

Clinico-Pathological Correlation in Dermatopathology

A 65-Year-Old Male with Primary Central Nervous System Diffuse Large B-Cell Lymphoma on Nivolumab with Oral Mucositis and Targetoid Plaques

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Abstract

Background/Aims: The development of programmed cell death-1 (PD-1) inhibitors has greatly improved patient outcomes in the treatment of a variety of advanced malignancies. These novel immunotherapies are not without adverse effects, the most common of which are dermatologic. **Methods:** We report our experience with an atypical erythema multiforme-like eruption in a patient with primary central nervous system diffuse large B-cell lymphoma treated with nivolumab. **Results:** The patient presented with oral mucositis and scattered erythematous papules which progressed to targetoid purpuric plaques with hyperkeratotic centers. Histopathology demonstrated interface dermatitis with dyskeratotic keratinocytes and pigment incontinence. The patient experienced improvement of the eruption with discontinuation of nivolumab and on systemic and topical glucocorticoids. **Conclusion:** As PD-1 inhibitors become more widely used in the treatment of advanced malignancies, the early recognition and treatment of rare dermatologic toxicities remain of great importance.

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Case Report

A 65-year-old Asian-American man with multiply recurrent primary central nervous system diffuse large B-cell lymphoma previously treated with high-dose methotrexate and rituximab was placed on the programmed cell death-1 (PD-1) inhibitor, nivolumab. Past medical history was otherwise not significant. The patient tolerated therapy well, achieving

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radiographic partial response and moderate clinical improvement. One week following his 8th cycle of nivolumab, he developed a sore throat and white plaques on the tongue and palate which did not improve on nystatin or oral fluconazole. The plaques progressed into painful oral ulcerations over several weeks, limiting the patient's oral intake. On admission, the patient was found to have punched-out orolabial ulcers on a white-yellow base with hemorrhagic crusting on the lips. A full skin exam also revealed penile erosions and scattered small pink macules and papules on the palmar hands and plantar feet.

The patient's next nivolumab infusion was deferred and he was empirically started on intravenous acyclovir. Testing for HSV, including DFA and culture of oral lesions, was negative, and workup for mycoplasma antibodies and pemphigus/pemphigoid antibodies was initiated. Throat culture grew normal flora. Despite the negative results for HSV, the clinical appearance of the patient's lesions was highly suspicious for HSV and secondary erythema multiforme (EM), and after slow improvement, he was discharged on oral acyclovir suppression therapy.

The patient was restarted on nivolumab and received his next infusion 5 days after discharge. Two weeks later, while still on acyclovir, the patient reported worsening oral pain and increasingly pruritic and enlarging lesions on the lower extremities, hands, and feet. He was evaluated by his local dermatologist who initiated a steroid taper and recommended inpatient evaluation.

On readmission, the patient had significant oral mucositis including hemorrhagic crusting and ulceration of the orolabial surface. He also had penile erosions and large targetoid purpuric plaques, some with hard, keratotic papular centers, on the extremities, palms, and soles (Fig. 1). The targetoid plaques were associated with significant pruritus and appeared to arise in the same locations as the scattered pink macules and papules noted from his initial admission.

Histopathologic examination of representative lesions on the patient's legs demonstrated interface dermatitis with dyskeratotic keratinocytes and pigment incontinence (Fig. 2). HSV DFA, culture, and serologies were negative. Mycoplasma and pemphigus/pemphigoid antibody panels from the patient's first admission returned negative. Altogether, the patient was reassessed to have an EM-like reaction to nivolumab given the negative virologic testing for HSV and nonspecific biopsy findings consistent with EM in the correct clinical context. Other possibilities including mycoplasma-induced rash and mucositis and paraneoplastic pemphigus were considered less likely given the negative antibody panel.

The patient completed a prednisone taper and was given topical augmented betamethasone ointment for the lesions on the body, as well as a regimen of oral oxycodone, oral dexamethasone swish and spit, and "magic mouthwash" swish and spit for the oral lesions with steady improvement. On a postdischarge visit approximately 4 weeks following the final inpatient encounter, oral mucositis had completely resolved. Penile erosions were almost completely healed with the exception of a 3-mm eroded macule. Cutaneous plaques were fading with resolution of the keratotic papules.

Discussion

Since their introduction, PD-1 inhibitors such as nivolumab have revolutionized the treatment of advanced malignancies. In targeting the T-cell inhibitory receptor PD-1, these monoclonal antibodies relieve the "brakes" placed on T-cell activity by tumor cells and promote tumor-directed immune activity [1]. However, PD-1 inhibitors are not without side effects and have been associated with several immune-related adverse events (irAEs), thought to arise from general enhancement of immunologic activity. Most common among these irAEs are dermatologic side effects [2].



Fig. 1. Representative mucosal and cutaneous findings. **a** Oral mucositis with ulceration and a white-yellow base on the upper and lower vermilion lips with overlying hemorrhagic crust. Similar-appearing ulcers were also noted on the hard palate and on the inferior surface of the tongue (not displayed). **b** Dorsal hand with scattered target-shaped plaques with a pink outer rim and central keratotic papule or eroded macule.

