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Letter to the Editor

Successful treatment with intravenous immunoglobulin and rituximab for bronchiolitis obliterans associated with paraneoplastic pemphigus

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Abbreviations: bronchiolitis obliterans (BO); computed tomography (CT); direct immunofluorescence (DIF); enzyme-linked immunosorbent assay (ELISA); immunofluorescence (IF); paraneoplastic pemphigus (PNP)

Key words: bronchiolitis obliterans; envoplakin; enzyme-linked immunosorbent assay; follicular dendritic cell sarcoma; paraneoplastic pemphigus; periplakin

Dear Editor,

We report a patient suffering from paraneoplastic pemphigus (PNP) with follicular dendritic cell sarcoma complicated with bronchiolitis obliterans (BO).

A 13-year-old boy with a 2-month history of painful ulcers on the buccal mucosa and a 1-month history of dyspnea was referred to our hospital. A posterior mediastinal mass (4.9 x 5.0 x 4.8cm) had been found by lung computed tomography (CT) in the previous hospital. The patient had erosive lesions on the buccal mucosa, the tongue and the lips (Fig. 1a,b). A biopsy specimen from the oral mucosa showed only erosions without any mucous membrane epithelia, and direct immunofluorescence (DIF) findings for depositions of immunoglobulins and complements were inconclusive. Indirect immunofluorescence (IIF) staining using normal human skin sections as a substrate detected circulating IgG antibodies against the keratinocyte cell surface. IIF staining using rat bladder sections revealed circulating IgG antibodies to the transitional epithelium at a titer of 1:40. Immunoblot analysis using epidermal extracts as a substrate showed positive immunoreactivity to the 210-kDa envoplakin and the 190-kDa periplakin. Anti-desmoglein 3 antibodies were negative by ELISA, although anti-desmoglein 1 antibodies were weakly positive. His respiratory symptoms rapidly worsened. Chest CT evaluation demonstrated bronchial wall thickening and a mosaic pattern of perfusion in the lungs (Fig. 1c). Pulmonary function tests revealed obstructive impairment. His lung disease was diagnosed as BO associated with PNP. The posterior

mediastinum tumor was surgically resected and the histopathological diagnosis was follicular dendritic cell sarcoma. He was treated with betamethasone at 2.5~1.5 mg/day and with 6 courses of IVIG (Fig. 1e). After the surgery followed by oral betamethasone, the titers of serum anti-periplakin and anti-envoplakin autoantibodies measured using our in-house ELISA[1] quickly decreased to below the cutoff values. Although the oral ulcers gradually improved, his respiratory function worsened. Then, rituximab (monoclonal antibody against CD20) (600mg) was administered four times and the worsening of his respiratory function started to decelerate, resulting in a stable condition. For the 6 years of follow-up, his respiratory symptoms have remained stable. Follow-up chest CT scans (Fig. 1d) and the results of pulmonary function tests have also been stable: forced expiratory volume in 1 second % (FEV_1%) around 35 %; vital capacity (VC) about 3.2 liter (approximately 70 % of the predicted value).

Recently, the efficacy of rituximab therapy for refractory autoimmune bullous diseases including PNP has been confirmed.[2,3] It was reported that the BO did not improve with cyclosporin, steroid, rituximab and IVIG in a case of PNP.[4] However, the BO in the present PNP patient was successfully treated with the combination therapy of oral betamethasone, IVIG and rituximab.

Pulmonary damage, mostly due to BO, is the main cause of death in PNP. In the present patient, the BO gradually worsened, even after the serum anti-periplakin and anti-envoplakin autoantibodies had significantly fallen

from the administration of oral betamethasone and IVIG. The exacerbation of BO even after the disappearance of anti-periplakin and anti-envoplakin autoantibodies in our patient could suggest that neither anti-periplakin nor anti-envoplakin autoantibodies are related to the pathogenesis of BO.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest for this article.

References

1 Muro Y, Sugiura K, Shiraki A *et al.* Detection of autoantibodies to periplakin and envoplakin in paraneoplastic pemphigus but not idiopathic pulmonary fibrosis using full-length recombinant proteins. *Clin Chim Acta* 2014; 429: 14-17.

2 Kurihara Y, Yamagami J, Funakoshi T *et al.* Rituximab therapy for refractory autoimmune bullous diseases: A multicenter, open-label, single-arm, phase 1/2 study on 10 Japanese patients. *J Dermatol* 2019; 46: 124-130.

