

## MINI-REVIEW

# Beyond Zoster: Sensory and Immune Changes in Zoster-affected Dermatomes: A Review\*

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**Neuroepidermal tropism of varicella-zoster virus accounts for cutaneous and nerve lesions following herpes zoster. Skin lesions heal in a few weeks and may or may not leave visible scars. Nerve lesions involve peripheral sensory fibres, sometimes causing permanent damage that results in partial denervation of the affected dermatome. The effects of the nerve injury involve the sensibility function, thus causing neuralgia, itch, allodynia, hypo- or anaesthesia, as well as the immune function that is related to neuropeptide release, thus altering immune control in the affected dermatome. The neuro-immune destabilization in the zoster-infected site paves the way for the onset of many and various immunity-related disorders along the affected dermatome. Key words: herpes zoster, immunocompromised district, post-herpetic itch, post-herpetic neuralgia, Wolf's post-herpetic isotopic response.**

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Varicella and herpes zoster are distinct clinical entities caused by the varicella-zoster virus (VZV). Entry of VZV is through the mucosa of the upper respiratory tract and oropharynx. Initial multiplication at this entry portal results in the random dissemination of the virus via the blood and lymphatic system to the skin and mucosal surfaces (varicella). From cutaneous and mucosal lesions VZV passes into the contiguous endings of sensory nerves and is transported centripetally up to the corresponding sensory ganglia. In ganglion somatosensory cells it establishes a dormant, immunity-controlled infection that persists for life (latent infection). When the immune control falls to a critical level due to ageing or immunosuppression, VZV re-activates within the sensory ganglia, causing neuronal necrosis and intense inflammation, a process that is often accompanied by severe

neuralgia, descends centrifugally through the sensory nerves, causing intense neuritis, and is released by the nerve endings in the skin or mucosal surfaces innervated by the affected neural segment, where it replicates producing the characteristic cluster of vesicles (herpes zoster). Importantly, herpes zoster occurs most often in dermatomes where the varicella rash is most dense, namely those innervated by the first (ophthalmic) division of the trigeminal nerve and by the spinal sensory ganglia from T1 to L2 (1). In immunocompromised patients, herpes zoster may affect more than one dermatome, even if the dermatomes are non-contiguous and bilateral (herpes zoster duplex), or it may last a long time with no tendency to heal (chronic varicella zoster virus infection). Interestingly, both the events may occur simultaneously, as reported recently (2).

## HISTOLOGICAL CHANGES IN ZOSTER

Skin biopsies of VZV-infected dermatomes show a reduction in the dermal nerve network, in particular as concerns unmyelinated C-fibres and thinly myelinated A- $\delta$  fibres (3, 4). In patients with severe post-herpetic neuralgia, the density of nerve endings in the papillary dermis and epidermis of the affected dermatome is reduced significantly. Interestingly, the extent of this reduction, which in some cases may be dramatic (less than 150 epidermal neurites/mm<sup>2</sup> instead of the normal more than 1,500 epidermal neurites/mm<sup>2</sup>), parallels the severity of the patient's neuralgia (4). In any case, partial denervation is the common hallmark in the skin of the affected dermatome in all zoster patients.

There are contrasting findings regarding the number of Langerhans' cells in the VZV-infected dermatomes. These cells normally contact epidermal neurites to form the neuro-immune cutaneous system (5). An investigative study of 5 patients with zoster showed no differences in the number of Langerhans' cells in previously zoster-affected and normal-control skin biopsies (6), whilst loss of Langerhans' cells was found in a previously zoster-affected dermatome in a patient with cutaneous T-cell lymphoma (7).

No data are available concerning the number of other immune cells (memory T cells, regulatory T cells) in the zoster-affected skin.

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## SENSORY CHANGES IN ZOSTER-AFFECTED DERMATOMES

A variety of neurological complications may ensue from the herpes zoster episode. As a consequence of a sensory-specific virus infection, the predominating symptoms are largely sensory, although autonomic and motor disorders can also appear because of "bystander" degeneration of the autonomic and motor neurons that are adjacent to infected somatosensory cells. The most common and important sensory trouble is post-herpetic neuralgia (PHN), which complicates approximately 15% of cases of herpes zoster in patients over 60 years of age. PHN ranges from constant pain (described as burning, aching, throbbing), intermittent pain (stabbing, shooting), to stimulus-evoked pain, also known as mechanical allodynia. This is pain elicited by stimuli that do not normally induce pain (1). Patients with allodynia may indeed suffer severe pain on even minimal contact with the affected skin by stimuli as trivial as the touch of clothing on their body, a hat on their head, a gentle touch, or a breeze on their skin.

