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Toxic epidermal necrolysis occurring with immune checkpoint inhibitors

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Abstract

Nivolumab and ipilimumab are immune checkpoint inhibitors (ICIs) used in the management of advanced malignancies including malignant melanoma. Although several cutaneous adverse events have been reported with these immunotherapy agents, toxic epidermal necrolysis (TEN) secondary to ICIs is rare. We report a 67-year-old man with TEN occurring during nivolumab and ipilimumab co-therapy and review published cases to highlight the challenges in recognizing and managing these patients. ICI-induced TEN can present atypically with delayed onset in comorbid, immunosuppressed patients with an associated high mortality rate. Prompt recognition and drug withdrawal are essential to improve outcomes. High dose systemic corticosteroid has also been recommended for the management of ICI-induced TEN, unlike other drug-induced TEN for which optimal immunomodulatory treatment is still debated.

Keywords: immune checkpoint inhibitors, nivolumab, ipilimumab, toxic epidermal necrolysis

Introduction

Immune checkpoint inhibitors (ICIs) are immunotherapy agents used in advanced hematological and solid organ malignancies with significant anti-tumor effect [1,2]. They are monoclonal antibodies which target cytotoxic T lymphocyte antigen-4 (CTLA-4; e.g. ipilimumab), programmed death receptor-1 (PD1; e.g. nivolumab), or programmed death ligand-1 (PDL1;

e.g. atezolizumab), [1]. Inhibition at these immune checkpoints increases cytotoxic T-cell activity against cancer cells resulting in effective tumor regression and control [2]. However, this enhanced T-cell action is non-specific and if directed against normal tissue can contribute to several inflammatory effects termed immune-related adverse events (irAEs), [1,2].

A wide range of irAEs have been described involving the skin, gastrointestinal tract, and respiratory tract, as well as hepatic, renal, endocrine, and neurological systems [1,2]. Skin-related irAEs occur most commonly with a reported incidence of 37% to 70% with anti-CTLA-4 antibodies and 17% to 40% with anti-PD1/anti-PDL1 antibodies [3]. These include morbilliform and lichenoid rashes, pruritus, vitiligo, mucositis, and bullous eruptions [1-3]. Most of these cutaneous reactions are low grade and treatment can often be continued [1,3].

In contrast, we report a case of toxic epidermal necrolysis (TEN) occurring during co-therapy with nivolumab and ipilimumab and review reported cases of ICIs-induced TEN to highlight the management challenges and the importance of early recognition.

Case Synopsis

A 62-year-old man presented with a widespread painful eruption progressing over five weeks. His medical history included hypertension, non-insulin-dependent diabetes mellitus, and stage 3C melanoma of the right foot with multiple, non-resectable in-transit metastases for which he was

