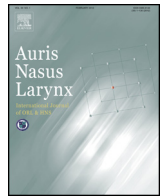




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Nasal manifestations of IgG4-related disease: A report of two cases

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ABSTRACT

IgG4-related disease (IgG4-RD) is a recently recognized clinical disease entity characterized by elevated serum IgG4, tumefaction, tissue infiltration of IgG4-positive plasma cells and fibrosis. IgG4-RD may occur, either synchronously or metachronously, in a variety of organs throughout the body. We describe herein two representative cases of the nasal manifestations of IgG4-RD, characterized by diffuse, crusty, erosive lesions on nasal mucosa. Oral steroid administration was effective in treating these nasal manifestations. We report a decrease in IgG4 positive plasma cell infiltrates in nasal mucosa biopsy specimens after steroid therapy, demonstrating that infiltration of IgG4-positive cells is reversible.

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1. Introduction

IgG4-related disease (IgG4-RD) is a recently recognized clinical disease entity characterized by elevated serum IgG4, tumefaction, tissue infiltration of IgG4-positive plasma cells and fibrosis. Chronic pancreatitis associated with high serum IgG4 and IgG4-positive plasma cell infiltration was first reported as IgG4-RD in 2001 [1]. In 2004, IgG4-positive plasma cell infiltration was observed in salivary gland tissue in patients with Mikulicz's disease [2]. Subsequently, infiltration of IgG4-positive plasma cells into various other organs was reported [3].

In 2011, comprehensive diagnostic criteria for IgG4-RD [4] were proposed by the Japanese Ministry of Health, Labour and Welfare IgG4 team; IgG4-RD may occur, either synchronously or metachronously, in a variety of organs throughout the body and may be present in a certain proportion of patients with a wide variety of diseases, including chronic sialadenitis (known as Mikulicz's disease and Küttner tumor), autoimmune pancreatitis, hypophysitis, Riedel thyroiditis, interstitial pneumonitis, interstitial nephritis, prostatitis, lymphadenopathy, retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pseudotumor [3].

Recently, other workers in the field have reported nasal manifestations of IgG4-RD [5–11], and also suggest that IgG4-positive plasma cells might target the nasal cavity or paranasal sinus. However, the clinical and pathological features of nasal lesions associated with IgG4-RD remain controversial and whether IgG4-related rhinosinusitis is a distinct, independent disease is still unclear.

In this study, we report two characteristic cases of IgG4-RD with nasal manifestations. We diagnosed these cases using the comprehensive diagnostic criteria for IgG4-RD [4] and the consensus statement on the pathology of IgG4-RD [12].

2. Case reports

2.1. Case 1

A 79-year-old man presented to our outpatient clinic with rapid-onset dysphagia and hoarseness associated with left vocal fold paralysis. Neck-chest CT and brain MRI imaging revealed hypophysitis, swelling of bilateral submandibular glands, and mediastinal lymphadenopathy. Blood tests revealed elevated serum IgG (2000 mg/dL) and IgG4 (432 mg/dL) levels and hypocomplementemia. We eliminated potential sarcoidosis, and IgG4-RD was suspected. One month later, left vocal fold paralysis had recovered spontaneously and the patient required no medication. Four months later, he complained of nasal obstruction. We detected diffuse erosive, crusty lesions on nasal mucosa

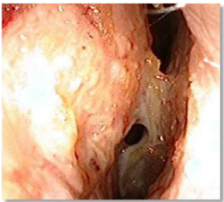
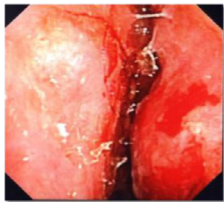
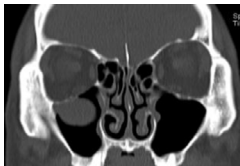
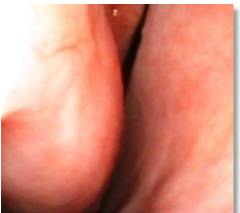
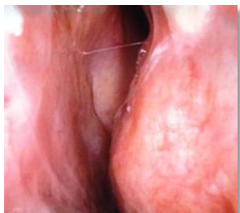
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Table 1

Clinical and pathological features of the three cases.

