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Pembrolizumab-associated pyoderma gangrenosum in a patient with metastatic squamous cell carcinoma

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Abstract

Pyoderma gangrenosum (PG) is a rare, ulcerative neutrophilic dermatosis that has been reported in association with certain medications. Recognition of medications that trigger PG may help to better understand the pathogenesis of the condition and to provide earlier diagnosis and treatment for affected patients. Herein, we report a case of new-onset PG following initiation of the checkpoint inhibitor pembrolizumab for the treatment of metastatic cutaneous squamous cell carcinoma. Our case was resistant to intralesional corticosteroid therapy, but ultimately improved with systemic corticosteroids and cessation of pembrolizumab.

Keywords: immune checkpoint inhibitor, immunotherapy, neutrophilic dermatosis, pembrolizumab, programmed death 1 inhibitor, pyoderma gangrenosum, skin toxicity

Introduction

In June 2020, the U.S. FDA approved the programmed death-1 (PD1) inhibitor pembrolizumab for the treatment of recurrent or metastatic cutaneous squamous cell carcinoma (SCC), [1]. Programmed death 1 inhibitors activate anti-tumor T cell responses but may also interfere with immune tolerance. As a result, they frequently trigger adverse cutaneous effects, including lichenoid, maculopapular, psoriasiform, and immunobullous reactions [2,3]. Neutrophilic dermatoses have been more rarely reported with checkpoint blockade [4]. Pyoderma gangrenosum (PG) is a non-infectious neutrophilic dermatosis which commonly presents with a painful, erythematous pustule or papule that rapidly expands to a necrotic ulcer with undermined, violaceous borders [5]. Herein, we report a case of new onset PG lesions following pembrolizumab treatment initiation for metastatic cutaneous SCC.

Case Synopsis

A 78-year-old gentleman with a history of SCC of the right scalp treated with surgical excision developed metastatic spread to the left parotid four years after initial diagnosis. He underwent left parotidectomy and modified radical neck dissection, which showed poorly differentiated metastatic SCC involving the parotid gland and 23/26 positive lymph nodes. Despite adjuvant therapy with radiation and the epidermal growth factor receptor inhibitor cetuximab, he developed metastases to the liver, spleen, abdominal lymph nodes, and bones. He began pembrolizumab 200mg IV every three weeks with near resolution of metastatic disease after three months of treatment.

He initially developed a pruritic maculopapular exanthem two months after starting pembrolizumab, which flared following infusions and improved with medium-high potency topical corticosteroids. However, 5 months after pembrolizumab initiation he developed three new painful back lesions (**Figure 1A)**. He lacked systemic symptoms or a history of prior similar lesions. On

