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Immunocompromised Districts of Skin: A Case Series and a Literature Review

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Abstract

BACKGROUND: The concept of immunocompromised districts of skin has been developed by Ruocco and helps to explain certain aspects of the macromorphology of skin diseases. This concept unites the isomorphic response of Koebner and the isotopic response of Wolf.

CASE REPORTS: We present different cutaneous conditions which can lead to immunocompromised districts of skin such as scars, radiodermatitis, lymphedema, disturbed innervation or mechanical friction etc. Typical and rarer skin disorders associated with them are discussed and illustrated by their observations.

CONCLUSION: At this moment, we wish to inform dermatologists and non-dermatologists about Ruocco's concept and its implications.

Introduction

The skin is one of our main protective tissues to support body homeostasis. Protection is generated by the dynamic structure of the outmost part of skin, the stratum corneum, and supported by specific cells such as melanocytes (UV-protection), Langerhans cells (antigen control), Mast cells and macrophages (innate immunity), lymphocytes (including γδ T cells, innate lymphoid cells - specific immunity), and Merkel cells (neuroimmunology). Keratinocytes, sweat glands and sebaceous glands are part of the innate immune system [1], [2], [3].

Skin failure is one of the most important causes of mortality in the intensive care units [4], [5]. It has been defined as loss of temperature control with the inability to maintain the core body temperature, and failure to prevent percutaneous loss of fluid, electrolytes and protein, and failure of the skin barrier function [6].

However, impairment of skin function is quite often seen in a sectorial area. Different pathways may lead to sectorial skin function impairment such as trauma, infection, or vascular dysfunction. The sectorial impairment of immune and other functions of skin has been described by the term Ruocco's immunocompromised districts (ICD's) [7]. It unites different phenomena such as isomorphic (Koebner) and isotopic (Wolf) responses of skin and helps to understand macromorphology of dermatoses. Although the concept had been developed during the last decade, it has yet to gain widespread knowledge [8], [9].

In this review article, we will provide a collection of clinical examples supporting the concept ICD from our departments.

Skin grafts as ICD's

Autologous split skin grafts are a mainstay for defect closure after trauma and tumour surgery. Split skin is not a primary vascularized graft. Grafts survive initially by the oxygen supply from the wound bed. Skin grafts have to establish their blood vascularisation. Grafts are not passive but can secrete soluble mediators involved in wound healing [10]. During the first 48 h after transplantation, the graft is bulged by plasmatic fluid. Neo-angiogenesis leads to improved supply of oxygen and nutrients. Pre-vascularization of grafts further enhances therapeutic effects [11].

Graft-associated wound healing may show some peculiarities compare to "normal" wound healing. For instance, there is no involvement of sweat gland progenitors in grafts [12]. Skin grafts are not primarily vascularized. Both T and B lymphocytes, natural killer cells, and last not least antigen-presenting cells will infiltrate the graft only after successful neovascularisation. This results in changes of local immunity, as demonstrated by case reports on localised bullous pemphigoid in sites of grafting [13]. Nevertheless, split skin grafts preserve peculiarities of functionality for a long period [14].

The occurrence of eczema restricted donor sites of split skin grafts has rarely been observed [15], [16], [17]. Eczema or atopic dermatitis is a common disease. The basic pathogenetic mechanism is disturbances of skin barrier function, dysregulated immune response, and disturbances of gut and skin associated microbiome. The leading symptom is itch [18], [19], [20].

Split skin grafts are characterised by a barrier function impairment, demonstrated by increased transepidermal water loss (TEWL) [14]. In split skin grafts, cutaneous adnexae such as hair follicles, sebaceous and sweat glands are absent. Sweat and sebaceous glands, however, are involved in innate immunity and regulate skin hydration among other functions. This creates a certain vulnerability.

Disturbances of local innervation as a cause of ICD – SKINTED and acquired nevus teleangiectaticus

Sympathetic neurons localised in the spinal cord project to paravertebral or prevertebral ganglia and synapse with relatively long postganglionic fibres innervating blood vessels, lymphoid tissue and organs. The vagus nerve, with cell bodies residing in the brainstem medulla oblongata, is the main nerve of the parasympathetic division of the autonomic nervous system, innervating peripheral visceral sites. Vagus nerve efferent cholinergic fibres project to visceral organs. Acetylcholine represents the principal neuro mediators released from postganglionic fibres. This molecule interacts with G protein-coupled muscarinic acetylcholine receptors that mediate among others exocrine function of skin glands. The availability of molecular sensors for detecting pathogen fragments and inflammatory molecules on both neurons and immune cells allows their simultaneous involvement in inflammatory responses [21]. If neural components are impaired, this will harm the control of tissue homeostasis

The infrapatellar branches of the saphenous nerve may be damaged by either trauma or surgery with resultant anterior or anteromedial pain and an associated lateral area of altered sensation. The acronym SKINTED (surgery of the knee, injury to the infrapatellar branch of the saphenous nerve, traumatic eczematous dermatitis) describes the eruption of eczematous lesions in the skin after total knee endoprosthesis [22].

