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ORIGINAL ARTICLE

Natural developing process of immunoglobulin G4-related sialadenitis after submandibular gland excision: a retrospective cohort study

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Abstract

Objective This study aimed to evaluate the long-term outcome and quality of life of IgG4-related sialadenitis (IgG4-RS) patients after submandibular gland (SMG) excision without immunomediate therapy.

Materials and methods This retrospective review included patients with IgG4-RS who did not undergo further treatment following SMG excision. All patients diagnosed with IgG4-RS between January 1955 and December 2012 at the Department of Oral and Maxillofacial Surgery, Peking University School of Stomatology, were enrolled. The main outcome measures included postoperative IgG4-RS progression rate and differences between patients with and without recurrent disease. The degree of subjective oral dryness was evaluated using the summated xerostomia inventory (SXI); the objective secretory function was assessed by whole saliva flow rate measurements. Serological findings were analyzed during the follow-up.

Results SMG excision was adopted in all of the 83 patients. The median follow-up period was 108 (range 7–396) months. Clinical progression was observed in 54.2% of cases. Patients with other organ involvement (OOI) indicated higher progression rate to a significant extent ($P = 0.015$, HR = 2.108). The annual progression rate was 20.7% in the group with OOI and was 14.1% in the group without OOI. All cases showed higher levels of serum IgG4; the level was in positive correlation with follow-up time when no therapy was added. 82.4% of cases experienced xerostomia after the surgery, and the degree of dry mouth in patients underwent bilateral resection was significantly more severe than those in unilateral resection.

Conclusions Surgical excision of involved SMG cannot control the disease progression, which is not recommended for treatment of IgG4-RS. Differential diagnosis is crucial in order to prevent irreversible organ loss and relevant salivary gland dysfunction.

Key Points
• *Surgical excision of involved SMG cannot control progression of IgG4-RS.*

Keywords IgG4-related sialadenitis · Surgery · Treatment · Xerostomia

Introduction

IgG4-related disease (IgG4-RD) is an increasingly classified, immune-mediated, fibro-inflammatory condition characterized by enlargement of involved organ and lymph plasma cell infiltration and often accompanied serum IgG4 level elevation [1]. Virtually all organs can be affected by the disease, but the most commonly affected tissues include the pancreas, salivary glands, kidneys, retroperitoneum, periorbital tissue, and lymph nodes [2, 3]. When IgG4-RD affects the salivary glands, the condition is called IgG4-related sialadenitis (IgG4-RS) [4].

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Despite relapse [5, 6] and scantly mentioned steoid-related side effects [7, 8], steroid administration is the first-line therapy for IgG4-RD, and patients generally exhibit a good treatment response. Surgical interventions, stated as amenable therapeutic option in some long-standing highly fibrotic cases, have been used to treat specific target organ such as ocular adnexa, but the long-term efficacy of submandibular gland (SMG) excision alone has not yet been reported. Whether the developing process of IgG4-RS could be controlled without immunotherapy remains unclear. Oral dryness is among the most common symptoms and obviously influences the quality of life in IgG4-RS patients [9]. However, few studies have investigated the secretory function in patients who underwent SMG excision surgery without additional systemic steroid therapy.

To elucidate the natural developing process of IgG4-RS after SMG excision without systemic immunomediate therapy, we performed a retrospective study with a median follow-up duration of 108 months. The efficiency of single surgery to control IgG4-RS and the quality of life in these patients were evaluated.

Patients and methods

The study protocol was approved by the Ethics Committee for Human Experiments of Peking University School of Stomatology. All patients provided informed written consent for the use of their data before the procedure were performed, and the possible outcomes were explained to them during the follow-up period.

Patients and clinical data

This was an exploratory retrospective cohort study. We conducted a search of all patients with SMG enlargement between January 1955 and December 2012 in the surgical pathology database at Peking University School of Stomatology. One thousand forty-three SMG specimens pathologically described as abundant lymphoplasmacytic infiltration in pathology reports were reviewed and re-stained using hematoxylin and eosin (HE) and immunohistochemical techniques. The procedures were the same as described in our previous study[10].

A flowchart of patient selection is shown in Fig. 1. Records review included data of patients diagnosed with IgG4-RS and treated by surgical excision of SMG. None of these patients underwent immuno-regulatory treatment before surgery. Patient age, gender, duration of SMG enlargement, symptoms at disease onset, postoperative follow-up duration, presence of allergies, involved organs, and outcomes were retrieved from their medical records. The sites of lesions at initial visit were determined by reviewing CT scans or ultrasonic examinations. Eighty-nine patients with probable IgG4-RS were enrolled; the cases were divided into definite and probable IgG4-RS based on results of laboratory test according to the comprehensive diagnostic criteria for IgG4-RD [11, 12].

