

Chronic Sclerosing Sialadenitis (Küttner Tumor) Is an IgG4-associated Disease

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Background: Chronic sclerosing sialadenitis is a fibroinflammatory disease of the salivary glands, characteristically of the submandibular gland. One prior Asian study proposed that chronic sclerosing sialadenitis is a part of the spectrum of IgG4-associated disease. This association has not been confirmed in Western populations. We therefore, investigated the relationship between IgG4 and chronic sclerosing sialadenitis, and compared the histomorphologic features of this condition with those of chronic sialadenitis-not otherwise specified, Sjögren syndrome, and lymphoepithelial sialadenitis.

Materials and Methods: We evaluated 13 cases of chronic sclerosing sialadenitis and compared them with 15 cases of chronic sialadenitis-not otherwise specified, 8 lip biopsies from individuals with Sjögren syndrome, and 4 cases of lymphoepithelial sialadenitis. Immunohistochemistry for IgG, and IgG4 was carried out. IgG4-positive plasma cells were quantified and the IgG4/IgG ratio was calculated.

Results: Seven patients with chronic sclerosing sialadenitis were female and 6 were male. Their mean age was 61 years (range: 27 to 80). Twelve chronic sclerosing sialadenitis cases involved the submandibular gland (bilaterally in 3) and in 1 there was a parotid lesion. Three of these 12 cases had manifestations of IgG4-associated systemic disease. Morphologically these specimens had preservation of lobular architecture, hypercellular interlobular fibrosis, florid lymphoid hyperplasia, and numerous plasma cells. Obliterative phlebitis was observed in 6 cases. The histologic features of chronic sclerosing sialadenitis were reminiscent of autoimmune pancreatitis, and were either not observed or were present only focally in cases of chronic sialadenitis, Sjögren syndrome, and lymphoepithelial sialadenitis. Eleven of 12 evaluable cases showed an increased number of IgG4 plasma cells with a mean of 229/high-power field (HPF) (range 75 to 608) and an overall IgG4/IgG ratio of 0.86 (range 0.5 to 1). The only patient whose biopsy lacked IgG4-positive plasma cells had pathologic evidence of cytomegalovirus infection. Chronic sclero-

sing sialadenitis cases, in comparison with the other 3 groups studied, showed a significantly higher number of IgG4 positive plasma cells ($P < 0.05$). Patients with chronic sialadenitis-not otherwise specified had a median number of only 16 IgG4-positive plasma cells/HPF (range 2 to 44), with an IgG4/IgG ratio of 0.14 (range 0.02 to 0.28). The Sjögren syndrome patients had a median of 1 IgG4-positive plasma cell/HPF (range 0 to 3), with an IgG4/IgG ratio of 0.02 (range 0 to 0.07). Patients with lymphoepithelial sialadenitis had a median of 0 IgG4-positive plasma cells per HPF.

Conclusion: Chronic sclerosing sialadenitis has a characteristic morphologic appearance. This morphologic appearance, in conjunction with the elevated IgG4 expression, distinguishes chronic sclerosing sialadenitis from other inflammatory diseases of the salivary glands. Chronic sclerosing sialadenitis belongs to the spectrum of IgG4-related diseases.

Key Words: Küttner tumor, chronic sclerosing sialadenitis, Sjögren syndrome, lymphoepithelial sialadenitis, IgG4, plasma cells

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Chronic sclerosing sialadenitis (also known as Küttner tumor) is a relatively uncommon and underrecognized cause of salivary gland enlargement that characteristically affects the submandibular salivary gland. This disease may clinically mimic Sjögren syndrome, and mucosa-associated lymphoid tumor (MALT) lymphoma. The disease was originally described by H. Küttner in 1896, who reported a “hard swelling” of 1 or both submandibular glands.^{3,19} Chronic sclerosing sialadenitis typically presents in middle-aged to elderly patients with a slight male predominance. The histologic features of chronic sclerosing sialadenitis are a well-defined mass lesion with preservation of lobular architecture, marked lymphoplasmacytic inflammation, formation of lymphoid follicles, sclerosis, acinar atrophy, obliterative phlebitis, and the absence of prominent lymphoepithelial lesions.^{3,18} Chronic sclerosing sialadenitis shows a predilection for the submandibular gland, although parotid gland involvement has also been described.²⁵ Earlier authors associated chronic sclerosing sialadenitis with inspissated secretions and sialoliths.^{3,14,26} However, the presence of a prominent lymphoplasmacytic infiltrate and lymphoid follicles, combined with the finding of unusual cytotoxic

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T cell populations, suggest an immune-mediated process.^{15,27} More recently, a group of Japanese researchers have shown that some examples of sclerosing sialadenitis have abundant IgG4-positive plasma cells that can possibly link it to autoimmune pancreatitis.¹⁸ Only limited information was available on these cases, and these findings have not been confirmed in Western populations.

