Eosinophilic Chronic Sinusitis with IgG4-Related Disease: Steroid Therapy or Endoscopic Surgery?

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Abstract
Objective
Sinonasal lesions with IgG4-related disease (IgG-RD) have been reported recently. Although the previous reports noted cases of IgG4-RD with rhino-sinus involvement, there are no reports regarding eosinophilic chronic rhinosinusitis (ECRS) with IgG4-RD. We experienced five cases of ECRS with IgG4-related disease which differed from cases involving sinonasal lesions that were reported previously.

Methods
We retrospectively investigated clinical records from patients who had both chronic rhinosinusitis with nasal polyps (CRSwNP) and IgG4-RD. All five patients had their diagnosis confirmed by the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score criteria for the diagnosis of ECRS.

Results
Peripheral eosinophilia (6.3-12.3%) was observed in all five patients. All five patients showed a dominant shadow of the ethmoid sinuses on computed tomography (CT) scans. The patients were selected for steroid therapy; four cases were administered prednisolone therapy, and one case was treated with nasal steroid spray. After steroid therapy, nasal polyps disappeared in all the patients. CT examination showed improvement in the nasal cavity and paranasal sinuses after steroid therapy in all patients. Therefore, endoscopic sinus surgery was not necessary.

Conclusion
We present five cases of ECRS with IgG4-RD which showed improvement after steroid therapy, demonstrating that steroid therapy was effective for this kind of CRSwNP.

Keywords
IgG4-Related Disease; Eosinophilic Chronic Rhinosinusitis

Abbreviations
IgG-RD: IgG4-Related Disease;
ECRS: Eosinophilic Chronic Rhinosinusitis;
CRSwNP: Chronic Rhinosinusitis with Nasal Polyp;
JESREC: Japanese Epidemiological Survey of Refractory
Eosinophilic Chronic Rhinosinusitis;
CT: Computed Tomography;
PSL: Prednisolone; ESS, Endoscopic Sinus Surgery;
TSLP: Thymic Stromal Lymphopoietin;
IL: Interleukin;
Th2: T Helper 2 Type;
Pre: Pre-Treatment;
Post: Post-Treatment

1. Introduction
Immunoglobulin G4-related disease (IgG4-RD) is a systemic disease characterized by elevated serum levels of IgG4, and a mass or hyperplastic formation showing the fibrous tissue infiltrated by lymphoplasmacytic cells with a predominance of IgG4-positive plasma cells [1, 2]. IgG-RD can involve one or multiple organs. Mikulicz’s disease (IgG4-related dacryoadenitis and sialadenitis) and Küttner’s tumor are typical diseases in the field of otolaryngology [1, 2]. Sinonasal lesions with IgG-RD have been reported recently [3, 4]. However, this new clinical entity is not well known. We experienced five IgG-RD patients who had chronic rhinosinusitis with nasal polyp (CRSwNP) that was diagnosed as Eosinophilic Chronic Rhinosinusitis (ECRS) [5], and retrospectively investigated these cases.

2. Materials and Methods
2.1 Patients
We examined CRSwNP patients with IgG4-RD diagnosed between 2010 and 2015 at Kyushu University Hospital. All patients were definite cases according to the comprehensive diagnostic criteria for IgG4-RD [6], IgG4-related kidney disease [7], Mikulicz disease [1], and autoimmune pancreatitis [8].

2.2 ECRS
ECRS was confirmed by the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score. The JESREC score was calculated according to each individual score (bilateral disease sites, nasal polyps, CT findings, and peripheral eosinophilia). When the JESREC score was 11 or higher, the case was diagnosed as ECRS [5]. Eosinophil-related fungal rhinosinusitis including allergic fungal rhinosinusitis was excluded.

2.3 Study Design
We performed a retrospective review. The following data points were extracted from the medical records: gender, age, nasal symptoms, medical histories, nasal endoscopy, grade of nasal polyps [9], pathology, computed tomography (CT) examination, including Lund and Mackay CT grading scores [10], serum IgG4 (mg/dL), serum eosinophil (%), JESREC score, and treatments for IgG4-RD.

2.4 Ethical Standards
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Institutional Review Board approval was obtained from the Kyushu University (protocol #29-71).

3. Results
3.1 Patients (Table 1)
Five CRSwNP patients were identified according to the diagnostic criteria for IgG4-RD including Mikulicz’s disease, sclerosing pancreatitis, autoimmune pancreatitis, and IgG4-related kidney disease. All the patients underwent biopsies from the lesion (lacrimal gland, submandibular gland, stomach and kidney) to examine the histopathology. There were no cases under the diagnostic criteria for IgG4 related sclerosing cholangitis.

The male to female ratio was 4:1. The mean age of the patients at the time of the diagnosis was 59 years (range, 48 to 75 years). The follow-up period ranged from 30 to 63 months (average 50 months). Two of five patients had bronchial asthma. Patient characteristics are summarized in Table 1.

