Immunoglobulin G4-Related Disease in The Head and Neck: Two Case Reports and Literature Review

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Immunoglobulin G4-related disease (IgG4-related disease) is a fibroinflammatory disorder defined by elevated serum IgG4 level and plasma cells tissue infiltration accompanied by fibrosis or sclerosis. In this article, we report two patients of IgG4 syndrome: a 60-year-old male with complaints of nasal congestion, rhinitis, anosmia and hearing loss, and a 28-year-old female with bilateral orbital and parotid gland swelling. Histopathological findings and high serum IgG4 level confirmed diagnosis of IgG4-related disease. Both patients were treated successfully with glucocorticoids and methotrexate. Herein, we also review clinical presentations of IgG4-related disease in head and neck, and related diagnostic and therapeutic approach.

Keywords: Immunoglobulin G4-related disease; Mikulicz’s syndrome; Sjögren’s disease.

CASE REPORT

Case 1– A 60-year-old male admitted to our clinic with complaints of nasal congestion, rhinitis, anosmia and hearing loss. A 28-year-old female reported bilateral orbital and parotid gland swelling. Histopathological findings and high serum IgG4 level confirmed the diagnosis of IgG4-related disease. Both patients were successfully treated with glucocorticoids and methotrexate. Herein, we review the clinical presentations of IgG4-related disease in the head and neck, and the related diagnostic and therapeutic approach.
anosmia, and hearing loss accompanied by some episodes of fever without cough or any other remarkable symptoms that had been aggravated during the last three months. Except for a history of dry eye, he did not mention any special disorder in himself or his family. Physical examination showed generalized muscle weakness.

With primary diagnoses of sinusitis and ear infection, some paraclinical evaluations were requested. Computed tomography scans of paranasal sinuses showed opacity and widening of ostiomeatal complex but his ears were normal. A few days later, bilateral parotid and submandibular salivary glands swelled. Serological tests and lymph node biopsies were performed to clarify the situation. Laboratory examination revealed negative antinuclear antibodies profile, increased erythrocyte sedimentation rate (80 mm/h), and high IgG4 titer (405 mg/dL) (normal 6.2-112 mg/dL). Other serologic examinations for infectious diseases such as cytomegalovirus, herpes simplex virus, Epstein-Barr virus, mycoplasma, and hepatitis B and C viruses were negative but serum IgG4 was elevated. Abdominal and chest computed tomography scans were unremarkable. Histopathological examination of salivary glands showed focuses of numerous lymphoid follicles with germinal centers, extensive fibrosis, and abundant IgG4+ plasma cell infiltration. Thus the diagnosis of IgG4-related disease was confirmed and treatment was started with steroid. To reduce steroid-induced adverse effects, methotrexate was added to the treatment regimen. After three months of follow-up, patient’s symptoms improved significantly. One year after the end of treatment, patient was healthy and symptom free.

**Case 2—** A 28-year-old female referred to our clinic with bilateral proptosis and parotid swelling from three months ago. She had a history of bilateral parotid swelling from six months ago, as well as chronic sinusitis and mild asthma. Her problem started three years ago with bilateral upper eyelid swelling that improved by using prednisolone. However, discontinuation of treatment due to pregnancy caused symptoms to relapse at second trimester of pregnancy.

In physical examination, visual acuity and neurologic examination were normal. There was no eye or mouth dryness. Hyperpigmented patchy lesions were observed on left leg and both hands, and bilateral eye and neck swellings were detected as well.

Chest-X-ray and abdominal ultrasound were unremarkable. Chest computed tomography scan showed right hilar lymphadenopathy and local plural thickening in posterior part of left hemithorax. Head and neck magnetic resonance imaging (MRI) indicated multiple hypointense signal foci in T2 in orbital muscles and cervical lymph nodes (Figure 1). Sputum smear and culture were negative for acid fast bacilli. Thyroid function tests and other biochemical parameters were normal.

![Figure 1. Orbital magnetic resonance imaging with hypointense signal foci in T2 in the orbital muscles.](image-url)
Orbital mass biopsy was performed and histopathological exam showed numerous lymphoid follicles with germinal centers, fibroid bundles and infiltration of IgG4+ plasma cells and eosinophils in lacrimal gland (Figure 2). Results of serologic assays including anti nuclear antibody profile and complement C3, C4 and CH50 were in normal ranges but serum IgG4 level was elevated (817 mg/dL) (normal range: 6.2-112 mg/dL).

