A case of pembrolizumab-induced toxic epidermal necrolysis with a delayed developmental timeline

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Key words: 2-hit mechanism; atypical presentation timeline; cancer care; cutaneous toxicity; delayed developmental timeline; delayed onset; immune checkpoint inhibitors; immune-related adverse event; immunotherapy; oncodermatologist; oncodermatology; PD-1 inhibitors; pembrolizumab; pembrolizumab-induced; PIRME; progressive immunotherapy-related mucocutaneous eruption; Stevens-Johnson syndrome; toxic epidermal necrolysis; toxicity.

INTRODUCTION

Immunotherapy has emerged in recent years as a crucial treatment strategy for a range of nonresectable cancers.[1] Programmed death-1 (PD-1) inhibitors enhance the immune system's capacity to recognize and fight cancer cells.[1] As a side effect of this more active immune system, patients often experience immune-related adverse effects.[1] Most commonly, PD-1 inhibitors induce cutaneous side effects, with overall rates of adverse cutaneous events as high as 42% in prior studies.[2] Most of these events are mild, but severe reactions, including Steven–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), can occur.[2,3]

Because immune checkpoint inhibitor (ICI)-induced SJS/TEN can exhibit different features and follow a different developmental timeline from classic SJS/TEN, Molina et al[4] have proposed reclassifying these reactions as "Progressive Immunotherapy-Related Mucocutaneous Eruption (PIRME)." Here, we report a case of TEN secondary to pembrolizumab to highlight the atypical presentation and developmental timeline that can be seen with PD-1 inhibitor-induced SJS/TEN, as well as to consider the case's fit within the proposed PIRME framework.

Abbreviations used:

PD-1:	programmed death-1
SJS:	Steven–Johnson syndrome
TEN:	toxic epidermal necrolysis
PIRME:	progressive immunotherapy-related mucocutaneous eruption

CASE REPORT

A 63-year-old man with metastatic non-small cell lung cancer initially presented with pink cornflake-like papules and plaques scattered on the upper portion of the chest, back, and shoulders after completing 3 cycles of pembrolizumab, pemetrexed, and carboplatin over 7 weeks.

Pemphigus foliaceus was considered given the initial morphology, but positive IgG basement membrane zone antibody reactivity on direct immunofluorescence and increased IgG BP230 serum antibody levels raised the consideration of pemphigoid.

Although the appearance of the rash did not improve on topical steroids, the patient was relatively asymptomatic and was maintained on topical therapy alone. Follow-up visits at 1, 3, and 5 months did not indicate worsening of symptoms. Carboplatin was discontinued after 4 months, per the clinical trial protocol. At week 34, the patient was prescribed doxycycline.

Two weeks after starting doxycycline and 9 months after starting pembrolizumab, the patient worsened significantly and presented with

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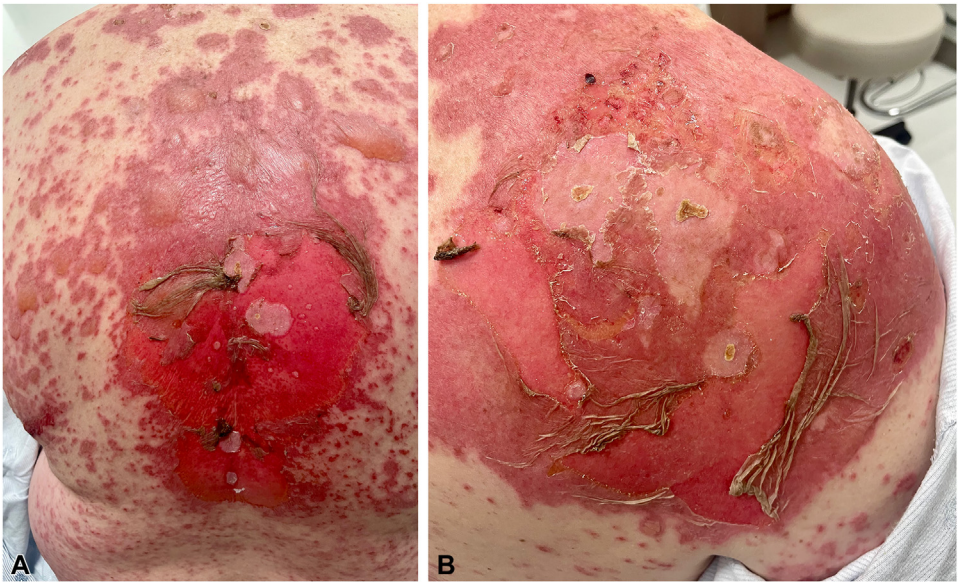

