

## BRIEF ARTICLES

## A Postherpetic Isotopic Response Presenting as a Granuloma Annulare-Like Inflammatory Reaction

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### ABSTRACT

Isotopic response refers to the occurrence of a new, unrelated cutaneous disease occurring at the same location of a previous healed disease. The etiology of isotopic responses is still not completely understood. Theories have included that viral particles may lead to the development of the second disease, the destruction of nerve fibers by herpes zoster may lead to an indirect influence on the immune system, an alteration of microcirculation from inflammation that causes future insults to localize to the same site, and an exaggerated and atypical hypersensitivity reaction to tissue antigens, viral antigens, or immune complex deposition. A wide variety of disease processes have been reported as the second disease in an isotopic response.

Here, we discuss a case of an isotopic response following herpes zoster in which the second disease involved a granuloma annulare (GA)-like inflammatory reaction that resolved and recurred. These findings support the theory that the skin affected by herpes zoster is affected in a way that makes it a focus for the manifestation of further skin diseases.

### INTRODUCTION

“Wolf’s isotopic response” refers to the occurrence of a new, unrelated cutaneous disease occurring at the same location of a previous healed disease.<sup>1-3</sup> It has been considered to be analogous to but distinct from the Koebner phenomenon, or isomorphic response, which describes the appearance of the same disease at another location induced by injury.<sup>1-3</sup> Consequently, “isotopic” means “at the same place,” and “isomorphic” means “the same morphology”.<sup>2</sup> Here, an isotopic response is described in a patient who had herpes

zoster, who subsequently developed a granuloma annulare (GA)-like inflammatory reaction in the affected area of herpes zoster that resolved and then recurred.

### CASE PRESENTATION

A 73-year-old male presented to the dermatologist one month after being diagnosed with herpes zoster by his primary care physician. When he presented, he complained of a pruritic rash on his right chest and back. Physical examination revealed zosteriform distribution of erythematous papules and plaques on his

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right chest and back (Figure 1). In addition, he had a severe eruption of the right axilla consisting of erythema, erosion, oozing, and crusting.

Biopsy of the back showed a perivascular infiltrate of lymphocytes with histiocytes in the dermis between and among collagen bundles in a palisaded pattern with sparse collections of mucin, consistent with GA or a GA-like process (Figure 2). Cultures of the axilla revealed the persistence of varicella zoster virus, along with a mixed bacterial infection consisting of *Escherichia coli*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. The eruption was treated with clobetasol cream resulting in clinical resolution within 2 weeks. The mixed infection of the axilla was treated with valacyclovir (1 gram twice daily for 7 days) and sensitivity-based treatment with linezolid (600 mg twice daily for 10 days) with clinical resolution within 2 weeks.

However, 5 weeks later, he developed erythematous papules and plaques in a zosteriform distribution in the previously affected area of his right trunk (Figure 3). Histopathological examination again revealed granulomatous dermatitis with lymphocytic infiltrate, suggestive of GA or a GA-like process. PAS and Fite stains were negative, and immunohistochemical staining for *Treponema pallidum* was negative. After 4 weeks of treatment with oral prednisone therapy (40 mg daily for 7 days, then 20 mg daily for 7 days) and clobetasol topical steroid therapy, the lesions had substantially resolved, with only faint erythema present at the previously involved sites.

## DISCUSSION

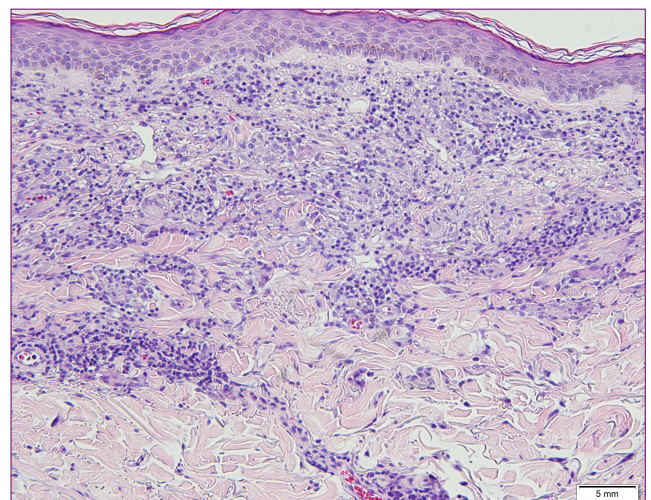
In this isotopic response, herpes zoster was the first disease, and the second disease was a GA-like inflammatory reaction. This

patient's presentation was complicated by the presence of an infection in the axilla involving multiple bacteria and active herpes zoster. What is interesting about this presentation is the resolution and subsequent recurrence of a GA-like inflammatory reaction in a zosteriform distribution in the setting of an isotopic response.

