ORIGINAL ARTICLE

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Clinical outcomes and pathological characteristics of immunoglobulin G4-related ophthalmic disease versus orbital inflammatory pseudotumor

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Background/Aims: This study investigated the clinical and pathological features of immunoglobulin G4 (IgG4)-related ophthalmic disease. To clarify the features, we compared IgG4-related ophthalmic disease and orbital inflammatory pseudotumor.

Methods: We retrospectively reviewed the medical records of 103 patients who were initially diagnosed with orbital inflammatory pseudotumor, and identified 16 cases in which the diagnosis was based on surgical biopsy and for which data in medical records were sufficient for analysis. Immunohistochemical staining of pathological specimens for IgG and IgG4 was performed. Finally, six of IgG4-related ophthalmic disease patient and 10 of orbital inflammatory pseudotumor patient were analyzed.

Results: The IgG4-related ophthalmic disease group had more IgG4-positive plasma cells and a higher IgG4/IgG plasma cell ratio than the orbital inflammatory pseudotumor group. Collagenous fibrosis and lacrimal gland involvement were significantly more frequent in the IgG4-related ophthalmic disease group. Dense lymphocyte infiltration, obliterative phlebitis, and bilateral lesions were more frequent in IgG4-related ophthalmic disease, but the differences were not significant. The recurrence-free period was shorter in the IgG4-related ophthalmic disease group ($p = 0.035$).

Conclusions: The location of the lesion (lacrimal gland), count and ratio of IgG4-positive plasma cells, and collagenous fibrosis aid the diagnosis of IgG4-related ophthalmic disease in patients with idiopathic orbital mass-like lesions. In addition, maintenance therapy should be considered in patients with IgG4-related ophthalmic disease to prevent recurrence.

Keywords: IgG4-related ophthalmic disease; Collagenous fibrosis; Recurrence; Clinical outcome

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INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a chronic fibro-inflammatory disorder that can affect various organ systems [1]. Formerly known as autoimmune-related sclerosing pancreatitis, this disease was first identified as IgG4-RD in the early 2000s [2,3]. IgG4-RD is characterized by a tumor-like lesion, storiform

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fibrosis, obliterative phlebitis, and IgG4-rich lymphoplasmacytic infiltration [4]. The diagnosis of IgG4-RD is difficult because the clinical course and symptoms of this disease can mimic those of a tumor and immune-mediated disorders, such as Sjögren's syndrome and sarcoidosis [5]. Integrating histopathologic examinations of the involved organ, elevated serum IgG4 level, and characteristic clinical findings are important to distinguish IgG4-RD from other diseases [6].

IgG4-RD affecting the orbit or ocular adnexa is recognized as Mikulicz's disease and orbital inflammatory pseudotumor [1,7]. IgG4-related ophthalmic disease can affect not only the lacrimal gland, but also the ocular adnexa, including the muscles, nerves, and soft tissue. Orbital inflammatory pseudotumor is treated with systemic glucocorticoids therapy, and radiotherapy has been tried in refractory cases [8]. Glucocorticoids therapy is used for the initial treatment and as maintenance therapy for IgG4-RD. The standard treatment for IgG4-RD is based on expert consensus, whereas the therapies for orbital inflammatory pseudotumor remain controversial [5]. Therefore, distinguishing IgG4-RD from other idiopathic inflammatory conditions is important.

This study compared the baseline characteristics, clinical course, and pathological features of IgG4-related ophthalmic disease and orbital inflammatory pseudotumor. We also investigated the recurrence rates of IgG4-related ophthalmic disease and orbital inflammatory pseudotumor after glucocorticoids therapy.

METHODS

Patients

We retrospectively reviewed the medical records of patients who were initially diagnosed with orbital inflammatory pseudotumor at our hospital, a tertiary-care university hospital and referral center, between January 2008 and December 2014. A total of 103 patients with orbital inflammatory pseudotumor were identified. The initial diagnosis of orbital inflammatory pseudotumor was based on the detection of a mass-like lesion by computed tomography or magnetic resonance imaging. Subjects in whom a definite cause of the orbital mass, such as malignancy, and those whose medical records were missing data were excluded from the analysis. Of the 103 patients, 16 had sufficient clinical information and pathological specimens. IgG and IgG4 staining was performed on specimens from these 16 patients. IgG4-RD was diagnosed based on a pathology review using the consensus diagnostic criteria for IgG4-RD and clinicopathological correlation [4]. We defined orbital inflammatory pseudotumor as an idiopathic inflammatory pseudotumor of the orbit that was unrelated to IgG4-RD. All experiments were conducted in accordance with the Declaration of Helsinki (1964). This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC16RISI0177). The informed consent was waived.

