

Clinical Evaluation of Sinonasal Lesions in Patients With Immunoglobulin G4-Related Disease

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Abstract

Objectives: Immunoglobulin G4-related disease (IgG4-RD) is a systemic disease entity characterized by elevated serum IgG4 and extensive IgG4-positive plasma cell infiltration of various organs. Patients with IgG4-RD show nasal manifestations with chronic rhinosinusitis. The objective of this study was to evaluate the clinical characteristics of sinonasal lesions in patients with IgG4-RD.

Methods: We evaluated radiological findings of sinonasal lesions in 79 patients with IgG4-RD who were divided into 3 groups according to severity. We also compared serological findings, including serum IgG4 and IgE levels, and eosinophil counts.

Results: Rhinosinusitis was found in 41 patients (51.9%). Although there were no significant differences in the serum IgG4 and IgE levels of the groups, there was a significant increase in eosinophil counts ($445 \pm 311.9/\text{mm}^3$) in Group C. Furthermore, 14 of the 41 patients with rhinosinusitis (34.1%) showed improvement after prednisolone administration. Patients with IgG4-RD and serum eosinophilia tend to also have sinonasal lesions.

Conclusions: Rhinosinusitis is common in patients with IgG4-RD, and its pathogenesis can be similar to eosinophilic chronic rhinosinusitis.

Keywords

IgG4-related disease, paranasal sinus, rhinosinusitis, eosinophil, IgE, IgG4

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a newly categorized disease that has received much attention in the past decade.^{1–4} The hallmarks of IgG4-RD are lymphoplasmacytic tissue infiltration with a predominance of IgG4-positive plasma cells accompanied by fibrosis, obliterative phlebitis, dacryoadenitis, and elevated IgG4 levels.^{2,3} Most often, diagnosis is made in patients with IgG4-related dacryoadenitis and/or sialadenitis (so-called Mikulicz's disease), which was once believed to be a subset of Sjögren's syndrome and type 1 autoimmune pancreatitis (AIP).^{3,4} Immunohistochemical detection of increased IgG4 levels in involved tissues is important because IgG4 is a surrogate marker that enables exclusion of its neoplastic mimics. The involved organ systems are numerous and include the salivary and lacrimal glands, pancreas, bile duct, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidneys, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast tissues.^{1–5}

In the otorhinolaryngological field, several reports have described nasal manifestations associated with IgG4-RD.^{6–10} Cases with massive or tumorous lesions in nasal/paranasal sinus cavity and typical histopathological features are considered IgG4-RD; however, it is now clear that rhinosinusitis lies outside the IgG4-RD spectrum and can be associated with increased numbers of IgG4-positive plasma cells in tissue.^{10,11} Therefore, careful consideration is required when sinonasal lesions including rhinosinusitis are diagnosed as associated with IgG4-RD, although it is also true that patients with rhinosinusitis complicated with IgG4-RD show certain characteristic features.⁶ In this study, we

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sought to clarify the features and location of sinonasal lesions, particularly rhinosinusitis, in IgG4-RD by a retrospective evaluation of the clinical features of sinonasal lesions in patients with IgG4-RD.

Materials and Methods

Subjects

We examined 79 patients with IgG4-RD (36 males and 43 females). All patients had previously consulted doctors at Sapporo Medical University and its related facilities between April 2000 and March 2013. Immunoglobulin G4-related disease was diagnosed according to the Japanese Society for Sjögren's syndrome, 2008,¹² and the comprehensive diagnostic criteria for IgG4-RD in 2011.¹³ In addition, our institutional pathologists provided diagnoses according to the 2012 Consensus Statement for Clinical Pathologists.¹¹ Briefly, IgG4-RD was diagnosed as follows: (1) symmetrical swelling of at least 2 pairs of lachrymal, parotid, or submandibular glands for at least 3 months; (2) serum IgG4 >135 mg/dl; (3) >40% of IgG+ plasma cells being IgG4+ and >10 cells/high powered field of biopsy sample; and (4) 2 of the following histopathological features: dense lymphoplasmacytic infiltration; fibrosis, arranged at least focally in a storiform pattern; and obliterative phlebitis. Submandibular gland biopsy was performed in all 79 cases for clinical and pathological diagnosis. Allergic rhinitis was diagnosed on the basis of medical history, symptoms, nasal cytology, and specific IgE to aeroallergens. Serum samples were obtained before therapy. Biopsy specimens were obtained from the inferior turbinates and maxillary sinus mucosa of 4 patients who consented to nasal cavity biopsy. Formalin-fixed paraffin-embedded blocks of these tissues were analyzed.

