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Intravenous immunoglobulin efficacy on pembrolizumab induced severe toxic epidermal necrolysis

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Pembrolizumab is an immune checkpoint inhibitor used in many different cancers. Several immune-related adverse events (irAEs) have been associated with pembrolizumab, including toxic epidermal necrolysis. Here, we are presenting a patient with non-small cell lung cancer that developed toxic epidermal necrolysis 3-days following initiation of pembrolizumab. Following high-dose steroid therapy, intravenous immunoglobulin 2 g/kg was initiated and resulted in complete resolution of all his irAEs. To our knowledge, this is the first reported case of total re-epithelialization and resolution of immune checkpoint inhibitor-induced toxic epidermal necrolysis following the use of intravenous immunoglobulin. *Anti-Cancer Drugs* 33: e738–e740 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Pembrolizumab has been approved by the Food and Drug Administration and belongs to a group of drugs termed immune checkpoint inhibitors. Pembrolizumab specifically is an anti-programmed death-1 (PD-1) receptor mAb that is used in several different cancers, including but not limited to, non-small cell lung cancer, endometrial cancer, breast cancer and melanoma [1]. Since checkpoint inhibitors interfere with the body's normal immune system, it has been shown that they are frequently associated with immune-related adverse events (irAEs). These can include dermatitis, pneumonitis, hypothyroidism and colitis [2].

Cutaneous irAEs are quite frequent in patients that are treated with PD-1 inhibitors and are commonly described as maculopapular rashes [3]. Other severe dermatologic complications can occur, including erythema multiforme, lichenoid and morbilliform reactions [4]. Rarely, Steven–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported as irAEs. SJS/TEN are life-threatening bullous drug eruptions that on a few occasions have been linked to anti-PD-1 antibodies [4,5]. Finally, approximately 23% of patients with SJS/TEN following the initiation of PD-1/programmed cell death ligand-1 (PD-L1) inhibitors died following the onset of a reaction [6].

Here, we are reporting on a severe case of TEN 3-days following the initiation of pembrolizumab for the treatment of non-small cell lung cancer (NSCLC) with complete resolution of symptoms after intravenous immunoglobulin (IVIG) therapy.

Case presentation

A 65-year-old Caucasian male was diagnosed with metastatic NSCLC squamous type. PD-L1 status expression was <1% while, epidermal growth factor receptor, ROS1 and ALK were wild-type. Next-generation sequencing on his tumor sample revealed different somatic mutations as seen in Tables 1 and

Table 1 Genomic alterations found in tumor sample

Gene	Mutation	Amino acid change	% Frequency
MYCN	c.691G>C	p. Ala231Pro	28.26
MAP3K1	c.365C>T	p. Ala122Val	61.19
CSMD3	c.2246G>C	p. Arg749Pro	15.32
OR4M2	c.347C>A	p. Thr116Lys	8.49
TP53	c.746G>T	p. Arg249Met	18.03