Laboratory data

Peripheral blood was collected from 28 (33.7%) patients during follow-up at medical laboratory for at least once. Serologic analyses were performed for antinuclear antibody(ANA), IgA, IgM, IgE, total IgG, and subclasses of IgG using the Array 360 Immunoassay Assay Protein Serology Chemistry Analyzer System (Beckman Coulter, Fullerton, CA, USA). Anti-SS-A and anti-SS-B antibodies were tested by western blotting. The final serological result was taken as standard if multiple measurements were employed. The relationship between serum IgG4 levels and age, gender, duration of follow-up, internal organ involvement, number of involved organs, history of allergy, and progress tendency was analyzed.

Clinical outcome assessments

During the follow-up period, computed tomography (CT), ultrasonographic examinations, and/or MRIs were carried out to identify the anatomic locations of lacrimal glands and salivary glands lesions in 41 (49.4%) patients. The presence of SMGs and parotid glands (PGs), sublingual glands (SLGs), and lacrimal glands (LGs) enlargement or lymphadenopathy were confirmed by imaging findings as follows: head and neck CT scans, 19 (22.9%) patients; ultrasonography examination, 20 (24.1%) patients; and MRIs, 6 (7.2%) patients. The other 42 patients without subjective symptom or refused to undertake imaging examinations received physical examinations administered by specialists in otolaryngology head and neck surgery or oral and maxillofacial surgery to exclude potential escape from diagnosis. Systemic involvement was assessed likewise: generally, 22 (26.5%) patients underwent whole-body screening; 16 (19.3%) patients had thorax, abdomen, or pelvic region CT scanning; 5 (6.0%) patients received ultrasonographic examination only; and 1 (1.2%) patient underwent 18F-fluorodeoxyglucose positron emission tomography. The remaining 61 patients claimed no persistent bodily symptom related to IgG4-RD and refused to undergo systemic screening.

Clinical involvement was designated existent if it was noted in medical records from rheumatologists or oral and maxillofacial surgeons. Radiological involvement was deemed present if it was reported in CT, MRI, PET-CT, or ultrasonography examination by radiologists. We identified organ involvement either clinically or radiologically or both. The decision to perform each examination depended

