

Abundant IgG4-Positive Plasma Cell Infiltration Characterizes Chronic Sclerosing Sialadenitis (Küttner's Tumor)

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Abstract: Chronic sclerosing sialadenitis (CSS) is a cryptogenic tumor-like condition of the salivary gland(s). While immune-mediated processes are suspected in its pathogenesis, and CSS is occasionally reported to be associated with sclerosing pancreatitis, an IgG4-related disease, the exact immunopathologic processes of CSS remain speculative. In this study, we examined the clinicopathologic findings of CSS (12 cases) in comparison with sialolithiasis (8 cases) and Sjögren's syndrome (13 cases), and tried to clarify whether CSS is an IgG4-related disease or not. Submandibular gland(s) were affected in all cases of CSS. CSS cases could be divided into two types: 5 cases were associated with sclerosing lesions in extrasalivary glandular tissue (systemic type), while only salivary gland(s) were affected in the remaining 7 cases (localized type). In the former type, which showed male predominance, bilateral salivary glands were frequently affected, and eosinophilia and elevations of γ -globulin and IgG in serum were frequently found. Histologically, all cases of CSS showed marked lymphoplasmacytic infiltration admixed with fibrosis and the destruction of glandular lobules. Obliterative phlebitis was found in the affected salivary glands in all cases of CSS. Immunohistochemically, the proportion of IgG4/IgG-positive plasma cells was more than 45% in CSS, while it was less than 5% in controls. The resemblance of the clinicopathologic features of CSS with those of sclerosing pancreatitis suggests the participation of a similar immunopathologic process with IgG4 disturbance in CSS. The abundance of IgG4-positive plasma cells in the lesions would be useful for distinguishing CSS from other forms of sialadenitis.

Key Words: autoimmune pancreatitis, sclerosing pancreatitis, Küttner's tumor, multifocal fibrosclerosis, Mikulicz's syndrome

(*Am J Surg Pathol* 2005;29:783–791)

Chronic sclerosing sialadenitis (CSS), which was first described by Küttner in 1896,²⁰ is a rare chronic inflammatory disorder of the salivary gland and most commonly affects the submandibular gland.^{8,16} Clinically, CSS presents with a firm swelling of the salivary gland, and differentiating it from neoplasm is said to be difficult.^{8,16} Because of this feature, this disease has been referred to as Küttner's tumor.⁵ While CSS is not infrequently associated with sialoliths, the sialolithiasis may be a secondary process.^{5,12} Monoclonal and oligoclonal cytotoxic T-cell populations found in the affected salivary gland of CSS patients may suggest an immune-mediated process against intraductal agent(s).^{15,23,27} It is also suggested that secretory dysfunction of salivary glands may lead to inspissation of saliva in the ducts and chronic inflammation in CSS.^{15,23,27} However, the exact etiology of CSS remains unknown.

CSS is sometimes associated with similar sclerosing lesions in extrasalivary glandular tissues such as bile duct (sclerosing cholangitis) and retroperitoneum (retroperitoneal fibrosis).^{21,24,28} Such cases are referred to as multifocal fibrosclerosis, and CSS could be regarded as one manifestation of multifocal fibrosclerosis. In addition, there have been several reports of an association between CSS and sclerosing pancreatitis.^{7,32} Recent studies showed that sclerosing pancreatitis, which is also called autoimmune pancreatitis or lymphoplasmacytic sclerosing pancreatitis, is a unique IgG4-related disease.^{10,32} Patients with sclerosing pancreatitis have high serum concentrations of IgG4,¹⁰ which is the rarest subclass (less than 6%) of IgG in normal subjects.²⁹ In addition, many IgG4-positive plasma cells are histologically detectable in the affected pancreas.^{11,17,32} These clinicopathologic features suggest the involvement of IgG4 and its disturbance in the pathogenesis of sclerosing pancreatitis. Interestingly, we previously detected many IgG4-positive plasma cells in the affected salivary glands of 2 patients with sialadenitis and sclerosing pancreatitis, both of whom were histologically diagnosed

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as CSS.³² This experience prompted us to speculate that disturbance of IgG4 was involved in the pathogenesis of not only sclerosing pancreatitis but also CSS. However, there have been few descriptions on the participation of IgG4 in CSS or sialadenitis,^{17,32} and no comprehensive study of the relationship between IgG4 and CSS has been reported.

In this study, we examined the clinicopathologic features of CSS with similarities to sclerosing pancreatitis and also analyzed the involvement of IgG4-positive plasma cells in CSS immunohistochemically. The goal of this study is to determine whether CSS is an IgG4-related disease or not.

MATERIALS AND METHODS

Patients and Materials

A total of 12 cases of CSS (8 males and 4 females; age, 52–75 years) were examined (Table 1), and 8 cases of sialolithiasis (5 males and 3 females; age, 22–82 years) and 13 cases of Sjögren's syndrome (SS) (13 females; age, 41–77 years) were used as a control. All of these cases were collected from the files of the Department of Human Pathology, Kanazawa University Graduate School of Medicine and affiliated hospitals between 1990 and 2004. All patients with CSS were cryptogenic, and the diagnosis was made based on clinical data and pathologic findings. All cases of CSS underwent surgical resection or biopsy based on clinical diagnosis of salivary gland tumors. Specimens showed histologic findings corresponding to those of CSS,^{5,8,12,15,16,23} and no preceding lesion(s) such as sialolith or mechanical obstruction

of the salivary duct was identifiable, macroscopically or microscopically. Case no. 4 of CCS was previously reported in detail.²⁸

All patients with sialolithiasis presented with painful swelling of the submandibular gland and underwent surgical resection. Sialoliths were macroscopically identifiable in resected specimens. The diagnosis of SS was made clinicopathologically in all cases; all patients presented with xerostomia or keratoconjunctivitis sicca, and were found to have antinuclear antibodies (ANA). All patients underwent lip biopsies (minor salivary glands).

