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Case Report

Case Report of a Patient with IgG4-Related Disease in the Sinuses and Eye Orbit

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Abstract

IgG4-related disease is an inflammatory systemic disease characterized by IgG4-positive plasma cell infiltration, which rarely involves the paranasal sinuses or ocular orbits. The aim of this study is to report the case of a patient who was diagnosed as having IgG4-related disease in the paranasal sinuses and orbit, to review the literature on this topic, and to discuss the diagnosis and management of IgG4-related disease. When the patient visited the hospital, invasive fungal sinusitis was suspected after the initial evaluation and emergent endoscopic sinus surgery was performed. However, the final pathology results led to the diagnosis of IgG4-related disease. Steroid pulse therapy was given to the patient three times, but the patient's symptoms did not improve. Guidelines for diagnosis and management of IgG4-related diseases are still inadequate, and additional research will be necessary.

Keywords: Immunoglobulin G4-Related Disease

Introduction

Immunoglobulin G4 (IgG4)-related disease is a chronic inflammatory systemic disease caused by lymphocyte and IgG4-positive plasma cell tissue infiltration, accompanied by fibrosis and occasionally by increased numbers of circulating IgG4 [1, 2]. Early diagnosis of the disease is difficult as its progression is slow, and its symptoms are unspecific; some cases get discovered due to long-term swelling or functional deterioration from fibrosis, and others get found by chance during unrelated imaging tests [1]. IgG4-related disease started being recognized as a systemic disease during the 2000s [3]. In 2001, an association between autoimmune pancreatitis and an elevated serum IgG4 level was reported, and in the following year, IgG4-positive cells were detected infiltrating pancreatic tissues [4].

Additional reports of IgG4-positive cells infiltrating other organs have led to the recognition that the disease is systemic [3]. In 2011, a consensus on the nomenclature and histopathology associated with IgG4-related disease was reached at an international symposium, and guidelines have been published after subsequent symposiums [5]. Swollen salivary and lacrimal glands, lymphadenopathy, and type 1 autoimmune pancreatitis are common IgG4-related disease findings, but IgG4-related diseases have also been reported in the ocular orbits, posterior peritoneum, lungs, kidneys, aorta, bile duct, ears, sinuses, nasal cavity, thyroid gland, prostate, meninges, liver, skin, heart, interstitial membrane, and other organs [6].

In this paper, we report the case of a man with a lesion in the sinuses along the orbit in whom invasive fungal sinusitis was suspected initially, but who was diagnosed as having IgG4-related disease based on the pathology results after surgery. In a previous cohort study, IgG4-related disease has been reported in the orbits in 22% of the cases, and in the sinuses in 4% of the cases [6]. Few IgG4-related disease cases appearing in the orbit or sinuses exist, and the cases in which the disease occurred in both the orbit and sinuses are even scarcer [7]. Our case involves a man with IgG4-related disease in both the sinuses and orbit; we review the literature on the diagnosis of and treatment for IgG4-related disease in cases like this one.

Case Report

An 83-year-old man with a medical history of hypertension and diabetes mellitus visited the hospital due to visual acuity

impairment and pain in the left eye that had begun about a month before and which were accompanied by intermittent postnasal drip and sputum. During the physical examination done in cooperation with an ophthalmologist, he had left eye visual acuity impairment (HM, hand motion) and left relative afferent pupillary defect (Figure 1). A nasal endoscopy identified a suspicious polypoid change in the left nasal cavity without nasal secretion (Figure 2). A Computed Tomography (CT) scan result showed a mass of soft tissue with irregular margins involving the left pterygopalatine fossa, and the left sphenoid, ethmoid, and maxillary sinuses. In addition, swellings of the left optic nerve, and the left inferior and left medial rectus muscles were shown with bone destruction and sclerotic changes in the sinuses and orbit, suggesting left orbital infiltration (Figure 3).

