

High prevalence of IgG4-related lymphoplasmacytic infiltrative disorder in 25 patients with orbital inflammation: a retrospective case series

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bjophthalmol-2013-303131>).

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Received 16 January 2013

Revised 22 April 2013

Accepted 20 May 2013

ABSTRACT

Aims To evaluate retrospectively the prevalence of positive IgG4-immunostaining in orbital tissue of patients with idiopathic orbital inflammation and to compare the clinical, radiographic and pathologic features among patients with and without IgG4-positive cells.

Patients and methods 25 patients with biopsy-proven idiopathic orbital inflammation examined from January 2006 through December 2011 were included. Immunohistochemistry with IgG and IgG4 immunostaining from biopsy specimens of all patients was performed. Tissue with more than 10 IgG4-positive plasma cells per high-power field and with a ratio of IgG4+/IgG+ plasma cells of more than 40% was scored as positive. Histopathologic features, demographic and clinical data, radiologic findings, treatment and follow-up information for each patient were analysed.

Results Immunohistochemical staining showed 10 cases (40%) were IgG4 positive. The symptoms and signs included eyelid or periorbital swelling/mass in all, pain (3/10), extraocular muscle restriction (3/10), proptosis (5/10) and/or decreased vision (4/10). Demographic and clinical findings of these patients did not differ from those with IgG4-negative cells. The presence of positive IgG4-immunostaining in orbital tissue was significantly associated with characteristic pathological features (more background fibrosis, lymphoid hyperplasia, plasma cells and phlebitis).

Conclusions Finally, 40% of patients with biopsy-proven orbital inflammation were classified as IgG4-RD, with typical histological features, but without specific clinical or radiological findings.

INTRODUCTION

First described in 1903, idiopathic orbital inflammatory (IOI) disease, also known as orbital pseudotumour, accounts for approximately 10% of all orbital 'tumours'. IOI is characterised by extraocular orbital and adnexal inflammation without any identifiable causes.¹⁻³ Diagnosis involves exclusion of other aetiologies, and surgical biopsy is often required to rule out lymphoma. The histopathologic hallmarks of IOI are a mixed, non-specific inflammatory infiltrate and fibrosis of varying degrees⁴ (figures 1 and 2).

IgG4-related disease (IgG4-RD) is a newly recognised entity characterised by IgG4-positive plasma cells and T-lymphocyte infiltration into various organs. The disease was initially described in

relation to autoimmune pancreatitis in 2001, but, to date, it has been reported in several other organs, including orbital tissues.⁵ Since the first histological demonstration in 2007 that IgG4-RD might also affect orbital tissues,⁶ to our knowledge, six case series have been published (a total of 94 patients). All except two studies involved Asian populations.⁷⁻¹⁵

The purpose of our investigation was to evaluate retrospectively the frequency of positive IgG4-immunostaining in orbital tissues among patients with IOI identified over a 6-year period and to compare clinical, radiologic and histopathologic features of patients with or without a positive diagnosis of IgG4-RD.

METHODS

This retrospective study was approved by our institutional review board. A retrospective chart review was performed for all adult patients with the diagnosis of IOI, who underwent an orbital biopsy at our institution from January 2006 to December 2011. All patients who met the following criteria were enrolled: (1) extraocular orbital and adnexal involvement; (2) onset after age 18 years; and (3) biopsy-proven IOI. These included patients with dacryoadenitis, myositis (one or more extraocular muscles) and orbital infiltrative inflammation. Furthermore, the biopsy examinations had identified non-specific, non-granulomatous inflammation. Patient records were reviewed for the following: demographic information; clinical neuro-ophthalmic findings; biopsy location and results; pre-existing disease; neuroimaging studies (eg, cranial MRI and CT scans); treatment; and course of disease. The archived biopsy specimens were evaluated independently by two pathologists (LD and AC) and the following histopathologic features were quantified: background fibrosis, taking note of storiform patterns (ie, matted and irregularly whorled),¹⁶ lymphoplasmacytic infiltrate, follicular hyperplasia, numbers of eosinophils and obliterative phlebitis or phlebitis without obliteration of the lumen. Similar to the study by Plaza *et al*,⁷ each feature was quantified as absent (0) or present in a small amount (1), moderate amount (2) or marked amount (3).