Laboratory Data

We retrospectively analyzed the following laboratory data for CSS and control cases at first presentation; eosinophilic leukocytes in the peripheral blood, serum γ -globulin, IgG, ANA, anti-SSA antibody, anti-SSB antibody, and antineutrophilic cytoplasmic antibody. The serum IgG4 level was not examined in any cases in this study.

Histologic Examinations and Immunohistochemistry for IgG and IgG4

Surgically resected or biopsied specimens of salivary glands were fixed in neutral formalin and embedded in paraffin. Surgically resected or biopsied specimens of the bile duct (case nos. 1 and 4), pancreas (case no. 5), cervical lymph node (case no. 3), and prostate (case no. 5) were similarly processed. More than twenty 4- μ m-thick sections were cut from each paraffin block, and several of them were stained with hematoxylin and eosin and elastica van Gieson (EVG).

TABLE 1. Main Clinicopathologic Features of Chronic Sclerosing Sialadenitis in This Study

Case No.	Age (yr) /Sex	Location	Size of Tumorous Lesion (cm)	Treatment	Extrasalivary Gland Lesion	Cervical Lymphadenopathy
Systemic type						
1	75/M	Submandibular gl. right	4.7	Surgical resection	Sclerosing cholangitis	Absent
2	60/M	Submandibular gl. left	4.5	Surgical resection	Sclerosing pancreatitis	Present
		Submandibular gl. right	4.8	Surgical resection		
3	63/M	Submandibular gl. left	3.0	Biopsy	Lacrimal gland swelling	Present
		Submandibular gl. right	2.0	No treatment		
4	61/M	Submandibular gl. left	2.0	Surgical resection	Sclerosing cholangitis	Absent
		Submandibular gl. right	2.0	Surgical resection		
5	65/M	Submandibular gl. left	3.0	No treatment	Sclerosing pancreatitis, Prostatitis	Absent
		Submandibular gl. right	5.0	No treatment		
		Minor salivary gl. multiple	<1.0	Excision biopsy		
Localized type						
6	70/F	Submandibular gl. left	3.1	Surgical resection	Absent	Present
7	52/F	Submandibular gl. right	3.0	Surgical resection	Absent	Absent
8	72/M	Submandibular gl. left	1.5	Surgical resection	Absent	Absent
9	73/M	Submandibular gl. left	2.5	Surgical resection	Absent	Absent
10	70/F	Submandibular gl. left	3.8	Surgical resection	Absent	Absent
		Submandibular gl. right	4.0	Surgical resection		
11	55/F	Submandibular gl. left	2.5	Surgical resection	Absent	Absent
		Submandibular gl. right	3.5	Surgical resection		
12	59/M	Submandibular gl. left	2.7	Surgical resection	Absent	Present

gl, gland.

The rest were used for the immunostaining for IgG and IgG4. Histologic features were comprehensively assessed by three pathologists (S.K., Y.Z., and Y.N.).

Immunostaining of IgG and IgG4 was performed using a mouse monoclonal antibody against human IgG (Dako, Glostrup, Denmark), and a mouse monoclonal antibody against human IgG4 (Zymed Laboratory Inc, San Francisco, CA), respectively. Deparaffinized sections were microwaved for 20 minutes in ethylenediaminetetraacetic acid buffer (pH 8.0). After the blocking of the endogenous peroxidase and incubation in normal goat serum for 20 minutes, the sections were incubated overnight at 4°C with the primary antibody. These sections were then incubated for 1 hour at room temperature with goat anti-mouse immunoglobulins, which were conjugated to peroxidase-labeled polymer (Envision+, Dako). Diaminobenzidine tetrahydrochloride was used as the chromogen, followed by light counterstaining with hematoxylin. Negative controls were evaluated by substituting the primary antibody with nonimmunized mouse serum. IgG- or IgG4-positive plasma cells is counted at 5 different high power fields (HPF, 10× eyepiece and 40× lens) with intense inflammation, and the ratio (percentage) of IgG4-positive plasma cells/IgG-positive plasma cells was calculated in each case. Both the right and left submandibular glands were examined histologically and immunohistochemically in 3 cases of CSS showing bilateral glandular involvement (case nos. 1, 4, 7, and 8). The ratio of IgG4/IgG-positive plasma cells in several extrasalivary gland lesions was also calculated in case nos. 1, 4, and 5.

Statistics

Values are given as the mean $\pm$ SD (SD). Means of two groups were compared with the Mann-Whitney *U* test. Values of *P* < 0.05 were regarded as statistically significant.