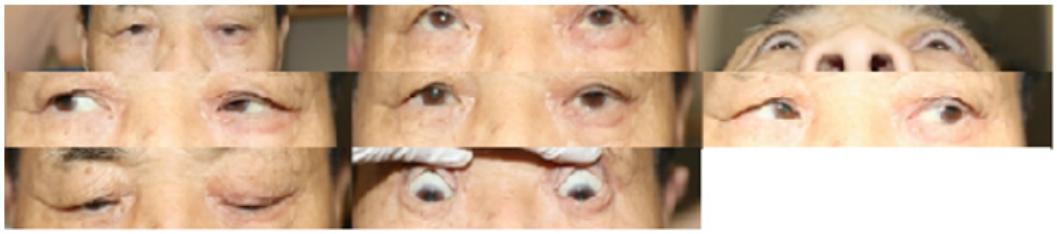

Figure 1: Photographs showing extraocular muscle examination results. Initially, the patient exhibited visual acuity impairment (hand motion) in the left eye and left relative afferent pupillary defect, but extraocular muscle gaze limitations were absent.

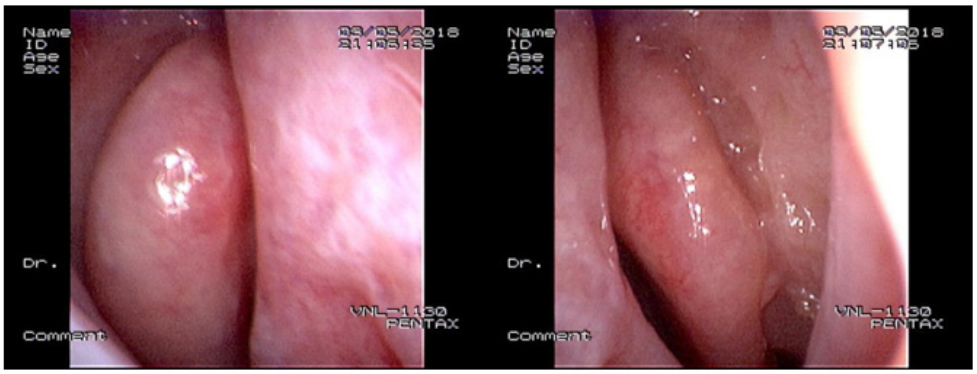

Figure 2: Nasal endoscopy images. **(A)** The right nasal cavity lacked specific findings. **(B)** The left nasal cavity had a polypoid change in the middle meatus.

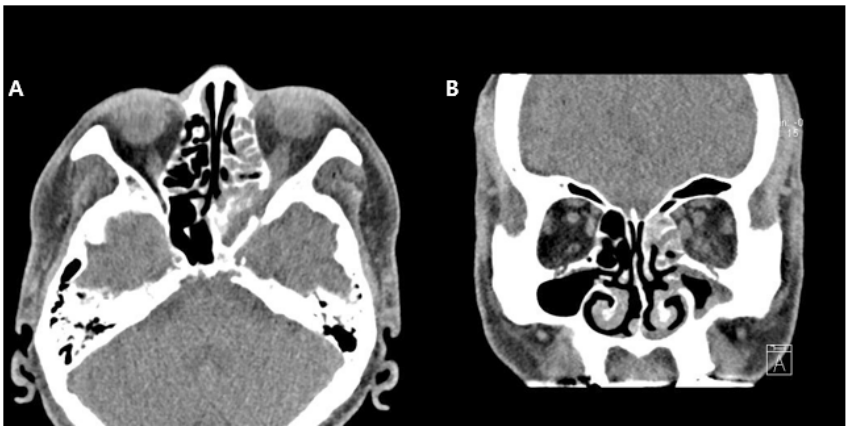

Figure 3: PNS Computed Tomography (CT) images. The initial CT images revealed an ill-defined soft tissue mass in the left pterygopalatine fossa and sphenoid sinus with bony destruction and sclerotic changes. The axial and coronal views show bony erosions and widening at the inferior and superior left orbital fissures and the left optic canal, and infiltrations at the left orbit with swellings of the left optic nerve, and inferior and medial rectus muscle in addition to diffuse mucosal thickening and enhancement of the left maxillary, ethmoid, and sphenoid sinuses.