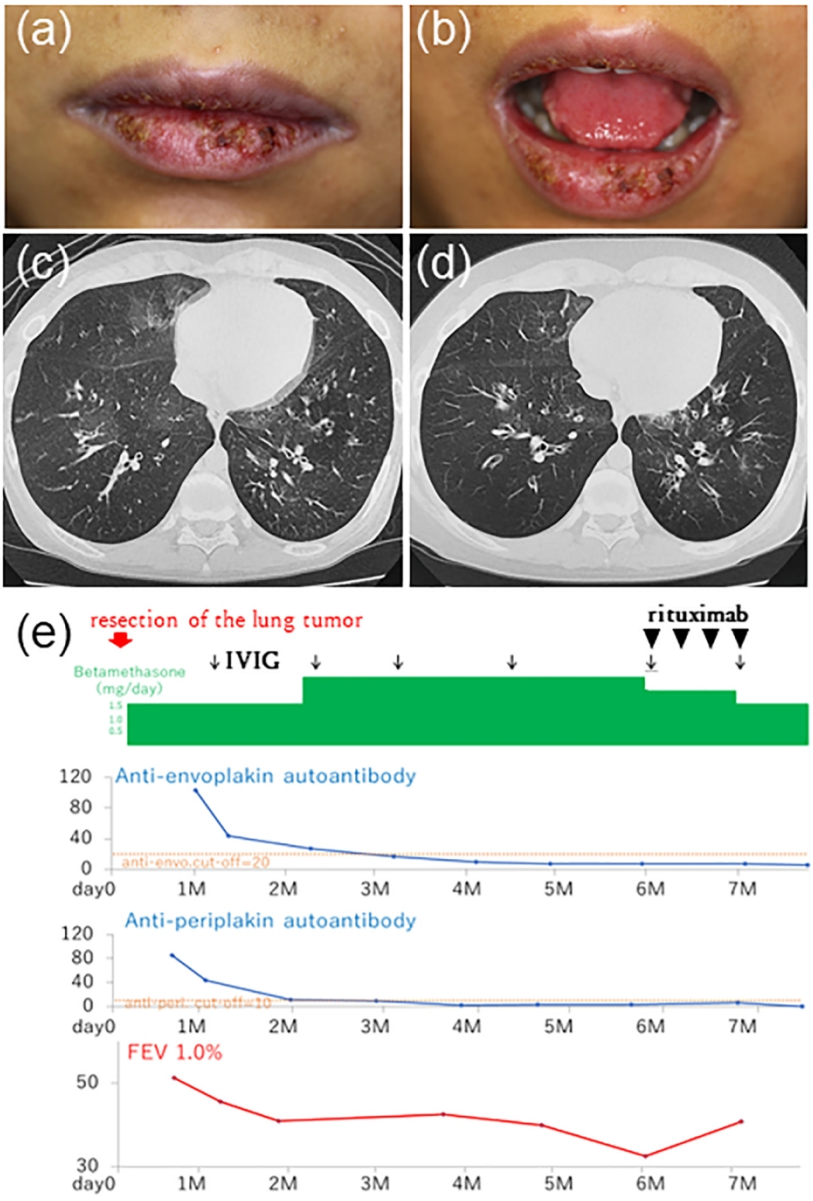
3 Kikuchi T, Mori T, Shimizu T *et al.* Successful treatment with bendamustine and rituximab for paraneoplastic pemphigus. *Ann Hematol* 2017; 96: 1221-1222.

4 Namba C, Tohyama M, Hanakawa Y *et al.* Paraneoplastic pemphigus associated with fatal bronchiolitis obliterans and intractable mucosal erosions: Treatment with cyclosporin in addition to steroid, rituximab and intravenous immunoglobulin. *J Dermatol* 2016; 43: 419-422.

Figure legends

Figure 1. Clinical features, chest CT findings and clinical course with serum anti-envoplakin and anti-periplakin autoantibody titers in the present patient

(a, b) Erosions and crusts are observed on the lips and the tongue. (c) A mosaic pattern of perfusion and bronchial wall thickening suggesting BO are seen in the patient's chest CT image before the rituximab treatment. (d) Findings of BO including bronchial wall thickening and a mosaic pattern of perfusion have been largely stable in follow-up chest CT scans for the 6 years after the introduction of the rituximab treatment. (e) After the introduction of systemic betamethasone, the serum anti-envoplakin and anti-periplakin autoantibodies decreased. However, the patient's respiratory function gradually worsened and rituximab was administered. His respiratory function then started to improve. Day 0 is the day of the patient's initial visit to our hospital. ↓, intravenous immunoglobulin; ▼, rituximab; FEV1.0%, forced expiratory volume in 1 second %.



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