RESULTS

Main Clinical Features

Main clinical features of 12 cases of CSS are shown in Table 1. In case nos. 1, 2, 3, 4, and 5, the CSS was associated with extrasalivary glandular lesions such as sclerosing cholangitis and sclerosing pancreatitis; whereas in case nos. 6, 7, 8, 9, 10, 11, and 12, it was not associated with such lesions. The former type of CSS was designated as systemic, and the latter as localized. The average age of patients with the systemic type and localized type was 63.8 and 65.3 years, respectively. Patients with systemic type CSS were all males, while with localized CSS included 4 females and 3 males. Submandibular glands were affected in all CSS cases, and in addition, patient no. 5 showed multiple swelling of minor salivary glands around the lower lip. Bilateral submandibular glands were affected in 6 cases; bilateral involvement was more common in systemic (4 of 5 cases) than localized (2 of 7 cases). CSS patient nos. 2, 3, 5, 10, and 11 presented with bilateral submandibular glandular lesions at first examination, while patient no. 4 first presented with a lesion of the left submandibular gland and underwent surgical excision, and 1 year later, developed swelling of right submandibular gland. All patients with CSS except patient nos. 3 and 5 underwent

surgical resection of submandibular glands, while only biopsies from the left submandibular gland in case no. 3 and from minor salivary glands around the lower lip in case no. 5 were available. After the diagnosis of CSS, patient nos. 3 and 5 were followed up without any medication or surgical treatment, and the salivary glandular lesions spontaneously regressed. Tumor size was measured by radiologic imaging or physical examination (case nos. 3 and 5) or in the resected specimens (the remaining cases). Cervical lymphadenopathy was evident in 2 cases of systemic type and 2 cases of localized type.

Association of Extrasalivary Gland Lesions

In case no. 1, irregular stenosis of hepatic ducts was found, and choledochectomy was performed based on the clinical diagnosis of hilar cholangiocarcinoma. The pathologic diagnosis of the hepatic duct was sclerosing cholangitis. In case no. 2, swelling of the pancreatic head was evident, and a diagnosis of sclerosing pancreatitis was made radiologically. During follow-up without any treatment, the pancreatic swelling spontaneously regressed. Patient no. 3 had swelling of the bilateral submandibular glands and bilateral lacrimal glands. These clinical features corresponded to Mikulicz's syndrome. He did not show any symptoms of SS, such as xerostomia or keratoconjunctivitis sicca. He underwent biopsies of the left submandibular gland and a cervical lymph node. Thereafter, the swelling of lacrimal gland improved spontaneously. Patient no. 4 presented with jaundice and liver dysfunction 20 months after salivary gland resection. Endoscopic retrograde cholangiopancreatography revealed stenosis of the common hepatic duct, and a pathologic examination of choledochectomy specimens showed sclerosing cholangitis. Patient no. 5 was found to have jaundice and swelling of the pancreatic head and underwent pancreatoduodenectomy because pancreatic cancer could not be excluded. The diagnosis of sclerosing pancreatitis was made histopathologically. Additionally, patient no. 5 had a history of swelling of the prostate and transurethral electroresection for suspicion of prostate cancer. Diffuse lymphoplasmacytic infiltration with glandular destruction was observed histologically.

Laboratory Data

Eosinophils in peripheral blood and serum γ -globulin level were examined in all cases of CSS, and IgG and ANA were measured in 8 cases (case nos. 1–5, 8, 11, and 12) and 7 cases (case nos. 1–5, 8, and 11), respectively. Eosinophilia was found in 3 of 5 systemic cases (case nos. 1, 3, and 5), and in 2 of 7 localized cases (case nos. 7 and 12). Three of 5 systemic cases (case nos. 1, 2, and 5) and 2 of 7 localized type (case nos. 10 and 11) showed an elevation of the γ -globulin fraction (20.6%–41.0%; normal range, <20.4%). The serum IgG level was elevated in 3 of 5 systemic cases (case no. 1, 4520 mg/dL; case no. 2, 2510 mg/dL; case no. 5, 2730 mg/dL), and 1 of 3 localized cases (case no. 12, 2040 mg/dL) (normal range, 700–1600 mg/dL). ANA was detected in 3 of 5 systemic cases (case nos. 1, 2, and 4) and in none of 2 localized cases. Eosinophilia, hypergammaglobulinemia, a high IgG level, and ANA were commonly observed in the systemic type of CSS, although the serum IgG concentration and ANA were not examined in cases

of localized CSS. Anti-SSA antibody and anti-SSB antibody, and anti-neutrophilic cytoplasmic antibodies (perinuclear type and cytoplasmic type) were measured only in case nos. 3 and 12, respectively, and were negative in both cases.

Histologic Findings of Salivary Glands

Chronic Sclerosing Sialadenitis

Tumorous lesions in surgically resected specimens were relatively well circumscribed and were composed of a dense lymphoplasmacytic infiltration with an irregular and dense fibrosis in 12 cases. These chronic sclerosing inflammatory lesions distributed diffusely in periductal or interlobular connective tissue and also within lobules with variable destruction or atrophy of the salivary glandular lobules or acini (Fig. 1A–C). Lymphoid follicles with germinal centers were found in all cases except case nos. 3 and 6. Eosinophilic infiltration was conspicuous in case nos. 1, 2, 7, 11, and 12, while they were scattered in the remaining cases. These inflammatory processes were localized within the salivary gland, and no extension of the lesions beyond the fibrous capsule to the adjacent tissues was evident. Obliterative phlebitis, which meant the vein totally or partially occluded with inflammatory cell infiltration and fibrosis, was easily identifiable in all CSS cases on EVG staining (Fig. 1D). No microscopic sialolith or microabscess was detected in any case of CSS. Lymphoplasmacytic infiltration was scattered in nontumorous areas of the affected salivary glands.

Histopathologic features in the affected salivary glands did not differ between the systemic type and localized type, or between the left and right glands in 4 cases with bilateral involvement (case nos. 2, 4, 10, and 11).