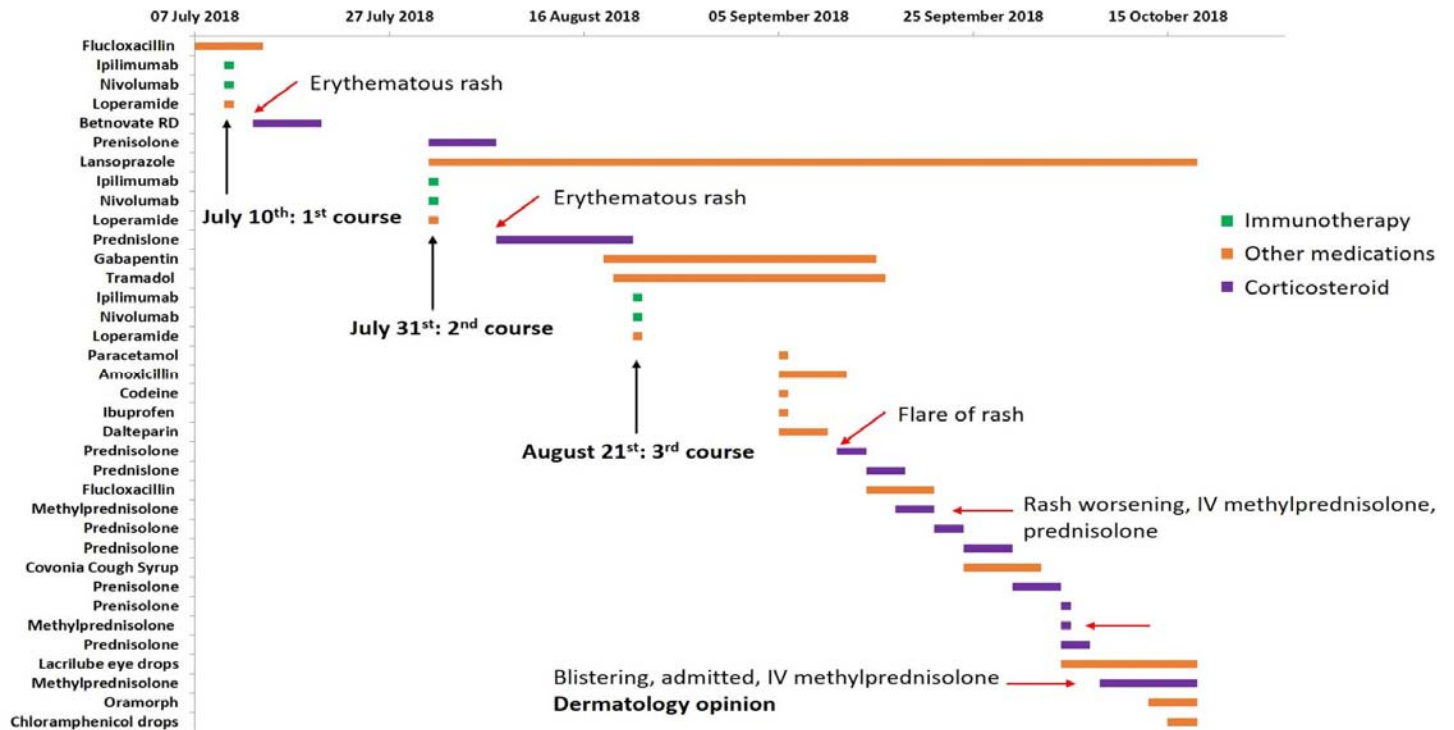


Figure 1. Gantt chart illustrating the evolution of skin changes in relation to the drug history.

undergoing combination immunotherapy with nivolumab and ipilimumab. A full skin and drug history revealed that an intermittent erythematous, non-desquamating rash occurred after each course of immunotherapy, graded as one-to-two on the common terminology criteria for adverse events (CTCAE), [4]. This was treated by either topical, oral, or intravenous corticosteroid by the oncology team with partial or complete resolution (**Figure 1**). Three weeks after his third course of ICI therapy, he

developed a progressively worsening rash and at seven weeks presented with blistering and desquamation which was not responsive to high-dose corticosteroid and prompted a dermatological review.

On examination, he had an extensive erythematous eruption with tense blisters and epidermal detachment affecting over 30% of his body surface area with oral mucosal involvement (**Figure 2**). His body temperature and pulse rate were normal.



Figure 2. Toxic epidermal necrolysis at presentation with widespread erythema (>30% body surface area) with blistering and epidermal detachment affecting trunk and limbs.

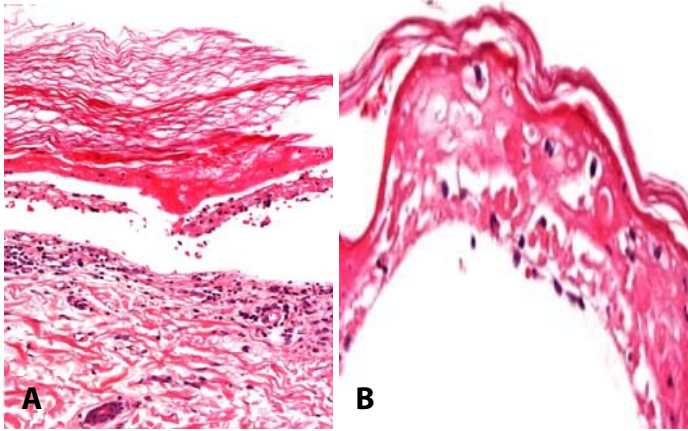


Figure 3. Histology demonstrating sub-epidermal split, full thickness epidermal necrosis with dyskeratotic cells and inflammatory cell infiltrate composed mainly of lymphocytes.

