IgG4 Related Disease of the maxillary sinus - a case report

JOHN MATHEW THOMASMATHAI
Department of Rheumatology,
CHRISTIAN MEDICAL COLLEGE

Abstract:
Immunoglobulin G4 related disease (IgG4-RD) is a fibroinflammatory disorder which can affect any tissue or organ. It is characterized by tissue swelling with lymphoplasmacytic infiltrates rich in IgG4 positive plasma cells, irregularly whorled pattern of fibrosis and often elevated serum IgG4 levels. Previously described conditions that represent manifestations of IgG4-RD include (1,2) IgG4-related pancreatitis, IgG4-related sclerosing cholangitis, Mikulicz disease, Sclerosing sialadenitis (Kttners tumor), Inflammatory orbital pseudotumor, IgG4-related retroperitoneal fibrosis, IgG4-related aortitis or periaortitis, Riedels thyroiditis, pulmonary inflammatory pseudotumors, IgG4-related kidney disease, IgG4-related hypophysitis and IgG4-related pachymeningitis. The disease shows a good initial response to glucocorticoids. Second line agents which have showed response include azathioprine and Mycophenolate mofetil (3,4). B cell depletion therapy with Rituximab have also been tried effectively (5-7).

Keyword: IgG4 Related Disease, IgG4 levels, IgG4 positive plasma cells, Maxillary sinus, Deflazacort, Azathioprine, Mycophenolate mofetil

INTRODUCTION
Immunoglobulin G4 related disease is an increasingly recognized rare entity. This could involve a single organ or multiple organs, with local symptoms based on the organ involved. Early aggressive treatment is warranted to prevent permanent irreversible damage. Hence it is important to be able to suspect and diagnose this condition. We describe a patient with involvement of the maxillary region and the response to treatment

CLINICAL PRESENTATION
A 22 year old student from Chittoor in Andhra Pradesh, presented to us with complaints of pain of the left pre-auricular region for the past 2 years. He also gave history of difficulty in mouth opening and intermittent headache of the left temporal region for the last 6 months. There was no history of ear discharge or hearing loss. There are no nose or throat complaints. He did not have any other known comorbidities. No history of substance abuse. There were no systemic symptoms Examination findings:
There was fullness seen around the left orbital region. There was a bony hard swelling 1cm × 2 cm along the lateral aspect of left maxilla extending into the buccal region. It was tender on palpation. There was trismus with mouth opening of only 1 finger breadth. There was mild left proptosis. The tympanic membranes were intact bilaterally. Eye movements and vision were normal. There were no lymph nodes palpable. Other systems on examination were normal.

INVESTIGATIONS:
The CT scan of the head and neck showed an ill-defined subtle enhancing soft tissue lesion involving the left maxillary sinus. The lesion was approximately 6×3×3.5 cm eroding the walls of the sinus with destruction of medial wall. Medially it was filling the infundibulum with mild extension into the nasal cavity. Superiorly the lesion was destroying the floor of the left orbit with intraorbital extension. Posterolaterally the lesion was extending into and filling the left masticator space. There was soft tissue density involving the left cavernous sinus and pituitary fossa. The CT images are shown in Fig. 1 and 2.

Fig. 1 Arrow head pointing the infiltrative mass lesion

Fig. 2 Intracranial extension with contrast enhancement

The liver functions showed an albumin/globulin ratio of 8.2/3.8, with normal liver enzymes. The bloodcounts and renal functions were normal. The inflammatory markers were raised. A rigid nasal endoscopy under general anaesthesia showed Pale nasal mucosa bilaterally. A small hypertrophic mass was noted on the left nasopharynx from which biopsy was taken. A Proliferative friable pink mass filling the left maxillary sinus was sent for histopathological examination, Mycobacterial and fungal culture.

PATHOLOGY:
Maxillary sinus mass: Grossly there were fragments of grey white to dark brown soft tissue. The microscopy showed fragments of respiratory mucosa with subepithelial oedema and mild infiltrates of lymphocytes and plasma cells with occasional eosinophils (Fig 3). Separately lying fibrous tissue was present with perivascular onion skinning of collagen fibers (Fig 4). There was no allergic mucin.
There were no granulomas. Special stains for fungal microorganisms were negative. There was no evidence of malignancy. Immunohistochemistry showed IgG4 positive plasma cells, maximum of up to 10-15/hpf in foci (Fig 5). Ratio of IgG4+/IgG+ plasma cells was 5-10%.