Controls

In sialolithiasis, sialoliths were macroscopically identifiable. The affected salivary glands showed mild to moderate

lymphoplasmacytic infiltration with variable neutrophils in the periductal area and lobules. Little or no eosinophilic infiltration was seen. The ducts of the salivary glands were variably dilated and occasionally associated with the accumulation of neutrophils (microabscess) within their lumens. Dense fibrosis was observed around stone-containing ducts and extended into lobules. Lip biopsies (minor salivary glands) of SS showed lymphoplasmacytic infiltration associated with parenchymal atrophy. In neither sialolithiasis nor SS was obliterative phlebitis evident on EVG staining.

Immunohistochemistry for IgG and IgG4

The results of immunostaining of IgG and IgG4 are shown in Figures 2 to 4 and Table 2. IgG-positive plasma cells were more conspicuous and diffusely distributed in the affected salivary glands of CSS patients (Fig. 2A) and mild or moderate in controls (Fig. 2C). The numbers of IgG-positive plasma cells per high power field in CSS cases ranged from 100.2 to 323.6/HPF. By contrast, in sialolithiasis and SS, the numbers of IgG-positive plasma cells were relatively small (5.0–82.8/HPF in sialolithiasis and 7.2–87.8/HPF in SS) (Figs. 2C, 3; Table 2). Immunostaining of IgG4 revealed that a majority of IgG-positive plasma cells infiltrating the lesions of all cases of CSS were positive for IgG4 (Fig. 2B). Numbers of IgG4-positive plasma cells in CSS ranged from 62.2 to 232.4/HPF (Fig. 3; Table 2). In contrast, IgG4-positive plasma cells were rarely found in sialolithiasis and SS (<2.8/HPF in sialolithiasis and <1.4/HPF in SS) (Figs. 2D, 3; Table 2). There was a significant difference in the number of IgG-positive plasma cells and of IgG4-positive plasma cells between CSS and either sialolithiasis or SS (Table 2). However, there were no differences in number between the systemic and localized type of CSS, or between the right and left submandibular glands in 4 cases of CSS affecting the bilateral glands (case nos. 2, 4, 10, and 11). The extrasalivary gland tissues available in case nos. 1, 4, and 5 showed a prominent infiltration of

FIGURE 1. Histopathology of chronic sclerosing sialadenitis. A, Dense fibrosis subdivides the submandibular gland, and a marked lymphoplasmacytic infiltration with germinal centers is associated with destruction and atrophy of the salivary gland lobules. Periductal fibrosis is also evident (hematoxylin and eosin, original magnification $\times 100$). B, There is nearly a complete loss of acinar cells with severe interstitial fibrosis and a marked lymphoplasmacytic infiltration (hematoxylin and eosin, original magnification $\times 400$). C, Severe lymphoplasmacytic infiltration with several eosinophils and fibrosis around the duct are observed (hematoxylin and eosin, original magnification $\times 400$). D, Obliterative phlebitis is evident (Elastic-van Gieson stain, original magnification $\times 200$). *a+*

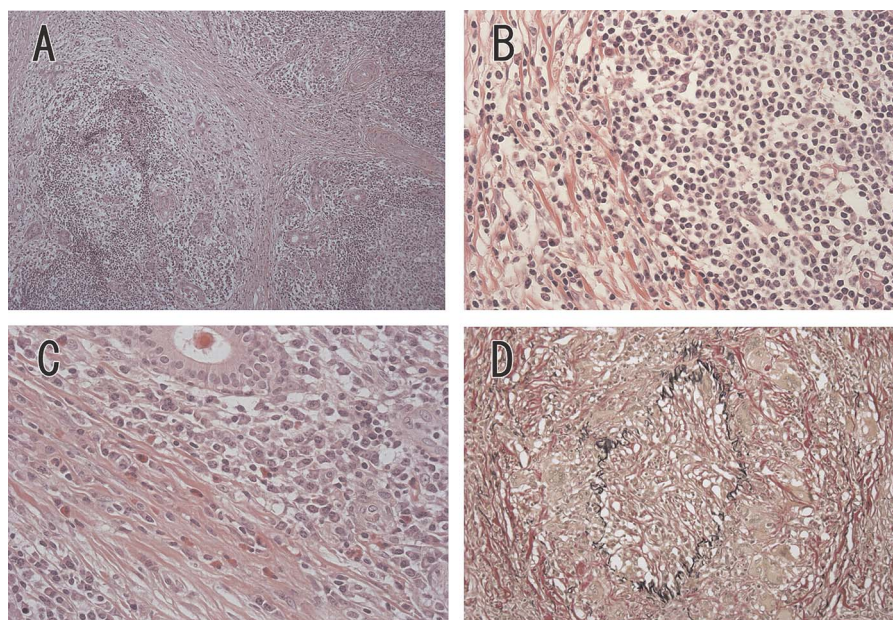


FIGURE 2. Immunostaining of IgG and IgG4 in chronic sclerosing sialadenitis and Sjögren's syndrome. A and B, Chronic sclerosing sialadenitis (surgically resected specimen). Many IgG-positive plasma cells are infiltrating in the salivary gland (A), and a majority of these plasma cells are positive for IgG4 (B). Immunostaining of IgG (A) or IgG4 (B) and hematoxylin (both, original magnification $\times 400$). C and D, Sjögren's syndrome (lip biopsies). Moderate numbers of IgG-positive plasma cells are infiltrating the salivary glands (C), and only a few of them are positive for IgG4 (D). Immunostaining of IgG (C) or IgG4 (D) and hematoxylin (both, original magnification $\times 400$). *az*

