Case Report

International Journal of
Dermatology and Venereology

OPEN

Pembrolizumab-Induced Erosive Lichenoid Reaction in a Patient With Metastatic Lung Adenocarcinoma: A Case Report

Federico Venturi[1,2,*], Barbara Melotti[3], Martina Lambertini[1,2], Aurora Alessandrini[1,2], Andrea Ardizzoni[2,3], Emi Dika[1,2]

[1] Oncologic Dermatology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna 40138, Italy; [2] Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna 40138, Italy; [3] Medical Oncology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna 40138, Italy.

Abstract

Introduction: Immune-related adverse events induced by immune checkpoint inhibitors are quite common. Cutaneous lichenoid immune-related adverse events are among the most frequent. However, oral lichenoid adverse reactions are extremely rare.

We herein describe a patient who was treated with pembrolizumab for metastatic lung cancer and developed an erosive oral lichenoid reaction induced by immunotherapy.

Case presentation: An 87-year-old man treated with pembrolizumab for metastatic lung adenocarcinoma developed multifocal erosions of the oral mucosa with multiple small, irregular, hyperkeratotic areas. Histopathological examination showed epithelial necrosis and a dense band-like layer of an inflammatory infiltrate of lymphocytes and histiocytes within the upper dermis. Direct immunofluorescence was negative for both IgG and C3. A diagnosis of erosive oral lichenoid reaction of the mucosa induced by immunotherapy was established. Pembrolizumab treatment was withheld and concomitant topical and systemic steroids were started. After 1 month, the drug-related toxicity was ameliorated and immunotherapy was re-introduced.

Discussion: Only one other case of pembrolizumab-induced erosive lichen planus of the oral mucosa has been described to date. Previously reported drug-induced lichenoid rashes were mainly localized on the skin. Clinically, the main differential diagnoses of lichenoid erosive lesions are bullous immune-related disorders. In our patient, histological examination combined with negative results of both direct immunofluorescence and enzyme-linked immunosorbent assays confirmed the diagnosis of erosive lichenoid drug reaction.

Conclusion: Clinicians should be aware of lichenoid involvement of the oral mucosa because related pain and food intake difficulties may seriously compromise treatment compliance. Prompt treatment of oral drug-related reactions may prevent interruption of immunotherapy and improve patients' quality of life.

Keywords: immunotherapy, drug reaction, erosive lichenoid reaction, case report

** Corresponding author: Dr. Federico Venturi, Oncologic Dermatology Unit, IRCCS Azienda Ospedaliera Universitaria di Bologna, Bologna 40138, Italy; Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna 40138, Italy. E-mail: federico.venturi@hotmail.it.*

Author contributions: FV was involved in patient care, data collection, and drafted the manuscript. BM, ML, AA(Aurora Alessandrini), AA(Andrea Ardizzoni), and ED reviewed and edited the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

Data sharing statement: Not applicable.

Conflicts of interest: The authors declared that they have no conflicts of interest.

Copyright © 2023 Hospital for Skin Diseases (Institute of Dermatology), Chinese Academy of Medical Sciences, and Chinese Medical Association, published by Wolters Kluwer, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

International Journal of Dermatology and Venereology (2025) 8:3

Received: 26 April 2023, Revised: 21 May 2023, Accepted: 26 July 2023,

Published online: 2 August 2023. doi: 10.1097/JD9.0000000000000335

Introduction

Immune-related adverse events (IrAEs) induced by immune checkpoint inhibitors are quite common, and among them, cutaneous lichenoid IrAE has emerged as one of the most frequent.[1-2] However, oral lichenoid adverse reactions are extremely rare. We herein describe a patient who was treated with pembrolizumab for metastatic lung cancer and developed an erosive oral lichenoid reaction of the mucosa induced by immunotherapy.

Case report

An 87-year-old man treated with pembrolizumab for metastatic lung adenocarcinoma (stage IVa based on AJCC 2018) for 8 months presented with multifocal erosions of the oral mucosa. The patient's medical history was negative for other relevant conditions and concomitant medications.

Oral cavity examination revealed white crossing lines presenting in a reticulated pattern and mainly located

on the buccal mucosa, palate, and inner portion of the lips. Additionally, erosive and atrophic elements were observed with multiple small, irregular, hyperkeratotic areas (Fig. 1A). The symptomatology had been worsening during the previous 2 weeks, impairing food intake. The patient had experienced dysgeusia, xerostomia, and pain since the first month after pembrolizumab treatment initiation. No cutaneous, eyes and vulva mucosal, or nail reactions were observed.

Histopathological examination showed epithelial necrosis and a dense band-like layer of an inflammatory infiltrate of lymphocytes and histiocytes within the upper dermis. We performed direct immunofluorescence on a mucosal biopsy specimen to exclude autoimmune bullous disease, and the result was negative for both IgG and C3. Moreover, enzyme-linked immunosorbent assays were negative for anti-desmoglein-1 antibody, anti-desmoglein-3 antibody, and anti-BP180 antibody. Hepatitis C and B virus antibodies were negative. Pharyngolaryngitis was excluded after otolaryngologic evaluation.

A diagnosis of erosive oral lichenoid reaction of the mucosa induced by immunotherapy was established (G2 NCCN 2022). According to the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, pembrolizumab treatment was withheld and concomitant topical and systemic steroids (clobetasol propionate 0.05% ointment and prednisone 1 mg/[kg·d]) were started. After 1 month, the drug-related toxicity was ameliorated (Fig. 1B) and immunotherapy was re-introduced. In the 8 months follow up since the lichenoid drug reaction, patient is still under treatment with pembrolizumab and showed two other relapses well tolerated with topical steroids.

