

Isolated IgG4-related Disease of Sphenoid Sinus Manifesting as Blindness

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ABSTRACT

Introduction: IgG4 related disease is a rare entity which can affect almost all parts of the body. The available literature of this entity related to paranasal sinuses is very limited.

Presentation of case: We present a case of isolated sphenoid sinus affliction by IgG4 related sclerosing disease manifesting as blindness, which recovered fully with pulsed steroid therapy.

Discussion: We present this case in view of developing insights toward diagnosis and management of IgG4 related sclerosing disease in paranasal sinuses, specifically the sphenoid sinus.

Conclusion: IgG4 disease involving paranasal sinuses (PNS) is rare entity and is managed with pulse methylprednisolone and immunomodulator drugs. Considering the limit of understanding of etiopathogenesis of this disease, surgeon needs to keep this differential diagnosis in mind. It may present atypically like isolated sinus involvement and optic neuritis.

Keywords: IgG4-related disease, Sphenoid sinus, Optic neuritis.

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INTRODUCTION

IgG4-related sclerosing disease is a systemic disorder characterized by infiltration of various organs with IgG4-positive plasma cells and T-lymphocytes.¹ Pathogenesis of IgG4-related sclerosing disease has not been clearly established. It may represent a hyper-sensitive/allergic reaction or an autoimmune disease.² We report a rare case of IgG4-related disease in the sphenoid sinus. Isolated sphenoid sinus involvement leading to optic neuritis and manifesting as blindness has not been reported earlier in the literature.

CASE REPORT

A 31-year-old gentleman presented to our hospital with history of recurrent episodes of frontal headache, vomiting and fever for the past one and a half years. He was evaluated in his hometown 3 months before coming here and was found to have a mass in the sphenoid sinus on CT scan. He underwent an endoscopic sinus surgery, details of which were not known. There was no improvement in his

symptoms following the surgery. Two months after the surgery, he started developing progressive diminution of vision, first in the left eye followed by the right. On presentation, he had complete loss of vision bilaterally. There was no history of loss of consciousness, seizures, head trauma, abnormal movements, stiffness of limbs or bowel and bladder dysfunction. There was no history of sensory deficits or other cranial nerve involvement. There was no rash, alopecia, photosensitivity, joint pain or weight loss. There was no past history of any neuropsychiatric morbidity, substance abuse or long-term drug intake. He did not have any known medical illness.

On ENT examination, there was a deviated nasal septum to right with synechiae between the right middle turbinate and septum. Bilateral ethmoidectomy cavities were seen.

Ophthalmology examination revealed bilateral relative afferent papillary defect and only perception of light bilaterally and fundus showed blurring of the optic disk margin bilaterally.

On neurological examination, higher mental functions were normal. All cranial nerves except optic nerve were normal. Motor system, sensory system, reflexes and gait were normal. All other systems were normal. There was no cerebellar dysfunction and meningeal signs were absent. The CSF analysis was normal. His visual evoked potential study showed anterior pathway dysfunction. SSEP tibial study was normal. Vasculitis markers were negative. Auto immune work up was also found to be negative.

In view of the fundoscopy not showing any evidence of raised intracranial pressure and venous pulsations being well seen, clinical localization was made to the retrobulbar optic nerve. Other cranial nerves were normal on examination. Meningeal signs were absent. MRI scan revealed complete opacification of the sphenoid sinus which was isointense to gray matter on T2-weighted imaging and diffuse enhancement on T1-weighted images (Fig. 1). There was meningeal enhancement in the anterior cranial fossa and along the clivus. Minimal degree of enhancement was also noted on both sides along the optic nerve before the chiasm suggesting optic neuritis (Fig. 2). CT scan showed soft tissue mass in the sphenoid sinus causing erosion of its lateral wall (Fig. 3). He was posted under general anesthesia for an endoscopic exploration and biopsy from the sphenoid sinus. Intraoperatively, a friable mass was seen filling the

