Programmed cell death protein-1 inhibitor–induced granuloma annulare and hypertrophic lichen planus masquerading as squamous cell carcinoma

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INTRODUCTION
Pembrolizumab is a humanized monoclonal antibody against programmed cell death protein-1 (PD-1) and is an effective treatment for advanced non–small cell lung cancer1 and advanced melanoma.2 PD-1 functions as a checkpoint of the effector stage of the immune system and inactivates T cells when they reach tumors.2 Systemic adverse events of checkpoint inhibitors include fatigue, fever, chills, and infusion reactions. Skin rash is the most common immune-related adverse event associated with checkpoint monoclonal antibody therapy, which can manifest as maculopapular rash, urticarial dermatitis, lichenoid dermatitis, bullous pemphigoid, Stevens-Johnson syndrome, and toxic epidermal necrolysis.2,3

We report a case of hypertrophic lichen planus (HLP) mimicking squamous cell carcinoma (SCC) as well as granuloma annulare (GA) associated with pembrolizumab.

CASE REPORT
A 79 year-old white man with PD ligand 1–positive stage IV non–small cell lung cancer started treatment with pembrolizumab, 200 mg once every 3 weeks, shortly after diagnosis in 2016. His medical history included a 50-pack-year smoking history, chronic obstructive pulmonary disease, and hypothyroidism. The patient also had a history of oral lichen planus, which was medically managed by an oral surgeon with maintenance low-dose doxycycline of 20 mg daily with good control of his disease. The patient’s lichen planus was localized to the oral mucosa, and he had no history of cutaneous lichen planus. Approximately 6 weeks after initiating therapy with pembrolizumab, the patient presented to the dermatology clinic for evaluation of an enlarging mildly pruritic rash on his arms, legs, and upper back. Physical examination found innumerable hyperkeratotic and necrotic papulonodules and ulcerations on the extremities (Figs 1, A and B) and scattered multicentimeter serpiginous nonscaly, erythematous plaques on the upper back and forearms (Fig 2, A and B). Coinciding with the onset of these cutaneous lesions, the patient experienced a flare of his oral lichen planus, and his dose of doxycycline was increased from 20 mg daily to 40 mg twice daily. He had no history of skin cancer and no genital lesions.

The differential diagnosis of these lesions was broad given the patient had 2 morphologically distinct lesions. Although the annular plaques on the back were most suggestive of annular lichen planus or GA, sarcoidosis was also considered, given...
that cases of sarcoidosis induced by pembrolizumab have been reported.\(^4\) The differential diagnosis of the papulonecrotic lesions included conditions more commonly seen in association with \textit{BRAF}\(^5\) inhibitors, such as eruptive keratoacanthomas, SCCs, lichen planus, lichenoid drug eruption, sarcoidosis, infection, nodular vasculitis, and lymphomatoid papulosis.

Punch biopsies of the anterior thigh, medial thigh, and upper back were performed. Histologic examination of the medial thigh and anterior thigh lesions found downward proliferations of dysplastic squamous epithelium confined to the hyperplastic epidermis consistent with early evolving, well-differentiated SCC (Fig 3, \textit{A} and \textit{B}). Histologic examination of an upper back lesion showed a palisading granulomatous infiltrate in the dermis consistent with GA (Fig 3, \textit{C}).

Pembrolizumab was held, and because of the severe pain associated with the ulcerated lesions, a trial of oral prednisone, 40 mg/d, was started with input from the hematology-oncology team. There was dramatic improvement in all lesions with most lesions completely flattening and only few residual areas of hyperkeratosis. The GA lesions on the upper back completely resolved. Repeat biopsy of the left forearm was performed and demonstrated hyperplastic epidermis with an associated lichenoid mononuclear cell inflammation, consistent with lichen planus (Fig 3, \textit{D}). In the setting of the patient’s recent oral lichen planus flare and dramatic response to prednisone, a diagnosis of HLP was made on clinicopathologic correlation.

\textbf{DISCUSSION}

Monoclonal antibodies that block co-inhibitory immune checkpoint molecules, such as PD-1, include pembrolizumab and nivolumab, which are used to improve prognosis in patients with advanced lung cancer and melanoma. Although this allows for immune tolerance, an unchecked immune response

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image1}
\caption{\textbf{A} and \textbf{B}. Six weeks after initiating therapy with pembrolizumab, the patient presented with numerous hyperkeratotic and necrotic papulonodules and ulcers on the extremities.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image2}
\caption{The patient had multiple erythematous annular serpiginous plaques without scale on the upper back (\textit{A}) and forearms (\textit{B}).}
\end{figure}
can lead to autoimmune-like or inflammatory side effects leading to systemic adverse events including fatigue, diarrhea, and hypothyroidism.

