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Comorbid Diseases of IgG4-Related Sialadenitis in the Head and Neck Region

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Objectives/Hypothesis: To further recognize the comorbid diseases of immunoglobulin G4-related sialadenitis (IgG4-RS) in the head and neck region and to observe the response of these conditions to immunomodulatory therapy.

Study Design: Retrospective review.

Methods: The symptoms of comorbid diseases and medical histories in 51 patients (24 men, 27 women; median age, 55 years) diagnosed with IgG4-RS were analyzed. Thirty-six patients received immunomodulatory therapy and were followed up for 10.4 ± 5.9 months. Computed tomography (CT) examination was performed before and after therapy.

Results: Rhinosinusitis occurred in 58.8% patients, and manifested with the symptoms of nasal obstruction, nasal xerosis, and hyposmia. In addition, 43.1% patients had allergic rhinitis. Lymphadenopathy was identified in 74.5% patients. Lacrimal gland swelling occurred in 78.4% patients. Extraocular muscles, otologic organs, skin and superficial soft tissue, and cranial nerves were also involved. All of the lesions were relieved after immunomodulatory therapy. The Lund-Mackay scores decreased (9.6 ± 5.6 to 1.0 ± 2.2) according to CT analyses ($P < .05$). Mean CT volumes of the swollen lymph nodes and lacrimal glands decreased from 1.21 ± 0.61 cm^3 to 0.59 ± 0.35 cm^3 and from 2.25 ± 1.35 cm^3 to 0.70 ± 0.32 cm^3, respectively ($P < .05$) after treatment.

Conclusions: IgG4-RS could potentially develop with involvement of ocular adnexa, sinonasal cavities, ears, lymph nodes, skin and superficial soft tissue, and cranial nerves in the head and neck region. Immunomodulatory therapy could be effective in controlling both the comorbid diseases of IgG4-RS and sialadenitis of the major salivary glands.

Key Words: IgG4-related sialadenitis, comorbid diseases, head and neck, rhinosinusitis, lymphadenopathy, ocular adnexa, salivary gland.

Level of Evidence: 4

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INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized systemic immune-mediated disease characterized by dense lymphoplasmacytic infiltrates, storiform fibrosis, and elevated serum IgG4 levels.[1] It was first described by Hamano et al. in 2001 as sclerosing pancreatitis, and it was not until 2003 that its status as a systemic disease was taken seriously when extrapancreatic manifestations were identified.[2,3] Thus far, more than 40 different organs have been reported to be involved in IgG4-RD, including the pancreas, salivary and lacrimal glands, biliary system, and lungs.[4]

In the head and neck region, salivary gland involvement in IgG4-RD, or IgG4-related sialadenitis (IgG4-RS), is the most common lesion, and has been described in detail.[5,6] However, the comorbid diseases of IgG4-RS in the head and neck region have only been described as separate lesions in different studies or reported as special cases with multiple organ involvement. The frequency of ocular adnexal, sinonasal cavity, ear, lymph node and cranial nerve involvement in IgG4-RS is unclear, and most of the clinical manifestations have not been well studied.[7]

In this study, we focus on the comorbid diseases in IgG4-RS patients, and attempt to 1) achieve a better recognition of the spectrum of this systemic disease in the head and neck region and 2) observe the response of these lesions to immunomodulatory therapy.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee for Human Experiments of the Peking University School of Stomatology. Informed consents were obtained from all the patients included in this study.

Additional Supporting Information may be found in the online version of this article.

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TABLE I.
Symptoms Associated With Immunoglobulin G4-Related Sialadenitis.