IgG4, the rarest of IgG subtypes, represents 3% to 6% of total IgG in the serum of normal subjects. IgG4 differs from other IgG isoforms in the composition of the hinge region because of a 25% to 75% loss of covalent interaction between the heavy chains. This intrinsic weakness leads to a dynamic exchange between Fab arms and the formation of bispecific, functionally monovalent antibodies.^{1,28} The exchange of half-molecules decreases the effectiveness of the antibodies that activate complement, and cross-link identical antigens poorly.²⁸

High serum and tissue levels of IgG4 have been linked to autoimmune pancreatitis, an idiopathic inflammatory illness affecting other exocrine glands.¹² In recent years, it has been recognized that patients with autoimmune pancreatitis may, in addition, have an involvement of numerous extrapancreatic sites, such as kidney, lung, liver, gallbladder, lymph nodes, and salivary glands.^{4,6,7,32} In contrast, some patients may present with primary extrapancreatic disease and have no evidence of a concurrent pancreatic lesion.^{5,11} This has led researchers to postulate that autoimmune pancreatitis is part of a disease spectrum for which a variety of names have been suggested, including “IgG4-related sclerosing disease” or “IgG4-related systemic disease.”^{7,16} Chronic sclerosing sialadenitis, if IgG4 related, may be a component of IgG4-related systemic disease.

We undertook this study in a Western population of patients with chronic sclerosing sialadenitis to validate the findings of the Japanese study. We also compared chronic sclerosing sialadenitis with other inflammatory conditions of salivary glands, with an emphasis on identifying a clinically relevant, steroid-responsive IgG4-associated subset.

MATERIALS AND METHODS

Case Selection

A computer-assisted search of pathology files at the Massachusetts General Hospital and histologic review of identified cases disclosed 13 patients with chronic sclerosing sialadenitis (Küttner tumor) diagnosed between 1992 and 2008. For comparison, we selected 15 patients with chronic sialadenitis-not otherwise specified of the submandibular gland, 8 Sjögren syndrome patients diagnosed by lip biopsy, and 4 patients with lymphoepithelial sialadenitis of the parotid gland. Patients with chronic sialadenitis-not otherwise specified did not have clinical and morphologic features of chronic sclerosing sialadenitis. Clinical data and follow-up information were obtained. Institutional Review Board approval was received from the Partners Healthcare System.

Histology and Immunohistochemistry

All slides were reviewed, and the area with the greatest number of plasma cells was included in a tissue microarray that was composed of 5 mm cores of tissue. Each tissue microarray included a core of pancreatic tissue from a well-characterized case of autoimmune pancreatitis and this served as a control. An elastic stain was carried out in selected cases. Slides were cut for hematoxylin and eosin analysis, and immunohistochemistry for IgG4 (Invitrogen, CA; dilution 1:200), and IgG (Dako, 1:800). Additional immunohistochemical stains were carried out on selected cases: CD20 (prediluted; Ventana), CD3 (prediluted; Vision Biosystems/Novocastrol), Bcl-2 (Prediluted; Ventana), bcl-6 (1:10; Dako), polyclonal κ light chain (1:2600; Dako), polyclonal λ light chain (1:1400; Dako), expression of immunoglobulin light chains for κ and λ using the Ventana ISH iView kit with probes κ and λ . Staining was done on BenchMark XT-automated tissue staining systems (Ventana Medical Systems, Inc., Tucson, AZ) using validated protocols. Antigen detection was carried out using *UltraView* diaminobenzidine chromogen (Ventana Medical Systems, AZ). Three high-power fields (HPF) with the densest concentration of IgG4-positive plasma cells were quantified (HPF area = 0.2375 mm²). Immunoreactive plasma cells were counted within the same 3 fields on the slide stained for IgG. The ratio of IgG4 to IgG positive plasma cells was calculated for each case.

RESULTS

Clinical Features

Chronic Sclerosing Sialadenitis (13 Patients)

The clinical, pathologic, and immunohistochemical results are summarized in Table 1. Seven patients were female and 6 were male. Their mean age was 61 years (range 27 to 80). All patients presented with a chief complaint of a neck mass. Twelve chronic sclerosing sialadenitis cases involved the submandibular gland, with bilateral involvement in 3. One patient had a parotid gland lesion. None had a history of recurrent sialadenitis or sialolithiasis. Associated autoimmune diseases included 1 case of Graves' disease.

Evidence of Systemic IgG4-related Disease

Three of the 13 patients (23%) showed clinical or pathologic evidence of a systemic IgG4-related disease. One patient presented with a pancreatic mass, retroperitoneal fibrosis, lung nodules, bilateral renal nodules, and generalized lymphadenopathy. His overall presentation was worrisome for a lymphoproliferative process. However, biopsies of the submandibular gland, lung, and kidney all showed histologic features of systemic IgG4-associated disease. Moreover, increased IgG4-positive plasma cells were identified at all 3 sites and the serum IgG4 level of the patient was markedly elevated. He was treated with glucocorticoids with complete resolution of clinical symptoms and

TABLE 1. Summary of Clinicopathologic Features of IgG4-associated Sialadenitis (Küttner Tumor) Versus Chronic Sialadenitis-not Otherwise Specified, Sjögren Syndrome and Lymphoepithelial Sialadenitis