In all cases, 4 µm paraffin-embedded sections had been prepared from the biopsy specimens. For this study, specimens were dewaxed, rehydrated

To cite: Deschamps R, Deschamps L, Depaz R, *et al*. *Br J Ophthalmol* Published Online First: [please include Day Month Year] doi:10.1136/bjophthalmol-2013-303131

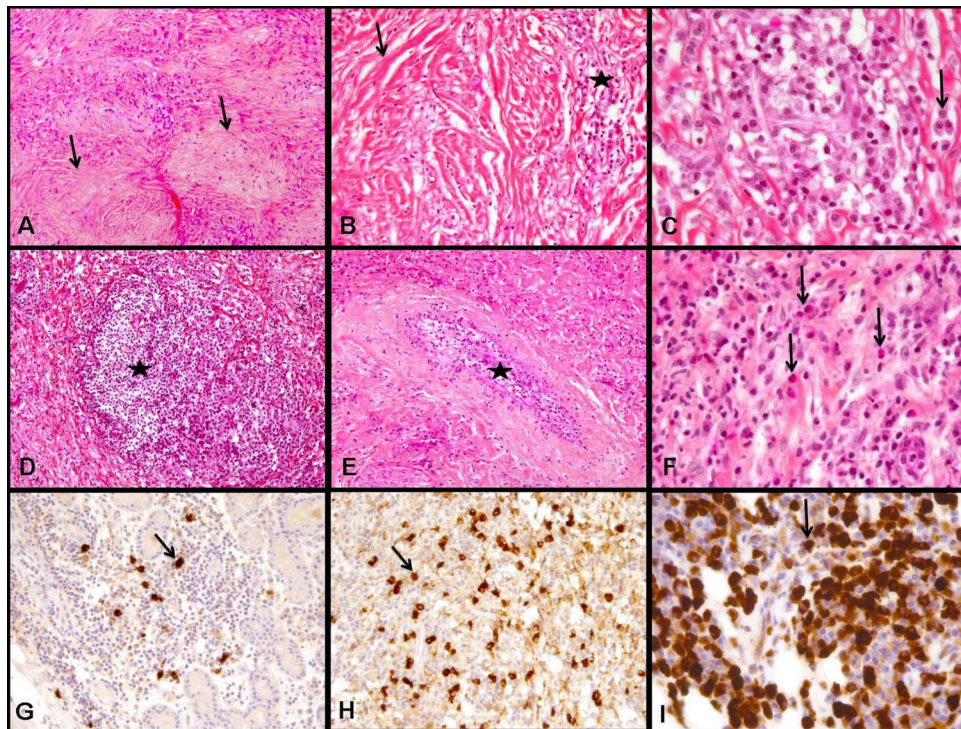
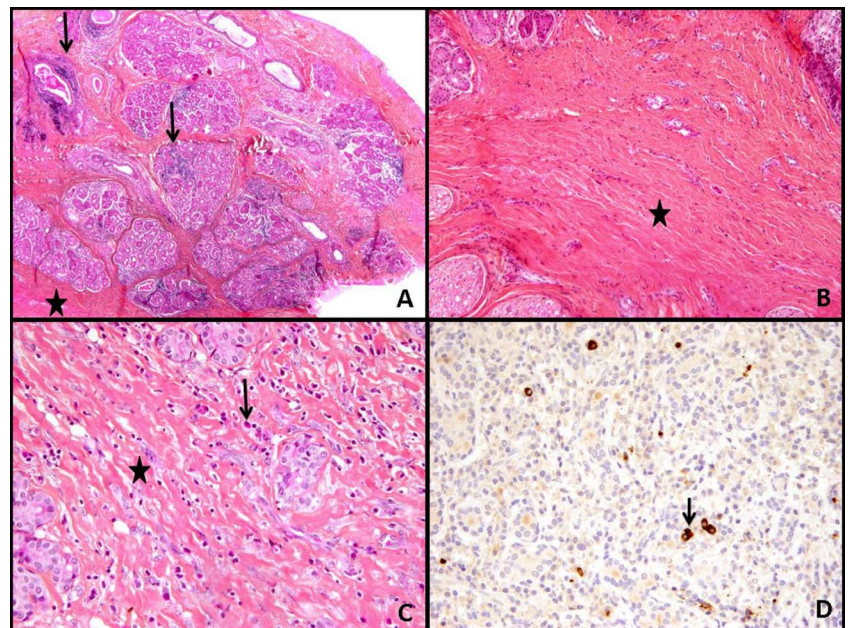


