Wolf Isotopic Response Manifesting as Postherpetic Granuloma Annulare
A Case Series

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• Context.—Wolf isotopic response has infrequently been reported in the literature, mainly as isolated case reports.

Objective.—To aid in recognition of the occurrence of postherpetic granuloma annulare for accurate histologic interpretation of granulomatous dermatitides.

Design.—We report 5 cases of patients with Wolf isotopic response manifesting as granuloma annulare, developing in a site of previous herpes zoster, and discuss the clinicopathologic findings.

Results.—Previous infection with herpes zoster or herpes simplex virus was found in 5 of 5 cases reported. The differential diagnosis of a dermal lymphohistiocytic infiltrate with multinucleated giant cells includes postherpetic granuloma annulare.

The phenomenon of developing a unique skin disease at the site of another unrelated and healed skin disease was first termed isotopic response by Wolf et al1 in 1995. This is distinctly different from an isomorphic response, also known as the Koebner phenomenon, which describes the development of the same disease at a site of damaged or traumatized skin. Wolf isotopic response has infrequently been reported in the literature, mainly as isolated case reports. Recognition of the occurrence of this phenomenon is important for dermatologists and dermatopathologists. We add to the literature 5 cases of Wolf isotopic response, manifesting as granuloma annulare with a perineurovascular and/or perifollicular pattern of inflammation and developing in a site of previous herpes zoster, and discuss the clinicopathologic findings.

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MATERIALS AND METHODS

Following institutional review board approval, the Partners Pathology Database was searched for “granuloma” and “zoster.” Five cases of granuloma annulare occurring at the site of prior herpes zoster were identified between 2006 and 2011 and included in this study. The clinical history and histopathology were reviewed by a dermatologist and dermatopathologist. The criteria for the diagnosis of granuloma annulare included, but were not limited to, a nonnecrotizing granulomatous infiltrate in the dermis. Histopathologic evaluation also included evaluation for an interstitial pattern of the lymphohistiocytic infiltrate (consistent with “incomplete” granuloma annulare) or a palisading pattern with central necrobiosis (granuloma annulare, common variant), increased dermal mucin deposition (highlighted by colloidal iron stain), presence of multinucleated giant cells, elastophagocytosis, and eosinophils. In all cases, special stains, including tissue Gram (Brown-Hopps), periodic acid–Schiff with diastase digestion, Grocott methenamine silver, acid-fast bacilli, and Fite, yielded negative findings for bacterial, fungal, and mycobacterial organisms. No polarizable foreign material was identified with polarization microscopy. Immunohistochemical stain results for herpes simplex virus 1 (HSV1), herpes simplex virus 2 (HSV2), and varicella zoster virus (VZV), when performed, were reported as negative.

RESULTS

Case 1

A 64-year-old man with a history of chronic lymphocytic leukemia presented with pruritic, pink, smooth, firm papules on the skin, some coalescing, in a zosteriform distribution from C8 to T5 on the right side of the back to T2 to T3 on the right anterior chest and C8 to T1 on the medial aspect of the right upper extremity (Figure 1). The patient...
reported that the eruption correlated exactly to the area that had been affected by a herpes zoster infection 2 months before. A 1.5-mm punch biopsy specimen was obtained from the right pectoral and right forearm. Histologic analysis for both tissue sites showed a nonnecrotizing histiocytic dermal lymphohistiocytic infiltrate with scattered multinucleated giant cells, some demonstrating elastophagocytosis (Figure 2). Perifollicular and perineural lymphohistiocytic infiltrate was identified. A colloidal iron stain demonstrated a mild increase in interstitial mucin deposition. Immunohistochemical staining for VZV was negative. VZV DNA was not detected by polymerase chain reaction testing of the formalin-fixed, paraffin-embedded tissue block. The patient was treated with clobetasol propionate ointment twice a day and oral doxepin 25 mg before bedtime, with much improvement noted within 1 month.

Case 2

A 64-year-old woman presented with pruritic, erythematous, flat-topped papules, some coalescing, in a zosteriform distribution on the left side of the abdomen and back involving the T8 dermatome at the site of herpes zoster, which was treated with resolution 4 weeks earlier. Her primary care physician had given her valacyclovir 1000 mg twice a day for 7 days, without resolution of symptoms. An urgent referral to dermatology was requested and a 3-mm biopsy specimen was obtained from the right side of the abdomen. Histologic analysis demonstrated an interstitial, folliculocentric, and perineurovascular lymphohistiocytic infiltrate (Figure 4) with increased dermal mucin deposition confirmed by colloidal iron staining, consistent with interstitial or “incomplete” granuloma annulare. Herpes simplex virus 1, HSV2, and VZV stain results were negative. No treatment was necessary, as the lesions resolved shortly thereafter.

