IgG4–Related Sclerosing Sialadenitis
– Report of Three Cases –

Ji Seon Bae · Joo Young Kim¹
Sang Hak Han¹ · Seung-Ho Choi
Kyung-Ja Cho¹

Departments of Otorhinolaryngology and
¹Pathology, Asan Medical Center, University of
Ulsan College of Medicine, Seoul, Korea

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Corresponding Author
Seung-Ho Choi, M.D.
Department of Otorhinolaryngology, Asan Medical
Center, University of Ulsan College of Medicine,
388-1 Pungnap-dong, Songpa-gu,
Seoul 138-736, Korea
Tel: +82-2-3010-4560
Fax: +82-2-472-7898
E-mail: shchoi@amc.seoul.kr

Kyung-Ja Cho, M.D.
Department of Pathology, Asan Medical Center,
University of Ulsan College of Medicine, 388-1
Pungnap-dong, Songpa-gu, Seoul 138-736, Korea
Tel: +82-2-3010-4560
Fax: +82-2-472-7898
E-mail: kjc@amc.seoul.kr

*Ji Seon Bae and Joo Young Kim contributed
equally to this work.

Chronic sclerosing sialadenitis, Mikulicz disease or Küttner tumor has been recently recognized
as a spectrum of IgG4-related sclerosing disease. IgG4-related disease is characterized by a high
serum IgG4 level and tissue infiltration of IgG4-positive plasmacytes. We report three cases of
chronic sclerosing sialadenitis with variably associated systemic involvement. All patients pre-
sented with a submandibular mass or swelling, and all the resected submandibular glands showed
diffuse lymphocytic infiltration, lymphoid follicles, and septal fibrosis. Two of the specimens re-
vealed numerous IgG-positive plasma cells, most of which were IgG4-positive on immuno-
histochemical staining. One of them was associated with dacrtyoadenitis and hypophysitis. The other
patient had ureteroreal lesions. Immunohistochemical study was unavailable in remaining one
case, but the histologic features along with elevated IgG level and associated pancreatitis sup-
ported the diagnosis. All patients received steroid therapy postoperatively and are doing well.
Salivary gland involvement in IgG4-related fibrosclerosis should be recognized in systemic medi-
cal pathology.

Key Words: Chronic sclerosing sialadenitis; IgG4-related sclerosing disease

CASE REPORTS

Case 1

A 56-year-old woman presented with bilateral submandibular swelling since last 1.5 years. She had a medical history of di-
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abetaes mellitus and had been treated with medications since 1998. Ultrasonography showed diffuse parenchymal heterogeneity with lobulation of both submandibular glands. Bilateral submandibular gland resection was performed and the excised salivary glands were diffusely enlarged, measuring up to 5 × 2.5 × 2.5 cm, with focal fibrosclerotic areas (Fig. 1A). The microscopic findings revealed multifocal patchy areas of lymphocytic infiltration with follicle formation and septal fibrosis (Fig. 1B). The infiltrates often involved the blood vessels and nerves and caused obliterative phlebitis-like features (Fig. 1C). Parenchymal atrophy was heterogeneous throughout the gland. Immunohistochemical stains revealed perifollicular presence of numerous IgG-positive plasma cells, most of which were positive for IgG4 (Fig. 1D). Postoperative study showed high titers of serum IgG (1,710 mg/dL; normal range, 700 to 1,600 mg/dL) and IgG4 (5.74 mg/dL; normal range, 0.06 to 1.21 g/L), but showed no autoantibodies including anti-SSA (Ro) and anti-SSB (La). Interestingly, levels of not only IgG4, but also IgG1 and IgG2 were elevated (Table 1). Additional computed tomography (CT) images showed diffuse enlargement with enhancement of both the lacrimal glands and the pituitary gland. Sjögren’s syndrome was excluded on the basis of histologic and laboratory findings. Other organs, including the pancreas, were not thoroughly evaluated. The patient received oral prednisolone (5 mg/day) therapy, and the follow-up magnetic resonance imaging showed an improved state of the pituitary lesion. The

Table 1. Laboratory findings

<table>
<thead>
<tr>
<th>Case</th>
<th>IgG (mg/dL)</th>
<th>IgG1 (g/L)</th>
<th>IgG2 (g/L)</th>
<th>IgG3 (g/L)</th>
<th>IgG4 (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,710 (700-1,600)</td>
<td>9.68 (3.65-9.41)</td>
<td>8.57 (1.65-5.45)</td>
<td>0.94 (0.32-1.16)</td>
<td>5.74 (0.06-1.21)</td>
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<td>2</td>
<td>2,050</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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</tr>
<tr>
<td>3</td>
<td>1,950</td>
<td>5.33</td>
<td>12.10</td>
<td>0.28</td>
<td>0.31</td>
</tr>
</tbody>
</table>

N/A, not available.
lacrimal gland enlargement was reduced during physical examination at follow-up.

