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RESEARCH PAPER

The impact of IgG-4-ROD on the diagnosis of orbital tumors: A retrospective analysis

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ABSTRACT

This study was to determine the prevalence of immunoglobulin G4 (IgG4)-related orbital disease (IgG4-ROD) among patients who have previously undergone biopsy and were diagnosed to have idiopathic orbital inflammatory disease (IOID) or orbital lymphoproliferative disease (OLD), namely, lymphoma and benign reactive lymphoid hyperplasia (BRLH). This is a retrospective cross-sectional study. The charts and slides of all patients who underwent biopsies and were histopathologically diagnosed to have either IOID or OLD were reviewed. Demographics, clinical features, initial histopathological diagnoses, treatment received, and final outcome were noted. Using the diagnostic criteria for diagnosis for IgG4 disease, those cases that would classify as "possible IgG4-related disease (IgG4-RD)" were reviewed, reclassified, and reassigned a diagnosis of IgG4-ROD. We reviewed 105 patients' clinical charts. Of these 105 patients, upon reviewing the histopathology, 18 (17.15%) patients were found to fit the diagnostic criteria for possible IgG4-ROD. Of these 18 patients who were now reassigned the diagnosis of IgG4-ROD, the most common previous histopathological diagnosis was found to be IOID, for eight patients (44%), then BRLH, which was noted in five patients (27.8%), followed by lymphoma, which was noted in two patients (11.1%). Previously diagnosed cases of IOID and OLD were found to fulfill the criteria for IgG4-ROD. Given the advent of recent diagnostic and histopathological techniques, all cases of suspected IOID and OLD should be screened for IgG4-ROD and all previously diagnosed cases must be closely followed up, given the systemic implication of IgG4-RD. Histopathological reassessment of previously diagnosed cases may be considered.

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Introduction

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a systemic inflammatory pathology that was first described in 2001 and for which the diagnostic criteria have been only recently defined.[1,2] The disease was originally diagnosed as part of the spectrum of autoimmune pancreatitis.[2] The fact that it involves multiple organs with different manifestations presents a challenge to diagnosis and differentiation from other inflammatory diseases.[3,4] The diagnostic criteria include both clinical parameters and histological findings in tissue samples taken from a suspect lesion.[5] The currently accepted criteria for diagnosis are[6,7]:

(1) Diffuse swelling or masses located in one or more organs.
(2) Histological findings: the presence of plasma cell infiltration and fibrosis (certain organs, such as the pancreas, should also reveal obliterative phlebitis) and a ratio of IgG4 cells/IgG cells of >40%, as well as >10 positive plasma cells (IgG4/high-power field).
(3) Increased serum IgG4 levels.

The presence of the first two criteria enables diagnosis and the presence of all three criteria establishes a definitive diagnosis. There are four types of human serum IgG, numbered according to their serum concentrations. IgG4 is an IgG antibody that represents less than 5% of the total and its main function is presumed to be anti-inflammatory.[8] Unlike the rest of the IgG group, IgG4 is unable to activate the complement components, it has a low affinity for Fc receptors on the leukocytes, and it is able to remove IgG1 and IgE from their binding sites.[8] Several studies showed this antibody to have a role in the development of antigen tolerance.[8,9] The currently leading theory is that IgG4-related disease is an overreaction of the body following

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exposure to an external antigen and not an autoimmune disease. The nature of the disease, expressed mainly as local inflammatory response without tissue destruction, also supports this theory.[9,10]

Information on the disease's ophthalmic manifestation is mainly based on case studies and small case series. Most of the patients described in the literature were diagnosed when orbital biopsies were performed for suspected lymphoproliferative disease and in cases of idiopathic orbital inflammation (IOI) that was refractory to standard treatment.[11,12,13,14] The most common reported clinical manifestation was periorbital swelling and proptosis with or without diplopia.