A Magnetic Resonance Imaging (MRI) was ordered for a more precise examination of the degree of tissue infiltration and to differentiate a possible fungal sinusitis from a malignant tumor. In T2 imaging, we found a mass of low signal intensity involving the left pterygopalatine fossa, the left cavernous sinus, the left masticator space, and the left superior ophthalmic vein, with perineural enhancement of the left optic nerve. Also, the image showed thickening of the left extraocular muscles and diffuse mucosal thickening and enhancement of the left maxillary, ethmoid, and sphenoid sinuses with focal bony erosions on the left orbit (Figure 4). Thus, we performed an urgent operation on suspicion of invasive fungal sinusitis. The procedure included left middle meatal antrostomy, left frontoethmoidectomy, and left sphenoidotomy with the removal of surrounding granulation tissues.

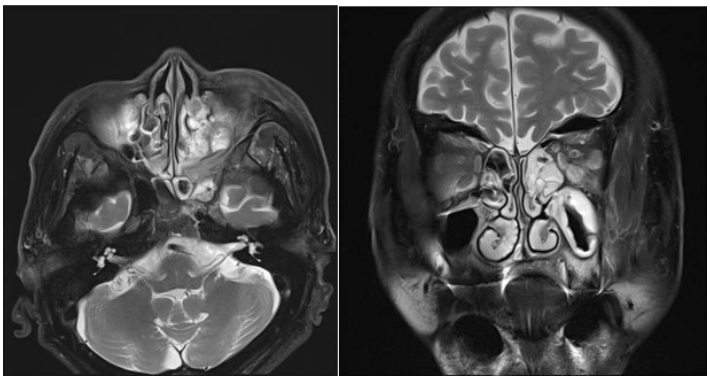

Figure 4: PNS Magnetic Resonance Imaging (MRIs). Initial MRIs showed an ill-defined T2 low SI mass in the pterygopalatine fossa with enhancement and bone destruction, extending to the left cavernous sinus, orbit, and masticator spaces with mild engorgement of the left superior ophthalmic vein. Diffuse perineural enhancement of the left optic nerve and thickening of the extraocular muscles are also shown. The images also reveal diffuse mucosal thickening and enhancement of the left maxillary, ethmoid, and sphenoid sinuses with focal bony erosion of the left orbit.

We ordered a frozen section examination of the granulation tissue of the posterior ethmoid cells but found no fungus or malignancy, and only inflammation was reported. We found a 2 × 3 cm defect in the medial wall of the left orbit with protruding tissue, but otherwise, the orbital wall was intact. The left orbital pain, visual impairment, and left relative afferent pupillary defect persisted after the operation, suggesting the existence of optic neuritis. Therefore, we prescribed daily methylprednisolone (250 mg) for 4 days, and the left visual acuity improved to 20/200 [8]. During the steroid tapering period with oral prednisolone, the patient was discharged from the hospital at his request due to personal reasons. The pathology results of the permanent sections revealed no fungus, and only severe infiltration with plasma cells and mild fibrosis were detected.

Additional Immunohistochemistry (IHC) tests revealed IgG4-related plasma cells (≥10 cells per High Power Field (HPF) and an IgG4+/IgG+ plasma cell ratio ≥40%, leading to the diagnosis of IgG4-related disease (Figure 5) [9]. The patient received rhinologic and ophthalmologic treatments from a hospital near his residence after discharge from our hospital. He was readmitted to our hospital because of aggravation of swelling in the left eye, visual acuity impairment, and headache. He was readmitted to our hospital 2 weeks after the discharge date because of aggravation of swelling in the left eye, visual acuity impairment, and headache. The physical examination for left visual acuity revealed the absence of even light perception. Moreover, we found gaze limitations in all directions for the left eye and left eye palpebral ptosis (Figure 6).