Case 2

A 62-year-old male presented with bilateral submandibular masses since last 4 months. He had a past medical history of stent insertion in the left ureter due to ureteric stricture in 2005, however, the accurate cause of the stricture was not known at that time. The head and neck CT revealed focal mass-like geographic low attenuation lesions with mild enhancement of submandibular glands. The abdominal CT showed a wedge-shaped

![Figure 2](image)

**Fig. 2.** One of the resected submandibular glands shows partial consolidation with pinkish-white, solid cut surface (A). Microscopically, the submandibular glands show severe interstitial fibrosis with marked lymphoplasmacytic infiltration (B), which is positive for IgG4 immunohistochemical staining (C).

![Figure 3](image)

**Fig. 3.** (A, B) Microscopically, septal fibrosis and lymphoplasmacytic infiltration are identified.
IgG4-related sialadenitis is a recently established condition which is thought to be a part of systemic sclerosing disease. For unknown reasons, the disease characteristically affects the submandibular glands. In 1888, Johann von Mikulicz-Radecki reported enlarged lacrimal and salivary glands with mononuclear cells infiltration, and in 1933, Sjögren described swelling of the major salivary gland which was termed as Sjögren’s syndrome. Furthermore, in 1896, Küttner described chronic sclerosing sialadenitis. Recent studies reported that the pathogenesis of MD and KT is associated with the unusual cytotoxic T cell mediated process, and these entities have been recently recognized as a part of the spectrum of IgG4-related sclerosing disease. IgG4 CSS is distinguished from Sjögren’s syndrome in that it typically presents in the older age group with slight male predominance, persistent swelling, none to slight sicca syndrome, good response to steroid therapy, elevated serum IgG4/IgG ratio, negative antinuclear antibody and anti-SSA/SSB, and abundant IgG4-positive plasma cells in tissue.

The pathogenesis of IgG4-related sclerosing disease is not completely understood. Increased serum levels of IgG and IgG4 and the presence of several autoantibodies in patients with pancreatitis raises a possibility of autoimmunity. Also the presence of common targets in the pancreas and other exocrine organs, such as carbonic anhydrase (CA)-II, CA-IV, lactoferrin, and pancreatic secretory trypsin inhibitor, distributed in the ductal cells of the pancreas and other organs has been suggested. Recent studies have revealed immune complex deposition within tissues in IgG4-related sclerosing disease on electron microscopy. Increased levels of CD25-high expressing regulatory T cells and decreased levels of naive (CD45RA+) regulatory T cells have been reported to be associated with autoimmune pancreatitis. Regulatory T cells usually inhibit immune responses by producing interleukin-10, however, they may also help to differentiate B lymphocytes into IgG4+ plasma cells. Biphasic mechanism of the disease, comprising of ‘induction’ and ‘progression,’ has been proposed. Disease induction occurs due to an immune response to self-antigens and molecular mimicry, and this leads to a Th1 response and progresses to a Th2 response, differentiating B cells into plasma cells.

Although the role of IgG4 is unknown at present, IgG4 participates as a common pathological component of sclerosing lesions in various organs, such as autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, tubulointerstitial nephritis, and interstitial pneumonia. The lacrimal glands and pituitary gland are the least commonly involved organs in IgG4-related disease as recently described.

In the present study, case 1 showed elevated serum IgG and IgG4 levels, while case 3 showed elevated IgG level and normal range of IgG4 level at the time of the test. However, the histologic features of the submandibular gland and the presence of
autoimmune pancreatitis in case 3 strongly support the diagnosis of IgG4 CSS. Also, if the follow-up data using oral prednisolone is favorable, it may help to confirm the diagnosis. Although serum IgG and IgG4 levels were not checked in case 2, the intraglandular presence of numerous IgG4 positive plasma cells supported the diagnosis of IgG4 CSS.

The cases in the present study are the first descriptions of IgG4 CSS cases in Korea. All cases showed lymphoplasmacytic infiltration in the resected submandibular gland specimens and elevated serum IgG and/or IgG4 levels. The three cases differed in the type and extent of systemic involvement. Case 1 had accompanying dacryoadenitis and hypophysitis, case 2 had previous ureteral stricture, and case 3 had accompanying pancreatic and bile duct involvement. The reported IgG4 CSS cases were accompanied with retrobulbar neuritis,3 cholangitis, cholangiitis, pancreatitis,1 and prostatitis. It appears that systemic involvement in IgG4 CSS is variable in combination case by case, and may vary with time.

In summary, it is not yet determined whether IgG4 CSS is a specified disease entity and the role of plasma cells is specific, however, salivary gland involvement in IgG4-related fibrosclerosis should be recognized in systemic pathology to avoid unnecessary surgery and to seek systemic evaluation.

REFERENCES