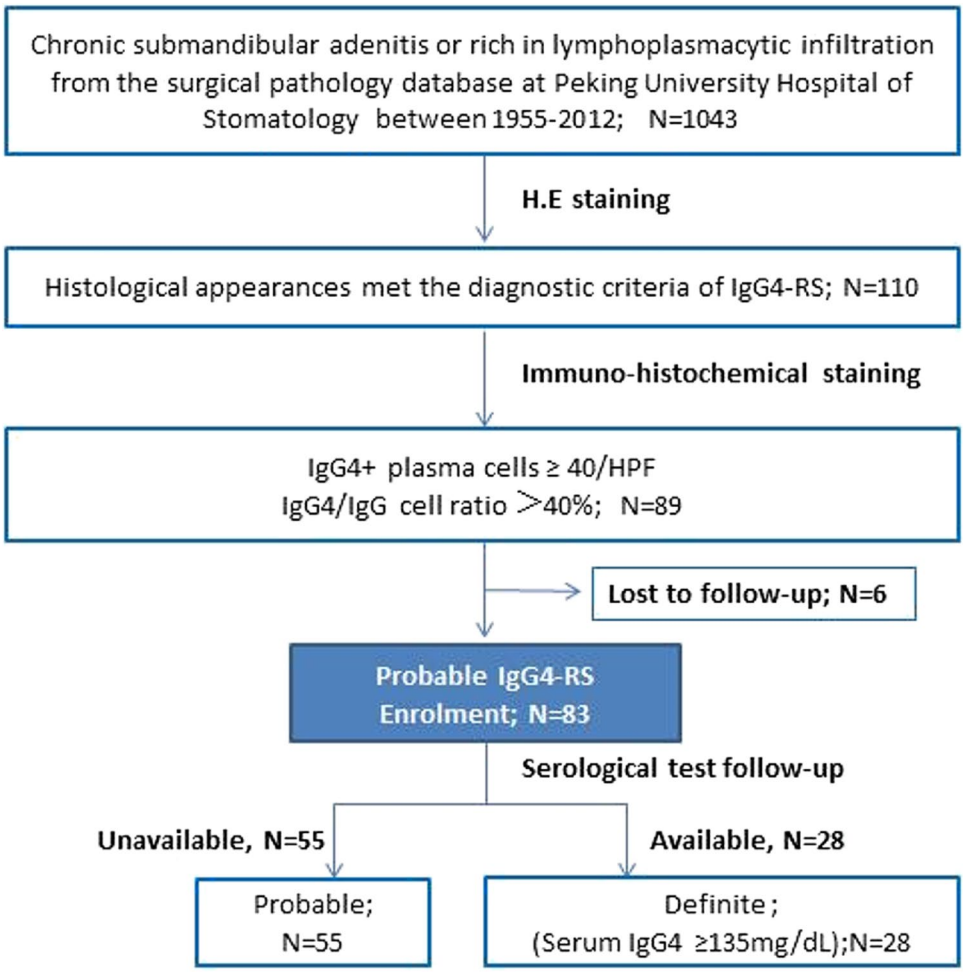

Fig. 1 Flowchart of patient selection of IgG4-RS

on clinical suspicion and preference of the treating physicians. Malignancy was diagnosed based on pathological manifestations by pathologists, with emphasis on commonly associated organs included in IgG4-RD responder index (IgG4-RD RI) [13].

We defined clinical remission as having no organ involvement. Clinical progression was defined by a new development or aggravation of pre-existing abnormal findings upon physical examination or imaging studies. Patients with an increase in serum IgG4 levels alone were not defined as having clinical progression, but in a serologically unstable condition.

Salivary gland function assessments

To determine the degree of subjective oral dryness, a total of 74 (89.2%) patients were assessed using the summated xerostomia inventory (SXI) [14]. Whole saliva was collected as previously described [15] in 22 (26.5%) patients; saliva flow rates at rest and under stimulation with 2.5% citric acid solution for 5 min were calculated, respectively.

Statistical analysis

Data distribution was evaluated according to Kolmogorov-Smimov test of normality. Serum IgG4 concentrations in mg/L were log-transformed to approximate normality. The normally distributed data between groups were analyzed using Student *t* tests, and a one-way analysis of variance (ANOVA) was used to compare the groups. Categorical variables were analyzed with Pearson Chi-square test or Fisher's exact test. We performed univariate analyses, followed by the log-rank test, and multivariate analyses, followed by the Cox hazard model to determine risk factors for progression after surgical treatment. The Spearman rank correlation was used to analyze the relationships between serum IgG4 levels and clinical features. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS v23.0 for Windows.

Results

Baseline characteristics and affected organs

Eighty-nine patients were included in this study, 47 (52.8%) men and 42 (47.2%) women with a mean onset age of 58.4 ± 13.3 years and a median disease duration of 4 months. According to CDCI, 28 (31.5%) and 71(79.8%) of patients were definite and probable IgG4-RD, respectively. The demographic features and organ involvement findings at disease onset are listed in Table 1. Overall, we observed 56 (62.9%) and 33 (37.1%) patients with unilateral and bilateral SMG involvement. The other anatomic sites affected were identified as follows: being the most frequent parotid ($n = 6$, 6.7%), sublingual ($n = 4$, 4.5%), and lacrimal glands ($n = 4$, 4.5%). Cervical lymph node swelling was noted in 46 (51.7%) cases. The primary clinical diagnosis included tumor ($n = 64$, 71.9%), inflammation ($n = 18$, 20.2%), Mikulicz's disease ($n = 4$, 4.5%), and Sjögren syndrome ($n = 3$, 3.4%). However, the postoperative pathological diagnosis were chronic inflammation of submandibular gland ($n = 76$, 85.4%), Sjögren syndrome ($n = 8$, 9.0%), and Mikulicz's disease ($n = 5$, 5.6%). Patients with bilateral SMG involvements tended to have had a longer duration of symptoms than those with unilateral SMG involvement ($P = 0.011$). More notably, it was shown that 87.3% of the unilateral SMG enlargement cases were diagnosed with neoplastic diseases, which was significantly higher than cases in the bilateral SMG enlargement group (45.5%).

The prevalence of allergies was 43.8% in our cohort; allergy-related symptoms of patients with IgG4-RS were allergic rhinitis; a total of 22 (24.7%) patients had a history of allergic rhinitis in the first diagnosis. Additionally, more patients with bilateral SMG involvements (group B) than unilateral SMG involvement (group A) experienced