Case 3

A 49-year-old woman presented with pruritic, clustered, erythematous papules along the right side of the abdomen involving the T8 dermatome at the site of herpes zoster, which was treated with resolution 4 weeks earlier. Her primary care physician had given her valacyclovir 1000 mg twice a day for 7 days, without resolution of symptoms. The herpetic infection had been treated with valacyclovir 1000 mg 3 times a day for 10 days with no scar formation. A 3-mm punch biopsy specimen was obtained from the left temple. Histologic analysis revealed a granulomatous dermatitis with a perineurovascular distribution of the infiltrate including multinucleated giant cells and plasma cells. Immunohistochemical stain results for HSV1, HSV2, and VZV were negative. A colloidal iron stain highlighted increased interstitial mucin. The patient was treated with another course of valacyclovir 1000 mg, 3 times a day for 10 days, without resolution of symptoms. Upon pathologic review, the patient was treated with triamcinolone 0.1% ointment twice a day with resolution noted in 1 month.

Case 4

A 57-year-old woman presented with painful, erythematous, edematous papules coalescing into a plaque studded with pseudovesicles on the left side of the chest. The eruption had a 2-month history and a dermatomal distribution which, upon further questioning, corresponded exactly to the area previously affected by a herpes zoster infection 4 weeks before. The herpetic infection had been treated with valacyclovir 1000 mg 3 times a day for 10 days with no scar formation. A 3-mm punch biopsy specimen was obtained from the left temple. Histologic analysis revealed a granulomatous dermatitis with a perineurovascular distribution of the infiltrate including multinucleated giant cells and plasma cells. Immunohistochemical stain results for HSV1, HSV2, and VZV were negative. A colloidal iron stain highlighted increased interstitial mucin. The patient was treated with triamcinolone 0.1% ointment twice a day with resolution noted in 1 month.

Case 5

A 52-year-old woman presented with pruritic, poikiloderma skin in a dermatomal distribution along the left side of the chest, shoulder, and upper back. The eruption appeared approximately 2 months before presentation. The patient had been diagnosed with herpes zoster at the same location 7 years earlier. A 4-mm punch biopsy specimen was obtained from the left clavicle. Histologic analysis revealed vascular ectasia and superficial interstitial and perifollicular and perineurovascular granulomatous reaction with increased mucin (colloidal iron stain examined), with occasional lymphocytes and eosinophils, consistent with postherpetic granuloma or an interstitial granuloma annulare–like tissue reaction. The patient was treated with triamcinolone 0.1% ointment twice a day, with resolution noted in 1 month.

The results for all cases are summarized in the Table.
COMMENT

All reported cases of Wolf isotopic response have occurred after herpes zoster or herpes simplex infection, although herpes viral infection is not always associated with a subsequent isotopic eruption. While granulomatous reactions are the most commonly reported eruptions developing at the site of prior herpes zoster or simplex infection, nongranulomatous processes may also occur. These include leukemic infiltration, lymphoma, lichen planus, morphea, reactive perforating collagenesis, melanoma metastases, angiosarcoma, and infections. Given this broad range of dermatologic disorders, including malignancy, that can present in a zosteriform distribution, a skin punch biopsy is recommended for confirming the diagnosis in clinically atypical cases.

The histologic differential diagnosis of postherpetic granuloma annulare includes idiopathic granuloma annulare; sarcoidosis; foreign-body–type giant cell reactions, such as to silica, zirconium, beryllium, and tattoo pigments (most commonly to red); metastatic Crohn disease; and infections such as tuberculoid leprosy and tuberculosis. All 5 cases of postherpetic granuloma annulare reported herein demonstrated a lymphohistiocytic infiltrate including multinucleated giant cells with a perineurovascular and/or perifollicular pattern. This pattern of infiltration has not previously been reported, to our knowledge, and may represent a histopathologic clue to the diagnosis of Wolf isotopic response manifesting as granuloma annulare. Although the histomorphology of postherpetic granuloma annulare is not entirely specific, the finding of a dermal lymphohistiocytic infiltrate with multinucleated giant cells has frequently been noted in reports of postherpetic granulomatous dermatitis. This finding is unusual for idiopathic granuloma annulare and sarcoidosis. Variable histologic findings in postherpetic eruptions include presence of eosinophils or plasma cells within the infiltrate, palisading, necrobiosis, elastosis, elastophagocytosis, interstitial mucin, and lymphocytic “cuffing” of histiocyte aggregates in a tuberculoid fashion. Postherpetic granulomatous dermatitis may also rarely present as a granulomatous vasculitis with involvement of medium-sized arteries or granulomatous folliculitis. Thus, clinicopathologic correlation, as well as awareness and recognition of this entity, are important for diagnosis.

As opposed to the isomorphic response, or Koebner phenomenon, which describes the development of the same morphologic disease entity at another location on the body, the isotopic response refers to the appearance of a new disease process within the same location as a previous disease. Indeed, the word isotopic, literally translates to homogenous (iso-, Greek for “homogenous”) and place (topic, Greek for “place”). The time period between the occurrence of the first disease in this phenomenon and the second is highly variable, with some reports documenting an interval of days and others reporting an interval of years. Interestingly, the detection of herpesvirus DNA is rare and typically only documented when dealing with a short interval between the first and second diseases (typically less than 4 weeks). This suggests that persistence of herpesvirus may not be responsible for the underlying pathogenesis, which remains unknown.

