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IgG4-Related Ophthalmic Disease: Pooling of Published Cases and Literature Review

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Abstract In recent years, IgG4-related ophthalmic disease (IgG4-ROD) has emerged as a common cause of orbital inflammation, accounting for a substantial proportion of idiopathic orbital inflammation and lymphoid hyperplasia. The last pooled analysis of published cases was conducted in 2012, but a large number of new cases have been added to the literature since then. In this review, we present the demographic, clinical, histological, and treatment data for 172 published cases of biopsy-confirmed IgG4-ROD. Results are accompanied by a review of the relevant literature.

Keywords Immunoglobulin G4 · Orbital · Orbit · Ocular · Dacryoadenitis · Lacrimal

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Introduction

IgG4-related disease (IgG4-RD) is a systemic, tumefactive condition characterized by two cardinal histopathological features: tissue infiltration by IgG4-bearing plasma cells and fibrosis, which is usually storiform in character. Obliterative phlebitis, tissue eosinophilia, and a raised serum IgG4 titer are common but do not occur in all cases or all organs [1]. Sites commonly involved by IgG4-RD are the pancreas, hepatobiliary tract, salivary glands, lymph nodes, orbit, and lung [2, 3]. IgG4-RD unites numerous fibro-inflammatory conditions and clinical syndromes, many carrying antiquated eponymous names that were previously thought to be unrelated. These include autoimmune pancreatitis, Küttner's tumor (sclerosing sialadenitis), Riedel's thyroiditis, multifocal fibrosclerosis, Ormond's disease (idiopathic retroperitoneal fibrosis), Mikulicz disease (bilateral lacrimal and salivary gland disease), and a subset of idiopathic orbital inflammation (IOI), previously labeled orbital inflammatory pseudotumors [4, 5].

IgG4-related ophthalmic disease (IgG4-ROD), the preferred nomenclature for IgG4-RD affecting the ocular adnexa or orbit, is a common manifestation of IgG4-RD. A large IgG4-RD disease registry in North America found ophthalmic involvement in 23 % of all IgG4-RD cases [6••]. Japanese reviews of IgG4-related pancreatitis, the most thoroughly researched manifestation of IgG4-RD, have found lacrimal gland swelling in 4 to 34 % of cases [7–9].

Retrospective reviews of archived biopsy specimens have found that IgG4-ROD accounts for a substantial proportion of cases previously classified as IOI and lymphoproliferative disease. Using diagnostic criteria of >10 IgG4+ plasma cells/high power field (hpf) and IgG4+/IgG+ cell ratio >40 %, IgG4-ROD has been found to account for 6 to 40 % of IOI [10, 11••, 12], 50 % of benign lymphoid hyperplasia [11••], and 6 to 23 % of orbital lymphoproliferative disease [12, 13]. Using the

diagnostic criteria of >30 IgG4+/hpf and/or IgG4+/IgG+ >40 %, a large Japanese study (n=1014) found that IgG4-ROD accounted for 22 % of orbital lymphoproliferative disease [14•].

The differential diagnosis of IgG4-ROD includes Sjögren syndrome, lymphoma, sarcoidosis, granulomatosis with polyangiitis (GPA or Wegener's granulomatosis), thyroid-associated orbitopathy, infection, and histiocytic disorders including xanthogranuloma, Erdheim-Chester disease, and Rosai-Dorfman disease [6••, 15]. High concentrations of IgG4+ plasma cells have been reported in several of these conditions, including mucosa-associated lymphoid tissue (MALT) lymphoma [13, 16, 17], sarcoidosis, GPA [18], and histiocytic disorders [19]. For this reason, the diagnosis of IgG4-ROD should only be rendered in the setting of supportive histopathological and clinical features, as described below.

Diagnostic Criteria for IgG4-ROD

Consensus-based diagnostic criteria for IgG4-ROD are still being refined, and published diagnostic algorithms have not been validated. Four sets of diagnostic criteria for IgG4-ROD have been proposed to date.

