Nivolumab associated vasculopathy: A novel mechanism

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapeutics by targeting key mechanisms by which tumor cells evade immunosurveillance. Monoclonal antibodies, which blockade cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1) or its ligand (PD-L1) were initially found to improve survival in metastatic melanoma, but are now approved for treatment of a variety of cancers.

The blocking of immune checkpoints increases both the number of cytotoxic T lymphocytes and their clonal diversity, which enables an enhanced immune response against cancerous cells.[1] In a few predisposed individuals, this also enables loss of physiologic self-tolerance and, consequently, immune-related adverse events (irAEs). The anti-CTLA-4 monoclonal antibody, ipilimumab, has been associated with the most irAEs, including diarrhea, colitis, hepatitis, and cutaneous reactions.[2,3] The anti-PD-1 monoclonal antibodies, pembrolizumab and nivolumab, have also been associated with similar reactions but with lesser frequency and severity.[1-3] With the increased usage of ICIs in the treatment of cancers, it is of the utmost importance that clinicians are aware of and monitor for irAEs, of which the spectrum continues to expand. We present a novel cutaneous irAE presenting as multifocal ulceration and eschar formation secondary to cutaneous small-vessel vasculopathy associated with nivolumab.

Abbreviations used:

ICI(s):	immune checkpoint inhibitor(s)
CTLA-4:	cytotoxic T-lymphocyte antigen-4
PD-1:	programmed cell death protein 1 (PD-1) or its ligand (PD-L1)
irAE(s):	immune-related adverse event(s)

CASE REPORT

A 45-year-old Caucasian woman with metastatic melanoma presented to the inpatient dermatology service with painful retiform purpura and associated ulcerations on her trunk and extremities. She had a history of a pT1a melanoma status post wide local excision 8 years ago. Four months prior to presentation, she discovered an expanding axillary mass prompting computed tomography and positron emission tomography. Subsequent axillary node biopsy confirmed metastatic melanoma. Shortly thereafter, she was initiated on high-dose nivolumab single-agent therapy (240 mg every 2 weeks). It was after her fourth cycle of nivolumab that she presented to our service with painful, dusky, indurated plaques on her breasts, lower portion of the abdomen, proximal parts of the legs, and buttocks, covering approximately 30% of her total body surface area (Fig 1). Initial punch biopsies from the left side of the abdomen showed epidermal necrosis with coagulative necrosis of small vessels and necrosis of eccrine coils. Frank thrombosis of dermal vessels was not visualized at that time.

Eleven days later, she again presented to our service, where it was found that the original dusky areas had evolved into ulcerations with overlying eschars. Repeat incisional biopsies showed extensive epidermal and dermal necrosis with an interstitial dermal neutrophilic infiltrate and small-vessel thrombotic vasculopathy (Fig 2). Laboratory tests, including polymerase chain reaction for SARS-CoV-2, Factor V Leiden, c-antineutrophil

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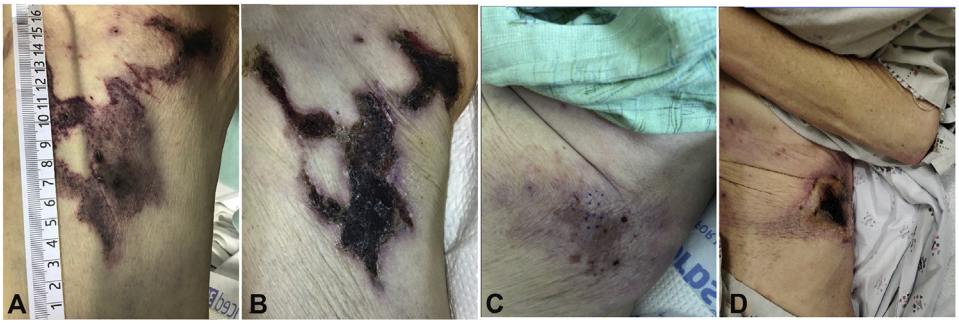

Fig 1. Clinical images depicting the progression of the patient's cutaneous lesions. Violaceous indurated plaques with few areas of ulceration on the anterior upper aspect of the patient's right leg on readmission **(A)** and their progression to eschars **(B)**. A similar lesion was observed on the patient's left flank **(C)**, and its progression over the course of 2 weeks is seen in **(D)**. Similar lesions were present on the upper portion of the patient's left leg, right flank, both buttocks, and both breasts.

cytoplasmic antibodies/p-antineutrophil cytoplasmic antibodies, prothrombin time/partial thromboplastin time/international normalized ratio, protein C and S levels, antiphospholipid antibodies, cryoglobulins, cryofibrinogens, and complement levels were unremarkable. A peripheral blood smear failed to reveal schistocytes or any evidence of a hypercoagulable state. Repeat blood cultures, tissue stains for bacterial, fungal, and mycobacterial organisms were consistently negative. The patient showed no evidence of renal compromise, and Von Kossa tissue stain of an incisional biopsy specimen showed no evidence of calciphylaxis. Given the timing of the lesions and exclusion of other etiologies, nivolumab therapy was determined as the cause of her vasculopathy and was subsequently held. Apixaban was initiated, resulting in the cessation of new lesion formation and halting the progression of her current lesions. Unfortunately, due to radiographic evidence of continued progression of her melanoma, she was discharged on hospice.