Acquired nevoid telangiectasia results from a segmental dilatation of papillary plexus vessels. It is asymptomatic. The disease indicates spinal or neuromuscular complaints with disturbed autonomic vascular nerve function (Figure 1) [23].

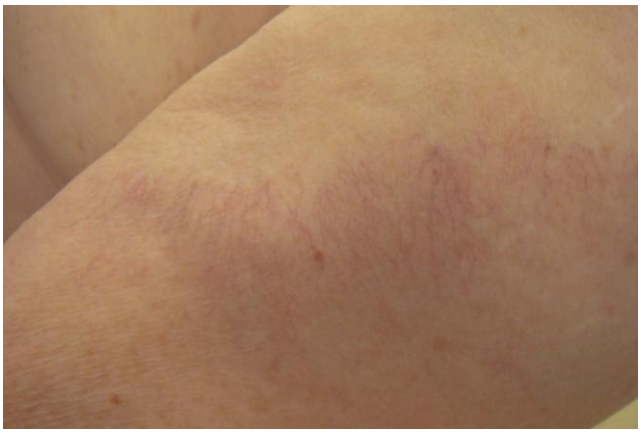

Figure 1: Acquired nevoid telangiectasia

In addition to trauma, infections of the nervous system have to be considered as a cause of ICD. Herpes zoster is caused by the varicella-zoster virus (VZV or herpes virus type 3). The primary infection leads to varicella. During the viraemic period of primary infection, VZV infects sensible dorsal spinal nerve ganglia and/or cephalic nerve ganglia. VZV lies dormant in the nervous system – neurons and glia satellite cells – for years. Endogenous reactivation of viral infection occurs after impairment of immune surveillance. Herpes zoster temporarily alters the function of neurons and ganglia leading to a painful inflammatory response [24].

Wolf's isotopic response describes the onset of secondary skin disease on the site of healed

herpetic lesions [25], [26]. We observed the development of hypertrophic scars and keloids four weeks after herpes zoster infection in a 28-year-old female while she was pregnant. She had not been treated by antiviral drugs during the acute infection and suffered from post-herpetic neuralgia [27].

A 66-year-old male patient with severe facial herpes zoster developed 5 days after zoster remission specific cutaneous zosteriform lesion of his pre-existent B-cellular chronic lymphatic leukaemia [28].

Lymphatic impairment as a cause of ICD

Lymphedema is caused by failure to drain protein-rich interstitial fluid and can be primary or secondary. Chronic lymph stasis has several consequences, including lipogenesis, fibrosis, inflammation, lymphangiogenesis, and immunosuppression. Lymphedema disrupts immune cell trafficking which leads to localised immunosuppression, predisposing to chronic inflammation, infection, and malignancy. Thus, lymphatic impairment can result in localised skin disease in an ICD [8].

We observed intralymphatic histiocytosis (IH), a rare disease with livedoid, erythematous to violaceous patches and plaques near articular metal implants [29]. The development of Stewart-Treves syndrome (angiosarcoma) in chronic arm lymphedema of breast cancer patients illustrates the importance of an intact lymphatic vasculature for cancer surveillance and prevention (Figure 2) [30].

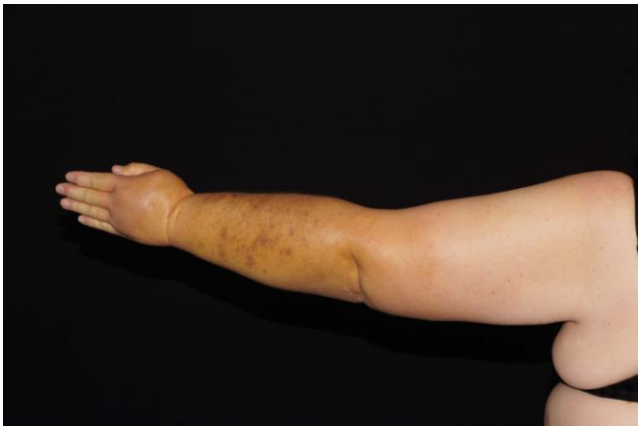

Figure 2: Stewart-Trewes syndrome in a breast cancer patient after lymph node dissection and radio-chemotherapy

Stretch marks as ICD's

Stretch marks are common during pregnancy and periods of a rapid increase of body weight or muscle mass. They are characterised by disturbances in the connective tissue and increased TEWL. Inflammatory dermatoses like psoriasis and lichen planus but also pigmentary disorders like vitiligo have been observed in stretch marks [31], [32].

The autoimmune disease herpes gestationis develops during the last trimester of pregnancy. It is characterised by vesico-bullous eruptions in striae distensae associated with pruritus [33].

