Atypical laboratory presentation of paraneoplastic pemphigus associated with Castleman disease

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INTRODUCTION

Because of variability in clinical and histopathologic findings, the diagnosis of paraneoplastic pemphigus (PNP) frequently relies on the combination of direct immunofluorescence and indirect immunofluorescence (IIF). Here we present a unique case of PNP associated with Castleman disease in which IIF on rat bladder substrate was negative, but enzyme-linked immunosorbent assay (ELISA) for anti-envoplakin antibodies was positive.

Abbreviations used:

ELISA:	enzyme-linked immunosorbent assay
IIF:	indirect Immunofluorescence
PNP:	paraneoplastic pemphigus
PV:	pemphigus vulgaris

CASE REPORT

A 40-year-old previously healthy man presented with a 4-month history of extensive blistering of the mouth, chest, and back. He was initially treated by an outside dermatologist with prednisone, 40 mg daily, and azathioprine, 100 mg twice daily, without improvement. Examination found several discrete erosions along the lips, tongue, and buccal mucosa and multiple erythematous scaly erosions and plaques on the chest and back. Biopsy of the gingiva found suprabasilar discohesiveness with acantholytic cells and diffuse mixed inflammatory infiltrate. Direct immunofluorescence found IgG positivity and speckled C3 positivity at the epithelial cell membrane. IIF on monkey esophagus substrate was positive for intercellular antibodies without associated basement membrane staining. Based on these results, a diagnosis of pemphigus vulgaris (PV) was initially favored. Chest radiograph, obtained for an indeterminate QuantiFERON Gold test, incidentally found an abnormality concerning for a mediastinal mass. Further immunologic workup found negative IIF on rat bladder substrate; however ELISA for anti-envoplakin antibodies was positive to 6.3 (cutoff ≥ 1.0). ELISA for anti-desmoglein 1 and 3 antibodies was negative. Mediastinal biopsy found a low-grade spindle cell neoplasm. After incomplete resection, the final pathology finding was consistent with Castleman disease. Outside positron emission tomography–computed tomography results were normal, supporting a diagnosis of unicentric Castleman disease.

After tumor resection, the patient continued treatment with a prolonged prednisone taper and 2 rituximab infusions. Over time, there was significant improvement, although periodic development of new oral ulcers and gingival bleeding required increased steroid dosing (Fig 1). Seven months after tumor resection, the patient began to notice mild shortness of breath with exertion. Pulmonary function testing found severe irreversible obstructive disease most consistent with bronchiolitis obliterans. The patient's pulmonary status has remained stable after the initiation of treatment with inhaled fluticasone and montelukast. Recent chest computed

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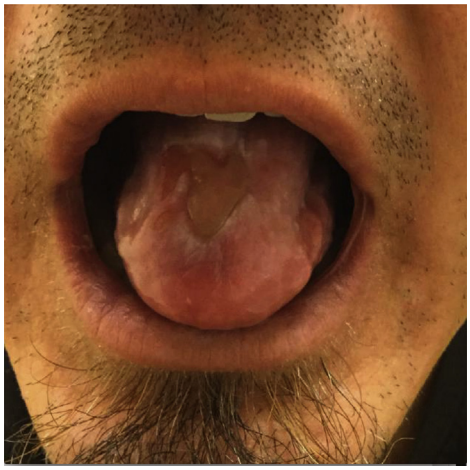

Fig 1. Dorsal midtongue. At his most recent visit, the patient had a new ulcerated plaque on his midtongue with yellow/white fibrinous pseudomembrane.

tomography found a new 16-mm nodule in the area of prior resection, suspicious for recurrent disease. Therapeutic options including repeat rituximab infusions are currently being considered.

DISCUSSION

Castleman disease is the third most common neoplastic disorder associated with PNP.[1] To our knowledge, this is the first case of PNP associated with Castleman tumor in which IIF on rat bladder epithelium was negative but ELISA for anti-envoplakin antibodies was positive. Initial IIF findings were more consistent with PV; however, subsequent ELISA testing, coupled with the clinical findings of Castleman disease and pulmonary involvement, is strongly supportive of PNP. Among recent studies, sensitivity and specificity of IIF on rat bladder have ranged from 74% to 86% and 98% to 100%, respectively.[2,3] The sensitivity and specificity of anti-envoplakin ELISA have ranged from 63% to 82% and 98% to 100%, respectively.[2-4] Of note, anti-envoplakin ELISA is currently available primarily for research use. This case supports the notion that there may be clinical value in using anti-envoplakin ELISA as part of the routine diagnostic workup for PNP, particularly for cases in which laboratory analysis is initially inconclusive. It also serves as a reminder for clinicians to retain a high index of suspicion for PNP when patients are recalcitrant to treatment for PV.

The progression of pulmonary disease in this case is also noteworthy. Bronchiolitis obliterans develops in up to 93% of cases of PNP associated with Castleman disease.[5] Respiratory failure is often rapidly progressive and is the most common cause of death in these patients.[5,6] This case is unusual in that, despite evidence of severe obstructive disease, our patient's pulmonary symptoms have been mild and stable for nearly 2 years.

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