Dermatologic toxicity is the most common immune-related adverse event of PD-1 inhibitors and includes maculopapular rash, Sweet syndrome, and urticarial dermatitis. Although the exact mechanism of toxicity is unknown, coexpression of a common antigen on the patient’s tumor cells and at the dermoepidermal junction has been proposed. Rarely, lichenoid dermatoses, bullous pemphigoid, and Stevens-Johnson syndrome have also been observed. A recent prospective study found that 22% of patients with stage IV melanoma who were treated with anti–PD-1 antibodies had cutaneous reactions ranging from mild rash to bullous drug eruptions, and 15% of patients went on to have vitiligo. Biopsy-proven lichen planus developed in one of the patients.

HLP is a form of lichen planus characterized by epidermal hyperplasia and pruritus. Lichen planus is a mucocutaneous inflammatory disease that frequently arises in the skin and oral mucosa and is characterized by flat-topped violaceous papules on the skin. Histopathology of HLP includes hyperorthokeratosis, lichenoid infiltrate with occasional eosinophils, no cytologic atypia, and no deep extension beyond the papillary dermis. The exact pathogenesis of HLP is unknown, but basal keratinocyte degeneration by induction of apoptosis affected by CD8+ T cells is believed to be involved in this autoimmune process. HLP is clinically and histologically similar to SCC, and multiple cases of HLP transforming into SCC have been reported. In the literature, there have been at least 5 patients with HLP that was mistakenly diagnosed as SCC, which highlights the importance of distinguishing the 2 conditions to minimize unnecessary treatments, such as surgical excision. As Levandoski et al states, important clinical features that are helpful for differentiating HLP from SCC include hyperkeratotic plaque(s) on the distal extremities including plaques with follicular accentuation, Wickham striae, negative history of sun damage, and no predisposing factors for multiple SCCs; histological features include lichenoid dermatitis with eosinophils, hyperorthokeratosis, no cytologic atypia, absence of marked elastosis, no deep extension beyond the papillary dermis, and no lymphovascular or perineural invasion. In this case, the patient’s history of oral lichen planus and the eruption of numerous lesions bilaterally on upper and lower extremities were clinically more consistent with lichen planus. Furthermore, although apoptotic keratinocytes can be found in SCC, their distribution limited to the basal layer of the epidermis as Civatte bodies is characteristic of lichen planus. Histologically, SCC is frequently a low-power diagnosis; however, high-power inspection of the dermoepidermal junction to look for this clue may also facilitate diagnosis.

GA is thought to be caused by a delayed-type hypersensitivity, the cause of which is unknown. Some have hypothesized that GA arises secondary to an immune-mediated, type III reaction, leading to chronic vasculitis or cell-mediated immunity with expression of lymphokines, resulting in sequestration of macrophages and histiocytes in the dermis. Histologically, in addition to the classic palisading granulomas, GA shows blood vessel wall fibrinoid changes, thickening, or occlusion. GA is most commonly related to diabetes and hyperlipidemia but has also been described in association with malignancies and infections. Triggers have included vaccinations and medications including allopurinol, topiramate, and tumor necrosis factor-α inhibitors. To our knowledge, there have been no cases of GA
associated with PD-1 inhibitors or other chemotherapeutic agents.

Patients with immune-related dermatologic events secondary to PD-1 inhibitors should be evaluated with clinical assessment with or without biopsy. Standard treatment for immune-related adverse events includes corticosteroids, anti–tumor necrosis factor medications, and antihistamines.

To our knowledge, this is the first reported case of GA and HLP mimicking SCC associated with the use of monoclonal antibodies against PD-1. It highlights the importance of vigilantly monitoring patients treated with checkpoint inhibitors for skin rashes. This case also demonstrates the importance of distinguishing between HLP and SCC, as this is critical for initiation of appropriate treatment. Furthermore, the patient’s development of HLP within the context of a flare of his previously diagnosed oral lichen planus underscores that PD-1 inhibition, and subsequent immune tolerance, can exacerbate autoimmune conditions.

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