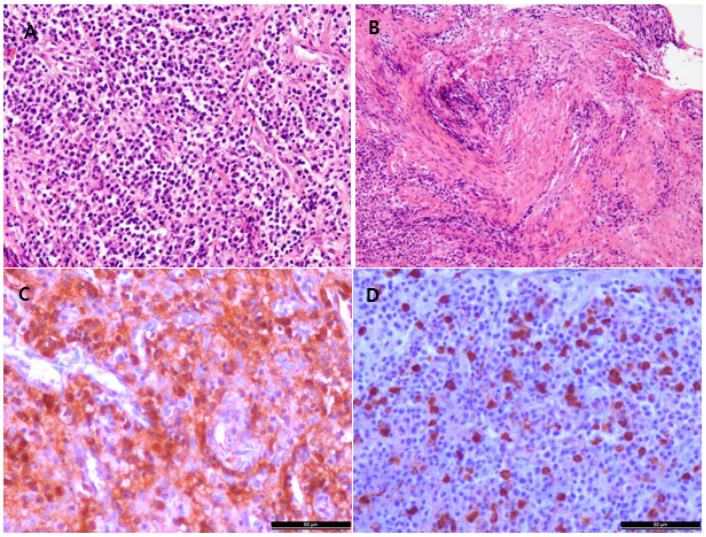

Figure 5: Microscopic pathology results of biopsy of sinus tissues from the patient. **(A)** Dense infiltration by inflammatory cells, which consist of lymphocytes and plasma cells. (H&E x200) **(B)** Fibrosis with IgG4-related disease-typical whirly pattern (storiform fibrosis). (H&E x400). **(C)** Immunostaining for IgG plasma cells (x400). **(D)** Immunostaining for IgG4 plasma cell (x400). Presence of >10 IgG4-positive cells per high power field and an IgG4+/IgG+ plasma cell ratio > 40% suggesting IgG4-related disease.

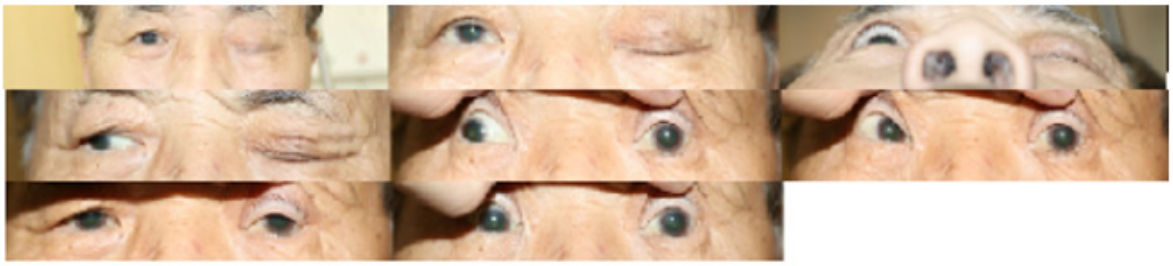

Figure 6: Photographs showing extraocular muscle examination results after the operation. The left eye had visual acuity aggravation (no light perception) and extraocular muscle gaze limitations in all directions (grade IV) with palpebral ptosis.

The blood tests for examination of IgG4-related disease revealed serum IgG and IgG4 levels of 1133 mg/dL and 85.7 mg/dL, respectively. A new MRI revealed a smaller mass in the left pterygopalatine fossa, cavernous sinus, masticator space, and superior ophthalmic vein than the previous MRI had shown, but diffuse perineural enhancement was apparent in the left optic nerve. The thickening of the left extraocular muscles, and the mucosal thickening of the left maxillary, sphenoid, and ethmoid sinuses observed were similar to the previous MRI findings (Figure 7). According to the comprehensive diagnostic criteria of IgG4-related disease, our patient could not be diagnosed as having definite IgG4-related disease due to the serum level of IgG4 being lower than 135 mg/dL [10]. However, the histopathological and clinical findings satisfy the criteria, so the patient was diagnosed as having a probable IgG4-related disease [10].

