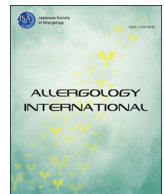




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Letter to the Editor

A case of refractory chronic rhinosinusitis with anti-desmoglein 3 IgG4 autoantibody

Dear Editor,

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a systemic, refractory, chronic inflammatory disease characterized by high serum IgG4 levels and histopathological findings of IgG4-positive plasma cell infiltration and fibrosis.^{1,2} Although recent reports have documented cases of refractory chronic rhinosinusitis (CRS) accompanied by IgG4 infiltration (IgG4-CRS),^{3–5} the underlying mechanism remains unknown.

Desmoglein 3 is an autoantigen of Pemphigus vulgaris (PV), an autoimmune blistering mucocutaneous disease.⁶ Here, for the first time, we report a case of refractory CRS with treatment-recalcitrant nasal polyposis accompanied by infiltration of IgG4 autoantibody specific for desmoglein 3. This case was diagnosed as Mikulicz's disease because of bilateral submandibular and lacrimal glands swelling. We assessed the relationship between IgG4-CRS and desmoglein 3 autoantibody.

A 42-year-old male who visited outpatient clinic of our hospital complained severe nasal obstruction of both sides, and also mass lesion in bilateral submandibular regions in July 2013. Initial medical examination revealed polyps in both nasal cavities and a deviation of the nasal septum toward to the right nasal cavity. Computed tomography (CT) of the paranasal sinuses and neck revealed bilateral sinusitis and bilateral submandibular and lacrimal glands swelling. Serum IgG4 and IgG levels were 383 (normal, 4.8–105 mg/dL) and 1931 mg/dL (normal, 870–1700 mg/dL), respectively. Anti-desmoglein 1 antibody and anti-PB180 antibody were negative (<3; normal, <3); anti-desmoglein 3 antibody was very high (4390; normal, <3). Eosinophil proportion were 7830/ μ L and 6.3% (normal, <7%). The pharynx, oral mucosa, and skin were normal, showing no lesions by whole body CT.

Endoscopic sinus surgery (ESS) and biopsy of the left side of the submandibular gland under general anesthesia were performed in January 2015. The patient was then prescribed an antihistaminic agent and a nasal steroid spray. Although the nasal and paranasal mucosa showed slight swelling after ESS, the nasal condition improved and has remained healthy during follow up.

Nasal and paranasal sinus mucosa and submandibular gland tissue obtained during surgery were fixed in neutral-buffered formalin, embedded in paraffin, and sectioned. Immunohistochemical staining was performed with mouse anti-human desmoglein 3 (Hycult Biotech, The Netherlands) and mouse anti-human IgG4

antibodies (Nichirei, Tokyo, Japan), and hematoxylin. Desmoglein 3 staining was observed at cell membranes of the nasal epithelial cells, the nasal, paranasal gland cells and submandibular gland cells (Fig. 1A,C). Less staining was observed in paranasal mucosa than nasal mucosa. IgG4 staining was observed in the nasal epithelial cells, the nasal, paranasal gland cells and submandibular gland cells (Fig. 1B,D). The desmoglein 3 staining areas were almost the same as the IgG4 in certain areas, although all were not the same. The nasal and paranasal lamina propria, and submandibular gland tissue, showed many IgG4-positive cells, with typical tissue fibrosis or sclerosis (Fig. 1E). Histopathological imaging of all tissues showed lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells >50%) (Fig. 1E,F).