Injection sites, stings and bites as an ICD

Intralesional injections of corticosteroids may lead to an ICD. Verma (2007) observed the development of a verrucous carcinoma on the foot of an Indian female patient at the injection site [34].

Wilmer et al., (1998) reported on benign lymphangioendothelioma (acquired progressive lymphangioma) at the site of a tick bite [35]. This uncommon benign lesion should be distinguished from well-differentiated angiosarcoma and patch-stage Kaposi's sarcoma [36].

Chronic osteomyelitis after limb trauma can lead to malignant transformation known as Marjolin's ulcer [37].

Previous sites of radiotherapy as ICD's

Chronic radiodermatitis occurs from 6 months up to 30 years after radiotherapy treatment. The skin develops telangiectasia, pigmentary changes, skin atrophy, dermal fibrosis, and keratoses. There is an ongoing activation of myofibroblasts in the connective tissue induced by transforming growth factor-beta 1 [38]. Sites of chronic radiodermatitis may be prone to delay non-melanoma skin cancer development. Wollina (2016) reported three patients with basal cell carcinomas in such ICD's more than 40 years after irradiation [39].

A 78-year-old female patient presented with a 3 cm large soft tissue defect on the frontotemporal left side with exposed bone and inflammatory soft tissue on the edges of the defect. About 35 years ago, she had undergone combined neurosurgery with skull trepanation and radiotherapy for an oligodendroglioma. Three years ago, sandwich transplantation with the dermal template and meshed skin graft failed. Recently she presented with a chronic ulcer, and a complex defect repair was performed after exclusion of a second malignancy. This is another example of an ICD [40].

Anastrozole is a non-selective aromatase inhibitor for adjuvant breast cancer therapy in postmenopausal women. Cutaneous adverse events have been reported. 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, a non-selective aromatase inhibitor. 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 segmental erythema multiforme-like drug eruption by anastrozole represents another example of the concept of ICD [41].

Tattoos as ICD's

Tattoos are pigmented areas of traumatised skin. Tattoo inks bear health risk. They may contain hexavalent chromium (Cr [VI]), which is carcinogenic to humans and a dermal sensitiser, benzene or naphthalene, known as carcinogens, and acrylates, known as sensitisers, among others [42], [43]. While contact dermatitis or infections are seen in tattoos, cancer development is a rare event and probably coincidental [44], [45].

The pigment particles are foreign bodies and can induce a chronic inflammatory response such as sarcoidal granulomas [46], [47], [48]. These granulomas are not identical with cutaneous sarcoidosis. However, true cutaneous sarcoidosis has also been observed in tattoos but less common [49], [50].

Surgical scars as ICD's

Surgery may possess several risks including bleeding, infection, hypertrophic scars or keloid formation. Surgical scars may also be the site of manifestation of other disorders since they represent an IDC.

Koebnerization by scars has been reported for psoriasis [51], lichen sclerosis et atrophicus [52], necrobiosis lipoidica [53], and vitiligo [54]. Scar sarcoidosis is another representative of such dermatoses [55].

In women after open abdominal surgery, cutaneous endometriosis may develop. This uncommon condition is characterised by the presence of an abdominal mass, period and non-period pain. Diagnosis needs to be confirmed by histopathology [56].

A greatly feared complication after surgery represents pyoderma gangrenosum – a primary sterile neutrophilic dermatosis (Figure 3) [57], [58].

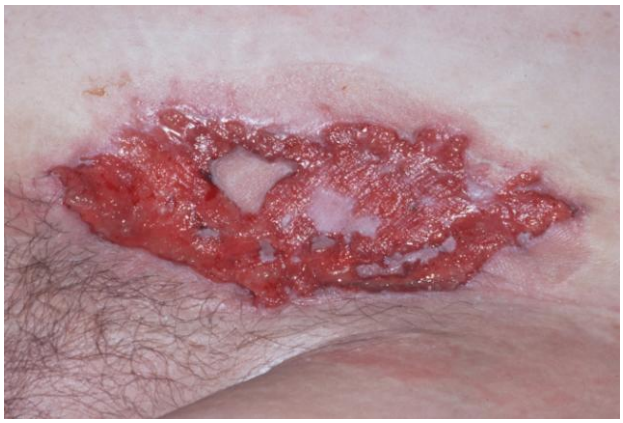

Figure 3: Pyoderma gangrenosum in in a scar from section caesarea

We observed a 63-year old man, who developed a verrucous carcinoma of skin in the scar of knee total endoprosthesis (Figure 4).