DISCUSSION

The most common irAEs are cutaneous, occurring in 30% to 40% of patients on anti-PD-1/PD-L1 monotherapy and 47%-68% of patients on anti-CTLA-4 monotherapy.[4] The majority of cutaneous reactions are mild and classified grade 1 or 2 by the Common Terminology Criteria for Adverse Events.[1,4] Severe reactions, grade 3 or higher, occur in approximately 2% to 3% of patients on ICI monotherapy and 4% to 10% of patients on ICI combination therapy.[1] Only a handful of instances of ICI-associated vasculitis have been reported. Castillo et al,[5] Tomelleri et al,[6] and Ho et al[7] have reported cases of cutaneous leukocytoclastic vasculitis.[5-7] However, there is only one reported case of ICI-associated vasculopathy, namely the one by Aburahma et al[8] who described a case of a 71-year-old man who developed antiphospholipid syndrome secondary to nivolumab monotherapy.[8] They reported prolonged prothrombin time, activated partial thromboplastin time, and the presence of an antiphospholipid antibody.[8]

On multiple occasions our patient had unremarkable laboratory findings with regard to prothrombin time, activated partial thromboplastin time, international normalized ratio, full hypercoagulable workup (including antiphospholipid antibodies), peripheral blood smears, and blood and tissue cultures. This, in conjunction with the paucity of reported cases of ICI-associated vasculopathy, contributed to a delay in confirming the diagnosis. While no mechanism has been elucidated, it is clear given the histopathologic findings and exclusion of other causes of vasculopathy that nivolumab is implicated. Of note, a necrotizing vasculitis with secondary thrombus formation was considered. However, the neutrophils displayed an interstitial pattern, suggesting that their presence was secondary to necrosis, rather than a within-vessel pattern as would be seen in vasculitis. The possibility of a concurrent vasculitis/vasculopathy was also considered; however, the patient responded to anticoagulation therapy without requiring immunosuppression, further supporting the diagnosis of vasculopathy. The clinical presentation, which included retiform purpura with subsequent eschar formation, also supports this diagnosis.

In summary, we present the second case, to our knowledge, of immunotherapy-associated small-vessel vasculopathy. Though a direct mechanism was not identified, the temporal association with the initiation of immunotherapy and response to cessation of treatment supports an etiologic role. Vasculopathy should therefore be included in the increasingly growing list of

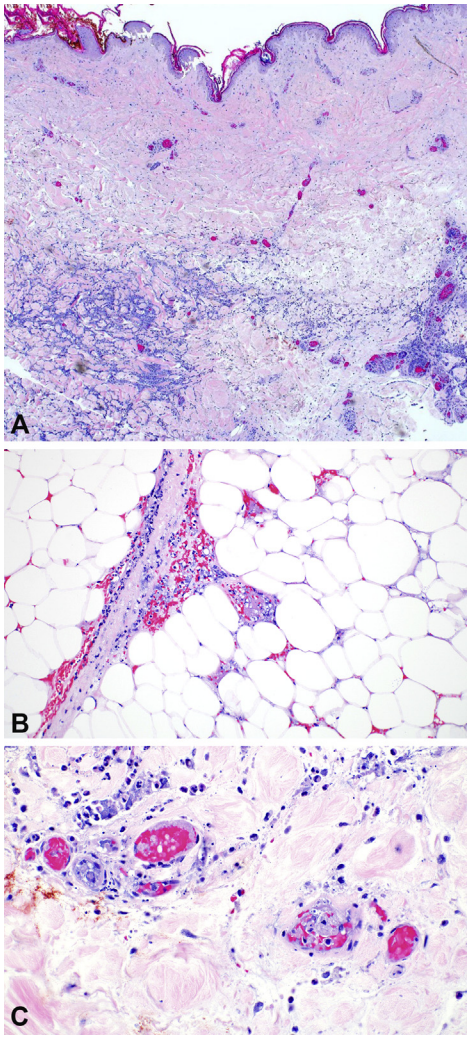

Fig 2. A, Histopathologic images displaying extensive epidermal and dermal necrosis with an associated scattered infiltrate of interstitial neutrophils. **B,** Small vessels with fibrin microthrombi as well as neutrophilic infiltrates in the subcutaneous septae. **C,** Small vessels in the mid dermis with vascular congestion and early fibrin microthrombi. A neutrophilic infiltrate is observed within the interstitial space, but it does not involve vessel walls (Hematoxylin-eosin—stained tissue sections; original magnifications: **A,** ×40, **B,** ×100, and **C,** ×400, respectively).

cutaneous irAEs, and, if detected, prompt anticoagulation should ensue.

Conflicts of interest

None disclosed.

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