Pembrolizumab-induced toxic epidermal necrolysis: A rare cause of severe adverse drug reaction

Dear Editor,

Stevens-Johnson syndrome/toxic epidermal necrolysis is the most dreaded adverse cutaneous drug reaction and is potentially fatal, if not promptly managed.[1] It is reported with medications such as non-steroidal anti-inflammatory drugs, anticonvulsants, antibiotics (beta-lactam), allopurinol and barbiturates; immune checkpoint inhibitors can also result in Stevens-Johnson syndrome/toxic epidermal necrolysis uncommonly. Pembrolizumab is a highly selective humanised monoclonal IgG4 antibody, directed against the programmed cell death-1 protein receptor on the cell surface. It is being increasingly used to treat unresectable/metastatic malignancies, melanoma and lymphoma and has shown good efficacy.[2] We present a case of pembrolizumab-induced toxic epidermal necrolysis in a patient with metastatic squamous cell carcinoma of the penis.

A 55-year-old male, a known case of moderately differentiated squamous cell carcinoma of the penis, post-chemo-radiotherapy, was diagnosed with progressive disease and metastases to the heart, lung and liver. He was being treated with oral gefitinib 250 mg, an epidermal growth factor receptor (EGFR) inhibitor, once daily for the last three months. However, in view of progressive metastatic disease, gefitinib was stopped; pembrolizumab 200 mg was administered as an intravenous infusion and was planned as three weekly injections. Two weeks later, he developed fever, redness of eyes, reddish rash on the trunk and painful oral ulcers. General and systemic examinations were within normal limits. Dermatological examination showed widespread erythematous to purpuric macules and a few bullae and erosions involving the face, trunk and extremities, constituting approximately 45% of body surface area [Figure 1]. Oral mucosa showed multiple erosions and there was haemorrhagic crusting of the lips. Bilateral conjunctiva showed chemosis [Figure 2]. A provisional diagnosis of toxic epidermal necrolysis was made with toxic epidermal necrolysis specific severity of illness score (SCORTEN) of the patient being 4 out of 7 (one point each for age >40 years; malignancy, epidermal detachment >10% and blood urea 42 mg/dL), indicating significant (60%) risk of mortality. The score on Naranjo adverse drug reaction probability scale was 6 indicating a "probable" association with pembrolizumab. Baseline haematological and biochemical parameters were within normal limits except for blood urea nitrogen (42 mg/dL) and serum creatinine (1.8 mg/dL). Histopathology of skin showed acantholysis, basal keratinocyte apoptosis and sub-epidermal bulla formation with inflammatory infiltrate of neutrophils and lymphocytes in the dermis. Direct immunofluorescence was negative for immunoglobulin G (IgG), immunoglobulin M (IgM),

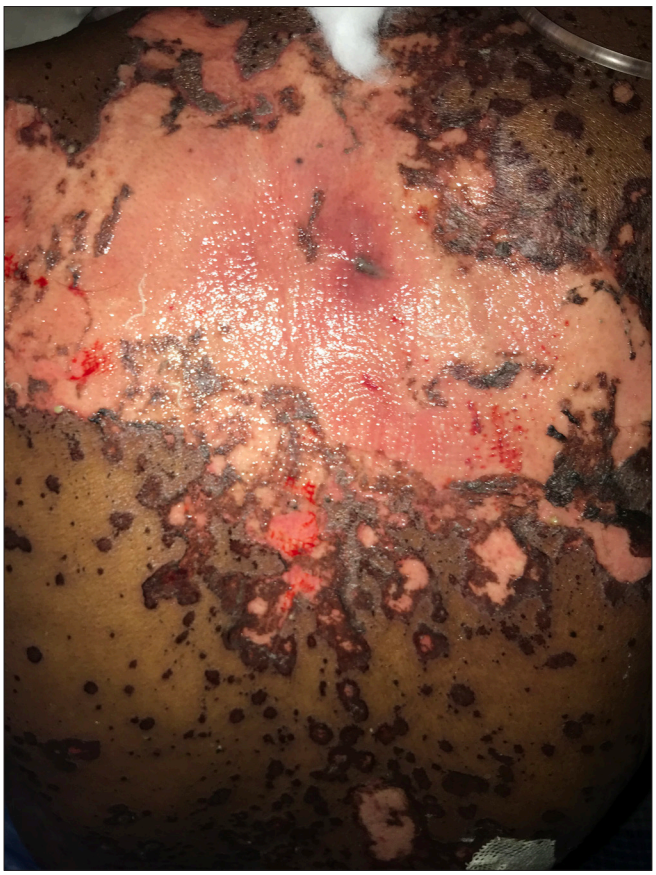

Figure 1: Pembrolizumab-induced toxic epidermal necrolysis showing involvement of trunk with sheet-like detachment of the skin

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Figure 2: Pembrolizumab-induced toxic epidermal necrolysis showing erosions involving face, conjunctival congestion, chemosis and crusting over the lips

immunoglobulin A (IgA) and complement 3 (C3). No viral cytopathic changes were seen. Pembrolizumab was withheld and cyclosporine 250 mg (5 mg/kg) in two divided doses was started. The patient continued to develop new lesions after 72 hours and was given intravenous immunoglobulin in a dose of 2 gm/kg body weight over two days.[3] Cyclosporine was continued for 10 days in the same dose. The patient responded well with no new lesions and healing of pre-existing erosions. However, the patient succumbed to complications of toxic epidermal necrolysis in the form of sepsis with multi-organ dysfunction syndrome and underlying metastatic carcinoma after about two weeks despite all possible care.