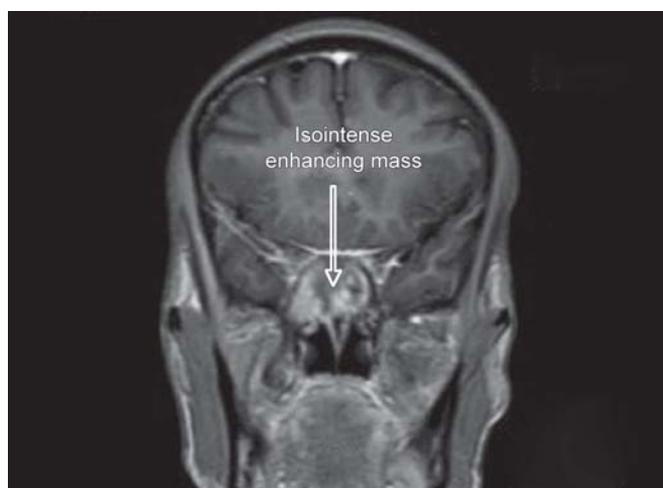


Fig. 1: MRI scan showing mass in sphenoid sinus, isointense to gray matter

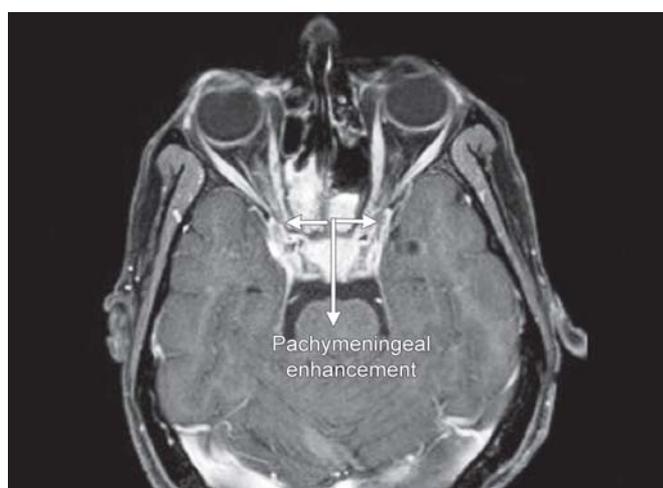


Fig. 2: MRI scan showing pachymeningeal enhancement along the optic nerve

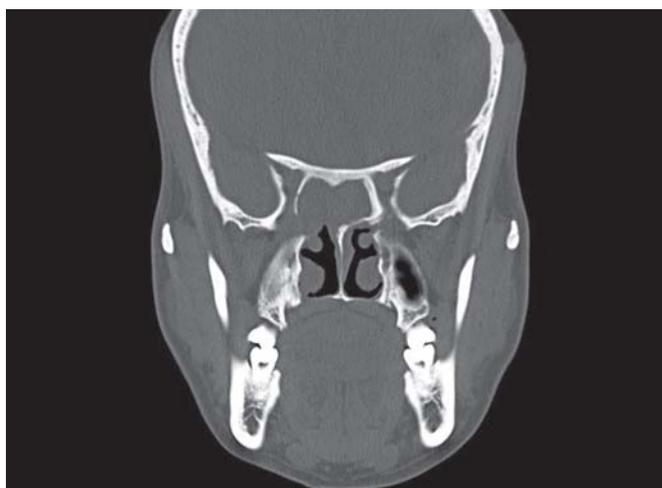


Fig. 3: CT scan showing soft tissue mass in sphenoid sinus eroding lateral wall

sphenoid sinus. Tissue was sent for histopathology, Xpert TB PCR and fungal culture.

Histopathology revealed a plasmacytic infiltrate (Fig. 4). Immunohistochemistry showed all plasma cells to be IgG

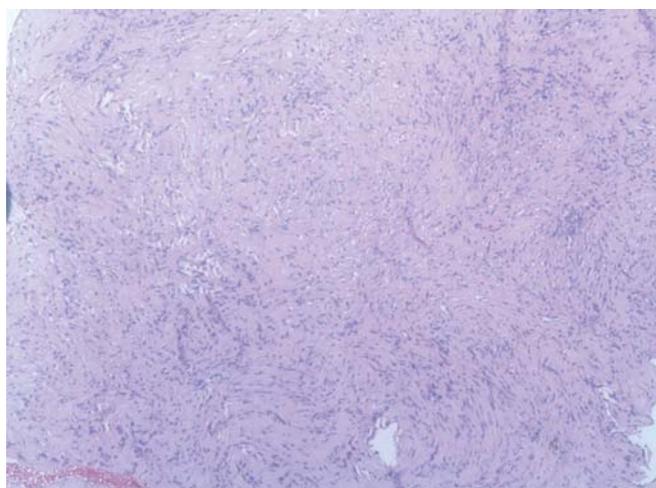


Fig. 4: Storiform fibrosis with scattered inflammatory cells on histopathological examination

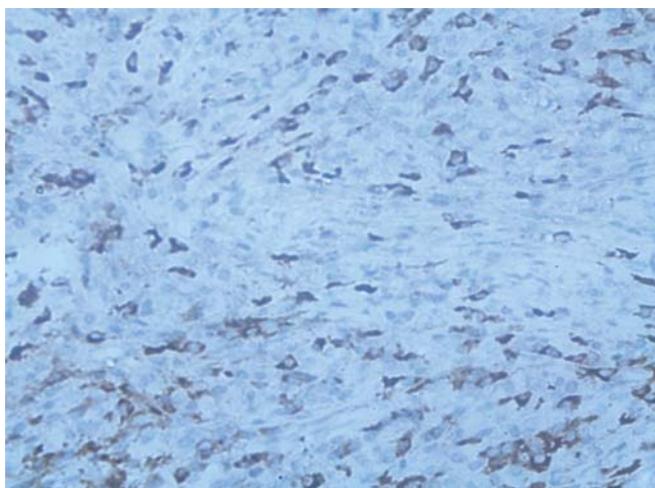


Fig. 5: $\times 40$, IgG4 positive plasma cells on immunohistochemistry

positive with IgG4 positive plasma cells being 20 to 30/high-power field (Fig. 5). Dense infiltrate of CD138 plasma cells were present with a mixture of kappa and lambda light chain-bearing cells. Cells were negative for CD56. Presence of fibrosis was also seen. The IgG4+/IgG plasma cell ratio was seen to be 35 to 40%. Xpert TB PCR and fungal cultures were negative.