Diagnosis of IgG4-related disease was made based on histopathological findings and high serum concentration of IgG4. Treatment was started with high dose of prednisolone (1 mg/kg) and then methotrexate was added to reduce steroid-induced side effects. As the patient was cushingoid, the response to steroid therapy was not too favorable and her blood glucose increased by therapy. We were unable to stop the treatment since steroid tapering and reducing steroid dosage caused relapse of symptoms. Patient may be a candidate for other new therapies like B cell depletion therapy with rituximab.

**DISCUSSION**

Immunoglobulin G4-related disease has been recognized as a systemic condition since 2003.\(^5\),\(^14\) Since then, many medical conditions such as Mikulicz’s syndrome, Kuttner tumor, and Riedel’s thyroiditis which were known as organ-specific disorders are considered as part of IgG4-related disease spectrum.\(^15\)

Immunoglobulin G4-related disease is a chronic relapsing systemic fibroinflammatory disease that can affect any organ with a common key pathological feature including tendency to form inflammatory lesions rich in IgG4-positive plasma cells, storiform fibrosis, phlebitis, and often an elevated IgG4 serum concentration (in 60-70% of patients).\(^16\)

The prevalence of IgG4-related disease in males is significantly higher than females except for that of the head and neck involvement (such as saladenitis) which is seen in males and females equally. This gender distribution is in contrast to other autoimmune diseases that mimic IgG4-related disease.\(^17\) In our study, IgG4-related disease with head and neck involvement occurred in a middle-aged male and a young female that is consistent with the above mentioned gender predominance.

Almost any organ may be affected by IgG4-related disease, usually in the middle-aged and elderly patients.\(^18\) IgG4-related disease symptoms are referable to the specific target organ that may be different from those of other organs.\(^6\),\(^17\),\(^19\) IgG4-related disease appears as a mass lesion or diffuse enlargement of organ in most cases which develops gradually and comes to attention usually due to the organ swelling.\(^6\),\(^17\),\(^20\),\(^21\) as observed in the head and neck region with orbital and parotid swelling and neck lymphadenopathy in our patients. Multi-organ involvement occurs in about 60-90% of patients.\(^22\) Lymphadenopathy in IgG4-related disease is common (40%) and mediastinal, hilar, intra-abdominal, and axillary lymph nodes are the most commonly involved.\(^21\) In our patients, clinical features of disease were limited to the head and neck and there was no multi-organ involvement at diagnosis. Hilar adenopathy was observed only in our second patient.

In the head and neck region, various organs including skin,\(^23\) thyroid,\(^24\),\(^25\) paranasal sinuses,\(^26\) ears,\(^27\),\(^28\) orbit,\(^29\),\(^30\) and salivary glands may be involved.\(^31\) The most commonly involved organs by IgG4-related disease in the head and neck region are lacrimal and salivary glands (40%).\(^15\),\(^31\),\(^32\)
Bilateral or unilateral simultaneous swelling of lacrimal, parotid and salivary glands (previously known as Mikulicz disease) and chronic sclerosing sialadenitis (known as Kuttner tumor in the past) were previously known as subtypes of SS.\textsuperscript{4,16,33-36} Both of the above mentioned disorders are now considered as part of the spectrum of IgG4-related disease.\textsuperscript{31} IgG4-related disease can be differentiated from SS by lower rate of xerophthalmia, xerostomia and arthralgias as well as higher rate of allergic rhinitis, bronchial asthma, autoimmune pancreatitis, and interstitial nephritis.\textsuperscript{31,36-38} Low rate of autoantibodies, including rheumatoid factor, antinuclear antibodies, anti-Sjögren's-syndrome-related antigen A, anti-Sjögren's-syndrome-related antigen B, higher serum IgG4 and immunoglobulin E concentrations and better response to steroid therapy are other findings that can help differentiating IgG4-related disease from SS.\textsuperscript{31,36-38} These differences enabled us to rule out Kuttner tumor in our first patient and Mikulicz disease in our second patient.