Fig 1. Toxic epidermal necrolysis. **A,** Patient with erythematous patches and plaques with bullae and desquamation spanning 30% to 40% of body surface area. **B,** Sheet-like desquamation seen on the back of the shoulder.

widespread painful, peeling skin. Examination showed widespread, crusted pink and dusky plaques, erosions, and tense bullae on 30% to 40% of the trunk and extremities. Lesions on the back coalesced with sheet-like desquamation and demonstrated Nikolsky positivity (Fig 1, *A*, *B*). Erosions were noted on the mucosal lower lip, but there was no evidence of ocular or genital involvement.

Laboratory tests were notable for mildly elevated bullous pemphigoid antigen 230 (BP230), normal BP180, normal eosinophil count, and negative herpes simplex virus polymerase chain reaction swab of oral erosions. A fresh frozen dermatopathology specimen from the upper portion of the back showed full thickness epidermal necrosis with rare eosinophils, with permanent sectioning showing a necrotic blister roof with epidermal re-epithelialization and subtle interface change. Direct immunofluorescence was negative.

A diagnosis of TEN was rendered, and treatment with pembrolizumab and pemetrexed was discontinued immediately. The patient was admitted to the hospital under the care of burn specialists, receiving 1.5 mg/kg/d of intravenous methylprednisolone and 3 g/kg/d of intravenous immunoglobulin for 4 days. The patient was maintained on doxycycline throughout the inpatient treatment.

Patient was seen 9 days after discharge with all prior lesions resolved and no new lesions observed. A new chemotherapy regimen was commenced 5 weeks after discharge, and the patient showed no signs of recurrence 6 months postdiagnosis.

DISCUSSION

TEN is a rare and life-threatening reaction requiring immediate attention, and its appearance within the context of immunotherapy is noteworthy, as immunotherapeutic agents are becoming increasingly prevalent in tumor management.[1,5]

Although doxycycline had been prescribed shortly before the TEN presentation, we still considered pembrolizumab more likely to be the agent driving the reaction, as there have been many more cases of SJS/TEN attributed to pembrolizumab than to doxycycline, despite the latter's more widespread usage. Evaluating the case in light of the PIRME framework, we find it possible that the doxycycline played a role in the cutaneous eruption via the kind of "2-hit" mechanism described by Molina et al,[4] whereby "ICIs reduce immune tolerance induce heightened sensitivity to subsequent drug exposures, leading to a florid exacerbation of an otherwise benign drug reaction." Under the PIRME framework—and, we believe, in our case—the final TEN-like reaction represents an acceleration of the initial mild, pemphigoid-like symptoms, rather than the *de novo* initiation of a new reaction.[4]

In contrast to the cases presented by Molina et al,[4] however, our patient was continued on the potentially "concomitant" doxycycline. His swift and full recovery implies either that the doxycycline did not

play a significant role in the escalation of symptoms or that, under the PIRME model, the concomitant medication does not continue to cause significant symptoms in the face of immunosuppressive treatment. Given the long half-life of pembrolizumab[3] and the durability of the ICI response, a diagnosis of TEN or PIRME in patients on PD-1 inhibitors should be met with immediate, aggressive treatment. Although it was not done in this case, the PIRME framework allows for the possibility of restarting the ICI after recovery, if deemed clinically necessary.[4]

It has been previously reported that ICI-induced SJS/TEN typically develops more slowly than traditional TEN, which typically presents within 3 weeks of starting the causative medication,[6] but even for ICI-induced TEN the onset in this case was unusually delayed: in a recent review, no cases of pembrolizumab-induced SJS/TEN were reported with onset times of >24 weeks; here it was roughly 36, which also equaled the longest PIRME onset duration reported by Molina et al.[4,7]

The nomenclature around severe ICI-induced cutaneous adverse events ("PIRME," "TEN-like," and "2-hit mechanism") is still developing, but providers with patients on PD-1 inhibitors should note the timelines and patterns present in cases such as ours and maintain a close watch on any cutaneous side effects, emphasizing to patients the importance of regular follow up and attentiveness to sudden changes, especially in light of the introduction of new medications at any stage of treatment. Our patient ultimately had a favorable outcome, which is consistent with other reported cases of ICI-induced TEN, but the decision of which (if any) medications to continue during and after treatment is a difficult one, and more exploration in this area as we gain an understanding of the immunopathologic process would be worthwhile.

Conflicts of interest

None disclosed.

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