Viewpoint

The immunocompromised cutaneous district and the necessity of a new classification of its disparate causes

Stefano Caccavale, Ajith Prasanna Kannangara[1], Eleonora Ruocco

Locus minoris resistentiae can be defined as a site of the body that offers lesser resistance than the rest of the body to the onset of disease. There are many reports of privileged localization of cutaneous lesions on injured skin which represents a typical condition of locus minoris resistentiae. Köbner phenomenon, namely the appearance of new lesions pertaining to a previously present skin disorder at the sites of trauma or other insult, is itself a clear example of locus minoris resistentiae in dermatology. The possible causes of the phenomenon are many and multifarious.[1]

The opposite of locus minoris resistentiae has not been considered so far, though examples of body sites that offer resistance to the onset of disease are not rare. In 1991, the Renbök (inverted writing of Köbner) phenomenon was described by Happle *et al.* as normal hair growth in psoriatic patches noted in a patient with co-occurrence of psoriasis and alopecia areata.[2] The new term locus maioris resistentiae, a site of the body that offers greater resistance than the rest of the body to the onset of disease might well define this opposite condition. Renbök phenomenon typically represents an example of locus maioris resistentiae.

Herpes-infected areas are known to be privileged sites for either harboring or rejecting a wide range of multifarious disorders (infections, tumors, dysimmune reactions). The phenomenon is labeled isotopic response when a new disease occurs on the herpes-infected site (locus minoris resistentiae) or isotopic non-response when the herpes-infected site is selectively spared by a cutaneous eruption that is diffuse elsewhere (locus maioris resistentiae). The term isotopic response (or non-response) was mainly used for herpetic infections. Afterward, the prevailing term became Wolf's post-herpetic isotopic response or non-response (post-herpetic meaning a consequence of a varicella-zoster virus or herpes simplex virus infection). However, the cause of an isotopic response is far from being singular (herpetic infection).[3]

It has been well known that all types of cutaneous scars are vulnerable sites for the development of neoplasms, infections and dysimmune reactions. The complex underlying mechanisms have lately been included into the concept of the "immunocompromised cutaneous district."[4] This term denotes a regional immune dysregulation caused by failure of lymph flow or altered neuropeptide release. The local alteration of the immune response, depending on the neurotransmitters and immune cells involved in the immunodestabilized cutaneous site can be either defective (favoring the development of opportunistic infections or tumors) or overactive (favoring the development of immune disorders).[4]

Since 2009, the year when the concept was fully developed and published, several cases of immunocompromised cutaneous district have been

Department of Dermatology, Second University of Naples, Naples, Italy, [1]Department of Dermatology, Base Hospital Balapitiya, Ministry of Health, Sri Lanka

Address for correspondence: Dr. Stefano Caccavale, Department of Dermatology, Second University of Naples, Via Sergio Pansini 5, 80131 Naples, Italy.
E-mail: stefano85med@libero.it

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identified.[5-12] Several factors can be responsible for localized immune dysregulation including chronic lymph stasis, herpetic infections, ionizing or ultraviolet radiation, burns, all kinds of trauma, tattooing, intradermal vaccinations and others. Whatever the cause, an immunocompromised district may become a vulnerable site, prone to developing opportunistic infections, tumors, or dysimmune reactions strictly confined to the district itself; the opposite may also occur with systemic immune disorders or malignancies that selectively spare the district.

What is the pathomechanism of this phenomenon? What is the defect that leads to local immune dysregulation in these areas? Immune response of a given cutaneous region is the result of a complex set of cellulor interactions, each with multiple regulatory points, based on the normal trafficking of immunocompetent cells through lymph channels and on the signals that the neuromediators released by peptidergic nerve fibers send to cell membrane receptors of immune cells. Any obstacle to lymph circulation or interference in the communications between peripheral neuromediators and immune cells can significantly alter local immune response.[5] The pathomechanisms involved in this sectorial immune destabilization may reside in locally hampered lymph drainage that hinders the normal trafficking of immunocompetent cells, damage to sensory nerve fibers that release immunity-related peptides, or both. To support this concept, we have focused on radiation dermatitis and burns in which the lymph network is profoundly disrupted with abnormal dilation of some vessels and obstruction of others. This results in an obvious obstacle to the trafficking of immune cells. Moreover, peripheral nerve fibers are throttled by dermal fibrosis and, in burn scars, the number of these fibers with relevant nerve endings proved to be significantly reduced, similar to what occurs in varicella-zoster virus-affected dermatomes, which also are known to be immunocompromised cutaneous districts. The locally altered interplay between immune cells conveyed by lymph vessels and neuromediators running along peripheral nerve fibers deprives the injured skin districts of normal immunological functions. According to the contingent circumstances depending on immune cells and neuropeptides involved, the regional immune dysregulation may manifest differently at different times, i.e., reduction of immunity facilitating the onset of opportunistic infections or tumors, excess of immunity responsible for dysimmune reactions or immune disorders.[5] For example, we have recently observed a case of localized psoriasis occurring exclusively on both saphenectomized lower limbs of a woman.

The injuring events capable of rendering a skin region a potential immunocompromised district are various, numerous and most of the times identifiable by means of a careful clinical history. A newly coined terminology to indicate each specific cause responsible for the occurrence of an immunocompromised cutaneous district should be proposed. We believe that a new categorization of the disparate causes of an immunocompromised district will simplify the understanding of this phenomenon. As further new observations continue to be reported on the subject, changes and revisions in the proposed classification may take place.

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There are no conflicts of interest.

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