CASE REPORT

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Herpes Zoster Granulomatous Dermatitis: A Rare but Memorable Complication

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There have been reports of benign and cancerous cutaneous reactions developing at the site of resolved herpes zoster weeks to years after the acute infection. This case study describes a 71-year-old male patient with herpes zoster granulomatous dermatitis, a manifestation of postherpetic isotopic response. His medical history was significant for Graves' disease and chronic myelomonocytic leukemia. After presenting to the emergency department, he was diagnosed with herpes zoster generalisatus. Approximately two months after receiving treatment for herpes zoster, multiple firm subcutaneous nodules appeared on his neck. An excisional biopsy was performed to rule out leukemia cutis. The specimen displayed extensive dermal lymphohistiocyte infiltration, marked by central necrosis and atypical T cells. Tests for tuberculosis and leukemia were negative. At follow-up, an excisional biopsy of the recurrent neck nodules confirmed diffuse dermal infiltration and central necrosis. Based on the clinical and pathological findings, he was diagnosed with herpes zoster granulomatous dermatitis. He was administered systemic and topical steroid therapy over one month, after which the lesions and associated symptoms improved. Wolf's isotopic response refers to the occurrence of a new skin disease at the site of an already healed, unrelated skin disease. This phenomenon is frequently overlooked—especially following herpes zoster. Healthcare practitioners should know Wolf's isotopic response to ensure accurate diagnosis and avoid potential oversight of malignant diseases.

Key Words: Granuloma, Herpes zoster, Herpes zoster granulomatous dermatitis, Wolf's isotopic response

INTRODUCTION

Herpes zoster (HZ) is characterized by unilateral dermatomal pain and a rash. The condition results from the reactivation of latent varicella-zoster virus within neurons. HZ occurs sporadically, with an average incidence ranging from 2 to 5 cases per 1,000 people in community-dwelling populations. The incidence of HZ increases with age, and HZ-related complications are also age-associated¹. Diminished cell-mediated immunity often affects the elderly, potentially leading to a higher prevalence of comorbidities. Additionally, regardless of age, immunocompromised patients demonstrate an increased risk of complications².

HZ-related complications are cutaneous—such as disseminated or recurrent zoster—as well as neurological, ophthalmological, and visceral presentation³. Numerous documented cutaneous disorders emerge at the site of resolved HZ following an acute infection⁴. This case study presents a

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Fig. 1. Clinical presentation of the patient at his first biopsy where (A) multiple painful erythematous papules are visible on the chest and abdomen and erythematous-to-violaceous crusty patches on the left flank (B-E). Multiple, painful clustered erythematous papules on the bilateral upper and lower extremities and (F) several firm subcutaneous nodules are apparent on the patient's neck.

case of herpes zoster granulomatous dermatitis (HZ-GD) that developed after disseminated HZ.



Fig. 2. (A) Histopathological findings showing central necrosis [Hematoxylin & eosin (H&E), ×40] and (B) diffuse dermal infiltration of lymphocytes and histiocytes with central necrosis surrounded by multinucleated giant cells and epithelioid cells (H&E, ×100) (C) Dense lymphocytic infiltration around the adnexa (H&E, ×100) and (D) atypical T lymphocytes are visible in the dermis (H&E, ×400).

CASE REPORT

A 71-year-old male patient presented to the emergency room with a three-day history of painful erythematous vesicular lesions over his face, neck, trunk, and extremities. Laboratory tests revealed elevated inflammatory markers, including an increased erythrocyte sedimentation rate, leukocyte count, and creatinine. His medical history was significant for Grave's disease; he had been using methimazole for 20 years. Additionally, he was recently diagnosed with chronic myelomonocytic leukemia and undergoing hydroxyurea treatment. A dermatology consultation was requested to manage the skin lesions associated with HZ.

While hospitalized, he received a two-week course of intravenous acyclovir and saline wet dressings. The hydroxyurea he took to treat his Graves' disease was suspended during this time. His HZ lesions soon improved; however, there was evidence of leukemia progression during followup, and the hydroxyurea was reintroduced. Around two months after the HZ lesions were resolved (Fig. 1A-E), he developed firm subcutaneous nodules on his neck, and the HZ lesions reappeared (Fig. 1F).

An incisional biopsy was performed on a nodule from the left side of his neck to investigate the possibility of leukemia cutis. Histopathological examination revealed diffuse dermal



Fig. 3. Site of prior herpes zoster lesions now resolved. Multiple asymptomatic dusky red patches are evident across the patient's chest, abdomen (A), and bilateral upper extremities (B, C). (D-F) Multiple firm subcutaneous nodules are apparent on the patient's neck.



