Clinics in Dermatology (2016) **34**, 654–657

ELSEVIER

Clinics in Dermatology

Comment and Controversy
Edited by Stephen P. Stone, MD

Loco-regional immune default: The immunocompromised district in human and comparative dermatology

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Abstract Lately, the innovative concept of an immunocompromised cutaneous district (ICD) has been introduced to explain why a previously injured cutaneous site may become in time a privileged location for the onset of opportunistic infections, tumors, and immune reactions. The injuring events capable of rendering a skin region a potential ICD are various, numerous, and most of the time identifiable by means of a careful clinical history. The reason that only a small minority of injured skin areas actually becomes ICDs, with subsequent opportunistic localization of a second and unrelated skin disorder, is presently unknown.

The ICD is a conceptual entity that is not limited to human dermatology. It can also apply to veterinary medicine. Development of sarcomas at the injection site in cats after routine vaccination and, occasionally, administration of pharmaceutical products, as well as insertion of any foreign body, is a repeatedly documented event. Antigen load, persistent inflammation, and fibroblastic proliferation are thought to be important factors predisposing to the onset of fibrosarcoma in cats.

Recently, it has been hypothesized that a local immunosuppression caused by inhalant glucocorticoids may have favored the development of regional demodicosis in cats. In our opinion, injection-site sarcomas and feline localized demodicosis can be considered examples of veterinary ICDs.

The immunocompromised district in humans: General concepts

Identifying a vulnerable area of the body has always aroused great interest in humans. There are countless reports of privileged localization of cutaneous lesions on injured skin, which represents a typical condition of *locus minoris resistentiae*.[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. The term *locus maioris resistentiae* (LMR), a site of the body that offers greater resistance than the rest of the body to the onset of disease, well defines this opposite condition.[1]

It has been well known for a long time that all types of cutaneous scars are preferred sites for the development of neoplasms, infections, and dysimmune reactions. The complex underlying mechanisms have lately been included into the concept of an *immunocompromised cutaneous district* (ICD). This term denotes a regional immune dysregulation caused

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http://dx.doi.org/10.1016/j.clindermatol.2016.04.009
0738-081X/

by lymph flow failure or altered neuropeptide release. The local alteration of the immune response, depending on the neurotransmitters and immune cells each time involved in the immunodestabilized cutaneous site, can be either defective (which favors the outbreak of opportunistic infections or tumors) or overactive (which favors the outbreak of immune disorders).[1]

Although the concept of immunocompromised district was developed only 8 years ago, paradigmatic instances of it, concerning the "opportunistic" onset of malignancies on lymphedematous and immunocompromised lower limbs, were published more than 30 years ago. They dealt with cases of Stewart-Treves syndrome, unilateral Kaposi sarcoma, coexistent basal cell carcinoma, and paucilesional Kaposi sarcoma; all tumors appeared on and were restricted to lower limbs with documented alteration of both lymph flow and immune response. At that time, the concept of cutaneous ICD had not been focused on yet. Since 2009, the year when the concept was fully developed and published, identifying a case of cutaneous ICD has become a common occurrence.[1]

The factors responsible for a localized immune dysregulation are multifarious, being represented by chronic lymph stasis, herpetic infections, ionizing or ultraviolet radiation, burns, all sorts of trauma, tattooing, intradermal vaccinations, and others of a disparate nature.[1–21] Whatever the cause, in time, an ICD may become a vulnerable site, prone to developing opportunistic infections, tumors, or dysimmune reactions strictly confined to the district itself; however, the opposite may also occur, with systemic immune disorders or malignancies that selectively spare the district.

In any case, the immunologic behavior of an ICD is different from that of the rest of the body. The pathogenesis involved in this sectorial immune destabilization may reside in locally hampered lymph drainage that hinders the normal trafficking of immunocompetent cells, or damage to sensory nerve fibers that release immunity-related peptides, or both conditions.[1]

Recently, a newly coined terminology, indicating each specific cause responsible for the occurrence of an ICD, has been proposed.[21] The new classification, based on the well-known isomorphic and isotopic skin reactions, encompasses additional clinical conditions (isomosaictopic, isovaccinetopic, isotattootopic, isoneuraltopic, and isolymphostatic response and nonresponse) that have not been clearly defined.[21]

Identification of an ICD in human dermatology is an important standpoint for both diagnostic and prevention purposes. In fact, knowing that a previously injured or diseased cutaneous site may in time harbor secondary skin disorders, different from the first one, can provide a diagnostic aid in some circumstances. Being aware of how vulnerable an injured or diseased skin site may be for an entire lifespan should alert both the physician and the patient to keep the site under special observation. Any new lesion appearing on that site should promptly be investigated by all means and, when necessary, immediately treated (infections, dysimmune reactions) or removed (neoformations, tumors).

The immunocompromised district in veterinary dermatology

The concept of the ICD has not been focused on yet in veterinary medicine. The ICD is a conceptual entity that is not limited to human dermatology. It can also apply to veterinary medicine.

The Köbner phenomenon, namely the appearance of new lesions pertaining to a previously present skin disorder at the sites of trauma or other insult, which is well known in humans and represents the simplest instance of ICD, has also been described in veterinary dermatology. A good example of this is provided by the reported development of new lesions in three sites, where the hair coat had been clipped in a Labrador retriever affected by contact-triggered pemphigus foliaceus.[22]

An emblematic example of injuring event capable of rendering a certain skin region a potential ICD in animals is represented by the onset of the so-called feline injection-site sarcoma (FISS). In cats, invasive sarcoma is the most serious adverse effect after vaccination as well as nonvaccinal injectables, so that the term *vaccine-associated sarcoma* has been changed to feline injection-site sarcoma.[23]

The first tumor diagnosed as a fibrosarcoma arisen on a vaccinated area was noted in 1983.[24] The first report of a possible link between vaccination and development of fibrosarcomas at injection sites in cats was published in 1991 (reviewed in reference 25). At first, only correlations with rabies and feline leukemia virus vaccinations were found. Subsequent studies found that several vaccines, including those against feline panleukopenia virus, feline herpesvirus 1, and feline calicivirus, could be involved in the development of the tumor. A specific role for a virus (feline immunodeficiency virus, feline leukemia virus, papillomavirus, polyomavirus, herpesvirus) has never been reported.[26,27]

Many inactivated veterinary vaccines contain aluminum hydroxide, an insoluble aluminum compound, or other aluminum derivatives as adjuvant. Aluminum was detected in a number of FISS cases using electron probe microanalysis[28] and was identified as gray-brown material by Irwin's histochemical reaction,[27] suggesting the possible role of aluminum material as foreign-body carcinogen in cats.

The interval between injection and detection of sarcoma varies from 1 to 3 years. This long potential lag time, not initially recognized, has resulted in great confusion about which products can cause sarcomas. Interestingly, in addition to vaccines, FISS has also been described after the injection of other medications.

Long-acting antimicrobials or steroids had been administered to cats affected by sarcoma more frequently than to normal cats.[29] Development of FISS shortly after meloxicam injection in an unvaccinated cat was described.[30] A case of FISS at the site of a cisplatin injection was reported.[31] Lufenuron was correlated with the development of fibrosarcoma in the site of injection.[32] Other agents, such as nonabsorbable suture material[33] and microchips,[34] have also been associated