

A Case of IgG4-related Orbitopathy

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Abstract

IgG4-related disease is an immune-mediated disorder affecting almost all major organs of the body. A 62-year-old male, who was diagnosed with an orbital tumor and a nasal-orbital communicating tumor of the left eye, underwent endoscopic endonasal removal of the orbital tumor and fenestration of the ethmoid sinus. The tumor originated in the orbital tissue and showed pathological changes associated with IgG4-positive chronic inflammation. He was diagnosed with IgG4-related orbital disease. At 4 months of follow-up after surgery, there was no recurrence.

Keywords: IgG4-related disease; Orbital disease; IgG4-positive

Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated disorder, characterized by infiltration with IgG4-positive plasma cells [1] that affects almost all major organs of the body. IgG4-related orbital disease (IgG4-ROD) involves elevated serum levels of IgG4 and infiltrated IgG4-positive plasma cells in the ocular adnexa [2,3]. Because IgG4-ROD has recently emerged as a disorder with a challenging diagnosis, this case report is presented to improve awareness of it.

Case Report

A 62-year-old male presented on May 23, 2016, with swelling of the left eye for the previous 1 year. The swelling had been progressively aggravated without treatment. The patient also presented with mild left-sided proptosis without red eye, pain, blurring, or diplopia, and there was no rhinorrhea, bleeding, or fever. His history of past illness included high blood pressure and diabetes mellitus for 5 years, coronary heart disease for 1 year, and abnormal liver functioning for 1 year (with medical treatment).

The ophthalmic examination concluded that vision in both eyes was 1.0 and intraocular pressures (IOP) were 15 mmHg (right eye) and 16 mmHg (left eye). There was mild swelling around the orbit, with no obvious mass, and the orbital pressure was T+1. The left eyeball was displaced towards the laterosuperior, and the proptosis of the left eye was 2 mm more than the right eye. Eye movement towards the medial inferior was limited. The examination of the anterior and posterior segments was normal. A computed tomography (CT) scan showed a homogeneous mass in the medial inferior of the left orbital, 32 mm × 17 mm, with the approximate shape of an ellipse. Its border was unclear, and it adhered to the medial rectus and inferior rectus. There was a homogeneous mass in the left ethmoid sinus, and the inferior rectus was enlarged (Figure 1A and B). A pulmonary CT scan showed double emphysema, a patchy shadow in the left lung (considered inflammation). Biochemical tests showed a bilirubin level of 21.10 μm a direct bilirubin level of 4.40 μm and a blood glucose level of 7.01 mM. The level of c-reactive protein was normal. A thyroid function test showed that thyroid-stimulating hormone, free thyroxine, and anti-thyroglobulin antibody were normal. The patient underwent

endoscopic endonasal removal of the orbital tumor and fenestration of the ethmoid sinus. The tumor originated in the orbital tissue, involving the oppression of the ethmoid sinus. It was purple-red and soft, with a capsule that adhered tightly to the medial rectus and surrounding tissues. It was 33 mm × 15 mm × 10 mm (Figure 2).

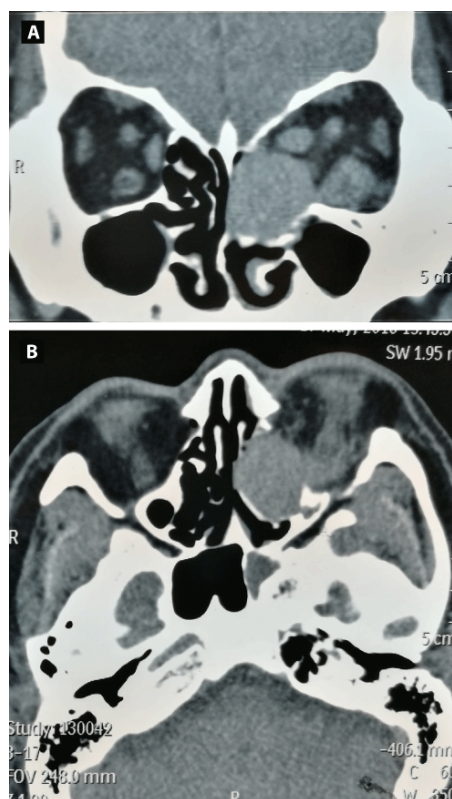


Figure 1: Computed tomography (CT) scanning. Coronal (A) and axial (B) CT scanning showed a tumor with ill-defined margins, close to oval in shape, located interiorly in the left orbit and intruding into the left ethmoidal cells. The inferior rectus muscle was enlarged.

