Zosteriform dermatoses-A review

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Abstract

The zosteriform distribution of cutaneous lesions is a common disease pattern in dermatology. It describes a unilateral girdle-like distribution restricted to the sensitive nerve territory of a dermatome. Three different pathogenic pathways can lead to a zosteriform pattern. The neural pathway uses the axons of a nerve ganglion for viral transport to a specific dermatome. The archetype is Herpes Zoster (HZ) followed by Zosteriform Herpes Simplex Virus Type (HSV) I infection. The Blaschko line pathway uses the Blaschko lines that represent embryonic migration patterns, mimicking a dermatomal distribution, particularly on the trunk. The isotopic pathway defines a dermatosis that exclusively develops on the site of a previously healed HZ eruption.

Before a zosteriform eruption, a history of prior HZ guides the diagnosis to the isotopic pathway, mainly represented by granulomatous reactions followed by among others, lichen planus, vasculitis and basal cell carcinoma. With no prior history of HZ recent eruptions orientate towards HZ and zosteriform HSV, whereas chronic eruptions should primarily evoke cutaneous metastases, principally from breast, ovary and lung carcinoma.

This review summarizes the relevant literature and presents a clinical algorithm for the differential diagnosis of zosteriform dermatoses.

Introduction

Pattern recognition is an important diagnostic tool in clinical dermatology. The zosteriform pattern is defined as an unilateral and belt or girdle-like presentation of a dermatosis along the sensory nerve territory of a dermatome [1-3].

Although Herpes Zoster (HZ) is the archetype of a zosteriform dermatosis, a large series of other infectious, neoplastic, inflammatory and miscellaneous dermatoses may also present a zosteriform distribution (Table 1).

This paper reviews the three pathogenic mechanisms of the zosteriform pattern and proposes a diagnostic algorithm helping the dermatologist in the differential diagnosis of zosteriform dermatoses.

Materials and methods

A PUBMED search was performed without restriction of publication date using the following keywords: Varicella Zoster Virus (VZV), varicella, herpes zoster, Herpes Simplex Virus (HSV), herpes simplex, genital herpes, zosteriform, zosteriform dermatoses, segmental, segmental dermatomes, dermatome, dermatomal distribution, isomorphand isotopic dermatoses. This research revealed 220 publications relevant to the subject and included for this review.

Pathogenesis

Cutaneous diseases presenting a zosteriform distribution answer to 3 different pathogenetical pathways.

The neural pathway

The neural pathway is classically at the origin of HZ [1-3]. The reactivation of latent VZV infection in the neural cell bodies and the satellite cells of the Dorsal Root Ganglia (DRG) results in the replication and synthesis of new viral particles that are transported anterogradely via the microtubular system of the axons to the skin. Once arrived at the free nerve endings between the basal keratinocytes and around the perifollicular free nerve endings, the viral particles egress and are captured by surface receptors on keratinocytes. Once internalized, viral replication leads to the appearance of the cytopathic effect in the host cell, finally leading to its cell death with the liberation of new viral particles. This epidermal cytopathic effect leads to the desiccation between infected keratinocytes and intra-epidermal blister formation, responsible for the clinically observed vesicular lesions in an unilateral clustered dermatomal distribution. HZ skin lesions occupy a more or less important part of a dermatome, depending on the number of infected axons involved and afflicted by viral reactivation in the DRG. Further cutaneous extension and spreading beyond the dermatomal limits can also be due to the spread of VZV from keratinocyte to keratinocyte, especially in the immunocompromised patient or in the patient with atopc dermatitis or other predisposing skin diseases. In some instances, HZ can affect more than one adjacent dermatome. Exceptionally, more than one non-adjacent dermatomes or bilateral eruptions are encountered [4]. The unilateral character is not always respected as minor nerve projections frequently extend to the contralateral side [5]. Indeed, it was recently demonstrated that numerous dermatomal maps were inaccurate and subject to significant variations [5]. A novel evidence-based dermatome map (Figure 1) is presented with the most consistent tactile dermatomal areas for each spinal dorsal nerve root found in most individuals. In contrast to previous data, overlap and interindividual variability seem more common than previously thought [5].

