Erythema nodosum-like panniculitis associated with immune checkpoint inhibitor therapy: Two cases reporting a rare cutaneous adverse event

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INTRODUCTION

Erythema nodosum (EN) is the most common form of panniculitis and typically presents as painful erythematous nodules on the shins, and may be associated with systemic symptoms including fever and arthralgia.[1,2] Histopathology demonstrates septal panniculitis with an inflammatory infiltrate, which includes neutrophils in the early stage and lymphocytes and multinucleated giant cells in the late stage.[1] A wide variety of etiologies are associated with EN, including infections, sarcoidosis, rheumatologic disorders, inflammatory bowel disease, autoimmune disorders, medications, and malignancies.[1,2] Recently EN-like panniculitis has been reported as a rare cutaneous adverse effect in association with immune checkpoint inhibitors (ICPis).[3-6] In this report, we present 2 additional patients who developed EN-like panniculitis in the setting of ipilimumab and nivolumab and pembrolizumab treatment, respectively, and review the clinical and histologic presentations, impact on cancer therapy, and response to treatment.

Abbreviations used:

EN: erythema nodosum
ICPi: immune checkpoint inhibitor

CASE DESCRIPTIONS

Case 1

A 50-year-old woman with vulvar melanoma treated with ipilimumab and nivolumab for 4 months and subsequently nivolumab monotherapy for 6 months presented with painful erythematous nodules on the left ankle and right shin. On examination, several red, tender subcutaneous nodules on the lower parts of both legs were observed (Fig 1). A review of systems was negative for fever, arthralgias, pharyngitis, and other upper respiratory symptoms, and there were no changes in her medications. A punch biopsy of the right leg demonstrated thickening of septa within the adipose tissue with focal granulomas and an inflammatory infiltrate composed of lymphocytes, histiocytes, and occasional neutrophils, consistent with EN-like panniculitis (Fig 2, *A* and *B*). Laboratory tests for antinuclear antibodies, C-reactive protein, erythrocyte sedimentation rate, and hepatitis B and C were all negative. Special stains were negative for fungi, acid-fast bacilli, and bacteria, and tissue cultures were negative for bacterial, fungal, and atypical mycobacterial organisms. Chest x-ray appeared normal and specifically revealed no hilar lymphadenopathy. A trial of high-potency topical steroid ointment (augmented betamethasone dipropionate 0.05%) was prescribed for 2-3 weeks with clinical resolution of the nodules. She remained on therapy with nivolumab without recurrence. She eventually developed distant metastases and her therapy was changed to regorafenib.

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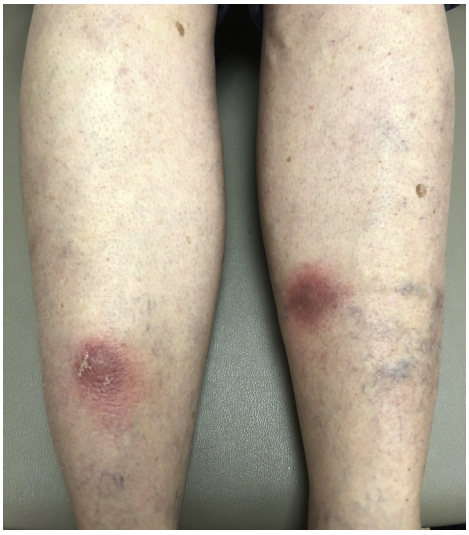

Fig 1. Clinical image of erythema nodosum-like panniculitis associated with immune checkpoint inhibitor therapy. Erythematous, tender nodules and plaques on both lower extremities.

Case 2

A 73-year-old woman with metastatic renal cell carcinoma who had received pembrolizumab for 7 weeks and axitinib for 3 weeks presented with a painful eruption on the bilateral legs. She first noted swelling of the left ankle, which was followed by swelling of the right ankle followed by painful erythematous lesions on the lower parts of both legs. Her leg pain became severe, and she required a walker for ambulation. She denied fever, chills, arthralgias, or other systemic symptoms, including pharyngitis and other upper respiratory symptoms, with the exception of recent weight loss. There were no other medication changes. On examination she had red, tender nodules and plaques on the bilateral shins, dorsal feet, and calves. Laboratory tests for antinuclear antibodies, C-reactive protein, erythrocyte sedimentation rate, serum angiotensin converting enzyme, tuberculosis, and hepatitis B and C were all negative. A telescoping punch biopsy of the left lower leg demonstrated unremarkable epidermis and dermis with thickened fibrous septae in the subcutis and a lymphohistiocytic infiltrate consistent with EN-like panniculitis. A computed tomography scan of the chest showed no hilar lymphadenopathy. Tissue cultures were obtained and were negative for bacterial, fungal, and atypical mycobacterial organisms. The patient was started on minocycline 100 mg twice daily and clobetasol ointment 0.05% with significant improvement after several weeks without the emergence of new lesions. Following a subsequent pembrolizumab infusion, she had a severe recurrence of EN-like panniculitis requiring prednisone (40 mg taper over 2 weeks) with prompt clinical improvement. Given the severe reaction impacting quality of life and oncologic response to therapy, pembrolizumab was temporarily held with plan to restart upon clinical improvement. Axitinib therapy was continued but then held a month later due to other adverse effects including diarrhea and neurologic sequelae. Pentoxifylline 400 mg twice daily was added as adjuvant therapy with minocycline to help with symptoms of pain associated with the EN-like panniculitis. The patient also developed autoimmune neuritis as a likely immune-related adverse event, and pembrolizumab was permanently discontinued. Her most recent scans demonstrated complete response of her tumor. Unfortunately, she passed away a few months later from sudden respiratory decompensation of unknown cause.