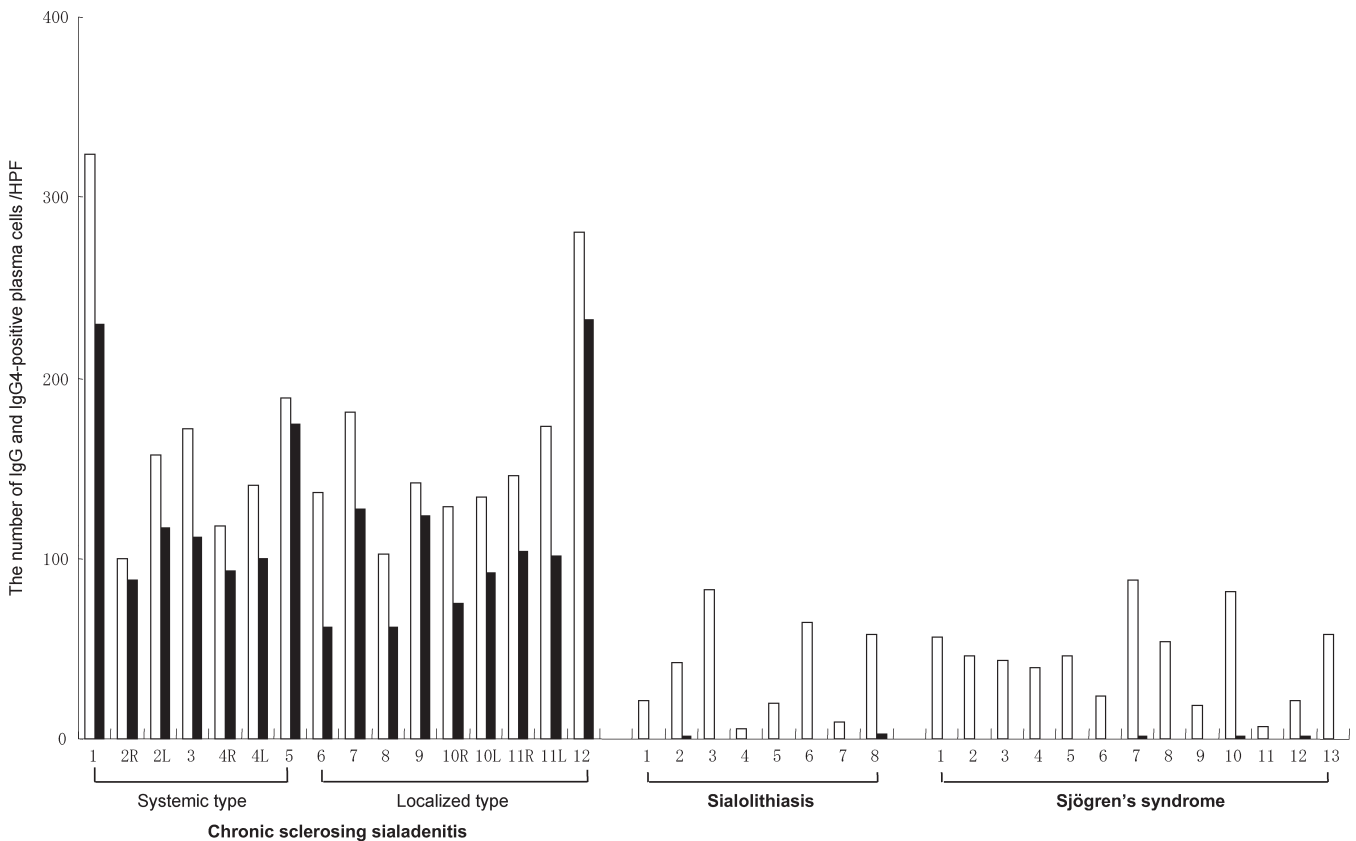
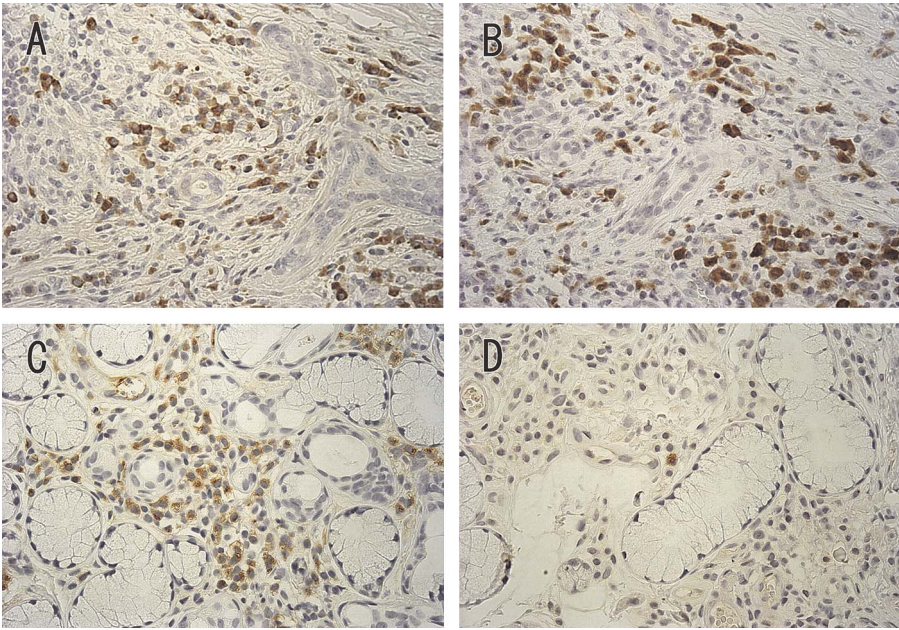


FIGURE 3. Distribution of the number of IgG- (white bars) and of IgG4-positive plasma cells (black bars) in the salivary gland tissue of individual case of chronic sclerosing sialadenitis (12 cases), sialolithiasis (8 cases), and Sjögren's syndrome (13 cases). Number of IgG-positive plasma cells and of IgG4-positive plasma cells are higher in all cases of chronic sclerosing sialoadenitis in comparison with those in sialolithiasis and Sjögren's syndrome ($P < 0.05$). There is no difference in the number of IgG- or IgG4-positive plasma cells between the right and left salivary glands in bilateral chronic sclerosing sialoadenitis (case nos. 2, 4, 10, and 11). In sialolithiasis and Sjögren's syndrome, mild to moderate IgG-positive plasma cell infiltration is seen, while IgG4-positive plasma cells are very rare. HPF, high power field; L, left salivary gland; R, right salivary gland.

