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Special Issue: Global Dermatology-2

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Editorial

Innovations and Innovative Approaches or Pseudo-Innovations in the Context of General Globalization? It's Time to Wake Up!

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Keywords: innovations; global progress; pseudo innovations; critical opinion; neglected carcinomas; medical mistakes.

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Abstract

Globalisation, scientific and technical progress are the basis of numerous innovative therapies for oncologic and non-oncologic diseases. It is another matter how much and by whom they are desired, and whether they have to be applied. When and how often? Innovative approaches should go towards simplification, universal distribution and application while at the same time analysis between the potential initial investment and the achieved final result should be made. An illustrative example for this is the targeted therapy for melanoma with its low baseline criteria or basic rules for its surgical treatment. Another example could be the confocal microscopy in the context of dysplastic nevus syndrome. Therapies for various autoimmune diseases should also be considered critically. In the current OAMJMS issue, as well as in some of our other ideas and statements reported also in OAMJMS, we are trying to answer at least to a part of these dilemmas, to provoke a critical point of view and to ask some simple questions: “Should any innovation be considered as a face value? Which is potentially beneficial for our patients? How could we regulate the processes to minimise the need for expensive medications for certain diseases? And, of course, we are also turning to our own mistakes by visualising the results of them!

The essential questions in the context of progress and evolution in medicine and evolution, in general, affect some common human wisdom that is often ignored. We desire to be always first, move forward, and meanwhile be rich, desirable, glorified and famous … these two mutually exclusive directions or states of mind, I do not know, ... maybe ... maybe they are the reason to repeat our mistakes and not to learn from history as a whole? Perhaps the conditions for achieving one or another of the goals above are mutually exclusive, which gives rise to our subsequent absurd and sometimes inconsistent with the common-sense decisions? We are not able to think humanely, universally, reasonably and/or wisely, and meanwhile not prejudicing the interests of the status quo or someone? And if you harm those – you will be imposed “an embargo” by all possible means. The least of all is the financial one. Even a public reprimand, and ... a universal denial is possible! And here we come to the choice ... making the right decisions: black or white? Our decisions are followed by absurd consequences, or the lack of explicitness or the presence of a half-way policy in our decisions is followed by absurdities. Grey colour is undesired; it is for the politicians. In general, positioning is important. It results in a failure or rise. But not in “flickering”.

Or maybe these statements or rhetorical questions are wrong? And we should be chameleons? And surely there are such? At least I do not know any chameleons in medicine. Do you? Absurdities are a common human impediment caused by mercenary motives, by difficult to achieve, mutually exclusive desires inconsistent with healthy logic, and why not partly due to pure egoism?

Take melanoma and the new 2017

classification, for example? Think about the lack of an adequate response to questions related to therapeutic recommendations in any individual melanoma patient? All the way, up to the lack of personalisation of medicine in the early stages of the disease. What is this, ... you will ask? We will discuss it a bit later! Or ignoring important articles from magazines with a high impact factor? With very high impact factor! And with the highest impact factor! Is this not a serious problem – medical, human, health-related, personal? Magazines looking for results from multicentre double-blind, and I would specify – sometimes "totally blind" studies, although based on originally mistaken baselines? And how could this be admitted? Self-criticism is inherent to highly intelligent individuals only, and these are not always represented in high-quality, high impact magazines. I would ask, are there any editors in those magazines who have not seen "living patients"? At the meetings of the magazine boards, they usually announce that they will release 2-3 articles, just like that? A pure desire! Because their fingers "itch" to do so! So, how shall we then solve the problems related to innovative therapeutic approaches and classifications? By turning for advice to whom? Why can an editor of such a magazine publish 160 articles, say in NEJM, or 500 articles in Lancet, and cannot give a good answer to the question, "Why are you rejecting my article"? Or the answer is, "... because we have some other good articles and there is no room for you, unfortunately, but ... try somewhere else!" Or try again later! In other words, the spots are reserved for others? Unfortunately, I did not know that bookings were to be made early!? And do we have to leave a deposit, hahaha? By bank transfer or endowment? Next time I will ask this question ... I will do, for sure! When should I post an article that is better than 1,000 other articles … which is the right moment and are there any vacant spots … or maybe articles are less frequently released in general? Another interesting question would be, "When will logic triumph over lobbyism and selfishness? Is Christmas time convenient for you?" And when will you consider not only studies sponsored by the pharmaceutical industry, but also the "cast-iron arguments" of sound logic? These sometimes weigh more than sponsorship and fake magnanimity!

Why are certain general human and medical or humanity issues being rudely ignored? Why are two surgical interventions necessary in certain patients, where just one is sufficient [1] [2]? Why the high-frequency ultrasound approach is not introduced as a diagnostic option at least in some melanoma patients [1][2][3]? Why don't we define the fields of surgical safety more clearly [1]? Is it necessary to treat melanomas of different tumour thickness equally and those of the same tumour thickness – differently? Who could ensure the freedom to choose a resection field, or in other words, its variability? All these questions have no definitive answer and are left without any possible discussion or optimisation, which is, in fact, a simple and not impossible approach. If we look a little deeper and a bit earlier into the "shared problems", perhaps we would also conclude that such "severe neoplasm" therapy is not so difficult? That the clarification of the "starting points" or the so-called "baseline criteria" ... might contribute to the lack of necessary progress about the millions of funds invested in a targeted therapy at a later stage? Funds that could be spent somewhere else? The more we ask these questions, the more we should think about whether these criteria are real, workable, applicable and enforceable? And who created them? Why do they remain unchanged for such a long time despite the misconceptions they contain? And above all, who has an interest in this? And for how long? Because, maybe ... "TIME IS MONEY", ... someone said! And someone else ... that "medicine is business"!

Recently, we had patients with melanoma of more than 16 and 8 mm who were successfully treated just surgically? Without any dissemination data. Until eight years ago, chemotherapy or polychemotherapy was the standard of care in these patient groups? And all of a sudden it was sunk to the bottom? Targeting, or OMICS appeared? What would we say now if someone suggested dacarbazine, for example, in metastatic melanoma? Or prophylactically maybe?

There is light in the tunnel, definitely, but the adaptation of tumour cell is amazing. Melanoma depends on multiple factors, and OMICS therapy (following a genetic typing test) is not available to all or at least to the majority of mortal individuals! Apparently, apart from "Europe at two speeds", there is also a "different speed" medicine!

And what shall we say about confocal microscopy? Patients with dysplastic nevi? And patients with identical clinical, dermatoscopic and histopathological signs of two or more lesions? Protect them from progression? And/or from excisions? It was found that borderline, dysplastic and/or normal melanocytic lesions in a patient (whether with dysplastic nevi syndrome or not) ... could show a different gene pool (based on OMICS analysis or another type of testing) and a different progression trend within an indefinite period, wasn't it? Well then? Who needed such innovation? I see that even the world's dermatoscopy guru-Prof. Giuseppe Argenziano has been a bit sceptical over the years about dermatoscopy and confocal microscopy ... but my observation is indirect, tacit (personal observations)? Or maybe his age has told its heavy word and suppressed his emotionality? And then, the next step is reconciliation? Who knows? Or is my interpretation wrong? Or, rather, his scepticism about explicit statements on final diagnosis results from his long experience and the lack of definitiveness or reduced degree of definitiveness (of methodologies) about the final diagnosis!? Then his response to the lectures would be, "Then cut it! That's simple!" And I agree with him, but I would like to add that here we

come to the following problem, “We have to know exactly when to cut it and how to cut it! And that’s not very simple. It’s complicated, very ... complicated.” It’s a bit easier through the dermatoscope and in front of the screen! Problems will start only afterwards. “What problems?”, You will ask.

Figure 1: Patient with advanced basal cell carcinoma of the forehead, treated inadequately or initially semi-invasive. Gradual progression of the disease and involvement of the eyelid. Started therapy with Vismodegib presents half-way success

And here, right here, during the categorisation of treatment groups of melanoma patients, while choosing an approach, we start “limping”, not “stumbling”, but literally “limping”, and limping seriously! What field should we use to make the “cut”? Simply put but well thought out! Shall we use a high-frequency ultrasound testing, try one-step melanoma surgery, explain this individual approach to the patient, determine his/her mental condition and possible reactions. Or should we proceed with excision and possible re-excision, i.e. follow the guidelines? Are the clinically determined limitations consistent with the histological ones? Why the guidelines recommend no re-excision if there is a discrepancy of shared limitations? Should I divert from the guidelines and ask for an individual consent from the patient? How shall I make sure that I am on the right track? Scars, lesion localisation, side effects, type of anaesthesia? Why no re-excisions are recommended at least in patients with nodular and superficial melanomas and established differences (different clinical and histological limitations following the resection) … by the international guidelines? Isn’t the histologically proven field of safety more important than the clinical one!? This has not been commented so far!???? We could define it as an individual approach and personalised therapy. Personalization that is 100 times more important than personalised, targeted therapy in advanced stage patients (Figs 1-4). As early personalisation may determine the risk of progression, and late one 1) is much more expensive, and 2) constitutes a constant daily struggle. Late personalisation results in progression (Figs. 1-4). It is like chasing the wind. Then, each patient should set their personalised therapy priorities. Or, if I may repeat myself, “We don’t have money, so we have to start to think!”

So, if Prof. Giuseppe Argenziano would excuse me for that statement, but I will explicitly state: 1) “The task of the dermatologic surgeon, the thinking dermatologic surgeon, the trying to think and thinking at least from time to time ... the dermatologic surgeon is much more responsible than the dermatologist's or confocalist’s task!”

It is one thing to watch the screen and say what should be done, and another … as they say … is simply, “Just do it!”

Figure 2: Patient with locoregional metastatic squamous cell carcinoma on the temple region. Massive locoregional metastatic process with facial paresis. Treated with cryotherapy with no histological verification of a tumour performed before it

Some time ago, as a child ... I enjoyed watching Kung Fu movies and was excited to the highest degree ... I often tried to imitate those characters, but in the course of time I found out it was not quite simple, as it required serious preparation (physical and mental). Moreover, despite the effort, implementation of practised movements is not always successful in practice. But: Just cut it ..., I still think it's a good expression! A pretty good expression. And I stopped watching movies! Or I do it less and less frequently!

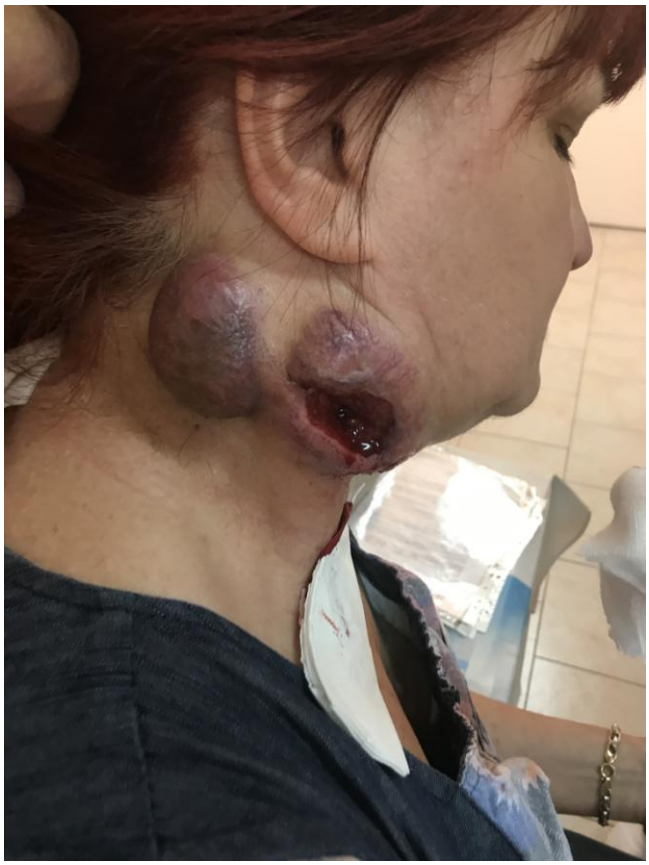

Figure 3: Patient with massively evolved local metastatic process within a histologically proven ameloblastic carcinoma. Surgical intervention is planned for removing the giant metastases, parotid gland and sublingual gland. Afterwards, postoperative radiotherapy will be conducted

Dear colleagues and friends from brotherly Macedonia, I hope that this new edition of the dermatological book within the high-quality OAMJMS of our highly valued and internationally recognized friend, scientist and colleague Prof. Mirko Spiroski, will give valuable highlights to all of us on how we should or should not proceed in certain situations! What are the new trends in vitiligo treatment, how to deal with rare clinical cases to achieving maximum safety of our patients? What should we expect from inadequate treatment of skin cancers and are our mistakes rectifiable? Is traditional medicine the most reliable one? Shall we observe the guidelines, and when this is not desired or at least "inhuman"? The thing is that before being therapists, we are still and ... I would say, though rarely ... or less and less frequently, also people! The problems we face as clinicians and dermatosurgeons surpass by several levels of complexity those of the initial conservative judgment and treatment recommendations in melanoma patients. More importantly, personalised medicine should be launched and is launched exactly at that stage and not at the terminal stage. Personalization should not be a mere equivalent of cash flows and targeted treatment, as well as of shamelessly expensive OMICS analyses?! Personalization is free of charge! Or at least should be! Personalization is our time, enthusiasm, satisfaction to win, our medical mind, medical thought, medical approach. Personalization is our human duty!

For estimation is determined by the radical nature of the approach and the clear rules – two things that are currently missing in the melanoma treatment, for example, worldwide. Now and until now. Let's hope this will change in the future, but the desire to change the status quo is one thing, and real actions – something else. Upgrading of a system that has been somewhat built as a "sand tower", is unthinkable for some... colleagues ... and lobbies in medicine – at least for now. Then, the forecast should also remain relatively the same. As well as our expectations. Plus, the applause at congresses and cocktails for how great we are!

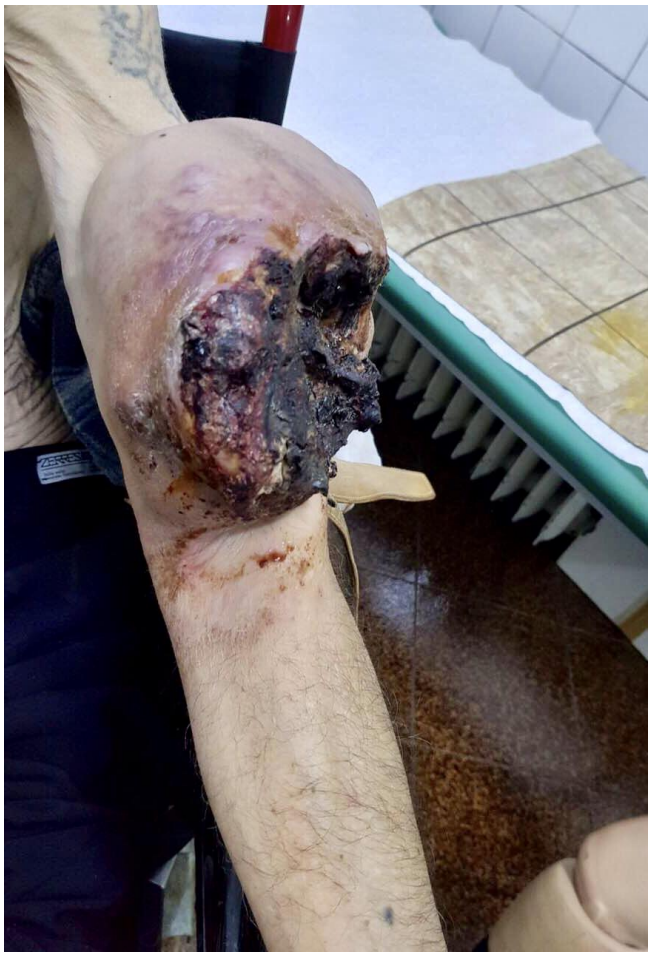

Figure 4: Giant tumour of the skin with bone tissue involvement in an elderly patient with poor social status. Subsequently, an amputation of the hand was performed

Of course, we should not be absolute pessimists. Criticism is necessary to realise at times or be aware of what we are forced to do or have done so far. And for what reasons. It is not easy to get to that point! Some people live all their lives without realising what they are doing and why they do it? Even to their last breath, it remains a dilemma for them. Was it right? I don't know?

I began realising what I was doing just after 17 years of work experience. More or less. And I am pleased to have a vision and a quest for something I want to change. The system put pressure on me; I followed the rules created by others until ... I had a little spare time to do some thinking. Even of my inadequate actions, which were not to be neglected after all? And I discovered my and our omissions ... as I had no choice, let alone a lobby! And money too! Then I could only be "logically aggressive". That was the only thing I was left! I had no choice!? The logically determined verbal aggression (as some say) based on "cast iron facts", expressed as tragic-comedy scenario (such as this editorial, for example) is maybe our only chance to impose innovative, different, unconventional opinion, to impose a change, generate positive energy to make our colleagues leave their comfort zone and bring one or another action or undertaking to a successful end. Because success is discomfort. And this is certain. Stick to early personalisation (Figs 1-4).

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Basic Science

Early Regenerative Modifications of Human Postmenopausal Atrophic Vaginal Mucosa Following Fractional CO_2 Laser Treatment

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Keywords: Vaginal atrophy; Postmenopausal; Fractional CO_2 laser; Laser treatment; Regenerative

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Abstract

BACKGROUND: Postmenopausal women experience undesired symptoms that adversely affect their quality of life. In the recent years, a specific 12 - week fractional CO_2 laser treatment has been introduced, with highly significant relief of symptoms.

AIM: The aim of this paper is the identification of the early modifications of structural components of atrophic vaginal mucosa induced by laser irradiation, which is responsible for the restorative processes.

MATERIAL AND METHODS: We investigated by microscopical, ultrastructural and biochemical methods the modifications of the structural components of postmenopausal atrophic vaginal mucosa tissues after 1 hour following a single fractional laser CO_2 application.

RESULTS: In one hour, the mucosal epithelium thickens, with the maturation of epithelial cells and desquamation at the epithelial surface. In the connective tissue, new papillae indenting the epithelium with newly formed vessels penetrating them, new thin fibrils of collagen III are also formed in a renewed turnover of components due to the increase of metalloproteinase - 2. Specific features of fibroblasts support stimulation of their activity responsible of the renewal of the extracellular matrix, with an increase of mechanical support as connective tissue and stimulation of growth and maturation to epithelium thanks to new vessels and related factors delivered.

CONCLUSION: We found the activation of regenerative mechanisms expressed both in the connective tissue - with the formation of new vessels, new papillae, and new collagen - and in the epithelium with the associated thickening and desquamation of cells at the mucosal surface.

Introduction

Vaginal atrophy (VA) is common clinical condition due to a decline in ovarian estrogens' production. In women with VA, it is possible to observe a macroscopic narrowing and shortening of the vaginal canal and a microscopic thinning of the vaginal mucosa (often associated with inflammation).

VA is a physiological process occurring after menopause, but it can develop in some other conditions such as after bilateral ovariectomy, chemotherapy for breast cancer, pelvic radiotherapy, and also during breast - feeding.

Moderate and severe VA can determine genital and urinary symptoms like vaginal dryness, dyspareunia, vaginal burning, dysuria, urinary urgency, urinary incontinence and a higher likelihood

to develop urinary tract infections (UTIs).

Different authors have reported the clinical safety and efficacy of a fractional CO_2 laser treatment protocol (MonaLisa Touch™), including three office sessions performed at an interval of 30 days one after the other, with a significant improvement in the genital and urinary symptoms [1][2][3][4][5][6] as well as in the sexual function [7]

Salvatore and Zerbinati [1][2][3] described the following important histological changes after this treatment protocol:

• a thickening of the epithelium, with the maturation of epithelial cells and desquamation at the epithelial surface as in premenopause;

• a new formation of papillae indenting the epithelium with newly formed and extended small vessels;

• in the connective tissue underlying the epithelium, the formation of new thin fibrils and morphological features of fibroblasts supporting a renewal of the extracellular matrix with functional restoration.

All these events are part of the regenerative effect on the vaginal tissue of the fractional CO_2 laser treatment. However, no - one has yet described its onset, and when and how the initial tissue modifications occur.

In this study, we aimed to identify the first modifications features (1 hour following one laser application) responsible for the starting regenerative mechanisms in vaginal postmenopausal atrophic mucosa after fractional CO_2 laser treatment.

Methods

In this study, during a surgical procedure for prolapse in a postmenopausal woman (63 years) and with the informed consent of the patient, we evaluated atrophic vaginal mucosa biopsies, before treatment and 1 hour after a single fractional CO_2 laser application. The CO_2 laser (SmartXide2 V2LR, Monalisa Touch®, DEKA, Florence, Italy) was set to a single spot size of 200 µm, and an optomechanical scanner was used to induce a spot sequential targeting in each energy pulse (D - pulse) with dot power 30 W, dwell time 1000 µs, dot spacing 1000 µm and stack parameter 2.

Mucosal biopsies (before any treatment as a control, and one hour after laser irradiation) were taken, immediately immersed in the fixative solutions and processed according to standard procedure with paraffin and epoxy resin embedding, respectively for light and electron microscopy. Particular care was used for correct orientation of biopsy samples, both in the embedding and sectioning phases of the preparative procedure, to prevent incorrect observations. The sectioning plane for all preparations was rigorously perpendicular to the epithelial surface, the thickness of all sections (pre - and post-treatment biopsies) was the same (5 µm), and the staining of sections was made at the same time and in the same solutions of dyes.

For light microscopy, some sections were stained with Hematoxylin and Eosin for verifying the correct orientation of mucosa samples, others with trichromic for a general view of the mucosal structural organisation, others with Picrosirius red (see above).

For high resolution light microscopy and electron microscopy, semithin (0.2 µm) and ultrathin sections were cut from epoxy resin (Epon 812) embedded specimens, after fixation with a glutaraldehyde/paraformaldehyde (2.5/2%) solution in Sodium cacodylate buffer followed by Osmium tetroxide 1.33% solution in s - Collidine buffer and dehydration before embedding. Semithin and ultrathin sections were obtained by an ultramicrotome Reichert Ultracut. Semithin and ultrathin sections were stained, respectively, with toluidine blue and uranyl acetate/lead citrate.

Specific analysis of sections for light microscopy was made using a staining method based on Picrosirius red, a dye which not only stains specifically collagen fibres but also enhances the collagen birefringence [8][9][10]. Picrosirius red was used as a solution 0.1% of Sirius red F3B in a saturated aqueous solution of picric acid for one hr at room temperature. The sections to be compared, all with the same thickness, were stained for the same time in the same dye solutions. Fainty staining with Hematoxylin was also used for nuclei.

At the light microscope provided with a setting of circularly polarised light, Picrosirius red stained fibres can be differentiated through a scale of different colours. Birefringent structures (collagen fibres) in the connective tissue of lamina propria were highly visible not only as brilliant structures, but some of them appeared Red/Orange, and others appeared Green/Yellow. In the scale of colours, Red/Orange structures are representing thick collagen fibres, while Green/Yellow is representing thin fibres [11].

On this basis, in the sections of the same thickness (5 µm) observed with circularly polarized light, it has been possible to apply a computerized morphometric analysis through a specific thresholding of the colour scale, permitting the identification and the evaluation of thick collagen fibres (mature), and thin collagen fibres (immature, the most recently formed), these last as expression of the onset of regenerative mechanisms of the extracellular matrix.

Microscopic observations were made at a light microscope Carl Zeiss Axiophot provided, for

circular polarising microscopy, with suitable filters in the condenser stage and the microscope tube. Images were recorded through a microscope digital 5 megapixels CCD camera Nikon DS - Fi2.

Computerized morphometric analysis was also performed. As the most reliable tool, it was used ImageJ (NIH, version 1.51a), a well - known software recognised as the standard tool by the international scientific community.

The following different steps were used as ImageJ tools, operative sequence and related meanings are reported: - File open; - Image, Type RGB color; - Adjust, Color Threshold: adjust Hue, Saturation, Brightness for the interactive selection of the Red/Orange or Yellow/Green threshold values to have a mask exactly superposed to the structures of interest to be saved in two different channels.

The Hue upper value for Red/Orange must be separated by a significant wider cleft from the lower Hue value for Yellow/Green to prevent superposition of data and a double evaluation into the two channels of the same structures (a value of 8 was evaluated as good).

In this study the values were:

Red channel: Hue 0 - 34, Saturation 106 - 255, Brightness 106 - 186.

Green channel: Hue 44 - 118, Saturation 106 - 255, Brightness 106 - 186.

- Save as: Red/Orange and Yellow/Green were saved as the single images of the two different channels.

For a correct comparison of results, obtained from sections of the same thickness and stained at the same time and in the same staining solutions, the values of Hue, Saturation, Brightness thresholds were maintained the same for all the microscopic preparations.

In the following step, each one of the images representing the two channels has to be converted into a digital one.

- Image, Type, 8bit before the following step.

- Image, Adjust, Threshold: it means to extract from each selected continuous tone image, a binary image. So the areas of interest corresponding to the defined masks (Red or Green) are constituted by black pixels (signal) on a white background. These images are ready for the measurements.

- Edit, Selection, Select all

- Analyze, Select particles. Select the following parameters: Display results, Summarize, Add to Manager, In situ show. The area % occupied in the reference frame of 2560 x 1920 sq pixels is so obtained and registered for comparison.

Zymography. Vaginal mucosa samples collected by biopsy were suspended in 10 mM phosphate buffer, pH 7.4 (1 mL) and then submitted to homogenization by using a Potter - Elvehjem homogeniser. The homogenate obtained was centrifuged at 12000 rpm for 10 min and the supernatant transferred into Eppendorf tubes and stored at - 80°C until the moment of use. The protein concentration of cellular extracts was determined using the bicinchoninic acid assay [12]. Aliquots of cellular extracts containing 30 µg of proteins were run on 10% Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS - PAGE) containing 0.1% gelatin. After electrophoresis and washing with 2.5% Triton X - 100 (30 min), gels were incubated 24 hr at 37°C with 100 mM Tris - HCl, 10 mM CaCl2, pH 7.4. Gels were stained with Coomassie Brilliant Blue and destained with 20% methanol, 10% acetic acid. The proteolytic activities were quantified after gels scan using Image J software.

Results

In this paper, we were able to identify very early structural modifications, at 1 hour after treatment, of vaginal mucosa in a postmenopausal woman treated with one fractional CO2 laser. These modifications will be enhanced and stabilised with more applications in clinical practice, restoring a healthy condition to vaginal mucosa with relief of undesired symptoms affecting women quality of life.

The comparison between two slices from two biopsies samples of the same postmenopausal woman is represented in Figure 1, before (1a) and 1 hour (1b) after fractional CO_2 application.

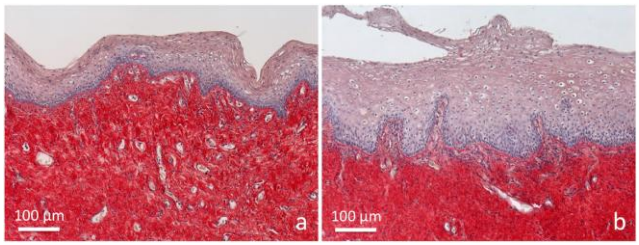

Figure 1: Samples of vaginal mucosa respectively a) before and b) 1 hour after laser application. a) The epithelium does not present any superficial desquamation, and its basal surface appears relatively smooth. The connective tissue is intensely stained; b) the epithelium is thicker, formed by bigger cells distributed in very numerous layers. At the surface, it appears desquamating in the vaginal lumen. The connective tissue is penetrating into epithelial indentations as deep bell-shaped structures constituting newly formed papillae. Papillae are formed by a loose connective tissue with small and thin fibrils inside, faintly stained by Picrosirius red. Many penetrating small vessels, are observable inside them. Light microscopy (not polarised light), sections 5 µm thick. Picrosirius red and fainty Hematoxylin staining

Before treatment (Figure 1a) the vaginal epithelium was constituted by few layers of cells,

densely packed, with dark nuclei and few cytoplasm. No signs of epithelial desquamation were detectable. The connective tissue appeared formed by thick and densely packed bundles of collagen fibres. No papillae were detectable.

At 1 hour after laser application (Figure 1b), the epithelium appeared much thicker, formed by numerous layers of cells, bigger and with clearly observable desquamation at the epithelial surface. The connective tissue was also different, with numerous papillae deeply indenting the epithelium. The most superficial part of the connective tissue underlying the epithelium and constituting the papillae appeared lighter; inside it a rich network of small blood vessels was detectable. Inside papillae at higher magnification (Figure 2), blood capillaries appeared differently oriented, some longitudinal, some obliquous, others transversally sectioned.

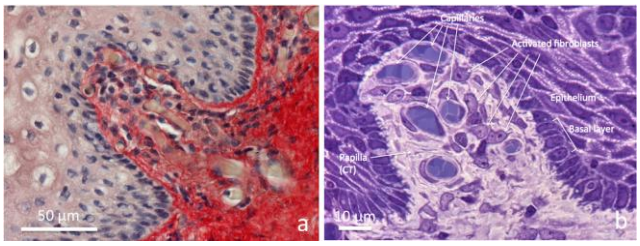

Figure 2: Connective tissue bell-shaped papillae in vaginal mucosa samples 1 hour after laser application. a) Paraffin section (5 µm) stained with Picrosirius red and light Hematoxylin, b) semithin section (0.2 µm) from resin embedded specimen, stained with toluidine blue. a) at the centre towards the high left, the connective tissue of papilla seem "pushing" underneath the epithelium by the growing connective tissue rich in vessels. In the loose and faintly stained connective tissue of papilla, very thin red fibrils between blood capillaries are observable. b) The semithin section permits high-resolution light microscopy. Transverse sections of blood capillaries, small pericytes around endothelium and fibroblasts with clear nuclei and well visible nucleoli, and basophilic cytoplasm are observable. Into the epithelium facing the connective tissue, the basal layer appears organised by a single row of cuboidal cells with basophilic cytoplasm. Light microscopy (not polarised light)

The thin endothelial wall of capillaries appeared surrounded by a light extracellular matrix in which very fine fibrils, often intermingled between them, were well identifiable in Picosirius red stained sections (Figure 2a). The cellularity inside papillae was represented mainly by endothelial cells and fibroblasts.

In semithin sections (0.2 µm) from epoxy resin embedded specimens (Figure 2b), further details on the structures inside papillae were observable. The very thin endothelium of capillaries appeared surrounded by flattened pericytes and the extracellular matrix, particularly rich in ground substance, was faintly stained due to the presence of very thin fibrils widely distributed and differently oriented. Here, big and compacted bundles of collagen fibres were absent. Many fibroblasts were easily identifiable inside papillae, due to clear nuclei rich of euchromatin, in which nucleoli were detectable for their intense basophilia. Their cytoplasm also was basophilic, with a uniformly distributed basophilia. At the electron microscope, the cytoplasm of fibroblasts was particularly rich in profiles of the rough endoplasmic reticulum (RER), represented by a lot of membranous cisternae with many ribosomes attached to the cytoplasmic surface of membranes (Figure 3).

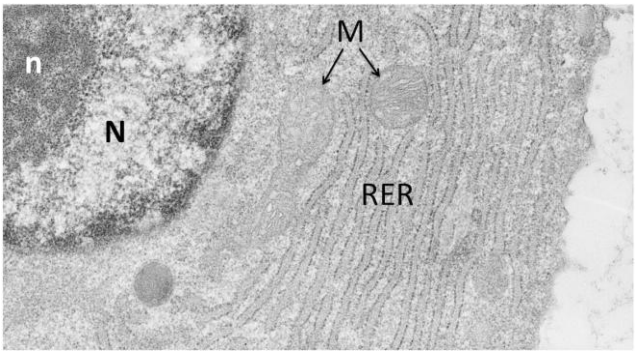

Figure 3: Electron micrograph representing a papillary fibroblast. Part of the nucleus (N) rich in euchromatin is showing inside a compacted nucleolus (n). In the cytoplasm, a highly extended rough endoplasmic reticulum (RER) rich in ribosomes, containing inside cisternae a finely filamentous material, is well visible. M: mitochondria

In the epithelium, the basal layer was well recognisable (Figure 2b), as formed by highly ordered cuboidal cells, which in the living tissue are continuously providing cells both to the same basal layer and to the upper layers of the epithelium for maturation and superficial desquamation. In the lower part of epithelium facing the represented papilla (Figure 2b), the basal surface of the epithelial cells of the basal layer appeared provided with many protrusions, as small feet anchoring to the basement membrane, as into the most of the functionally active premenopausal vaginal epithelium. In the upper third of papilla (Figure 2b), the basal part of epithelial cells appeared smoother, less or not provided with small basal protrusions, as a sign of the dynamic growth of the epithelium in the apical part of the newly formed and still developing papilla.

Picrosirius red staining did not exhaust its potentiality only with selective staining of collagen and enhancement of its birefringence but using circularly polarised microscopy; it permitted the identification and differentiation of big bundles of collagen (mature) and smaller fibres and fibrils (newly formed) through a scale of colours.

We have applied to digital images of microscopic fields of histological preparations, stained with Picrosirius red and observed at the circularly polarised microscope (Figure 4), a suitable colour channel selection for identification of different collagen fibres (Figure 5). As analytically illustrated in the Methods section, we used ImageJ software and computerized morphometric analysis for extracting from the digital images the percent areas occupied by thick fibres appearing Red/Orange and thin fibres appearing Green/Yellow on identical 2560 x 1920 sq

pixels standard reference frames. The segmentation thresholds for both control and treated samples were maintained the same.

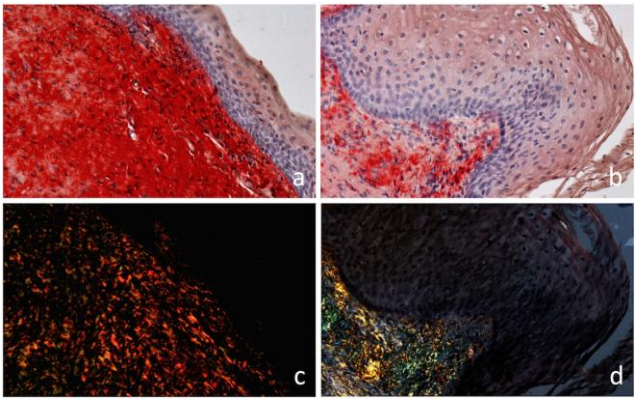

Figure 4: Samples of vaginal mucosa respectively a) and c) before, b) and d) 1 hour after laser application. Picrosirius red stained sections. a) and b) observed with not polarised light. a) atrophic mucosa with a relatively thin epithelium formed by small compacted cells, and connective tissue intensely stained. b) epithelium appears much thicker, with big cells desquamating at the epithelial surface. The connective tissue of papilla is mainly formed by thin fibrils. The same sections, observed at the circularly polarised light microscope, are represented in b) and c) respectively. The visible coloured structures are constituted by collagen fibres which, without any additional filter, are showing different colours, appearing red, or orange, or green or yellow. This is due to different collagens and specific interactions with the Sirius red stain. The epithelium is not visible because it does not contain birefringent structures

The resulting percentage areas of collagen profiles in the Green/Yellow channel and the Red/Orange channel, respectively for controls and treated, are represented in Figure 6.

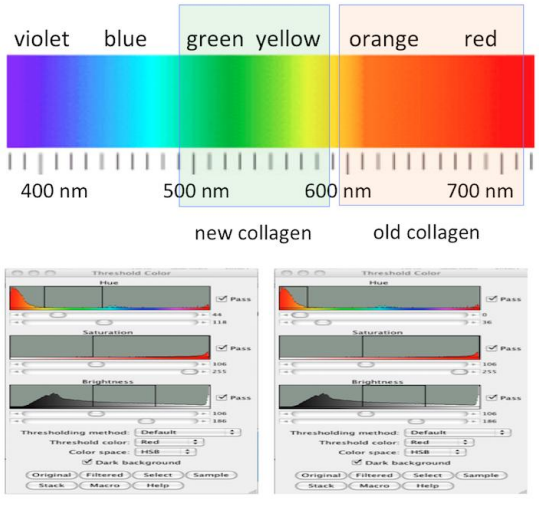

Figure 5: The tool used for computerised morphometric analysis is represented (in detail described in Materials and Methods), with the selected colour bands which have permitted the selected evaluation of the green/yellow and the red/orange fibres. The tool "Adjust colour threshold" was used for segmentation of sampling areas, extracting from each preparation the green/yellow appearing thin fibres and the red/orange appearing thick fibres to be evaluated

The result of the treatment shows respect to the control, a significant increase of thin fibres (Figure 6), not only in the newly formed papillae but also in the lamina propria of the vaginal mucosa.

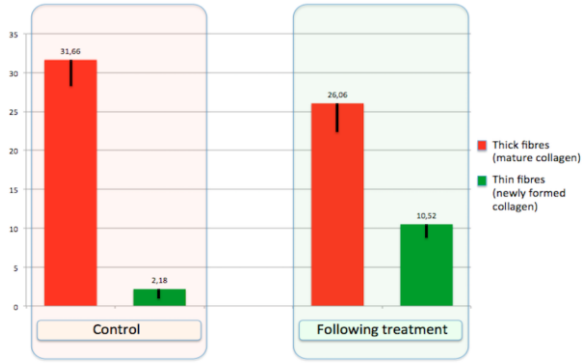

Figure 6: Results from the computerized morphometric analysis performed on the connective tissue of lamina propria in Picrosirius red stained sections. Comparison between the percentage area occupied by thick fibres (red columns, mature collagen) over a reference frame and the percentage of the area occupied by thin fibres (green columns, immature/newly formed collagen) over a corresponding reference frame, respectively in samples controls (before) and in samples 1 hour after fractional CO2 laser treatment

At last, the zymographic analysis of MMP - 2 (Figure 7) demonstrated an increase of the active form of MMP - 2 and a corresponding decrease of latent MMP - 2 form, suggesting and confirming the early starting of the enzymatic pathway for collagen turnover.

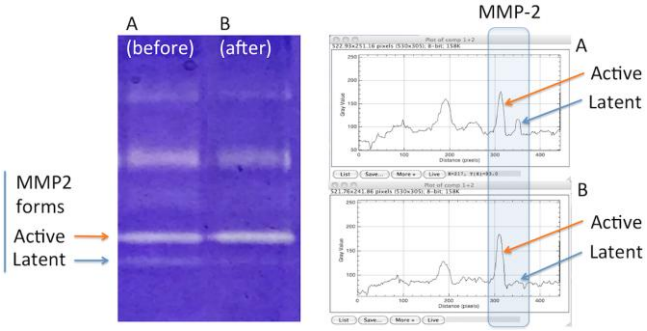

Figure 7: Zymograms obtained by electrophoresis and related densitometry plots of activity bands of active and latent MMP-2 forms from a) control, and b) following treatment

These features are realistically representing the demonstration of the very early onset of the regenerative mechanisms in the connective tissue, with related trophic stimulation of growth and maturation of the epithelium. These regenerative mechanisms, started so early, will be enhanced and then stabilized with following laser applications with relief of symptoms as an effective treatment, consisting in three laser applications with follow up at 12 week [1][2][3][4][5][6], resulting in a long-lasting renewed and rejuvenated mucosa.

Discussion

In the premenopausal fertile age women, the vaginal mucosa is presenting as a well-structured bilayer of tissues, with a squamous stratified, not keratinised epithelium formed by many layers of cells and a lamina propria of connective tissue. Numerous projections of the connective tissue are expanding in the underface of the epithelium forming characteristic indentations as papillae. Papillae constitute very important mechanical and trophic structures. They are representing not only a significant increase of structural link between the epithelium and the connective tissue but also a functional link permitting a much better diffusion of nutrients to the stratified epithelium through a much more extended surface. Through the basement membrane, the connective tissue results firmly anchored to the epithelium through different collagens, fibronectin, proteoglycans, glycosaminoglycans, and glycoproteins synthesised by fibroblasts.

Another highly significant function of papillae is closely related to a rich presence of blood capillaries, permitting a high rate of metabolic support (water, ions, mineral salts, oxygen, etc.) to the epithelial cells, particularly to the intermediate and superficial layers of the very thick stratified epithelium.

In premenopause, the structure of the epithelium is undergoing to cyclic changes during the ovarian cycle, and it is maintained by the influence of estrogens, particularly during the follicular phase. For the most of cycle, epithelial cells are synthesising glycogen, which is stored in the cells and, through maturation and migration toward the surface is delivered by the shedding cells at the epithelial surface, constituting a sort of secretion. The delivery of glycogen, considering that vaginal wall is lacking glands, is very important for maintaining a correct physiological microenvironment supporting vagina health.

When in postmenopausal women estrogens secretion declines and almost completely stops, vaginal mucosa undergoes to dramatic changes, both structural and functional. The epithelium becomes much thinner, constituted by few layers of small cells, the synthesis and storage of glycogen are highly reduced, and shedding rate is very low or absent.

The benefits of fractional CO_2 laser treatment of vulvovaginal atrophy in postmenopausal women have been clearly demonstrated in some recent papers concerning a 12 - week treatment with histological analysis at time 0, after 1 month and after 2 months [1][2][3][4][5][6][13]. Also, the effectiveness of this treatment has been demonstrated even in women with a history of breast cancer [14][15].

But very early modifications on atrophic vaginal mucosa treated with laser irradiation - as in this study (1 hour after one fractional CO_2 laser application) - have never been reported in the literature.

In this paper, early structural modifications of atrophic vaginal mucosa in postmenopausal women after a very short time (1 hour after one fractional CO_2 application) have been studied, to identify the structures as the first involved in the starting of regenerative mechanisms. Also, we have also considered the role of metalloproteinase MMP - 2, well known as an interstitial collagenase [16], by zymography technique, an efficient method based on electrophoresis of bis-acrylamide gels copolymerized with a protein substrate [17]. The degree of digestion of the substrate into the zymograms by purified gelatinase - A (MMP - 2, the matrix metalloprotease of interest extracted from bioptic samples) is proportional to the enzyme loading, and varying the incubation time results in a shift in the linear range of the assay [18]. In this assay system, active and latent forms of MMP - 2 show the same degree of digestion, allowing reliable comparability of quantitative assessment of MMP - 2 activity, as modifications of the of the latent/active forms. In our observations, the increase of MMP - 2 active forms and the corresponding decrease of the latent form in the biopsy 1 hour following treatment, constitutes a significant indication of production and degradation of collagen, as the stimulation of a new equilibrium occurring in the regenerative process of the connective tissue. These results are in some respect similar to those obtained following photobiomodulation energy transfer in the skin [19], even if in the reported paper it was used a photosensitizer and the evaluation of the effects was made after a longer time. The results of zymography analysis concerning MMP - 2, indicating higher expression level of MMP - 2 active form and lower MMP - 2 latent form in the biopsy of mucosa 1 hour following fractional CO_2 laser treatment, are in agreement with our histological and morphometric findings showing an increase of thin collagen III fibres and a decrease of the thick collagen I fibres (Figure 6).

Our observations on vaginal mucosa samples are demonstrating that vaginal mucosa tissues were modified, involving both connective tissue and epithelium. The connective tissue, particularly in the most superficial part, appeared as a loose connective tissue rich in ground substance and very fine collagen fibrils (finely stained by Picrosirius red), containing a lot of small vessels. Newly formed well detectable papillae - absent in the atrophic mucosa - expanding underneath the epithelium, are constituting a striking modification of the connective tissue after fractioned CO_2 laser application. Realistically, the presence of a lot of vessels into papillae is an important factor stimulating epithelial metabolism. The epithelium, following treatment, is much thicker than control, with intermediate and superficial layers constituted by bigger cells. At the epithelial surface, evident desquamation is detectable (Figure 1b), with cells

shedding in the vaginal lumen. These features are consistently supporting a very early restoration onset of the differentiative/maturative mechanisms of epithelial cells.

Related to the possible mechanisms involved in such striking modifications of atrophic vaginal mucosa, some papers on skin treated with fractional CO_2 laser - where a connective tissue is closely facing a stratified epithelium (in that case keratinized) and where papillae are constitutive elements - were published supporting the increase in growth factors following CO_2 laser application [20][21][22]. One of these reports interesting immunohistochemical evaluations of cytokines delivered in the skin following fractional CO_2 irradiation [22]. More specifically, in that paper have been reported increases of TGF - β (stimulating synthesis of matrix proteins, such as collagen), bFGF stimulating angiogenetic activity with endothelial cell migration and proliferation), EGF (stimulating the re-epithelization), PDGF (stimulating fibroblasts to produce extracellular matrix components), and VEGF (regulating vasculogenesis and angiogenesis), starting immediately after laser irradiation, with evaluations performed until to 30 days. Though observed in the skin, the increase in these factors following fractional CO_2 laser application, starting immediately after irradiation, well couples with our findings reported in this paper on the very early modifications of atrophic vaginal mucosa following fractional CO_2 laser irradiation.

Our microscopic and ultrastructural findings demonstrate the formation of new vessels and the morphological features related to the stimulation of fibroblast activity, with a new production of connective tissue matrix components (as the increase of newly formed thin collagen fibrils), the growth of epithelium and the activation of epithelial cell differentiative mechanisms (glycogen synthesis). In particular, as evident by our observations, the expression of these mechanisms is observed in the epithelium in the suprabasal and in the intermediated layers of cells (big cells with an extended cytoplasm in which begins to be stored newly synthesised glycogen), and in the connective tissue. Inside papillae, particularly, fibroblasts are presenting features - such as an extended rough endoplasmic reticulum (the site of synthesis of procollagen molecules [23], an euchromatic nucleus provided with a clearly detectable nucleolus, and mitochondria (Figure 3) - supporting an active engagement of these cells in the renewal of collagen (and other molecular components of the extracellular matrix).

Owing to our use of the dye Sirius red, Picrosirius red is intensely staining collagen and enhances collagen birefringence [11]. Other Authors demonstrated the advantages of this technique compared to traditional methods [9][11][24][25][26], also useful for studying the differential distribution of the structurally distinct collagen types [11] or the collagenolysis with related stimulation of new collagen synthesis, into vesical prolapse lesions [27].

Due to the variability of the traditional trichrome staining which does not always stain collagen fibres with the same colour and some fibres do not stain at all [26], in contrast, the enhancement of collagen's natural birefringence by Picrosirius red stain reveals more collagen than can be seen after trichrome staining. With this method, even fine collagen fibres can also be identified due to their enhanced birefringence [26].

The enhancement of birefringence is highly specific for collagen because many Sirius red dye molecules link parallel to the long axis of each collagen molecule, both thick and very thin as single or few tropocollagen molecules [27].

In our study, we used circularly polarised light rather linear polarised light. The advantage of this choice is that all collagen fibres appear bright regardless of their orientation within the section plane [10][26], permitting a reliable quantitative analysis. Owing to the different colours observed, red-orange or green-yellow (Figure 4 c, d), this is due to the degree of polymerisation and packing of collagen molecules and their 3D organisation. Big bundles of highly packed collagen molecules (red/orange) or thin bundles of few molecules of collagen (green/yellow), are reflecting distinct patterns of physical aggregation and the different content of mature, old collagen (collagen I), and immature, newly formed collagen (collagen III) [11][19][27].

Due to the enhancement of natural birefringence of collagen by Picrosirius red staining, it has been possible to detect even very thin collagen fibres, not detectable with other staining methods, as a trichrome stain for example [26]. As thickness and compactness of collagen increases, the colour of the fibre changes from green to yellow, to orange to red. Due to the thickening of collagen fibres as they mature, as in the wound healing, a prevalence of green fibres realistically is indicating a remodelling or a relatively newly formed matrix [26][28][29][30].

Our findings obtained by circular polarising microscopy applied to Picrosirius red stained sections from vaginal mucosa biopsies taken 1 hour after one fractional CO_2 laser application, are furtherly supporting the very early starting of regenerative mechanisms. They realistically begin firstly in the connective tissue with the renewal of the extracellular matrix and the formation of new vessels and papillae and develop stimulating the thickening of the epithelium, supporting at the same time the maturation of epithelial cells. A restored synthesis and storage of glycogen occur, followed by desquamation with the delivery of glycogen in the vaginal lumen. Here glycogen is hydrolyzed to glucose, feeding Lactobacilli vaginalis with the production of lactic acid. Lactic acid acidifies the inner vaginal environment restoring the healthy acidic vaginal pH [31][32]. The mucosal surface is so moistened, and at the same

time, the colonization of yeasts and potentially pathogenic bacteria are inhibited [31][32].

In conclusion, microscopic modifications of postmenopausal vaginal mucosa 1 hour after fractional CO_2 laser treatment have never been reported in the literature.

In this paper, we have presented the onset of very early structural modifications of the epithelium and connective tissues of postmenopausal vaginal mucosa 1 hour following one fractional CO_2 laser application. Such modifications are suggesting the activation of regenerative mechanisms expressed both in the connective tissue - with the formation of new vessels, new papillae, and new collagen - and in the epithelium with the associated thickening and desquamation of cells at the mucosal surface. Furthermore, the specific properties of the PicroSirius Red staining which enhances the natural birefringence of collagen, using circular polarising microscopy, permitted to obtain a further reliable demonstration of an effective early remodelling of the extracellular matrix.

In clinical practice, these early restoring modifications will be enhanced and stabilised with a long-lasting effect by subsequent laser applications in an effective, experienced plan as a clinical treatment that ensures to vaginal mucosa of postmenopausal women a renewed healthy condition.

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Basic Science

In Vitro Evaluation of the Biosafety of Hyaluronic Acid PEG Cross-Linked with Micromolecules of Calcium Hydroxyapatite in Low Concentration

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Keywords: hyaluronic acid; biosafety; calcium hydroxyapatite; human keratinocytes; Neauvia Stimulate

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Abstract

OBJECTIVE: Neauvia Stimulate is biocompatible, injectable hyaluronic acid (HA) filler (26 mg/ml) PEG cross-linked with 1% of calcium hydroxyapatite (CaHA) for facial soft-tissue augmentation that provides volume to tissues, followed by process of neocollagenesis for improving skin quality.

AIM: The aim of the present study is to evaluate the biosafety of the product (Lot. 160517-26-1/2 PEG) on human keratinocytes cultured in vitro.

MATERIAL AND METHODS: The experimental model proposed, despite being an in vitro system, allows the derivation of useful information to predict the possible activity of the product in further in vivo application. Human keratinocytes (HaCaT cells) were treated with the product for 24h at increasing concentrations of product respect to control (untreated cells).

RESULTS: The biosafety of the product to be tested has been evaluated performing different methods: MTT test, NRU test, Kenacid Blue assay. Moreover, any possible effect on the structure, morphology, and viability of cells has been evaluated.

CONCLUSION: In conclusion, the results obtained by the different methods show that the product Neauvia Stimulate® does not cause any cytotoxic effect and does not affect the correct structure and morphology of cells cultures.

Introduction

Neauvia Stimulate (MatexLab SA, Lugano, CH) is a product which combines pure hyaluronic acid of probiotic origin (*Bacillus Subtilis*) cross-linked with PEG (poly-ethylene-glycol) and micromolecules (10-12 μm size) of calcium hydroxyapatite in low concentration (1%). The product could be considered a "composite" filler (completely biocompatible and degradable) with both volumizing effects, typical of the HA filler cross-linked polymer [1][2][3], and a collagenesis activity. The latter is obtained by the action of calcium hydroxyapatite that stimulates the

skin self-production of collagen [4][5][6].

The aim of the present work is to evaluate the *in vitro* biosafety, in term of cytotoxicity and modification of the cellular structure and morphology, after treating human keratinocytes cultured *in vitro* with the product Hyaluronic Acid Hydrogel 26 mg/ml PEG cross-linked with Calcium Hydroxyapatite 1% (Lot. 160517-26-1/2 PEG), named Neauvia Stimulate. The experimental model proposed, despite being an *in vitro* system, allows the derivation of useful information to predict the possible activity of the product in further *in vivo* applications.

Materials and Methods

Sample preparation

The product Neauvia Stimulate was weighed and dissolved at the concentration of 5 mg/ml in complete medium constituted by DMEM with 10% fetal bovine serum (FBS), one mM L-glutamine and antibiotics (100 UI/ml penicillin and 100 µg/ml streptomycin). SLS (Sodium Lauryl Sulphate), well-known cytotoxic substance, was used as positive control and was prepared as described for the product.

Cell cultures

Keratinocytes are the most represented cell type in the epidermis cells. They grow from the base of the epidermis where cells multiply and then migrate to the surface of the skin producing lipids, natural factors of hydration and keratin. Human immortalised keratinocytes used in the assay were a human cell line (HaCaT, code BS CL 168). The cell line was grown in conditions of complete sterility and maintained in incubation at 37°C with 5% carbon dioxide (CO_2) atmosphere.

Cytotoxicity assay (MTT test)

The MTT test is a colourimetric cytotoxicity assay used to test cell proliferation and viability based on mitochondrial efficiency. The MTT, a tetrazolium salt that, in case of cells metabolical activity, is reduced from the highly reducing mitochondrial environment of viable cells by the action of mitochondrial dehydrogenase. MTT reduction leads to the formation of formazan crystals (Fig. 1) - insoluble in the culture medium, but soluble in DMSO - which gives the typical purple colour to the mitochondria of viable cells. Contrarily, in suffering or dead cells, since active mitochondria are lacking, MTT will not be reduced resulting in a less intense purple colour [7]. For the direct relationship between cellular respiration and viability, MTT is considered a good assay to identify the non-cytotoxic concentrations of the product Neauvia Stimulate.

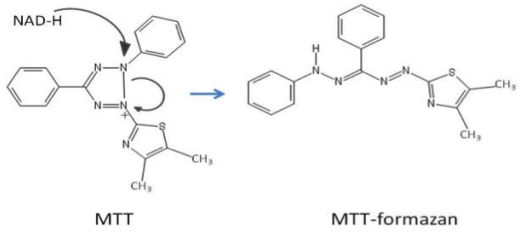

Figure 1: MTT reduction in formazan. The reaction is catalysed by succinate dehydrogenase

For the preparation of the assay, HaCaT cells were homogeneously seeded in 96-well plates at a density of 1.5 x 10^4 cells-per-well and incubated at 37°C with 5% CO_2 humidified atmosphere. After 24 h, cells were treated (six replicates for each of the eight different concentrations) starting with a concentration of 5 mg/ml up to the final one of 0.039 mg/ml through a serial dilution of 1:2. Cells treated with SLS were used as positive control (Ctrl+, starting concentration 5 mg/ml in complete medium).

Incubation was performed for 24 h. Following, ten µl of MTT stock (5 mg/ml in PBS) were added to HaCaT cells at 37°C for two h. The medium was then removed, and 100 µl of DMSO was added to the cells. Subsequently, absorbance was measured at a wavelength of 570 nm using a microplate reader. Cell viability was calculated measuring the difference in optical density of each of the eight concentrations of the tested product concerning control (untreated cells) (8). Data were processed using Photox v. 2.0 for IC_{50} calculation, which is the concentration of the product that determines the 50% of cell viability.

Cytotoxicity assay (NRU test)

The NRU cytotoxicity assay is a colourimetric test based on the ability of viable cells to incorporate the dye in lysosomes [9]. Neutral Red (NR, Sigma) is a weak cationic dye that readily penetrates cell membranes and accumulates intracellularly in lysosomes, thereby providing direct information on the cell membrane integrity and, indirectly, on the viability of cells. For the preparation of the assay, cells were seeded and treated as previously described. At the end of the treatment, cells were examined under a phase-contrast microscope and washed in PBS. One hundred µl of the NR medium was then added and cells were incubated for three h at 37°C, 5% CO_2. After the medium has been discarded, an acetic acid solution was added to extract the NR from cells, and the reading of the absorbance was performed at 540 nm wavelength using a microplate reader (Tecan Sunrise). Cell viability was calculated as previously described.

Cytotoxicity assay (Kenacid Blue assay)

The Kenacid Blue test is a colourimetric cytotoxicity assay used to test cell viability based on the ability of a dye to bind cellular proteins [10]. The Kenacid Blue assay system measures total biomass by staining proteins (total biomass) with a specially developed dye creating a simple, accurate, and highly reproducible test. For the preparation of the assay, cells were seeded and treated as previously described. Cells were then washed with PBS and fixed with a 3% glutaraldehyde solution for 20 min at room temperature. Fifty µl of the Kenacid Blue Acid Stain Solution was added to each well for 20 min at room temperature. At the end of the incubation, the medium was then discarded, and cells were washed with an acetic acid solution (5% in 10% ethanol). Finally, 100 µl of Kenacid Blue Assay Extraction Solution was added to each well for 20 min at room temperature with gentle shaking. Subsequently, the absorbance was read at 570 and 690 nm wavelength using a microplate reader. Cell survival was calculated as previously described.

Evaluation of cell viability

Cell viability has been evaluated by "LIVE/DEAD" (Life Technologies Ltd) commercial kit that uses two different fluorescent probes, the red-fluorescent nucleic acid stain, propidium iodide, and the SYTO® nine green-fluorescent nucleic acid stain for the determination of live and dead cells. The SYTO 9 penetrates all cells, those with intact and damaged membranes. In contrast, propidium iodide penetrates only cells with damaged membranes, causing a reduction in the SYTO 9 stain fluorescence when both dyes are present. For the preparation of the assay, cells were homogeneously seeded onto glass coverslips (22 x 22 mm), placed inside Petri dishes (35 x 10 mm), at a density of 1 x 10^5 cells, and incubated at 37°C, with 5% CO_2 humidified atmosphere. After 24 h, cells were treated with two concentrations of the product, equal to 2.5 mg/ml and 1.25 mg/ml, demonstrated to be non-cytotoxic and with the best solubility in the culture medium. After 24 h treatment, an appropriate mixture of the two dyes was added to each dish for 15 min. Samples were then stored protected from light and analysed using fluorescence microscopy.

Evaluation of cell morphology

The hematoxylin and eosin (EE) staining, commonly used in the microscopic study of animal tissues and histopathology routine, has been used to evaluate any possible effect on cell cultures after the treatment with the product Neauvia Stimulate. For the preparation of the assay, cells were seeded and treated as described in the previous paragraph. At the end of the treatment, cells were washed and fixed in methanol; subsequently, a 1% hematoxylin-eosin solution has been added to each slide. After having carefully removed the stain, coverslips has been mounted on microscope slides to promote the drying.

Evaluation of cell structure

For the study on the effects on the cytoskeleton due to the treatment with the product Neauvia Stimulate®, a fluorescent Phalloidin molecule has been used to detect the microfilaments of F-actin [11] in immunofluorescence. For the preparation of the assay, cells were seeded and treated as previously described. After the treatment, HaCaT cells were fixed with 4% paraformaldehyde for 20 minutes at room temperature and then incubated with the antibody Alexa Fluor® 488 phalloidin at room temperature. After this period, the excess of phalloidin and any residues were removed through two further washes in PBS and the nuclei stained with Hoechst 33258. The coverslips were then mounted on slides and analysed by confocal microscopy.

Results

Results are reported in charts, and images containing the measurements obtained by cell cytotoxicity assays and the evaluation of cell viability, structure and morphology after treatment with the product Neauvia Stimulate concerning control HaCaT cells. Data represented as the mean of at least two independent experiments performed in single.

Evaluation of cell cytotoxicity

HaCaT cells were incubated and treated for 24 h with eight different concentrations of the product Neauvia Stimulate®, along with an appropriate positive control, to identify a possible cytotoxic effect on cell cultures and the concentrations to use in the following assay.

Fig. 2 shows the results of the cytotoxicity tests. It is possible to note that, at all concentrations tested and in all the three assays, the product Neauvia Stimulate did not cause a decrease in cell viability so to calculate the IC_{50} value and, consequently, the product did not show cytotoxic activity.

The concentrations of 1.25 mg/ml and 2.5 mg/ml were chosen for the following assays for their best solubility in the culture medium.

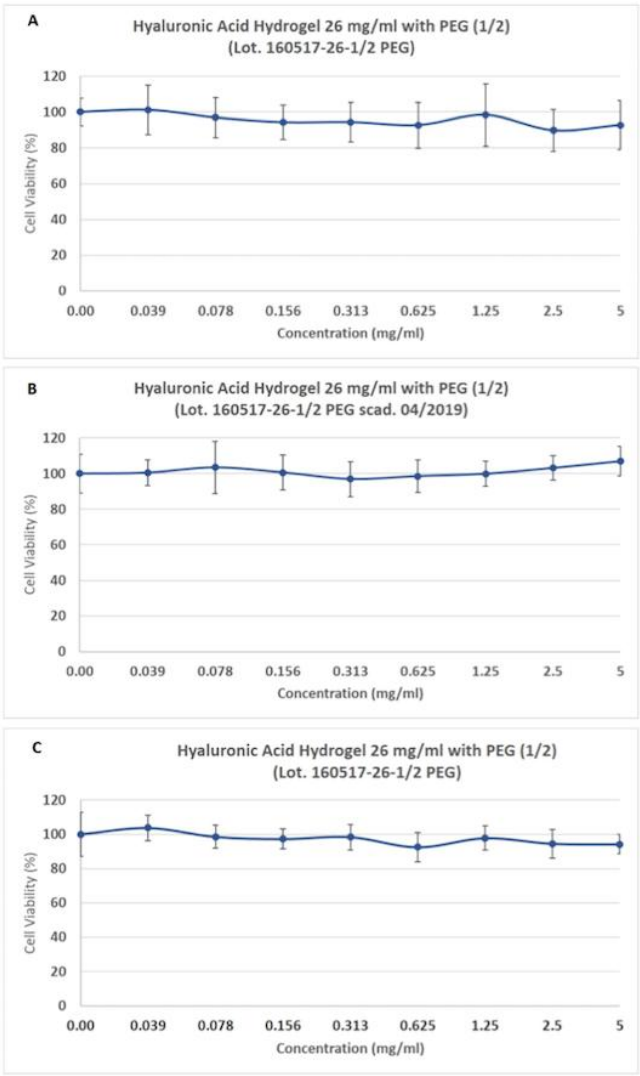

Figure 2: Graphics of cell viability obtained after 24 h treatment of HaCaT cells with the product Neauvia Stimulate®. (A): MTT test; (B) NRU test; (C) Kenacid Blue assay

Evaluation of cell viability

HaCaT cells were incubated and treated for 24 h with the concentrations of 1.25 mg/ml and 2.5 mg/ml of the product Neauvia Stimulate®, along with an appropriate positive control. Fig. 3 shows the representative images obtained with a fluorescence microscope of the results of the LIVE/DEAD assay. Analysing the images, it is clear that none of the two concentrations tested determines a variation in cell viability and that the number of stained cells in green (live) is comparable to the control (untreated cells). In contrast, it is evident an alteration of viability after treatment with SLS, with a decrease in the total number of observed cells and increased mortality (cells stained in red) compared to the control.

Evaluation of cell morphology

HaCaT cells were incubated and treated for 24 h with the two previously described concentrations of the product Neauvia Stimulate®, along with an appropriate positive control.

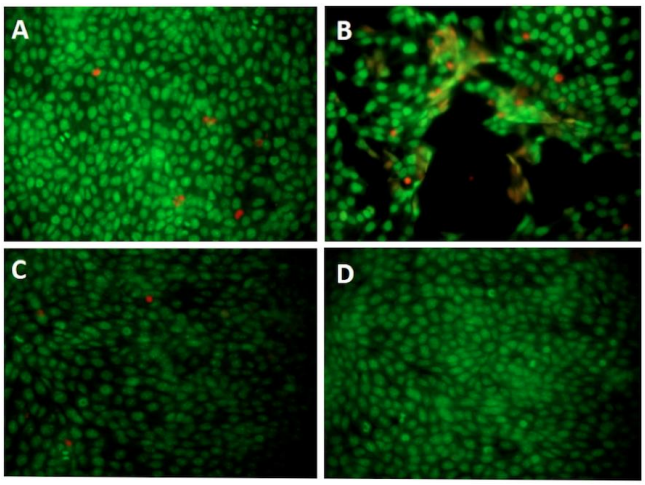

Figure 3: Images obtained using a fluorescence microscope of the staining with LIVE/DEAD kit after 24 h treatment with the product Neauvia Stimulate®. A) Ctrl (untreated cells); B) SLS (Ctrl+); C) product 2.5 mg/ml; D) product 1.25 mg/ml

Fig. 4 shows the representative images in optical microscopy of the results of the Hematoxylin-Eosin test for each tested condition. None of the two concentrations of the product does alter the cell morphology when compared with the untreated control. It is also evident an alteration of the cell morphology induced by the SLS, with a remarkable decrease in the total number of observed cells and a modification of the normal morphology of the HaCaT cells compared to the negative control.

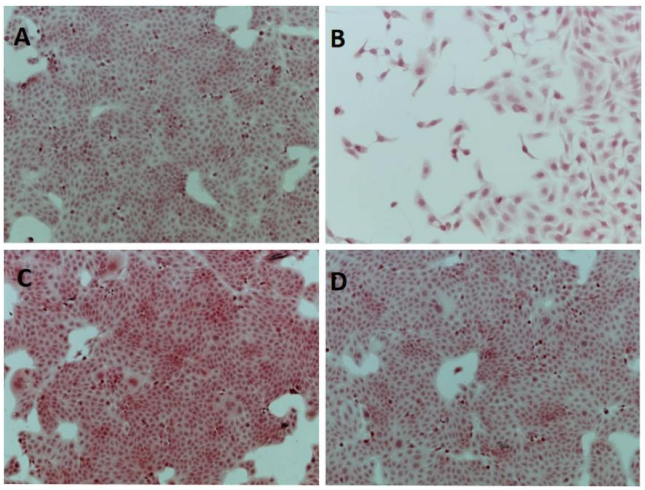

Figure 4: Optical microscopy images related to EE staining after 24 h treatment of HaCaT cells with the product Neauvia Stimulate®. A) control (untreated cells); B) SLS (Ctrl +); C) product 2.5 mg/ml; D) product 1.25 mg/ml

Evaluation of cell structure

HaCaT cells were incubated and treated for 24 h with the two previously described concentrations of the product Neauvia Stimulate®, along with an

appropriate positive control. Fig. 5 shows the representative images in confocal microscopy of the results obtained by the cytoskeleton's structure evaluation. Analysing the images, it is clear that none of the two tested concentrations determines an alteration in the structure of cytoskeleton (stained in green) compared to the control (untreated cells). In contrast, it is evident an alteration of the structure after treatment with SLS, with a decrease of the F-actin labelled and a decrease in the total number of observed cells.

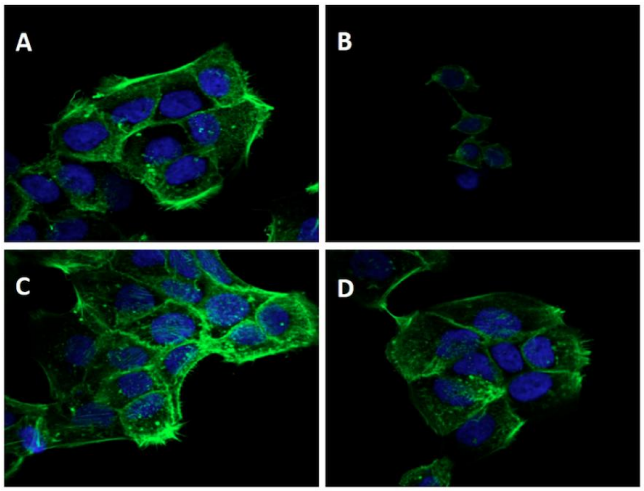

Figure 5: Images obtained using a confocal microscope of the staining with Phalloidin after 24 h treatment with the product Neauvia Stimulate®. A) Ctrl (untreated cells); B) SLS 0.1 mg/ml (Ctrl+); C) product 2.5 mg/ml; D) product 1.25 mg/ml

Discussion

From the results obtained using *in vitro* tests, we can conclude that the product Neauvia Stimulate® does not induce any cytotoxicity effect after 24 h treatment in human keratinocytes at the tested conditions. Moreover, the analyses performed with the two concentrations resulted to be with the best solubility in cell culture medium, do not cause any alteration of cell viability, cell morphology, and structure, showing results comparable to control cells, which were not treated.

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Basic Science

In Vitro Evaluation of the Sensitivity of a Hyaluronic Acid PEG Cross-Linked to Bovine Testes Hyaluronidase

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Keywords: Hyaluronic acid; Sensitivity to hyaluronidase; N-acetyl-D-glucosamine; Neauvia Intense; Poly ethylene glycol

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Abstract

Neauvia Intense is biocompatible, injectable hyaluronic acid (HA) filler PEG cross-linked for facial soft-tissue augmentation that provides volume to tissues. The aim of the present study is to evaluate the sensitivity of Neauvia Intense in hyaluronidase from bovine testes in a time-course analysis. The test is based on the colourimetric determination of the N-acetyl – D - glucosamine (NAG) released by the hyaluronidase in standardised conditions. The in vitro conditions involve the treatment of Neauvia Intense with a known concentration of the enzyme (6080U/ml). The NAG content was determined at different times to assess the kinetics of the degradation (1h, 3h, 6h, 24h, 48h, 72h, 120h, and 168h); the Ehrlich's reagent was used for the colourimetric quantification, by the method described by Reissing and colleagues. The intensity of the violet colour developed after the chemical reaction was proportional to the NAG present in each sample. A microplate reader at 585 nm read the absorbance. The amount of NAG released by the product was proportional to the time of incubation with bovine hyaluronidase, reaching a plateau after 168 hours.

Introduction

Hyaluronic acid (HA) is a high-molecular-mass linear anionic polysaccharide without branching side - chains, composed of 2000 - 25000 disaccharide units formed by glucuronic acid and N – acetyl – D - glucosamine (NAG), which are linked by β(1,4)-glycosidic bond, reaching 105 – 107 Da in molecular mass [1][2][3][4][5]. HA is a major component of the extracellular matrix in the human body, as it is present in the skin, synovial fluid, loose connective tissues, umbilical cord, vitreous body of the eye and cartilage [6] Several biological functions are fulfilled by this molecule, as it plays a major role in the organization and integrity of the extracellular matrix, thereby participating in the preservation of the form and the spatial arrangement of tissue components. It is also involved in numerous biological and physiological functions, such as cell motility, cell-matrix adhesion, and cell proliferation, water homeostasis of tissues or joint lubrication [7]. Thanks to the HA molecule's capability to absorb a large volume of water, it can

hydrate tissues and finally to maintain the moisture of the skin [8][9].

The degradation of the HA molecule occurs in the body by three mechanisms: the attack by free radicals, enzymatic processes (hyaluronidases) or thermally [10]. The hyaluronidases are endoglycosidases that cleave HA, reducing its viscosity [11]. Hyaluronidases could be classified into three groups according to their mechanism of action and end products: mammalian hyaluronidase (testis tube), leech/hookworm hyaluronidase and microbial hyaluronidase [12][13]. Mammalian and microbial hyaluronidases act on the β -1, 4 - glycosidic linkages of HA, while the leech/hookworm hyaluronidase degrades the β - 1, 3 - glycosidic bond; all of them degrade the HA molecule and produce oligosaccharides of different chain length [14][15]. These enzymes are normally employed for several purposes, such as the prevention of tissue damage after the extravasation of different substances, for oedema reduction [16] and to prevent the diffusion of several substances injected subcutaneously [17][18][19][21].

In the last decade, HA has been considered, in aesthetic medicine, as an ideal substance to be used to augment the skin volume, being highly biocompatible, non-immunogenic and capable of binding water to a large extent [22]. In order to increase the biomechanical properties and the resistance to enzymatic break down of natural HA containing preparations, various methods have been developed for chemical modification or cross-linking of native HA into gels by covalent links, resulting in larger and most stable derivatives that retain HA biocompatibility and biodegradability in vivo [23][24].

In the HA hydrogel evaluated the crosslinking reaction occurring with cross-linking agents based on epoxides, in a strongly basic environment with the formation of ether bonds C – O - C, which is among the most solid and consequently the most resistant to degradation.

The reaction consists in the epoxide ring opening, in the simultaneous deprotonation of the hydroxyl group (in a basic environment is more nucleophilic than the carboxylic deprotonated group) and in the formation of the bond C – O - C.

The crosslinker used for this type pf reaction to create Neauvia Hydrogel was PEGDE (Figure 1).

In aesthetic medicine, hyaluronidases are used for dissolving the injected hyaluronic acid filler, eliminating nodules, correcting the injection of excessive quantities of injected filler, or avoiding ischemic complications derived from this practice [25][26]. The literature reported a wide range of techniques to analyse the in vitro degradation rate of crosslinked HA hydrogels by the hyaluronidase enzyme [27][28]: change in viscosity, in water content, gel plate assay in Petri dishes or colourimetric assays for the released glucuronic acid.

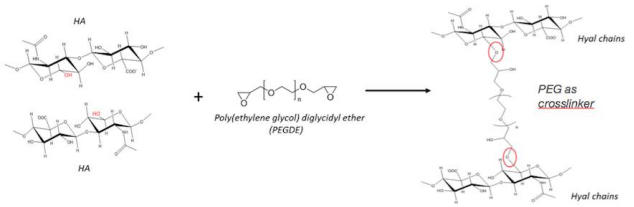

Figure 1: Hyaluronic acid (HA) crosslinking with poly(ethylene glycol) diglycidyl ether (PEGDE)

The aim of the present work is to evaluate the sensitivity to a bovine hyaluronidase enzyme of Neauvia Intense®(MatexLab SA, Lugano, CH), a product composed of pure hyaluronic acid of probiotic origin (Bacillus Subtilis) PEG cross-linked (polyethylene glycol) [29][30][31].

Materials and Methods

Chemicals and instruments

The sensitivity of Neauvia Intense®(MatexLab SA, Lugano, CH) to hyaluronidase was tested. This product is composed of pure hyaluronic acid of probiotic origin (Bacillus Subtilis) PEG cross-linked (polyethylene glycol) to obtain a 3D hydrogel matrix, that could be considered a completely biocompatible and degradable hydrogel, with volumizing effect, typical of the HA filler cross-linked polymer

Type I - S hyaluronidase from bovine testis was purchased from Sigma Aldrich (ref. H3506, 451Units/mg); all other chemicals were of the highest purity available.

The absorbance was measured using a Multiskan - Go (Fisher Scientific) spectrophotometer.

Sample preparation

Neauvia Intense® was weighed (0.2g) and placed in the bottom of glass tubes. The tubes were then centrifuged for 5min at 1000g in a refrigerated bench centrifuge (Megastar 600R, VWR) equipped with a swinging bucket rotor. At the end of the centrifugation, thin pellets firmly attached at the bottom of the tubes were obtained.

Hyaluronidase sensitivity test

To measure the degradation rate of the hyaluronidase on hydrogels, a Type I - S hyaluronidase from bovine testes (Sigma Aldrich; ref.

H3506, 451 Units/mg) was prepared at the concentration of 6080U/ml in an isotonic phosphate-NaCl buffer at a pH of 7.4 [2]. The glass tubes containing the gel pellets and the hyaluronidase solution were pre-incubated separately for 10min at 37°C. Then, 100 µl of the enzyme solution was added gently onto the surface of the gels and, after the incubation for 1h, 3h, 6h, 24h, 48h, 72h, 120h and 168h the enzymatic reaction was stopped by the addition of 0.1ml of a potassium tetraborate solution (0.8 mol/L, pH 9.1), followed by a stirring with a vortex mixer and heating for 3min at 100°C. The tubes were then cooled at room temperature, and the released NAG was assayed.

Assay of the released NAG

The measurement of the released NAG was performed according to the Reissig et al. method [1]. Briefly, a diluted 1:10 Ehrlich's reagent (Sigma Aldrich) in acetic acid was added to the tubes. The samples were vortexed and incubated for 20min at 37°C, to develop a violet colour, proportional to the released NAG content in each sample. The tubes were centrifuged at 1000 g for 15min to remove the gel fragments and the turbidity in the reaction. Then, the samples were read with a microplate reader (Multiskan-Go, Fisher Scientific) at 585 nm wavelength against the blank prepared with the only phosphate buffer and the Ehrlich's reagent.

Results

Hyaluronidase sensitivity test

To measure the degradation rate of Neauvia Intense, the product was weighed and incubated with a constant concentration of hyaluronidase enzyme. The amount of NaHA (mg) contained in the weighed product was reported in Table 1.

Table 1: Amount of NaHa (mg) contained in each sample. The indicated values correspond to the mean of at least two measurements ± SD for each time of analysis

NaHAcontent (mg/g)	Time	Weight (g) sample	NaHA (mg) amount in the sample
28	1h	0.208±0.002	5.810±0.048
28	3h	0.204±0.010	5.707±0.0273
28	6h	0.204±0.007	5.705±0.188
28	24h	0.197±0.004	5.516±0.112
28	48h	0.201±0.003	5.614±0.090
28	72h	0.205±0.003	5.734±0.084
28	120h	0.207±0.001	5.793±0.020
28	168h	0.202±0.000	5.662±0.000

The results of the time - course degradation of crosslinked HA by hyaluronidase are reported in Table 2.

Table 2: Absorbance values obtained after incubation of the samples with hyaluronidase and the relative amount of NAG (mg) released. The indicated values correspond to the mean of at least two measurements ± SD for each time of analysis

Time	Abs (585nm)	Abs per g of NaHA	total mg of NAG released	mg NAG/g released
1h	0.117±0.020	0.020±0.003	0.350±0.059	1.687±0.281
3h	0.181±0.050	0.032±0.008	0.540±0.141	2.657±0.713
6h	0.227±0.032	0.040±0.010	0.678±0.094	3.322±0.354
24h	0.312±0.083	0.057±0.004	0.933±0.247	4.735±1.245
48h	0.537±0.0105	0.096±0.020	1.605±0.315	8.001±1.552
72h	0.795±0.080	0.139±0.013	2.379±0.234	11.613±1.114
120h	0.867±0.074	0.150±0.012	0.593±0.221	12.529±1.027
168h	0.829±0.001	0.146±0.000	2.481±0.004	12.271±0.019

Results obtained after different times of incubation of Neauvia Intense® with a constant amount of hyaluronidase enzyme (Figure 2) showed an increase in the absorbance values (585 nm) concerning the blank sample.

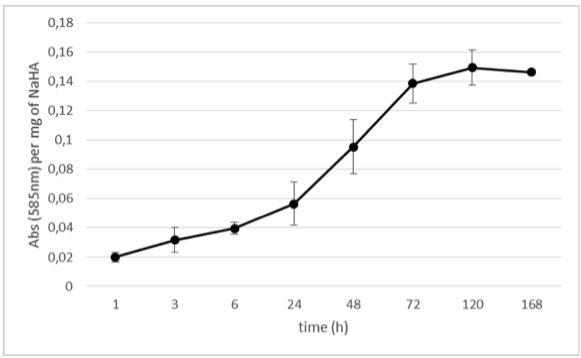

Figure 2: Absorbance values obtained after the incubation of Neauvia Intense® with the hyaluronidase enzyme for different times of treatment. Gel wt= 0.2g; Vol hyaluronidase = 100µl; Conc. hyaluronidase sample= 6080 U/ml;Temp= 37°C. Each point is the mean of at least two measurements ± SD

Interpolating these data with a standard NAG curve (data not shown), the amount of NAG (µg) released per g of product was calculated (Figure 3).