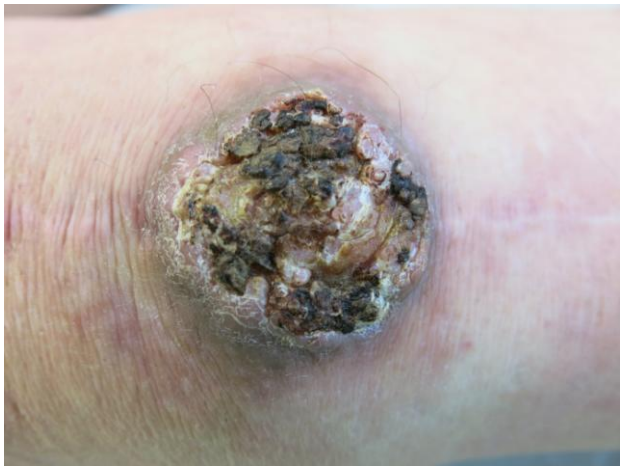

Figure 4: Verrucous carcinoma in the scar after knee total endoprosthesis

Burn scars as ICD's

The burn wound is characterized by alterations of immune cell composition. Even in the early stage they contain significantly greater numbers of T-cells, primarily αβ T-cells with a suppressor phenotype. In contrast, the γδ T-cells are diminished, and the expression of the early activator CD69 is decreased 9-fold in the burn wound. This causes and ICD [59].

Deep burn scars seem to facilitate secondary

malignancies. With a delay of a year to decades squamous cell carcinoma, basal cell carcinoma and, to a lesser extent, melanoma has been reported [60]. Rarely, burn-induced tumours of histiocytic origin have been observed in a few cases. Vanhooteghem and Theate (2018) reported a 66-year-old male patient suffering from severe large stage 3 burn on the leg. Fifty-five years later, this patient developed large extraosseous osteosarcoma on the scar [61].

Chronic friction as an ICD

Chronic friction is a thread to the epidermal barrier. Typical clinical findings of chronic friction are callus, corn, black heel and post-inflammatory hyperpigmentation – in particular in the skin of colour [62].

Friction can cause koebnerization of different, mostly inflammatory dermatoses such as atopic or occupational dermatitis [63], [64], lichen planus, vitiligo [65], frictional hypermelanosis [66], frictional keratosis of the nipple during breastfeeding or the hyperkeratosis of buccal mucosa seen in morsicatio buccorum [67]. Friction plays an obvious role in the manifestation of hidradenitis suppurativa (*syn:* acne inversa) [68]. In obese patients, boils often develop at the site of friction (Figure 5). Sitting with closed-legs on hard ground can cause callosities above the ankles, also known as Yoga sign [69]. Another example of a frictional dermatosis is pretibial alopecia [70].

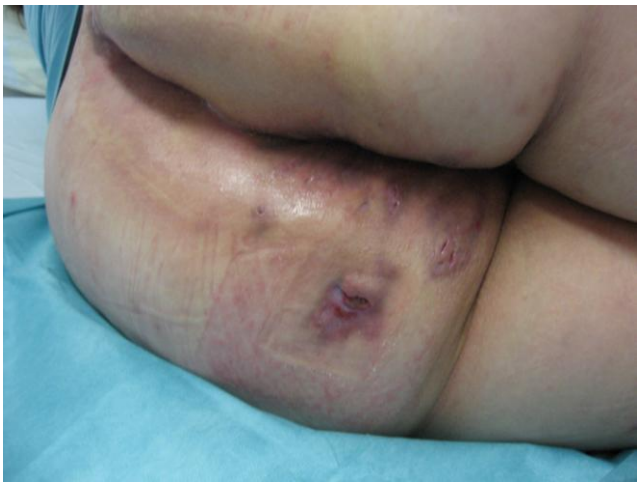

Figure 5: Acne inversa/hidradenitis suppurativa boils gluteal in an area of friction

Epilation sites as an ICD

Eyebrow threatening is a popular procedure in India. There is several complications that have been reported including the appearance of verrucae, folliculitis, pseudofolliculitis, hyperpigmentation, and depigmentation, including the koebnerization of vitiligo [71], [72].

Laser hair removal also can induce koebnerization. There are reports on reactive perforating collagenosis and vitiligo induced by laser hair removal [73], [74].

Table 1: Immunocompromised districts of skin

Major alteration(s)	Underlying disorders
Connective tissue disturbances	scars, stretch marks, chronic radiodermatitis, burns
Lymphatic impairment	lymphedema
Disturbed nerval function	herpes zoster, spinal or neuromuscular complaints with disturbed autonomic vascular nerve function
Impaired epidermal barrier	skin graft recipient and donor sites, burns
Local immunosuppression	steroid injections, chronic radiodermatitis, burns
Chronic exposure to foreign bodies	tattoos

Conclusions

The concept of ICD has broadened our view on localised immune dysfunction in the skin. These areas are prone to develop secondary skin disorders, both benign and sometimes malignant. The pathogenesis is not completely understood and does not seems to be uniform. Loss of barrier function, loss of skin glands important for innate immunity, disturbed vascular function, connective tissue alterations, disturbed innervation or chronic exposure to foreign bodies are possible mechanisms (Table 1). Future research is necessary to develop strategies to reconstitute ICD's to gain full immunologic competence again.