Nasal symptoms
Nasal obstruction
Rhinorrhea
Decreased olfactory sensation
Nasal xerosis
Allergic rhinitis
Ocular symptoms
Swelling of eye lids
Ocular movement restriction
Visual disturbance
Otologic symptoms
Audition decrease or dysaudia
Tinnitus
Skin manifestations
Subcutaneous nodules
Skin rash
Enlargement of lymph nodes

Patients

The study comprised 51 patients who were referred to the Department of Oral and Maxillofacial Surgery at Peking University School of Stomatology between August 2011 and November 2014. IgG4-RS was diagnosed according to the following criteria: 1) persistent (>3 months) swelling of single or multiple major salivary glands; 2) serum IgG4 concentration >135 mg/dL; 3) histopathologic and immunohistochemistry examination showing marked lymphocyte and plasmacyte infiltration and fibrosis as well as infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells/high powered field; and 4) exclusion of other diseases that present with glandular swellings, such as sarcoidosis and lymphoproliferative disease.[8] Basic clinical data, including age and sex, were collected. Besides enlargement of the salivary glands, comorbid symptoms that lasted for at least 3 months or medical history associated with the ocular adnexa, sinonasal cavities, ears, lymph nodes, skin and superficial soft tissue were recorded in detail (Table I). Thirty-six patients (70.6%) received immunomodulatory therapy with intravenous methylprednisolone at a dose of 200 mg for 3 days and 40 mg for 3 days, followed by oral prednisone 0.6 mg/kg/d, which was gradually tapered to a maintenance dose of 5 mg/d. Cyclophosphamide was also administered at a dose of 400 mg once every 2 to 4 weeks. All the previous symptoms were reevaluated more than 3 months after the initiation of the treatment.

Computed Tomography

All patients underwent computed tomography (CT) scanning from the base of the skull to the hyoid. The CT scan was performed using an eight-slice scanner (BrightSpeed; GE Medical Systems, Waukesha, WI). The CT images were analyzed by an experienced radiologist and two oral and maxillofacial surgeons who were blinded to the clinical information. The evaluation of rhinosinusitis was based on the Lund-Mackay staging system, which assigned a value of 0, 1, or 2 to each of the following sinuses: maxillary, anterior ethmoid, posterior ethmoid, frontal, and sphenoid. Score assignments were 0 if the sinus was totally patent, 1 if the sinus was partially opacified, and 2 if the sinus was completely opacified. The osteomeatal complex was scored either 0 if not occluded or 2 if occluded.[9,10] Lymph nodes with a long diameter greater than 1.5 cm or a short diameter greater than 0.8 cm were recorded as swollen,[11] and the largest lymph node was reconstructed by volume rendering of the CT images (see Measurement of the Volume of the Lacrimal Glands and Lymph Nodes).[12] The lacrimal glands were also reconstructed in the same way as the lymph nodes, and the glands were judged to be swollen if their volume was larger than the normal value (see Measurement of the Volume of the Lacrimal Glands and Lymph Nodes, and Supporting Table I in the online version of this article). Other radiological abnormalities associated with the ocular adnexa, ears, skin, superficial soft tissue and cranial nerves were also observed and recorded in detail. All of the patients receiving immunomodulatory therapy were reevaluated during follow-up.

Statistical Analysis

Continuous variables were summarized as means ± standard deviation; categorical variables were expressed as numbers and percentages. Continuous variables in two groups were compared using the Student *t* test. All tests followed the significant level of .05. The analyses were carried out using SPSS 20.0 (IBM, Armonk, NY).

RESULTS

Of the 51 IgG4-RS patients included in the study, 24 were men and 27 were women (male:female ratio, 1:1.25). Their median age was 55 years (range, 9–89 years). All the patients complained of single or multiple major salivary glands swelling for more than 3 months. Forty-nine patients (96.1%) revealed elevation of serum IgG4 levels. Histopathologic and immunohistochemistry examinations of the swollen salivary glands were also consistent with the diagnosis criteria of IgG4-RD in all patients.

Thirty (58.8%) patients complained of rhinosinusitis, and their main symptoms were nasal obstruction (28 patients), nasal xerosis (22 patients), and hyposmia (17 patients). Among these patients, 22 also had allergic rhinitis. In 14 patients, rhinosinusitis presented as the first symptom, prior to enlargement of the salivary or lacrimal glands. According to the CT analyses, 34 (66.7%) patients showed different degrees of sinonasal mucosa thickening (Fig. 1A), and their mean Lund-Mackay score was 9.0 ± 5.3. Destruction or sclerosis of the bony walls of the sinuses was not observed.