Although the diagnosis of IgG4-related disease is based on the combination of clinical feature, serology, imaging, histopathology and immunohistochemistry findings, histopathology is the gold standard and key component for diagnosing IgG4-related disease.\textsuperscript{39,40} The unique histopathological characteristics of IgG4-related disease include three major features of dense lymphoplasmacytic infiltrate, storiform fibrosis, and phlebitis.\textsuperscript{16,40} Based on the guidelines developed and approved in 2011 by experts in “Consensus statement on the pathology of IgG4-related disease”, presence of at least two of the three major histological features is required for definitive histological diagnosis of IgG4-related disease. However, it should be considered that storiform fibrosis and obliterative phlebitis may be absent or non-significant in organs such as the lymph nodes\textsuperscript{41} as well as salivary and lacrimal glands.\textsuperscript{30}

Increased number of IgG4+ plasma cells or an elevated ratio of IgG4+/IgG+ in the tissue are of diagnostic value in immunostaining, although the latter can be a more powerful evidence\textsuperscript{41,42} since infiltration of IgG4+ plasma cells may be seen in some non IgG4-related disease inflammatory lesions.\textsuperscript{43} Elevated serum IgG4 concentration (>135 mg/dL) is another characteristic of the disease, although serum IgG4 concentration may be normal in 30-40% of patients with histopathologically confirmed IgG4-related disease.\textsuperscript{44} Some of the specific histopathological and immunostaining characteristics such as lymphoplasmacytic infiltration, fibrosis and infiltration of IgG4+ plasma cells as well as elevated serum IgG4 concentration were observed in both of our patients with head and neck involvement.

The main differential diagnosis of IgG4-related disease is SS. In histopathologic examination, both of these disorders show marked lymphocytic infiltration but IgG4-related disease can be differentiated from SS by lymphoid follicles formation, lower lymphocytic infiltration and marked IgG4+ plasma cells infiltration (>10 IgG4+ cells/HPF) with a ratio of IgG4+ to IgG+ cells of more than 40%, which is never seen in SS. Also, polyclonal B-cell proliferation is seen only in IgG4-related disease but not in SS.\textsuperscript{9,16,17,34-36,45,46} Kuttner tumor and Mikulicz's syndrome, which were observed in our patients, are two similar disorders that both share a common feature of sialadenitis and now are considered as IgG4-related disease.\textsuperscript{17} Histology of Kuttner tumors shows severe fibrosclerotic lesions with infiltration of IgG4+ plasma cells\textsuperscript{9} but fibrosis is less severe in Mikulicz's syndrome. Therefore, it is difficult to differentiate them from each other.\textsuperscript{17} In our patients, differential diagnosis of Kuttner tumor and Mikulicz's syndrome from IgG4-related disease was challenging and highly elevated serum IgG4 guided us to diagnose IgG4-related disease in the head and neck region.

Magnetic resonance imaging may be beneficial in diagnosis of IgG4-related disease with head and neck involvement. Imaging findings of IgG4-related disease differ based on involved organ. Imaging of IgG4-related disease in head and neck lesions such as lacrimal gland, orbital mass and pituitary reveals hypointense signal in T\textsubscript{2} of MRI,\textsuperscript{47} which was observed in MRI of our second patient. So, the diagnosis of IgG4-related disease should be suggested for T\textsubscript{2}-weighted hypointense enhancing lesions of the head and neck such as lacrimal glands, as in our second patient, and further investigations should be performed. However,
making a definitive diagnosis by imaging findings alone is challenging.

Glucocorticoids are the treatment of choice and the first line of therapy in IgG4-related disease and most of patients have good response to this treatment except for those with extensive fibrosis. Good response to glucocorticoids is so remarkable that it may further confirm the diagnosis and even help to discriminate it from other similar diseases such as SS. Other medications such as methotrexate, azathioprine or mycophenolate mofetil may be used to reduce adverse effects of long-term steroids usage. In addition, recent studies have shown significant efficacy of B cell depletion therapy with rituximab in refractory patients. In conclusion, further histopathological, imaging and pharmacological evidence should be provided for better understanding and clarifying various aspects of head and neck involvement in IgG4-related disease. Currently, it is not possible to establish a definitive diagnosis of head and neck involvement in IgG4-related disease by only one of the mentioned methods although its diagnosis is similar to involvement of other organs. A combination of histopathological, immunohistochemistry, imaging and serologic studies should be considered for distinct diagnosis of IgG4-related disease in the head and neck region.

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