Figure 1 Histopathologic and immunohistochemical findings for IgG4-positive patients. (A) Patient 5; marked storiform fibrosis (arrows) (H&E, original magnification $\times 100$). (B) Patient 3; marked storiform fibrosis (arrow) with inflammatory infiltrate (asterisk) (H&E, $\times 200$). (C) Patient 3; numerous plasma cells (arrow) in inflammatory infiltrate (H&E, $\times 200$). (D) Patient 3; lymphoid follicular hyperplasia (asterisk) (H&E, $\times 100$). (E) Patient 6; obliterative phlebitis (asterisk) (H&E, $\times 200$). (F) Patient 7; numerous eosinophils (arrows) intermingled with plasma cells (H&E, $\times 400$). (G) Patient 10; some plasma cells expressed IgG4 (arrow) (immunostaining, $\times 200$). (H) Patient 3; numerous plasma cells expressed IgG4 (immunostaining, $\times 200$). (I) Patient 1; high plasma cell infiltrates expressed IgG4 (immunostaining, $\times 400$).

and stained with an immunohistochemical technique, where a monoclonal IgG4 antibody (clone HP6025; Binding Site, Birmingham, UK) and a polyclonal IgG-antibody (reference 65-066-1, ICN) were applied with an automated immunohistochemical stainer (Leica Bond-Max, Nanterre, France). For each specimen, we counted IgG4-positive plasma cells in three high-power fields (HPF) or more depending on the size of the biopsy

sample; at least three HPF were adequate for counting in all cases. The pathologists (LD and AC) selected HPFs with the highest density of plasma cells with IgG4-positive staining ('hot spots'). Counting was performed with a $40\times$ objective and a $10\times$ eyepiece on a Leica DM 2000 microscope. Each HPF covered an area of 0.196 mm^2 . The mean number of IgG4-positive plasma cells in 'hot spots' was calculated for each

Figure 2 Histopathologic and immunohistochemical findings for IgG4-negative patients. (A) Patient 13; mild fibrosis (asterisk) with a light inflammatory infiltrate around excretory duct or close to lacrimal acini (arrows) (H&E, original magnification $\times 25$). (B) Patient 13; mild fibrosis (asterisk) without lymphoplasmacytic infiltrate (H&E, $\times 200$). (C) Patient 11; background fibrosis (asterisk) and mild inflammatory infiltrate with eosinophils (arrow) (H&E, $\times 200$). (D) Patient 11; few plasma cells expressed IgG4 (arrow) (immunostaining, $\times 200$).



specimen. The diagnostic criterion for the classification of IgG4-positive orbital tissue was defined as a mean of more than 10 IgG4-positive plasma cells per HPF and a ratio of IgG4+/IgG+ plasma cells of more than 40% (diagnosis of 'probable' IgG4-RD).¹⁷ Patients were classified as IgG4 positive or IgG4 negative according to this criterion.

Categorical variables were compared between patients classified as IgG4 positive or IgG4 negative with the χ^2 test or the two-tailed Fisher's exact probability test. Student unpaired *t* tests were performed to compare age between groups. The level of significance was taken as $p < 0.05$.

RESULTS

This study included 25 patients with IOI, 8 men and 17 women, ranging in age from 20 to 83 years (mean 45.9 years). Among these patients, 21 were Caucasian and 4 were from sub-Saharan Africa. None was of Asian origin. The symptoms and signs of IOI included pain ($n=8$), swelling/mass ($n=23$), proptosis ($n=11$), diplopia or extraocular muscle restriction ($n=10$) and decreased vision ($n=10$). Four patients (15%) had bilateral involvement (two positive and two negative for IgG4). The mean symptom duration before diagnosis (from recognition of the initial clinical signs and symptoms to the first evaluation in our institution) was 6 months (range 9 days to 3 years). Twenty-one patients underwent an MRI, and 19 patients received a CT scan. The clinical features, radiological features, disease course and treatment for IgG4-positive and IgG4-negative patients are displayed in table 1. Table 2 summarises the histomorphologic findings from biopsy specimens. Table 3 shows a comparison of patient clinical pathologic variables.