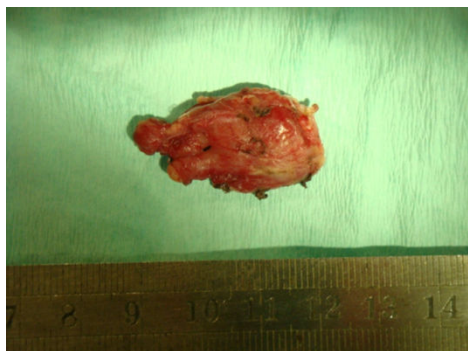


Figure 2: The appearance of the tumor. It was nearly elliptical, dark red, with an approximate size of 33 mm × 15 mm × 10 mm.

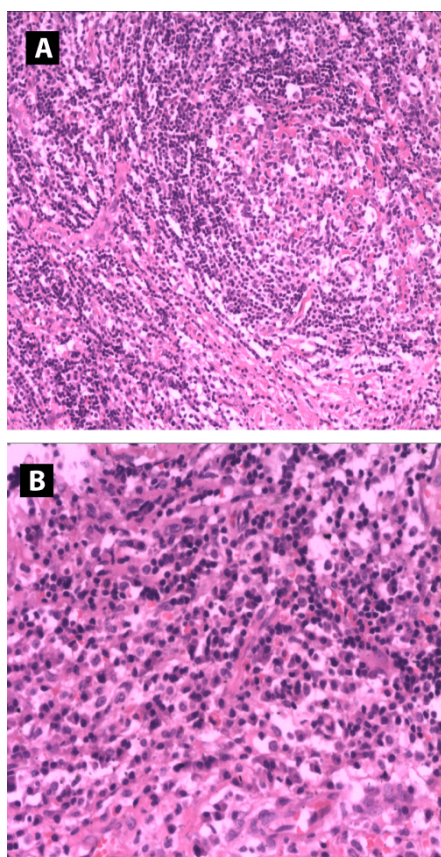


Figure 3: Light microscopy of the tumor stained with hematoxylin and eosin (H&E). (A) Low power magnification (×100) showing inflammatory cell infiltration and hyperplasia of fibrous tissue. A lymph node follicle is also seen. (B) H&E staining showing that the inflammatory cells include abundant plasma cells, lymphocytes, and eosinophilic granulocytes.

The pathological specimens showed chronic inflammation of connective tissue, increased fibrous tissue, and small blood vessel hyperplasia infiltrated with lymphocytes, plasma cells, and eosinophil's, with visible lymphoid follicles (Figures 2, 3A and 3B).

Immunohistochemical examination was positive for IgG, with >40% cells positive for IgG4/IgG, and 50–60/HPF (high power field) for IgG4-positive cells (Figure 4A and B). The patient was diagnosed with IgG4-ROD. In this case, orbital soft tissue and extra ocular muscles have been involved. Histological pattern show IgG4-related orbital inflammation and orbital myositis. Visual acuity and IOP were normal after surgery. Corticosteroids (40 mg) were administered orally every morning, with a 10 mg reduction every 2 weeks, tapering to 3 months of continuous treatment using 5 mg. At the regular follow-up at 4 months, there was no tumour recurrence and no other autoimmune disorder related to the original one.

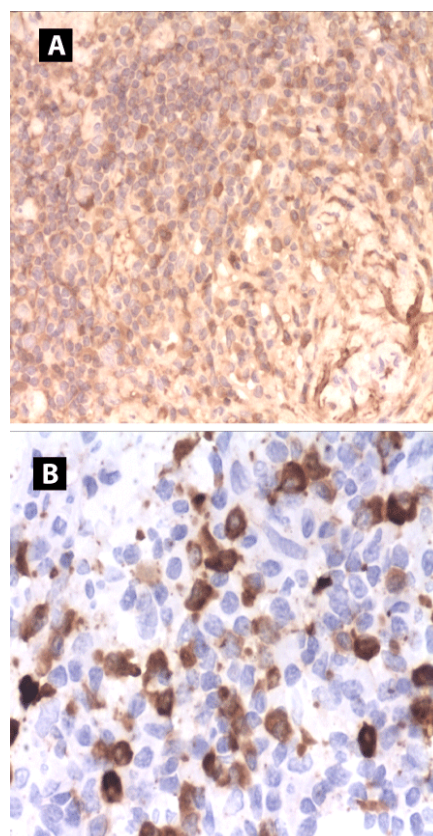


Figure 4: Immunohistochemical staining of tissues. (A) Immunohistochemistry staining showing a high proportion of plasma cells (brown color) that were positive for IgG (×200). (B) Abundant IgG4-positive plasma cells (brown color) are shown (×400).

