IgG4-related sialadenitis
Pearls and Pitfalls in Management

Nobuo OHTA1) Kazuya KURAKAMI1) Akihiro ISHIDA1) Yusuke SUZUKI1) Takatoshi FURUKAWA1) Tsukasa ITO1) Tomoo WATANABE1) Motoyasu SUGIYAMA1) Seiji KAKEHATA1)

1) Dept. of Otolaryngology, Yamagata Univ. School of Medicine
**Conception**

- Retroperitoneal fibrosis
- Interstitial nephritis
- Auto-immune pancreatitis
- Sclerosing cholangitis / hepatitis
- Pseudotumor of mammary gland
- Prostatitis
- Pachymeningitis
- High serous IgG4 IgG4(+) plasmacytes fibrosis
- Auto-immune adenohypophysisis
- Mikulicz’s disease
- Kuttner’s tumor
- Riedel’s thyroiditis
- Mediastinal fibrosis
Diagnosis of IgG4-related Mikulicz’s disease

1. Visual confirmation of symmetrical and persistent swelling in more than two lacrimal or major salivary glands.

2. Raised serum levels of IgG4 (>135 mg/dl).

3. Infiltration of IgG4-positive plasma cells into the lacrimal and/or salivary tissue (IgG4(+)/IgG(+) plasma cells >50%)

※ Criterion 1 and either 2 or 3.

※ Exclusion of other diseases such as sarcoidosis, Castleman’s disease, Wegener’s granulomatosis, lymphoma, cancer and so on.
Introduction

IgG4-related disease is a systemic disease with associated IgG4-positive lymphocytic and/or plasmacytic infiltrations of many organs whole the body.

Infiltrations of IgG4-positive plasmacytes are often observed in salivary glands, thyroid, pancreas, bile duct, and retroperitoneum. Sclerosing salivary glanditis (such as Kuttner’s tumor), autoimmune pancreatitis (AIP), primary sclerosing cholangitis (PSC), and retroperitoneal fibrosis may be IgG4-related sclerosing diseases.

We report ten cases of IgG4-related sclerosing disease and its management.
Case 1: 56 years old, male

- Complaint: bilateral submandibular swelling
- Past and family history: nothing notable
- Present illness:
  From 2003, he was treated with steroid for left lacrimal glanditis by ophthalmologist.

In summer 2007, he complained of bilateral submandibular swelling without pain, so he consulted an otolaryngologist. The swelling repeatedly improved with steroid and deteriorated without steroid, and enlarged slowly.

Therefore, in March 2008, he was introduced to us.
Present medical condition:
- Bilateral submandibular swelling; diam. 6 cm; hard, elastic, with poor mobility.
- Bilateral lacrimal gland swelling.
- No swelling of neck lymph nodes.

Laboratory data:
- WBC 7500/ml, CRP 0.2 mg/dl,
- GOT 25 mg/dl, GPT 19 mg/dl, AMY 351 IU/l
- anti-SS-A/B antibody (Ab) negative (-),
- anti-nuclear Ab (-),
- sIL-2R 1690 U/ml,
- IgM 56 IU/ml, IgA 110 IU/ml, IgE 2640 IU/ml
- IgG 3070 mg/dl (normal: 607—1621)
- IgG1 561 mg/dl (normal: 315—855)
- IgG2 663 mg/dl (normal: 64—455)
- IgG3 59 mg/dl (normal: 23—196)
- IgG4 1750 mg/dl (normal: 11—157)
MRI:

Fig. 2: a, b. Bilat. swelling of submandib. gland (a. axial, b. coronal),
c. Bilat. swelling of lacrimal gland.
FNAC from submandibular gland: class II

Pathological findings:

Fig. 3: a. Specimen, b. H-E stain, c. IgG4-specific stain: diffuse invasion of lymphocytes, destruction of acinus.
Clinical course:

Fig. 4: a. Submandib. gland first exam: Symmetric swelling. 
b. Eyelids at first exam: Symmetric swelling. 
c. CT; AIP onset: Diffuse swelling of pancreas. 
d. Submandib. gland post-op. 
e. Eyelids after therapy: Swelling reduced. 
f. Abdominal CT after therapy: Swelling of pancreas reduced.
Clinical course:

- Maintenance with PSL 5 mg has prevented recurrence.
- We will continue to follow up systemic condition from now on.
Case 2: 47 years old, female

Complaint: bilateral submandibular swelling; thirst.
Past history: hypertension
Family history: nothing notable
Present illness:
  In August 2006, she complained of abnormality of smell perception.
  In February 2007, she consulted an otolaryngologist. Although she was treated, smell perception did not improve.

From 26 February she was treated with PSL 15 mg. Symptoms improved temporarily, but recurred without steroid. Additionally, thirst and dry eyes appeared. On 7 May, she had bilateral submandibular swelling and dry mouth. On resumption of steroid, symptoms reduced.
February 2009: introduced to us.
MRI:

- **Axial:** symmetric swelling of submandibular gland.
- **Coronal:** symmetric swelling of submandibular glands.