	IgG4-associated Sialadenitis (CSS)	Chronic Sialadenitis, NOS	Sjögren Syndrome (Lip Biopsy)	Lymphoepithelial Sialadenitis
Age in years (mean)	61	55	56	50
Sex M:F	6:7	3:2	1:7	1:1
Focal lesion/diffuse involvement	8 focal 5 diffuse	6 focal 9 diffuse	0 focal 8 diffuse	0 focal 4 diffuse
Interlobular cellular fibrosis	13/13 (100%)	1/15 (6%)	0	0
Bland acellular interlobular fibrosis	0	15/15 (100%)	0	0
Periductal inflammation	7/13 (54%)	7/15 (47%)	0	0
Marked lobular chronic inflammation with sheets of plasma cells	13/13 (100%)	2/15 (13%)	0	0
Phlebitis	9/13 (69%)	0	0	0
Obliterative phlebitis	6/13 (49%)	0	0	0
Follicular hyperplasia	13/13 (100%)	8/15 (53%)	0	4/4 (100%)
Florid follicular hyperplasia	13/13 (100%)	0	0	4/4 (100%)
Lymphoepithelial lesions	2/13 (15%)	0	1/8 (12%)	4/4 (100%)
Mean IgG4 per HPF (range)	229 (75-608)	16 (2-44)	1 (0-3)	6 (0-22)
IgG4/IgG ratio	0.86	0.14	0.02	0.04

CSS indicates chronic sclerosing sialadenitis; NOS, not otherwise specified.

improvement in the radiologic appearance. The patient remains well 6 years after presentation.

Another patient presented with submandibular gland enlargement that was followed by lacrimal gland disease 1 year later. Biopsy of the lacrimal gland was consistent with an inflammatory pseudotumor. The patient subsequently developed parotid gland enlargement and was found to have a pancreatic mass on computed tomographic imaging of the abdomen. His serum levels of IgG4 were not measured, and he was subsequently lost to follow-up.

One patient had persistent peripheral lymphadenopathy involving cervical, hilar, and paratracheal lymph nodes. Six patients have not developed additional symptoms of IgG4-related systemic disease after a mean follow-up of 6 years (range 1 to 12). Clinical information was unavailable for 3 patients.

Chronic Sialadenitis-not Otherwise Specified (15 Patients)

Nine patients were male and 6 were female. Their median age was 55 years (range 22 to 76). Chief complaints from this cohort were a neck mass (n = 5), recurrent sialadenitis (n = 4), and acute neck swelling and pain (n = 3). All patients had involvement of submandibular glands.

Sjögren Syndrome (8 Patients)

Seven patients were female and 1 male. Their median age was 56 years (range 40 to 68). All patients had clinical and immunologic features that were consistent with Sjögren syndrome. Patients presented with dry mouth (n = 5) and/or arthralgias and myalgias (n = 4). All 7 Sjögren syndrome patients tested had histories of autoantibodies, including anti-Ro/SSA (6 patients) and anti-La/SSB (3 patients). One patient did not have

documentation of an immunologic evaluation at our institution.

Lymphoepithelial Sialadenitis (4 Patients)

Two patients were female and 2 were male. Their median age was 50 years (range 24 to 65). One patient had bilateral parotid involvement and 2 had evidence of unilateral parotid enlargement. None of these patients had clinical or immunologic evidence of Sjögren syndrome. Data on the clinical presentation was unavailable for 1 patient.

Pathologic Findings

Chronic Sclerosing Sialadenitis

Eight of the 13 cases (62%) had well defined, circumscribed lesions that involved between 30% and 80% of the submandibular gland (mean 50%). In the remaining 5 cases (including the parotid lesion), the entire gland was involved. All chronic sclerosing sialadenitis lesions had consistent and characteristic morphologic features, notably: preservation of lobular architecture, dense lymphoplasmacytic inflammation within the lobules, large irregular lymphoid follicles with expanded geographic germinal centers, sheets of plasma cells, and acinar atrophy. The lobules were separated by a distinctive form of fibrosis that was characterized by a highly cellular proliferation composed of plump fibroblasts, small lymphocytes, numerous plasma cells, and occasional eosinophils (Fig. 1). This appearance is similar to the inflammatory proliferation seen in autoimmune pancreatitis.

