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Pembrolizumab-induced oral lichen planus pemphigoides with mucous membrane pemphigoid preceding lichen planus

KEYWORDS
Programmed cell death 1 inhibitor;
Pembrolizumab;
Immune-related adverse event;
Mucous membrane pemphigoid;
Lichen planus

The programmed cell death protein 1 (PD-1) inhibitor pembrolizumab is used for various advanced malignancies.[1] Several reports mention pembrolizumab-associated mucocutaneous immune-related adverse events,[1] including lichen planus pemphigoides (LPP) with bullous pemphigoid features with cutaneous lichen planus (LP).[2,3] Pembrolizumab-induced oral LPP related to mucous membrane pemphigoid (MMP) has not been reported. This case report described a rare case of pembrolizumab-induced oral LPP wherein oral lichen planus (OLP) arose after MMP.

An 82-year-old patient was referred to our department. He had a history of diabetes and had undergone pembrolizumab therapy since January 2021 for lung metastasis of right renal pelvic carcinoma. One week before the initial visit, the patient began experiencing oral mucositis, affecting the entire oral cavity (Fig. 1A). He was diagnosed with severe pembrolizumab-induced oral mucositis. Topical betamethasone ointment (0.05 %) and azulene sodium sulfonate with 4 % lidocaine gargle were prescribed. However, the oral symptoms did not improve. A biopsy of a lower lip mucosal ulcer revealed submucosal inflammatory cell infiltration (Fig. 1B). Direct immunofluorescence microscopic image showed complement 3 (C3) and immunoglobulin G (IgG) deposition in the basement membrane zone (BMZ) and vascular wall (Fig. 1C). Bullous pemphigoid 180 (BP180) NC16A was positive (366.0 U/mL) in enzyme-linked immunosorbent assay. A dermatologist diagnosed papules on the shoulder and abdomen as asteatotic eczema. The oral findings confirmed the diagnosis of pembrolizumab-induced MMP. Pembrolizumab was discontinued in June 2021, and doxycycline (100 mg), topical betamethasone ointment (0.05 %), and azulene sodium sulfonate with 4 % lidocaine gargle were prescribed. The anti-BP180 antibody levels decreased (Fig. 1D), and the oral manifestations improved gradually.

Pembrolizumab was restarted in September 2021. Oral manifestations subsequently flared with white lines and erosive and ulcerative mucositis (Fig. 1E), but levels of anti-

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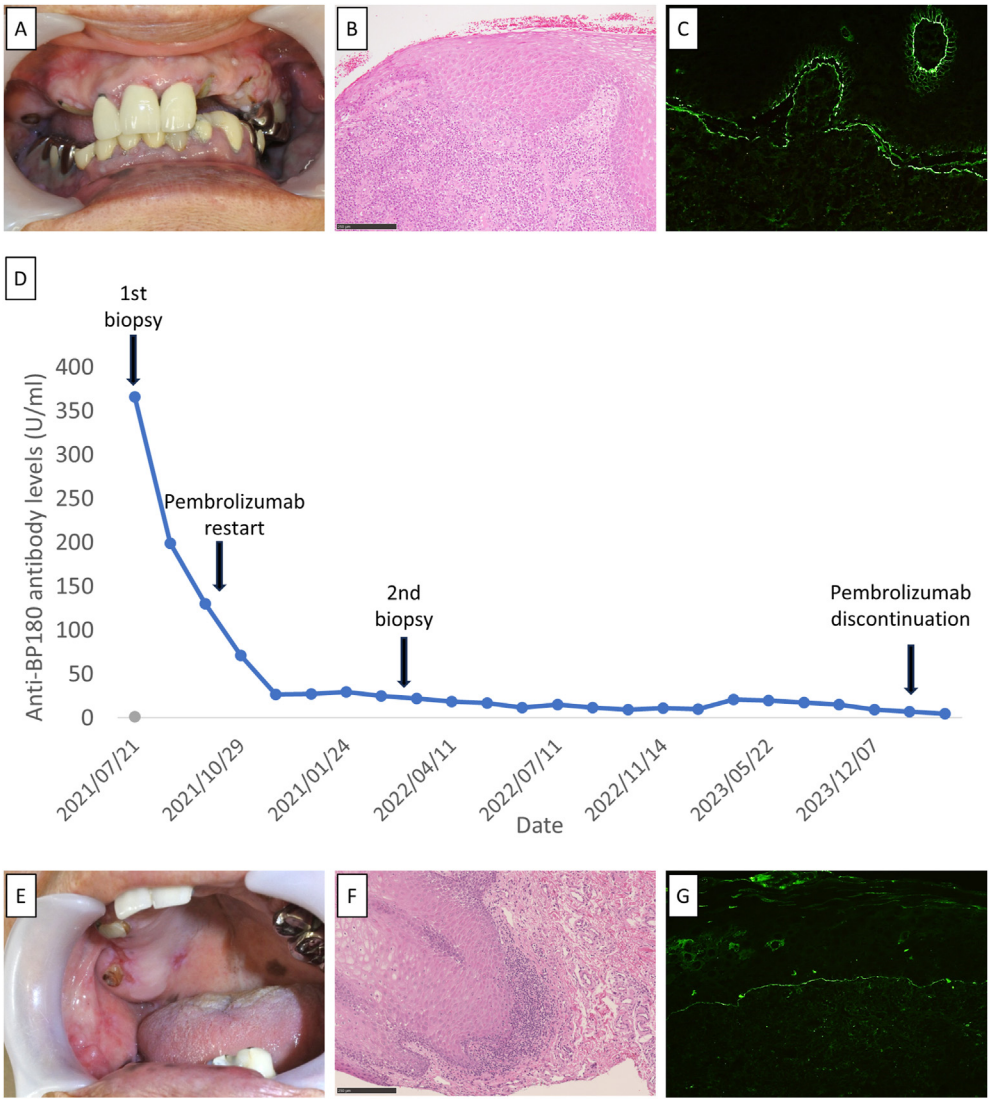