Discussion

The etiology and epidemiology of IgG4-RD are unknown. IgG4-RD often occurs in elderly males. It has been estimated that the incidence of this disorder in Japan is 0.28–1.08/100,000 [4,5]. IgG4-RD can affect almost all major organs of the body. The most common site is the **pancreas**, followed by the parotid, bile duct, liver, lung, and lymph nodes [4–6]. The orbital tissue is also often involved, with a prevalence of 3.6–12.5% [1,7–10]. The current diagnostic criteria of IgG4-RD include [11]: single or multiple organ swelling, either symmetrically or locally, with the formation of a mass; serum IgG4>1.35 g/L; and

pathological results involving lymphocyte and IgG4⁺ plasma cell infiltration, with typical tissue fibrosis, IgG4⁺ cells/IgG⁺ cells >40% in a biopsy, and IgG4⁺ cells >10/HPF. However, approximately 60–70% of patients have elevated serum levels of IgG4 [12], so IgG4-RD cannot be completely excluded using this parameter [13]. Recent studies have shown that the serum IgG4⁺/IgG⁺ ratio may be more sensitive and specific in the diagnosis of early and single organ-limited development of IgG4-RD [14–16]. IgG4-ROD has been increasingly diagnosed on the basis of clinical manifestations, imaging, blood tests, and histopathological examinations [17,18]. The diagnostic criteria for IgG4-ROD not yet firmly. The Japanese study group on IgG4-ROD advocates a ratio of IgG4⁺/IgG⁺ cells 40% and the number of IgG4⁺ cells 50 cells/HPF [19]. Typical histologic findings, such as storiform-type fibrosis and obliterative phlebitis may be absent in lacrimal gland involvement [20].

IgG4-ROD can occur at any age, and there is no significant difference in prevalence between males and females [21]. Patients often show unilateral or bilateral long-term, painless orbital swelling and proptosis, and impairment of visual acuity is not obvious. The conjunctiva is generally not involved, although the mass is accompanied by peripheral lymphadenopathy [22–24]. A primary tumor with an irregular boundary can be found using imaging. PET/CT can highlight multifocal disease to detect involvement of distant organs [25]. In contrast to the surrounding normal tissue, IgG4-ROD involves the orbit, lacrimal gland, extra ocular muscles, retrobulbar soft tissue, suborbital nerve, optic nerve, the sclera, uvea [26], and even the cavernous sinus and intracranial areas, with impairment of lacrimal glands being the most common symptom [27]. The pathological features of IgG4-ROD involve lymphocytes and plasma cells infiltrated to different levels, sclerosis, and formation of reactive lymphoid follicles. Eosinophils are sometimes involved, with IgG4-positive plasma cells [22–24,28].

Differential diagnosis involves a mucosa-associated lymphoid tissue (MALT) lymphoma. One type of extranodal marginal zone B-cell lymphoma, which is the most common type, occurs in the conjunctiva, lacrimal gland, orbit, eyelids, and other parts of the eye. Although there are no specific clinical manifestations, there is eyelid swelling, ptosis and conjunctival edema, and a painless mass can usually be touched. If the conjunctiva is involved, “salmon meat-like” changes are visible [29]. Unlike an orbital MALT lymphoma, the pathological examination lacks lymphoid epithelium lesions, lymphoid cells such as monocyte-like B cells, diffuse CD20-positive B cells, restriction of light chains, an abnormal immunophenotype, and clonal immunoglobulin gene rearrangement [30]. An inflammatory pseudotumor involves moderate amounts of lymphocyte and plasma cell infiltration, with significant spindle cells (myofibroblasts and spindle cells), without phlebitis, immunohistochemical staining of spindle cells that are actin positive or CD68 positive, and no increase in the number of IgG4-positive plasma cells [31]. Sjogren's syndrome involves an **autoimmune disease**, characterized by keratoconjunctivitis sicca, dry mouth, and intermittent swelling of the salivary or lacrimal glands, more common in elderly females. Treatment with steroids is unsatisfactory. The anti-SS-A and anti-SS-B levels are positive, and the serum level of IgG4 is normal [32,33].