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VZV, in particular the epidermo-neurotropism [6-18]. other alpha-herpesviruses share a number of identical features with dermatoses.

Benign and malignant tumors

<table>
<thead>
<tr>
<th>Primary cutaneous tumors</th>
<th>Inflammatory dermatoses</th>
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<tbody>
<tr>
<td>- Angiosarcoma</td>
<td>Lichen planus</td>
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<tr>
<td>- Kaposis’s sarcoma</td>
<td>Lichen aureus</td>
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<td>- Squamous cell carcinoma</td>
<td>Lichen sclerous</td>
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<tr>
<td>- primary cutaneous T-cell lymphoma</td>
<td>Darier’s disease</td>
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<td>- primarycutaneous B-cell lymphoma</td>
<td>Pityriasislichenoides</td>
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<td></td>
<td>Morphea</td>
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<td>Granuloma annulare</td>
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<td>Cutaneous metastases</td>
<td>GVHD</td>
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<td>- Gastrointestinal cancer</td>
<td>Connective tissue hamartomas</td>
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<td>- Breast carcinoma</td>
<td>Epidermal hamartomas</td>
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<td>- Endometrial cancer</td>
<td>Perforating collagenosis</td>
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<td>- B-cell chronic lymphocytic leukemia</td>
<td>Porokeratosis</td>
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<tr>
<td>- Hodgkin’s lymphoma</td>
<td>Pigmentary disorders</td>
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<td>- Nodal T-cell lymphoma</td>
<td>Progressive cribiform and zosteriform</td>
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<td>- Ovary carcinoma</td>
<td>hyperpigmentation</td>
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<tr>
<td>- Pulmonary cancer</td>
<td>Spitz nevi</td>
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<tr>
<td>- Leiomyoma</td>
<td>Arteriovenous malformations</td>
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<td>- Mesothelioma</td>
<td>Unilateral dermato malcavernous</td>
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<td>- Renal carcinoma</td>
<td>hemangiomatosis</td>
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<td>- Melanoma</td>
<td>Transient acantholyticdermatosis</td>
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<td>- Prostate</td>
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<td>- Merkel cell carcinoma</td>
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<td>Ecrinespiradenoma</td>
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<td>Neura</td>
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<td>Trichoepitheliomas</td>
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Table 1. Benign and malignant, inflammatory and miscellaneous zosteriform dermatoses.

HSV type I and type II also use the neural pathway. In fact, these other alpha-herpesviruses share a number of identical features with VZV, in particular the epidermo-neurotropism [6-18].

The nerve fibers may also function as anatomical substrate for perineural progression of breast cancer cells and Squamous Cell Carcinoma (SCC) cells, probably related to the neurotropic character of these cells. SCC presents neurotropism through its ectodermal origin [19,20]. The presence of Neural Cell Adhesion Molecules (N-CAM) does however not always equal neurotropism in SCC. Probably, other cell surface markers may also confer neurotropism [21,22]. Schwannomas can also follow a nerve distribution, called segmental Schwannomas [23]. Multiple palissaded encapsulated neuromas are a rare benign neural skin tumor that also may exhibit a dermatomal pattern [24]. Furthermore, this pattern can be found in OTA naevi, with melanocytic progression along the nerve fibers. In general, neoplastic growths deriving from cells originating from the neurectodermal crest are more prone than other cell types to present zosteriform metastatic migration.

The Blaschkoid pathway

Embryonic migration of cutaneous cell populations is directed by ectodermal development patterns. During embryogenesis, when the presence of the primitive line gives the embryonic disk bilateral symmetry, precursory cells start to proliferate on the midline and grow in transversal direction from this line. These migration patterns can become visible when genetic mosaicism occurs, ie two or more genetically distinct cell populations derived from a genetically homogeneous zygote. These lines are called Blaschko lines and represent the boundaries between genetically normal and abnormal cell populations [25]. This phenomenon typically affects the keratinocytes, fibrocytes and melanocytes, etc. Furthermore, these patterns change from one cell type to another and also depend on the timing of the occurrence of the mosaicism. Five types of Blaschkos lines are distinguished including the classic (narrow and broad), checkerboard, phyllloid, patchy and lateralization patterns [25].