	Case 1	Case 2
Age, Sex	79, M	59, M
Serum IgG4(IgG) (mg/dL)	432 (2000)	514 (1750)
Serum IgE (mg/dL)	19	572
WBC (/ μ L)	4320	5460
CRP (mg/dL)	0.37	0.08
Initial symptoms	Dysphagia, Hoarseness	Submandibular swelling
Nasal symptoms	Nasal obstruction	Hyposmia
Allergic history	None	Cough variant asthma, Allergic rhinitis
Nasal findings (before treatment)		
CT images		
IgG4+ cells (/HPF), IgG4+/IgG+ cells	240, 30% (nasal mucosa) 132, 65% (submandibular gland) 90, 53% (submandibular lymph node)	100, 50% (nasal mucosa) 220, 70% (submandibular gland)
Fibrosis	- (nasal mucosa) + (submandibular gland) - (submandibular lymph node)	+ (nasal mucosa) - (submandibular gland)
Phlebitis	- (nasal mucosa) + (submandibular gland) - (submandibular lymph node)	- (nasal mucosa) - (submandibular gland)
Lesions of IgG4-RD	Hypophysitis, lymphadenopathy Chronic sclerosing sialadenitis Rhinitis	Chronic sclerosing sialadenitis Rhinitis Autoimmune pancreatitis
Treatment	Oral steroid	Oral steroid
Nasal findings (after treatment)		

WBC: white blood cell count; CRP: C-reactive protein; HPF: high-power field.

(see Table 1). A nasal mucosa specimen showed chronic inflammation with dense infiltration of IgG4-positive plasma cells (240/HPF) and an IgG4/IgG ratio of 30% (Fig. 1A, B). Storiform-fibrosis and obliterative phlebitis were not observed. One year later, he had swelling and sclerosis of bilateral submandibular glands also and swelling of submandibular lymph nodes. Biopsy specimens of the left submandibular gland and a submandibular lymph node excluded the possibility of malignant lymphoma. The submandibular gland showed dense infiltration of inflammatory cells and hyalinized fibrosis (Fig. 1B), infiltration of IgG4-positive plasma cells (132/HPF) and a high IgG4/IgG ratio (65%) (Fig. 1C), but obliterative phlebitis was not observed. The submandibular node also showed dense infiltration of IgG4-positive plasma cells (90/HPF) and a high IgG4/IgG ratio (50%) (Fig. 1D). The patient was diagnosed with IgG4-RD (definite) with hypophysitis, lymphadenopathy, chronic sclerosing sialadenitis and rhinitis. After oral

prednisolone (starting at 0.6 mg/kg/day) treatment, the swelling of the bilateral submandibular glands and lymph nodes was relieved and his nasal mucosa and serum IgG4 level were normalized.

2.2. Case 2

A 59-year-old man presented to our outpatient clinic with right submandibular swelling. He had a history of cough variant asthma and allergic rhinitis. We detected a swelling of the bilateral submandibular glands (4-cm in diameter) and elevated serum IgG4 (514 mg/dL) with IgG (1750 mg/dL). One month later, the patient complained of hyposmia and presented with diffuse, erosive, crusty lesions on nasal mucosa (see Table 1). Biopsy specimens from the submandibular gland (Fig. 2A, B) and the inferior turbinate mucosa (Fig. 2C) showed dense infiltration of IgG4-positive plasma cells and a high IgG4/IgG ratio

