

Pembrolizumab-induced Toxic Epidermal Necrolysis in a Patient with Metastatic Esophageal Adenocarcinoma

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ABSTRACT

Adverse cutaneous reactions associated with the immune checkpoint inhibitor (ICI) pembrolizumab are well documented, yet life-threatening reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are infrequent.^{1,2} We present a case of pembrolizumab-induced TEN in a patient with metastatic esophageal adenocarcinoma who was successfully treated with cyclosporine and systemic corticosteroids.

KEYWORDS: Stevens-Johnson syndrome, toxic epidermal necrolysis, pembrolizumab, cyclosporine

CASE REPORT

A 77-year-old white man with metastatic esophageal adenocarcinoma presented to his outpatient oncologist with an acute onset pruritic morbilliform eruption that began 24 hours after his fourth cycle of folinic acid, fluorouracil, and oxaliplatin (FOLFOX)/trastuzumab and second cycle of pembrolizumab (**Figure 1A**). He was treated with methylprednisolone 80 mg IV, diphenhydramine 25 mg IV, and sent home with an eight-day low dose oral prednisone taper (40

mg PO maximum dose). Seven days later, he returned given rash persistence for which he received an additional dose of methylprednisolone 80 mg IV and was initiated on an additional course of oral steroids (60 mg PO maximum dose). Two days later, he demonstrated bullae and presented to the Emergency Department. Physical examination revealed a hemodynamically stable, non-toxic appearing patient with a diffuse morbilliform eruption, scattered dusky foci, flaccid bullae on the abdomen and back, tense palmoplantar bullae, and sacral and medial buttocks with full-thickness desquamation. Orogenital and ocular mucosal surfaces were spared. Nikolsky and Absoe-Hansen signs were positive. Total body surface area (BSA) approached 90% (**Figure 1B**). He reported fevers and fatigue.

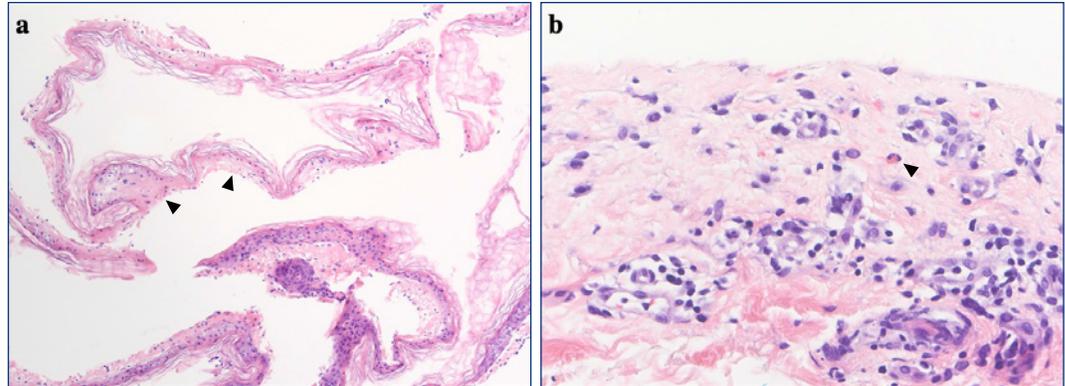
The patient was admitted to the trauma intensive care unit (TICU) and was started on prednisone PO 1 mg/kg/day. Skin biopsy revealed full-thickness epidermal necrosis with subjacent sparse superficial perivascular lymphocytic inflammation with few admixed eosinophils (**Figure 2**). Direct immunofluorescence (DIF) studies were negative for IgA, IgM, IgG, C3, and fibrinogen deposition.

Clinicopathologic correlation confirmed a grade IV immune-related cutaneous adverse event (ir-CAE) presenting

Figure 1. Clinical progression of pembrolizumab-induced TEN. (A) Diffuse pruritic morbilliform eruption noted in the setting of recent pembrolizumab infusion, prior to eruption of painful bullae. Photo taken 24 hours after pembrolizumab infusion. **(B)** Diffuse dusky morbilliform eruption with areas of frank desquamation. Photo taken 10 days after pembrolizumab, on day 1 of hospitalization. **(C)** Continued reepithelialization following combination therapy with cyclosporine and high dose oral prednisone. Photo taken on day 17 of hospitalization. **(D)** Near complete re-epithelialization after combination therapy with cyclosporine and high dose oral prednisone. Photo taken on day 24 of hospitalization.



Figure 2. Histopathologic findings in pembrolizumab-induced TEN. **(A)** Full-thickness necrosis of detached epidermis (hematoxylin and eosin stain, original magnification $\times 100$). **(B)** Dermis with sparse superficial perivascular predominantly lymphocytic inflammation and rare eosinophils (hematoxylin and eosin stain, original magnification $\times 400$).



as TEN. SCORTEN was 3, indicating a mortality risk of $>35.5\%$.³ Review of medications revealed infusion with combination FOLFOX, trastuzumab, and pembrolizumab approximately 6 weeks prior to presentation without adverse cutaneous events. He underwent a subsequent infusion with FOLFOX and trastuzumab 4 weeks prior to presentation, again without adverse cutaneous events. Twenty-four hours prior to initial cutaneous eruption and 9 days prior to presentation for hospitalization, the patient was again administered an infusion with combination FOLFOX, trastuzumab, and pembrolizumab. Due to acute cutaneous eruption after the second exposure to pembrolizumab, and the known association of PD-1 inhibitors with ir-CAEs, pembrolizumab was favored as the culprit drug. A PubMed literature search and Litt's Drug Eruption and Database review failed to identify FOLFOX and trastuzumab as culprits of SJS/TEN. Thus, pembrolizumab was held indefinitely.

