Nivolumab-induced systemic vasculitis

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INTRODUCTION

Nivolumab is a fully human IgG4 monoclonal immune checkpoint inhibitor antibody that inhibits programmed cell death-1 receptor (PD-1), augmenting the host antitumor response.[1] Nivolumab has been associated with immune-related adverse events (irAEs)[2] such as colitis. In addition, various cutaneous adverse events have been reported and the 3 most common findings included lichenoid eruptions, eczema, and vitiligo.[3] We report a patient with squamous cell carcinoma of the right maxillary sinus on nivolumab who had vasculitis of the jejunum and leukocytoclastic vasculitis of the skin successfully treated with high-dose systemic steroids and plasma exchange.

Abbreviations used:

Ab:	antibody
CT:	computerized tomography
CTLA-4:	cytotoxic T-lymphocyte—associated protein 4
irAEs:	immune-related adverse events
PD-1:	programmed cell death-1 receptor

CASE REPORT

A 62-year-old man with squamous cell carcinoma of the right maxillary sinus underwent right radical maxillectomy, right neck dissection, and right orbital exenteration in April 2016. Two months after the surgeries, the patient had pulmonary metastasis on imaging and was started on palliative cisplatin, fluorouracil, and cetuximab therapy. However, a repeat computerized tomography (CT) scan after 4 cycles of this therapy showed worsening cavitary and nodular metastatic lesions in the lungs bilaterally, indicating progression of disease. He was subsequently switched to nivolumab in November 2016, which was interrupted between December 2016 and March 2017 for surgical reconstruction of his forehead.

Three weeks after reinitiation of nivolumab therapy, the patient presented to the emergency room with a 3-day history of abdominal pain, nausea, vomiting, diarrhea, and rash. The rash started on his legs then spread to his thighs and trunk. He denied history of similar rashes. The patient denied fevers, chills, chest pain, dyspnea, cough, dysuria, joint pain, joint swelling, numbness, and sensory loss.

On skin examination, he had palpable and nonpalpable purpura on bilateral distal legs, popliteal fossae, posterior thighs and back (Fig 1). There was no other skin or mucosal involvement.

CT scan of the abdomen and pelvis showed marked dilatation of the proximal and midjejunum with contrast enhancement of the mucosa and wall edema, suggestive of vasculitis (Fig 2, *A*). There was no occlusion of the superior mesenteric artery.

Two punch biopsies with histopathologic examination found blood vessels in the papillary dermis with fibrinoid necrosis, neutrophils, nuclear dust, and extravasated red blood cells (Fig 3). In addition, direct immunofluorescence showed no immune reactants detected in the epidermis, dermoepidermal junction, or vessel walls for IgG, IgA, IgM, and C3. These features were consistent with leukocytoclastic vasculitis.

Laboratory results were negative for the following: hepatitis B and C serologies, quantiferon-TB gold, HIV antibody (Ab), cytomegalovirus serologies, cryoglobulin, histone Ab, antinuclear Ab, antineutrophil cytoplasmic screen, $\beta 2$ glycoprotein 1 Abs, C1q binding immune complex, myeloperoxidase Ab, proteinase-3 Ab, cardiolipin Abs, lupus anticoagulant, antiphospholipid Abs, and rheumatoid factor.

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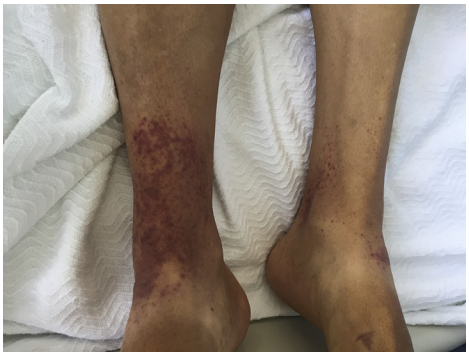

Fig 1. Palpable and nonpalpable purpura on bilateral distal legs. The right side is worse than the left side.

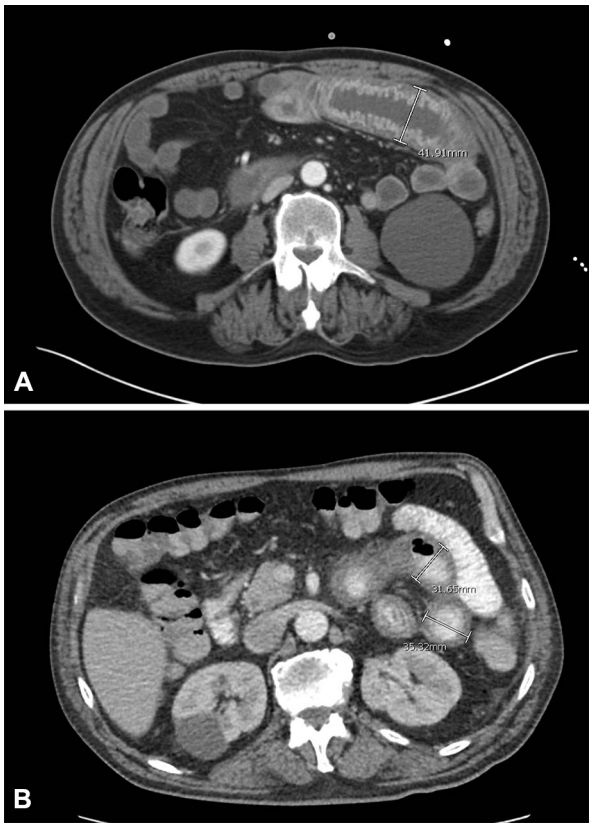

Fig 2. A, CT of the abdomen and pelvis with contrast showed marked dilatation of the proximal and midjejunum, up to 4.2 cm, with contrast enhancement of the mucosa and wall edema. **B**, A repeat CT angiogram of the abdomen after 2 days of plasma exchange and high-dose methylprednisolone showed decrease in jejunal dilatation.