Table 2 Copy number variants found in tumor sample

Gene	Variant class	Copy number variants
COL11A1	Amplification	6.28

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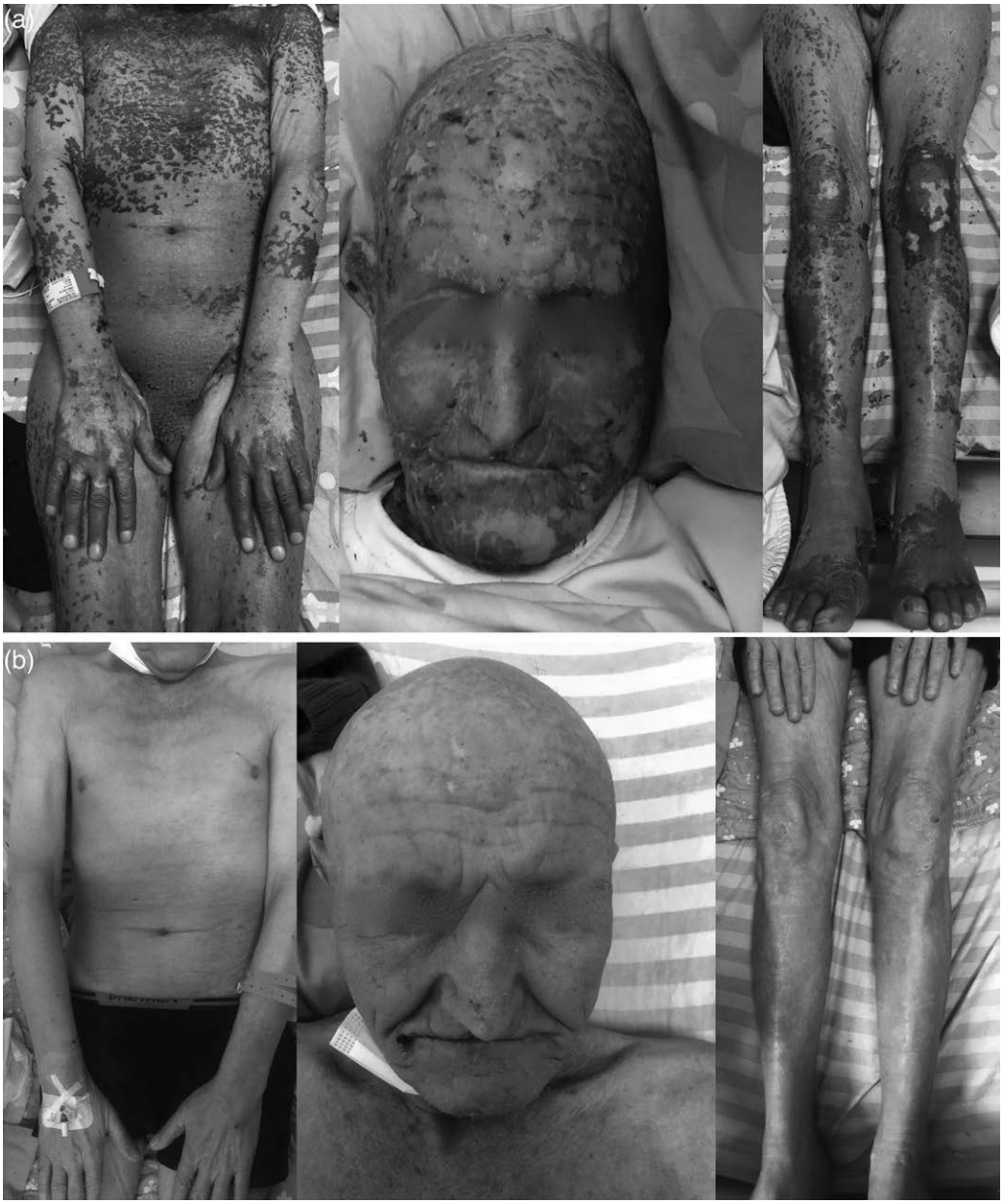
Fig. 1



(a) Widespread epidermal detachment involving the face, chest, upper and lower limbs with a positive Nikolsky sign. (b) Resolution of skin lesions 2-weeks following intravenous immunoglobulin therapy.

2. His medical history is significant for hypertension and smoking. His medications include ramipril and amlodipine. There is no personal or family history for dermatologic or autoimmune diseases. This patient received two cycles of combination chemotherapy, including carboplatin and paclitaxel without any significant side effects. On 3 December he received his first dose of pembrolizumab 200 mg.

On 11 December, he presented to the hospital with chest pain, nausea, vomiting and a whole-body maculopapular erythematous skin rash that first appeared on 6 December (3-days following drug initiation). He was then admitted for myocarditis, gastritis, esophagitis and suspected SJS/TEN. Gastritis and esophagitis were then confirmed by gastroscopy. Electrocardiogram and troponin levels confirmed myocarditis. Intravenous (i.v.) steroid therapy with methylprednisolone 2 mg/kg was initiated without significant improvement. Therefore, pulse steroid therapy with methylprednisolone 500 mg was given for 3 days with mild improvement. He was

then transferred to the ICU due to widespread epidermal detachment which involved the face, chest, back, upper and lower limbs (Fig. 1a). In the ICU, he was treated with high-dose steroid therapy and IVIG total dose of 2 g/kg with an impressive clinical improvement (Fig. 1b). He showed complete re-epithelialization on 30 December. The skin punch biopsy confirmed the diagnosis of TEN.

Discussion

Toxic epidermal necrolysis is a life-threatening bullous drug reaction that begins as an erythematous maculopapular rash that leads to epidermal detachment. By definition, TEN involves >30% of body surface area. TEN is thought to be due to apoptosis of epithelial keratinocytes by cytotoxic CD8+ T lymphocytes [7]. TEN is most commonly linked to nonsteroidal anti-inflammatory drugs, antibiotics and allopurinol [8].

Here we present a very interesting case of an NSCLC patient with PD-L1 status less than 1%. Following one cycle of pembrolizumab, he developed early onset irAEs in multiple organs, including esophagitis, gastritis, myocarditis and life-threatening toxic epidermal necrolysis. After high-dose steroidal therapy and IVIG treatment, the patient experienced complete resolution of all his irAE including TEN.

The guidelines for the treatment of immune-checkpoint inhibitor adverse events related to TEN include intravenous methylprednisolone 1–2 mg/kg and for corticosteroid-unresponsive cases, IVIG or cyclosporin can be considered [4].

After review of the literature, there have only been two reported cases of IVIG use in patients unresponsive to high-dose steroidal therapy, all of which died [9,10]. To our knowledge, this is the first reported case of complete resolution of irAEs after initiation of IVIG therapy.

Conclusion

Here we described a case of life-threatening pembrolizumab-induced TEN. To our knowledge, this is the first reported case of pembrolizumab-induced TEN with complete resolution following the use of IVIG. Therefore, physicians should be made aware of this life-threatening drug reaction and its association with this widely used medication.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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