References

1. Kanitakis J. Anatomy, histology and immunohistochemistry of normal human skin. Eur J Dermatol. 2002; 12:390-9.

2. Elias PM. Stratum corneum defensive functions: an integrated view. J Invest Dermatol. 2005; 125:183-200. https://doi.org/10.1111/j.0022-202X.2005.23668.x PMid:16098026

3. Salimi M, Ogg G. Innate lymphoid cells and the skin. BMC Dermatol. 2014; 14:18. https://doi.org/10.1186/1471-5945-14-18 PMid:25427661 PMCid:PMC4289267

4. Inamadar AC, Palit A. Acute skin failure: Concepts, causes, consequences and care. Indian J Dermatol Venereol Leprol. 2005; 71:379-85. https://doi.org/10.4103/0378-6323.18007

5. Wollina U, Nowak A. Dermatology in the intensive care unit. Our Dermatology. 2012; 3:298-303. https://doi.org/10.7241/ourd.20124.65

6. Irvine C. 'Skin failure' a real entity: discussion paper. J R Soc Med. 1991; 84:412-3. https://doi.org/10.1177/014107689108400711 PMid:1865448 PMCid:PMC1293332

7. Ruocco V, Ruocco E, Piccolo V, Brunetti G, Guerrera LP, Wolf R. The immunocompromised district in dermatology: A unifying pathogenic view of the regional immune dysregulation. Clin Dermatol. 2014; 32:569-76. https://doi.org/10.1016/j.clindermatol.2014.04.004 PMid:25160098

8. Ruocco E, Puca RV, Brunetti G, Schwartz RA, Ruocco V. Lymphedematous areas: privileged sites for tumors, infections, and immune disorders. Int J Dermatol. 2007; 46:662. https://doi.org/10.1111/j.1365-4632.2007.03244.x PMid:17550576

9. Ruocco V, Brunetti G, Puca RV, Ruocco E. The immunocompromised district: a unifying concept for lymphoedematous, herpes-infected and otherwise damaged sites. J Eur Acad Dermatol Venereol. 2009; 23:1364-73. https://doi.org/10.1111/j.1468-3083.2009.03345.x PMid:19548975

10. Maarof M, Law JX, Chowdhury SR, Khairoji KA, Saim AB, Idrus RB. Secretion of wound healing mediators by single and bi-layer skin substitutes. Cytotechnology. 2016; 68:1873-84. https://doi.org/10.1007/s10616-015-9940-3 PMid:26768914 PMCid:PMC5023561

11. Chen L, Xing Q, Zhai Q, Tahtinen M, Zhou F, Chen L, et al. Pre-vascularization enhances therapeutic effects of human mesenchymal stem cell sheets in full thickness skin wound repair. Theranostics. 2017; 7:117-31. https://doi.org/10.7150/thno.17031 PMid:28042321 PMCid:PMC5196890

12. Lu C, Fuchs E. Sweat gland progenitors in development, homeostasis, and wound repair. Cold Spring Harb Perspect Med. 2014; 4:a015222. https://doi.org/10.1101/cshperspect.a015222 PMid:24492848 PMCid:PMC3904096

13. Ghura HS, Johnston GA, Milligan A. Development of a bullous pemphigoid after split-skin grafting. Br J Surg. 2001; 54:447-9. https://doi.org/10.1054/bjps.2001.3601 PMid:11428779

14. Kim YJ, Kim MY, Lee PK, Kim HO, Park YM. Evaluation of natural change of skin function in split-thickness skin grafts by noninvasive bioengineering methods. Dermatol Surg. 2006; 32:1358-63. https://doi.org/10.1111/j.1524-4725.2006.32306.x PMid:17083588

15. Sahin C, Noyan N, Ergun O, Sever C, Kulahci Y. Eczema in full-thickness skin graft. J Burn Care Res. 2013; 34:e58. https://doi.org/10.1097/BCR.0b013e31825adb43 PMid:22929528

16. Harnack K, Miemiec E, Waldau W. Endogenous eczema in a split-thickness skin graft. Dermatol Monatsschr. 1972; 158:28-32.