Image Analysis

Data from pretreatment computed tomography (CT) were obtained by using a standard clinical protocol; 3-mm contiguous images were obtained in the axial and coronal planes. Each sinus CT image was scored in a blinded fashion by 3 otolaryngologists who used the Zinreich system,¹⁴ which enables a greater level of inflammatory gradation in comparison to the Lund-Machay system widely used for CT evaluation of rhinosinusitis. This system divides the rhinosinusitis inflammation on CT images into 4 strata with intervals of 25% and yields an inflammation score on a 5-point scale. Magnetic resonance imaging was also performed in all patients for differential diagnosis to detect rhinosinusitis and other diseases, including tumorous lesions.

The patients were divided into 3 groups according to the Zinreich score: group A is none (Zinreich score = 0-1), group B is mild (2-19), and group C is severe (≥ 20 or including 5-score-sinus).

Table 1. Clinical Findings of All Patients in This Study.

Median age of disease onset (y)	60.3 $\pm$ 12.9
Sex ratio (M:F)	36:43
Mean total IgG level (mg/dl)	2447.5 $\pm$ 1408.2
Mean total IgG4 level (mg/dl) (%)	851.8 $\pm$ 718.3 (25.5 $\pm$ 9.9)
Mean total IgE level (IU/ml)	384.6 $\pm$ 565.4
White blood cells (/ml)	5764.9 $\pm$ 1612.0
Peripheral blood eosinophils (%)	4.8 $\pm$ 5.0
Peripheral blood eosinophils (/mm ³)	262.7 $\pm$ 249.4
Complication with asthma, n (%)	16 (20.3)
Complication with allergic rhinitis, n (%)	44 (55.7)

Immunohistochemistry

For all immunostaining, monoclonal antibodies were reacted with steam for 24 hours at 4°C after blocking endogenous peroxidase activity in tissue sections. Anti-IgG4 antibody (mouse anti-human IgG4; The Binding Site, Birmingham, UK) at a dilution of 1:500 was used as the primary antibody. The secondary antibody (biotinylated anti-mouse IgG [H + L]; Vector Laboratories, Burlingame, California, USA) was used at a dilution of 1:500. Nuclear staining with hematoxylin was performed after indirect peroxidase staining of nasal mucosa specimens collected from the patients with IgG4-RD. To identify IgG4-producing cells, gland specimens were stained with anti-CD138 antibodies (CD138; Biogenesis, Poole, UK) diluted to 1:250.

Statistical Analysis

Analysis of variance was used to evaluate significant differences between groups. Data are expressed as mean $\pm$ standard deviation. *P* values <.05 were considered to indicate statistical significance.

