

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

Aleksandra Vojvodic¹, Michael Tirant^{2,3}, Veronica di Nardo², Torello Lotti², Uwe Wollina^{4*}

¹Department of Dermatology and Venereology, Military Medical Academy of Belgrade, Belgrade, Serbia; ²Department of Dermatology, University of Rome "G. Marconi", Rome, Italy; ³Hanoi Medical University, Hanoi, Vietnam; ⁴Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Academic Teaching Hospital, Dresden, Germany

Abstract

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***Correspondence:** Uwe Wollina, Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Academic Teaching Hospital, 01067 Dresden, Germany. E-mail: uwollina@gmail.com

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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 $\gamma\delta$ 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-Treves 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 lymphangi endothelioma (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 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 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 $\alpha\beta$ T-cells with a suppressor phenotype. In contrast, the $\gamma\delta$ 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 threat 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

Eye-brow 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 neural 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 seem 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.

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