Patient consent declaration

The patient gave the written informed consent about his case publication, including the images and other disease details.

Discussion

Only one other case of pembrolizumab-induced erosive lichen planus of the oral mucosa has been described to date.[3] Previously reported lichenoid rashes were mainly localized on the skin.[4-5] Several hypotheses for the pathogenesis of this condition have been proposed,[1] and recent data have shown that blocking the programmed cell death protein 1 (PD-1) pathway significantly increases the proliferation of peripheral blood T lymphocytes in patients with oral lichen planus, implying that PD-1 plays an important role in negatively modulating self-reactive T-cell-mediated immune responses in oral lichen planus.[6-7] Our patient's history was negative for any drug intake, so other drug-induced lichenoid reactions were exclude.

Clinically, the main differential diagnoses of lichenoid erosive lesions are bullous immune-related disorders. This was particularly relevant in our case because both lichenoid dermatitis and bullous dermatitis are listed among dermatologic IrAEs. In our patient, the histological examination combined with the negative results of both direct immunofluorescence and enzyme-linked immunosorbent assays confirmed the diagnosis of erosive lichenoid drug reaction. Importantly, patients treated with anti-PD-1 antibody may show positivity for anti-BP180 autoantibody with no immunobullous reaction. A hypothetic justification for this positivity is related to BP180 expression not only in the basement membrane zone but also on the surface of non-small cell lung carcinoma or melanoma cells. The limitations are that the incidence rate of immunotherapy-induced lichenoid reactions is unclear, and further studies comparing a larger number of similar cases are warranted to improve the diagnostic accuracy.

In conclusion, lichenoid eruption during immunotherapy should always be acknowledged, and clinicians should be aware of lichenoid involvement of the oral mucosa because related pain and food intake difficulties may seriously compromise treatment compliance. Prompt treatment of oral drug-related reactions may prevent interruption of immunotherapy and improve patients' quality of life. Increased awareness among clinicians will aid in the early recognition and appropriate management of this rare entity.

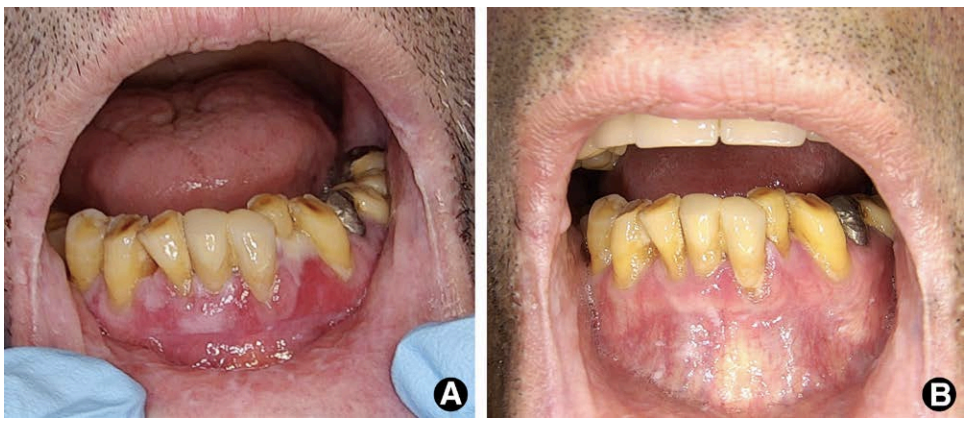

Figure 1. Clinical presentation of erosive lichenoid reaction in a patient with metastatic lung adenocarcinoma treated with anti-PD-1 antibody (pembrolizumab) before (A) and after (B) steroid treatment.

References

[1] Obara K, Masuzawa M, Amoh Y. Oral lichenoid reaction showing multiple ulcers associated with anti-programmed death cell receptor-1 treatment: a report of two cases and published work review. J Dermatol 2018;45(5):587–591. doi: 10.1111/1346-8138.14205.

[2] De Giorgi V, Colombo J, Trane L, et al. Cutaneous immune-related adverse events and photodamaged skin in patients with metastatic melanoma: could nicotinamide be useful? Clin Exp Dermatol 2022;47(8):1558–1560. doi: 10.1111/ced.15215.

[3] Bhattacharyya I, Chehal H, Migliorati C. Severe oral erosive lichenoid reaction to pembrolizumab therapy. Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130(5):e301–e307. doi: 10.1016/j.oooo.2020.06.014.

[4] Veronesi G, Scarfì F, Misciali C, et al. An unusual skin reaction in uveal melanoma during treatment with nivolumab: extragenital lichen sclerosus. Anticancer Drugs 2019;30(9):969–972. doi: 10.1097/CAD.0000000000000819.

[5] Dika E, Ravaioli GM, Fanti PA, et al. Cutaneous adverse effects during ipilimumab treatment for metastatic melanoma: a prospective study. Eur J Dermatol 2017;27(3):266–270. doi: 10.1684/ejd.2017.3023.

[6] Sibaud V, Eid C, Belum VR, et al. Oral lichenoid reactions associated with anti-PD-1/PD-L1 therapies: clinicopathological findings. J Eur Acad Dermatol Venereol 2017;31(10):e464–e469. doi: 10.1111/jdv.14284.

[7] Bhardwaj M, Chiu MN, Pilkhwal Sah S. Adverse cutaneous toxicities by PD-1/PD-L1 immune checkpoint inhibitors: pathogenesis, treatment, and surveillance. Cutan Ocul Toxicol 2022;41(1):73–90. doi: 10.1080/15569527.2022.2034842.