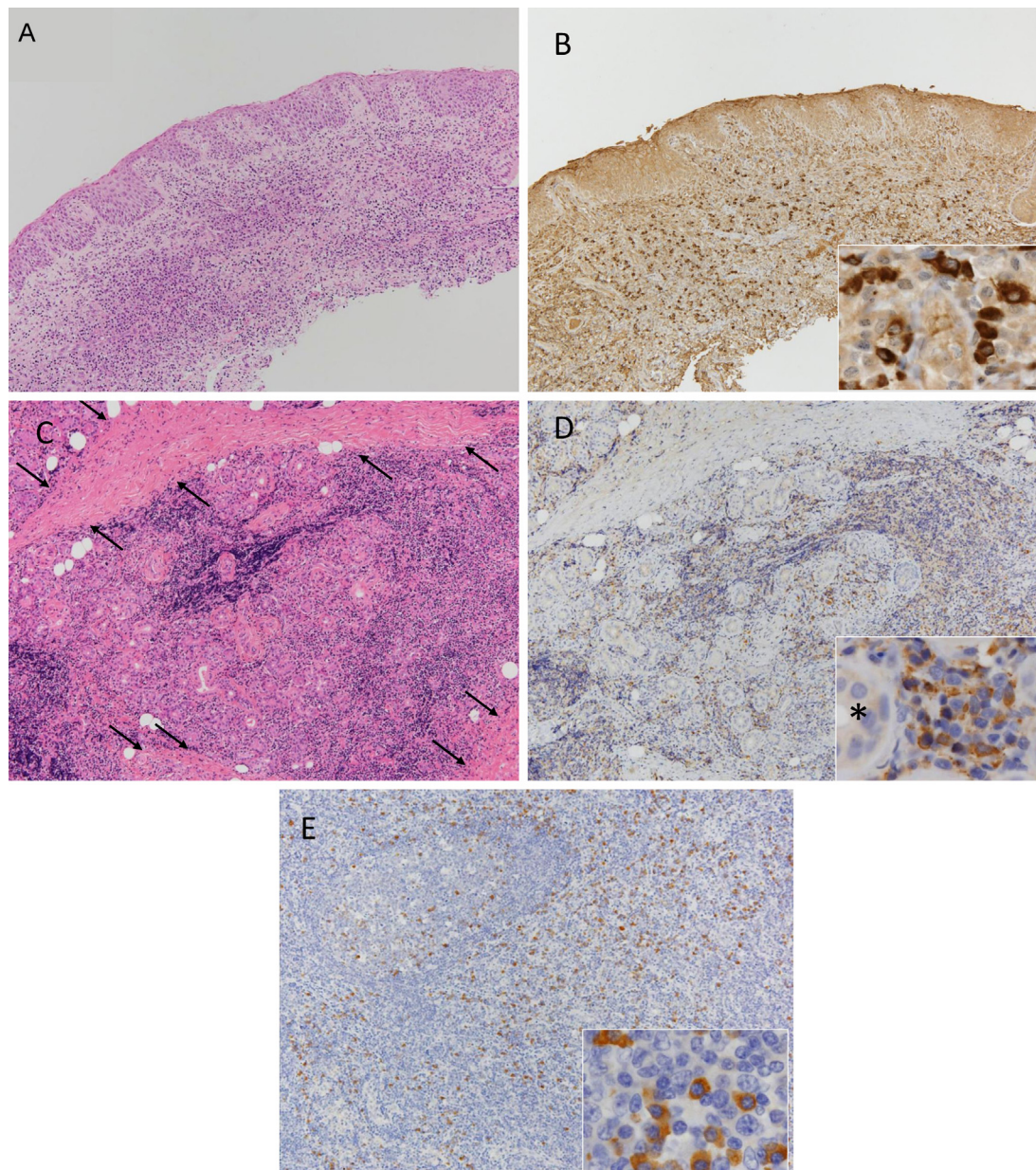


Fig. 1. Pathological results: Case 1.

(A) Hematoxylin and eosin (H&E) staining of nasal mucosa showed dense inflammatory cell infiltration. $\times 100$. (B) IgG4 immunostaining showed dense infiltration of IgG4-positive plasma cells. Original magnification, $\times 100$; inset, $\times 600$. (C) H&E staining of submandibular gland showed infiltration of dense inflammatory cell infiltration. Arrows indicate hyalinized fibrosis. $\times 100$. (D) IgG4 immunostaining of submandibular gland and (E) IgG4 immunostaining of submandibular lymph node showed dense infiltration of IgG4-positive plasma cells. Original magnification, $\times 100$; inset, $\times 600$.

(submandibular gland; 220/HPF, 70%; nasal mucosa; 100/HPF, 50%) with fibrosis (Fig. 2A and B, arrows). The patient was diagnosed as IgG4-RD (definite) with chronic sclerosing sialadenitis and rhinitis. After oral prednisolone (starting at 0.6 mg/kg/day) treatment, his nasal mucosa was normalized and the hyposmia was improved. Biopsy specimens from the inferior turbinate nasal mucosa after treatment showed a marked decrease in IgG4-positive plasma cells (3/HPF) and an IgG4/IgG ratio of 5% (Fig. 2D). Oral prednisolone administration was tapered and then suspended after one year. His serum IgG4 persisted at a high level independently of the dose of oral prednisolone. Two years later, the patient was diagnosed with autoimmune pancreatitis and has been followed up regularly without general steroid administration.

This trial of inferior turbinate biopsy for patients with suspected IgG4-RD was approved by the Institutional Review Board of Tokyo Metropolitan Geriatric Hospital (No. 260213).

Informed written consent for the usage of tissues was obtained from all patients.