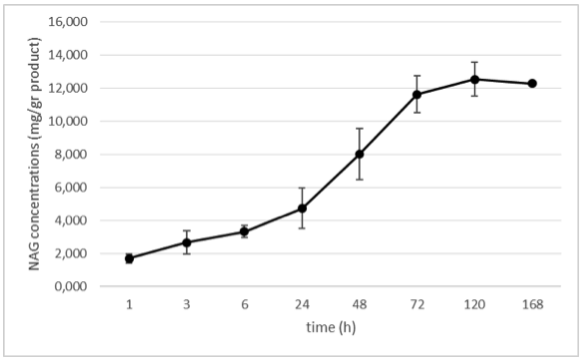

Figure 3: NAG amount (mg/g) released after different times of incubation of Neauvia Intense® with the hyaluronidase enzyme. Gel wt= 0.2g; Vol hyaluronidase = 100µl; Conc. hyaluronidase sample= 6080 U/ml;Temp= 37°C. Each point is the mean of at least two measurements ± SD

It is possible to note that the amount of NAG released increased with time and eventually levelled off from 120h of incubation on, suggesting complete digestion of the initial NaHA content in the sample.

In this study, the sensitivity of the product Neauvia Intense to a hyaluronidase from bovine testes was assayed. The growing interest of the aesthetic medicine sector in the use of such enzymes to dissolve or correct the injected hyaluronic acid filler, also avoiding misplacement HA complications derived from this injection practice, has been the starting point to deepen the mechanisms of action of the hyaluronidase on the Neauvia Intense product.

In detail, the method has been set up defining a determined quantity of product that was incubated with a constant concentration of hyaluronidase (6080 U/ml) at 37°C for a period ranging from 1 h to 168 h. The amount of NAG released, evaluated by the use of the Ehrlich's reagent, was calculated from the absorbance values measured at determined times of analysis and was considered as the factor corresponding to the degradation rate of the hydrogel caused by the enzymatic digestion process. The calculation was based on the interpolation of the absorbance values obtained from each sample with the values obtained for the standard NAG curve in µg. To this end, the centrifugation step of the final medium reaction before the absorbance measurement was necessary to remove the turbidity and small gel fragments still present in the tube [32].

The obtained results showed that the product Neauvia Intense, put in contact with a constant concentration of hyaluronidase enzyme, released a NAG quantity directly proportional to the incubation time and reached a plateau (maximum observed absorbance value) after 120h, monitored until 168h of contact with the enzyme. This has been considered the evidence that the hyaluronidase enzyme reached the highest levels of NAG release and consequently the maximum level of degradation of the HA molecule contained in the hydrogel.

The obtained results demonstrated that the Neauvia Intense product is sensitive to the bovine testes hyaluronidase, by a time course analysis that examined the rate of degradation of the HA molecule present in the hydrogel. Moreover, it is possible to conclude that the hyaluronidase brought to a complete degradation of the amount of Neauvia Intense product, in the experimental conditions performed, after 120h of treatment with the enzyme in an in vitro assay.

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Clinical Science

Carbon Dioxide with a New Pulse Profile and Shape: A Perfect Tool to Perform Labiaplasty for Functional and Cosmetic Purpose

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Keywords: labia minora hypertrophy; labial reduction; vulvar surgery; dermatologic cosmetic gynecologic surgery; labiaplasty, nymphoplasty; Carbon Dioxide Laser CO_2

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Abstract

OBJECTIVE: To describe the benefits and safety of using Carbon Dioxide Laser in multi-pulse modalities when performing labiaplasty and anatomical variants approach for functional and cosmetic indications.

DESIGN: This is a prospective, descriptive case series study.

SETTING: Private Practice Quirofano Calculaser Megacentro Pinares Pereira Colombia.

POPULATION: One Hundred and twelve women seeking labia minora labiaplasty for functional and cosmetic reasons were enrolled in the study protocol from June 2013 to June 2016. Labia minora labioplasty and anatomical variants approach were performed with Carbon Dioxide laser Multi-pulse modalities DEKA M.EL.A Florence Italy

MAIN OUTCOME MEASURES: Good Cosmetic results, functional and sexuality improvement

RESULTS: Dramatic changes in the VAS and VSQ were detected after the surgical procedure. All the participants reported a high degree of satisfaction, felt more confident with their partners during sexual encounters, and the procedure was well tolerated.

CONCLUSION: Laser Carbon Dioxide Laser with a new pulse profile and shape seems to be a safe and precise surgical tool to perform this type of procedures, optimal biophysical and bio stimulative laser-tissue interactions allow delicate vulvar tissues to shorten downtime.

Introduction

Increasing number of patients are seeking medical attention, due to concerns about labia minora hypertrophy related to cosmetic, functional, and sexual concerns [1]. Gynecologists from around the world are nowadays confronted with an increasing demand for labia reduction surgery, the National Health Service (NHS) in the United Kingdom reported at least the doubling of the number of labia reductions carried out in the UK in 2004 compared with 1998 [2].

Hodgkinson was one of the firsts to publish a description of a labiaplasty procedure in 1983 [3]. Rouzier and colleagues presented their experience with a large series of patients [4]. Labiaplasty technique has also been described by many other authors, such as Munhoz [5], Maas [6], Giraldo [7], and Rauso [8]. These techniques were performed with common surgical techniques, without the aid of

energy source or laser devices. Pardo and colleagues reported hemostatic advantages of using laser devices when performing this procedure, with high rates of patient satisfaction and few rate of complications [9].

Laser energy sources have been used in gynaecology for more than three decades [10]. There are many described advantages, such as bactericidal, bio-regenerative and bio-stimulating effects on tissues, which allows better healing, faster recovery, less pain and better aesthetic results.

This study aimed to demonstrate the benefits and safety of multi-pulsed CO_2 Laser when performing a labiaplasty procedure and to demonstrate with histological samples the lateral thermal damage between the different pulses.

Materials and Methods

In the present study protocol, were enrolled one hundred and twelve women aged between 15 and 62 years (mean 32.63) attending a private cosmetic gynaecology unit from January 2013 to January 2016, seeking labia minora labiaplasty for functional and cosmetic indications. The main indications for labiaplasty were identified as: functional (40%), cosmetic (30%), sexual (20%), and cultural (10%).

The Gonzalez Labia Minora Hypertrophy Classification was used to determine the degree of hypertrophy and to choose the best technique to be performed in each patient [11]. The Visual Analog Scale (VAS) was used to compare the degree of satisfaction and comfort with sexual partners during intercourse. The Vulvovaginal Symptom Questionnaire (VSQ) was used to measure symptoms, emotions, life-impact, and sexual-impact before and after surgery. The first seven questions of the VSQ comprise symptoms subscale (itching, burning, hurting, irritation, dryness, discharge, and odour). Women who answered "Yes" to any of the first seven symptoms questions were considered to have vulvovaginal symptoms, and sexual impact (Yes to ≥1 out of 4 sexual impact subscale items).

Statistical analysis was performed using SPSS 11.5.1 (SPSS, Chicago, Illinois. the USA). Quantitative variables deal with the following parameters: mean, median, and standard deviation before and after surgery.

Labiaplasty was performed with a Carbon Dioxide Laser 10,600 nm (Deka M.E.LA., Florence, Italy) in different pulse modes, profile, and shape, to achieve efficient cutting and coagulation during the procedure. Labiaplasty was carried out in the surgical room under regional or general anaesthesia; meantime procedure was about 60 minutes. The surgeon preferred technique was the Grees technique [12], which allows the appropriate approach of common vulvar anatomical variants.

Results

Outcomes were analyzed with validated tools: Vulvovaginal Symptom Questionnaire (VSQ) and Visual Analog Scale (VAS) before and at least one month after CO_2 Laser labiaplasty. An image report has been carried out (Fig. 1).

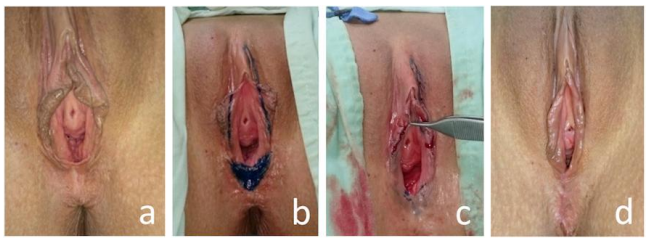

Figure 1: a) Labia minora hypertrophy II-A-A (Gonzalez Classification); b) Pre-surgery markings; c) Immediate post-surgery; Right side DP mode; Left side SP mode; d) 2-month post-surgery

All the patients completed the study, scores for overall satisfaction and comfort with partners during sexual intercourse were dramatically improved after surgery in both groups respectively 7.3 ±1.6 to 2.3 ± 0.89, and 7.4 ± 1.0 to 1.89 ± 0.74 (Tables 1 and 2).

Table 1: Visual Analogue Scale (VAS) for overall satisfaction, before and after surgery, expressed as mean value standard deviation

Visual Analogue Scale (VAS)	Before Surgery	After Surgery
Baseline	7.3 ± 1.0	2.3 ± 0.89

Overall Vulvovaginal Symptom Questionnaire (VSQ) before surgery was 7.0 ± 0.79 and after Labiaplasty 0.65 ± 0.63.

Table 2: Visual Analogue Scale (VAS) for self-confidence during intercourse, before and after surgery, expressed as mean value standard deviation

Visual Analogue Scale (VAS)	Before Surgery	After Surgery
Baseline	7.4 ± 1.0	1.89 ± 0.74

For women reporting one or more vulvovaginal symptom, before surgery 70.5% (n = 79/112) reported emotional impact (Yes to ≥1 out of 4 emotional impact subscale items) and 94.6% (n = 106/112) reported lifestyle impact (Yes to ≥1 out of 5 lifestyle impact subscale items) from these symptoms. For sexually active women reporting vulvovaginal symptoms, 83% (n = 93/112) reported sexual impact (Yes to ≥1 out of 4 sexual impact subscale items).

One month after surgery the percentage was

found to be dramatically lower as follows: for women reporting one or more vulvovaginal symptom, after surgery 10% (n = 11/112) reported emotional impact (Yes to ≥1 out of 4 emotional impact subscale items), and 8% (n = 7/112) reported lifestyle impact (Yes to ≥1 out of 5 lifestyle impact subscale items) from these symptoms.

Table 3: Domains of vulvovaginal symptoms from the Vulvo Vaginal Symptom Questionnaire (VSQ), expressed as a percentage. n is the correlated number of women over the total 112 enrolled ones

	Before Surgery	After Surgery
VSQ Score	7.0 ± 0.79	0.65 ± 0.63
Emotional Impact	70.5% (n=79)	10% (n=11)
Lifestyle Impact	94.6% (n=106)	8% (n=7)
Sexual Impact	83% (n=93)	7% (n=6)

For sexually active women reporting vulvovaginal symptoms, 7% (n = 6/112) reported sexual impact (Yes to ≥ 1 out of 4 sexual impact subscale items) (Table 3).

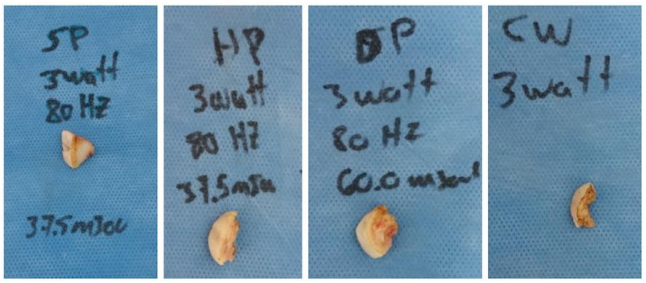

Figure 2: Samples cut with different modes (3W, 80 Hz): SP, HP, DP, CW

Biopsies of the excess skin of the vulva were obtained to corroborate histological changes after CO_2 Laser Labiaplasty (Fig. 2). Lateral thermal damage (TRT) was measured in millimetres with traditional staining methods Hematoxylin and Eosin (Fig. 3).

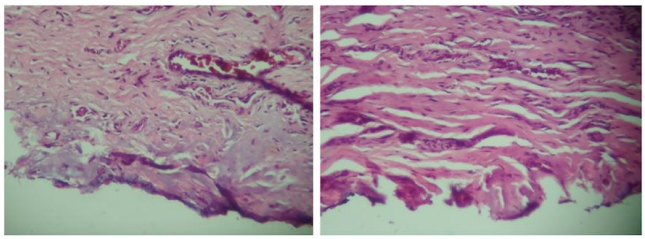

Figure 3: Samples stained using Hematoxylin and Eosin. Left) DP cutting mode TRT 1.3 mm. Right) SP cutting mode TRT 1.1 mm

Discussion

Vulvovaginal symptoms are common and present in an important percentage of patients with labia minora hypertrophy. Many of these patients have emotional, lifestyle, and sexual discomforts due to these symptoms. A labiaplasty with the right indication and performed by a high skilled cosmetic gynaecology surgeon can improve sexuality, self-esteem and overall satisfaction in symptomatic patients suffering from this condition.

CO_2 Laser with new pulse profile and shape seems to be a safe and precise surgical tool to perform this type of procedure. Optimal biophysical and bio-stimulating laser-tissue interactions allow delicate vulvar tissues to shorten downtime.

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Epidermoid Cysts – A Wide Spectrum of Clinical Presentation and Successful Treatment by Surgery: A Retrospective 10-Year Analysis and Literature Review

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Keywords: Epidermoid cysts; Pathogenesis; Skin; Surgery; Gardner syndrome; Lowe syndrome

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Abstract

Epidermoid cysts are common benign lesions of hair-bearing, and less often glabrous skin. They can also occur in oral mucosa and internal organs. In case of cutaneous lesions, an epidermal punctum is a clinical diagnostic hallmark. The clinical presentation is variable leading to some differential diagnoses. Diagnosis of epidermoid cysts needs histopathological confirmation – not only of the potential of malignant transformation. The treatment of choice is surgery. We report a retrospective analysis of 2159 epidermoid cysts treated surgically. Most of the cases can be performed under local anaesthesia. The complication rate of 2.2% is low. To avoid relapses, the cyst wall has to be removed completely. Rare genetic disorders with multiple cysts are Gardner and Lowe syndrome.

Introduction

Epidermoid cysts are slow-growing benign subcutaneous lesions imposing as nodules or tumours. The lesions can either be congenital or acquired. Histologically, the cysts are lined by stratified epithelium and filled with a keratinous mass. An epidermal punctum is a hallmark of clinical diagnosis. Young males are the most affected subgroup, but any age and gender might be involved [1].

These cysts can develop in any area of the body with about 7% occurring in the head-and-neck region. Extracutaneous development has been observed in the oral cavity and intraosseous, and in various internal organs including the cerebrum [2][3][4]. Secondary infection and inflammation due to wall rupture are possible complications. The cyst wall tends to become thicker after that what implies complete surgical excision [5].

Giant epidermoid cysts > 5 cm in diameter can cause problems, especially in the head-and-neck region but also in other regions such as the sole [6-8]. Malignant transformation of an epidermoid cyst is a rare event but possible. Squamous cell carcinoma, basal cell carcinoma, and Merkel cell carcinoma have been observed [9][10][11].

Material and Methods

We analysed the files of the Department of Dermatology and Allergology, Academic Teaching Hospital of Dresden, during the years 2007-2017. We focused on those patients who were treated surgically. We analysed the anatomical distribution, the occurrence of giant epidermoid cysts defined by a diameter of more than 5 cm, complications and surgical outcome.

Results

We identified 2159 tumours in 1753 patients. The sex ratio was 2.9:1 for males to females. The mean age was 32.5 years (SD ± 18.3 years; range 16 to 83 years). The major localizations were head-and-neck region (73.4%), trunk (15.1%), extremities (9.8%), and genitals (1.7%).

Inflammation and or infection were noted in 16.8%. In these cases, antibiotic drug therapy was performed before surgery. The rupture was noted histologically in 23.7%. Giant epidermoid cysts were observed in 2.1%.

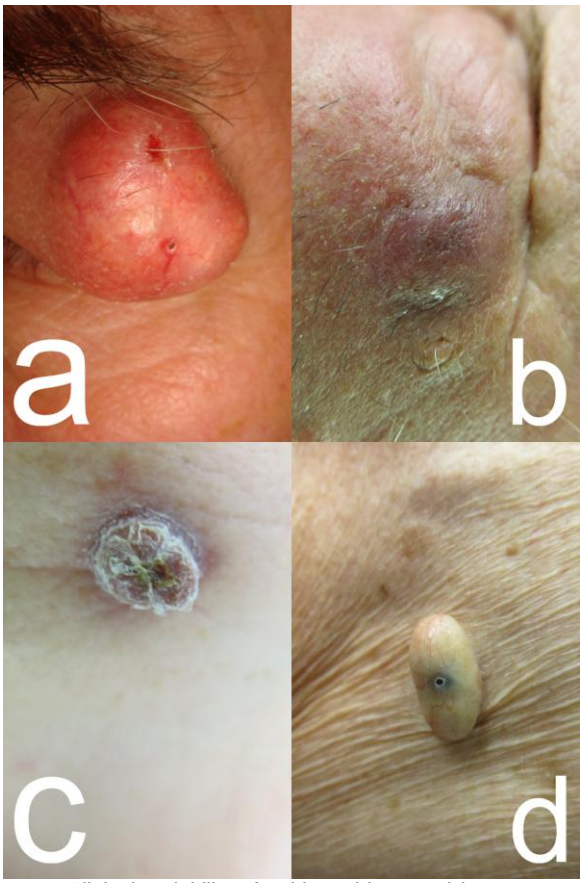

Figure 1: Clinical variability of epidermoid cysts; (a) Large cysts of the lateral brow imposing as a lipoma; (b) Retroauricular inflammatory cyst in a cancer patient – here a cutaneous metastasis was suspected; (c) Ruptured cyst of submandibular localisation; (d) Pediculated cyst on the trunk

The variability of clinical presentations is illustrated in Fig. 1. This has led to a variety of suspected diagnoses such as lipoma, hidrocystoma, dermoid cyst, trichilemmal cyst, steatocystoma, pyoderma, cutaneous metastasis and benign adnexal tumours of the skin.

Histopathology was performed for all cases removed by surgery. We did not observe a single malignant transformation among our tumours.

Surgery was realised with local anaesthesia in 98.9%; the remaining cases were treated under general anaesthesia. Postsurgical complications were noted in 2.2%, such as wound dehiscence, secondary bacterial infection, or hypertrophic scarring. Infectious complications were more frequent in diabetic patients and patients with iatrogenic immunosuppression.

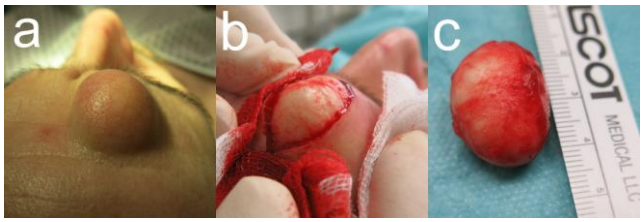

Figure 2: Surgery of a large epidermoid cyst of the glabella. (a) Clinical presentation; (b) Preparation of the cyst after mobilisation. (c) Surgical specimen

A selection of clinical presentations and surgery is added (Fig. 2 and 3). To avoid skin sagging after removal of large or giant epidermoid cysts removal of an epidermal sheet is recommended.

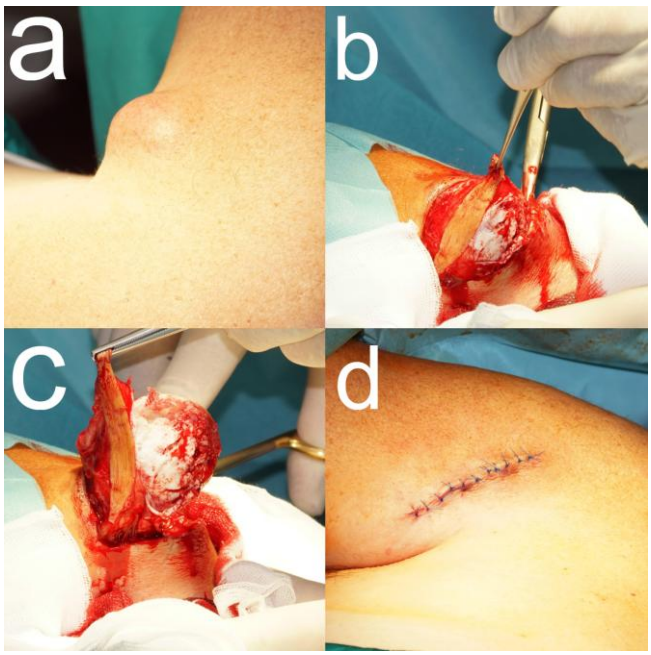

Figure 3: Surgery of a giant epidermoid cyst of the forearm. (a) Clinical presentation; (b) Preparation of the cyst leaving a small epidermal sheet for fixing with the forceps and mobilisation with a small scissor; (c) presentation of the surgical specimen; (d) Defect closure by tissue advancement and tow layered suturing

Discussion

Although the preferred localisation of epidermoid cysts is hair-bearing skin, they have also been seen on the glabrous skin and mucous membranes. Acquired cysts are thought to develop after blunt, penetrating trauma form either hair follicle infundibulum or eccrine sweat ducts [12]. The role of human papilloma virus in epidermoid cyst pathogenesis has been debated [13].

Multiple epidermoid cysts suggest a genetic background. They can occur in Gardner syndrome caused by mutations in the adenomatous polyposis coli gene [14], or in Lowe syndrome, an X-chromosomal oculo-cerebral-renal disorder caused by mutations of the OCLR1-gene [15].

We did not observe these genetic disorders among our patients. Epidermoid cysts of the subcutaneous tissue raise some possible differential diagnoses (Table 1).

Table 1: Differential diagnoses of subcutaneous epidermoid cysts

Entity	Remarks
Dermoid cysts	Ectodermal cysts may contain squamous epithelium and dermal contents
Trichilemmal cysts	Often on the scalp, family history, multiple, trichilemmal keratinisation
Pilomatricoma	Common in children, mostly head-and-neck region, hard, painless
Lipoma	Common, often soft, composed of mature adipocytes with a fibrous capsule

While small cysts may be treated by CO2- or erbium-YAG-laser [16][17][18][19], larger cysts need a surgical approach with cold steel [3][7][8]. Since skin sagging is a possible outcome after removal of larger cysts, a small sheet of the epidermis above the cyst is excised. This allows an individualised adaption of the surgical margins. To avoid relapses, complete removal of the cyst wall is mandatory. All epidermoid cysts removed surgically should be subjected to histopathological confirmation, to ensure complete excision and avoid misdiagnosis. Possible malignant transformation, although not seen in our cases, is another important argument for regular histopathologic analysis [20].

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Intralesional Diode Laser 1064 nm for the Treatment of Hidradenitis Suppurativa: A Report of Twenty Patients

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Keywords: diode laser; 1064 nm; hidradenitis suppurativa; human treatment; chronic inflammatory disease

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Abstract

AIM: Hidradenitis suppurativa (HS) is a chronic inflammatory disease, commonly characterized by painful, deep dermal abscesses and chronic draining sinus tracts. Recently, laser and light-based therapies have become more commonly used in the management of HS.

MATERIAL AND METHODS: We report 20 HS patients treated with a 1064 nm wavelength, emitted from a diode laser, launched in an optical fibre through intracavitary modalities.

RESULTS: Each patient underwent four laser sessions, one every two weeks. we recorded a significative reduction (31%) of Sartorius score from 28.55 ± 13.04 to 19.75 ± 12.29 after 4 laser sessions ($p < 0.05$). No one has had a worsening of the disease.

CONCLUSION: Intralesional diode laser 1064 nm can be a good treatment option for patients with moderate and localized hidradenitis suppurativa, because it is minimally invasive, doesn't have significant complications and provides a rapid post-treatment recovery.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory disease, commonly characterized by painful, deep dermal abscesses and chronic draining sinus tracts [1][2]. Classically, pharmacologic agents ranging from antibiotics, isotretinoin, acitretin, anti-androgens and various biological agents such as Adalimumab and Infliximab, and surgical therapies have been effective for reducing lesion activity, and inflammation and have been shown to be helpful to treat the disease [3][4]. In several cases, these medications provide only transitory results, and they cannot act in the prevention of future recurrences or disease progression. No single agent has been proved to show overwhelmingly positive outcomes [5][6][7]. Recently, laser and light-based therapies have become more commonly used in the management of HS. Different kinds of laser-based therapies have been studied over the last years. The laser can act in 2 different modalities, selective and ablative. Intense Pulsed Light (IPL) and lasers like NdYag, Alexandrite and Diode act selectively and are considered the most useful in Hurley stage I-II, because of their ability to reduce the number of hair follicles, sebaceous glands, and consequently to

reduce the bacterial load; the CO2 laser acts in ablative modality and seems to be more useful in Hurley stage II-III [8][9].

We report 20 HS patients treated with a 1064 nm wavelength, emitted from a diode laser, launched in an optical fibre through intracavitary modalities.

Materials and Methods

Twenty patients were recruited at the University Federico II of Naples, Section of Dermatology, from May 2016 to January 2017. The authors declare that their research complied with the guidelines for human studies and welfare regulation and the subjects participating in the research have given their informed consent. All patients were recommended to a wash-out period from any topical and systemic medications.

We excluded patients with significant comorbidities and those who were pregnant.

Each patient underwent four laser sessions, one every two weeks.

Hurley stage, Sartorius score and PGA were registered before starting laser therapies and at the end of these (after eight weeks - 4 sessions). Responses were classified as complete (improved by 65% or more), good (between 40% and 65%), partial (between 15% and 40%) and no response (less than 15%). Hidradenitis Suppurativa Clinical Response (HiSCR) was used as another tool to evaluate clinical response to the treatment.

Dermatology Quality of Life Index (DLQI) was recorded to judge the impact on the quality of life of HS patients before starting treatment and two weeks after the end of the study.

A diode laser with a wavelength of 1064nm in pulsed operation, launched in fibre from 300-600 µm (coated glass fibre polycarbonate) was used for the clinical study. This laser was supplied by Eufoton.

A standard energy fluence of 250 J/cm^2 has been used, employing different diameters fibres depending on the type of the lesion and its anatomical localisation. In any case, the energy thresholds of 2500J on 10 cm^2 were never exceeded.

Energy is delivered by a micro-variable pulse train from 150 to 350 milliseconds by the selected power energy.

The fibre size (400-600 microns) and the energy power selected (6 - 8 - 10 Watts) took into account the physiological condition of the lesion and the surrounding skin.

Local anaesthetic (Mepivacaine hydrochloride with epinephrine) was injected directly into the anatomical area involved by the disease, at the superficial subcutaneous plane.

A 30 G needle was used, and approximately 1 ml anaesthetic solution per cm^2 was administered.

The infiltration was practised until obtaining tumescence of the concerned area. This procedure, particularly effective in controlling pain, was made possible thanks to the low water absorption for the wavelength of the laser.

Performed anaesthesia, the intervention included the identification of the orifices of suppurating lesions, the introduction of the optical fibre inside them and the subsequent decontamination-denaturing by the direct action of the laser on the pathological tissue. From the day of the laser-surgical procedure, all patients were subjected to an oral antibiotic treatment with azithromycin 500 mg once daily for three days. Four treatment sessions were performed, one every two weeks.

Results

The open clinical study was conducted in twenty patients aged between 18 and 44 years (mean age 26.6 ± 7.84) suffering from HS; anatomical sites involved by HS were the axillae, the groin, buttocks, the brisket and the infra-mammary fold (Table 1).

Table 1: The open clinical study was conducted in twenty patients aged between 18 and 44 years (mean age 26.6 ± 7.84) suffering from HS; anatomical sites involved by HS were the axillae, the groin, buttocks, the brisket and the infra-mammary fold

Patient	Age	Gender	Anatomical site involved	Hurley	Sartorius	PGA
1	22	Male	Axillae (left and right), Groin (left)	2	45	Moderate
2	24	Male	Groin (left and right)	1	25	Mild
3	18	Female	Brisket, Axillae (left and right), Inflammatory fold	2	44	Moderate
4	27	Female	Axillae (left and right)	1	18	Mild
5	29	Male	Groin (left and right), Buttock	2	40	Moderate
6	19	Female	Brisket	1	20	Mild
7	40	Female	Axillae (left and right)	2	40	Moderate
8	38	Male	Axillae (right)	1	12	Mild
9	21	Female	Brisket, Axillae (left and right), Groins (left and right)	2	38	Moderate
10	26	Female	Axillae (left), Inflammatory fold	1	13	Mild
11	20	Female	Axillae (left and right)	2	48	Moderate
12	19	Female	Brisket	1	16	Mild
13	44	Female	Axillae (left and right)	2	40	Moderate
14	23	Female	Axillae (left)	1	18	Mild
15	22	Male	Groin (left and right)	1	18	Mild
16	39	Male	Groin (left and right), Buttock	2	35	Moderate
17	30	Female	Axillae (left and right)	2	28	Moderate
18	27	Female	Axillae (left and right), Groin (right)	2	45	Moderate
19	19	Female	Axillae (left)	1	10	Mild
20	25	Female	Axillae (left and right)	1	18	Mild

50% of patients had a Hurley stage I, while the remaining subjects had a Hurley stage II; no patient with Hurley stage III was recruited.

All results are showed in Table 2. In summary, we recorded a significative reduction (31%) of Sartorius score from 28.55 ± 13.04 to 19.75 ± 12.29 after 4 laser sessions ($p < 0.05$).

Table 2: Fifty percentages (50%) of patients had a Hurley stage I, while the remaining subjects had a Hurley stage II; no patient with Hurley stage III was recruited. We recorded a significative reduction (31%) of Sartorius score from 28.55 ± 13.04 to 19.75 ± 12.29 after four laser sessions ($p<0.05$). In particular, we registered the following clinical response: 1 patient with a complete response (improved by 65% or more); 7 patients with a good response (between 40% and 65%); 10 patients with a partial response (between 15% and 40%); 2 no response (less than 15%). No one has had a worsening of the disease. HiSCR, which is considered a useful tool in detecting changes after treatment, was achieved in 13 patients (65% of patients). Most notably HiSCR was achieved in 60% of patients with Hurley II and 80% patients with Hurley I

Patient	Sartorius T0	Sartorius T1	HiSCR (A - achieved / NA - Not achieved)	Complete response (improved by 65% or more)- C Good response (between 40% and 65%) - G Partial response (between 15% and 40%) - P No response (less than 15%) - N
1	45	40	NA	12% - N
2	25	15	A	40% - P
3	44	28	A	37% - P
4	18	10	A	45% - G
5	40	40	NA	0% - N
6	20	16	NA	20% - P
7	40	30	A	25% - P
8	12	6	A	50% - G
9	38	28	A	27% - P
10	13	6	A	54% - G
11	48	40	NA	17% - P
12	16	8	A	50% - G
13	40	30	NA	25% - P
14	18	8	A	56% - G
15	18	6	A	67% - C
16	35	22	A	38% - P
17	28	16	A	43% - G
18	45	28	A	38% - P
19	10	8	NA	20% - P
20	18	10	A	45% - G

In particular, we registered the following clinical response:

- One patient with a complete response (improved by 65% or more)
- Seven patients with a good response (between 40% and 65%)
- Ten patients with a partial response (between 15% and 40%)
- Two no response (less than 15%).

No one has had a worsening of the disease.

HiSCR, which is considered a useful tool in detecting changes after treatment, was achieved in 13 patients (65% of patients). Most notably HiSCR was achieved in 60% of patients with Hurley II and 80% patients with Hurley I.

In parallel with clinical improvement, we registered a marked improvement in the quality of life of patients undergoing the treatment, showed by DLQI values reduction ($p = 0.0307$).

Most patients (18 of 20) tolerated the procedure without any symptoms. Adverse effects included postoperative pain, erythema, and mild swelling. One patient complained of fever and an influenza-like illness, which resolved itself. Serious adverse side effects, suppuration or infections did not occur.

Discussion

In several cases of HS patients, medical therapy is unsatisfactory, and it is very difficult to identify the way to stop the progression of the disease.

Laser treatment could represent an alternative therapy for the early stages of HS. Selective lasers, such as NdYag, Alexandrite and Diode, can be very useful in the early stage of disease [9][10]. On the other hand, ablative lasers are usually used in the worst cases. There are very few data in literature focused on the use of diode laser to improve symptoms of HS. The rational of the diode laser can be explained by the reduction in the number of hair follicles.

Downs et al. achieved a partial improvement of hidradenitis suppurativa with a sweating reduction following four treatments with a 1450 nm diode laser [11].

In 2011 *Sehgal et al*. reported favourable outcomes in a case report of Axillary HS using diode laser 800 nm after six sessions at an interval of 3 – 4 months (energy 34 J/cm 2, pulse duration 110 – 140 ms) [12].

Valladares-Narganes LM and colleagues reported twenty-seven patients affected by hidradenitis suppurativa treated with intralesional photodynamic therapy using a diode laser attached to an optical cable. They recorded very good results in almost 80% patients with best results achieved in isolated fistulas, axillary, sacral and breast locations, where the majority of cases are found [13].

A histopathological survey demonstrated the mechanism of action of the 1064 nm Nd: Yag laser in the treatment of HS: this type of laser penetrates the follicular unit and, through a selective photothermolysis, causes the destruction of organized inflammatory lesions in the superficial to mid dermis. The wavelength 1064 nm in the near-infrared electromagnetic spectrum selectively targets hair shafts and follicles via absorption by the melanin chromophore [15].

The wavelength used in our research can perform similarly and to get stackable results. Recently has been published an experience on 7 HS patients treated with photodynamic therapy with intralesional methylene blue and a 635 nm light-

emitting diode lamp. After six months, five patients (71%) maintained remission of the disease in the treated area. Photodynamic therapy has been used for its ability to reduce bacterial biofilms, which is a common finding in hidradenitis lesions [16].

Also, some published clinical and histopathological data suggested that the Nd: YAG microsecond pulsed laser in optical glass fiber was able to sterilize by selective photoantisepsis all the affected areas and was also able to decrease the inflammation in the surrounding tissue [17]. Laser treatment proposed in our survey conjugate the laser action (1064 nm wavelength able to destroy follicular unit and organized inflammatory lesions) with the intralesional application of the light that allows reaching different depths (from the superficial to mild dermis). Treatment efficacy has been proved by the reduction of Sartorius score and by HiSCR. It is important to underline that only 4 patients had a marginal improvement and no one got worse.

Moreover, in comparison to surgery, our laser is less invasive; it has been performed under local anaesthesia and therefore does not require hospitalization. Also, the treatment is well tolerated by patients with very few adverse events, which don't limit patient's life (days of absence from work). This laser can be a good alternative for those patients that are not responsive to medical therapy. It can be performed in patients undergoing biologic treatment because it doesn't increase the risk of immunosuppression and does not induce autoantibodies formation, therefore can repeatedly be used without complications.

The main restrictions of our survey are the small sample, but it is important to underline that prevalence remains uncertain and HS is frequently misdiagnosed as a simple infection.

In conclusion, the intralesional Diode laser 1064 nm can be a good treatment option for patients with moderate and localized hidradenitis suppurativa, because it is minimally invasive, doesn't have significant complications and provides a rapid post-treatment recovery.

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Dermatofibrosarcoma Protuberans: Retrospective Single Center Analysis Over 16 Years

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Abstract

Dermatofibrosarcoma protuberans (DFSP) is rare mesenchymal neoplasia with a high risk of local recurrence but a low risk of metastatic spread. Tumor cells express CD34 and show a characteristic translocation t(17;22)(q22;q13). We analysed the documented cases at the Department of Dermatology and Allergology between 08/2001 and 08/2017. The diagnosis had been confirmed by histology and immunohistology in all cases. We identified four adults and a pediatric patient with DFSP. All patients were treated by wide surgical excision and controlled by three-dimensional histologic margin control. We observed no recurrence and no metastatic spread. We discuss prognostic factors and emerging treatments.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is rare mesenchymal neoplasia of skin and soft tissue. Most cases develop on trunk and extremities as nodules or plaques, sometimes hyperpigmented. The hyperpigmented type is also known as Bednar a tumour. There is a wide age range, although incidence shows a peak between the second and fifth decade of life.

Diagnosis is made by histology, immunohistology and cytogenetic analysis [1].

DFSP is characterised by a relatively high risk of local recurrence but low risk of metastatic spread. In most cases, a chromosomal translocation can be found: t(17;22)(q22;q13). Thereby, the genes *COL1A1* and platelet-derived growth factor (PDGF)-beta fuse. This leads to an autocrine stimulation loop involving PDGF-beta and PDGF-beta receptor [2].

We analysed our files for DFSP-patients, treatment, and outcome and discussed emerging treatments.

Material and Methods

We analysed the files of the Department of Dermatology and Allergology, Academic Teaching

Hospital Dresden during a 16-year period, i.e. 08/2001 to 08/2017. Demographics, tumour characteristics, treatment and outcome, were investigated.

Results

We were able to identify five patients with a histologically confirmed diagnosis of DFSP. Maximal tumour diameter was between 2 and 4 cm. All tumours were staged T1(≤ 5 cm of tumour diameter on trunk and extremities), N0, M0, G1 (low grade). All tumours were ordinary DFSP without fibrosarcomatous transformation. One tumour was hyperpigmented (Bednar type).

The youngest patient was a 10-year-old girl with a rapidly growing, painless nodule of the chest (Fig. 1). A diagnostic skin biopsy was taken, that revealed large uniform spindle cells reactive with CD34 but negative for S100. Several mitoses were noted. The proliferative fraction as measured by Ki67-reactivity was 1%. A tumour was removed by wide surgical excision with 2 cm safety margin and complete removal of soft tissue down to the muscle fascia by slow Mohs technique. 3-dimensional histologic margin control was performed. The resulting defect was closed by tissue advancement flap after wide subcutaneous mobilisation of wound margins. Healing was uneventful. The 5-year follow-up was relapse-free.

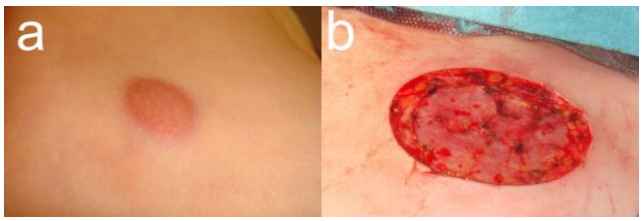

Figure 1: Juvenile dermatofibrosarcoma protuberans on the chest of a 10-year-old girl. (a) Clinical presentation of a well-circumscribed plaque; (b) Defect after wide excision

The remaining patients were adults aged 24, 27, 43, and 61 years of age. The sex ratio for the adult patients was 1:1. One female patient was referred with a recurrence after first surgery elsewhere. The localisation was a shoulder, hip, epigastrium and under belly (Fig. 2).

The safety margins were 1 – 4 cm according to German guidelines [3][4]. In all patients, tumour-free margins were documented. In 4 of five tumours, only one surgical session was necessary, in a single tumour two sessions were needed to obtain tumour-free margins.

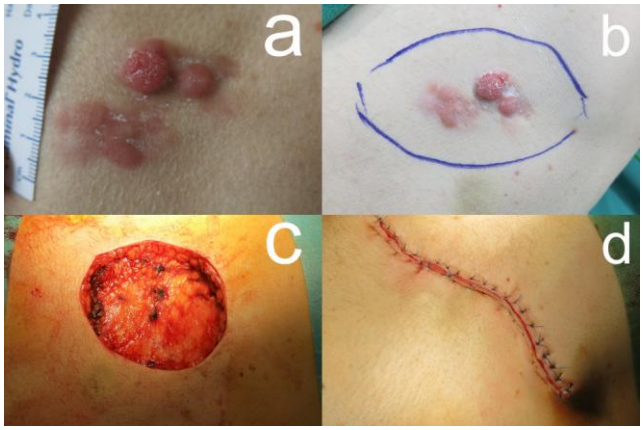

Figure 2: Nodular dermatofibrosarcoma protuberans on the underbelly of a 61-year-old male patient. (a) Clinical presentation; (b) Safety margins; (c) Defect after wide excision; (d) Defect closure by tissue advancement

Tumor cells were positive for CD34 but negative for S100, desmin, pan-cytokeratin, epithelial membrane antigen, and actin. The proliferative index was 1% to 10% measured by Ki67 reactivity. Tumor staging excluded metastatic spread.

Defect closure could be realised by tissue advancement flaps; no grafts were needed. During follow up of up to 7 years neither recurrence nor metastasis was noted.

Discussion

DFSP is rare mesenchymal neoplasia composed of CD34-positive spindle cells. The incidence of this tumour has been estimated between 0.4 and 4.1 patients per million person-years [5][6][7]. The 10-year survival is 99.1%. Negative factors for the unfortunate outcome are higher age, male sex, black race, and anatomic location of the limbs and head [7][8].

Recently, fibrosarcomatous differentiation has been identified as a risk factor for local recurrence [9]. The transformation also increases the rate of metastasis (risk ratio 5.5) and death from disease (risk ratio 6.2) [10]. The fibrosarcomatous transformation is accompanied by an activation of the Akt-mTOR signalling pathway [11]. Treatment of choice is wide tumour excision. Safety margins of 2 cm had a recurrence rate of 1% [12][13][14]. Patients treated with classic or slow Mohs technique have significantly lower recurrence rates [15][16].

DFSP is unresponsive to classical chemotherapy. PDGF-beta, KIT and Abelson murine leukaemia viral oncogene homolog 1 (ABL) inhibitor imatinib mesylate achieved an objective response rate of about 50% in DFSP [17]. In metastatic disease,

imatinib mesylate resulted in median survival progression of ≥ 19 months. The fibrosarcomatous transformation had a less favourable outcome [18][20]. Emerging new drug therapies for advanced or metastatic DFSP are multikinase inhibitors pazopanib [21] and regorafenib [22].

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Automatic Artificial Hair Implant: Safety and Efficacy in Androgenetic Alopecia. A Prospective Study with a Highly Biocompatible Fiber

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Abstract

AIM: A multi - centre two years the long prospective open clinical study was conducted in five countries located in four different continents from May 2015 to evaluate the clinical safety and efficacy of Automatic Biofibre hair implant in male and female androgenetic alopecia. Biofibre®is a CE/TGA certified medical grade polyamide fibre suitable for implantation.

MATERIAL AND METHODS: A total of 213 patients were enrolled in the study. Patients were assessed pre - operatively by Hamilton scale grading and the percentage of scalp covered by hair. All the patients underwent Biofibre hair implantation by a standardised surgical technique followed by adequate post-operative care. Efficacy of the implant was evaluated by surgeons and patients bimonthly for the first year and trimonthly during the second year. Any adverse effects were recorded during these visits.

RESULTS: At the completion of the study period, a total of 194 patients concluded the trial and the results were statistically evaluated. Both Hamilton scale grading and covered area percent improved at the end of the study, and subjective and objective evaluations revealed satisfactory results. Side effects were reported in only 18 cases (9.27%) which were easily controlled by either topical or systemic treatment in 8 to 10 days.

CONCLUSION: Overall a successful result was noticed in 97.94% of patients with great psychological satisfaction.

Introduction

Clinical experience with synthetic hair implantation began in Japan in the '70s and rapidly spread all over the world as the correction of male pattern baldness has always been a much sought-after cosmetic surgical procedure. However, various complications occurred due to the rampant use of this technique by non - qualified personnel, poor patient selection, unsterile operating conditions, and non - biocompatible implant material [1]. Subsequently, in 1983, an FDA ban was issued against the implantation of synthetic fibres, such as monoacrylic, polyacrylic, polyester and natural processed human hair [2], owing to the rising unpopularity for this procedure amongst various dermatologists and surgeons due to the many adverse outcomes encountered [3].

With the advancements in biomedical technology, many biocompatible inorganic materials have come up, which have been more successful and have resulted in many fewer complications. Subsequent studies from Europe focused on biocompatible synthetic fibres and a better technique of insertion with proper medical protocols was conducted to prevent complications such as secondary infection or inflammation [4]. Investigations

on suture materials revealed that a specific polyamide mixture resulted in fewer foreign body reactions. These medical-grade polyamides were therefore selected to develop a biocompatible fibre for scalp implantation, a human hair-like, melt dyed fibre suitable for human use (Biofibre®, Medicap srl, Italy).

The UE in 1996 recognised the artificial hair implant technique as medical act and included artificial hair in the medical devices list, therefore submitting it all safety standard requirements [5, 6]. In the same year also Australian TGA approved artificial hair use by qualified doctors in suitable clinics.

Materials and Methods

Biofibre®is a sterile, inert, UV - resistant, highly bio - compatible, medical-grade polyamide fibre which is 0.08 - 0.09 mm thick and 160 - 460 mm long suitable for male and female implantation [7].

Approved colouring agents are incorporated at the molecular level during the liquid extrusion phase by creating a stable compound with no colour migration. Biofibre® hair is available in 13 colours, three different shapes (straight, wave, curly) and three different lengths (15 cm, 30 cm, 45 cm). The fibres can be washed and dried like natural hair, but they should not be bleached or permanently waved. One end of the fibre carries an open knot to anchor it to the scalp tissue and to allow fibrosis. The special reversible knot allows total fibre extraction in case of need with no residues in the scalp. Histological studies have shown that a keratin shield surrounds the implanted fibres facing bacterial introduction [8]. This study began in May 2015, and 213 patients were enrolled in the trial from five investigational centres in agreement with the principles of the Declaration of Helsinki. All patients signed an informed consent form and were included according to the following inclusion and exclusion criteria (Table 1). The patients came from 4 different continents to have trials, resulting in having different climate, habits and ethnicity.

Table 1: Patient inclusion and exclusion criteria

Patient inclusion and exclusion criteria	
Inclusion Criteria	**Exclusion criteria**
Age 25 to 65	psychological disorders
Clinical diagnosis of androgenetic alopecia and grading with Hamilton scoring	dermatitis or any dermatosis of the scalp
Good general health without any other pathology of the scalp	chronic metabolic disorders, immunodeficiencies, allergies
Patients willing to return for follow up	patients not willing to return for follow up, or with reduced therapeutic compliance
Informed consent	jobs where hygiene could not be guaranteed and maintained

Demographic and anamnestic information was collected with special regards to previous medical or surgical treatments and any known allergies. All patients underwent a preliminary dermatological checkup followed by biochemical blood profiles. All patients were tested for hypersensitivity by implanting only 100 fibres as a test implant. If there were no hypersensitivity reported in six weeks, 500 - 1200 fibres were further implanted per session at a gap of minimum three weeks till a satisfactory cosmetic result was obtained.

A standard operative technique was used for all the patients in all the centres and a similar post-operative care was provided to avoid bias due to different operators. A special needle- containing automatic implanter was used to implant the fibre. This instrument allows the operator to reach the right depth in the scalp implanting the fibre until the knot reaches the galea capitis. The fibres were spaced at a minimum interval of 2 mm. Special attention and care were paid by the operating surgeon to avoid implanting two fibres at the same point and giving any traction to the implanted fibre to avoid displacement of the fiber superficially. Topical as well as systemic antibiotics were prescribed to all cases for the next seven days. In addition to this, all patients were asked to use an antiseptic shampoo on alternate days for seven days and avoid tar - based shampoos.

The post - operative evaluation included: efficacy (as judged by Hamilton scale grading, covered area percent, surgeon and patient's subjective evaluation) and safety (as judged by adverse events). Clinical examination and scalp hygiene assessment were done bimonthly for the first year and every three months for the second year. The additional assessment was also done in case of any adverse events.

Results

A total of 213 cases of different origins and ethnicities were enrolled in the study, out of which 194 cases completed the trial. Only 19 cases underwent test implantation and were excluded from the study for the following reasons (three cases developed a hypersensitivity reaction to test implants, six patients opted out due to personal reasons, and ten cases were lost to follow up).

Table 2: Patients with previous alopecia treatments. Is it possible to move this table under the relative text reference

Topical treatments	91 patients (46.91%)
Systemic treatments	24 patients (12.37%)
Surgery	18 patients (9.28%)

Male patients represented the majority of the study population: 165 men (85.05%) vs 29 female (14.95%). The average age was 42 (± 4.78), with an age range of 25 - 65 years, 133 patients (68.56%) had taken previous treatments for alopecia (Table 2):

Food and/or respiratory allergies were detected in 19 subjects (9.79%). However, in these

patients, no hypersensitivities were reported to the test implants. The average number of implanted fibres was 2302 (SD2.805; size 200.9) ranging from 300 to 16000.The average duration of pain and tenderness in the implant area was 2.3 days (SD 4.096; se 0.2933) ranging from 1 - 20 days. A diagrammatic comparison of the Hamilton scale grading before and after the trial showed dramatic improvement (Fig. 1) with the majority of the patients being in Hamilton grade II after implantation.

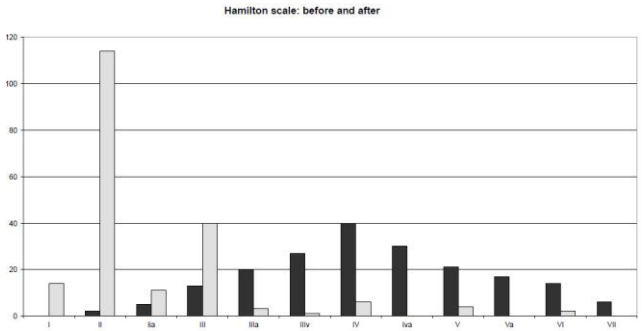

Figure 1: Grey - before; black – after hair implantation

Both subjective (physicians and patients') and efficacy evaluation data which were recorded on a three-grade scale (1 = slight improvement, 2 = moderate improvement, 3 = marked improvement) showed moderate to marked improvement at the end of the study. Average patients, surgeons' and efficacy evaluation grades were 2.54, 2.53, and 2.34 respectively.

Table 3: Paired T-test for Hamilton Scale Grading

Paired T-test for Hamilton Scale Grading
average grade before: 4.52
average grade of 2.33
t = 20. 823
p < 0.0001

Overall a successful result was noticed in 97.94% of the patients with psychological satisfaction. Paired T-test for Hamilton Scale Grading and Covered Area Percent gave statistically significant results (Table 3, 4).

Table 4: Paired T-test for Covered Area Percent

Paired T-test for Covered Area Percent
average % before: 61.5
average % after: 85.3
t = -23.3
p < 0.0001

An annual rate of 10.61% was noticed. Careful maintenance of post-operative scalp hygiene and use of appropriate products contributes to reducing the fall rate and recurrent folliculitis. These fibres were found safe in 90.73% of cases. Adverse events were clinically classified into three categories (insignificant, mild, and moderate) and were observed in only 18 cases (9.27%), (Table 5, Fig. 2a).

Table 5: Complication rate in patients

	No. of patients	%
Insignificant	2	1.03
Mild	12	6.18
Moderate	4	2.06

Insignificant adverse events like fibre curling were observed in two cases (1.03%). Curling of the fibre is often caused by wrong products application and does not affect the scalp.

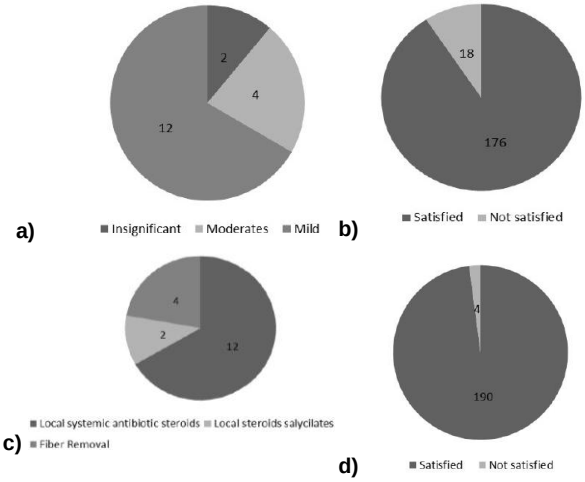

Figure 2: a) Complication; b) results; c) therapy; and d) results after hair implant therapy

Mild side - effects comprising localised slight inflammation and infection were recorded in 12 cases (6.18%) which improved thanks to topical anti-inflammatories and antibiotics with an average healing time of 10.8 days. Staphylococci (aureus and epidermoids), Streptococcus pyogenes, and corynebacteria (acnes and other strains) were the microbial species repeatedly grown in the cultures in these cases. Poor scalp hygiene, excessive perspiration, dirty headgears, secondary seborrhea, inadequate skin care were identified as the main risk factors.

Moderate adverse events observed in four cases (2.06%) also required some fibre removal, when frank abscess or pustular inflammation were not controlled by topical and systemic therapy. In these cases, microbiological cultures revealed Staphylococcus aureus infection and systemic antibiotic therapy (teicoplanin 400 mg. daily, im) was added to the local treatment in order to control infections. No residual damage or permanent scarring was observed during the follow up period in any of these cases .In none of the cases did we record any further complications after healing (Fig. 2 b, c, d).

The results of this clinical trial demonstrate that Biofibre® hair implantation provides satisfactory results in both male and female cases of androgenetic alopecia. Patients with psychological disorders, autoimmune diseases, immunodeficiencies, lack of personal hygiene have to be excluded [9][10].

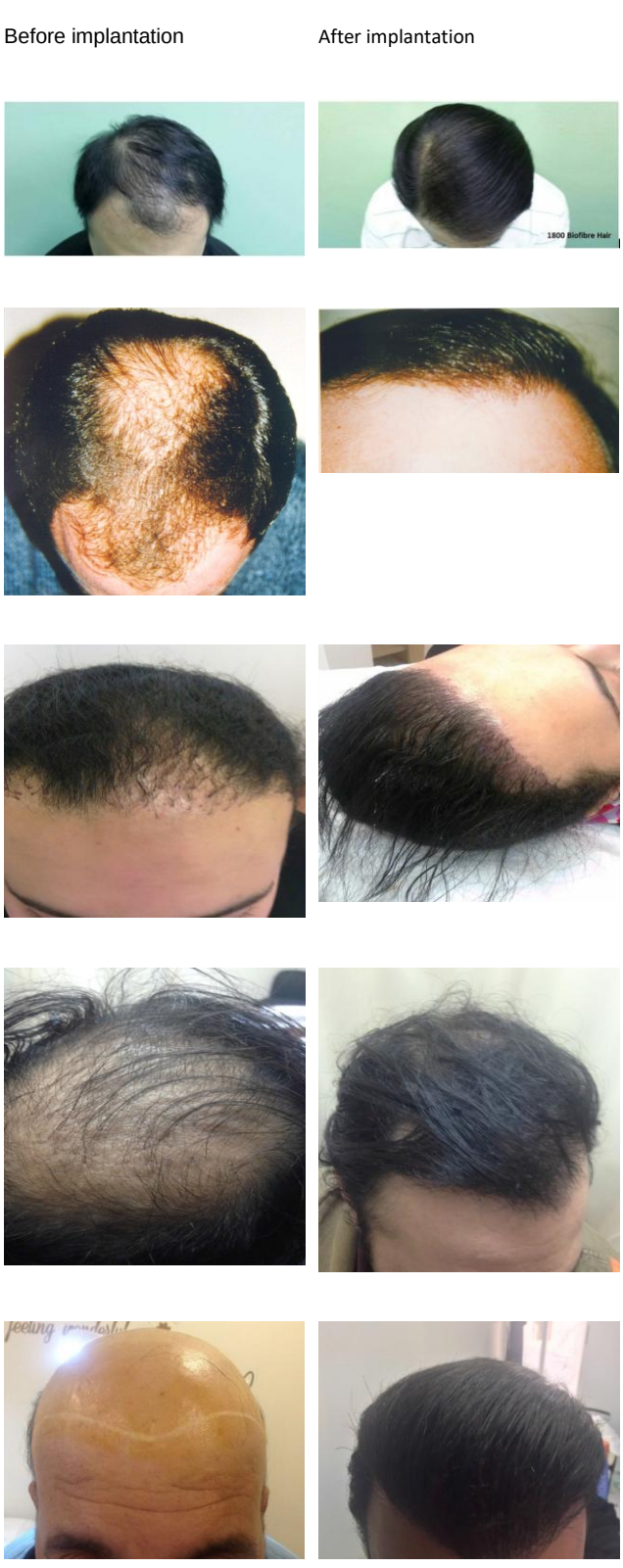

Figure 3: Several patients before (left) and after hair implantation (right)

Use of biocompatible hair implant fibres, modern automatic equipment, careful selection of patients, respect of pre - and post-implant protocol and correct after care are essential requirements to achieve the expected results. If the medical protocol indications are respected, this technique represents a safe and efficacious method to treat androgenetic alopecia with immediate aesthetic results providing immense psychological comfort [11][12][13] to the male and with particular attention to female patients [14]. Use of wrong substances, of unsuitable treatment and a lack of hygiene or correct after-care can compromise the expected result. If problems appear and can't be successfully treated, a complete fibre removal is performed without residues [15][16]. The Biofibre hair implant procedure can also be performed in combination with other hair restoration techniques such as follicular unit hair transplantation to maximize final aesthetic result or in case of scarce donor - area [17][19]. It is also an appropriate technique to cover scalp scars such as post-burn and post-traumatic scars [20][21]. Several implant tests on alopecia total are and alopecia areata cases are taking place with encouraging results.

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Successful Treatment with UVA 1 Laser of Non - Responder Vitiligo Patients

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Keywords: Vitiligo; UVA1; Laser Alba 355®; Repigmentation; Safe profile

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Abstract

The Authors discuss their experience in treating non-responder vitiligo patients with a UVA-1 laser. Laser Alba 355® is an innovative device of target UVA - 1 phototherapy. The present report suggests that UVA1 laser could be an applicable therapeutic option in patients with vitiligo, also for the ones who did not respond to the more conventional phototherapies.

Introduction

Vitiligo is an important cutaneous pigmentary disorder, characterised by the progressive loss of melanocytes and/or by their dysfunction, resulting in hypopigmented skin areas which progressively become amelanotic. Despite new researches and progress, the pathogenesis of vitiligo is still enigmatic. Nowadays most evidence support that vitiligo is a T - cell-mediated autoimmune disease, maybe triggered by oxidative stress, and associated with an underlying genetic predisposition [1][2][3][4].

Clinically, the condition is characterized by milk-white macules and patches, varying in size, form, and distribution. Because of the clinical appearance of the patients, vitiligo is often associated with psychological distress and reduction of patient's life quality index [5].

Classically, vitiligo treatments are unsatisfactory and challenging. Despite the continuous introduction of innovative medical and surgical therapies, phototherapy is the mainstay of vitiligo repigmentation (Table 1) [6].

Table 1: Conventional phototherapies available for vitiligo treatment

Phototherapies
Broadband UVA
PUVA therapy
Topical PUVA
PUVA sol therapy
Bath PUVA
Broadband UVB
Narrow band UVB

The aim of this multicenter observational study was to evaluate the efficacy and safety of Laser Alba 355 in the treatment of 21 patients affected by vitiligo vulgaris, who had been unsuccessfully treated with other conventional phototherapies.

Patients and Methods

We evaluated 21 subjects (14 female, seven male), aged from 23 to 48 years, who suffered from stable or active vitiligo vulgaris for more than three years and less than six years. Lesions were variously localised (Table 2).

Table 2: Distribution of vitiliginous macules in our patients

Side of Lesion	Number of Patients
Face	17
Trunk	9
Arm	13

In the past, all of them have been treated with different phototherapies, without good clinical results. In details, 18 patients had been treated with a complete session of PUVA therapy; the other 3 stopped the treatment because of the gastric toxicity of psoralen. Successively, all patients completed the treatment with UVB broadband of clinical responses; patients had been successively treated with narrow-band UVB (311nm) total body. None of them achieved a repigmentation rate more than 30%. In the recent past (5 months), none of them had been treated for the cutaneous disease.

We decided to treat the patients with UVA - 1 laser using Laser Alba 355®, a laser technology based on UVA - 1 spectrum with a wavelength of 355 nm (Table 3). They had been irradiated once a week at a dosage of 120 J/cm², for 24 weeks.

Table 3: Laser Alba 355 ® technical features [7]

Laser Source	Solid state pumped laser diode (DPSS)
Active Material	Neodymium-doped yttrium orthovanadate (Nd: YVO4)
Wavelenght	355 nm
Maximum Output	7W
Beam Size	2.5 mm
Beam Quality	TEM00
Beam Divergence	1.5 mrad
Power Stability	<1%
Repetition Pulse Rate	20-25 kHz
Maximum Energy per Pulse	0.35 mJ
Pulse Width	10-15 ns
Brightness	For 20000 hours
Cooling System	Air

The time of emission and spot diameters were regulated by the operator, based on the clinical characteristics of the patients.

For all patients, digital photographs of the vitiliginous lesions have been obtained before the start and at each treatment session. The response to the treatment was determined by assigning to each lesion a 0% score before therapy and a second percentage value at the end of the same, to represent the level of repigmentation (Table 4).

Table 4: Classification of clinical response by the repigmentation rate

Clinical response	Repigmentation rate
Excellent	>75%
Marked	50-75%
Moderate	25-50%
Minimal	< 25%

Results

At the end of the treatment, we evaluated the repigmentation rate achieved by every single patient treated with Laser Alba 355®. 17 patients (81%) achieved excellent results, with a re - pigmentation rate bigger than 75%. Three patients (14%) achieved a marked improved of the clinical findings with a repigmentation rate between 50-75%. Only one patient showed minimal response to the phototherapeutic treatment.

No differences in repigmentation had been described for the different localisation of the lesions.

In general, the treatment had been well tolerated by all patients. Besides a mild, transient, post-therapy erythema and itching sensation, we did not observe other side effects.

Discussion

In this multicenter study, we evaluated the treatment of 21 patients affected by a stable or active form of localised vitiligo with Laser Alba 355®, an innovative targeted phototherapy device, with a peak of emission of 355 nm [7].

Like common UVA - 1 device, the biological effects of UVA - 1 laser are mainly mediated by the formation of reactive oxygen intermediates, during the mitochondrial oxidative phosphorylation, which may damage DNA, lipids, proteins and cellular organelles. This fact may exert different biochemical effects, such as inhibition of immune responses and stimulation of melanocytes [8][9].

The most important advantage in the use of Laser Alba 355®, is the possibility to treat only skin lesions, sparing uninvolved skin areas. This fact allows the operator to use higher doses achieving better results in less time and in a safer way, reducing the side effects due to radiation.

In conclusion, laser Alba 355® is an

innovative device of target UVA - 1 phototherapy. The present report suggests that UVA1 laser could be an applicable therapeutic option in patients with vitiligo, also for the ones who did not respond to the more conventional phototherapies.

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Micro - Focused Phototherapy Associated To Janus Kinase Inhibitor: A Promising Valid Therapeutic Option for Patients with Localized Vitiligo

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Keywords: Vitiligo; Micro – phototherapy; BIOSKIN EVOLUTION®; Janus kinase inhibitor; Tofacitinib; Repigmentation

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Abstract

BACKGROUND: Vitiligo is an acquired pigmentary cutaneous disease, characterised by the progressive loss of melanocytes, resulting in hypopigmented skin areas which progressively become amelanotic. Classically, vitiligo treatments are unsatisfactory and challenging. Despite the continuous introduction of new therapies, phototherapy is still the mainstay for vitiligo repigmentation.

AIM: The aim of this multicenter observational retrospective study was to evaluate the efficacy and safety of the nb - UVB micro - phototherapy (BIOSKIN EVOLUTION®), used alone or in associations with an oral Janus kinase inhibitor (Tofacitinib citrate), in the treatment of stable or active forms of localised vitiligo.

MATERIAL AND METHODS: Fifty eight patients had been treated with n-UVB micro-photootherapy (Group A); 9 patients had been treated with phototherapy plus Tofacitinb citrate (Group B).

RESULTS: Among Group A, 42 patients (72%) obtained a re-pigmentation rate higher than 75%, with a medium value of 77%. 11 patients (19%) achieved a marked improvement of the clinical findings with a repigmentation rate between 50-75%; 4 patients (8%) showed a moderate response with a lesional repigmentation of 25-50%. Only one patient (1%) had a poor response to the phototherapeutic treatment

CONCLUSION: Nb - UVB micro-focused phototherapy is one of the most effective therapeutic options for vitiligo treatment. The association of micro-focused phototherapy to Tofacitinib citrate seems to provide better clinical results in term of repigmentation rate.

Introduction

Vitiligo is an acquired, chronic, cutaneous hypopigmentary disorder, which results in the progressive loss of melanocytes from the epidermis and its appendages.

Even if the precise aetiology and pathobiology of the disease are still unclear [1], recent data support that vitiligo is a T - cell-mediated autoimmune disease, maybe triggered by oxidative stress [2]. Many data support the autoimmune nature of the disease, such as the evidence of autoimmune T cells epidermotropic T cells exerting anti melanocytic cytotoxicity activity [3], the presence of circulating antibodies versus melanocyte antigens [4][5], the association with another kind of autoimmune syndromes [6], and the clinical response to immunosuppressive therapies [7]. Since the deep psychological impact of vitiligo on patients and their quality of life [8], to treat the disease is very important.

The aim of this multicenter observational retrospective study was to evaluate the efficacy and safety of the nb - UVB micro - phototherapy (BIOSKIN EVOLUTION®), used alone or in associations with an oral Janus kinase inhibitor (Tofacitinib citrate), in the treatment of stable or active forms of localized vitiligo.

Patients and Methods

This observational retrospective study has been conducted in Italy, Germany, Croatia, Bulgaria, America and Australia.

We evaluated 67 subjects (44 women, 23 men), aged from 25 to 61 years, who suffered from stable or active vitiligo Vulgaris by more than 2 years and less than 10. In the recent past (more than 5 months), none of them had been treated for the cutaneous disease. Nine of those patients (7 women, 2 men) were also affected by rheumatoid arthritis since more than 3 years (mean duration: 5 years). Those patients were in treatment with Tofacitinib citrate (10 mg/die), an oral Janus kinase inhibitor. We decided to treat all the patients with BIOSKIN EVOLUTION®; a special cold light generator micro-focused phototherapy. BIOSKIN EVOLUTION® can provide a spectrum of intensity up to 400 mW/cm^2 with a peak of emission at 311 nm.

Patients had been irradiated once every three weeks for a total of 12 sessions, with an average dose of 50 mW/cm^2. The starting dose of irradiation was 20% less than the minimal erythema dose (MED), which had been evaluated on a vitiliginous area of each patient, during a test, performed 3 days before the treatment.

Time of emission and spot diameters were regulated by the operator, on the base of the clinical characteristic of the patients. In the following sessions of treatment, we progressively increased the irradiation dose by 20% until the development of erythema was noted. When was noted, the dose of the following treatment was diminished by 20% in the erythematous area.

For all patients, digital images of the cutaneous lesions, both with normal ambient light and with Wood's lamp, have been obtained before the treatment beginning and at each session, for all the treatment period. Response to the treatment was determined by assigning to each lesion a 0% score before therapy and a second percentage value at the end of the same, to represent the level of repigmentation.

Results

At the end of the treatment, we evaluated the repigmentation rate achieved by every single patient treated with BIOSKIN EVOLUTION® alone (Group A) or in association with oral Tofacitinib citrate (Group B). Among Group A, 42 patients (72%) obtained a re-pigmentation rate higher than 75%, with a medium value of 77%. Eleven patients (19%) achieved a marked improvement of the clinical findings with a repigmentation rate between 50 - 75%; four patients (8%) showed a moderate response with a lesional repigmentation of 25 - 50%. Only one patient (1%) had a poor response to the phototherapeutic treatment. In any case, we did not observe side effects.

Surprising, the Group B patients showed better results in term of repigmentation rate in comparison to the patients of Group A. All the 9 subjects achieved a nearly complete re-pigmentation of the vitiliginous areas, with a re -pigmentation rate of 92%. Also in Group B, we did not observe side effects.

Discussion

In this retrospective study, we evaluated the treatment of 67 patient affected by a stable or active form of localised vitiligo with BIOSKIN EVOLUTION®, a micro-focused phototherapy device (peak of emission of 311 nm), used alone or in association to oral Tofacitinib citrate, an oral Janus kinase inhibitor.

As we had supposed, the study confirms the effectiveness and safe-profile of nb - UVB micro-focused phototherapy in the treatment of localised forms of vitiligo. As well known, nb - UVB micro-focused phototherapy is now considered as one of the best treatment for localised vitiligo. As the classical phototherapeutic devices, the micro-focused one act stimulating silent melanocytes and modulating the immune skin system. Differently by classical devices, the micro-focused one has the major advantages that, treating only skin lesions, the operator may use more appropriate doses achieving better results in less time and in a safer way, reducing the side effects due to radiations [9][10][11]. Moreover, another important data has emerged from our retrospective study: the combination of BIOSKIN EVOLUTION® to systemic Tofacitinib citrate, allows to achieve better clinical results in term of repigmentation rate.

Tofacitinib citrate is an oral Janus kinase inhibitor. Janus kinases (JAKs) are intracellular protein kinases, crucial for the transmission of extracellular cytokines and cells communication. Even if they act in different ways (e.g. cells growth and maturation), JAKs have a fundamental role for innate

and adaptive immunity. Recent data have shown that their up-regulation is implicated in autoimmune disorders (e.g. rheumatoid arthritis), which may be successfully treated with JAKs inhibitors, such as Tofacitinib citrate, for their immunosuppressive and anti-inflammatory actions [13][14][15].

In our case, patients treated with micro-focused phototherapy plus Tofacitinib citrate achieved better results in term of repigmentation (repigmentation rate of 92%) than phototherapy alone. This can be explained by the imbalance of proinflammatory cytokines, mainly derived from The/Thl7 lymphocytes, in vitiligo [16].

In conclusion, nb - UVB micro-focused phototherapy is one of the most effective therapeutic options for vitiligo treatment. The association of micro-focused phototherapy to Tofacitinib citrate seems to provide better clinical results in term of repigmentation rate. New studies have now to be conducted to elucidate the exact mechanism of actions and the possibility to use this therapeutic protocol for the treatment of vitiligo.

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Clinical Science

An Innovative Therapeutic Protocol for Vitiligo: Experience with the Use of Fraxel Herbium Laser, Topical Latanoprost and Successive Irradiation with UVA - 1 Laser

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Keywords: Vitiligo; Fraxel Herbium laser; Latanoprost; UVA1 laser; Repigmentation

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Abstract

Despite the continuous introduction of innovative therapies for vitiligo, today none of them provide constant and excellent results in term of repigmentation. The authors report their experience in treating a localised form of vitiligo with a new protocol consisting in the use of a Fraxel Herbium laser, and in the following application of topical Latanoprost solution and, one day after, in lesional irradiation with UVA1 laser.

Introduction

Vitiligo is an acquired, chronic, cutaneous disease, characterised by milky white macules and patches, due to the progressive loss of melanocytes from the epidermis and its appendages. Because the colour contrast between the pigmented skin and the cutaneous lesions, vitiligo is an important cause of psychological distress and reduction of the life quality index so that treating the disease is fundamental [1][2]. Vitiligo treatment has two main goals: the first one is to halt the disease progression; the second one is to induce the lesions' repigmentation, achieving an acceptable cosmetic result. In the last years, several therapeutic options, both medical and surgical, have been proposed for vitiligo (Table 1) [1][3][5].

The aim of this multicenter study was to evaluate the efficacy and safety of an innovative combination treatment, based on the use of a Fraxel Herbium laser, the successive topical application of Latanoprost, and, finally, one day after, by the

irradiation with UVA - 1 laser.

Table 1: Main therapeutic options for vitiligo

MEDICAL THERAPIES	Topical and/or systemic corticosteroids Phototherapy: oral PUVA, topical PUVA, bath - PUVA, sol PUVA, nb - UVB, UVB - microphototherapy, UVA - 1 microphototherapy Excimer laser Topical calcineurin inhibitors Topical Vitamin D analogues Pseudocatalase Topical 5 - Fluoracil Topical prostaglandin E2 analogue Systemic antioxidants Low dose medicine Depigmentation therapy Camouflage
SURGICAL THERAPIES	Tissue grafting technique: suction blister grafting, split thickness grafting Miniature punch grafting Follicular unit grafting Smash grafting Cellular grafting techniques: non - cultured epidermal suspensions, melanocyte culture

Patients and Methods

We evaluated 30 subjects (19 female, 11 male), aged from 20 to 58 years (mean age: 34 years), who suffered from stable or active forms of localised vitiligo vulgaris for more than 18 months and less than five years (Table 2).

In the past six months, none of them had been treated for the cutaneous disease. After obtaining the informative consent, we decided to treat the patients with an innovative therapeutic protocol consisting of 3-phases sequential treatment of skin lesions.

Table 2: Distribution of the vitiliginous patches in our patients

Body part	Number of patients
Trunk	12
Face	9
Arms and legs	25

Initially, we treated the vitiliginous lesions with a single passage of Fraxel Herbium laser (Valseriana® Fraxel Herbium Laser), with a wavelength of 1540 nm and an energy level of 1800 mJ/P. Immediately after obtaining columnar areas of epidermal ablation, we applied Latanoprost 0.005% (Xalatan®) solution onto each skin lesion (1 drops every 2.5*2.5 cm^2 lesion).

The day after, we irradiated the skin lesions with a UVA1 laser (Laser Alba 355®, the wavelength of 355 nm) for 20 minutes. The treatment has been repeated every 21 days, for nine months (total session).

For all patients, digital photographs of the cutaneous lesions, with normal ambient light and Wood's lamp, have been obtained before the start and at each session, for all the treatment period. Response to the treatment was determined by assigning to each lesion a 0% score before therapy and a second percentage value at the end of the same lesion, to represent the level of repigmentation.

Results

At the end of the treatment, we evaluated the repigmentation rate achieved by every single patient treated with the innovative protocol.

Twenty-seven patients (90%) obtained a re-pigmentation rate higher than 75%, with a medium value of 88% (Figure 1). The other three patients (10%) achieved a marked improvement of the clinical findings with a repigmentation rate between 50-75%.

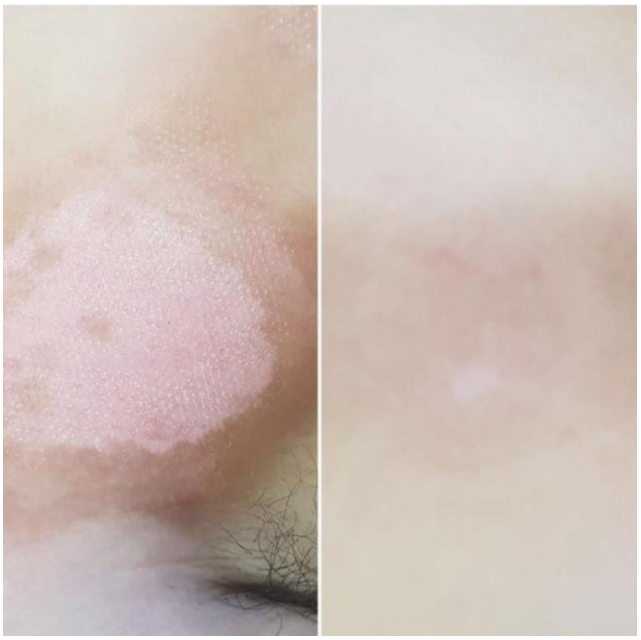

Figure 1: Progressive rapid repigmentation of Vitiligo patches after treatment with Laser Fraxel Herbium, local application of Latanoprost solution and UVA1 irradiation

We did not observe any difference in repigmentation for lesions with different localisation.

In any case, we did not observe side effects, apart for a transient inflammation (erythema and oedema) and itchy sensation in the treated area.

Discussion

In this study, we evaluated the treatment of 30 patient affected by a stable or active form of localised vitiligo with a new therapeutic protocol consisting of a 3 - phases sequential treatment of skin lesions.

At first, we used a Fraxel Herbium laser (Valseriana® Herbium laser) with a wavelength of 1540 nm and high energy level of 1800 mJ/P. We performed only one laser passage for each lesion to achieve micro-areas of epidermal ablation [6].

Immediately after the laser treatment, we applied Latanoprost 0.005% ocular solution (1

drop/2.5*2.5 cm^2 lesion).

Latanoprost solution is a prostaglandin F2 alpha (PGF2a) analogue, normally used in the treatment of glaucoma. Since the evidence of it's periocular and iridal pigmentation side effects, Latanoprost has been evaluated for the treatment of cutaneous hypo-pigmentation, showing to be effective especially in combination with different therapies (e.g. phototherapy) [7][8].

The day after, we irradiated the skin lesions with a focused UVA1 laser with a wavelength of 355 nm and an energy level of 25 J/cm^2 (Laser Alba 355®) for 20 minutes.

As the classical UVA1 phototherapy devices, Laser Alba 355® acts both stimulating melanocytes and inhibiting the immune responses which lead to the formation of skin lesions. In detail, it has been shown that UVA - 1 can induce the apoptosis of T lymphocytes and to inhibit effector T- cells, through the direct inhibition of dendritic cells, and through the production of interleukin 10 (IL - 10) and the decrease of tumour necrosis factor-alpha (TNF - alpha) [9].

In contrast to the classical devices, Laser Alba 355® has the major advantages that, treating only skin lesions, it acts in a safer way reducing the side effects due to radiations and achieving better aesthetic results regarding less colour contrast between a vitiliginous and vitiliginous skin [9][10]. In our case, all patients treated with the innovative combination therapy achieved good results in term of repigmentation (repigmentation rate of 88%) without relevant side effects, apart from a transient inflammation and erythema.

In conclusion, the association of Fraxel Herbium laser, topical Latanoprost solution and focused UVA1 laser seems to provide good clinical results in term of repigmentation rate, without side effects.

All the patients were satisfied by the innovative protocol treatments, not only for the achieved aesthetical results but also for its limited number of sessions.

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Case Report

Subungual Exostosis in a Young Soccer Player

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Keywords: Surgery; exostosis; nail; verruca vulgaris; treatment outcome

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Abstract

BACKGROUND: Subungual exostosis is a relatively uncommon, benign osteocartilaginous tumor of the distal phalanx of the toes or fingers in young adults, considered as a rare variant of osteochondroma. Differential diagnoses include subungual verruca (viral wart), pyogenic granuloma, osteochondroma, amelanotic subungual melanoma and glomus tumour. Misdiagnosis and total onychodystrophy frequently occur as a result of late treatment or inadequate treatment strategy. Dermoscopy could be a useful technique, involved in the diagnostic process, although X-ray examination and histopathology are mandatory for the diagnosis.

CASE REPORT: We report a rare case of subungual exostosis of the great toe associated with repeated trauma of the nail bed. The lack of radiographic and histopathological examination could lead to misdiagnosis and inadequate treatment. Although completely benign, subungual exostosis should be considered in differential diagnosis of nail bed tumors in young adults, in order to avoid associated complications and unneeded aggressive surgical interventions.

CONCLUSION: Complete excision of the lesion and delicate separation from the underlying nail bed structures results in total resolve of the problem, by providing the lowest risk of recurrences.

Introduction

Subungual exostosis (SE) is a relatively uncommon, benign osteocartilaginous tumor of the distal phalanx of the toes or fingers, considered as a rare variant of osteochondroma [1][2].

First described by Dupuytren in 1847, SE is the most common nail tumor of young adults, representing a benign bony proliferation of the distal phalanx with unknown etiology [2][3].