Fifteen (29.4%) patients complained of lymph node swelling, which occurred as the first symptom in four patients. Physical examinations showed that 14 patients had swelling of the cervical lymph nodes, mainly located in the submandibular region (Fig. 2). Two patients had masses in the tail of the parotid gland, which appeared as benign tumors but were eventually proven to be lymph node swellings on histopathological and immunohistochemical examinations. According to the CT analyses, lymphadenopathy was present in 38 (74.5%) patients. Among these patients, the submandibular lymph nodes and superior deep cervical lymph nodes were the most commonly involved; the lymph nodes in the parotid region were involved in four patients. No

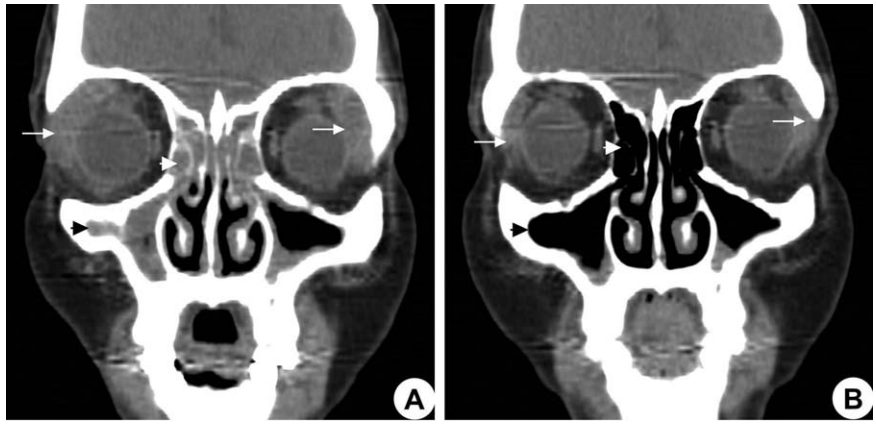

Fig. 1. Immunoglobulin G4-related sialadenitis in a 51-year-old woman. (A) A coronal contrast-enhanced computed tomography scan shows bilateral lacrimal gland (arrows) and sinonasal cavity involvement (arrowhead). (B) At 4 months after treatment, both the enlargement of the lacrimal glands (arrows) and the diffuse thickening of the sinonasal mucosa (arrowhead) have improved.

necrosis of the lymph nodes was observed. The mean volume of the swollen lymph nodes, as determined by the volume rendering of the CT images, was 1.42 ± 1.06 cm^3, and the largest volume was 5.52 cm^3.

Ocular adnexal involvement was common and mainly presented as swelling of the eyelid. In our study, palpation revealed bilateral and unilateral enlargement of the lacrimal gland in 33 (64.7%) patients and one (2.0%) patient, respectively, whereas CT showed bilateral and unilateral enlargement of the lacrimal gland in 35 (68.6%) and five (9.8%) patients, respectively. No patient complained of ocular movement restrictions or visual disturbances. Nevertheless, swelling of the extraocular muscles was observed in three patients (Fig. 3A).

Nine patients complained of decreased audition, four of them combined with tinnitus. Another two patients complained of dysaudia. No obvious imaging abnormalities of the temporal bone were detected on CT, except in one patient with increased density of the middle ear and mastoid sinus (Fig. 4A).

Swelling of the zygomatic and paraorbital region was observed in one patient and was demonstrated to be soft tissue involvement due to IgG4-RD. CT showed thickening of the subcutaneous tissue with no clear boundary (Fig. 5A). Increased density of the subcutaneous tissue was observed in another two patients, one of whom also showed thickening of the platysma.

Cranial nerve involvement occurred in one patient, and was detected as unilateral enlargement of the infraorbital nerve on CT (Fig. 6); no clinical symptoms or signs related to the nerve involvement were present.