DISCUSSION

ICPis enhance the immune system's antitumor activity but may also cause immune-related adverse events, of which dermatologic toxicities are among the most common ones.[7] Dermatologic immune-related adverse events may manifest as vitiligo-like leukoderma and various inflammatory eruptions, including lichenoid, eczematous, immunobullous, exanthematous, psoriasiform, and granulomatous patterns, and, although uncommonly, severe cutaneous adverse reactions.[7] To the best of our knowledge, only a few other cases of panniculitis associated with ICPis have been reported in the literature.[3-6]

EN-like panniculitis associated with ICPis clinically resembles EN with erythematous plaques favoring the anterior aspects of the lower extremities as seen in this report, consistent with other cases in the literature.[3-6] Interestingly, 1 patient with ocular melanoma developed EN-like panniculitis while receiving nivolumab and later developed a sarcoidosis-like syndrome.[3] Additionally, 2 other patients with ovarian cancer and melanoma developed EN-like panniculitis without sarcoidosis-like syndrome, mimicking disease recurrence while being treated with ipilimumab and nivolumab.[4] Two additional cases of granulomatous lobular panniculitis have been reported in melanoma patients receiving ICPi therapy, 1 of whom had systemic symptoms, including fever and oligoarthritis, which resolved with systemic corticosteroid therapy.[5,6] EN-like panniculitis may flare on ICPi rechallenge as seen in case 2, but several reported cases demonstrated clinical resolution without recurrence when immunotherapy was recommenced.[3,5]

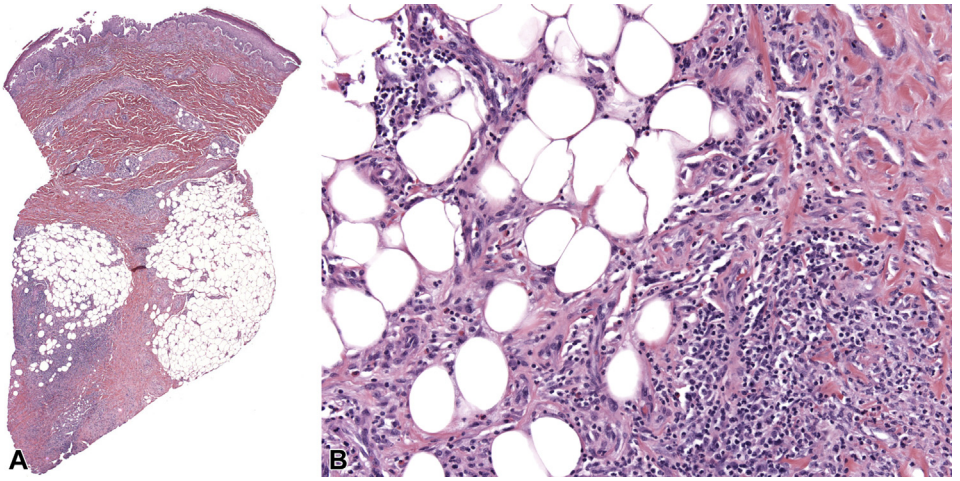

Fig 2. A, **B** Histopathologic features of erythema nodosum-like panniculitis associated with immune checkpoint inhibitor therapy. Thickening of septa within the adipose tissue with focal granulomas and an inflammatory infiltrate composed of lymphocytes, histiocytes, and occasional neutrophils in case 1. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×20; **B**, ×200.)

Evaluation of presumed EN-like panniculitis in patients on ICPi therapy should include a comprehensive review of systems, medication reconciliation, skin biopsy, as well as tissue cultures and chest imaging to evaluate for ICPi-associated sarcoidosis in the appropriate clinical setting. The decision to adjust cancer therapy should be based on the severity of the disease and associated systemic symptoms. In our report, patient 2 had severe pain impacting ambulation and improved promptly with administration of systemic corticosteroids and interruption of ICPi therapy, while patient 1 had a milder presentation and was treated with topical corticosteroids and continuation of immunotherapy. Furthermore, patient 2 was treated with minocycline as a steroid-sparing option, given previous evidence of efficacy in recalcitrant EN.[8] It may be reasonable to apply a similar approach of systemic corticosteroids and interruption of immunotherapy in severe cases of EN-like panniculitis impacting quality of life or with systemic symptoms, whereas milder presentations may be treated conservatively with topical corticosteroids, non-steroidal anti-inflammatory drugs, and continuation of immunotherapy. Further investigation is needed to determine whether EN-like panniculitis is associated with response to immunotherapy.

This report of 2 cases provides further support that EN-like panniculitis is a dermatologic adverse effect of ICPi therapy, the pathogenesis of which is currently unknown. The scope of dermatological toxicities secondary to ICPi treatment is wide, and a better understanding of novel as well as rare cutaneous adverse effects is critical for dermatologists and oncologists caring for cancer patients.

Conflicts of interest

Dr Leventhal served on the advisory boards of La Roche Posay, Bristol Meyer Squib, and Sanofi Genzyme and Regeneron. Authors Pach, Moody, Ring, Panse, Zhang, and Deverapalli have no conflicts of interest to declare.

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