In 2010, Masaki et al. [20] published diagnostic criteria for IgG4-related Mikulicz disease that required (1) swelling of two pairs of lacrimal, parotid, or submandibular glands and either (2) serum IgG4≥135 mg/dL or (3) fibrosis and lymphoplasmacytic infiltrate with IgG4+/IgG+ cell ratio >50 %. In 2011, Umehara et al. [21] proposed comprehensive diagnostic criteria for IgG4-RD (Table 1). For "probable" IgG4-RD, the criteria required >10 IgG4+/hpf, IgG4+/IgG+ >40 %, lymphoplasmacytic infiltrate, and fibrosis.

In 2012, Deshpande et al. [22] proposed consensus-based diagnostic criteria for IgG4-RD. For "histologically highly suggestive" IgG4-RD involving the lacrimal gland, the criteria required (1) >100 IgG4+/hpf and IgG4+/IgG+ >40 % and (2) at least one of lymphoplasmacytic infiltrate, fibrosis, or obliterative phlebitis.

In 2014, the Japanese Study Group for IgG4-RD proposed a revision of the 2011 comprehensive diagnostic criteria [15]. The new criteria de-emphasized the importance of fibrosis, included trigeminal nerve enlargement and germinal center formation as supportive features, and proposed new diagnostic levels of IgG4 staining. For "probable" IgG4-ROD, the criteria require (1) orbital mass lesion or ocular adnexal swelling and (2) a lymphoplasmacytic infiltrate demonstrating *either* >50 IgG4+/hpf or an IgG4+/IgG+ >40 %.

Table 1 2011 comprehensive diagnostic criteria for IgG4-related disease [21]

1. Swelling or masses in single or multiple organs
2. Lymphoplasmacytic infiltrate, fibrosis, >10 IgG4+ plasma cells/high power field, and IgG4+/IgG+ cell ratio >40 %
3. Serum IgG4≥135 mg/dL

"Definite" IgG4-RD is diagnosed when all criteria are met. "Probable" IgG4-RD is diagnosed when criteria 1 and 2 are met

The aim of this review was to pool clinical, histological, and management data from all published cases of IgG4-ROD and present the findings alongside a review of the relevant literature.

Methods

A literature search on IgG4-ROD was conducted in December 2014 using PubMed. The search was performed on all fields for "immunoglobulin G4" and "IgG4," combined with various synonyms for anatomic structures of the orbit and ocular adnexa. We included all English language publications of biopsy-confirmed IgG4-ROD clearly demonstrating >10 IgG4+ plasma cells/hpf, IgG4+/IgG+ cell ratio >40 %, and histopathological features supportive of the diagnosis. Publications that did not meet the inclusion criteria but had specific relevance to IgG4-ROD were also reviewed. The reference lists of included publications were searched for additional relevant articles. Studies which combined data on IgG4-ROD and IgG4-related sialadenitis were excluded from the pooled analysis.

For each published case of IgG4-ROD, the following information was recorded: demographic information (ethnicity, age, gender), clinical features and organ involvement, serum IgG4 concentration, histopathological features (lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, IgG4+/hpf, IgG4+/IgG+), and management data (treatment, response, duration of follow-up). Case series' findings were summarized for parameters which were not systematically reported by all cases.

The subgroups of cases demonstrating >50 IgG4+ cells/hpf and >100 IgG4+ cells/hpf were identified. The Mann-Whitney U test and the chi-square test were used to compare the age and gender of these subgroups with all identified cases. Statistical analysis was performed on SPSS Statistics 22 (Armonk NY, IBM Corp), and p<0.05 (two-tailed) was considered significant.

Results and Discussion

One hundred seventy-two cases met the inclusion criteria. Of these, 100 cases (58 %) demonstrated >50 IgG4+/hpf. In 54 cases (31 %), it was unclear whether IgG4+/hpf was >50 because the cell count was reported as within a range that spanned across 50, for example ">10" or "30-99." Sixty-two cases (36 %) demonstrated >100 IgG4+/hpf. The age and gender of cases with >50 IgG4+/hpf and >100 IgG4+/hpf were not significantly different to cases with >10 IgG4+/hpf. The

characteristics of the IgG4-ROD cases with >10 IgG4+/hpf are presented below, accompanied by a review of the relevant literature.

Patient Demographics

The ratio of cases from Asian centers to cases from Western centers was 2.4 to 1. Median age was 57 years. The male to female ratio was 1.1 to 1, while IgG4-RD in general tends to affect men more than women [5].