Mikulicz's disease is one of the pathologies most influenced by the finding of IgG4-RD. It is an inflammatory disease that simultaneously involves both tear glands and submandibular or parotid glands. It had formerly been considered part of the Sjögren disease spectrum. Recent studies have shown that Mikulicz's disease has elevated IgG4 levels and characteristic IgG4-RD findings in biopsy, and it is now considered part of the IgG4-RD spectrum[15,16]. A recent study showed that 45% of the affected patients also have evidence of systemic disease on positron-emission tomographic computerized tomography (PET-CT), and the search for a systemic disease has now become routine in patients suspected as having this disease.[17,18]

The majority of patients diagnosed as having IOI rarely undergo diagnostic biopsy since they respond well to steroids. Therefore, it is very difficult to assess the true prevalence of orbital IgG4-RD. Recent retrospective works have thus far examined the prevalence of IgG4-RD in patients undergoing biopsy for suspected orbital lymphoproliferative disease; it ranged from 23% in one Japanese study to 5.6% in a study conducted in the United States.[19,20] This, however, does not reflect the true incidence in the population.

Methods

We aimed to determine the prevalence IgG4-RD among patients who underwent orbital biopsies for suspected orbital IOI and/or orbital lymphoproliferative disease (OLD) in the Department of Ophthalmology at the Sheba Medical Center from 1996 to 2011.

The charts of all patients who underwent biopsies for suspected orbital masses were reviewed. Demographics, clinical features, initial histopathological diagnoses, treatment received, and final outcome were noted. Only those with conclusive histopathological diagnosis were retained. On the basis of their etiology, the lesions were classified and the final subset that was of interest contained those that are most commonly the differential diagnoses of IgG4-ROD: idiopathic orbital inflammatory disease (IOID) and lymphoproliferative lesions (lymphoma and benign reactive lymphoid hyperplasia [BRLH]). The charts of these patients were reviewed along with their histopathology slides. The samples were fixed in 10% formaldehyde and embedded in paraffin. Serial sections (4 μm) were cut from each paraffin-embedded tissue block, and several sections were stained with hematoxylin and eosin and also immunostained for IgG4-expressing cells. Immunohistochemistry was performed using an automated Benchmark XT slide stainer (Ventana Medical Systems, Tucson, AZ). Paraffin-embedded tissue sections were deparaffinized using EZ Prep (Ventana Medical Systems) and pretreated with the standard CC1 protocol for antigen retrieval. Immunostaining for IgG4 expression was performed using a mouse monoclonal antibody against human IgG4 (Binding Site, Birmingham, UK). The degree of infiltration was be scored as none, mild, moderate, or marked, according to the number of IgG4-positive plasma cells seen on high-power field (HPF) in each specimen, and the areas with the highest density of IgG4-positive plasma cells were also evaluated. The presence of more than 10 plasma cells positive for IgG4/HPF was considered a positive test result for IgG4-RD. Two masked observers performed the cell counting. Paraffin sections of the patients identified with IgG4-related disease were stained following the Elastica–Masson method and immunostained with a mouse monoclonal antibody against human CD138 (Dako, Glostrup, Denmark). The IgG4-positive/CD138-positive plasma cell ratio was calculated. Using the aforementioned diagnostic criteria, those cases that would classify as "possible IgG4-RD" were reviewed and all demographic, clinical, and radiological information was collected.

Results

We reviewed 105 patients' clinical charts and slides. All the patient's slides were reexamined after staining for IgG. Of these 105 patients, 18 (17.15%) patients were found to fit the diagnostic criteria for possible IgG4 RD: namely, with a positive history of an orbital mass, histopathological evidence of plasma cell infiltration and fibrosis, and a ratio of IgG4 cells/IgG cells of <40%, as well as >10 positive plasma cells (IgG4/HPF). With regard to the cell count, which was performed by the masked observers, no discordance was found between the findings of the observers in any of the cases that fit the diagnostic criteria for IgG4-related orbital disease (IgG4-ROD), suggesting a high degree of agreement.

Of these 18 patients who were now reassigned the diagnosis of IgG4 RD, the most common previous histopathological diagnosis was found to be IOID, in eight patientts (44%). BRLH, which was noted in five patients (27.8%), was the next most common diagnosis, followed by lymphoma, which was noted in two patients (11.1%). The complete list is given in Table 1.

In the newly assigned IgG4 RD group, the mean age of presentation was 46.8 years (range: 9–71 years; SD: ±19.42). A female predilection was noted, with 11/18 (61.1%) patients being female.