Significantly, acellular and hyalinized fibrosis was either absent or identified only focally. Phlebitis was evident in 9 cases, obliterative in 6 and nonobliterative in 3. An elastic stain confirmed the presence of obliterative phlebitis in 2 cases. A periductal pattern of inflammation was seen in 7 cases, but was never as prominent as the

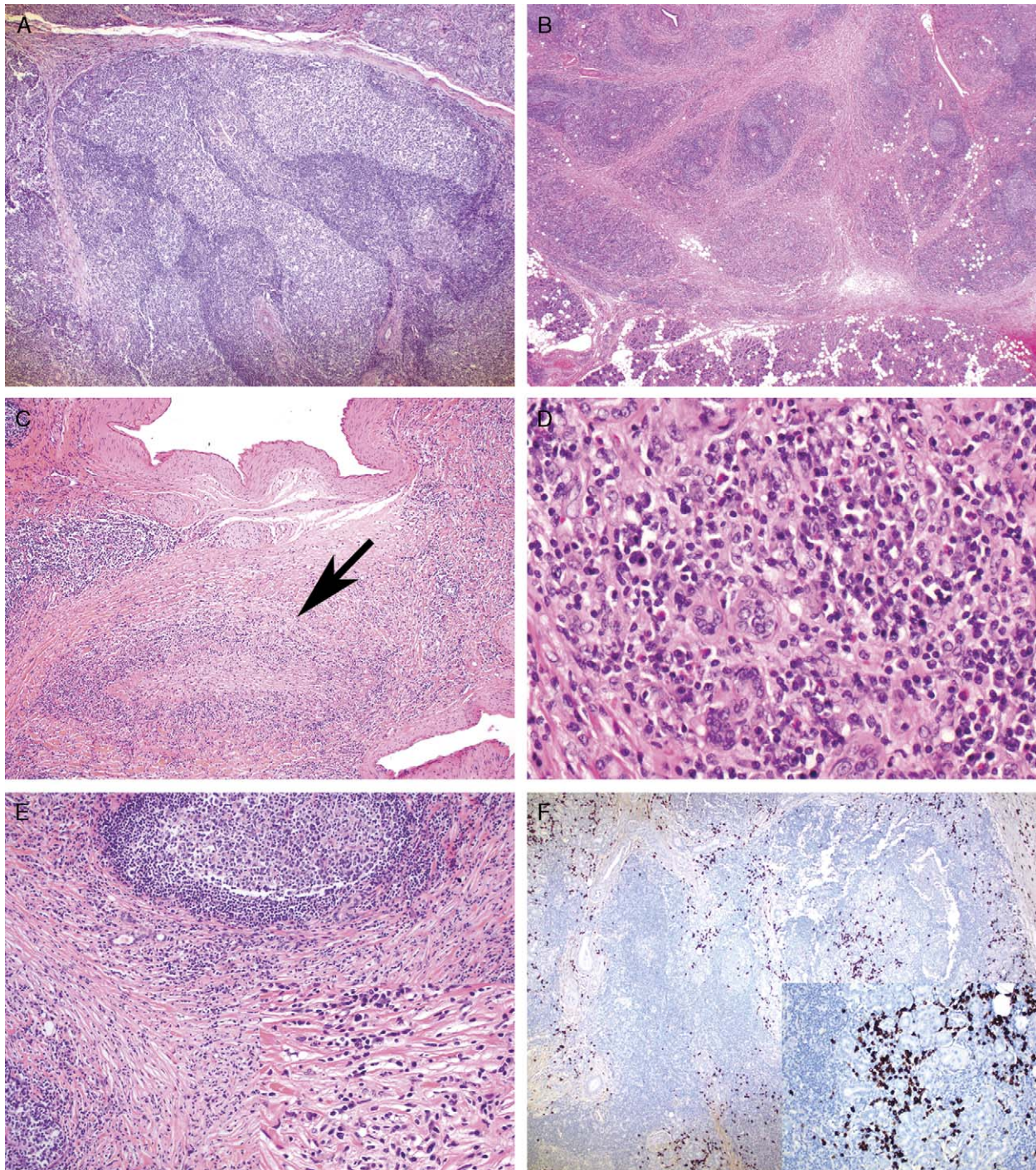


FIGURE 1. Chronic sclerosing sialadenitis cases show a consistent morphologic appearance that includes large geographic germinal centers (A), accentuation of lobular architecture (B), obliterative phlebitis (arrow). Note also the accompanying artery; the arteries frequently accompany veins and help in localizing an obliterated vessel (C), large number of plasma cells in the lobules (D), hypercellular interlobular stroma consisting of lymphocytes, plasma cells, and fibroblasts (E), Greater than 75 IgG4 positive plasma cells/ high-power field (HPF) were identified in 12 of 13 chronic sclerosing sialadenitis cases.

intralobular inflammatory component. Rare lympho-epithelial lesions were noted in 2 cases. The marginal zone was not expanded and lymphocytes were mostly round and small without evidence of atypia.

One submandibular excision from a 13-year-old patient had a histologic appearance similar to the other chronic sclerosing sialadenitis cases, but this salivary gland lesion also showed prominent intranuclear and

intracytoplasmic viral inclusions within epithelial cells consistent with cytomegalovirus infection. This case was, therefore excluded from the chronic sclerosing sialadenitis cohort.

Chronic Sialadenitis-not Otherwise Specified

Sialoliths were identified in 8 gross specimens. Six patients had well defined, focal lesions that involved between 30% and 50% of the submandibular gland. Nine patients had diffuse glandular involvement. Eight of the 15 excisions showed microscopic evidence consistent with the presence of intraductal calculi as evidenced by a markedly dilated salivary duct with focal squamous metaplasia of ductal epithelium. A prominent periductal inflammatory response was seen in 7 cases and periductal fibrosis in 4.