Results

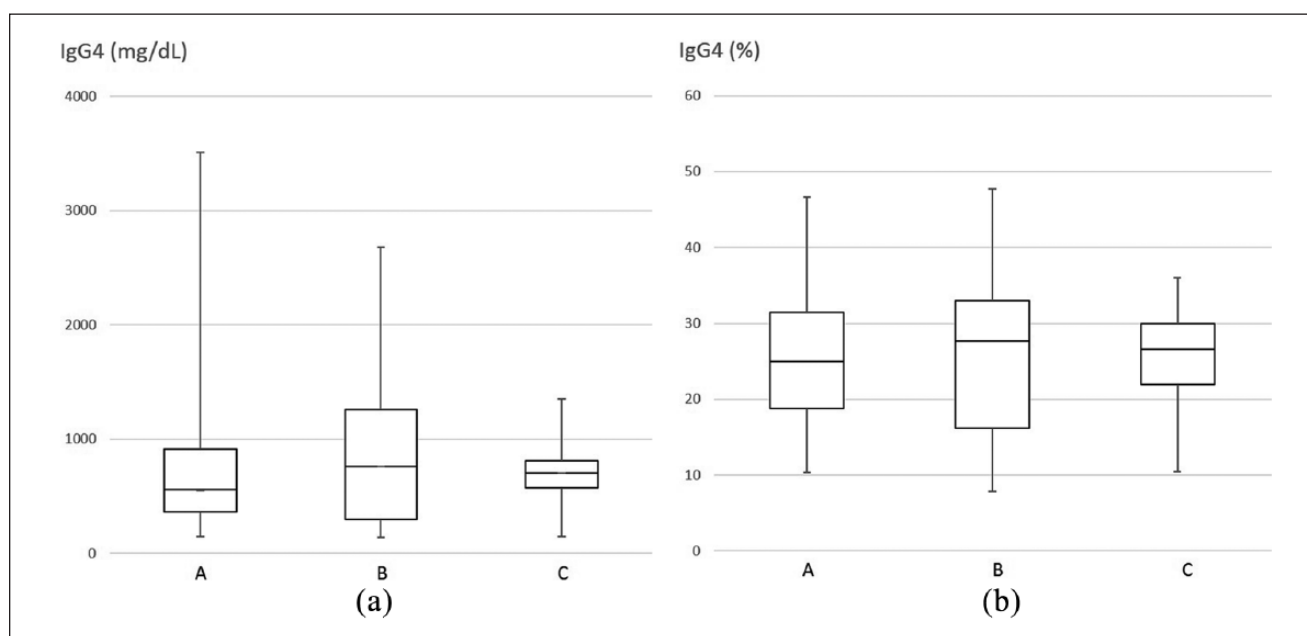
Clinical Findings

The clinical features of the patients are summarized in Table 1. The patients were middle-aged to elderly and included more women than men. Hypergammaglobulinemia (IgG ≥ 1800 mg/dl) was found in 45 patients (57.0%). All patients showed elevated serum IgG4 (>135 mg/dl). Eosinophil counts were highly variable (262.7 $\pm$ 249.4/mm³, 4.8% $\pm$ 5.0%). Complications associated with bronchial asthma and allergic rhinitis are shown in Table 1. Almost half of the patients had allergic rhinitis, and approximately 20% had bronchial asthma.

A comparison of the clinical findings is shown in Table 2. Rhinosinusitis was found in almost half of all patients (51.9%); sinusitis was more common in group A, followed

Table 2. Comparison of Each Group According to Clinical Findings.

	Group A (None)	Group B (Mild)	Group C (Severe)
No. of patients (%)	37 (46.8)	31 (39.2)	10 (12.7)
Mean score	0.11	4.8	24.3
Mean total IgG4 level (mg/dl) (%)	851.8 ± 718.3 (25.5 ± 9.9)	863.7 ± 683.6 (25.6 ± 11.6)	719.5 ± 369.5 (24.9 ± 7.8)
Mean total IgE level (IU/ml)	384.6 ± 565.4	444.1 ± 725.8	271.3 ± 226.6
White blood cells (/ml)	5964.9 ± 1783.0	5512.9 ± 1637.2	5893.0 ± 619.9
Peripheral blood eosinophils (%)	4.2 ± 4.0	4.2 ± 3.6	9.0 ± 9.0
Peripheral blood eosinophils (/mm ³)	236.9 ± 256.0	230.7 ± 201.0	445 ± 311.9
Complication with asthma, n (%)	5 (13.5)	7 (22.6)	4 (40.0)
Complication with allergic rhinitis, n (%)	18 (48.6)	20 (64.5)	6 (60.0)

**Figure 1.** The (a) IgG4 subset serum levels and (b) serum IgG4/IgG ratio in each group. There were no significant differences between groups.

by groups B and C. One patient (1.3%) with a massive lesion that was not atypical rhinosinusitis was excluded. Bronchial asthma was highest in group C (40.0%), followed by groups B (22.6%) and A (13.5%). Allergic rhinitis was similar in all groups.

Serological findings are shown in Figures 1 and 2. There was no difference in IgG4 (Figures 1a and 1b) or IgE levels (Figure 2a) between groups. Although there was no significant difference in the peripheral blood eosinophil counts of groups A and B ($P = .998$), the differences between groups A and C ($P = .0063$) and between groups B and C ($P = .0074$) were significant (Figure 2b).

Effect of Steroid Therapy

The initial dose of prednisolone was 0.6 to 0.8 mg/kg/day and gradually decreased to around 5 to 10 mg/day.