An ELISA was developed to detect anti-human desmoglein 3 autoantibodies in serum. Briefly, 48-well microplates, pre-coated with human desmoglein 3, were incubated with serum from this case (5 $\times$, 20 $\times$, and 80 $\times$ dilutions) overnight at 4 °C. Plates were then assayed for IgG 4 using peroxidase-conjugated anti-human IgG4 monoclonal antibodies (Beckman Coulter, USA). 3,3',5,5'-tetramethyl-benzidine substrate reagent (Dako Corp., Glostrup, Denmark) was added for color development. The reaction was stopped with 1 N H₂SO₄, and OD₄₅₀ was measured. We examined the serum of 3 desmoglein 3 antibody-negative CRS cases, 2 with a high level and 1 with a normal level of IgG4, as controls. Anti-desmoglein 3 autoantibodies were detected in all serum concentrations in this case. Serum from the 3 control patients with CRS showed no increase in absorbance at any dilution with IgG4 (Fig. 2).

In this case, some IgG4-positive cells found in the paranasal lamina propria showed morphology similar to previously reported paranasal mucosa plasma cells that produced IgG4.^{3–5} Furthermore, some epithelial and gland cells were stained by anti-IgG4 antibodies, suggesting the presence of some autoantigens specific for IgG4 in the epithelial and gland cells.

One of several desmoglein isoforms, desmoglein 3 is characteristically expressed in the lower half of the epidermis and in wider zones of the oral mucosal epithelium, from basal to prickle cell layers.⁷ Zuckerman *et al.* reported desmoglein 3 in normal nasal mucosa and nasal polyps.⁸ We confirmed desmoglein 3 in cells of the epithelial layer and glands in the nasal and paranasal mucosa.

Diagnostic criteria for IgG4-related Mikulicz's disease are symmetrical swelling of at least 2 pairs of lachrymal, parotid, or submandibular glands for at least 3 months, elevated serum IgG4 levels (>135 mg/dl), or histopathological features including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma

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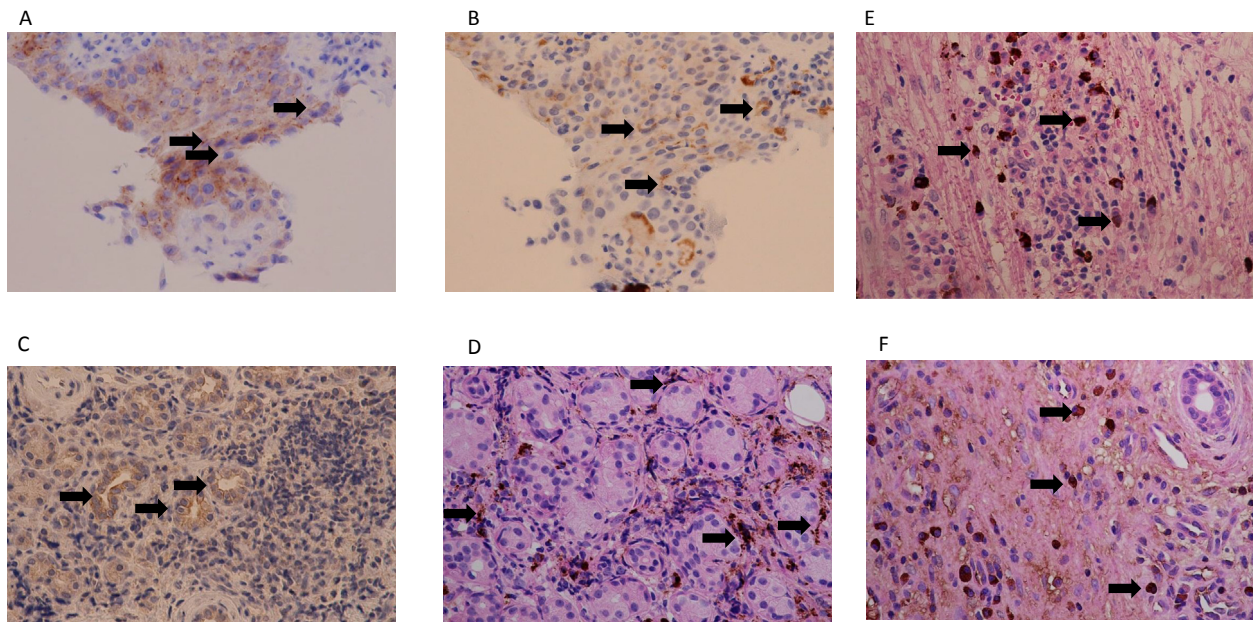


