

## Case Report

# IgG4-related sclerosing disease located on the right maxilla: a case report and review of literature

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**Abstract:** IgG4-related sclerosing disease is an immunologic disease which involves multiple organs, and it was always misdiagnosed as inflammation or malignant tumor. The salivary and lacrimal glands are always related when it occurs in the maxillofacial region. The histopathology of the lesion is most important in the diagnosis of the IgG4-related sclerosing disease. To make a definite diagnosis, clinical manifestation and increasing of serum IgG4 are also needed. We received a patient who had a hard mass of the right maxilla and a swollen left lacrimal gland. After series examinations, we made a confirmed diagnosis of the patient as IgG4-related sclerosing disease. IgG4-related sclerosing disease was rarely been reported and occurred extremely rare in maxilla. This case report detailed the experience of us to make a definite diagnosis for the patient and discussed the pathogenesis, diagnosis and treatment methods of IgG4-related sclerosing disease by consulting the previous articles.

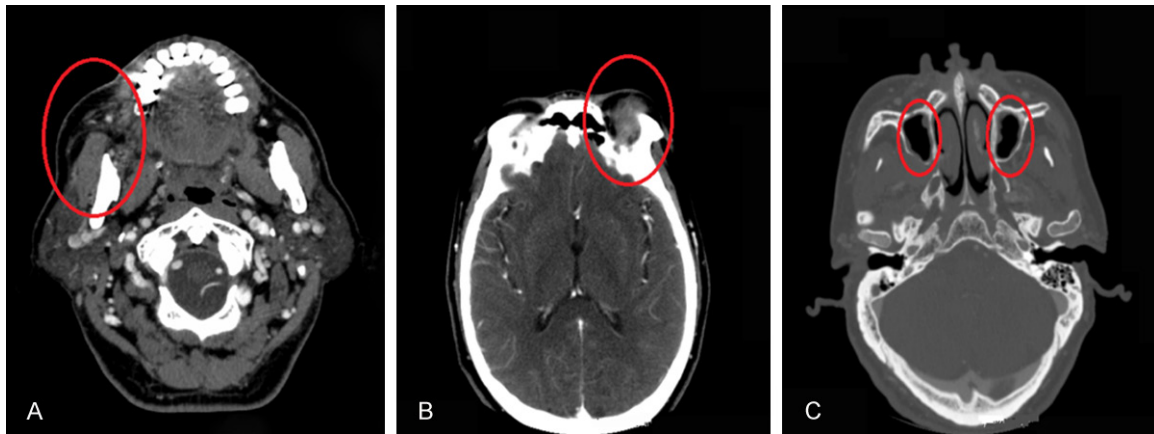
**Keywords:** IgG4-related sclerosing disease, histopathology, maxilla, diagnosis