Approximately 4 months after prednisolone administration, CT was performed to evaluate treatment efficacy. As shown in Figure 3, 9 patients in group B (29.0%) and 5 in group C (50.0%) showed improvement in rhinosinusitis. Fourteen of the 41 patients who were complicated with rhinosinusitis (34.1%) showed improvement after prednisolone administration without the use of other drugs, such as macrolide antibiotics.

Histopathological Analysis

Histopathology was performed in 4 Group B patients. Hematoxylin and eosin stains in the maxillary sinus mucosa showed diffuse fibrosis and lymphoplasmacytic infiltration (Figure 4a). In addition, IgG4-positive plasma cells were elevated in the sinus mucosa (Figure 4b) and were positive for the CD138 plasma-cell marker.

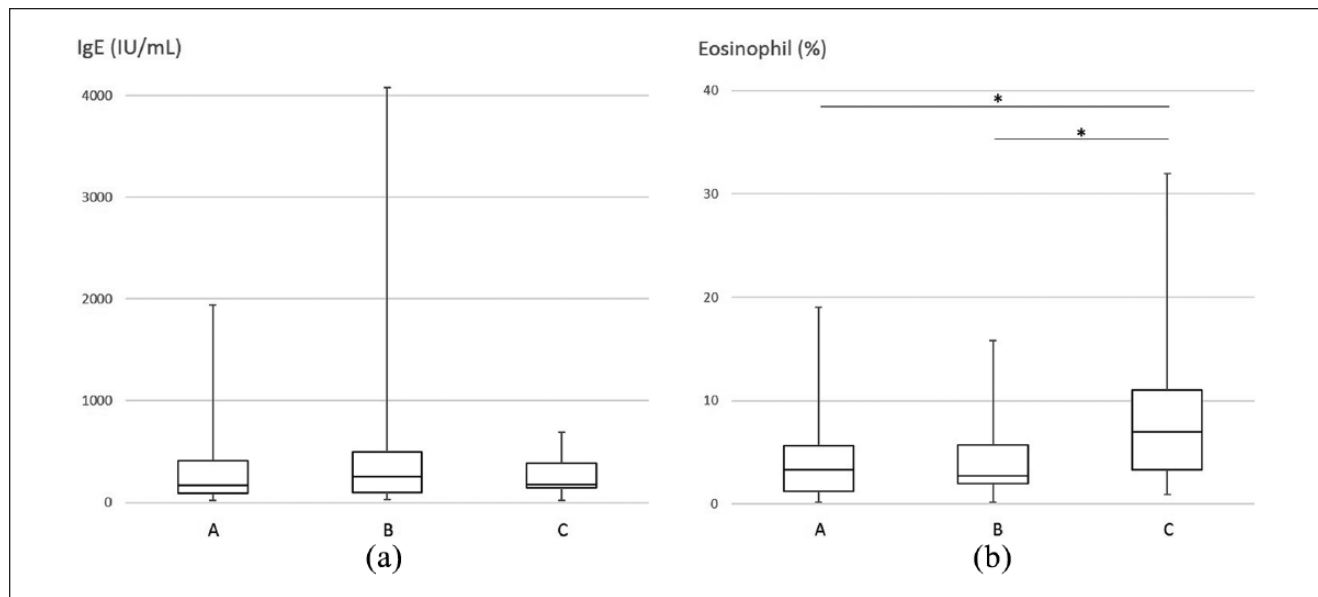


Figure 2. (a) Serum IgE and (b) eosinophil counts. Although there were no significant differences in serum IgE levels, significant differences were found between groups A and C and between groups B and C. * $P < .05$.

