

# Differential diagnosis of IgG4-related sialadenitis, primary Sjögren syndrome, and chronic obstructive submandibular sialadenitis

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## Abstract

Our aim was to differentiate IgG4-related sialadenitis, primary Sjögren syndrome, and chronic obstructive submandibular sialadenitis by analysing clinical, radiographic, and pathological features. Fifty-five patients, 50, and 50 were enrolled, respectively and their baseline characteristics and serological, sialographic, and pathological findings compared. The male:female ratio for IgG4-related sialadenitis was 1:1.2 for primary Sjögren syndrome 1:15.7, and for chronic obstructive submandibular sialadenitis 1:0.92. Numbers with enlarged salivary glands were 55, 16, and 50; with xerostomia 26, 48, and 0; with a history of allergy 26, 4, and 6, and with coexisting systemic disease 12, 19, and 0 ( $p=0.14$ ). Mean (SD) serum IgG4 concentrations were 109.1 (97.9), 4.9 (1.9) g/L, and 5.3 (1.6) g/L,  $p<0.001$  in all cases. Sialography showed enlargement of the gland, dilatation of the duct, and slightly decreased secretory function in IgG4-related disease; obvious sialectasia and decreased secretory function in Sjögren syndrome; and dilatation of Wharton's duct and filling defects in obstructive sialadenitis. Histopathological examination showed lymphoplasmacytic infiltration with storiform fibrosis, lymphoplasmacytic inflammation and lymphoepithelial lesions, and dilatation of the duct with epithelial metaplasia in the three groups, respectively. The number of IgG4-positive plasma cells was 123 (45)/HPF, 8 (3)/HPF, and 5 (4)/HPF, while the IgG4/IgG-positive cell ratio was 71.7 (13.9)%, 4.6 (2.5)%, 18.9 (19.7)%, respectively ( $p<0.001$ ). The three conditions have different clinical, radiographic, and pathological features that provide important clues to the differential diagnosis. Serological and histological tests are important, and comprehensive consideration is necessary.

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**Keywords:** Salivary glands; IgG4-related sialadenitis; Primary Sjögren syndrome; Chronic obstructive submandibular sialadenitis; Differential diagnosis

## Introduction

Immunoglobulin G4-related disease is an increasingly-recognised, systemic, immune-mediated disease that is

characterised by dense lymphoplasmacytic infiltrates, storiform fibrosis, and raised serum IgG4 concentrations.<sup>1</sup> Immunoglobulin G4-related sialadenitis is a part of it, and is characterised by enlargement of single or multiple salivary or lacrimal glands, or both, with reduced secretion of saliva.<sup>2</sup>

Because of its close relation to Mikulicz disease, IgG4-related sialoadenitis was thought to be identical to primary Sjögren syndrome,<sup>3</sup> which is characterised by xerophthalmia

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and xerostomia as a result of immune-mediated destruction of the exocrine glands and enlargement of the salivary glands.<sup>4</sup>

Chronic obstructive submandibular sialadenitis is one of the most common disorders of the submandibular glands, and is characterised by obstruction of the ductal system by various factors.<sup>5</sup> Though a sialolith is the most common cause, radiolucent sialoliths are hard to detect. There is an ill-defined group with intermittent swelling of the gland but not typical obstruction or infection, which shares the histological features of chronic obstructive submandibular sialoadenitis. Clinically, advanced disease may manifest itself as a firm submandibular gland, and might be identified as a tumour or Küttner tumour.<sup>6</sup> However, recent studies have indicated that some patients with Küttner tumours develop high serum concentrations of IgG4, together with IgG4-positive plasma cell infiltration, indicating a strong resemblance between IgG4-related sialoadenitis and chronic obstructive disease.<sup>7</sup>

The three conditions are therefore completely different, but they do have several similarities, and differential diagnosis is important for treatment and evaluation of prognosis.<sup>8</sup> We have therefore retrospectively analysed their clinical, radiographic, and pathological features, with the aim of establishing clear distinctions between them.

## Patients and methods

The study protocol was approved by the Ethics Committee for Human Experiments of the Peking University School of Stomatology (Beijing, China). Informed consent was obtained from all patients.

