Case Report

# Toxic Epidermal Necrolysis During Cotherapy with Ipilimumab and Nivolumab


## Abstract

Ipilimumab and nivolumab are human monoclonal antibodies used in cancer therapy. Ipilimumab targets cytotoxic T-lymphocyte-associated antigen and nivolumab acts against programmed death receptor-1. Both drugs have extensive side effect profiles with high rates of cutaneous involvement. We present a 57-year-old male with stage IV esophageal/gastroesophageal junction adenocarcinoma that developed histologically confirmed toxic epidermal necrolysis (TEN) 6 days after cotreatment with ipilimumab and nivolumab. He presented with diffuse erythematous macules with confluence and large flaccid bullae with scrotal and mucosal involvement. He improved significantly following drug cessation, steroids, and antibiotics. TEN has been reported with ipilimumab and/or nivolumab, as have other severe drug reactions including Stevens–Johnson syndrome and erythema multiforme major. As a true dermatologic emergency, TEN should be recognized as a potential complication of ipilimumab, nivolumab, and other immune checkpoint inhibitors, so clinicians can quickly recognize the condition and initiate therapy.


**Keywords:** *Drug rash, immunotherapy, ipilimumab, nivolumab, toxic epidermal necrolysis*


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## Introduction

Ipilimumab and nivolumab are human monoclonal antibodies used to treat a variety of cancers, including gastroesophageal (GE) adenocarcinoma.[1,2] Ipilimumab targets cytotoxic T-lymphocyte-associated antigen and nivolumab acts against programmed death receptor-1 (PD-1). Both drugs have extensive side effect profiles with high rates of cutaneous involvement. Nearly 44.7% of patients on ipilimumab and 43.5% of patients on anti-PD1 therapy experience cutaneous irAEs during therapy.[1,2] Toxic epidermal necrolysis (TEN) and similar conditions have been reported in conjunction with both drugs.[3-8] We present a patient on ipilimumab and nivolumab with histologically confirmed TEN and review the current literature on the topic.

## Case Report

A 47-year-old Caucasian male with stage IV esophageal/GE junction adenocarcinoma metastatic to the liver and lungs presented with skin rash 6 days after receiving a single combined dose of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg). The patient reported fever, eye swelling and erythema, and rash on his trunk. Over the next several days, eye symptoms progressed and the rash continued to spread [Figures 1 and 2]. Methylprednisolone dose pack was initiated 2 days after rash onset; however, symptoms worsened and he developed mouth sores and tenderness, so he was transitioned to intravenous steroids.

The examination showed diffuse erythematous macules coalescing into patches on the chest and back. Large, flaccid bullae and scattered smaller bullae, as well as pustules, were noted on the entire trunk. Nikolsky and Asboe-Hansen signs were positive. Erythematous macules were present on the bilateral upper and lower extremities. Examination of the genitals demonstrated poorly defined erosions and erythema of the scrotum, with sparing of the meatus of the penis. Examination of the oral mucosa showed crusting of the lips, areas of ill-defined gray macerated tissue on the hard palate, and several gray ulcers on the inferior lip. Punch biopsy of the abdomen showed full-thickness epidermal necrosis consistent with TEN. He was initially assessed as having 54% total body surface area involvement, and calculated



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severity-of-illness score for TEN (SCORTEN) 3 on examination, translating into a mortality risk of 35.3%. He was admitted to the burn unit for management.

All unnecessary medications were discontinued and his immune checkpoint inhibitor (ICPI) infusions were held. Treatment was initiated immediately with methylprednisolone 1 mg/kg IV BID. Topical therapies included wraps with clobetasol 0.05% ointment to severely affected areas with unroofed vesicles and hemorrhage, triamcinolone 0.1% ointment to extremities, and petrolatum to blistering and eroded areas. During hospitalization, he remained afebrile with no signs of bacterial superinfection. Rash initially worsened [Figure 3] with new bullae formation up to 6 days after initiating steroids. After 10 days of intravenous steroids, the rash was clinically improved and the patient was released for outpatient management. Nikolsky's sign was negative at discharge. He continued the topical treatments and transitioned to an oral steroid taper.

At follow-up 4 days after discharge, examination showed signs of secondary impetiginization with cultures positive for methicillin-resistant *Staphylococcus aureus* (MRSA). Treatment was initiated with Bactrim double-strength (DS) twice daily and bleach washes, and after several days, his condition was markedly improved. Topical steroids were replaced with white petrolatum and oral steroid taper was continued.