Due to progression of dusky cutaneous patches, prednisone PO was increased to 2 mg/kg/day and cyclosporine PO 4 mg/kg/day was initiated. The patient developed blood pressure lability and leukopenia; initiation of IV cefazolin effected improvement. Leukopenia was trended and favored to be multifactorial, attributed to TEN and cyclosporine. Reduced desquamation, decreased bullae formation, and early re-epithelialization were observed on day four of therapy, after which cyclosporine and prednisone were tapered.

On day seventeen of hospitalization, the patient was transferred to a step-down unit to continue down-titration of cyclosporine and prednisone as re-epithelialization progressed (**Figure 1C**). The patient was discharged on day twenty-four with near total re-epithelialization (**Figure 1D**).

Following discharge, the patient completed tapers of cyclosporine and prednisone totaling three and nine weeks of therapy, respectively. He demonstrated complete re-epithelialization with patches of residual lower extremity dyspigmentation, and intermittent dysesthesias of his right anterior thigh. During the final two weeks of his prednisone taper, he developed multiple vertebral compression fractures, and three months later, sustained traumatic fractures after a fall. He continued treatment for metastatic

esophageal adenocarcinoma without pembrolizumab, and had three months of progression free survival. A small brain metastasis was successfully treated with gamma knife radiation. Continued follow-up is ongoing.

DISCUSSION

Ir-CAEs related to ICI therapy may involve cutaneous and extracutaneous systems. Pembrolizumab is an ICI initially approved for advanced melanoma in 2014 that was subsequently authorized for managing various malignancies including advanced small cell lung cancer, esophageal carcinoma, and classical Hodgkin Lymphoma.⁴ Approximately 30-40% of patients receiving pembrolizumab may develop dermatologic complications, yet SJS/TEN has been reported infrequently.⁵ Reports on the PD-1 inhibitor nivolumab suggest that dermatologic adverse events are the earliest to develop, with a median time to onset of five weeks.⁶ However, ir-CAEs such as SJS/TEN may present at anytime during therapy.^{1,2} Ir-CAEs are graded in severity according to morphology and BSA; morbilliform eruptions involving $>30\%$ BSA and skin sloughing $<10\%$ BSA both signify a grade III ir-CAE.⁷ In relation to ICI therapy, TEN is defined as skin sloughing covering $\geq 30\%$ BSA with associated erythema, purpura, or epidermal detachment and signifies a grade IV ir-CAE.⁷ Differentiating ir-CAEs is paramount to management and impacts cancer therapy decisions; SJS/TEN dictates discontinuation of the implicated ICI.

In our patient, pembrolizumab-induced TEN demonstrated a prodromal morbilliform-like eruption that became dusky prior to bulla formation and desquamation. Mucosal involvement is a nearly universal feature of SJS/TEN and part of traditional diagnostic criteria. However, the relative lack of mucosal involvement in our and another reported patient suggests that this feature may represent a unique SJS/TEN phenotype.^{1,2} Thus, clinicians should maintain high clinical suspicion for pembrolizumab-induced SJS/TEN even if mucosal involvement is absent; skin biopsy is essential in differentiating this entity from the spectrum of pembrolizumab-associated ir-CAEs, including bullous pemphigoid.⁸

Our patient improved after treatment with high-dose prednisone and cyclosporine, the latter of which reduces lymphocyte proliferation. Intravenous immune globulin (IVIg) was not part of our management strategy in accordance with published ir-CAE management recommendations in the *Journal of the American Academy of Dermatology*.¹ Cyclosporine's mechanism of action theoretically positions it as an ideal treatment for SJS/TEN, which is thought to represent a T-cell mediated delayed hypersensitivity reaction. The use of cyclosporine for SJS/TEN remains controversial with recent systematic reviews suggesting little to no benefit over supportive care.⁹ However, our case adds to reports suggesting the efficacy of cyclosporine in managing pembrolizumab-induced SJS/TEN, which, given its unique phenotype, may respond differently to medical interventions than other forms of SJS/TEN.^{1,2,9,10} In addition, our patient's adverse effects secondary to prolonged high dose systemic corticosteroid therapy for SJS/TEN emphasizes the need to closely monitor for extracutaneous complications of corticosteroids such as osteopenia.

With continued use of targeted cancer therapies, clinicians must maintain a high degree of suspicion for SJS/TEN in patients receiving pembrolizumab or other ICIs demonstrating blistering and/or skin sloughing even in the absence of mucosal symptoms. Cyclosporine may effect rapid cutaneous improvement in patients with pembrolizumab-induced SJS/TEN.

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Disclosures

The authors have no conflict of interests to declare.

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