We reviewed the data for 55 patients with IgG4-related sialadenitis, 50 with primary Sjögren syndrome, and 50 with chronic obstructive submandibular sialadenitis who were diagnosed between August 2011 and May 2015 at Peking University School of Stomatology. IgG4-related sialadenitis was diagnosed from the serological and histological findings in patients with persistent (>3 months) swelling of the major salivary glands,<sup>9</sup> and primary Sjögren syndrome from the revised European criteria.<sup>10</sup> Chronic obstructive submandibular sialadenitis was diagnosed according to the following criteria: history of recurrent painful and periodical swellings of the involved gland; radiopaque appearance of submandibular calculi or filling defects and dilatation of Wharton's duct; and histopathological appearances with periductal lymphocytic, plasma cell, neutrophilic, and eosinophilic infiltration.

We recorded personal and clinical information including age and sex; clinical signs and symptoms including enlargement of the lacrimal or salivary glands, or both; xerophthalmia or xerostomia; history of allergic diseases (including asthma and allergic rhinitis); associated systemic coexisting diseases; and duration of symptoms.

The total serum concentrations of IgG and its subclasses were measured in all patients with IgG4-related sialadenitis, 12 with Sjögren syndrome, and nine with chronic sialadenitis.

Serum antinuclear antibody (ANA) and anti-SS-A/Ro and anti-SS-B/La antibodies were measured in all patients in the first two groups, and nine with chronic sialadenitis. Detailed information is given in Supplementary information.

Thirty-three glands in 22 patients with IgG4-related sialadenitis were examined by parotid sialography, as were 42 patients with Sjögren syndrome, while 14 glands in 12 IgG4-RS patients with IgG4-related disease and eight with submandibular sialadenitis were examined by submandibular gland sialography (Supplementary information). Occlusal projections and lateral submandibular gland projections were obtained for 36 patients with submandibular sialadenitis.

Histopathological and immunohistochemical examinations of the major salivary glands were made for all patients with IgG4-related disease and submandibular sialadenitis, together with 12 patients with Sjögren syndrome (Supplementary information), and reviewed by two pathologists. Three identical HPF with the greatest density of IgG-positive and IgG4-positive plasmacytes were quantified, and the IgG4-positive:IgG-positive plasmacyte ratio was calculated.

Student's *t* test, analysis of variance, and the chi square test were used to assess the significance of differences, as appropriate, with the aid of IBM SPSS Statistics for Windows (version 20.0 IBM Corp, Armonk, NY), and probabilities of less than 0.05 were accepted as significant.

## Results

### Clinical features

There were 25 men and 30 women in the IgG4-related sialadenitis group, all of whom had enlargement of the salivary glands (Tables 1 and 2). Only one patient gave a history of periodic swellings and remissions of the involved gland. Xerostomia and xerophthalmia were complained of by 26 (supplemental Fig. 1A) and 10 patients, respectively. An allergic disease history was reported by 26 patients. The systemic comorbidity rate included autoimmune pancreatitis (*n* = 5), sclerosing cholangitis (*n* = 1), interstitial pneumonia (*n* = 6), and a lesion in the cardia (*n* = 1).

There were three men and 47 women in the primary Sjögren group. Moderate to severe xerostomia was complained by 48 patients (supplemental Fig. 1B) and xerophthalmia by 28. Recurrent enlargements of the submandibular, parotid, and lacrimal glands were found in 2, 14, and 2 patients, respectively (Table 1). A history of allergic disease was reported by 4 patients. The number with coexisting systemic disease included disorders of the joints (*n* = 15), kidneys (*n* = 3), liver (*n* = 2), and the haematopoietic system (*n* = 1).

There were 26 men and 24 women in the group with chronic obstructive submandibular sialadenitis, but only one had bilateral swelling. Thirty-two gave a history of swelling after meals, while 11 had persistent swelling without discomfort. There were no other signs of exocrine gland swelling. No patient had xerostomia (supplemental Fig. 1C), except the

Table 1

Number of involved salivary and lacrimal glands in patients with IgG4-related sialadenitis and primary Sjögren syndrome.

Involved glands	IgG4-related sialadenitis (n = 55)			Primary Sjögren syndrome (n = 50)		
	Bilateral	Unilateral	Total	Bilateral	Unilateral	Total
Submandibular	40	13	53	1	1	2
Parotid	28	5	33	9	5	14
Lacrimal	34	1	35	1	1	2
Sublingual	26	0	26	0	0	0
Accessory parotid	9	0	9	0	0	0

Table 2

Clinical, serological, and immunohistochemical features of patients with IgG4-related sialadenitis, primary Sjögren syndrome, and chronic obstructive submandibular sialadenitis. Data are number of patients except where otherwise stated.