17. Constantini N. Eczema of Thiersch's graft following radical surgery. Arcisp S Anna Ferrara. 1954; 7:169-79.

18. Elias PM, Steinhoff M. "Outside-to-inside" (and now back to "outside") pathogenic mechanisms in atopic dermatitis. J Invest Dermatol. 2008; 128:1067-70. https://doi.org/10.1038/jid.2008.88 PMid:18408746 PMCid:PMC2675555

19. Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016; 387:1109-22. https://doi.org/10.1016/S0140-6736(15)00149-X

20. Wollina U. Microbiome in atopic dermatitis. Clin Cosmet Investig Dermatol. 2017; 10:51-6. https://doi.org/10.2147/CCID.S130013 PMid:28260936 PMCid:PMC5327846

21. Pavlov VA, Chavan SS, Tracey KJ. Molecular and functional neuroscience in immunity. Annu Rev Immunol. 2018; 36:783-812. https://doi.org/10.1146/annurev-immunol-042617-053158 PMid:29677475 PMCid:PMC6057146

22. Verma SB, Mody BS. Explaining a hitherto nameless condition: 'SKINTED'. Clin Exp Dermatol. 2009; 34:e465-6. https://doi.org/10.1111/j.1365-2230.2009.03522.x PMid:19747315

23. Wollina U, Barta U, Uhlemann C, Oelzner P. Acquired nevoid telangiectasia. Dermatology. 2001; 203:24-6. https://doi.org/10.1159/000051698 PMid:11549795

24. Wollina U. Variations in herpes zoster manifestation. Indian J Med Res. 2017; 145:294-298.

25. Wolf R, Wolf D. Tinea in a site of healed herpes zoster (isoloci response?). Int J Dermatol. 1985; 24:539. https://doi.org/10.1111/j.1365-4362.1985.tb05561.x PMid:4066096

26. Wolf R, Wolf D, Ruocco V, Ruocco E. Wolf's isotopic response: The first attempt to introduce the concept of vulnerable areas in dermatology. Clin Dermatol. 2014; 32:557-60. https://doi.org/10.1016/j.clindermatol.2014.04.002 PMid:25160096

27. Verma SB, Wollina U. Herpes zoster in pregnancy leading to keloids and post herpetic neuralgia: A double whammy? Indian Dermatol Online J. 2013; 4:158-9. https://doi.org/10.4103/2229-5178.110646 PMid:23741683 PMCid:PMC3673390

28. Wollina U, Schönlebe J. Disseminated specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia - Wolf's isotopic response following herpes zoster infection. J Dtsch Dermatol Ges. 2016; 14:179-81. https://doi.org/10.1111/ddg.12670 PMid:26283648

29. Darling MD, Akin R, Tarbox MB, Stetson CL, Patterson JW, Tchernev G, et al. Intralymphatic histiocytosis overlying hip implantation treated with pentoxifilline. J Biol Regul Homeost Agents. 2015; 29(1 Suppl):117-21.

30. Bennewitz A, Langner D, Schönlebe J, Heinig B, Koch A, Wollina U. Stewart-Treves-Syndrom beim sekundären Arm-Lymphödem neun Jahre nach invasiv-duktalem Mammakarzinom. Lymph Forsch Praxis. 2013; 17:16-8.

31. Verma SB. Vitiligo precipitated by striae: a little known entity. J Eur Acad Dermatol Venereol. 2009; 23:357-8. https://doi.org/10.1111/j.1468-3083.2008.02844.x PMid:18554226

32. Verma SB. Striae: stretching the long list of precipitating factors for 'true koebnerization' of vitiligo, lichen planus and psoriasis. Clin Exp Dermatol. 2009; 34:880-3. https://doi.org/10.1111/j.1365-2230.2009.03312.x PMid:19489859

33. Wollina U, Degen KW, Konrad H, Schönlebe J. Itching stretch marks and bullous lesions in a pregnant woman. Int J Dermatol. 2004; 43:752-4. https://doi.org/10.1111/j.1365-4632.2004.02356.x PMid:15485535

34. Verma SB. Verrucous lesion on dorsum of the foot. Indian J Dermatol Venereol Leprol. 2007; 73:281. https://doi.org/10.4103/0378-6323.33654 PMid:17682297

35. Wilmer A, Kaatz M, Mentzel T, Wollina U. Lymphangioendothelioma after a tick bite. J Am Acad Dermatol. 1998; 39:126-8. https://doi.org/10.1016/S0190-9622(98)70416-5

36. Guillou L, Fletcher CD. Benign lymphangioendothelioma (acquired progressive lymphangioma): a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma: clinicopathologic analysis of a series. Am J Surg Pathol. 2000; 24:1047-57. https://doi.org/10.1097/00000478-200008000-00002 PMid:10935645

37. Bula P, Bula-Sternberg J, Wollina U, Haroske G, Bonnaire F. [Marjolin's ulcer: malignant transformation of a crural ulcer due to posttraumatic chronic osteomyelitis]. Unfallchirurg. 2010; 113:149-54. https://doi.org/10.1007/s00113-009-1671-5 PMid:19859679

38. Martin M, Lefaix J, Delanian S. TGF-beta1 and radiation fibrosis: a master switch and a specific therapeutic target? Int J Radiat Oncol Biol Phys. 2000; 47:277-90. https://doi.org/10.1016/S0360-3016(00)00435-1

39. Wollina U. Basal cell carcinoma in the area of chronic radiodermatitis - 3 case reports with long-term follow-up. Georgian Med News. 2016; (254):7-10.

