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Nivolumab-Induced Cutaneous Medium-Vessel Vasculitis in a Patient with Metastatic Melanoma: A Case Report and Literature Review

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Abstract

An immune checkpoint inhibitor-associated vasculitis is an exceedingly rare occurrence. We describe a case of cutaneous vasculitis developing in a patient with metastatic melanoma who presented with non-classic clinical findings of tender indurated erythematous plaques with overlying scale on the bilateral shins four months after starting adjuvant nivolumab therapy. The patient had improvement with prednisone treatment, but developed recurrence of the lesions following the prednisone taper. A biopsy of the right lower extremity revealed a medium-vessel vasculitis, an uncommon immune-related adverse event of nivolumab therapy. Treatment with a ten-week prednisone taper and intralesional triamcinolone injections led to complete resolution, and nivolumab was held indefinitely.

Introduction

Advances in our understanding of the pathogenesis of melanoma have led to the approval of ipilimumab, an anti-CTLA-4 antibody, as well as nivolumab and pembrolizumab, anti-PD-1 antibodies, for the treatment of advanced melanoma. These agents upregulate T-cell activity by blocking immune checkpoints, driving immunity to tumor-associated antigens, and leading to tumor reduction or resolution [1]. Immune checkpoint inhibitors (ICI) have revolutionized the management of patients with metastatic melanoma, making tumor regression possible in nearly 50% of patients, compared to a historical less than 10% [2]. However, toxicity resulting from T-cell overstimulation remains a significant concern. ICI expose patients to a number of immune-related adverse events (irAEs), including common toxicities of the dermatologic, gastrointestinal, and endocrine systems, as well as rarer toxicities of the neurological, cardiovascular, and pulmonary systems, which can be fatal [3]. Among dermatologic manifestations, the frequency of ICI -induced cutaneous vasculitis is lower than that of other irAEs, and information about this condition remains limited. Herein, we present a case of a cutaneous medium-vessel vasculitis following PD-1 inhibitor immunotherapy, which was successfully managed with systemic and intralesional steroids.

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Case presentation

An 87-year-old female presented to her primary care physician after self-detecting an asymptomatic nodule on her scalp. A shave biopsy was performed, and histopathology identified nodular malignant melanoma at least 2.2 mm Breslow depth with no ulceration, no perineural invasion, no microsatellites, 11 mitoses/mm^2, positive lateral and deep margins, and a positive BRAF V600E activating mutation. The patient underwent wide excision with full-thickness skin graft of the left posterior scalp and sentinel lymph node biopsy of the left upper neck, which revealed a positive node. The final diagnosis was clinical stage IIA and pathologic stage IIIC melanoma (pT3a, pN2c, cM0). The patient received adjuvant treatment with monthly nivolumab.

Four months after starting nivolumab, the patient presented to her primary care physician with tender indurated erythematous plaques with overlying scale on the bilateral shins. She was prescribed 0.05% fluocinonide ointment to use twice daily. However, her cutaneous findings were unchanged when she presented to oncology one month later (**Figure 1A-B**). At this time, she had no fevers, chest pain, cough, dyspnea, abdominal pain, hematochezia, arthralgias, or neuropathies. PET scan was notable for multiple foci of increased uptake within the dermal and subcutaneous layers of the bilateral lower extremities, as well as hilar, mediastinal, and supraclavicular adenopathy, and scattered ground-glass opacities in the bilateral lung bases. PET findings were attributed to an intense immune response in the setting of immunotherapy. MRI of the brain was without evidence of metastatic disease. Laboratory tests, including CBC and CMP, were unremarkable, hepatitis B surface antigen and hepatitis C antibodies were undetectable, and urinalysis was without proteinuria. Nivolumab was held after the fifth cycle due to grade two cutaneous toxicity. She was treated with 30 mg of prednisone daily for one week, and the lesions significantly improved. Prednisone was tapered by 10 mg per week, but the nodules recurred and progressed after she finished the course.