In all, 36 patients (70.6%) received immunomodulatory therapy. Among them, 23 patients suffered from rhinosinusitis, 27 cases revealed lymphadenopathy by CT scan, 29 showed swollen lacrimal glands, three of them also with swollen extraocular muscles. Eleven patients complained of decreased audition or dysaudia, and two

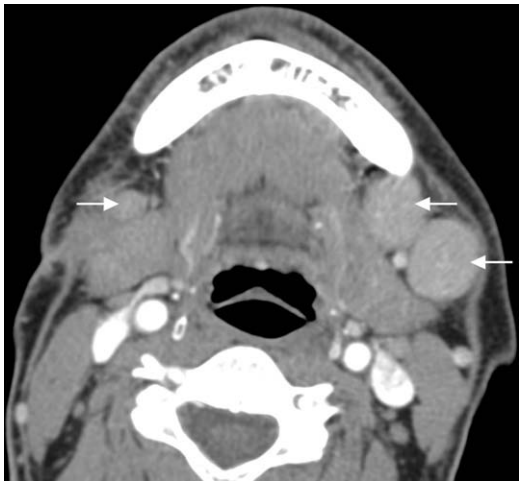

Fig. 2. Lymphadenopathy in immunoglobulin G4-related sialadenitis patient. An axial contrast-enhanced computed tomography scan shows bilateral lymph node enlargement in the submandibular space (arrows) in a 57-year-old man.

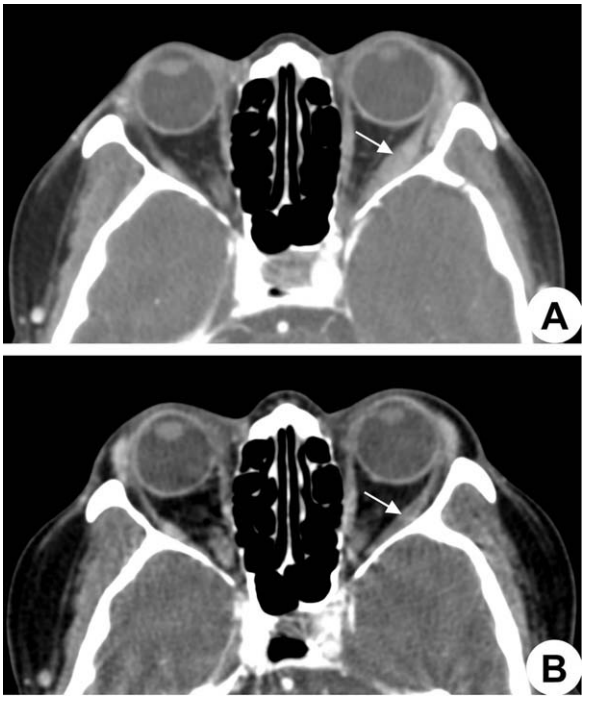

Fig. 3. Immunoglobulin G4-related sialadenitis in a 55-year-old woman with extraocular muscle involvement. (A) Axial contrast-enhanced computed tomography scan reveals swelling of the left lateral rectus muscle (arrow). (B) The swollen muscle has returned to its normal size 12 months after treatment (arrow).

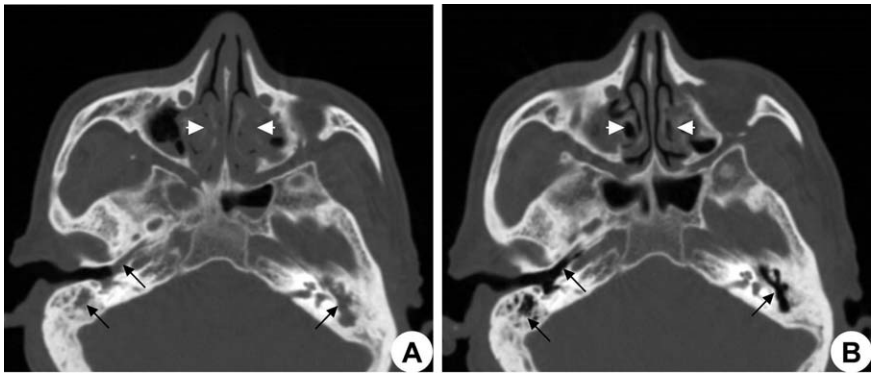

Fig. 4. Immunoglobulin G4-related sialadenitis in a 57-year-old man with dysaudia. Axial plain computed tomography scans reveal bilaterally increased density in the middle ear and mastoid sinus (arrows) as well as thickening of the sinonasal mucosa (arrowheads) (A) and evident relief after immunomodulation therapy (B).

