Leukocytoclastic Vasculitis-Induced Lower Leg Ulceration in the Course of Immune Checkpoint Inhibitor Therapy for Advanced Malignant Melanoma: A Case Report

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Abstract

Immune checkpoint inhibitors (ICIs) have expanded therapeutic options for advanced malignancies, offering new hope for conditions once deemed untreatable. However, the advent of ICIs has introduced a spectrum of immune-related adverse events (irAEs), including leukocytoclastic vasculitis (LCV), a rare but significant complication. This case report describes development of LCV after treatment with nivolumab and ipilimumab in a 70-year-old man with malignant melanoma, highlighting the diagnostic and management challenges of such irAEs. Despite extensive investigation, conventional pathology failed to identify the immune complexes typically associated with LCV. The clinical presentation, alongside a detailed medical history and the exclusion of infections, medications, and autoimmune diseases, was crucial in establishing a diagnosis. Ulcer resolution following discontinuation of ICI therapy and initiation of steroids further support the conclusion that LCV was an irAE in this patient. This case underscores the need for vigilant monitoring for irAEs for the variable onset after ICI therapy and the importance of thorough history-taking to guide diagnosis and treatment. With ICIs becoming increasingly prevalent in oncology, the incidence of ICI-induced ulcers like LCV is expected to rise, necessitating heightened awareness and multidisciplinary approaches to patient care.

Keywords: Immune checkpoint inhibitors; Leg ulcer; Leukocytoclastic vasculitis; Case reports

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic landscape for a range of advanced malignancies, including non-small cell lung cancer and urothelial cancer, marking a significant shift in the treatment of conditions previously considered unresponsive to existing therapies [1]. This innovation extends to the field of dermatologic surgery, where agents such as pembrolizumab, nivolumab, and ipilimumab have become integral in management of advanced malignant melanoma. Unfortunately, adverse events related to such immune modulation, known as immune-related adverse events (irAEs), encompass a broad spectrum of adverse effects affecting multiple organ systems as a result of activation of immune pathways.

The most common irAEs are fatigue and dermatological conditions such as erythema, with symptomatology varying based on the specific ICI used [1]. Manifestations resembling rheumatoid conditions are noted in 1%–10% of patients treated with ICIs, whereas vasculitis is considerably less common [2]. This report describes a case in which lower leg ulcers developed as a rare manifestation of vasculitis in the context of...
ICI therapy, underscoring the critical need for awareness and understanding of this potential complication. Consent was acquired from the patient for the use of his images and data in this case report.

Case

The patient was a 70-year-old man under the care of the department of plastic and reconstructive surgery, diagnosed with malignant melanoma on his left great toe. Three years earlier, he had undergone wide local excision of the primary lesion along with dissection of the left inguinal lymph nodes. Histopathology confirmed malignant melanoma with more than 1% PD-L1 expression and no evidence of \textit{BRAF} mutation.

ICI therapy with pembrolizumab was initiated 2 months postoperatively as adjuvant treatment. The patient received 12 cycles at 200 mg every 3 weeks, with an escalated dose of 400 mg for the 13th and 14th cycles. Six months into the therapy, intransit metastases developed on the ipsilateral thigh. Despite repeated local excisions and ongoing pembrolizumab treatment, including an increased dosage, the lesion remained uncontrolled.

\textbf{Fig. 1.} Clinical photographs during the clinical course. (A) The patient’s right lower leg in the 4th week following the second cycle of nivolumab and ipilimumab during the second treatment attempt, showing relatively clear skin before onset of symptoms. (B) Progression of the patient’s condition 1 week subsequent to the time point shown in (A), highlighting development of significant purpura on the right lower leg. (C) The patient’s right lower leg 2 months following cessation of nivolumab and ipilimumab therapy. The purpura has resolved but persistent ulcers are evident.
Subsequently, due to apparent resistance to pembrolizumab, the treatment was replaced with a combination of nivolumab 80 mg and ipilimumab 200 mg. After two cycles of this regimen, growth of the local lesion was arrested. Unfortunately, the patient's treatment course was complicated by development of colitis and pneumonitis, suggesting irAEs.

A trial of dacarbazine was undertaken but was soon discontinued because of lack of efficacy, leading to cessation of all pharmacological treatments. Palliative radiation therapy was then initiated.

Given the previous partial response, in consultation with oncologists, the patient elected to retry nivolumab and ipilimumab combination therapy. However, following two additional cycles, the irAEs recurred, necessitating discontinuation of the ICIs. In the third year following the initial surgery, and within 5 weeks following the second additional cycle, multiple poorly demarcated purpura with elevated lesions appeared on the contralateral side. These lesions had not been present at 4 weeks from the completion of the second cycle. Therefore, a punch biopsy was performed (Fig. 1A and B). The biopsy revealed neutrophilic infiltration around dermal vessels, extravasation of red blood cells within dermal collagen fibers, and

**Fig. 2.** Histopathological findings of the wound biopsy. A histopathological image of hematoxylin and eosin staining at ×40 magnification demonstrating infiltration of neutrophils around the dermal vessels, extravasation of red blood cells in the dermal collagen fibers (arrows), and nuclear dust (arrowheads) consistent with leukocytoclastic vasculitis.