IgG4-ROD is a disorder discovered in recent years, so there is a general lack of clinical experience. Furthermore, there is presently no consistent treatment option, although corticosteroids have been used as a first-line treatment. A retrospective analysis of the SMART IgG4-RD database in Japan showed that 122 patients with IgG4-RD

dacryoadenitis and/or sialadenitis were effectively treated with corticosteroids. In addition, rituximab is another important option, which has been shown to be effective for controlling steroid-refractory IgG4-ROD; **radiation therapy** may also be of use.

The present case affected the monocular orbit. The histopathological specimens showed chronic inflammation of connective tissue, with increased fibrous tissue, small blood vessel hyperplasia, and infiltration of lymphocytes that were all consistent with a diagnosis of IgG4-ROD. The immunohistochemical examination showed that the IgG4⁺ cells were 40–60/HPF and the IgG4⁺ cells/IgG⁺ cells were >40% positive, in accordance with the diagnostic criteria of IgG4-ROD. The patient's orbital muscles and adipose tissue were impaired, although no lacrimal glands were involved, and no dry eye or other symptoms were observed. Endoscopic endonasal removal of the orbital tumor was performed, together with glucocorticoid therapy, with significant positive effects with minimal **trauma**. This protocol directly removed the local lesions, and effectively relieved tissue compression. This treatment protocol was consistent with the protocol of Lora. There was no tumor recurrence and no other systemic symptom was found during the 4-month follow-up. The possible involvement of an orbital IgG4-related disease was considered. Four weeks after surgery, the serum level of IgG4 was 1.29 g/L. However, it is impossible to completely exclude the possibility of the involvement of other organs. Even if the IgG4-related disorder affected the orbit, it is impossible to eliminate the possibility of other organ involvement. At least a 6-month follow-up is necessary to eliminate recurrence, and IgG4-related disorders should also be considered.

References

- Andrew N, Kearney D, Selva D (2013) IgG4-related orbital disease: a meta-analysis and review. *Acta Ophthalmol* 91: 694-700.
- Berry-Brincat A, Rose GE (2012) Idiopathic orbital inflammation: a new dimension with the discovery of immunoglobulin G4-related disease. *Curr Opin Ophthalmol* 23: 415-419.
- Takahira M, Kawano M, Zen Y, Minato H, Yamada K, et al. (2007) IgG4-Related Chronic Sclerosing Dacryoadenitis. *Arch Ophthalmol* 125: 1575-1578.
- Kamisawa T, Okamoto A (2008) IgG4-related sclerosing disease. *World J Gastroenterol* 14: 3948-3955.
- Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, et al. (2012) A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol* 22: 1-14.
- Carruthers MN, Stone JH, Khosroshahi A (2012) The latest on IgG4-RD: a rapidly emerging disease. *Curr Opin Rheumatol* 24: 60-69.
- Hamano H, Arakura N, Muraki T, Ozaki Y, Kiyosawa K, Kawa S (2006) Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. *J Gastroenterol* 41: 1197-1205.
- Takuma K, Kamisawa T, Anjiki H, Egawa N, Igarashi Y (2010) Metachronous extrapancreatic lesions in autoimmune pancreatitis. *Intern Med* 49: 529-533.
- Ebbo M, Daniel L, Pavic M, Sève P, Hamidou M, et al. (2012) IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. *Medicine (Baltimore)* 91: 49-56.
- Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, et al. (2012) Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 22: 21-30.
- McNab AA, McKelvie P (2015) IgG4-related ophthalmic disease. Part I: background and pathology. *Ophthalmol Plast Reconstr Surg* 31: 83-88.
- Kamisawa T, Zen Y, Pillai S, Stone H (2014) IgG4-related disease. *Lancet* 6736: 1-12.