The most common presenting complain among these patients was the presence of a mass or orbital/eyelid swelling, which was seen in 11 patients (61.1%), followed by proptosis in nine patients (50%) and ptosis, which was observed in seven patients (38.9%). The other presenting complaints included pain and diplopia. An overwhelming majority (16/18) of the patients presented with unilateral disease (88.9%). Within the larger cohort of 105 patients, nine were found to have bilateral disease: five with a final diagnosis of lymphoma and four patients with IOID. Two of those nine bilateral cases were found to be IgG4 positive (20%). On imaging with computed tomography scans, the most frequently observed findings was lacrimal gland enlargement (7/18; 38.9%), followed by extraocular muscle enlargement, which was seen in five patients (27.8%), orbital mass in four patients (22%), and a preseptal mass and optic nerve lesion were seen in one patient each. The details of the radiological findings are summarized in Table 2.

We compared the clinical and demographic characteristics of two groups of patients: those who now fit the IgG4 criteria and those who did not have IgG4 disease. The parameters compared included age, gender, presenting sign, disease duration, and laterality. The independent samples were tested using Levene's test for equality of variances, the chi-squared test, and the *t*-tests. However, no single clinical characteristic was found to be significantly higher in either group. However, we believe that that groups compared here had too few subjects to reflect a statistically significant difference.

The treatment modalities included oral steroids, radiation, systemic chemotherapy, and radiation therapy, depending on the clinician's plan as per the earlier diagnosis.

Table 1. Summary of the previous diagnoses of the cases that were reclassified as IgG4-related orbital disease.

Previous diagnosis	Number of cases	Percentage
Lymphoma	2	11.1%
Idiopathic orbital inflammation	8	44.4%
Sarcoid-like granulomatosis inflammation	1	5.6%
Low-grade leiomyosarcoma	1	5.6%
Thyroid eye disease	1	5.6%
Benign reactive lymphoid hyperplasia	5	26.8%
Total	18	100.0%

Table 2. Summary of the radiographic findings on computed tomography (CT) scans in IgG4-related orbital disease patients in the study.

Radiographic finding	Frequency	Percentage
One EOM enlargement	3	16.7%
Multiple EOM enlargement	2	11.1%
Lacrimal gland involvement	7	38.9%
Orbital mass lesion	4	22.2%
Preseptal involvement	1	5.6%
Optic nerve involvement	1	5.6%
Total	18	100.0%

Note. EOM, extraocular muscle.

Discussion

According to Ferry et al., in a survey of 38 patients previously diagnosed as IOID or chronic dacryoadenitis, 15 were positive for IgG4 disease and five were probable for IgG4 disease without all of the characteristics.[21] In clinical presentation, according to Andrew et al., painless eyelid swelling and mass is the most common symptom, followed by proptosis with or without diplopia.[18] According to Deschamps et al., IgG4-positive patients presented most commonly with painless eyelid or periocular swelling, followed by proptosis and diplopia.[22] Wu at al., in their retrospective analysis of 172 published cases, found that eyelid swelling and mass effect was the most common symptom seen in 78–100% of the cases, followed by proptosis, which was seen in 29–56% of cases.[23] This correlates with our findings: In our study, the common presenting symptoms were eyelid swelling and mass, followed by proptosis. According to Andrew et al., IgG4-RD affects males and females equally. This is in sharp contrast to IgG4-related pancreatitis, which has a strong male predilection.[18] Deschamps at al. reported that out of their 10 IgG4-RD patients, seven were female; this was correlated with our study, in which 61% of the positive patients were female.-[21]Wu et al. found the female to male ratio to be 1:1.[23] The mean age of presentation was found to be 49.7 years by Dechamps et al., whereas Andrew et al. reported the age of presentation in their cohort to be 55.5 years; Wu found the median age to be 57 years, while in the study by Ferry et al. it was 64 years.[18,21,22,23] Our mean age in positive patients was found to be 46.8 years.