exhibited soft-tissue involvement. The follow-up time ranged from 4 to 27 months (mean, 10.4 ± 5.9 months). Besides the decreased volume of the involved salivary glands, all of the patients with rhinosinusitis reported a remission of their discomfort and regaining of their olfactory sensation within 7 days from when the treatment began (Fig. 1B). Their Lund–Mackay scores decreased from 9.6 ± 5.6 to 1.0 ± 2.2 ($P < .05$). The swollen lymph node volume decreased from 1.21 ± 0.61 cm^3 to 0.59 ± 0.35 cm^3 ($P < .05$; two swollen lymph nodes were excised for biopsy). The volume of the swollen lacrimal glands decreased significantly from 2.25 ± 1.35 cm^3 before treatment to 0.70 ± 0.32 cm^3 after treatment ($P < .01$), with the swollen extraocular muscles returning to their normal size as well (Fig. 3B). All the patients with decreased audition or dysaudia stated improvement of audition, and the increased density of the middle ear and mastoid sinus was also decreased (Fig. 4B). All of the abnormal clinical and imaging appearances of the involved soft tissue recovered after treatment (Fig. 5B).

DISCUSSION

IgG4-RS, as an important part of IgG4-RD, is an autoimmune disease mainly involving the salivary and lacrimal glands.[6] However, as a systemic disease, the spectrum of IgG4-RD in the head and neck includes almost all organs or tissues.[7]

The involvement of the nasal cavity and paranasal cavity has recently been included in the spectrum of IgG4-RD.[13] However, only a few studies and several case reports have focused on or mentioned nasal involvement.[13–15] The main nasal symptoms of IgG4-RS are nasal obstruction, nasal crusting, nasal discharge, and hyposmia.[13,14] CT demonstrates a soft-tissue shadow in the nasal sinuses,[16] and bone destruction can occasionally be observed.[17,18] According to an epidemiological investigation performed in 11 cities in China, the prevalence of allergic rhinitis ranged from 8.1% to 21.4%,[19] whereas allergic rhinitis occurred in 22 patients (43.1%) in our series, indicating the close relationship between IgG4-RD and allergic disease. Dryness in the nasal cavity was also common, which is consistent with the observation of a decreased number of nasal glands in IgG4-RD patients.[14] Recent epidemiological research about chronic sinusitis (CRS) conducted in seven cities in China also achieved a 8.0% prevalence.[20] In our series, 30 patients (58.8%) had rhinosinusitis, and their main nasal symptoms were nasal obstruction (54.9%), nasal xerosis (43.1%), and hyposmia (33.3%). Despite the lack of histological specimens, we suggest that nasal involvement is common in IgG4-RS because of its higher prevalence in these patients than in the Chinese general population and its good response to immunomodulatory therapy. In 14 patients, rhinosinusitis presented as the first symptom, prior to the enlargement of the salivary or lacrimal glands. Nasal biopsy is a safe and useful diagnostic tool; however, it may be not specific for the diagnosis of IgG4-RD.[15] In fact, typical storiform fibrosis

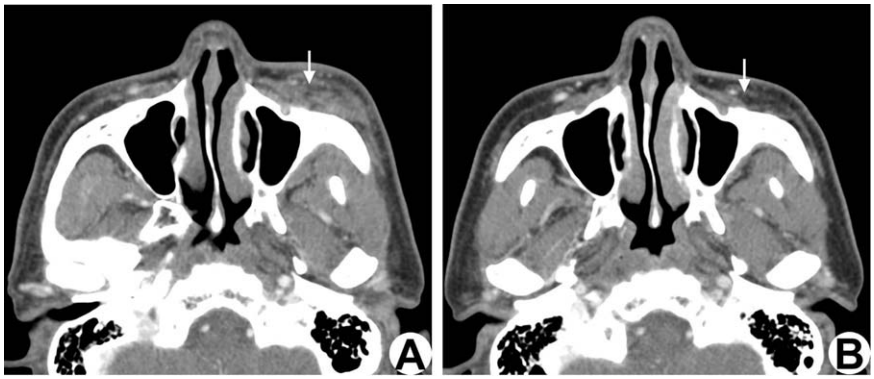

Fig. 5. Skin and superficial soft tissue involvement in immunoglobulin G4-related sialadenitis patient. A 58-year-old man with swelling of the zygomatic and paraorbital region. Axial contrast-enhanced computed tomography scans show subcutaneous tissue thickening with no clear boundary (arrow) (A) and complete reversal of this change after therapy (B).