The lobules had evidence of lymphoplasmacytic inflammation that was mild in 8 cases, moderate in 5, and severe in 2. In contrast, severe lobular inflammation was noted in all chronic sclerosing sialadenitis cases. Acini were atrophic and intercalating ducts were frequently surrounded by markedly thickened basement membranes. Lymphoid follicles were present in the lobules and adjacent to large ducts in 8 cases. However, in comparison with the chronic sclerosing sialadenitis cases, the lymphoid follicles were both fewer in number and smaller in size (Fig. 2).

The fibrous stroma separating the lobules was uniformly paucicellular, lacked an inflammatory infiltrate, and was composed of hyalinized collagen. The interlobular fibrosis ranged from mild (2 cases) to moderate (5 cases) to severe/dense (8 cases). Cellular fibrosis, as noted in chronic sclerosing sialadenitis specimens, was focally seen in only 1 case; however, the majority of the interlobular stroma in this case was qualitatively and quantitatively similar to the other chronic sialadenitis-not otherwise specified cases. There was no evidence of phlebitis or lymphoepithelial lesions in this group.

Sjögren Syndrome

The lip biopsies showed a mild, focal lymphoplasmacytic infiltrate with preservation of the gland architecture (Fig. 2). No cases had lymphoid follicle formation, fibrosis, sclerosis, or phlebitis. One patient had a small lymphoepithelial lesion.

Lymphoepithelial Sialadenitis

The parotid gland excisions showed uniform histologic involvement of the entire gland. The acini were replaced by a dense lymphoid infiltrate with reactive follicular hyperplasia and prominent, widespread lymphoepithelial lesions (Fig. 2). Plasma cells were rare and eosinophils absent. There was no evidence of interlobular fibrosis.

Immunohistochemistry Results

The IgG4 positive plasma cells showed strong reactivity and thus these plasma cells were relatively easily enumerated. In an occasional case a nonspecific background stain was noted; however, the intensity of

the immunoreactivity allowed for the easy identification of IgG4 positive plasma cells. All 11 evaluable chronic sclerosing sialadenitis cases showed increased numbers of IgG4 positive-staining plasma cells. The median number of IgG4-positive plasma cells per HPF was 229 (range 75 to 608). The IgG4/IgG ratio was 0.86 (range 0.5 to 1.0). These IgG4-positive plasma cells were noted within the inflamed lobules, interlobular septae, and occasionally within germinal centers. The patient with evidence of CMV infection showed only a single IgG4-positive plasma cell.

In comparison, patients with chronic sialadenitis-not otherwise specified had a significantly lower median number of IgG4-staining plasma cells compared with the chronic sclerosing sialadenitis cases: 16/HPF (range 2 to 44) versus 229 (range 75 to 608) ($P = 0.001$). Thus, the chronic sclerosing sialadenitis cohort showed significantly higher numbers of IgG4 positive plasma cells ($P = 0.001$) (Fig. 3). Similarly, IgG4-positive plasma cells were scant to absent in the Sjögren syndrome cohort with a median of 1 (range 0 to 3) cell per HPF and IgG4/IgG ratio of 0.02 (range 0 to 0.07) (Fig. 3, 4). Three of the lymphoepithelial sialadenitis cases entirely lacked IgG4-positive plasma cells. In 1 case a lymphoid follicle containing 22 IgG4-positive plasma cells per HPF was identified.

In addition, immunohistochemistry for CD20, CD3 and κ and λ light chains were carried out on 7 cases of chronic sclerosing sialadenitis. The CD20 positive B cells were confined to the follicles, with many interfollicular T cells. Plasma cells were polytypic with immunohistochemical stains and in situ hybridization (carried out on 1 case) for κ and λ immunoglobulin light chains. The follicles expressed Bcl6 (carried out on 2 cases) and were negative for Bcl2 (carried out on 3 cases). These results support a reactive process in all cases and do not suggest lymphoma.

DISCUSSION

Only 1 earlier study based in Japan has examined the relationship between chronic sclerosing sialadenitis and IgG4-related systemic disease.¹⁸ These authors found that the number of IgG4-positive plasma cells ranged from 62.2 to 232.4/HPF (mean 118) with an IgG4 to IgG ratio that ranged from 0.46 to 0.93 (mean 0.72). Our study, conducted on Western patients, confirmed these results. The number of IgG4-positive plasma cells was significantly higher in patients with chronic sclerosing sialadenitis as compared with other inflammatory conditions of salivary gland, including chronic sialadenitis-not otherwise specified, Sjögren syndrome, and lymphoepithelial sialadenitis. Chronic sclerosing sialadenitis cases showed more than 75 IgG4-positive plasma cells/HPF, whereas the cases in the other 3 groups had fewer than 50 IgG4-positive plasma cells/HPF. Furthermore, the IgG4/IgG ratios readily distinguished chronic sclerosing sialadenitis from the other inflamed salivary glands studied. The only patient with "chronic sclerosing sialadenitis" who