## Introduction

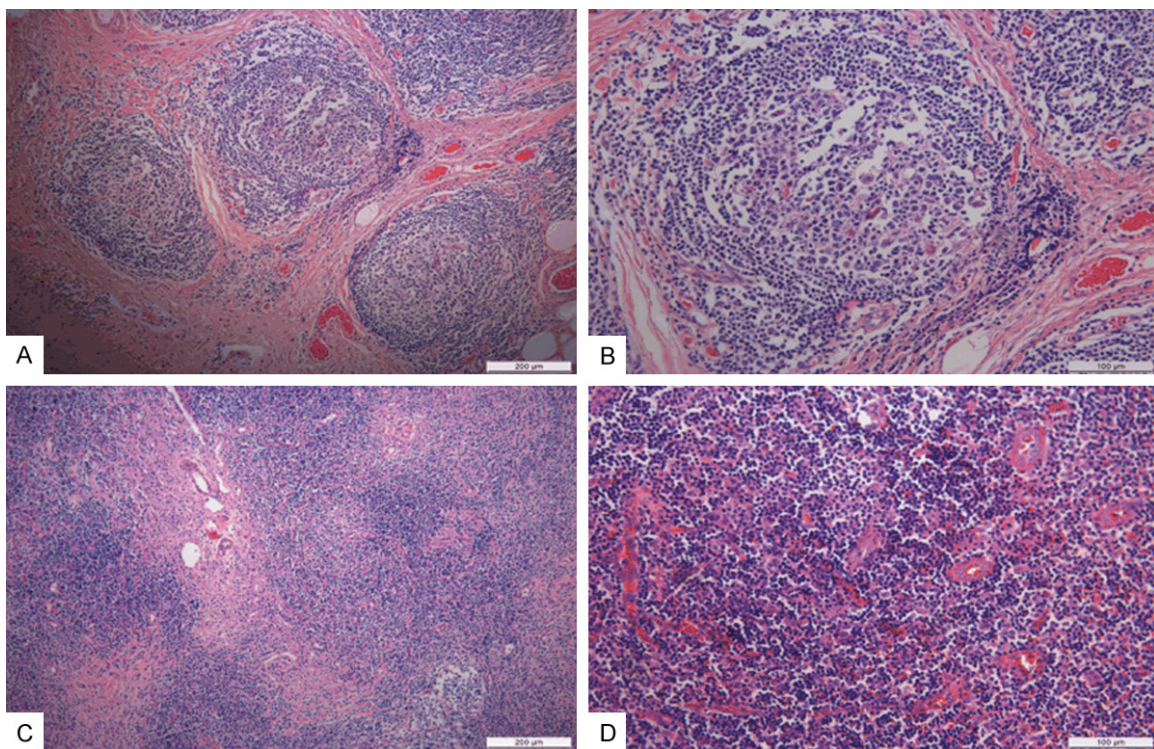
IgG4-related sclerosing disease which also called IgG4-related autoimmune disease is a new immune regulating sclerosing disease which involves multiple organs [1]. The designation of this disease appeared formally in the medical publications in 2003, and before this time the kind of diseases were usually misdiagnosed as individual organ diseases like autoimmune pancreatitis, fibrosis of mediastinal inflammatory, Küttner's tumor, Mikulicz's disease and so on [2]. IgG4-related sclerosing diseases used to appear in the elderly, the organs like kidney, aorta, peritoneum, lymph node are widely involved. IgG4-related sclerosing disease can affect orbital and orbital tissues, salivary gland, sinus or other organs in the maxillofacial region [3]. The Mikulicz's disease and Küttner's tumor which happened in the salivary glands of the maxillofacial region are now classified as IgG4-related sclerosing diseases, they are distinguished with Sjogren's syndrome and malignancy for amount of IgG4 positive plasmacyte infiltration and multiple organs involved [4, 5].

The methods of diagnose for IgG4-related sclerosing disease include tissue biopsy, imaging examination and so on. Among these, histopathology is the gold standard for most cases, the infiltration of IgG4 positive plasma cells in the tissue should be measured. The serum increase of IgG4 is also needed in some diagnosis of IgG4-related sclerosing disease [1]. However, the treatment of IgG4-related sclerosing disease haven't got a clear standard yet, according to the severity of patient's condition, the size of the lesion and the range of the organs are involved. Medication treatment for IgG4-related sclerosing disease is the most common method. However, many patients' lesions located on the superficial parts, at this time surgical excision can also reach a good prognosis [6, 7].

We have recently detected a special patient who had a tough pseudotumor located on his right maxilla. The tumor tend out to be 2 cm × 1 cm size large, meanwhile the patient got a swollen left lacrimal gland and ethmoiditis on both sides. After surgical excision of the lesion, we made an immunohistochemical diagnosis of the pseudotumor. Based on the pathological



**Figure 1.** Computed tomography shows an irregular density image in the space of the right masticatory muscle (A), left lacrimal gland swelling (B), and inflammations of the bilateral maxillary sinus (C).



**Figure 2.** Hematoxylin-eosin stain of the right maxilla mass. We can see the formation of lymphatic follicles (A, 100× B, 200×), large numbers of lymphocytes and plasmacytes infiltrated (C, 100×) and obviously fibrosis of the collagen (D, 200×) in the lesions.

