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Case Report

Association of Programmed Cell Death 1 Inhibitor with Circumorificial Plasmacytosis

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Keywords

Circumorificial plasmacytosis · Checkpoint inhibitors · Pembrolizumab · Thymic carcinoma · Immunotherapy side effects

Abstract

Introduction: The development of immune checkpoint inhibitors is considered one of the most important advances in cancer treatment. Pembrolizumab is an immune checkpoint inhibitor against programmed death-1 (PD-1) receptors that has demonstrated antineoplastic activity against various malignancies, including non-small cell lung cancer, melanoma, and triple-negative breast cancer. Pembrolizumab is associated with numerous adverse reactions including mucosal and cutaneous reactions referred to as immune-related adverse events. These events can impact patient quality of life and lead to dose reduction or discontinuation of the medication. A comprehensive understanding of pembrolizumab's toxicities is crucial for the initiation of treatment. ***Case Presentation:*** We present the case of a 27-year-old man with stage IVB thymic carcinoma with a bulky anterior mediastinal mass, bilateral jugular, bilateral peritracheal, and bilateral cardiophrenic lymphadenopathies, and a small pericardial effusion. He received pembrolizumab IV every 3 weeks for 53 cycles over 39 months. The patient developed bleeding oral lesions approximately 38 months after treatment with pembrolizumab. ***Conclusion:*** The patient's pembrolizumab treatment was not interrupted and the perioral rash ultimately improved after treatment with steroids.

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Introduction

Pembrolizumab is a US Food and Drug Administration-approved drug with complex indications, including the treatment of many advanced solid tumor malignancies [1]. Pembrolizumab is a humanized monoclonal IgG4 kappa anti-programmed death-1 (PD-1) antibody that does not activate Fc receptors or the complement cascade, consequently inhibiting cytotoxic response [2]. Adverse reactions can affect any organ system, with the skin being one of the most commonly affected organs [3]. Additionally, there have been numerous reports of mucosal adverse effects (AEs), secondary to pembrolizumab therapy [4–6]. We report a case of circumorificial plasmacytosis (CP) in a patient with stage IVB thymic carcinoma undergoing treatment with pembrolizumab. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary Figure 1 (for all online suppl. material, see https://doi.org/10.1159/000535015).

Case Report

A 27-year-old man with stage IVB thymic carcinoma was diagnosed 7 years ago. He initially presented with a 7.7 × 7.1 cm bulky anterior mediastinal mass, bilateral jugular, bilateral peritracheal, and bilateral cardiophrenic lymphadenopathy with small pericardial effusion. Biopsy of the mediastinal mass revealed a primary lymphoepithelioma-like thymic carcinoma with metastatic Epstein-Barr virus-positive undifferentiated carcinoma from peripheral right neck lymphadenopathy. He received neoadjuvant therapy with five cycles of carboplatin and paclitaxel. The patient underwent surgical excision of the thymus, pericardium, part of the involved lung, and regional lymph nodes. Pathological examination confirmed poorly differentiated lymphoepithelioma-like thymic carcinoma with local invasion of the pericardium and lungs with regional metastatic adenopathy. The patient received three cycles of adjuvant cisplatin-etoposide-based chemoradiation. The patient did well and underwent ablation of pulmonary recurrence 2 years later. Surveillance imaging 4 years after surgery revealed recurrent bilateral mediastinal adenopathy. He was treated with pembrolizumab IV every 3 weeks for 53 cycles over 39 months. He tolerated the treatment well, except for bilateral pruritus of the eyes, which responded to antihistamine and abdominal pain managed with omeprazole after negative upper endoscopy. The patient developed bleeding oral lesions approximately 38 months after the pembrolizumab therapy. On exam, there were numerous lesions. One lesion on the left inner cheek was quarter sized, red, and fissured. There were an additional 4 lesions under the patient's tongue. The patient's throat and gums were without lesions, redness, or bleeding. There were no white patches or enlarged lymph nodes. There was also no drainage, foul odor, or bleeding observed. The patient was prescribed dexamethasone mouthwash for discomfort and inflammation and was referred to oral surgery for further evaluation.

Oral surgery evaluation revealed a 4.0 × 3.0 cm red and fissured soft tissue with redundancy in the left inner cheek. There was a second similar lesion measuring 2.0 × 3.0 cm on the left lower inner lip (Fig. 1, 2). Four small red lesions were observed under the patient's tongue. The patient noted these patients were painful. Again, there was no drainage, foul odor, or bleeding present at the time of evaluation. It was recommended the patient have these lesions biopsied by ENT.

Biopsy of the lesions from the buccal mucosa and lip revealed infiltration of mature plasma cells beneath the epithelium (Fig. 3, 4). There was no evidence of granulomatous or lichenoid-like inflammation noted on pathology report. Serum protein electrophoresis and

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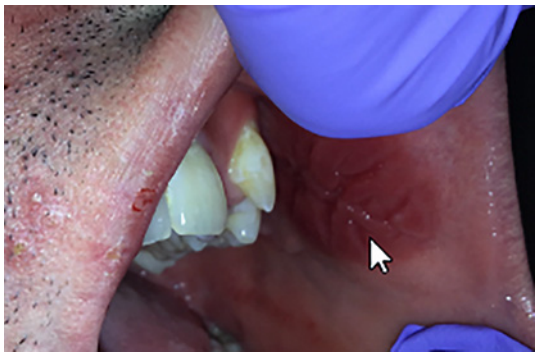

Fig. 1. Buccal lesion.