Fig. 1. **A:** Nasal mucosa with desmoglein 3 staining. Desmoglein 3 staining was observed at cell membrane of the nasal epithelial cells (black arrows). **B:** Nasal mucosa with IgG4 staining. IgG4 staining was observed at cell membrane of the nasal epithelial cells (black arrows). **C:** Submandibular gland with desmoglein 3 staining. Desmoglein 3 staining was observed at cell membrane of the submandibular gland cells (black arrows). **D:** submandibular gland with IgG4 staining. IgG4 staining was observed in the submandibular gland cells (black arrows). **E:** Nasal mucosa with IgG4 staining. The nasal lamina propria, showed many IgG4+ plasma cells (black arrows), with typical tissue fibrosis or sclerosis. **F:** Nasal mucosa with IgG staining. The nasal lamina propria, showed many IgG+ plasma cells (black arrows). IgG4+ plasma cells/IgG+ plasma cells was >50%.

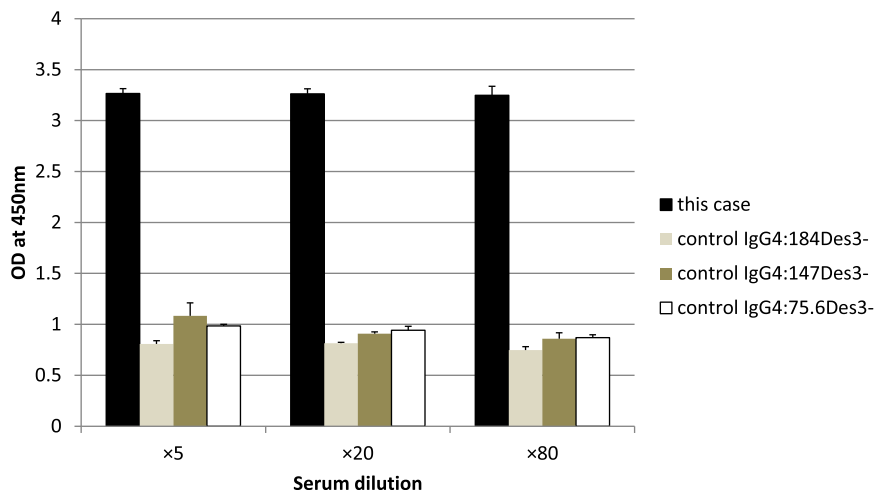


Fig. 2. Reaction between IgG4 and desmoglein 3 by ELISA.

cells/IgG+ plasma cells >50%) with typical tissue fibrosis or sclerosis.⁹ This case fulfills all diagnostic criteria.

In this case, IgG4 may have caused chronic inflammation because of its autoimmunity to desmoglein 3, and intractable CRS and sialodacryoadenitis persisted. In addition to IgG4, other IgGs, IgA, and IgE are implicated in refractory CRS and sialodacryoadenitis. Tan reported that nuclear-targeting autoantibodies, such as anti-dsDNA IgG and IgA antibodies, were found in increased levels in nasal polyps, particularly in patients requiring revision surgery for recurrence.¹⁰ Similarly, there may be other autoantigens, such as desmoglein 3, in the paranasal mucosa of patients with

intractable CRS, and in the submandibular and lacrimal glands of those with Mikulicz's disease. Some IgG4 might bind to other autoantigens, therefore all staining area with desmoglein 3 were not the same as with IgG4.

This case report was approved by the Ethical Review Board of the Toho University Medical Center Sakura Hospital (2012-103), and we obtained informed written consent from this patient.

Conflict of interest

The authors have no conflict of interest to declare.

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