The mechanism involved in the lancinating pain of early PHN is presumably due to the VZV-induced demyelination of sensory nerve fibres. In fact, a loss of myelinic sheath in two or more adjacent neurites results in the close apposition of denuded axons, which permits action potentials to spread laterally from one axon to another (ephaptic neurotransmission). As a consequence of this "electrical" (as opposed to chemical) neurotransmission, multiple nociceptors are triggered (or "fired") on minimal stimulus causing severe jolts of pain (8). Demyelination mainly involves fast-conducting afferent fibres (A- $\delta$ ) and somehow preserves slowly-conducting ones (C fibres), which would explain why even the lightest mechanical stimuli generate abnormally long-lasting and painful sensations (hyperaesthesia including mechanical allodynia) (8).

In some cases, a prolonged period of hyperaesthesia may unexpectedly bring about a complete loss of touch and pain sensibility (anaesthesia) in the VZV-affected dermatome. This is similar to what occurs with all known sensory systems (tinnitus may precede progressive hearing loss, visual hallucinations can precede blindness, paraosmia can precede anosmia, dysgeusia often precedes or accompanies ageusia) and is a neuronal plasticity adaptive mechanism (8). Simply, a reduction in incoming signals from the periphery due to afferent nerve injury produces enhanced electrical activity of the target central neurons, resulting in an initial increase and subsequent decrease or total loss of the sensory function.

In addition to, or instead of, the classic symptoms of pain and mechanical allodynia, some patients complain of severe itching (sometimes associated with numbness) in the affected dermatome, especially in the cases of herpes zoster involving the head or neck (8). The post-herpetic

itch (PHI), which is found in approximately 4% of all herpes zoster patients, may precede (pre-herpetic), accompany (herpetic) or follow (post-herpetic) the onset of cutaneous lesions (9). In one patient PHI started 5 years after the zoster episode, indicating how complex the basic pathomechanism of this late complication can be. It has been proposed that generation of PHI may be related to spontaneous firing of denervated central itch-specific neurons or, alternatively, it may be due to relative preservation of peripheral itch-specific neurons from adjacent, uninjured dermatomes after PHN (8). Severe chronic itch may be even more disabling and harmful than chronic pain, because of the injury that constant scratching can cause. Normally, people stop scratching at the onset of pain, but, if neuropathic itch is co-localized with loss of protective pain sensation (anaesthesia), patient scratching can cause painless injuries. In this light Oaklander's report is emblematic (8). After ophthalmic zoster, a patient developed such irrepressible PHI with concomitant loss of pain sensibility that the persistent painless scratching of her desensate scalp and skull, led to self-induced brain injury (Fig. 1).

## IMMUNE CHANGES IN ZOSTER-AFFECTED DERMATOMES

Besides conducting sensorial stimuli centripetally, sensory nerve fibres also modulate the skin immune response centrifugally by secreting neuromediators (such as substance P, vasoactive intestinal peptide, calci-



Fig. 1. Dramatic effects of sensory changes in the zoster-affected dermatome. Self-inflicted brain injury resulting from irrepressible post-herpetic itch and co-localized post-herpetic anaesthesia in the trigeminal area (first division) that had been affected by herpes zoster one year previously (8, with Editor's permission).

tonin gene-related peptide) that interact with membrane receptors of immune cells (mastocytes, lymphocytes, Langerhans' cells) (5). It is therefore not surprising that, in the VZV-infected dermatomes, damage to and reduction of the sensory nerve fibres (3, 4, 8), which contain and release neuromediators (10), can result in immunity-related disorders. The first experimental investigation on this subject was carried out in 1969 with the histamine test, which showed decrease or absence of the axon flare in dermatomes affected with severe PHN (3). However, pioneering clinical observations, dating back to 1955, made by the world-famous British neurologist, Wyburn-Mason, had already indicated a sort of immune destabilization in zoster-affected dermatomes in 25 patients in whom malignant tumours (breast carcinomas, basal and squamous cell carcinomas) developed at the site of a previous herpes zoster (11). One of the most striking examples of the connection existing between zoster infection and tumour onset in the herpes-healed site is the report by Hudson et al. (12) of a patient with an angiosarcoma of the head whose topography traced precisely the trigeminal areas (first and second branches) that had been affected by herpes zoster 10 years previously (Fig. 2). A large series of "opportunistic" disorders, namely primary or metastatic tumours, infections and immune reactions may appear in the dermatomes that have been infected by VZV as a consequence of the destabilization of local immunity produced by the viral damage to sensory nerve fibres