The classic type is the most common with patterns in a V shape on the back and in an S shape on the antero-lateral portion of the trunk [26-28]. This classic pattern can further be divided into narrow (1a) and broad (1b) bands. This distribution pattern is often difficult to distinguish from dermatomes, in particular on the trunk.

The isotopic pathway

The isotopic phenomenon is defined as a dermatosis that only develops and remains restricted to the site of a previous other healed dermatosis [29-31]. The most typical examples are dermatoses occurring on the site of healed previous HZ, explaining the zosteriform distribution. Granulomatous reactions are the most commonly encountered.

The exact origin of the isotopic pathway remains unclear but it may be related to VZV-induced alterations in epidermal and dermal components of the skin immune system, favoring the occurrence of some dermatoses without expressing themselves on non-previously involved skin.

Several hypotheses have been advanced. A transient immune silencing may be suspected as demonstrated by the sparing of primary cutaneous T-cell lymphoma (pCTCL) extension on the site of previous HZ involving the left T8 dermatome. Immunohistochemical analysis of a clinically uninvolved patch revealed absence of CD1a+ cells in the epidermis, consistent with loss of Langerhans cells (LC) in the areas spared by pCTCL. There was no loss of LC in areas affected by pCTCL. This is an unusual inhibition of pCTCL by a prior viral infection. The loss of LCs in the clinically spared skin suggests a role...
for LC in the epidermotropism of lymphocytes in pCTCL [32]. The same phenomenon is observed with the avoidance of allergic contact dermatitis lesions at the site of florid HZ, suggesting an inhibition or an incapacitating action of VZV on the epidermal LCs conducting to a transitory silencing of the antigen presenting capacities of the cutaneous immune system [33].

Another hypothesis suggests a delayed type hypersensitivity reaction to the persistence of residual viral glycoproteins in the dermis [34]. In recently resolved cases of HZ, VZV DNA could still be retrieved from granulomatous skin reactions by PCR [35-37]. In cases of granulomatous reactions occurring later after the resolution of HZ, no viral DNA was evidenced [38-43]. In granulomatous reactions affecting elderly previous HZ sites, the presence of the gE and gBVZV envelope glycoproteins, highly resistant to enzymatic degradation, was evidenced by immunohistochemistry, whereas viral DNA was not found [41]. Not only VZV antigens and DNA could be found in zosteriform granulomatous reactions but also HSV [41,44]. As there is no residual viral DNA in the granulomatous reactions developing later after the resolution of HZ, the treatment rather requires topical corticosteroids [41] or intralesional corticosteroids than antivirals [45].

A third hypothesis is a local neuro-immune deregulation set off by alphaherpesvirus-induced lesions of dermal sensory nerve fibers [46].

Other dermatoses than granulomatous reactions are far less common and their pathogenesis remains largely unclear (Table 2).

### The algorithm of the differential diagnosis of zosteriform dermatoses

The first distinction is to determine whether the patient has previously presented HZ or not at that particular site.

**Patient with a previous history of HZ at the site of the zosteriform eruption**

If the patient presents a zosteriform dermatosis that is restricted to the site of a previous HZ eruption, the differential diagnosis has to be made among the zosteriform isotopic responses (Table 2) [26,30,31]. The site of healed HZ is the most usual area to develop isotopic responses. Indeed, in a case-series review, 52 out of 58 cases of isotopic responses were localized on healed sites of previous HZ (30). Recently healed HZ sites are particularly prone to develop a large series of various granulomatous reactions, including granulomatous dermatitis, granulomatous vasculitis (Figure 3), sarcoidal granuloma, granulomatous folliculitis, granuloma annulare, granuloma formation, tuberculoid granuloma [34,47-73].