Pathology review

We reviewed pathology specimens for lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis. Immunohistochemical stains were performed on formalin-fixed, paraffin-embedded 4 μm-thick tissue sections. Primary antibodies were mouse monoclonal for IgG (Thermo, Loughborough, UK) and IgG4 (Roche, Indianapolis, IN, USA). The sections were deparaffinized in xylene for 15 minutes, subsequently rehydrated and rinsed in distilled water. Assays were then performed using the Ventana NX automated immunohistochemistry system (Ventana Medical Systems, Tucson, AZ, USA). We counted number of IgG positive plasma cell per high power field and IgG4 positive plasma cells to IgG positive plasma cells ratio. All pathologic review was performed by a pathology expert.

Demographic, clinical, and laboratory profiles

Patients' demographic characteristics (age, sex, and disease duration) and clinical data and laboratory data were collected at the time of diagnosis. The treatment and outcomes of IgG4-related ophthalmic disease and orbital inflammatory pseudotumor were compared, as were recurrence rates. Recurrence was defined as an increase in mass size and relapse of the initial symptoms and signs. The analysis of recurrence included only the first recurrence.

Statistical analysis

The Mann-Whitney *U* test was used to compare continuous values between groups. Categorical variables, such as proportions, were compared between groups using the chi-square test or Fisher exact test. Values of

$p < 0.05$ were considered to be statistically significant. Recurrence rates were studied using the Kaplan-Meier method and compared between groups using the log-rank test. For the Kaplan-Meier study, the time scale was defined as the time from first diagnosis. All tests were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline demographic, laboratory, and pathological data of patients with IgG4-related ophthalmic disease and orbital inflammatory pseudotumor

Six of the 16 patients were diagnosed with IgG4-related ophthalmic disease according to consensus diagnostic criteria [4]. Pathological findings for the 16 patients are presented in Table 1.

Table 2 shows a comparison of the demographic, laboratory, and pathological findings from patients with IgG4-related ophthalmic disease and those with orbital inflammatory pseudotumor. The IgG4-related ophthalmic disease group had a higher IgG4 count, higher IgG4/IgG ratio, presence of collagenous fibrosis, lacrimal gland involvement on pathological analysis, and higher eosinophil count. The eosinophil count was significantly higher in the IgG4-related ophthalmic disease group, although only one patient (patient no. 2) had definite eosinophilia. Case 6 only showed definite storiform fibrosis. Fig. 1 displayed representative pathologic findings and clinical photo of IgG4-related ophthalmic disease of present study.

Clinical profiles of patients with IgG4-related ophthalmic disease and orbital inflammatory pseudotumor

All patients with IgG4-related ophthalmic disease had mass-like lesions at the orbital part of lacrimal gland, whereas orbital inflammatory pseudotumors were located in muscles, nerves, and soft tissues around the orbit. All patients with IgG4-related ophthalmic disease complained of eyelid swelling, whereas the most frequent complaint in the orbital inflammatory pseudotumor group was exophthalmos. Half of the patients with IgG4-related ophthalmic disease had bilateral lesions, but the frequency of bilateral lesions did not differ significantly between groups. Only one patient (patient no. 6) had a concurrent extraocular lesion at the time of diag-

Table 1. Pathological features of patients with IgG4-related ophthalmic disease and orbital inflammatory pseudotumor

Patient	IgG4-positive plasma cells, /HPF	IgG4/IgG ratio, %	Dense lymphoplasmacytic infiltration	Storiform fibrosis	Collagenous fibrosis	Obliterative phlebitis
#1	190	60.0	+	–	+	+
#2	100	45.0	+	–	+	–
#3	170	50.0	+	–	+	–
#4	100	40.0	+	–	–	–
#5	350	87.5	+	–	+	–
#6	350	70.0	+	+	+	+
#7	80	20.0	+	–	+	–
#8	2	2.5	–	–	–	–
#9	0	0	+	–	–	–
#10	2	10.0	–	–	–	–
#11	5	6.0	–	–	–	–
#12	3	9.0	–	–	–	–
#13	0	0	–	–	–	–
#14	2	10.0	+	–	–	–
#15	3	0.4	+	–	–	–
#16	2	0.5	+	–	–	–

IgG4, immunoglobulin G4; IgG4-RD, IgG4-related disease; HPF, high power field.