Although the proportion of cases from Asia is high, this may be accounted for by research on IgG4-RD being concentrated in this region. There is no evidence to suggest the existence of racial or geographic variation in IgG4-ROD, and histopathology reviews from Western and Asian centers have reported similar disease frequencies [10, 11••, 13, 14•].

Histopathology

IgG4 Staining

Figure 1 shows the intensity of IgG4 staining in all published cases of IgG4-ROD for which both IgG4+/hpf and IgG4+/IgG+ ratio were quantified. The IgG4+/IgG+ ratio was 0.41–0.49 in 18 % of cases, 0.5–0.59 in 18 % of cases, 0.6–0.69 in 13 % of cases, 0.7–0.79 in 11 % of cases, 0.8–0.89 in 11 % of cases, and ≥0.9 in 29 % of cases.

The IgG4-ROD cases were distributed approximately evenly among the IgG4+/IgG+ ratio deciles. We have previously reported that non-specific orbital inflammations are not organized into discrete IgG4+ and IgG4− groups but span a continuum from no IgG4 staining to intense staining [11••]. The intensity of IgG4 stain that should be considered diagnostic of IgG4-ROD is therefore not self-defining, and proposed diagnostic levels are necessarily derived from an expert opinion.

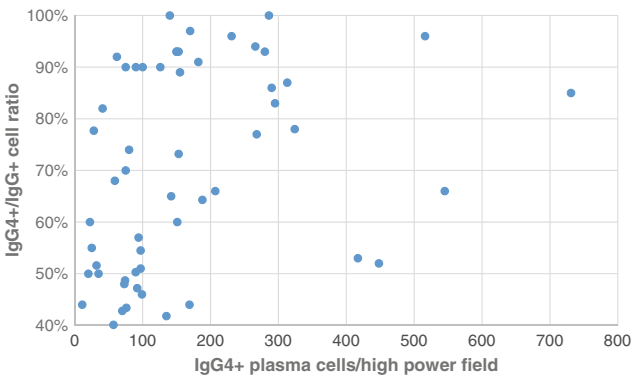

Fig. 1 IgG4+ plasma cells/high power field and IgG4+/IgG+ cell ratio for published cases of IgG4-related ophthalmic disease. *Each circle* represents a case

Supportive Histopathological Features

Lymphoplasmacytic infiltrate and fibrosis were listed as disease features in the vast majority of reports. Storiform fibrosis was reported in around 10 % of cases and obliterative phlebitis in less than 10 %.

The high frequency of lymphoplasmacytic infiltrate and fibrosis among published cases of IgG4-ROD underpins these as cardinal histopathological features. The intensity of these features varies significantly between cases, creating a spectrum of histological patterns in IgG4-ROD, which may be classified into three subsets: pseudolymphomatous, mixed, and sclerotic [23]. The histopathology of IgG4-ROD can change dramatically over time, and since different cases will be biopsied at different stages in the disease course, this may contribute to the wide spectrum of histopathology observed in IgG4-ROD [24, 25]. The lymphocytic infiltrate in IgG4-ROD comprises a histologically bland mixture of B and small T cells, usually but not always with a predominance of the latter.

Fibrosis in IgG4-ROD can occur at disease onset in primary sclerosing cases or as a histopathological endpoint of lesions that were once hypercellular ('burnt out' IgG4-ROD) [24–27]. Fibrosis in IgG4-RD is typically 'storiform'; however, in orbital IgG4-ROD, this pattern is observed infrequently. In our center, storiform fibrosis was present in only 6 % of IgG4-ROD, with most cases instead exhibiting a lamellar pattern of fibrosis [11••]. However, one series reported presence of storiform fibrosis in all cases [6••].

Obliterative phlebitis is rare in IgG4-ROD and cannot be relied upon as a diagnostic adjunct. As such, the 2014 diagnostic criteria for IgG4-ROD do not include it as a supportive feature. Thus, obliterative phlebitis should be considered an organ-specific rather than a disease-specific feature. Interestingly, Deschamps et al. reported a high rate of non-obliterative phlebitis in their series of IgG4-ROD [10]. We previously hypothesized that the low rate of obliterative phlebitis in IgG4-ROD, a diagnosis most commonly found upon biopsy of lacrimal gland tissue, is an artifact of the tiny lacrimal veins being difficult to identify once obliterated [11••].