40. Wollina U, Nowak A, Tchernev G, Lotti T. Chronic scalp ulcer 35 years after skull trepanation surgery and radiotherapy for oligodendroglioma: A further example of immunocompromised cutaneous districts. Open Access Maced J Med Sci. 2017; 6:55-7. https://doi.org/10.3889/oamjms.2018.019 PMid:29483982 PMCid:PMC5816315

41. Wollina U, Schönlebe J, Heinig B, Tchernev G, França K, Lotti T. Segmental erythema multiforme-like drug eruption by aromatase inhibitor anastrozole - first case report and another example of an immunocompromised district. Open Access Maced J Med Sci. 2018; 6:79-81. https://doi.org/10.3889/oamjms.2018.026 PMid:29483990 PMCid:PMC5816324

42. Bocca B, Senofonte O, Petrucci F. Hexavalent chromium in tattoo inks: Dermal exposure and systemic risk. Contact Dermatitis. 2018; 79:218-25. https://doi.org/10.1111/cod.13051 PMid:29998510

43. Schreiver I, Hutzler C, Andree S, Laux P, Luch A. Identification and hazard prediction of tattoo pigments by means of pyrolysis-

gas chromatography/mass spectrometry. Arch Toxicol. 2016; 90:1639-50. https://doi.org/10.1007/s00204-016-1739-2 PMid:27209489 PMCid:PMC4894928

44. Kluger N, Koljonen V. Tattoos, inks, and cancer. Lancet Oncol. 2012; 13:e161-8. https://doi.org/10.1016/S1470-2045(11)70340-0

45. Wollina U. Severe adverse events related to tattooing: a retrospective analysis of 11 years. Indian J Dermatol. 2012; 57:439-43. https://doi.org/10.4103/0019-5154.103062 PMid:23248361 PMCid:PMC3519250

46. Wollina U, Gruner M, Schönlebe J. Granulomatous tattoo reaction and erythema nodosum in a young woman: common cause or coincidence? J Cosmet Dermatol. 2008; 7:84-8. https://doi.org/10.1111/j.1473-2165.2008.00368.x PMid:18482009

47. Leverenz DL, Henderson C, Shah A. Atypical cutaneous presentations of sarcoidosis: two case reports and review of the literature. Curr Allergy Asthma Rep. 2018; 18:40. https://doi.org/10.1007/s11882-018-0794-6 PMid:29904803

48. Tchernev G, Lotti T, Wollina U, Cardoso JC, Popova LV, Maximov GK, et al. Sarcoidosis in A. C. Milan (1899)? Open Access Maced J Med Sci. 2018; 6:99-102. https://doi.org/10.3889/oamjms.2018.049 PMid:29483997 PMCid:PMC5816331

49. Kluger N. Cutaneous complications related to tattoos: 31 cases from Finland. Dermatology. 2017; 233:100-9. https://doi.org/10.1159/000468536 PMid:28441655

50. Grosse J, Menhart K, Schmidbauer B, Hellwig D. Cutaneous manifestation of sarcoidosis in lower-back tattoo with increased uptake of 18F-FDG. Clin Nucl Med. 2018; 43:454-5. https://doi.org/10.1097/RLU.0000000000002061 PMid:29538031

51. Alolabi N, White CP, Cin AD. The Koebner phenomenon and breast reconstruction: Psoriasis eruption along the surgical incision. Can J Plast Surg. 2011; 19:143-4. https://doi.org/10.1177/229255031101900411 PMid:23204886 PMCid:PMC3269195

52. Mendieta-Eckert M, Ocerin-Guerra I, Landa-Gundin N. Lichen sclerosus et atrophicus in a surgical scar treated with fractional laser. J Cosmet Laser Ther. 2017; 19:106-8. https://doi.org/10.1080/14764172.2016.1262955 PMid:27911123

53. Prieto-Torres L, Bernárdez C, Hernández-Ostiz S, Pastushenko I, Ara-Martin M, Requena L. Necrobiosis lipoidica developing within a surgical scar in a non-diabetic patient: Type III Koebner phenomenon (isomorphic response), Wolf's isotopic response or Ruocco's immunocompromised cutaneous district? Indian J Dermatol Venereol Leprol. 2017; 83:233-6. https://doi.org/10.4103/0378-6323.197389 PMid:28071608

54. Khurrum H, AlGhamdi KM, Bedaiwi KM, AlBalahi NM. Multivariate analysis of factors associated with the Koebner phenomenon in vitiligo: An observational study of 381 patients. Ann Dermatol. 2017; 29:302-6. https://doi.org/10.5021/ad.2017.29.3.302 PMid:28566906 PMCid:PMC5438936

55. Tchernev G, Cardoso JC, Chokoeva AA, Verma SB, Tana C, Ananiev J, et al. The "mystery" of cutaneous sarcoidosis: facts and controversies. Int J Immunopathol Pharmacol. 2014; 27:321-30. https://doi.org/10.1177/039463201402700302 PMid:25280023