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Table 2. Clinical, laboratory, and pathological characteristics of patients with IgG4-related ophthalmic disease and orbital inflammatory pseudotumor

Characteristic	IgG4-RD (n = 6)	Orbital inflammatory pseudotumor (n = 10)	*p* value
Age, yr	54 (43–58)	54 (41–65)	0.828
Male sex	4 (66.7)	8 (80.0)	0.604
Follow-up duration, mon	34 (24–46)	43 (27–71)	0.386
IgG4-positive plasma cell count	180 (95–350)	2 (1–3)	0.001
IgG4/IgG plasma cell ratio, %	55.0 (45.0–70.0)	2.5 (0.4–10.0)	0.001
Maximum size	23 (19.41–25.16)	24.96 (12.11–38.09)	0.724
White blood cell count	7,365 (5,283–8,508)	7,190 (4,825–7,430)	0.828
Eosinophil count	179.43 (150–385)	99.26 (56–168)	0.016
Segmented neutrophils, %	48.45 (42.45–56.43)	60.6 (49.75–66.35)	0.092
Hemoglobin	13.65 (13.10–14.80)	14 (13.40–14.90)	0.913
Platelet count	245 (169–292)	238 (204–274)	0.828
Dense lymphocyte infiltration	6 (100)	5 (50.0)	0.093
Storiform fibrosis	1 (16.7)	0	0.375
Collagenous fibrosis	5 (83.3)	1 (10.0)	0.008
Obliterative phlebitis	2 (33.3)	0	0.125
Lacrimal gland involvement	6 (100)	0	< 0.001
Bilateral lesions	3 (50.0)	1 (10.0)	0.118
Recurrence	4 (66.7)	3 (30.0)	0.302

Values are presented as median (interquartile range) or number (%).
IgG4, immunoglobulin G4; IgG4-RD, IgG4-related disease.