Lymphoid follicles with germinal centers and a mild to moderate eosinophilic infiltrate are common in IgG4-ROD. In a review of IgG4-ROD from our center, germinal centers were present in 44 % of cases and were not limited to cases with a dense lymphoplasmacytic infiltrate [11••]. Both germinal centers and eosinophilic infiltrate were significantly more common in IgG4-ROD than IOI and benign lymphoid hyperplasia.

Clinical and histopathological features can be suggestive of IgG4-ROD, but quantification of the IgG4+ infiltrate is essential for diagnosis. Three non-overlapping high-power fields

with the highest concentration of IgG4+ cells should be selected for counting. IgG+ cells should be counted in these same areas on a slide cut from adjacent tissue. A high-power field of ×400 magnification (×40 objective with ×10 eyepiece) is standard and is advocated in both the 2012 and 2014 diagnostic criteria for IgG4-ROD. However, the field size will vary depending on the microscope's optics. In publications on IgG4-ROD, this size has been reported to vary from 0.058 to 0.55 mm^2, a difference of factor 10 [28]. As this introduces inconsistencies in diagnosis between centers, Deshpande and colleagues have endorsed the use of a "standard" field area of 0.237 mm^2 and published correction factors for calculating IgG4+ cell counts according to the field number of the eyepiece [22].

Clinical Features

Of cases that reported laterality, 68 % were bilateral and 32 % were unilateral. Cases may present with eyelid swelling or mass effect (78–100 %), proptosis (29–56 %), diplopia or restriction of eye movements (12–33 %), orbital pain (17–33 %) and decreased visual acuity (up to 40 %) [10, 11••, 30•, 34].

Compared to IOI in which orbital pain is a common feature [29], pain may be less common in IgG4-ROD cases. Extraocular muscle (EOM) involvement may present with painful diplopia and proptosis [6••]. However, motility limitation in IgG4-ROD is more commonly attributable to mass lesions than IgG4-related myositis [30•]. Scleral involvement may present with scleral injection, pain, and blurred vision [31, 32]. Compressive optic neuropathy from orbital apex IgG4-ROD has been reported [25]. Nasolacrimal duct involvement should be considered in patients with IgG4-RD who develop epiphora [6••].

Duration of symptoms prior to presentation can vary widely. The reported mean durations range from 4 to 61 months [11••, 33•, 34]. In our center, approximately half of the cases had a subacute or insidious onset, with symptoms of orbital mass effect developing gradually, often with minimal or no signs of inflammation [11••].

Radiological Features

In IgG4-ROD, the most commonly used imaging modalities are computed tomography (CT) and magnetic resonance imaging (MRI) [35–37]. Structures involved by IgG4-ROD include the lacrimal gland (62–88 % of cases), orbital fat (29–40 %), EOM (19–25 %), and trigeminal nerve (10–39 %) [6••, 30•]). Other structures which may be involved include the orbital septum, sclera, optic nerve [10, 38], eyelid [6••, 39], conjunctiva [40], and lacrimal sac [41].

On CT and MRI, IgG4-ROD mass lesions characteristically show well-defined margins, homogenous internal architecture and contrast enhancement, and bone remodeling without destruction [42]. Compared to brain gray matter, lesions show isoattenuation on precontrast CT, isointensity on T1-weighted precontrast MRI, and hypointensity on T2-weighted precontrast MRI [42]. However, these imaging features are non-specific.

Trigeminal nerve enlargement has emerged as a useful diagnostic sign that can help differentiate IgG4-ROD from other tumefactive conditions of the orbit. Radiological reviews of IgG4-ROD have reported trigeminal nerve enlargement in 24 % (4/17 cases) [43], 29 % (20/68 cases) [44], 39 % (25/65 cases) [30•], and 50 % (8/16 cases) of cases [35]. In addition, one study ($n=14$) found that 50 % of patients with infraorbital nerve (ION) enlargement had IgG4-ROD [45•]. Studies have found the ION to be significantly thicker in IgG4-ROD than both controls and lymphoproliferative disorders [35, 44]. ION enlargement may also have prognostic value as one study found that it was associated with higher serum IgG4 and multiple organ involvement [44]. Nerve involvement in IgG4-ROD is usually epineural and axon-sparing but can occasionally cause pain, paresthesia, or numbness [30•, 45•, 46].

