Intravenous immunoglobulin efficacy on pembrolizumab induced severe toxic epidermal necrolysis

Waleed Kiana, Melanie Zemelb,*, Firas Elobrac, Adam A. Sharbd, Dina Levitasa, Yarden Assabagd, Farouq Alguayne, Alexander Yakobsona Keren Rouvinova and Lior Fuchsf

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 2022, 33:e738–e740 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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 2.
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.

Reference
1 du Rusquec P, de Calbiac O, Robert M, Campone M, Frenel JS. Clinical utility of pembrolizumab in the management of advanced solid tumors: an evidence-based review on the emerging new data. Cancer Manag Res 2019; 11:4297–4312.
2 Bae S, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L, Korenstein D. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 2018; 360:k793.
3 Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2018; 54:139–148.
4 Brahmer JR, Laczetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al.; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018; 36:1714–1768.
5 Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28(suppl 4):iv119–iv142.
6 Cai ZR, Lecours J, Adam JP, Marciil I, Blais N, Dallaire M, et al. Toxic epidermal necrolysis associated with pembrolizumab. J Oncol Pharm Pract 2020, 26:1259–1265.
7 Lerch M, Mainetti C, Terzioli Beretta-Piccoli B, Harr T. Current perspectives on Stevens-Johnson syndrome and toxic epidermal necrolysis. Clin Rev Allergy Immunol 2018; 54:147–176.
8 Ward KE, Archambault R, Mersfelder TL. Severe adverse skin reactions to nonsteroidal antiinflammatory drugs: a review of the literature. Am J Health Syst Pharm 2010; 67:206–213.
9 Griffin LL, Cove-Smith L, Alaukhar H, Radford JA, Brooke R, Linton KM. Toxic epidermal necrosis (TEN) associated with the use of nivolumab (PD-1 inhibitor) for lymphoma. JAAAD Case Rep 2018; 4:229–31.
10 Vivar KL, Deschaine M, Messina J, Divine JM, Rabionet A, Patel N, et al. Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy. J Cutan Pathol 2017; 44:381–384.