The proposed possible triggering factors include constant irritation of the bone, previous trauma and longstanding infection [1]. Two inherited conditions could be manifested as subungual exostosis, namely multiple exostoses syndrome and multiple exostoses-mental retardation syndromes [3]. Although completely benign, SE must be differentiated between a number of other subungual tumors, both benign and malignant [4]. There are increasing evidences of histological differences between subungual exostosis and subungual osteochrondroma. Histologically, subungual exostosis has a fibrocartilaginous cap whereas osteochondroma has distinctive hyaline cartilage [5]. When the diagnosis is made, simple surgical removal of the exostosis is effective and well- tolerated treatment option [6].

Case report

A 7-year-old otherwise healthy male patient presented with a small painful, raised skin lesion under the nail plate, on the medial edge of the right hallux, with one year history of duration.

A lobulated nodule of bony-hard consistency, measuring around 1 × 1 cm located on the medial aspect of the right great toe was established within the clinical examination. Elevation and destruction on the nail plate in the affected area was also presented (Fig. 1a).

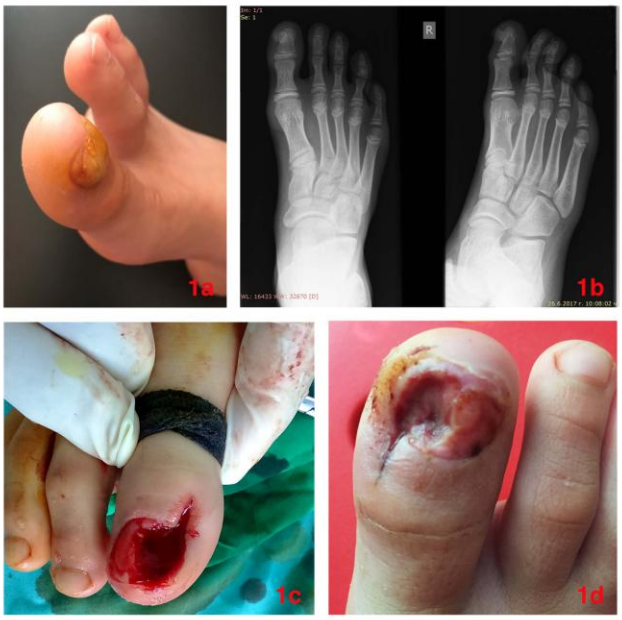

Figure 1: 1a - Clinical manifestation of a subungual exostosis, presented as a firm, painful lesion, with eroded surface, on the medial aspect of the right great toe, under the distal half of the nail plate; 1b - X-ray examination of the foot showing mature bone projecting from the distal end of the terminal phalanx of the right halux forming a Y-shaped bifurcation; 1c - Intraoperative images of a marginal excision of subungual exostosis of the great toe; 1d - The operative wound after resection of the exostosis. At the bottom - a well-rounded macroscopic intact bone, the incision is extended proximally to cure the medial part of the nail matrix in order to narrow the future nail and avoid its ingrowth

Mild pain was reported by the patient, when pressure was applied on the right great toe. A history of preceding chronic trauma was available, as the patient was a soccer player. The initial diagnostic consideration was a subungual verruca vulgaris. Radiography of the right foot revealed a lesion composed of mature bone stemming from the dorso-medial end of the terminal phalanx of the right hallux forming a Y-shaped bifurcation (Fig. 1b). The lesion was excised under general anesthesia, with complete removal of the cartilaginous cap by curetting to normal trabecular bone (Fig. 1c,d). Histopathological examination of a fragment of excised lesion established mature trabecular bone covered by a well-developed fibrocartilaginous cap located in the deep dermis (Fig. 2a,b,c,d).

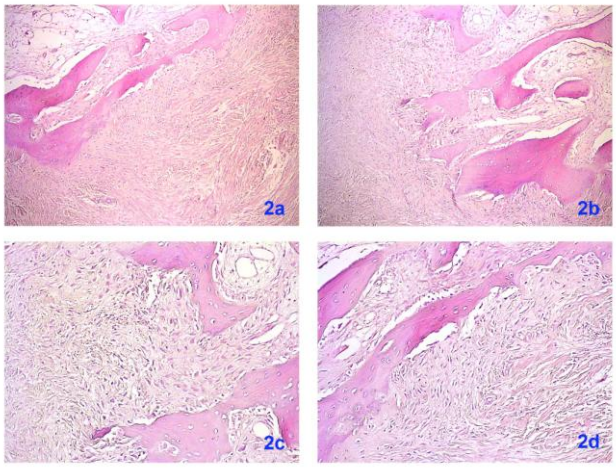

Figure 2: a, b – Histological findings (HE x100) - Loosely arranged spindle cells with mitotic activity, but no cytologic atypia, zonation (zonation phenomenon). The central cellular portion matures into trabecular bone surround by a well-developed fibrocartilaginous cap; 2c,d -(HE x 40) The lesion tends to mature toward the periphery producing osteoid rimmed with osteoblasts

The morphological findings cover a large number of criteria for a histological profile of the underneathing exostosis (underneathing zone heteropic ossification). The clinical, radiographic and histopathological data support the diagnosis of subungual exostosis.

Discussion

Subungual exostosis is usually presented with a solitary lesion, which appears like a small firm lesion, located deep to the free edge of the nail in children and young adults [1].

The most common site of affection is the inner or medial aspect of the great toe, and less common SE could affect the fingers, especially the index and middle fingers [2][3]. Although it can occur at any age, half of the reported cases described patients under 20 years of age, with female predominance of the gender distribution [3].

Many possible causes have been implicated in the etiopathogenesis of SE, such as: trauma, chronic infections, tumor, hereditary abnormality, or activation of a cartilaginous cyst [4][6]. The condition may also represent cartilaginous metaplasia occurring in response to acute or chronic irritation [7][8].

The differential diagnosis of subungual exostosis includes verruca vulgaris, subungual fibroma/fibrokeratoma, pyogenic granuloma, glomus tumor, subungual epidermal inclusion cyst, achromic malignant melanoma, squamous cell carcinoma of the

nail bed, melanotic whitlow, osteogenic sarcoma and enchondroma [7]. Radiological findings may establish the diagnosis in the majority of cases [7]. Radiographically, the lesion is approximately 1 cm in diameter and projects from the dorsal or dorsomedial aspect of the distal portion of a terminal phalanx. It is composed of mature trabecular bone with attachment to the phalanx; the free end is flat, cupped and smooth, or irregular [9]. There is a large radiolucent cartilaginous cap [3]. There is no cortical disruption or other abnormality of the distal phalanx [9]. Dermoscopy could be another useful technique, involved in the diagnostic process, although X-ray examination and histopathology are mandatory for the diagnosis [10]. The dermoscopic features include vascular ectasia, hyperkeratosis, onycholysis, and ulceration [10].

Specific operative and nonoperative strategies vary widely and there are no articles comparing directly one technique with another. The most successful therapeutic approaches involved curettage, burr or rongeur debridement down to the base of the stalk to avoid recurrence, with preservation of the nail bed when possible [1][6].

We report a rare case of subungual exostosis on the great toe associated with repeated trauma of the nail bed. Although completely benign, the lack of radiographic and histopathological examination could lead to misdiagnosis and inadequate treatment. Delayed diagnosis occurred in approximately 10% of the cases and total onychodystrophy occurred in more than 10% of the patient as a result [1]. Complete excision of the lesion and delicate separation from the underlying nail bed structures results in the lowest rate of recurrences and future complications.

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Case Report

Chronic Scalp Ulcer 35 Years after Skull Trepanation Surgery and Radiotherapy for Oligodendroglioma: A Further Example of Immunocompromised Cutaneous Districts

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Keywords: Chronic scalp ulcer; Oligodendroglioma; Second malignancy; Complex reconstruction; Immunocompromised cutaneous district

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Abstract

BACKGROUND: Chronic ulcers of the scalp have a variety of underlying pathologies. In case of cancer patients, a second malignancy must be excluded.

CASE REPORT: A 78-year-old female patient presented to our department with a large soft tissue defect on the frontotemporal left side. The lesion was about 3 cm in diameter with exposed bone and inflammatory soft tissue on the edges of the defect. About 35 years ago, she had undergone a combined neurosurgery with skull trepanation and radiotherapy for an oligodendroglioma. Three years ago, sandwich transplantation with the dermal template and meshed skin graft failed. Now she re-presented with inflammatory ulcer borders. A complex defect repair was performed after exclusion of a second malignancy.

CONCLUSION: Chronic scalp ulcers may be the result immunocompromised cutaneous districts and need a complex reconstruction.

Introduction

Chronic scalp ulcers have a variety of differential diagnoses – vascular, infectious, developmental etc. In cancer patients, second malignancies are not uncommon. Focusing on the skin, chronic scars and chronic radiodermatitis are prone to non-melanoma skin cancer development [1]. Radiotherapy is a risk factor for cutaneous angiosarcoma [2, 3].

Radiotherapy has also possible adverse effects on vascularity of tissues with subsequent tissue fibrosis and/ or ulceration [4].

Here we present a case of an elderly female patient with the development of a chronic scalp ulcers suggesting second non-melanoma skin cancer after primary treatment of oligodendroglioma. We also discuss the defect closure.

Case report

A 78-year-old female patient presented to our department with a large soft tissue defect on the frontotemporal left side (Fig. 1a). The lesion was about 3 cm in diameter with exposed bone and inflammatory soft tissue on the edges of the defect. The inflammatory changes developed only recently and have been the reason for the consultation.

About 35 years ago, she had undergone a neurosurgery with skull trepanation for an oligodendroglioma.

Three years ago an excision of fibrous tissue suggestive of squamous cell carcinoma was performed with a defect closure by meshed graft on a dermal template, also known as sandwich transplantation. Histology excluded a malignancy but demonstrated a chronic nonspecific inflammatory reaction with calcinosis cutis. The transplant, however, was lost.

Her medical history was remarkable for hemiparesis, aphasia and epilepsy, repeated urosepsis, suprapubic cystostoma and cholecystectomy.

On examination, we observed an exposed bone frontotemporal with inflammatory and necrotic changes of the surrounding soft tissue. We decided to remove the altered soft tissue and bony surface and defect closure by the rotational flap.

Surgery was performed under general anaesthesia. The soft tissue was removed with a safety margin of 1 cm. The bony surface was refreshed by a rose head burr driven by a pneumatic power drill. The outer table of the skull was completely milled exposing diploic veins to obtain better vascular supply. A one mm thick dermal template made of collagen and elastin was fit in and reconstituted with Ringer's solution. The defect was closed by a large rotational flap after extensive mobilization of the soft tissue from underlying bone. The defect was sutured by a braided, surgical suture composed of polyethylene terephthalate (Ethibond®, Ethilon) (Fig. 1 b, c).

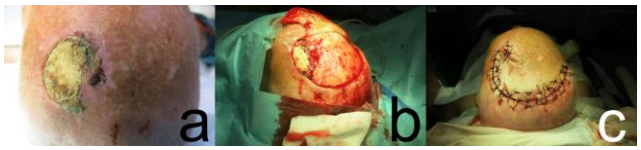

Figure 1: Chronic scalp ulcer 35 years after surgery and radiotherapy of oligodendroglioma. (a) Initial clinical presentation of necrotic exposed bone and soft tissue alterations suggestive of a second malignancy; (b) Surgical situs after removal of altered soft tissue und necrotic bone with exposure to diploic veins; (c) After complete closure by rotational flap on dermal template

Histology of soft tissue revealed a chronic granulomatous inflammatory reaction with comedo-like structures and epithelial cysts. No cytological atypia and no malignancy at all.

Discussion

Oligodendrogliomas belong to the World Health Organization grade II slow growing central nervous (CNS) tumours. The present patient had a treatment for oligodendroglioma 35 years ago. In that time, surgery and radiotherapy were the cornerstones of treatment. Upfront surgical maximal safe resection has been shown to improve overall and progression-free survival [5, 6].

Surgery and radiotherapy may have a long-term impact on surrounding tissues, which may create a certain vulnerability of that part of the anatomy. Several types of bone pathology in the setting of radiotherapy are known, such as advanced osteoradionecrosis, pathologic fractures and non-unions. In the case of CNS targeted radiotherapy decreased vascularity of irradiated skull may cause impairment of overlying soft tissue structures [7, 8].

The sectorial impairment of immune and other functions of skin has been described by Ruocco using the term "immunocompromised cutaneous districts" (ICD)[9-11].

We suggest that iatrogenic ICD has caused the delayed chronic soft tissue defect in our case. In such a situation, minor impairment of microcirculation can cause catastrophic sequelae leading to chronic ulceration. This would explain why the first attempt to cover the defect in 2012 by sandwich transplantation [12] failed.

Scalp ulcerations often need a complex approach for closure with consideration of bony structures and soft tissue [13]. We used the rose head burr driven by a pneumatic power drill to remove necrotic bone and to expose diploic veins in the cancellous skull [14]. A collagen-elastin dermal template was fit in and a large rotational flap was prepared to cover the defect.

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Case Report

Successful Treatment of Reticular Blue Veins of the Lower Eyelid by Long-Pulse Nd: YAG – Case Report with 8-Year Follow-Up

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Keywords: Facial esthetics; Reticular facial veins; Periocular rejuvenation; Nd: YAG laser; Treatment

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Abstract

BACKGROUND: Facial reticular blue veins are of esthetic concern. Most often these veins develop on the lower lids. The safest and most effective way of treatment is by vascular lasers.

CASE REPORT: We report on a successful reticular vein treatment using a long-pulsed 1064 nm Nd: YAG laser. We present a follow-up of 8 years with constant esthetic improvement without unwanted adverse events.

CONCLUSION: There was no relapse demonstrating the efficacy of Nd: YAG laser.

Introduction

Superficial and visible veins in the face can represent an aesthetic concern. Reticular blue veins occur most frequently in the lower eyelids toward the lateral portion of the orbit. These vascular structures around the eyelids are more visible because of the specific anatomical characteristics of the region with no or limited subcutaneous fat beneath the thin skin. They become more visible in patients with fair skin, after weight loss and during ageing. The veins are asymptomatic and the main concern is related to the aesthetic aspect. The desire of the patient is to eliminate the appearance of these dilated and protruding reticular veins. The management of periorbital veins is part of periorbital rejuvenation [1].

Despite all risks and side effects sclerotherapy using sodium tetradecyl sulfate, transection and cautery, extraction (phlebectomy) and electro cauterization remained during a long time the main treatment options [2]. The safety profile of certain techniques, such as sclerotherapy, is questionable in this region where complications related to vision would be catastrophic. Currently, the most effective and safe method for treating these cosmetically unattractive veins in the periocular region is the laser [3].

Case report

We present a case of a 41-year-old female patient with a reticular vein in the lower lid (blue periocular lower eyelid vein, patient skin photo type Fitzpatrick II) (Fig. 1 a, b). No previous treatment was done. After a clinical examination, she was treated with three consecutive sessions of laser. The

parameters of the long-pulsed 1064 nm neodymium-doped yttrium aluminium garnet (Nd: YAG) laser were as follows: fluence ranging from 100 to 125 J/cm2 with a 2.5 mm and 4.0 mm spot size. The pulse width ranged from 3 msec to 15 msec (Synchro and Smartepil, Deka, Italy).

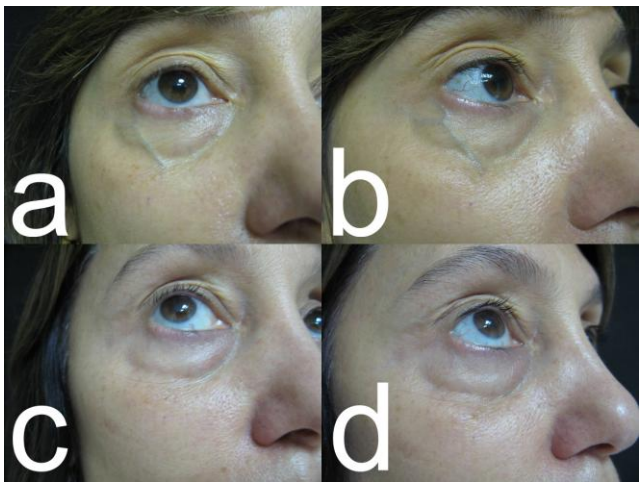

Figure 1: a, b - Reticular vein in lower eyelid; c, d Result 8 years after laser treatment

The sessions were performed monthly. No topical or local anaesthesia was used. The eyes were protected with specific eye wear. Cryogen spray was used before and immediately after laser shot. Erythema and mild oedema occurred. No other side effects were observed. The vein was effectively treated and absorbed after the third session.

The patient was satisfied with the result and returned for consultation 8 years later for another reason (Fig. 1 c, d). The affected region previously treated with the laser presented no skin pigmentation and no evidence of reticular vein recurrence.

Discussion

Laser treatment of vascular structures is dependent on the selected wavelength. The pulse width of the laser must be shorter than the target's thermal relaxation time, which is the time required for the target to lose half of its peak temperature following irradiation. And finally, the fluence has to be sufficient to achieve the desired tissue response within an appropriate time interval [4].

Laser treatment of facial veins or telangiectasia has been reported with different sources of laser including the diode, potassium titanyl phosphate (KTP), copper-bromide, Nd: YAG lasers and pulsed dye lasers among other. Treatment aims to achieve blanching without causing a skin or burn lesion with a consequent resorption of the vein [5][6][7].

Thread-like constriction is the desired treatment endpoint of the vascular laser. This is a consequence of complete vascular occlusion by a thrombus. Cavitation can cause haemorrhage when a thrombus fails to occlude the vessel completely [8]. In vitro experiment found that vessel constriction was due to the constriction of thrombus induced by laser irradiation. The theoretical investigation revealed that the mechanism for the effective reduction of energy density by multi-pulse Nd: YAG laser was due to enhanced light absorption of the blood with thrombus formation [9][10].

The long-pulsed Nd: YAG laser at 1064nm demonstrated to be a safe, simple, effective and fast treatment in the treatment of superficial vein in the eyelid [11][12][13]. Eremia and Li (2002) were the first who reported on Nd: YAG laser in 8 patients with periorbital reticular veins. Their treatment parameters consisted of a fluence between 125-150 J/cm^2 with a 6 mm spot size and pulse widths of 75-100 msec. They also employed cryogen spray like us. However, they did not report on the long-term outcome.

We used a smaller spot size of 4 mm with a much shorter pulse width between 3 to 15 msec. This has been recommended based on mathematical modelling of vascular response to laser irradiation. In general, for selective photothermolysis the laser pulse duration should be similar to the thermal relaxation time of targeted vessels (Anderson & Parrish 1983). For vessels with a diameter between 30 µm and 300 µm, a relaxation time between 1 to 100 msec has been calculated (Mordon & Bourg-Heckly 2016) [14].

Here we report on the successful treatment of lower lid vein with a follow-up of 8 years. There was no relapse demonstrating the efficacy of Nd: YAG laser.

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Case Report

Simultaneous Occurrence of Balanoposthitis Circumscripta Plasmacellularis Zoon, Phimosis and *in Situ* Carcinoma of the Penis: Case Report with An Unusual Ulcerated Polypoid Variant of Zoon's Disease and a Carcinoma *in Situ* of Reserve Cell Type

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Keywords: Balanitis plasmacellularis Zoon; Morbus Queyrat; Penile cancer; Carcinoma in situ; Circumcision; Pimosis; HPV

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Abstract

BACKGROUND: Zoon's balanitis is a benign disease characterized by an asymptomatic, chronic, solitary, shiny, red-orange plaque of the glans and/ or prepuce. In rare cases of Zoon's disease, penile squamous cell carcinoma developed in the chronic inflammatory lesions.

CASE REPORT: We report on a 68-year-old male patient presenting with phimosis and coexistent Zoon's disease and penile carcinoma in situ treated successfully by circumcision.

CONCLUSION: Coexistence of both lesions in contrast to the development of cancerous lesions within pre-existent Zoon's disease is a very rare observation.

Introduction

Zoon's balanitis is characterized by an asymptomatic, chronic, solitary, shiny, red-orange plaque of the glans and/ or prepuce. In contrast to Morbus Queyrat which is a carcinoma in situ, Zoon's disease is a benign lesion [1]. In rare cases of Zoon's disease, penile squamous cell carcinoma developed in the chronic inflammatory lesions [2][3][4].

The disorder develops in uncircumcised adult to elderly men. Nevertheless, in rare cases, females and circumcised men can be affected [5][6]. Etiology and pathogenesis are not well understood but irritant contact balanitis is widely accepted [7].

Histologically, the early lesions show a thickened parakeratotic epithelium. Epidermal oedema accompanied by a dense upper dermal band of lympho-histiocytic inflammatory cells including many plasma cells, dilated capillaries, extravasated red blood cells, and hemosiderin deposition develop. There are a greater proportion of IgG4-positive plasma cells in the lesions, but no signs of cicatrication are found. Later on, a thinned and scant spongiotic epithelium occurs, siderophages may be found in the dermis. Subdermal clefts and lozenge keratinocytes can occur. The lesions don't show cytological atypia or epithelial dysplasia [8][9][10]. As far as we know, Zoon's balanitis is not caused by infection with human papilloma virus (HPV) [11].

Diagnosis is based on clinical pattern and confirmation by histopathology. Noninvasive techniques such as dermoscopy or reflectance confocal microscopy seem to have a potential to differentiate the being lesion from precancerous and cancerous penile imitators [12][13].

Case report

A 68-year-old male patient presented with an asymptomatic reddish papular lesion of the foreskin (Fig. 1). Reposition of the foreskin was not completely possible indicating phimosis.

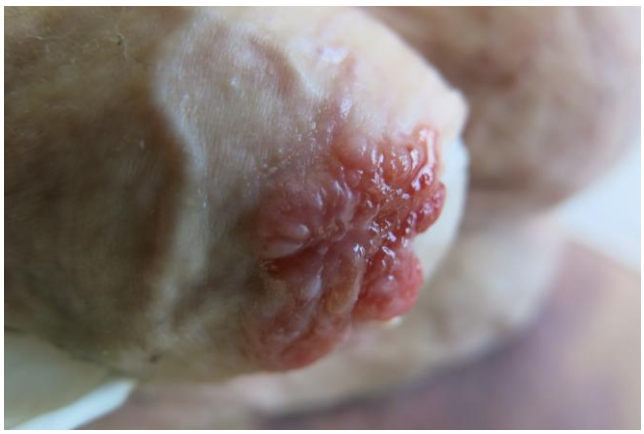

Figure 1: Strawberry-like reddish papules of the penis – clinical presentation of carcinoma in situ

His medical history was positive for diabetes mellitus and prostate adenoma. Surgical excision in combination with circumcision to correct phimosis was performed with penile root anaesthesia using 1% prilocaine solution (Fig. 2).

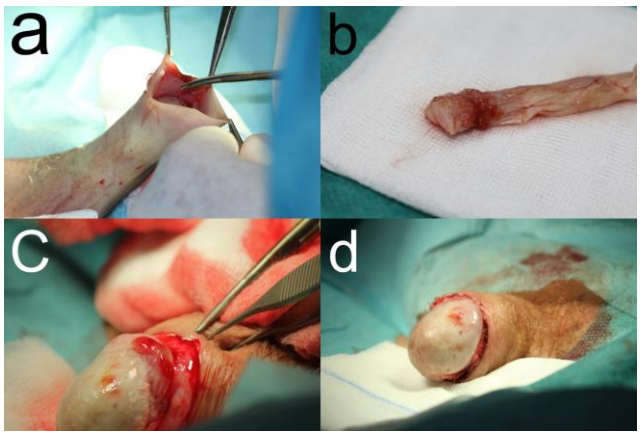

Figure 2: (a) Circumcision of the penis to remove the in situ carcinoma and to correct phimosis; (b) Surgical specimen; (c) Erosive Zoon's disease; (d) After suturing

After removal of foreskin, two shiny reddish ulcerated lesions of the glans penis became visible and were also completely excised (Fig. 2c). The wound was closed with 4/0 absorbable polyglactin sutures (Vicryl rapid®; Ethicon; Norderstedt, Germany) (Fig. 2d). Healing was unremarkable.

Histology: An epidermal in situ carcinoma of the reserve cell type with circumscribed plump taps but complete basal cell membrane (Periodic acid Schiff's reaction and collagen type IV) was observed, associated with a variable dense lichenoid inflammatory infiltrate of the upper dermis (Fig. 3a, b). Locally, hemosiderin depots were seen. R0-resection.

The erosive lesions of the glans penis were characterized as chronic erosive balanophosthitis with a band-like, partly polypoid, and chronic inflammatory reaction, numerous capillaries, surrounded by giant cells. The inflammatory infiltrate was dominated by plasma cells. No epithelial dysplasia, no cytological atypia were observed (Fig. 3 c, d).

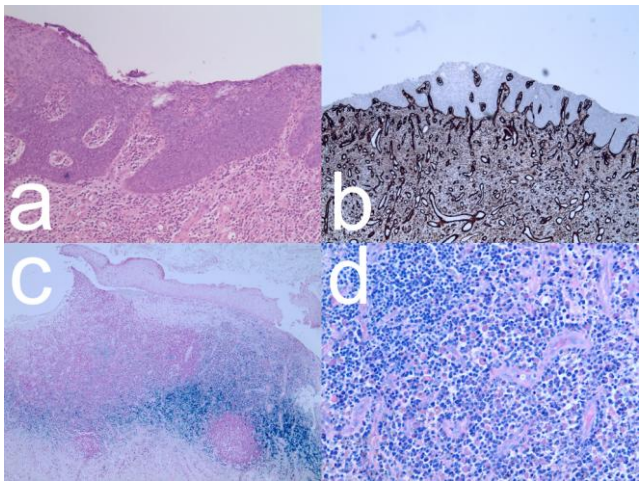

Figure 3: Histopathology. (a) Carcinoma in situ with plump epithelial taps (hematoxylinin-eosin x 10). (b) Collagen IV immmunoperoxidase staining showing an intact basal cell membrane (x 4). Erosive Zoon's disease with lichenoid dermal inflammatory infiltrate (c; x 4), composed of plasma cells and lymphocytes (d; x 20)

The findings confirmed the diagnoses of penile in situ carcinoma associated with secondary phimosis and ulcerous Zoon's disease.

Discussion

Carcinoma in situ (CIS) of the penis is an uncommon condition among Caucasians, most frequently presenting as red macules or plaques. Early recognition and treatment are important, as progression to invasive penile cancer has been reported in up to 1/3 of cases [14]. European Association of Urology (EAU) guidelines recommend local excision with or without circumcision, laser therapy with carbon dioxide laser or

neodymium:yttrium-aluminium-garnet (Nd: YAG) laser, photodynamic therapy, and topical therapy with 5-FU or 5% imiquimod cream [16].

We performed surgery with circumcision to achieve an R0-status of the cancerous lesion and to correct phimosis in one setting. After circumcision, two ulcerated polypoid lesions, diagnosed as Zoon's disease became visible. We removed them surgically to obtain histologic confirmation. Our differential diagnosis was penile cancer. In case of uncomplicated Zoon's disease, often topical treatment is used primarily.

In contrast to other inflammatory penile disorders, Zoon's disease is usually refractory to topical therapy and systemic antibiotics/ antimycotics. Recently, photodynamic therapy has been used in selected cases but this is not an established treatment [17].

Zoon's disease can be treated relatively easily by circumcision or alternatively by ablative erbium-YAG-laser therapy [18][19]. The latter is a less invasive procedure with no down-time.

The simultaneous occurrence of carcinoma in situ of the reserve cell type and polypoid, ulcerated Zoon's disease hidden by phimosis demonstrates exemplary the diagnostic and therapeutic problems of penile diseases in elderly males. Early diagnosis is of particular importance to avoid invasive penile cancer with severe consequences [20].

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Case Report

Advanced Pretibial Melanoma (APM): Clinicians Behaviour As Triggering Factor?

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Keywords: melanoma; seborrheic keratosis; imitation; surgery; risk behaviour; outcome

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Abstract

BACKGROUND: Pigmented lesions represent a broad spectrum of clinical conditions, both benign and malignant. The precise diagnosis is often a challenge, while the clinical diagnostic criteria could be misleading, as a result of the frequently atypical presentation of otherwise completely benign in nature lesions. The variety of therapeutic options for benign pigmented lesions including shave curettage, local laser destruction, electrocoagulation removal could sound enticingly both for the physician and patient, but they destroy the possibility for histological examination and provide a deceptively feeling of calm, that the problem is solved. If there is even a minimum chance for misdiagnosis, the risk could be a human life. Furthermore, a simple surgical excision could provide total resolution of the problem, with correct histological verification and further therapeutic measurements, if needed.

CASE REPORT: We present a case of a patient, with advanced pretibial melanoma with multiple lung metastases, misdiagnosed as a seborrheic keratosis, treated with shave-curettage 6 months earlier, as we want to emphasize the importance of the correct therapeutic method in all cases with pigmented lesions with unknown origin, in order to minimize the risk of dramatic consequences of misdiagnosis of melanoma. So, we want to ask you- is this risk justified?

CONCLUSION: So, we want to ask you - is this risk justified?

Introduction

Pigmented lesions represent a broad spectrum of clinical conditions, both benign and malignant [1]. The precise diagnosis is often a challenge, while the clinical diagnostic criteria could be misleading, as a result of the frequently atypical presentation of otherwise completely benign in nature lesions [1]. In contrast, numerous malignant keratinocyte cutaneous tumours could also be atypically presented, especially in their pigmented variants, where the precise clinical diagnosis is almost impossible [2]. Furthermore, while the treatment of pigmented lesions includes several approaches, from local destruction to incision biopsy, and the clinician's choice depends on the nature of the cutaneous lesion, mistakes could be quite dangerous, as in the presented case. The implication of dermoscopy in routine dermatologic practice achieve an improvement of the malignant/benign diagnostic ratio in excised lesions, leading to a more appropriate selection of pigmented lesions referred to surgery [2]. In another hand, is this risk justified, if the bet is a human life?

Case report

A 71-year-old Caucasian female patient, presented with a 6-months history of rapidly increasing in size pigmented lesion, located on the medium front part of her right lower leg. The lesion has been presented for many years, occurring as

small pigmented maculae, gradually increasing in size. Two years ago, the lesion had been removed by shave curettage, with the clinical observation of pigmented seborrheic keratosis. No, follow up had been recommended to the patient. A couple of months after the procedure, the lesion occurred again, but rapidly increased its size from a small coin to a palm. Clinical examination revealed well-demarcated, oval-shaped, dark-brown to the black uneven coloured pigmented lesion, measuring approximately 15/5 cm, irregularly bordered, covered with yellow crusts and partially ulcerated surface, located on the frontal medium part of the right lower leg (Fig. 1a,b).

Burning sensations and formications of the same leg were presented as subjective complaints. Arterial hypertension, controlled with medicine and status post thrombosis of v. popliteal dextra, with patch plastic autogenous, performed two years ago, were reported from the medical history. Family history was negative for cutaneous diseases. Total surgical excision of the lesion was performed under local anaesthesia; with the field of safety margins 1cm. Histological examination verified the diagnosis of melanoma, with a tumor thickness of 4 mm.

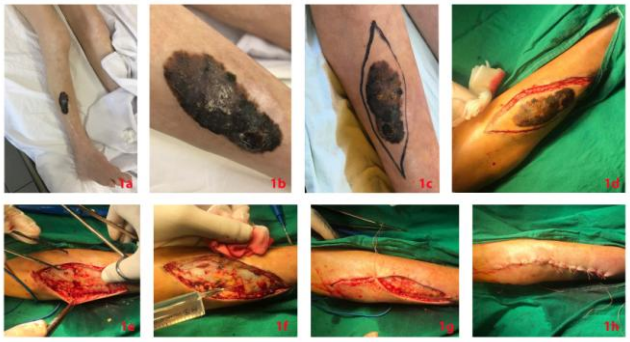

Figure 1: a,b – a Clinical manifestation of advanced pretibial melanoma, 6 months after shave curettage of the so-called "seborrheic keratosis"; 1c – Preoperative marking of the surgical safety margins; 1d, e, f, g – Intraoperative findings: Elliptic surgical excision under local anesthesia; 1h- Postoperative findings. Closing of the wound with single stitches

Laboratory blood tests established elevated level of glucose (6.5 mmol/l), direct bilirubin (4.4 mmol/l), alcal phosphatase (185 UI/l), LDH (2381 UI/L) and hsCRP (101.8 mg/l). The performed screening vie X-ray revealed multiple metastases in both of the lungs, with maximal diameter 40 mm. The diagnosis of melanoma staged IV was made.

One metastasis was referred for BRAF testing, as therapy with BRAF and MEK inhibitors was planned, while pembrolizumab was considered in case of negative BRAF status.

Discussion

Although most often benign, small pigmented lesions remain the most significant diagnostic challenge, both in naked-eye and in dermatoscopic examinations, particularly in the diagnosis of small melanoma [3]. When considering the diagnosis of pigmented lesions, a balance between therapeutic aspects and cosmetic concerns have to be taken into account, with attention for the differential diagnosis between benign and malignant lesions [4]. The variety of therapeutic options for benign pigmented lesions including shave curettage, local laser destruction, electrocoagulation removal could sound enticingly both for the physician and patient, but they destroy the possibility for histological examination and provide a deceptively feeling of calm, that the problem is solved [2].

Nevertheless, the recurrence rate is the smallest problem that should be taken into consideration. The most severe challenge in such cases is the correct differentiation between the benign and potentially malignant nature of the lesion that must be treated [4]. As it was already mentioned, the diagnosis is not often correct even with dermoscopy or confocal microscopy, although these diagnostic weapons could be high sensitive and precise [5][6]. When considering a pigmented lesion with unknown origin, once should always keep in mind that the incidence of primary cutaneous melanoma has been increasing dramatically for several decades, as this kind of tumour is responsible for the majority of skin cancer-related deaths. Furthermore, the most important diagnostic point is the early diagnosis and treatment with simple excision, because if the 5 year-survival rate for patient in stage I is 95% AND 70-90% for stage II, these percents decreased dramatically up to 15% in patients with stage IV [7]. If there is even a minimum chance for misdiagnosis, the risk could be a human life. Furthermore, a simple surgical excision could provide total resolution of the problem, with correct histological verification and further therapeutic measurements, if needed [7].

We present a case of a patient, with advanced pretibial melanoma with multiple lung metastasis, misdiagnosed as a seborrheic keratosis and treated with shave-curettage 6 months earlier. We want to emphasize the importance of the correct therapeutic method in all cases with pigmented lesions with unknown origin, in order to minimize the risk of dramatic consequences of misdiagnosis of melanoma. So, we want to ask you- is this risk justified?

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Case Report

The Role of Complex Treatment in Mixed Leg Ulcers – A Case Report of Vascular, Surgical and Physical Therapy

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Keywords: Leg ulcer; Mixed vascular type; Sandwich transplantation; Percutaneous transluminal angioplasty; Transdermal CO_2; Surgery

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Abstract

BACKGROUND: Leg ulcers are a burden to patients, their families and society. The second most common cause of chronic leg ulcers is the mixed arterio-venous type. An 80-year-old female patient presented to our department due to painful enlarging chronic leg ulcer of mixed arteriovenous origin on her left lower leg. She suffered from peripheral arterial occlusive disease stage I and chronic venous insufficiency Widmer grade IIIa, and a number of comorbidities.

AIM: The aim of our ulcer treatment was a complete and stable wound closure that was hampered by arterial occlusion, exposed tendon, and renal insiffuciency.

CASE REPORT: To improve the prognosis for ulcer surgery, we performed percutaneous transluminal angioplasty, transcutaneous CO_2 and deep ulcer shaving. The wound was closed by sandwich transplantation using elastin-collagen dermal template and meshed split skin graft. She had a 100% graft take with rapid reduction of severe wound pain.

CONCLUSION: Complex approaches are necessary, to gain optimum results in leg ulcer therapy in mixed leg ulcers. Therapeutic nihilism should be abandonend.

Introduction

Leg ulcers are among the most common conditions seen in dermatologic department. Patients often present with chronic and disabling wounds. The spectrum of underlying disease causing leg ulcers is remarkably broad, although the most common cause in Western countries is chronic venous insufficiency (CVI). The second commons are mixed venous-arterial ulcers [1].

Leg ulcers are a symptom of an underlying chronic cause. In every case, a search for the underlying cause is necessary to provide the appropriate treatment for the patient. The pillars of treatment are compression therapy, vascular surgery, leg ulcer shaving and transplantation. Smaller ulcers may heal by conservative treatment [2][3][4].

Leg ulcer surgery is based upon sufficient arterial blood supply, deep ulcer shaving to remove bacterial biofilm, avital tissue and necrosis, and fibrosis shifting a chronic non-healing wound into an acute wound with a better prognosis. Grafts to cover the wound can be made from the patient's own, uninjured skin (autografts), or applied as a sheet of bioengineered skin grown from donor cells (allograft). Preserved skin from other animals, such as pigs, has also been used (xenografts) [5].

The take rate after deep ulcer shaving and meshed grafts in venous and venous-arterial leg

ulcers was 91% in our own department but decreased down to 80% in case of dystrophic calcifications [3]. Other negative factors for graft take are insufficient shaving, extensive fibrosis, clotting disorders, immunosuppression, and predominant arterial ulcers [6] while the ulcer size is not predictive for graft failure [7].

But even in patients with arterial problems, successful leg ulcer shaving and grafting is possible with an interdisciplinary approach.

Case report

The 80-year-old female patient presented to our department due to painful enlarging chronic leg ulcer of mixed arteriovenous origin on her left lower leg. Leg ulcers were known for many years. Her medical history was remarkable for peripheral arterial occlusive disease stage I and chronic venous insufficiency Widmer grade IIIa [8]. In 2016, she underwent endovascular laser therapy of vena saphena magna and sclerotherapy of vena saphena parva.

Percutaneous transluminal angioplasty (PTA) was performed in March 2016 because of a relapsing stenosis of the distal arteria fibularis sinistra and the arteria poplitea sinistra. In July 2016, PTA was repeated and stent-assisted recanalization was realized.

She suffered from atrial fibrillation treated by phenprocoumon and beta-blocker. In 2016 she had a cardiac decompensation with pleural effusions due to a highly stenotic aortic valve. She got a synthetic aortal valve in November 2016 in combination with a bypass surgery for 2-vessel coronary stenosis.

She also suffered from chronic renal insufficiency stage III and coxarthrosis of right hip joint. Contact sensitization to para-phenylenediamine, lanoline, benzoyl peroxide, and chlorhexidine-digluconate had been confirmed by patch tests.

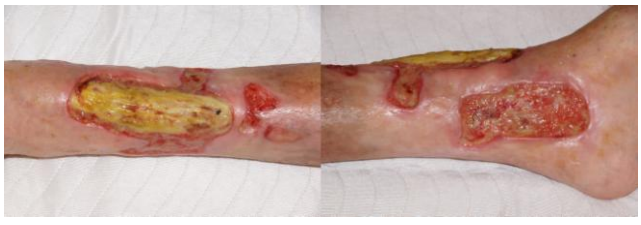

Figure 1: Clinical presentation of mixed arteriovenous leg ulcers of the left lower leg

On examination, we found a 14 x 7 cm large pretibial leg ulcer with exposed tendon. There was a second ulcers of 10 x 7 cm size above the left malleolus medialis (Fig. 1 a & b). Both ulcers had a malodorous wound covering. Surrounding skin was erythematous, scaly and xerotic. Pain was 9 on the visual pain scale. We took a biospy to exclude a malignant ulcer and other differential diagnoses such as calciphylaxis (Fig. 2). Histopathology revealed nonspecific changes.

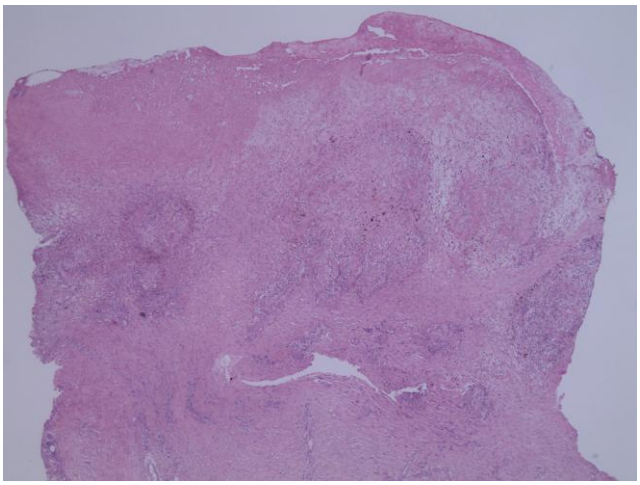

Figure 2: Histopathology of the biopsy from the leg ulcer showing nonspecific inflammation and ulceration (HE x 4)

Microbiological swabs from the wound revealed two strains of Staphylococcus aureus and Corynebacterium striatum.

An arterial vascular investigation showed a systemic blood pressure of 155/90 mmHg on the left side.

Closure pressure of the arteria tibialis posterior before treatment was 90 mmHg (right leg) and due to the ulceration it could not be assessed on the left leg, closure pressure of arteria dorsalis pedis was 95 mmHg (right leg) and 70 mmHg (left leg). The ankle-brachial pressure index (ABPI) was 0.86 on the right side and 0.64 on the left side.

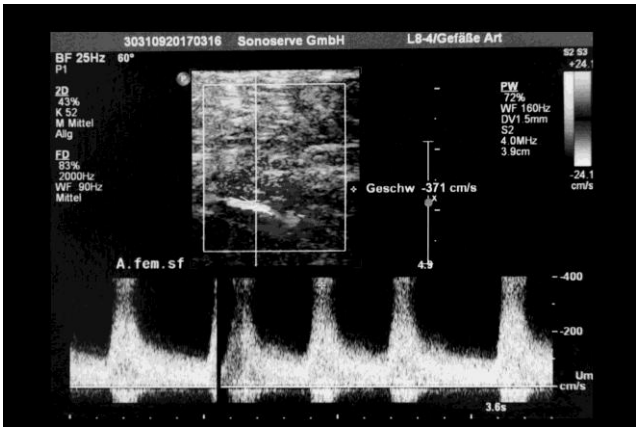

Figure 3: Duplex sonography of left A. fermoralis superficialis

Using Duplex sonography, a high-grade stenosis of the left distal in distal arteria femoralis superficialis (Vmax 350 cm/s) was observed. Another

stenosis was found in arteria poplitea at the transition P2/P3 (Fig. 3).

PTA was successfully performed before leg ulcer surgery.

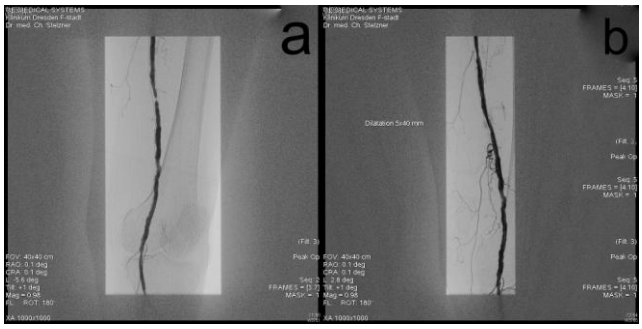

Figure 4: Angiography of A. femoralis superficial of the left leg before and after PTA

After PTA, closure pressure of the arteria tibialis posterior was 140 mmHg (right leg) and 160 mmHg (left leg), closure pressure of arteria dorsalis pedis was 140 mmHg on both sides. The ankle-brachial pressure index (ABPI) was 0.9 on the right side and 1.03 on the left side.

Acral light plethysmogram demonstrated on both legs powerful post stenotic curves. It also excluded a relapse after endovascular laser therapy.

We decided to perform deep ulcer shaving in combination with sandwich meshed graft transplantation in general anesthesia. The ulcers were conditioned with anti-septic wound covers (Cutimed sorbact gauze, Cutimed sorbact hydroactive dressing), multiple necrosectomies, and daily transcutaneous application of CO_2 for 30 min [9].

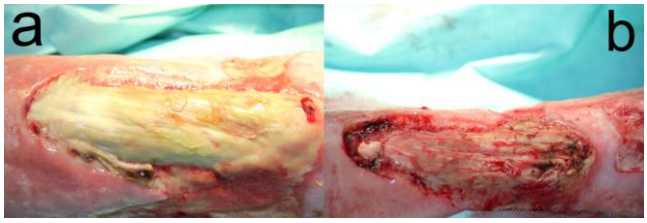

Figure 5: Aggressive surgical debridement of the leg ulcer: (a) before and (b) after the procedure

Ulcer surgery was realized in May 2017 with antibiotic prophylaxis (Unacid 3 g i.v./day for one week followed by Unacid PD oral tablets 2 x 2/day for 10 days). Using an electrodermatome, all necrotic and avital tissue was removed. Exposed tendon was completely covered by dermal template (Matriderm®, Dr. Suwelack Skin and Healthcare Ltd., Billerbeck, Germany). Eventually, the meshed graft was fixed by tissue tacker. We used silicone Adaptic touch above the grafts and sterile gauze compresses before compression bandages were applied.

Five days after surgery the transplant was stable but the wound ground was wet. To stabilize the graft topical treatment with Betaisodona solution, Cutimed sorbact gauze, and Adaptic touch silicone gauze was performed on a daily basis. Surrounding skin was treated initially with a combination of betamethasone and fusidinic acid (Fucicort ointment) and later on by moisturizer (Dermatop basic cream). The leg ulcers healed completely (Fig. 6). The pain was rated 2 on the visual pain scale.

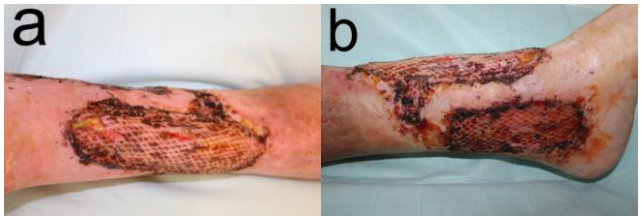

Figure 6: Stable and complete meshed-graft take on day 11 after surgery

We recommended a lower leg flat knitted compression stocking, compression class I.

Discussion

Chronic leg ulcers are a great burden for the individual patient and society. Pain reduction and infection control are major targets in leg ulcer treatment [10]. Despite the fact that most patients are treated conservative by various dressings, ointments, physical therapies, and compression the outcome of patients who underwent surgery is the most favorable regarding the need for additional treatment and evidence of post-intervention claims for symptomatic varicose veins [11].

In contrast to patients with venous leg ulcers, patients with mixed leg ulcers are significantly older, have lower body mass index, a history of smoking, and more comorbid conditions. Ulcer pain is highly prevalent. Mixed arteriovenous leg ulcers were associated with lower health related quality of life, greater mobility impairments, and more deficits in self-care and usual activities [12].

In the present case a symptomatic stenosis of infrapopliteal arteries was evident. We performed a PTA in our Department of Angiology. Meta-analyses of infra-popliteal PTA show technical success rates of up to 90% [13][14]. Leg ulcer healing rates, however, are not improved by primary stent implantation [15][6].

In case of exposed tendons, however, the take rate of skin grafts is low. We developed a sandwich technique to overcome this problem. A dermal template consisting of non-crosslinked collagen and elastin (Matriderm) is used to cover the tendon. After reconstitution of the template by Ringer's solution, a meshed skin graft is placed

above. The dermal template supports a rapid neoangiogenesis and pretends the adhesion of the graft to the tendon itself [17][18].

Using PTA at first place allows leg ulcer surgery in mixed arteriovenous leg ulcers with arterial stenosis. Sandwich transplantation is capable to cover wound with exposed tendons. After PTA, mild compression ensures an optimal healing.

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Case Report

Neurofibromatosis Type 1 with Massive Ventricular Polyposis: First Report in the Medical Literature

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Keywords: NF1; surgical removal; polyposis ventriculi; neurofibromas; Billroth II

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Abstract

BACKGROUND: Neurofibromatosis type 1 (*NF1*) is a multisystemic disorder with genetic background, characterised by specific cutaneous findings, skeletal dysplasias, and growth of both benign and malignant nervous system tumours. *NF1* is caused by mutations in the *NF1* gene, situated in chromosome 17q11.2, with an autosomal dominant pattern of inheritance and clinical manifestation of neurofibromas, malignant peripheral nerve sheath tumour, optic and non-optic nerve gliomas, congenital heart disease, cardiovascular and cerebrovascular disease and orthopaedic disorders. The incidence of gastrointestinal manifestations of *NF1* is relatively low, compared to neurological disorders, presenting approximately in 5 to 25% of the patient, but later in life.

CASE REPORT: We present a patient with *NF1*, ventricular polyposis and attentional disorders with cognitive phenotype, while both of her daughters also present with cutaneous manifestations of *NF1*.

CONCLUSION: To the best of our knowledge, this is the first reported case of *NF1* with ventricular polyposis as a gastrointestinal manifestation in the mother and *NF1* with no signs of inner organ involvement in both of her daughters.

Introduction

Neurofibromatosis type 1 (NF1) is a multisystemic disorder with genetic background, characterised by specific cutaneous findings, skeletal dysplasias, and growth of both benign and malignant nervous system tumours [1][2]. NF1 is caused by mutations in the NF1 gene, situated in chromosome 17q11.2, which provides instructions for making a protein called neurofibromin, produced in many cells, including nerve cells and specialised cells surrounding nerves (oligodendrocytes and Schwann cells) [3]. Neurofibromin acts as a tumour suppressor, and therefore, mutations in the NF1 gene lead to the production of a nonfunctional version of neurofibromin, incapable to regulate cell growth and division [3].

The clinical signs and symptoms vary widely among affected people, usually beginning in early childhood [1]. One of the most typical manifestations represents the so-called café-au-lait spots wich can be single or multiple, gradually increasing in size [1][2]. Tumors like neurofibromas can arise along nerves throughout the body [2].

Clinical diagnosis of NF1 requires the presence of at least 2 of the following 7 criteria: 1) Six

or more café-au-lait spots or hyperpigmented macules =5 mm in diameter in prepubertal children and 15 mm postpubertal; 2) Axillary or inguinal freckles (>2 freckles); 3) Two or more typical neurofibromas or one plexiform neurofibroma; 4) Optic nerve glioma; 5) Two or more iris hamartomas (Lisch nodules); 6) Sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis; 7) First-degree relative (mother, father, sister, brother) with NF1 [2].

Case report

A 78-year old female patient presented with complaints of malaise, and weakness. Attentional disorders with cognitive phenotype, depressive and suicide attentions (from 1985), spondyloarthritis, sub compensatory ocular peripheral syndrome, lumbar osteochondrosis, right-sided lumbosacral radicular syndrome, vertebral syndrome and gonarthrosis on the right (from 2003) were reported from the medical history as comorbidities with long-standing duration. Ulcus callosum gastric was also reported as accompanied disease and polyposis ventriculi, treated with resection ventriculi (Billroth II) in 2004. The patient had been hospitalised in 2007 with pain in the epigastrium and abdomen. Abdominal ultrasonography had established well circumscribed, heterogeneous solid tumour formation, measuring 4 cm, in the pylori-antral part of the stomach, resembling cholelithiasis, polyp or a mesenchymal tumour. Further fibro gastroscopy had revealed three polyps, one measuring 15/10 mm, and the others 2/3 cm, with ulcerated surface and wide basis. The diagnosis of hyperplasiogenic polyposis ventriculi was made, based on the fibro gastroscopic findings and histological examination. The polyps had been removed on a later stage.

Clinical examination revealed multiple nodular and tumour-like formations, measuring from 1 to 5 cm, disseminated on the whole body and extremities, with a smooth surface and regular borders (Fig. 1a). The same clinical findings were observed in patient's daughters, both of them with long-standing duration and progressive behaviour for dissemination (Fig. 1b,c,d,e).

The conducted paraclinical blood tests revealed the decreased level of erythrocytes (3.18 10^12/l), haemoglobin (65.0 g/l), hematocrit (0.21 l/l) and increased plated cells count (562.0 10^9/l). Abdominal ultrasonography did not reveal any abnormalities in structure or function of the inner organs. Irigoscopy established hypotonic and hypokinetic dyskinesia of colon ascendens. Fibrogastroscopy findings were indicative of chronic active gastritis.

The diagnosis of massive ventricular polyposis, associated with neurofibromatosis type I, affecting the patients and her daughters was made. All of the patients did not undergo genetic examination.

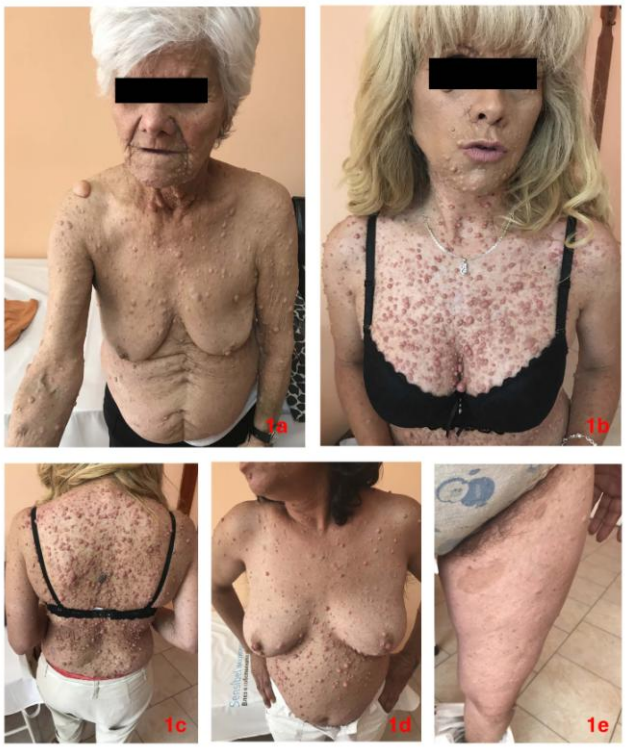

Figure 1: 1a,b – Clinical manifestation of a 78-year-old female patient with NF 1 and ventricular polyposis; 1c,d,e,f – Clinical manifestation of NF1 in both patient's daughters

Discussion

Neurofibromatoses refer to 3 genetically inherited disorders, which are clinically and genetically distinct diseases, including NF1, neurofibromatosis type 2 and Schwannomatosis.

NF1 also known as Von Recklinghausen's disease or peripheral neurofibromatosis, is the most common form of neurofibromatosis represents up to 90% of the cases [3]. It has an autosomal dominant pattern of inheritance, with one mutated copy of the NF1 gene in each cell, which is inherited from an affected parent in about half of the cases [2][3]. Sporadic new mutations are responsible for the other half of the cases, with no family history of the disorder [2]. In contrast to most of the autosomal dominant conditions, two copies of the NF1 gene must be altered to trigger tumour formation in neurofibromatosis type 1, as the mutation in the second copy of the NF1 gene occurs during a person's lifetime in cells surrounding nerves [1]. It is not clear enough how mutations in the NF1 gene lead

to the other features of neurofibromatosis type 1, such as café-au-lait spots and learning disabilities or autism [4]. On the other hand, it is established that children and adolescents with NF1 are at increased risk for wide-ranging behavioural, developmental, and cognitive impairments, all decreasing quality of life [4].

Furthermore, an interesting research by Jonas RK. et al (2017) observed significantly reduced neural activity across multiple brain regions involved in higher-order semantic processing and motivation in patients with NF1 relative to controls and atypical age-associated changes in neural activity in patients with NF1, such that during risk-taking, neural activity tended to decrease with age in controls, whereas it tended to increase with age in patients with NF1 [5]. The more commonly encountered manifestations of NF 1 include plexiform neurofibromas, malignant peripheral nerve sheath tumour (MPNST), optic and non-optic nerve gliomas, congenital heart disease, cardiovascular and cerebrovascular disease, and orthopaedic disorders [1][3]. Other signs and symptoms may include high blood pressure, bone abnormalities, lisch nodules, learning disabilities and attention deficit, hyperactivity disorder; autism spectrum disorder, larger than average head size, short stature [1]. The incidence of gastrointestinal manifestations of NF 1 is relatively low, compared to neurological disorders, presenting approximately in 5 to 25% of the patient, but later in life [3]. Gastrointestinal symptoms include visceral neurogenic tumours, gastrointestinal stromal tumour and neuroendocrine tumours and clinical signs could include abdominal pain, dyspepsia, vomiting, anaemia, melena, hematemesis, hematochezia, intussusception, volvulus, small bowel obstruction, fever and abdominal mass [3].

To the best of our knowledge, this is the first reported case of NF1 in a three-member family, with different clinical manifestation and associated symptoms, including ventricular polyposis in the mother and no signs of inner organ involvement in her daughters.

Although there is no general cure for NF1, surgery can be used to remove tumours that cause pain or a loss of function, press on vital structures, obstruct vision, or grow rapidly [1][2]. Annual examinations and screening are mandatory, as the patient's morbidity is a result of the associated complications [3].

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Case Report

Van Lohuizen Syndrome – A Case Report with a Diagnostic Delay of Four Years

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Keywords: Cutis marmorata telangiectatica congenita; Van Lohuizen syndrome; vascular-cutaneous disorders

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Abstract

BACKGROUND: Cutis marmorata telangiectatic congenital or Van Lohuizen syndrome is a rare vascular disorder that may be associated with other congenital malformations. Around 300 cases have been reported so far.

CASE REPORT: We present a 4-year-old girl with Van Lohuizen syndrome of the leg, but without any other malformations.

CONCLUSION: Neonatal lupus erythematosus may resemble congenital vasculopathy, but histopathology and immune-serology are characteristic.

Introduction

Van Lohuizen – a female paediatrician from the Netherlands - first described a congenital vascular-cutaneous disorder in 1922 - cutis marmorata telangiectatica congenita [1]. Its aetiology is unknown, and the occurrence is spontaneous. The clinical presentation is a combination of cutis marmorata with telangiectasia. Skin atrophy or ulcerations are sometimes present. The cutaneous features show a tendency of improvement over time [2]. The most common associated cutaneous malformations include port-wine stains and hemangiomas [3].

Other associated anomalies may affect any organ of the body, such as the eye, skeleton, brain, kidneys, etc. [4].

We report the case of a female patient with van Lohuizen syndrome not associated with other anomalies.

Case report

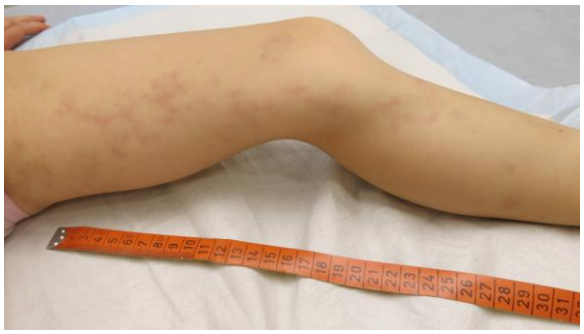
A 4-year-old girl was referred with her parents to our department for consultation. She had segmental skin disorders in her left leg that showed an enlargement during the last three months.

The girl was born from a non-consanguineous marriage. It is the first child of a healthy mother. Her delivery was uncomplicated on time. Skin changes were observed at birth demonstrating hyperpigmented macules of a reticular pattern and telangiectasia. The changes were unresponsive to temperature.

Her further development was unremarkable.

There was no evidence of skeletal, motoric, neuronal or ophthalmologic malformations. She was monitored on a regular basis by her paediatrician and neither laboratory, nor functional abnormalities were noted. Hyperpigmentation partially faded away by time. There was neither atrophy nor ulceration at any time.

a)



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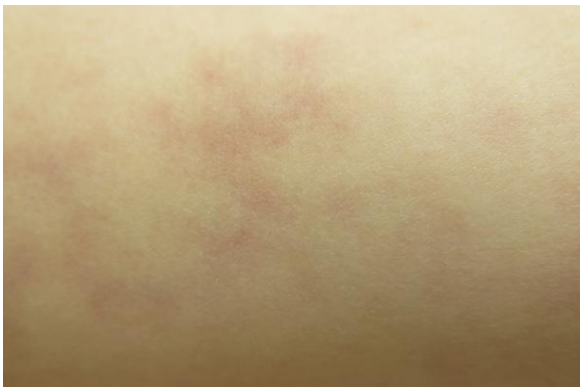

Figure 1: Van Lohuizen syndrome on the leg in a 5-year-old girl. (a) Overview, (b) detail of the hyperpigmented reticular patches

We observed a reticular slightly hyperpigmented pattern on the inner side of the thigh and lower leg. This feature was associated with telangiectasias. On palpation, the whole lesion remained painless. The parents were informed about the benign nature of the vascular-cutaneous disorder. Based on medical history and clinical presentation the diagnosis of Van Lohuizen syndrome was confirmed. The treatment is impossible and in the present case also unnecessary.

Discussion

Van Lohuizen syndrome (OMIM 219250) is a rare congenital disorder with no clear gender prevalence caused by genetic mosaicism. No specific mutations have been discovered until the present moment [5]. Around 300 cases have been reported so far [6]. The diagnostic criteria include three major criteria such as congenital reticular (marmorated) erythema, the absence of venectasia, and unresponsiveness to local warming. Furthermore, two or more minor criteria should be present such as fading of erythema within two years, telangiectasia within the affected area, port-wine stain, ulceration within the affected area, and atrophy within the affected area [6]. Our patient fulfilled the three major and two of the minor criteria.

There are many differential diagnoses. The closest disease to Van Lohouizen syndrome is congenital livedo reticularis, where ulceration and phlebectasia do not occur. It is part of the congenital livedo reticularis-megalencephaly syndrome (OMIM 602501) being caused by mosaic *PIK3CA* gene mutations [7]. Other differential diagnoses include Klippel-Trenaunay syndrome and Sturge-Weber syndrome. The latter is caused by mosaic *GNAQ* gene mutation *c.548G>A* [5]. Neonatal lupus erythematosus may resemble congenital vasculopathy, but histopathology and immune-serology are characteristic [8].

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Case Report

A "Yellow Submarine" in Dermoscopy

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Keywords: histiocytic sarcoma; dermoscopy; yellow colour; CD68; WHO classification lymphomas

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Abstract

BACKGROUND: Histiocytic sarcoma (HS) is an extremely rare, non-Langerhans cell tumor. HS affects especially adults, its etiology is unknown yet. Skin could be interested by papules or nodules, single or multiple.

CASE REPORT: A Caucasian man in his late 40s came to our clinic for a naevi evaluation. During the visit, a rose papulonodular lesion was observed in the lumbar region. This lesion was completely asymptomatic, and it had been there for an indefinite period. The clinical evaluation revealed that the lesion appeared elevated, of 9 x 15 mm in dimension, symmetrical and of a homogeneous pinkish colour. The videodermoscopical evaluation revealed a homogeneous yellow central pattern, polymorphic vessels, an eccentric peripheral pigmentation and a white collar. An excisional biopsy was performed. The morphology and the expression of CD163, CD68 and/or lysozyme to the immunophenotypic analysis, revealed the true nature of the lesion.

CONCLUSION: HS is usually diagnosed at an already advanced clinical stage and it has a high mortality rate even today. Dermoscopy, showing a yellow and distributed homogeneously colour, can facilitate its hard diagnosis.

Introduction

Histiocytic sarcoma (HS) is an extremely rare, non-Langerhans cell disorder with morphologic and immunophenotypic evidence of histiocytic disorders [1]. HS affects all ages, but it is more common in adults (46–55 years). The aetiology of this disorder is unknown [2]. Systemic symptoms (such as fever, night sweats, and weakness) and other skin, hepatosplenic or intestinal manifestations could appear. For some years there has been confusion about this type of a tumour and its terminology. Nonetheless, thanks to the advances in knowledge in the field of genetics and biology in recent years, we are today able to classify and recognize these kinds of hematologic neoplasms.

The latest WHO classification of lymphomas, published in 2008 [3] and updated in 2016 [4], describes the HS within the histiocytic and dendritic cells neoplasms; this group includes pathologies which share the same functional properties of their normal counterpart (phagocytosis and/or processing and presentation of antigens) rather than their cell of origin [4].

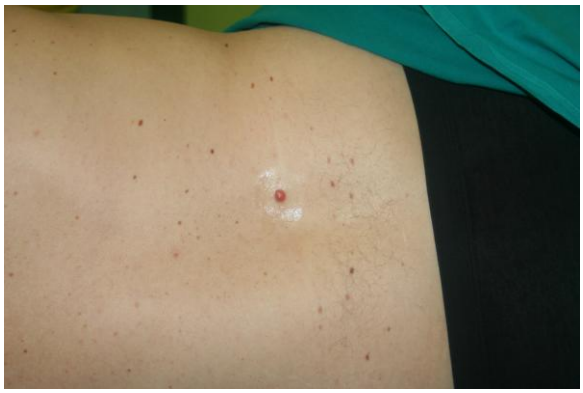
Case Report

A Caucasian man in his late 40s came to our clinic for a naevi evaluation.

During the visit, a rose papulo-nodular lesion was observed in the lumbar region (Figure 1: A, B). This lesion was completely asymptomatic, and it had been there for an indefinite period. The clinical evaluation showed that the lesion appeared elevated,

of 9x15 mm in dimension, symmetrical and a homogeneous pinkish colour.

A)



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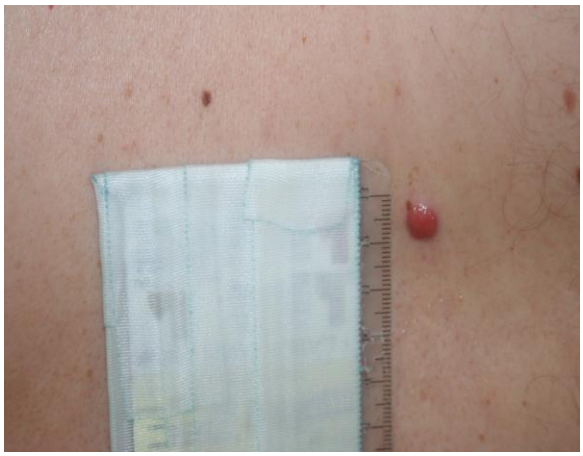

Figure 1: Clinical evaluation (A, B)

Suspecting a malignant lesion, also a videodermoscopy of the lesion was also immediately performed, and this revealed a homogeneous yellow central pattern, polymorphic (arborizing, dotted and glomerular) vessels, an eccentric peripheral pigmentation and a white collar (Figure 2).

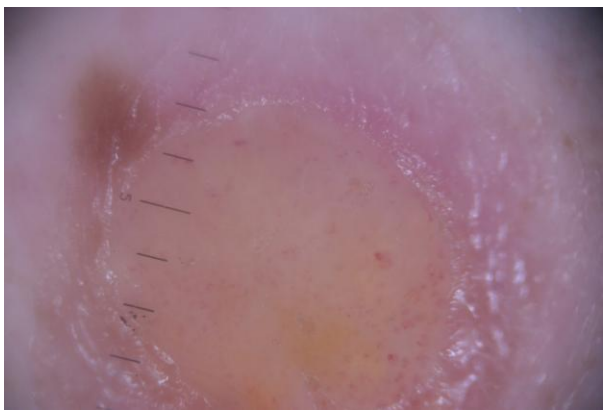

Figure 2: Dermoscopic evaluation

An excisional biopsy was performed. The morphology showed a diffuse proliferation of large cells, with grooved and indented nuclei and abundant eosinophilic cytoplasm (Figure 3: A, B). The immunochemistry of the surgical specimens showed cells with positivity for CD68, CD163 and CD4, with negativity for S100, CD34 and HMB45 (Figure 4). The Ki67 index was about 18% (Figure 4).

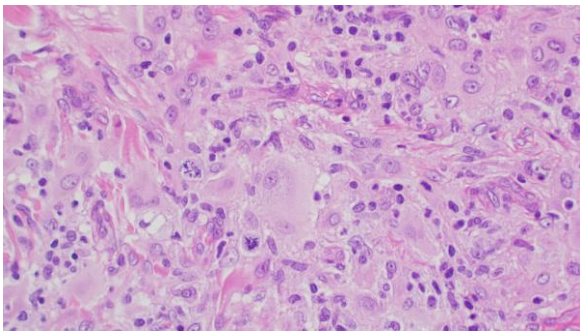

Figure 3: Morphology

The patient has always been in good health and was not taking any drugs. He had a skin type II according to Fitzpatrick's classification; he did not suffer from any skin diseases and did not have melanoma familiarity. In the previous check-ups of neavi no atypical lesions had been observed.

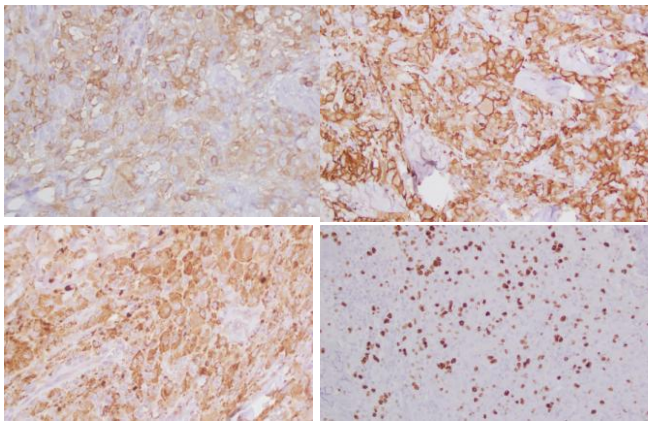

Figure 4: Immunophenotype (first line, from left to right: CD4, CD68; second line, from left to right: CD163, Ki67). [Courtesy of Dr Mancini C., Unità Operativa di Anatomia e Istologia Patologica, Dipartimento Diagnostico, Università degli Studi di Parma]

Discussion

Even though the lymph nodes are the most common site of HS presentation, the gastrointestinal tract, the soft tissue and the skin could also be affected. Skin manifestations can be isolated or associated with systemic involvement. A cutaneous HS could appear as single or multiple papules and nodules of a light colour. The clinical differential diagnosis must take into account other cutaneous lesions: amelanotic melanoma, B or T cell lymphoma, dermatofibroma, dermatofibrosarcoma protuberans, juvenile xanthogranuloma, etc.

With dermoscopy, the cutaneous HS is predominantly yellow, distributed homogeneously.

This colour, in dermoscopy, was investigated by Cavacchini et al. some years ago [5]. In the case of HS, the yellow may appear in various shades and is the background to some polymorphic vessels (arborising, dotted or glomerular) and a white-pinkish collar. In fact, the presence of polymorphic vessels represents a highly risky dermoscopic pattern that can be seen not only in amelanotic melanoma or Spitz naevi [6] but also in other malignant lesions, such as an HS. When confronted with this kind of lesion, excisional biopsy is the most accurate diagnostic method. The morphology is characterized by large atypical pleomorphic cells with eosinophilic cytoplasm and large, round to oval, irregular nuclei [1].

The immunophenotype is characterized by the expression of one or more histiocytic markers, such as CD163, CD68 and lysozyme [1]. CD163, a haemoglobin scavenger receptor whose expression is limited to neoplasms of macrophage/histiocytic lineage, is more specific than CD68, and a strong immunoreactivity for this antigen is suggestive of histiocytic differentiation [2]. The Ki-67 index is variable. Staging studies, including imaging studies such as computed tomography (CT) or a combined positron emission tomography (PET/CT), should be performed after the diagnosis to determine the extent of the disease.

Unfortunately, HS is usually diagnosed at an already advanced clinical stage, and it does not have a good response to chemotherapy. This tumour has a high mortality rate and, in fact, most patients die from the progressive disease within two years [7].

Due to the aggressive course and the limited treatment options of this tumour, performing a careful clinical and dermoscopic evaluation is essential to help the final histological diagnosis. Over the last ten years, there has been various case reports in the literature regarding patients with cutaneous or subcutaneous histiocytic sarcoma. Only one of them [8] focused on the use of dermoscopy on this kind of lesion.

Dermoscopy, a non-invasive analysis technique, used especially for the early detection of melanoma, an instrument that is becoming increasingly widespread and more commonly used in dermatology clinics; it represents a tool which helps increase the low clinical sensitivity of the naked eye [9].

In conclusion, the early diagnosis of a rare and malignant tumour-like HS currently remains hard. However, dermoscopy can facilitate it and lead to quickly performing an excisional biopsy, thus improving the prognosis for patients.

When dermoscopy notices the colours pink or black in a lesion, it should indicate to dermatologists that something may be wrong. Nevertheless, yellow too could be suspicious, and it is a wake-up call in dermoscopy… beware of the “yellow submarine”!

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Case Report

Segmental Erythema Multiforme-Like Drug Eruption by Aromatase Inhibitor Anastrozole – First Case Report and another Example of an Immunocompromised District

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Keywords: Erythema multiforme; Adverse skin reaction; Aromatase inhibitors; Anastrozole; Breast cancer

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Abstract

Anastrozole is a non-selective aromatase inhibitor for adjuvant breast cancer therapy in postmenopausal women. Cutaneous adverse events have been reported. We observed a 64-year-old female patient with a medical history of locally advanced breast cancer of her right breast that was treated with radiotherapy and adjuvant drug therapy with anastrozole. She developed a segmental bullous eruption limited to the cancer-affected breast. Cessation of the aromatase inhibitor and systemic therapy with prednisolone cleared the lesions completely. This is the first report of a segmental erythema multiforme like drug eruption by anastrozole and another example of the concept of the immunocompromised district of skin.

Introduction

Anastrozole is a non-selective aromatase inhibitor approved for adjuvant treatment of early-stage, hormone receptor-positive breast cancer in postmenopausal women or for women after adjuvant tamoxifen therapy for breast cancer. The compound is more effective than tamoxifen in the reduction of breast cancer relapse after surgery. Studies demonstrated that overall survival with anastrozole was better than with tamoxifen [1][2]. The most important adverse effects are an increased risk of bone fractures and myalgia/arthralgia. Other adverse events include fatigue, diarrhoea, xerostomia, xerophthalmia, and head ache. Dry skin, alopecia, pruritus, allergic reactions, skin rash, and acne have also been reported [3][4].

We report unusual, localised, cutaneous side effects of anastrozole.

Case report

A 64-year-old female patient was referred to us for localised skin blisters on her right breast.

Her medical history was positive for an invasive lobular breast cancer with a diffuse infiltration of the pectoralis muscle (May 2015), pT4a, pN0, M0, L0, V0, Pn0, Rx, G2. She had been treated with radiotherapy and docetaxel. Since March 2016, she had been treated with aromatase inhibitor anastrozole. First skin eruptions occurred in August 2016. A skin biopsy at that time excluded both malignancy and an autoimmune bullous disease. One week before the first presentation to the Department of Dermatology and Allergology, larger hemorrhagic blisters developed with a maximum diameter of 5 cm.

On examination, the breast was edematous, slightly erythematous (Fig. 1 a-c). No palpable lymph nodes were found. Diagnostic ultrasound of axillary, supra- and infraclavicular lymph nodes and abdomen remained unremarkable.

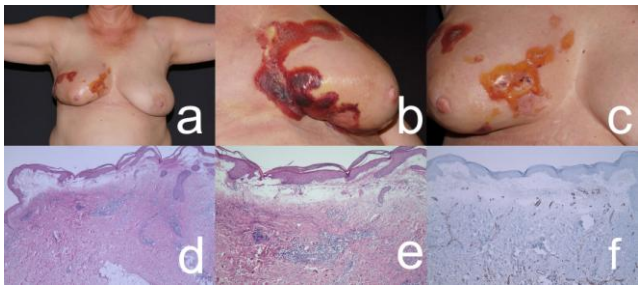

Figure 1: (a) Segmental erythema multiforme-like eruption due to anastrozole; (b) and (c) details with bullous, partly hemorrhagic eruptions; (d-f) histopathology; (d) overview (Hematoxylin-eosin, x2); (e) Detail with massive subepidermal edema and inflammatory infiltrate (hematoxylin-eosin, x4); (f) absence of atypical vascular proliferations (CD34, immunoperoxidase, x2)

Microbiology from blister fluid demonstrated minimal amounts of Acinetobacter ursingii, Moxarella osloensis, Staphylococcus capitis, and coagulase-negative Staphylococci.

Routine laboratory investigations revealed no signs of inflammation. C-reactive protein was 1.8 mg/L (normal range < 5 mg/L).

The blister fluid was subjected to cytological analysis. No malignant cells were identified. A skin biopsy was taken. A massive subepidermal oedema was observed with a superficial perivascular, and interstitial lymphomonocytic inflammatory infiltrate (Fig. 1d,e). Atypical vascular proliferations could be excluded by immunohistochemistry (CD31 and CD34) (Fig. 1 f).

The final diagnosis of erythema multiforme-like skin eruption due to anastrozole was confirmed.

The patient was treated initially with 100 mg prednisolone and 20 mg pantoprazole per day. Prednisolone was tapered down. For topical treatment, bethametasone/ fusidic acid ointment was applied. The blisters healed and oedema regressed. A medical bra was subscribed. Close follow-up was advised since aromatase inhibitor therapy was ceased.

Discussion

Anastrozole is a non-selective aromatase inhibitor for the adjuvant treatment of breast cancer. Skin rash, pruritus and dry skin have been reported to occur in 10%, 10%, and 2% respectively [2].

Rare cutaneous adverse events are lichen sclerosus vulvae, erythema nodosum, subacute cutaneous lupus erythematosus, micropapular pruritic eruption, and cutaneous vasculitis [6][7][8][9].

Our patient presented with hemorrhagic bullae in a segmental arrangement, localised only to the breast that was affected by breast cancer and exposed to radiotherapy before. The histological diagnosis was an erythema multiforme-like eruption.

Erythema multiforme is a mucocutaneous hypersensitivity reaction showing varying degrees of blistering and ulceration. The aetiology includes herpes simplex virus and other infections, food additives, and drugs. Genetic factors can predispose individuals to severe drug reactions [10][11].

Anastrozole is known to induce cutaneous adverse events, but why was the eruption limited to the right breast? The explanation comes from the concept of immunocompromised districts of skin [12]. The immunocompromised district of skin is an area more vulnerable than the rest of the body mainly due to a local dysregulation of skin associated immune system. Several possible factors can be responsible for this, but radiotherapy and lymphedema are definitively involved in the present case. Another case was reported in the literature, with disseminated erythema multiforme after radiotherapy and anastrozole therapy [13].

For differential diagnosis, cutaneous lymphomas [14], atypical pityriasis rosea [15], bullous pemphigoid [16], and lupus erythematosus [17] must be considered. Histopathology and immune serology allow differentiation.

To the best of our knowledge, this is the first report on segmental bullous erythema multiforme-like drug eruption to anastrozole.

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Case Report

Chronic Encapsulated Seroma Persisting for Three Years after Abdominoplasty and a Successful Surgical Solution

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Keywords: Pseudocapsule; Chronic seroma; Abdominoplasty; Capsulectomy; Surgery; Scarpa's fascia

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Abstract

Abdominoplasty is listed among five most common esthetic surgical procedures in the Western World. Despite all efforts, abdominoplasty bears a high risk of complications. We observed a 39-year-old-woman with previous classical abdominoplasty performed elsewhere three years ago. Clinical examination demonstrated a swollen and tense abdominal mass. Laboratory findings were normal. Clinical examination was completed by abdominal ultrasonography which demonstrated both, a significant fluid volume in this area and a dense fibrous "capsule". The diagnosis was a late or chronic encapsulated seroma with a thick pseudocapsule or "bursa". We performed a revision abdominoplasty with a standard supra-fascial dissection. Surgical resection of infra-umbilical flap containing skin, subcutaneous tissue and capsulectomy were performed under general anaesthesia. A new umbilicus was created attaching small skin flaps in the muscular fascia. No drains were used. We observed no seroma formation. Follow up after six and ten months was unremarkable. The fibrous pseudocapsule of chronic seroma results in different degrees of deformities, abdominal scar deviation and asymmetry. Surgical capsulectomy combined with revision abdominoplasty with preservation of Scarpa's fascia and placement of progressive tension sutures resulted in being effective and leads an esthetic outcome without seroma recurrence.

