Postherpes zoster programmed death-1 inhibitor–associated zosteriform granulomatous reactions

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Key words: granulomatous; immune-related adverse event; pembrolizumab; programmed death-1; zosteriform.

INTRODUCTION

Immune checkpoint inhibitors (ICPIs) that inhibit programmed death-1 (PD-1) or its target receptor have side effect profiles consisting of "immune-related adverse events," which include varied cutaneous reactions. Although eczematous and lichenoid reactions are most common, granulomatous reactions have also been reported.[1] We report 2 cases of patients who developed granulomatous reactions in the distribution of a previous herpes zoster eruption while receiving treatment with pembrolizumab, which is a unique manifestation of Wolf postherpetic isotopic response in the immunotherapy setting.

Abbreviations used:

GA: granuloma annulare
GD: granulomatous dermatitis
ICPI: immune checkpoint inhibitor
PD-1: programmed death-1

CASE REPORTS

Case 1

A woman in her 50s, previously treated with chemotherapy for metastatic triple-negative inflammatory breast cancer, presented with a pruritic papular eruption along the C7-C8 dermatome of her upper right arm (Fig 1). Six months earlier, the patient developed herpes zoster involving the same dermatome and received valacyclovir with resolution of the cutaneous reaction; however, she experienced persistent postherpetic neuralgia. Four weeks before the onset of eruption, carboplatin chemotherapy was replaced with pembrolizumab monotherapy. After cycle 1, the patient developed pembrolizumab-induced thyroiditis, and after cycle 2, she developed mauve, grouped, polygonal, and flat-topped papules extending from the upper right side of her back to the ulnar aspect of her hand without vesicles, scaling, or nail involvement. A punch biopsy was performed, which revealed necrotizing granulomatous dermatitis (GD) and a mixed perivascular inflammatory infiltrate with mucin, consistent with the findings of granuloma annulare (GA) (Fig 2, *A*). The distribution of her rash suggested Wolf postherpetic isotopic response in the setting of a pembrolizumab-induced granulomatous reaction. She was treated with triamcinolone cream. Her pembrolizumab immunotherapy was not interrupted, and she was maintained on acyclovir for prophylaxis.

Case 2

A woman in her 80s having metastatic lung adenocarcinoma with elevated PD-1 ligand-1 expression and hyperthyroidism presented with clustered reddish brown 2-3-mm macules and thin papules involving the left side of her postauricular and preauricular skin, jawline, and posterior aspect of the neck with associated burning, which were persistent for 1 month. The patient developed herpes zoster involving the V3 and C3 dermatomes 1 month

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Drs Guggina and Nguyen are co-last authors.
Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.
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JAAD Case Reports 2020;6:1201-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.09.017

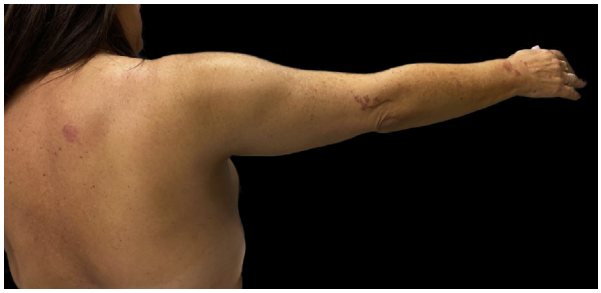

Fig 1. Case 1. Groups of mauve papules distributed along the C7-C8 dermatome.

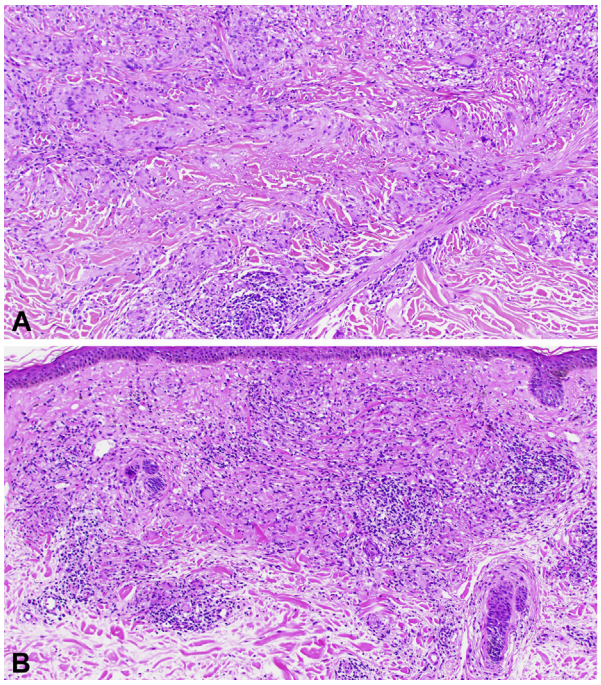

Fig 2. **A**, Case 1 histopathology. The sections demonstrate an infiltrate comprising mononucleated cells and multinucleated histiocytes palisading around the areas of degenerated collagen and mucin. **B**, Case 2 histopathology. The sections demonstrate a loose nonpalisaded granulomatous infiltrate without degenerated collagen or increased mucin. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×100; **B**, ×100.)

after the initiation of pembrolizumab. Then, about 6 months later, the patient presented to our clinic with a new cutaneous eruption, which started after cycle 10 of therapy. A punch biopsy revealed interstitial and focal nodular collections of histiocytes forming loose granulomas in the dermis, consistent with the findings of GD (Fig 2, *B*). Her history of herpes zoster in the same distribution suggested Wolf postherpetic isotopic response in the setting of pembrolizumab-induced GD. Her treatment included the application of topical corticosteroids to the affected region for 2-3 months, which resulted in improvement and flattening of lesions and initial resolution of pruritus. She was continued on pembrolizumab and experienced a recurrence of burning and pruritus along the neck and jawline, which was managed with intermittent application of triamcinolone cream and oral antipruritics.