56. Lopez-Soto A, Sanchez-Zapata MI, Martinez-Cendan JP, Ortiz Reina S, Bernal Mañas CM, Remezal Solano M. Cutaneous endometriosis: Presentation of 33 cases and literature review. Eur J Obstet Gynecol Reprod Biol. 2018; 221:58-63. https://doi.org/10.1016/j.ejogrb.2017.11.024 PMid:29310043

57. Wollina U. Pyoderma gangrenosum--a review. Orphanet J Rare Dis. 2007; 2:19. https://doi.org/10.1186/1750-1172-2-19 PMid:17433111 PMCid:PMC1857704

58. Verma SB. Atypical pyoderma gangrenosum following total knee replacement surgery: First report in dermatologic literature. An Bras Dermatol. 2009; 84:689-91. https://doi.org/10.1590/S0365-05962009000600020 PMid:20191186

59. Rani M, Schwacha MG. The composition of T-cell subsets are altered in the burn wound early after injury. PLoS One. 2017; 12:e0179015. https://doi.org/10.1371/journal.pone.0179015 PMid:28575063 PMCid:PMC5456360

60. Yoo JJ, Kim HS, Kim JH, Joo M, Kim KJ, Park S, Jet al. Clinical features and treatment outcomes of skin cancer arising from burn scar: a single-institution experience. Tumori. 2014; 100:26-30.

61. Vanhooteghem O, Theate I. A rare extraskeletal osteosarcoma appearing after 55 years on a large stage 3 burn scar. Case Rep Dermatol Med. 2018; 2018:5185604. https://doi.org/10.1155/2018/5185604 PMid:29971170 PMCid:PMC6008689

62. Wollina U. Disorders Caused by Physical and Chemical Damage. In: Burgdorf WHC, Plewig G, Wolff HH, Landthaler M (Editors): Braun-Falco's Dermatology, 3rd edition. Berlin, Heidelberg: Springer-Verlag; 2009:598-616.

63. Bennike NH, Johansen JD, Menné T. Friction from paper and cardboard causing occupational dermatitis in non-atopic individuals. Contact Dermatitis. 2016; 74:307-8. https://doi.org/10.1111/cod.12530 PMid:27040878

64. Wollina U, Heinig B, Tchernev G, França K, Lotti T. Unilateral palmar callus and irritant hand eczema - underreported signs of dependency on crutches. Open Access Maced J Med Sci. 2018;6:103-4. https://doi.org/10.3889/oamjms.2018.031 PMid:29483998 PMCid:PMC5816272

65. Verma SB. Dermatological signs in South Asian women induced by sari and petticoat drawstrings. Clin Exp Dermatol. 2010; 35:459-61. https://doi.org/10.1111/j.1365-2230.2009.03587.x PMid:19758377

66. Wollina U, Tchernev G, Lotti T. Frictional dermatosis in a courier driver. Open Access Maced J Med Sci. 2017; 5:541-2. https://doi.org/10.3889/oamjms.2017.108 PMid:28785356 PMCid:PMC5535681

67. Wollina U. Krebsvorläufer an der Mundschleimhaut? MMW Fortschr Med. 2017; 159:7. https://doi.org/10.1007/s15006-017-0144-y PMid:29071646

68. Verma SB, Wollina U. Callosities of cross legged sitting: "yoga sign"--an under-recognized cultural cutaneous presentation. Int J Dermatol. 2008; 47:1212-4. https://doi.org/10.1111/j.1365-4632.2008.03823.x PMid:18986470

69. Boer J. Should hidradenitis suppurativa be included in dermatoses showing koebnerization? Is it friction or fiction? Dermatology. 2017; 233:47-52. https://doi.org/10.1159/000472252 PMid:28505620

70. Zhao J, Cohen PR. Frictional alopecia of the distal legs: case series and review. Dermatol Online J. 2016;22(8).

71. Verma SB. Vitiligo with koebnerisation due to eyebrow plucking by threading. J Cosmet Dermatol. 2002; 1:214-5. https://doi.org/10.1111/j.1473-2165.2002.00069.x PMid:17147543

72. Verma SB. Eyebrow threading: a popular hair-removal procedure and its seldom-discussed complications. Clin Exp Dermatol. 2009; 34:363-5. https://doi.org/10.1111/j.1365-2230.2008.02920.x PMid:19021633

73. Doshi SN, Levy ML, Markus R. Koebnerization of reactive perforating collagenosis induced by laser hair removal. Lasers Surg Med. 2003; 32:177-9. https://doi.org/10.1002/lsm.10158 PMid:12605422

74. Zainab J. Koebnerization of reactive perforating collagenosis induced by laser hair removal. J Cosmet Dermatol. 2011; 10:72-3. https://doi.org/10.1111/j.1473-2165.2010.00542.x PMid:21332919