Paraneoplastic pemphigus manifesting in a patient treated with pembrolizumab for urothelial carcinoma

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Key words: anti-programmed-death-1; dermatologic toxicities; immune checkpoints inhibitors; immune-related adverse event; paraneoplastic pemphigus; pembrolizumab; urothelial carcinoma.

INTRODUCTION

Paraneoplastic pemphigus (PNP) is a rare, highly fatal autoimmune blistering disease occurring in the setting of occult or confirmed neoplasms. The clinical hallmark of PNP is recalcitrant, painful mucositis, which may be accompanied by polymorphic cutaneous eruptions.[1] In the era of onco-dermatology, manifestations of PNP or PNP-like immune-related adverse events (irAE) are rare in patients receiving immune checkpoint inhibitor (ICI) therapy.[2] The diagnosis of PNP is confirmed by skin biopsy with histopathologic evaluation and immunologic studies.[1] We present a case of PNP associated with the administration of the ICI, pembrolizumab, in the treatment of metastatic urothelial carcinoma.

Abbreviations used:

ICI: immune checkpoint inhibitor
irAE: immune-related adverse events
PNP: paraneoplastic pemphigus

CASE REPORT

A 57-year-old Caucasian woman with metastatic urothelial carcinoma was referred to our service for a 7-month history of mucosal blisters, which started while she was receiving pembrolizumab therapy. She had a history of high-grade urothelial carcinoma with focal squamous and sarcomatoid features involving the dome of the bladder. She received 6 cycles of neoadjuvant dose-dense methotrexate, vinblastine, adriamycin, and cisplatin, followed by complete cystectomy with bilateral pelvic lymphadenectomy and the development of an ureteroileal conduit. Pathologic evaluation revealed metastatic urothelial carcinoma with extranodal extension involving 1/28 lymph nodes, and adjuvant treatment with pembrolizumab (200 mg intravenous, 6 cycles) was initiated. After 9 months of therapy, she remained without evidence of active disease but developed painful ulcers of the oral cavity and genital mucosa. She had no other evidence or history of irAE. Pembrolizumab was discontinued, and a slow prednisone taper was prescribed. She pursued therapy with oral steroids and intralesional steroid injections for several months without relief.

On referral to our clinic, physical examination revealed numerous ulcers with extensive granulation predominantly on the dorsal aspect of the tongue and inferior vermillion lip (Figs 1 and 2). She also had painful erosions of the labia majora. Full skin examination revealed no other areas of involvement.

A biopsy of the lower lip mucosa was performed. Microscopic analysis revealed lichenoid interface mucositis with subepithelial clefting (Fig 3). A perilesional biopsy, taken for direct immunofluorescence, revealed a linear layer of immunoglobulins and complement deposition along the basement membrane and weak intercellular staining (Fig 4). Enzyme-linked immunosorbent assay testing was

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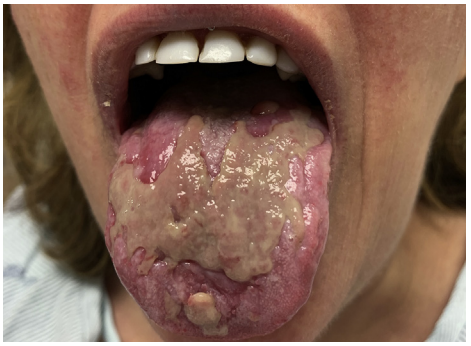

Fig 1. Extensive ulceration of the inferior vermillion lip and tongue with overlying crust and granulation tissue.

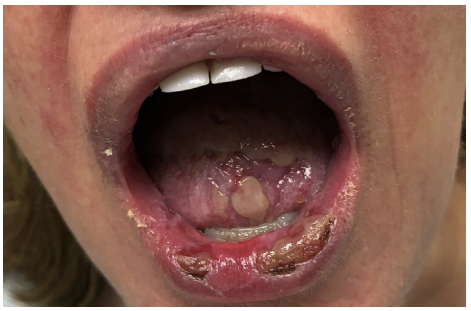

Fig 2. Painful ulcerations of the tongue.

positive for antibodies towards desmoglein 3 as well as bullous pemphigoid antigens 180 and 230. Medication review was negative for any thiol or non-thiol causes of drug-induced pemphigus.

The clinical and histologic findings in combination with the mixed pattern on DIF were highly suggestive of PNP. High-resolution chest tomography performed to rule out bronchiolitis obliterans, a high mortality complication of PNP, showed no evidence of disease. Treatment was initiated with intravenous rituximab, 375 mg/m2 weekly, for 1 month, along with high-dose oral steroids. Six weeks post rituximab, her genital involvement resolved, and her oral mucosal disease substantially improved (Fig 5). Corresponding to this, anti-DSG 3, -bullous pemphigoid antigens 180, and 230 antibodies returned to normal. Subsequently, she developed worsening oral ulceration, so a plan was made to repeat the course of rituximab with the addition of intravenous immunoglobulin.

DISCUSSION

PNP is most commonly associated with lymphoproliferative disorders, which are present in up to 84% of reported cases.[1] Carcinomas of epithelial origin, as in our patient, account for less than 10% of the cases.[1] While PNP is almost always associated with an active neoplasm, PNP has rarely been

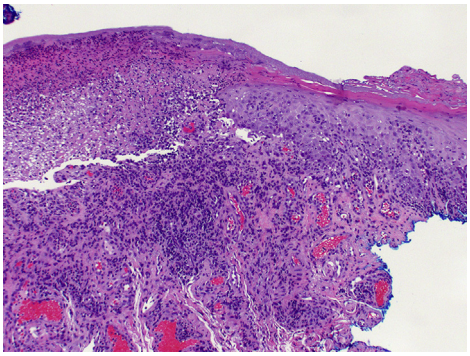

Fig 3. PNP. Squamous mucosa with ulceration (left), lichenoid lymphohistiocytic infiltrate, and focal subepithelial cleft (center) (hematoxylin-eosin−stain; original magnification, ×100).