Introduction

Abdominoplasty is listed among is one the five most common esthetic surgical procedures in the Western World. Techniques, patients care and settings have been improved and modified in the last decades. Abdominoplasty is a measure of primary body shaping and has been additionally fueled by bariatric surgery [1].

Despite all efforts, abdominoplasty bears a higher risk of complications compared to other esthetic procedures. Scar problems, cutaneous flap necrosis, hematoma formation, infections, thrombo-embolic events, and seroma formation are described in the surgical literature [2][3][4][5].

Seroma formation is among the most common complications and has been reported in about five to 50 % of cases [5]. A chronic seroma may develop later a fibrous encapsulation.

The reason for this is largely unknown. Interruption of lymphatic flow and shear forces between tissue layers were discussed as contributing factors. Nevertheless, encapsulation represents a severe complication after abdominoplasty [6]. In such a case, repeated aspiration does not achieve a complete remission. Instead of this, complete surgical removal is necessary.

Case Report

A 39-year-old-woman with previous classical abdominoplasty performed elsewhere three years ago was referred to our surgical department with an enlargement of her abdominal region (Fig. 1a-c). According to the patient, three weeks after the surgery she experienced a palpable swelling in the surgical region. The clinical diagnosis was a seroma which was drained by aspiration by her surgeon. Five days after this initial aspiration a new seroma was drained. In the last three years, there was a continuous recurrence of seromas. She has undergone aspiration with the evacuation of the serous fluid numerous times.

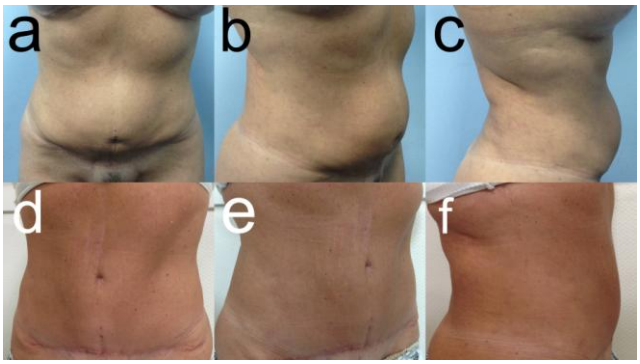

Figure 1: (a-c) A 39-year-old woman presenting for treatment of her abdominal projected region. Treatment results ten months later (d-f)

The patient arrived at our consultation with a projected aspect of her abdomen and with some flotation and aesthetic deformity. The enlargement of the region was evident upon clinical inspection without other signs or symptoms of inflammation or infection. The umbilicus was abnormally located (too low), and the entire aspect of the region was compromised. Clinical examination also demonstrated a swollen and tense abdominal region. Laboratory findings were normal. Abdominal ultrasonography demonstrated both, a significant fluid volume in this area and a dense fibrous “capsule”. The diagnosis was a chronic encapsulated seroma with a thick pseudocapsule or “bursa”. We performed an aspiration of approximately 540 mL of viscose serous and sanguine fluid. The liquid was sent to microbial examination, which revealed no contamination.

A revision abdominoplasty was performed with a standard supra-fascial dissection. Surgical resection of infra-umbilical flap containing skin, subcutaneous tissue and the entire capsule of the affected area was performed (capsulectomy under general anaesthesia) (Fig. 2). No muscular plication was done. Progressive tension sutures using Monocryl 4-0 suture were placed to avoid dead space [7].

A new umbilicus was created attaching small skin flaps in the muscular fascia. No drains were used. Smooth dressings were applied during the next three weeks without compression.

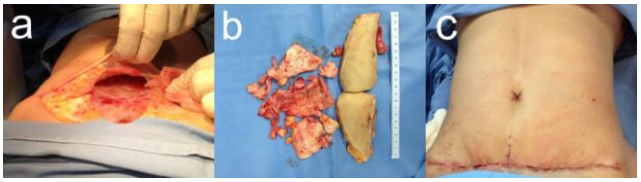

Figure 2: Surgical resection of an encapsulated late seroma of the abdomen. (a) Operation situs. (b) Infra-umbilical flap is containing skin, subcutaneous tissue and the entire capsule of the chronic seroma. (c) Final aspect with umbilicus reconstruction

We observed no complications such as wound hematoma, infection, dehiscence, or recurrence of seroma after revision surgery. Follow up after six and ten months was unremarkable (Fig. 1 d-f).

Discussion

Postoperative seroma formation remains the most frequent complication following abdominoplasty. Usually seroma appears shortly after the abdominoplasty with a peak incidence eleven days after surgery [8].

If not detected or adequately treated, a fibrous pseudocapsule can develop that transforms the seroma into a chronic encapsulated condition. The seroma pseudocapsule is composed of fibrous tissue with eosinophilic hyaline degeneration of collagen and a mild inflammatory, predominantly lymphocytic, infiltration. It lacks an epithelium on its inner surface.

Differential diagnoses include hernias, chronic expanding organized hematoma, cystic lesions of epithelial, mesothelial, and other origin (germ cell tumors, sex cord gonadal stromal tumors, cystic mesenchymal tumors, fibrous wall tumors, and infectious cystic peritoneal lesions), lymphangiomas and posttraumatic oily pseudocysts [9][10][11]. The fibrous pseudocapsule of chronic seroma results in different degrees of deformities, abdominal scar deviation and asymmetry. Surgical capsulectomy was followed by revision abdominoplasty with preservation of Scarpa’s fascia and placement of progressive tension sutures [7][12]. Thereafter special garments were used leading to an esthetic outcome without seroma recurrence.

Damage of lymphatic vessels of the abdominal wall muscular fascia probably affects lymphatic drainage in the undermined surface after a classical abdominoplasty [6]. The most frequently used method for decreasing early seroma frequency has probably been the use of closed suction drains. Several studies disclosed, however, that drains do not

result in a decreased seroma incidence [12]. In contrast, progressive tension sutures decreased the rate of seroma from 26% to 4% [13] and from 9% to 2% [14], respectively.

Other methods for reducing complications are described in the literature for seroma. Those recommendations include quilted sutures to reduce dead space and fibrin glue. In a meta-analysis covering 15 studies with > 1,800 patients, only the abdominoplasty with preservation of Scarpa's fascia or placement of progressive tension sutures was associated with a significantly reduced incidence of seroma compared with standard abdominoplasty. Abdominoplasty with the application of fibrin glue was similar to standard abdominoplasty regarding seroma development [15][16].

Although seromas usually resolve with multiple aspirations, some can often become chronic and lead to the development of a pseudocapsule or pseudobursa clinically apparent by (scar) asymmetry. This condition requires reoperation with complete resection of the entire compromised tissue [17][18]. As shown in our patient, the outcome after well-performed procedure is esthetically and functionally excellent.

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Case Report

Acute Forefoot Phlegmon – A Complication of Intravenous Heroin-Addiction

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Keywords: Phlegmon; Skin and soft tissue infection; Intravenous drug abuse; Heroine; Treatment; Forefoot

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Abstract

Infections of the skin and soft tissues (SSTI) are clinical entities with variable presentations, causes, and levels of clinical severity. They are frequent in emergency departments. The most common pathogen in the Western World is *Staphylococcus aureus*. SSTI may provide a hint to underlying pathologies such as diabetes and other states of immune compromise. Here we present a 41-year-old non-diabetic male patient with pain and swelling of the left forefoot but not any recent trauma. Microbiology identified streptococci. The medical history was positive for intravenous heroin abuse. The diagnosis of forefoot phlegm due to drug addition was confirmed. Treatment was realised by a combination of intravenous antibiosis and drainage. Intravenous drug addiction is a significant risk factor for SSTI.

Introduction

In the Western World, diabetic foot is the leading cause of soft tissue infections of the forefoot. The most common pathogens are bacteria, but mycotic and viral infections are also possible. SSTI of the forefoot ranges from superficial to deep infections to necrotising fasciitis. SSTI cause annually about 850 000 hospitalizations in the US [1][2][3][4].

Case Report

A 41-year-old male patient presented to the emergency department. He reported pain and swelling in the left forefoot but denied any recent trauma. He had slightly increased the peripheral temperature of 37.6^0 Celsius. On examination, we observed swelling of the forefoot with an injection mark but without sharply demarcated erythema (Fig. 1). He had small erosion on the lateral part of his Vth toe. On demand, he mentioned an earlier self-injection of heroin on both sites. There was no discharge from the wounds. The lymph nodes in the left groin were palpable and painful. Laboratory investigations revealed an elevated C-reactive protein of 65 mg/L (normal range < 5 mg/L) and an increased leukocyte count of 63 Gpt/L. A microbial swab was positive for streptococcal spp. Magnetic resonance tomography excluded the involvement of fascia, muscles and bone. He was submitted to the Department of Orthopedic Surgery. Treatment was realised by a combination of intravenous cefuroxime 2 x 1.5 g for ten days and drainage. Healing was complete.

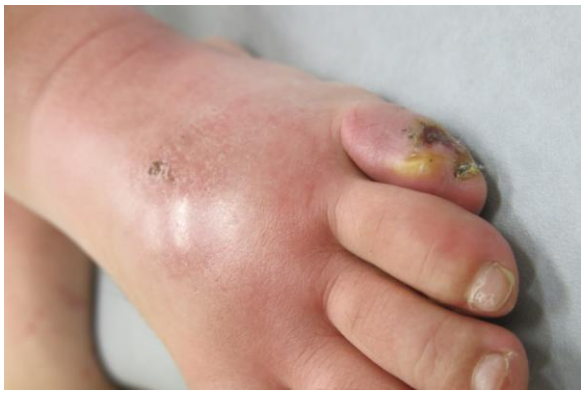

Figure 1: Forefoot phlegmon due to intravenous heroin use, small erosion on the Vth toe

Discussion

Intravenous drug addiction is a significant risk factor for SSTI. The presentation of intravenous heroin users to emergency departments is significantly above average [5][6]. Skin and soft tissue infections (SSTI) are the most common cause of hospital admission of injection drug users. Abscesses are the most frequent type of SSTI. Wound infections with rather unusual germs like Clostridium (C.) botulinum, C. novyi, tetanus or anthrax have been observed in heroin injectors, especially after subcutaneous or intramuscular injection of heroin ("skin popping") [7][8][9].

In the present case, neither abscess formation and nor erysipelas (cellulitis) was noted but a forefoot phlegmon due to streptococcal infection. The disease was treated with intravenous antibiosis with drainage. Complete healing was achieved.

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Case Report

Neglected Under Lip Cancer

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Keywords: Lip cancer; Neglected; Chemotherapy; Surgery; Cetuximab

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Abstract

The lip represents an anatomical area of the interface between the skin and oral mucosa. It is, therefore, not entirely surprising that SCC of the lip exhibits mixed features between cutaneous and oral mucosal SCC, namely regarding risk factors and biological behaviour. The main risk factors for lip SCC include ultraviolet radiation exposure, low phototype, tobacco and alcohol use, and immunosuppression. Lip SCC usually presents clinically as a nodule or a tumour with a keratotic surface that commonly ulcerates. There is often a background of actinic cheilitis. The particularly exuberant presentation of our case can most probably be explained by the long evolution of a tumour before the patient reached medical attention. Patients with regional lymph node metastasis are usually offered regional lymph node dissection (usually of the neck). Radiotherapy and/or chemotherapy may be used in advanced cases, particularly in unresectable tumours, tumours with high-risk features and metastatic disease. The large size of a tumour in our case, most probably due to its long evolution, highlights the importance of timely diagnosis to avoid such extreme presentations and the consequent need for more aggressive treatment.

Introduction

The lip represents an anatomical area of the interface between the skin and oral mucosa [1]. It is, therefore, not entirely surprising that SCC of the lip exhibits mixed features between cutaneous and oral mucosal SCC, namely regarding risk factors and biological behaviour [1]. The main risk factors for lip SCC include ultraviolet radiation exposure, low phototype, tobacco and alcohol use, and immunosuppression [1]. Poor oral hygiene and dental status are also very frequent findings in patients with this neoplasm [2]. Recently, it was found that use of photosensitive drugs, particularly hydrochlorothiazide, may significantly increase the relative risk of lip SCC [3].

Case Presentation

A 94-year-old female was presented to the dermatology department with a large ulcerated tumour of the lower lip that was evolving for seven years. The patient lived in a rural area in Bulgaria and had a

history of significant chronic sun exposure. Clinical examination disclosed a large tumoural mass occupying virtually the whole extension of the vermillion of the lower lip and extending to the surrounding perioral skin (Figs. 1a, 1b, 1c, 1d). The lesion was markedly exophytic with an ulcerated friable surface covered with black haemorrhagic crusts (Figures 1a to 1c). Oral cavity examination revealed poor oral hygiene and dental status (Figure 1d). Incisional biopsy was consistent with squamous cell carcinoma (SCC). The patient is currently scheduled for surgical treatment.

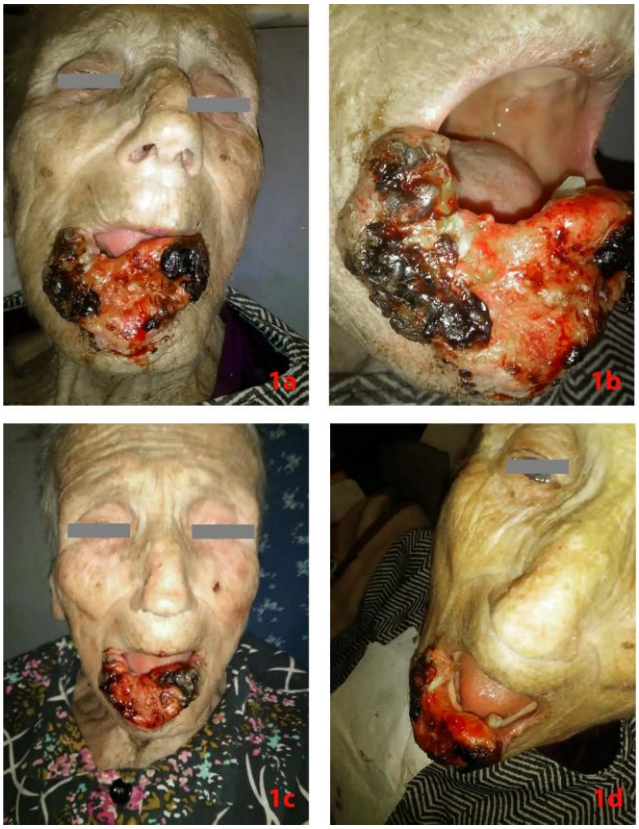

Figure 1: (1a-1d) A tumoural mass occupying virtually the whole extension of the vermillion of the lower lip and extending to the surrounding perioral skin. The surface of a tumour is covered with black haemorrhagic crusts (Figures 1a to 1c). Poor oral hygiene and dental status (Figure 1d)

Discussion

First-line treatment of lip SCC is surgical excision, whenever possible [4]. Patients with regional lymph node metastasis are usually offered regional lymph node dissection (usually of the neck) [4]. Radiotherapy and/or chemotherapy may be used in advanced cases, particularly in unresectable tumours, tumours with high-risk features and metastatic disease [4].

Regarding prognosis, lip SCC displays intermediate behaviour between cutaneous SCC and SCC of the oral mucosa, with an overall 5 - year survival rate of 82,1% [5]. The risk of nodal metastasis varies widely with primary tumour staging (e.g. T1 tumours have the nodal disease in 3, 4 to 7% of cases, whereas in T4 tumours this percentage may vary from 17 to 100%, depending on the studies). Lip SCC is thus considered a high-risk category within the group of cutaneous SCC [1][2][5]. Additional prognostic factors include the degree of differentiation of a tumour, depth of invasion and perineural invasion [1][2][3][4][5][6]. In a recent study, elderly (over 80 years-old) and non-white patients were found to have a poorer prognosis [6].

The large size of a tumour in our case, most probably due to its long evolution, highlights the importance of timely diagnosis to avoid such extreme presentations and the consequent need for more aggressive treatment (Figs.1a-1d).

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Case Report

Cutaneous Leishmaniasis – A Case Series from Dresden

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Keywords: Leishmaniasis; Protozoa; Cutaneous infection; Traveler's diseases; Displaced people

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Abstract

Leishmaniasis is world-wide one of the most common infectious disorders caused by protozoa. Due to the climate change, there is a risk of further spread of the disease to central and northern Europe. Another important issue is the high number of refugees from Syria since Syria is one of the hot spots of Old World leishmaniasis. We report on single-centre experience with leishmaniasis in the capital of Saxony, Dresden, during the years 2001 to 2017. We noted a substantial increase in the last five years. Once a very rare exotic disorder in Germany, cutaneous leishmaniasis has become a reality and physicians should be aware of it. A significant number of cases are from Syrian refugees; other cases had been acquired by tourists in the Mediterranean region!

Introduction

The climate change has the potential for distribution and epidemiology of skin diseases. In case of infectious dermatoses, climate may modulate the distribution of both, pathogens and vectors [1].

Leishmaniasis is a protozoal disease with cutaneous, mucocutaneous and visceral subtypes. World-wide, about two million people are affected. Pathogens are Trypanosoma-like Leishmania with the major subgenera Leishmania and Viannia. Around 20 species have been identified so far.

Cutaneous leishmaniasis is classified into Old World- and New World- disease. Also, there is mucocutaneous and visceral leishmaniasis, also known as Kala-Azar [2].

The classical distribution of leishmaniasis is Central and South Americas, China, Sri Lanka, the Indian subcontinent, North, East, West and Central Africa, Middle East, and the Mediterranean. Transmission occurs by blood-sucking female insects of the genus Phlebotomus (Old World) and Lutzomyia (New World). Pathogen reservoir includes rodents, canine, feline, and humans. The incubation period may vary between some weeks and several months. The protozoa are located intracellular and modify the host response reactions immunologically [3].

Entomological investigations suggest changes in the geographical distribution of Leishmania vectors. An increased risk for vectors has been calculated for the European Atlantic coast, Austria, Germany, and Switzerland [4]. In Germany, there are two possible mosquito vectors, i.e. Phlebotomus (P.) mascittii and P. pernicious [5]. In Northern Italy, Ixodes ricinus had been identified as another possible vector since 7.5% of all tick bites had a positive polymerase chain reaction (PCR) for Leishmania (L.) infantum [6]. PCR plus sequencing and/ or multiple restriction enzyme

digestions (RFLP) is now considered as gold standard in diagnosis [7].

We report on cutaneous leishmaniasis cases, diagnosed and treated at our department during the years 2001 - July 2017.

Patients and Methods

This is a single-centre retrospective study using the patient files at the academic teaching hospital Dresden-Friedrichstadt from January 2001 to July 2017. All patients that could be identified by diagnosis of cutaneous leishmaniasis were included.

Results

We identified nine patients – 6 males and three females – with age between 1.5 years and 33 years. Five patients were refugees from Aleppo, Syria (Table 1).

Table 1: Cutaneous leishmaniasis 2001-17 (PR, partial remission; CR, complete remission)

No.	Age years	Sex	Infection from	Clinical presentation	Diagnosis	Treatment and outcome
1 [3]	18	m	Northern Italy tourist	verrucous plaque, nose	histology	fluconazole 2 x 200 mg/d, CR after 7 months
2 [3]	16	f	Syria tourist	papule, cheek	histology	intralesional injections of 20 mg/ kg body weight meglumine stibnite every 3 days, CR after 1.5 months
3	33	m	Crete business trip	papule, cheek	histology	itraconazole 200 mg/d for 6 weeks, CR after 8 weeks
4	6	m	Syria refugee	nose, cheek, elle bow		3 x glucantime 1.5 mg/ 5 ml every week, CR after 5 weeks
5	10	m	Syria refugee	partly verrucous plaques, corner of the mouth, ear, hand	clinical	3 x glucantime 1.5 mg/ 5 ml every week, CR after 5 weeks
6	9	m	Syria refugee	indurated plaques, eyebrow, cheek, ear	clinical	3 x glucantime 1.5 mg/ 5 ml every week, CR after 5 weeks
7	14	m	Syria refugee	partially ulcerated plaques, hands, lower arm	histology	3 x glucantime 1.5 mg/ 5 ml every week, CR after 5 weeks
8	2	f	Syria refugee	papules, cheek	clinical	3 x glucantime 1.5 ml/ 5ml every week, PR after 5 weeks
9	1.5	f	Sicily tourist	ulceration cheek	PCR *L. infantum*	paromomycin ointment, CR after 8 weeks

All cases were identified since 2013; there was not a single case before. The lesions developed up to 6 months before a diagnosis was confirmed. Major differential diagnoses were pyoderma and infected insect bites. The diagnosis was confirmed by histologic proof of intracellular amastigotes in eosin-hematoxylin or Giemsa stains. Four cases occurred in a single family. Here, we decided to confirm clinical diagnosis in the oldest child only. In another infant, infected with Sicily, polymerase chain reaction (PCR) was performed at the Benhard-Nocht-Institute for Tropical Medicine, Hamburg. PCR was positive for Leishmania spp., sequencing excluded L. braziliensis and L. major complex but confirmed L. donovani complex. Eventually, L. infantum infection could be belayed. Other infections were acquired during holidays in Northern Italy and Crete, Greece.

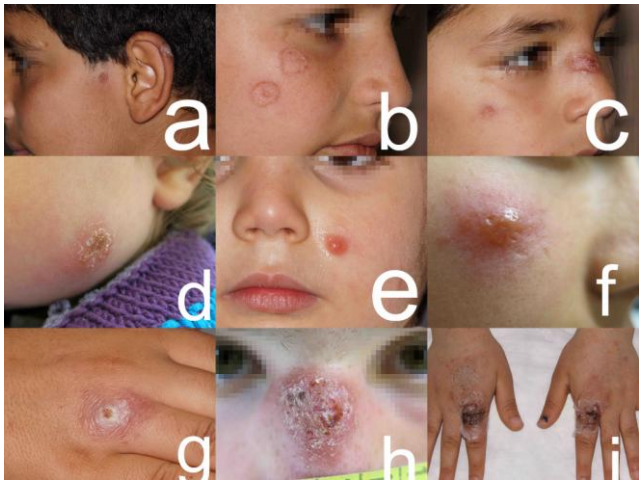

Figure 1: Clinical presentations of Old World cutaneous leishmaniasis. (a) Plaques; (b) Atrophic plaques; (c) Plaque with elevated borders; (d) Ulcerated plaque with eschar; (e) Firm nodule; (f) Abscess-like nodule; (g) Erosive plaques; (h) Verrucous plaque; (i) Eczematous lesions

We used pentavalent antimonials (Glucantime) (n = 5), meglumine stibnite (n = 1), azole derivates (n = 2) or paromomycin ointment (n = 1) to treat our patients. Eight patients achieved a complete remission (CR), one achieved a partial remission (PR). In the latter two cases, treatment is continued. Treatment was well tolerated. To reduce the injection-associated pain, topical lidocaine/prilocaine ointment (EMLA® cream) was applied. We observed single delayed oedema after the second injection of glucantime on the cheek. With systemic corticosteroids, oedema disappeared within three days.

Cutaneous leishmaniasis healed leaving scars (n = 7) and/or post-inflammatory hyperpigmentation (n = 4).

Discussion

We identified nine cases of cutaneous leishmaniasis (Old World) in the last 16 years. All but one patient were infants, children and adolescents [8][9][10]. Five patients were from Aleppo, Syria, coming to Saxony as refugees. The most common sites affected, were head-and-neck region and hands not covered by clothes. In Aleppo and the surrounding northern area of Syria, L. major is the major pathogen [11]. L. infantum is the dominant species in Sicily [12].

In Germany 130 cases of leishmaniasis were registered from September 2000 and May 2007 with

96 cutaneous and mucocutaneous disorders. Tourists represented the greatest group [13]. In Europe EuroTravNet identified three hot spots for Leishmania infections in Europe, i.e. Spain, Malta, and Italy [14]. The largest outbreak of European leishmaniasis occurred in 2009 in Fuenlabrada, Spain, with 90 adult patients with either localised Leishmania lymphadenopathy or visceral leishmaniasis (81%) [15].

In recent years, refugees and asylum seekers from the Middle East and North Africa have become more important in that manner. The official number of refugees registered in Saxony was 69,900 in 2015. In May 2017, around 25,000 refugees and asylum seekers officially lived in Saxony [16]. Outbreaks of cutaneous leishmaniasis have been reported from refugee camps in Lebanon and Turkey [17][18][19], but neither from Switzerland nor Germany [20][21][22].

Another important source of infections are pets serving as a pathogen reservoir. Canine and feline infections from animals taken by tourists to endemic regions of the Mediterranean, and dogs and cats imported from there represent a risk factor for leishmaniasis spread in Central Europe [23].

Treatment is dependent on clinical symptoms. Miltefosine, pentavalent antimonials, paromomycin and azole derivates are treatment options. Recently, case reports about successful photodynamic therapy have appeared, but systematic trials are missing [7][9]. In general, the safety of drug therapy is good. The adverse effects associated with miltefosine were vomiting, nausea, kinetosis, headache, diarrhea, and an increase in aminotransferases and creatinine. The most frequently reported clinical adverse effects of pentavalent antimonials and pentamidine were musculoskeletal pain, gastrointestinal problems, and headache. Electrocardiographic QTc interval prolongation and increase in liver and pancreatic enzymes were also seen [24]. We observed a facial edema after second injection with glucantime, that responded rapidly to systemic corticosteroids. The third injection was tolerated well.

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Case Report

Lip Repair after Mohs Surgery for Squamous Cell Carcinoma by Bilateral Tissue Expanding Vermillion Myocutaneous Flap (Goldstein Technique Modified by Sawada)

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Keywords: Non-melanoma skin cancer; Squamous cell carcinoma; Lower lips; Flaps; Defect closure

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Abstract

Squamous cell carcinoma is the most common malignancy of the lower lip. Environmental factors such as ultraviolet light exposure, arsenic and smoking are contributing factors to the increasing incidence. Mohs surgery is the treatment of choice ensuring the lowest recurrence rates. The closure of the surgical defects, however, can be a challenge. Multiple and versatile methods of reconstructing vermilion defects have been described. Among these options, Goldstein developed the adjacent ipsilateral vermilion flap based on an arterialized myocutaneous flap. The original technique was modified by Sawada based on bilateral adjacent vermilion advancement flap for closure of central vermilion defects. We report the use of bilateral flaps - Sawada's technique (instead of unilateral as suggested by Goldstein) in medium (2 cm of extension) to large defects (> 2 cm) to achieve an effective and functional reconstruction of vermillion defects after Mohs surgery for lip cancer.

Introduction

The vermilion and cutaneous mucosa line of the lips represents an important role regarding esthetics and functionality of the face. The Vermilion has a unique anatomic structure with proper texture, colour, movement and function. This anatomical region also works as an important structure in interpersonal relationship and as strong sphincter [1].

The lips have a high incidence of skin tumours. The majority of lower lip tumours are squamous cell carcinomas (SCCs), in contrast to the upper lip where basal cell carcinomas (BCCs) dominate. The precursor of lip SCC is chronic actinic cheilitis. Exposure to ultraviolet radiation, smoking, and arsenic are the major environmental factors contributing to its carcinogenesis [2][3][4]. Lip SCC has an intermediate risk of metastatic spread, higher than cutaneous SCC and lower than oral mucosa SCC [5]. Mohs surgery is the procedure with highest cure rates [6], but proper lip reconstruction can represent a challenge. Oncologic, functional and esthetic aspect must be ideally considered to choose the appropriate treatment [7].

Multiple and versatile methods of reconstructing vermilion defects have been described. Among these options, Goldstein developed the adjacent ipsilateral vermilion flap based on an arterialized myocutaneous flap. This composite flap is

stretched to span the deficient area [8]. The original technique was modified by Sawada based on bilateral adjacent vermilion advancement flap for closure of central vermilion defects [9].

We suggest the use of bilateral flaps - Sawada's technique (instead of unilateral as suggested by Goldstein) in medium (2 cm of extension) to large defects to achieve an effective and functional reconstruction of vermillion defects.

Case report

A 71-year-old female patient with a chronic lesion of her the lower lip presented to us (Fig. 1). The lesion appeared approximately four months ago. She had a history of sun exposure (non-professional), diabetes mellitus type II, hypertension and previous tumour surgeries for lung cancer and pharynx carcinoma eight years ago.

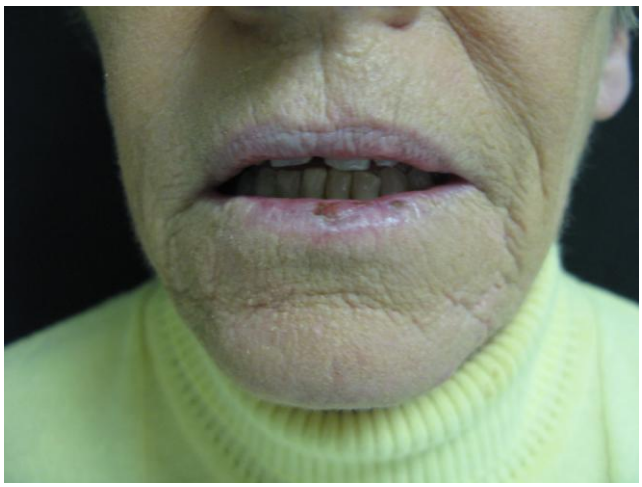

Figure 1: Squamous cell carcinoma of the lower vermillion

Under local anaesthesia and sedation, the lesion was removed in one single piece including Vermillion, skin, muscle and mucosa with a longitudinal dimension of 2 cm. Frozen section evaluation by the pathologist demonstrated tumour-free surgical margins. The final pathology report described an SCC of the lower lip, invasion to Clark level II. There was no vascular or perineural infiltration. The tumour was staged T1.

Bilateral vermilion flap (Goldstein's technique) was prepared for defect closure. Special attention was paid to avoid damage to the vascular plexus. The flaps were advanced medially. Mucosa, muscle and cutaneous mucosa line were sutured (Fig. 2). There were no complications in the post-operative period.

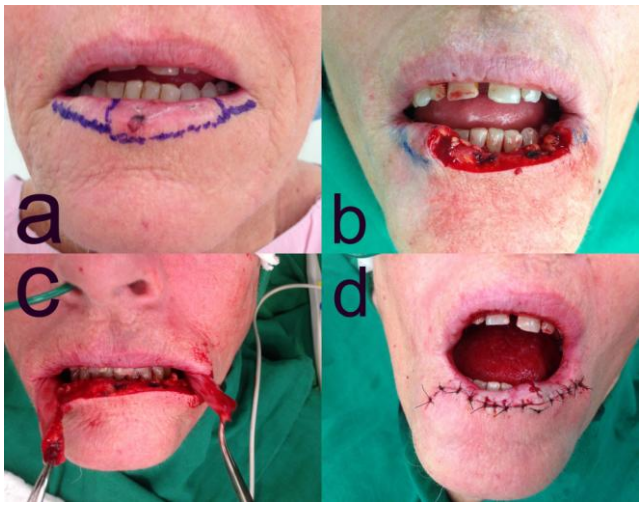

Figure 2: Surgery. (a) Surgical plan is observing a good margin limit resection. Bilateral expanding vermillion-myocutaneous flap was designed; (b) large defect after complete tumour excision; (c) Bilateral flaps were dissected; (d) the flaps were advanced medially. Note that two Burow's triangles of compensation had been removed

The last follow-up four years after the surgery demonstrated no relapse. The esthetic aspect was very nice and the scars well dissimulated. There was no interference in the functionality of the mouth or lips especially no lip incontinence. Muscular activity was fully preserved (Fig. 3).

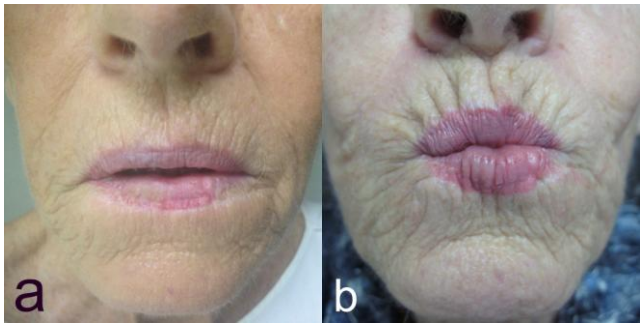

Figure 3: Four years post reconstruction without tumour relapse. (a) Good functionality and satisfactory esthetic result; (b) Functionality was maintained, and the lips and mouth as sphincter were preserved

Discussion

Lower lip defects after cancer removal are a challenge for reconstruction. A loss of labial continence increases the risk of dysphagia and sialorrhea, with negative effects on esthetics, function and health-related quality of life [10][11][12].

Various techniques have been developed over time to improve functionality and esthetics [8][9][10][11][12][13][14][15][16][17]. Although multiple-step procedures such as the Abbé - Estlander

flap can yield good results [13], single step procedures are favoured by patients. The Karapandzic flap [14] and the Bernard–Burrow–Webster procedure [15][16] are two long-established surgical techniques for lower lip reconstruction. While the Karapandzic flap preserves the sensibility, microstomia is a common outcome. The Bernard–Burrow–Webster flap allows a larger site mobilisation but may result in some degree of lip incontinence. The staircase technique is an option for closure of medium-sized defects with or without muscular involvement [17].

The bilateral tissue-expanding vermillion myocutaneous technique was used in the present case with good functional and esthetic outcome. If it is necessary, small Burow's triangle of compensation can help the reconstructive approach. The expanded flap has different anatomic structures which allow an effective stretching (advancement) towards the ipsilateral border defect. In general, bilateral flaps generate less tension in the distal portion of the flaps. They can be created smaller than a singular flap. Smaller flaps have more viability and are safer than bigger flaps. The muscular activity of the musculus orbicularis or is maintained since preparation of the flaps does not cut the muscular fibres. Last but not least, this one-stage procedure can be done under local anaesthesia as an outpatient procedure.

To avoid tumour recurrence, a three-dimensional surgical margin examination (Mohs technique in our case) is warranted [6]. The surgical technique for defect closure must be individualized depending on tumour stage, patients' needs, and availability of resources.

In conclusion, bilateral tissue-expanding vermillion myocutaneous flap for lip repair demonstrated to be a safe, useful and versatile technique in the reconstruction of vermillion defects. Adequate esthetic outcome and functionality of the region can be achieved as long as oncological and anatomic characteristics are properly considered.

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Case Report

Ulcerating Lichen Planopilaris – Successful Treatment by Surgery

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Keywords: Lichen planus; Lichen planopilaris; Scalp ulceration; Surgery; Combined tissue advancement and extension

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Abstract

Lichen planus is a T-cell mediated autoimmune disorder affecting the skin and mucous membranes. Ulcerating lichen planus is uncommon mostly on oral and genital mucosa but not skin. Lichen planopilaris, however, is a subtype of lichen planus affection hair follicles and leading to permanent scarring alopecia. We report a case of lichen planopilaris of the scalp with multiple alopecic patches ulceration – a hitherto unreported clinical feature. The patient was treated surgically, and the defect could be closed by combined tissue advancement and extension.

Introduction

Scarring alopecia is an end stage of various underlying pathologies such as trauma, chronic inflammation, deep follicular infection, collagen vascular disorders and lichen planopilaris (LPP) [1][2]. In 1994, Kossard described the peculiarities of frontal fibrosis alopecia of women with similar histopathology as LPP but with the limitation to the frontal hair line. LPP, in contrast, has multifocal areas of involvement [3][4].

We describe the very unusual presentation of a postmenopausal female with ulcerating LPP of the scalp and the successful surgical treatment.

Case report

A 56-year old postmenopausal female patient with progressive scaring alopecia caused by LPP for more than five years was referred to our department because of chronic ulceration of the capillitium.

On examination, we observed large alopecia lesion (about 10 cm in diameter on the capillitium) with a fronto-parietal localised 1.5 x 1.5 large ulcer covered by a scab. There was some putrid secretion. We took a swab for microbiology demonstrating large amounts of *Staphylococcus aureus*. After removal of the scab, a scalp ulcer with sharp borders became visible (Fig. 1).

Routine laboratory disclosed a C-reactive protein of 9.51 mg/L (normal range < 5 mg/L).

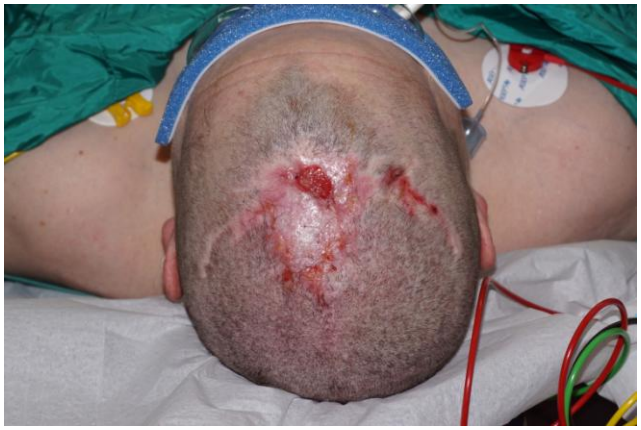

Figure 1: Frontal scalp ulceration within patches of scarring alopecia

We performed a complete excision of the ulcer in general anaesthesia (Fig. 2). The lesion was closed after wide undermining of the wound borders by combined tissue advancement and extension using lateral relief cuts (Fig. 3).

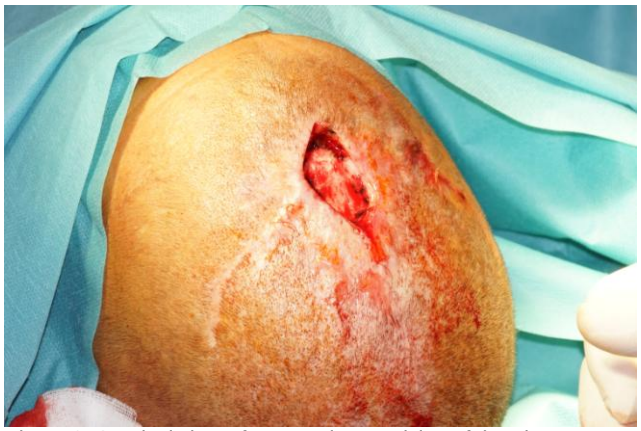

Figure 2: Surgical situs after complete excision of the ulcer

Antibiotic prophylaxis was realised with 1,500 mg cefuroxime one hour before surgery. Healing was uneventful. We observed no relapse of the ulceration.

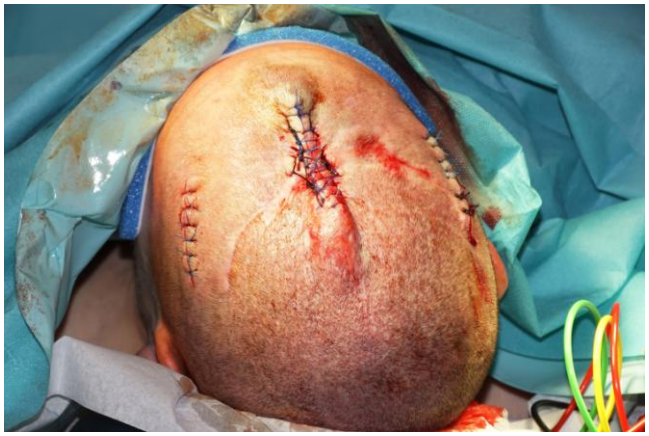

Figure 3: Defect closure by tissue advancement combined with bilateral extension

Histopathology demonstrated a skin ulcer centrally with chronic polypoid granulating inflammation. In the periphery, a stronger fibroblastic inflammation was noted. In the surrounding skin, there was perifollicular fibrosis and lichenoid lymphocytic inflammation in the isthmus and infundibular areas of the follicles leading to their destruction. Elastic fibres were almost completely missing.

Discussion

LPP is a follicular variant of lichen planus. It is characterised lichenoid lymphocytic infiltrates, perifollicular fibrosis and destruction of hair follicles. Apoptotic cells are found in the outer root sheath. Common findings are scarring alopecia, scalp dysesthesia, erythema, and perifollicular hyperkeratosis. The disease has a female preponderance and a peak in the forth to the sixth decade of life [5][6][7].

LPP can be subdivided into the following variants: classic LPP, frontal fibrosing alopecia of Kossard, and Graham-Little syndrome. The latter, also known as Lasseur-Piccardi-Graham-Little syndrome, is characterised by GLPS is an unusual variant of LPP characterized by multifocal scarring alopecia of the scalp, non-scarring alopecia of the axillae, and/or pubis and follicular lichen planus (LP) involving the trunk and extremities [8].

Treatment is usually a medical one with topical or intralesional corticosteroids, topical calcineurin inhibitors, systemic hydroxychloroquine and cyclosporine A [9][10][11].

While LPP is not known for ulcerations, lichen planus ulcerations may be uncommon but represent a very severe subtype of the disease. Oral lichen planus is often ulcerative [12]. Treatment of ulcerative plantar lichen planus needs systemic immunosuppression and often surgery [13][14].

The scalp ulcer in our patient was at least clinically comparable to squamous cell carcinoma. In long-standing LPP of the scalp, SCC has occasionally been observed [15].

Treatment of choice was complete surgical excision and defect closure by tissue advancement and extension [16].

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Case Report

Sarcoidosis in A. C. Milan (1899)?

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Keywords: Sarcoidosis; Sarcoid - type reaction; Cutaneous granuloma; Molecular mimicry; Tattoo; Exogenous pigment

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Abstract

The pathogenesis, diagnosis and therapy of sarcoidosis as an autonomous disease are subjects of spirited discussions, which haven't found definitive conclusion yet. Distinguishing between sarcoidosis and sarcoid-like reactions (sarcoid - type granulomas) is not currently a medical "gold standard" and is not implemented in clinical practice. This leads to 1) misinterpretation of numerous available data; 2) difficulty in the interpretation of other unverified data, which is often followed by 3) inappropriate or inadequate therapeutic approach. Similarly to many other diseases, in sarcoidosis and sarcoid - types of reactions the concept of personalised approach and therapy should also be introduced. This methodology of clinical guidance is difficult, complex and not always achievable in the current medical status and relations (doctor-patient relationship; financial factor; time factor). It is appropriate to note that in some cases the guidelines or the so-called standards are neglected or not possible to put into practice with the aim of better therapeutic practices and strategies, as well as the achievement of optimal final clinical results (especially in patients with sarcoid granulomas). The sarcoid granuloma, even when it is sterile, should not be considered as the equivalent of sarcoidosis, i.e., sarcoidosis as an autonomous disease. Sure enough, exactly because of this fact, the personalised approach should not be an exception, but it has to gradually become a rule in medical practice. When clinical decisions are conformed to some of the latest modern concepts, officialised in the international databases, often the achieved results can be much better.

We present a patient with a tattoo of AC Milan (1899) on his right arm, who subsequently developed localised sterile sarcoid granulomas in the area of the tattoo. Later the process became generalised on his whole body's skin, lungs and lymph nodes. It is unclear for the moment whether this condition should be interpreted as sarcoidosis as an autonomous disease or, instead, as a sarcoidal type of reaction with subsequent generalisation due to cross-reactivity against antigens present in other tissues with similarities to the exogenous pigments. Following the modern concepts regarding the pathogenesis of these two conditions, we introduced, in this case, an innovative, non-standard approach: 1) systemic and local immunosuppressive therapy, combined with 2) recommendation for immediate surgical excision of the tattoo to remove the possible trigger of molecular and antigen mimicry.

Introduction

At the current stage of knowledge the definition of sarcoidosis as an autonomous disease, as well as the differentiation between sarcoidosis and sarcoid - type reactions, remain unclear and a serious clinical and diagnostic challenge [1].

An accurate distinction between these two concepts is crucial because it presumes completely different clinical behaviour and therapeutic strategies [2]. On the other hand, it is a very serious question whether the term sarcoidosis has to be reconsidered as a non-autonomous disease but rather as a reaction pattern [3].

We present an interesting patient with histopathologically - proven sarcoid granulomas and discuss the possible pathogenetic relationship between the disturbance of tissue homeostasis and granuloma formation.

Case report section

Anamnesis

A 42 – year - old male patient presented to the department of dermatologic surgery due to a rash on his right tight. Pruritus leading to scratching and bleeding was reported as a subjective complaint. The symptoms occurred one year and a half after performing a tattoo with the logo of the football team AC Milan (1899). The patient noticed thickening of the skin under the blazon, exactly in the area of the red pigment, which had started to disappear (Fig.1 a).

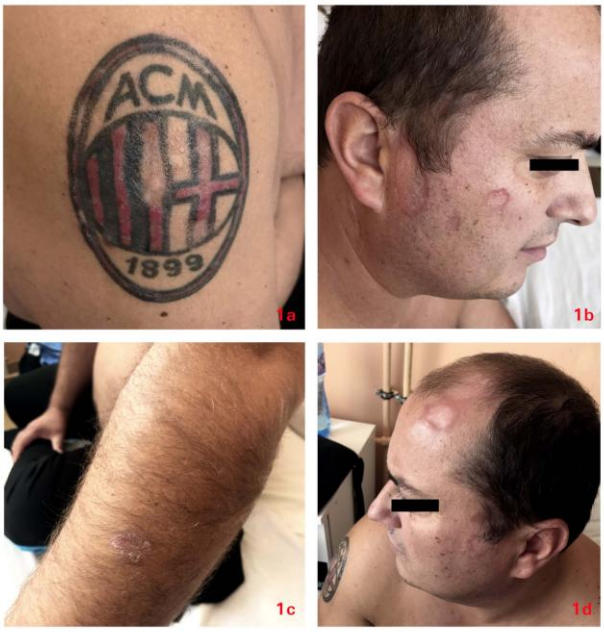

Figure 1: a – Thickening of the skin under the blazon, coinciding with the area of the red pigment, which has started to disappear

The patient had histologically proven cutaneous sarcoidosis from 03/2014. Therapy with methylprednisolone 60mg/day, with gradual tapering of the dose, was started. In 02/2015 systemic sarcoidosis was additionally proved histologically after a biopsy of endobronchial granulations. Throughout several months, dermatologic and pulmonary consultations were performed as well as control CT and chest radiography. Meanwhile, the dosage of methylprednisolone was slowly reduced or increased according to disease fluctuations. According to the more recent data, methylprednisolone was prescribed in the following doses: 01-03/2017 x 15 mg/d; 04-06/2017 x 10 mg/d; 06-09/2017 x 5 mg/d.

In 09/2016, treatment with methotrexate at a dose of 20 mg weekly was prescribed for six months, followed by reduction of the dose to 10 mg weekly until 09/2017 when the treatment was suspended. By the regular follow-up tests, the treatment mentioned above was considered inefficient.

QuantiFERON test and serological tests (anti-HCV and HBsAg) were negative.

Physical examination

Disseminated annular lesions with the atrophic centre and raised edges, well demarcated from the surrounded skin were observed on the scalp, face, trunk and upper limbs (Fig.1 b, c, d). Enlarged inguinal lymph nodes were identified by palpation.

Ancillary tests

Laboratory tests revealed elevated ESR – 18 mm/h (< 11 mm/h); WBC - 31.0/l (3.5 - 10.5/l); Crystal - 9.0/l (-); Plasma uric acid - 526.0 mol/l (< 410 mol/l). Microbiological analysis of a skin swab identified S. aureus, sensitive to amoxicillin, cefuroxime, ciprofloxacin and clindamycin.

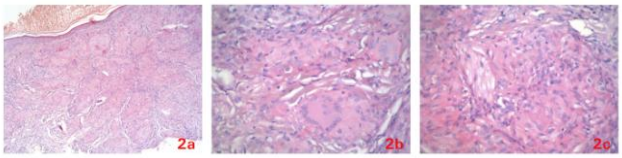

Figure 2: Radiographic images taken in the last 15 months show relatively stable pulmonary findings, which persist in spite of the systemic treatment

Chest radiography detected bilateral hilar enlargement with irregular borders, consistent with hilar lymphadenopathy (Fig. 2). An infiltrate with perihilar paracardial localisation could not be excluded. Horizontal linear opacities between the medium and lower lobes of the right lung were also reported (Fig. 3).

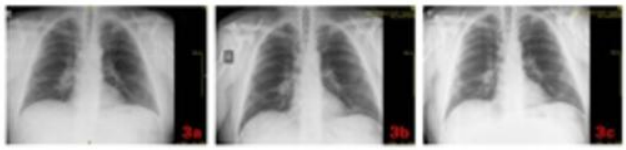

Figure 3: a, b, c - Chest radiography detected bilateral hilar enlargement with irregular borders, which can be associated with hilar lymphadenopathy. An infiltrate with perihilar paracardial localisation cannot be excluded. Horizontal linear opacities between the medium and the lower lobes of the right lung were also observed

Ultrasound examination revealed splenomegaly and enlarged bilateral inguinal lymph nodes as well as enlarged cervical lymph nodes on the right side of the neck, dorsal to the sternocleidomastoid muscle. Echocardiography detected upper-bound volume on the left ventricle, right ventricle dilatation and elevated pulmonary artery pressure in the right atrium. Biopsy from 10/2017 revealed sarcoid granulomas. After endocrinology consultation, the patient was diagnosed with

hyperuricemia and started therapy with allopurinol.

Treatment and outcome

To eradicate the infectious process he underwent treatment with ciprofloxacin 100mg 2 x 2/d i.v. and local dressings with Jodasept® unguent, resulting in successful results.

The patient was diagnosed with skin and systemic sarcoidosis. According to the clinical consultations he performed, treatment was inefficient and did not lead to any significant improvement of the pulmonary changes. Furthermore, the progression of the cutaneous lesions of sarcoidosis was observed. Therefore, a therapy with methylprednisolone 60 mg/d i.v. and azathioprine 2 x 50 mg/d for three days was prescribed. The ambulatory treatment proceeded with methylprednisolone 40 mg/d with a dose reduction of 4 mg per week; azathioprine 50 mg 2 x 1/d; esomeprazole 40 mg/d and local application of pimecrolimus 1%/15 g cream 2 x /d. Also, the patient was referred to a plastic and reconstructive surgery department for surgical excision of his tattoo to permanently remove the exogenous pigment.

Discussion

Once more, we focus the attention of our colleagues and the dermatologic community on the pathogenesis of sarcoidosis, still defined as an “autonomous disease”, a concept that, in our opinion, should be reconsidered. A sarcoid granuloma is not equivalent to the disease sarcoidosis because it is observed as a result of 1) possible paraneoplastic manifestation, resulting from cross-reaction between antigens of the self and cancer antigens; 2) reaction pattern (cross-mediated or direct immunity) against several microbiological agents [1]. Is sarcoidosis such a wide-spectrum disease?

One of the difficulties in distinguishing sarcoidosis as an autonomous disease from sarcoidal-type reactions comes from their main common feature, which is the presence of epithelioid cell granulomas [3]. However, there is no “gold standard” for systematic diagnostic approach and prediction of clinical behaviour in cases of histologically proven epithelioid cell granulomas [4]. The definition of sarcoidosis states that it is a disease characterised by the presence of non - caseating epithelioid cell granulomas in several organs and tissues [5]. By definition, granulomas in sarcoidosis are sterile, so the presence of any identifiable immunogenic triggering agents makes it more accurate to refer to this reaction as a sarcoidal type of reaction pattern [6][7]. In our opinion, sterile sarcoid granuloma should not equate to sarcoidosis disease. The triggering mechanisms that induce sarcoid-like reactions may be categorized as following: 1) local reaction to infectious agents (leprosy, atypical mycobacterial infections, deep fungal reactions, etc.) [8][9][10]; 2) noninfectious but immunogenic antigens (inorganic compounds) [11][12]; 3) tumors (paraneoplastic sarcoid type of reaction) [13][14]. Our concepts of sarcoid - type reaction are based on the assumption that it may be provoked, in predisposed patients, by cross-reaction to immunogens or tumour antigens, so its pathogenesis is closely related to the generation of cross - mediated immunity presenting as molecular (antigen) mimicry. This phenomenon occurs by the similarity between certain amino acid sequences in the triggering antigens and molecular structures in the body [15]. The precise distinction between these two terms is extremely important because misdiagnosis may lead to the introduction of inappropriate treatment. Immunosuppressive therapy, which is recommended as first-line treatment for sarcoidosis, can enhance a tumour or infectious progression in patients afflicted by those conditions, with all its deleterious consequences for the patient [16][17][18].

Blau syndrome (BS), for example, is a rare autosomal dominant autoinflammatory disease characterised by the clinical triad of dermatitis, arthritis, and uveitis. It is caused by mutations in nucleotide-binding oligomerisation domain-containing protein - 2 (NOD2) gene [19]. It is unclear whether and to what extent this autoinflammatory syndrome overlaps with congenital or early-onset sarcoidosis, which is most probably genetically determined [20]. It is a somewhat disturbing fact that the mechanism of granuloma formation in these patients is completely different from the one that originates similar types of granulomas in patients with certain forms of cancer or deep mycosis. Sarcoid granulomas are obviously the final result of diverse pathogenic mechanisms, which are, in turn, activated by different specific diseases [1][21].

Would it be accurate to define existing sarcoidosis as a disease occurring by 1) congenital genetic defect; 2) paraneoplastic reaction; 3) parainfectious or infectious disease, as well as the incorporation of inorganic material via inhalation or skin contact?

According to our observations, sarcoid-like reactions could be determined by the capability of the organism (or a genetically determined predisposition) for reacting against different kinds of antigens. These antigens could be either exogenously incorporated into the body or generated by the tissue homeostasis (de novo) as seen in the process of carcinogenesis. This abnormality of tissue homeostasis is the main trigger of sarcoid-like reactions [22]. Thus, clinicians should be cautious in the approach to this kind of reactions. In case of a histological diagnosis of sarcoid granulomas, it is of great importance to exclude: 1) different forms of tumours; 2) infectious

diseases with diverse origin. Following the standard definition of sarcoidosis and starting immunosuppressive therapy may lead to a significant risk of potentiating cancer progression or worsening of an underlying infection, which may have fatal consequences, as we already unravelled.

In conclusion, we consider the present case of a patient with a sarcoid-like reaction secondary to a tattoo, as an illustrative example of our theory of antigen mimicry as the mechanism leading to granuloma formation in genetically predisposed individuals. The persistence of symptoms in spite of treatment with corticosteroids followed by methotrexate in combination with corticosteroids is not unique in the setting of sarcoidosis or sarcoid type reactions. In such patients, we hypothesise that it is of vital importance to eliminate the trigger of molecular mimicry, which may potentially lead to normalization of the tissue homeostasis and the immune response. It remains an open question: Sarcoidosis – does it exist?

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Case Report

Unilateral Palmar Callus and Irritant Hand Eczema – Underreported Signs of Dependency on Crutches

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Keywords: Leg amputees; Crutches; Mechanical forces; Hyperkeratosis; Friction; Cheiropompholyx; Palmar skin

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Abstract

Leg amputees who can't use prostheses and patients with arthritis are often dependent on crutches. Their chronic use can exert significant friction forces. The palmar skin will respond by forming a hyperkeratotic callus. We report for the first time unilateral palmar callus formation caused by friction from using crutches. Another possible adverse effect is the triggering of irritant contact dermatitis by the handholes of crutches. We report two cases with hand dermatitis due to the chronic dependence on crutches and discuss treatment options.

Introduction

The skin is a barrier to the external environment. Chronic mechanical forces lead to cutaneous responses such as bullae, callus, corn or ulceration. The type of responses is dependent upon the amplitude and frequency of mechanical stressors [1].

The callus is epidermal hyperplasia and hyperkeratosis following mild to moderate rubbing under mechanical stress and friction. They can be due to occupation, sports or peripheral neuropathy [2][3][4]. They have to be differentated from the genetically heterogeneous palmoplantar keratodermas, characterised by erythema and hyperkeratosis [5][6]. Epidermolysis or acantholytic dyskeratosis may be present or absent.

Here we focus on underreported side effects of chronic use of crutches.

Case reports

1. A 66-year-old male patient was referred to our outpatient clinic since he had a hyperkeratotic plaque on the heel of his hand. On examination, we observed a 5 x 4 cm large hyperkeratotic, yellowish hard plaque on the heel of his right hand (Fig. 1).

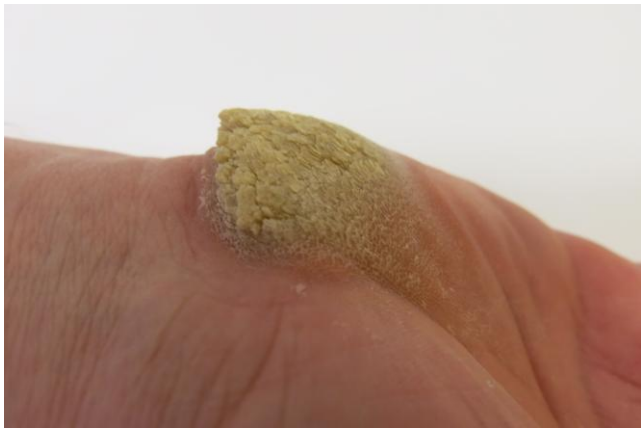

Figure 1: Unilateral massive callus formation on the heel of the hand

The other hand was unchanged. He reported no response to rubbing with a pumice stone after soaking the hand in hot water, topical retinoids, and topical urea- or salicylic acid-containing ointments. He had an upper leg amputation after an accident on his right side. He used to walk with two crutches. The diagnosis of a callus caused by crutches was made. He was offered surgical removal of the callus and a modification of his crutches to reduce the frictional forces.

2. A 50-year-old female was referred from the rheumatologists due to palmar lesions. She suffered from rheumatoid arthritis and used crutches for walking. On examination, we observed an eczematous infiltrated and lichenified skin of the thenar and antithenar of her hand. From time to time she developed itching vesicles in this area (Fig. 2).

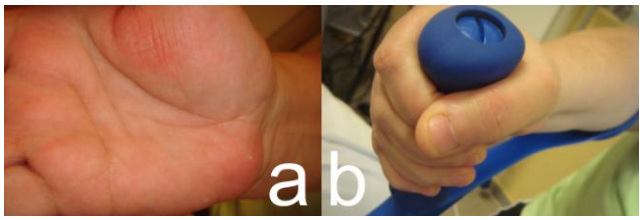

Figure 2: Chronic irritant hand eczema. (a) Clinical presentation; (b) the responsible handhole

When she was using the crutches for a longer time, continuously her hands became hyperhidrotic. A patch test series was positive for nickel only. The diagnosis of mechanically triggered hand eczema and cheiropompholyx was made due to the use of crutches. We prescribed antihidrotic topical solutions and topical corticosteroids and recommended a change of the handholes.

Discussion

Crutches are an aid for handicapped people such as leg amputees, patients with severe arthritis, vertigo, rheumatologic disorders, after surgery etc. Their use aims to improve or secure a certain degree of mobility. Sometimes they are the source of complaints. Here we reported two cases with cutaneous lesions of the palms. The first patient needed the crutches due to amputation of his right leg. Although the preferred localization of calluses is the feet and legs, they have also been seen on glabrous skin of fingers and hands as in our case. Calluses of the palms have to be differentiated from acquired and genetic hyperkeratosis of other etiologies [5][6]. These plaques are not only unsightly, but may become malodorous due to secondary bacterial and/or mycotic infection, or may become even painful.

In the presented male patient, we need a surgical removal and modifications of the handholes of the crutches. His unilateral callus formation was mainly due to the right-sided instability after complete loss of his right leg. In the second case, the rougher surface of the handhole caused a chronic irritant hand eczema that was from time to time worsened by cheiropompholyx. Hyperhidrosis can be an aggravating factor for eczema known from occupational dermatology [7]. It is quite typical in cheiropompholyx to have a type-IV nickel sensitization as in our case [8]. A contact allergy to the grip material could be excluded.

The recognition and treatment of hand dermatoses is of great practical importance for patients depending on the use of crutches.

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Case Report

Sweet's Syndrome (SS) in the Course of Acute Myeloid Leukaemia (AML)

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Keywords: Sweet syndrome; Acute leukaemia; Complete response; Epirubicin

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Abstract

Firstly described by Robert Douglas Sweet in 1964, febrile neutrophilic dermatosis is a disabling, not only cutaneous disorder, clinically characterised by fever and painful erythematous nodules, with a typical background of neutrophilia. Sweet's syndrome (SS) is a chronic inflammatory reactive disorder of unknown cause and incompletely established pathogenesis, although an interplay between genetic and environmental factors, including infections, is likely to occur. A significant part of cases has been demonstrated to be linked with malignancies, especially in the hematologic setting. Because of the underlying disease and related therapeutic measures, SS may present atypical clinical course, whereas the response to treatment is strictly dependent on the concurrent hematologic disease. Herein we describe a case of a lady who had a refractory form of SS, resulted in a paraneoplastic cutaneous disease, and AML. Surprisingly, clinical remission of SS followed cytotoxic chemotherapy while hematologic disorder obtained a further complete response.

Introduction

Sweet syndrome (SS), or acute febrile neutrophilic dermatosis [1], is a rare inflammatory condition characterised by painful cutaneous nodules and neutrophilic infiltrate in the dermis, in the absence of vasculitis. SS is a potentially disabling disease, significantly associated with malignancies (15-20% of cases). Among these, hematologic neoplasms, particularly acute myeloid leukaemia (AML) and myelodysplastic syndromes are the most commonly reported [2][3].

Herein we describe a case of a lady who had a refractory form of SS, resulted in a paraneoplastic cutaneous disease, and AML. Surprisingly, clinical remission of SS followed cytotoxic chemotherapy while hematologic disorder obtained a further complete response.

Case report

A 72 – year - old woman was admitted in 2015 because of several erythematous lesions on the dorsal surfaces of both the lower extremities. They were initially suspicious for pyoderma gangrenosum,

so she was treated with oral prednisone and gentamicin ointment topically, with partial response. Six months later similar lesions recurred at the same anatomical sites, now presenting as erythematous, painful, popular and nodular skin lesions, showing pustule sporadically on the top (Fig 1a, 1b). The patient was afebrile, with slight leucocytosis, Erythrocyte Sedimentation Rate >20mm/hour and positive CRP protein. Anamnestic personal data were positive for COPD and Charcot Marie-Tooth disease, whereas a family history of leukaemia was referred. A skin biopsy was performed, showing a dense neutrophilic dermal infiltrate without vascular aspects of leukocytoclasia; the morphological findings covered the highest number of criteria for the diagnosis of acute neutrophilic dermatosis (Figs 1c, 1d, 1e 1f).

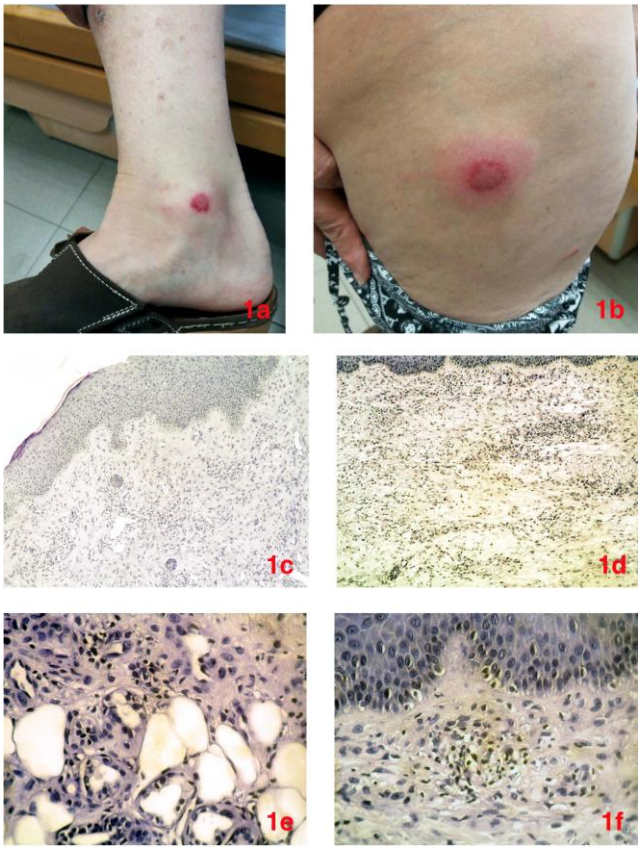

Figure 1: Nodular skin lesions localised at legs (a) and thighs (b). Incisional biopsy revealed normal epidermis and dense inflammatory infiltrate in the dermis (c), mainly composed of lymphocytes and histiocytes (d) [Haematoxylin and eosin stain, x40]. The infiltration extended to the subcutaneous adipose tissue (e), showing a pale neutrophilic background (f) [Haematoxylin and eosin stain, x100]

In the meanwhile, she was commenced on oral prednisone (0.75 mg/kg for five days and gradual tapering of the dosage) achieving only temporary relief of signs and symptoms with recurrence of manifestations. A hematologic consultation was also obtained together with blood exams: anemia [RBC at 2,600,000 mmc (n.r. 4,200,000-5,400,000), HGB at 89 g/L (n.r. 120 - 160), thrombocytopenia [PLT at 42,000 (n.r. 130,000-260,000)] and the presence of blasts, prompted a bone marrow examination that revealed 43% of blasts and multilineage dysplasia. A diagnosis of acute myelogenous leukaemia was made, cytogenetics also supporting the diagnosis through the evidence of deletion of 5q [- 5/del (5q)]. Gene mutations in fms - related tyrosine kinase - 3 (FLT3) gene [*FLT3* - internal tandem duplication] were also found.

Supportive care for cytopenia was established, using erythropoietin, red blood cells transfusions with iron chelation therapy and platelet transfusions.

Treatment with cytarabine (200 mg daily for seven days) plus epirubicin (75 mg daily for three days) was started. Methylprednisolone 40 mg/day intravenously was also prescribed and tapered over two weeks. Supportive antibiotics, including vancomycin and meropenem, were added during the hospital stay.

Cytostatic therapy was well tolerated without serious adverse effect, except for neutropenia, which required occasional dose reduction. After the first cycle, a complete remission of cutaneous manifestations of SS happened, with the improvement of blood values and marrow histology after three cycles. The patient is also undergoing the fourth cycle of treatment with further hematologic improvement and no new skin lesions.

Discussion

Sweet's syndrome, or acute febrile neutrophilic dermatosis, is an uncommon, severe cutaneous condition, characterized by the abrupt development of painful, tender, erythematous plaques, fever greater than 38°C, and a nodular perivascular neutrophilic dermal infiltrate without evidence of vasculitis on histologic examination [1][3].

Although frequently idiopathic, similarly to other diseases in this 'reactive' setting4, SS may develop in association with other systemic disorders or in the presence of identifiable triggers, including underlying autoimmune disorders, pregnancy, antecedent vaccination, drug assumption, inflammatory bowel disease, or infections [5][6].

The so-called 'malignancy-associated Sweet's syndrome' accounts for 15-20% of total cases of SS, and occurs in the association, or as a consequence, with both haematological and visceral malignancies [2].

In this setting, AML constitutes the most reported in clinical practice [2][7].

In fact, SS could present as a paraneoplastic cutaneous manifestation or as a drug-induced SS due

to medications commonly used in the treatment of AML [8].

The aberrant production of both pro-inflammatory cytokines (IL - 6, TNF - alpha) and signalling molecules, that has been demonstrated in AML and SS, may affect neutrophil function, finally contributing to the dermal clumping of the mature neutrophils [7][9].

According to with literature, SS is relatively rare in general population whereas it occurs in about 1% of patients with AML [6].

It also occurs more commonly in females and at various stages, including pre-diagnosis, at diagnosis, at the commencement of therapy, during remission and with relapse [7][10], thus representing such as a "marker" of AML disease activity.

Dealing with the data by Kazmi et al., [7], about 33% of patients receive the diagnoses of SS and AML at the same time, whereas another third of them during treatment of relapsed disease, and 29% during primary induction of chemotherapy. About diagnostic criteria, anaemia and thrombocytopenia are present in almost all patients, with fever being reported only in two-thirds of cases, as well as neutrophilia and elevated erythrocyte sedimentation rate. Clinical manifestations were classically multifocal, diffuse and asymmetrical. Cytogenetic characterisation revealed mainly changes in chromosome 5 (38% of cases) [7].

Glucocorticoids, either topical or systemic, together with antibiotics and wound care, represent the mainstays of SS therapy [11].

Although they showed to be highly efficacious, some recalcitrant cases may significantly benefit from the treatment of the underlying AML, and of infections, through the restoration of normal granulocyte function.

Our case was consistent with the above-mentioned characteristics. Initial cutaneous manifestations were probably underestimated, because of not typical features of the lesions, and the diagnosis of leukaemia might be obscured by steroid administration.

Anyway, although rare and sometimes difficult to be discovered because of the wide spectrum of differential diagnoses, when SS is established, the physician should keep a high index of suspicion to search underlying malignancies. In the same way, sign and symptoms of SS have to be searched for the diagnosis of AML.

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Case Report

Idiopathic Scrotal Calcinosis – A Case Report

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Keywords: Scrotum; Idiopathic calcinosis; Scrotal cysts; Surgery; Histopathology

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Abstract

Idiopathic scrotal calcinosis is a rare disorder presenting with firm and painless nodules on the scrotal skin. The most common site is the frontal aspect of the scrotum whereas the dorsal aspect with the transition to the perineum is rarely involved. Surgery is the gold standard of treatment.

Introduction

Inguinoscrotal disorders can be chronic disorders or emergencies like testicular trauma or torsions [1].

Table 1: Scrotal cysts and tumours

Entity	Remarks
Epidermal Cyst	Stratified lining epithelium, filled with keratin and debris May occur in Gardner syndrome Can lead to secondary calcinosis Cancerization is very rare
Cutaneous ciliated cyst	Rare benign lesion, very rare in males Female predominance (here on the legs)
Steatocystoma multiplex	Uncommon benign tumours of the pilosebaceous unit Stratified squamous epithelium without granular layer Filled with sebum Mutations in KRT17 gene
Eruptive vellus hair cyst	Stratified squamous epithelium with granular layer Multiple vellus hair shafts inside
Pilomatricoma	Rarely on scrotal skin Firm nodules, mostly single tumours Islands of epithelial cells composed of ghost cells in the centre surrounded by basaloid cells
Idiopathic scrotal calcinosis	No epithelial lining

Scrotal nodules and cysts are rare findings. If they are asymptomatic, the diagnostic delay may be for several years or even decades. Table 1 provides an overview of scrotal cysts and tumours [2].

We report on a rare case of extensive idiopathic scrotal calcinosis treated surgically.

Case report

A 46-year-old male patient presented with asymptomatic nodules of the scrotal skin for diagnosis and treatment. He reported the slow development of multiple lesions within the last ten years. He was otherwise healthy and did not have any medications or allergies.

On examination, we observed more than 30

firm subcutaneous cysts of variable size attached to the scrotal skin. On palpation, they were firm but painless. Their size varied form 3 mm to 4 cm (Fig. 1). Inguinal lymph nodes were impalpable. We performed surgical excision in general anaesthesia.

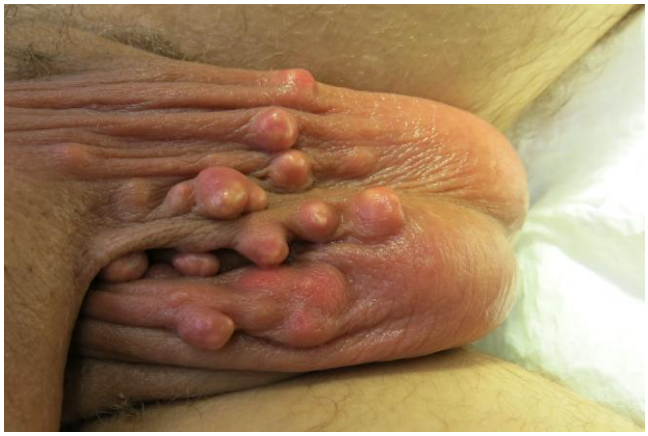

Figure 1: Multiple scrotal tumours – idiopathic scrotal calcinosis of the anterior aspect of the scrotum

The tumours were subjected to histopathological examination. On examination, pseudocystic formations with a fibrotic tissue around calcium deposits of variable size could be seen. There was no epithelial lining (Fig 2).

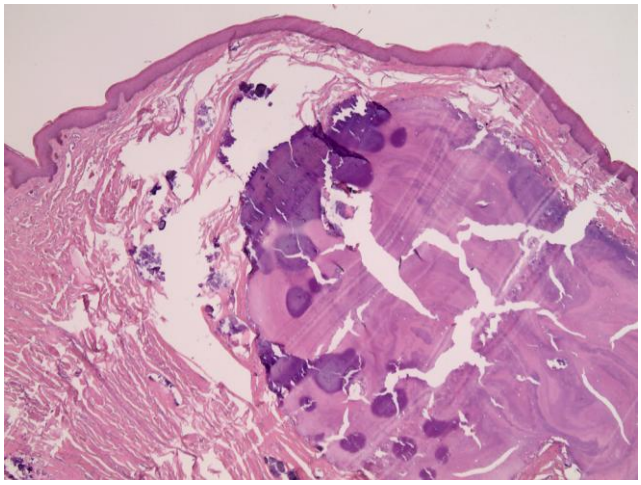

Figure 2: Histopathology of idiopathic scrotal calcinosis with coarse calcifications (hematoxylin-eosin x 10)

Healing was unremarkable. The patient was discharged on the second day after surgery.

Discussion

Firm nodules of the scrotal skin are rare. They can arise from pre-existing cysts like sebaceous cysts or steatocystoma multiplex or develop de novo. The latter is designated idiopathic scrotal calcinosis. The major difference to calcified cysts is the complete absence of a lining epithelium [3]. Surgery is the treatment of choice.

The senior author of this paper (UW) noted during his decades of experience in clinical dermatology that idiopathic calcinosis and scrotal cysts are mainly localised an the anterior aspect of scrotal skin. Scrotal skin is a product of cloacal membrane ectoderm forming the labioscrotal folds [4].

There are some differential diagnoses to idiopathic scrotal calcinosis (Table 1). Multiple epidermal cysts of the scrotum [5][6][7], sebaceous cysts [8], steatocystoma multiplex [9]. Larger cysts need surgery; smaller ones can be subjected to laser therapy with either carbon dioxide or diode laser [10][11][12]. A linear nick with a radiofrequency electrode works well in enucleating the cysts intact as long as they are not melded together with the surrounding tissue [12].

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Case Report

Para - And Intraurethral Penile Tumor - Like Condylomatosis

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Keywords: HPV associated lesions, surgery, lasers, therapeutic approach, paraurethral location

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Abstract

Condyloma acuminata represents an epidermal manifestation, associated with the epidermotropic human papillomavirus (HPV). They have been reported as the most common sexually transmitted disease, with prevalence exceeding 50%, increased up to 4 times, within the last two decades, as the most common side of affection are the penis, vulva, vagina, cervix, perineum, and perianal area, with increased prevalence in young, sexually active individuals. Increased attention should be focused on lesions, caused by types, with moderate (33, 35, 39, 40, 43, 45, 51-56, 58) or high risk potential (types 16, 18) for malignant transformation, leading to further development of cancers of anus, vagina, vulva and penis, as well as cancers of the head and neck . A provident of coexistence of many of these types in the same patient could be seen in approximately 10-15% of patients, as the lack of adequate information on the oncogenic potential of many other types complicated the treatment and the further outcome. Although the variety of treatment options, genital condylomata acuminata still show high recurrent rate to destructive topical regiments, because of the activation of the viruses at some point, which emphasise the importance of virus- eradication, instead only of the topical destruction of the lesions. Despite decreasing the recurrent rate, the most important goal of immunisation is the reduction of the incidence of HPV-associated squamous cell carcinomas using either the quadrivalent (Silgard/Gardasil) or the bivalent (Cervarix) HPV (human papillomavirus) vaccine. We present a patient with periurethral condylomata acuminate, who refused performing of a biopsy for determining the virus type, as we want to emphasize the importance of the virus - treatment in all cases of genital warts, instead only of topical destruction of the lesions, not only because of the recurrence incidence rate, but also because of the well - known oncogenic potential of some HPV - types, as well as the unknown potential of various underestimated types, in contrast.

Introduction

Condyloma acuminata represents an epidermal manifestation, associated with the epidermotropic human papillomavirus (HPV) [1]. HPV is most often acquired via sexual transmission in sexually active individuals, vertical transmission or extragenital contact in younger patients, rarely in children [2]. They have been reported as the most common sexually transmitted disease, with prevalence exceeding 50%, increased up to 4 times, within the last two decades [2]. The most common site affected are the penis, vulva, vagina, cervix, perineum, and perianal area, with increased prevalence in young, sexually active individuals [1][[2]. Uncommon, but also reported sides of invasion are oropharynx, larynx, and trachea [2]. Up to 90% of the genital warts are related to HPV 6 and 11 types, with no neoplastic potential [2]. Increased attention should be focused on lesions, caused by types, with moderate (33, 35, 39, 40, 43, 45, 51-56, 58) or high risk potential (types 16, 18) for malignant transformation, leading to further development of cancers of anus, vagina, vulva and penis, as well as cancers of the head and neck [1][3]. A provident of

coexistence of many of these types in the same patient could be seen in approximately 10-15% of patients, as the lack of adequate information on the oncogenic potential of many other types complicated the treatment and the further outcome [3].

Case Report

A 26-year-old Caucasian, otherwise healthy male patient presented with 6 - months history of papillomatous lesions, affecting his glans penis and orificium urethrae was reported. No accompanying diseases, neither medication was reported. Patient-reported brave heterosexual behaviour and promiscuity. The papillomatous lesion was observed within the clinical examination, located on gland penis, exclusively affecting the paraurethral area, measuring approximately 3 cm in diameter (Fig. 1).

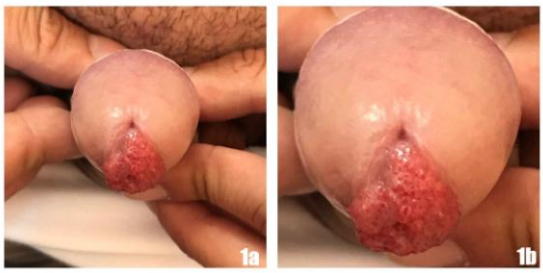

Figure 1: a, b Papillomatous lesion, located on gland penis, affecting orificium urethrae in a 26-year-old male patient

HPV - DNA testing with PCR for high-risk HPV viruses was not performed, because of the patient's refusal for biopsy. Paraclinical examinations did not reveal any abnormalities. HIV, HBsAg, anti - HBC and TPHA test were negative. The diagnosis of condylomata acuminata was made.

Topical treatment with imiquimod 5% was initiated. Subsequent laser therapy with pulsed dye laser was planned for a total resolution of the symptoms if such was not achieved with topical treatment. A vaccination with anti - HPV vaccine was also planned for the later stage for prevention of further relapses.

