CASE REPORT

Orbital Manifestations of Immunoglobulin G4-Related Disease in Bilateral Lacrimal Glands, Optic Nerves, Trigeminal Nerves, and Maxillary Sinuses

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ABSTRACT

Immunoglobulin G4 (IgG4)-related disease is characterised by numerous aggregates of IgG4-positive plasma cells in multiple organs. We report two patients who had bilateral proptosis associated with extensive inflammation bilaterally in lacrimal glands, optic nerves, trigeminal nerves, and maxillary sinuses. The patients were treated as idiopathic orbital inflammation syndrome with corticosteroid pulse therapy. As symptoms relapsed upon tapering, a reassessment of immunohistochemical stains of the lacrimal glands confirmed the diagnosis of IgG4-related disease. During 2 years of follow-up, the inflammation regressed spontaneously without any medical treatment in the first patient; however, inflammation in the other patient progressed, and he lost his vision. The extensive orbital involvement, characteristic pathological findings, and slowly progressive clinical course might help practitioners differentiate orbital IgG4-related disease from presumed idiopathic orbital inflammation syndrome.

Keywords: Idiopathic orbital inflammatory syndrome, IgG4-related disease, Mikulicz disease

INTRODUCTION

The hallmark findings of the orbital immunoglobulin G4 (IgG4)-related disease (IgG4-RD) are lymphoplasmacytic infiltration, abundant IgG4-positive plasma cells, elevated serum IgG4 level, and bilateral involvement.¹ With increased awareness of IgG4-RD, the diagnosis is increasingly recognised in patients who were previously considered as cases of idiopathic orbital inflammation syndrome (IOIS).² We documented two orbital IgG4-RD patients, who were very similar in clinical, pathological, and serological manifestations. However, the outcomes were different after 2 years of follow-up.

CASE REPORTS

Case I

A 60-year-old male presented with bilateral proptosis that had progressed for 5 years. He had no history of diabetes or other systemic disease. His right parotid gland was resected 7 years previously and he was thought to have suffered from Sjögren syndrome (SS). His visual acuity was 20/40 (OU). Bilateral ptosis and limitation of eye movements were noticed. Visual field examinations showed bilateral constriction. Thyroid function, thyroid antibodies, antinuclear antibody (ANA), rheumatoid factor (RF),

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and anti-SS-A and anti-SS-B antibodies were normal. Magnetic resonance imaging showed bilateral perineural enhancement of optic nerves, enlargement of lacrimal glands, thickening of maxillary sinus mucosa, and bilateral hypertrophy of the trigeminal nerves in the cavernous sinus; in addition, the infraorbital and supraorbital branches in the orbit were enlarged (Figure 1a–d). The abdominal echo imaging revealed normal bile duct, pancreas, and kidney. However, a painless elastic mass was found near the right subclavicular muscle.

A lacrimal gland biopsy revealed lymphoplasmacytic inflammation (Figure 1e). Pulse intravenous steroid therapy with 1 g methylprednisolone daily for 3 days dramatically relieved his symptoms of ptosis, extra-ocular muscle (EOM) limitation, and visual field constriction, and the right cervical mass also subsided. However, the symptoms of EOM limitation recurred upon tapering of oral

prednisolone to 5 mg daily at the fourth week after initial treatment. We reassessed the immunohistochemistry and found a high ratio of IgG4- to IgG-positive plasma cells in the lacrimal gland (Figure 1f) and in previously resected parotid gland tissue. In addition, the serum IgG4 level was elevated to 912 mg/dL, and the serum level of IgG4 was 86.4% of the level of IgG. Therefore, orbital IgG4-RD was diagnosed. With discontinuation of the oral prednisolone due to intolerable upset stomach, the inflammation regressed completely 1 year after the initial treatment, and there was no evidence of recurrence during a further 12 months of follow-up.

Case 2

A 58-year-old male without known systemic disease had experienced painless progressive proptosis,

FIGURE 1 Orbital magnetic resonance image and histopathological photograph case 1. (a) Axial view showing bilateral prominent lacrimal glands (arrow). (b) Thickened maxillary sinus mucosa and hypertrophy of infraorbital nerves (arrow) were evident. (c) Coronal view showed bilateral perineural enhancement of optic nerves (white arrowhead in the insert), as well as prominent hypertrophy of supraorbital (grey arrow) and infraorbital nerves (white arrow). (d) Bilateral hypertrophy of the trigeminal nerves (arrow) in the cavernous sinus. (e) Biopsy specimen of lacrimal gland showed lymphoplasmacytic infiltration around preserved acinar structure (haematoxylin-eosin stain, original magnification $\times 200$). (f) Immunohistochemical stain of lacrimal gland using anti-IgG antibody (left half) and anti-IgG4 antibody (right half) showing the high ratio of IgG4-positive cells against IgG-positive cells.