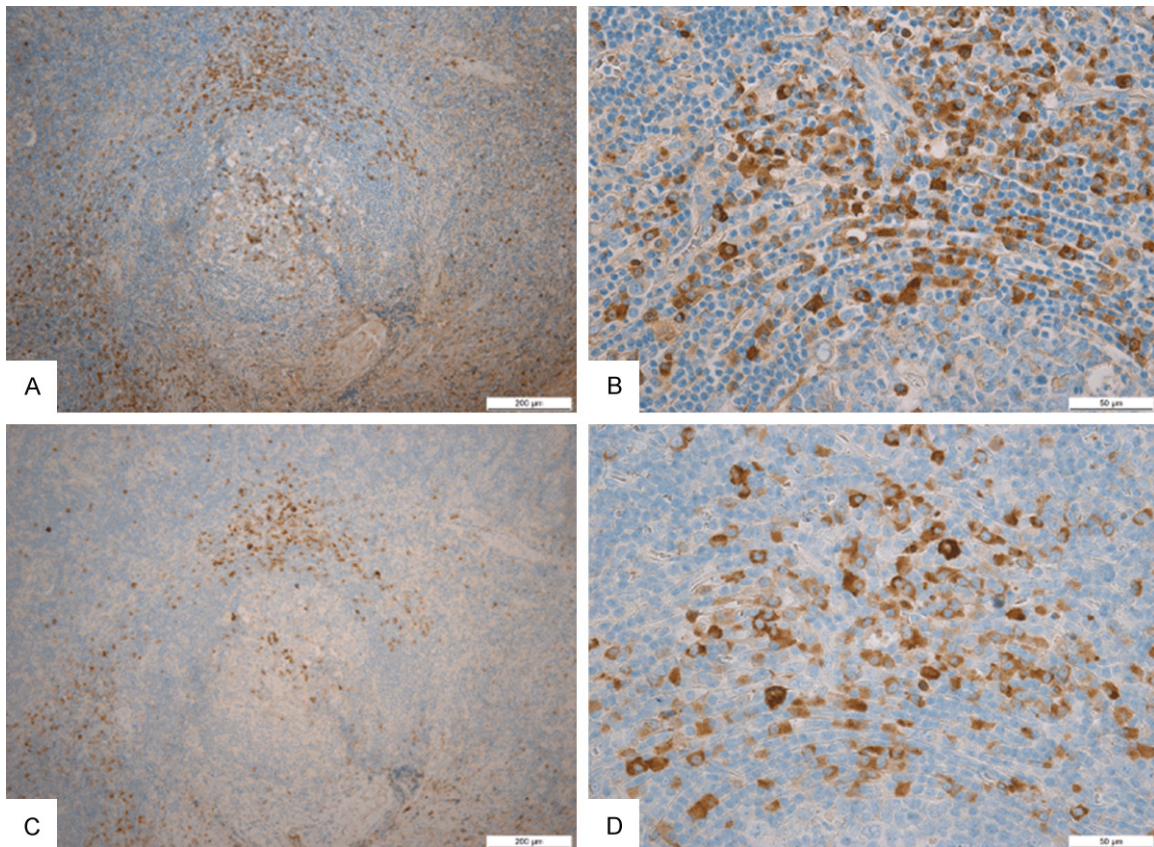
findings, the patient was at last diagnosed as IgG4-related sclerosing disease.

#### Case report

A 67 years old man underwent an operation of right lacrimal sac in Shenzhen Ophthalmic Hospital on May 14th 2015 for the obstructed right lacrimal sac. However, after operation the

computed tomography spotted an occupancy lesion on the body of the right upper jaw and near the infratemporal fossa, so he was suggested to the Department of Oral and Maxillofacial Surgery in the Peking University Shenzhen Hospital. The patient described that he noticed a walnut size lump on his right facial unintentionally 6 years ago, since there was no pain or any discomfort, he didn't care about it.





**Figure 3.** Immunohistochemistry of the right maxilla mass. The infiltration of IgG-positive plasma cells (A, 100× B, 400×). The infiltration of IgG4-positive plasma cells (C, 100× D, 400×). We can see more than 20 IgG4 positive plasma cells each HPF and the ratio of IgG4 positive to IgG positive plasma cells was above 40%.