ION enlargement has been defined as vertical nerve diameter greater than that of the optic nerve on coronal section [35, 45•]; however, ION diameter can be overestimated in cases where the infraorbital canal runs oblique to the coronal plane. The results of one study suggest that the reference range for normal vertical ION thickness is 2.0–3.3 mm (95 % confidence interval) [44].

The differential diagnosis for periocular nerve enlargement includes IgG4-RD, sarcoidosis, IOI, and neoplasms of lymphoid, neurogenic, or epithelial origin. Imaging features favoring IgG4-ROD include bilateral nerve thickening, involvement of multiple nerves particularly the ION, involvement of the entire length of EOMs from origin to insertion, sinus disease, and orbital and extra-orbital mass lesions [30•, 35, 36, 45•].

Extra-Ophthalmic Involvement

The detection of extra-ophthalmic disease depends on the completeness of the systemic work-up. With comprehensive systemic work-up, extra-ophthalmic disease may be found in 71–100 % of cases [47•]. Extra-ophthalmic IgG4-RD may present synchronously or metachronously to ophthalmic disease. Commonly involved structures are the salivary glands and lymph nodes. Involvement of the kidney or urinary tract, pancreas, sinuses, lungs, arteries, thyroid gland, skin, prostate, pituitary gland, liver, bile duct, nerves, retroperitoneum, and pericardium has also been reported.

There are currently no consensus-based guidelines regarding appropriate systemic work-up for a patient with a new diagnosis of IgG4-ROD. In our center, the systemic work-up includes physical examination giving particular attention to lymph nodes and salivary glands, complete blood picture, serum protein electrophoresis, serum electrolytes, liver function testing and renal function testing. Some authors have recommended systemic imaging (including the neck, chest, abdomen, and pelvis) for all cases upon diagnosis, even those without clinical or biochemical evidence of organ dysfunction [47•]. In our center, cases of bilateral IgG4-ROD were more likely to have systemic involvement than unilateral cases. Thus, bilateral IgG4-ROD may be an indication for systemic imaging. It should be noted that the detection of extra-orbital IgG4-RD mass lesions may change management by strengthening the rationale for systemic treatment (e.g., prednisolone or rituximab) over local treatment (e.g., intraorbital corticosteroid injection). Furthermore, it is not known if early treatment of asymptomatic disease results in better long-term outcomes, although since IgG4-RD is thought to be a fibrosing process, this is biologically plausible. Suitable imaging modalities include CT with contrast enhancement [31], fluorodeoxyglucose positron emission tomography (FDG-PET) [48], and gallium scintigraphy [33•]. A drawback of FDG-PET is that it is unsuitable for imaging the kidney and pituitary gland [49], two sites where IgG4-RD is well described. It is important that the patient's primary care physician is informed of the diagnosis of IgG4-RD, so that should the patient develop organ dysfunction in the future, IgG4-RD is ranked appropriately in the differential diagnosis.

Serum Biomarkers

Serum IgG4 level and serum IgG4/IgG ratio have been proposed as biomarkers of disease activity that can inform management [39]; however, a clear role for monitoring serum IgG4 has not been established. The proportion of IgG4-ROD cases with normal serum IgG4 has varied from 0 to 37 % in different studies [6••, 39]. High serum IgG4 in IgG4-ROD has been associated with both bilateral and extra-ophthalmic disease [6••, 34]; very high serum IgG4 (>900 mg/dL) has been associated with a longer duration of symptoms [33•].

Recently, Wallace and colleagues reported that circulating IgG4+ plasmablasts are a more sensitive biomarker of IgG4-RD than serum IgG4. Increased numbers of IgG4+ plasmablasts (detected using flow cytometry) are present in the peripheral blood of patients with IgG4-RD, regardless of their serum IgG4 status, rendering this a potentially useful biomarker for diagnosis, assessing response to treatment, and determining the appropriate time for retreatment [50].