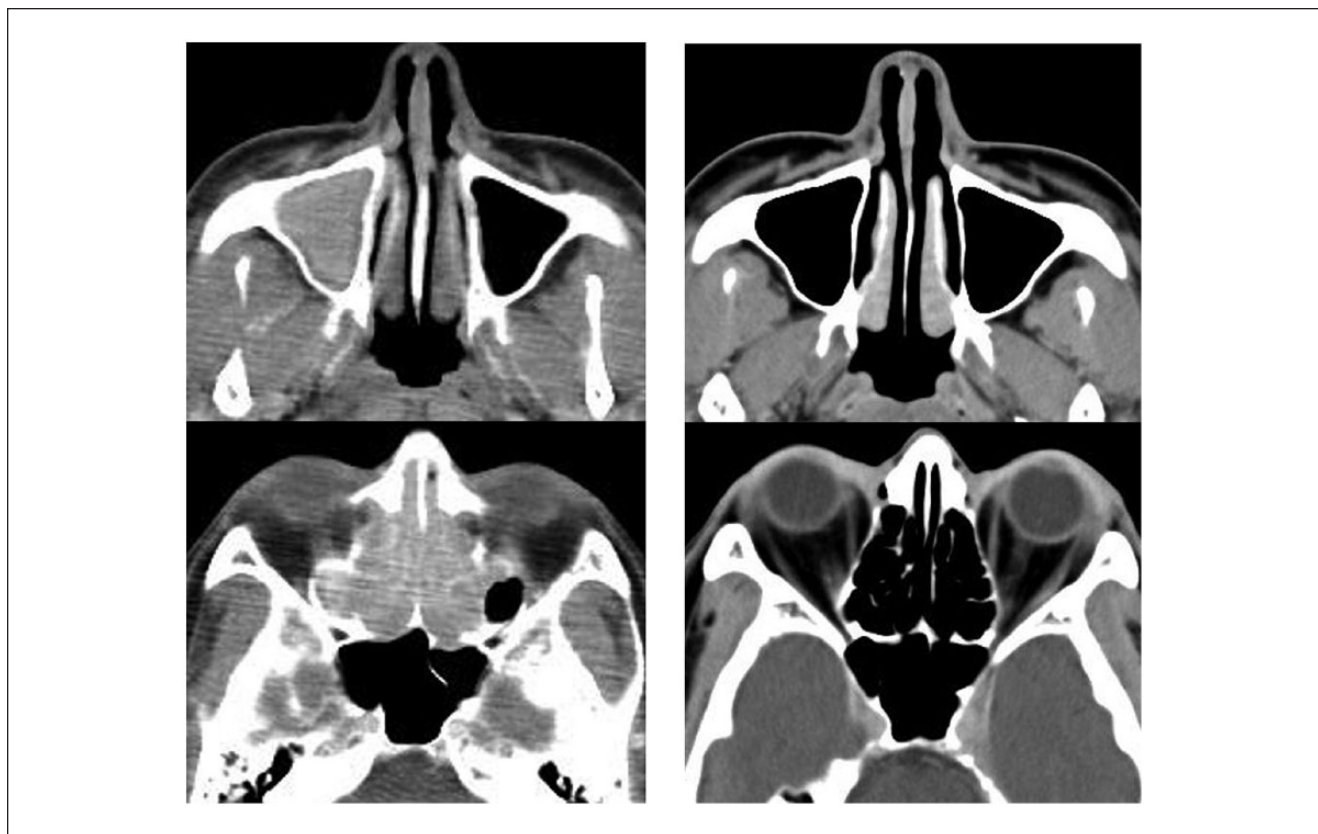


Figure 3. Paranasal computed tomography (CT) before treatment (left panels) and after treatment (right panels). Pretreatment CT revealed a diffuse lesion with soft tissue density in the right maxillary sinus and bilateral ethmoid sinuses. After treatment, CT findings revealed improvement in the opacification of these sinuses.