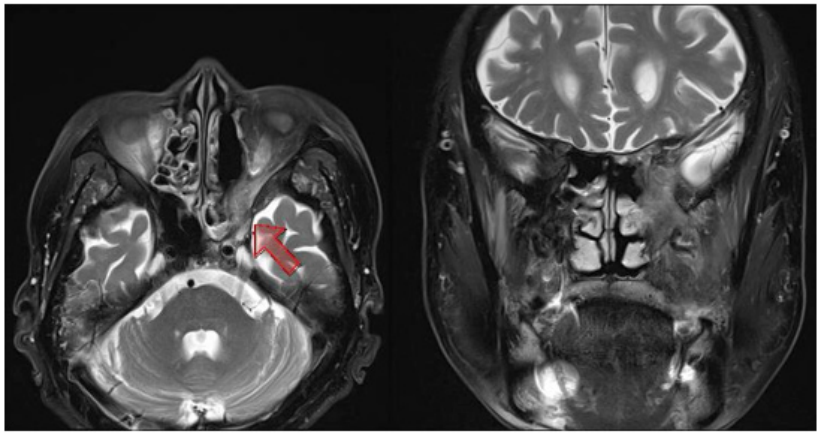

Figure 7: PNS Magnetic Resonance Images (MRIs) after the operation for comparison with pre-operative MRIs. The postoperative images showed a slightly smaller ill-defined mass in the pterygopalatine fossa (red arrow) compared with the pre-operative mass, but still extending to the left cavernous sinus, left orbit apex, left masticator space, and suspicious of middle cranial fossa via foramen rotundum and vidian canal. Diffuse perineural enhancement of the left optic nerve was again noted, suggesting optic neuritis. The left extraocular muscles seemed smaller but still thick with enhancement.

It is possible that the patient initially had a higher serum IgG4 level, which decreased with the steroid treatment because the hematological study was done after the steroid treatment. We prescribed steroid pulse therapy with a higher dose than the previous therapy. The patient received IV methylprednisolone (500 mg/day for 3 days), but he experienced no symptomatic changes. We decided to prescribe additional therapy with IV methylprednisolone (1 mg/day for 3 days), but the treatment was ineffective, and we tapered the corticosteroid with PO prednisolone for 17 days. We also tried a stellate ganglion block and other conservative measures, but the headache, left otalgia, visual loss, and extraocular muscle movement limitations persisted. In addition, we considered trying an immunomodulator or rituximab known as another treatment for IgG4-related disease, but due to the patient's personal circumstances he was discharged from the hospital without further treatment [1].

Discussion

Patients suspected of having IgG4-related disease require examinations to rule out other diseases like malignant tumors and inflammatory and infectious diseases [1]. In our case, in the initial imaging study of the patient, mass in paranasal sinuses with surrounding tissue infiltration was observed, and we first suspected the possibility of invasive fungal sinusitis. In addition, we determined that it is necessary to rule out the possibility of an inflammatory disease, such as granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and sarcoidosis, or proliferative lesion like lymphoma and other types of malignant solitary tumor [1]. Blood tests for serum IgG4, IgG, IgE, and CBC aid the diagnosis when IgG4 is above 135 mg/dL [1]. However, the serum IgG4 level may be elevated in other diseases such as malignant tumors, allergic or autoimmune diseases, and this characteristic is not limited to IgG4-related disease [11, 12].