Indeed, for the cases described in this report, cytopathic changes characteristic of herpes viral infection, such as nuclear molding, “ground glass” chromatin, and multinucleation, were lacking in both epidermis and adnexal...
epithelium. Interestingly, prominent involvement of folliculosebaceous units, sometimes exclusively, and/or perineural involvement of the infiltrate, are typically reported to represent early herpes zoster.\(^8\) In herpes zoster, it is postulated that the virus is transported from dorsal root ganglia to skin via myelinated axons, with nerve endings at the hair follicle isthmus leading to folliculosebaceous and subsequently, to epidermal spread of the virus.\(^2\) Herpes viral antigens have also been reported to occupy dermal histiocytes.\(^2\) This suggests a possible link between herpes viral infection and the development of postherpetic granuloma annulare, particularly given the histologic finding of a perineurovascular and/or perifollicular lymphohistiocytic infiltrate with multinucleated giant cells in our cases.

One hypothesis for the development of an isotopic response following herpes virus infection, as suggested by Ruocco et al.,\(^14\) is that neural alteration may be the inciting event; the virus acts as an antigen, as herpesvirus affects sensory nerve fibers, resulting in the release of neuropeptides that locally modulate immune and angiogenic responses. Others\(^25\) suggest that an inflammatory dermatosis is conducive for the development of an isotopic response, as it results in variations of local vascular network. Another report\(^26\) suggests that the development of a chronic granulomatous folliculitis, following a herpes zoster infection, may be related to a delayed-type hypersensitivity reaction to incompletely degraded varicella zoster envelope glycoproteins. Perineural and/or perifollicular inflammation was noted for all cases reported herein and may aid in narrowing the histopathologic differential diagnosis of granulomatous dermatitis.

Wolf isotopic response links pathogenetically distinct skin diseases to a zosteriform pattern, which can often present a diagnostic dilemma. Recognition of this phenomenon is important for accurate clinicopathologic diagnosis and may advance our understanding of the underlying pathophysiologic processes contributing to isotopic responses and help inform targeted therapies.\(^9,10\)

### CONCLUSION

In conclusion, we report the cases of 5 patients who developed granuloma annulare with multinucleated giant cells and a perineurovascular and/or perifollicular pattern of infiltrate at the site of prior herpes zoster. In spite of its unclear etiology, Wolf isotopic response remains an interesting phenomenon, which should be considered in the differential diagnosis for any patient with a history of zoster who presents with a zosteriform dermatitis having a granuloma annulare–like histomorphology.

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**Summary of Clinical and Histopathologic Findings for all Cases**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex</th>
<th>Site</th>
<th>Histopathology</th>
<th>Polarizable Foreign Material</th>
<th>Special Stain Results(^a)</th>
<th>Herpes IHC(^b)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64/M</td>
<td>R back/anterior chest</td>
<td>G, F, N, M, C, E, B, P</td>
<td>Not identified</td>
<td>Negative</td>
<td>Negative</td>
<td>TC</td>
</tr>
<tr>
<td>2</td>
<td>64/F</td>
<td>L neck/upper chest</td>
<td>G, N, M, C, E, B, P(^c)</td>
<td>Not identified</td>
<td>Negative</td>
<td>Negative</td>
<td>ILC</td>
</tr>
<tr>
<td>3</td>
<td>49/F</td>
<td>R abdomen and back</td>
<td>G, F, N, M, C, P</td>
<td>Not identified</td>
<td>Negative</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>57/F</td>
<td>L temple</td>
<td>G, F, N, M, C, B</td>
<td>Not identified</td>
<td>Negative</td>
<td>Negative</td>
<td>TC</td>
</tr>
<tr>
<td>5</td>
<td>52/F</td>
<td>L chest/shoulder/back</td>
<td>G, F, N, M, C, E</td>
<td>Not identified</td>
<td>Negative</td>
<td>Not performed</td>
<td>TC</td>
</tr>
</tbody>
</table>

Abbreviations: B, necrobiosis; C, colloidal iron stain confirmed increased mucin deposition; E, presence of eosinophils; F, perifollicular lymphohistiocytic infiltrate; G, nonnecrotizing granulomas; IHC, immunohistochemistry; ILC, intralesional corticosteroids; L, left; M, multinucleated giant cells; N, perineurovascular lymphohistiocytic infiltrate; P, elastophagocytosis; R, right; TC, topical corticosteroids.

\(^a\) Brown-Hopps (tissue Gram stain), periodic acid-Schiff with diastase digestion, Grocott methanamine silver, acid-fast bacilli, and Fite.

\(^b\) Immunohistochemical stains for herpes simplex virus 1, herpes simplex virus 2, and varicella zoster virus.

\(^c\) No hair follicle was present in this sample, precluding evaluation for a perifollicular infiltrate.

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**References**


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