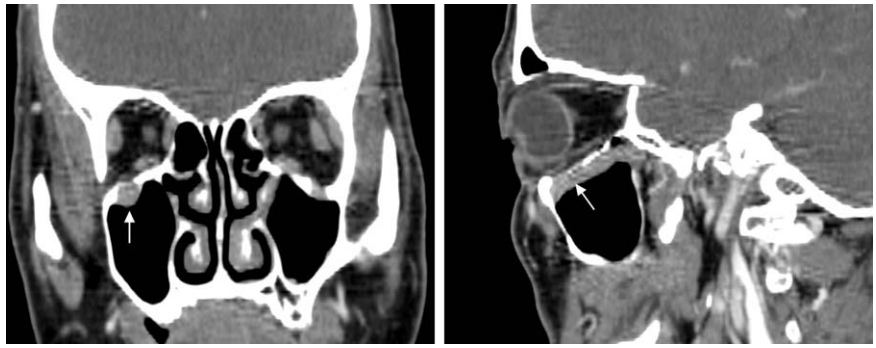

Fig. 6. Immunoglobulin G4-related sialadenitis in a 57-year-old man with cranial nerve involvement. Coronal (left) and sagittal (right) contrast-enhanced computed tomography scans exhibit enlargement of the right infraorbital nerve (arrows).

is not commonly observed in the nasal mucosa, and the diagnostic value of the immunohistochemical staining of the nasal mucosa for IgG4 remains controversial, as IgG4-positive cell infiltration is also observed in common allergic rhinitis, chronic rhinosinusitis, Wegener granulomatosis, rhinoscleroma, Rosai-Dorfman disease, and fungal infection.[21] Nonetheless, we suggest that the involvement of the sinonasal cavities is an important part of diagnosis and evaluation of IgG4-RS, owing to its remarkably high prevalence. As the symptoms, the imaging manifestations, and even the pathological appearances of IgG4-related sinonasal cavity involvement are nonspecific, it is quite difficult for ear, nose, and throat surgeons to identify patients of this relatively low-prevalence systemic disease from thousands of chronic rhinosinusitis and allergic rhinitis patients, especially when nasal symptoms are the only discomfort. But one should consider the disease if the clinical examination shows swelling of salivary glands and/or lacrimal glands, or if the patient has a history of resection of salivary glands or a history of pancreatitis, cholangiolitis, or retroperitoneal fibrosis. Unnecessary invasive therapy could then possibly be avoided.

Lymphadenopathy occurred in 74.5% patients in our series, and its frequency could be as high as 80% in patients with IgG4-related pancreatitis.[22,23] Submandibular lymph nodes and superior deep cervical lymph nodes were the most commonly affected, though lymph nodes in the parotid region were also affected in some patients. Lymphadenopathy may precede, coexist with, or follow the other lesions of the disease.[24] In our study, swelling of the lymph nodes was the first symptom in four patients. The diagnosis of IgG4-RD in such patients is challenging because of the lack of histological and immunohistochemical features that are specific to IgG4-related lymphadenopathy.[24,25] Clinical and laboratory findings are helpful to reach the correct diagnosis, but the lack of these features cannot rule out this disease.[26] In one study, almost half of the patients with IgG4 lymphadenopathy progressed to develop salivary gland lesions during follow-up.[27] Therefore, when the diagnosis is unconfirmed, close follow-up is necessary. All of the patients with lymphadenopathy responded well to immunomodulatory therapy, as the volume of the swollen lymph nodes decreased.