Patients considered positive for IgG4

Ten patients (10/25; 40%) were considered positive for IgG4, including three men and seven women, with a mean age of 49.7 years (range 26–81; table 1). The mean follow-up time was 22.7 months (range 4–73 months) and two patients were followed for less than 6 months. The symptoms and signs of IOI in these patients included eyelid or periocular swelling/mass ($n=10$), pain ($n=3$), extraocular muscle restriction ($n=3$), proptosis ($n=5$) and decreased visual acuity ($n=4$). Eight had unilateral involvement. Four (40%) patients presented with a history of allergic manifestations and three with a mild eosinophilia. The lacrimal gland was the most commonly affected site of the orbit on neuroimaging (eight patients). Swollen extraocular muscles were present in four cases, and an extension to the orbital apex was observed in one case. The lesions appeared as a hypointense signal on T2-weighted images in all patients who underwent an MRI. All MRIs showed homogeneous enhancement after contrast injection. Neither calcification nor erosion in adjacent bone was detected on CTs. Three patients had a medical history suggestive of inflammation in other sites (table 1). Seven of eight patients treated with corticosteroids responded to initial doses with improvement. In three cases, ocular symptoms deteriorated during tapering off or after discontinuation. Five patients continued taking corticosteroids. A man who failed to respond to oral steroids received intravenous methylprednisolone and infliximab, and he showed marked improvement. Two patients were treated only with surgical excision, because they exhibited mild signs and/or a reduction in lesion size after biopsy surgery.

Patients considered negative for IgG4

Fifteen patients (15/25; 60%) were considered negative for IgG4, including 5 men and 10 women, with a mean age of

43.3 years (range 20–83; table 1). The mean follow-up time was 21.9 months (range 2–47 months). For 12 patients, the mean number of IgG4-positive plasma cells was 10 or smaller and in three cases, the ratio of IgG4+/IgG+ cells was less than 40% (two of these three patients had marked fibrosis and moderate lymphoplasmacytic infiltrate). All except two patients had eyelid or periocular swelling/mass, and five patients reported pain. Extraocular muscle restriction was seen in seven patients; proptosis and decreased visual acuity were found in six cases. Neuroimaging revealed an enlargement of the lacrimal gland for 10 patients. Five patients had swollen extraocular muscles, and two exhibited extensions to the orbital apex and/or to the cavernous sinus (one case). The lesions appeared as hypointense signals on T2-weighted images in all patients who received MRIs except three; two with a lesion that appeared as a high-intensity signal and one with a lesion that appeared as a mixed-intensity signal. All MRIs showed homogeneous enhancement after contrast injection. Neither calcification nor erosion in adjacent bone was observed on CTs. Five patients were treated only with surgical excision (one was lost to follow-up). Ten patients were treated with corticosteroids. Five patients relapsed during tapering. Five patients required immunosuppressive drugs.

DISCUSSION

In the present study, 40% of patients with IOI were diagnosed with orbital IgG4-RD.

Our results were consistent with results of Kubota *et al* (10 of 24 patients; 42%) and differed slightly from results of Sato *et al* (21 of 78 patients with orbital lesions; 27%), Plaza *et al* (11 of 21 patients, 52%) and Takahira *et al* (16 of 26 patients with orbital inflammation and without lymphomas, 61%).^{7–10}

We found that patients with positive IgG4-immunostaining had eyelid or periocular swelling, most often painless, and they sometimes presented with proptosis, diplopia and visual loss. Overall, clinically they did not differ significantly from patients who were IgG4 negative. Only two patients with an IgG4-positive biopsy exhibited bilateral lesions. This contrasted with prior case series, but unilateral involvement was reported in various case reports.^{14 18–21} A medical history of lesions other than orbital lesions was found in patients who were IgG4 positive more often than in those who were IgG4 negative (3 vs 1 patient, respectively). However, statistical comparisons were not performed, due to the lack of data for some patients. Previous studies have shown a frequency of extraorbital lesion ranging from 22% to 71%.²²