Discussion

Conventional treatment options for condylomata acuminata vary between chemical (podophyllotoxin) and physical destruction methods, which are painful and less effective, with high recurrence rates [1]. Intraurethral fluorouracil and lidocaine instillation have also been reported with a variable degree of effectiveness [1]. The use of immunotherapies is preferred recently, including topical application of imiquimod 5% cream, cimetidine and intralesional or systemic interferon [4].

Laser therapy has also been applied with satisfactory therapeutic response in otherwise resistant or recurrent lesions [4]. Application of a Pulsed dye laser-therapy is reported as a safe, effective, satisfactory and less traumatic compared to other options for treatment of genital warts [4]. Ultrasonic surgical aspiration, electrocautery fulguration and cryosurgery have been also used successfully [1][4].

Although various treatment options, genital condylomata acuminata still show high recurrent rate to topical destructive treatment options, because of the activation of the viruses at some point, which emphasize the importance of virus- eradication, instead only of the topical destruction of the lesions [3]. Despite decreasing the recurrent rate, the most important goal of immunization is the reduction of the incidence of HPV-associated squamous cell carcinomas using either the quadrivalent (Silgard/Gardasil) or the bivalent (Cervarix) HPV (human papillomavirus) vaccine [3].

We present a patient with periurethral and intraurethral condylomata acuminate, which refused performing of a biopsy for determining the virus type, as we want to emphasize the important of the virus-treatment in all cases of genital warts, instead only of topical destruction of the lesions, not only because of the recurrence incidence, but also because of the well-known oncogenic potential of some HPV-types, but also the unknown potential of various underestimated types, in contrast.

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Case Report

Giant Pendulous Carcinosarcoma – Squamous Cell Carcinoma-Type - of the Leg – A Case Report and Review of the Literature

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Keywords: Non-melanoma skin cancer; Cutaneous carcinosarcoma; Leg; Histopathology; Surgery

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Abstract

Cutaneous carcinosarcoma (CCS) is a rare non-melanoma skin cancer with a biphasic growth pattern. A tumour is composed of epithelial and mesenchymal cells that show clonality. In most cases, CCS develops in the head-and-neck region on the chronic sun-exposed skin of males. Here, we describe an 80-year-old female patient who developed a giant, pendulous CCS on the leg. A tumour was surgically removed. We found no evidence of metastatic spread.

Introduction

Cutaneous carcinosarcoma (CCS) also known as sarcomatoid carcinoma is a rare non-melanoma skin cancer occurring mainly on sun-exposed skin of elderly males. The tumour is biphasic, i.e. composed of epithelial and mesenchymal elements. Various subtypes have been described such as a basal cell, pilomatrical, squamous cell, and trichoblastic [1][2].

The neoplastic cells show coexpression of keratins and vimentin – in particular, the spindle cells. Also, coexpression of p53, p16 and p63 has been reported in epithelial and spindle cells [3]. CCS display multiple copy number variations (CNVs) and copy-neutral loss of heterozygosity (CN-LOH). Furthermore, epithelial and spindle cells share the same clonality [4][5].

Here we report a case of CSS – squamous cell type – of the leg.

Case report

An 80-year-old female patient was referred to our department. The primary reason for hospital admission was an edematous swelling of the right leg and slight increase of fibrinogen to 4.96 g/L (normal range: 1.8-4.5). Duplex sonography revealed a 3-storey deep venous thrombosis of the right leg. Since the bandages had to be removed for diagnostics, a giant exophytic, pendulous, malodorous tumour became apparent. Therefore, she was referred to our department.

Her medical history was remarkable for breast cancer 1995, renal cell carcinoma 2015, and chronic lymphatic leukaemia. She suffered from type II diabetes mellitus and arterial hypertension. She had secondary lymphedema of the arm after axillar dissection 1995.

On examination, we observed a 9 cm x 7 cm large, partially ulcerated, pendulous tumour on her upper right leg (Fig. 1).

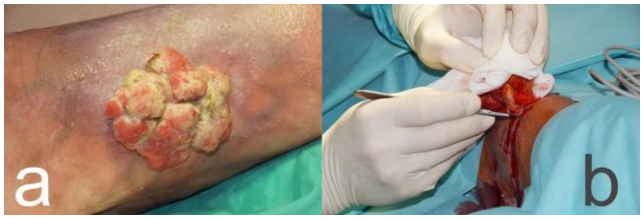

Figure 1: Clinical presentation of cutaneous carcinosarcoma of the leg (a). During surgery, the pendulous growth is apparent (b)

Laboratory findings: Leucocytes 11.71 Gpt/L (normal range: 3.8-11), erythrocytes 3.86 Tpt/L (4.2-5.4), hypochromic erythrocytes 14.6% (< 2.5%), microcytic erythrocytes 2.4% (< 1.5%), hemoglobin 6.4 mmol/L (7.4-10.7), hematocrit 0.336 (0.37-0.47), C-reactive protein 69.6 mg/L (< 5).

Imaging techniques did not reveal any metastatic spread.

Treatment was surgically excised with wide excision (2 cm safety margin) and primary closure by tissue expansion. Healing was uneventful.

Histopathologic examination of the specimen was performed. Histological examination showed a polypoid ulcerated tumour with structures of squamous cell carcinoma associated with the overlying epidermis, and beneath structures of a malignant spindle cell component in parts seeming one component transit into the other. The interlacing cords of epithelial cells extended from the epidermis and the ulcerated tumour surface to the intermediate dermis (Fig. 2a). Some of the deeper situated cords developed bulbar formations resembling glandular structures (Fig. 2b). However, ductal formations were completely missing.

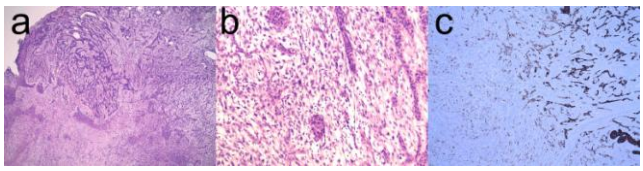

Figure 2: Histopathology of cutaneous carcinosarcoma (sarcomatoid carcinoma) of skin. (a) Overview, demonstrating the transition between epithelial and mesenchymal cells (Hematoxylin-eosin - HE x 20). (b) Detail (HE x 100). (c) Expression of CK5/6 (Immunoperoxidase x 40)

In both cellular components, immunohisto-chemistry demonstrated expression of cytokeratins (CK 5/6 and PanCK). In particular, in the spindle cell component, there was coexpression with vimentin, which was interpreted as clues to sarcomatoid dedifferentiated squamous cell carcinoma (CCS) (Fig. 2).

The patient also received low-molecular-weight heparin certoparin–sodium 8,000 U subcutaneously per day to treat the deep vein thrombosis.

Discussion

CCS is a rare tumour entity initially described by Dawson in 1972 [6]. We report a case of squamous cell type CCS on the leg of an elderly woman. The localisation on the leg is a rarely reported clinical feature since most of these tumours develop on the chronic sun-damaged skin of the head and neck region [1][2][3].

We could identify only three case reports with CCS of the leg – one in a 32-year-old female with a burn scar [7], another case of a 52-year-old female with a very rare myofibroblastic sarcomatous variant [8], and a last one of a 54-year-old male [9].

In the present case, we observed an ulcerated malodorous tumour that raised several differential diagnoses in a patient with multiple neoplastic disorders, including metastasis of breast or renal cancer, SCC, Merkel cell carcinoma, amelanotic melanoma, osteosarcoma, and rhabdomyosarcoma [10][11][12][13]. By histologic examination, a CCS of squamous cell subtype could be confirmed.

Cutaneous SCC can be associated with reactive fibroblastic proliferation. These spindle cells, however, do not co-express vimentin and keratin as seen in our case (Fig. 2c). In SCC epithelial-mesenchymal transition (EMT) is required for tumour invasion and dissemination. This is accompanied by overexpression of transcriptional factors Twist and ZEB1 [14].

Basosquamous carcinoma, also known as metatypical basal cell carcinoma (BCC), is a rare subtype of BCC. It occurs in two subtypes – mixed and intermediary. The mixed type shows focal keratinisation with a parakeratotic centre. The intermediary type is characterised by a network of narrow strands composed of an outer row of dark-staining basaloid cells and an inner layer of larger cells appearing lighter. Some of these tumours may express smooth muscle actin or myosin [15].

Cutaneous adenosquamous carcinoma is extremely rare neoplasia composed of malignant squamous and glandular cells without co-expression of keratin and vimentin. Luminal cells express cytokeratin 7. All tumour cells express cytokeratin 5/6

and p63. Cutaneous adenosquamous carcinoma is considered as a locally aggressive high-risk subtype of SCC [16].

BCC with ductal and glandular differentiation is very uncommon. The preferred tumour localisation is the eyelids. The glandular structures demonstrate an apocrine differentiation [17]. In contrast to our case, no co-expression of keratin and vimentin was reported. The present tumour had some glandular-like bulbar formations but no ductal parts.

The tumour was ulcerated, and ulcerated CCS of the hand had been described previously [18].

Our patient presented initially because of leg swelling caused by deep vein thrombosis. Tumors can alter the clotting system by various events including circulating tumour cells. Both ovarian and uterine carcinosarcoma-induced deep venous thrombosis have been reported [19][20].

The treatment of choice is surgery. Despite R0-resection, in one study, 27% of cases developed metastatic disease [21]. Negative prognostic factors are histologic subtype, age, tumour size > 2 cm, and nodal status. Patients with basal or squamous cell carcinoma-type CCS have a mean age of 72 years with clear male dominance. The 5-year disease-free survival is 70%. In contrast, adnexal CCS occurs in younger patients (mean age 58 years) and those have only a 25% 5-year disease-free survival [22].

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Case Report

Another Case of Interdigital Located "Metastasing Hematoma"?

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Keywords: Melanoma; Hematoma; Dermatoscopy; Misdiagnosis; Sentinel lymph node

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Abstract

Interdigital spaces could be an area of affection of a various cutaneous conditions, most of them with benign origin. The spectrum of differential diagnosis of pigmented interdigital lesions with a recent occurrence is not so wide, in contrast. When considering pigmented lesions in the interdigital area, the most harmless differential diagnosis is a traumatic hematoma. But what would happen if we based our therapeutic behaviour or suspicious and unconfirmed harmless diagnosis, instead of considering the real life-threatening once with priority, if we kept in mind that acral lentiginous melanoma has rather an aggressive course and is the main cause of death in skin cancer patients? We present a case of misdiagnosed interdigital melanoma, treated as a hemangioma with curettage, with almost fatal consequences, in regard to uncontrolled tumor progression as a result of the wrong traumatic procedure in one hand, and the lack of adequate screening and follow up, leading to progress of the disease with lymph node metastasis and poor prognosis in general. We want to emphasise the importance of acral lentiginous melanoma with an unusual location in the differential diagnostic plan because, despite the early detection, early eradication with simple excision could save a life, or at least could provide a better prognosis.

Introduction

Interdigital spaces could be an area of affection of a various cutaneous conditions, most of them with the benign origin, including tinea, eczema, pyogenic granuloma, interdigital neuroma, scabies eruption, etc. [1]. Fungal infections are the most commonly among them in elderly, within the spectrum of dermatological diseases [2].

They are usually presented with maceration and desquamation of the plantar surface of the foot, with or without nail involvement and rarely pigmented [2]. The spectrum of differential diagnosis of pigmented interdigital lesions with a recent occurrence is not so wide, in contrast. When considering pigmented lesions in the interdigital area, the most harmless differential diagnosis is a traumatic hematoma [1][3].

But what would happen if we based our therapeutic behaviour or suspicious and unconfirmed harmless diagnosis, instead of considering the real life-threatening once with priority, if we kept in mind that acral lentiginous melanoma has rather an aggressive course and is the main cause of death in skin cancer patients [3]?

Case report

A 58-year-old, otherwise healthy male patient, presented to the dermatologic clinic, because of a dark lesion on his right foot. The patient has noticed the pigmentation five months ago and went to another clinic for diagnosis and treatment. The lesion was diagnosed several times as hematoma and had been treated initially with curettage, according to patient's history. Four months later, the lesion occurred again and rapidly increased in size. Malaise and loss of appetite were reported as additional subjective complaints. A dark brawn with black uneven coloured irregularly bordered pigmented macule was observed within the clinical examination, affecting the first interdigital space of the right foot and the surrounding skin on the plantar surface of the foot.The lesion was partially ulcerated, covered with yellow crusts and macerated surface right between the great and second toe (Fig. 1a). The conducted paraclinical examination did not reveal significant abnormalities in the total blood count and biochemistry. Ultrasound examination did not detect abdominal organ involvement but enlarged unilateral inguinal lymph nodes. Packages of enlarged lymph nodes were observed in the right inguinal fold, one measuring 19/8mm and two additional (measuring 10/10 mm) with the ultrasonographic characteristic of metastasis. The patient was referred for surgical treatment. The cutaneous lesion was removed by surgical excision under local anaesthesia, with 0.5 cm field of safety margins in all direction (Fig. 1b, c).

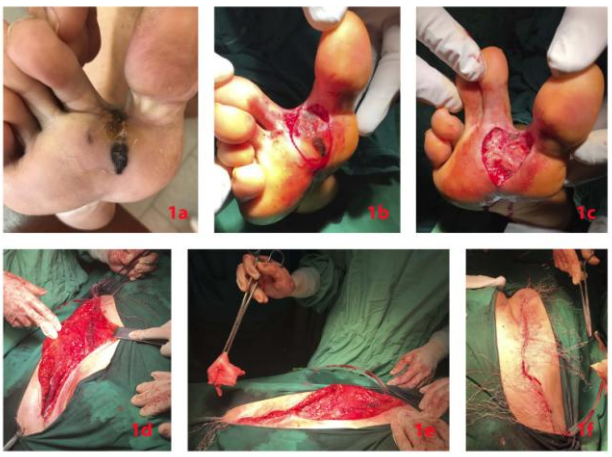

Figure 1: a – Clinical manifestation of interdigital acral lentiginous melanoma, four months after curettage for hematoma; b, c – Intraoperative findings. Surgical excision of the interdigital melanoma, under local anaesthesia; d, e, f – Intraoperative findings of the lymph node dissection. Dark coloured packages of enlarged lymph nodes with a firm texture, measuring 2,5 cm were established intraoperatively. Enlarged lymph nodes were observed in the obturator whole, with the same characteristic. A lymph node was found in the pelvis immediately adjacent to the v. iliaca external, infiltrated the vein wall. A partial resection of the vein was performed, as the same was reconstructed with a single stitch

Lymph node dissection was also performed under general anaesthesia, and retroperitoneal entrance toward the iliac and femoral vessels (Fig. 1d. e). Dark coloured packages of enlarged lymph nodes with a firm texture, measuring 2.5 cm were established intraoperatively. Enlarged lymph nodes were observed in the obturator whole, with the same characteristic. A lymph node was found in the pelvis immediately adjacent to the v. iliaca external, infiltrated the vein wall. A partial resection of the vein was performed, as the same was reconstructed with a single stitch on Karel. Radical lymph dissection was performed in a femoral, obturator and paraphiliac area (Fig. 1f).

Histological examination of the cutaneous lesion revealed moderately atypical cells with vesiculous nuclei, suspicious for melanoma, with tumour thickness 2 mm (Breslow).

Histological examination of the dissected lymph nodes verified total and non-total metastasis from melanoma, some with capsular infiltration, some of them without.

Postsurgical period underwent without complications, as the patient was referred for a PET - Scan in 2 months. In case of negative results for an active metastatic process, a strictly follow up would be recommended. In contrast, in case of a positive result for an active metastatic process, a BRAF testing of metastasis will be performed, considering further BRAF and MEK inhibitors as a therapeutic behaviour in case of subsequent received.

Discussion

Although melanoma is one of the most distributed tumours among the white-skinned population, tumours located on unusual sides are detected early less frequently, which decreased the favourable of the prognosis in these patients [4]. Furthermore, as a subtype of acral lentiginous melanoma, interdigital melanoma, is relatively uncommon in the Caucasian population, in contrast to Asians and Africans, and therefore, it is frequently unrecognised for a prolonged period of time, as a result from its asymptomatic nature and often atypical clinical manifestation [5]. The prognosis for patients' survival depends on the stage of disease, but tends to be worse than with other subtypes of melanoma [6]. The often misdiagnosis and delay in diagnosis are statistically associated with a poor prognosis and relatively low survival rate, partly as a result from the advanced stage in which the tumor is usually diagnosed [4, 7]. Even histopathologically, the very early signs of acral melanoma are difficult to identify [7]. Dermoscopic criteria are also no always capable to detect early acral lentiginous melanoma, and usually caused confusion in considering further

adequate therapeutic managements [8].

We present a case of misdiagnosed interdigital melanoma, treated two times as a hemangioma with curettage, with almost fatal consequences, in regard to uncontrolled tumor progression as a result from the wrong traumatic procedure in one hand, and the lack of adequate screening and follow up, leading to progress of the disease with lymph node metastasis and poor prognosis in general.

We want to emphasise the importance of acral lentiginous melanoma with an unusual location in the differential diagnostic plan, because, despite the early detection, early eradication with simple excision could save a life, or at least could provide a better prognosis.

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Case Report

Psoriasiform Dermatophytosis in a Bulgarian Child

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Keywords: Dermatophytosis; Terbinafine; Psoriasiform pattern, Misdiagnosis; Kogoj

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Abstract

Although tinea capitis is the most common fungal infection in children, significant changes have been reported in its epidemiology worldwide, as a result from certain geographic, climatic and cultural differences in one hand, as well as the changes in its etiologic pattern. The clinical manifestation of the infection and the stage of inflammation vary from mild desquamation to severe suppurative indurated plaques in kerion - like pattern, depending on the nature of the etiologic agent and the host-immune response. We report a case of tinea capitis profunda, caused by Trichophyton verrucosum in a 5 – year - old male patient, presented as a severe scalp and cutaneous desquamation, resembling histopathologically psoriasis, associated with severely indurated ringworm plaque in the temporal area. The performed histological examination revealed a psoriasiform pattern, without the typical Munro abscesses or Kogoj pustules. With the presented case, we want to emphasize the importance of the host's immune reaction to zoophilic dermatophytes, such as Trichophyton verrucosum, resulting in severe and often atypical clinical manifestation, as well as the possible "Id reaction", to avoid or minimise misdiagnosis and delayed therapy. The presented patient was treated with topical oleum acidy salicylic 10% and Terbinafine 125 mg daily with significant resolution of the complaints within the following two months.

Introduction

Although tinea capitis is the most common fungal infection in children, significant changes have been reported in its epidemiology worldwide, as a result from certain geographic, climatic and cultural differences in one hand, as well as the changes in its etiologic pattern [1]. All of the three genera dermatophytes can cost the infection – Epidermophyton, Trichophyton and Microsporum [2]. Most important among them are still Microsporum Canis, Trichophyton verrucosum et. mentagrophytes [1]. The clinical manifestation of the infection and the stage of inflammation vary from mild desquamation to severe suppurative indurated plaques in kerion - like pattern, depending on the nature of the etiologic agent in one hand, as well as the host's immune response in other [1]. Furthermore, new etiological agents have been implicated in the aetiology of the disease, mostly associated with atypical clinical manifestation in indigent patients [2].

Case Report

A 5 – year - old male patient presented with a 6 - months history of desquamation of the scalp. Initially, the symptoms had been poorly presented, as

a mild dandruff-like eruption, but gradually became more pronounced. One month ago, a well-demarcated erythematous lesion occurred at the left temporal area of the scalp, while the hairs gradually fall in the affected area. Subjective, the condition was accompanied by mild itching. No family history, nor comorbidities, neither medication were reported. Clinical examination revealed erythematous and edemas plaque, without hairs, with severe induration and inflammation, located on the left temporal area of the scalp, while severe desquamation was observed, covering the whole scalp surface and the left cheek (Fig. 1).

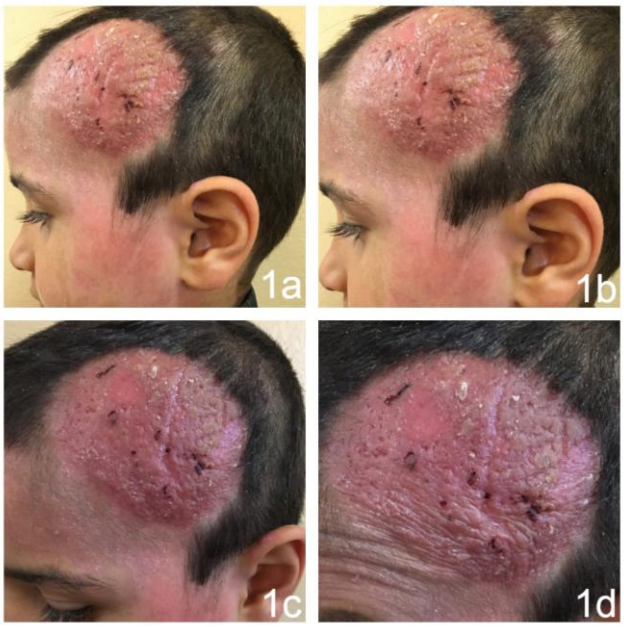

Figure 1: a, b - Clinical manifestation of tinea capitis profunda in a 5 - year - old patient; c, d - Closer view of the tinea capitis profunda and scalp desquamation, resembling psoriasis

Histopathological examination after performed scalp biopsy revealed a psoriasiform pattern, while the mycological examination of scales on Sabouraud agar, established growth of Trichophyton verrucosum. The diagnosis of tinea capitis profunda was made. Patient was treated with topical application of oleum acid salicylic 10% and systemic administration of Terbinafine 125 mg daily with significant resolution of the complaints within the following 2 months.

Discussion

It is well known that zoophilic dermatophytes usually cause more severe inflammation, with Kerion Celsii pattern, due to the delayed type of allergic immune reaction and further releasing of Th2 cytokines from mononuclear leukocytes, and increased serum levels of IgE and IgG4 [3]. The immune response in severe infiltrative cases, caused by zoophilic dermatophytes, as Trichophyton verrucosum, could be so strong in healthy individuals that it could lead not only to the so called “Bruno Block phenomenon”, which represents a further resistance to fungal infection with the same localization, but also to severe, deep infiltration and suppuration, which is otherwise unusual in non-immune-suppressed patients [4]. Despite this, the clinical manifestation in such severe cases could lead to diagnostic challenges and therapeutic delay.

Other atypical manifestation of tinea capitis, with widespread eruption could be a result from the so called “Id reaction” [5]. It is clinically presented as disseminated symmetrical cutaneous eruption, either follicular, or psoriasiform, typically in response to a scalp ringworm of Kerion-type, caused by Trichophyton verrucosum, as in the presented case [5]. In such cases, mycological examination of body scales is negative as a rule, while the condition is incorrectly interpreted as psoriasis, associated with tinea capitis profunda [5].

We report a case of tinea capitis profunda, caused by Trichophyton verrucosum in a 5-year-old male patient, presented as a severe scalp and cutaneous desquamation, resembling psoriasis, associated with severely indurated ringworm plaque in the temporal area. The performed histological examination revealed psoriasiform pattern, without the typical Munro abscesses or Kogoj pustules in the histological slides.

With the presented case, we want to emphasize the importance of the host’s immune reaction to zoophilic dermatophytes, such as Trichophyton verrucosum, resulting in a severe and often atypical clinical manifestation, as well as the possibility of the “Id reaction”, in order to avoid or minimize misdiagnosis and delays in therapy.

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Case Report

A Patient with Multiple Keratinocytic Cancers (MKC): Uncommon Presentation in a Bulgarian Patient

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Keywords: skin cancer; surgery; island flap; basal cell carcinoma; squamous cell carcinoma

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Abstract

Keratinocyte skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common cancer occurring in people with fair skin, worldwide. Despite all known triggers, several suggested contributors are still investigated. We will focus our attention on the personal history of previous cancers and radiation exposure as occupational risk factors, as in the presented case. We report a patient, with multiple BCCs, and subsequent occurrence of a SCC on photo-exposed area of the face, as we want to emphasize the importance of strict following up of these patients, regarding the risk for developing new tumors in short periods of time, no matter if the triggering exposure factor is known from the history, or not. Although keratinocytes tumours are associated with the low mortality rate, we focus the attention on the fact, that the history of non-melanoma skin cancer is associated with increased mortality.

Introduction

Keratinocyte skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common cancer occurring in people with fair skin, worldwide [1]. The highest incidence has been reported in Australia, because of the higher cumulative UV-exposure, with higher prevalence among man after 60 years of age, with the higher domination of BCC, than SCC [1][2]. Exposure to UV radiation is the primary triggering factor for malignant transformation in both-melanoma and non-melanoma cancers, although the pattern of exposure that gives rise to different types of tumours appears to vary [2]. Other risk factors, playing role in the cancer genesis of these kinds of tumors include: patient's phenotype (light-coloured skin, eyes and hair), personal and family history of skin cancer, exposure to ionizing radiation, arsenic, and certain petroleum products, previous PUVA therapy, xeroderma pigmentosum, Basal cell nevus syndrome, immunosuppression and variety of precancerous skin conditions [3]. Most of the cases are the result of the

simultaneous contribution of many risk factors [3]. While UV-exposure from the sun is the most important risk factor for all skin cancer, the risk of basal cell and squamous cell skin cancers also increases with age [1]. Despite the morbidity, the gender distribution also depends on age. BCC develops in people under the age of 52, more commonly in women than men, while after 52, BCC is more common in men [2]. Squamous cell carcinoma is considered to occur equally in both men and women up to the age of 47, while after the age of 47, SCC becomes more common in men [1][2].

Despite all known triggers, several suggested contributors are still investigated. We will focus our attention on the personal history of previous cancers and radiation exposure as occupational risk factors, as in the presented case.

Case report

An 83-year-old, fade-skin, blue-eyed Caucasian male patient was admitted for a second time in the clinic for dermatologic surgery, with a medical history of multiple non-melanoma skin cancers in the past couple of years. The occasion of the certain hospitalisation was a recently occurred tumour formation, located on his left infratemporal area. Clinical examination revealed a nodular formation, with the ulcerated surface, covered with yellowish crusts and raised pearl-like edges, affecting the skin of the left preauricular, infratemporal area (Fig. 1a).

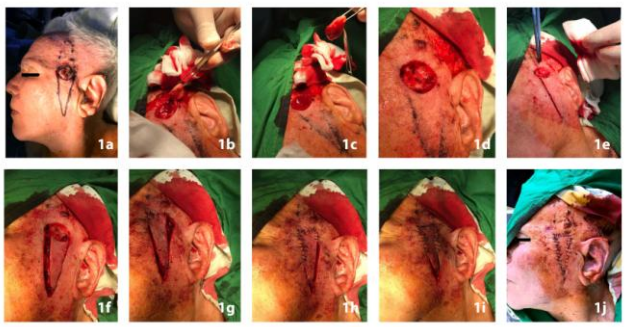

Figure 1: a - Clinical manifestation of a tumour, prior the surgical excision; b, c, d, e - Intraoperative finding. Oval shaped excision of a tumour with the preparation of the island flap; f - Postoperative findings. The surgical wound is closed with single stitches

Arterial hypertension, diabetes type II and prostate hyperplasia were reported as comorbidities, controlled with medications. Dermatologic history was positive for previous keratinocyte tumours, including eight basal cell carcinomas, excited within the first hospitalisation in the clinic, and four more BCCs, excited previously. Occupational history was positive for risk factors, as the patient had been working as a welder, in radiation conditions with X - rays. The conducted screening panel, including laboratory blood tests, lung X-ray and abdominal ultrasonography did not reveal any significant abnormalities or organ involvement. The patient was referred for surgical treatment with island flap under local anaesthesia. The tissue, surrounding the tumour was resected by deep oval excision, toward the underlying muscle (Figs. 1 b, c, d). Two additional excisions were performed, forming a triangle (Fig. 1 e, f, g, h). The proximal and distal part of the flap was gently dissected in depth, for easier further transposition. The proximal part of the flap was slightly cut and transported proximately, with adaptation to the edges of the primary cutaneous defect (Fig. 1 e, f, g, h). Stepwise adjustment of the cutaneous island to the newly created bed was performed next, as the blood supply and innervation of the transported area were preserved (Fig. 1 e, f, g, h, i, j). The postsurgical period underwent without complications. Histopathological examination of the resected tumour verified the diagnosis of SCC (Fig. 2 a, b, c, d).

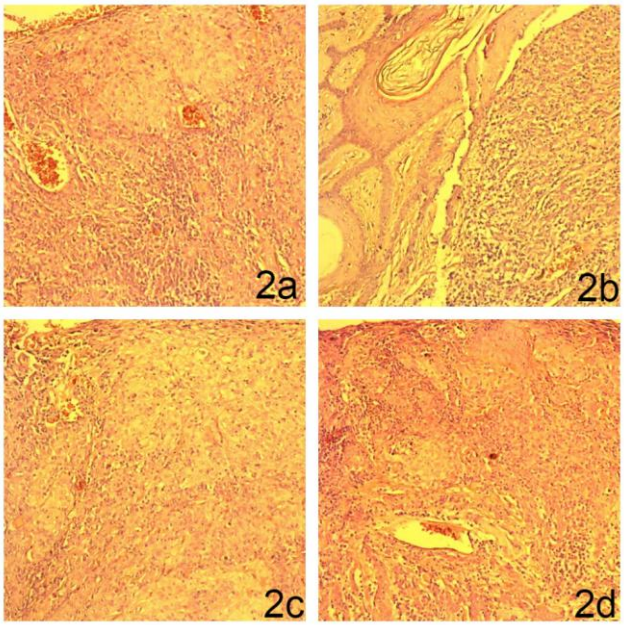

Figure 2: Histopathological findings, confirming the diagnosis of SCC (H&Ex100): a - Aggregates of atypical epithelial cells invading the dermis. The nonspecific inflammatory infiltrates with lymphocytes and plasma cells; b - Lobules and nests of atypical, acantholytic keratinocytes. Premature cornification with free-floating neoplastic keratinocytes. Cellular aggregates with vascular appearance; c, d - Aggregates of atypical epithelial cells invading the dermis. The nonspecific inflammatory infiltrates with lymphocytes and plasma cells. Erythrocytes contained in pseudovascular spaces. Moderate mitotic activity. Premature cornification

Discussion

Multiple keratinocyte tumors may occur in the framework of inherited conditions, such as Gorlin-Goltz syndrome (caused by a mutation in a tumor-suppressor gene, known as the patched 1 gene

(*PTCH1*) and xeroderma pigmentosum, as well as a result from several hereditary syndromes that are associated with increased risk for development of BCCs, including Bazax - Dupre - Christol syndrome, Rombo syndrome, multiple hereditary infundibulocystic BCCs syndrome, basaloid hematoma etc. [4]. On the other hand, many immune-related conditions are also associated with increased keratinocyte carcinoma risk [5]. While usually most of the mentioned conditions are caused by certain mutations and have been associated with additional abnormalities, in the genesis of an-syndromic multiple keratinocyte tumours should be based on the environmental factors predominantly, mainly the UV exposure and personal history [6]. And if the cumulative dosage of UV radiation leads to DNA damage in all individuals, it is certainly unclear whether multiple keratinocyte tumours could appear in all individuals, exposed to same triggering factors, as radiation for example.

But it is well - known that the 3 - year cumulative risk for developing a BCC is 44% higher with at least a 10 - fold increase in the incidence compared with the rate in a comparable general population, while the cumulative risk of a subsequent SCC after a primary SCC is 18%, or at least a 10 - fold increase in incidence compared with the incidence of first tumors in a comparable general population [6]. Furthermore, the established risk of developing BCC in a patient with previous SCC is almost equal to the same in a patient with a primary BCC, for developing a new BCC, but it is lower for subsequent development of SCC in a patient with primary BCC [6].

Varies treatment options have been implicated in non-melanoma skin cancers, including surgical and non - surgical technique's [8]. The choice of treatment approach depends on several factors, including 1) the location of the lesion; 2) the type of a tumour; 3) the patient's age and comorbidities [8]. Surgical management may involve standard elliptic surgical excision of a primary tumour and Mohs micrographic surgery [8][9]. Although other possible modalities include locally destructive methods, such as cryotherapy, curettage, electro cautery and radiation, it is established that surgical management is the preferred one [9]. When dealing with face - located lesions, the defect closing and further reconstruction for the best aesthetic result could be challenging. Despite the primary closure, skin grafting, and local and free flaps are used in providing best cosmetic results and optimal defect closing [9]. Local flaps, including rotational techniques, Limberg flap, island flaps and V - Y advancement flaps, are usually performed in small and medium-size defects, depending on defects' shape and surgeon preferences, while skin grafting is recommended in larger surgical wounds [9].

In the presented case, we report a patient, with multiple BCCs in the past, and subsequent occurrence of a SCC on photo-exposed area of the face, as we want to emphasize the importance of strict following up of these patients, regarding the risk for developing new tumors in short periods of time, no matter if the triggering exposure factor is known from the history, or not. Although keratinocytes tumours are associated with low fertility rate, we focus the attention on the fact, that the history of non-melanoma skin cancer is associated with increased mortality, as the high prevalence of these tumours elevates the importance of the possibility of associated subsequent mortality from other causes also [7]. Early detection is an essential part of the therapeutic process, while surgical excision is the most appropriate treatment choice.

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Case Report

Diffuse Normolipemic Plane Xanthoma (DNPX) of the Neck without Xanthelasma Palpebrum

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Keywords: Diffuse normolipemic plane xanthoma; Non-Langerhans histiocytosis; Histology; Treatment; Xanthelasma palpebrarum

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Abstract

Diffuse normolipemic plane xanthoma (DNPX) is an uncommon subtype of non-Langerhans histiocytosis. DNPX is characterised by xanthelasma palpebrarum, diffuse plane xanthoma of the head, neck, trunk, or extremities, and normal plasma lipid levels. The neck is the most common site. We report about a 62-year-old female Caucasian patient, who developed an asymptomatic fine wrinkling and loose skin on the neck and décolleté about three years ago. The skin colour became yellowish. Xanthelasma was absent. Histopathology of a skin biopsy confirmed the diagnosis of DNPX. The patient had a medical history of chronic myeloblastic leukaemia. No other laboratory abnormalities were found. Laser treatment was offered but opposed by the patient.

Introduction

Diffuse normolipemic plane xanthoma (DNPX) was first described by Altman and Winkelmann in 1962 [1]. It is now considered as an uncommon subtype of non - Langerhans histiocytosis [2].

DNPX is characterized by xanthelasma palpebrarum, diffuse plane xanthoma of the head, neck, trunk, or extremities, and normal plasma lipid levels. The neck is the most common site [1][3]. Xanthelasma palpebrarum usually appears first [1].

The clinical presentation is characterised by the presence of symmetric, asymptomatic, yellowish-orange plaques [1][2]. Oral lesions are extremely rare [3].

In histology, foam cells (macrophages), and variable numbers of Touton giant cells, lymphocytes, and foamy histiocytes are present; sometimes only foam cells can be seen [4][5].

DNPX has been associated with systemic diseases, particularly multiple myeloma and monoclonal gammopathy [4][5][6]. In other cases, malignant haematological or lymphoproliferative disorders have been observed [7][8].

Case report

A 62-year-old female Caucasian patient developed an asymptomatic fine wrinkling and loose skin on the neck and décolleté about three years ago.

The skin colour became yellowish (Fig. 1).

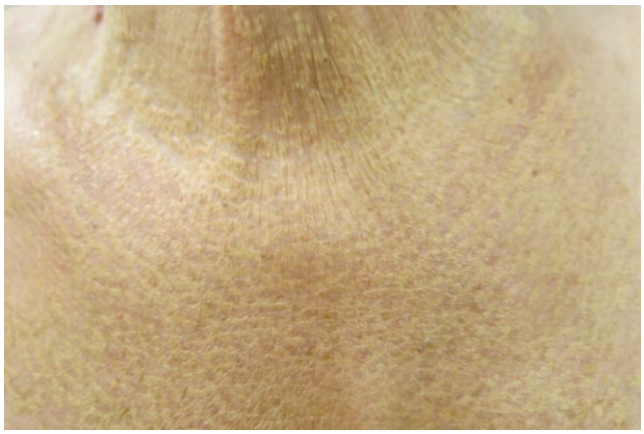

Figure 1: Diffuse plane yellowish plaques on neck and décolleté

No other body areas were involved. Her medical history was remarkable for chronic myeloblastic leukaemia without chemotherapy. She did not take any medical drugs. The family history was negative for skin diseases. Laboratory investigations of metabolic abnormalities remained unremarkable. A skin biopsy revealed an atrophic epidermis and a massive infiltration of the upper and mid-dermis by CD68 positive macrophages including foam cells. Here, elastic fibres were somewhat reduced. No calcifications were noted (Fig. 2).

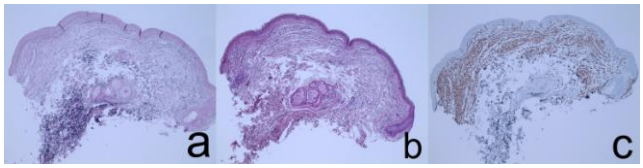

Figure 2: Histopathology of diffuse normolipemic plane xanthoma (x 4). (a) Elastica stain, (b) hematoxylin-eosin, and (c) immunoperoxidase for CD68

The diagnosis of DNPX was confirmed. Ablative laser therapy was mentioned, but treatment was not warranted.

Discussion

DNXP is part of the Langerhans cell histiocytes-spectrum [9]. No standardised treatment is available yet. However, cladribine (2-chlorodeoxyadenosine) is a candidate drug since it is particularly metabolised, phosphorylated and concentrated in lymphocytes, macrophages/ histocytes and Langerhans cells. The active compound is 2-chloroadenosine triphosphate. Cladribine has been used successfully in Langerhans cell histiocytosis of different types including plane xanthoma [10]. There are case reports on regression of DNPX during treatment (of associated disorders) with cyclosporine A [11] or bexarotene [12]. DNPX can be treated by ablative lasers such as erbium-YAG laser [13][14].

DNXP itself does not cause significant health problems although it can be esthetically annoying. Of greater importance is the fact, that DNXP has been observed in association with monoclonal gammopathy, monoclonal gammopathy of unknown significance (MGUS) and plasmacytoma [4][5][6][7][8][14][15][16]. In our case, chronic myeloblastic leukaemia was evident. Under this view, DNXP may have a marker function for unknown myeloproliferative disorders and dermatologists should be familiar with this uncommon entity.

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Case Report

Locally Advanced Basal Cell Carcinoma with Intraocular Invasion

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Abstract

We present a 103 - year - old patient, with duration of complaints of about ten years. The initial complaint had been presented as a small nodule, located on the eyebrow, which subsequently ulcerated and encompassed larger regions of the upper and lower eyelids. For the past three years, the patient also had complaints of a worsening of his vision, without seeking for medical help. Within the dermatological examination, an intraocular and periocular localised tumour was established, characterised by a raised peripheral edge and central ulceration. More careful examination revealed that the bulb was fully consumed. The patient refused further diagnosis and treatment. Advanced basal cell carcinomas with intraocular invasion are rare in general. If the patient refuses surgery, radiotherapy and systemic therapy with modern medications such as Vismodegib or Sonidegib are available as treatment options.

Introduction

Basal cell tumours can be easily treated in their early stages [1]. However, with the larger tumour growth, the more extensive treatment is needed [1]. Some special locations (eyelids, nose flap, lips, auricle) pose a challenge for the surgeon to remove the tumour entirely with proper margins and to retain functionality and satisfactory aesthetic appearance at the same time [1]. Furthermore, large, neglected tumours, especially located in the face region, demand complex reconstructive procedures after excision, i.e. local reconstruction techniques, free grafts, advanced, island, pedicle or microvascular flaps [1].

Case Report

A 103 - year - old male patient, a peasant from the Bulgarian mountain region, presented with a reddish facial lesion. The reported complaints were from the last ten years. The lesion had occurred as a small papule on the medial part of the right eyebrow, followed by gradual enlargement and ulceration on a later stage, leading to complete loss of the upper eyelid (Fig. 1 a, b). The diagnosis of multicentric basal cell carcinoma (BCC) was made clinically and histopathologically. Any treatment was denied.

Neglected patients are one of the major

contributing factors for the development of mutilating, horrifying and aggressive BCC - a rare, but potentially fatal cutaneous tumour [1]. Basal cell carcinoma occurs in the area of the head in 85 - 90% of cases, often above the line connecting the mouth corner with the ear lobe [2]. They are less often found in the lower part of the face and on the scalp [1].

Figure 1: A) 103-year-old male patient with oozing and crusted periocular lesion; B) Detail with loss of lids and eye

Discussion

In 10 - 15% of the cases, BCC is found on the neck, trunk and limbs. The affected area is commonly closely related to the exposure to ultraviolet radiation [3]. Although BCC could be rarely metastatic, it has a potential for tremendous and life - threating regional destruction in some locations, leading to severe disfigurations as in the presented case [1][2].

Two systemic treatments options that target the hedgehog pathway have become available recently for patients with advanced BCC: sonidegib (Odomzo; Novartis) and vismodegib (Erivedge; Roche). Based on results from a noncomparative study (the 200 mg arm of the BOLT trial) [3], sonidegib was approved recently in the United States and European Union for the treatment of adults with locally advanced BCC (laBCC) who are ineligible for curative surgery or radiotherapy [4][5]. Similarly, vismodegib is indicated for the treatment of adults with symptomatic metastatic BCC or adults with laBCC who are ineligible for surgery or radiotherapy, approved based on a single-arm trial (ERIVANCE) [6][7].

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Case Report

Seborrheic Pemphigus, Antigen Mimicry and the Subsequent-Wrong Diagnostic and Therapeutic Approach?

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Abstract

It is well-established that drugs could be leading cause of occurrence of numerous diseases, including pemphigus, being either inducer or triggering factor of the autoimmunity. Despite medications, it should be kept in mind that chronic or acute infections are also capable of being a trigger in various types of cutaneous eruptions, including pemphigus. The rapidly obtained and uncompleted history for accompanied medication leads to general mistakes in the subsequent treatment approach, as the first step in such cases is discontinuation of the drug-inductor. The absence of this information guaranties the fail of the treatment. On the other hand, the lack of performed screening for chronic or acute hepatitis and tuberculosis is not the only mistake, regarding the high dosage of immunosuppressors that have been planned as regiment and the possible fatal effect on the infection's spread or exacerbation, but also because of the possible triggering ability of chronic or acute infection, which may play also a key role in the generation of antigen- or molecular- mimicry, as a potential source of antibodies reactive with various tissue antigens. It turns out that although the diagnosis of pemphigus in regular cases is usually not a challenge, the treatment occasionally could be, just because of a simple pitfall in anamnesis and screening, as in the presented case. Herein, we present a case of a patient with seborrheic pemphigus, which is strongly demonstrative for these statements, as we want to emphasise the importance of the first and the most powerful clinician's weapons – the patient's history and thorough examination.

Introduction

Pemphigus is a part from the large group of autoimmune bullous diseases with variable clinical manifestation, but common histological and immunofluorescence characteristics, causing blisters and erosions both on the skin and mucous membranes, as a result from autoimmunity to desmosomal cadherins [1]. Pemphigus is divided into two groups, based on the level of acantholysis in the epidermis - pemphigus vulgaris (histologically presented with suprabasal acantholysis) and superficial pemphigus [1][2]. The superficial acantholysis could be seen in pemphigus foliaceus and its milder subtype - pemphigus seborrheicus (PS), which is limited only to seborrheic areas [3]. The other superficial variant is pemphigus erythematosus, also known as Senear - Usher syndrome, which is characterized by immunologic markers both for pemphigus foliaceus and lupus erythematosus, but uncommon mucous membrane involvement [2][3].

Although both genetic and exogenous, stress-related factors have been implicated in the

etiopathogenesis of pemphigus in general; antigenic triggering is not yet fully understood [4]. However, it is well-established that drugs could be leading cause of occurrence of the disease, being either inducer or triggering factor [4]. The thorough medical history for accompanying medication is an essential prerequisite for the successful clinical management of pemphigus of any type, as the lack of improvement is often related to simply pit falls in anamnesis, which is unacceptable at the current stage of scientific knowledge. Despite medications, it should be kept in mind that chronic or acute infections are also capable of being a trigger in various types of cutaneous eruptions, including pemphigus [5].

Herein, we present a case, which is strongly demonstrative for these statements, as we want to emphasise the importance of the first and one of the most powerful clinician's weapons - the patient's history, as well as the mandatory screening for infections, prior the introduction of high dosage immunosuppressors.

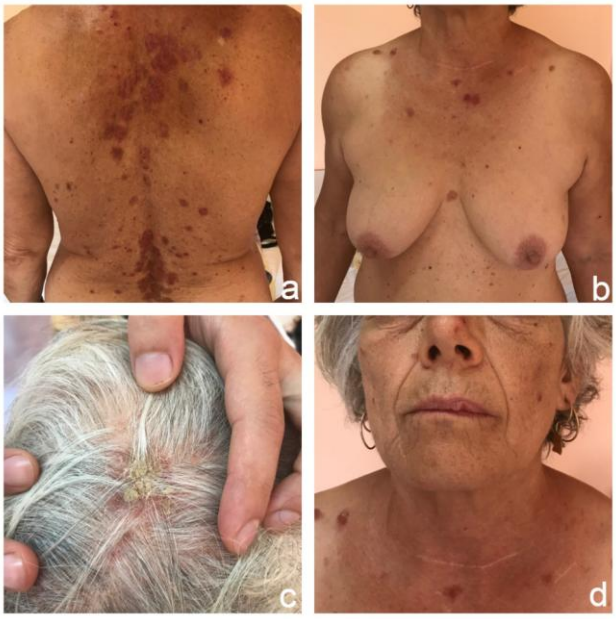

Figure 1: a, b, c, d - Clinical manifestation of a drug-induced pemphigus seborrhoicus, a year after the initial diagnosis

Case report

A 67 - year - old Caucasian female patient presented with one - year history of spontaneous occurrence of painful erosions on the skin and nasal mucosa. The patient had been diagnosed with seborrheic pemphigus. Seven months prior the current hospitalisation, histologically and immunofluorescently verified and treated in another University dermatological department. The presented medical history reported systemic administration of methylprednisolone x 40 mg i.m/daily, azathioprine 50 mg – 2 x 1 table/daily for one month. The current hospitalisation in a medical institute of MVR - Sofia, Department of Dermatology, Venereology and Dermatologic surgery, was because of the lack of any improvement of the conducted treatment and occurrence of new cutaneous lesions in contrast. The clinical examination revealed multiple blisters and erosions, partially covered with yellow - brownish crusts, disseminated on the seborrheic areas on the sun-exposed zone of the décolletage, presternal, interscapular and paravertebral spaces (Fig.1 a, b). Same lesions were observed on the scalp, while superficial erosions were affected the nasal mucosa and paranasal skin (Fig. 1 c, d). The thorough medical history revealed systemic administration of captopril 25 mg, because of mild arterial hypertension with long-lasting duration. The whole serological screening for HBsAg, Anti Hbs, HIV and quantiferon tests was performed. The revealed titer of antinuclear antibodies (ANA) was 1:100, anti HCV - negative, HIV - negative, quantiferon test - negative, but the anti HBcore total test - positive.

The patient was referred for evaluation of virus load in peripheral blood, to differentiate between chronic and acute infection, as a possible trigger for antigen/ molecular mimicry, which would require adequate therapy, as no such examinations, not therapy had been introduced to that point. The rest of the results from the conducted laboratory blood tests were within the normal range. The histological examination after biopsy demonstrated pseudoepitheliomatous, hyper- and parakeratosis in the epidermis with mononuclear perivascular infiltration in the dermis. The immunofluorescent examination confirmed the diagnosis pemphigus, with intercellular deposition of IgG and C3 in the epidermis. Diagnose of drug-induced seborrheic pemphigus was made, based on the clinical and laboratory findings. The administration of captopril was switched to valsartan 80 mg.

Systemic administration of methylpred-nisolone in a daily dose of 1mg/kg with subsequent reduction and azathioprine 2x50 mg daily was planned as a therapeutic regiment, in case of obtaining negative results from the virus load. Meanwhile, the patient was treated with topical application of clobetasone proprionate 0.05% and oral antihistamines.

Discussion

Since the first reported case of drug-induced pemphigus by penicillamine in 1969 [6], and captopril in 1980 [7], numerous types of drugs have been

implicated in the etiopathogenesis of pemphigus, either as triggers, or exacerbates of the disease, including phenytoin and carbamazepine [4, 8]. Wolf R. et al. suggest back in 1991 that clinical course and behavior of the disease depends mainly on the type of the drug, as the authors first report pemphigus-induced by drugs containing a sulfhydryl radical (as penicillamine) showed spontaneous recovery in up to 52.6%, after the drug discontinuation, in contrast to only 15% spontaneous recovery in pemphigus-induced by other drugs [6]. Since then, it is known that drugs with sulfhydryl radicals induce pemphigus, while drugs without sulfhydryl radicals trigger the occurrence of the disease in predisposed individuals, as the mechanism of drug-induced pemphigus is related mainly to drug's potential to induce acantholysis [8][9].

Despite penicillamine, it is well-established that antihypertensive drugs, namely ACE - inhibitors can trigger pemphigus or induce exacerbation, resembling the mode of action of b - blockers in worsening of psoriasis, gold - provoking lichen ruber planus, estrogens - lupus, etc. [8]. The drug may act either as the main etiological factor for occurrences of otherwise mild and therapeutic responsible with drug discontinuation or as a triggering factor, resulting in idiopathic pemphigus, which is usually more therapeutic - resistant, even after discontinuation of the drug [10]. The investigated autoimmune response is similar in drug-related and non-drug induced disease; both showing have tissue - bound and serum autoantibodies to DSG1 and/or DSG3, suggesting a similar underlying molecular mechanism [11]. While the clinical and histological findings in ordinary pemphigus and the drug-induced one are quite similar and they do not allow such differentiation, the clinician should obtain a very thorough medical history, to avoid deterioration of the disease, in contrast to otherwise correct therapeutic behaviour [8]. However, despite the current state of scientific knowledge, and the lower incidence of drug-induced seborrheic pemphigus recently, inadequate diagnostic and therapeutic behavior could be still seen not only among hypertension specialists, but also among dermatologist, who are obviously not aware that severe pemphigus, which is therapeutically resistant and aggressive in its clinical behavior, may be caused by drugs or triggered by infections also [5][8].

Despite drugs, various bacterial, viral and parasitic agents can activate the T - or B - cellular immunity with subsequent autoimmune response to certain cutaneous tissues, in the framework of so-called Antigen Mimicry [5][12]. And while generation of antibodies in pemphigus subtypes could be as a response to different infectious antigens by antigen mimicry and subsequent epitope spreading, the screening for underlying bacterial or viral trigger and its subsequent elimination are as many essential preconditions for achieving of a clinical remission or satisfactory therapeutic response, as discontinuation of eventual drug - inductor [5, 12]. If both mechanisms could be implicated in the etiopathogenesis, the careful history and adequate screening for underlying infectious trigger should be the first step when dealing with pemphigus. Furthermore, it turns out that although the diagnosis of pemphigus in regular cases is usually not a challenge, the treatment occasionally could be, just because of simple pit falls in anamnesis, as in the presented case. The rapidly obtained and uncompleted history for accompanied medication leads to general mistakes in the subsequent treatment approach, as the first step in such cases is discontinuation of the drug-inductor. The absence of this information guaranties the fail of the treatment. On the other hand, the lack of performed screening for chronic or acute hepatitis and tuberculosis is not the only mistake, regarding the high dosage of immunosuppressors that have been planned as regiment and the possible fatal effect on their spread or exacerbation, but also because of the possible triggering ability of chronic or acute infection, which may play a key role in molecular mimicry, as a potential source of antibodies reactive with various tissue antigens [5]. Our patient achieved significant clinical resolution of the symptoms, soon after the discontinuation of the medication with captopril, a very simple step which can provide rapid and uncomplicated treatment and should be considered in earlier stages of the disease.

With the presented case, we want to emphasize the importance of thorough medical history, in which simply pit falls may vitiate the treatment outcome and prognosis, but also the mandatory need of performance of screening for acute and chronic infection, prior the introduction of high dosage systemic immunosuppressors, including quantiferon test for tuberculosis and hepatitis serology, as a potential source of antigen/molecular mimicry, which is capable to produce antigens, complicating the pathogenesis of otherwise drug-induced pemphigus of various type.

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Case Report

Peri - and Intraocular Mutilating Advanced Squamous Cell Carcinoma: "Monsters Inside Your Body"?

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Keywords: Periocular malignancies; Surgery; Mohs; Cetuximab; Endoxan

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Abstract

Periocular malignancies represent between 5% and 10% of all types of skin cancers. The incidence of eyelid (but also the periocular located) malignancies seems to differ in distribution across the continents. The incidence of eyelid tumours (but also the periocular located tumours) in a predominantly white population determined that BCC is the most common malignant periocular eyelid tumour in whites. This finding has been replicated consistently throughout the literature, with BCC representing 85–95% of all eyelid malignancies, SCC representing 3.4 - 12.6%, Seb Ca representing 0.6 - 10.2%, and both melanoma and Merkel cell carcinoma representing less than 1%. Most periocular skin cancers are associated with ultraviolet radiation (UVR) exposure. Ultraviolet radiation causes local immune suppression, which, coupled with DNA abnormalities in tumour suppressor genes and oncogenes, leads to the development of skin cancers. We are presenting a 62 - year - old patient with a small nodule about 2 cm away from the lower lid of his left eye. A tumour was surgically treated. Several years later there was a tumour relapse, treated with radiotherapy and subsequent chemotherapy with Endoxan and Cisplatin. After the second relapse, he was treated surgically in general anaesthesia by orbital exenteration, removal of the orbital floor and resection of zygomatic bone and the maxillary sinus. A couple of months later, he developed a tumour relapse in the scars and the area of a primary tumour with tumour progression. A possible therapy with Cetuximab or radiation therapy was discussed as a possible treatment option.

Introduction

Periocular SCC is a tumour with a possible unfavourable outcome, when not treated efficiently primarily. A recent study from Australia investigated the recurrence of SCC according to TNM classification. They observed a recurrence rate of 5.3% (12/226 patients) for primary tumors and 20% (5/25 patients) for recurrent tumors (P = 0.019). Recurrences also occurred in T1 tumours. Higher T stage was significantly associated with both perineural invasion and local recurrence [1].

Perineural invasion capacity of periocular SCC bears a significant risk of orbital involvement and the need subsequent orbital exenteration [2]. There is a great variety of reconstructive procedures, but orbital prothesis and simple split skin grafts may be helpful as well [3].

Adjuvant treatment with targeted tumour therapy is under investigation. Cetuximab has achieved a response rate of ≤ 47 %, erlotinib and gefitinib – to other epidermal growth factor tyrosine kinase inhibitors are under investigation in adjuvant and neoadjuvant settings [4][5][6].

Case presentation

A 62 - year - old male patient presented in 2009 with a small nodule about 2 cm away from the lower lid of his left eye. His medical history was positive for hypertension and unspecified hepatitis. The tumour was surgically removed elsewhere (Fig. 1 a, b).

Figure 1: a, b - Mutilating postoperative results and tumour relapse

It was a squamous cell carcinoma (SCC), but the resection was obviously not R0. There was a relapse, and the tumour developed rapidly until 2013. From 09.09.13 to 13.09.13 radiotherapy had been performed. In March 2014, he received a single course of systemic chemotherapy with endoxan and cisplatin because of a second relapse. Computerized tomography (CT) revealed extended osteolysis of left sinus maxillaries, nasal bone and orbital bone. The polypoid soft tissue process involved not only sinus maxillaries and overlying subcutaneous adipose tissue but ocular bulbus as well. Chemotherapy was stopped.

He was treated surgically in general anaesthesia by orbital exenteration, removal of the orbital floor and resection of zygomatic bone. The tumour resection included the maxillary sinus. The orbital defect was covered by temporal muscle. The soft tissue defect was closed by fronto-parietal rotational flap, buccal plasty, and a mesh graft obtained from his upper leg. A couple of months later, he developed a tumour relapse in the scars and the area of a primary tumour with tumour progress.

Discussion

The standard treatment for all eyelid carcinomas is surgical excision with negative margins, although controversy still exists regarding the recommended margins for each specific malignancy [7]. Mohs micrographic surgery has become the most common method of managing both BCC and SCC [8]. The benefits of this procedure lie in its capacity to determine margin control during excision and preserve the greatest amount of normal tissue [8]. This is especially significant in the eyelid and medial canthus, where large excisions can have devastating effects on the appearance and function of the eyelids [8]. Both frozen and permanent sectioning has been used for histologic assessment of surgical margins [8]. There does not seem to be a consensus in the literature regarding the preferred margin control technique for nonmelanoma malignancies [8].

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Case Report

Mucoepidermoid Carcinoma (MEC) of Parotid Gland with Massive Cutaneous Involvement: Bilateral Pedicle Advancement Flap (U - Plasty) As Adequate Surgical Approach

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Abstract

Neoplasms of the major and minor salivary glands are morphologically and a clinically diverse group of neoplasms which lead the clinician to diagnostic and management challenges. This article aims to report a case of mucoepidermoid carcinoma in 83 – year - old woman who presented in the dermatology clinic with a tumour mass in the left auricular area. The patient complained of pain and abnormal bleeding of the mass. The lesion was examined, and surgical treatment was performed. A tumour was extirpated, and partial resection of both the parotid gland and the sternocleidomastoid muscle was done. Lymphatic dissection was performed. Post recovery was uneventful with no functional defects and abnormalities. The pathohistological result confirmed the diagnosis of mucoepidermoid carcinoma of the parotid gland with massive infiltration of the skin and the subcutaneous tissue. Lymph nodules with total metastasis of mucoepidermoid carcinoma and capsular invasion were additionally presented. Postoperative radiation therapy was planned.

Introduction

Cancers of salivary glands are rare malignancies. They represent only 5% of all head and neck malignancies [1]. The most common cancer among salivary glands' tumours and especially the major salivary glands is the mucoepidermoid carcinoma of the parotid gland (75%) [2] Mucoepidermoid carcinoma is a malignant epithelial neoplasm [2]. It is composed of multiple cell types which include: epidermoid cells, mucous producing cells and intermediate type cells [3]. It presents with a prominent cystic growth. Based on its histology characteristics, including the cell types, cellular differentiation, growth and invasion, cytologic atypia, mucoepidermoid carcinoma are graded as low, intermediate or high grade [3]. It is more common in women than men and usually affects women in their fifth decade [4].

Also, it is thought that there is a clear predilection for white race [5]. Little is known about the

aetiology of mucoepidermoid carcinoma, but low-dose radiotherapy used for benign diseases as acne and obstructive lesions of the lymphoid tissue is probably involved in its pathogenesis [5].

Case report

We report a case of an 83 – year - old female patient with a painful and easily bleeding mass in the left auricular area present for one year. The lesion was examined preoperatively, and surgical management was planned. Patient history included: arterial hypertension. On physical examination: a firm five/ 5cm mass was palpated in the left auricular region. The mass was painful and easily bleeding by touch (Fig. 1a).

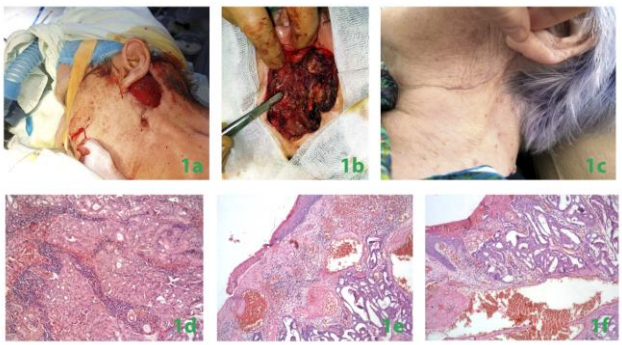

Figure 1: A - Preoperative aspect before the excision of the tumor; B - Intraoperative aspect after the excision of the tumor; C - Immediate post-operative result; D - Lobules of cells with abundant eosinophilic cytoplasm with one focus of keratinization (on the left) representing one area of squamous differentiation; multiple areas of ductal and glandular differentiation are also seen; E - Detail of the tumour in the the superficial reticular dermis in an area of glandular differentiation composed of multiple interconnected lumina lined by smaller cells with more scant cytoplasm than those seen in the squamous areas

No lymphadenopathy was clinically detected. The results of routine blood tests were within normal ranges. General anaesthesia was performed. After cleaning and disinfection of the surgical field, an incision was performed. The cutaneous incision was made preauricular near the mandibular border, and the tumour was surrounded by healthy tissue. Tumor extripation and partial resection of the parotid gland has been performed. After hemostasis, a platysma myocutaneous flap was made. The mandibular ramus of the facial nerve in the area of the posterior facial vein was reached and after that following the pathway of the mandibular nerve the main trunk of the facial nerve was reached (Fig 1b).

Once the main trunk of the facial nerve was exposed, the tumour mass was completely extirpated, and both the sternocleoidal muscle and the parotid gland were partially resected because of the massive tumour infiltration. The neoplasm was extirpated with reached negative surgical borders using the bilateral pedicle advancement flap. Two pathologically changed lymph nodules in the area of the digastricus muscle were removed. After partial removal of the superficial parotid gland and the tumour, the cut surface of the parotid remnant was sutured. Hemostasis was achieved. The subcutaneous tissue and the skin incision were closed. Closed suction drainage was maintained. A thin layer of gauze was placed on the wound. The sutures were removed ten days after the operation.

Discussion

Histologically, MEC is a tumour composed of three types of cells: epidermoid, mucous producing and intermediate cells [3][4][5]. Based on its histological findings it is classified as low, intermediate or a high-grade tumour [5]. Low grade and intermediate grade appear as well - demarcated with pushing margins, but in difference, the intermediate one more often presents with a perineural invasion [5].

High-grade tumours are being characterised by the infiltrative border, diverse of cell abnormalities as anaplasia, necrosis and atypical mitoses and invasion: perineural and angiolymphatic [5].

MEC of the parotid gland clinical manifestation includes very often asymptomatic swelling [5]. There is an average latency period which is one year or may vary widely [6].

All grade of MEC is treated with surgical resection as a definitive treatment [5][6][7][8][9]. A low and intermediate grade of tumours often undergoes primary surgical excision [5][6][7][8][9][10]. High-grade tumours treatment course includes surgical excision with wide margins followed by radiotherapy [5][6][7][8][9][10]. Neck dissection is necessary if there are local metastasis as in our case [5][6][7][8][9][10]. It is known that low-grade tumours behave with more benign nature and the high grade are highly aggressive [6][7]. Intermediate grade presents more like a low grade, but they should be treated as high grade because they demonstrate predilection to nodal metastasis like the high-grade tumours [6][7].

Prognosis depends on three main factors: clinical stage, histological grade and treatment [6]. Distant MEC metastases relate to a poor prognosis [3]. The survival rate for patients with distant metastases is 2.3 - 2.6 years [3].

The differential diagnoses spectrum is wide and includes necrotising sialometaplasia, mucocele, inverted papilloma or cystadenoma, cystadenocarcinoma, primary or metastatic epidermoid carcinoma, and low-grade polymorphic

adenocarcinoma [6].

It seems that genetic factors of MEC appear to do not have a prognostic meaning [3]. Many MEC's have been reported in cytogenetical analyses to have the t(11:19), (q21 p13.1) translocation [3]. Immunological factors like a high proliferating cell nuclear antigen score lead to a less surviving percentage of the patients [11].

Post-operative radiotherapy has been shown to have an advantage in the survival of patients with tumours larger than 4 cm, and it is not shown as it for patients with smaller tumours [5]. Post-operative radiotherapy is indicated in patients with tumours which are larger than 4 cm [5].

MEC is a challenge to the clinicians because of it its biological behaviour [7]. In our clinical case, we present one of its many different behaviours. As firstly, it was assumed as a cutaneous tumour involving the parotid gland, but it turned out to be the opposite like MEC of the parotid gland with massive infiltration in the skin of the head.

However, cutaneous metastases occur in 0.7 - 10 % of all patients with cancer [12]. ¼ of these percentages is for the skin of the head and neck [12]. Any malignant neoplasm could have potential to metastasize to the head and neck [12].

Patients who were treated with MEC should be followed up closely for life to prevent late recurrence [13]. The morphological manifestation of MEC has some similarities with clear cell bronchogenic squamous carcinoma [14]. The cell proliferation is important criteria for measuring the MEC aggressiveness [14].

In conclusion, mucoepidermoid carcinoma is the most common malignant tumour of the salivary glands. It is a challenge to the clinicians and especially for the dermatologists. According to the literature, it apperas to be a treatable disease.The prognosis is in a great relation on not only the tumor stage, but also the histological grade of the lesion.

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Case Report

Violet - Colored Inguinal Located Cutaneous Tumour?

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Keywords: B cell lymphoma; T cell lymphoma; anaplastic large; surgery; chemotherapy; systemic involvement

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Abstract

Anaplastic large cell lymphoma (ALCL) represents an aggressive CD30 – positive T cell lymphoma, as it is the second most common T cell lymphoma and 2% to 5% of all non - Hodgkin lymphomas. The cutaneous involvement can be primary or secondary within systemic ALCL, resembling inflammatory and other neoplastic lesions both clinically and cytologically. Various pigmented cutaneous tumours with a different origin, cutaneous metastasis and B-cell lymphoma must be carefully considered in the differential diagnostic plan. While simple surgical excision is usually curative, with good prognosis, systemic involvement must also be excluded. We present a case of a patient, with clinically unspecific single violet nodular lesion, as the only clinical manifestation of ALCL. The diagnosis was confirmed histologically, as the surgical excision was enough therapeutic management, regarding the early disease stage. Further following up with the patient is mandatory, because of the high recurrence rate. We want to emphasise the diversity of clinical manifestation of ALCL, regarding the importance of its early diagnosis and treatment.

Introduction

Anaplastic large cell lymphoma (ALCL) is the second most common T cell lymphoma and 2% to 5% of all non-Hodgkin lymphomas [1][2]. It represents an aggressive CD30 - positive T - cell lymphoma, with three subtypes, exhibiting a chromosomal translocation involving the ALK gene and the expression of ALK protein [3]. Although no current risk factors have been identified, some studies have shown an increased risk of incidence (up to 18 times) in association with breast implants for augmentation [3]. An increased risk of malignant T - cell lymphoma in patients with atopic dermatitis has also been reported [4]. The disease more often affects young and middle-aged adults, with mild male predominance and with rapid progression and generalisation [4]. The cutaneous involvement can be primary or secondary within systemic ALCL [2], resembling inflammatory and other neoplastic lesions both clinically and cytologically [1]. Although fine needle biopsy aspiration cytology is usually useful for the correct diagnosis, most of the cases present in advanced stages and usually have been excited regarding the wide spectrum of differential diagnosis [2][3].

Case Report

A 63 – year - old male patient presented to the department of dermatologic surgery, because of

an elevated violet tumor-like formation on the inner side of his right hip. The lesion occurred approximately 20 days ago, accompanied by occasional spontaneous bleeding and mild discomfort. The patient had been treated with topical antibiotics for almost ten days, without any therapeutic result. Neither family history, not comorbidities were reported.

Clinical examination revealed a nodular tumour-like formation with erythematous-violet discolouration, located on the medial side of the right hip (Fig. 1a). Enlarged lymph nodes were not detected on palpation. Laboratory blood tests were within the normal range. The patient was referred for surgical removal of the lesion. Elliptic surgical excision with 0.5 cm surgical margins was performed under local anaesthesia (Fig.1 b, c, d).

The histopathological examination of a fragment of the excited lesion revealed diffuse dermal infiltrate of atypical cells. The atypical cells were with prominent, centrally located nuclei. Simultaneously a mixed inflammatory infiltrates also detectable at the histology slides (Fig. 1 g, h, i). The findings were indicative of primary cutaneous anaplastic large T - cell lymphoma.

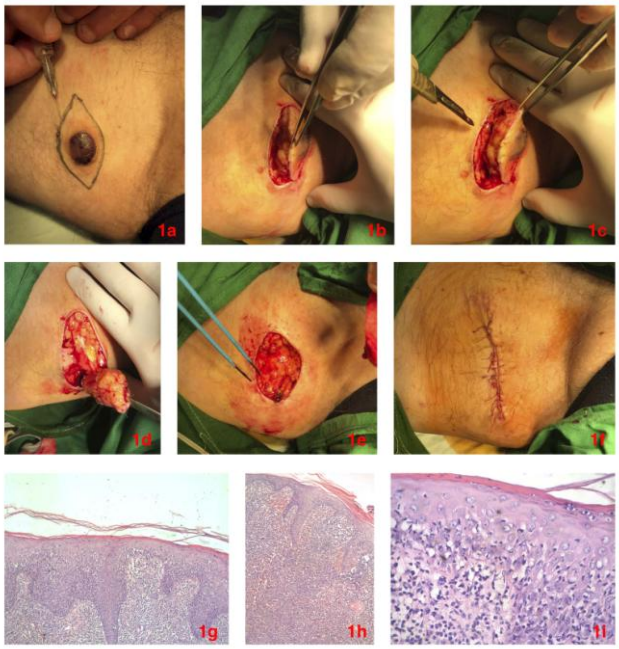

Figure 1: a – Clinical manifestation of a primary cutaneous anaplastic large cell lymphoma, presented as a single violet nodule in the medial aspect of the right hip; b, c, d, e, f – Intraoperative findings. Surgical excision of the lesion; g, h, f – Histological findings. Diffuse dermal infiltrate of atypical cells with prominent centrally located nuclei, with simultaneously presented mixed inflammatory infiltrate

The patient was referred for hospitalization in the haematology department for further screening for systemic involvement, which was not detected at this stage. Additional immunohistochemistry was planned for confirmation of the diagnosis, as well as spinal punction and serum flow cytometry.

Discussion

Primary cutaneous ALCL can be present clinically as single or multifocal nodules that ulcerate spontaneously, have autoregressive behavior and high rate of recurrence [5]. Regional lymph node invasion could be a sign for extracutaneous dissemination [5]. The diagnosis is confirmed by histological features such as diffuse, non-epidermotropic infiltrate, and anaplastic large lymphoid cells of immunohistochemistry CD30+, CD4+, EMA-/+, ALK-, CD15- and TIA1-/+. [5]. Surgical removal of the lesion, radiotherapy or low-dose methotrexate is reported treatment of choices [5].

In the presented case, a clinically unspecific single violet nodular lesion was the only clinical manifestation of ALCL. Diagnosis was confirmed histologically, and surgical excision was enough therapeutic management in regard to the early disease stage. Prognosis is good and does not depend on lymphatic invasion in general. Further following up of the patient is mandatory because of the high recurrence rate [1].

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Case Report

Disseminated Porokeratosis with Idiopathic Thrombocytopenia - Case Report and Literature Review of Porokeratosis and Related Disorders

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Keywords: Porokeratosis; Acitretin; Betamethasone; Outcome; Therapy; Cryosurgery

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Abstract

BACKGROUND: Porokeratosis is characterised by one or more atrophic patches surrounded by a distinctive peripheral keratotic ridge, typically found on sun-exposed areas, with several clinical variants and typical histological findings. Despite ultraviolet radiation, varies antibody - related autoimmune disease treated with systemic steroids and other immunosuppressive conditions such as chronic liver disease, HIV and organ transplantations have been implicated in its etiopathology.

CASE REPORT: We present a case of porokeratosis, associated with idiopathic thrombocytopenia in 74 - year old, otherwise healthy male patient, as we discuss the previously reported associated disorders.

CONCLUSION: Regarding all of the polymorphism of clinical presentation, associated disorders and treatment responses, we could conclude that disseminated porokeratosis is still an unknown well disorder, which will continue to surprise the physicians in future. The screening and follow up of the patients is mandatory in all cases because as we see, porokeratosis has multiple unexpected faces, which require circumstantial clinical and paraclinical behaviour.

Introduction

Porokeratosis represents a clonal disorder of keratinisation, first described in 1983 as a chronic parakeratotic skin disorder [1]. The condition is characterised by one or more atrophic patches, typically found on sun-exposed areas, surrounded by a distinctive peripheral keratotic ridge, called the cornoid lamella [1][2]. Several clinical variants have been described, as the most common among them include classic porokeratosis of Mibelli (PM), disseminated superficial actinic porokeratosis (DSAP) and its nonactinic variant disseminated superficial porokeratosis (DSP), linear porokeratosis, porokeratosis palmaris et plantaris disseminata (PPPD), punctate porokeratosis, which might represent a variant of PPPD [1][2][3].

Much less commonly reported clinical subtypes include porokeratosis ptychotropica (a verrucous variant localised in the gluteal region) [3], porokeratoma, also referred to as porokeratotic acanthoma [4], porokeratotic adnexal ostial nevus (PAON) - a rare congenital disorder of keratinization with eccrine and hair follicle involvement [5]. Although aetiology is not well - established, exposure to ultraviolet radiation, organ transplantation, chemotherapy, repetitive trauma, liver failure, chronic renal failure, hepatitis C, HIV, and other diseases associated with immunosuppression are considered risk factors which activate abnormal clones of keratinocytes [3]. Gene mutations in mevalonate

pathway enzymes have also been implicated in etiopathology, such as mevalonate kinase (MVK), phosphomevalonate kinase (PMVK), mevalonate decarboxylase (MVD), and farnesyl diphosphate synthase (FDPS), as c.746 T > C and c.875A > G of the MVD gene are most common mutations [1][6]. Beside the immunosuppression variety of disorders associated with the condition, disseminated superficial porokeratosis has been reported in systemic lupus erythematosus (SLE) patient with long-term corticosteroid treatment [7], patients with diabetes mellitus [8] and associated with haematological disorders such as Hodgkin's disease and B-cell lymphoma [9].

Here we present a patient with disseminated porokeratosis, associated with idiopathic thrombocytopenia. To the best of our knowledge, this is the first report of disseminated superficial porokeratosis, associated with idiopathic thrombocytopenia.

Case report

A 74 – year - old male patient presented with 2 - months history of erythematous rash on the lower legs, accompanied by itching. The clinical examination revealed multiple individual erythematous, slightly atrophic macules and papules, with brownish discolouration, surrounded by peripheral keratotic ridge, resembling cornoid lamella, disseminated on the chest, back and lower extremities (Fig. 1 a, b, c, d).

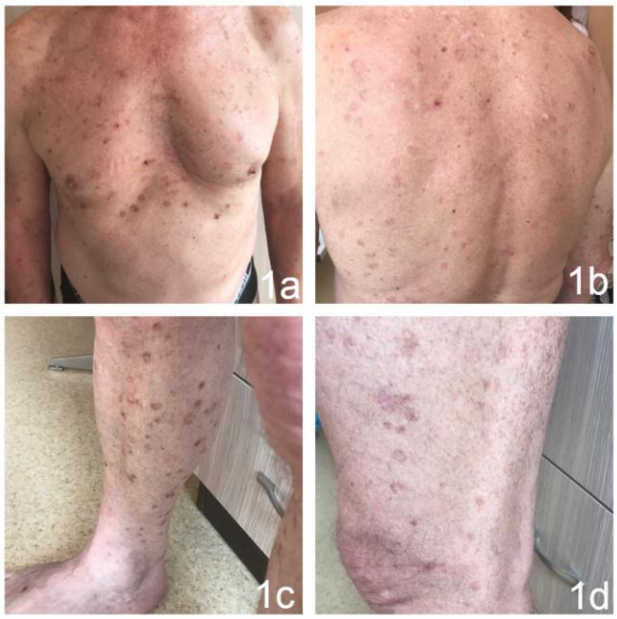

Figure 1: a, b – Clinical presentation of disseminated porokeratosis on chest and back in 74-year-old male patient; c, d – Clinical presentation of disseminated porokeratosis on lower legs, with closer view of cornoid lamella

Multiple excoriations and linear defects, from scratching, were also established. The conducted paraclinical blood examinations revealed decreased plated cells count (107.0 10^9/l) and increased cholesterol (8.4 mmol/l: HDL - 2.43, LDL - 5.33 mmol/l). The performed imaging diagnostic screening did not reveal organ pathologies. The histopathological examination after performed biopsies obtained focal absence of the granular layer, dyskeratotic cells observed in the subjacent upper spinous layer.

A mild lymphocytic infiltrate were seen around an increased number of capillaries in the underlying dermis.

Dermis showed a non-specific inflammatory cell infiltrate. Epithelium deep to the tier was vacuolated and devoid of a granular cell layer (Fig. 2 a, b). Dyskeratotic cells were observed in the subjacent upper spinous layer (Fig. 2 c). Keratin-filled epidermal invagination with an angulated, parakeratotic tier (cornoid lamella) (Fig. 2 d).

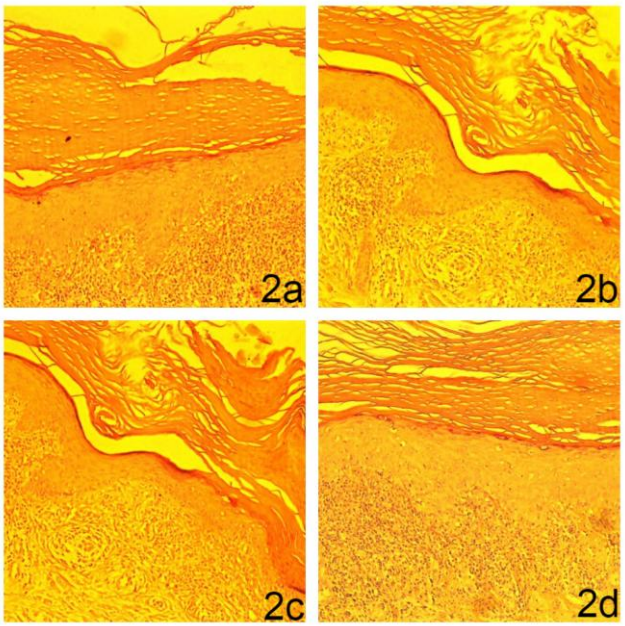

Figure 2: Histological findings; a, b - Focal absence of the granular layer, dyskeratotic cells observed in the subjacent upper spinous layer. A mild lymphocytic infiltrate were seen around an increased number of capillaries in the underlying dermis. Dermis showed a non-specific inflammatory cell infiltrate. Epithelium deep to the tier was vacuolated and devoid of a granular cell layer; c - Dyskeratotic cells were observed in the subjacent upper spinous layer; d - Keratin-filled epidermal invagination with an angulated, parakeratotic tier (cornoid lamella)

The diagnosis of disseminated superficial porokeratosis, associated with idiopathic thrombocytopenia was made, based on the clinical examination, laboratory and histological findings. A systemic administration of acitretin 10 mg was initiated with local application of vitamin D3 analogue (calcipotriol) and corticosteroid (betamethasone), combined in one commercial product as a gel, without

a satisfactory therapeutic response within the following two weeks. Cryotherapy was initiated in combination with systemic acitretin and calcipotriol, combined with a corticosteroid. Regarding the thrombocytopenia, the dose of acitretin was not increased. The satisfactory therapeutic response was achieved in one month.