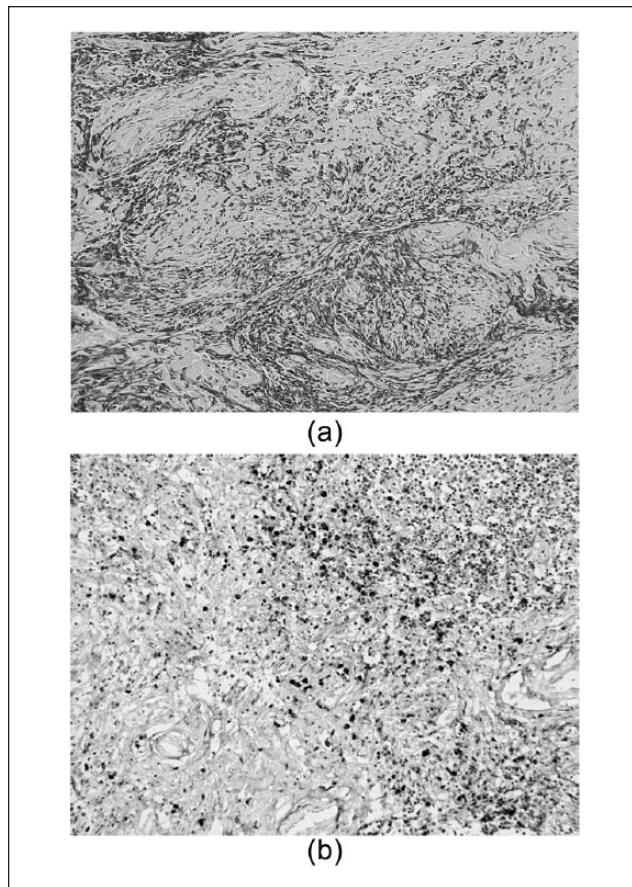


Figure 4. Histopathological findings of the maxillary sinus mucosa biopsies (100×). (a) Hematoxylin and eosin stain shows an irregular whorled pattern of fibrosis and lymphoplasmacytic infiltration. (b) Immunohistochemical staining for IgG4 shows infiltration by abundant IgG4-positive plasma cells.

Patient With a Mass Lesion in the Paranasal Sinus

Clinical examination of IgG4-RD shows characteristic diffuse/localized swelling or masses in single or multiple organs.¹¹ Only 1 patient (1.3%) appeared to fulfill this condition (Figure 5); however, the patient did not consent to histopathological examination, so we were unable to confirm the diagnosis of an IgG4-related sinonasal lesion. According to the comprehensive diagnostic criteria,¹³ a diagnosis of IgG4-related sinonasal lesion was considered possible for this patient.⁷⁻¹⁰ After 3 months of prednisolone administration, the lesion was diminished.

Discussion

In this study, we examined the clinicopathological findings of sinonasal lesions in patients with IgG4-RD. Approximately 50% of the patients showed sinonasal lesions on CT, and the



Figure 5. T2-weighted magnetic resonance image shows massive lesions in the left maxillary sinus at the anterior wall and left nasal cavity.

patients in group C showed high eosinophil counts in the peripheral blood. In addition, the lesions improved after steroid therapy.

The hallmarks of IgG4-RD are tissue infiltration by abundant IgG4-positive plasma cells accompanied by fibrosis and obliterative phlebitis.^{11,13} IgG4-positive plasma cell infiltration has been identified in various diseases and clinical conditions. Inflammatory diseases associated with elevated IgG4-positive plasma cells include rhinosinusitis, oral inflammatory disease, primary sclerosing cholangitis, anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis, inflammatory bowel disease, Rosai-Dorfman disease, splenic sclerosing angiomatoid nodular transformation, cutaneous plasmacytosis, perforating collagenosis, and autoimmune atrophic gastritis.¹¹ These conditions, including rhinosinusitis, consistently show IgG4-abundant inflammation, and all lack the characteristic histopathological features of IgG4-RD; therefore, rhinosinusitis is no longer considered an IgG4-related disease.^{11,13} However, recent histological findings of the paranasal sinus mucosa have shown fibrosis with dense infiltration by IgG4-positive plasma cells.⁸ In this study, biopsy specimens of the maxillary sinus mucosa revealed abundant infiltration of IgG4-positive plasma cells and the histopathological characteristics of IgG4-RD. This matter requires further consideration to determine whether massive or tumorous sinonasal lesions as well as rhinosinusitis complications with patients with IgG4-RD can be included in the spectrum of IgG4-RD.

Although the pathogenesis of IgG4-RD remains unclear, several studies have suggested a causative role for T helper

type 2 (Th2) cells.¹⁵⁻¹⁷ A subset of patients with AIP have longstanding histories of allergies and serum IgE elevation or manifest atopic symptoms such as allergic rhinitis, bronchial asthma, and atopic dermatitis.^{18,19} In our patients, we observed serum IgE elevation (384.6 ± 565.4 IU/mL) and higher prevalence of bronchial asthma (20.3%) and allergic rhinitis (55.7%) than of asthma²⁰ and rhinitis.²¹ On the other hand, 41 of the 79 patients with IgG4-RD (51.9%) had findings of rhinosinusitis, a greater frequency than the rates of which incidental sinus mucosal abnormalities are found in the general population, between 15% and 37% according to CT findings.²² We suggest the high prevalence of sinus abnormalities in patients with IgG4-RD may be influenced by serum IgE elevation and/or complication of allergic involvement.