He was seen for follow-up about 1 month after rash onset. Examination showed tan reticulated macules on the shoulders and violaceous to erythematous plaques on the trunk, arms, and legs. Several fluctuant nodules were present, and wound culture from incision and drainage of the left thigh was positive for MRSA. Bactrim DS and oral prednisone taper were continued in addition to skin-directed therapies: mupirocin to abscesses and white petrolatum to residual rash. Continued improvement was noted 3 weeks later.

## Discussion

TEN is typically a drug-induced mucocutaneous reaction associated with life-threatening outcomes and is a true dermatologic emergency. It is characterized clinically by widespread sloughing of the skin and mucosal surfaces. TEN is included on a spectrum of conditions that also includes erythema multiforme (EM) major and Stevens–Johnson syndrome (SJS), which have been classified by Bastuji-Garin et al. based on the severity of epidermal detachment [Table 1].[9] Specific dermatological features of TEN include skin pain, dusky erythema, flaccid bullae, and skin erosions that display shedding of the epidermis with lateral pressure, known as the Nikolsky's sign.[10] TEN also commonly presents with painful inflammation and ulceration of the mucosal surfaces, with oral involvement in 71%–100%, ocular involvement in 50%–78%, and genital involvement in 40%–63%.[10]

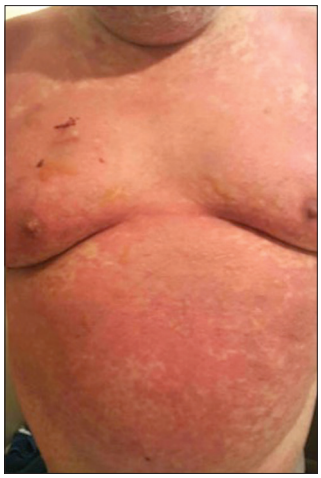

**Figure 1: Anterior trunk with erythematous macules coalescing into patches 5 days after rash onset.**

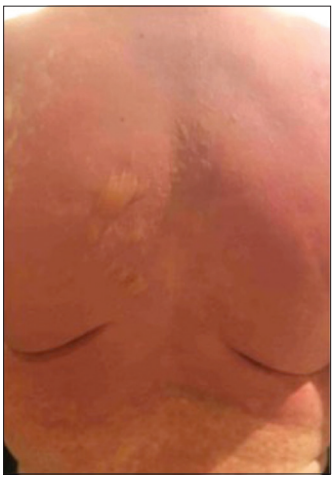

**Figure 2: Posterior trunk with bullae and erythematous macules coalescing into patches 5 days after initial onset.**

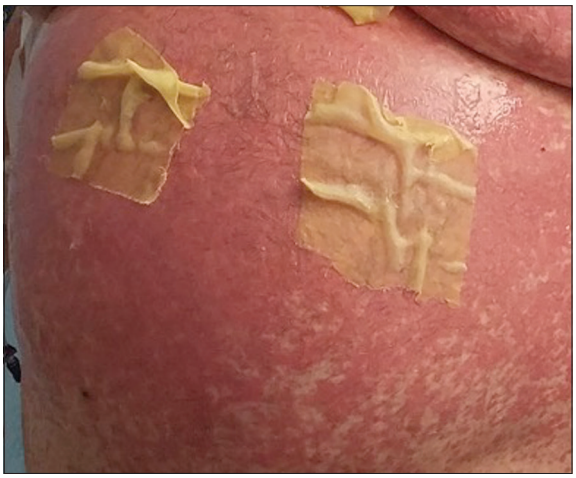

**Figure 3: Anterior trunk with worsening bullae and erythematous macules coalescing into patches 2 weeks after initial onset.**

The majority of TEN cases are associated with drug hypersensitivity, with onset typically between 7 days and

8 weeks of drug exposure.[10] It is widely accepted that T-cells are responsible for epidermal necrosis, but the mechanism of T-cell activation is unclear. One theory is that following drug exposure, drug metabolites bind covalently to cellular peptides and act as antigens capable of activating a systemic immune response. Alternatively, there is evidence that drugs noncovalently bind to major histocompatibility complex I, inducing a T-cell specific response. The outcome is widespread tissue damage characterized histologically by full-thickness epidermal necrosis. The prognosis of TEN can be rapidly assessed using the SCORTEN, which associates the presence of specific independent risk factors with mortality rate.[5]

If TEN is suspected, any potentially causative medications should be discontinued immediately.[11] Patients should be admitted to a burn unit for supportive care, as intensive nursing care is accustomed to patients with severe epidermal damage. Systemic therapies for TEN include intravenous immunoglobulin and corticosteroids. Based on the presenting symptoms, consulted specialists commonly include ophthalmology, urology, and/or otolaryngology, as involvement of mucosal surfaces and subsequent scarring increases the risk of permanent complications.