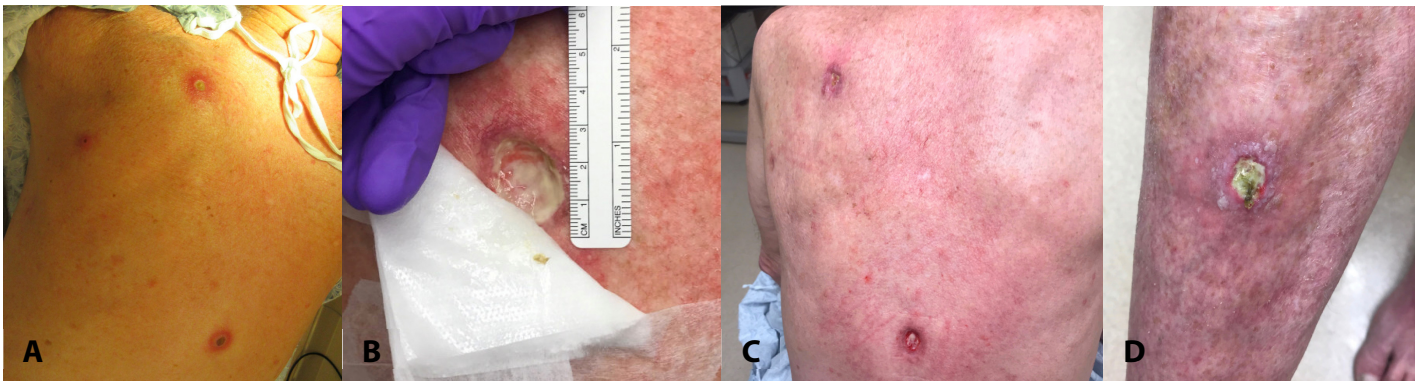

Figure 1. ***A)*** *Pre-treatment images showed three erythematous plaques with central ulceration.* ***B)*** *Two months after presentation. Despite treatment with intralesional triamcinolone, the back ulcerations continued to expand and developed erythematous, slightly undermined borders.* ***C)*** *Persistent ulcerations three months after presentation prior to systemic corticosteroids.* ***D)*** *Ulcer on right shin that developed in area of minor trauma.*

cutaneous examination, he had three ulcers with erythematous-to-violaceous, undermined borders on the back. Out of concern for an adverse reaction to pembrolizumab, a biopsy of an ulcer edge was performed, which showed florid acute and chronic inflammation in the dermis with a prominent neutrophilic component and microabscess formation (**Figure 2**). Gram, fungal, and acid-fast stains were negative for microorganisms. The lesions were treated with intralesional triamcinolone 20mg/mL and local wound care consisted of collagen matrix dressings, mupirocin, and non-adherent gauze. Despite this, the ulcer continued to expand over the subsequent three months (**Figure 1B, C)**. He also developed an expanding ulcer on the right shin at an area of minor trauma (**Figure 1D)**. After 9 months of pembrolizumab, he developed immune-mediated colitis diagnosed by flexible sigmoidoscopy with biopsy; pembrolizumab was stopped and he was started on oral prednisone. The ulcerations on his back and shin completely healed over two months while on the corticosteroid taper. He has remained off pembrolizumab without recurrence of his ulcerations or metastatic SCC over two years of follow-up.

Case Discussion

Pyoderma gangrenosum is a rare, ulcerative neutrophilic dermatosis which may occur in association with medications. It was previously a diagnosis of exclusion, but in 2018 validated criteria were published to establish a diagnosis of PG (**Figure 3**), [5]. Our case met criteria for PG based on a neutrophilic infiltrate on biopsy without evidence of infection, pathergy on the leg after minor trauma, pain and peripheral erythema at ulcer sites, multiple ulcerations including on the anterior leg, and improvement within a month of starting prednisone.

Two cases of PG have previously been reported in association with ipilimumab, a different type of

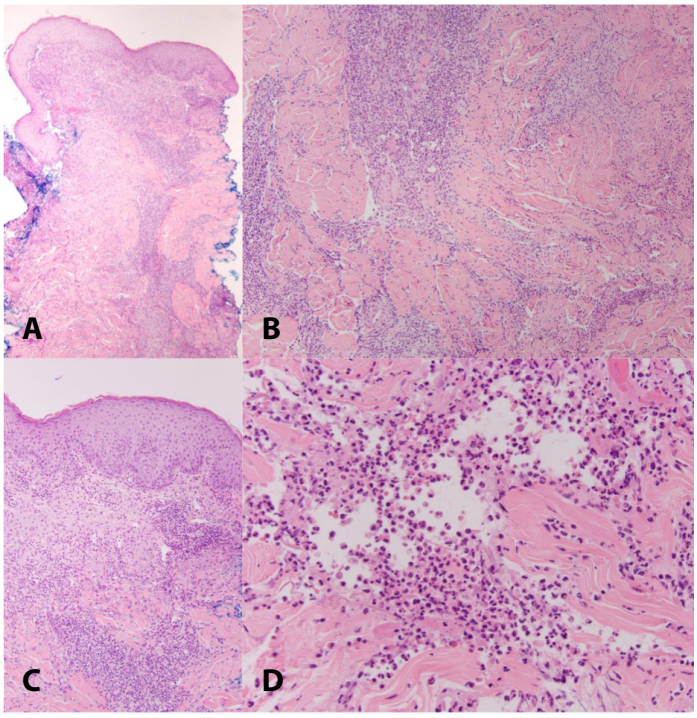

Figure 2. *Histopathology of ulcer border three weeks after onset. Punch biopsy showed florid acute and chronic inflammation in the dermis with a prominent neutrophilic component and microabscess formation. Gram, fungal, and acid-fast stains were negative for microorganisms. H&E,* ***A)*** *10×,* ***B)*** *20×,* ***C)*** *20×,* ***D)*** *40×.*