**Fig. 3.** Clinical photograph of the right shin post skin graft surgery. One month after surgery, the split-thickness skin graft has demonstrated successful engraftment. Lesions distal to the graft site have healed, resulting in scar formation.
nuclear dust. These findings are characteristic of leukocytoclasia, which is a hallmark of the pathological diagnosis of leukocytoclastic vasculitis (LCV) (Fig. 2). No melanoma markers or autoantibodies were detected by immunohistochemistry. The LCV was clinically attributed to ICI therapy.

Two months following cessation of ICIs and a brief course of steroid therapy, the purpura resolved, but the ulcers persisted (Fig. 1C). The ulcers were subsequently managed with wound bed preparation and closure by skin grafting (Fig. 3).

**Discussion**

ICIs function as antagonists targeting CTLA-4 or PD-1 receptors. CTLA-4 is an inhibitory receptor on T lymphocytes and downregulates the immune response [3]. Similarly, PD-1 interacts with its ligands, PD-L1 and PD-L2, to modulate the immune system [3]. By inhibiting these receptors, ICIs can potentiate the activity of T lymphocytes against malignant neoplasms, albeit with an increased risk of provoking autoimmune disorders [1]. Common skin involvement, accounting for more than 30% of irAEs and presenting as maculopapular rash, dermatitis, itching, and depigmentation, is generally mild and does not require cessation of therapy [4,5]. In contrast, vasculitis, a rare irAE with a frequency of less than 1%, typically requires discontinuation of ICIs [6].

Daxini et al. [7] have documented that ICI-associated vasculitis can involve vessels of any size and that the onset can vary significantly from the first to 15th cycle of treatment, with a median onset of 3 months.

LCV results from deposition of immune complexes in small venules of the skin and is triggered by various factors, including infections, medications, microorganisms, viruses, autoantibodies, and chronic hepatitis [8]. It typically manifests as palpable purpura located primarily in the upper layers of the skin in gravity-dependent areas, such as the lower limbs, buttocks, and back, while internal organ involvement is rare [8].

Characteristic pathological features of LCV include deposition of multinucleated white blood cells, extravasation of red blood cells, fibrinoid necrosis, and leukocytoclasia (i.e., nuclear dust formed from destruction of multinucleated cells) [8].

The differential diagnosis includes paraneoplastic vasculitis, which is vasculitis occurring in association with malignant neoplasms, particularly hematologic cancers [1]. This type of vasculitis often develops within a year of cancer diagnosis and frequently involves the skin [9].

In our case, LCV may have developed in response to factors such as infection, medication, or malignancy. In terms of medication history, the patient was taking gabapentin, a calcium channel blocker, a proton pump inhibitor, apixaban, nicorandil, tamsulosin, and steroids; however, none of these medications had been recently initiated. Serological tests for hepatitis virus were negative, and no other findings indicative of bacterial infection were observed. An autoantibody screen for autoimmune disease was negative. Despite thorough pathological evaluation, immune complexes, which were suspected as a causative factor, were not identified. According to Sams [10], the pathology of this condition is markedly dynamic, and the window for accurately identifying the immune cause is confined to 18–24 hours after onset of symptoms. Samples obtained too soon might not reflect the relevant changes, while those obtained after this critical period may have undergone phagocytosis, rendering the true etiology elusive in a clinical setting.

In our case, based on the clinical history and presentation, we concluded that the LCV was an irAE induced by nivolumab and ipilimumab. Consequently, these agents were discontinued, and immunosuppressive therapy with steroids was initiated. The actual onset of the irAE is presumed to have occurred in the 5th week after the completion of the second cycle of combination therapy. The ulcers did not recur following treatment. The clinical course further indicated that the ulcers were a result of vasculitis as an irAE. Consistent with other literature, cessation of ICIs and the initiation of steroids were necessary for treatment [5,6,11-13]. Additional immunosuppressive therapy may also be warranted depending on the severity and progression of the patient’s response [11].

While this case contributes important clinical observations regarding the irAEs of ICI therapy, its findings are limited by the constraints of a single case study. The direct causality between the ICIs and LCV, though suggested by clinical outcomes, remains hypothetical without further corroborative studies. Future research with larger subject groups is necessary to validate these conclusions.

In conclusion, given the growing indications for ICIs and their growing prevalence in the treatment of various types of malignancy, it is anticipated that there will be an increase in the incidence of ulcers induced by these agents. As pathology alone may not pinpoint the etiology, meticulous history-taking that includes the timing of symptom onset, medication history, and accompanying illnesses is imperative for accurate diagnosis of the cause of the ulcers.
Conflict of interest

No potential conflict of interest relevant to this article was reported.

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