Table 1 Baseline characteristics of 89 patients with probable IgG4-RS

	All patients ($n = 89$)	Unilateral SMG enlargement (Group A, $n = 56$)	Bilateral SMG enlargements (Group B, $n = 33$)	*P*-value
Male:female ratio	1.12:1	0.87:1	1.54:1	0.196
Age (years, mean ± SD)	58.4 ± 15.4	60.1 ± 13.3	55.6 ± 18.3	0.18
Course of disease (months, min–max)	4 (0.5–84)	2 (0.5–84)	4 (0.5–48)	0.011*
Parotid gland				
Unilateral, n (%)	2 (2.2)	1 (1.8)	1 (3.0)	1.00
Bilateral, n (%)	4 (4.5)	1 (1.8)	3 (9.1)	0.281
Sublingual gland				
Unilateral, n (%)	1 (1.1)	0 (0.0)	1 (3.0)	0.371
Bilateral, n (%)	3 (3.4)	1 (1.8)	2 (6.1)	0.637
Lacrimal gland				
Unilateral, n (%)	3 (3.4)	3 (5.4)	0 (0.0)	0.457
Bilateral, n (%)	1 (1.1)	0 (0.0)	1 (3.0)	0.371
Cervical lymphadenopathy	46 (51.7)	25 (44.6)	21 (63.6)	0.678
Internal organs				
Pancreas, n (%)	2 (2.2)	1 (1.8)	1 (3.0)	1.00
Biliary system, n (%)	2 (2.2)	2 (3.6)	0 (0.0)	0.528
Lung, n (%)	4 (4.5)	3 (5.4)	1 (3.0)	1.00
Kidney, n (%)	2 (2.2)	2 (3.6)	0 (0.0)	0.528
Pituitary gland, n (%)	1 (1.1)	1 (1.8)	0 (0.0)	1.00
Allergy history, n (%)	39 (43.8)	24 (42.9)	15 (45.5)	0.811
Rhinitis, n (%)	22 (24.7)	11 (19.6)	11 (33.3)	0.148
Oral dryness, n (%)	37 (41.6%)	17 (30.4)	20 (60.6)	0.001**
Preoperative diagnosis				
Tumor	64 (71.9)	49 (87.3)	15 (45.5)	
Inflammation	18 (20.2)	6 (10.7)	12 (36.4)	
Mikulicz's disease	4 (4.5)	1 (1.8)	3 (9.1)	
Sjögren syndrome	3 (3.4)	0 (0.0)	3 (9.1)	0.000**

*Statistically significant was defined as two-tailed $P < 0.05$

xerostomia; the percentage of oral dryness in group B (60.6%) was higher than that in group A (41.6%), $P<0.001$.

Treatment and clinical outcomes

The initial treatment included unilateral and bilateral SMG excision. Fifty-six and 25 patients received gland excision of single and double sides due to its unilateral and bilateral nature. Eight out of the 33 bilateral cases involved operation of only the unilateral lesions. Ten unilateral cases underwent secondary contralateral SMG excision at 7–37 months after the initial surgery of SMG. No medication was administrated at first diagnosis.

As six patients had no further visit in record since initial visit, the follow-up rate was 93.3% ($n=83$), with a median postoperative follow-up period of 108 (7–396) months. Overall, clinical progression occurred in 45 (54.2%) patients, at 7 to 72 months (median: 18 months) after surgical excision of the swollen SMG. New-onset locations were SMG ($n=31$), PG ($n=11$, 5 unilateral cases and 3 bilateral cases), LG ($n=32$, 4 unilateral cases and 14 bilateral cases), SLG ($n=4$, two bilateral cases), pancreas ($n=4$), lung ($n=2$), bile duct ($n=2$), kidney ($n=2$), retroperitoneum ($n=1$), and pituitary ($n=1$). Kaplan–Meier analysis showed that progression occurred in 56.9% patients (SE: 0.057) within 72 months. Moreover, patients with other organ involvement (OOI) exhibited a higher progression rate than those without OOI ($P=0.015$, HR = 2.108, Fig. 2). The annual progression rate was 20.7% in the group with OOI and 14.1% in the group without OOI.

Serum IgG4 levels and influencing factors

In the 28 cases in whom IgG and its subclasses in peripheral blood were measured, laboratory data showed that all 28 patients had high IgG4 serum levels (≥ 1350 mg/dL), with the median serum IgG4 level of 7890 mg/dL (range 2030–19,400 mg/dL). As is shown in Table 2, results of Spearman correlation analysis indicate positive correlation between serum IgG4 levels and time of follow-up (r = 0.404), internal organ involvement (r = 0.402), and disease progression (r = 0.581). The level of IgG was elevated in 18 patients (64.3%). A total of 9 patients (32.1%) had an increased level of IgG2, and 22 subjects (78.6%) showed elevated IgE level. The reaction to anti-SSA, anti-SSB, and anti-ANA was negative in all of the 28 patients.