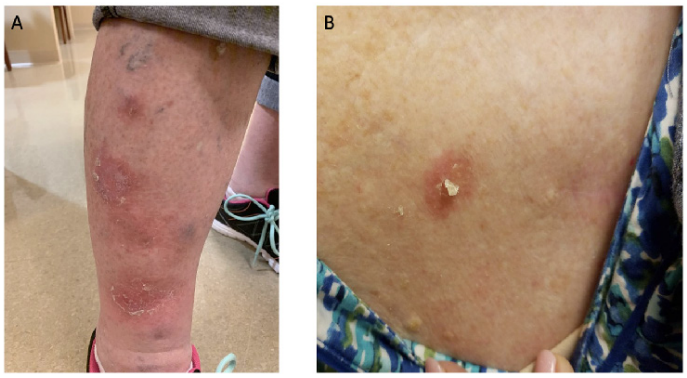

Figure 1: Indurated erythematous plaques with overlying scale were present on the bilateral shins.

The patient was referred to dermatology and a punch biopsy of the left lateral calf was performed. She was restarted on a 10 mg daily dose of prednisone, and once again the lesions recurred when she had tapered to 5 mg. Biopsy results revealed a medium-vessel vasculitis with overlying pseudoepitheliomatous hyperplasia, mixed inflammation, and fat necrosis with suppuration (**Figure 2A-C**). PAS, gram, and AFB stains were negative for microorganisms. Given the timing of onset of her lesions in relation to the initiation of immunotherapy and the pathology findings, her vasculitis was attributed to nivolumab therapy. Nivolumab was therefore discontinued indefinitely. Nine nodules on the bilateral shins were treated with 10 mg/mL in tralesional triamcinolone injections, and she began a slow prednisone taper starting at 10 mg daily over ten weeks. Three nodules were treated with a second round of triamcinolone injections three months later. Subsequently, the cutaneous vasculitis completely resolved and has since remained quiescent.