	IgG4-related sialadenitis	Primary Sjögren syndrome	Chronic obstructive submandibular sialadenitis	P value
No of patients examined:	55	50	50	
Male: female ratio	1:1.2	1:15.7	1: 0.92	<0.001
Mean (SD) age (years)	55 (14)	53 (16)	48 (14)	0.055
Mean (SD) duration of history (months)	55 (13)	52 (19)	37 (16)	<0.001
Salivary gland swelling	55	16	50	<0.001
Multiple salivary/lacrimal gland swellings	48	10	1	<0.001
Xerostomia	26	48	1	<0.001
Xerophthalmia	10	28	0	<0.001
Hypersensitivity diseases	26	4	6	<0.001
Systemic coexisting diseases	12	19	0	0.139
No of serum immunoglobulin tests:	55	12	9	
Raised serum IgG concentration	28	7	0	<0.001
Raised serum IgG4 concentration	53	0	0	<0.001
Mean (SD) IgG concentration (g/L)	187.9 (81.1)	166.2 (20.9)	129.0 (15.5)	0.062
Mean (SD) IgG4 concentration (g/L)	109.1 (97.9)	4.93 (1.9)	5.3 (1.6)	<0.001
No of serum autoantibody tests:	55	50	9	
Anti-SSA (positive)	1	32	0	<0.001
Anti-SSB (positive)	0	20	0	<0.001
Antinuclear antibody (positive)	0	32	0	<0.001
No of immunohistochemical stains:	55	12	50	
Mean (SD) IgG-positive plasma cells (/HPF)	170 (47)	158 (32)	42 (44)	<0.001
Mean (SD) IgG4-positive plasma cells (/HPF)	123 (45)	8 (3)	5 (4)	<0.001
IgG4:IgG ratio (%)	71.7 (13.9)	4.6 (2.5)	18.9 (19.7)	<0.001

only bilateral case. Six patients had a history of allergy, and none had a coexisting condition (Table 2).

### Laboratory findings

Serum IgG concentrations were raised in 28 patients in the IgG4-related group, 29 of the primary Sjögren patients, and none of the other patients. The differences did not differ significantly in the first two groups ( $p = 0.129$ ) and were higher than that in the other group ( $p < 0.01$ ). Serum IgG4 concentrations were raised in 53 patients in the IgG4-related group, and zero in the other patients ( $p < 0.001$ ). Other laboratory findings are shown in Table 2.

### Radiographic characteristics

Parotid gland sialography showed that nine glands were enlarged in the patients with IgG4-related disease. The main duct was dilated in 27 patients and this appeared to be regularly around the hilum (supplemental Fig. 2A). One patient

had simultaneous dilatation of the branch duct and two punctate sialectasia. All others had ductal systems within the normal range. There was residual contrast medium in five patients. Sialography of the submandibular gland showed that glands were enlarged in 10 patients. Wharton's duct was dilated, particularly around the hilum, in nine (supplemental Fig. 2C). The emptying function of the submandibular gland could hardly be assessed in four patients because of excess injection of contrast medium. Residual contrast medium was found in eight of the remainder.

Nineteen of the patients with Sjögren syndrome had abnormal dilatation of the duct and 28 had punctate, globular, or cavitary sialectasia (supplemental Fig. 2B). Thirty had residual contrast medium.

Occlusal and lateral plain films showed radiopaque calculi in 19 of the patients with chronic obstructive sialadenitis, and sialography showed dilatation of Wharton's duct in all patients, which filled defects in the ducts in two (supplemental Fig. 2D). Five had residual contrast medium.