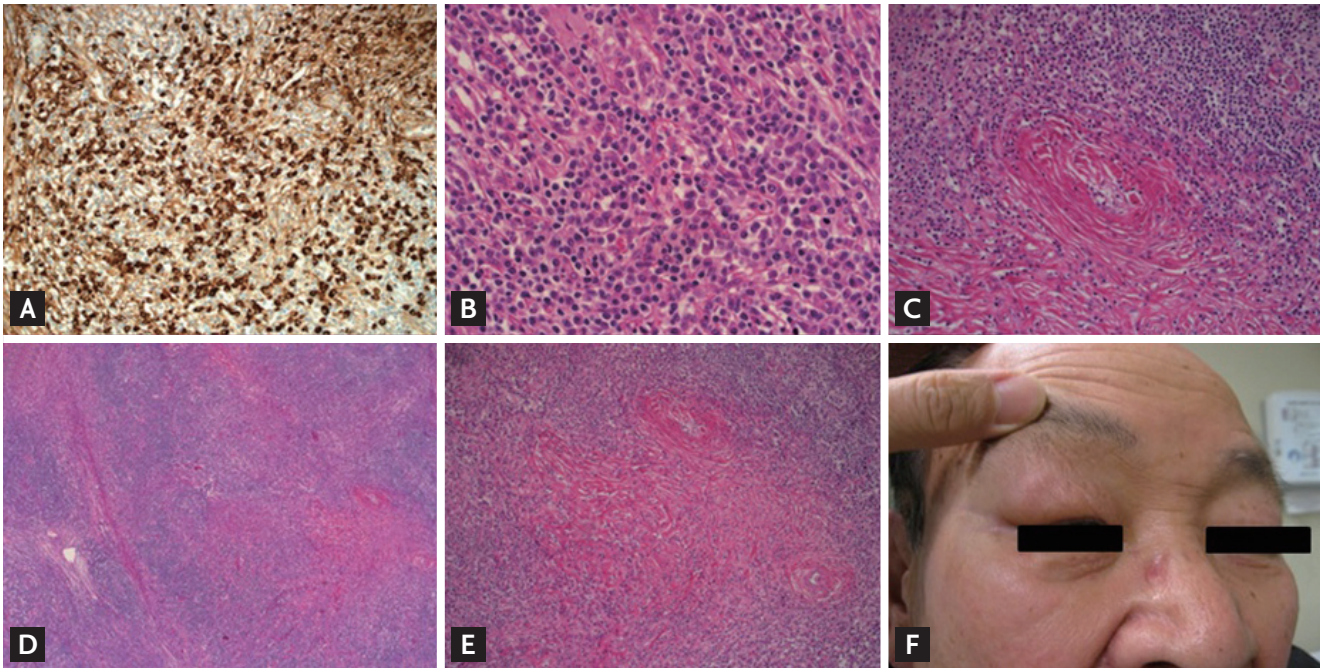

Figure 1. Representative images of pathologic and clinical finding. (A) Immunoglobulin G4 (IgG4)-positive plasma cell infiltration (IgG4 stain, ×200); (B) dense lymphoplasmacytic infiltration (×400); (C) obliterative phlebitis (×100); (D) collagenous fibrosis (×40); and (E) storiform fibrosis (×100). (F) Incidious swelling of both eyelid was the first symptom (H&E).

nosis. Detailed clinical profiles are presented in Table 3.

Clinical outcomes of IgG4-related ophthalmic disease and orbital inflammatory pseudotumor

All patients were treated initially with prednisolone (1 mg/kg for 1st week, 0.6 mg/kg for 2nd week, 0.3 mg/kg for 3rd week, 0.1 mg/kg for 4th week), and patients in both groups entered remission after the initial glucocorticoids therapy. Glucocorticoids therapy was not maintained in any patient. Recurrence was more frequent in patients with IgG4-related ophthalmic disease than in those with orbital inflammatory pseudotumor (66.7% vs. 30.0%), but the difference was not significant (Table 2). Although the recurrence rate did not differ significantly, recurrence occurred significantly earlier in patients with IgG4-related ophthalmic disease, as determined by a log-rank test (Fig. 2). The mean recurrence periods were 1 month in patients with IgG4-related ophthalmic disease and 5 ± 5.3 months in those with orbital inflammatory pseudotumor. Cox regression analysis was performed to survey independent risk factors of recurrence-free period, and there was no statistically significant risk factor (data not shown).

DISCUSSION

IgG4-RD is a new disease entity that can involve most parts of the body. Its etiology is not fully understood.

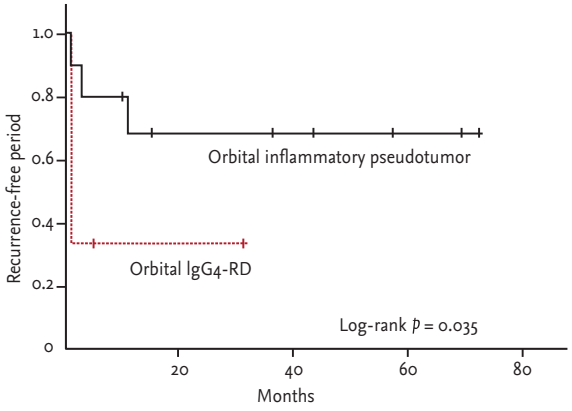

Figure 2. Recurrence-free period of immunoglobulin G4 (IgG4)-related ophthalmic disease and orbital inflammatory pseudotumor. The recurrence-free period was significantly shorter in the IgG4-related ophthalmic disease group, as determined by the log-rank test ($p = 0.035$).

Table 3. Clinical features of patients with IgG4-RD and orbital inflammatory pseudotumor

Patient	Age, yr	Sex	Symptom	Location	Bilateral lesion	Maximum size, mm
#1	58	M	Eyelid swelling	Lacrimal gland	–	25.16
#2	28	M	Eyelid swelling	Lacrimal gland	–	19.41
#3	53	M	Eyelid swelling	Lacrimal gland	–	25.08
#4	58	F	Eyelid swelling	Lacrimal gland	+	20.92
#5	43	F	Eyelid swelling	Lacrimal gland	+	19.33
#6	81	M	Eyelid swelling	Lacrimal gland, left submandibular gland	+	25.72
#7	54	M	Exophthalmos	Retrobulbar mass	–	24.96
#8	46	M	Binocular diplopia	Ocular muscle	–	12.11
#9	36	M	Exophthalmos, ophthalmalgia	Ocular muscle	–	33.00
#10	64	M	Eyelid swelling	Eyelid	+	38.09
#11	70	F	Decreased visual acuity	Brain, optic nerve, soft tissue	–	26.80
#12	55	M	Exophthalmos	Ocular muscle, fat tissue	–	24.22
#13	49	M	Ophthalmalgia	Ocular muscle	–	29.37
#14	65	F	Decreased visual acuity	Ocular muscle	–	8.11
#15	30	M	Exophthalmos, decreased visual acuity	Ocular muscle	–	15.55
#16	71	M	Exophthalmos	Ocular muscle	–	43.85

IgG4-RD, immunoglobulin G4-related disease.