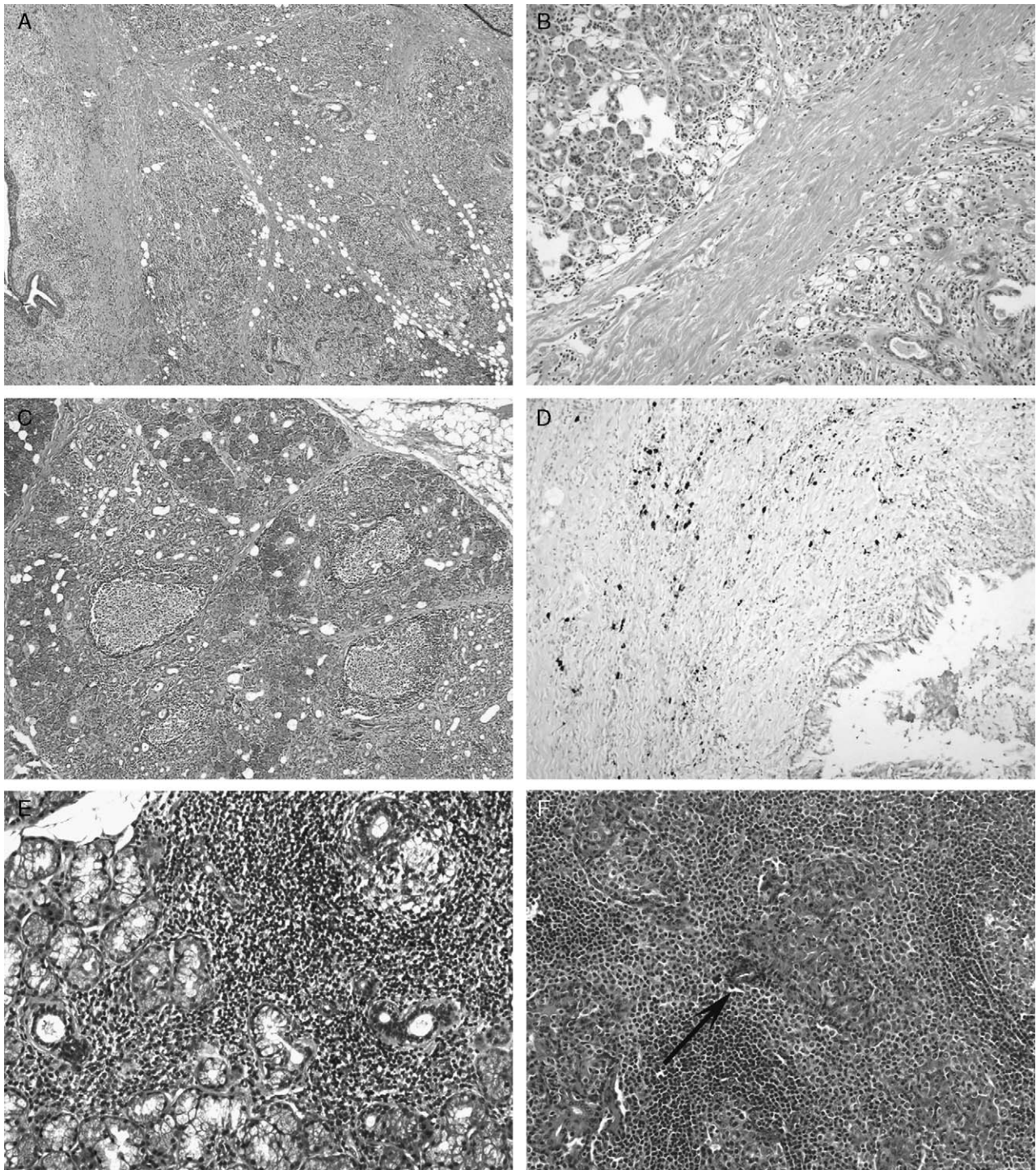


FIGURE 2. In contrast to chronic sclerosing sialadenitis, chronic sialadenitis—not otherwise specified showed relatively acellular interlobular fibrosis (A, B), both fewer and smaller germinal centers (C). Some cases of chronic sialadenitis—not otherwise specified showed numerous IgG4 positive plasma cells; however, they were less than 50/ high-power field (HPF) (D). A lip biopsy from an individual with Sjögren syndrome with a lymphoid tissue infiltrating minor salivary gland tissue (E). Lymphoepithelial sialadenitis showing lymphoepithelial lesions (arrow) (F).

lacked IgG4-positive plasma cells within her salivary gland was the 13-year-old patient with evidence of CMV sialadenitis.