Discussion

Porokeratosis is considered as an autosomal dominant inherited disorder with the variable clinical presentation, but unified histological characteristics of cornoid lamella [1][2]. The approximate age of onset is 45 - 50 years, although the reported cases range between 27 - 84 years [1][2]. Although it is believed that the sun-exposed areas are mainly affected, the most common regions of occurrence are extremities, the buttocks, and genitogluteal region, while facial lesions are rare [2][4]. It is believed that ultraviolet radiation is the triggering factors in genetically predisposed individuals [2]. On the other hand, various antibody-related autoimmune diseases treated with systemic steroids and other immunosuppressive conditions such as chronic liver disease, HIV and organ transplantations have also been implicated in its etiopathology [11]. Despite that, our literature review established cases of association between disseminated porokeratosis and pyoderma gangrenosum [10], a case of dermatomyositis [12], scleroderma [13], Sjogren syndrome [14] and rheumatoid arthritis [15]. Authors suggest that immunosuppressant therapy is the reason for the occurrence of the porokeratosis [10][11]. Although disseminated superficial porokeratosis has rarely been reported in association with internal malignancy, its occurrence in patients with hepatitis C virus-related hepatocellular carcinoma, cholangiocarcinoma, and ovarian cancer suggests a paraneoplastic nature of the cutaneous disease [16]. Furthermore, porokeratotic lesions can give raise of bowenoid lesions and squamous cell carcinoma as precancerosis trigger with aggressive behaviour and poor prognosis [17]. A porokeratotic lesion, showing histological changes during his disease, including cellular atypia, dysplasia, and invasive squamous cell carcinoma is known as “malignant superficial porokeratosis” [18]. Sporadic case reports in the literature represents porokeratosis in patient with polycythemia rubra vera [19], pseudoxanthoma elasticum [20], multiple myeloma [21] and myelodysplastic syndrome [22][23]. Although rare, benzylhydrochlorothiazide - induced porokeratotic lesions in stable porokeratosis of Mibelli accompanied by eosinophilic spongiosis have also been reported [24].

Although hematologic disorders are not uncommonly accompanied by disseminated porokeratosis, we couldn’t find a case of porokeratosis associated with idiopathic thrombocytopenia (as in the presented case) within our thorough literature revue, encompassing the available reported cases between 1984 and present date. Although various treatment options have been implicated with various degrees of success, including topical diclofenac, vitamin D 3 analogs, 5-fluorouracil, retinoids, 5% imiquimod, photodynamic therapy, carbon dioxide laser and oral retinoids, therapy with good response is rather poor [1][2]. Reports of disseminated superficial actinic porokeratosis treated with vitamin D 3 analogs are rare in general; with no satisfactory enough effect obtained with calcipotriol monotherapy [25][26]. Simultaneous application of vitamin D3 analog (calcipotriol) and corticosteroid (betamethasone), combined in a one commercial product as a gel is reported as a promising, more effective new entity, because of the simultaneous synergetic effects of the substations, which normalize the proliferation of the keratinocytes by calcipotriol on one hand, and the reducing of the inflammation by the corticosteroid, on another [27].

Considering the polymorphism of clinical presentation, the variety of associated disorders and the differences in the treatment responses, we could conclude that disseminated porokeratosis is still an unknown well disorder, which will continue to surprise the physicians in future. The screening and follow up of the patients is mandatory in all cases because as we see, porokeratosis has multiple unexpected faces, which require circumstantial clinical and paraclinical behaviour.

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Case Report

Medium Sized Congenital Melanocytic Nevus with Suspected Progression to Melanoma during Pregnancy: What's the Best for the Patient?

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Abstract

BACKGROUND: Congenital melanocytic nevi (CMN) are pigmented skin lesions usually present at birth. Rare varieties can develop and become clinically very large. Although they are benign nevomelanocytic neoplasms, all CMN may be precursors of the melanoma, regardless of their size. Individual risk of malignant transformation of melanocyte is determined by simultaneous action of exogenous and endogenous factors. The major exogenous risk factor is ultraviolet radiation. Leading roles among the endogenous factors are attributed to skin phenotype, gene mutation, sex hormones and their significance.

CASE REPORT: We present a case of a 27 – year - old pregnant female patient with a congenital melanocytic nevus, which increased significantly in size, during her pregnancy. Estrogen levels increase during pregnancy and clinical evidence has suggested that melanocytes are estrogen - responsive. Nevi in a pregnant patient would exhibit increased expression of estrogen receptor β (ERβ) and thus enhanced the potential to respond to altered estrogen levels.

CONCLUSION: All pigmented skin lesions should be carefully observed during pregnancy by a dermatologist due to the increased risk of malignant transformation, associated with the endocrine dependence. All lesions with visible changes should be removed surgically with appropriative anaesthesia.

Introduction

Despite aesthetic, congenital melanocytic nevi can cause health problems. Usually they are classified by size: small (< 1.5 cm in diameter), medium (1.5 – 19.9 cm) and large or giant (≥ 20) [1]. Independently of their size, all congenital melanocytic nevi are associated with increased risk of development of melanoma [1]. The risk of malignant transformation is higher in giant congenital nevi, and they should be carefully monitored biopsied if indicated [2].

The most prominent and predictable progression could be seen in the middle sized melanocytic nevi by dermoscopic and clinical evaluation, because:

1. The giant congenital melanocytic nevi often show areas which are clinically and dermoscopically difficult to differentiate from melanoma [3]. In these cases (patients with giant congenital melanocytic nevi) surgical excision is rarely due to the enlarged size of the lesions [4][5]. Confocal laser dermoscopy and PET CT can be useful to diagnose melanoma [6].

2. Small congenital melanocytic nevi or so-

called congenital pseudomelanomas are often clinically and dermoscopically indistinguishable from real melanomas. Histopathological verification of the above-mentioned lesions are also subjected to lively discussions; therefore differentiation of melanoma is extremely difficult.

These two facts are giving a new perspective on diagnosis and choosing of the most appropriate treatment option for the medium-sized melanocytic nevi, namely by surgery [3][4][5]. Progression of normal and dysplastic nevi to melanoma during pregnancy is an interesting topic which at the moment does not find a definitive solution [7].

Case report

We present a case of a 27 – year - old female patient, with a pigmented lesion measuring 3 x 5 cm, located above the right gluteal area since early childhood. The lesion was asymptomatic and had not shown any changes in size or colour for the last 20 years. There was no evidence of significant comorbidities or medical treatment. During pregnancy, the patient noticed peripheral enlargement of the lesion as well as the intensification of the dark hue. The latest changes prompted the patient to seek medical consultation at the dermatological clinic. A large melanocytic nevus was established within the clinical examination, located above the right gluteal area with asymmetric shape, uneven boundaries at the periphery, no uniform colour in the different areas of the lesion as well as the difference in diameter – east, west, north, south, but no elevation of the lesion.

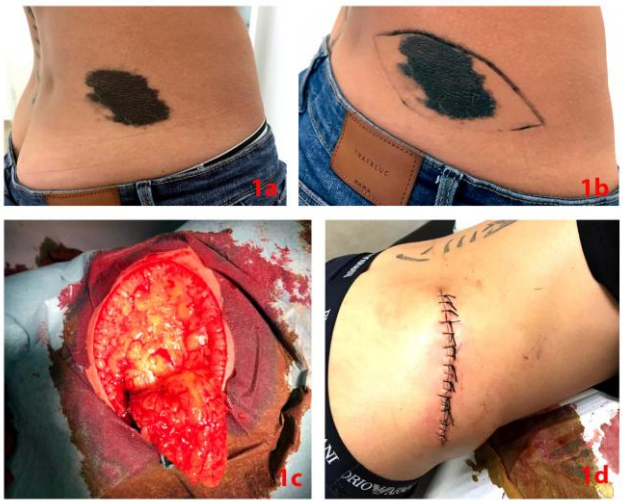

Figure 1: a, b) Clinical view of the lesion located above the right gluteal area; c, d) Consecutive stages within the excision of the lesion

The diagnosis of medium-sized congenital melanocytic nevus was confirmed by the medical history, dermoscopic and clinical signs of dysplasia and progression during pregnancy. The lesion was surgically removed under local anaesthesia (Fig.1 a, b, c, d). The histopathological evaluation concluded the diagnosis of medium-sized congenital pigmented congenital melanocytic nevus with minimal cytological atypia and clear surgical margins.

Since pregnancy is a sure risk factor for the progression of normal nevi to dysplastic or dysplastic nevi to melanoma, we recommend surgical treatment as a preferable option.

Discussion

It is well known that the frequency and prognosis of melanoma in women are influenced by hormonal and reproductive factors [7]. It is also well established that the prognosis and survival rate in premenopausal women is better than postmenopausal [8]. In the last years there has been increased interested and discussion about the impact of pregnancy on nevi and their malignant transformation [7][9][10]. New theories and approaches have been advanced to explain the interplay between hormones and pathological changes in nevi [11]. One of the hypotheses is the influence of estrogen expression. Beneficial and protective effects on the skin have estrogen receptors: estrogen – receptor α (ERα) and estrogen - receptor β (ERβ) [12]. Significant differences in the concentrations of these receptors have been established in sections of melanocytic lesions and those with healthy skin as well as in pregnant and non- pregnant women's skin [13]. Subtype β is a predominant receptor in melanocytes and its protective function is well known [12]. ERβ is antagonist against uncontrolled cell- proliferation and tumor growth [12][14]. An increased in the immunoreactivity for ERβ was observed in normal nevi during pregnancy [15]. The immunoreactivity for ERβ was found to decreases with such deeply extending cells [16][17]. Loss of ERβ expression and its presumed inhibitory effects may promote transformation into melanoma, which is a key event in neoplastic progression [18]. Several studies show reduced expression of ERβ in metastatic stages of malignant melanoma [19], in the presence of a greater thickness of the dysplastic nevi [20]. The clinical implications of such altered ERβ expressions remains underestimated. Different hypothesis explains the higher risk of malignancy during pregnancy with the increased levels of male sex hormones- androgens [21]. There is a theory that endocrine effect reduces after first pregnancy. During second and third pregnancy the risk of development of malignant melanoma (MM) is lower due to the presence of antibodies against tumor-associated fetal antigens. Thus, during first pregnancy the risk of malignant transformation is increased, while every subsequent

pregnancy has a protective effect [22]. Recently, mutations in two tumor suppressive gens - BAP1 (BRCA - associated protein 1) and BRAF (V - raf murine sarcoma virus oncogene homolog B1) have been associated with increased susceptibility for development of MM and other atypical epithelial lesions [23][24]. Screening for mutation/loss/ inactivation of BAP1 and BRAFV600E can be performed by immunohistochemistry. Most melanocytic lesions show positive BAP1 nuclear staining. BRAFV600E is positive in 5% of congenital melanocytic nevus [23][25]

The potential relationship between dysplastic nevi and malignant transformation during pregnancy is underestimated [26][27]. However, all pigment skin lesions should be carefully observed during this period [26][27]. In our case of a 27 – years - old pregnant woman, with CMN, which significantly increased its size and changed its colour and therefore, we decide to remove the lesions surgically, because of the increased risk of malignant transformation.

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Case Report

Once in a Blue Moon … Rare Adnexal Tumor: From the Clinical and Videodermoscopical Aspects to the Mohs Surgery and the Histological Diagnosis

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Abstract

The adnexal tumours are a very heterogeneous group of lesions, more and more studied in the literature. The squamoid eccrine ductal carcinoma (SEDC) is a rare malignant variant that combines ductal structures with squamous differentiation.

We report a case of dermoscopic and histological diagnosis of SEDC, treated with Mohs Surgery and with no recurrence of a tumour after 12 months of follow up.

Introduction

Cutaneous adnexal tumours can be a diagnostic challenge for the pathologist and the dermatologist, because of the rarity and the complexity of these lesions. According to the traditional view, sweat gland tumours are divided into eccrine and apocrine. Nowadays, this classification has been modified because many of these tumours may have both eccrine and apocrine variants [1]. Squamoid eccrine ductal carcinoma (SEDC) is an extremely rare neoplasm with a tendency for local recurrence but low metastatic potential [1]. Less than 20 cases have been reported in the literature so far.

We report herein the case of an SEDC with its clinical and dermoscopic evaluation, treated with deferred Mohs surgery.

Case report

A 75 – year - old man, with a history of colon cancer and benign prostatic hypertrophy, addressed the Department of Plastic Surgery in October 2015 to

remove a nodular ulcerated lesion on the right temporal region of the face. No clinical pictures were taken. The histological diagnosis was that of a poorly differentiated squamous cell carcinoma, with acantholytic features, with perineural invasion and extended to the deep surgical margin. The patient underwent two subsequent radicalizations to reach free surgical margins.

In June 2016, the patient addressed to our Dermatologic Clinic for a recurrence of the lesion, in the same area (Figure 1).

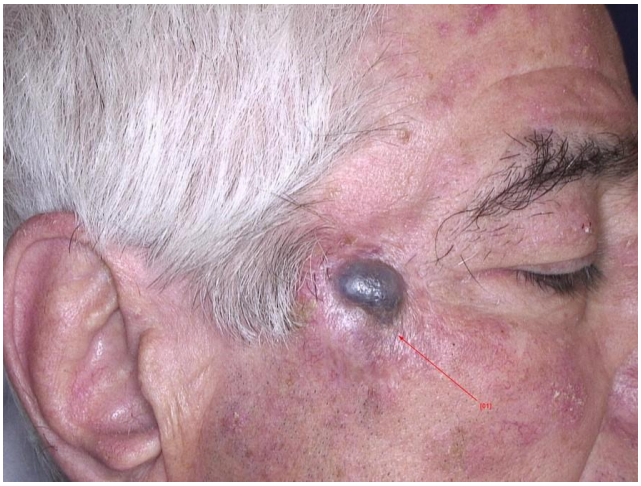

Figure 1: Bluish nodular lesion, after two months by its occurrence, at the temporal region in patient's face, in location of previous surgery

The lesion was a bluish, exophytic nodule, approximately 2 cm in diameter, soft to palpation. Contextually, a videodermatoscopy was performed (Figure 2). Videodermatoscopy showed a homogeneous, structureless, blue-white colour lesion with reddish - purple lacunar areas and irregular vessel at the periphery; the lesion was furthermore free of any specific criteria of melanocytic or non - melanocytic tumour.

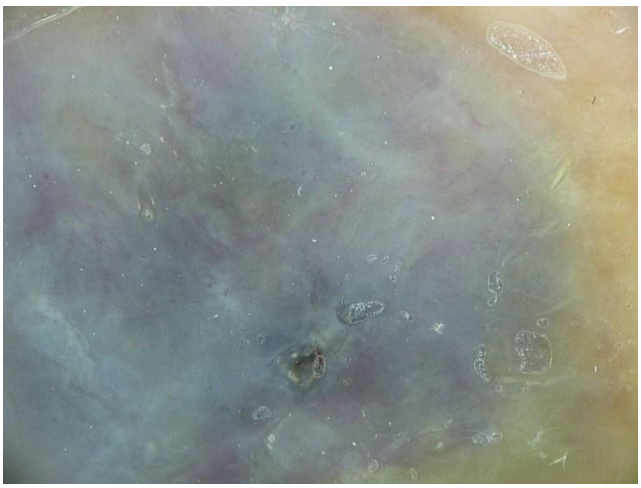

Figure 2: Videodermoscopy aspect of the lesion

In consideration of the patient's personal history and the high risk of the dermoscopic image, deferred Mohs surgery was performed. Once established the absence of tumour cells at the margins, a dermo-epidermal skin graft was used to cover the surgical wound.

The histopathology examination showed a dermal proliferation with squamous and ductal differentiation. The lesion had an infiltrative growth pattern and perineural invasion. The final diagnosis was squamoid eccrine ductal carcinoma.

The 12 - months follow up was negative for recurrence.

Discussion

An adnexal tumour is nowadays a very huge and heterogeneous group of lesions. The rarity of this kind of lesions precludes drawing any solid conclusions concerning their line of differentiation, to the diagnosis and their biological behaviour [2].

The variety of names reflects the different approaches of authors who have emphasised a particular aspect of the neoplasm, describing it in the word itself (e.g. squamoid aspect, syringoid aspect, etc.) [2].

The terms "eccrine carcinoma" or "eccrine ductal" are used by different authors to indicate a malignant tumour with the proliferation of ductal structures. Nevertheless, because normal eccrine and apocrine ducts are indistinguishable, it is easy to confuse the two groups of lesions. [2] Moreover, the squamoid eccrine ductal carcinoma (SEDC) variant presented by our patient shows a variable degree of atypia. It combines ductal structures, usually towards the deep margin of the neoplasm, with squamous differentiation, usually towards the tumour surface (Figure 3 A, B).

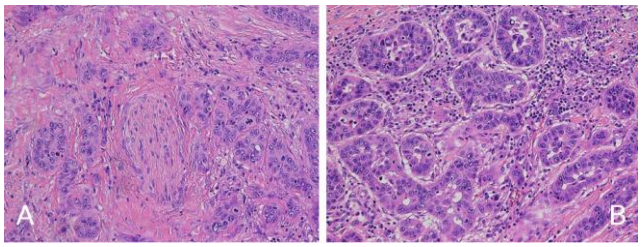

Figure 3: Histopathology revealed a dermal proliferation with squamous and ductal differentiation

The histological diagnosis is, therefore, difficult and could be confused with a squamoid tumour (like the squamous carcinoma). In particular, this misdiagnosis could be expected in superficial biopsies, which are not able to show the ductal proliferation predominant in the deeper part of a tumour [1]. Perineural and lymphovascular spread are

present in the 10% of cases [1]. Avraham et al. [3] highlight how in this rare adnexal tumour with eccrine differentiation, it's just the tumour depth and the lymphovascular invasion which are important survival factors, compared, for example, to the size of the neoplasm.

The SEDC usually presents clinically as a non - distinctive nodule or plaque on the head/neck or, less frequence, on the extremities, with a higher incidence in elderly and male patients [4]. Due to its rarity and non - specific clinical appearance, it is difficult to differentiate it from other malignant cutaneous lesions. Dermoscopy helps the diagnosis. In our case, dermoscopy revealed a blue-whitish colour structureless lesion with uneven reddish purple lacunar areas and linear irregular vessel at the periphery. Also, the lesion was free of any specific criteria of melanocytic or non - melanocytic tumour. In literature, the dermoscopic aspect of eccrine poroma and eccrine porocarcinoma is described. To our knowledge, this is the first case describing the dermoscopic aspect of an SEDC, and the blue aspect of this lesion has awakened our interest. The blue colour in dermoscopy is studied by different authors because, although it could be present in benign and malignant lesions, it is closely linked to melanoma (in particular if associated with other specific dermoscopic aspects). Our case would suggest that, albeit once in a blue moon, blue colour can be tricky and hide a rare malignant tumour, like SEDC. For this reason, if in doubt, do not hesitate in front of a dermoscopic blue lesion: cut it out.

About tumour behaviour, SEDC is a tumour with low risk of metastasis, in approximately 10% of cases has a local recurrence, as also proved by our patient (who had two recurrences of a tumour). Considering the malignancy of the lesion, the high risk of recurrence and perineural/lymph nodes invasion, an intracervical check of the margins would be desirable to reach a complete neoplasm extirpation.

Unfortunately, due to the relative rarity of SEDC, there have been no randomised studies comparing the traditional surgery with the Mohs Surgery (or other surgical treatments). However, a recent review [5] considers the three cases in the literature of SEDC treated with Mohs Surgery and highlighted the efficacy of this surgical modality for this type of a tumour (Figure 4 A, B).

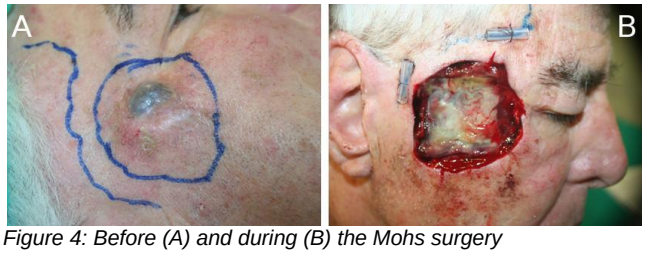

Figure 4: Before (A) and during (B) the Mohs surgery

The follow up of our patient at 12 months (Figure 5), which shows no recurrence of the lesion, confirms it.

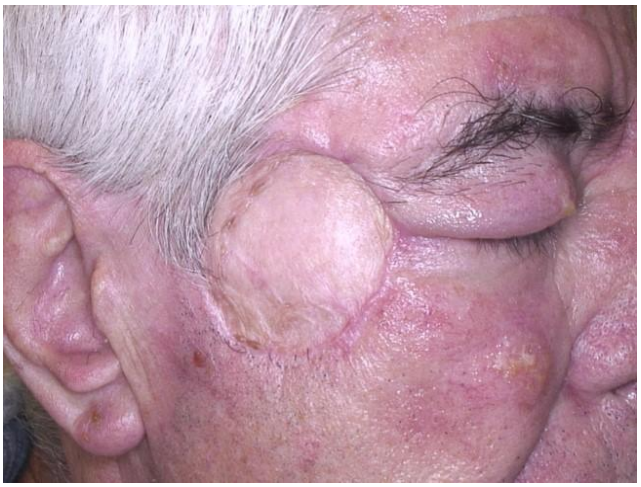

Figure 5: Follow up at 12 months

In conclusion, the squamoid eccrine ductal carcinoma (SEDC) is a rare adnexal tumour with a high risk of recurrence and perineural and lymphovascular invasion. Clinically It appears as a nodule or a plaque in elderly and male patients. An early clinical diagnosis is difficult. The dermoscopy, characterised by a blue-whitish colour and irregular reddish purple lacunar areas, could help the diagnosis. The morphology is similar to a squamous carcinoma; nevertheless, also a ductal proliferation is present in SEDC.

The Mohs Surgery is the most efficient surgical treatment for this type of neoplasm.

A close follow - up it's important to evaluate possible recurrences.

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Case Report

Small Dysplastic Congenital Melanocytic Nevi in Childhood as Possible Melanoma Imitators

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Keywords: Nevi; Small congenital nevi; Surgical approach; Melanoma imitators; Treatment; Melanoma; Histopathological evaluation

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Abstract

Small pigmented lesions in children can represent a significant diagnostic challenge. If the diagnostic features and therapeutic approach are relatively well established in large and giant nevi, there is still much controversy regarding small and intermediate-sized congenital pigmented lesions that can lead to significant diagnostic challenges, both clinically and dermoscopically, and consequently to difficulty in defining the optimal approach in such cases. Although dermoscopy can be useful in the diagnosis of pigmented lesions, the diversity of clinical and dermoscopic features of pigmented nevi in children usually hinder the differentiation between them and melanoma. Histological findings after resection often show surprising results that do not correspond either to the clinical nor the dermoscopic features. With the present case, we want to emphasise the variable natural behaviour of melanocytic lesions in children, which sometimes leads to unnecessary surgical excisions, which should be avoided in pediatric patients.

Introduction

Pigmented lesions in children can provide significant diagnostic challenges [1]. Melanocytic nevi can be present at birth, although in a minority of cases they may not be clinically apparent until one to two years of age, and acquired later in life [1]. Congenital melanocytic nevi (CMN) are classified based on size and morphologic features [2]. Small CMN is less than 1.5cm in greatest diameter; intermediate CMN is between 1.5 - 10 cm in greatest diameter and large CMN are greater than 20 cm in greatest diameter, while the giant CMN corresponds to a CMN that is greater than 50 cm in diameter [1][2]. Although moles are frequently seen in the pediatric population, fortunately, the general incidence of malignant melanoma in children is low [2]. More than 50 melanocytic nevi, clinically atypical lesions, family

history of melanoma, excessive ultraviolet radiation exposure, fair skin and eyes, and immunosuppression are considered as risk factors for the occurrence of melanoma in childhood [1]. If the risk of melanoma arising in large and giant CMN is approximately 2 - 5% over a lifetime, a significant proportion of this risk is present in the first decade of life [2].

Therefore, it is recommended that large or giant CMN should be referred to an experienced dermatologist and a pediatric surgeon at birth for close follow - up and discussion of the risks and benefits of surgical intervention [2]. Also, if the diagnostic and therapeutic behaviour is well - known in large and giant nevi, small and intermediate congenital pigmented lesions could lead to significant diagnostic challenges, both clinically and dermoscopically [3]. Furthermore, although challenging, proper diagnosis of pigmented lesions in children is essential for the successful clinical outcome, prevention of unnecessary surgical excision and prognosis in general [3].

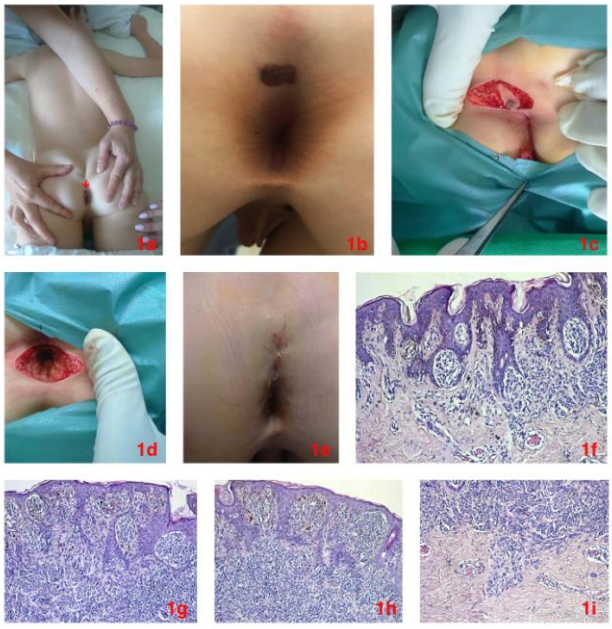

Figure 1: a, b - Clinical presentation of irregularly bordered pigmented lesion, location in rima ani in an 8 - year old male patient, clinically and dermatoscopically suspicious for malignant melanoma; c, d – Intraoperative findings. Surgical excision of the lesion; f, g, h, i – Histological findings. Compound melanocytic lesion with the irregular architecture of the junctional component, with mild cytological pleomorphism, lentiginous hyperplasia and variably sized and shaped nests (1f to 1h). However, maturation of the intradermal component is adequate (1i)

Case report

An eight-year-old male patient was admitted to the Dermatology department for evaluation of two pigmented lesions, present since birth. There were no comorbidities or medications. No family history of dermatologic diseases was reported by the patient's mother. Clinical examination revealed multiple pigmented lesions, disseminated all over the body. Two of them were larger than the remainder, clinically resembling dysplastic nevi or melanoma. An oval-shaped pigmented macule, with partial induration, measuring 1.5cm, irregularly bordered, with uneven colouration from light to dark brown and black was seen in rima ani (Fig.1 a, b). An oval-shaped dark brown - coloured pigmented macule, measuring 1 cm, was observed in the right scapular area of the back (Fig.1 a, b).

The dermoscopic findings and clinical appearance of both lesions were suspicious for malignant melanoma. An enlarged lymph node was detected on palpation in the right inguinal fold. Laboratory blood tests examination did not reveal any significant abnormalities. The enlarged lymph node was confirmed by ultrasonography, revealing a 7.4/3.3 mm in diameter lymph node in the right inguinal fold, with preserved structure. No additional enlarged lymph nodes were detected in the left inguinal or axillary folds. Abdominal ultrasonography did not reveal any pathological abnormalities. The lesions were surgically removed with elliptic surgical excision under general anaesthesia and safety margins of 0.8cm (Fig. 1 c, d).

Histological examination confirmed the diagnosis of melanocytic nevus in both lesions (Fig. e, f, g, h, i). Systemic antibiotic treatment was initiated in the postsurgical period, due to the enlarged lymph node, which normalised its size in two weeks.

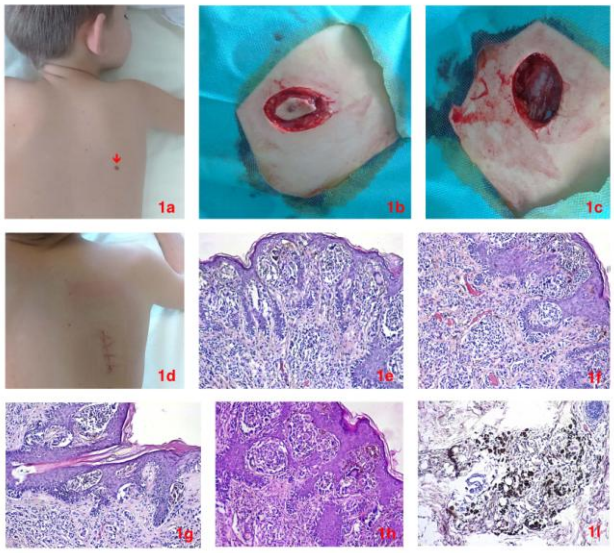

Figure 2: 1a - Clinical presentation of the second suspicious lesion, located on the back of the same patient; 1b, c, d – Intraoperative findings. Surgical excision of the lesion; 1e, f, g, h, i – Histological findings. Similar findings as in panel 1, with irregularity in the architecture of the junctional component, mild cytological pleomorphic and rare scattered suprabasal melanocytes (1e and 1g)

Discussion

Between 1% and 6% of infants are born with a congenital melanocytic nevus and between 2% and 6% of the population have a Congenital Naevus - Like Nevi (CNLN) [2].

It has been postulated that CMN could present in a wide diversity of patterns, forming the concept of so-called “nevus volatility” in childhood, being more likely to both develop new nevi and to have nevi that disappeared during follow - up [2][3]. On the other hand, the concept of “nevus volatility” in children is supported by the clinical and dermoscopic presentation of nevi in children, which is often confusing even for well - trained dermatologists [3]. CMN can first appear as macular lesions with irregular borders, strongly resembling superficial spreading malignant melanoma [3]. The irregular border of most of the nevi in children could be interpreted as a sign of melanocytic progression, which will clinically present as the growth of the nevus [1][2]. In contrast to the irregular border in adolescents, this pattern in children could simply mean that a given nevus is still growing [1][3]. They can be of one colour or multicoloured, from tan to dark brown to black, but most important, nevi in childhood may undergo some changes during the first few years of life [3]. Additional brown macules or papules can develop within the lesion, or the nevus could become infiltrated as a raised plaque [3]. Further confusion could be provided by the changing in nevus’ colour - progressively darkening or lightening [4][5]. This often requires surgical excisions as a cautionary measure for these patients. The lack of well-qualified pathologists in the field of dermatopathology often leads to misdiagnosis of melanocytic nevi as melanoma, resulting in unnecessary second excisions, sentinel lymph node biopsies, etc. This stems from the fact that melanocytic lesions in children may exhibit certain features that look worrisome on the microscope to the unwary pathologist, for example, an architectural disorder of the junctional component, upward migration of melanocytes and variable cytological pleomorphism.

In addition to colour variation, congenital melanocytic nevi in children, especially the giant ones, are also more likely to be associated with satellite lesions and benign proliferative nodules within the lesion that can resemble melanoma [3]. All of these clinical diversities give rise to the diversity of dermoscopic patterns, which can also be confusing [4]. Furthermore, although considered as diagnostic tools, which improve the diagnosis in general, algorithms and checklists, such as Menzie's method, the seven-point checklist, pattern recognition, and the ABCD algorithm [2][3] are not so helpful when dealing with the differential diagnosis between melanocytic nevi and melanoma in children.

Most CMN is characterised by globular or reticular dermoscopic pattern, while overlap of the globular and reticular patterns was seen in less than 2% of nevi [5]. Zalaudek I et al. (2006) have shown that globular pattern and uniform pigmentation predominated in children, while the reticular or homogeneous patterns and central hyperpigmentation was predominantly seen in the group of individuals aged 16 - 30 years [6]. Despite the age, a site-dependent variation of dermoscopic patterns of small and medium congenital melanocytic nevi has also been reported [5].

Although dermoscopy can be useful in the diagnosis of pigmented lesions, the diversity of clinical and dermoscopic features of pigmented nevi in children usually make the distinction between them and melanoma difficult. With the present case, we want to emphasise the variable natural behaviour of melanocytic lesions in children, which sometimes leads to unneeded surgical excisions, which should be avoided in pediatric patients.

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Review Article

Chimeric Monoclonal Antibody Cetuximab Targeting Epidermal Growth Factor-Receptor in Advanced Non-Melanoma Skin Cancer

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Keywords: cetuximab; epidermal growth factor receptor; non-melanoma skin cancer; targeted treatment; skin toxicities

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Abstract

BACKGROUND: Non-melanoma skin cancer (NMSC) is the most common malignancy in humans. Targeted therapy with monoclonal antibody cetuximab is an option in case of advanced tumor or metastasis.

AIM: We present and update of the use of cetuximab in NMSC searching PUBMED 2011-2017.

METHODS: The monoclonal antibody cetuximab against epidermal growth factor receptor (EGFR) has been investigated for its use in NMSC during the years 2011 to 2017 by a PUBMED research using the following items: "Non-melanoma skin cancer AND cetuximab," "cutaneous squamous cell carcinoma AND cetuximab," and "basal cell carcinoma AND cetuximab", and "cetuximab AND skin toxicity". Available data were analyzed including case reports.

RESULTS: Current evidence of cetuximab efficacy in NMSC was mainly obtained in cutaneous SCC and to a lesser extend in BCC. Response rates vary for neoadjuvant, adjuvant, mono- and combined therapy with cetuximab. Management of cutaneous toxicities is necessary. Guidelines are available.

CONCLUSIONS: Cetuximab is an option for recurrent or advanced NMSC of the skin. It seems to be justified particularly in very high-risk tumors. There is a need for phase III trials.

Introduction

Non-melanoma skin cancer (NMSC) is the most common malignancy in humans, with basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) as the dominant tumor types [1]. As major risk factors the following findings could be identified: age ≥ 50 years of life, Fitzpatrick's phototype I or II, and increased chronic exposure to natural or artificial ultraviolet (UV) irradiation. Other known risk factors include immunosuppression, solid organ transplantation, and use of tanning beds [1][2][3][4][5][6].

Logically, the reduction of UV-exposure seems the major goal in primary prevention [1]. The three pillars of current treatment for localized disease are surgery with wide excision, Mohs surgery for recurrent tumors or special localizations such as the face, and radiotherapy [1].

The role of chemotherapy and targeted therapy in NMSC seems to be confined to advanced cases, where surgery has become impossible or is contraindicated, and to metastatic disease [8][9][10][11][12].

Cetuximab is a chimeric monoclonal antibody against epidermal growth factor receptor (EGFR) and had been FDA-approved for head and neck SCC in conjunction with radiotherapy [12].

We present and update of the use of cetuximab in NMSC searching PUBMED 2011-2017.

BCC

BCC is the most common human cancer. Age-adjusted BCC incidence (cases per 100,000 person-years) was 360.0 in men and 292.9 in women in a recent population-based study in Olsmedt county, Missouri [13]. In contrast to cSCC, BCC does not increase cancer-related mortality [14]. BCC develops as a result of the interplay between ultraviolet radiation (UVR) and genotype with somatic mutations (Smoothed) and germline mutations/polymorphisms. The role of UVR exposure and BCC is not as clear as in cSCC [15].

Prognostic factors of BCCs are tumor size, histological subtype, tumor location, margins, and recurrence. The first line treatment of BCC is wide excision or Mohs surgery dependent on the site of tumor growth. In relapsed tumors, Mohs surgery provides a better outcome with a lower recurrence rate. Radiotherapy is an alternative for patients, who refuse surgery or where surgery is contraindicated. For advanced BCC, Smoothened (SMO) inhibitors vismodegib and sonidegib have been FDA approved [8][9].

Cutaneous SCC

Cutaneous SCC (cSCC) is the second most common NMSC. The age-adjusted cSCC incidence (cases per 100,000 person-years) has been calculated as high as 207.5 for men and 128.8 for women in Olmsted country [13]. The rate of metastasis has been estimated between 1.9 to 2.6%. Risk factors for metastatic spread are the maximum diameter, poor histological differentiation and particular anatomical localizations such as lip, cheek, and ear [16].

The risk of recurrence, metastases, and mortality can be further stratified. High-risk and very high-risk tumors are the possible indication for the use of cetuximab.

High-risk tumors (HRSCC) are characterized by localization in the head-and-neck region, maximum diameter of more than 2 cm, invasion into the subcutaneous adipose tissue, poor differentiation, recurrence or occurrence in a previously irradiated area, and immunosuppression [16].

Very high-risk SCC (VHRSCC) include tumors with perineural, lympho-vascular, parotid, cartilaginous or bony invasion, in-transit, regional or distant metastases [17].

Studies of cetuximab in cutaneous SCC 2011-17

In 2011, the first phase II trial included 36 patients with SCC. Disease control was obtained in 69% after 6 weeks of treatment. Patients received a 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly for at least 6 weeks with 48 weeks follow-up. In this study, three related serious adverse events were observed - two grade 4 infusion reactions and one grade 3 interstitial pneumonitis. Grade 1 to 2 acne-like rash occurred in 78% of patients and was associated with prolonged PFS [18].

Table 1: Results of cetuximab therapy in cSCC 2011-2017 (disease-free survival – DFS, overall survival – OAS, complete response – CR, partial response – PR, stable disease – SD, progressive disease – PD)

No.	Metastases	Best response	Outcome	Remarks	Reference
36	lymph node	2 x CR 8 x PR 15 x SD 6 x PD 5 x not assessable	1 x at 6 months	in part with surgery phase II trial	[18]
1	lymph node	CR after 6 weeks	DFS 7 months	1st line	[19]
1	satellites	CR	> 6 months	plus volumetric modulated arc-radiotherapy	[20]
8	-	3 x CR 2 x PR 1 x PD	3- >21 months 6-18 months	6 x with radiotherapy	[21]
4	2 x lymph node	3 x CR	1 x relapse after 6 months, median disease-free survival 20.5 months		[22]
1	lung, pleura, lymph nodes	PR after 6 months	-	cetuximab plus paclitaxel	[23]
3	-	1 x CR after 16 weeks 2 x PR 1 x PR	DFS 16 months PR for 17 and 18 months died from other reasons		[24]
6	-	3 x CR 2 x PD 1 x intolerance	median 3 years	in combination with surgery VHRSCC	[17]
17	bone or visceral	4 x PR	-	penile & scrotal, cetuximab alone or with cisplatin	[25]
6	all metastatic	67% disease control at 4 to 8 weeks	mean overall survival 25 ± 16.2 months		[26]
1	-	CR	-		[27]

There have been a number of retrospective case series and case reports been published since then (Table 1). Cetuximab has been used as 1st – 3rd line therapy, alone or in combination with surgery, radiotherapy or chemotherapy [17][18][19][20][21][22][23][24][25][26][27].

Cetuximab in advanced BCC 2011-2017

Cetuximab has also been used in patients with advanced BCC [11]. The safety profile is not different from SCC patients. However, Karapurakal et al. (2015) used a lower starting dosage of 125 mg/m^2 increased to 250 mg/m^2 or 300 mg/m^2. Their dosages varied from 125 mg/m^2 once a month to 300 mg/m^2 once a week. The authors did not explain the reason for these dose variations. Two patients achieved a CR, the other 2 had a PR. During a median follow-up of 12 months overall survival was 100%. Mean disease-free survival was one month. Three of their four patients suffered from Gorlin-Goltz syndrome [22].

Management of adverse effects

Skin toxicity is the most common adverse effects of cetuximab. Treatment is based on skin moisturizers and sunscreens [28]. In a retrospective trial on gastrointestinal cancer patients, prophylactic and reactive treatment for acne-like rash was equally effective [29].

Treatment of the papulopustular rash includes topical use of erythromycin or metronidazole for mild cases, and systemic tetracyclines or retinoids for skin toxicities grade ≥2 with temporary interruption of cetuximab therapy [30]. The incidence of skin toxicity seems to be lower in smokers but the incidence of anorexia is higher compared to non-smokers [31].

Topical vitamin K3 (menadione) is not effective in the prevention of cutaneous toxicity nor does it change the expression of EGFR in skin [32].

In conclusion, there are increasingly more data available on the use of targeted therapy in advanced NMSC although controlled prospective, randomized, placebo-controlled phase III trials are still missing. From the available data, cetuximab seems to be effective as monotherapy after surgery. The safety profile is not different from approved indications such as advanced colorectal and head-and-neck cancer. In contrast to hedgehog inhibitor vismodegib approved for advanced BCC, second cSCC have not been observed with cetuximab therapy of NMSC [33][34][35][36].

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Review Article

Artificial Hair: By the Dawn to Automatic Biofibre® Hair Implant

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Abstract

Since the beginning of the twentieth century, there have been attempts at creating artificial hair to treat baldness. Major evolution took place at the end of 1970's when, unfortunately, artificial hair treatments were applied without appropriate medical controls, resulting in sub-standard results from the use of unsuitable materials and technique. The large improper use of this technique in North America from no medical personnel and with dangerous fibres led the Food and Drug Administration (FDA) to suspend the procedure in 1983. In Europe, a new trial on artificial hair procedure started at the beginning of 1990's.

In 1995 the European Union (UE) recognised the artificial hair implant as a legitimate medical treatment and outlined the rules related to that procedure. In 1996, biocompatible fibres (Biofibre®) produced by Medicap® Italy were approved by the UE Authorities and by the Australian Therapeutic Goods Administration (TGA) as medical devices for hair implant. An effective medical protocol was developed during the following years to provide correct guidelines for appropriate treatment, and to reduce possible related complications. Automatic Biofibre® hair implant represents the last achievement in this hair restoration technique with significant advantages for the patients.

Introduction

The very first experiences with artificial hair implants date back to the beginning of the twentieth- century as recorded by a USA patent [1]. In 1930 Dr. M. Sasagawa reported his experiments with the implantation of cut human hair [2]. Nonetheless, its greatest evolution did not take place until the 1970's. In 1976, Dr S. Yamada and Dr. K. Fukuta presented their technique to JMJ [3]. From 1976 fierce competition within the North American market resulted in a number of different companies offering inadequately tested fibers for human hair replacement with very negative results [4][5][6]. In those years, the technique was often being performed inappropriately by non-medical operators, in non-medical environments and without any medical protocol. That led to frequent complications (severe infection, inflammation, broken hair embedded in the scalp, etc,) resulting from unsuitable materials and techniques. In the USA, the above situation provoked a Government inquiry followed, in 1983, by a ban on the implantation with special reference to the materials utilized at that time as human hair and colored industrial fibers such as polyester, modacrylic and polyacrylic fibers (FDA, June 13, 1983) [7]. During the following years, some European companies specialized in the bio-medical field started researching on artificial hair in cooperation with University Departments. In 1993 biocompatible fibers (Biofibre®) were developed in Italy by Medicap company. From 1993 onward clinical trials [8][9][10]

and histological studies [11][12] were performed with encouraging results, leading to additional research on the biocompatible material field and medical protocol application. In 1995 the UE recognized the artificial hair implant technique as a medical act, setting that strict and ethical medical protocols must be followed to ensure the safety of implants and minimize complications [13]. In consequence of this regulation, all fibers to be used for this practice have to be compulsory approved and certified as CE medical devices. The approval of this methodology was a great advantage for patients since it legally prevented the procedure from being performed by unqualified people. From the beginning of the 2000's many cases of patients treated by artificial hair implant were worldwide presented to the scientific community [14][15][16][17], getting favorable outcome and interest also for USA doctors. On 2007, a study about the use of Biofibre® hair implant to treat scalp scars was published [18] as an additional indication for this technique. In 2011, Biofibre® hair implant was included in an academic text of cosmetic dermatology [19] at the World Congress of Cosmetic Dermatology (WCOCD). In 2013, the first Automatic machine for Biofibre® hair implant was presented by Medicap Italy with significant advantages for the technique [20]. In 2014 was released the new high-density version of Biofibre®, named as MHD® hair, which allows triple hair quantity with the same number of implants. Such fibres are presently used for the crown area only allowing very mild aftercare and the very quick result, while for the front hairline the single Biofibre® is recommended to ensure a more natural aesthetic result. Recent PubMed publications bring additional evidence of the reliability of the present artificial hair implant technique [21].

Materials

The safety of implant fibres has to be assured. At the same time, good aesthetic quality and durability must also be considered to maintain the expected results over time. The main features required are biocompatibility, resistance to traction, the absence of capillarity, resistance to physical-chemical stress, low tissue trauma, and good aesthetic qualities. Biofibre® medical hair prosthetic fibres meet all the biocompatibility and safety requirements established by international standards committees for medical devices. They are available in 13 colours (Fig.1), with different lengths (15, 30 or 45 centimetres) and in various shapes (straight, wavy, curly and afro) to satisfy different patients requests. Presently, they are also available in the new high-density version, MHD®, which allows for each implant to have three hairs implanted as the final result. This fibre is used for the crown area only, while for the front hairline the single Biofibre® is recommended. The instruments used for the procedure are also very important. The special hooked needles are less traumatic according to diameter and shape. These instruments also ensure easy work for the physician and best comfort for the patient. Automatic Biofibre® hair implant device represents a valuable solution to encounter such requirement.

Figure 1: Biofibre® is available in 13 colours, with different lengths (15, 30 or 45 cm) and in various shapes (straight, wavy, curly and afro)

Indications

Biofibre® hair implant is carried out thanks to minor surgery. It is indicated for diffuse alopecia or hair thinning both for male and female patients (Fig. 2a-be Fig. 3a-d).

a) b)

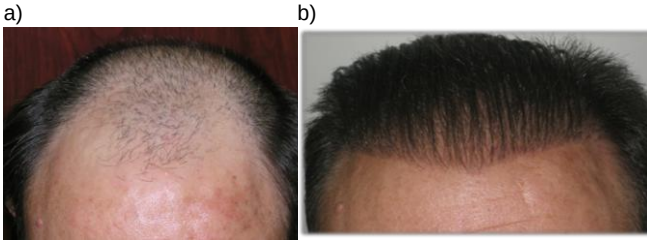

Figure 2: a): Patient with androgenetic alopecia; b): Final results after five implant sessions with 4000 Biofibre® as a whole

This technique ensures an immediate aesthetic result and sufficient quantity of hair in a short time without requiring any donor area. It is a very soft surgery not requiring hospitalisation and can be used alone or in combination with other hair restoration techniques to improve final aesthetic results when required [15][17] or in case of the poor donor area. It is also performed to correct scars or scalp burns (Fig. 4a-b). This technique is not indicated for implant on the temples, on low frontal

hairline, scalp areas with very thin dermal tissue (such as the sideburns) or in case of the pathologically atrophic scalp.

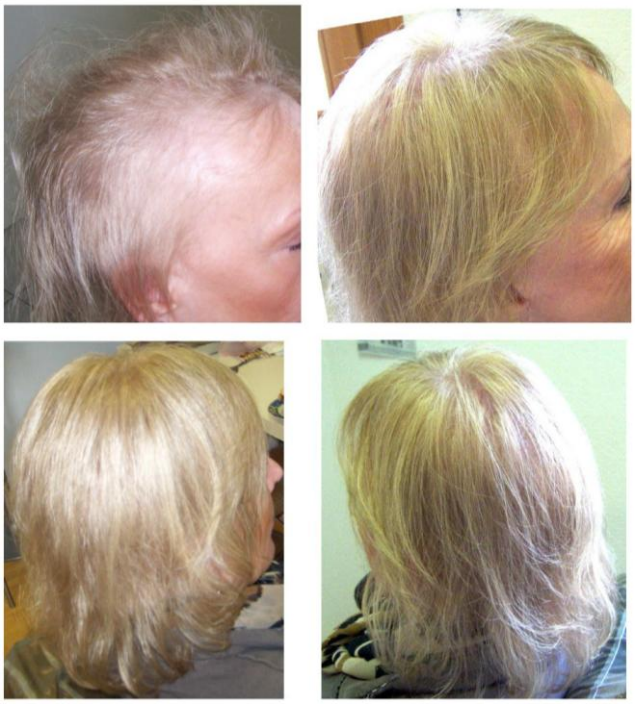

Figure 3: A 53 years old woman with chronic telogen effluvium (upper left); Final results after three implant sessions with 2000 Biofibre® as a whole (upper right, down)

Patient's selection

It is important that patients are previously selected and well informed about the correct aftercare protocols and the pros and cons of this procedure. Biofibre® hair implant is not indicated in patients with diabetes mellitus, hepatitis A, B and C, autoimmune diseases, chronic scalp diseases, severe psychosis, not stabilised alopecia areata, when there is lack of personal hygiene, or with employment in dusty or dirty environments. A preliminary screening of the patient, including blood testing, is essential before proceeding with an implanted test. Blood tests list include: Complete blood count, Urea, Creatinine, Bilirubin (total and direct), Gamma-Glutamyl Transferase (GGT), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Fibrinogen, Treponema Pallidum Haemagglutination (TPH), Anti-HIV, Hepatitis A-B and C Markers/Hbsag, Erythrocyte Sedimentation Rate (ESR), Venereal Disease Research Laboratory (VDRL), Prothrombin Time (PT), Partial Thromboplastin Time (PTT), C Reactive Protein, Fasting Blood Sugar Levels, Serum protein electrophoresis, Urinalysis, and Electrocardiogram**.** Before proceeding with implant sessions, a small number of implant tests must be performed.

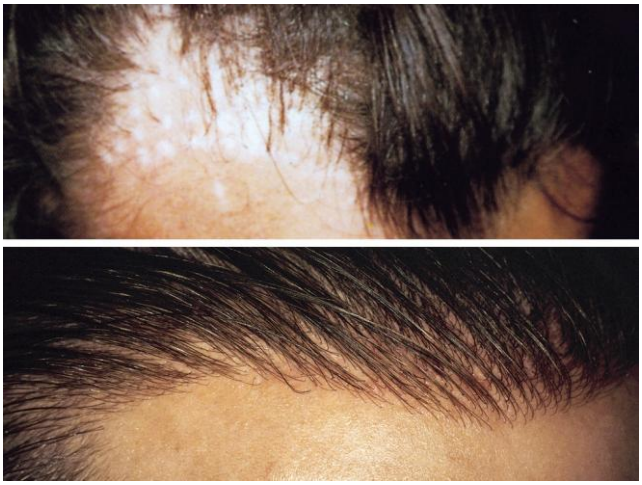

Figure 4: Patient with two frontal scars (upper); Final result after two implant sessions with 1500 Biofibre® as a whole (down)

They should be observed every one week over a period of at least one month. If not significant problems are observed, larger sessions can be performed at intervals of 1 month each.

Implant Technique and Medical Protocol: From the Stone Age To Now

A correct hair implant procedure requires a combination of safe fibres, suitable implant instruments, trained doctors, careful patient selection, and proper after-care follow-up. Selection of a suitable patient is important. A preliminary visit with tolerance testing allows the exclusion not only of those patients who are not suitable for the fibres implants but also those who have contraindicating skin conditions. Patient must avoid smoking, drinking alcohol for two days before implant, and taking salicylic acid for at least three days before surgery. Before starting the implant, the implant area must be carefully disinfected. The tolerance implant test is performed with 100 fibres and results are evaluated weekly and after four weeks. The implant technique is based on small hooking needles that go out the implanter and hook the Biofibre® root (reversible knot®), placing it under the scalp at galea level. In this way, the root can be held by the fibrous tissue and avoid premature hair loss. The implanter performed by automatic machine allows reaching always the right deepness (Fig. 5). The procedure is performed under local anaesthesia and in one hour up to 600 Biofibre® are usually implanted. A small quantity of local anaesthesia is recommended initially, with repeated administration in case of need. The local anaesthesia commonly used is carbocaine or lidocaine 2% with adrenaline 1:100.000. The suggested quantity of anaesthesia is 1 cc per 200 Biofibre®. The average implant is

about 1000 Biofibre® per session, respecting the appropriate distance between each fiber.

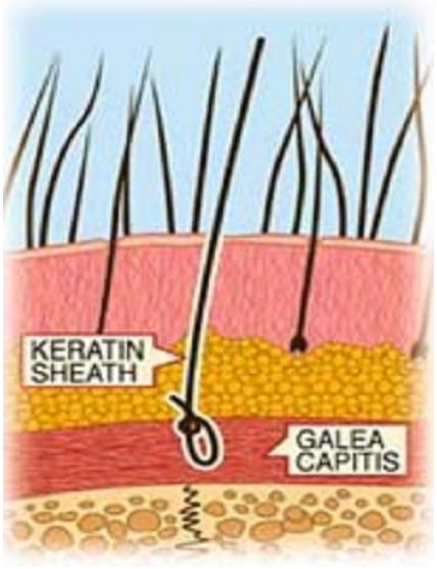

Figure 5: Right implant deepness of Biofibre® performed by automatic machine to allow best retention rate

The implantation is performed to grant the appropriate directional orientation of the fibres to avoid unwished traction and to enhance the final appropriate aesthetic result. Implants performed by the automatic machine minimise implant trauma and hastens cicatrization of the implanted area by allowing a higher degree of fixation, thereby allowing a quicker, better aesthetic result. At the end of the implant procedure, the scalp is disinfected with betadine solution. For large implant sessions, an ice pack protected by sterile gauze is applied for 5 minutes on the scalp. Then the fibres are finally combed with a large toothcomb, holding them at the base to prevent surfacing and the risk of premature fall. The first cleaning with ketoconazole shampoo is suggested after three days. Systemic antibiotic coverage is recommended for one week after the implant, allowing adjustments in therapy depend upon local circumstances and patient's medical history. The patient must avoid sports, sauna and other activity that can increase sweating for the first three weeks until cicatrisation takes place. Also, should avoid smoking and drinking alcohol for one week after implant session. Before proceeding with the following implant sessions, a four week of pause has to be respected.

Follow Up / After Care Protocol

Maintenance of scalp hygiene and periodic medical check-ups are required to keep the expected aesthetic results. Follow-up is very important to check the patient's scalp conditions and prevent possible complications such as infection or inflammation. Biofibre® after-care protocol consists of regular follow up, proper scalp hygiene, use of suitable products, and avoidance of dangerous products or treatments such as hair bleaching, permanent waving, thermal shocks, and hair curlers. Various behaviours that can lead to side effects with the implant procedure include lack of patient hygiene or lack of asepsis during the procedure, excessive density or quantity of implanted fibres in one session, a traumatic implant procedure, personal fibre intolerance, incorrect choice of implant area, and failure in after-care procedures. Most of these problems can be solved with appropriate therapies and change of habits. When the problem is recurrent or cannot be easily resolved with appropriate antibiotics and/or corticosteroid therapy, it may be necessary to proceed with fibre removal. The reversible knot of Biofibre® does not allow the fibre to fall out from the implant area, but allow it to be pulled out entirely with appropriate traction with no remains (Fig. 6).

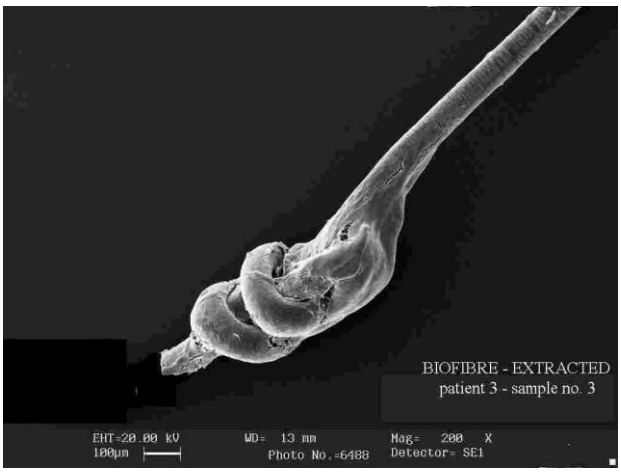

Figure 6: a Reversible knot of Biofibre® after extraction. No remains stay embedded on the scalp, allowing prompt restitution ad integrum of scalp

This ability to remove the implant contributes to the overall safety of the procedure since once removed; the scalp is healed after several days without scars [14]. Special attention has to be reserved to the scalp sebum.

Sebum is an important and useful natural shield for the scalp, but when it is in excess, it must be removed before it leads to sebum accumulation around implanted fibres that can cause early fibre loss and may predispose the patient to a scalp infection. Sebum accumulation can be avoided by gently massaging the scalp with a soft toothbrush during the shower once every two weeks according to the patient scalp, or they can be easily removed periodically with forceps extraction at the implant clinic. After that, the scalp must be cleansed with an antiseptic spray (e.g. chlorhexidine).

Clinical and Histological Studies

The implant technique was validated with clinical studies and scientific research from the 1990's onwards [8][9][10][18][21]. Differences in the results achieved during these years represent a constant improvement of the technique and related protocols. A recent clinical study about hair implant conducted on 133 patients (95 men and 38 women) for three years has shown very satisfactory results (Fig. 7a-7c).

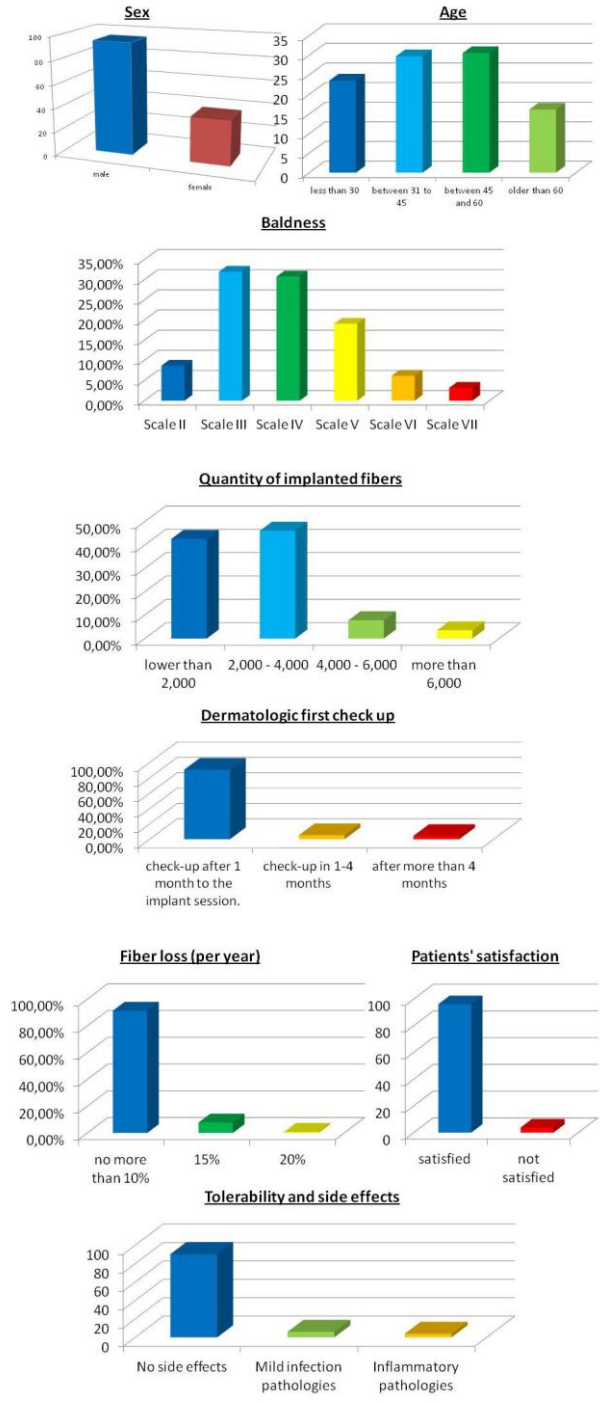

Figure 7: a): clinical features of the patients; b): technique information; c): efficacy and tolerability of implants

The most represented age group of this study was between 30 and 60. These patients underwent implants of up to 6000 Biofibre® (average of 5-6 implants in three months). Fiber loss was not more than 10% per year in 91.4% of the cases, 15% to 7.8% of the cases, and 20% in 0.8% of the cases. 96.2% of the patients stated that they were satisfied with the results of the implant, while 3.8% were not satisfied. As for post-implantation tolerance and complications, 90.3% of the patients recorded no difficulties after surgery. Of the remainder, 5.9% developed mild infections and 3.8% presented with inflammatory changes, mainly from the use of inappropriate chemical substances. Resolution of the scalp infectious and inflammatory issues occurred in an average of 15 days with the use of systemic antibiotics and/or local corticosteroid therapy. In 2.1% of the cases (3 patients), it was necessary to remove the fibres, which was accomplished without leaving any lasting scars.

Histological studies after three years [11][12][21] on Biofibre® (Fig. 8a-8d) have shown that each fibre appears surrounded by a fibrous layer, hindering bacterial penetration. Thin diameters and proper distances between the fibres reduced the occurrence of rejection phenomena. Histopathologically, a sort of infundibulum comprised of Malpighian epithelium, similar to the cutaneous one, formed around the implanted fibre. We can consider it as the basis for adequate fibre anchorage. A moderate, controlled inflammatory infiltrate was noticed. In the middle and deep reticular dermis, the fibre is in contact with collagen. In the hypodermis, no inflammatory infiltrate was noticed.

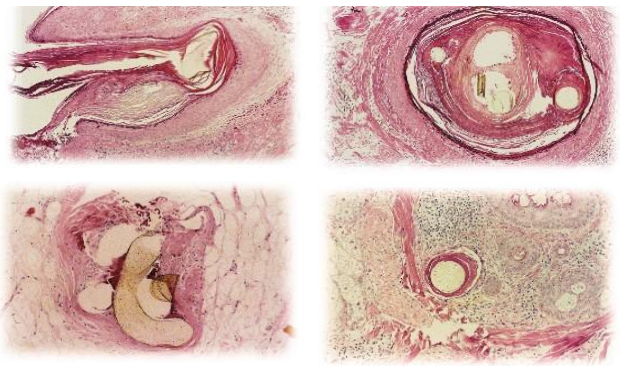

Figure 8: Within the pseudo-infundibula, a compact keratin layer adheres closely to the fibres. In the middle and deep reticular dermis, the fibres are surrounded by a small amount of focally granulomatous chronic infiltrate. In the deepest dermis and hypodermis, the fibres are surrounded by fibroplasia, and no inflammatory infiltrate is noted. (Courtesy of Dr PA Fanti, Lab of Dermatology Histopathology, University of Bologna, Italy)

Discussion

The problem of alopecia affects both sexes and all ages. Between the main surgical techniques

for solving the problem of common baldness, the implant of biocompatible fibres Biofibre® has to be listed. This is a non-traumatic technique, which is performed under local anaesthesia and enables the implantation of the desired quantity of hair, the immediate excellent aesthetic result with a natural appearance, and the accompanying psychological and physical rebound. Artificial hair will not age – i.e. it will not turn white. Biofibre® hair implant is indicated to cover thinned and/or bald areas in case of irreversible alopecia. It is also very successful in alopecia of cicatricial origin (scars, burns). Emerging studies are proving its efficacy in case of total alopecia areata. Post-operative patients are advised to avoid hair dyes with ammonia, hair bleaching, permanent waving, excessive heat, hair curler and thermal shocks, and violent brushing. The disadvantages of this technique are that the implanted “hair” will not grow. It needs some periodical re-touches to keep the expected aesthetic result. Patients with unbalanced diabetes, hepatitis, autoimmune diseases, chronic scalp diseases, or unstable forms of alopecia areata are not suitable for this technique. Implant in some scalp areas must be avoided: temples, the low front line on the forehead, and over very thin or atrophic scalp. Spontaneous Biofibre® hair implants loss is very subjective as it is influenced by many factors such as the patient’s scalp and habits, the climate and the implant procedure. The use of automatic Biofibre® hair implant devices reduces the average implant loss since they allow to place the fibres always in the right depth and angle orientation.

Local infections are mostly due to poor hygiene of the patient and lack of the after-care protocol. Local inflammation is normally caused by the use of the patients of improper products. Fiber extractions although very rare, allow a prompt solution of the problem without remains.

Pre-operative patient selection, mutual consent of patient, appropriate implant equipment, asepsis of the operation field, preparation of the patient, correct implant techniques and medical protocols, compatibility tests, implant on suitable implant areas, patient records, post-operative treatment and drug prescription, aftercare patient instructions providing forbidden products and a treatments list, periodical check-ups and post-implant management must be followed.

In conclusion, why Synthetic Hair Implant is approved in many Countries and not in some others is still mysterious. We tried here to provide the main technical changes, which made this technique safe and effective. Biofibre® Hair Implant is a soft surgery technique, performed under local anaesthesia by a manual implanter or by an automatic machine with certified medical fibres. This technique allows immediate aesthetic result, without patient downtime and with relevant psychological comfort for the patient. It can be considered an efficient hair restoration technique for male and female patients in cases of androgenetic alopecia, hair thinning and scars. Conditions for the success of the implant are suitable patient selection, healthy scalp, compliance with the implant and post-implant medical protocol, correct patient after-care and periodical medical check-up. Clinical and histological studies demonstrated that Biofibre® hair Implant is safe and well tolerated by patients, and can be totally reverse if needed. It can be used alone or in combination with other hair restoration techniques. Studies about implant on total alopecia areata are successfully taking place.

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Review Article

Health and Illness in History, Science and Society

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Abstract

Health is a fundamental human right. The World Health Organization defines it as a "state of complete physical, psychological and social well - being and not merely the absence of disease or infirmity". The health of individuals, however, is also linked to the environment in which they live and especially to their ability to adapt and integrate into their life context. The relationship with the environment is extremely important because it is that interaction that outlines the concept of normality compared to pathology. Such normality needs to be contextualised by gender, geographical origin and by the individuals' living conditions: as a matter of fact, what is normal for a young person may differ from what is normal for a senior one. That is to say, the concept of health is indeed relative and it is the result of an interesting evolution of the concept of illness. From the first approaches - dealing with the mere treatment of the symptoms - to the promise of a free-from-pain society, science and economics have played a significant role in redefining the dualism health/ illness. The article reflects on these two concepts, health and illness, in history and nowadays, and discusses the future of the medical science.

Introduction

Analysing the concept of illness is a rather complex task. Just like for the concept of health – presented by the philosopher Hans - Georg Gadamer as a "[...] general feeling of personal well-being [which] appears mostly when we, in our feeling of personal well-being, are open to new things, are ready to start new business, without considering demands made on us" [1] - there is an important dimension of relativity that needs to be considered: it could be stated that, in the presence of illness, there is a significant change in the functionality of an organ or the entire organism. W. E. Boyd maintains that "illness is a change of the condition in which the organism is in perfect harmony with its environment [...]" [2].

The concept of illness has evolved. In the past, it was linked to the presence of microbes. Later, the emphasis was placed on the constitution and the environment. Nowadays, illness is seen as a system that the body puts in place to find again its lost balance [3] In ancient times, feeling ill concerned the individual only; today, a state of illness can be diagnosed by a physician by objective criteria. Therefore the concept of illness can be seen from many different perspectives.

It is interesting to note that, in the English language, there are three terms to indicate a pathological state: illness, which identifies the personal emotional state connected to the loss of health; disease, which refers to the objective, biological and measurable dimension of it - strictly linked to the physician's activity - and sickness, which

refers instead to the public dimension of the disease and highlights the link between illness and society.

Compared to the ontological model, which aims at eliminating the symptoms, the functional/relational model considers the illness as a dynamic event, an endogenous reaction to the break of a balance. In this perspective, body and mind are inseparable: it is the entire organism that becomes ill, not the single organ. In this model, the physician/patient relationship is crucial, and the physician promotes self - healing processes [4]. Western medicine fully adheres to the so-called scientific method, intended as a set of rules that governs the process of acquiring knowledge. Key elements of the scientific method are the experimental observation of a natural event, the formulation of a general hypothesis in which this event occurs, and the ability to control the hypothesis through subsequent observations.

Science, after a long period in which it was interpreted as true in an absolute sense, completely changed after Albert Einstein, who, with his theory of relativity, laid the basis of quantum physics. Almost simultaneously, the aetiological agents of infectious diseases were discovered, and the first effective remedies to control them were introduced. At first, the arsenical compounds discovered by Paul Ehrlich – which were capable of inhibiting bacterial growth - and then the first antibiotics. Medicine thus became somewhat omnipotent, promising a free-from-pain society. The discoveries of the new physics did not affect the certainties of the twentieth-century medicine. This lack of integration has led the scientific - medical thinking to the reality we experience today.

The relationship between health, nutrition and environment

We cannot speak of health and illness without considering the issue of the environment. As stated by Paul Crutzen – who was awarded the Nobel Prize in Chemistry in 1995 – we might call the geological age in which we live as Anthropocene, that is the era ruled by men. For thousands of years, human beings used for their nutrition and needs plants, seeds and animals: a whole biological world, the result of millions of years of evolution. The richness and variety of our food is the result of extraordinary natural biodiversity. With the arrival of the Modern Era, a gradual extinction of animal and plant species has begun. Alterations and destructions have become exponential: over the last fifty years, we lost more biological heritage than in any previous era. Furthermore, the disappearance of a plant or an animal involves the impossibility of survival of other species connected to them.

In the nineties, some multinational corporations put on the market a variety of genetically modified (GM) corn, soybean and cotton seeds never seen before in the entire history of farming. To date, no epidemiological investigation has ever been conducted to reassure the general public on the effects of GMOs on human and animal health.

GMOs do not exist in nature: they are the result of a manipulation that - to a certain extent – removes the natural barriers between species. An example of how genetic manipulation might influence the health of entire populations is the one concerning the manipulation of cereals [5].

In the last few years, the use of hyper-fertilised wheat has led to an artificial increase of its gluten content: plus 12% compared to a standard one. Gluten is a lipoprotein found in wheat flour which mainly derives from the combination, through water, of two molecules: glutenin and gliadin. This increased concentration of gluten proteins, often three times more than the one our ancestors' organisms were used to, makes the wheat very different from the "old" and best-tolerated ones. The selection of such wheats is surely the cause of many gluten-related health problems. Our organism has not evolved enough to digest a large amount of these substances. Gluten sensitivity and the coeliac disease are only two of several pathologies related to this issue.

The influence of economics on the treatment of illness

Economic sustainability is now an issue to which health policies for prevention and treatment are inextricably linked. In recent decades, the healthcare expenditure in Western countries has shown a steady increase and health today is the most important sector of the economy of a nation. Western countries annually spend on healthcare a significant part of their gross domestic product (GDP). The United States in 2003 spent $ 5,635 - the 14% of GDP - for every single citizen: only $ 1,500 out of this amount were spent for the annual consumption of drugs per capita. Our country in 2005 spent €125 billion that is 7.8% of GPD [6].

The causes of this huge expenditure for acute and chronic diseases are multiple and complex. According to Voltaire, the physician's art would be to entertain the patient until nature heals him. Today, instead, we are witnessing the opposite phenomenon: many conditions, once considered as physiological, can now be considered as subject to therapeutic intervention.

Normal phenomena such as shyness, baldness, apathy, ageing, fatigue and unhappiness

are considered as conditions that can be cured: new diseases that must be treated, often in a costly way [7].

Current challenges and future directions in medical science and health care policies and practice

The framework of the current situation is the increase in the number of diagnoses that, in industrialised countries, has reached grotesque dimensions. It is believed that Homo Sapiens had about 40,000 among diseases, syndromes and disorders. Fortunately, there is a remedy for most diseases. Nowadays the pharmaceutical industry keeps investing in research; however, it spends more for marketing than for innovation. About a third of the revenues and a third of the staff are used only to sell medicines [8].

The issues discussed so far call for a profound reflection about the future of the medical science: a modern health care system will be sustainable only if prevention policies are developed, through the protection of the environment and the promotion of correct eating habits.

It is fundamental, after all, to highlight that - to proceed in this regard - it is necessary to consider the role that culture has always played in the perception that every single person has about taking care of himself/herself. The link between health and care is an interesting topic that is being currently considered by social studies: in particular, the influence that culture and society have on people and their way of keeping healthy is being investigated. Research that starts from the assumption that “culture, as a complex system, is a way of organizing individuals and the relationships that connect them” [9].

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Review Article

Cutaneous Microembolism of Fingers and Toes

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Keywords: Microembolism; Skin; Infections; Tumors; Metabolic disorders; Autoimmune disorders; Coagulation disorders; Physical factors; Vascular occlusive disease

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Abstract

A macro vascular embolism is a well-known emergency. In contrast, cutaneous microembolism is a lesser known symptom. However, cutaneous microembolism of fingers and toes is a red flag symptom for vascular emergencies. The underlying cause may involve infectious, immunological, metabolic and physical disorders, coagulation disorders and malignancies. Early recognition can help to live safe.

Introduction

Vascular micro embolism results in acute pain and subsequent tissue necrosis. Typical causes for this emergency event are an embolus due to atrial fibrillation or thoracic outlet syndrome, or aneurysm of the ulnar artery [1]. Deep venous thrombosis can result in venous gangrene [2]. Another but rare cause is paradoxical embolism due to patent foramen ovale [3].

In contrast, cutaneous micro embolisms are less known in the dermatologic literature and may be easily overlooked. Lesions may not be limited to the acral region. Intermittent painful reddish, bluish macules of the finger tips and toes are a red flag for cutaneous micro embolism leading to the cutaneous vascular-occlusive crisis. In this short review, we will discuss possible causes and consequences.

Cutaneous microemboli

Cardiac disorders

The same conditions that show a higher risk for micro embolism may sometimes cause macroembolism of fingers or toes (Fig. 1). The latter may be overlooked in emergency care.

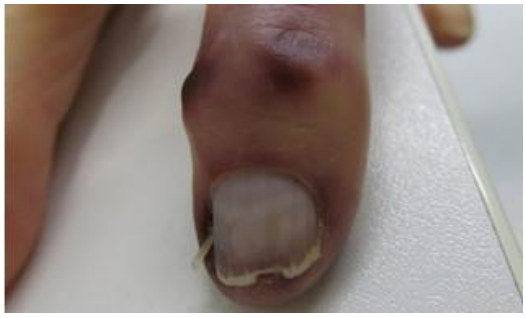

Figure 1: Arterial microembolism of the finger in a 74-year-old female patient with cardiac arrhythmia

Sepsis and another infectious disease

The most common cause of cutaneous microembolism is bacterial septicemia, leading to small pustules, papules and ulcers known as ecthyma gangrenosum (Fig. 2). Bacterial embolisms and vasculitis (bacterial vasculopathy) are responsible [4][5][6][7]. Although different bacteria can cause septicemic vasculitis, meningococci are the major cause in immunocompetent patients. In particular, meningococcemia is characterized by a typical triad of persistent fever, arthralgia, and cutaneous rash [8]. In contrast, bacterial toxins induce petechia, ecchymosis, purpura fulminans, and larger ulcerations [9].

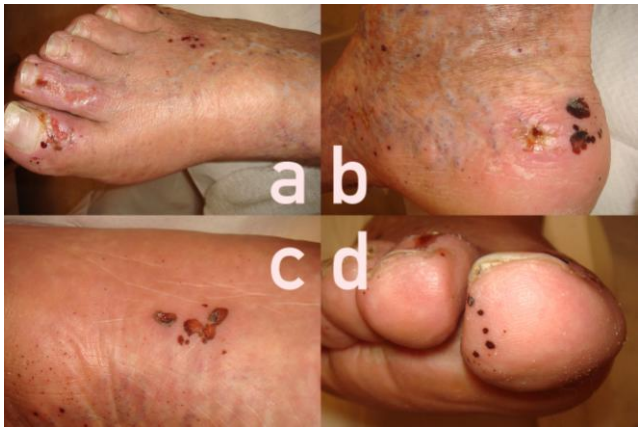

Figure 2: Arterial microembolism in a male patient (79-year-old) due to bacterial septicaemia. (a) Foot with macular lesions and digital ulcers. (b) Detail of the heel. (c) Detail of the plantar region. (d) Macular lesions on the tip of the toes

Systemic fungal infections such as aspergillosis have to be considered in case of atypical signs and symptoms of sepsis, even in immunocompetent patients [10]. In any case of suspected septicemia, patients should be immediately be transferred to an intensive care unit.

A recently, re-emerging infectious disease is anthrax caused by Gram-positive Bacillus anthracis. Cutaneous anthrax presents typically with non-tender cutaneous ulcers with black eschar, oedema, or malignant pustules, and a history of butchering, or dressing/washing of cattle/goat or their meat. Fingers and hands can be the site of primary infection [11]. Treatment with systemic penicillin, amoxicillin or ciprofloxacin in combination with flucloxacillin for two weeks results in high cure rate [11][12].

Metabolic disorders

Crystal cholesterol embolisation is a multisystem ischemic damage characterised by the occlusion of small vessels with cholesterol crystals that originate from ruptured atherosclerotic plaques lining the walls of major arteries. It can cause acute cutaneous microembolism. Selective arteriography will demonstrate mild stenosis. Anticoagulation is not recommended. Treatment of choice is filter-assisted stenting of the affected artery to prevent further embolisation [13].

Tumors and myeloproliferative disorders

Cardiac myxoma often presents with uncharacteristic symptoms. Cutaneous manifestations are often transient and non-specific. Rodríguez Bandera et al. (2015) presented a case of a 36-year-old woman with a 6-month history of intermittent, painful, violaceous, non-blanching macules on the thumb and fingertips of the left hand and right ankle. An urgent echocardiogram demonstrated an atrial mass, with subsequent histopathology confirming the clinical suspicion of atrial myxoma. Excision of a tumour avoided serious complications in this patient [14].

Cancers may alter the clotting system leading to a hypercoagulable state. Thromboembolism is a well-known risk factor for cancer patients with pulmonary embolism as the leading symptom [15]. Stelzner et al. (2012) reported on digital ischemia due to a hitherto unrecognised metastatic colon carcinoma. Anti-cancer treatment is the treatment of choice. In the acute setting, anticoagulation is required. In contrast, routine thrombo-prophylaxis to prevent venous thromboembolism in solid cancer patients is not recommended [16].

Polycythemia vera is marked by arterial and venous thromboembolism. There is a report of painful purple toes in two patients presenting normal peripheral pulses caused by this myeloproliferative disease [17]. Cytoreductive therapy keeping hematocrit threshold beneath 45% represents the cornerstone in the therapeutic approach [18].

Coagulation disorders

Factor V Leiden mutation is an inherited blood coagulation disorders, resulting in resistance to activated protein C and a significantly increased risk of deep leg vein thrombosis. In rare cases, it may cause arterial embolism of the upper extremities [19]. Dorweiler et al. (2003) reported about a 24-year-old woman with acute onset of critical ischemia of her left thumb and index finger. Intra-arterial angiography revealed an embolus in the distal radial artery and a thrombotic occlusion of the digital artery of the thumb and index finger. Immediate surgical embolectomy combined with subsequent local intra-arterial lysis for three days, anticoagulation, and prostaglandin E resulted in a rapid a complete remission [20].

Mechanical vascular damage

The hypothenar hammer syndrome is a type of secondary Raynaud's phenomenon, occurring mainly in subjects who use the hypothenar part of the

hand as a hammer. Occlusion and/or aneurysm of the ulnar artery results from repeated strikes of the hook of the hamate on the superficial palmar branch of the ulnar artery. In a series of 47 patients, multiple occlusions of the digital arteries were observed in 57.4% of cases [21]. Conservative approaches include calcium channel blocker or buflomedil alone or in combination with oral platelet aggregation inhibitors. Other options are hemodilution and prostacyclin analogue therapy. Despite conservative measures, some patients need vascular surgery [22][23].