3. Discussion

These two cases of IgG4-RD are characterized by elderly men and diffuse, crusty, erosive lesions on the nasal mucosa. Oral steroid administration was effective in treating these nasal manifestations. We identified a decrease in IgG4 positive plasma cell infiltration in nasal mucosa biopsy specimens after steroid therapy, demonstrating that the infiltration of IgG4-positive cells is reversible (Case 2).

The main pathological features of IgG4-RD are considered to be (1) dense lymphoplasmacytic infiltration, (2) increased numbers of IgG4-positive plasma cells (or an elevated IgG4/IgG ratio), (3) fibrosis, arranged at least focally in a storiform pattern, and (4)

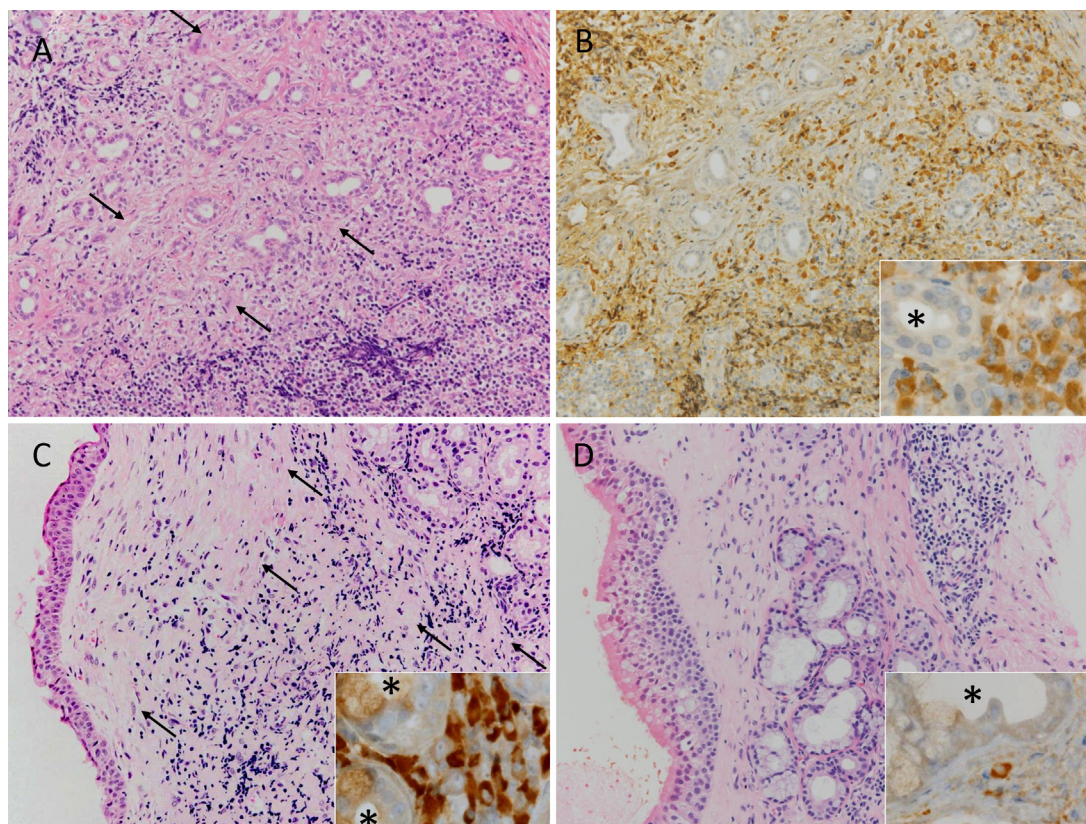


Fig. 2. Pathological results: Case 2.

(A) H&E staining of submandibular gland showed dense inflammatory cell infiltration. Arrows indicate fibrosis. $\times 100$. (B) IgG4 immunostaining of submandibular gland showed dense infiltration of IgG4-positive plasma cells around submandibular glands (asterisk). Original magnification, $\times 100$; inset, $\times 600$. (C) H&E staining of nasal mucosa before steroid therapy showed dense inflammatory cell infiltration and fibrosis (arrows). IgG4 immunostaining (inset) showed infiltration of IgG4-positive plasma cells around nasal glands (asterisk). Original magnification, $\times 100$; inset, $\times 600$. (D) H&E staining of nasal mucosa after steroid therapy showed a marked decrease in inflammatory cell infiltration. IgG4 immunostaining (inset) showed a decrease in IgG4-positive plasma cells around nasal glands (asterisk). Original magnification, $\times 100$; inset, $\times 600$.