IgG4-ROD has been associated with evidence of enhanced T-helper cell type 2 (Th2) activity, including raised serum IgE [33•, 34], blood eosinophilia [11••], and elevated expression of the Th2 cytokines interleukin (IL)-4, IL-5, and IL-10 [51]. Furthermore, allergic disease and tissue eosinophilia are common in IgG4-ROD. These findings suggest that IgG4-ROD is caused by immune dysregulation skewed towards a Th2 phenotype. It is not known whether immune dysregulation is a cause or a consequence of IgG4-RD; to answer this question, it might be helpful to investigate whether allergic disease precedes or follows the diagnosis of IgG4-RD in patients.

Management

There is currently no consensus on defining response to treatment, and different studies have used different endpoints [27]. Treatment response has often been reported using non-specific descriptors such as "good" and "significant." Furthermore, many studies did not distinguish between clinical and radiological response. A standardized IgG4-RD responder index has been proposed to help researchers compare outcomes of treatment [52].

Of cases that reported response to corticosteroids, 95 % improved on the treatment. However, relapse was reported to occur in 72 % of cases. 17 cases improved on rituximab and 1 had no response. 9 cases were given additional cycles of rituximab as maintenance therapy.

A minority of IgG4-ROD cases has settled following the debulking effect of biopsy and did not require specific treatment [11••, 33•].

Corticosteroids are considered to be first-line treatment for IgG4-ROD, and the response is usually excellent but unsustained, which is underscored by the fact that over half of published IgG4-ROD cases have suffered relapses. The typical starting dose for oral prednisolone is 0.6–1 mg/kg/day for 1–2 weeks, tapered over the following 5–8 weeks. If disease flares occur during taper, the dose is increased and tapered more slowly, typically over 10 to 12 weeks. In cases of disease localized only to the orbit, intraorbital injection of corticosteroids may also be considered [40, 53•].

The high rate of disease relapse following corticosteroid treatment necessitates low-dose maintenance therapy or additional pharmacotherapies in the majority of cases. One large series of IgG4-related dacryoadenitis and/or sialadenitis (IgG4-DS) (n=122) reported that 50 % of cases suffered at least one relapse within 7 years of initial treatment with corticosteroids [49]. Although many of the IgG4-DS cases were adequately controlled on <5 mg/day oral prednisolone, a study of IgG4-ROD (n=9) found that disease was controlled with 9–20 mg/day oral prednisolone [47•]. Risk factors for relapse may include concomitant autoimmune pancreatitis, low steroid dose for initial treatment, male gender, younger age of onset, and normal serum IgG4 in patients with known extra-ophthalmic involvement and high serum rheumatoid factor in

the 6 months following treatment [33•, 54]. Serum IgG4 level before and after treatment has not been shown to predict early relapse [33•, 55]. Factors predictive of a poor response to corticosteroids may include severe fibrosis and lower serum IgG4 prior to treatment [39].

Rituximab and radiotherapy have generally been reserved as second-line agents for patients with steroid-resistant or steroid-intolerant disease [6••, 39, 53•]. Rituximab is usually given as monotherapy but has occasionally been used in combination with chemotherapy agents [56]. Rituximab induces apoptosis of immature and mature B lymphocytes, including those destined to become IgG4-bearing plasma cells. Stem cells regenerate the B cell population over the following 6 months. Various dosing regimens have been used for rituximab induction therapy in IgG4-ROD; more common regimens include two doses of rituximab 1000 mg IV separated by 14 days [6••] or four doses of rituximab 375 mg/m^2 IV at weekly intervals [53•]. Following induction, the patient can either be observed or can commence rituximab maintenance therapy, comprising additional treatment cycles given periodically. The decision to use maintenance therapy is empiric, although rising serum IgG4 level and increasing blood IgG4+ plasmablasts have been suggested to herald a disease flare and could potentially be used to guide management [50, 57]. Rituximab maintenance therapy is often used. If relapse occurs, rituximab re-induction therapy can potentially achieve disease control [53•]. Rituximab may occasionally fail to control cases of fibrosing IgG4-ROD [6••]. Rituximab is generally well tolerated but has a moderate risk of infusion reactions [53•] and a small risk of serious adverse effects including progressive multifocal leukoencephalopathy. For this reason, rituximab treatment for IgG4-ROD is usually administered by oncologists, hematologists, and rheumatologists experienced with its use.