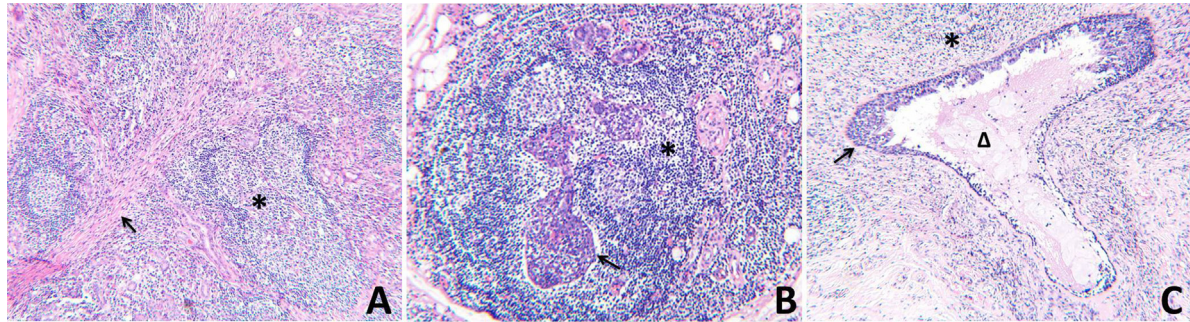


Fig. 1. Representative histopathological specimens. (A) Typical lymphoplasmacytic infiltration with irregular lymphoid follicles (\*) and storiform fibrosis (arrow) in IgG4-related sialadenitis (haematoxylin and eosin, original magnification  $\times 100$ ). (B) Lymphoplasmacytic inflammation (\*) and lymphoepithelial islands (arrow) in primary Sjögren syndrome (haematoxylin and eosin, original magnification  $\times 200$ ). (C) Dilatation of the duct, intraductal mucous deposit ( $\Delta$ ), ductal epithelial metaplasia (arrow) and periductal lymphoplasmacytic infiltration (\*) in chronic obstructive submandibular sialadenitis (haematoxylin and eosin, original magnification  $\times 100$ ).

### Histopathological and immunohistochemical features

Histopathological examination of IgG4-related specimens showed acinar atrophy with preservation of the lobular architecture and pronounced lymphoplasmacytic infiltration with large, irregular, lymphoid follicles with expanded germinal centres and prominent cellular interlobular fibrosis (Fig. 1A). Periductal collagen sheaths and eosinophilic infiltration were common. Specimens of the major salivary gland from the patients with Sjögren syndrome showed acinar atrophy with pronounced lymphoplasmacytic inflammation and lymphoepithelial lesions (Fig. 1B). Lymphocytic infiltration into the ducts was common, whereas eosinophilic infiltration and interlobular fibrosis were rare. Dilatation of the duct with lymphoplasmacytic infiltration ( $n = 37$ ), epithelial metaplasia ( $n = 28$ ), and intraductal mucous deposits ( $n = 21$ ), respectively, were present in the chronic sialadenitis group (Fig. 1C).

On immunohistochemical analyses there were considerably increased IgG4-positive cells and IgG4:IgG-positive cell ratios in all specimens in the IgG4-related group, but in none of the other specimens. IgG-positive lymphoplasmacytic cells were abundant in both the IgG4-related and Sjögren's specimens (Table 2).

### Discussion

We have presented the results from three different entities with different therapeutic principles.<sup>11–13</sup> However, because they share similar clinical features, differentiation is crucial. Here we have compared their features.

Epidemiologically, IgG4-related sialadenitis is a rare disorder that affects mostly Asians.<sup>14</sup> The female:male ratio varies among studies but there are no obvious sex differences, and the age at diagnosis is generally 50–70 years.<sup>2,15</sup> The prevalence of Sjögren syndrome ranges from 0.03% to 2.7%, with a strong female propensity, and the age of onset is usually the fourth – fifth decades.<sup>12,16</sup> Chronic obstructive submandibular sialadenitis is one of the most common dis-

orders of the salivary glands, and we could find no particular sex predominance.

IgG4-related disease is characterised by swelling of the salivary glands.<sup>2</sup> Multiple enlargement of the exocrine glands was common among our patients, and the submandibular gland was the most common. The swelling is firm, painless, and persistent. In comparison, swelling of the gland is not so common in primary Sjögren disease, accounting for less than half the patients in our study and being common in the parotid gland. Although the submandibular gland was enlarged in every patient in the chronic sialadenitis group, it was mostly unilateral and characterised by meal-induced swelling and, occasionally, pain.

Primary Sjögren disease mainly involves the exocrine glands, and typically presents with xerophthalmia and xerostomia. It can affect swallowing, and may lead to oral candidiasis or rampant caries.<sup>13</sup> Xerostomia and xerophthalmia occasionally occur in IgG4-related patients, and in a previous study we found decreased salivary flow rates, but less so than in the Sjögren group.<sup>2</sup> Chronic obstructive sialadenitis is a topical disease, and xerostomia is rare.