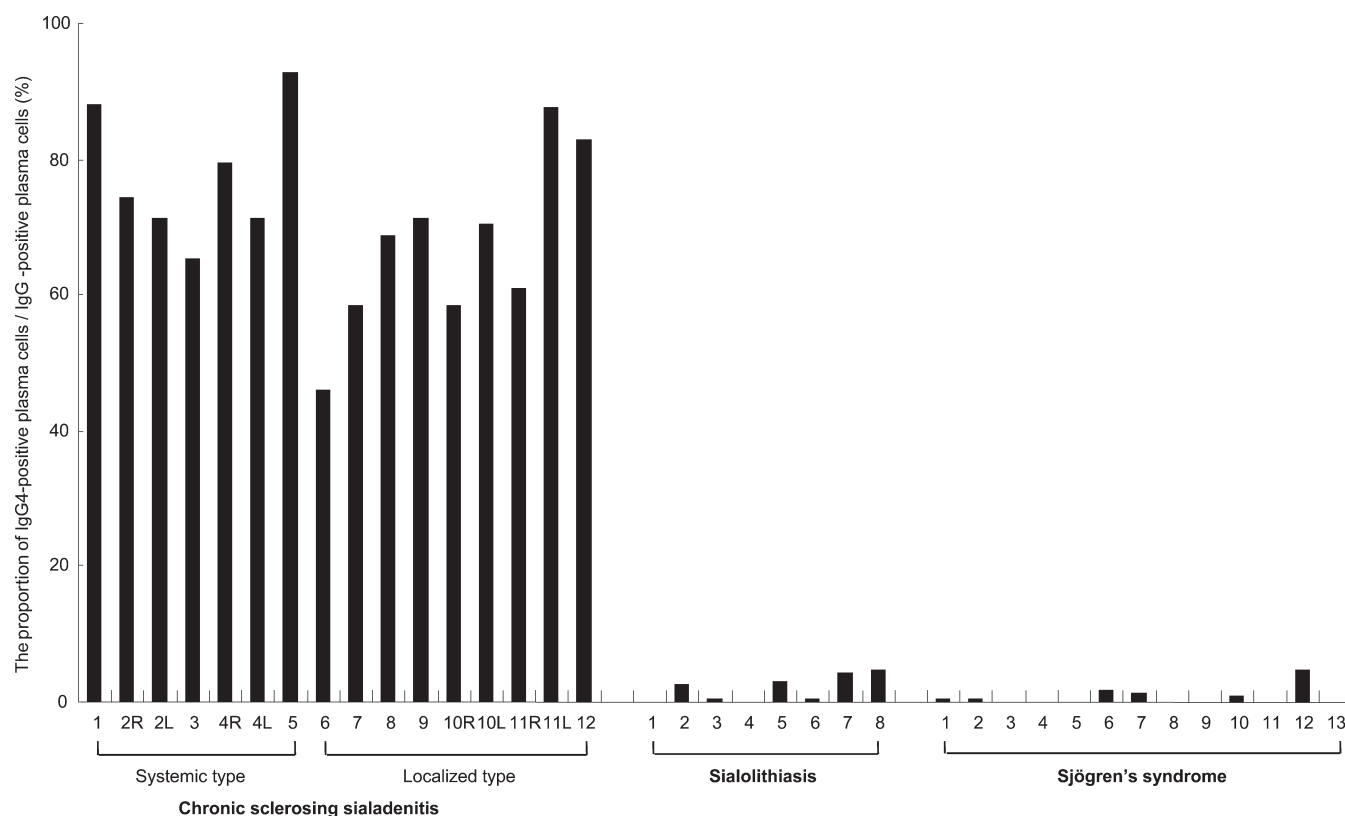


FIGURE 4. Distribution of the proportion of IgG-positive plasma cells/IgG4-positive plasma cells in the salivary gland of individual cases of chronic sclerosing sialadenitis (12 cases), sialolithiasis (8 cases), and Sjögren's syndrome (13 cases). The proportion in chronic sclerosing sialadenitis ranges from 50% to 93%, while that in sialolithiasis and Sjögren's syndrome ranges from 0% to 4%. The difference between chronic sclerosing sialadenitis and sialolithiasis or Sjögren's syndrome is significant ($P < 0.05$). There are no differences in the percentage between the right and left salivary glands in bilateral chronic sclerosing sialadenitis (case nos. 2, 4, 10, and 11). HPF, high power field; L, left salivary gland; R, right salivary gland.

IgG- and IgG4-positive plasma cells as seen in the salivary gland. The proportion of IgG4/IgG-positive plasma cells in the common bile duct (case no. 1) was 81.3%, that in the common bile duct (case no. 4) was 60.9%, that in the pancreas

(case no. 5) was 87.6%, and that in the prostate (case no. 5) was 91.7%.