As previously reported, our study showed that patients who were IgG4 positive were heterogeneous in disease severity, course and prognosis.¹⁶ Of note, although most patients required the typical steroid therapy and showed good clinical response, two out of 10 patients did not receive steroid therapy, because they showed symptom resolution after surgery alone. Similar findings were previously described by Sato *et al* (six patients), Takahira *et al* (three cases) and Kubota *et al* (three cases).^{8–10}

In our study, the IgG4-positive and IgG4-negative groups were distinctly different pathologically. In particular, they showed significant differences in background fibrosis (storiform type in two cases), presence of phlebitis and the levels of plasmacytic and lymphocytic infiltration. The biopsies of patients with high IgG4 staining had a morphologic appearance characteristic of IgG4-RD, including a dense lymphoplasmacytic infiltrate and background fibrosis (storiform type in three cases). Obliterative phlebitis is a major histopathologic criterion associated with IgG4-related disease but prior studies also showed

Table 1 Clinical and radiographic data for IgG4-positive and IgG4-negative patients

Patient/ sex/age	Location	Pain	Eyelid or periocular swelling/mass	EOM restriction	Proptosis	Decreased visual acuity	Other clinical history	Abnormal laboratory findings	Follow-up, mo	Initial therapy	Course
IgG4 positive (n=10)											
1/F/31	LG, EOM, orb	Yes	Yes	Yes	Yes	No	Iodine allergy	Eosinophilia, phg	18	CS	PR. No recurrence
2/F/81	LG	No	Yes	No	No	No	Breast carcinoma, pacemaker		7	Surgery alone	No recurrence. Asymptomatic
3/M/40	Orb, ON	No	Yes	Yes	Yes	Yes	Malaria	Eosinophilia, phg	38	CS	Relapse. Surgery, CS, Remicade. PR
4/F/57	LG, EOM, orb, ON	Yes	Yes	No	No	Yes	Ovarian cystectomy, eczema,chronic urticaria		8	CS	PR. CS
5/F/52	Orb, LG	Yes	Yes	No	Yes	Yes	Retinal detachment	High ESR and CRP levels	73	CS	Relapse. Surgery. CS
6/F/65	Orb, EOM,ON	No	Yes	No	Yes	Yes	Nephritis, bladder carcinoma, diabetes mellitus		4	CS	No recurrence. CS
7/F/28	LG, orb, apex, EOM	No	Yes	Yes	Yes	No	Asthma; recurrent sinusitis; left optic neuritis 1 and 4 years earlier	Eosinophilia, high CRP level	5	CS	CR. Relapse. CS
8/M/55	LG	No	Yes	No	No	No	Iodine allergy, bronchomediastinal lymphadenopathy		12	CS	Stable. CS
9/M/26	LG	No	Yes	No	No	No			15	CS	PR. No recurrence
10/F/62	LG	No	Yes	No	No	No	Thyroidectomy		47	Surgery alone	Asymptomatic. No recurrence
IgG4 negative (n=15)											
11/F/20	Orb	Yes	Yes	Yes	No	No			3	Surgery alone	Stable
12/F/26	LG	Yes	Yes	No	No	No			30	Surgery alone	Asymptomatic. No recurrence
13/F/32	LG	No	Yes	No	No	No		Eosinophilia	5	CS	Relapse. Surgical
14/M/83	Orb	No	Yes	No	No	No	Diabetes mellitus, pacemaker, hypertension		Lost during follow-up	Surgery alone	NA
15/F/53	LG	No	Yes	No	No	No	Diabetes mellitus		9	CS	CR. No recurrence
16/F/53	LG, orb, ON	No	No	No	Yes	Yes	Hypertension, Hashimoto thyroiditis, collagenous colitis		40	CS	PR. Relapse. PR with Methotrexate and CS
17/M/20	LG, orb, ON	Yes	Yes	Yes	No	Yes		Phg	15	CS	PR. No recurrence
18/F/43	EOM	Yes	Yes	Yes	No	No		High CRP	47	CS	PR. Relapse. Methotrexate and CS
19/F/34	LG	No	Yes	No	No	No			6	Surgery alone	Stable
20/M/35	Orb, EOM, LG	No	Yes	Yes	Yes	No	Epilepsy		2	CS	CR
21/F/21	LG	No	Yes	No	No	No	Recurrent sinusitis	Phg	31	Surgery alone	Stable. No recurrence
22/F/54	LG, EOM, ON	No	Yes	Yes	Yes	Yes	Myocardial infarction	High CRP level	44	CS	PR. Relapse. Methotrexate and CS. CR
23/M/53	Orb, ON	No	Yes	Yes	Yes	Yes	Amblyopia		11	CS	PR. Methotrexate and CS. Relapse
24/F/58	Orb, apex, EOM, ON	Yes	No	Yes	Yes	Yes	Recurrent sinusitis, hearing loss 1 year earlier	High ESR	43	CS	PR. Cyclophosphamide and CS. No recurrence
25/M/65	Orb, Cav, ON, EOM, LG	No	Yes	No	Yes	Yes		High ESR	20	CS	CR. No recurrence