IgG4-related disease is closely related to allergic diseases,<sup>17,18</sup> and we found that significantly more patients gave a history of allergic disease in the IgG4-related group than in the other two. Increased serum IgE concentrations, eosinophilic infiltration, or shared cytokines involved in inflammatory reactions, or both, may have played a part.<sup>19</sup>

IgG4-related sialadenitis and primary Sjögren syndrome are systemic diseases that can coexist with disorders of other organs. The prevalence of these in the two groups did not differ significantly, but the range was quite different. Internal organs were often involved in IgG4-related disease, with the pancreas, biliary system and liver, distant lymph nodes, respiratory system, urinary system, and retroperitoneal soft tissues being the most commonly involved.<sup>20</sup> However, 30%–70% of the Sjögren patients had systemic involvement, including arthritis, skin rashes, and respiratory, and kidney diseases.<sup>21</sup> Careful analysis of the medical history and comprehensive physical examination is necessary for differentiation.



Most IgG4-related patients had raised serum IgG4 concentrations, but the other patients did not. In contrast, serum anti-SS-A, anti-SS-B, and ANA positivity was rare among IgG4-related patients and common among Sjögren patients, serving as one of the most important diagnostic criteria between them.<sup>10</sup> One IgG4-related patient reacted to anti-SS-A, but because anti-SS-A positivity has been reported in 1.6% healthy people,<sup>22</sup> we speculate that this case is one of that 1.6%. All related serological tests were within normal ranges in patients with chronic submandibular sialadenitis, which indicates that serological tests are important for their differential diagnosis.

Sialography is often used for the diagnosis of Sjögren syndrome. Sialectasia and a “cherry-blossom appearance” are typical findings,<sup>23</sup> and were seen in two-thirds of our patients. However, only two IgG4-related patients showed punctate sialectasia on parotid sialograms. Residual contrast medium indicating decreased secretion from the parotid gland was less common among IgG4-related patients than among the Sjögren group, as the IgG4-related patients each had a dilated main duct with clear borders, and the part around the hilum was the most commonly involved. The appearance is different from the lace-like or onion-like pattern of the main duct in Sjögren syndrome. No filling defects were found in Wharton’s duct in IgG4-related patients, as opposed to those with chronic sialadenitis whose occlusal and lateral projections of the submandibular gland show radiopacities when stones were present. Considering the various features of the three diseases, sialography is effective for differentiation, particularly between IgG4-related disease and Sjögren syndrome, whereas for the other group plain films are the first choice.

Histopathological and immunohistochemical signs and symptoms are considered the gold standard for diagnosis. In this study, all IgG4-related patients presented the typical dense lymphoplasmacytic infiltration, large, irregular lymphoid follicles, storiform fibrosis, and pronounced IgG4-positive plasma cells.<sup>17</sup> Although lymphoplasmacytic infiltration and lymphoid follicles were also seen in Sjögren specimens, the fibrosis was slight and fibroblasts were absent, while IgG-positive cells were common and IgG4-positive cells were rare. Lymphoepithelial lesions and myoepithelial islands were common in Sjögren specimens, but not in IgG4-related ones. Dilatation of the duct featured in chronic sialadinitis, as did intraductal mucous deposits, epithelial metaplasia and lymphoplasmacytic infiltration. Fibrosis could also be seen, mainly in the periductal regions. There were no IgG4-positive plasma cells. These pathological features suggest that different target tissues are involved in the three diseases: glandular interstitial tissue in IgG4-related disease, glandular parenchyma in Sjögren, and the ductal system in chronic sialadenitis.

Despite the statistical differences among the three conditions, the crossover in symptoms makes it hard to diagnose a patient with unexplained salivary gland enlargement, particularly those with chronic obstructive sialadenitis with bilateral enlargement of the submandibular duct, or a submandibu-

lar gland that was firm histologically with obvious fibrosis. Serology could distinguish them sometimes, but not every time, and a general review of all the signs and symptoms may be necessary in some cases. Histopathological tests could be the most powerful but the last step for diagnosis, and occasionally, wait-and-see is a useful approach.

## Conclusion

Despite looking similar in some ways, IgG4-related sialadenitis, primary Sjögren syndrome, and chronic obstructive submandibular sialadenitis usually have distinct clinical, radiographic, and histopathological features that provide important clues to their differential diagnosis. Serological and histological tests are the two most powerful, while a number of variables may also have to be taken into consideration.

## Conflict of interest

We have no conflicts of interest.

## Ethics statement/confirmation of patients’ permission

The study was approved by the Ethics Committee for Human Experiments of the University School of Stomatology. Informed consent was obtained from all patients.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bjoms.2016.10.021>.

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