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Before the concept of IgG4-RD was introduced, different diagnoses were used for different organ systems, including Mikulicz's disease, Küttner's tumor, inflammatory pseudotumor, and retroperitoneal fibrosis [1]. An elevated serum IgG4 level in patients with sclerosing pancreatitis was the first clue that led to the establishment of the concept of IgG4-RD [2]. Recent evidence based on pathological reviews and laboratory data supports the mechanism of IgG4-RD. IgG4-RD is considered to be a type 2 help T cell (Th2)/regulatory T cell (Treg)-driven condition, and cytokines produced by Th2 and Treg are thought to induce the fibrosis, excessive production of IgG4 and IgE, eosinophilia, and allergic reaction found in patients with IgG4-RD [9]. Eosinophilia, eosinophil infiltration in the affected organ, and accompanying allergic disease are some of the characteristics of IgG4-RD [1]. In our series, definite eosinophilia was observed in only one case of IgG4-related ophthalmic disease, although the circulating eosinophil count was significantly higher in the IgG4-related ophthalmic disease group than in the orbital inflammatory pseudotumor group.

Biopsy of the affected organ is mandatory for the diagnosis of IgG4-RD. The major histopathological features of IgG4-RD are dense lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis [4]. Obliterative phlebitis was infrequent in our series, consistent with reports that this condition is unusual in patients with IgG4-related ophthalmic disease [10]. A Japanese study group published diagnostic criteria for IgG4-related ophthalmic disease, and claimed that fibrosis was not necessarily a feature of this disease (Supplementary Table 1) [11]. However, the expert consensus obtained at the international symposium on IgG4-RD holds that typical storiform fibrosis is uncommon, whereas collagenous fibrosis is common, in IgG4-RD of the lacrimal gland [4]. We observed collagenous fibrosis in almost all patients with IgG4-related ophthalmic disease. This finding is consistent with previous study [4], and our study support that collagenous fibrosis is more common than typical storiform fibrosis in IgG4-related ophthalmic disease. Two previous studies reported that about 90% of IgG4-related ophthalmic disease is located in the lacrimal glands [12,13], and we obtained similar results. This finding suggests that the lacrimal gland is the most frequent site of IgG4-related ophthalmic disease. Therefore, biopsy should be considered when an orbital mass is found in the lacrimal gland to differentiate IgG4-RD from other diseases of the lacrimal gland, such as Sjögren's syndrome [5]. A previous comparison of IgG4-related ophthalmic disease and idiopathic sclerosing orbital inflammation (ISOI) showed that IgG4-related ophthalmic disease had a better response than ISOI to initial therapy [12]. In our series, both groups had good responses to the initial therapy; this discrepant result may be due to the relatively aggressive clinical course of ISOI. Our study included patients with orbital inflammatory pseudotumor as the control group, whereas the previous study included patients with ISOI as the control group. Our study showed that the recurrence-free period was shorter in patients with IgG4-related ophthalmic disease than orbital inflammatory pseudotumor; this finding is important because our study is the first to compare the recurrence of IgG4-related ophthalmic disease and orbital inflammatory pseudotumor. Experts agree that the initial therapy for IgG4-RD is glucocorticoids therapy, and that glucocorticoids maintenance and immunosuppressant therapy can prevent relapse in some cases [5]. In our study, IgG4-related ophthalmic disease recurred 4 weeks after the cessation of glucocorticoids therapy in two-thirds of cases. Therefore, the maintenance of a low-dose glucocorticoids regimen and the addition of an immunosuppressant after initial glucocorticoids therapy should be considered in patients with IgG4-related ophthalmic disease.

IgG4-RD has been reported to occur more often in men and in those older than 50 years of age [1,14]; we observed similar results. In addition, bilateral involvement has been reported in 70% to 90% of IgG4-related ophthalmic disease cases [12,15]. We found that half of our patients with IgG4-related ophthalmic disease had bilateral lesions, and one patient with IgG4-related ophthalmic disease had concurrent parotid gland involvement. The frequent bilateral involvement of the orbit and the involvement of other organs may occur because IgG4-RD is an immune-mediated systemic inflammatory condition that can affect almost every organ system [9].