Cav, cavernous sinus; CR, complete response; CRP, C reactive protein; CS, corticosteroids; EOM, extraocular muscles; ESR, erythrocyte sedimentation rate; LG, lacrimal gland; mo, month; ON, optic nerve; orb, orbit; phg, polyclonal hyperglobulinaemia; PR, partial response.

that it is not a common feature of orbital inflammation with IgG4-positive plasma cells¹²: it was detected in only two of the 21 samples (9.5%) by Sato *et al*,⁸ in accordance with our result (one among 10 patients).

Although the biopsy specimens of patients who were IgG4 positive revealed the characteristic morphologic features of IgG4-RD, our study could be criticised for using a low threshold to classify tissue as IgG4 positive,²³ in accordance with the recent Japan consensus.¹⁷ In other analyses of IgG4 immunostaining, a variety of cut-off thresholds have been proposed ranging from 10 to >100 IgG4-positive cells/HPF. We chose a cut-off threshold of 10 similar to three prior case series,^{7 8 13} More recently, newer consensus criteria for the diagnosis of IgG4-RD have been published.²⁴ Those investigators emphasised that 'the diagnosis of IgG4-RD is based primarily on the morphological appearance on biopsy. The tissue IgG4 count and IgG4:IgG ratios are of secondary importance'; they also suggested that >100 IgG4-positive plasma cells per HPF would be a more appropriate cut-off threshold for lacrimal gland biopsy samples. They referenced a study by Cheuk *et al*,¹² which included five cases of chronic sclerosing dacryoadenitis with abundant IgG4-positive cells in lacrimal gland. Only one of our patients displayed a similar level, with 150 IgG4-positive cells per HPF. In previous studies by Sato *et al*⁸ and Takahira *et al*,¹⁰ only four of 21 and one of 16 cases, respectively, of IgG4-related orbital inflammation displayed more than 100

IgG4-positive cells. None of the four patients reported by Matsuo *et al*¹³ reached this threshold. In the cohort studied by Plaza *et al*,⁷ two of 11 patients considered positive for IgG4 had less than 30 IgG4-positive cells/HPF (others had >30 positive cells per HPF without more detailed information). To our knowledge, the mean number of IgG4+ cells/HPF was not available in three other studies.^{9 14 15} Finally, the variability of the cut-off value could reflect the heterogeneity of the IgG4 immunostaining, which may occur even in different areas of the same biopsy. In 2012, the consensus statement on the pathology of IgG4-RD proposed that counting should only be performed in areas with intense IgG4 'hot spots', as performed in the present study.²⁴ Another variable to consider is the area (HPF) covered by the light microscope. The most frequent HPF area is 0.237 mm² (with a 0.55 mm diameter for a 22 mm eyepiece); with our light microscope, the HPF area was smaller (0.196 mm²). This must be kept in mind when interpreting our results, because this may have led to underestimated results. The HPF area is rarely reported in studies that report IgG4-positive cell counts.²² We were aware that analysis of serum IgG4 concentrations would have provided more accurate diagnosis; however, unfortunately, this analysis was not performed in this retrospective study. Of note, approximately 30% with biopsy-proven IgG4-RD have normal serum IgG4 levels.^{16 25}