Even in patients with normal display levels, the possibility of IgG4-related disease should not be ruled out, considering the sensitivity of the serum IgG4 level, as in the previous study about 10% of patients diagnosed with either probable or definite IgG4-related disease showed normal serum IgG4 levels [11]. The comprehensive diagnosis criteria for IgG4-related disease include: (1) swelling or lump that may cause long-term infiltration, (2) serum IgG4 >135 mg/dL, and (3) histopathology showing (i) infiltration with lymphocytes and plasma cells with fibrosis and (ii) more than 10 IgG4-positive cells at high resolution. A definite IgG4-related disease diagnosis is declared if the IgG4/IgG ratio is larger than 0.4 and if criteria (1), (2), and (3) are all satisfied. A probable IgG4-related disease diagnosis involves meeting criteria (1) and (3), and a possible IgG4-related disease diagnosis involves meeting criteria (1) and (2) [13].

The histopathologic diagnosis unique to IgG4-related disease comprises lymphoplasmacytic cellular infiltration, spiral fibrosis, and obliterating phlebitis, but the features may vary depending on the organs infiltrated. For instance, spiral fibrosis or obliterating phlebitis are rarely found in the salivary glands or lymph nodes, and obliterating phlebitis is rare in orbital disease [9, 13-15]. In terms of the immunohistochemistry, 10 or more IgG4-positive plasma cells per HPF (x400) and an IgG4/IgG ratio $\geq$ 0.4 are common findings [9, 13-15]. Additionally, 18F-FDG PET-CT can be helpful for the diagnosis and to decide whether to perform a biopsy [16]. IgG4-related disease is a newly recognized disease, lacking enough reported cases to ensure the reliability of its diagnostic criteria, and as mentioned, only a few cases with sinus and orbit infiltrations exist. Despite the general agreement on the diagnostic criteria for IgG4-related disease, an international consensus is still needed [10].

Also, the current comprehensive criteria require biopsies that cannot always be performed depending on the organs being infiltrated [10]. In our patient, the diagnostic criteria for IgG4-related ophthalmic disease were met for imaging studies (enlargement of ophthalmic tissue) and for histopathological findings (ratio of IgG4+ cells to IgG+ cells of 40% or above, or more than 50 IgG4+ cells per HPF), suggesting a "probable" IgG4-related ophthalmic disease [10, 17]. However, the lack of unified criteria for IgG4-related disease infiltrating the sinuses demands that criteria be varied in consideration of the organs infiltrated. Among the current criteria such as organ infiltration and serum IgG4 and biopsy, the last one is the most crucial criterion, and probable IgG4-related disease cannot be diagnosed without biopsy; therefore, when the disease infiltrates organs that are not amenable to biopsy, an accurate diagnosis and provision of available treatments are highly difficult [10].

Suspecting IgG4-related disease during its initial stages is difficult, and a better diagnostic algorithm is required to decide whether to implement examinations during the early stages. An established criterion for IgG4-related treatment is also lacking. In general, after an initial dosage of methylprednisolone (0.5-0.6 mg/kg/day) or prednisone (30-40 mg/day) for 2-4 weeks, the doses are decreased by 5-10 mg for 1-2 weeks, and once they reach doses as low as 2.5-5 mg/day, treatment is maintained for 6 months to 3 years [14, 18, 19]. However, steroid is not always effective, and specific treatment methodologies depending on the infiltrated organs have not been established. Steroid-sparing approach such as using immunosuppressants or B cell depletion is also known to have improved the IgG4-related disease in some cases, but the consensus on dosage, dosing period, and combination therapy of these methods are still lacking and further research for establishing detailed treatment methods are necessary [1, 18].

Addition, whether sinonasal ventilation or optic nerve decompression through surgical treatments as well as medical treatments would be helpful in IgG4-related sinonasal or ophthalmic disease is unknown. If surgery is done for a patient with suspected IgG4-related sinonasal disease, it should be clarified whether removal of a minimal amount of lesion for biopsy is enough or removal of all the lesion of the sinus should be done. In all, we presented the case of a patient with IgG4-related disease that did not improve even after surgery and steroid therapies and highlighted the need for studies to develop evidence-based guidelines for diagnosis and treatment.

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