On the basis of unique histologic appearance of chronic sclerosing sialadenitis and the uniform presence of increased numbers of IgG4-positive plasma cells in both

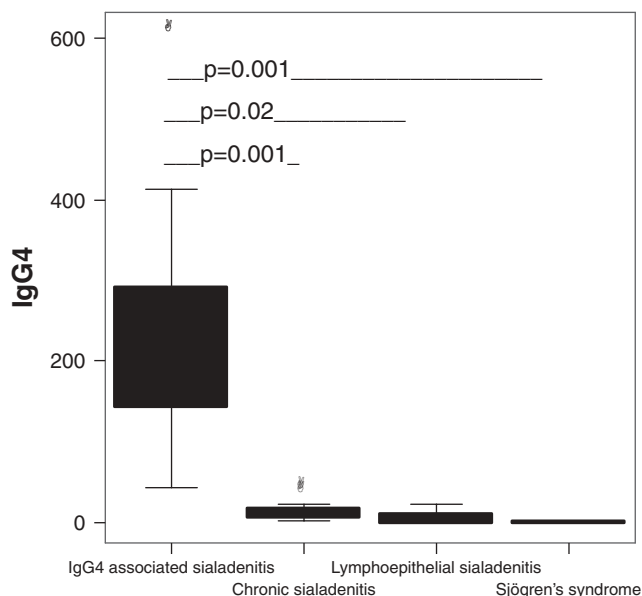


FIGURE 3. Boxplot illustrating IgG4 counts in inflammatory disorders of the salivary gland.

studies¹⁸ and the characteristic histomorphologic appearance, we propose replacing the eponym “Küttner tumor” with the term “IgG4-associated sialadenitis.” Three of the 10 cases on which follow-up information was available showed other manifestations of IgG4-associated systemic disease. Significantly, in a prior study from Japan, 5 of 12 patients (42%) showed evidence of a systemic IgG4-related disease.¹⁸ This terminology would bring the salivary gland nomenclature in line with the term used for other systemic manifestations of this disease.¹¹ Furthermore, this proposed

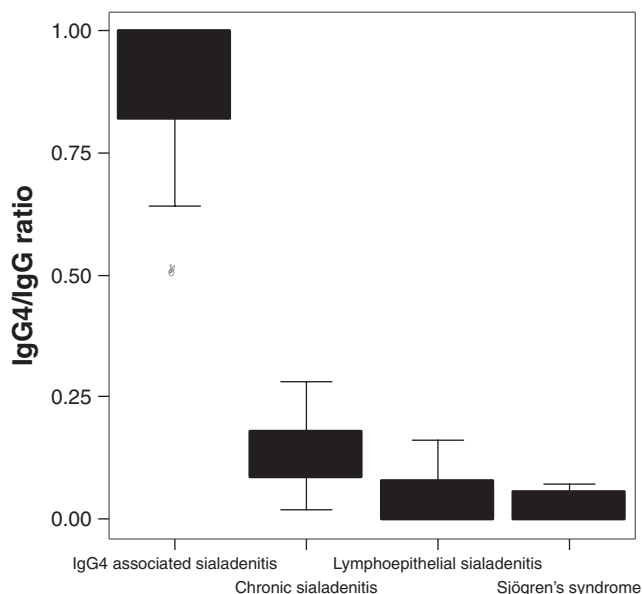


FIGURE 4. Boxplot illustrating IgG4/IgG ratios in inflammatory disorders of the salivary gland.

term would bring into focus both the systemic nature of the disease and the appropriate therapy, that is immunosuppressive drugs.^{8–10} Nonetheless, we acknowledge the fact that a change in nomenclature will require additional studies, and furthermore a better understanding of the role of IgG4 in this disease.

Recognition of IgG4-associated sialadenitis (Küttner tumor) is important clinically, because IgG4-related disease has been proven to be steroid-sensitive, thus potentially obviating the need for surgical procedures. On the basis of our case review, we believe that chronic sclerosing sialadenitis has a characteristic morphology and is also readily recognized based on histologic grounds. Chronic sclerosing sialadenitis (IgG4-associated sialadenitis) is differentiated from chronic sialadenitis-not otherwise specified by the presence of a prominent cellular interlobular fibrosis composed of plump fibroblasts, lymphocytes, and plasma cells. In contrast, chronic sialadenitis-not otherwise specified, related to sialolithiasis or other miscellaneous conditions is characterized by a bland, acellular interlobular fibrosis. All IgG4-associated sialadenitis cases were characterized by florid follicular hyperplasia with large, irregular geographic lymphoid follicles. In contrast, cases with chronic sialadenitis-not otherwise specified showed fewer lymphoid follicles that were smaller, when present. Obliterative phlebitis is frequently noted in chronic sclerosing sialadenitis, and an elastic stain may be required to unmask this feature. Approximately half of the cases in the chronic sialadenitis-not otherwise specified cohort showed markedly dilated salivary ducts with erosions or squamous metaplasia of the ductal epithelium, consistent with the presence of an intraductal stone. Intraglandular stones were not identified in the IgG4-associated sialadenitis cases that we studied.

The classic presentation of salivary gland enlargement in Sjögren syndrome involves the parotid glands. Isolated submandibular gland enlargement in the absence of clinically-evident parotid disease is highly unusual in Sjögren syndrome.² In contrast, parotid gland involvement in IgG4-associated sialadenitis is less common compared with submandibular gland disease. Minor salivary tissue in patients with Sjögren syndrome shows mild lymphoplasmacytic inflammation without sheets of plasma cells and lacks lymphoid follicular hyperplasia or evidence of interlobular fibrosis. Lymphoepithelial lesions are typically not well developed and are therefore, not required for a diagnosis.