Sogabe et al. reported the radiographic findings of IgG4-RD in a study detailing 65 patients. In their study, the most common finding was lacrimal gland swelling. Other findings included extraocular muscle involvement and finally followed by diffuse orbital involvement.[24] Cheuk et al., Sato et al., and Plaza et al. all demonstrate that lacrimal gland involvement is the most common finding in IgG4-RD.[2,16,19] Deschamps et al. also found that lacrimal gland

involvement was the most common finding, which was corroborated by Wu et al.[22,23] This is corroborated by our findings, as our most common radiographic finding was lacrimal gland enlargement, followed by extraocular muscle (EOM) involvement, which was followed by an orbital mass. For laterality, we found nine bilateral cases out of the total 105 cases. Two of these nine bilateral cases (20%) were found to be IgG4 positive. According to Andrew et al., 68% of the patients were bilateral and 32% were unilateral (Table 3).[18]

This study, being a retrospective study, has its limitations. There was no attempt at long-term evaluation, such as extended follow-up and outcomes. Furthermore, since this was retrospective in nature, it was not feasible to call the patients back and do further tests such as serum IgG4 that would help establish a "definitive diagnosis"; our study therefore presents the cases of "possible IgG4-RD," those that meet two of the three diagnostic criteria. This, however is acceptable in the diagnosis and management of this disease entity.[17]

Previously in the literature, it has been reported that IgG4-RD can mimic ocular lymphoma. Karamchandani et al. reported that in their study, out of 164 biopsies of the ocular region for suspected lymphoma, they identified six cases of IgG4 disease, four of which were previously unrecognized. In their series, six cases demonstrated increased plasma cells in a background of sclerosis and increased absolute numbers of IgG4-expressing cells. They highlighted the difficulty in diagnosing IgG4-related sclerosing disease in the ocular region. Furthermore, using their findings as the basis, they recommended that specimens from biopsies of the ocular adnexa for which a definitive diagnosis of lymphoma is not established undergo further workup for IgG and IgG4, particularly if increased plasma cells and sclerosis are present.[20]

Orbital IgG4-related disease must be differentiated from idiopathic orbital inflammation and ocular adnexal marginal zone B-cell lymphoma to ensure appropriate and effective treatment.[25]In theory, it is essential to understand the concepts of orbital inflammatory disease. Orbital inflammatory disease is a general umbrella term used to indicate any inflammatory process within the orbit. The cause for inflammation can be attributable to many disease processes, such as Wegner's granulomatosis, sarcoidosis, and systemic lupus erythematosis, among a host of other causes. However, while discrete and classifiable diseases can be implicated in many cases, up to 5–8% of cases have no discernible cause on biopsy and are hence labeled idiopathic orbital inflammation (IOI).[26]

Histologically, these cases usually show a pleomorphic inflammatory cellular response and a fibrovascular tissue reaction. A spectrum of granulomatous inflammation is noted, admixed with nongranulomatous inflammation and fibrosis.[27]As Linfield and colleagues have reported, the recent discovery that IgG4 has a causative role in a subtype of IOI indicates that IOI cases should be investigated for IgG4-related disease.[26] In contrast, classical IgG4-related orbital disease shows dense lymphoplasmacytic infiltrate that is rich in IgG4+ plasma cells (IgG4+ PC), storiform fibrosis, and obliterative phlebitis. Immunohistochemical analysis shows IgG4-positive plasma cells, which differentiate IgG4-related disease from other inflammatory conditions arising from the ocular adnexa and benign reactive lymphoid hyperplasia.

There were two cases in our study that were diagnosed retrospectively as IgG4-RD but that were earlier reported were as extranodal marginal zone B-cell lymphoma (EMZL). Kase et al. have reported the case of IgG4-related inflammation of the orbit simulating

Table 3. Comparison of demographics and symptomatology in IgG4 disease in our literature review.

Name of study	Number of patients in study	Number of patients: IgG-4 + disease	Median age (years)	Gender	Laterality	Systemic symptoms	Common radiologic findings	Histology characteristics	Clinical features
Ferry et al.[21]	38	15: definite (39.5%) 5: probable (52.6%)	64	1:1 F:M	Unilateral: 60% Bilateral: 40%	10%: Lesions in other anatomic sites	Orbital soft tissue: 21% Lacrimal gland: 15%	All showed lymphocytoplasmic infiltrate and fibrosis	N/A
Wu et al.[23]	172	172	57	1:1 F:M	Unilateral: 32% Bilateral: 68%	N/A	LG: 88% OF: 40%	Lymphocytoplasmic infilatrate and fibrosis 100%	ES: 100% Proptosis: 56% OF: 33%
Deschamps et al.[22]	25	10 (40%)	49	8.3:1 F:M	Unilateral: 80% Bilateral: 20%	12%: Lesions in other anatomic sites	LG: 80% EOM: 40%	Lymphocytoplasmic infiltrate and fibrosis	ES: 100%
Andrew et al.[18]	N/A	N/A	55.5	1:1 F:M	N/A	N/A	N/A	Lymphocytoplasmic infiltrate and fibrosis	ES: most common in cited studies

