Wolf’s Isotopic Response: A Case Report

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Abstract
We report the case of a 53-year-old white female who presented with a mildly pruritic rash on the left chest wall, left shoulder, and left posterior neck of two weeks’ duration. Patient history included herpes zoster several months prior, and clinicopathologic findings supported perifollicular granulomatous dermatitis as an isotopic response following a healed herpes zoster episode—a rare phenomenon known as Wolf’s isotopic response (WIR). In WIR, a new skin disorder occurs at the site of another, unrelated, and already healed skin disease. In many cases of WIR, the initial dermatosis is herpes zoster, and the isotopic response is a granulomatous process. The suggested pathophysiology involves local immune dysregulation due to peripheral nerve damage. Our patient’s WIR resolved spontaneously after symptomatic treatment for pruritus.

Introduction
When injured skin looks healed and normal, the logical assumption is that the skin has returned to its non-injured state. But in 1995, Wolf et al. coined the term “isotopic response” to describe the occurrence of a new skin disorder at the site of another, unrelated, and already healed skin disease.1 (The term was later expanded to “Wolf’s isotopic response” to avoid any apparent correlation with radioactive isotopes, which are unrelated.)

Wolf’s isotopic response (WIR) is a rare phenomenon, with fewer than 200 cases reported in literature.2 WIR should be distinguished from Koebner’s isomorphic response, isomorphic meaning “same morphology” and indicating the recurrence of the original disease at the original site of injury. Since the isotopic response often follows a herpes reaction, the term “post-herpetic isotopic response” (PHIR) is often used. We describe a perifollicular granulomatous dermatitis arising as an isotopic response following a healed herpes zoster episode.

Case Report
A 53-year-old white female presented for a mildly pruritic rash on the left chest wall, left shoulder, and left posterior neck of two weeks’ duration. The rash consisted of 1 mm to 3 mm, discrete and confluent, firm whitish papules on an erythematous base (Figures 1, 2). This eruption was non-tender and without lymphadenopathy. The patient reported an episode of herpes zoster about three to four months prior, which had lasted six weeks. Based on clinical examination, a differential diagnosis of post-herpetic dermatitis such as granuloma annulare, unilateral eruptive xanthomas, or colloid milia was supported.

Two punch biopsies were performed, both of which indicated perifollicular granulomatous dermatitis (Figure 3, H&E, 40x). Pathology reported, “Sections demonstrate essentially unremarkable epidermis. Within the dermis is a superficial and deep predominantly perifollicular spilling into the interstitial collagen lymphohistioctic infiltrate with ill-formed collections of the epithelioid histiocytes with associated multinucleated giant cells. Neutrophils and eosinophils are not identified.” Additionally, there was no mucin, elastophagocytosis, or necrobiosis. Pathology concluded, “The cutaneous pattern of injury is quite supportive of the clinical impression of post herpetic granulomatous dermatitis. Residual (active) herpes viral cytopathic changes are not identified. Special stains performed on both biopsies (GMS and AFB) are negative for fungal organisms and acid-fast bacilli, respectively.”

Based on the clinical and histopathologic findings, the diagnosis of post-herpetic granulomatous dermatitis as a secondary isotopic response to a primary herpetic infection was made. With the original herpes zoster dermatosis already resolved, the patient’s secondary granulomatous reaction was treated symptomatically for pruritus, and the eruption soon spontaneously resolved.

Discussion
WIR is used to describe the occurrence of a new skin disorder at the site of another, unrelated, and already healed skin disease. In most cases, the initial dermatosis is herpes zoster, although the condition is also seen with herpes simplex virus, varicella, thrombophlebitis, and scrofuloderma.1,3,4 Although many consider isotopic responses a herpes-specific phenomenon, Wolf’s definition included a wider range of initial dermatoses, which would have implications for the underlying pathophysiology.5

The dermatoses that appear on healed sites are mainly granulomatous and lichenoid reactions but may also be infiltrations by hematologic malignancies, skin tumors, and infections.1-6 In a large review of 188 cases of PHIR, 64 were granulomatous reactions, 37 were malignant tumors, 27 were dysimmune reactions, 17 were infections, 15 were leukemic or lymphomatous infiltrations, 12 were comedonic-microcystic reactions, and 17 were “other.” The interval from the first dermatosis to the second has been reported as anywhere from days to years.7,8

In general, WIR occurs due to the continuation of microscopic and physiologic changes in apparently
healed skin. The most widely accepted theory of its pathogenesis points to cutaneous nerve damage that, in addition to altering sensation, may alter immunity. This could lead either to hyperactivity, which could cause an inflammatory process such as granulomatous or lichenoid dermatitis, or to immune suppression, which could lead to tumor infiltrations such as leukemia cutis or infectious diseases. The pathophysiology of herpes virus supports this theory, as herpes viruses infect and damage peripheral cutaneous nerves, and local immune dysregulation will occur due to a change in the release of neuromediators like substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide. This pathogenesis may or may not apply to isotopic responses to dermatoses other than herpes. In cases involving herpes, the actual virus does not seem to play a direct role, as studies and case reports rarely demonstrate viral DNA in the isotopic lesions except when the interval between the dermatoses is short. It has also been suggested that incompletely degraded varicella zoster envelope glycoproteins may cause a delayed-type hypersensitivity reaction. Others theorize the initial inflammation may disrupt the local vascular network, leading to an isotopic response.

Supporting the hypothesized pathophysiology of immune dysregulation is the phenomenon known as “inverse isotopic response” or “isotopic nonresponse,” in which a second dermatosis spares the site of previous skin injury. In one case, a widespread cutaneous T-cell lymphoma spared a resolving herpes zoster lesion.

In a case series of WIR manifesting as post-herpetic granuloma annulare, a unique histopathology was found. Findings included a perineural vascular or perifollicular pattern of lymphohistiocytic infiltration, including multinucleated giant cells that occurred following a herpes zoster or herpes simplex infection. These findings are unusual for idiopathic granuloma annulare. Although our case involved a nonspecific granulomatous dermatitis, the finding of perineural and/or perifollicular inflammation may help narrow the histopathological diagnosis down to post-herpetic granulomatous dermatitis. This correlates with a herpes pathophysiology in that the virus travels along nerves to nerve endings at the hair follicle isthmus, leading to folliculosebaceous spread.

Treatment in our case involved easing the patient’s pruritus. Since herpes DNA is rarely found in the isotopic lesion, especially when the interval between the two dermatoses is many months apart, antiviral therapy is not indicated. Treatment of herpes zoster does not correlate with a decrease or an increase in the rate of PHIR. Underlying malignancy such as lymphoma or leukemia has been observed in cases of WIR and PHIR, so biopsy is recommended for clinically atypical cases.

Conclusion

The WIR phenomenon sheds light on the physiology of the skin. Some authors have used the term “post-herpetic isotopic response” (PHIR) when dealing with reactions following a herpes dermatitis, which may be beneficial since pathphysiology may differ based on the initial dermatitis. It is important to be aware of the WIR phenomenon, as it may be under-recognized. Routinely inquiring specifically about a patient’s herpes-related medical history may help with diagnostic accuracy.

References