Lymphoepithelial sialadenitis involving the parotid gland may or may not be associated with Sjögren syndrome. Regardless of the etiology of lymphoepithelial sialadenitis, however, the condition is characterized by numerous, florid lymphoepithelial lesions, defined as a proliferation of ductal epithelial cells with the formation of lymphoepithelial islands and cystic dilatation of peripheral ducts.¹³ The inflammatory infiltrate is predominantly lymphocytic with only rare plasma cells. Lymphoepithelial sialadenitis does not feature the interlobular fibrosis of IgG4-associated sialadenitis and lacks the elevated numbers of IgG4 positive plasma cells.

IgG4-associated sialadenitis must be also distinguished from non-Hodgkin lymphoma of the salivary gland. The most common type of lymphoma in this location is extranodal marginal zone lymphoma (MALT), characterized by a diffuse proliferation of neoplastic marginal zone B cells, scattered large, transformed lymphoid cells, intact or disrupted reactive germinal centers, and lymphoepithelial lesions. Some MALT lymphomas have a plasmacytic differentiation with aggregates or sheets of plasma cells that may be small and mature or are cytologically abnormal, showing enlargement, nuclear irregularity, or presence of Dutcher bodies. MALT lymphomas are also characterized by the extension of B cells beyond lymphoid follicles. Immunohistochemical stains are helpful in reliably making a distinction between MALT lymphoma and IgG4-associated sialadenitis. If plasma cells are part of the neoplastic clone, clonality will be shown on paraffin sections by staining for κ and λ immunoglobulin light chains. Rarely, MALT lymphoma may arise from a Küttner tumor. In that case, the typical architectural features of chronic sclerosing sialadenitis are associated with an atypical monomorphous lymphoid infiltrate with monotypic expression of immunoglobulin light chains.²⁴

In recent years, there has been much interest in the Japanese literature regarding the historic term “Mikulicz disease.” Mikulicz disease was described in the 1890s in a 42-year-old man with bilateral parotid, submandibular, and lacrimal gland enlargement.^{20,21} In the 1950s, such cases were related to Sjögren syndrome and considered to be a subset of that condition.^{22,23} Recently, some cases were again separated from Sjögren syndrome in the clinical literature because the patients lacked anti-Ro/SSA and anti-La/SSB antibodies and responded quickly to glucocorticoids.^{30,31} These particular patients had increased serum levels of IgG4 and prominent tissue infiltration of IgG4, leading to the hypothesis that Mikulicz disease is part of IgG4-related systemic disease. In these studies IgG4-positive plasma cells were increased both in the lip biopsy specimens and in the lacrimal and submandibular glands.

Mikulicz disease has been reported to have prominent lymphoepithelial lesions and we consider Mikulicz disease to fall under the current terminology of lymphoepithelial sialadenitis.^{13,20–23} The 4 patients with lymphoepithelial sialadenitis in our study had very few to absent IgG4-positive plasma cells. Furthermore, none of the lip biopsies associated with Sjögren syndrome showed increase in IgG4+ plasma cells. The cases reported by Yamamoto seem to lack lymphoepithelial lesions.³⁰ Therefore, our findings do not seem to support the reintroduction of the historic term Mikulicz disease in the pathologic classification of Sjögren syndrome and lymphoepithelial sialadenitis. Instead, we propose that individuals with elevated numbers of IgG4 (> 50 per HPF) belong to the group of patients with IgG4-associated systemic disease.

This study highlights the growing awareness of the concept of IgG4-associated systemic disease. The disease was initially recognized in the pancreas (autoimmune pancreatitis) and the biliary tree. The recognition that autoimmune pancreatitis is an IgG4-associated disorder came in the early

years of the twenty-first century. Involvement of the gallbladder, tubular gut, lung, kidney, breast, retroperitoneum, and aorta by this disease is now well recognized.^{6–9,17,29} In addition to the IgG4 plasma cells, we believe that careful attention to morphologic features is critical to arrive at a diagnosis of IgG4-associated sialadenitis. The unifying morphologic features of this disease are cellular fibrosis with embedded lymphocytes and plasma cells with or without obliterative phlebitis.

In summary, this is the first study to show that in a Western population chronic sclerosing sialadenitis is an IgG4-related disease. Chronic sclerosing sialadenitis has a characteristic morphologic appearance that aids in its identification. In conjunction with high levels of tissue IgG4, this condition is distinguishable from other inflammatory lesions in the salivary gland including Sjögren syndrome, lymphoepithelial sialadenitis, and chronic sialadenitis-not otherwise specified. The prompt recognition of this IgG4-associated systemic disease (with or without the involvement of the pancreas) is vital in both treating these patients appropriately and conservatively with steroids, and for recognition of the not so uncommon multiorgan nature of involvement, a finding that is frequently diagnostically challenging.

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