DISCUSSION

Reported granulomatous reactions to ICPIs are rare but include GA, GD, granulomatous panniculitis, and, most commonly, sarcoidosis-like reactions (Table 1).[1] ICPI-induced GA manifests with the onset of lesions between 6 weeks and 8 months after initiating anti-PD-1 therapy. The eruptions appear with erythematous, annular plaques and pink papules, commonly localized to the dorsal arms and upper side of the back before spreading bilaterally to the legs.[2,3] Histopathology revealed necrobiotic collagen and mucin surrounded by palisaded histiocytes and lymphocytes. Treatment with topical and oral steroids was found to be effective in all reported cases, with a definitive resolution of GA at the completion of PD-1 therapy.[2-4] The eruptions appear with erythematous or violaceous coalescing papules and plaques involving the torso and extremities. Although the reported cases of ICPI-induced GD are mainly mild (grade 1, low body surface area involvement, and little to no impact on quality of life), a severe reaction (grade 3, >50% body surface area involvement, and impact on quality of life) has been reported.[5] Histopathology revealed dermal histiocytic infiltrate with sparing of the epidermis. Similar to that for GA, the mainstays of treatment are topical and oral steroids; however, several cases of GD did not resolve fully until an average period of 21 weeks after the cessation of immunotherapy.[6]

ICPIs function by disrupting the immunologic response and can thus cause adverse reactions that are autoimmune or inflammatory in nature, such as granulomatous reactions. It is hypothesized that the blockade of PD-1 by pembrolizumab induces Th1 and Th17 immune-cell hyperactivity, causing granuloma formation.[1] Previous studies have demonstrated that immunotherapy-induced GA and GD were less likely to be associated with systemic granulomatous disease; in contrast, systemic manifestations, including thyroiditis, are more likely to be associated with sarcoid-like reactions.[1]

Wolf postherpetic isotopic response manifests as the occurrence of an unrelated eruption at the exact site of a previous, resolved herpes zoster infection, and granulomatous infiltrate is commonly noted in this phenomenon.[7] Two previous cases of ICPI-induced postherpetic granulomatous reactions

Table I. Spectrum of granulomatous reactions associated with immune checkpoint inhibitor therapy[1,4,7,8]

	Time to symptoms*	Morphological characteristics	Clinical distributions	Histologic features	Treatment strategies	Associated immune-related adverse events
Cutaneous granulomatous reactions						
Sarcoidosis-like reactions (n = 59)†	From 1 to 27 months Average: 6.3 months	Subcutaneous nodules or skin-colored papules and plaques, occasionally within tattoos or scars	Face, neck, and upper extremities	Noncaseating granulomatous dermatitis	Systemic steroids	Pulmonary and ophthalmologic involvement, thyroiditis
Granulomatous panniculitis (n = 4)	From 5 weeks to 10 months Average: 5.3 months	Tender subcutaneous nodules	Lower extremities	Mixed septal and lobular granulomatous panniculitis	Topical or systemic steroids or hydroxychloroquine	Pneumonitis, sarcoidosis-like reaction
Granuloma annulare (n = 7)	From 6 weeks to 8 months Average: 4.3 months	Pink papules, annular plaques	Extremities	Necrotizing and palisading granulomatous infiltrate	Topical or systemic steroids	Hypertrophic lichen planus, vitiligo
Granulomatous dermatitis (n = 7)	From 2 days to 5 years Average: 3 weeks	Coalescing papules and plaques	Extremities and trunk	Superficial, perivascular and interstitial granulomatous infiltrate	Topical or systemic steroids or topical calcineurin inhibitors	Acneiform and morbilliform eruptions, generalized pruritus, hepatitis, and pancreatitis
Less common cutaneous granulomatous reactions						
Granulomatous foreign body reactions (n = 1)	4 weeks	Coalescing pink papules	Extremities and trunk	Granulomatous inflammatory response with lichenoid and perivascular distribution	Systemic steroids	

Adapted from Tables I and II reported by Cornejo et al.[1]

*Time ranges reported from first dose of immunotherapy.

†The summary of reactions is based on the data from previous case reports. The number of case reports included in each summary is indicated by "n" values.

have been reported, both in the context of nivolumab therapy.[7,8] The additional cases of GA and GD in our study in the context of pembrolizumab therapy suggest that this phenomenon is a class effect of the PD-1 inhibitors. In the 4 reported cases, the granulomatous reaction occurred between 6 months and 2 years after initial herpes zoster eruption and the histology was inconsistent with an active herpes virus infection.[7,8] Although the patients in this report had full resolution with topical therapy, in the case reported by Martín-Carrasco et al,[7] nivolumab-induced GD did not resolve with topical corticosteroids or topical calcineurin inhibitors. Assi et al[8] reported the treatment of postherpetic GA exclusively with emollients and the resolution of the eruption only after the interruption of pembrolizumab therapy, emphasizing a correlation between PD-1 therapy and these rare immune-related adverse events, distinct from the isolated postherpetic granulomatous reactions. Although the pathogenesis of Wolf postherpetic isotopic response remains unknown, previous hypotheses have implicated delayed-type hypersensitivity and altered local immune modulation that predisposes the impacted dermatomes to future immune conditions, such as iatrogenic immune dysregulation.[8] Recent guidelines have underscored the importance of ruling out infection and systemic disease when treating the skin reactions in patients on immunotherapy; therefore, the recognition of this postherpetic phenomenon can preclude additional testing.[9] Thus, these cases present an interesting phenomenon of immune dysregulation confounded by 2 different etiologies and highlight the importance of considering Wolf postherpetic isotopic response when treating zosteriform lesions.[10]

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