Treatments used less frequently for IgG4-ROD have included immunosuppressants (azathioprine, methotrexate, mycophenolate, cyclophosphamide, and cyclosporine), infliximab, and surgical decompression of vision-threatening disease [6••].

IgG4-ROD and Lymphoma

Compared to the general population, IgG4-RD patients are at 3.5 times higher risk of developing malignancies [58]. The malignancies that can develop include lung cancer, colon cancer, and lymphoma, in particular MALT lymphoma.

IgG4-ROD needs to be distinguished from MALT lymphoma [59]. However, IgG4 staining is not sufficient for differentiation, as a proportion of MALT lymphomas display IgG4 staining. In a large study of orbital lymphoproliferative disease (n=1014), 10 % of the 448 MALT lymphomas displayed IgG4 staining [14•]. In another study of ocular adnexal MALT lymphoma (n=111), IgG4+ plasma cell infiltrate was present in 9 % of cases [60]. It has been hypothesized that IgG4-positive MALT lymphomas may be due to either (1) the coexistence of IgG4+ plasma cells and MALT lymphomas which do not produce IgG4 or (2) MALT lymphomas directly producing IgG4 [14•].

Additional investigations are recommended to distinguish IgG4-ROD from lymphomas, which are characterized by B lymphocyte predominant infiltrate and a monoclonal lymphocyte population [6••, 61]. To characterize the lymphocytic infiltrate, immunophenotyping by flow cytometry and immunohistochemistry may be done. Molecular genetic analysis (polymerase chain reaction or Southern blot hybridization) is a more sensitive measure of monoclonality and detects rearrangement of the Ig heavy chain or T cell receptor genes. It is particularly useful when the morphology and immunophenotype are indeterminate. Strong consideration should be given to performing flow cytometry and/or molecular genetic analysis when the diagnosis of IgG4-ROD is contemplated and not only when lymphoma is suspected from the clinico-radiological picture. Clinicians should therefore ensure that fresh tissue for flow is collected when performing biopsies in suspected cases of IgG4-ROD.

Conclusions

In this review, we identified 172 published cases of biopsy-confirmed IgG4-ROD. At least 58 % had >50 IgG4+/hpf, 36 % had >100 IgG4+/hpf, and the IgG4+/IgG+ ratio deciles were relatively evenly distributed between 40 and 100 %. IgG4-ROD has a median age of onset of 57 years, has no gender predilection (in contrast to extra-ophthalmic IgG4-RD), is bilateral in over half of cases, presents with orbital mass effect occasionally accompanied by erythema and pain, and is steroid responsive but usually recurrent. Lymphoplasmacytic infiltrate (sometimes with lymphoid follicles) and fibrosis (occasionally storiform) are ubiquitous histological features; however, their relative intensity may vary substantially between cases and change over time.

The frequent revision of IgG4-ROD diagnostic criteria has been a necessary inconvenience. Inevitably, wherever boundaries are drawn will find the seeds of dispute. Decisive staining cutoffs will only come from identification of unifying clinical features, unifying disease biomarkers, or elucidation of a unifying etiology. Until there is international and unanimous agreement on IgG4-ROD diagnostic criteria, it is important that authors meticulously publish complete case details so that the literature can be retrospectively interrogated as diagnostic criteria change.

Soon, prospective trials for IgG4-ROD will begin investigating trends revealed by the retrospective literature. It is important that a coordinated, organized approach is taken so that trials are comparable and can be amalgamated for meta-

analysis. This will require high levels of collaboration, a comprehensive and systematic classification system for categorizing cases, and standardized definitions for important treatment end points such as treatment response and relapse. Other research topics of high priority are the development of pragmatic guidelines for the appropriate systemic work-up of new cases and the identification of disease biomarkers that can inform management and prognosticate.

Compliance with Ethics Guidelines

Conflict of Interest Albert Wu, Nicholas H. Andrew, Alan A. McNab, and Dinesh Selva declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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