Fig 3 respiratory mucosa with subepithelial oedema and mild infiltrates of lymphocytes and plasma cells with occasional eosinophilis

Fig 4 perivascular onion-skinning of collagen fibers shown by green arrow

Fig 5 Immunohistochemistry with arrow showing IgG4 positive plasma cells

Nasopharyngeal mass:
Grossly they were multiple dark brown soft tissue pieces. Microscopy showed fibro-collagenous tissue covered by pseudo stratified ciliated columnar epithelium with dense infiltrates of lymphocytes, few histiocytes and plasma cells with lymphoid follicle formation. There was no evidence of malignancy. This was suggestive of reactive lymphoid hyperplasia.
The fungal and Mycobacterial cultures were negative. The serum IgG4 levels were elevated.

CLINICAL COURSE:
Based on the clinical features, CT scan findings of an infiltrative mass, and the histopathological findings and elevated IgG4 levels a diagnosis of IgG4 related disease was made. He was started on deflazacort at a dose of 1.2 mg/Kg (equivalent to prednisolone 1 mg/Kg). At review after two weeks he reported 30% improvement in pain. The IgG4 levels also dropped significantly as shown in table.
At this visit Mycophenolate mofetil was started at 500mg twice daily for a week and increased to 1000 mg twice daily and continued. At the next follow up, 6 weeks after start of steroids he reported a 60% reduction in facial pain. At the end of 6 weeks, the deflazacort were tapered at a frequency of 6mg every 2 weeks. At the subsequent visit after 3 months he reported to be totally pain free. Due to changes in his financial status he expressed inability to continue Mycophenolate mofetil, and hence he was started on Azathioprine in lieu of Mycophenolate mofetil. The Azathioprine is being given at a dose of 2 mg/Kg. During these visits the orbital fullness and the swelling over the left maxilla persisted, but became non tender. On review 5 months after the start of treatment he remained pain free, and reported improvement in mouth opening. Objectively he has 2 finger mouth opening. The IgG4 levels came to within the normal range as shown in Table 1. The repeat CT scan showed reduction in contrast enhancement and size of intracranial, maxillary and intraorbital disease as shown in Fig. 6 and 7, which corresponds to Fig 1 and 2 respectively.

**Fig. 6 CT image corresponding to fig. 1 after treatment showing reduction in size of the lesion**

**Fig 7 CT image corresponding to fig. 2 after treatment showing reduction in size and contrast enhancement**

**Table 1**

**DISCUSSION:**

IgG4-related disease is a condition where there is inflammation and fibrosis characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis and elevated serum IgG4 concentrations many a times(8). A significant proportion of these patients have normal IgG4 levels(9). A good response to glucocorticoids is typical, as seen in our patient who had 30% improvement in pain after two weeks of steroids. The etiopathogenesis of IgG4 related disease is poorly understood. There are pointers towards an allergic or autoimmune disorder (10–12). Other diseases in which IgG4 levels could be increased include Castleman’s disease, allergic diseases, Churg strauss syndrome and Sarcoidosis among others.
The disease can involve one or multiple organs. Patients generally do not have any constitutional symptoms. The organ system involvement which have been described include autoimmune pancreatitis, IgG4 related sclerosing cholangitis, salivary or lacrimal gland tumors, retroperitoneal fibrosis, aortitis, periaortitis, Reidel’s thyroiditis, fibrous variant of Hashimoto’s thyroiditis, lung and pleural disease, tubulointerstitial nephritis, skin, liver, breast, pituitary, meningeal, prostate or pericardium. The optimum treatment of IgG4 RD has not been established. There are no randomized trials on treatment. The general approach has been to give high dose steroids. The second line agents which have been used include Azathioprine or Mycophenolate mofetil. Rituximab has also been tried(5–7). Sustained benefit may be observed in treated patients, but relapses are common after discontinuation of therapy.

REFERENCES:
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