FIGURE 2 External eye, histopathological photographs, and orbital magnetic resonance images of case 2. (a) Initial presentation. (b) Photograph of his last visit after no treatment for 11 months. (c) Coronal view showed remarkable hypertrophy of extraocular muscles. (d) Axial view showing bilateral prominent lacrimal gland. (e) Biopsy specimen of lacrimal gland showed lymphoplasmacytic infiltration. (haematoxylin-eosin stain, original magnification $\times 200$). (f) Immunohistochemical stain of lacrimal gland using anti-IgG antibody (left half) and anti-IgG4 antibody (right half) showing the ratio of IgG4-positive cells against IgG-positive cells was 40%.

ectropion for 3 years (Figure 2a). His visual acuity and visual field were difficult to evaluate due to severe ptosis and dry eye symptoms. There was a right exotropia and EOM limitation bilaterally. Laboratory examination revealed eosinophilia and an elevated serum IgG4 level of 2310 mg/dL (the serum level of IgG4 was 72% of the level of IgG). Magnetic resonance imaging in the brain showed hypertrophy of the lacrimal glands and extraocular muscles bilaterally (Figure 2c, d). There was no abnormal finding upon

echo imaging of the abdomen. A lacrimal gland biopsy (Figure 2e) showed an IgG4- to IgG-positive ratio of 40% (Figure 2f), confirming the diagnosis of IgG4-RD. Pulse therapy with 1 g methylprednisolone per day for 5 days only partially relieved his symptoms of EOM limitation and lower eyelid swelling. The symptoms recurred upon tapering of oral prednisolone at the second week after initial treatment, when the patient was at a dosage of 40 mg per day. The second pulse therapy was not effective. Due to

economic reasons, the patient refused further treatment. Later, he presented at our outpatient service with severe proptosis (Figure 2b) and bilateral vision loss after 13 months.

DISCUSSION

IgG4-RD is an emerging entity characterised by numerous aggregates of IgG4-positive plasma cells in multiple organs, including the orbit³ and salivary gland.⁴ The current consensus of the clinical diagnostic criteria for IgG4-RD⁵ includes serum IgG4 concentration greater than 135 mg/dL, tissues contain IgG4-positive plasma cells greater than 10 per high power field (HPF), and an IgG4/IgG-positive plasma cell ratio greater than 40% in patients with diffuse or localised tumefactions. According to the comprehensive criteria, our two patients were categorised as definite IgG4-RD. Its signs and symptoms include lid and periorbital swelling, which are mostly painless. Some patients have proptosis and ocular motility restrictions; few patients have visual loss^{1-3,6}; and patients commonly have bilateral involvement.^{1,3}

To date, scattered cases of orbital IgG4-RD with lesions involving the lacrimal glands, extraocular muscles, trigeminal nerves, cavernous sinuses, and optic nerve sheaths have been reported.^{1,2,7} Our patients had simultaneous inflammation of bilateral paranasal sinuses, orbital contents, and intracranial extensions. Although there was sequential parotid gland enlargement followed by orbital manifestations in the first patient, the patient's symptom was more extensive than typically seen in Mikulicz disease.^{4,8} Interestingly, there was no cutaneous sensory loss regardless of trigeminal branch hypertrophy.^{9,10}

The featured histopathology of orbital IgG4-RD includes dense lymphoplasmacytic infiltration, follicular hyperplasia, and background fibrosis in lacrimal gland tissues.^{1,2} However, obliterative phlebitis is rare in lacrimal glands in comparison with other tissues.^{2,3,11,12} It is difficult to differentiate IOIS from IgG4-RD without specific IgG4 staining.³ Therefore, performing a biopsy and staining plasma cells for IgG4 is warranted to differentiate IgG4-RD from IOIS, especially in cases with diffuse involvement¹³ that are refractory to steroid treatment.^{2,3} IgG4-RD involving the salivary and/or lacrimal gland (also termed Mikulicz disease) shares histological similarities with Sjögren syndrome (SS). Hence, the initial diagnosis of SS, as in our first patient, might not be uncommon. In addition to common histological features such as myoepithelial islands and ectopic germinal centre, the SS patients present more apoptosis of acinar and ductal cells than the IgG4-positive plasma cell-infiltrated cases.⁴ The pathogenesis of the two diseases is also proven to be different based on

the overexpression of interleukin-21 in patients with IgG4-related dacryoadenitis and sialadenitis but not in those with SS.¹⁴