Vasculitis and autoimmune connective tissue disorders

Vasculitis and autoimmune connective tissue disorders may cause digital ulcers, mostly by vasculitis but sometimes by micro embolism too (Fig. 3). Digital ulcers are more frequently seen in systemic sclerosis, anti-phospholipid syndrome, and Wegener's granulomatosis [24][25]. Immunosuppressive treatment of the underlying cause and adjuvant targeted vascular therapy are necessary. In systemic sclerosis, limited evidence suggests that iloprost, sildenafil and tadalafil may improve ulcer healing. Tadalafil has shown some protective effect as well [26].

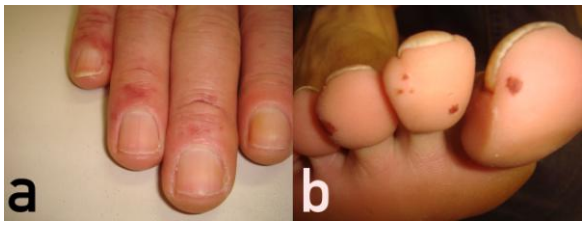

Figure 3: Arterial microembolism in a 49-year-old male patient with systemic lupus erythematosus. (a) Periungual erythema. (b) Cutaneous microembolism of the toes

Another promising approach is the use of autologous adipose-derived stromal vascular cells. A phase I open-label clinical trial (NTC01813279) assessed the safety of subcutaneous injection of the autologous adipose-derived stromal vascular fraction. There was a 33.1% decrease in hand pain, an 88.3% decrease in the Raynaud Condition Score, and a decrease in the number of digital ulcers number 22 and 30 months after treatment [27]. In anti-phospholipid syndrome, warfarin/ phenprocoumon or clopidogrel plus aspirin are appropriate treatments [28].

Physical factors

Perniones (frost bites) are caused by exposure to cold. They are an important differential diagnosis of cutaneous micro embolism [29]. We have seen a female patient presenting perniones together with clinical signs of a cutaneous micro embolism on the toes (Fig. 4). This can be explained by increased blood coagulability in experimental frost bites [30].

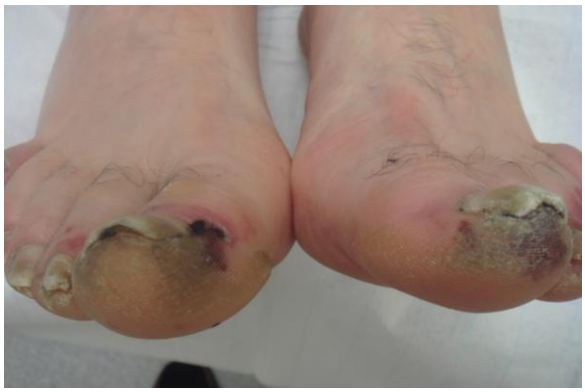

Figure 4: Combination of perniones and cutaneous micro embolism on the toes

Differential diagnoses

Suspicion of cutaneous micro embolism warrants the confirmation by histopathological examination. There are some other disorders that need consideration because they also affect acral regions of the body. The majority of acral necrosis is due to small vessel disorders like diabetic angiopathy (predominance of toe ulcers) [31], scleroderma (finger ulcers are more frequent than toe ulcers) [32], thrombangiitis obliterans (predominant finger ulcers) [33], calciphylaxis [34], or rare entities such as autoimmune inflammatory syndromes like stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) with associated interstitial lung disease (OMIM #615934) [35].

In conclusion, cutaneous microembolism of fingers and toes is a red flag symptom for vascular emergencies. The underlying cause is not uniform, and so is the treatment. Dermatologists should be able to recognise this particular type of macro-vascular compromise and act as a pilot to ensure early diagnosis and treatment.

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Review Article

Unconventional Treatments for Vitiligo: Are They (Un) Satisfactory?

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Abstract

The authors show a brief overview of the vitiligo's unconventional therapies. A part for well-documented effectiveness of L-phenylalanine, PGE2 and antioxidant agents in the treatment of vitiligo, for the other therapeutical approaches more investigations are needed.

Introduction

Despite the numerous therapies of proven efficacy available for vitiligo treatment, in the last decades new unconventional drugs had been introduced for the correction of cutaneous disease.

The authors show a brief overview of the vitiligo's unconventional therapies.

Alpha Lipoic Acid

Alpha lipoic acid is an organosulfur compound with important antioxidant properties. It is commonly found in many dietary products, such as tea, wine, beer, vegetable (e.g. broccoli, spinach), fruit and soy products [1]. Moreover, Alpha lipoic acid is found in yeast, kidney and liver. Recently, it is produced in laboratory for medical purpose. Alpha-lipoic acid is used for the treatment of different disorders, such as diabetes, HIV/AIDS, cancer, liver and eye diseases, and others. It is generally administrated orally at various dosages, ranging from300 to 1,800 mg daily.

Due to its antioxidant properties, recently, alpha-lipoic acid has been proposed in the treatment of vitiligo, to prevent the destruction of melanocytes by

free radicals. It is generally used as adjuvant therapy in association to more conventional treatments (e.g. corticosteroids, phototherapy). Recent data underline its safe profile and effectiveness in terms of acceleration of cutaneous repigmentation in vitiligo patients [2][3).

Flavonoids

Flavonoids (also known as Bioflavonois) are polyphenolic compounds, with antioxidants, anti-inflammatory and anti-microbial properties. They are widely found in plants and in many dietary products (e.g. wine, beer, tea, onions, blueberries, bananas, all citrus fruits, dark chocolate and others). Because their antioxidant action, flavonoids have been proposed as supplements in the treatment of vitiligo patients [4].

A particular mention is due to quercetin, a member of flavonoids, which has been evaluated, both in vitro and in vivo, for the treatment of the pigmentary disease [1]. Different studies underline how quercetin is able to protect keratinocytes and melanocytes by the oxidative damage, suggesting its effectiveness as adjuvant oral therapy in vitiliginous patients [5][6). Moreover, it has been observed how the topical application of quercetin may prevent ultraviolet radiation cellular damage [7].

Fluorouracil

Fluorouracil (also known as 5-fluorouracil or 5-FU) is a pyrimidine analog of the antimetabolites family, used in oncology for about 40 years, because of its anticancer properties.

By some decades, it has been also used by dermatologist for the topical treatment of vitiligo [8]. The drug has been observed to be safe and effective in inducing repigmentation. Better results have been achieved in patients, who previously underwent to an epidermal abrasion (e.g. classical dermabrasion, cutaneous laser ablation), of skin lesions [9][10].

Recently, Capebetacina has been also proposed for vitiligo treatment.

Capecitabine is an oral prodrug of 5-FU, used in the treatment of metastatic colon and breast cancers. It has been observed how its use cause cutaneous hyperpigmentation [11][12]. At the moment, more studies have to be conducted to evaluate the potential use of the drug in the treatment of vitiligo.

Glutathione (GSH)

Glutathione is a well-known antioxidant able to protect cellular components by oxidative stress damage. Recently, some studies underline how its oral use as supplement may be useful in preventing cells photo- damage [13][14]. Unfortunately, more data are needed for its potential use in the treatment of vitiligo.

L-DOPA

L-DOPA is an amino acid, normally produced from the amino acid L-tyrosine by the enzyme tyrosine hydroxylase. It is the precursor of some neurotransmitters (dopamine, noradrenaline and adrenaline), and of the melanin.

In medicine, it is used in the clinical treatment of Parkinson's disease and dopamine-responsive dystonia.

In seventies, by the description of neuromelanin loss from the substantia nigra in Parkinson’s patients, some authors hypotezed its potential use in vitiligo treatment. Unfortunately, only few cases reported its efficacy in vitiligo. First was Grainger who described the beard repigmentation in a Parkinson patient treated with L-DOPA [15]. Successively, Goolamali repoted the repigmentation of vitiliginous patients treated with levoDOPA plus UV lights [16]. In the same period, Woolfson et al treated 16 patients, affected by vitiligo, with a topical preparation of L-DOPA 10% or 20% in a fatty alcohol/propylene glycol base. The results were unsatisfactory [17]. Since then, while no other studies confirmed the utility of the drug in therapy of the pigmentary disease, different studies underlined the role of L-DOPA in inducing vitiligo [18].

Levamisole

Levamisole is an antihelminthic agent, which has been observed to have important immunoregulatory properties [19]. For this property, the drug has been used in the treatment of vitiligo. Few studies demonstrated how Levamisole may be considered as a valid and therapeutic tool, able to arrest the course of the disease and to induce repigmentation [20]. Even if the drug may be uses alone, the association with conventional therapies (e.g. corticosteroids) seems to be more effective [21].

L-Phenylalanine

L-Phenylalanine is an essential α-amino acid, which is used to biochemically form proteins, coded for by DNA. L-Phenylalanine is the natural precursor for tyrosine, which is further converted into cathecholamines (dopamine, noradrenaline and adrenaline) or in the cutaneous pigment melanin. L-Phenylalanine may be introduced with dietary products (e.g. eggs, chicken, liver, beef, milk, cheese, soybeans) or nutritional supplements (e.g. aspartame), which are industrially produced by use of Escherichia coli, a bacterium able to produce large amount of phenylalanine and others amino acids [22]. The amino acid is usually safe, except for people affected by phenylketonuria, a rare genetic disorder charaterized by the inability to metabolize phenylalanine because of the lack of the enzime phenylalanine hydroxylase.

L-Phenylalanine is widely used in medicine for the treatment of different diseases (e.g. depression, attention deficit-hyperactivity disorder, Parkinson's disease, chronic pain, osteoarthritis, rheumatoid arthritis).

Because it is a precursor of melanin [23], dermatologists use the amino acids as a therapeutic tool for vitiligo treatments.

L-Phenylalanine may be administrated both orally (50 – 100 mg/kg of body weight) or topically, and provide better results if combined with UV exposure. The oral administration of phenylalanine (50 – 100 mg/kg of body weight) combined with UVA exposure (also known as PAUVA) is well-known therapy for vitiligo since long time. It is generally well-tolerate and provide quite good results in term of repigmentation rate [24]. Recently, a variant of the classic PAUVA has been experimented. It consists in the oral intake of khellin encapsulated in L-phenylalanin stabilized phosphatidylcholine liposomes, in combination with ultraviolet light therapy (both UVA and UVB). The treatment (also known as KPLUV) has been shown to be effective and safe for the treatment of vitiligo patients [25].

Different therapeutic options are based on the oral and topical application of L-Phenilalanin plus ultraviolet radiation, both natural (sol-therapy) or artificial (UVA or nb-UVB) [26]; and on the oral and topical L- phenylalanine, associated to local clobetasol propionate, and UVA/sunlight [27]. Both the protocols have provided good results in term of repigmentation.

On the other hand, there is the possibility to treat vitiliginous patches with topical L-phenylalanine (cream with L-Phenylalanine 10%), alone, or better, in association with phototherapy/target phototherapy [28]. Finally a mention is due to the introduction of an innovative combined treatment, which is based on the topical application of a cream composed by phenylalanine, cucumis melo extract, and acetyl cysteine, followed by the irradiation with target nb-UVB. The therapeutic protocol has been seen to be effective and safe for vitiligo treatment [29].

Melagenine

Melagenine is an alcohol extract of human placenta, which has been proposed for the topical treatment of vitiligo patients [30]. Even if the exact mechanism of action is still unclear, it seems to stimulate the melanoblast and melanocyte proliferation and the melanogenesis [31]. Classically, it is applied twice a day, alone or in association with ultraviolet radiation. Interestingly, a pilot study underlines the effectiveness of topical melagenine in combination with 20 minutes of infrared exposure twice daily, in the repigmentation of scalp vitiligo [32]. Recently a new formulation of melagenine (Melagenina plus) has been formulated; it consists in a alcohol human placental extract with calcium. The drug is applied once a day, and seems to be effective in stimulating the repigmentation [33]. No side effects had been described in the use of both Melagenine and Melagenine plus. Unfortunately, no recent data are available on the use of melagenine in vitiligo.

Metals

Zinc is a metal, which has many vital functions in human, such as regulation of RNA and DNA metabolism, signal transduction, gene expression, cofactor for enzymes and antioxidant defense system, and cellular apoptosis [34]. It can be assumed with animal-sourced food (e.g. meat, fish, shellfish, fowl, eggs, dairy), food plants (sesame, poppy, mustard, beans, nuts, grains, pumpkin seeds, sunflower seeds and others) and dietary supplements.

Recently, it has been proposed for vitiligo treatment, in association to conventional therapies, such as topical corticosteroid [35]. Unfortunately, the few data, which are today available, don’t support its efficacy in the treatment of the pigmentary disorder.

Minoxidil

Topical Minoxidil (2% or 5%) is a vasodilator drug, which is used topically to treat different forms of hair loss (e.g. male androgenetic alopecia, female

androgenetic alopecia, alopecia areata and other) [36]. Even if exact mechanism of action is not well understood, it seems possible that, by widening blood vessels, Minoxidil allows more oxygen and nutientes to the hair follicles.

About its potential use in vitiligo treatment, only the study of Srinivas et al. reports its efficacy. The authors described how the association of the daily use of topical 2% Minoxidil with alternate day PUVA, was able to induce local hyperthricosis and marker repigmentation in two vitiligo patients [37].

Unfortunately, no other studies about Minoxidil in vitiligo have been conduced and some clinical reports underline controversial results, such as the appearance of leucoderma after the use of the drug [38].

Minerals

Since the discovery of the role of oxidative stress in the pathogenesis of vitiligo, some minerals with proved antioxidative effects, such as Selenium and Manganese, have been proposed as adjuvant oral therapies for the treatment of the skin disease, in association to more conventional therapies (e.g. phototherapy). Unfortunately, today only few studies are available on their use, in terms of both dosage and efficacy [39][40][41].

Omega-3 polyunsatured fatty acids

Omega-3 fatty acids are polyunsaturated fatty acids, with antioxidant and anti-inflammatory properties.

In medicine, they are administrated for the treatment of different disorders, such as cardiovascular diseases, rheumatoid arthritis, atopic diseases, neurodegenerative disorders, cognitive problems, and others [42][43]. They can be assumed with different foods (e.g. fish, fish and krill oils, fruits) or as industrial supplements.

Recently, omega-3 fatty acids have been proposed for vitiligo treatment and to limit the side effects due to phototherapies [1]. Unfortunately, no data are available.

Prostaglandin E2 (PGE2)

Prostaglandin E2 is a member of prostaglandins, a group of hormone-like substances that participate in a wide range of body functions (e.g. uterine contraction, control of blood pressure, modulation of inflammation). In details, PGE2 is an immunomodulatory agent, capable to stimulate melanocytes [44].

In the last years, a topic gel composed by PGE2 has been introduced for the treatment of vitiliginous patients. The drug has been observed to be effective both used alone or in combination with topical corticosteroids or target nb-UVB phototherapy [45][46][47]. No relevant side effects have been described.

Pseudocatalase

In the last years, topical cream cointaning pseudocatalase has been proposed as a valid therapeuthic tool for vitiligo. The drug acts reducing the free radicals and improving the catalase action. Generally, it is applied twice a day. Better results seem to be achieved when pseudocatalase is associated to sol-therapy, UVA or nb-UVB [48][49]. Unfortunately, not all the research confirm this data: some studies underline how the use of pseucocatalase, used alone or associated to UVR, doesn't add any beneficial [50][51].

Resveratrol

Resveratrol is a natural phenol, with marked antioxidant and anti-inflammatory properties. It may be assumed with diet (e.g. wine, peanut, cocoa) or artificial supplements. Recent studies show how its suppletion may be useful in vitiligo treatment, also in association to the classical PUVA-therapy [52][52][53].

Soybeans

Soybeans (also known as soya beans) are a type of legume, particularly rich in flavonoids, which explain how they can be used in vitiliginous patients to halt the oxidative stress phenomenon [1].

Recently, researchers have isolated by soybeans an oestrogen, called Genistein. Few study suggest how its oral and topical administration, are useful in reducing the cell damage by UVR, suggesting a possible adjuvant use of Genistein to phototherapy [54].

Tars

Tars are oily, viscous material, consisting mainly of hydrocarbons, produced by the destructive distillation of organic substances such as wood, coal, or peat. In past, they had been widely used for the topical treatment of psoriasis, both alone or in association to UVR. Because of their antinflammatory and immunosuppressive effects, tars had been also proposed for the treatment of vitiligo [55]. Actually they are not used, not only for the limited data on their effectiveness, but also for their toxicity and carcinogenic effects.

Vitamins

Vitamins are organic compounds, essential for the normal human growth and development, and for its healthy maintenance. Even if some of them are synthesized by the body organs, the others must be assumed with foods or supplements.

Because of the beneficial effects of some vitamins on the skin, since long time dermatologists used to prescribe them for the treatment of different cutaneous diseases. Also for vitiliginous patients, some vitamins have been observed to be useful. Among them, there are: vitamin A, B12, C and E [56].

Different studies underline how an oral supplement of those vitamins is indicated in the treatment of vitiliginous patients, because of their antioxidant properties. Interesting are the good results in term of repigmentation, achieved in vitiliginous patients treated with phototherapy associated to oral vitamins C and E, which are natural photoprotectors [1][57].

In conclusion, a part for well-documented effectiveness of L-phenylalanine, PGE2 and antioxidant agents in the treatment of vitiligo, for the other therapeutical approaches more investigations are needed.

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Review Article

Arthrospira Platensis – Potential in Dermatology and Beyond

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Abstract

The search for natural products with benefits for health in general and of potential for treating human disease has gained wider interest world-wide. Here, we analyse current data on the microalga Arthrospira platensis (AP), that has been used in nutrition since ancient times in Fare East and African communities, for medical purposes with a focus on dermatology. Extracts of AP have been investigated in vitro and in vivo. The alga is rich in proteins, lipopolysaccharides and gamma-linolenic acid. AP extracts, phycocyanin compounds and polysaccharide calcium spirulan (Ca-SP) have been evaluated in various models. It could be demonstrated, that AP has significant antioxidant activity, prevents viruses from entry into target cells and inhibits the colonisation of wounds by multi-resistant bacteria. Furthermore, anti-cancer activity was documented in models of oral cancer, melanoma, and UV-induced non-melanoma skin cancer.

Introduction

Arthrospira (formerly: Spirulina) platensis (AP) is one of the photoautotrophic, planktonic, filamentous green-blue algae that have become of medical interest. It has been used as a protein-rich nutrient since ancient times for instance by the Kanem in Tchad, in Japan and Korea. Seventy percent of dry matter of AP is proteins [1]. The water-soluble fraction of proteins contains molecules between 11,000 and > 300,000 kDa [2]. This plant is very rich in gamma-linolenic acid (GLA) which is produced by the alga by direct desaturation of linoleic acid [1][3][4]. AP also has a high content of vitamin B complex, carotene, and ascorbic acid [5].

The whole cells of AP and lipopolysaccharides isolated from these cells are immunomodulatory in rabbits leading to the production of macro - and microglobulin antibodies [6].

In this review, we focus on medical indications for the possible use of AP in dermatology.

Antiviral activities

An aqueous extract of AP containing lipopolysaccharides as well as a fraction depleted of polysaccharides and tannins inhibited HIV - 1 replication in human T - cell lines, peripheral blood mononuclear cells (PBMC), and Langerhans cells (LC). The 50% inhibitory concentration (IC_{50}) of

extract for PBMC growth ranged between 0.8 and 3.1 mg/ml. In vitro, the extract inactivated HIV - 1 directly, i.e. viral entry and fusion [7].

In a small phase I trial, five HIV - infected, treatment naïve adult patients took algae extracts from either AP or brown seaweed Undaria pinnatifida or a mixture of both for 3 to 13 months. No toxicities were observed, but a bB stabilisation of the CD4 cell count and virus load was found. Both parameters improved after 13 months [8].

Allophycocyanin from AP neutralised in vitro the enterovirus 71 - induced cytopathic effects in both human rhabdomyosarcoma cells and African green monkey kidney cells with an IC50 of approximately 0.045 ± 0.012 μM. Allophycocyanin was active in the state of viral adsorption and post-adsorption, respectively. However, the antiviral activity was superior when added to the cell cultures before viral infection. Allophycocyanin delayed the viral RNA synthesis in infected cells and reduced thereby enterovirus - 71 - induced apoptosis [8].

Aqueous extracts of AP and purified calcium spirulan (Ca-SP) were investigated for their potential in human herpes simplex virus 1(HHV1) and 8 (HHV8) infections. Ca-SP represents a sulfated polysaccharide mainly composed of rhamnose, that is capable of chelating calcium. In vitro, Ca-SP inhibited HHV1 infection of Vero cells with an IC50 of 0.04 μg/mL and HaCaT cells with an IC50 of 0.07 μg/mL. AP extract was lesser effective. Ca - SP inhibited the delivery of viral protein VP16, that is necessary for viral attachment to target cells, in a dose-dependent manner. In an observational trial, 198 adult female patients, who underwent a procedure for permanent lip makeup and had a history of previous herpes labialis, were included. Patients received herpes prophylaxis with either topical ointment containing AP extract and Ca - SP, topical acyclovir or systemic acyclovir/ valacyclovir. Herpes reactivation was observed in about 20% with systemic medications, 90% with topical acyclovir, and 60% with topical AP extract/ Ca-SP [10]. In conclusion, topical AP extract/ Ca - SP was more effective in this open trial than topical acyclovir.

HHV8 is responsible for cutaneous Kaposi sarcoma. Tissue cultures of human RPE - 1 cells were infected by HHV8. The IC50 for Ca-SP for HHV8 titer reduction and reduction of DNA copies in treated versus untreated controls was 1.5μg/mL. Ca - SP inhibited the uptake of viral ORF45 tegument protein by target cells in a dose-dependent manner [10].

Antioxidant activity

It was shown that a protean extract of AP is a potent free-radical scavenger for both hydroxyl and peroxyl radicals and inhibits microsomal lipid peroxidation. The major component of this activity is the phycobiliprotein C - phycocyanin [11].

C - phycocyanin has been evaluated in several models of inflammation. It was shown to reduce oedema, histamine release from mast cells, myeloperoxidase activity of macrophages, and the concentrations of prostaglandin-E2 and leukotriene LTB4 in inflammatory lesions [12].

Chinese researchers succeeded in the crystallisation of the selenium-containing phycocyanin from the selenium-rich by the hanging-drop vapour diffusion techniques [13]. Indian researchers developed a method of purification of C - phycocyanin [14].

Experimental studies have been performed to analyse the potential of AP as a matrix for the production of selenium - and iodine-containing pharmaceuticals [15].

More recently, the potential of algae extracts on diabetic nephropathy was investigated in a mouse model. Oral administration of phycocyanin (300 mg/kg) for ten weeks protected against albuminuria and renal mesangial expansion. The compound also normalised tumour growth factor-β and fibronectin expression. Phycocyanin was capable of normalising urinary and renal oxidative stress markers and the expression of NAD(P)H oxidase components. Similar antioxidant effects were observed following oral administration of phycocyanobilin (15 mg/kg) for two weeks. Phycocyanobilin also inhibited NADPH dependent superoxide production in cultures of renal mesangial cells [16].

By the use of one-step high-speed counter-current chromatography (HSCCC) with ethanol-ammonium sulfate, another major antioxidant could be isolated: a α - acidic polysaccharide, composed of major glucose, slight rhamnose and mannose, with a molecular weight of 12.33 kDa [17].

Reactive oxygen species and mitochondrial dysfunction have been implicated in doxorubicin-induced and tilmicosin-induced cardiotoxicity [18][19] and ciclosporin A-induced and cisplatin-induced nephrotoxicity [20][21]. In mice and rat models of these diseases, extracts from AP exhibited dose-dependent cytoprotective activities. Concerning cardiomyocytes, C - pyocyanin has been identified as the most active compound to protect cells from mitochondrial dysfunction, lipid and protein peroxidation thereby diminishing apoptosis [22].

Liver injury by liver toxins like dibutyl nitrosamine precursors [23], carbon tetrachloride [24], lead acetate [25], deltamethrin [26], and drugs such as acetaminophen [27] or cisplatin [28] can be diminished by AP extracts.

Anti-inflammatory, anti-pyretic, and anti - hyperalgesic effects

C-phycocyanin is a selective inhibitor of cyclooxygenase - 2 (COX-2), that is upregulated during inflammation and induces apoptosis in macrophages [29][30]. In a carrageenan-induced thermal hyperalgesia animal model C - phycocyanin was investigated for anti-inflammatory and anti-hyperalgesic effects. C - phycocyanin inhibited the overproduction of nitric oxide (NO) and prostaglandin E2 by suppression of inducible NO synthase and COX-2. Also, there was an attenuation of TNF -alfa formation and tissue infiltration by neutrophilic granulocytes [31].

Antipyretic activity of AP was demonstrated in Brewer's Yeast induced pyrexia in rats. The anti-inflammatory potential had been evaluated in rat paw oedema induced by prostaglandin E2 injection. In both models, AP extract revealed dose-dependent efficacy [32].

Wound healing potential

Using an in vitro model with cultivated human dermal fibroblast various extracts of AP have been screened for a wound healing promotion. Aqueous extracts stimulated both proliferation and migration of fibroblasts and enhanced the closure rate of wounds within 24 hours after treatment. Methanolic and ethanolic extracts supported fibroblast proliferation too but failed to support migration and wound closure. The plant extracts were further characterised: Cinnamic acid, narigenin, kaempferol, temsirolimus, phosphatidylserine isomeric derivatives and sulphoquinovosyl diacylglycerol supported proliferation. The authors concluded that AP might pose potential medical use to treat chronic wounds especially in diabetes mellitus patients [33].

Colonization of chronic wounds with bacteria including methicillin-resistant Staphylococcus aureus (MRSA) is an increasing health problem [34]. Of interest for wound treatment is the fact that topical Maresometrade mark containing lipids and all other components of microalgae in an encapsulated form, is capable of inhibiting dermal colonisation by several MRSA strains and by vancomycin-resistant strain MU50. In animal models, MRSA colonisation was reduced by 3 - 4 log units in comparison to controls [35].

Gunes et al. (2017) used an aqueous AP crude extract in a concentration of 1.125% in a skin cream. The formulation enhanced wound healing in HS2 keratinocyte cell cultures [36].

Anti-cancer potential

The first published data on the possible anti-cancer potential of AP extracts came from dimethylbenz(a)anthracene - induced squamous cell carcinomas (SCC) of hamster buccal pouch as a model of oral SCC. Phylogenies from algae extract induced complete response in 30% and partial response in 70% of animals treated twice weekly by intratumoral injections [37].

In a model investigating the early epithelial changes leading to oral SCC, buccal pouches of the Syrian hamsters were painted with 7, 12 - dimethylbenz[a]anthracene. Supplementation of the diet with AP extracts diminished epithelial dysplasia during 14 weeks of this study [38] and 32 weeks in a long-term study [39]. In the latter study, the progression to SCC was reduced by AOP extracts as well.

By using an in vitro model of invasion of tumour cells through reconstituted basement membrane (Matrigel)/fibronectin-coated filters, the potential of Ca-SP isolated from AP was evaluated. Ca-SP significantly inhibited the invasion of B16 - BL6 melanoma, Colon 26 M3.1 carcinoma and HT - 1080 fibrosarcoma cells. Ca - SP also inhibited migration of tumour cells on laminin but failed on fibronectin. This effect was accompanied by prevented adhesion of B16-BL6 melanoma cells to Matrigel and laminin but did not affect the adhesion to fibronectin. Experimental lung metastasis was significantly reduced by co-injection of B16-BL6 cells with Ca - SP. In B16-BL6 spontaneous lung metastasis model, several intra-venous injections 100 µg of Ca - SP diminished the tumours lung colonisation [40].

Non-melanoma skin cancer is induced by ultraviolet (UV) light exposure, natural and artificial. UVB (280 - 320nm) irradiation of skin induces the formation of 8-oxo - 7,8-dihydroguanine (8 - oxoG) by UV-induced reactive oxygen species. Ogg1 gene encodes a repair enzyme that removes 8 - oxoG - DNA. Ogg1 - knock out (KO) mice, missing the repair enzyme, have become an established model for UVB-induced skin cancer [41]. In Ogg1 - KO mice fed with AP extracts, skin tumours developed about seven weeks later than in control animals without AP extracts. Furthermore, the number of tumours was lower in AP-treated animals, but the ratio of malignant versus benign skin tumours remained unaffected by AP. The authors could further demonstrate, that AP lead to a reduced acute UVB-induced inflammation (ear swelling and erythema). AP downregulated signalling proteins such as p38 mitogen-activated protein kinase, kinase/c-Jun N-terminal kinase, and extracellular signal-regulated kinase after UVB exposure in mice [42]. AP extracts from their anti-inflammatory, and anti-oxidative potential may be beneficial in UV - induced skin cancer. However, studies in humans are warranted before conclusions.

In conclusion, AP is a source of various, partially identified and purified compounds with potential health benefits and activities in the prevention or treatment of some human pathologies, ranging from infections to environmental disorders, chronic wounds and cancer. Despite the vast advantages in basic research and in in vitro and in vivo models of disease, human trials are sparse. A better standardization of natural products and randomized controlled trials in human disease are necessary before final conclusions. Nevertheless, the potential of natural products as AP should not be underestimated [43].

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Review Article

Vitiligo in Children: A Better Understanding of the Disease

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Abstract

Vitiligo is an important skin disease of childhood. The authors briefly discuss the etiopathobiology, clinics and comorbidities of the disease.

Introduction

Vitiligo is an acquired, chronic, pigmentary disorder characterized by the progressive loss of cutaneous melanocytes and abnormality in their normal function, resulting in hypopigmented skin areas which progressively become amelanotic [1].

Different studies underline how half of vitiligo patients develop the disease before the age of 20 years old and how about 25% of them develop the disease before the age of 8 [2].

In pediatric age, vitiligo may represent a deep psychological trauma for both patients and their parents, and leads to a poor quality of life [3]. Even if the treatment of the disease is mail goal for dermatologists, a better understanding of vitiligo may be helpful for a better management of the patient.

Etiology

As well-known, vitiligo is inherited in a non-Mendelian, multifactorial and polygenic pattern.

A part for gene encoding molecules relevant for the normal melanogenesis (e.g. TYR which encode for Tyrosinase), recent studies show a strong association of vitiligo with particular HLA haplotypes (HLAs-A2, -DR4, -DR7, and –DQB1*0303) and other genes (Tab. 1) which are implicated in both cellular and humoral immunity [4][5][6]. Because the possible

associated to different autoimmune diseases, in future, the recognition of the genetic background should be helpful to recognize eventual comorbidities and personalized focused treatment.

Table 1: some of gene which may be alterated in vitiligo patients

Gene	Protein	Function	Comorbilities
RERE	Atrophin like protein 1	Regulation apoptosis	
PTPN22	Lymphoid specific protein tyrosinase phosphatase nonreceptor 22	Regulation T cell receptor signaling	Type 1 DM, Grave's disease, RA, Addison's disease, psoriasis, IBD
CTLA4B	Cytotoxic T lymphocytes antigen 4	Inhibition of T cells	Type 1 DM, Grave's disease, Hashimoto's thyroiditis, IBD, SLE
FOXP1	Forkhead box P1	Regulation of lymphoid cell development	
TSLP	Thymic stromal lymphoprotein	Regulation of T cell and DC maturation	
CCR6	Chemokine receptor type 6	Regulation of B cell differentiation	IBD, AR, Grave's disease
IL2RA	Interleukin 2 receptor	Regulation of lymphocyte response to bacteria	Type 1 DM, Grave's disease, RA, multiple sclerosis, SLE
GZMB	Granzyme B	Mediator of T cell and NK apoptosis	
FOXP3	Forkhead box P3	Regulation of T-reg	

Environmental factors

Many data support the deep impact of environmental factors in the development of vitiligo. First at all, there is the evidence of a variable prevalence of the disease in different countries, which range from 0.1 to 2.0%.

Then there are the data about the incidence of the disease among familiarities. It has been estimated that most of the cases of vitiligo are sporadic and up to 20% of patients report an affected relative. Moreover, the incidence of concordance of vitiligo in monozygotic twins is only 23% [7].

Different environmental factors (Tab. 2) may trigger the disease: their recognition would be fundamental to limit the incidence and progression of the skin disease.

Table 2: Trigger factors which may be involved in vitiligo onset

Physical stress: major illness, surgical operations, accidents
Intercurrent infections and repeated antibiotic- intake
UVR and sunburns
Chemical factors: Thiols, Phenols, Catechols, Mercaptoamines, Quinones and their derivatives
Endocrine factors: pregnancy
Malnutrition: malnutritional habits, intake of preserved, stale, junk flood
Psycho-social insecurity/shocks

Pathobiology

Today the exact pathobiology of vitiligo is still unclear. Even if multiple theories have been proposed (Tab. 3), recent data support that vitiligo is a T-cell mediated autoimmune disease, triggered by oxidative stress [8]. In melanocytes, the progressive accumulation of reactive oxygen species (ROS) causes DNA damage, lipid and protein peroxidation. Many are the proteins altered, showing partial or complete loss of their functionality. In particular tyrosinase is found to be inhibited by the high concentrations of hydrogen peroxide [9]. Also keratinocytes are significantly altered by oxidative stress, leading to a deficit of their trophic support to melanocytes [10].

Table 3: Pathobiological theories for vitiligo

• Oxydative stress theory
• Autoimmune theory
• Neurohumoral theory
• Autocytotoxic theory
• Biochemical theory
• Melanocytorrhagy theory
• Theory of decreased melanocyte lifespan
• Inflammatory theory

Clinic of vitiligo

Classically, vitiligo is characterized by asymptomatic white macules, varying in form and size. Although it is more often localized on body folds, periorificial and sun-exposed areas, vitiligo may affect different part of the body, both cutaneous and mucosal. Occasionally, patients may show the damage of the hair follicles' melanocytes, which result in depigmentated hairs (also known as "leukotrichia"). Characteristic is the Koebner's phenomenon, consisting in the development of new lesions at sites of skin trauma.

Table 4: Clinical variant of vitiligo [11-12]

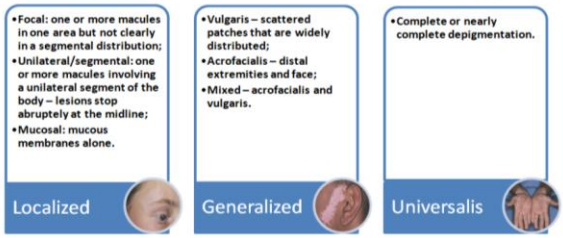
Type of vitiligo	Characteristics
Punctata vitiligo	little, punctuate-like, depigmented macules
Follicular vitiligo	vitiligo involving the follicular reservoir with poor cutaneous lesions
Inflammatory vitiligo	erythematous halo surrounding the white patches
Trichrome vitiligo	hypo-pigmented area between the central amelanotic zone and the peripheral normal skin
Quadrichrome vitiligo	variant of trichrome vitiligo with foci of repigmentation at the follicular osti
Pentachrome vitiligo	lesions show the occurrence of five shade of color, by white to black
Blue vitiligo	bluish appearance of skin color

In addition to such more common clinical features, vitiligo patients may also show abnormalities of the melanocytes localized in different districts (e.g. eyes, ears, brain, heart and lungs) [13].

Classification

Another classification of the skin disease, often preferred to the first one, is based on the clinical feature and natural history of vitiligo (Tab. 6) [14].

Table 5: classification of vitiligo on the basis of the disease distribution



Recognize the type of vitiligo has important implication for the management of the patient, because for each form there is a different prognosis (Tab. 7).

Table 6: Classification of vitiligo based on the clinical feature and natural history of the disease

Types	Characteristics	Subtypes
Segmental vitiligo (SV)	One or more vitiliginous patches, in a linear or flag-like pattern of mosaicism, with a unilateral dermatomal distribution	Unisegmental Bisegmental Multisegmental
Non-segmental vitligo (NSV)	Heterogeneous group of pigmentary disorders with different localization, usually in a symmetric pattern	Acrofacial Mucosal (more than 1 side affected) Generalized Universal Mixed (associated with segmental vitiligo) Rare forms
Unclassified or indeterminate		Focal Mucosal (only one side)

Comorbidities

The increased risk of developing autoimmune diseases of vitiligo patients is a well-known data (Tab. 8) [15].

Table 7: Prognosis of different forms of vitiligo

- Localized – stable, regressive
- Generalized – progressive, systemic, possible association with other autoimmune diseases
- Universalis – common association with comorbidities

Even if at the moment no laboratory biomarker are available to evaluate the possible association with autoimmune comorbidities, it is recommended to rule out the presence of associated diseases thought the commonest autoimmune antibodies and clinical laboratory data (Tab. 9).

Table 8: common autoimmune diseases associated to vitligo

- Alopecia areata
- Atopic dermatitis
- Autoimmune hemolytic anemia
- Autoimmune thyroid disease
- Diabetes mellitus
- Inflammatory bowel disease
- Morphea
- Multiple sclerosis
- Pemphigus vulgaris
- Pernicious anemia
- Psoriasis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Others

Finally, even if more rare especially in childhood, recent studies underline the possible association of vitiligo with different diseases, such as endocrinologic ones (e.g. hypoparathyroidism) and systemic inflammatory disorders (e.g. obesity, metabolic syndrome) [16].

Table 9: Antibodies and laboratory data to be checked in a patient with vitiligo

Ab to be checked • Routine ○ Anti-thyroid peroxidase Ab (ATPO) ○ Anti-thyroglobulin Ab (ATG) ○ Anti-thyroid ○ Anti-parietal gastric cell antibody ○ Total IgE • Second line ○ Anti-nuclear Ab (ANA) ○ Additional autoantibodies (only if patient's history, family history and/or laboratory parameters highlight a strong risk of additional autoimmune disease or if endocrinologist /immunologist advice if multiple autoimmune syndrome detected
Laboratory data • Thyroid stimulating hormone (TSH) • Eosinophil count • Vitamin B12 • Folic acid

In conclusion, vitiligo may be considered as a spectrum of diseases with different clinical presentations, unknown etiology, fragmented genetic data and pathobiological hypothesis. We strongly affirm the importance of a better knowledge of the etio-pathobiology and clinic of the disease, for a better management of the patients.

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Review Article

Integrative Dermatology – The Use of Herbals and Nutritional Supplements to Treat Dermatological Conditions

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Abstract

From humble beginnings at the dawn of time to it's advanced and successful status today, this essay traces the history of natural medicine and the development of integrated dermatology to what it is today. Some of the most well-known natural (international and Australian) products with an application in dermatology are discussed. The history and functions of the Psoriasis Eczema Clinic and the products developed by its founder, Prof. Michael Tirant, are explained.

Introduction

Integrative Dermatology is a relatively new term coined to describe treatment therapy that combines Complementary Medicine with Dermatology in the treatment of dermatological conditions. It was first explored in Fitzpatrick's Dermatology in General Medicine, Chapter 241 - Complementary and Alternative Medicine in Dermatology, published in 2007. The authors stated that "Complementary and Alternative medicine (CAM) in dermatology encompasses a wide variety of methods of diagnosis and treatment that either supplement or substitute for conventional dermatologic practice, drawing on an expanded knowledge base that includes CAM, conventional practice, and the latest research findings. Its diagnostic and therapeutic choices are made by combining these three knowledge bases, in what might also be termed integrative dermatology" [1].

In the late 70's and early 80's, the main treatment options for dermatological conditions were exclusively in the domain of mainstream or conventional medicine. However, in some western countries, Complementary Alternative Medicine (CAM) was becoming more popular. As patients began to seek alternative treatment approaches using natural therapies to treat their skin conditions, CAM practitioners, including naturopaths, began to experiment with western herbal medicine and traditional Chinese medicine to meet the needs of their patients. Naturopaths tended to rely heavily on anecdotal and traditional treatments from historical

data rather than on scientific research results.

History of Mainstream Medicine/Allopathic Medicine for Dermatological Conditions

Mainstream medicine, although effective, mainly focused on providing symptomatic relief using topicals and/ or systemic, either as orals or injectables. Corticosteroids were first introduced in the treatment of psoriasis in 1952 with the topical application of hydrocortisone. Later, the steroid molecule was fluoridated which allowed more potent steroids like fluocinolone acetonide, betamethasone valerate and clobestadol propionate to be developed. These were then enhanced with occlusive dressings or by using combination therapies with salicylic acid and tars [5].

The 50's also saw the introduction of folate inhibitors like methotrexate, in both topical and as systemic preparations. In the 70's, Retinoids, analogues of Vitamin A, began to be used, especially for erythrodermic and pustular psoriasis, again as topical and systemic, with the first clinical trial on Isotretinoin undertaken in 1972. Later, other second-generation Vitamin A analogues, Etretinate (Retinoic Acid) and Acitretin were introduced as either topical and/or systemic. In the mid 80's analogues of Vitamin D (Calciprotriol) was found to also be of benefit in the topical treatment of psoriasis and by the mid-90s oral calcitriol (Vitamin D) became available [5][6][7].

Phototherapy was and is still one of the most common treatment options for psoriasis, with narrowband UVB (nbUVB) or psoralen ultraviolet A (PUVA) the most widely used applications. In the 50's, Dr John Ingram developed a treatment regimen using ultraviolet B (UVB) radiation in conjunction with coal tar and anthralin paste, and by the 70's, broadband UVB was found to be effective in clearing mild forms of psoriasis, whilst ultraviolet A (UVA) irradiation in combination with either oral or topical application of psoralen, was also being used. By the 80's narrowband UVB (nbUVB) was found to be effective in treating psoriasis [8].

With the advent of biologics to treat autoimmune diseases such as Rheumatoid Arthritis, researchers experimented during the 90's in the treatments of various systemic and cutaneous diseases. Biologics are protein molecules produced by recombinant DNA technology, which target the specific sites in the immune - pathogenesis pathway of the diseases by blocking these pathways. Because of the specific action on the immune system, biologics are considered to have fewer side effects compared to the traditional immune - suppressants. However, the use of biologics is still limited because of the unknown long-term safety profile and various aspects of the biologics [9].

History of Complementary Alternative Medicine (CAM) and CAM Therapies for Dermatological conditions

Complementary Alternative Medicine (CAM) is mainly focused on treating the human body as a whole in the hope that the dermatological condition would benefit from their treatment(s). CAM includes naturopathic compounded creams using herbal ingredients, herbal systems and nutritional supplementation and “detox” diets.

The history of CAM and the treatment of dermatological conditions are founded on the use of specific herbs solely developed based on locally available plants and through trade in ethnobotanical remedies. Various schools of herbal use developed regionally in Europe,

the Middle East, Africa, India, China, Japan, Australia, and the Americas. The best-known systems still in use today are the Ayurvedic herbs originated from India, herbal treatments developed as part of traditional Chinese medicine (TCM) in China, and Western Herbal Medicine developed in the United States and based on European and Native American traditions and later influenced by TCM [10].

Unlike the developing countries where traditional medicine remains entrenched in the treatment of various conditions including skin conditions, Europe and the United States saw a steady decrease during the 1900's in the use of herbal treatments and the number of herbalists, as purified extracts and synthetic chemical drugs became available. However, from the 70's onwards there has been a steady resurgence in the use of herbal treatments and the number of visits to CAM practitioners. The causes for this are varied including:- the increase in the identification of serious side effects of chemical drugs, the increased cost of mainstream medications, the lack of long-term efficacy of mainstream medication and a general desire to return to nature, natural remedies and an alteration to diet to include organic produce. Thus herbal remedies, including those for skin conditions, are continually gaining greater popularity among patients and to a lesser degree greater tolerance and/ or acceptance among General Practitioners [10].

In the United States, the number of visits to CAM practitioners has grown rapidly, estimated to have increased from 427 million in 1990 to 629 million in 1997. This 1997 figure exceeded the number of

visits Americans made to all primary care physicians in the United States during that same year. Furthermore, it is estimated that between 50% and 75% of the US population is using some form of CAM at a given time [11].

In the European Union, there are approximately 150,000 dual-trained doctors, meaning trained in conventional medicine and a particular CAM modality. In addition to these dually trained doctors, there are in the order of 180,000 non-doctor CAM practitioners. However, the prevalence rates of the main therapies in use are much harder to define, as statistical records are basic at best and therapies monitored and reporting methods differ from country to country. As an example, for Herbal Medicine (31 studies), the prevalence rates varied from 5.9 - 48.3% of the population studies. However, herbal medicine was not well defined (it may have been included in naturopathy, folk medicine or traditional Chinese medicine) and different categories including medical herbalism, herbal remedies, herbal teas and Phytotherapy [12].

Notwithstanding the number of alternate therapies that are included under the banner of CAM, for this review, the following will be considered: TCM, Ayurveda and Western Herbal Medicine and Naturopathy.

Traditional Chinese Medicine

The conceptual foundation of TCM is entirely different from that of western medicine. TCM is centred on the five solid organs − heart, liver, spleen, lung, and kidney and six hollow viscera − large and small intestine, urinary bladder, stomach, gall bladder, and 'triple burners'. These 'structures' are connected by conduits and vessels with 'Qi' (energy) and blood circulating through them. There is no equivalent counterpart in conventional Western medicine for Qi. TCM treatment is based on the diagnosis of the individual as a whole rather that the Western mainstream medical approach which typically concentrates on the disease. TCM uses a process called 'syndrome identification', whereby the practitioner makes a dynamic conceptualisation of the individual's situation and comes up with a 'pathophysiologic status' (the type of disharmony) for the individual; this status is called 'zheng' or 'syndrome'. The therapeutics used to restore the harmony within the host and between the host and their environment are determined by the identified 'syndrome' [13].

Because TCM views all diseases as patterns of symptoms that correspond to individual disorders or syndromes, the aim is to treat the pattern disorder which is the cause of the problem and not the disease itself. For example, one of the common patterns in acne is “Lung Heat” and is seen as the most common pattern in a teenager. It is important to note that not all patients with acne are treated in the same way. A TCM treatment protocol might include a combination of Acupuncture, Chinese herbs in either raw, tinctured or pill form, external herbal washes or creams and dietary advice.

TCM and Acupuncture

The World Health Organisation recognises acupuncture as a suitable treatment for a wide variety of different conditions [14]. Acupuncture means to puncture with a needle. Acupuncture is usually, but not always, combined with herbal medicine. The needles are small, sterile and disposable. Patients do not normally feel any pain, although they may experience a feeling of warmth, tingling, dull ache or a heavy sensation, which the Chinese call 'sour'.

In many Asian countries, skin diseases are customarily treated with acupuncture. However, there have been very few controlled studies published. In a randomised controlled clinical trial on chloasma, acupuncture had a significantly better effect than vitamins C and E. Some evidence favouring acupuncture treatment of herpes zoster (human (alpha) herpes virus) has been reported. It has been established that acupuncture has an anti-pruritic effect. This has been shown experimentally in volunteers, suggesting that acupuncture could be used in clinical conditions associated with pruritus. Acupuncture with dermal needles has traditionally been used in the treatment of neurodermatitis, with confirmation of its effect in a controlled clinical trial “Treatment of 60 cases of neurodermatitis with three-step seven-star needling therapy”, published in the Journal of Guiyang Chinese Medical College, 1998. Acupuncture, particularly ear acupuncture, has also been used in the treatment of acne vulgaris. In one study published in 2012 a single-blind clinical trial on 84 outpatients with psoriasis vulgaris by auricular therapy (ear acupuncture) combined with a TCM Yin Xie ling Formula, reported reduction scores in the treatment group of 74.4% [14][15].

TCM and Chinese Herbs

The herbal medicine used in TCM can come in various forms. The most common form of prescription involves a selection of herbs specifically chosen for the patient and “cooked”, usually by the

patient as a decoction (tea). The cooking time can be over hours, and most patients find that the actual decoctions are not very palatable. Tinctures are herbal preparations made in alcoholic bases and pills are also prescribed. Up to 8 to 12 pills may be taken twice per day, as the pills are made of herbal plant material, not concentrated chemicals.

In one clinical trial carried out at the Hospital for Sick Children, London, England, a Chinese physician, Dr. Luo, formulated a mixture of 10 herbs for the treatment of atopic dermatitis, consisting of Clematis armandii, Dictamnus dasycarpus, Glycyrrhiza glabra, Ledebouriella satellites, Lophatherum gracile, Rehmannia glutinosa, Paeonia lactiflora, Potentilla Chinensis, Tribulus Terrestris, and Schizonepeta tenuifolia. In this double-blind, placebo-controlled crossover study, there was a clear distinction between the genuine TCM therapy and the placebo herbs. With the active herbs, there was a median decrease in erythema of 91.4% and a decrease in the extent of surface involvement of 85.7% [16].

Washes are decocted herbs that are used externally on the body, usually twice daily. Depending on the herbal prescription proposed the purpose was to assist with various symptoms including extreme itching, heat, ulcerations as well as the healing of the skin.

A 1 - year follow - up with both children and adults who chose to continue to use TCM showed a persistent benefit with only minimal side effects.

This is in contrast to the clinical deterioration of patients who elected to discontinue use of TCM in the ensuing year. It is of interest to note that many of the patients, both children and adults, who chose to continue TCM, were able to decrease the frequency of their TCM to less than daily use, while still others were able to discontinue treatment altogether without experiencing a relapse [16].

TCM and Diet

Dietary therapy in TCM is considered extremely important as all foods possess a certain “nature”, which include Cold, Hot, Sweet, Sour etc., which can affect the body. During a consultation, the TCM practitioner usually advises the patient to avoid certain foods considered to potentially aggravate the condition. The patient is also advised to eat more of the foods that are beneficial for the condition. For example, it is important to avoid hot spicy foods in skin conditions as they create more heat in the body and hence more redness or itching.

Ayurvedic Medicine

Ayurveda originates from India, and the Ayurvedic system of medicine describes a wide range of etiological factors for dermatological disorders. The etiological factors include physical, physiological, psychological, psychosocial, and hereditary and Papakarma (sinful activities) aspect. Ayurveda emphasises threefold therapeutic management based on (avoiding causative factors) for almost all types of disorders including dermatological disorders. Ayurvedic therapy is probably the hardest for non-Indian Practitioners to comprehend as the combined use of herbal formulas with chants, mantras, gems etc. is far more complicated and foreign. Most of the herbs described for the management of dermatological disorders in Ayurveda are “Rasayana drugs” [17].

Various studies on “Rasayana drugs” suggest the following therapeutic properties:

- Immunomodulator
- Adaptogenic
- Antioxidant
- Nootropic
- Antistress

In Ayurveda, “Rasayana drugs” are considered very important for the management of dermatological disorders. Skin health is restored and maintained by directly targeting the different layers and cells of the skin involved in the process of skin ageing & dysfunction and also in the pathogenesis of a disease. Diet modification or dietary supplementation is also very much emphasised in the Ayurvedic system of medicine for the prevention, as well as management, of disorders including skin conditions. The diet rich in Amla (Indian gooseberry), Lavana (salt) and Katu Rasa (pungent, spicy), milk, curd, jaggery (cane sugar), and a diet which is unbalanced should be avoided.

The recommended diet includes old wheat, old barley, pulses like Moonga (brown beans), Masoor (red lentils), Arhar (split pigeon peas), honey, Patola (Luffa cylindrical – vegetable from the gourd family), Neem (leaf), garlic, old Ghrita (ghee) and Tikta Rasa (bitter herbal juices). Also, Triphala (made up of these three fruits, dried and powdered - Amalaki (Emblica officials or Phyllanthus emblica), haritaki (Terminalia chebula) and bibhitaki (Terminalia bellirica)) is important [17].

In Ayurveda, the therapy in the form of “Rasayana drugs” and diets cannot be effective unless the body channels are properly cleansed, and toxic materials are eliminated. Samshodhan (detoxification) is believed to purify or cleanse all the body tissues and bring about the harmony of bio-

humours to obtain long-lasting beneficial effects. So, Ayurvedic practice is to incorporate divine therapy or psychological therapy including chanting Mantras, the spiritual use of herbs and gems, sacrifices, offerings and washing with ceremonial penances, fasting, and other rituals for social wellbeing etc. [17].

There have been published “trials” on the success of Ayurvedic treatments for psoriasis and vitiligo, but these studies are difficult to assess. As an example, in one study patients were randomly divided into two groups. Koshtha Shuddhi was done using Eranda bhrushta haritaki (6g at night with ushnodaka) for both groups for three days before starting the treatment. A total of 111 patients were selected for the study and divided into two groups - A and B. Group A (45) patients were given “Navayasa Rasayana Leha” and “Dhatryadhyo lepa” for the external application while Group B (49) patients were given Medhya Rasayana tablet along with the application of Dhatryadhyo lepa.

The duration of the study was three months, and follow-up was done for one month. Both the groups showed equally good results on improving the quality of life in the patients regarding Dermatology life quality index and Psoriasis disability index.

The study was also coupled with Laboratory investigations and a DLQI and Psoriasis Disability Index (PDI) questionnaire.

1. Blood – Hemoglobin (Hb), total count (TC), differential count (DC), erythrocyte sedimentation rate (ESR), total red blood cells (RBC), and peripheral blood picture.

2. Urine – Routine and microscopic examination.

3. Biochemical – Fasting blood sugar (FBS), serum creatinine, serum glutamate oxaloacetate transaminase (SGOT), serum calcium, total protein, albumin/globulin (A/G) ratio.

The study did not show any PASI scoring nor were the results of the laboratory investigations detailed. The authors only reported on the DLQI and the PDI results. The overall effect on PDI showed that both the therapies had highly significant relief ($P< 0.001$), but percentage wise, group A showed better relief by 72.20% whereas group B showed relief by 65.99%. While DLQI showed beneficial effects of therapy, group A showed 70.26% relief, whereas group B showed 67.64% relief [18].

Western Herbal Medicine (WHM), Naturopathy and Dermatological Conditions Western Herbal Medicine (WHM) covers the following therapies:- Herbal medicine, Phytotherapy, Botanical medicine, Medical herbalism, Herbalism.19 Herbalists are defined as health practitioners who engage in extemporaneous compounding of herbs for therapeutic purposes for individuals under their care and are broadly classified under Western, or European, herbal practice. Two systems of knowledge are identified within

Western herbal medicine: Evidence-based medicine (EBM) and Traditional Knowledge (TK) [20].

EBM has developed as a way to evaluate and generate biomedical knowledge, and to link research findings with clinical application. “Evidence-based medicine is defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.” [21].

Traditional Knowledge is used to cover a range of fields, which are referred to as Traditional Ecological Knowledge, Indigenous Knowledge and Folk Knowledge. All of these terms relate to the knowledge which has been developed by indigenous and traditional cultures about their environment [22].

Plants and their secondary metabolite constituents, have a long history of use in modern WHM and certain systems of traditional medicine, and in mainstream medicine are the sources of important drugs such as aspirin (from willow bark), digoxin (from foxglove), quinine (from cinchona bark), and morphine (from the opium poppy) [23].

Since the latter half of the twentieth century, monographs on selected herbs have become available from some sources, including the European Scientific Cooperative on Phytotherapy (ESCOP, 1999), German Commission E (Blumenthal et al., 1998) and the World Health Organization (WHO, 1999).

The WHO monographs classify the herb according to a number of criteria including botanical, synonyms and vernacular names; the herbal part commonly used such as leaf, stem, root, flower etc., its geographical distribution, tests used to identify and characterize the herb (including macroscopic and microscopic examination and purity testing), the active principles (when known), dosage forms and dosing, medicinal uses, pharmacology, contra-indications and adverse reactions.

Other resources that provide detailed information about herbal products in current use include the Natural Medicines Comprehensive Database and the European Commission on herbal medicinal products in the European Union (EU) [24].

Naturopathy

Naturopathy incorporates traditional natural remedies including herbal remedies, nutrition,

acupuncture, traditional Asian medicine, hydrotherapy, and other modalities. Overall, naturopathy focuses on the use of non-toxic, natural remedies. In the US and Canada, Naturopathic Practitioners are trained as family and general physicians and can be registered as doctors. However, in most other countries, this level of training or recognition has not occurred [20]. The tenets of Naturopathy seem worthy:

- First, do no harm
- Use the healing power of nature, the body's innate healing power
- Treat the underlying cause of the disease, not just the symptoms
- Treat the whole person – holistic health
- Educate the patient about their health
- Focus on preventing disease

Some of the modalities involved in Naturopathic Medicine [20], include:

Clinical Nutrition - Naturopathic Practitioner, has the belief that diet is the basis for health, hence encouraging their patients to adopt an appropriate healthy diet, which is the first step towards correcting health problems. Naturopathic Practitioners may use specific individualised diets, fasting, and nutritional supplements.

Lifestyle Counselling and Stress Management - Mental attitudes and emotional states are considered to be important elements in healing and cause of disease. Naturopathic Practitioners are trained in counselling, stress management, hypnotherapy, and biofeedback.

Botanical Medicine - Plants have powerful healing properties. Many pharmaceutical drugs have their origins in plant substances. Naturopathic Practitioners use plant substances in varied forms for their healing effects and nutritional value.

Physical Medicine - Naturopathic medicine includes methods of therapeutic manipulation of muscles and bones. Naturopathic Practitioners may also employ therapeutic exercise, massage, hydrotherapy, bio - electrical therapies, ultrasound, and the use of heat and cold applications.

TCM – Some Naturopathic Practitioners are trained in the fundamentals of TCM and diagnosis. They may use acupressure, and Chinese herbal medicine to promote healing. With additional training and licensure, they may also perform acupuncture.

Homeopathic Medicine - Homeopathic medicines are very small doses of natural substances that stimulate the body's self-healing response with minimal or no side effects. Homeopathy is a popular topic for debate, even from its inception.

Natural Childbirth - In the US and Canada Naturopathic Doctors also offer Natural Childbirth care, provided they undergo additional speciality training. They offer prenatal and postnatal care using appropriate diagnostic and treatment techniques.

Minor Office Procedures - Naturopathic Practitioners with the appropriate training can perform in-office minor surgery including repair of superficial wounds and removal of foreign bodies, warts and cysts with local anaesthesia. Both Herbalists and Naturopaths use their understanding of herbs and dietary modification to treat the body as a whole. They both use a combination of tinctures (usually an alcohol base with herbal infusions), herbal powders and tablets as well as compounded topical creams and lotions. Naturopaths also use nutritional supplementation (mineral, vitamin, amino acids and others) to treat their patients.

An outline of various CAM treatment options for skin conditions including Mode of Action, Properties, Adverse Effects and Drug Interactions follows below:

Traditional Chinese Medicine in Dermatology

Chinese medicine has a long history of treating skin-related symptoms, with previous reviews identifying 174 different herbs that have been used for skin conditions, however western clinical trials and the literature on TCM therapies and formulations for skin conditions, remain scant. Any studies that are published have usually been conducted in China and are often small and uncontrolled. The formulations in these studies are either not specified, or if ingredients are given, then amounts are not, the formulations are not easily replicable outside the study settings and at times the botanical identification of the plant used is obscure as there are no monographs available. This makes it extremely difficult for western research scientists to do follow up and efficacy studies in a controlled setting (Table 1).

Table 1: Example One: Zemaphyte 25, 26, 27, 28

Treatment	Mode of Action and Properties	Ingredients
Oral treatment with daily decoctions	1. Reduction in number of dendritic cells and macrophages in the lesional skin 2. CD1a and CD23 MoDC expression inhibited 3. Allogeneic and autogenic stimulatory activity decreased 4. Induction of IL-10 production	*Ledebouriella saseloides Potentilla chinensis Clematidis armandii Rehmannia glutinosa Paeonia lactiflora Lophatherum gracile Dictamnus dasycarpus Tribulus terrestris Glycyrrhiza glabra Schizonepeta tenuifolia*

A Cochrane review in 2004, collated the reported adverse events from published clinical trials. Blood analysis, renal function and liver function were investigated in all three cross - over trials. No changes were observed for either treatment. A few minor

adverse events were reported with Zemaphyte, including dizziness, gastrointestinal upsets and one case of lichenoid eruption, mild abdominal distension and headaches. However, one serious adverse event resulting in an admission to hospital with a flare of eczema and associated bacterial infection was reported in one trial. Both patients had been taking the herbal tea- bag preparation. Blood tests showed no significant alterations except for one case where lymphocyte count fell transiently and with intermittent lymphopaenia being present for several years. Liver function abnormalities were observed in two children in the follow-up study but became normal after discontinuing the herbal therapy [29].

In one trial, a total of 35 adverse events were reported in 694 patients (5.04%), mainly gastrointestinal symptoms (2.58%) such as nausea, vomiting and mild diarrhoea.

Other adverse events included urticaria, photosensitivity, an exacerbation of eczema, night diuresis, discolouration of teeth and bilirubin creatinine values outside normal limits. Liver function values were raised in seven patients but returned to normal after treatment was discontinued [29].

A topical application using Shi Du Ruan Gao (SDRG) is shown in Table 2. No data was found on adverse events on the constituents of this formula.

Table 2: Example Two: Shi Du Ruan Gao (SDRG) 30, 31, 32

Treatment	Mode of Action and Properties Of some Ingredients*	Ingredients:
Topical twice daily application	*1. Indigo naturalism* has a mode of action which includes anti-inflammatory and antimicrobial. It is thought to modulate the proliferation and differentiation of keratinocytes in the epidermis. Also, it acts as an inhibitor of the infiltration of T lymphocytes. Since these processes are components of subsequent inflammatory reactions in psoriatic lesions, it has a possible application in this field. 2. In mice serum, *Phellodendron chinense* has been shown to significantly downregulate macrophage chemoattractant protein-1 (MCP 1), lipopolysaccharide-induced interleukin-6 (IL-6) and IL- 1β. *Cortex Phellodendri* has also been shown to inhibit inducible nitric oxide synthase (iNOS), activated nuclear factor-κB (NF-κB) by degradation and phosphorylation of IκBα, and attenuated phosphorylation of mitogen-activated protein kinases such as ERK1/2, p38, and JNK in mice treated with lipopolysaccharide. 3. According to TCM theory, Gypsum has astringent and granulating functions. It has been shown in research to promote skin wounds healing by accelerating the formation of micrangium and collagenoblast and the proliferation of granulation tissues.	***I**ndigo naturalis* (Qing Dai) *Cortex Phellodendri* (Huang Bai), Gypsum fibrosum preparatum (Duan Shi Gao) Calamine (Lu Gan Shi) *Galla chinensis* (Wu Bei Zi)

The restriction of access to Chinese clinical trials and databases plus the limited number of western clinical trials drastically reduces the potential to review recorded significant data. The trial data that has been published in western publications and online databases is restrictive and does not allow a definitive ruling on efficacy.

Ayurvedic Medicine in Dermatology

The difficulties outlined earlier in trying to assess. Ayurvedic medicine and clinical trials can be seen in the following example. In a 2013 trial, titled “Comparative effect of Navayasa Rasayana Leha and Medhya Rasayana tablet along with Dhatryadhyo Lepa in Eka kushta (psoriasis)”.

Table 3: Tablet One: Navayasa Rasayana Leha 31, 32, 33, 34, 35

Treatment	Mode of Action and Properties Of some Ingredients*	Ingredients:
Tablet - 2 gm twice a day.	**Dhatri** Reduces elevated levels of serum creatinine, urea nitrogen, TBARS ; decreased iNOS, COX 2 expression. Reduced hexachlorocyclohexane (HCH) & induced raisenin renal gamma glutamyltranspeptidase (GGT) activity. Protects against damaging effects of free radicals, non-radicals and transition metal-induced oxidative stress in the skin. When compared to diclofenac, exhibits anti-inflammatory activity in both acute and chronic model of inflammation. Prevention of immunosuppression through the restoration of phagocytosis and production of gamma-interferon by macrophages. Prevention of chromium-induced oxidative damage through decreased GSH and GPx activity in macrophages. Inhibition of matrix metalloproteinase levels, MMP-1, hyaluronidase activities, and promotion of pro- collagen content in UV-B induced skin photo ageing in fibroblasts by MTT assay. Exhibited a dose-dependent switching from anti- oxidant to pro-oxidant and immuno-modulatory property. Marked up-regulation of anti-inflammatory cytokine (IL-10) concentration. Efficient reduction of pro-inflammatory cytokine (TNF- α and IL-1β) levels. **Haritaki** Immunomodulatory activity of ripe *T. Chebula* fruits – this study showed an increase in the concentration of antioxidant enzymes, GSH, T and B cells. This increase plays an important role in immunity. The occurrence also enhances the concentration of melatonin in the pineal gland and the levels of cytokines. Gallic & chebulagic acid isolated from the extract of herbal medicine, Kashi (myrobalans: the fruit of *Terminalia chebula*) are the active principles that block cytotoxic t lymphocyte (ctl)-mediated cytotoxicity. **Chitraka** In inflammatory immune disorders, *Lumbago zeylanica* extract exhibits immuno- suppressive action. This occurs due these constituents - plumbagin, linoleic acid, nonylnonanoate & stigmasterol. **Bakuchi** The phenolic glycosides in the aqueous extract of *Psoralea corylifolia* inhibits keratinocytes replication in psoriasis. Several flavonoids from *P. corylifolia* exhibit inhibition on IL-6-induced STAT3 activation and phosphorylation and may, therefore, be useful in the treatment of inflammatory diseases	**Dhatri** - *Emblica Officinalis (*Indian Gooseberry) **Aksha** - *Terminalia bellirica* (tropical almond) **Haritaki** - *Terminalia chebula* (another type of tropical almond) **Vidanga** - *Embelia ribes* (flase black pepper) **Chitraka** - *Plumbago Zeylanica* (Ceylon Lead Wort) **Shuddha Bhallataka** - *Semecarpus anacardium* (related to the cashew) **Bakuchi** - *Psoralea corylifolia* **Loha Bhasma** – Iron oxide **Bhrungraj** - *Eclipta prostrata* (false daisy)

*Please Note: the mode of action has been compiled from several studies, reviews and scientific papers

This involved two groups, with each group taking a different tablet formulation (Tables 3 and 4) while both groups used the same topical formulation (Table 5) [31].

Table 4: Tablet Two: Medhya Rasayana 35, 36, 37, 38, 39

Treatment	Mode of Action and Properties Of some Ingredients*	Ingredients:
Tablet – 500 mg 2 tablets twice daily	**Vacha -** A herb which acts on the CNS with anticonvulsant, hypnotic, sedative, and tranquilising properties. After administration for six weeks, *Acorus calamus* resulted in decreased severity of depression as well as improved rehabilitation. It also showed a significant improvement in assessment based on the rating of symptoms on the Hamilton depression rating scale. In an experimental study on rats examining the spontaneous electrical activity and monoamine levels of the brain, the ethanol extract of AC exhibited a depressive action by changing electrical activity and by altering brain monoamine levels in different brain regions. The pharmacodynamic actions of α - Asarone and β - asarone exhibits many similarities to some well-established tranquillisers. A Study of the mechanism of the tranquillising action of α - asarone found that its sedative effect to be dependent on the depression of the ergotropic division of the hypothalamus. In monkeys, α - Asarone produced a prolonged calming effect. In rats, it decreased anxiety and resulted in reduced spontaneous motor activity without dulling perception. Also, it inhibited production of nitric oxide (NO), interleukin - 2 (IL - 2) and tumour necrosis factor - α (TNF-α). Treatment with *A. calamus* extract did not affect intracytoplasmic interferon - γ (IFN - γ) and expression of cell surface markers, CD16 and HLA - DR on human PBMC. It did, however, down-regulate CD25 expression. This study demonstrated the antiproliferative and immuno - suppressive potential of ethanolic extract of *A. calamus* rhizome in vitro. **Jatamansi -** Study results suggest efficacy in the prevention of lipid peroxidation. This is involved in cell membrane disruption and cell damage. The extract showed potential as a powerful oxidant, with high reducing power and inhibition of protein oxidation. It has potential as a scavenger of-of superoxide radicals and ROS. It also decreased DNA damage and protein carbonyls. Also, it is an effective iron chelator. **Jyotishmati -** also has antioxidant properties, and induces antioxidant enzymes. It limits hydrogen peroxide-induced toxicity in neuronal cells.	**Vacha -** *Acorus calamus* (sweet flag) **Haritaki** - *Terminalia chebula* (a type of tropical almond) **Jatamansi -** *Nardostachys jatamansi* (member of the Valerian family) **Jyotishmati -** *Celastrus paniculata* **Yashtimadhu -** *Glycyrrhiza glabra* **Shuddha Bhallataka -** *Semecarpus Anacardium* (related to the cashew) **Guduchi -** *Tinospora cordifolia* (moon seed) **Brahmi -** *Bacopa monnieri* (Waterhyssop) **Shankhpushphi -** *Convolvulus pluricaulis* (Bindweed)

*Please Note: the mode of action has been compiled from several studies, reviews and scientific papers

Unlike most medical dermatological clinical trials conducted on psoriasis, where the use of the Psoriasis Area Severity Index (PASI) scoring system is standard, in this trial the PASI scoring had been altered, and no detail was given on how the psoriasis lesions were assessed. Developed in 1978, PASI is an index used to express the severity of psoriasis, and it combines the severity (erythema, induration and desquamation) and percentage of the affected area to arrive at a final score, as depicted in Table 6.

Table 5: Topical - Dhatryadhyo Lepa 31, 40, 41, 42

Treatment	Mode of Action and Properties of some Ingredients	Ingredients:
Topical **Details as to the exact formulation were not specified, other internet sources – namely a PPT presentation by the authors indicated that the same ingredients as the tablet: Navayasa Rasayana Leha is used. However whether it was a wash, cream, ointment or poultice was not specified.** **It was applied twice daily.**	**Dhatri** A potent antioxidant is limiting oxidative stress-induced damage; it protects against ultraviolet-B irradiation-induced ROS and collagen damage in human dermal fibroblasts. Stimulates proliferation of fibroblasts in a concentration-dependent manner. Induces production of pro-collagen in a concentration and time-dependent manner. Marked decrease of Matrix metalloproteinases (MMP) - 1 production from fibroblasts *E. officinalis* extract acts as an effective agent in collagen metabolism. This enhances its abilities in cosmetic, mitigative and therapeutic applications. **Bakuchi** The extract exhibits antimicrobial activity against both grams positive and gram-negative skin pathogens.	**Dhatri** - *Emblica Officinalis* (Indian Gooseberry) **Aksha** - *Terminalia bellirica* (tropical almond) **Haritaki** - *Terminalia chebula* (another type of tropical almond) **Vidanga** - *Embelia ribes* (flase black pepper) **Chitraka** - *Plumbago Zeylanica* (Ceylon Lead Wort) **Shuddha Bhallataka** - *Semecarpus Anacardium* (related to the cashew) **Bakuchi** - *Psoralea corylifolia* **Loha Bhasma** – Iron oxide **Bhrungraj** - *Eclipta prostrate* (false daisy)

*Please Note: The mode of action has been compiled from several studies, reviews and scientific papers

The authors in the Ayurvedic trial stated that they used a scoring pattern made specifically for their study to assess the pattern of some symptoms, as given by the National Psoriasis Foundation, but do not clarify nor reference it. However, their method for assessment was based on the grades given below:

1. Complete Remission: 100% relief
2. Marked Improvement: 75% to 99% relief
3. Moderate Improvement: 51% to 74% relief
4. Mild Improvement: 25% to 50% relief
5. Unchanged: < 25% or No relief 31

Table 6: Topical - Dhatryadhyo Lepa 31, 40, 41, 42

Score	0	1	2	3	4
Erythema	0 = none	1 =mild	2 = moderate	3= severe	4 = very severe
infiltration	0 = none	1 =mild	2 = moderate	3= severe	4 = very severe
Parakeratosis	0 = none	1 =mild	2 = moderate	3= severe	4 = very severe
Score	0	1	2, 3	4, 5	6
Area 0/0	0	>10	10<30 30<50	50<70 70<90	90<100

This is very different from the universally accepted PASI scoring system. Furthermore, the rating was subjective, using the term “RELIEF”, rather than lesion improvement or clearing. Although Body Surface Area is mentioned, no details were given. Another drawback of the study was the inclusion of both plaque and guttate psoriasis patients, but there were no details as to the number of participants suffering from each type. The authors mentioned that some tests were conducted:

1. Blood – Hemoglobin (Hb), Total count of WBCs (TC), differential count of WBC (DC), erythrocyte sedimentation rate (ESR), Total red blood corpuscles (RBC), Peripheral Blood picture

2. Urine - Routine and Microscopic

examination

3. Biochemical - Fasting blood sugar (FBS), Serum creatinine, serum glutamic pyruvic transaminase (SGPT), Serum calcium, Total protein, the albumin-globulin ratio (A/G ratio) [31].

However, apart from the statement “Insignificant results were found in all laboratory parameters in both the groups”, no further details or actual pre- and post-treatment results were included in the findings.

The difficulty in being able to assess the efficacy of the treatment is due to the inconsistent and confusing reporting parameters. The parameters that were set and reported on have either been modified or do not have a workable translation or equivalent comparison that can be directly related to the western dermatological terminology or parameters used in mainstream clinical trials. Much of the data reported is referring to symptoms and possible modes of action that purely relate to Ayurvedic terminology and thus extremely difficult to properly translate and understand from a western medical point of view.

It was also extremely difficult to obtain safety assessments, adverse effects and contraindications on the majority of the Indian herbs used in this trial, as there are few comprehensive monographs available. A complete monograph for Psoralea corylifolia was the only one found, which included toxicity, acute toxicity, adverse effects, precautions and safety. All other monographs provided very basic information, often without any mention of any toxicity data.

Western Herbal Medicine and Naturopathic Medicine in Dermatology

In Europe, several of the traditional medicines have been studied in clinical trials and developed into modern registered drugs. For a number of these plant-based drugs, controlled clinical trials have proven their efficacy and can thus be prescribed in evidence-based medicine [71]. The European Medicines Agency (EMA) has established a Committee that reports on Herbal Medicinal Products (HMPC).

They issue scientific opinions on herbal substances and preparations, along with information on recommended uses and safe conditions. They require a full quality dossier for all herbal medicinal products as well as other fundamental principles that apply to all medicinal products including good manufacturing practice, pharmacovigilance and requirements on packaging and labelling. They classify herbal medicine products into 1) Herbal substances with Final European Union herbal monographs (alphabetical order) and 2) Herbal substances with Final European Union herbal monographs (according to therapeutic areas).

The lists are also divided into two groups of herbal medicinal products: a) well - established use: demonstrated with sufficient safety and efficacy data and b) traditional use: accepted by adequate safety data in conjunction with plausible efficacy.

For this paper, a few herbs have been selected, including Calendula Officinalis L., Melaleuca alternifolia, Myrrha, Centella Asiatica (L.) (Gotu Kola) and Aloe Vera to show their mode of action, interactions and adverse effects as discussed in Table 7.

Each of these herbs has been used as topical treatments in some clinical trials for various wound healing and skin conditions with differing results. Usually, the clinical trials are on the single herb at various doses and in various carriers, including creams, gels, and petroleum bases. This makes it exceptionally difficult to quantifiably state that a certain percentage of herbal extract “Y” is consistently efficacious in resolving a certain skin condition. Much research time and effort have been spent in trying to identify the active ingredients and therapeutic properties, including antimicrobial, antioxidant, and antiseptic.

In 2006, an evidence-based systematic review by the Natural Standard Research Collaboration was conducted on calendula. They concluded that much of the research had been done on animals and as such may be of limited use only when assessing viability in treating skin conditions. However, while recognising that traditionally, calendula has been used topically for treating minor wounds, burns and other skin problems, they found that there was no strong scientific evidence to support this use.

However, they felt that there was good scientific evidence to support the use of calendula in Radiation dermatitis [61]. Calendula can prevent oxidative stress, making it theoretically an ideal treatment for radiodermatitis. It is thought that this occurs via the numerous polyphenols contained in its extract. Polyphenols have many potentially therapeutic roles as antioxidants on the skin. The pylene glycol extract of Calendula has been studied, with results showing that it interferes with neutrophil radical oxygen species (ROS) and radical nitrogen species (RNS) generation, particularly nitric oxide, at concentrations as low as 0.2 μg/mL [46].