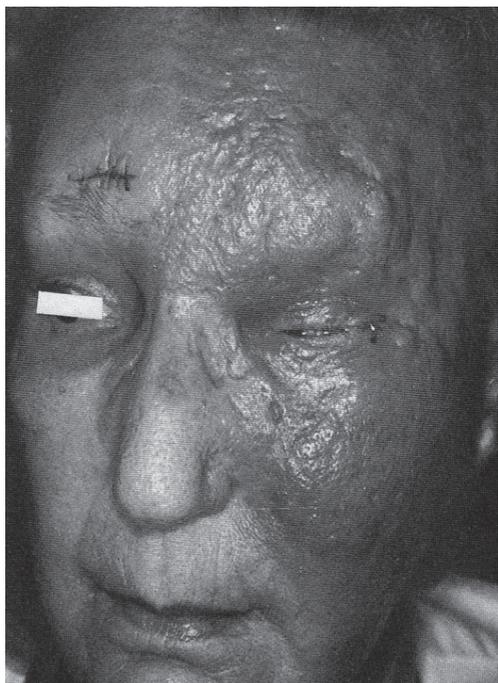


Fig. 2. Dramatic effects of immune changes in the zoster affected dermatomes (Wolf's isotopic response). Angiosarcoma of the head, the topography of which traced precisely the trigeminal areas (first and second divisions) that had been affected by herpes zoster 10 years previously (12, with Editor's permission).

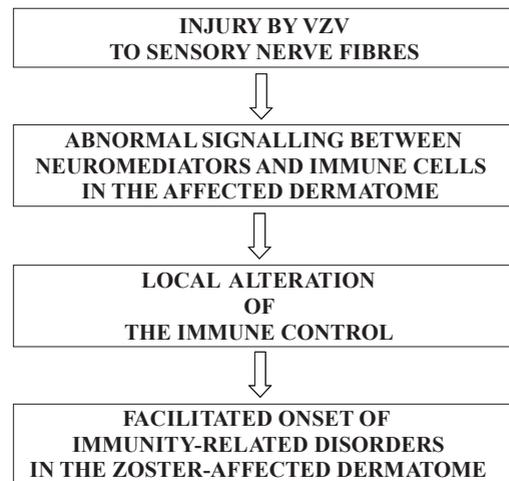


Fig. 3. Destabilization of immunity in the zoster-affected dermatome. VZV: varicella-zoster virus.

(Fig. 3). In fact, zoster-affected dermatomes become privileged sites for a subsequent development of heterogeneous disorders, featuring the well-defined "Wolf post-herpetic isotopic response" (PHIR) (13–25). This term describes the occurrence of a new disorder at the site of a previous and already healed herpetic infection, in most cases herpes zoster, with an extremely variable latency (days, weeks, months (18), years, decades (11)), no age or gender predilection, and unknown prevalence rate. An emblematic instance of PHIR is featured by an immunocompromised patient who developed herpes zoster in 7 disparate dermatomes and, 3 months after resolution of the zoster lesions, presented a granulomatous dermatitis with zosteriform distribution at the sites of the previous infection (16). Another demonstrative case of PHIR is that of the development of cutaneous melanoma metastases along 3 dermatomes that had been affected by a herpes zoster infection 10 years previously and had been photodocumented by the patient (17). Table I summarizes the 176 PHIRs we have collected (13–25). Although strikingly heterogeneous in nature, most of these cases have a possible common denominator, i.e. the local imbalance of the immune control. In fact, in the zoster-affected dermatome, immune response may become compromised or generally destabilized (either reduced or exaggerated). In some cases, this destabilization leads to a defective immune response (as denoted by the local outbreak of opportunistic infections, primary tumours, or metastases from internal malignancies); in other instances, destabilization results in excessive local immune reactions. Examples of excessive local immune reactions in the VZV-infected dermatomes are represented by the occurrence of lichen planus (20), lichenoid chronic graft-vs-host disease (21), psoriasis (22), acneiform lesions (23), drug-reactions (24), or even unclassifiable hyper-reactive skin lesions that were termed "post-zoster eosinophilic dermatosis" (25), all confined to (20–23, 25) or more intense in (24)

Table I. Skin diseases arising in dermatomes previously infected by varicella-zoster virus: Wolf's post-herpetic isotopic response (13–25)

Granulomatous reactions
Granuloma annulare
Sarcoidosis
Malignant tumours
Breast cancer
Basal cell carcinoma
Squamous cell carcinoma
Angiosarcoma
Kaposi's sarcoma
Metastases from cutaneous (melanoma) or visceral malignancies (zosteriform metastases)
Dysimmune reactions
Lichen planus
Lichen sclerosus et atrophicus
Graft-versus-host disease
Drug rash
IgA linear dermatosis
Psoriasis
"Post-zoster eosinophilic dermatosis"
Infections
Bacterial
Fungal
Viral
Miscellany
Acneiform lesions
Rosacea
Pseudolymphoma
Mucinosis

the skin previously compromised by VZV infection. Reduction or induction of immunity, which is confined to the zoster-affected dermatome, may depend on the immune properties of the specific neuromediators involved each time.