The proportion of IgG4/IgG-positive plasma cells in CSS, sialolithiasis, and SS is shown in Figure 4 and Table 2.

TABLE 2. Number of IgG4- or IgG-Positive Plasma Cells Per HPF and the Proportion of IgG4-Positive/IgG-Positive Plasma Cells in Chronic Sclerosing Sialadenitis, Sialolithiasis, and Sjögren's Syndrome

		IgG4 (no. per HPF)	IgG (no. per HPF)	IgG4/IgG (%)
CSS (12 cases)	Average $\pm$ SD	118.2 $\pm$ 51.7	163.6 $\pm$ 60.4	71.6 $\pm$ 12.5**†
	Range	62.2–232.4	100.2–323.6	45.8–92.8
(systemic type, 5 cases)	Average $\pm$ SD	130.5 $\pm$ 52.5	171.1 $\pm$ 73.7	77.3 $\pm$ 10.0**†
	Range	88.2–230.0	100.2–323.6	65.0–92.8
(localized type, 7 cases)	Average $\pm$ SD	108.6 $\pm$ 52.1	157.8 $\pm$ 51.8	67.1 $\pm$ 12.9**†
	Range	62.2–232.4	101.8–281.0	45.8–87.4
Sialolithiasis (8 cases)	Average $\pm$ SD	0.7 $\pm$ 0.9	37.6 $\pm$ 28.4	2.0 $\pm$ 2.0
	Range	0–2.8	5.0–82.8	0–4.9
Sjögren's syndrome (13 cases)	Average $\pm$ SD	0.3 $\pm$ 0.4	45.1 $\pm$ 23.7	0.7 $\pm$ 1.3
	Range	0–1.4	7.2–87.8	0–4.6

CSS, chronic sclerosing sialadenitis; SD, standard deviation of the mean; HPF, high-power field.

* $P < 0.05$ vs. sialolithiasis.

† $P < 0.05$ vs. Sjögren's syndrome.

That of IgG4/IgG-positive plasma cells in CSS cases ranged from 45.8% to 92.8%, while the percentage in controls (sialolithiasis and SS) was 0% to 4.9%. The proportion was significantly higher in CSS than in sialolithiasis ($P < 0.001$) and also SS ($P < 0.001$). There was no difference in the ratio in the submandibular glands between systemic type and local type, or between the right and left submandibular glands in 4 cases of CSS affecting the bilateral glands.

DISCUSSION

It was found in this study that the affected salivary glands of all CSS patients showed histologically a marked lymphoplasmacytic infiltration admixed with irregular and dense fibroplasia and obliterative phlebitis and also evident destruction or atrophy of glandular lobules. Eosinophils were also variably infiltrated within the lesions and even conspicuous in several cases. Interestingly, marked infiltration by IgG-positive and IgG4-positive plasma cells was detected immunohistochemically within the lesions. Interestingly, more than 45% of IgG-positive plasma cells were of IgG4-type in all CSS cases. In contrast, in sialolithiasis and SS cases, a variable number of IgG-positive plasma cells had infiltrated and less than 5% of IgG-positive plasma cells were of IgG4-type. Thus, a marked infiltration of IgG- and IgG4-positive plasma cells and, particularly, a high proportion of IgG4-positive plasma cells, seem to characterize CSS.

Interestingly, these histologic and immunohistochemical characteristics of CSS resemble those of sclerosing pancreatitis.^{19,22,32} That is, the latter was composed of marked lymphoplasmacytic infiltration with irregular and dense fibrosis, and the sclerosing inflammatory process destroyed the exocrine pancreatic acini considerably and also extended to the peripancreatic adipose tissue. Eosinophilic infiltration was conspicuous in some cases. Frequently, sclerosing pancreatitis presents with a tumor-like mass due to localized or exaggerated inflammatory changes in the pancreas. Such a feature is also a characteristic of CSS.^{5,8,16} More recently, in sclerosing pancreatitis, infiltration by abundant IgG4-positive plasma cells was detected in the affected pancreas and the serum level of IgG4 was frequently elevated.^{17,32} As mentioned above, marked infiltration of IgG4-positive plasma cells was a characteristic feature of CSS. It is likely that CSS may show an elevated serum IgG4 level, although serum IgG4 was not examined in the cases used in this study. These histologic and immunohistochemical similarities between CSS and sclerosing pancreatitis suggest a common pathogenetic process in these two diseases. Particularly, immunologic assault involving IgG4 disturbance could be a key process.

IgG4 is the rarest component among the IgG subclasses and only accounts for less than 6% of the total IgG fraction in the serum of healthy subjects.²⁹ So far, a high serum level of IgG4 has been reported in a limited number of pathologic conditions such as atopic dermatitis, pemphigus vulgaris, pemphigus foliaceus, and allergy in addition to sclerosing pancreatitis.^{1,14,25,29,30} In endemic pemphigus foliaceus, acquisition of an increased IgG4 response to desmoglein-1, an epidermal adhesion molecule, may play a key step in the pathogenesis. In CSS and sclerosing pancreatitis, similar

processes involving antigenic materials around the ducts of pancreas and salivary glands may be operative. Interestingly, several patients with CSS (patient nos. 3 and 5) showed spontaneous remission of CSS, and such spontaneous remission is also known in sclerosing pancreatitis,^{17,18,32} suggesting that the acquisition of an increased IgG4 response could be transient. Anyhow, it is mandatory to identify antigen(s) recognized by IgG4 and clarify the immunopathologic processes in these IgG4-related diseases including CSS.