Note. ES, eyelid swelling; LG, lacrimal gland; OF, orbital fat. F. female; M, male. N/A, not available.

extranodal marginal zone B-cell lymphoma.[28]They reported the case of a 72-year-old female who complained of bilateral eyelid swelling for 3 years. A magnetic resonance imaging (MRI) scan demonstrated two kinds of orbital lesions, one exhibiting a low density and the other of relatively high density, in proximity to each other. Laboratory tests in this case showed high serum IgG4 concentrations. Histologically the two masses were diagnosed as IgG4-related inflammation and EMZL, respectively. Kase et al. concluded that EMZL can arise from massive IgG4-related orbital inflammation. In our series, there were two cases that were previously diagnosed as lymphoma that histologically expressed IgG4 positivity. It may be hypothesized that these cases could represent a similar scenario where cases of IgG4-related orbital diseases developed lymphoma at the same location. Serum IgG4 levels, however, in our cases were not available to help in diagnosis. This further adds strength to the hypothesis that there could potentially exist a higher rate of lymphoma—localized or systemic—in patients that have IgG4-related inflammation.

We believe that our findings represent a paradigm shift in the histopathological diagnosis of orbital lesions. Previously published series of orbital tumors have shown that IOID is a relatively common diagnosis.[29] Given the recent advent of diagnostic tests that have enabled the diagnosis of IgG4-RD, one wonders how many of these IOID patients would have been diagnosed as IgG4-ROD.[17] IgG4-ROD is a diagnosis that requires different management and staging as compared to IOID. The patient must be evaluated for systemic involvement, as well as a detailed workup by a rheumatologist.[30] Salivary gland enlargement and diffuse lymphadenopathy must be looked for, in addition to renal and hepatic workup, as those organs can also be affected. Serum IgG4 levels should be obtained and may serve as a baseline test for treatment response.[30] Imaging of head, neck, chest, abdomen, and pelvis as well as whole body PET-CT may be performed if there is suspected soft-tissue involvement. Furthermore, there appears to be a connection between IgG4-ROD and lymphoma; it seems that the increased inflammatory response increases the incidence of lymphoma.[17,18] Thus, in the diagnosis of IgG4, the treating physician must be aware of this increased incidence of lymphoma and be fastidious in follow-up and quick to rebiopsy should the lesion recur. We believe this is one of the most significant ramifications of our study. It may be worthwhile to see how many patients of IgG4-ROD, who were diagnosed as IOID in the past, develop lymphoma over the long term.

In terms of treatment, corticosteroids are still the mainstay of treatment. There is evidence to show that the immense amount of fibrosis that is evident in these cases can lead to irreversible damage if not treated.[30] There have been good responses to Rituximab in recent studies.[17,30] There is not currently a single prospective long-term study reporting on treatment regimens and response in IgG4-RD, and there is also no current agreement on defining response to treatment. Since orbital involvement in IgG4 is relatively common, we must have a high index of suspicion in patients who present with an "IOID"-like picture. The diagnosis of IgG4 changes the management and subsequent follow-up, and hence, we believe there may be a potential benefit in reviewing previously diagnosed cases of IOI and benign lymphoproliferative conditions and screening them for IgG4-RD.

Our study reports the clinical characteristics of patients from Israel. While there have been anecdotal reports of previously diagnosed cases of IOID turning out to be IgG4-ROD on detailed examination, our study highlights that this proportion could be significant.[17,31] Both diseases have overlapping clinical and radiological features. However, the systemic implications of IgG4-ROD make our findings significant. Close follow-up of previously diagnosed IOID patients is warranted with a high degree of suspicion for lymphoma or multisystemic disease, as they could possibly indicate an IgG4-related etiology. IgG4-RD is a mimic of IOID; larger studies, however, are needed to corroborate our findings and establish their true clinical relevance.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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