Table 2 Correlations between serum IgG4 level and demographic and clinical features

	Mean ± SD/n/ median (P25, P75)	*r*	*P*-value
Age(years)	67.5 ± 11.7	0.361	0.059
Gender (male/female)	16/12	−0.143	0.468
SMG resection (unilateral/ bilateral)	17/11	−0.023	0.909
Allergy (yes/no)	14/14	−0.088	0.655
Time of follow-up (months)	84 (63,144)	0.404	0.033*
Internal organ involvement (yes/no)	19/9	0.402	0.034*
Progression (yes/no)	18/10	0.581	0.001**
Number of involved organs	2.00 ± 1.15	0.191	0.331

*Statistically significant was defined as two-tailed $P<0.05$

Subjective oral dryness and whole saliva flow rates

Of 74 patients who completed SXI survey, 33 patients (44.6%) had symptom of oral dryness at the time of diagnosis. However, 61 patients (82.4%) developed xerostomia

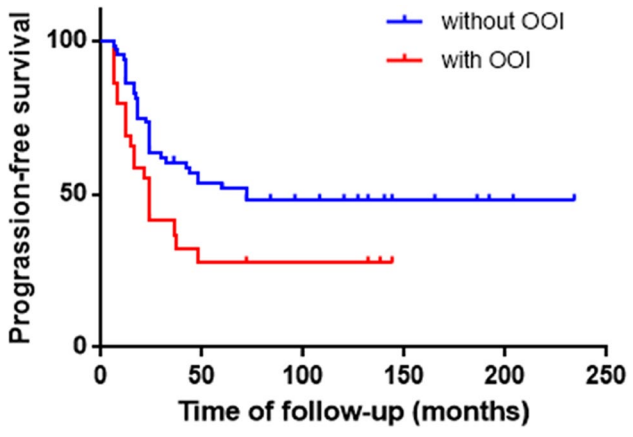

Fig. 2 Kaplan–Meier analysis of treatment outcomes in patients with IgG4-RS. Patients with OOI showed higher progression rate than those without OOI, $P=0.019$)

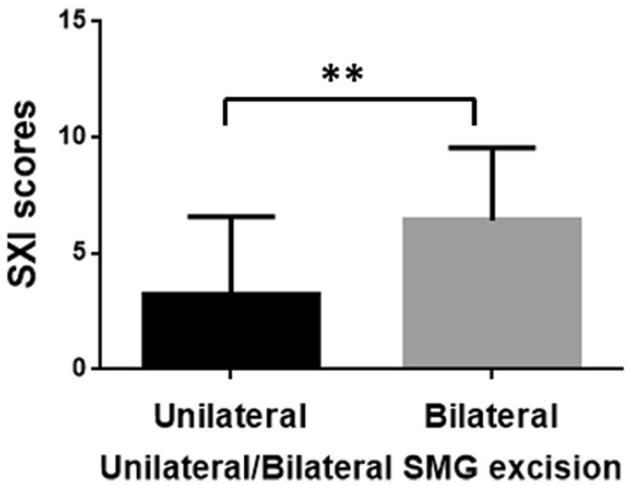

Fig. 3 SXI scores of IgG4-RS patients after SMG excision

postoperatively during follow-up. SXI scores for the unilateral and bilateral excision groups are shown in Fig. 3. Median SXI score in unilateral SMG excision and bilateral SMG excision group was 2.00 (P25-P75, 0–5.25) and 5.50 (P25-P75, 3.25–9.00), respectively. Degree of dry mouth in patients that underwent bilateral excision was significantly more severe than those in unilateral excision group ($P < 0.01$).

The whole saliva flow rate measured from 22 patients at rest was 0.03–0.24 (mean 0.13 ± 0.07) g/min, which was significantly lower than the normal value of 0.38 g/min ($P < 0.01$). Similarly, the stimulated saliva flow rate (mean 1.05 ± 0.38 g/min) was lower than the normal value of 1.35 g/min ($P < 0.01$) [16].

Discussion

With the deepening recognition of IgG4-RD as a systemic disease entity, glucocorticoids has, to date, been widely accepted as the first-line therapeutic intervention. Despite that several studies reported spontaneous regression of IgG4-RD without therapies [17–20], the conclusion is challenged by a paucity of long-term follow-up data in these cases. In this study, no spontaneous remission was found. A systemic review including 3034 subjects in 62 studies suggested that "wait and see" strategy was implemented in 13% of patients with IgG4-RD and 36.6% of patients with IgG4-RS, 60% of these cases experienced relapse or progression, rate doubles than that described as of patients treated with glucocorticoid regimens [21]. In a recent prospective trial of IgG4-RS from Japan, progression rate was 10.2% during a mean observation period of 2.67 years; in contrast, relapse rate in glucocorticoid-treated group was only 2.74% [22]. It was stated in recent consensus that therapy may induce rapid and more complete remission with fewer long-term complications than does waiting to treat [23]. Watchful waiting, thus, does not seem beneficial for the treatment of IgG4-RS. To clarify the issue, we investigated 83 Chinese IgG4-RS patients treated by SMG surgical excision solely and received no subsequent therapy. During the follow-up period, 54.2% of patients were found in progression, and an impaired salivary function was observed both subjectively and objectively. As was shown in our previously work, glucocorticoid regimen combined with steroid-sparing agents led to recovery and preservation of secretory function of salivary glands with relatively lower relapse rate of 32.5% in 55 months [24]. Shimizu et al. disclosed improvement of salivary secretion in patients with IgG4-RS after immunotherapy; interestingly, patients with duration of illness more than 2 years presented a reduced functional improvement [25]. Therefore, early intervention is required to protect against progressive fibrosis and potential organ dysfunction or complications.