The manifestations of IgG4-RD, with possible involvement of other organs, need to be identified promptly to take advantage of emerging therapeutic approaches. B lymphocyte depletion therapy with rituximab was reported anecdotally to demonstrate effectiveness in reducing the serum IgG4 level; however, a swift clinical response^{7,15} was limited to cases of IgG4-RD without extensive fibrosis.¹¹

In conclusion, we report two cases with long-term inflammation bilaterally of the lacrimal glands, optic nerves, trigeminal nerves, and maxillary sinuses. Pulse steroid therapy was only effective in one patient. Through careful clinicopathological correlation combining characteristic histopathological appearance, increased numbers of IgG4-positive plasma cells, radiological presentation, and the refractory clinical course, the diagnosis of IgG4-RD in both patients was definite.

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Note: Figures 1 and 2 of this article are available in colour online at www.informahealthcare.com/oph.

REFERENCES

- [1] Plaza JA, Garrity JA, Dogan A, Ananthamurthy A, Witzig TE, Salomao DR. Orbital inflammation with IgG4-positive plasma cells: manifestation of IgG4 systemic disease. *Arch Ophthalmol* 2011;129:421-428.
- [2] Deschamps R, Deschamps L, Depaz R, Coffin-Pichonnet S, Belange G, Jacomet PV, Vignal C, Benillouche P, Herdan ML, Putterman M, Couvelard A, Gout O, Galatoire O. High prevalence of IgG4-related lymphoplasmacytic infiltrative disorder in 25 patients with orbital inflammation: a retrospective case series. *Br J Ophthalmol* 2013;97:999-1004.
- [3] Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, Tanaka T, Takata K, Morito T, Kondo E, Yoshino T. Ocular adnexal IgG4-related disease has uniform clinicopathology. *Pathol Int* 2008;58:465-470.
- [4] Yamamoto M, Takahashi H, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Shinomura Y, Imai K. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. *Mod Rheumatol* 2006;16:335-340.
- [5] Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S,

- Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Nakamura S, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;22: 21–30.
- [6] Kubota T, Moritani S. Orbital IgG4-related disease: clinical features and diagnosis. *ISRN Rheumatol* 2012; Article ID 412896. doi: 10.5402/2012/412896.
- [7] Wallace ZS, Khosroshahi A, Jakobiec FA, Deshpande V, Hatton MP, Ritter J, Ferry JA, Stone JH. IgG4-related systemic disease as a cause of “idiopathic” orbital inflammation, including orbital myositis, and trigeminal nerve involvement. *Surv Ophthalmol* 2011;57:26–33.
- [8] Geyer JT, Deshpande V. IgG4-associated sialadenitis. *Curr Opin Rheumatol* 2011;23:95–101.
- [9] Rose GE, Wright JE. Trigeminal sensory loss in orbital disease. *Br J Ophthalmol* 1994;78:427–429.
- [10] Khine AA, Prabhakaran VC, Selva D. Idiopathic sclerosing orbital inflammation: two cases presenting with paresthesia. *Ophthalm Plast Reconstr Surg* 2009;25:65–67.
- [11] Stone Jh, Zen Y, Deshpande V. IgG4-related disease. *New Eng J Med* 2012;366:539–551.
- [12] Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Kloppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25:1181–1192.
- [13] Tsai RK, Cheng HH, Hsu SY, Lin HY. Intravenous pulse methylprednisolone therapy in patients with acute idiopathic orbital inflammatory syndrome. *Neuro-Ophthalmology* 2005;29:53–57.
- [14] Maehara T, Moriyama M, Nakashima H, Miyake K, Hayashida JN, Tanaka A, Shinozaki S, Kubo Y, Nakamura S. Interleukin-21 contributes to germinal centre formation and immunoglobulin G4 production in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz’s disease. *Ann Rheum Dis* 2012;71:2011–2019.
- [15] Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010;62: 1755–1762.