3.2 Pre-treatment Findings
All five cases were confirmed by the JESREC score criteria for the diagnosis of ECRS. The score ranged from 12 to 17. Three patients had dysosmia. Nasal congestion was observed in four patients. The grade of nasal polyps ranged from one to three. There was no hypertrophic lesion or mass formation associated with IgG4-RD in the nasal
cavities and sinuses. CT examinations predominantly showed soft attenuation lesions in bilateral ethmoid cells in all cases. Lund and Mackay CT grading scores was ranged from seven to 23. The percentage of serum eosinophils was increased in all patients (6.3-12.3%). The level of serum IgG4 was elevated (range; 743 to 1500, >135 mg/dl) in all patients. Two patients underwent biopsies from nasal polyps with IgG immunostaining. Therefore, all the patients did not have a confirmed presentation of equal or higher than 70 eosinophils/HPF by the histopathological examination from a nasal polyp. The histopathological examination of nasal polyps revealed infiltration of eosinophils, but no evidence of the specific findings associated with IgG4-RD (elevated IgG4-positive plasma cells: IgG plasma cells ratio, dense infiltration of plasma cells, fibrosis, storiform pattern, and obliterative phlebitis) in the tissue.

**Table 1: Patient's Characteristics and Findings Summarized**

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age</th>
<th>Diagnostic criteria</th>
<th>IgG4 related lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>51</td>
<td>IgG4 related lacrimal, orbit and salivary glands</td>
<td>Lacrimal, parotid, submandibular glands and Stomach</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>75</td>
<td>Autoimmune pancreatitis</td>
<td>Lacrimal, parotid gland Mediastinal, Hilum, Pancreas, Prostate, Retroperitoneal</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>48</td>
<td>Autoimmune pancreatitis</td>
<td>Lacrimal, submandibular glands, Pancreas, Liver, Abdominal LNs</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>62</td>
<td>IgG4-related kidney disease</td>
<td>Lacrimal, submandibular glands, and kidney</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>61</td>
<td>IgG4 related Mikulicz disease</td>
<td>Lacrimal, parotid, submandibular glands (Mikulicz), Mediastinal, Hilum, Pancreas, Prostate, Retroperitoneal</td>
</tr>
</tbody>
</table>

F; female. M; male. LNs; Lymph nodes.

### 3.3 Treatments for Sinonasal Lesions Including IgG4-RD (Table 2)

Four patients showed improvement of nasal findings after prednisolone (PSL) administration. The initial oral dose of PSL was started from 30mg or 40mg per day. The maintenance dose of PSL ranged from 1 to 7.5 mg per day. One case was treated with nasal steroid spray. Endoscopic sinus surgery was not performed in any of the patients.

**Table 2: Nasal Findings after Prednisolone (PSL) Administration**

<table>
<thead>
<tr>
<th>Case</th>
<th>Treatments</th>
<th>Initial</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral PSL 30mg/day</td>
<td>Oral PSL 5mg/day</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Oral PSL 30mg/day</td>
<td>Oral PSL 5mg/day</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Oral PSL 40mg/day</td>
<td>Oral PSL 7.5mg/day</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Intranasal steroid spray</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Oral PSL 40mg/day</td>
<td>Oral PSL 1mg/day</td>
<td></td>
</tr>
</tbody>
</table>

### 3.4 Post-treatment Findings (Figures 1, 2)

The olfactory disorders (dysosmia) were cured after the treatments in three patients. The complaint of nasal congestion improved in four patients. Nasal polyps disappeared in all the patients (Figure 1-A). CT examination after treatments (CT score) showed that the paranasal sinus lesions improved in all patients (Figure 1-B, 2). Peripheral blood eosinophils (%) decreased with treatment, except for one case (Figure 1-C). As for IgG4-RD, clinical and radiological responses to PSL were observed in all the patients (Figure 2). Serum IgG4 levels were decreased by treatment in all patients (Figure 1-D), and no relapse was noted.

**Figure 1:** Pre- and Post-Treatment Polyp Grade (A), CT Score (B), Serum Eosinophils (%), and Serum IgG4 (Mg/Dl, D)
4. Discussion

IgG4-RD is recognized as an immune-mediated systemic condition characterized by tumor-like swelling, and the infiltration of IgG4-positive plasma cells with a variable degree of fibrosis that affects a variety of organs [1]. Major salivary gland and/or lacrimal gland involvement is a common feature of IgG4-RD in the field of otolaryngology. It was previously called Mikulicz disease or Küttner’s tumor. Currently these diseases belong to the IgG4-related systemic disease spectrum [2].