Surgical excision remains controversial as standard treatment method for IgG4-RS. On one hand, clinical swelling of affected organ often raises concerns about tumor-like lesions; surgery was intended to treat mimicked conditions and pathologically proved unnecessary in retrospect [26]. In our cohort, 71.9% and 3.4% of cases were considered tumors and Sjögren syndrome, respectively, before operation. Our data showed that patients with unilateral SMG swelling are more often misdiagnosed as tumor, while bilateral cases are prone to be diagnosed with Sjögren syndrome and inflammatory diseases. Accordingly, improving understanding of correct diagnosis is essential, especially for unilateral involved cases. We have previously detailed clinical, radiographic, pathological, and serological features of IgG4-RS [27] and provided more clues on differentiation between IgG4-RS, primary Sjögren syndrome, Kimura's disease, and chronic obstructive submandibular sialadenitis [28, 29]. More recently, the comprehensive exclusion criteria of IgG4-RD had been proposed by all Japan IgG4 team, enabling accurate diagnosis of IgG4-RD and differential diagnosis from hyper interleukin-6 (IL-6) syndromes, plasma cell type Castleman disease (PC-CD), rheumatoid arthritis (RA), and other mimicked conditions [11]. Above all, biopsy lays the cornerstone of diagnostic utility in determining whether neoplastic diseases or non-specific chronic inflammatory conditions could be excluded [3, 10, 30].

On the other hand, according to the consensus statement regarding management of IgG4-RD in 2015, in some highly fibrotic cases with long-standing process, when poor response to steroids and refractory relapse was indicated, surgical intervention is amenable [23]. However, first-line option of surgical excision remains organ-specific. Ominato et al. reported that only 2 of 15 IgG4-dacryoadenitis cases (13.3%) treated with debulking surgery showed recurrence, but documented in 33–68% steroid-treated patients in other researches [31]. Tirelli et al. systemically reviewed all IgG4-RD in head and neck region and reported 25% of patients treated with surgical procedure alone experienced recurrence, approximately five times higher that underwent medical treatment only [32]. Generally, the duration of follow-up in literature was short, and also the clinical outcomes were assessed in different ways. In the present study, 83 patients were followed up with a median time of 108 months; progression was observed in 54.2% of these cases. Prevalence of progression was significantly higher than published data. In addition, we identified internal organ progression occurred in 12 cases in our series. These results indicate that IgG4-RS, as a local presentation of a distinct entity, and the disease progression should be controlled by systemic immunotherapy rather than SMG excision. As a

consequence, surgery treatment should not be recommended as first-line therapeutic method in patients with IgG4-RS.

We also observed a higher frequency of progression in patients with OOI at onset. Of 26 cases with OOI, 16 patients (61.5%) had a progression at new lesion, significantly higher than in cases without OOI (50.9%) in our cohort. The results concurred with a report by Yamamoto et al. [33]. In another study including 47 patients of IgG4-RD, patients with major salivary gland involvement showed higher prevalence of multiple organ involvement and higher basal disease activity [34]. Liu et al. retrospectively reviewed 428 cases of IgG4-RD in a single-center cohort and revealed that IgG4-RD with salivary gland lesions had more organs affected than salivary-gland-free IgG4-RD patients [35]. We described a higher progression rate in patients with multiple organ involvement, and serum IgG4 level was also correlated with involvement of internal organs, which is consistent with the progression condition.

So far, research and attention usually focus on diagnosis and treatment of the protean disease, with little data available on quality of life in those IgG4-RS patients. We highlighted the subjective xerostomia inventory scores and whole saliva flow rate to evaluate the quality of life in aspect to oral dryness. Mild to moderate xerostomia was observed in 66.7% of unilateral excised patients, but in 93.8% of bilateral excised cases. All of 22 cases showed lower saliva flow rate at rest, and 8 in 22 cases had decreased saliva flow rate under acid stimulation. These results indicated that surgical excision of SMG and the consequential organ loss would impair salivary function irreversibly. Therefore, surgical excision should not be considered as a therapeutic intervention for IgG4-RS patients.