In the event of an isotopic-zosteriform eruption on an more ancient site of previous HZ, cutaneous metastasis of a variety of internal malignancies should be considered as first hypothesis. Breast carcinoma cutaneous metastases (15/26 cases) are the most frequently observed, probably linked to the initial localization of breast cancer [30]. Squamous cell carcinomas, basal cell carcinomas, primary cutaneous lymphomas [74,75], leukemic infiltration (particularly B-cell) [76], melanoma and melanoma cutaneous metastases, angiosarcoma [77,78], basosquamous carcinomas, Kaposi’s sarcoma and Bowen’s disease are

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**Table 2. Differential diagnosis of isotopic-zosteriform dermatoses.**

<table>
<thead>
<tr>
<th>Granulomatous reactions</th>
<th>(granulomatous dermatitis, granulomatous vasculitis, sarcoidal granuloma, granulomatous folliculitis, granuloma annulare, granuloma formation, tuberculoid granuloma)</th>
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<tbody>
<tr>
<td>Lichen sclerosus</td>
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<td>Lichen planus</td>
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<td>Pseudolymphoma</td>
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<td>Morphea</td>
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<tr>
<td>Dermatophytoses</td>
<td><em>(Candida albicans, Epidermophyton floccosum, Trichophyton mentagrophytes)</em></td>
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<tr>
<td>Eruptive keratoacanthoma</td>
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<td>Cutaneous lymphoid infiltrates of B-cell chronic lymphocytic leukemia</td>
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<td>Primary cutaneous B-cell lymphoma</td>
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<td>Cutaneous metastases of angiosarcoma</td>
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<td>Skin metastases of breast carcinomas</td>
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<td>Melanoma</td>
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<td>Squamous cell carcinoma</td>
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<td>Basal cell carcinoma</td>
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<td>Lymphoma, leukemia cutis</td>
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<td>Kaposi’s sarcoma</td>
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Figure 2. Blaschko lines, with a zosteriform pattern on the trunk.

Figure 3. Post zoster granulomatosus vasculitis affecting the latero-anterior T7,T8.
Inflammatory dermatoses restricted to ancient HZ sites are more exceptional and comprise lichenoid Graft-Versus-Host-Disease (GVHD) [79-81], morphea [82,83] and localized chronic urticaria [84]. Infectious dermatoses are even more rare and include fungal granulomas [85], dermatophytosis [86] and molluscum contagiosum [87] (Table 2).

Another complication that can precisely occur at the site of healing or healed HZ is zosteriform keloid formation. In particular patients with a black skin are prone to this complication (Figure 4) [88-90]. The presence of VZV DNA in FXIIIa positive dermal dendrocytes might lead to a dysfunction, hence altering their important role in the scarring process [38,41]. As observed during other dystrophic scarring processes, comedo formation may be observed [91] and even cutaneous calcification in a zosteriform distribution [92].

**Patient without a previous history of HZ at the site of the zosteriform eruption**

If the zosteriform eruption is recent (<10-14 days), HZ is the most likely diagnosis (Figure 5). However, zosteriform HSV infections (Figure 6) are encountered in up to 25% of the cases initially diagnosed as HZ on a clinical base, particularly in the facial dermatomes [6-18,93]. The immunohistochemical distinction between HSV and VZV can readily and rapidly be performed on a Tzanck smear, with a high specificity and sensitivity [2]. This distinction is important in terms of dosing regimens, different for HSV and VZV infections [2].