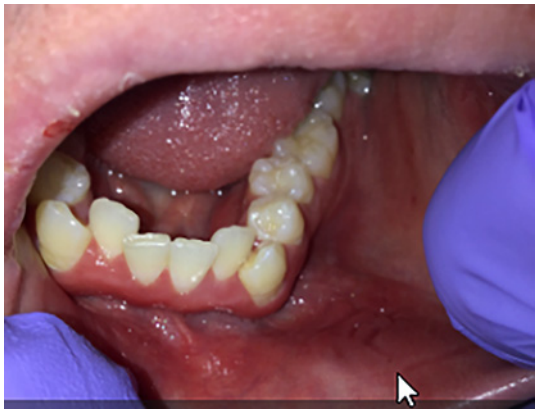

Fig. 2. Lower lip lesion.

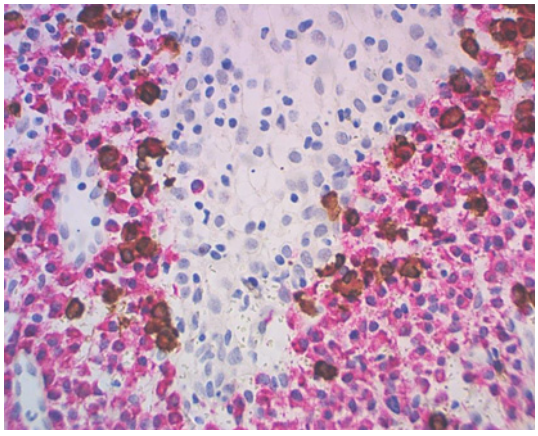

Fig. 3. Chromogenic in situ hybridization showing polytypic light chain pattern (kappa: red and lambda: brown, original magnification ×400).

PET scan were obtained to exclude monoclonal lymphoproliferative disorder and were ultimately not indicative of this condition. It was concluded that this was most likely circumorificial plasmacytosis induced by pembrolizumab. Ultimately, it was determined that the risk of cancer outweighed the risk of side effects at this time, so pembrolizumab treatment was continued.

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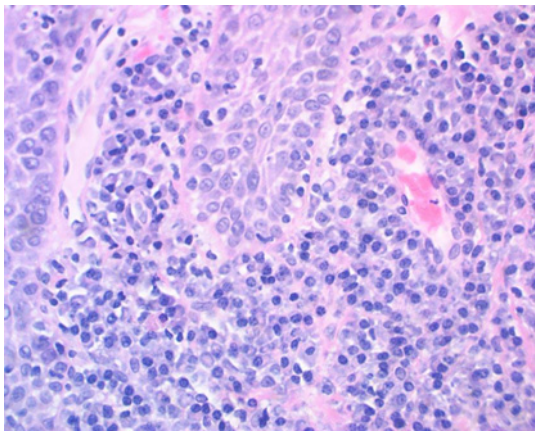

Fig. 4. Sheets of mature plasma cells beneath the epithelium (H&E, original magnification ×400).

Discussion

There is currently limited literature describing cases of CP associated with PD-1 inhibitors. However, numerous dermatological adverse effects (AEs) have been reported from pembrolizumab therapy. Most commonly, symptoms include rash, pruritus, and vitiligo [3]. Other noted AEs include xerosis, alopecia, stomatitis, urticaria, photosensitivity reactions, hyperhidrosis skin exfoliation, and hair color changes occurring at various doses [3]. One study even found that 42% of patients (35/83) developed cutaneous AEs attributed to pembrolizumab [7]. The incidence and risk of all-grade and high-grade events appeared to be low [8].

CP is a rare plasma cell proliferative disorder of the orifical mucous membranes and the etiology to date is unknown [9]. There have been few cases in the literature of CP secondary to PD-1 checkpoint inhibitors, like pembrolizumab [4]. There has been a case of severe mucositis secondary to pembrolizumab therapy [5]. It has been thought that CP due to pembrolizumab may be the result of activation of native T cells that are leading to differentiation and proliferation of polyclonal plasma cells [4].

Our patient's mucosal AEs were significantly delayed in onset. Similarly, it has been documented that cutaneous AEs have increasingly been recognized to have a delayed onset and prolonged duration when compared to AEs from other classic chemotherapies, but the onset of these toxicities can range from a few weeks to several months from initiation of treatment depending on the AE [10]. It has been suggested that patients who experience dermatological AEs have had more favorable outcomes [4, 11].

Our patient's CP was successfully treated with a 1-week course of oral steroids. Additionally, the patient's CT scan after lesion occurrence showed improvement when compared to previous scans, indicating a positive response to treatment. The patient has continued to tolerate treatment with pembrolizumab well and has not developed any further oral lesions.

Conclusion

Checkpoint inhibitors are integral to the treatment of numerous malignancies. As with many chemotherapeutic agents, there are numerous off-target effects. Our case demonstrates the delayed onset of CP induced by pembrolizumab therapy. As the use of checkpoint inhibitors continues to increase, providers should be aware of potential mucocutaneous AEs

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and their relevance to improved outcomes. Further research is needed to understand the mechanisms of these AEs and what they may mean for a patient's response to therapy and prognosis.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical approval was not required for this study in accordance with the local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.O. identified the case to be reported. Y.T. analyzed the data, completed the literature review, and prepared the manuscript. S.T., A.O., and R.C. assisted with data analysis, preparation of the manuscript, and its revisions. All authors have read and approved the final manuscript.

Data Availability Statement

The majority of the data analyzed for this publication are included within the article. Some details are not publicly available because of the potential risk of compromising confidentiality. Further inquiries can be made to the corresponding author, Dr. Sabo Tanimu, MD, USA.

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