There are certain limitations to this study. Firstly, given the retrospective nature, potential for bias cannot be ruled out. In spite of antigen retrieval using heat-induced method, potential antigen variation remains a valid concern, especially for long-stored specimens. Salivary glands and extra-salivary gland involvement were identified by diverse diagnostic utilities (CT/ultrasound /MRI /PET-CT); progression was defined either clinically or radiologically, which may cause under-estimation of the prevalence and progression status. Moreover, patients included in this study were diagnosed before the suggestion of IgG4-RS, thus making it difficult to detect asymptomatic lesions at early stage. Finally, the sample of laboratory data is missing at baseline; with our best effort, serum IgG4 level was measured in only 28 patients. However, our study derived from one of the largest single-center cohorts of IgG4-RS, and the length of follow-up after surgical excision providing strength on the natural course to progression.

In conclusion, surgical excision of enlarged SMG should not be considered as an option for patients with IgG4-RS due to high progression rate and irreversible organ function loss. Our study demonstrated that IgG4-RS with OOI were affected by a higher percentage of progression. So, differential diagnosis from tumors and non-specific inflammatory mass is essential based on clinical, radiological, serological, and histopathological findings.

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Declarations

Disclosures None.

References

1. Stone JH, Zen Y, Deshpande V (2012) IgG4-related disease. N Engl J Med 366(6):539–551. https://doi.org/10.1056/nejmra1104650
2. Cheuk W, Chan JK (2010) IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol 17(5):303–332. https://doi.org/10.1097/PAP.0b013e3181ee63ce
3. Kamisawa T, Zen Y, Pillai S, Stone JH (2015) IgG4-related disease. Lancet 385(9976):1460–1471. https://doi.org/10.1016/S0140-6736(14)60720-0
4. Geyer JT, Deshpande V (2011) IgG4-associated sialadenitis. Curr Opin Rheumatol 23(1):95–101. https://doi.org/10.1097/BOR.0b013e3283413011
5. Compochiaro C, Della-Torre E, Lanzillotta M et al (2020) Long-term efficacy of maintenance therapy with Rituximab for IgG4-related disease. Eur J Intern Med 74:92–98. https://doi.org/10.1016/j.ejim.2019.12.029
6. Sasaki T, Akiyama M, Kaneko Y et al (2018) Risk factors of relapse following glucocorticoid tapering in IgG4-related disease. Clin Exp Rheumatol 36 Suppl 112(3):186–189
7. Ebbo M, Daniel L, Pavic M et al (2012) IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. Medicine (Baltimore) 91(1):49–56. https://doi.org/10.1097/MD.0b013e3182433d77
8. Patel H, Khalili K, Kyoung KT et al (2013) IgG4 related disease: a retrospective descriptive study highlighting Canadian experiences in diagnosis and management. BMC Gastroenterol 13:168. https://doi.org/10.1186/1471-230X-13-168
9. Wang Z, Li W, Hong X et al (2016) Minor salivary glands function is decreased in hyposalivation-related diseases. Arch Oral Biol 69:63–70. https://doi.org/10.1016/j.archoralbio.2016.05.012
10. Zhang YY, Hong X, Wang Z et al (2020) Diagnostic utility of submandibular and labial salivary gland biopsy in IgG4-related sialadenitis. Clin Rheumatol 39(12):3715–3721. https://doi.org/10.1007/s10067-020-05097-1
11. Umehara H, Okazaki K, Masaki Y et al (2012) Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). Mod Rheumatol 22(1):21–30. https://doi.org/10.1007/s10165-011-0571-z
12. Satou A, Notohara K, Zen Y et al (2020) Clinicopathological differential diagnosis of IgG4-related disease: a historical overview and a proposal of the criteria for excluding mimickers of IgG4-related disease. Pathol Int 70(7):391–402. https://doi.org/10.1111/pin.12932