Ocular adnexal involvement is common in IgG4-RD patients, and almost 30% of these patients develop dacryoadenitis.[4] Our previous study has shown that 80% of IgG4-RS patients had lacrimal gland enlargement (data not shown). Besides the lacrimal glands, the extraocular muscles and optic nerve are also regarded as target structures of IgG4-RD, and their involvement results in ocular movement restrictions and occasionally visual disturbances.[28,29] Idiopathic orbital inflammatory disease has also been reported but has not been systematically explored. In our series, besides swelling of the eyelid, no obvious ocular symptoms were noticed. However, CT scans revealed that three patients (5.9%) had extraocular muscle swelling, which completely reversed after treatment.

Otologic manifestations of IgG4-RD are rarely reported and include hearing loss, mastoiditis, and otitis media.[30] In our series, nine patients complained of decreased audition, four of them combined with tinnitus, whereas another two patients complained of dysaudia. CT revealed otitis media in one patient. All the clinical symptoms and the radiological abnormality improved after treatment. The involvement of the ear is a part of the spectrum of IgG4-RD, and clinicians should be aware that it sometimes occurs as the first symptom.[31,32]

Lesions of the cranial nerves have recently been described in IgG4-RD, and the trigeminal branches are the most commonly involved.[33] Cranial nerve involvement mainly appears as a swelling of the nerve or occasionally as tumor-like masses. Fortunately, functional impairment seldom occurs, as inflammatory cells infiltrate mainly the interstitial substance, leaving the nerve fibers intact, as determined by histopathological observations.[33] One of our patients showed apparent unilateral infraorbital canal thickening, which is a sign of infraorbital nerve enlargement. Although another study focusing on orbital lymphoproliferative disorders showed that only patients with IgG4-RD exhibited infraorbital nerve enlargement,[34,35] other lesions, including lymphoma, sarcoidosis, neurofibroma, and schwannoma, should also be differentiated.

Skin and superficial soft-tissue involvement was observed in three patients in our series. One of them presented with subcutaneous nodules. The other two complained of itching, and an increase in the density of the subcutaneous tissue was detected on CT as well as platysmal thickening in one of these patients. No skin lesions at other locations or other types of lesions mentioned in the literature, including erythematous or brown papules,[36] were observed.

The spectrum of IgG-RD in the head and neck region is wide, and the clinical presentation varies, which makes reaching an accurate diagnosis highly challenging, especially when an uncommon manifestation occurs as the main complaint. All the lesions in this series were relieved after steroid therapy rather than surgery. Thus, a clear recognition and greater awareness of this disease may help clinicians to achieve an accurate diagnosis and avoid invasive treatments that may lead to permanent loss of the functions of important organs.

All of the patients included in this study were IgG4-RS patients with either single or multiple salivary glands involved, and most of their serum IgG4 levels were high. Early intervention seems necessary to avoid further fibrosis and damage of the secretory functions of the involved salivary glands as well as wider organ involvement.[37] Steroid therapy is regarded as a standard treatment for IgG4-RD.[38,39] In our study, the enlarged salivary glands, lacrimal glands, and cervical lymph nodes decreased, and the symptoms of rhinosinusitis and dysaudia were relieved after treatment. Our results indicate that immunomodulatory therapy is effective for IgG4-RS and its comorbid diseases in the head and neck, which is consistent with previous reports.[13,26,31,40] Recently, Alt et al. reported a case of localized IgG4-RD in the sphenoid sinus, with normal serum IgG4 level successfully treated by sphenoidotomy combined with nasal corticosteroid spray.[41] For the patients with IgG4-related disease isolated to the nasal cavity and/or paranasal sinus, topical application of steroids with or without limited surgery would be a good choice of treatment because it lessens the risks of steroid complications. A mean period of 10.4 ± 5.9 months for follow-up is relatively short for precise evaluation of our treatment protocol. This study is retrospective, which is a limitation. Therefore, further prospective investigation with long-term follow-up is necessary.

CONCLUSION

IgG4-RS could potentially develop with involvements of ocular adnexa, sinonasal cavities, ears, lymph nodes, skin and superficial soft tissue, and cranial nerves in the head and neck region. Immunomodulatory therapy could be effective for the control of both the comorbid diseases of IgG4-RS and sialadenitis of the major salivary glands.

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