Our study has several limitations. First, as it was a retrospective review, we could not fully evaluate data such as the serum IgG4 and IgE levels and circulating IgG4+ plasmablasts. A recent study of IgG4-RD revealed that circulating IgG4+ plasmablasts were correlated with disease activity [14], which could help physicians to select

patients who need maintenance therapy. In addition, immunohistochemical staining for IgG/IgG4 was not conducted initially in all patients included in our study. As a result, the diagnosis of IgG4-RD was missed and no patient received maintenance therapy to prevent recurrence. Second, this study is limited by its small sample.

Some patients initially diagnosed with orbital inflammatory pseudotumor were subsequently diagnosed with IgG4-related ophthalmic disease after the review of pathological findings. The most common site of IgG4-related ophthalmic disease was the lacrimal gland, and IgG4-related ophthalmic disease was frequently bilateral and could involve other organs. The pathological review showed that the typical features of IgG4-RD were more frequent in patients with IgG4-related ophthalmic disease. Finally, the recurrence-free interval was shorter in patients with IgG4-related ophthalmic disease than in those with orbital inflammatory pseudotumor; therefore, maintenance therapy should be considered for patients with IgG4-related ophthalmic disease.

KEY MESSAGE

1. Immunoglobulin G4 (IgG4)-related ophthalmic disease should be considered when patient present as idiopathic orbital mass, especially which involves lacrimal gland.
2. Most patients with IgG4-related ophthalmic disease may need maintenance therapy to prevent recurrence.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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REFERENCES

1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012;366:539-551.
2. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732-738.
3. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 2003;38:982-984.
4. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012;25:1181-1192.
5. Khosroshahi A, Wallace ZS, Crowe JL, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol 2015;67:1688-1699.
6. Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 2012;22:21-30.
7. Kubota T, Moritani S. Orbital IgG4-related disease: clinical features and diagnosis. ISRN Rheumatol 2012;2012:412896.
8. Lee JH, Kim YS, Yang SW, et al. Radiotherapy with or without surgery for patients with idiopathic sclerosing orbital inflammation refractory or intolerant to steroid therapy. Int J Radiat Oncol Biol Phys 2012;84:52-58.
9. Della-Torre E, Lanzillotta M, Doglioni C. Immunology of IgG4-related disease. Clin Exp Immunol 2015;181:191-206.
10. Sato Y, Notohara K, Kojima M, Takata K, Masaki Y, Yoshino T. IgG4-related disease: historical overview and pathology of hematological disorders. Pathol Int 2010;60:247-258.
11. Goto H, Takahira M, Azumi A; Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. Jpn J Ophthalmol 2015;59:1-7.
12. Sa HS, Lee JH, Woo KI, Kim YD. IgG4-related disease in idiopathic sclerosing orbital inflammation. Br J Ophthalmol 2015;99:1493-1497.
13. Song YS, Choung HK, Park SW, Kim JH, Khwarg SI, Jeon YK. Ocular adnexal IgG4-related disease: CT and MRI findings. Br J Ophthalmol 2013;97:412-418.
14. Wallace ZS, Deshpande V, Mattoo H, et al. IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients. Arthritis Rheumatol 2015;67:2466-2475.
15. Go H, Kim JE, Kim YA, et al. Ocular adnexal IgG4-related disease: comparative analysis with mucosa-associated lymphoid tissue lymphoma and other chronic inflammatory conditions. Histopathology 2012;60:296-312.

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Supplementary Table 1. Diagnostic criteria for IgG4 related ophthalmic disease, 2014

(1) Imaging studies show enlargement of the lacrimal gland, trigeminal nerve, or extraocular muscle as well as masses, enlargement, or hypertrophic lesions in various ophthalmic tissues (2) Histopathologic examination shows marked lymphocyte and plasmacyte infiltration, and sometimes fibrosis. A germinal center is frequently observed. IgG4+ plasmacytes are found and satisfy the following criteria: ratio of IgG4+ cells to IgG+ cells of 40% or above, or more than 50 IgG4+ cells per high power field (×400) (3) Blood test shows elevated serum IgG4 (≥ 135 mg/dL)

Diagnosis is classified as "definitive" when (1), (2), and (3) are satisfied; "probable" when (1) and (2) are satisfied; and "possible" when (1) and (3) are satisfied.
IgG4, immunoglobulin G4.