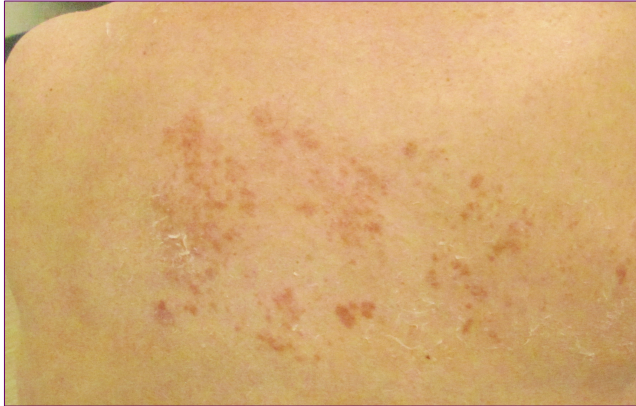
**Figure 1.** Granuloma annulare-like inflammatory reaction consisting of a zosteriform distribution of erythematous papules and plaques on the right back. This eruption extended to the right chest.



**Figure 2.** Histopathological findings consistent with granuloma annulare or a granuloma annulare-like process. There is a perivascular infiltrate of lymphocytes with histiocytes in the dermis between and among collagen bundles in a palisaded pattern with sparse collections of mucin.



**Figure 3.** Recurrence of a granuloma annulare-like inflammatory reaction consisting of a zosteriform distribution of erythematous papules and plaques on the right back. This eruption extended to the right chest.



The first disease in an isotopic response is frequently herpes zoster.<sup>2</sup> Herpes simplex, varicella, and thrombophlebitis also have been reported as first diseases in this phenomenon, but are less common.<sup>2</sup> Several types of cutaneous lesions and disease processes have occurred as the second disease in an isotopic response, including acneiform eruption, angiosarcoma, basal cell carcinoma, comedones, contact dermatitis, cutaneous metastasis from internal carcinoma, furunculosis, granuloma annulare, granulomatous vasculitis, impetigo, Kaposi's sarcoma, leukemia, lichen planus, lymphoma, morphea, molluscum contagiosum, pseudolymphoma, psoriasis, squamous cell carcinoma, xanthomatous changes, tinea, tuberculoid granuloma, and others.<sup>2,4,5</sup>

Multiple theories have been proposed to describe the localization of the second disease in an isotopic response, including viral etiology (viral particles lead to the development of the second disease), immunologic etiology (atypical and exaggerated hypersensitivity reaction to tissue antigens, viral antigens, or immune complex deposition), neural etiology

(destruction of nerve fibers may have an indirect influence on the immune system), and vascular etiology (alteration of microcirculation from inflammation may cause future insults to localize to the same site).<sup>2,6</sup> Evidence which supports the neural etiology include the expression of cell membrane receptors for neuropeptides, neurotransmitters, and hormones on immune cells and that cytokines can influence the peripheral and central nervous systems.<sup>6</sup> As herpes zoster is the most common first disease in an isotopic response and can cause destruction of the A-delta and C fibers in the mid and lower dermis, it may be that the neurological alteration and subsequent interaction with the immune system leads to the development of the second disease.<sup>6</sup> Additionally, the first disease may cause long-lasting immunologic changes, making an area of skin more susceptible to the development of a second disease.<sup>2</sup> Therefore, Ruocco et al.<sup>6</sup> support the hypothesis that there is an interaction between the neurological and immune systems, in which neural alteration leads to subsequent impairment of immunologic function. Viral and vascular mechanisms may be cofactors in this process.

Zosteriform granulomatous reactions at the sites of previously healed herpes zoster lesions have been described.<sup>7-9</sup> Granulomatous inflammatory infiltrates may represent delayed hypersensitivity reactions to varicella zoster virus glycoproteins or altered tissue antigens.<sup>8,9</sup> Granulomatous reactions may occur due to nerve damage and persisting viral particles, which may lead to the secretion of interleukin-4 and other inflammatory cells.<sup>5</sup>

Multiple diseases occurring simultaneously in a postherpetic isotopic response have been reported.<sup>5,10</sup> Here, there was a GA-

like inflammatory reaction that localized to the site of previously affected herpes zoster at separate points in time. These findings support the theory that skin previously affected by herpes zoster is altered in a way that makes it a focus for the manifestation of further skin diseases. While the interaction of the neurological and immune systems may play a role in this process, it is unclear how the milieu of inflammatory cells, cytokines, and neuropeptides may contribute to the development of such a wide array of second disease processes that have been reported in isotopic responses.

**Abbreviations:** Granuloma annulare (GA)

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