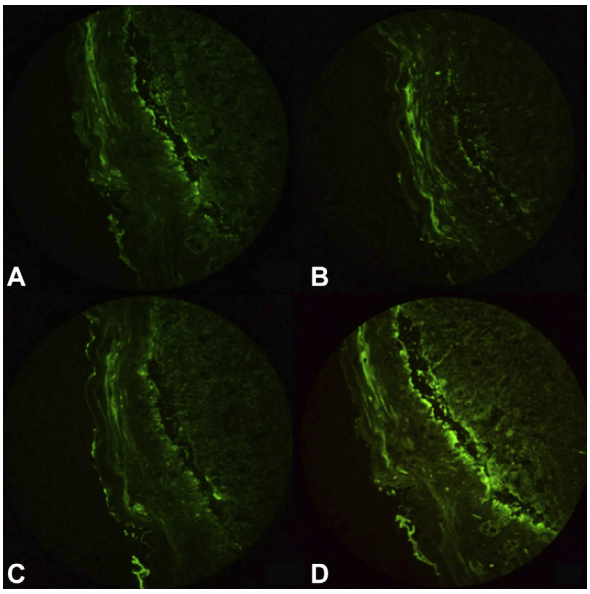

Fig 4. PNP. Direct immunofluorescence showing mixed pattern of basal layer linearity, subepithelial split, and some keratinocyte staining. **A**, IgG. **B**, IgM. **C**, IgA. **D**, C3. (original magnification, ×200).

reported in patients who are either in remission[3] or have no detectable underlying neoplasm.[4]

Through their immunomodulatory affects, ICIs such as pembrolizumab cause a variety of cutaneous irAEs. Bullous disorders are among the spectrum of cutaneous irAEs encountered from ICI therapy, most commonly bullous pemphigoid.[5] Oral and cutaneous lichen planus is also well described. Infrequently, subclinical PNP and PNP-like irAEs with absence of mucositis have been described in the context of ICI therapy.[2,6-8]

We strongly considered the differential diagnosis of oral erosive lichen planus, given the history of pembrolizumab combined with oral erosions.

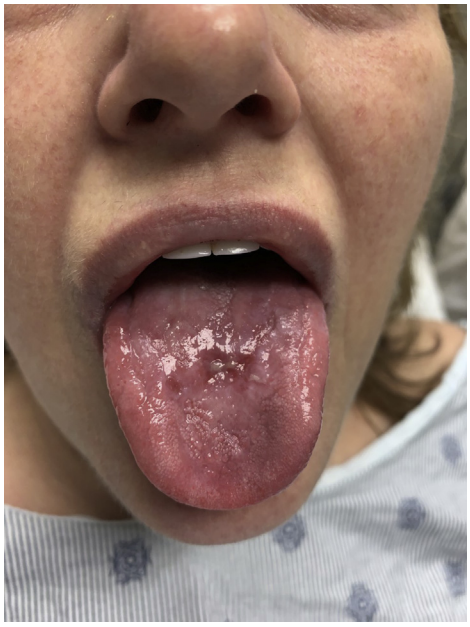

Fig 5. PNP. Clinical improvement 6 weeks following rituximab treatment and 10 weeks off prednisone.

However, the predominant involvement of the tongue and lower vermillion lip and the lack of Wickham's striae were clinically more consistent with PNP. The lichenoid infiltrate on histology could have been consistent with PNP or lichen planus. Anti-PNP antibodies were tested for, and the test came out negative; however, this was done after the patient received rituximab and demonstrated clinical improvement. The presence of 3 types of anti-basement membrane autoantibodies was further suggestive of an autoimmune bullous disorder along with weak immunofluorescence findings. Her considerable improvement with rituximab following a lack of clinical improvement after several months of steroid therapy was also supportive of the diagnosis.

To the best of our knowledge, this is the first case of PNP associated with programmed death receptor-1 in a patient with no known history of anti-PNP antibody positivity or previous clinical findings of PNP. However, it is impossible to determine whether PNP was a direct result of pembrolizumab, or if subclinical PNP was unmasked by pembrolizumab, as we did not have any previous serology results. Despite disease remission, our patient did not develop PNP until after several months of pembrolizumab treatment. Although rare, especially in a patient with no evidence of active malignancy, it is possible that the epithelial carcinoma contributed to the patient's PNP.

IrAEs can be life threatening and difficult to diagnose. PNP is a disease associated with high morbidity and mortality. Even with aggressive immunosuppression, management is difficult. Our patient's prolonged course prior to correct diagnosis was mitigated by multiple courses of oral steroids and intralesional steroid injections. These interventions likely dampened the effects of the programmed death receptor-1 inhibitor as well as the course of her PNP prior to starting rituximab. Correct diagnosis allowed for an appropriate steroid-sparing agent and close monitoring for associated complications such as bronchiolitis obliterans.

This case highlights the importance of interdisciplinary care between oncologists, dermatologists, and dermatopathologists in the ICI patient population. Clinicians should be aware of a possible association between pembrolizumab and PNP.

Conflicts of interest

None declared.

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