The patient had no hypertension, diabetes or family history of pancreatitis and immune diseases. The elemental oral and maxillofacial exams revealed a 2 cm × 1 cm size unpainful bulge on the body of right maxilla which was hard and had clear margin. Intraoral examination showed slightly swelling of the gingiva, however the salivary glands were normal and the secretion behaved limpid. A 1 cm × 1 cm size lymph node was detected under the right jaw while other lymph nodes were normal. Blood routine examination indicated that only leukocyte, monocyte and lymphocyte had a slightly increase.

The results of computed tomography showed an irregular density image of soft tissue in the space of the right masticatory muscle (**Figure 1A**). The range of the lesions downward extend to the infratemporal fossa, forward went through the inferior orbital fissure extend to the subcutaneous of right facial, inward broke through the lateral wall of ethmoidal sinus, the

properties the lesions were to be determined. The CT also showed lacrimal gland swelling on the left side, and inflammations were supposed to be found in bilateral lacrimal gland, ethmoid, sphenoid and maxillary sinus (**Figure 1B, 1C**).

For the diagnosis of the patient can't exclude malignancy of the maxilla, total removal of the mass under the general anesthesia was taken, and the specimen was sent to conduct a biopsy. The pathological examinations revealed diffuse infiltration of inflammatory cells in the muscular and fibrous tissue. Most of the inflammatory cells were lymphocyte with the formation of lymphatic follicles, and large numbers' of plasmocytes and few eosinophils were also found in the lesions (**Figure 2**). Immunohistochemical staining for IgG4 showed strongly positive for more than 100 IgG4 positive plasma cells can be seen in each HPF and the ratio of IgG4 positive to IgG positive plasma cells was approximately 60%. According to these two results, the pathology depart-

ment considered that the patient had an IgG4-related sclerosing disease.

Subsequently, the pathological sections of the patients were sent to the First Affiliated Hospital of Sun Yat-sen university for further diagnosed. They reported lymphatic follicles distribute intensively among the striated muscle, adipose and fibrous tissues, thousands of lymphocytes and plasmacytes infiltrated and obviously fibrosis of the collagen can also be noticed in the lesions (**Figure 2**). Immunohistochemical staining for IgG4 showed that more than 20 IgG4 positive plasma cell each HPF and the ratio of IgG4 positive to IgG positive plasma cells was approximately 40% (**Figure 3**), so they also expected the patient to be IgG4 related sclerosing disease. Moreover, the patient should make a detailed check-up of the body and serum levels of IgG4 as they suggested.

After the doctors had a consultation, the patient had department transference to the department of rheumatism and immunology in our hospital. The examination of multiple organs of the body was taken, and the results showed no diseased organs. Meanwhile, peripheral blood plasma examination indicated that the serum levels of IgG4 reached up to 1270 mg/dL and serum levels of IgG highly raised to 2379 mg/dL, both of which greatly exceeded the range of normal values. Based on all these results, the patient was finally diagnosed with IgG4-related sclerosing disease on the right maxilla with the lacrimal gland possibly implicated. The patient was at last advised to apply glucocorticoid drugs or immunosuppressive agents' therapy. After three months low-dose prednisolone (10 mg/day) therapy we came to a follow-up of the patient. The patient now showed no regrowth of the mass on the right maxilla and the swelling lacrimal gland diminished significantly.

### Discussion

Large numbers of hospitals report a new systemic disease in recent years, the lesions of the disease are mostly characterized by tumoral sclerosis, IgG4 positive plasma cells infiltration of the lesions and increasing peripheral blood IgG4 level [4, 6, 8]. This kind of diseases is called IgG4-related sclerosing disease and the patients are sensitive to steroid hormone therapy [9]. According to the statistics, high percent of these patients are from Asian and most of

them are Japanese, the lesions of the patients most commonly happened in the orbit, then the submandibular gland and rarely happened in the skin or other parts of the facial [6].