13. Masaki Y, Kurose N, Yamamoto M, Takahashi H, Saeki T, et al. (2012) Cutoff Values of Serum IgG4 and Histopathological IgG4+ Plasma Cells for Diagnosis of Patients with IgG4-Related Disease. *Int J Rheumatol* 2012: 580814.
14. Krzysztof O, Joanna L, Emilia B, Krzysztof B, Joanna M, et al. (2015) Immunoglobulin G4-related disease (IgG4-RD) in the orbit:mucosa-associated lymphoid tissue(MALT)-type lymphomas. *Med Sci Monit* 10: 1043-1050.
15. Oles K, Szczepanski W, Skladzien J, Okon K, Leszczynska J, et al. (2015) IgG4-related inflammatory orbital pseudotumors - a retrospective case series. *Folia Neuropathol* 53: 111-120.
16. Yamamoto M, Hashimoto M, Takahashi H, Shinomura Y (2014) IgG4 disease. *J Neuroophthalmol* 34: 393-399.
17. Goto H, Takahira M, Azumi A. Japanese Study Group for IgG4-Related Ophthalmic Disease (2015) Diagnostic criteria for IgG4-related ophthalmic disease. *Jpn J Ophthalmol* 59: 1-7.
18. Satoshi K (2014) IgG4-Related Disease: A Neuro-Ophthalmological Perspective. *J Neuroophthalmol* 34: 400-407.
19. Andrew N, Kearney D, Selva D (2013) IgG4-related orbital disease: a meta-analysis and review. *Acta Ophthalmol* 91: 694-700.
20. Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, et al. (2008) Ocular adnexal IgG4-related disease has uniform clinicopathology. *Pathol Int* 58: 465-470.
21. Kubota T, Moritani S, Katayama M, Terasaki H (2010) Ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder. *Arch Ophthalmol* 128: 577-584.
22. Plaza JA, Garrity JA, Dogan A, Ananthamurthy A, Witzig TE, et al. (2011) Orbital inflammation with IgG4-positive plasma cells:manifestation of IgG4 systemic disease. *Arch Ophthalmol* 129: 421-428.
23. Nguyen VX, De Petris G, Nguyen BD (2011) Usefulness of PET/CT imaging in systemic IgG4-related sclerosing disease. A report of three cases. *JOP* 12: 297-305.
24. Richard A Prayson (2015) Immunoglobulin G4-related ophthalmic disease presenting as uveitis. *J Clin Neurosci* 22:1848-1849.
25. Wallace ZS, Khosroshahi A, Jakobiec FA, Deshpande V, Hatton MP, et al. (2012) IgG4-related systemic disease as a cause of "idiopathic" orbital inflammation, Including orbital myositis, and trigeminal nerve involvement. *Surv Ophthalmol* 57: 26-33.
26. Sato Y, Notohara K, Kojima M, Takata K, Masaki Y, et al. (2010) IgG4-related disease: historical overview and pathology of hematological disorders. *Pathol Int* 60: 247-258.
27. Jie Y, Wei R (2010) Clinical Analysis of Diagnosis and Treatment of Ocular Adnexal Mucosa-associated Lymphoid Tissue Lymphoma. *Pro Modern Biomed* 10: 4298-4300.
28. Chen G, Cheuk W, Chan JK (2010) IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Chin J Pathol* 39: 851-868.
29. Yamamoto H, Yamaguchi H, Aishima S, Oda Y, Kohashi K, et al. (2009) Inflammatory myofibroblastic tumor versus IgG4-related sclerosing disease and inflammatory pseudotumor: a comparative clinicopathologic study. *Am J Surg Pathol* 33: 1330-1340.
30. Minato H, Watanabe K, Kurumaya H, Katayanagi K, Masuda S, et al. (2005) Abundant IgG4-positive Plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). *Am J Surg Pathol* 29: 783-791.
31. Ferry JA, Harris NL, Stone JH, Zukerberg LR, Lauwers GY, et al. (2010) Chronic sclerosing sialadenitis(Kuttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 34: 202-210.
32. Yajima H, Takahashi H, Yokoyama Y, Ishigami K, Shimizu Y, et al. (2015) Everyday clinical practice in IgG4-related dacryoadenitis and/or sialadenitis: results from the SMART database. *Mod Rheumatol* 25: 199-204.
33. Glass LR, Freitag SK (2015) Management of orbital IgG4-related disease. *Curr Opin Ophthalmol* 26: 491-497.