Serum eosinophilia and eosinophilic infiltration often occur in patients with IgG4-RD. Allergic immune responses can be induced by specific Th2 cytokines such as IL-4, IL-5, and IL-13, which promote serum eosinophilia and secretion of IgG4 and IgE.²³ Serum eosinophilia and IgE elevation induce IL-10 and transforming growth factor- β secretion from regulatory T-cells and increase IgG4 levels.²⁴ Serum IgG4 subsequently interferes with allergic reactions by competing with IgE in the immune response and binding to mast cells.^{4,15,25,26} Accordingly, serum eosinophilia and IgG4 elevation are simultaneously observed in some cases of IgG4-RD. In this study, serum hypereosinophilia was observed in group C (mean serum eosinophil: 9.0%), which showed high inflammation sinus scores, but not in groups A and B. Considering these findings, we suggest patients with IgG4-RD and serum eosinophilia tend to be complicated with sinonasal lesions; the pathogenesis may be similar to that of eosinophilic chronic rhinosinusitis (ECRS).

Eosinophilic chronic rhinosinusitis is a clinical entity of intractable chronic sinus inflammation accompanied by numerous infiltrations of activated eosinophils in the paranasal sinus mucosa and/or nasal polyps.²⁷ It is unclear whether the high eosinophil infiltration is accompanied by a shift to a more type 2-dominated response in ECRS patients. However, a hypoxic state in the paranasal sinuses activates endothelial cells and fibroblasts to release inflammatory mediators, leading to the promotion of inflammatory cell adherence to the endothelium. These include proinflammatory cytokines such as tumor necrosis factor alpha and interferon gamma, as well as Th2 cytokines, such as IL-4 and IL-13, even in non-atopic subjects.²⁸ These cytokine profiles are similar to that of IgG-RD.^{15,23} In addition, hypoxia-induced factors were upregulated in the tissue obtained from patients with IgG4-RD (unpublished data). Toll-like receptors (TLRs) are now recognized as part of the innate immune system in the human upper airway.²⁹ In IgG4-RD, TLR ligands are recognized by TLRs in monocytes and basophils, and activated basophils subsequently produce IL-13 to support Th2 cell-dominant inflammation.¹⁵ The Th2 cells

secrete IL-4 and IL-5, which promote Th2 cell self-propagation via differentiation of naive T-cells and activation of eosinophils, respectively. In ECRS, the nuclear factor kappa light chain enhancer of activated B cells (NF- κ B) pathway is activated through TLRs in the structural cells; thus, they can be considered to reflect hypersensitivity to external stimuli as part of the eosinophil recruitment.³⁰ Although the pathogenesis of both IgG4-RD and ECRS remains unclear, they share several similarities.

Immunoglobulin G4-related disease is characterized by a good response to glucocorticoids, and the sinonasal lesions of patients with IgG4-RD are also responsive to steroid administration.⁶ In our study, sinonasal CT findings revealed improvement of the sinus mucosal abnormalities in 34% of our patients after treatment, and this responsiveness is believed to be 1 of the characteristics of rhinosinusitis in patients with IgG4-RD similar to ECRS, which is also responsive to steroid therapy.²⁷ Although rituximab (RTX) is frequently used in Western countries, RTX is not covered by Japanese health insurance plans for patients with IgG4-RD and was therefore not used in this study. Carruthers et al³¹ reported a prospective open-label trial of RTX and demonstrated its efficacy as induction therapy for IgG4-RD without short-term glucocorticoid use. Yamamoto et al³² reported patient outcomes in long-term RTX-treated IgG4-RD and suggested that the indication for RTX is a definitive diagnosis by histological examination, younger age, and patients in which increasing the glucocorticoid dose is difficult due to complications. In other patients, 1 or 2 administrations of RTX do not induce or maintain complete remission of IgG4-RD, and others present with fading of the RTX effect.³² The primary etiology of IgG4-RD remains unclear. Although the polyclonal populations of lymphocytes and plasma cells increase, these increases are not etiologic but the result of other types of stimulation; thus, an effective treatment mechanism has been identified.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors alone are responsible for the content and writing of this paper.

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