Kamisawa et al reported that many IgG4-positive plasma cells were also evident in extrapancreatic organs such as the stomach and lymph nodes in patients with sclerosing pancreatitis, and proposed as a disease entity an IgG4-related systemic disorder.^{17,18} They regarded sclerosing pancreatitis as an exaggerated organ involvement of pancreas in an IgG4-related systemic disorder.¹⁸ There is now increasing evidence to suggest that IgG4-related tumorous lesions could occur in extrapancreatic tissue even in individuals without sclerosing pancreatitis. In this sense, IgG4-rich CSS could be an exaggerated manifestation of IgG4-related disease in the salivary glands. If so, CSS might be effectively treated with steroids as is true for sclerosing pancreatitis.^{9,11,13} Actually, there have been a few reports of CSS treated well using corticosteroid therapy.⁷

Obliterative phlebitis was observed in all cases of CSS. Obliterative phlebitis was determined as a histologic feature of IgG4-related diseases after Kawaguchi et al first reported the histopathology of sclerosing pancreatitis in 1991,¹⁹ and this phlebitis was easily and characteristically found in almost all cases of sclerosing pancreatitis.^{2,32} The extrapancreatic IgG4-related diseases reported so far also shared this histologic feature.³² While it is possible that the IgG4-related immune response may also involve the small veins in the affected tissue, the exact pathogenesis of obliterative phlebitis remains only speculative.

CSS could be divided into two categories in this study: a systemic type associated with chronic inflammatory sclerosing changes in extrasalivary glandular tissues, and a localized type affecting only the salivary glands. Of 5 cases of systemic-type CSS, abundant IgG4-positive plasma cell infiltration was shown in the extrasalivary glandular lesions in three cases (case nos. 1, 4, and 5). Pancreas in case no. 2 and lacrimal glands in case no. 3, in which histologic studies were not done, might have been also similarly affected because these lesions had spontaneously regressed in these 2 cases. Such a regression is one of the characteristics of IgG4-related diseases.^{17,18,32} Both the systemic and localized type of CSS showed a similar histopathology in the affected salivary glands, and the density of IgG- and IgG4-positive plasma cells and the ratio of IgG4/IgG-positive plasma cells were also similar. However, the systemic type showed male predominance, the frequent involvement of bilateral submandibular glands, and peripheral eosinophilia, whereas females were affected similarly by the localized type. The clinical features of systemic-type CSS share those of sclerosing pancreatitis, which also commonly affects middle-aged men and is frequently associated with para-pancreatic lymphadenopathy, eosinophilia, and retroperitoneal fibrosis.^{10,17,31,32} Indeed, case nos. 2 and 5 of CSS in this study were associated with

sclerosing pancreatitis. More studies are needed to explain the differences between these two types of CSS.

Case no. 5 showed an IgG4-related lesion in the prostate. While the involvement of the prostate seems strange from the standpoint of immune-mediated disease, there is now increasing evidence that IgG4-related diseases more commonly affect glandular tissues such as the pancreas and salivary gland. More recently, we also reported an IgG4-related inflammatory pseudotumor in the breast.³³ In this sense, the IgG4-related prostatitis in case no. 5 might be explainable based on the reports that this disease preferentially affects the glandular tissue.

Histologically, CSS is known to be difficult to distinguish from other forms of sialoadenitis.^{6,27} However, this discrimination is important and necessary in clinical practice because histologic similarities between CSS and sclerosing pancreatitis shown in this study suggest that CSS shares clinical features of sclerosing pancreatitis. CSS could be well treated with corticosteroid therapy same as sclerosing pancreatitis and other IgG4-related disease.^{19,32} In addition, CSS is sometimes associated with IgG4-related lesions in the extrasalivary glandular tissue(s); therefore, systemic medical survey is recommended for patients with CSS.

It has been a puzzle whether case no. 3 with swelling of the bilateral lacrimal glands and submandibular glands involves SS or not. However, the patient did not present with xerostomia or keratoconjunctivitis sicca. In addition, ANA, hypergammaglobulinemia, anti-SSA antibody, or anti-SSB antibody was not serologically detected, so we thought that CSS was likely in this case. Histologic and immunohistochemical studies of case no. 3 also support this diagnosis. There have been several reports on the occurrence of SS in patients with sclerosing pancreatitis or cholangitis.^{26,28} Most of these patients were reportedly negative for anti-SSA or anti-SSB antibodies,²¹ suggesting that they actually had CSS not SS.

Mikulicz's syndrome is chronic dacryoadenitis associated with enlargement of the salivary glands and lymphoepithelial lesions.^{3,4} This may be the result of Mikulicz's disease or a variety of other diseases, including sarcoidosis, malignant lymphoma, and viral infection. Mikulicz's disease, which is the most common cause of Mikulicz's syndrome, is histologically characterized by lymphoplasmacytic infiltration surrounding isolated epithelial nests (epimyoepithelial island). Interestingly, patient no. 3, whose disease clinically corresponds to Mikulicz's syndrome, showed IgG4-related sclerosing inflammation in a biopsy specimen from the left submandibular gland, suggesting that IgG4-related disease could manifest as Mikulicz's syndrome. It is interesting and also mandatory to clarify what proportion of Mikulicz's disease or syndrome is an IgG4-related disease.

In summary, this study suggests that CSS belongs to the IgG4-related disease spectrum and abundant IgG4-positive plasma cells in the affected salivary glands might relate to its pathogenesis. It seems mandatory to clarify the spectrum of IgG4-related disease and also the immunopathologic process(es) operative in this disease.

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