Pembrolizumab is a monoclonal antibody against programmed cell death-1 protein receptors on the cell surface. Programmed cell death-1 protein inhibitors produce durable responses in patients with advanced and metastatic squamous cell carcinoma.[4] It belongs to the group of immune checkpoint inhibitors and acts by enhancing the intrinsic ability of the immune system to destroy tumour cells and by doing so they also alter the immune tolerance and homeostasis leading to untoward effects, termed immune-related adverse events. Skin is a common site for these immune-related adverse events and can manifest as pruritus, morbilliform, psoriasiform, lichenoid, eczematous, immunobullous reactions and vitiligo.[5] Rarely

Table 1: Previous cases of SJS/TEN overlap and TEN due to pembrolizumab

Reference	Diagnosis	Age	Sex	Malignancy	Concomitant medications	Onset	Treatment	Outcome
Cai *et al.*[9]	TEN	63	Male	Metastatic adenocarcinoma lung	Nil	3 days after first cycle	Corticosteroid Cyclosporine	Recovered
Robinson *et al.*[7]	SJS/TEN	55	Female	Metastatic cervical squamous cell carcinoma	Nil	17 days after first cycle	Methylprednisolone	Recovered
Chow *et al.*[10]	TEN	63	Male	Metastatic lung adenocarcinoma	Perindopril, oxycodone, levetiracetam	17 days after 3rd cycle	Methylprednisolone, IVIG, cyclosporine	Recovered
Kian *et al.*[11]	TEN	65	Male	Metastatic non-small cell lung carcinoma	Perindopril, amlodipine	3 days after first cycle		Recovered
Marin *et al.*[12]	TEN	77	Male	Metastatic esophageal adenocarcinoma	Folinic acid Fluorouracil Oxaliplatin Trastuzumab	10 days after first cycle	Methylprednisolone cyclosporine	Recovered
Storandt *et al.*[13]	SJS/TEN	55	Female	Adenocarcinoma lung	Pemetrexed	6 months after first cycle	Methylprednisolone IVIG	Recovered
Aoyama *et al.*[14]	TEN	72	Female	Carcinoma lung	Pemetrexed Carboplatin celecoxib	14 days after second cycle	Methylprednisolone IVIG	Recovered
Choi *et al.*[15]	TEN	62	Male	Urothelial carcinoma	Nil	7 days after first cycle	Methylprednisolone	Recovered
Cao *et al.*[16]	SJS/TEN	69	Male	Carcinoma esophagus	Oxaliplatin Gimeracil Tegafur Oteracil	2 weeks after first cycle	Methylprednisolone IVIG Plasmapheresis	Recovered
Oguri *et al.*[17]	SJS/TEN	76	Male	Carcinoma lung	Denosumab Radiation	2 weeks after first cycle	Methylprednisolone IVIG	Fatal
Kumar *et al.*[18]	TEN	57	Female	Carcinoma lung	Nil	2 weeks after first cycle	Methylprednisolone Plasmapheresis Infliximab	Fatal

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, IVIG: Intravenous immunoglobulin

severe cutaneous adverse drug reaction like Stevens-Johnson syndrome/toxic epidermal necrolysis has also been reported. In addition to the skin, the mucosae (conjunctival, oral and genital) may also be significantly affected with the possibility of complications like blindness.[6] Exact mechanisms for the occurrence of life-threatening reactions like Stevens-Johnson syndrome/toxic epidermal necrolysis is unclear. Goldinger *et al.* suggested that the immune checkpoint inhibitors cause activation and proliferation of auto-reactive CD8+ T cells targeting keratinocytes with self-antigens leading to the occurrence of cutaneous drug reactions.[2]

Stevens-Johnson syndrome/toxic epidermal necrolysis following drugs like non-steroidal anti-inflammatory drugs (NSAIDS), anticonvulsants, antibiotics, allopurinol etc, occur acutely, usually within two weeks of administration of the culprit drug. However, the same reaction with pembrolizumab was reported to have a delayed onset (median of three weeks) and a prolonged course.[7] This atypical presentation could be explained by the pharmacokinetics of the drug. For example, anticonvulsant lamotrigine has a mean half-life of approximately 23–37 hours while pembrolizumab has a half-life of 23 days and takes a longer time to reach steady states, hence a delayed onset of reaction. In addition to the longer half-lives, the underlying mechanism of Stevens-Johnson syndrome/toxic epidermal necrolysis with commonly implicated drugs involve activation and proliferation of drug-specific T cells, occurring rapidly following drug exposure, while the process with checkpoint inhibitors like pembrolizumab is complex and involves proliferation of T cells directed against self-antigens in the skin, loss of peripheral immune tolerance before these reactions can fully manifest.[8] The cases of pembrolizumab-induced Stevens-Johnson syndrome/toxic epidermal necrolysis and toxic epidermal necrolysis published in the literature have been tabulated in Table 1.

Correct identification of culprit drug and its withdrawal, supportive care and administration of cyclosporine, steroids or intravenous immunoglobulin are the mainstay of treatment for reactions caused by usual drugs. However, the longer half-lives of immune checkpoint inhibitors and a different underlying mechanism usually cause a delayed and unpredictable response to treatment with a significantly increased risk of mortality (approximately 60%) as reported in various case reports. Plasmapheresis may be a useful treatment option, especially in cases with progressive rash and poor response to conventional treatment, considering the longer half-lives of these molecules.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest

There are no conflicts of interest.

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