In conclusion, this study was the first in a European country to compare the pathologic features of IOI among patients with and

Table 2 Histomorphologic findings from biopsy specimens for IgG4-positive and IgG4-negative patients

Patient	Background fibrosis	Follicular hyperplasia	Phlebitis	Plasmacytic infiltrate	Lymphocytic infiltrate	Eosinophils	IgG4+/IgG+ cells ratio (%)	IgG4+ cells/HPF (mean)
IgG4 positive (n=10)								
1	3	1	0	3	2	0	93	150
2	3	0	1 (no obliterative)	3	1	0	51	97
3	3 (storiform)	3	1 (no obliterative)	3	3	1	57	94
4	3 (storiform)	3	1 (no obliterative)	3	3	0	47.2	92
5	3	3	0	3	2	0	43.4	76
6	2	1	1 (obliterative)	2	2	1	48.7	74
7	3	1	1 (no obliterative)	2	3	3	40.1	57
8	2	0	0	2	3	1	34	49
9	3	0	0	1	1	0	51.6	32
10	1	1	0	1	2	1	77.7	28
IgG4 negative (n=15)								
11	3	3	0	2	2	3	19.5	26
12	3	0	0	2	2	0	16.8	24
13	1	0	0	1	2	0	32.7	18
14	2	1	0	2	2	1	ND	10
15	1	1	0	0	2	0	ND	3
16	0	1	0	1	2	0	ND	0
17	0	0	0	0	1	0	ND	0
18	2	0	0	0	1	0	ND	0
19	0	0	0	1	1	0	ND	0
20	1	0	0	0	1	0	ND	0
21	2	0	0	0	1	0	ND	0
22	0	0	0	0	1	0	ND	0
23	2	0	0	0	2	0	ND	0
24	1	0	0	0	1	0	ND	0
25	2	0	0	0	1	0	ND	0

ND, not done.

Table 3 Patient comparison according to their IgG4 status

	IgG4 positive (n=10)	IgG4 negative (n=15)	p Value
Sex M:F	3:7	5:10	1
Age (mean)	49.7	43.3	0.404
Clinical findings			
Pain	3	5	1
Eyelid or periocular swelling/mass	10	13	0.500
EOM restriction	3	7	0.978
Proptosis	5	6	0.697
Decreased visual acuity	4	6	1
Pathological findings			
Background fibrosis ≥ 3	7	2	0.009
Background fibrosis ≥ 2	9	7	0.040
Follicular hyperplasia ≥ 3	3	1	0.267
Follicular hyperplasia ≥ 2	3	1	0.267
Presence of phlebitis	5	0	0.005
Plasmacytic infiltrate ≥ 3	5	0	0.005
Plasmacytic infiltrate ≥ 2	8	3	0.005
Lymphocytic infiltrate ≥ 3	4	0	0.017
Lymphocytic infiltrate ≥ 2	8	7	0.211
Eosinophils ≥ 3	1	1	1
Presence of eosinophils	5	2	0.075

Significant values of p (<0.05) are in bold.
EOM, extraocular muscle.

without IgG4-positive cells. In this study, 40% of patients with biopsy-proven orbital inflammation could be retrospectively classified as IgG4-RD based on characteristic histological features, although they lacked specific clinical or radiological findings.

Contributors RoD, LyD: contribution regarding conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. RaD, GB, SC-P, CV, PVJ, MLH, PB, OGo, MP, AC and OGa: contribution regarding conception and design, and revising it critically for important intellectual content and final approval of the version to be published.

Competing interests None.

Ethics approval This retrospective 101 study was approved by our institutional review board.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Romain Deschamps, Lydia Deschamps, Raphael Depaz, et al.

Br J Ophthalmol published online June 12, 2013

doi: 10.1136/bjophthalmol-2013-303131

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