Immunity-related disorders due to peripheral neuropathy other than VZV-induced neuropathy have been observed. Clear examples are represented by a patient with acne confined to an area of post-traumatic trigeminal neuralgia (26) and the report of bullous pemphigoid restricted to the skin area of an amputation stump with gross abrupt cutting off of all nerve conduction (27).

## CONCLUSION

Due to its specific ectodermal (or neuroepidermal) tropism, VZV typically causes muco-cutaneous and neural lesions. Mucosal and skin lesions appear as characteristically grouped vesicles that heal spontaneously in a few weeks and may or may not leave visible scars. Nerve lesions mainly involve peripheral sensory fibres sometimes causing permanent damage that results in partial denervation of the affected dermatome. Since sensory nerves have a bidirectional conduction (centripetal as concerns sensibility function, centrifugal as concerns neuropeptide secretion), the VZV-induced damage can provoke both sensory symptoms (PHN, PHI, mechanical allodynia, hypo- or anaesthesia) due to altered sensibility and immune disorders (PHIR) ensuing from altered

neuro-immune cross-talk in the affected dermatome. While post-herpetic sensory symptoms have been well-known for a long time, it is only in the last two decades that immunity-dependent disorders occurring in a zoster-affected dermatome have been recognized, focused on and named Wolf's post-herpetic isotopic response (PHIR) (13–25). Regular signalling between sensory fibre-secreted neuropeptides and locally recruited immune cells is a basic requirement for a normal immune response in a given cutaneous district (5, 28). When nerve integrity is compromised, as occurs in zoster infection (3, 4), the neuropeptide release is altered inevitably affecting local immune control, even if there is no reduction in the immune cell "contingent" (6). If this contingent is reduced or lost (7) local immune control is obviously knocked-out. Bearing in mind that some neuropeptides (e.g. substance P) are immune function stimulators, while others (e.g. vasoactive intestinal peptide) are immune suppressors (5), one could argue that the PHIR can be either reduced or exaggerated depending on the type of neuropeptide involved in the nerve fibre damage. However, substance P (SP), vasoactive intestinal peptide and calcitonin gene-related peptide (CGRP) all co-localize in C-fibres (10, 29), while A- $\delta$  fibres contain and release CGRP rather than SP (30). It is also known that neuropeptide amounts may vary greatly in sensory nerve fibres, with different proportions of a single neuropeptide in different subsets of nerve fibres (29–31). Furthermore, depending on incidental circumstances, some neuropeptides can either enhance or inhibit particular immune/inflammatory cell functions (31). Taken together, these remarks may well explain the unpredictable immune behaviour subsequent to nerve lesion. In any case, to the best of our knowledge, neuropeptide amounts in the zoster-affected dermatome have never been appraised.

A large body of evidence has shown that the skin, the nervous system and immunity are not independent systems but are closely associated (neuroimmunocutaneous system) and use the same language of cytokines and neuromodulators (5, 10). When the neuroimmunocutaneous system is destabilized in a given district, whatever the cause (nerve lesion or infection, chronic lymph stasis, amputation trauma, radiodermatitis, thermal burn), the district itself becomes a vulnerable site, prone to harbour a wide range of immunity-related disorders (opportunistic infections, primary or metastatic tumours, immune reactions). This innovative unifying concept has been labelled as "the immunocompromised (or immunodestabilized) district" (15). In a unique, recently published report, skin cancer and discoid lupus erythematosus coexisted in the same burn scar (32). With regard to metastatic tumours, much of the current research on tumour biology indicates that, besides vascular and lymphatic channels, another route for the spreading of tumours is in and along nerve fibres, which provides strong evidence to support neuropeptide

signalling between the nerves and invading tumour cells (33).

In conclusion, the possible occurrence of many and various immunity-related disorders in the zoster-affected dermatomes (PHIRs) sheds light on the role played by the neuro-immune network in the skin. A better understanding of how neuropeptides are involved in these mechanisms could lead, in the very near future, to novel therapeutic strategies for immune and neoplastic disorders (30). In this connection, the report of a patient with acne restricted to an area of post-traumatic trigeminal neuralgia, which was treated successfully with capsaicin (26), is emblematic. In fact, this observation, by underscoring the role of substance P-mediated neurogenic inflammation in acne development, suggested the possibility of capsaicin treatment for such a condition. As to malignancies, further insight into neuropeptide effects might lead to development of new drugs able to interrupt or interfere with neuropeptide signalling between nerve fibres and invading cancer cells, thus blocking the spread of some tumours. On the basis of these new pathophysiological perspectives, the neuroimmunocutaneous system should be investigated further.

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