Table 7: Properties of selected herbs

Treatment Topical	Adverse Effects	Drug Interactions	Mode of Action and Properties
***Calendula Officinalis* L.** **46, 47, 48, 49, 50**	No allergic events occurred in the group (126 patients) given Calendula during the clinical trial. There is no evidence for phototoxic activities. The extract was found to cause allergy in 9 patients out of 443 (2.03 %) when assessed by patch testing method. Therefore a cross-sensitivity with other members of the Asteraceae cannot be excluded. Experimentally, the plant extract is a weak sensitiser. This is probably due to the lack of sesquiterpene lactones in Calendula flowers.	None reported	The polysaccharides isolated from an aqueous extract of *Calendula* flowers stimulates the phagocytosis of human granulocytes. *Calendula* flower extracts have been shown to exhibit anti - oxidative effects on liposomal lipid peroxidation induced by Fe + and ascorbic acid. *Calendula* extract contains numerous polyphenols which inhibit oxidative stress, At concentrations as low as 0.2 µg/mL, *Calendula* exhibits anti - oxidant qualities. It interferes with neutrophil radical oxygen species (ROS) and radical nitrogen species (RNS) generation, particularly nitric oxide *Calendula* inhibits lipoxygenase activity in vitro. It also significantly reduces monocyte chemotactic protein - 1, keratinocyte-derived chemokine, granulocyte colony-stimulating factor, IL - 1 alpha, and vascular endothelial growth factor (VEGF). Calendula exhibits anti-inflammatory activity via its active components - triterpenoids, faradiol monoester and free ester faradiol. Of these, the latter is the most active and exhibits the same effects as an equimolar dose of indomethacin. The extract of *Calendula* reduced pro-inflammatory markers including TNF - α, IL - 1β, (IL - 6), interferon-gamma (IFN - γ), c - reactive protein (CRP), and cyclooxygenase - 2 (COX - 2).
Melaleuca alternifolia **46, 47, 48, 49, 50**	Adverse skin reactions have been reported. These include mild pruritus, burning sensation, discomfort, irritation, stinging, erythema, and oedema. Allergic reactions have been reported. The frequency is not known. In rare cases, a burn - like skin reaction has been reported. Considerable systemic exposure may result from percutaneous absorption after topical application of Tea Tree oil and Tea Tree oil-containing products. This may occur especially when neat oil, body lotion and foot spray/powder is used (see appendix). The extent of systemic exposure to Tea Tree Oil from cosmetic products is uncertain due to inadequate availability of dermal absorption studies. In accidental poisonings, *Melaleuca aetheroleum* causes Central Nervous System depression and muscle weakness. These symptoms resolved within 36 hours. Classified as hazardous - R22 Harmful if swallowed - Swallowing can result in hallucinations, ataxia, diarrhoea, central nervous system depression, sleep or coma.	None reported	**Tea Tree Oil (TTO) -** suppresses inflammatory mediator production through activated human monocytes. These include lipopolysaccharide - induced tumour necrosis factor-α, IL-1β, IL-8, IL-10 and prostaglandin E2. Of these, lipopolysaccharide-induced tumour necrosis factor-α is often considered the most influential inflammatory cytokine. The water-soluble components of TTO can suppress the production of superoxide by human monocytes, but not neutrophils activated in vitro. TTO may enable neutrophils to be fully active in an acute inflammatory response and eliminate foreign antigens while suppressing monocyte production of superoxide and inflammatory mediators. It thereby prevents oxidative damage and the activation of other cells that are seen in more chronic inflammatory states. Micro-emulsion (stable dispersions of oil and water stabilised by an interfacial film of a surfactant, usually in combination with a co-surfactant) systems of 5% TTO from M*elaleuca alternifolia* are promising vehicles for transdermal drug delivery. The major component of TTO is Terpinen-4-ol. It has shown strong antimicrobial and anti-inflammatory properties. In vitro research has demonstrated that terminal-4-ol can inhibit the production of several inflammatory mediators (such as interleukins) by human peripheral blood monocytes.
Commiphora myrrha **51, 52, 53, 54, 55**	Allergic contact dermatitis has been reported.	Interaction with warfarin has been reported. –the anticoagulant effect of warfarin was reduced after aqueous extract of boiled roots of *Commiphora molmol* was taken orally. When taken orally, Gugulipid, a constituent of Myrrh, decreased the serum level of the drugs Diltiazem and Propranolol. Another component, *Z*-guggulsterone, increased the uptake of iodine by the thyroid gland as well as oxygen uptake in the liver and bicep tissues. This occurred when taken orally combined with some thyroid medications. Oral administration of myrrh may potentiate the effects of aspirin, non-steroidal, anti-inflammatory drugs, and warfarin. Oral guggulsterone was found to be a bile acid receptor and farnesoid X	Several sesquiterpenes (furanodesma-1.3- diene, current, furanodiene, furanodiene-6-one and metyhoxyfuranoguaia-9-one-8-one) have been found to have antibacterial, antifungal, analgesic and local anaesthetic effects. As demonstrated in vitro, myrrh contains terpenes with fairly potent antibacterial effect against several bacteria including the most common wound pathogen *S. aureus.* The mechanism of action is unknown. The phytochemical evaluation showed the presence of alkaloids, glycosides, steroids, terpenoids and flavonoids in the methanol extract of guggul. Flavonoids are the key metabolic compounds having anti-inflammatory, antihistaminic, antibacterial and antiviral properties. It has also shown a moderate scavenging effect against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. Guggul shows a definite pro-healing action due to the wound contraction ability of the oil and resin of scented myrrh. One reason for this ability could be via the enhanced proliferation of epithelial cells. As an incision wound treated by guggul shows greater tensile strength, it might be inferred that myrrh extracts not only increase collagen synthesis per cell but also aid in cross-linking of the proteins. This wound healing activity is likely to be attributed to its high content of terpenoids. Due to their astringent and antimicrobial properties, terpenoids are known to promote the wound healing process. This process could be responsible for wound contraction and increased rate of epithelization. Another component, sesquiterpene lactones, is known to possess antioxidant activity. This may contribute to the wound healing process and the promotion of rapid wound healing.

		receptor (FXR) antagonist both in vitro and in vivo. Topically–None known	
Centella Asiatica (L.) (Gotu Kola) ***56, 57, 58***	Administered in the recommended doses, C. asiatica is not toxic, and side effects are rare. When used externally, it may cause allergic reactions and burning. The sensitising effect of the triterpene fraction could be a potential cause of allergic contact dermatitis.	None Identified	*C. asiatica* affects extracellular matrix proteins deposition. It stimulates fibroblasts proliferation, activates the Smad pathway, increases collagen synthesis and decreases the activity of metalloproteinases, thereby increasing collagen deposition.
Aloe Vera Topical 59	Possible erythema, burning and stinging. Generalized dermatitis may occur in sensitive individuals. Anthraquinones, such as aloin and barbaloin, may cause allergic reactions.	None Identified	Topical and oral Aloe vera results in significantly increased collagen synthesis. This occurs due to two active components - Glucomannan, a mannose-rich polysaccharide, and gibberellin, a growth hormone. These interact with growth factor receptors on the fibroblast, thereby stimulating its activity and proliferation. Similarly, Aloe gel increases the collagen content in wounds and increases collagen composition type III. Collagen cross-linking is also stimulated. Wound contraction accelerated and resultant scar tissue is improved. After oral or topical treatment, the synthesis of hyaluronic acid and dermatan sulfate in the granulation tissue of a healing wound is increased. Aloe vera gel has been reported to have a protective effect against radiation damage to the skin. When aloe vera gel is applied to the skin, metallothionein (an antioxidant protein), is generated in the skin. This scavenges hydroxyl radicals and prevents suppression of superoxide dismutase and glutathione peroxidase in the skin. This also prevents UV-induced suppression of delayed-type hypersensitivity, via the decreased production and release of skin keratinocyte-derived immunosuppressive cytokines such as interleukin-10 (IL-10). Aloe vera inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid. Recently, the novel anti-inflammatory compound called C-glucosyl chromone was isolated from gel extracts. Aloe stimulates fibroblast which produces collagen and elastin fibres, resulting in more elastic and less wrinkled skin. Its cohesive effects on the superficial flaking epidermal cells soften the skin. The amino acids in Aloe also soften hardened skin cells, and due to its zinc content, it acts as an astringent to tighten pores. Its moisturising effects have also been studied in the treatment of dry skin associated with occupational exposure where *aloe vera* gel gloves improved skin integrity, decreased the appearance of fine wrinkles and decreased erythema. It also has an anti-comedonal effect. *Aloe vera* contains six antiseptic agents with an inhibitory action on fungi, bacteria and viruses - Lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols and sulfur.
***Centella Asiatica*(L.) (Gotu Kola)** Oral **56, 57, 58**	In recommended doses, orally administered *C. asiatica* may cause dyspepsia, nausea and headache. Exceeding the recommended dosage may result in dizziness and drowsiness. In diabetic patients, Gotu Kola may cause hyperglycaemia, whereas, in existing hyperlipidemia, elevated lipid levels may occur. When administered for 20– 60 days, there is increased the risk of hepatotoxicity of *C. asiatica* in humans. Due to its emmenagogic effects, the oral administration of Gotu Kola is to be avoided during pregnancy and lactation.	Medications for Diabetes and hyperlipidemia may need to be modified.	When administered orally, Asiaticoside, a constituent of *C. asiatica*, exhibited potent antipyretic and anti-inflammatory effects in lipopolysaccharide-treated rats. These effects could be associated with the inhibition of liver myeloperoxidase activity, a decrease of pro-inflammatory mediators, such as TNF-α and IL-6 levels, and inhibition of COX-2 protein expression and PGE2 production. Asiaticoside increases the level of anti-inflammatory IL-10 in serum and up-regulates heme oxygenase-1 (HO-1) expression, an enzyme which protects the liver. The presence of glycosides like asiaticoside, madecassoside as well as triterpenes in *Centella Asiatica* may help to explain its antiallergic, anti-pruritic as well as anti-inflammatory activities. Of these components, glycosides possess antioxidant, antiviral, antiallergic, and anti-inflammatory activities. Certain glycosides possess potent inhibitory activities against a wide array of enzymes - protein kinase C, protein tyrosine kinase & phospholipase A2. Other glycosides potentially inhibit prostaglandins, a group of pro-inflammatory signalling molecules. This is mainly due to inhibition of key enzymes involved in prostaglandin biosynthesis (lipoxygenase, phospholipase and cycloxygenase). This action provides the mechanism by which glycosides act as an anti-inflammatory. Analgesic is als associated with glycosides as well as with terpenes.
***Aloe Vera* Oral -60, 62**	(Group 2B). possibly carcinogenic to humans Known hypersensitivity to the active substance. Oral - Cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration - water and electrolyte depletion have been reported. Aloes should not be administered in cases of faecal impaction, acute or persistent gastro-intestinal complaints, for example, abdominal pain, nausea and vomiting. Possible electrolyte imbalance in patients with kidney disorders.	Patients taking cardiac glycosides, anti-arrhythmic medications, QT- prolongation medications, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking aloes concomitantly.	After oral *Aloe* Vera administration, two of its components - Glucomannan (a mannose-rich polysaccharide) and gibberellin (a growth hormone) interact with growth factor receptors on the fibroblast. This stimulates the fibroblast's activity and proliferation, resulting in significantly increased collagen synthesis. Following oral administration of Aloe, increased synthesis of hyaluronic acid and dermatan sulfate in the granulation tissue of a healing wound has been reported.

The Need for a New and Different Approach

In the 80's the need for a new and different approach became more and more apparent, as neither mainstream nor CAM seemed to be fulfilling the needs of the patient. In the past, both CAM and mainstream medicine remained at opposite ends and were never to interact. In the 80's, Dr Michael Tirant saw the opportunity to bring the two closer together, especially in the treatment of dermatological conditions, where he had developed very effective treatment protocols, including the use of bio - herbal actives.

The question was: "How could CAM and allopathic medicine be brought together to offer a more effective treatment approach, which has more longterm benefits for the patients?"

For a longterm solution to psoriasis or other dermatological conditions for that matter, it is vital to identify triggers of these conditions and understand the pathways of how they elicit a flare-up. His research identified many triggers, including drugs, infections, trauma, chemicals, alcohol, smoking, hormones, stress, diet, and lifestyle issues.

Interestingly, some of these triggers initiate a flare - up while others continue to exacerbate the condition. Scientific reports (internal publications) were written on individual triggers and circulated to doctors. Lectures and talks were organised at doctors' clinics and seminars to promote his findings. Unfortunately, he was not able to publish his findings as most journals declined publication because the findings were not scientific or legitimate.

He spent many years working on bacterial superantigens - how they could elicit a flare - up in psoriasis, and how they could be targeted using bio-herbal therapies. Many of the herbs that were tested during the initial stages possessed anti-inflammatory, antioxidant, anti-microbial (viral/bacterial/fungal), anti-pruritic and analgesic properties.

This brought in a very scientific and medical approach that resonated with doctors and formed a stepping stone for collaboration. The outstanding results achieved with patients helped to open doors, both in Australia and overseas, and brought more acceptance and credibility for his treatments.

Although there was a reluctance for his work initially, the medical fraternity has, over the years, started to accept that Tirant's protocols are effective in the treatment of many skin diseases. In Australia, doctors in Integrative practices started to incorporate his treatments with orthodox drugs and so began Integrative Dermatology in Australia. His treatment protocols are now used by patients and doctors in many countries around the world. His work is well published in collaboration with international dermatologists, through international clinical trials and confirmation of the efficacy of his treatments [63][64][65][66][67][68]69][70][71][72][73][74][75][76][77][78][79][80][81][82]. Interestingly, there are now also many publications confirming Tirant's findings on triggers of psoriasis.

His motto is – "we target the triggers and treat the symptoms". He has developed over 40 topical formulations for symptomatic relief and over 25 oral supplements to target triggering factors of many dermatological conditions including psoriasis, eczema, ichthyosis, rosacea, fungal infections and acne. The treatments are now used in many countries around the world.

The exact combination of herbal ingredients, specifically the essential oils, is carefully chosen for the treatment of a skin condition and is based on the therapeutic properties and bioactive plant compounds of the various ingredients. This creates a synergistic compounding effect of the actives that work on specific pathways.

Essential oils are highly complex mixtures of volatile compounds with some containing more than 100 different components. The major volatile constituents are hydrocarbons (pinene, limonene, bisabolene), alcohols (linalool, santalol), acids (benzoic acid, organic acid), aldehydes (citral), cyclic aldehydes (criminal), ketones (camphor), lactones (bergaptene), phenols (eugenol), phenolic ethers (anethole), oxides (1, 8 cineole) and esters (geranyl acetate). All these compounds may be classified into two main categories: terpenoids and phenylpropanoids.

Essential oil compounds are fat - soluble, and thus they had the ability to permeate the membranes of the skin before being captured by the micro-circulation and drained into the systemic circulation, which reaches all targets. Currently, no one study gives a clear explanation of the mode of action of essential oils. Given the complexity of their chemical composition, it would suggest a complexity that makes it difficult to identify the overall molecular pathway of action(s). It is quite possible that each of the constituents of essential oils may have its mechanism of action [83]

That said, there are several proposed cellular actions or mechanisms that may explain the anti-inflammatory activity of medicinal plants that have been observed in vivo. These mechanisms include anti-oxidative and radical scavenging activities, regulation of cellular activities of the inflammation-related cells - mast cells, macrophages, lymphocytes, and neutrophils. They have many actions including inhibition of histamine release and T - cell proliferation.

Table 8: Sominex - topical for treatment of psoriasis. Note: only a small number of the essential oils were discussed due to the long list of ingredients

Treatment	Mode of Action
Topical –	
83, 84, 85, 86, 87, 88, 89,	Zinc is required for collagen, and protein synthesis as low levels of zinc are associated with impaired wound healing.
90, 91, 92	Zinc is also required for cellular growth and replication and may assist in wound healing by reducing free radical activity and inhibiting bacterial growth.
Ingredients include: Zinc oxide Salicylic acid Sweet almond Oil Jojoba Seed Oil Avocado Oil Carrot Seed Oil Calendula extract Orange Oil Wheat germ Oil Apricot kernel Oil Lavender Oil Sandalwood Oil Patchouli Oil Emu Oil Bergamot Oil Rosemary oil Geranium Oil Evening primrose Oil Eucalyptus Oil Pine needle oil Chamomile oil Myrrh Oil Neroli Oil	Zinc serves as a cofactor in numerous transcription factors and enzyme systems including zinc-dependent matrix metalloproteinases (MMP). These augment auto-debridement and keratinocyte migration during wound repair.
	Zinc confers resistance to epithelial apoptosis through stabilising cellular membranes. It protects cells against reactive oxygen species (ROS) and bacterial toxins through anti - oxidant activity of cysteine-rich metallothioneins (MT) and superoxide dismutase.
	Salicylic acid facilitates desquamation by solubilising the intercellular cement that binds scales in the nail plate, thereby loosening the keratin and facilitating the penetration of other medicaments into the nail plate.
	The keratolytic effect of Salicylic acid may also provide an antifungal action because the disruption of the keratin also suppresses fungal growth. It also aids in the penetration of other antifungal agents.
	Salicylic acid also has a mild antiseptic action and possesses anti - inflammatory, ant I -pruritic, analgesic and antimicrobial properties. Its anti-inflammatory and analgesic action appears to be mediated by the inhibition of prostaglandin synthesis via the inhibition of the cyclooxygenase enzyme.
	Many of the essential oils are known for their hydrophobicity, which enables them to partition the lipids of the bacterial cell membrane and mitochondria. This disrupts the cell structures and renders them more permeable.
	Extensive leakage from bacterial cells or the exit of critical molecules and ions will lead to their demise.
	In general, it is proposed that most essential oils target microbial cell membranes, affecting their integrity or permeability or compromising membrane-associated functions (primarily respiration). This leads to fungal cell wall polymer degradation, membrane channel and pore formation, and damage to ribosomal inhibition of DNA synthesis and the cell cycle. Almost all of the essential oils have some antibacterial/antifungal functionality.
	Many of these essential oils are also known for their antioxidant properties. This is most often due to phenolic acids (gallic, protocatechuic, caffeic and rosmarinic acids), phenolic diterpenes (carnosol, carnosic acid, rosmanol, and rosmadial), flavonoids (quercetin, catechin, naringenin and kaempferol), and volatile oils (eugenol, carvacrol, thymol and menthol).
Topical –	
112, 113, 114, 115, 116,	Essential oils can inhibit the expressions of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS).
117, 118, 119	They can also increase the expression of anti-inflammatory cytokine IL-10 and inactivate nuclear transcription factor κappa B (NF-κB).
Zinc oxide Salicylic acid Sweet almond Oil Jojoba Seed Oil Avocado Oil Carrot Seed Oil Calendula extract Orange Oil Wheat germ Oil Apricot Kernel Oil Lavender Oil Sandalwood Oil Patchouli Oil Emu Oil Bergamot Oil Rosemary oil Geranium Oil Evening primrose Oil Eucalyptus Oil Pine needle oil Chamomile oil Myrrh Oil Neroli Oil	Chamomile oil contains alpha-bisabolol, which oxides A & B, and matricin (usually converted to chamazulene) and other flavonoids. These possess anti-inflammatory and antiphlogistic properties.
	A study in human volunteers demonstrated that the flavonoids and essential oils in chamomile penetrate below the skin surface into the deeper skin layers.
	This is important for its use as a topical antiphlogistic (anti-inflammatory) agent.
	One of the chamomile's anti-inflammatory activities involves the inhibition of LPS-induced prostaglandin E(2) (PGE2) release and attenuation of cyclooxygenase (COX-2) enzyme activity without affecting the constitutive form, COX-1.
	The polyphenols in chamomile oil exhibit anti-inflammatory effects due to the inhibition of pro-inflammatory biomarkers in THP1 macrophages. These can reduce inflammation in neurovascular units (NVU) at the site of migraine pain.
	Chamomile has neuro-protective effects because of the induction of reduced tissue NO levels.
	In vivo analysis of patchouli found that its anti-inflammatory activity occurred due to the regulation of mRNA expression of a panel of inflammatory mediators.
	These include TNF-α, IL-1β, iNOS and COX-2. Inhibition of COX-2 produces the analgesic, antipyretic, and anti-inflammatory effects typical of non-steroidal anti-inflammatory drugs (NSAIDs).
	Various essential oils or their constituents inhibit cytokine production. For example, a constituent of many essential oils, 1,8-cineol, inhibited TNF-α and IL-1β in human lymphocytes, α-humulene reduced TNF-α production and terpinen-4-ol suppressed the production of TNF-α, IL-1β,
	IL-8, IL-10 and PGE2 by LPS-activated monocytes.
	A constituent of Eucalyptus Oil,1.8-cineole (eucalyptol), has been reported to inhibit the production/synthesis of TNF-α, interleukin-1, leukotriene B4, and thromboxane B2 in inflammatory cells. Similar to acetylsalicylic acid, it also inhibits the production of prostaglandins and thromboxanes.
	The mechanism of the analgesic effects of the eucalyptus oils is not known. It is speculated that it may be linked to processes involved in the prevention of sensitisation of the nociceptor, down-regulation of the sensitised nociceptor and/or blockade of the nociceptor at peripheral and/or central levels.
	Eucalyptus oil effectively inhibits neutrophil migration as well as carrageenan-induced oedema.
Topical –	
112, 113, 114, 115, 116,	The main constituents of the resin from which Myrrh Oil is obtained are boswellic acids, which have been found to inhibit the synthesis of leukotrienes (inflammatory compounds produced when oxygen interacts with polyunsaturated fatty acids).
117, 118, 119	Boswellic acids have been found specifically to inhibit 5- lipoxygenase, the key enzyme of leukotriene biosynthesis. Leukotrienes, a family of lipid mediators, play a key role in the pathogenesis of inflammation.
Zinc oxide Salicylic acid Sweet almond Oil Jojoba seed Oil Avocado Oil Carrot Seed Oil Calendula extract Orange Oil Wheat germ Oil Apricot Kernel Oil Lavender Oil Sandalwood Oil Patchouli Oil Emu Oil Bergamot Oil Rosemary oil Geranium Oil Evening primrose Oil Eucalyptus Oil Pine needle oil Chamomile oil Myrrh Oil Neroli Oil	

They also modulate the enzymatic activities of arachidonic acid (AA) metabolising enzymes, such as phospholipase A2 (PLA2), cyclooxygenase (COX1 and COX 2), and lipoxygenase (LOX) and the nitric oxide (NO) producing enzyme, nitric oxide synthase (NOS). All of these pathways are involved in the activation and exacerbation of skin conditions [84].

An example of the ingredients contained in the topical treatment for psoriasis is shown in Table 8.

Oxidative stress is involved in the pathogenesis of psoriasis. In psoriasis, studies have revealed increased markers of oxidative stress and decreased antioxidant capacity in plasma, in white blood cells and skin.

The comprehension of the role of immune function in psoriasis could permit the management of this complex disease, which dramatically affects patients far beyond the skin. In fact, cytokines and growth factors released by activated T cells have been shown to display a prominent role in keratinocyte formation. Six of the essential oils in Dr Michaels® (Soratinex®) family of products (calendula, patchouli, geranium, neroli, myrrh (OME)), were studied for redox status of fibroblast primary culture from lesional psoriatic skin hyperproliferation.

The study focused on dermal fibroblasts, which are involved in the accelerating keratinocyte proliferation of developing psoriatic lesions. According to the results, the total antioxidant capacity of OME (at the 1:5000 dilution) resulted equivalent to 163.6mM Trolox, which indicated a very high antioxidant capacity for the provided oil mixture [93].

The preliminary experiment aimed at evaluating the effect of OME on cell viability. A further dose-dependent test was carried out in psoriatic fibroblasts in the presence of increasing OME concentrations ranging from 1:1000 to 1:10000. The results indicated that treatment with 1:5000 OME increased the viability of psoriatic fibroblasts by 37.9 ± 1.7% compared to untreated cells.

A significant decrease in intracellular ROS production was observed in OME-treated fibroblasts compared to untreated fibroblasts as revealed by confocal analysis [93].

The results indicated a strong protective, redox balancing effect of OME obtained from the vegetable oil mixture (Dr Michaels® Soratinex® family products) and if used at an appropriate concentration, significantly increases the viability and decreases intracellular ROS production in human psoriatic fibroblasts. A strong antioxidant effect of the OME obtained from Dr Michaels mixture of oils may be a reason for the effectiveness of the mixture in the topical treatment of psoriasis [93].

The oral supplement range consisted of a specific combination of herbs, either leaf, bark, root, stolen or bulb. The normal dose is one tablet twice daily, however for short periods in the acute stage, two tablets twice daily may be prescribed for 3 - 4 weeks.

Conclusion

Although initially considered unscientific, today many herbs have been scientifically trialled to elucidate their efficacy, mode of action and possible adverse events for them to be safely combined with modern medicine.

Today Integrative Dermatology is well-accepted internationally with many new practices starting in many countries, such as the USA.

Many integrative dermatologists combine integrative approaches in their clinics; such as minerals, herbal products, stress management techniques and clinical nutrition, to achieve the best outcomes for their patients.

These practitioners now realise that the best approach is one where the appropriate triggers for each patient are considered, as each is unique.

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Review Article

Herbal Compounds for the Treatment of Vitiligo: A Review

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Abstract

An overview of unconventional therapies for vitiligo is presented. Some herbal compounds may be considered as valid therapeutic tools for the treatment of vitiligo.

Introduction

Since ancient time, herbal products of different nature and effects had been used for the treatment of vitiligo. The Authors provide a brief overview of the herbal products available for the treatment of the pigmentary disease.

Ginkgo biloba

Ginkgo biloba (also known as “maidenhair tree”), is one of the oldest trees on Earth and its leaves and seeds had been largely used in medicine for a very long time. Ginkgo extracts have been shown to be effective for the treatment of different diseases, such as allergies, varicose vein, premenstrual syndrome, headache, vertigo and others [1]. In the last few years, gingko extracts have also been used for the treatment of vitiligo. The drug is formulated into a tablet of different dosage, which must be taken orally once to three times daily, for more than three months.

The exact mechanism of action of Ginkgo biloba in vitiligo is still unknown, but it seems to be related to the anti-inflammatory, immunomodulatory and antioxidant properties of the drug [2].

Many data support the efficacy of the herbal compound in controlling the activity of vitiligo and in inducing repigmentation of the white macules, especially if administrated with other conventional therapies (e.g. corticosteroids, phototherapies) [3][4].

Moreover, recent studies underline how the drug is also effective when administrated alone [2][5]. Unfortunately, the results in term of repigmentation are not uniform. This fact may be explained by different factors: the genetic differences of the analysed populations, the different type of Ginkgo biloba extracts, the treatment duration, the number of administrated doses per day [5]. The drug is safe and well-tolerated at therapeutic dosages (normal value: 120 mg/day). Only daily dosage > 240 mg may result in restlessness and gastrointestinal disorders. Patients on anticoagulants should only take ginkgo under medical supervision for a correct prescription, to avoid over-thinning of their blood and haemorrhaging.

Cucumis melo

Cucumis melo (also known as “Muskmelon”) is a species of Cucumis, plants of the Cucurbitaceae family. Cucumis melo extract is rich in antioxidants that naturally contain a high superoxide dismutase (SOD) (Table 1) activity, which has been proposed to be important in stopping the melanocytes d e construction by the oxidative stress in the first step of vitiligo. Recently, preliminary studies were conducted to evaluate the efficacy of a topical preparation, containing Cucumis melo superoxide dismutase (SOD) and catalase, in the treatment of vitiligo [6][7]. In each study, the gel preparation was applied to the skin lesions followed by irradiation with natural UV or artificial narrow band UVB. Even though the drug has been shown to be safe, there was no difference in repigmentation rate recorded compared to the patients treated only with the phototherapy. More interesting and promising is the use of a different topical formulation, containing phenylalanine, Cucumis melo extract, and acetyl cysteine. The association of the gel with nb - UVB target phototherapy has been observed to be safe and effective, leading to a better repigmentation of cutaneous lesions [8].

Khellin

Khellin is a naturally occurring furanochromone, derived from the plant Amni visnaga. The plant has been used as a herbal medicine for different purposes (e.g. kidney diseases, asthma and others), since ancient Egyptian times. Because of khellin side effects, including liver dysfunction and allergic reactions, analogues of khellin, with safer profiles and better efficacy, have been developed and introduced in medicine in the last decades for the treatment of vitiligo, where they provide good results in combination with UVA phototherapy. Even if the exact mechanism of action is unclear, khellin acts by stimulating melanocytes proliferation and melanogenesis [9]. Khellin may be administrated both systemically (oral administration) or topically. The association of oral Khellin to UVA is better known as KUVA therapy [10]. The treatment consists in the oral intake of khellin gelatin capsules and, after about 2.5 hours, in the patient’s irradiation with UVA. The therapeutic session is repeated 2 - 3 times a week. The treatment is quite safe and provides clinical results similar to PUVA therapy. Unlike psoralens, Khellins have less phototoxic, and DNA mutagenic effects but the long-term risk of carcinogenesis has to be determinate [11]. Like topical - PUVA, khellin may be applied topically and associated with UVA radiation (topical KUVA therapy) or natural UVR (sol - KUVA therapy). Even in this case, the risk of carcinogenesis has to be yet determinate [12]. More recently, topical khellin 4% has been successfully used in association to monochromatic excimer light 308 nm [13]. The clinical results regarding repigmentation rate and safe profile suggest how this combination may be useful for vitiligo treatment.

Ayurvedic medicine: Picrorhiza kurroa

Also, Ayurvedic medicine had tried to treat vitiligo with herbal products, such as Picrorhiza kurroa. Picrorhiza kurroa (also known as “Kutki” or “Kutaki”) is another khellin extract, with well - known hepatoprotective properties. More recently, researchers have proposed how the herbal extract has antioxidant and immune-modulating activities too (Table 1).

Table 1: Some of the most common herbal products used for vitiligo treatments, and their main components

Herbs	Active components
Cucumis melo	Cucumis melo superoxide dismutase
Green Tea	Epicatechin, epicatechin-3-gallate, epigallocatechin
Picrorhiza kurroa	Picroside I and picroside II
Polypodium leucotomos	p-coumaric, ferulic, caffeic, vanillic, 3,4 - dihydroxybenzoic, 4 - hydroxybenzoic, 4 - hydroxycinnamic, 4 - hydroxycinnamoyl - quinic, chlorogenic acids

Recently, a study investigated Picrorhiza Kuroda's potential use in association with phototherapy, in the treatment of vitiligo. The drug was administrated twice a day orally for three months. At the same time, patients were treated with methoxsalen photochemotherapy. The association of the two therapies has seen to provide a better result regarding repigmentation [14]. Another Ayurvedic herbal product which had been used for the treatment of vitiligo is the anarchic [15], topical concentrated pharmaceutical preparations of plants in the Anacardiaceae family. The drug seems to act as a

photosensitizing agent. Unfortunately, more data and research are needed.

Polypodium leucotomos

Polypodium leucotomos (also known as "Calaguala") is a species of tropical fern in the family Polypodiaceae. Its extracts, famous for their antioxidant and photoprotective properties (Table 1) [16], are used for the treatment of various skin diseases, such psoriasis, atopic dermatitis and others [17][18]. In the last few years, Polypodium leucotomos has been used as adjuvant therapy for vitiligo patients who were being treated with phototherapy. An interesting study underlines d how PUVA therapy plus oral Polypodium leucotomos led to a higher repigmentation than the photochemotherapy alone. A different study showed similar results with the combination of nb - UVB/oral Polypodium leucotomos in comparison to the single phototherapy [18][19].

Traditional Chinese Medicine (TCM)

Since ancient time, TCM had tried to treat vitiligo with different herbal products, used alone or, more often, in combination. Among the traditional Chinese products, psoralen plus UVA (PUVA therapy) had been considered as the first vitiligo treatment for several decades. Psoralen is a photosensitising compound, derived from Psoralea Cordyfolia, a Chinese herb, and other plants. TCM used to treat vitiligo by combining topical or systemic Psoralea seed extract, in association to UVA exposure for a long time. The mechanism of action of therapeutic protocols, such as the beneficial effects and the collaterals are well - known. Another well - known and characterized treatment option is the topical PUVA, based on the topical application of Psoralea extract or derived products, and in the successive exposure to a UVA source [20]. Among the other herbal products, many are the formulations available for the treatment of the pigmentary disorders (Table 2) (Table 3) [21][22][23][24].

Table 2: The most commonly prescribed Chinese herbs for vitiligo

Angelica Sinensis, Ligusticum wallichii, Tribulus Terrestris, Polygonum multiflorum, Fructus psoraleae, Radix Paeoniae Rubra, Rehmannia glutinosa, Glossy Privet Fruit, Eclipta Alba, Salvia miltiorrhiza, Liquorice, Angelica dahurica

They can be administered alone or in association with phototherapy. Unfortunately, for most of them, clinical trials are of poor quality or missing [25]. A particular mention is due to the "Barresi complex prescription", one of the most used for vitiligo treatment in the Uyghur medicine, which is an important part of TCM [26]. The formulation is composed of the hot water extract of five herbs (Psoralea corylifolia, Plumbago zeylanica, Brassica juncea, Nigella glandulifera, Vernonia anthelmintic). The efficacy of the drugs has been evaluated both in vivo and in vitro. In both studies, a good repigmentation has been observed, as the result of melanogenesis stimulation [27].

Table 3: Examples of TCM for vitiligo treatments

Main components:	
Treatment 1	Systemic treatment: walnut, red flower, black sesame, black beans, zhi bei fu ping, lu lu tong, and plums
Treatment 2	Systemic treatment: ligustrum, lycium, morus fruit, cuscuta, eclipta, epimedium (to restore liver and kidney), plus tang - kuei, red peony, cnidium, carthamus, persica, moutan, lithospermum (to promote circulation); plus tribulus, psoralea, cuscuta, black sesame seed, ho-shou-wu, angelica (to promote cutaneous pigmentation). Topical treatment: psoralea, cuscuta, tribulus, angelica, mume, sulfur, and various toxic metals
Treatment 3	Systemic treatment: Phase 1: bupleurum, tang-kuei, red peony, dalbergia, and pangolin scale (to regulate circulation and vitalize blood), plus ligustrum and eclipta (to nourish liver and kidney).Duration treatment: 3-6 months. Phase 2: astragalus, ginseng, tang-kuei, rehmannia, cnidium, cinnamon bark, millettia, psoralea, and epimedium (to regulate circulation and stimulate skin pigmentation). Treatment duration: several months. Topical therapy: psoralea.

Green Tea Polyphenols

Green Tea polyphenols are extracts of green tea leaves, which are used in medicine since ancient time. They act as anti - inflammatory, anti - oxidant, and immunomodulatory agents, mainly because of their composition in Epigallocatechin – 3 - gallate (EGCG) (Table 1) [28]. The drug can be administered both systemically and topically [29]. Recent data suggest how Green Tea polyphenols may be useful for vitiligo treatment, in stopping the oxidative stress of the melanocyte-unit [30].

Capsaicin

Capsaicin is one of the active component of chili peppers, plants of the genus Capsicum. Because its antinflammatory and antioxidant properties, the drug has been proposed as a therapeutic tool for vitiligo treatments. An experimental study recently

confirmed how the incubation of keratinocytes, taken by the perilesional skin of a vitiliginous patient, with capsaicin stopped the cellular damage by ROS [31].

Curcumin

Curcumin is a polyphenol derived from the golden spice turmeric (“Curcuma longa”).

Because of its numerous properties (e.g. antioxidant, anti - proliferative, anti - inflammatory, antiviral, antibacterial and antifungal properties), curcumin has been used for the treatment of different diseases [32].

Recently, a tetrahydrocurcumide cream has been used in association with nb - UVB for vitiligo treatments. The phototherapy was performed twice a week for 12 weeks. At the end of the therapeutic protocol, patients showed a slightly better repigmentation compared to the ones treated only with nb-UVB [33]. Finally, as with other antioxidants, curcumin may be orally administered as adjuvant therapy in vitiligo patients.

Pyrostegia venusta

Pyrostegia venusta (also known as “cipó – de – são - joão”) is a herb of the family Bignoniaceae, widely distributed in southern Brazil, where topical formulations are commonly used for the treatment of vitiligo. Even if its mechanisms of action are still under investigations, the herb seems to be effective for its antioxidant, anti-inflammatory and melanogenic properties [34].

Conclusions

Some herbal compounds may be considered as valid therapeutic tools for the treatment of vitiligo.

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Review Article

Acrocyanosis – A Symptom with Many Facettes

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Keywords: Acrocyanosis; hands and feet; vascular disorders; Raynaud syndrome; Connective tissue diseases; Adverse drug reactions; Tumors

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Abstract

Acrocyanosis is an uncommon complaint belonging to the acro-syndromes. It typically presents with coolness and bluish discolourations of hands, feet, ears, nose, lips and nipple. The most frequently affected parts of the body are the hands. This review discusses physical factors, vascular disorders, infectious diseases, haematological disorders, solid tumours genetic disorders, drugs, eating disorders, and spinal disease presenting as or leading to acrocyanosis.

Introduction

Acrocyanosis is an uncommon complaint belonging to the acro-syndromes. It typically presents with coolness and bluish discolourations of hands, feet, ears, nose, lips and nipple. The most frequently affected parts of the body are the hands. Discoloration and coolness may be permanent or temporary and the result of a peripheral functional vascular disease and reduced tissue oxygenation. A great variety of conditions and disorders may be responsible for acrocyanosis [1]. Chronic idiopathic has been identified as a cutaneous sign of a "latent" cardiovascular risk [2].

Physical factors

Cold can induce vasospasm of digital arteries and arterioles resulting in acrocyanosis. The major differential diagnosis is perniones (chilblains) [3]. Sojourn in high altitude can cause some systemic diseases. From a dermatological point of view, acrocyanosis is a possible consequence due to the combination of lowered oxygen pressure, wind and cold temperatures [4].

Vascular disorders

Raynaud's phenomenon is the most common underlying cause of acrocyanosis. It is characterised by paroxysmal reversible episodes of vasospasm, usually involving small peripheral vessels of the fingers or toes and resulting in a triple-colour change starting with pallor and followed by cyanosis and erythema. Attacks are typically triggered by cold or

emotional stress [5].

Primary Raynaud's syndrome must be differentiated from secondary Raynaud's phenomenon seen in scleroderma, mixed connective tissue disease, dermatomyositis, systemic lupus erythematosus or anti-phospholipid syndrome [6][7].

Thoracic outlet syndrome is a compression of the neurovascular structures in the area superior to the first rib and posterior to the clavicle. Paget-Schröetter syndrome is an effort-induced thrombosis of the upper extremity. It is the leading vascular disorder in male athletes. The combination of both disorders can either lead to painful or painless acrocyanosis [8][9][10].

Primary vasculitis, such as giant cell arteritis, granulomatosis with polyangiitis, or essential cryoglobulinemic vasculitis, can lead to peripheral ischemic manifestations including acrocyanosis [11].

Infections

Chikungunya is a mosquito-borne viral infectious disease that has emerged as a global pathogen. Three to seven days after mosquito bite fever, rash, severe joint and muscle pains, and arthritis develop. It can spread vertically from mother to unborn child. Neonates infected intrauterine with chikungunya present with severe symptoms and infrequently death. Acrocyanosis progressing to ischemic digits is a typical symptom [12].

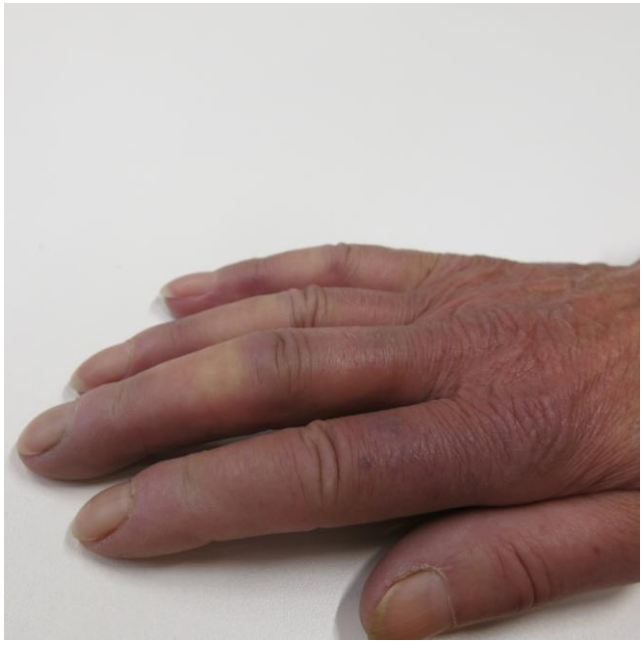

Figure 1: Acrocyanosis in a 74-year-old female with a herniated disk of the cervical spine. The differential diagnosis includes scleroderma, but sclerodactylia is absent

In rare cases of parvovirus B19 infection or lepromatous leprosy, acrocyanosis has been observed [13][14].

Persistent acrocyanosis with skin atrophy is a possible sign of late borreliosis – acrodermatitis chronic atrophicans (Herxheimer) [15].

Hematologic disorders

Cold agglutinin disease is a rare disorder with typical cutaneous signs such as livedo reticularis of the thighs, acrocyanosis and Raynaud's phenomenon upon cold exposure [16].

In rare circumstances, chronic lymphocytic leukaemia can be associated with cold agglutinin disease [17]. Acrocyanosis has been observed in Hodgkin's disease [18].

Essential thrombocythemia is a myeloproliferative neoplasm characterised by an increase in blood platelets. The most common cutaneous sign is itching, acrocyanosis, erythromelalgia, livedo reticularis, and Raynaud's phenomenon are rare but possible manifestations [19].

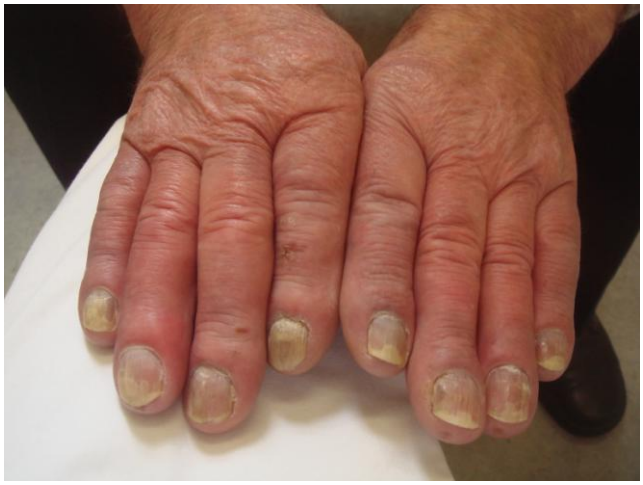

Figure 2: Peripheral sensory diabetic neuropathy with acrocyanosis and onychomycosis in a 78-year-old male

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes) syndrome is a rare systemic disease with the monoclonal proliferation of plasmacytes and slow progression. Cutaneous alterations are present in two-third of patients with diffuse cutaneous hyperpigmentation, and acrocyanosis [20].

Solid tumours

Acrocyanosis can be a rare symptom of extra-adrenal pheochromocytoma [21], intrahepatic carcinoid tumour [22], or endometrial adenocarcinoma [23]. This phenomenon has also been described under the terminus “paraneoplastic acral vascular syndrome” [24].

Genetic diseases

Aicardi-Goutières syndrome (AGS) caused by mutations in the *SAMHD1* gene is characterised by early-onset encephalopathy and chilblains. Additional findings include acrocyanosis and Raynaud's phenomenon [25].

Ethylmalonic encephalopathy is a rare metabolic disorder caused by mutations in the *ETHE1* gene. Neurodevelopmental delay and regression, pyramidal and extrapyramidal involvement, episodes of acrocyanosis, recurrent petechiae and chronic diarrhoea are cardinal features of the disease. Characteristic metabolic findings include lactic acidemia, elevated plasma C4 and C5 acylcarnitines, C4 and C5 acyglycines, and substantial ethylmalonic aciduria [26].

Other possible underlying genetic diseases of acrocyanosis include fucosidosis, and oxaliosis [27][28][29].

Drug-induced

Ergot alkaloids used for the treatment of headaches and migraine can cause acrocyanosis and hand or leg ulcers [30]. Particular attention has to be paid in case of antiretroviral therapy since alkaloid action can be potentiated due to an inhibition of cytochrome P450 [31].

Liposomal amphotericin-B and amphotericin-B deoxycholate used for the treatment of systemic fungal infections have been reported to cause acrocyanosis that was reversible after discontinuation [32][33].

A bilateral foot acrocyanosis developed in a patient suffering from multiple sclerosis during interferon-β-treatment [34].

Tumescent liposuction for liposuction is known to cause acrocyanosis as a possible adverse effect. In severe cases, cyanosis, tachypnea, tachycardia, hypotension, confusion, or even death may be observed. Methemoglobinemia has been noted with all anaesthetics, such as lidocaine, prilocaine or ripivocaine, and patient safety demands laboratory monitoring of methemoglobin [35].

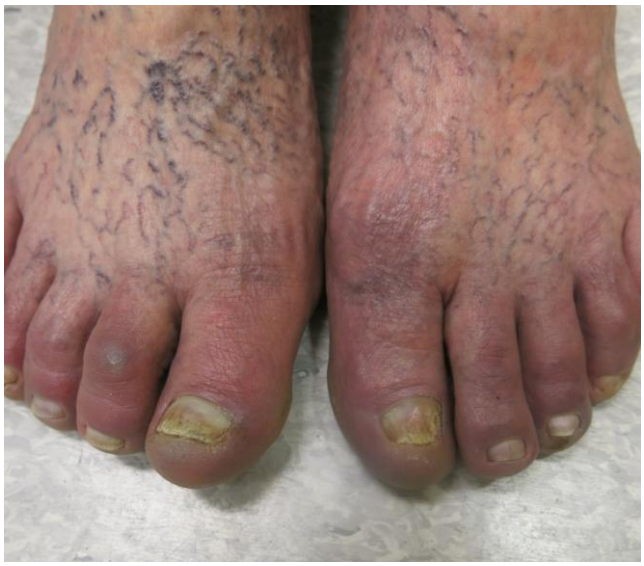

Figure 3: Acrocyanosis in a 71-year-old female after partial pulmonary resection due to malignant pheochromocytoma. The lesions developed with a delay of several months

Digital ischemia with acrocyanosis is a rare event during intravenous chemotherapy with gemcitabine, cisplatin or oxaliplatin [36]. Other drugs known to induce acrocyanosis are metoclopramide, imipramine, desipramin, and fluoxetine [27].

Eating disorders

Acrocyanosis is a possible cutaneous symptom of anorexia nervosa and bulimia nervosa due to persistent vasoconstriction associated with impairment of thermoregulation and reduced and delayed responsiveness to both vasodilator and vasoconstrictor agents [37][38].

Spinal disorders

Japanese authors described two male patients with cervical myelopathy, which exhibited peculiar vasomotor symptoms ("acro-erythro-cyanosis"). Continuous reddening, swelling and skin temperature increase were observed on both hands and feet or both hands. Cold stimulation resulted in paroxysmal cyanosis and a decrease in skin temperature [39].

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Review Article

Vitiligo in Children: A Review of Conventional Treatments

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Keywords: Childhood vitiligo; Conventional treatments; Topical treatments; Systemic treatments; Phototherapy; Combined treatments; Surgical therapies

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Abstract

Vitiligo is an important skin disease of childhood, which may lead to deep psychological trauma, resulting in a poor quality of life and low self-esteem. The Authors discuss a short review of the more conventional therapies available for the treatment of vitiligo in children.

Introduction

Vitiligo is an acquired, chronic, maybe autoimmune, pigmentary disorder characterised by white macules and patches, due to the progressive loss of cutaneous melanocytes and to an abnormality in their normal function [1].

Usually, it starts in childhood or young adult: it has been estimated that about 50% of patients develop vitiligo before the age of 20 years and about 25% of them develop the disease before the age of 8, with a mean age of 4 - 5 years [2].

In pediatric age, vitiligo may represent a psychological trauma for both patients and their parents, resulting in emotional disorders (e.g. anxiety, depression), poor quality of life scores, and low self-esteem [3].

Treating vitiligo and supporting patients to live their stigmatising condition, is the first aim of a dermatologist. Fortunately, nowadays different treatments, both medicals (Table 1) and surgical, are available.

Topical treatments

Topical corticosteroids (TCs)

The efficacy of topical corticosteroids in the treatment of vitiligo, especially of localised forms on the face and other body's area, is well - known since long time [4].

Table 1: Current traditional therapeutic options for vitiligo in children

Treatment modality	Drugs	Mechanism of actions	Side effect
Topical treatments	Calcineurin inhibitors	Immunomodulation	Burning sensation, erythema, transient pruritus; risk of malignancies?
	Calcipotriol	Repigmentation, immunosuppression	Transient burning or irritation
	Corticosteroids	Immunomodulation	Epidermal atrophy. striae, telangiectasia, glaucoma, tachyphylaxis, hypothalamus-pituitary axis suppression, Cushing's syndrome, growth retardation
Systemic treatments	Corticosteroids	Immunomodulation	Glaucoma, tachyphylaxis, hypothalamus-pituitary axis suppression, Cushing's syndrome, growth retardation
Phototherapies	PUVA (12yo), Topical PUVA, Topical PUVA sol, nbUVB	Repigmentation, immunomodulation	Erythema, itching or burning sensation; chronic actinic damage; psoralen toxicity (nausea, vomiting, abdominal pain, liver toxicity, cataracts)
Other therapeutic options: Combined therapies Camouflage Depigmentation therapy (monobenzyl ether of hydroquinone) Cognitive therapy and psychological support			

Steroids act as anti-inflammatory and immunosuppressant agents. Even if different classes of steroids are now available, the mid- potent ones (e.g. betamethasone dipropionate 0.05% cream, 0.05% clobetasol propionate ointment) are usually preferred for the treatment of young patients. The drugs may be applied once or twice a day, in consecutive or on alternate days. Different studies report a response rate of 45 - 60% in childhood vitiligo, with best outcome in inflammatory vitiligo [5].

Even if their use should be prolonged for several months, TCs are quite safe only if used for few weeks, not more than 2 - 4 months, to avoid local side effects (e.g. atrophy, striae, telangiectasia, hypertrichosis, acneiform eruption) and systemic ones due to the percutaneous absorption (e.g. tachyphylaxis, suppression of hypothalamic-pituitary-adrenal axis, Cushing's syndrome and growth retardation). In detail, the use of TCs on vitiligo patches of the face should be avoided or limited in time because of the higher risk of topical side effects, including glaucoma [6][7].

Topical calcineurin inhibitors (TCI)

Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are considered valid alternatives to TCs for the treatment of localised forms of vitiligo. They act as immunomodulator agents: by blocking calcineurin, they inhibit the cytokines expression [8].

As TCs, TCIs are indicated for the treatment of localised forms of vitiligo, also for the facial lesions where they seem to be safer than steroids. Usually, TCIs are prescribed twice a day.

Tacrolimus 0.1% seems to be more effective than pimecrolimus 1%, achieving a repigmentation rate similar to that of topical clobetasol propionate (0.05%) [9]. Pimecrolimus 1% is another valid option for the treatment of facial lesions, especially on the thinnest cutaneous areas, such as eyelids [10].

Usually, TCIs are safe and well tolerated. The most common side effects are burning sensation, transient pruritus and erythema at the side of the application. Because of the potential risk of malignancies (e.g. skin cancers and lymphoma), TCIs cannot be used in children < 2 years. The major limit to treat vitiligo with CIs is due to their costs [6].

Calcipotriol

Calcipotriol is a synthetic vitamin D3 analogue, which has been used for many years in the treatment of psoriasis for its ability to regulate the epidermal turnover.

Its use in vitiligo patients, start with the observations that its topical application, on psoriatic lesions, may cause perilesional hyperpigmentation. Even if the exact mechanism of action has to be elucidated, calcipotriol seems to stimulate melanogenesis and to halt the melanocytes destruction by T - cells [11].

Calcipotriol is applied once a day. It seems to be less effective than TCs, with variable results in term of repigmentation rate. Interesting, calcipotriol seems to stimulate repigmentation in both treated and untreated skin, and to continue its action also after treatment termination, leading to hypothesise a systemic effect of the drug applied topically [12].

The drug is well tolerated, and the most common side effects are represented by a transient burning sensation or irritation at the site of application. The treated sites should not be exposed to phototherapy to avoid cutaneous hyperpigmentation.

Systemic treatment

Systemic corticosteroids (SCs)

In patients affected by unstable vitiligo, another therapeutic option is the systemic administration of corticosteroids (e.g. betamethasone, methylprednisolone), which seem to be useful to stop the progression of the disease and to induce repigmentation. Due to the potential well-described side effects, SCs are usually administered for a short period or in pulsed a regimen [13][14]. The dosages of SCs are usually decided by the patient's characteristics. Recently, an oral mini-pulse therapy (OMP) has been proposed [15]. It consists of the morning intake of betamethasone (0.1 mg/kg body weight) on two consecutive days in a week for 12 weeks. After that, patients have to assume 1

mg/month for the following three months. The clinical results seem to be good, with minimal risk of side effects.

Phototherapies

Ultraviolet radiations (UVR), both in the range of UVB and UVA, are considered as a first line therapy especially for extensive vitiligo, because of their good efficacy and tolerance. The effects of UVR are both immunosuppression and stimulation of the melanocytes activity [16].

Today, a range of phototherapies are now available: oral PUVA; topical cream PUVA, bath PUVA; PUVA sol; narrow-band UVB. Broad band UVB should no longer be used because of the sunburn risk and low efficacy.

PUVA therapy

PUVA therapy consists of the oral intake of a photosensitizing psoralen (e.g. 8 - methoxypsoralen, 5 - methoxysporalen or 4, 5, 8 - trimethylpsoralen) followed by exposure to photoactivating UVA light (320 - 400 nm). Treatment is performed 2 - 3 times a week, increasing the dose of UVA on the base of patient's response. Because of psoralen's toxicity (e.g. gastric and ocular damage), PUVA therapy should not be performed in children < 12. The rate of repigmentation after oral PUVA is about 75% in 50-60% of the children with vitiligo [4]. The possible side effects are due to both radiations and psoralens. While the most common short- time side effects are erythema, pruritus, xerosis and phototoxic reactions; the long-term ones include chronic actinic damage and carcinogenesis [16].

Topical PUVA

A valid therapeutic option for children with vitiligo is the topical PUVA. It consists of the application of 0.1 - 0.01% 8-methoxypsoralen in hydrophilic petrolatum or ethanol onto the vitiligo skin, followed by exposure to UVA-irradiated with a dose of 0.12 - 0.25 J/cm². The treatment is done 1 - 3 times a week, increasing the UVA dose until mild erythema will develop. The treatment provides good results, similar to the systemic PUVA [4]. The acute and chronic side effects, due to UV radiations, are well described.

Topical PUVA sol

Similar treatment is the topical PUVA sol: after the topical application of a psoralen cream, the patient will be exposed to sunlight. Although the proven efficacy of the treatment, the risk of acute and chronic actinic damage are well documented [17].

Bath PUVA

Patients take a warm bath with 0.5 -1.0 mg/l 8 - MOP for 20 min before they are exposed to UVA [18][19].

Narrow - band UVB (nb - UVB)

Today, narrow-band UVB (nb - UVB, 311 nm) is considered a valid and safeness therapy for vitiligo, especially for children due to the lack of psoralens. It consists in the exposure to nb - UVB at the starting dose of 0.1 mJ/cm², followed by 20% increasing dose of UVR on a weekly basis, accordingly to the clinical response. Treatment is well - tolerated. The commonest acute side effects are pruritus and erythema. Apart from supposed photo-damages, long-term side effects are yet to be determined [16]. Recent studies show how nb - UVB is more active than topical and oral PUVA, and that the repigmentation achieved with nb - UVB is more persistent and more similar to the colour of the unaffected skin [20].

Combined treatments

In the last years, different types of combined therapies have been proposed for the treatment of vitiligo in children.

Topical corticosteroids may be used in combination with calcipotriol [20]. This type of association seems to provide better clinical results in term of repigmentation and fast response, also in patients who did not have a response to the use of steroids alone. Moreover, the combination calcipotriol -corticosteroids reduce the side effects due to each drug, leading to a safer treatment.

In progressive vitiligo, TCs may be associated to the oral ones [21]. Apart from the risks due to the steroids therapy, the protocol seems to be effective in halting the progression of the disease and in inducing skin repigmentation. Finally, a study underlines also how the combination of OMP to nb - UVB phototherapy should be superior in the treatment of unstable vitiligo, then the systemic corticosteroids used alone [22].

Topical treatments may also be associated to phototherapies. For example, many studies show how nb-UVB combined with different topical drugs (e.g. Corticosteroids, vitamin D analogues, tacrolimus, pimecrolimus, pseudocatalase) could be more efficacy than phototherapy alone [16][17][18][19][20][21][22][23][24]. In case of a combination, both TCI

and vitamin D analogues should be used after UVB, never before to avoid risks such as hyperpigmentation or skin cancer.

Cosmetic camouflage

Due to the deep psychological impact of vitiligo, which risks representing a real stigma for patients, the camouflage of vitiliginous areas is often recommended [25]. Today many products are available. The ideal cosmetic is non - allergenic, colour matching, easy to apply and to remove, water resistant and cost-limited.

Depigmentation therapy

Unresponsive, widespread vitiligo or universal forms may be addressed to a total depigmentation therapy with 20% monobenzyl ether of hydroquinone (MBEH) [26].

Cognitive therapy and psychological support

Among the different type of vitiligo's treatment, cognitive therapy and psychological support are strictly recommended for children with vitiligo and their parents, especially in the cases where it is clear the impact of the skin disease on their quality of life [27].

Surgical therapies

Surgical therapies are not recommended in childhood vitiligo and must to be limited to patients with stable localised lesions, unresponsive to the more conventional therapies. Surgical techniques in young children have to be also avoided because of their natural body growth in which lesions tend to extends, and they're difficult to stand still in the post-operative time [4][5][6].

Today, different types of surgical techniques are available (Table 2). Among them, the suction blister epidermal grafting (SBEG) is the best choice for childhood vitiligo.

Table 2: Surgical therapies for childhood vitiligo

	Technique	Mechanism of actions	Side effect
Surgical therapies	Mini punch grafts, suction blister epidermal grafts (SBEG), thin Thiersch grafts, transplantation of epidermal cell suspension, cultured melanocyte suspension, and cultured epidermis, combined therapies	Correction of the pigmentary disease	Cost factor and time consumption; inability to treat large areas; risk of infections; transient hyperpigmentation of recipient or donor site; risk of Koebner phenomenon at the graft site

Among the various surgical techniques, suction blister epidermal grafting (SBEG) has been found to be most convenient and effective for children and adolescents, with an excellent rate of repigmentation (> 75%) in over 80% of patients [28]. Face and lips obtain best results [29].

Other surgical procedures include mini punch grafts; thin Thiersch grafts; transplantation of epidermal cell suspension, cultured melanocyte suspension, and cultured epidermis. Finally, there is the possibility to combine surgical techniques with medical treatments. An excellent example is the microdermabrasion of cutaneous lesions, followed by the topical use of pimecrolimus 1% cream [30].

Apart for the normal problems due to an intervention (e.g. risk of infection), the major problems due to surgical vitiligo therapies are represented by the necessity of expert equipment, the cost and the time consumption. Treatments are not indicated in the case of large vitiliginous areas and/or in case of active vitiligo. Finally, there are the risks of transient hyperpigmentation of recipient or donor site, and of Koebner phenomenon at the graft site.

Conclusions

Vitiligo's treatment has two main goals: the first one is to halt the disease progression; the second one is to induce the lesions' repigmentation, achieving an acceptable cosmetic result. In the last years, several therapeutic options, both medical and surgical, have been proposed for vitiligo. The choice of the best therapy for childhood vitiligo is based on various factors, such as patient's age, psychological condition and expectation, distribution and extension of skin lesions, type of vitiligo (stable or not), availability and cost of the therapeutic options.

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Review Article

Use of Curcumin in Psoriasis

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Abstract

Curcumin is a polyphenol derived from the golden spice turmeric, which is widely used for different purposes, such as culinary spice and alimentary addictive, make - up and, finally, as a natural product for the treatment of different diseases, especially for the chronic inflammatory ones. Recently, curcumin has been proposed as a valid and safe therapeutic option for psoriasis.

Introduction

The traditional medicine, based on the administration of natural and herbal products for the treatment of several human diseases, has been employed by many different cultures throughout history, becoming today a real multi millionary industry, with a recorded cost of USD 10 billion/year [1].

Among the numerous herbal compounds available for the medical purpose, there is Curcumin, a polyphenol derived from the golden spice turmeric ("Curcuma longa"), of the Zinzigiberaceae family, characterised by many properties [2].

Since ancient time, Curcumin has been widely used for different purposes, such as culinary spice and alimentary addictive (e.g. ice cream, yogurt, orange juice, biscuits, popcorn, cakes, cereals, sauces, gelatins), make - up and, finally, as natural product for the treatment of different diseases, especially for the chronic inflammatory ones [3].

Although, its well - known effectiveness as a therapeutic herb, curcumin pharmacological properties have been scientifically proved only in the last century [4][5]. Today, it is clear how the wide range of use of curcumin in medicine is the result of its numerous properties, such as antioxidant, anti-inflammatory, anti - proliferative, anti-carcinogenic and anti-microbial ones [6][7].

In medicine, curcumin is used for the treatment of different diseases [3], like rheumatoid arthritis, eye diseases (e.g. chronic anterior uveitis, conjunctivitis), urinary tract infections, menstrual alterations, liver and gastrointestinal disorders (e.g. abdominal pain, inflammatory bowel disease) [3][8][9][10]. Furthermore, curcumin is used as adjuvant therapy for the treatment of skin cancers, chicken pox and wound healing [5][6].

Even if it may be assumed with diet, curcumin

is now formulated into tablets, at a different dosage, often associated to particular adjuvants (e.g. piperine, phospholipids), which lead to improving its absorption and bioavailability [11].

Curcumin and psoriasis

Psoriasis is a chronic, inflammatory, cell-mediated disease, which involves the skin, and sometimes joints, bones, tendons, ligaments, nails, and mucosal membranes. Although it may represent with different clinical variants, the most commonly described is the “vulgaris” one, which is characterised by erythematous round or oval lesions, covered by white-silvery scales. Cutaneous lesions are usually localised on the elbows, knees, scalp and lumbar-sacral region in a symmetric pattern, even if they can affect different body areas [12].

Despite the availability of different topical and systemic therapeutic options for the treatment of psoriasis [13][14][15][16][17], none of them provides excellent clinical results without the risk of side effects (Table 1).

Table 1: Common antipsoriatic therapies

Drugs		MoA
TOPICAL	Corticosteroids	Immunosoppressive; anti-inflammatory; anti-proliferative; vasocostriction
	Soothing: urea, allantoin, lanolin	Anti-inflammatory
	Keratolytics: salicylic acid 3 - 6%, Alpha - Hydroxy acids (lactic acid, propylene glycol), emollients, bath	↓ cell – to - cell cohesion in the stratum corneum → Help to remove accumulated scales or hyperkeratosis
	Anthralin (Dithranol, 1, 8 – Dihydroxy – 9 - anthrone)	Anti - proliferative effect; anti-inflammatory effect
	Tars (coal tars and wood tars)	Keratoplastic; anti-acanthotic; photosensitizing (absorption spectrum of 330-550 nm); vasocostrictive
	Retinoids: tarazotene	Normalize the abnormal differentiation of keratinocytes; antiproliferative affects on keratinocytes; ↓ expression of inflammatory markers on keratinocytes (e.g. HLA - DR, ICAM - I)
	Derivatives and analogues of vitamin D3: calcipotriol, tacalcitol, calcitriol	Regulation of epidermal hyperproliferation; enhancement of normal keratinisation; immunomodulating; anti-inflammatory; angiogenesis inhibition
	Calcineurin inhibitors: Tacrolimus, Pimecrolimus	Immunosuppression
PHOTOTHERAPY	PUVA therapy	Cell cycle arrest; immunosuppression
	UVB, nbUVB, excimer laser	Cell cycle arrest; immunosoppression
SYSTEMIC	Methotrexate	Antiproliferative; anti-inflammatory
	Acitretin	Normalize the abnormal differentiation of keratinocytes; antiproliferative affects on keratinocytes
	Cyclosporin A	Inhibition of CD4 T cells
	Fumaric acid esters	Immunomodulation
	Hydroxyurea	Regulation of proliferating cells
	Sulfasalazine	Antiinflammatory
	Mycophenolate mofetil	Immunomodulator
	6 - Thioguanine	Cell cycle arrest
BIOLOGICS	Etanercep, Infliximab, Adalimumab	Anti TNFα

In the last years, an increasing number of studies underline the potential use of curcumin in the treatment of psoriasis. Many are the evidence which supports its therapeutic efficacy. The first one is that curcumin, with its antioxidative property, may reduce the oxidative stress of psoriatic lesions [18]. More recently, two different studies showed how curcumin therapeutic efficacy might also be related to its ability in inhibiting the phosphorylase kinases, which are increased in psoriatic patients [19][20]. Also interesting are the results, achieved by Varma et Al., about the use of curcumin at 25 and 50 μM concentrations in the treatment of psoriatic - like cells (HaCaT cells), in vitro. The authors showed how curcumin was able to inhibit the proliferation of psoriatic - like cells, by the down-regulation of pro-inflammatory cytokines, such as interleukin - 17, tumour necrosis factor - α, interferon - γ and interleukin - 6. Moreover, curcumin significantly enhanced the skin - barrier function by the up-regulation of involucrin (iNV) and filaggrin (FLG) [21].

Recently, Kang D. et Al. have proved, on mice models, another important effect of curcumin, consisting in the inhibition of the potassium channels (subtypes Kv1.3) expressed on T cells, which seem to be involved in the onset of psoriasis. The anti-inflammatory properties of curcumin, have been confirmed by the finding that mice, showed in their serum a decrease of more than 50% level of inflammatory factors, including TNF - α, IFN - γ, IL - 2, IL - 12, IL - 22 and IL - 23 [22].

No study in vivo have shown side effects of curcumin in the treatment of psoriatic patients [23][24], and the U.S. Food and Drug Administration (FDA) has defined curcumin as “generally regarded as safe” (GRAS).

In conclusion, curcumin is a polyphenol derived from the golden spice turmeric (“Curcuma longa”). Because of its numerous properties (e.g. anti - oxidant, anti -proliferative, anti-inflammatory, antiviral, antibacterial and antifungal properties), curcumin has been used for the treatment of different diseases [25]. Recently it has been proposed for the treatment of psoriasis, where its efficacy seems to be the result of different mechanism of actions. Even if different studies, both in vitro and in vivo, have shown its efficacy and safe profile, further placebo-controlled studies are needed before recommending oral curcumin as a valid treatment for psoriasis.

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Review Article

Vitiligo in Children: What's New in Treatment?

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Abstract

Vitiligo is an acquired chronic hypopigmentary disorder, which usually stars in childhood. The Authors discuss a short review of the more innovative therapies for childhood vitiligo.

Introduction

Vitiligo is an acquired chronic hypopigmentary disorder, which usually stars in childhood. Even if today different kind of therapies, both medical and surgical, are available [1] (Table 1), none of them may be considered as a standard gold treatment for the variable results in term of repigmentation and the risk of side effects.

Fortunately, innovative treatments have been introducing to solve this problem. They consist in either innovation of conventional treatments and real new therapies.

Innovative phototherapeutic treatments

Among the conventional treatments for childhood vitiligo, phototherapies may be represent the most effective therapies, especially for generalised vitiligo [2].

Table 1: Current therapeutic options for vitiligo in children

Calcineurin inhibitors	Immunomodulation	Burning sensation, erythema, transient pruritus; risk of malignancies?
Calcipotriol	Repigmentation, immunosuppression	Transient burning or irritation
Corticosteroids	Immunomodulation	Epidermal atrophy, striae, telangiectasia, glaucoma, tachyphylaxis, hypothalamus-pituitary axis suppression, Cushing's syndrome, growth retardation
Corticosteroids	Immunomodulation	Glaucoma, tachyphylaxis, hypothalamus-pituitary axis suppression, Cushing's syndrome, growth retardation
PUVA (12yo), Topical PUVA, Topical PUVA sol, nbUVB	Repigmentation, immunomodulation	Erythema, itching or burning sensation; chronic actinic damage; psoralen toxicity (nausea, vomiting, abdominal pain, liver toxicity,

In the last decade's new techniques, both natural and artificial, are being introduced to achieve better clinical results in term of repigmentation, with fewer side effects (Table 2).

Table 2: Innovative modalities of phototherapy

The Dead Sea
Selective sunlight therapy
Excimer laser/ Monochromatic excimer light (MEL)
Focused microphototherapy
LASER ALBA UVA1 355nm

Natural exposure to the sunlight at the Dead Sea ("Dead Sea Climatotherapy")

It is now clear how at the Dead Sea, the sunlight travels below the normal sea level, attenuating the low range of UVB spectrum, which is the non - therapeutic ones. This fact explains how vitiliginous patients show a greater improvement in skin lesions after sunlight therapy in this special geographical area [3]. The therapeutical protocol varies by the characteristics of patients (e.g. skin phototype, age, comorbidities) and of their skin disease. In general, it consists of the daily session, with a gradual increase of the exposure time.

Many data support the efficacy of Dead Sea Climatotherapy (DSC) in inducing repigmentation and, not less important, in improving the quality of life of patients [4].

Interestingly, a study shows the opportunity to combine DSC with the topical application of a pseudocatalase cream, for achieving a faster repigmentation [5]. Pseudocatalase, however, is a controversial issue. One open trial from London, UK [6] and two randomised, double-blind trials – one from Iran and another one from Australia – could not demonstrate any beneficial effect of this compound compared to placebo [7][8].

Selective sunlight phototherapy

Another innovation is the selective sunlight phototherapy. Recently, a topical cream (PHOTOCIL®) has been introduced to selectively deliver nb - UVB therapy, when exposed to solar ultraviolet irradiation. The cream is composed by diethylamino hydroxy benzoyl hexyl benzoate and by alpha - glucosyl hesperidin, a glucosylated derivative of a natural plant flavonoid, formulated into a water and oil emulsion. It is applied on vitiliginous patches, while a broadband SPF 50 sunscreen is applied on the unaffected skin. The treatment seems to be effective and safe, providing good results in term of regimentation [9][10].

Excimer lasers

Among the artificial radiation therapies, excimer lasers are probably the oldest phototherapy to have been introduced for vitiligo treatment. They consist of xenon chloride lasers, delivering radiation of 308 nm, with a variable spot size (mean value: 15 - 25 mm). The therapeutic protocol varies on the bases of characteristics of patient, disease and delivery system. The therapeutic procedure schedules consist of two sessions in a week for 13 weeks. During the first session, the operator estimates the MED (Minimal Erythema Dose) of the patient in a vitiliginous area, to be able to set the first dose of radiation, corresponding to the MED decreased by 10%. During the following sessions, the dose increases gradually depending on the clinical response [11].

Excimer lasers are proved to be effective for the treatment of localised forms of vitiligo. The rate and speed of repigmentation vary accordingly with the site and duration of the disease. Lesions on the face and neck are highly respondent areas, while extremities show a slower response [12].

The treatment is quite safe. A part of a supposed chronic skin photo - damages, the more common side effects is represented by perilesional hyperpigmentation, burns, and folliculitis.

An excimer laser may be used alone or in association with topical therapies (e.g. tacrolimus, tacalcitol), which seems to provide better results in term of repigmentation [13].

Narrow - band UVB target phototherapy and narrow - band UVB micro-focused phototherapy

More innovative is the target phototherapy which allows the operator to treat only the hypopigmented areas, sparing the uninvolved skin.

While the mechanisms of action are the same of the classical phototherapy, the target phototherapy acts in a more precise way because, treating only vitiliginous patches, the operator can use a more appropriate dose of energy, leading to shorter duration and less frequent treatment sessions [14]. In the last years, many different target phototherapy devices have been introduced in the clinical practice. Among these, the last frontier of vitiligo therapy is

represented by the BIOSKIN EVOLUTION® device, a cold light generator micro-focused phototherapy (Table 3).

Table 3: Conventional phototherapy versus micro-focused phototherapy

Exposure to affected and unaffected skin areas	Treatment focused on skin lesions
Difficulty in treating certain skin areas (e.g. ear, nose)	Possibility to treat difficult areas thanks to a manoeuvrable hand piece
Slow delivery system, which needs longer treatment sessions	Quick delivery system. Treating only skin lesions, operators can also use higher doses of energy, achieving faster response on selected areas
Multiple and frequent visits to clinic	Shorten and less frequent visits
Bulky machines	Smaller device
Difficulty in treating claustrophobic patients and children, who may be afraid of the large device	Easy administration of the energy delivery and well tolerate - therapy

It consists of a short arc lamp generating a beam of visible, ultraviolet radiations, filtered to obtain only nb - UVB. BIOSKIN EVOLUTION® can provide a spectrum of intensity up to 400 mW/cm² and the peak of emission at 311 nm. The possibility to treat only vitiliginous patches, allows the operator to obtain lesional repigmentation, without an increase in the colour contrast between affected and not affected skin areas.

The therapeutic protocol (energy level, spot light, no. of the session, duration) is decided by the operator by patients' characteristics. The therapy is repeated once every three weeks, with the possibility to effect 2 sessions in the same day, for a total of 6 months.

Many data suggest how nb - UVB micro-focused phototherapy should be considered as first-choice therapy for localized vitiligo, where it may provide good clinical results in term of restoring pigmentation, patients' compliance, and safety [15][16].

UVA - 1 therapy

Recently, light therapy lamps with halogen-metal band confined to the high irradiance UVA1 (340 - 400 nm) have experienced a growing interest and used in dermatology. The well-documented immune-modulating effects of UVA - 1, make this type of phototherapy useful for the treatment of several skin diseases, such as atopic dermatitis, psoriasis, vitiligo and other [17].

The therapeutic procedure schedules for vitiligo, usually, consists in 3 - 5 sessions per week, with a starting dose of 20 - 30 J/cm^2, which is progressively increased in the following sessions to the full dose. The treatment is well tolerated. The most common side effects are tanning, erythema, pruritus and phototoxic reactions (eczema, urticaria). The long-term side effects are yet to be investigated [18].

UVA - 1 target laser

Laser Alba 355® is an innovative, focused laser technology based on UVA - 1 spectrum with a wavelength of 355 nm (Table 4).

Table 4: Clinical indication for Laser Alba 355®

CLINICAL INDICATIONS
Atopic dermatitis
Dyshidrotic dermatitis
Psoriasis
Pityriasis rosea
Prurigo
Urticaria pigmentosa/Mastocytosis
Localized scleroderma (morphea)
Systemic lupus erythematosus
Lichen sclerosis
Mycosis fungoides and another T-cell lymphoma
Others: Vitiligo, Graft versus host disease, Granuloma annulare, Necrobiosis lipoidica, Cutaneous sarcoidosis, Follicular mucinosis, POEMS syndrome, Scleromyxedema, Hypereosinophilic syndrome, Pityriasis lichenoides

It consists of an active medium and a Neodymium - doped yttrium orthovanadate (Nd: YVO4) crystal that is "energetically pumped" by another laser with 808 nm wavelength. The light emitted by the Nd: YVO4, at a wavelength equal to 1064 nm, is impulsed through an acoustic-optic crystal named Q - switch, producing a frequency of 20 - 50 kHz and transforming the laser light into an ultrashort pulsed light (25 nano sec). This pulse rate is higher than 40 kW, and it is sent to crystals to duplicate and triplicate the 1064 nm wavelength. Thus it produces a second (532 nm) and third (355 nm) harmonic wavelength delivery. The laser beam is then filtered by a harmonic separating mirror to select from this galvanometric head a 355 nm wavelength specific beam which is amplified and homogenate, before galvanometric head output, with a 2.5 mm spot and a pulse repeating potential up to 20.000 spots/second and designing variously shaped dimensional figures [19].

The use of Laser Alba 355® allows the treatment of selected affected skin areas so that the operator can use a more appropriate dose of energy, leading to shorter duration and less frequent treatment sessions. Time of emission and spot diameters are regulated by the operator, on the base of the clinical characteristic of individual patients. The treatment with Laser Alba 355® is well - tolerated. Acute side effects, such as erythema or pruritus, have rarely been described. Long-term side effects have yet to be determined.

Immunomodulatory agent: Neovir®

Neovir® is an i.m. Immunomodulatory agent, composed of sodium oxo – dihydro – acridinyl - acetate (ODHAA).

Normally, it is used to normalise impaired

immune system functions under various conditions, such as viral infections, immunodeficiency, oncological diseases and multiple sclerosis. An experimental study evaluated the efficiency of acridone acetic acid, sodium salt, in stopping active nonsegmental vitiligo progression. Sixty patients with active non - segmental vitiligo have been treated with ten intramuscular injections, every 48 hours, of ODHAA. Vitiligo progression was assessed in 1, 3, 6 and 12 months after treatment. The results of the preliminary study were excellent: sodium oxodihydroacridinylacetate showed high efficiency in achieving long-term stabilisation of nonsegmental vitiligo [20].

Melgain

In the last years, an Indian group of study developed a new topical drug (Melgain) for the treatment of vitiligo. It is a decapeptide derived from bFGF, which has to be applied topically once a day. Many data suggest how Melgain is effective in inducing repigmentation and particularly safe for treating children [21].

The combination of Melgain with target phototherapy has been demonstrated to be more effective.

Antioxidants

It is now clear, how oxidative stress of both melanocytes and keratinocytes, is an important pathogenic mechanism at the base of vitiligo progression [22][23]. In particular, the impairment of keratinocytes removes the trophic support to melanocytes and induces their consequent death. Among the mechanisms that have been proposed in the prevention of keratinocyte cell stress, SIRT1 positive modulation has been recently suggested. On this observation, recently resveratrol and more innovative agents have been proposed and successfully tested in vitiligo patients, to protect them by the disease's progression.

Low dose medicine (LDM)

Many studies underline how vitiligo is characterised by an unbalance of signalling molecules (e.g. growth factors, cytokines), that regulate the normal cross-talk between keratinocytes and melanocytes. In details, vitiligo is characterised by a hyper production of Th1 and Th17-related cytokines, with an inflammatory action (e.g. TNF - α, INF - γ, IL - 1, IL - 2, IL - 6, IL - 8, IL - 17). Recently, researchers and clinicians operating in the field of Low Dose Medicine (LDM) had investigated the possibility of treatment vitiligo with low dose cytokines, growth factors and neuropeptides. In details, it has been shown how the use of low oral dose anti-inflammatory cytokines (low dose Interleukin - 4 and Interleukin - IO; low dose anti-interleukin one antibody) and b - FGF, may be useful in restoring the altered keratinocytes-melanocytes cross-talk, leading to a skin repigmentation. The therapeutic protocol consists of the oral intake of 20 drops, twice a day, for 9 months of Low dose FGF, IL4, IL10 and IL1 [24][25].

Different observational studies demonstrated the efficacy and the safe profile of LDM in the treatment of vitiligo patients. The combination of the low dose cytokines with more conventional treatments (e.g. topical corticosteroids or micro-focused phototherapy) provide better results in term of repigmentation rate.

Conclusion

Even if asymptomatic and not life threatening, vitiligo is a disease psychologically devastating that have to be treated. Today different types of therapies are available but none of them provide excellent results in term of repigmentation rate and safeness. For this reason, new studies and experiment have to be conducted.

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Letter to the Editor

Comment on a Primary Cutaneous *Nocardiosis* of the Hand

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Abstract

Nocardia spp. are gram-positive, partially acid-fast bacteria which are lives in environmental sources and cause of various infection that called nocardiosis in animals and humans. Identification of this group of bacteria was important due to accurate diagnosis, patient management and prevention of antibiotic resistant among of bacteria. Molecular methods including PCR-RFLP and sequencing using housekeeping genes such as 16S rRNA, hsp65, rpoB and gyrB are recommended to accurate and reliable identification of nocardiosis.

Dear Editor,

Camozzota et al., recently published their report on A Primary Cutaneous Nocardiosis of the Hand [1]. *Nocardia* spp. is opportunistic environmental bacteria which are saprophytic lives in hospital environmental resources that through to the human body via inhalation of environment aerosols and cutaneous traumatic inclusion which cause of nocardiosis in immune disorder patients and even healthy individuals [2][3].

Nocardia species are identified using conventional test and molecular methods that phenotypic tests are laborious, time-consuming, expensive and need to expertise technicians while molecular methods such as direct sequencing of the *hsp65* (using pair primers of TB11: 5′-ACCAACGATGGTGTGTCCAT-3′ and TB12: 5′-CTTGTCGAACCGCATACCCT-3′) and 16S rRNA (whit primers 27f (5′-AGAGTTTGATCMTGGCTCAG-3′ and 1525r (5′-AAGGAGGTGWTCCARCC-3′) and PCR-RFLP are reliable, accurate and rapid for identification of nocardial infections especially in emergency cases for example in nocardial disseminated infections that necessary to urgent identifying *Nocardia* spp. before death of patients [3][4][5]. Based on the literatures, antimicrobial drug susceptibility of *Nocardia* species are different.

Also in many countries, Trimethoprim-sulfamethoxazole (TMP-SXT) is first choice for treatment of nocardiosis infection whereas reports have showed that high mortality rate of patients with brain abscess and disseminated which treated with sulfonamides alone [3]. Therefore, due to final diagnosis, appropriate treatment of patients *Nocardia* should be identified to the species level [3][6].

I'm request the authors attend to the following questions.

1. According to reports other aerobic actinomycetes including *Mycobacterium tuberculosis*, *non-tuberculosis mycobacteria* (NTM), *Gordonia*, *Rhodococcus* and *Tsukamurella* are similar to *Nocardia* spp. are same phenotypic features (microscopic evaluation and colony morphology); and can cause of cutaneous infections in human [7]. Please explain the *Nocardia* isolation method, which was not mentioned in the report.

2. Please clarify how *Nocardia* was identified to the species level.

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Authors reply

We very much appreciate the interest of Masoud Keikha in our recent case report on *Nocardiosis* of the hand. We are aware of high standard diagnostic procedures as described in your letter. However, the diagnostic opportunities are not easily available in daily practise. In our case the final diagnosis was obtained by culture.

In order to exclude *Mycobacteria tuberculosis*, Ziehl-Neelsen (acid fast stain) coloration was used. In addition we used Kinyoun stain, an acid-fast procedure used to detect species of the genus *Mycobacterium, Nocardia* and other species.

Unfortunately, it was not possible to identify the exact *Nocardia* specimen.

With kind regards,

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