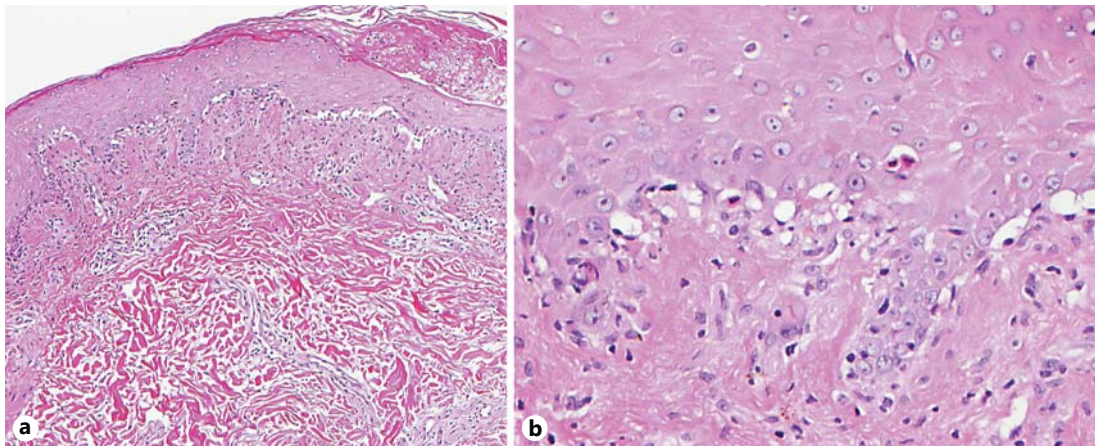


Fig. 2. Hematoxylin and eosin stain on biopsy of the papule on the leg demonstrating interface dermatitis with dyskeratotic keratinocytes and pigment incontinence. **a** Low power at $\times 100$. **b** High power at $\times 400$.

In a recent retrospective study, the most commonly reported dermatologic adverse events to PD-1 inhibitors were “maculopapular eruptions,” pruritus, and hypopigmentation [3]. These side effects are commonly mild with less than 10% presenting with a toxicity of grade 3 or higher [4]. Several case reports have also characterized less frequently seen dermatologic toxicities including lichenoid dermatitis [5], bullous disorders [6], and Stevens-

Johnson syndrome [7]. In one case series, a patient with metastatic melanoma treated with nivolumab developed bullous EM, as evidenced by confluent plaques and flaccid bullae on the trunk and extremities, with biopsy demonstrating a blister cavity with adjacent interface dermatitis and associated dyskeratotic keratinocytes [6]. Our patient, while demonstrating similar histology, presented with a unique clinical presentation of EM with targetoid lesions and hyperkeratotic centers not classically seen in EM.

Typically, the development of EM when secondary to an HSV infection is thought to be mediated by a Th1 response to viral antigens deposited in the skin [8]. This aberrant reaction could theoretically be triggered by the immune-enhancing effects of nivolumab. However, our patient had no detectable IgM or IgG antibodies to HSV, indicating no prior HSV exposure. The patient may thus have experienced a direct drug-induced EM-like eruption, which is thought to be mechanistically distinct from HSV-induced EM and occur via a tumor necrosis factor alpha-mediated mechanism [9]. It may not be entirely surprising that the use of a T-cell-activating drug could produce an EM-like reaction, especially given the altered immunologic milieu in the setting of hematologic malignancy.

This patient's EM-like eruption developed after 8 cycles of nivolumab, approximately 4 months after initiation. Interestingly, different forms of dermatologic irAEs appear to present following variable amounts of time on therapy. The common "maculopapular rash" is frequently observed within the first 2 weeks of therapy [4]. However, lichenoid dermatologic toxicities have been reported after an average of 88 days on therapy, while bullous pemphigoid eruptions have been seen after 102 days on therapy [10]. These data indicate the importance of continuing to consider nivolumab as a culprit for dermatologic presentations well after the onset of treatment.

In terms of management, current consensus suggests treatment with topical corticosteroids for grade 1 or 2 reactions and systemic corticosteroids for grade 3 or 4 reactions. Immunotherapy should be held for grade 3 reactions and permanently discontinued for grade 4 reactions [2]. However, we are strongly in favor of managing cutaneous eruptions aggressively to give patients the benefit of immunotherapy in the setting of advanced malignancy. In this particular case, due to participation in a clinical trial, immunotherapy was ultimately discontinued. The balance of risk and benefit is also made more nuanced by early evidence showing that dermatologic toxicities may be evidence of a strong response to immunotherapy and carry a positive prognostic value, further supporting the approach to attempt to cautiously treat through dermatologic adverse events [3]. Continued study of the relationship between therapeutic response and dermatologic toxicity is required to better inform our management of patients relying on immunotherapy for cancer treatment.

Statement of Ethics

The authors have no ethical conflicts to disclose. Patient consent was not required for this study given the nonidentifiability of the patient.

Disclosure Statement

The authors declare no conflicts of interest. This work did not receive any financial support.

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