He was started on 5 days of pulse methylprednisolone and monthly cyclophosphamide therapy. His vision improved to 6/6 bilaterally in 5 days and he was discharged on long-term oral glucocorticoid. Presently, he has completed 2 months of therapy and has normal vision bilaterally with no new complaints.

DISCUSSION

IgG4-related disease is a fibroinflammatory condition initially described in the pancreas. It is a novel clinical disease entity having a tendency to form tumefactive lesions at multiple sites, a dense lymphoplasmacytic infiltrate rich

in IgG4 and plasma cell and storiform fibrosis. This may not always have elevated serum IgG4 concentrations.³

The nomenclature of IgG4-related disease has continued to evolve. A group of Japanese investigators recently elected to use the term 'IgG4-related disease' for this condition, in preference to such potential alternatives as IgG4-related systemic disease, IgG4-related sclerosing disease, and IgG4-related multiorgan lymphoproliferative syndrome.⁴

The international symposium on IgG4-related disease held in Boston, Massachusetts in October 2011 put down the guidelines for organ-specific diagnostic criteria in IgG4-related disease. According to them, histology is the key component and there may be certain variability in the pathological findings across the organs.

The pathological sites involved in our case were sphenoid sinus, pachymeninges (radiology) and retrobulbar optic nerve (clinically and electrophysiologically). In view of the defect in the lateral wall of sphenoid sinus seen in CT scan and the previous history of surgery, a surgical mishap leading to blindness was considered but was ruled out as the loss of vision started many months after the surgery. There was no increased intracranial tension. Non-infectious granulomatous disease would have been the other most important cause with similar findings but the absence of granulomas went against that diagnosis.

The three major histopathological features associated with IgG4-related disease are (1) Dense lymphoplasmacytic infiltrate (2) Fibrosis, arranged at least focally in a storiform pattern (3) Obliterative phlebitis. Other histopathological features associated with IgG4-related disease are (1) Phlebitis without obliteration of the lumen (2) Increased numbers of eosinophils. However, in isolation, these latter two features are neither sensitive nor specific for the diagnosis of IgG4-related disease.³ The two features that are relatively inconsistent with the diagnosis of IgG4-related disease are the presence of epithelioid cell granulomas and a prominent neutrophilic infiltrate.

The histopathology in our case showed plasmacytic infiltrate with fibrosis and all plasma cells stained positive for IgG. IgG4 cells were 20 to 30/hpf. Also there were no features suggestive of granulomas.

Both histopathological features and immunohistochemical stains provide strong supportive evidence for the diagnosis of IgG4-related disease. In addition, careful correlation with the clinical scenario and imaging characteristics are necessary to arrive at a definitive diagnosis. Some researchers have suggested an IgG4+/IgG plasma cell ratio of 40% as a comprehensive cut off value in any organ.³ In our patient, the ratio was 35 to 40%.

The serum IgG4 concentration is often elevated in many patients dramatically, but serum concentrations of this

immunoglobulin are normal in up to 40% of patients with biopsy-proven IgG4-related disease.⁵

The consensus statement on the pathology of IgG4-related disease stated that in the absence of a more specific biomarker, in the appropriate clinical context, morphological features form the fundamental basis for the diagnosis. But the immunohistochemical stain for IgG4 has to be positive for diagnosis.³

In our patient, the auto immune markers like Rheumatoid factor, DS DNA, anti SSA, ANA, total complement, C3, C4, CRP, anti aquaporin 4 IIFT were all normal. c-ANCA and p-ANCA were also found to be within normal limits. Fungus culture and TB PCR test were negative. Moreover our patient had dramatic improvement on starting steroids.

A 3-tiered diagnostic terminology has been advocated for the pathological diagnosis of IgG4-related disease:³

(1) Histologically highly suggestive of IgG4-related disease (2) Probable histological features of IgG4-related disease (3) Insufficient histopathological evidence of IgG4-related disease.

In view of the expanding clinical spectrum and understanding, we can justify discussing our case as having probable histological features of IgG4 related disease.

Treatment of choice for IgG4-related sclerosing disease has been pulse therapy corticosteroids with other immunomodulator drugs like rituximab and cyclophosphamide.^{6,7} Although Steroid therapy is the primary treatment yet, it may fail in severe cases with irreversible sclerosis and fibrosis of orbital tissues.^{8,9}

A literature search revealed a report of IgG4 related perineural disease involving the optic nerve.¹⁰ There have also been 4 manuscripts in the literature of involvement of the paranasal sinuses with IgG4 related disease. This is the first report of isolated sphenoid sinus involvement leading to optic neuritis and ultimately manifesting as blindness.

CONCLUSION

IgG4-related disease remains a histopathological diagnosis in the appropriate clinical setting. The criteria for histopathologically definite IgG4 related disease are quite stringent. Considering the limited understanding of etiopathogenesis of this disease, the surgeon needs to keep this differential diagnosis in mind whenever dealing with atypical presentations of lesions in the paranasal sinuses.

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