The pathogenesis of IgG4-related sclerosing disease still remains unclear, previous research has shown that the development of disease might highly associated with the inflammatory factors secreted by Th2 and Treg cells, IL-4 and IL-13 secreted by Th2 cells and IL-10 secreted by Treg cells can promote plasmacyte infiltration, the formation of secondary lymphoid nodule and the secretion of IgG4 [10]. Some scholars also discovered that TGF- $\beta$ , a transcription factor secreted by Treg cells can promote fibrosis, maybe closely associated with the storiform fibrosis of the lesions [11]. Although the level of IgG4 in the local-pathological-changed tissues and the peripheral blood of the IgG4-related sclerosing disease patients obviously increased, the mechanism of IgG4 in the development of the disease has not made a clear conclusion yet.

The diagnostic criteria of the IgG4-related sclerosing disease including several points: Firstly, clinical examination showing characteristic diffuse or localized swelling or masses in single or multiple organs. Secondly, hematological examination shows elevated serum IgG4 concentrations ( $\geq 135$  mg/dl). At last, histopathologic examination shows marked lymphocyte, plasmacyte infiltration and fibrosis, meanwhile the infiltration of IgG4 positive plasma cells shows: the ratio of IgG4 positive/IgG positive cells larger than 40% and more than 10 IgG4 positive plasma cells per HPF. When all these symptoms are positive, the diagnosis can be definite, however, the diagnosis maybe just probable if only two of them are positive [12].

The IgG4-related sclerosing disease is less likely happened in the maxillofacial region except orbit and salivary glands, a small part of scholars discovered the lesions located in the pharyngeal space, nasal mucosa or the infratemporal fossa, and the maxilla is extremely rare [7, 8, 13]. The CT of our patient revealed that the lesion located on the body of the maxilla and extended to the infratemporal fossa with the destruction of the bone. According to these results, the diagnosis of the patient can't exclude sarcoma, osteofibroma, fibrous dysplasia and giant cell tumor of bone. Considering

these possibilities, the lesions would metastasize, we conducted expanded resection of the mass in the right facial and infratemporal fossa, and then subtotal maxillectomy was taken to make sure the pathologic tissues were resected completely. After immunohistochemical examination we suspected the patient to be IgG4-related sclerosing disease. Finally we conducted the serum IgG4 examination of the patient and it turned out to be 1270 mg/dL which was much larger than normal, so we made a definite diagnosis of the patient.

So far, glucocorticoids are the first-line drugs for most patients, for prednisolone, we usually use a starting dose of 0.6 mg/kg daily, 2-4 weeks later the dose is tapered gradually and the time of usage may last more than 3 years [9]. For patients in serious condition, the drug dosage should be larger, to avoid the side effect of long-term, heavy use of glucocorticoids, some researchers adopt immunosuppressive therapy at the same time. However, this kind of treatment hasn't been tested in plenty of clinical research, the effectiveness of this therapy method require further studies [14]. Rituximab is also used in the treatment of IgG4-related sclerosing disease. When the patients don't respond well to glucocorticoids therapy, rituximab can be a good choice for it can relieve the symptoms obviously and rapidly, and avoid the drug resistance after the abuse of glucocorticoids [15].

The exact pathogenesis of the IgG4-related sclerosing disease is still unknown, however the clinical manifestation, serum and imageological examination of this disease have no obvious specificity, so we always confuse it with tumor and other diseases. Since the low incidence of IgG4-related sclerosing disease, the diagnosis and treatment method are not perfect. In the case of head and neck, the IgG4-related sclerosing disease always happened in the lacrimal glands, salivary glands, skin and other parts, glucocorticoids therapy at early stage can get a good prognosis. However, in most cases due to the neglect and lack of experience of the clinical surgeons, the IgG4-related sclerosing disease is always misdiagnosed which can lead to the treatment failure. We should improve the understanding of IgG4-related sclerosing disease, positively check the patients which are suspicious and try our best

to take early diagnosis and treatment and then relieve the sufferings of the patients.

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### Disclosure of conflict of interest

None.

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