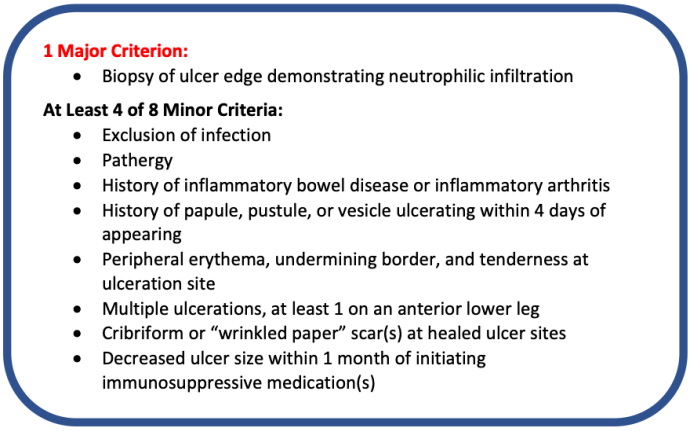

Figure 3. *Diagnostic criteria of ulcerative pyoderma gangrenosum as established by the 2018 International Delphi Consensus [5].*

checkpoint inhibitor which blocks binding to cytotoxic T lymphocyte-associated protein four [4]. This case suggests that PG can also occur with pembrolizumab therapy. Prior reported cases of ipilimumab-associated PG occurred 16 weeks after treatment initiation [4]. Our case occurred in similar time frame—approximately 5 months after pembrolizumab was started.

The mechanisms by which the PD1 inhibitors may trigger neutrophilic dermatoses or PG and its association with anti-tumor efficacy remain unclear. Although it has previously been suggested that PG is a disorder of innate immune dysregulation and altered neutrophil chemotaxis [6], there is evidence that T cells may play an important role in the pathogenesis of PG. Early lesions show a T cell, rather than neutrophil-dominant infiltrate and clonal expansion of T cells has been identified in the skin and circulation of patients with PG [7,8]. Alterations in T-cell immune tolerance induced by PD1 inhibitors may lead to T cell-mediated autoimmunity and the subsequent development of PG.

Notably, our patient presented with immune checkpoint inhibitor-induced colitis two months after onset of PG. Immune-mediated colitis is histologically similar to inflammatory bowel disease (IBD) but has more neutrophilic inflammation [9]. Future studies evaluating whether checkpoint inhibitor-associated neutrophilic dermatoses are associated with other immune-related adverse events would help to predict whether patients who present with neutrophilic dermatoses are at greater risk of additional organ system involvement and should be monitored more closely. An underlying predisposition may put some patients on checkpoint inhibitors at greater risk of developing both PG and other immune-related adverse events such as colitis.

Unless life threatening, cutaneous reactions of immune checkpoint blockade are ideally managed without stopping therapy. In our reported case, the PG ulcerations continued to expand despite treatment with intralesional corticosteroids and local wound care. The lesions did not resolve until pembrolizumab was stopped and systemic corticosteroids initiated after onset of colitis. However, dapsone, colchicine, and minocycline were potential future treatment options and may be considered in other similar cases.

Conclusion

Our case suggests that pyoderma gangrenosum can be associated with pembrolizumab treatment. Future studies evaluating the frequency of PG with PD1 inhibitors, successful treatment strategies, and associated immune-related adverse events will be of benefit as the approved treatment indications for pembrolizumab and other PD1 inhibitors continue to expand.

Potential conflicts of interest

The authors declare no conflicts of interest.

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