obliterative phlebitis [12]. The biopsy specimens from nasal mucosa in the present cases showed dense infiltration of lymphoplasmacytes and IgG4-positive plasma cells, but not storiform-type fibrosis or obliterative phlebitis. We found hyalinized fibrosis in the nasal mucosa and submandibular glands, which is commonly observed in chronic inflammation, but not in acute inflammation. Previous studies have also reported that in organs such as the lymph node, lung, minor salivary glands, and lacrimal glands, storiform-type fibrosis or obliterative phlebitis may be inconspicuous or absent [12]. Also, occurrence of fibrosis depends on the stage of a disease, because it takes time to build fibrosis in tissues. Nasal symptoms can be easily recognized, both subjectively and objectively, at an early stage, perhaps explaining why storiform-type fibrosis and obliterative phlebitis were absent in these cases. Fibrosis is a process of tissue repair induced by tissue damage. Therefore, the duration and degree of inflammation might be associated with a specific pattern of fibrosis. In addition, there is the possibility that storiform fibrosis and obliterative phlebitis were not detected because the nasal biopsy specimen was too small.

Some patients with IgG4-RD often complain of nasal symptoms such as nasal obstruction, nasal crusting and hyposmia. In 2009, Takano et al. reported the existence of nasal symptoms in IgG4-RD for the first time. They reported that patients with Mikulicz's disease often complain of hyposmia and that the nasal mucosa in these patients was infiltrated with IgG4-positive plasma cells [13,14]. At about the same time, cases of chronic rhinosinusitis with IgG4-RD began to be reported. Moteki et al. [8] described a type of sinusitis, with a high level of serum IgG4, for which steroid therapy is effective. Following the consensus statement on the

pathology of IgG4-RD [12], a variety of inflammatory disorders (oral inflammatory diseases, primary sclerosing cholangitis, anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis, etc.), lymphoma, malignancies and, interestingly, rhinosinusitis were demonstrated not to be IgG4-RD despite elevated numbers of infiltrating IgG4-positive cells. In regions that are exposed to inflammation every day e.g. in the oral or nasal cavity, infiltration of IgG4-positive plasma cells must occur easily. We should therefore expect false-positives in these areas, thus making the diagnosis and the placement of the nasal manifestations of IgG4-RD complicated. Rhinosinusitis is not currently included in the IgG4-RD spectrum, but several reports, including ours, have described that IgG4-positive plasma cells might target the nasal cavity or paranasal sinus. It is still unclear whether chronic airway inflammation such as rhinosinusitis is independent from the symptoms of IgG4-RD or causes IgG4-RD. Therefore, careful investigation of clinicopathological correlations will continue to be of importance.

In the present study, the two cases were elderly men and had characteristic rhinitis and chronic sialadenitis, with pancreatitis or hypophysitis also observed in one case. According to previous reports, the ages of patients with IgG4-RD in all groups were similar, with means from 59 to 68 years (ranges 42 to 79) [15]. Suzuki et al. [9] reported that 43.4% of patients with IgG4-RD had some nasal symptoms and 56.3% had numerous IgG4-positive plasma cell infiltrates in the nasal mucosa. These data indicate that characteristic rhinitis of elderly men has the potential to present with partial symptoms of IgG4-RD, and that accurate differential diagnosis with regard to other systemic symptoms such as sialadenitis or pancreatitis is therefore vital. Biopsy of the inferior

turbinate is easier and less invasive than biopsies of any other lesion, enables evaluation of sequential changes in pathology and may be useful in the assessment of any therapeutic effects. In future studies we plan to increase the sample size and include control groups in order to define more accurate and sensitive diagnostic criteria for IgG4-related rhinosinusitis.

4. Conclusion

We report two cases of characteristic nasal manifestations in IgG4-RD. Susceptible individuals are typically elderly men, present with diffuse, crusty, erosive lesions of the nasal mucosa, high sensitivity for steroid therapy, elevated serum IgG4, dense infiltration of IgG4-positive plasma cells without storiform fibrosis and obliterative phlebitis. Cases with such characteristics probably have IgG4-related rhinitis, and we should also consider other systemic symptoms of IgG4-RD. Biopsy of the inferior turbinate is a useful way to evaluate sequential changes in pathology and partial symptoms for IgG4-RD.

Conflict of interest

None.

Financial disclosure

None.

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