**Table 1: Classification of reactive skin disorders based on epidermal detachment**

| Condition | Clinical characteristics |
|---|---|
| EM major | Detachment of <10% of BSA plus localized target lesions |
| Stevens–Johnson syndrome | Detachment of <10% of BSA plus widespread erythematous or purpuric macules or flat atypical target lesions |
| Overlap SJS/TEN | Detachment between 10% and 30% of BSA plus widespread erythematous or purpuric macules or atypical target-like annular patches |
| TEN with spots | Detachment of >30% of BSA plus widespread erythematous or purpuric macules or flat atypical target lesions |
| TEN without spots | Detachment in large epidermal sheets >10% of BSA without macules or target lesions |

BSA: Body surface area, SJS: Stevens–Johnson syndrome, TEN: Toxic epidermal necrolysis, EM: Erythema multiforme. Reprinted [or adapted] from[9] with permission

Table 2 describes cases of TEN, SJS, and EM major reported with ipilimumab and/or nivolumab. All patients developed initial symptoms after their first or second treatment. Patient 2 received 12 cycles of nivolumab over 10 months, which was stopped due to tumor progression, and 42 days later received one dose of ipilimumab complicated by EM major. The author hypothesized that prior treatment with nivolumab may have contributed to EM major development. Patient 4 was initially on cotherapy with ipilimumab and nivolumab, and after the first treatment, developed a Grade 2 maculopapular rash that improved with systemic corticosteroids. Ipilimumab was discontinued and the patient continued nivolumab monotherapy. The rash worsened with each subsequent dose of nivolumab, and after the third monotherapy session, the patient developed signs consistent with TEN. Of note, patients 3 and 4 died from complications related to TEN, highlighting the severity of this condition known to have a mortality rate ranging from 25% to 30%[11].

This is the first report of a patient developing TEN after a single treatment with combination of ipilimumab and nivolumab. While it is difficult to determine the impact of cotherapy on TEN development from a single case, we attempted to identify unique aspects of this patient compared with those previously described. Of note, the time to reaction was much shorter in our patient than those

**Table 2: Reports of severe drug reactions associated with ipilimumab and/or nivolumab therapy**

| Patient number | Age (year)/sex | Primary cancer (stage) | Therapy and dose at the time of reaction | Time to reaction | Classification | Treatment |
|---|---|---|---|---|---|---|
| 1 | 50/male | Esophageal/GE adenocarcinoma (IV) | Ipilimumab 3 mg/kg, nivolumab 1 mg/kg×1 cycle | 6 days | TEN | Drug cessation, IV steroids, oral steroids, antibiotics |
| 2[3] | 37/female | Melanoma (IV) | Ipilimumab unknown dose ×1 cycle | 1 week | EM major | Drug cessation, IV steroids, oral steroids, IVIG |
| 3[4] | 64/female | Melanoma (IV) | Nivolumab, 3 mg/kg ×2 cycles | 4 weeks | TEN | Drug cessation, IV steroids, oral steroids, IVIG, cyclosporine |
| 4[5] | 50/female | Melanoma (IV) | Ipilimumab 3 mg/kg, nivolumab 1 mg/kg×1 cycle; nivolumab 3 mg/kg ×3 cycles | 12 weeks | TEN | Drug cessation, IV steroids, oral steroids, infliximab, IVIG, antibiotics |
| 5[6] | Unknown | Melanoma (IV) | Ipilimumab | Unknown | SJS | Unknown |
| 6[7] | 59/female | Nonsmall-cell lung adenocarcinoma (IV) | Nivolumab 3 mg/kg ×2 cycles | 3 weeks | SJS | Drug cessation, IV steroids, oral steroid |
| 7[8] | 63/female | Melanoma (IIIc) | Nivolumab 3 mg/kg ×2 cycles | 4 weeks | EM major | Drug cessation, IV steroids, antibiotics, valacyclovir |

IV: Intravenous, IVIG: Intravenous immunoglobulin, TEN: Toxic epidermal necrolysis, EM: Erythema multiforme, SJS: Stevens–Johnson syndrome

previously reported, possibly representing a cumulative effect of the two ICPIs. Further investigation is needed to determine whether patients developing TEN during ICPI cotherapy versus monotherapy consistently differ in clinical presentation and outcome. A double-blind Phase I dose-escalation study by Postow et al. revealed that more Grade III and IV IRAEs were reported during cotherapy with ipilimumab and nivolumab compared with patients receiving ipilimumab monotherapy (54% vs. 24%).[12] In light of these findings, it is important to recognize TEN as a potential complication of ipilimumab, nivolumab, and other ICPIs and understand the impact of co-therapy, so clinicians can quickly recognize the condition, discontinue the ICPI, and initiate therapy.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

The authors declared no conflicts of interest.

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