Fig. 4. (A) Areas of diffuse dermal lymphocytic infiltration with central necrosis (H&E, \times 40) surrounded by (B) multinucleated giant cells and epithelioid histiocytes (H&E, \times 100)

infiltration of lymphocytes and histiocytes with central necrosis, surrounded by multinucleated giant cells and epithelioid cells (Fig. 2A, B). We observed dense lymphocytic infiltration around the adnexa (Fig. 2C) and atypical T lymphocytes in high-power fields (Fig. 2D). Special staining showed positive results for cluster of differentiation (CD) 3 stain, with Ki-67 levels of 10%. Simultaneously, tests for cytokeratin (CK), CD20, acid-fast bacteria (AFB), and markers indicative of leukemia -such as myeloperoxidase, c-kit, CD34, and CD68-were all negative. Polymerase chain reaction testing for mycobacterium yielded negative results, excluding tuberculosis as a contributor to the observed caseous granuloma. A chest X-ray revealed left lower lobe peribronchial infiltration, and he was diagnosed with atypical pneumonia and initiated antibiotic therapy. Additional tests were negative, including the interferon-gamma release assay and sputum culture with AFB stain. Evaluation of T-cell receptor beta and gamma gene rearrangement-conducted to investigate the cause of atypical T lymphocytes-revealed polyclonality, thereby excluding lymphoma.

His HZ lesions worsened during follow-up, and he was readmitted to the hospital for a two-week course of intravenous acyclovir and saline wet dressings. The hydroxyurea prescribed to treat his Graves' disease was stopped while hospitalized. After two weeks of treatment, his dermatological symptoms improved (Fig. 3A-C), and hydroxyurea was restarted. However, the emergence of persistent multiple nodules on the face and neck (Fig. 3D-F), along with elevated pinkish patches along the HZ lesions—including the primary site on the left flank—prompted an excisional biopsy.

Pathological study revealed a diffuse dermal lymphocytic infiltration with central necrosis surrounded by multinucleated giant cells, epithelioid histiocytes, and perivascular inflammation (Fig. 4). Special staining for CD3 was positive, with Ki-67 levels of 10%. At the same time, CK, AFB, c-kit, and CD68 stains were negative. He was diagnosed with granulomatous disease based on the characteristic appearance of granulomas featuring central necrosis, surrounded by epithelioid histiocytes, lymphocytes, and perivascular as well as peri adnexal inflammation.

Considering the localization of these lesions within the prior HZ site, the patient was conclusively diagnosed with herpes zoster granulomatous dermatitis (HZ-GD). He was treated with topical corticosteroids (desonide 0.05%, desoximetasone 0.25%), antihistamines, and systemic corticosteroids (prednisolone 5 mg/day). Within one month, his symptoms were markedly improved.

DISCUSSION

Wolf's isotopic response refers to the emergence of a new skin condition at a site previously occupied by a different, unrelated skin disease. In contrast, the isomorphic response —known as the Koebner phenomenon and frequently observed in patients with psoriasis and lichen planus—refers to when a skin disorder recurs in areas previously subjected to injury or trauma^{5,6}.

The precise cause of Wolf's isotopic response remains unclear. However, HZ is this phenomenon's most frequently reported precursor condition⁶. Secondary disorders range from benign to malignant and include granuloma annulare, granulomatous vasculitis, sarcoid granuloma, tuberculoid granuloma, nonspecific granulomatous dermatitis, lichen sclerosus, eosinophilic dermatosis, atypical lymphoid proliferation, lymphoplasmacytoid lymphoma, T-cell lymphoma, leukemia cutis, and Kaposi sarcoma⁴.

Postherpetic isotopic response (PHIR), a manifestation of Wolf's isotopic response, can emerge following an episode

of HZ. While rare, PHIR occasionally manifests in immunocompromised individuals. While its underlying pathogenesis is poorly understood, it is unlikely to be directly induced by HZ, as herpes virus DNA rarely detects skin lesions except during the early stages. Alternatively, PHIR might be linked to local neuroimmune instability resulting from the release of neuropeptides due to damaged cutaneous nerve fibers⁶. While rare, PHIR encompasses a wide spectrum of secondary disorders ranging from benign to malignant. A granulomatous reaction is the most frequent manifestation in approximately 33.9% of PHIR cases⁷.

HZ-GD is rare and characterized by localized inflammation, primarily in immunocompromised individuals⁸. It typically occurs around 4.2 months after HZ onset and is more common in males⁵. Clinical presentation involves painful or pruritic nodules that follow a distribution similar to that of HZ⁹. Unlike HZ, vesicles are rarely observed in HZ-GD. Diagnosis involves evaluating the patient's history of HZ infection, underlying immunocompromising conditions, or medication usage. Clinical assessments should consider characteristic features like lesion distribution, affected areas, and accompanying symptoms⁴⁻⁷.

Confirmation of HZ-GD typically requires a skin biopsy to identify the presence of granulomas and the clustering of immune cells. Histopathologically, the granulomas appear composed of epithelioid histiocytes, giant cells, and lymphocytes encircling a central area of necrosis and accompanied by perivascular as well as perineural inflammation⁴.

There are no established treatment guidelines for HZ-GD; treatment is largely informed by clinical experience and reported cases. Various approaches have been tried, including topical, intralesional, and systemic corticosteroids, which have shown efficacy in many patients⁵.

There are limited reports about the specific occurrence of Wolf's isotopic response, particularly following HZ. In our case, granulomatous dermatitis has presented as a relatively benign course in the cases we have encountered. However, emphasizing that the spectrum of conditions manifesting as PHIR can encompass a broad range, from benign to malignant, is crucial. While this phenomenon is uncommon, PHIR must receive more recognition. This recognition is crucial to facilitate precise diagnoses and prevent any oversight regarding the potential occurrence of malignant diseases.

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CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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PATIENT CONSENT STATEMENT

The patient provided written informed consent for the publication and the use of his images.

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