13. Carruthers MN, Stone JH, Deshpande V et al (2012) Development of an IgG4-RD responder index. Int J Rheumatol 2012:259408. https://doi.org/10.1155/2012/259408
14. He SL, Wang JH, Li M (2013) Validation of the Chinese version of the summated xerostomia inventory (SXI). Qual Life Res 22(10):2843–2847. https://doi.org/10.1007/s11136-013-0420-y
15. Wang Z, Shen MM, Liu XJ et al (2014) Characteristics of the saliva flow rates of minor salivary glands in healthy people. Arch Oral Biol 60(3):385–392. https://doi.org/10.1016/j.archoralbio.2014.11.016
16. Navazesh M, Brightman VJ, Pogoda JM (1996) Relationship of medical status, medications, and salivary flow rates in adults of different ages. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81(2):172–176. https://doi.org/10.1016/s1079-2104(96)80410-0
17. Kubota T, Katayama M, Nishimura R et al (2020) Long-term outcomes of ocular adnexal lesions in IgG4-related ophthalmic disease. Br J Ophthalmol 104(3):345–349. https://doi.org/10.1136/bjophthalmol-2018-313730
18. Ohshima K, Sato Y, Yoshino T (2013) A case of IgG4-related dacryoadenitis that regressed without systemic steroid administration. J Clin Exp Hematop 53(1):53–56. https://doi.org/10.3960/jslrt.53.53
19. Kase S, Yamamoto T, Ishijima K et al (2013) Spontaneous regression of IgG4-related dacryoadenitis. Mod Rheumatol 23(5):1018–1021. https://doi.org/10.1007/s10165-012-0728-4
20. Seki N, Yamazaki N, Kondo A et al (2012) Spontaneous regression of lung lesions after excision of the submandibular gland in a patient with chronic sclerosing sialadenitis. Auris Nasus Larynx 39(2):212–215. https://doi.org/10.1016/j.anl.2011.01.025
21. Brito-Zerón P, Kostov B, Bosch X et al (2016) Therapeutic approach to IgG4-related disease: a systemic review. Medicine (Baltimore) 95(26):e4002. https://doi.org/10.1097/MD.0000000000004002
22. Yamamoto M, Takano KI, Takahashi H (2018) Early therapeutic intervention for IgG4-related dacryoadenitis and sialadenitis: the balance between risk of observaiton only and therapeutic adverse effects. J Rheumatol 45(9):1339–1340. https://doi.org/10.3899/jrheum.180163
23. Khosroshahi A, Wallace ZS, Crowe JL et al (2015) International consensus guideline statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol 67(7):1688–1699. https://doi.org/10.1002/art.39132
24. Hong X, Zhang YY, Li W et al (2018) Treatment of immunoglobulin G4-related sialadenitis: outcomes of glucocorticoid therapy combined with steroid-sparing agents. Arthritis Res Ther 20(1):12. https://doi.org/10.1186/s13075-017-1507-6
25. Shimizu Y, Yamamoto M, Naishiro Y et al (2013) Necessity of early intervention for IgG4-related disease--delayed treatment induces fibrosis progression. Rheumatology(Oxford) 52(4):679–683. https://doi.org/10.1093/rheumatology/kes358
26. Lee CM, Alalwani M, Prayson RA et al (2019) Retrospective single-centre analysis of IgG4-related disease patient population and treatment outcomes between 2007 and 2017. Rheumatol Adv Pract 3(1):rkz014. https://doi.org/10.1093/rap/rkz014
27. Li W, Chen Y, Sun ZP et al (2015) Clinicopathological characteristics of immunoglobulin G4-related sialadenitis. Arthritis Res Ther 17(1):186. https://doi.org/10.1186/s13075-015-0698-y
28. Hong X, Li W, Xie XY et al (2017) Differential diagnosis of IgG4-related sialadenitis, primary Sjögren syndrome, and chronic obstructive submandibular sialadenitis. Br J Oral Maxillofac Surg 55(2):179–184. https://doi.org/10.1016/j.bjoms.2016.10.021
29. Zhu WX, Zhang YY, Sun ZP et al (2021) Differential diagnosis of immunoglobulin G4-related sialadenitis and Kimura's disease of the salivary gland: a comparative case series. Int J Oral Maxillofac Surg 50(7):895–905. https://doi.org/10.1016/j.ijom.2020.05.023
30. Strehl JD, Hartmann A, Agaimy A (2011) Numerous IgG4-positive plasma cells are ubiquitous in diverse localized non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. J Clin Pathol 64(3):237–243. https://doi.org/10.1136/jcp.2010.085613
31. Ominato J, Oyoma T, Cho H et al (2019) The natural course of IgG4-related ophthalmic disease after debulking surgery: a single-centre retrospective study. BMJ Open Ophthalmol 4(1):e000295. https://doi.org/10.1136/bmjophth-2019-000295
32. Mulholland GB, Jeffery CC, Satija P et al (2015) Immunoglobulin G4-related diseases in the head and neck: a systemic review. Otolaryngol Head Neck Surg 44(1):24. https://doi.org/10.1186/s40463-015-0071-9
33. Yamamoto M, Yajima H, Takahashi H et al (2015) Everyday clinical practice in IgG4-related dacryoadenitis and/or sialadenitis: results from the SMART database. Mod Rheumatol 25(2):199–204. https://doi.org/10.3109/14397595.2014.950036
34. Martín-Nares E, Ángeles-Ángeles A, Hernandez-Molina G (2020) Major salivary gland enlargement in IgG4-related disease is associated with multiorgan involvement and higher basal disease activity. Mod Rheumatol 30(1):172–177. https://doi.org/10.1080/14397595.2019.1572575
35. Liu Y, Xue M, Wang Z et al (2020) Salivary gland involvement disparities in clinical characteristics of IgG4-related disease: a retrospective study of 428 patients. Rheumatology (Oxford) 59(3):634–640. https://doi.org/10.1093/rheumatology/kez280