If the eruption is more longstanding (>14 days), zosteriform primary skin cancers, including predominantly SCC (Figure 7), but also Kaposi’s sarcoma, angiosarcoma, pCTCL (Figure 8) and primary cutaneous B-cell lymphoma (pCBCL) should primarily be considered [30,31,78,94-109]. Zosteriform cutaneous metastases of internal malignancies have also to be discarded [110-165], in particular in the elderly patient with an abnormal long duration and a not precisely dermatomal distribution as well as in patients with a history of cancer. Cutaneous metastases of breast cancer (Figure 9) are the most frequently described, probably due to its primary localization in the T3 and T4 dermatomes. Other less frequently described cutaneous metastases are described, listed in term of decreasing number of publications; melanoma (n=10), leiomyoma (n=8), B-cell chronic lymphocytic leukemia (n=6), gastrointestinal cancer (n=5), renal cancer (n=4), pulmonary cancer (n=3) ovary cancer (n=2), mesothelioma (n=1) endometrial cancer (n=1), Hodgkin’s lymphoma (n=1), nodal T-cell lymphoma (n=1), and Merkel cell carcinoma (n=1) (Figure 10). These zosteriform cutaneous metastases are often a sign of poor prognosis and may commonly be initially misdiagnosed as HZ [109,166-169] or...
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as contact eczema [133,157]. In one study, 7 out of 15 cases of cutaneous zosteriform metastases were initially diagnosed as HZ and treated with antivirals [129]. Another study evidenced that 59% of the zosteriform cutaneous metastasis cases had previously been diagnosed as HZ at the time of the initial examination and that many of them also had received antiviral therapy [143]. Other reports also relate erroneous treatment with antivirals for zosteriform cutaneous metastases [166-168]. The localization of the zosteriform cutaneous metastases is not indicative in the determination of the primary neoplasm. Indeed, zosteriform cutaneous metastases may be observed in the vicinity of the initial cancer, or be ipsilateral or contralateral, adjacent or at a distance [109]. In some rare cases, the initial tumor was discovered by the presence of zosteriform skin metastases [144,168]. Some benign skin tumors may present a zosteriform pattern, especially eccrine spiradenoma [170-174] and trichoeoepitheliomas [175].

Among the zosteriform infectious skin diseases, one should distinguish the chronic VZV infections that are rare but commonly present a zosteriform distribution and borrow the same pathway as classic HZ [176]. Incidental cases of zosteriform Leishmaniosis have been described [177-180].

Zosteriform inflammatory dermatoses are uncommon but present a great variety, including drug reactions to levofloxacin, trimethoprim and cephazolin [181,182]. Zosteriform lichen planus is the most frequently reported type of zosteriform lichen [183-190] and should be distinguished from linear lichen planus. A distinction with a lichenoid HZ should also be considered, especially as the treatment of the latter requires antiviral therapy and not dermatocorticoids [191]. A punch biopsy with an immunohistochemical search for VZV readily distinguishes these entities [191]. Other types of lichen have been reported such as lichen aureus [192,193] and lichen sclerosus etatrophicus [194-196]. Exceptional cases are reported of zosteriform Darier’s disease [197-200], pityriasis lichenoides (Figure 11), acneitis (Figure 12), morphea [201] and linear atrophoderma of Moulin [202].

Other dermatoses that may present a zosteriform pattern include the zosteriform nevus spilus [203], zosteriform naevus spilus with melanoma [159], progressive cribiform and zosteriform hyperpigmentation [204,205], zosteriform bleu nevi (Figure 13) and OTA nevus [145,206-210] (Figure 14), zosteriform melanocytic hyperpigmentation (Figure 15), Spitz nevi [211], unilateral nevoid telangiectasia [212-216] and notalgia paresthetica [217]. Connective tissue [218-224] and epidermal hamartomas [225,226], perforating...
collagenosis [227], porokeratosis [228-231], arterio-venous malformations [232], epitheloid hemangioma [233], transient acantholytic dermatosis [234,235] and segmental vitiligo (Figure 16) may present with a zosteriform pattern [236-238].

**Diagnosis algorithm**

Figure 17 presents an algorithm helping the dermatologist in the differential diagnosis of an unilateral zosteriform eruption according to a history or not of previous HZ and taking into account the temporal evolution of the zosteriform dermatosis.

**Conclusion**

The first step in the differential diagnosis of a zosteriform dermatosis is to distinguish whether the eruption is restricted to a site of previous HZ or not. If not, recent zosteriform dermatoses include predominantly HZ and accessory zosteriform HSV. More longstanding zosteriform dermatoses evoke primarily cutaneous metastases, particularly in the elder patient, followed by a series of inflammatory and other miscellaneous dermatoses. If the eruption develops on the site of previous andrecently healed HZ, the most probable diagnosis is a granulomatous reaction and at the site of an ancient healed site of HZ, cutaneous metastases and skin cancer should primarily be considered.

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