On the other hand, ECRS is a subgroup of CRSwNP in Japan [5]. ECRS is divided from eosinophil-related fungal rhinosinusitis including allergic fungal rhinosinusitis [5]. Patients with ECRS present with loss of smell, nasal congestion, and sticky and viscous rhinorrhea with bilateral polyposis [5]. CT examination of ECRS shows dominant opacification of the ethmoid sinus [5]. The biopsy specimen of nasal polyps reveals a massive infiltration of eosinophils in the tissue [5]. Peripheral blood eosinophilia is a characteristic finding for ECRS. Asthma is often observed as a co-morbidity in ECRS [5]. Although endoscopic sinus surgery (ESS) with or without systemic steroid therapy has been performed in ECRS patients, there is a strong tendency of recurrence after ESS [5]. Recently a new diagnostic criterion for ECRS has been proposed by the JESREC study [5].

In the present study, we performed a retrospective review of CRSwNP with the diagnosis of IgG4-RD. Five patients were identified according to the diagnostic criteria for both JESREC score (≥11) and IgG4-RD. Sinonasal lesions with IgG4-related disease (IgG-RD) have been reported recently [3, 4, 11]. The previous reports noted cases of IgG4-RD with rhino-sinus involvement showing recurrent nasal bleeding, nasal crusting, and mass formation [3, 4]. In the present study, five cases showed none of these findings clinically. In addition, the nasal polyp biopsy specimen revealed no evidence of the specific findings associated with IgG4-RD. Therefore, the five cases seem to be different from the previous cases of rhino-sinus lesions with IgG-RD. Cases similar to the five cases reported in the present study were described in only one article. Takano et al. reported that rhinosinusitis was observed in 41 (51.9%) of 79 patients with IgG4-RD [11]. The report showed that 14 out of 41 patients (34%) showed improved rhinosinusitis after oral PSL administration, which was similar to that observed after ECRS [11]. The clinical courses of ECRS and IgG4-RD are variable, and the treatments are also varied. However, the most common treatment for both diseases is steroid therapy [2]. The steroid therapy was effective for all five cases in this study. Therefore, there was no longer a need for ESS in these five cases. This indicates that a trial of steroid therapy should potentially be the first line treatment for ECRS with IgG4-RD, in contrast to selecting ESS as the main therapy for ECRS.

Do these five cases belong to the newest category of CRSwNP associated with IgG4-RD (IgG4-related chronic sinusitis)? Were they IgG4-RD with incidentally detected ECRS? The answer is still unknown in the present study because adequate pathological examination with cytokines was not performed in the rhino-sinus lesions including nasal polyps. We performed biopsies from nasal polyps in two of five cases. These histopathological examinations revealed no evidence of the specific findings associated with IgG4-RD. Therefore, two of the five cases presenting with ECRS with IgG4-RD were thought to be different from cases of IgG4-RD involving sinonasal lesions, but this was not confirmed in the three remaining cases. The infiltration of IgG4-positive cells is not a specific finding of IgG4-RD, and can also be observed in common chronic sinusitis with polyps [12]. Therefore, it is necessary for diagnosis of the specific rhino-sinus lesions associated with IgG4-RD to be explained by pathological examination showing an elevated ratio of IgG4-positive plasma cells: IgG plasma cells, dense infiltration of plasma...
cells, fibrosis, storiform pattern, and obliterative phlebitis [13].

As for the relationship between ECRS and IgG4-RD, there are no reports that the patients had ECRS with IgG4-RD previously. In the present study, all five cases showed a peripheral eosinophilia. Peripheral eosinophilia is traditionally observed in the allergic conditions, including ECRS, but has also been described in IgG4-RD [2]. Eosinophil-predominant inflammation induced by thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33 may play a key role in the development and exacerbation of ECRS [14]. A previous report showed that increased induction and expression of TSLP, IL-25, and IL-33 from nasal epithelial cells contributes to the pathophysiology of ECRS. These epithelial cell-derived cytokines induce T helper 2 type (Th2) immune responses [2, 14]. Th2 induces the production of IgE and IgG4 isotypes. It has also been suggested that IgG4-RD is characterized by allergic manifestations and it is potentially driven by enhanced Th2 immune responses [2]. In a more elaborate report, it was shown that IL-33 produced by alternatively activated macrophages (CD68+CD163+20; M2) may have contributed to the pathogenesis of IgG4-RD via aberrant activation of Th2 immune responses [2,15]. Therefore, ECRS with IgG4-RD is speculated to be a unique inflammatory disorder characterized by a Th2 immune response. Further studies are necessary to investigate the relationship between ECRS and IgG4-RD.

**Conclusions**

1. Five patients had ECRS with IgG4-RD were reported.
2. Steroid therapy without surgery was performed in all cases.
3. Clinical and radiological responses were observed in all cases; no relapse occurred.
4. Histopathological examination and cytokine analysis are necessary to make a diagnosis of ECRS with IgG4-RD.

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**Conflicts of Interest**

The authors declare no conflicts of interest associated with this manuscript.

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