Laboratory data:

- WBC 4580/ml, sIL-2R 480 U/ml, anti-SS-A/B Ab, anti-nuclear Ab (-), IgG1 776 mg/dl, IgG2 702 mg/dl, IgG3 19.7 mg/dl, IgG4 531 mg/dl.

Clinical course:

- CT and MRI showed no abnormal organs.
- Symptoms have not reduced without PSL.
- We will continue our observations, because sclerosis may appear in other organs.
Clinical features of patients with IgG4 related disease

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Location(s)</th>
<th>IgG4 (IgG4/IgG;%)</th>
<th>IgG4 Local</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>56</td>
<td>S L</td>
<td>1750 (57.7)</td>
<td>++</td>
<td>AIP</td>
</tr>
<tr>
<td>F</td>
<td>60</td>
<td>S L</td>
<td>369 (22)</td>
<td>ND</td>
<td>AIP</td>
</tr>
<tr>
<td>M</td>
<td>47</td>
<td>S</td>
<td>664 (30.7)</td>
<td>ND</td>
<td>(–)</td>
</tr>
<tr>
<td>M</td>
<td>48</td>
<td>S L</td>
<td>210 (10.9)</td>
<td>++</td>
<td>(–)</td>
</tr>
<tr>
<td>M</td>
<td>59</td>
<td>S</td>
<td>724 (30.7)</td>
<td>++</td>
<td>AIP IP</td>
</tr>
<tr>
<td>M</td>
<td>73</td>
<td>S L</td>
<td>322 (13.7)</td>
<td>++</td>
<td>AIP M</td>
</tr>
<tr>
<td>M</td>
<td>59</td>
<td>S L</td>
<td>665 (24.9)</td>
<td>++</td>
<td>AIP</td>
</tr>
<tr>
<td>F</td>
<td>71</td>
<td>S L</td>
<td>822 (37.9)</td>
<td>++</td>
<td>RF</td>
</tr>
<tr>
<td>F</td>
<td>68</td>
<td>S L</td>
<td>726 (42.1)</td>
<td>++</td>
<td>(–)</td>
</tr>
<tr>
<td>F</td>
<td>38</td>
<td>P</td>
<td>223 (16.6)</td>
<td>ND</td>
<td>(–)</td>
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</tbody>
</table>

**Discussion**

Sclerosing sialadenitis, known as Kuttner tumor, appears as salivary gland enlargement. The lesion is always extensively firm. Histopathologically, the tumors usually present as areas of localized fibrosis characterized by lymphoplasmacytic infiltrate within the glands. IgG4 concentration measurement and IgG4 immunostaining of tissue specimens are required to rule out Sjögren’s syndrome, but Mikulicz’s disease and Kuttner tumor may be immunologically common diseases. Recently, Masaki et al. proposed a new clinical entity, IgG4-related systemic disease characterized by hyper-IgG4 -globulinemia and IgG4-positive plasma cell infiltration in the tissue. In our study, all of the patients had elevated serum IgG4 (>135 mg/dl), and IgG4-positive plasmacytes were observed in the affected salivary glands. Six patients with IgG4-related sclerosing sialadenitis with high ratios of IgG4/IgG and prominent infiltration of IgG4-positive plasmacytes in the involved salivary glands had systemic complications, including pancreatitis, retroperitoneal fibrosis, and/or inflammatory pseudotumor of the lung after the initial swelling of the salivary glands. These results suggest that IgG4 plays important roles in the pathogenesis of IgG4-related sclerosing sialadenitis and that IgG4 levels and the IgG4/IgG ratio can be used as additional parameters of disease activity and as biomarkers for potential life-threatening complications.
The association of malignancy in contiguity with IgG4-related sclerosing disease has been reported in the salivary glands, lacrimal glands, and pancreas. One of our patients with IgG4-related sclerosing sialadenitis had salivary duct carcinoma. These results suggest that progression from longstanding IgG4-related sclerosing disease to malignancy can occur; caution should therefore be taken in interpreting the nature of masses in patients with raised serum IgG4 levels and histological characteristics of IgG4-related systemic disease, because the differential diagnosis includes malignancy.

Good responses to corticosteroids are well known in IgG-4 related systemic diseases, but a standard steroid therapy regimen has not been established. Our patients showed excellent responses to steroid therapy, which was administered as prednisolone 20 to 30 mg daily for 1 to 2 weeks, then tapered. We confirmed a trend of decreasing swelling of the salivary glands 1 to 2 months after the start of steroid treatment, but the dosage and duration of treatment are not still clearly established. In addition, maintenance therapy with steroid medication needs to be investigated. Recently, mizoribine has been used for IgG4-related sclerosing disease and has proven to be effective for reducing symptoms and serum IgG4 levels. Therefore, further studies are required to more fully characterize IgG4-related diseases in more cases and to clarify the long-term outcomes.
Conclusions
Our results suggest that IgG4 plays important roles in the pathogenesis of IgG4-related sclerosing sialadenitis and that serum IgG4 levels and IgG4/IgG ratios may be used as additional parameters of disease activity and as biomarkers of potential life-threatening complications.

References
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