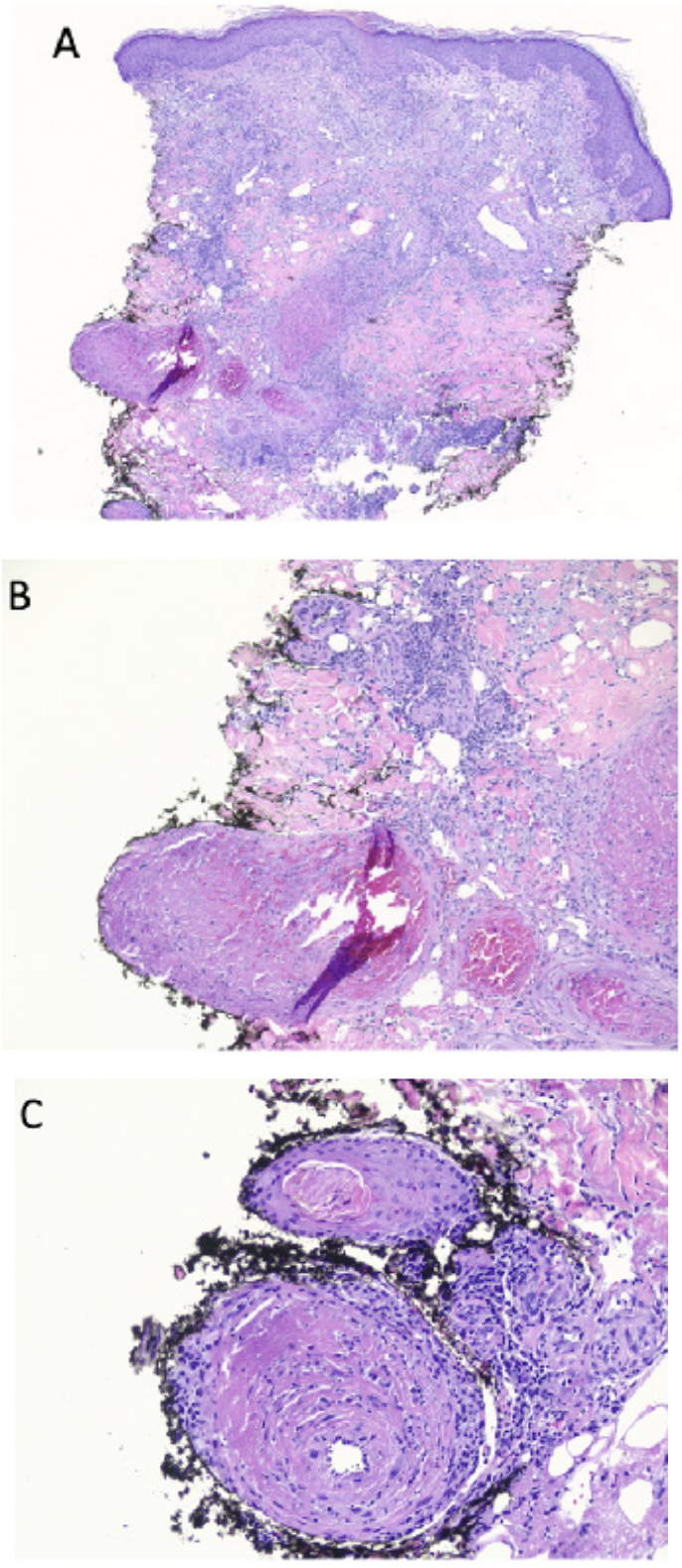

Figure 2: Punch biopsy demonstrated medium-vessel vasculitis with overlying pseudoepitheliomatous hyperplasia, mixed inflammation, and fat necrosis with suppuration.

Discussion

ICI have become the standard of care for patients with metastatic melanoma, and their increased frequency of use has led to new types of irAEs continuously arising. The most common irAEs are cutaneous, seen in up to 40% of patients on anti-PD-1 monotherapy and up to 68% of patients on anti-CTLA-4 monotherapy [4]. Cutaneous manifestations are graded 1 if they are asymptomatic, 2 if they are responsive to conservative measures, 3 if aggressive treatment is required, 4 if hospitalization is required, and 5 if death results [5]. Despite the frequency of cutaneous side effects, the incidence of immune-mediated vasculitis is uncommon, and nivolumab specifically has been associated with a less than 1% risk of vasculitis across clinical trials [6].

A previous systematic review of the literature has demonstrated 20 confirmed clinical cases of vasculitis after administration of ipilimumab (n=8), pembrolizumab (n=6), or nivolumab (n=5) [7]. The most common cancer type associated with immune-mediated vasculitis was melanoma, and most patients had either large-vessel vasculitis or vasculitis of the nervous system. There were only two cases of medium-vessel vasculitis induced by nivolumab, an isolated vasculitis of the peripheral nervous system and an asymmetric vasculitic neuropathy. To our knowledge, this is the first case to demonstrate a nivolumab-induced medium-vessel vasculitis with purely cutaneous manifestations.

The pathogenesis of ICI-induced vasculitis remains unclear, though it has been suggested that immune checkpoint signals may play a role in maintaining the immunoprivileged status of blood vessels [8]. All patients presenting with suspected cutaneous vasculitis should be evaluated for a concomitant systemic vasculitis with a complete blood count, creatinine, sedimentation rate, liver function tests, urinalysis, and chest x-ray [9]. It is critical that physicians be able to distinguish ICI-induced vasculitis from paraneoplastic vasculitis, such that they can manage patient symptoms most appropriately and safely in the setting of malignancy. Paraneoplastic vasculitis can be seen in patients with melanoma, but these cases resolve with chemotherapy or tumor resection. In contrast, ICI-induced vasculitis, as was seen in our patient's case, resolves following discontinuation of immunotherapy and treatment with corticosteroids.

In this case, we demonstrate a temporal relationship between the start of ICI therapy and the onset of a medium-vessel vasculitis with classic histological findings but a non-classic clinical presentation. The patient's symptoms resolved after discontinuation of immunotherapy and treatment with both systemic and intralesional corticosteroids. This case highlights the need for physicians to have a high index of clinical suspicion for vasculitis in a patient presenting with indurated erythematous plaques in the setting of ICI therapy. Early recognition is critical because immunotherapy must be held for cutaneous toxicity of grade 2 or higher, and physicians must promptly biopsy the lesions and initiate treatment with corticosteroids to avoid severe complications [6]. Vasculitis is a rare phenomenon associated with ICI, and our aim through this case report is to highlight the need to further investigate its pathogenesis as well as to facilitate physician recognition to prevent adverse patient outcomes.

Conflicts of interest: The authors declare no conflict of interest.

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