Figure 1 Clinical photographs, histopathological microphotographs, and direct immunofluorescence microphotographs of oral lesions in an 82-year-old male patient.
(A) Intraoral presentation at the initial visit showed severe oral mucositis affecting the entire oral cavity.
(B) Histopathological microphotograph of the first biopsy specimen from a lower labial mucosal ulcer showed a lymphoplasma cell infiltrate in the lamina propria (hematoxylin and eosin stain, original magnification, 100 ×).
(C) Direct immunofluorescence microphotograph of the first biopsy specimen showed a linear complement 3 (C3) deposition in the basement membrane zone and vascular wall (original magnification, 100 ×).
(D) The graph showed the changes in the level of anti-bullous pemphigoid 180 (BP180) antibodies, which decreased, even after discontinuation of the pembrolizumab.
(E) Intraoral examination at the second biopsy site showed white lines and erosive and ulcerative mucositis of the right buccal mucosa.
(F) Histopathological microphotograph of the second biopsy of the right buccal mucositis lesion showed a band-like, lymphocytic infiltrate in the lamina propria and the hyperplastic oral epithelium with saw-tooth rete ridges (hematoxylin and eosin stain, original magnification, 100 ×).
(G) Direct immunofluorescence microphotograph of the second biopsy, showed a linear immunoglobulin G (IgG) deposition at the basement membrane zone and vascular wall (original magnification, 100 ×).

BP180 antibodies remained low. A biopsy of a buccal mucositis lesion histopathologically revealed OLP (Fig. 1F). Direct immunofluorescence revealed IgG and C3 deposition along the BMZ (Fig. 1G). Sequential clinical and laboratory findings were consistent with a diagnosis of oral LPP. Systemic prednisone was withheld because of his desire not to use insulin. Oral diphenyl sulfone, cyclosporine gargle, and topical betamethasone ointment were prescribed. Oral

manifestations improved minimally; thus, pembrolizumab was discontinued in January 2024. Two months later, his oral manifestations were nearly in remission.

The oral LPP development was consistent with pembrolizumab-induced adverse events, given the onset at 4 months after its initiation, exacerbation on reinitiation, and remission of oral manifestations on ceasing pembrolizumab. Pembrolizumab-induced oral LPP has not been reported. In reports[2,3] of oral LPP with MMP unrelated to pembrolizumab use, MMP occurred after OLP. These reports mentioned that sequestered MMP antigens were exposed in BMZ tissue destroyed by OLP inflammation, under the concept of epitope spreading.[2,3] In this case, we surmised OLP developed after MMP. Based on the concept of epitope spreading, BMZ tissue was destroyed because of MMP inflammation, with exposed protein acting as secondary antigens of OLP. Mignogna et al.[3] described bidirectional shifts from MMP to OLP. However, oral LPP pathophysiology is controversial, and definite oral LPP diagnostic criteria are nonexistent.[4,5] Further study is necessary to elucidate these mechanisms.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

None.

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