Histological examination of a truncal skin biopsy demonstrated areas of subepidermal split and full-thickness epidermal necrosis with a lymphocytic inflammatory infiltrate with few eosinophils (**Figure 3**). Indirect immunofluorescence and auto-immune screen were negative. Routine bloods demonstrated a mild neutrophilia of $8.35 \times 10^3/\mu\text{L}$ ($2\text{--}7 \times 10^3/\mu\text{L}$), elevated urea at 9.2 mmol/L ($2.5\text{--}7.8 \text{ mmol/L}$) with normal serum glucose at 8.6 mmol/L and bicarbonate at 22 mEq/L ($22\text{--}29 \text{ mEq/L}$).

A diagnosis of TEN was made with an admission severity-of-illness score (SCORTEN) of 3 [6]. Subsequent doses of nivolumab and ipilimumab were withheld. Intravenous methylprednisolone (2mg/kg), initiated by the oncology team six days

prior to dermatology admission, was continued. The patient received supportive treatment with reverse-barrier nursing, daily antiseptic baths, blister decompression, emollients and skin dressings, fluid and temperature control, and ophthalmology care [6]. Initial skin swabs isolated staphylococcus aureus and he was treated with a seven-day course of intravenous flucloxacillin. He recovered well with 100% re-epithelialization at four weeks (**Figure 4**). Methylprednisolone was switched to oral prednisolone and gradually weaned. He remained well at twelve months post-discharge with no evidence of melanoma recurrence.

Case Discussion

Toxic epidermal necrolysis is a severe reaction characterized by widespread mucocutaneous blistering and sloughing, most commonly triggered by medications. Histologically, keratinocyte death is evident ranging from discrete cell apoptosis to full-thickness epidermal necrosis [7]. Despite the high rates of cutaneous irAEs associated with ICI therapy, severe and life-threatening skin reactions such as TEN are infrequent and occur in approximately 2% to 3% of patients treated with single-agent ICI [2,3]. The risk increases with combination treatment but ICI-induced TEN is still considered rare [1]. However, a few cases have now been reported (**Table 1**) with both single-agent and combination therapy involving nivolumab and ipilimumab. Cases of



Figure 4. Improvement at four weeks with re-epithelialization of trunk and limbs with post-inflammatory changes.

Table 1. Summary of reported cases of immune checkpoint inhibitors-induced toxic epidermal necrolysis, treatment used, and outcomes.

	Author, year	Age, gender	Primary cancer	ICI treatment	Time to TEN	Treatment of TEN	Outcome
1	Antonia et al., 2014 [10]	Unknown	Non-small cell lung cancer	Nivolumab +Ipilimumab	Unknown	Unknown	Death
2	Nayar et al., 2016 [5]	64, female	Melanoma	Nivolumab: 3mg/kg (x2 cycles)	4 weeks	IV MP: 1.5mg/kg/day Cyclosporine: 3mg/kg	Sepsis and death 4 months post admission
3	Vivar et al., 2017 [11]	50, female	Melanoma	Ipilimumab: 3mg/kg +Nivolumab: 1mg/kg (x1 cycle); Nivolumab: 3mg/kg (x2 cycles)	12 weeks	Prednisone: 1mg/kg/day Infliximab: 3mg/kg IV IG: 1mg/kg/day	Sepsis, multi-organ failure and death 6 days post admission
4	Kubicki et al., 2017 [9]	47, male	Oesophageal cancer	Ipilimumab: 3mg/kg +Nivolumab: 1mg/kg (x1 cycle)	6 days	IV MP: 2mg/kg/day	MRSA abscesses; discharged 10 days post admission, improved at 3 weeks follow-up
5	Griffin et al., 2018 [12]	54, male	Follicular lymphoma	Nivolumab: 3mg/kg	22 days	IV MP: 1g/day IV IG	Sepsis, multi-organ failure, death 58 days post admission
6	Logan et al., 2019 [13]	62, male	Choroidal melanoma	Ipilimumab: 3mg/kg +Nivolumab: 1mg/kg (x2 cycles)	4 days	IV IG: 2g/kg/day IV GCSF: 60 million units Cyclosporine: 1mg/kg	Multi-organ failure, death about 8 days post admission
7	This case	62, male	Melanoma	Ipilimumab: 3mg/kg +Nivolumab: 1mg/kg (x3 cycles)	7 weeks	IV MP: 2mg/kg/day	Discharged 26 days post admission, improved at 4 weeks follow-up