The combined history, clinical examination, and study findings strongly suggested the diagnosis of nivolumab-induced systemic vasculitis.

The patient received intravenous methylprednisolone, 1000 mg/d for 3 days, which was decreased to 50 mg for 2 days, then switched to oral prednisone. Oral prednisone was started at 60 mg/d with plans for a slow taper. He also received plasma exchange for the first 2 days to remove circulating nivolumab and thus reduce the likelihood of subsequent bowel perforation. After 2 days of high-dose methylprednisolone and plasma exchange, he showed radiographic improvement (Fig 2, *B*). At the time of discharge, symptoms of nausea, vomiting, and diarrhea had resolved. Purpura and petechiae were almost completely resolved. After a 1-week inpatient stay, he was discharged home in a stable condition.

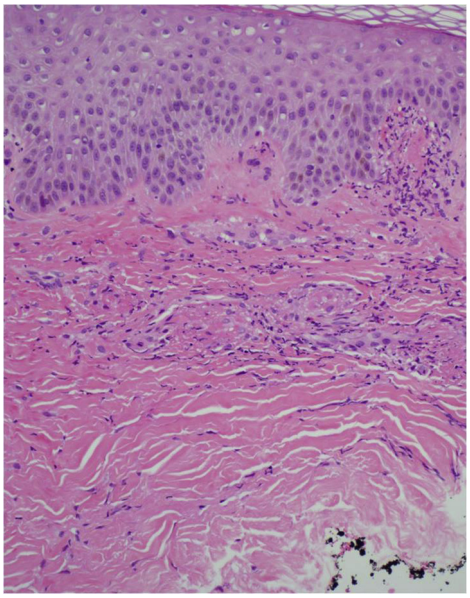

Fig 3. Several blood vessels in the papillary dermis show fibrinoid necrosis, neutrophils, nuclear dust, and extravasated red blood cells. (Hematoxylin-eosin stain.)

DISCUSSION

Approved by the US Food and Drug Administration for the treatment of melanoma, classical Hodgkin lymphoma, colorectal cancer, non–small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma,[4] nivolumab is increasingly used in oncology. The checkpoint inhibitors, including PD-1 and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitors, block co-inhibitory immune checkpoint molecules, turning the immune system against the tumor. However, this disruption of immune homeostasis can result in an unchecked immune response, possibly explaining the association of checkpoint inhibitors with irAEs. In general, irAEs with PD-1 inhibitors seem to be less common and less severe when compared with those caused by CTLA-4 inhibitors.[2,5,6] For example, grade 3 or 4 colitis is rare in patients treated with PD-1 blockade, reported in only 1.4% to 2.5% of such

patients as opposed to 7% in patients treated with a CTLA-4 inhibitor.[2,6] A wide spectrum of cutaneous adverse events with the use of PD-1 inhibitors has been reported, including morbilliform drug eruptions, pruritus, vitiligo, eczema, sarcoidosis, lichenoid eruptions, bullous pemphigoid, dermatitis herpetiformis, and psoriasiform dermatitis.[3,7,8] Some of these cutaneous adverse events, including pruritus, vitiligo, and eczema, have also been reported in patients taking a CTLA-4 inhibitor. In addition, these patients also had erythema multiforme, folliculitis, acneiform eruption, and Stevens-Johnson syndrome.[9]

Management of checkpoint inhibitor—induced irAEs varies depending on the grade of toxicity according to the Common Terminology Criteria for Adverse Events defined by the National Cancer Institute (1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = death related to toxicity). Grade 1 or 2 adverse events may be managed symptomatically or with topical medications for cutaneous reactions. Grade 3 or 4 adverse events such as colitis may require hospital admission, high doses of systemic steroids, or other immunosuppressive agents such as infliximab.[10]

Across clinical trials of nivolumab either as a single therapy or in combination with a CTLA-4 inhibitor, less than 1% of patients went on to have vasculitis.[7] With PD-1 pathways inhibited, antigen-presenting cells may provide insufficient negative signaling leading to nonphysiologic, and even pathologic sustained T-cell activation that may contribute to B-cell activity, increasing antibodies available for immune complex deposition or providing highly activated T cells to infiltrate and damage the walls of small vessels. Systemic vasculitis caused by nivolumab therapy involving both the small bowel and the skin, as seen in our patient, has not been reported to date. As the use of checkpoint inhibitors continues to increase, clinicians should be able to recognize the wide spectrum of associated adverse events.

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