IV GCSF, intravenous granulocyte colony-stimulating growth factor; IV MP, intravenous methylprednisolone; IV IG, intravenous immunoglobulins.

Stevens-Johnson syndrome and erythema multiforme major have also been described in association with ICIs [8,9].

The pathogenesis of ICI-induced TEN is not fully understood [3]. It is believed to be a direct effect of non-specific activation of cytotoxic T-cells [3]. Inhibition of CTLA-4 and PD1/PDL1 interaction by ICIs prevent deactivation and exhaustion of T-cells leading to increased T-cell activity [1,2]. These cytotoxic T-cells can target both tumor and non-tumor cells and cause apoptosis of normal keratinocytes resulting in TEN [1].

Managing ICI-induced TEN presents several additional challenges compared to usual TEN. Whilst TEN commonly occurs within 5 to 28 days of exposure to a culprit drug [7], ICI-triggered TEN can

present up to 12 weeks after administration and manifest atypically leading to delays in diagnosis and drug withdrawal [9,12]. Immune checkpoint inhibitors also have extended half-lives ($T_{1/2}$ ipilimumab=17 days; $T_{1/2}$ nivolumab=21 days), [12] with complete drug clearance of over 3 and 6 months respectively. This potentially results in protracted mucocutaneous toxicity persisting long after discontinuation of ICIs.

In terms of active treatment, although it is suggested that high-dose systemic corticosteroid given at the onset of TEN may be beneficial, its use remains controversial and not routinely recommended [6,14]. Conversely, in ICI-induced TEN, similar to other high-grade irAEs, administration of systemic corticosteroid is advocated and included in the

recently published guidance on the management of immunotherapy-related toxicities from the National Comprehensive Cancer Network [3]. Alternative immunosuppressants, such as cyclosporine and infliximab, can further be considered if corticosteroid is ineffective [1,3]. Accordingly, reported cases of ICI-induced TEN (**Table 1**) were almost exclusively treated with systemic corticosteroid, typically intravenous methylprednisolone 1-2mg/kg/day.

Of note, the mortality risk of ICI-induced TEN, based on published cases, appears to be 71% which is considerably higher than the overall risk usually associated with TEN [5], although this may represent an overestimation related to the limited number of cases and potential reporting bias. The sepsis rate is also noticeably high resulting from loss of the skin barrier in TEN, the protracted disease course owing to the long half-lives of ICIs, and the patients' immune-deficient status conferred by their

advanced malignancy and use of immunosuppressant medications [12].

Conclusion

Immune checkpoint inhibitors have so far demonstrated significant benefits on progression-free and overall survival across multiple cancer types including melanoma, Hodgkin lymphoma, and pulmonary and renal cancers [1-3]. As their use expands further, the incidence of irAEs and TEN will likely increase. This highlights the need to recognize ICI-induced TEN and the added challenges in managing these patients to ensure appropriate multi-disciplinary care to reduce infection and mortality rates [12].

Potential conflicts of interest

The authors declare no conflicts of interests.

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