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REVIEW

Systemic immunoglobulin G4 (IgG4) disease and idiopathic orbital inflammation; removing 'idiopathic' from the nomenclature?

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Abstract

The discovery of systemic disease related to raised tissue and serum immunoglobulin G4 (IgG4) is changing diagnostic and therapeutic practice in many medical specialties. Orbital inflammation remains a diverse and heterogeneous group of disorders that can pose a diagnostic and therapeutic challenge, but with improved understanding and corresponding diagnostic advances the previously expansive group of idiopathies is reducing. The recent discovery that IgG4 has a causative role in a subtype of, what is currently termed, idiopathic orbital inflammation is encouraging. The term 'idiopathic' can now be removed from the nomenclature for another subtype of orbital inflammation. IgG4 disease should be especially considered in patients with a bilateral dacryoadenitis and systemic features (eg, lung and gastrointestinal involvement). However, reports are emerging suggesting that IgG4 may be responsible for more diverse disease subtypes. The relationship between IgG4-related disease and lymphoma remains unknown but vigilance is required.
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Introduction

Inflammatory process afflicting the orbit can be attributed to a number of causes, both systemic and localised (Table 1).[1] Subclassification can be based upon temporary course (acute or chronic), morphological classification (local or diffuse), or anatomical location.[2] Discrete and classifiable diseases can be implicated, but 5–8%[1,3] have no discernible cause on biopsy and hence labelled idiopathic orbital inflammation (IOI). This benign, non-infective syndrome was first described in 1903[4,5] and recognised as a specific clinicopathological entity of 'an orbital mass that simulated a neoplasm but was histologically inflammatory' in 1905.[6] Previously, these were termed orbital pseudotumour but confusion over clinical and pathological diagnosis recommended a change in terminology to IOI.[2] This umbrella term of conditions that do not fit neatly into established diagnoses is one of the transition and continuing revision. There is no single feature that is pathognomonic. In fact, the history of IOI has been defined by what it is not. Improved knowledge and advances in investigational techniques have narrowed the once broad and expansive term 'idiopathic'.[7] Sarcoidosis, Wegener's granulomatosis and xanthogranulomatosis are now distinguishable and diagnosable with biochemical and immunological testing. IOI remains a diagnosis of exclusion but is it merely a 'tissue response to some other process not yet elucidated by available testing'.[8]

Immunoglobulin

Immunoglobulins are Y-shaped glycoproteins which form the humoral arm of the immune system, most commonly referred to as

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Table 1 Causes of orbital inflammation[1]

Idiopathic orbital inflammation
Systemic inflammatory disease
Autoimmune thyroid disease
Sarcoidosis
Wegener's granulomatosis
Crohn's disease
Systemic lupus erythematosus
Churg–Strauss syndrome
Erdheim–Chester syndrome
Histiocytosis X
Tolosa–Hunt syndrome
Giant cell arteritis
Idiopathic fibrosclerotic disorders
Periarteritis nodosa
Scleroderma
Sclerosing cholangitis
Neoplasm
Lymphoma
Lymphoproliferative disorders
Rhabdomyosarcoma
Choroidal malignant melanoma with extrascleral spread
Metastatic disease
Congenital malformation
Dermoid cyst
Lymphangioma
Infectious disease
Trauma

antibodies. Antibodies are secreted by activated B cells, which have responded and differentiated into plasma cells upon recognition of their cognate antigen. The two arms of the immunoglobulin encode the variable region, which provides the diversity required to recognise a vast repertoire of antigens. The stem of the Y-shaped structure is referred to as the constant region, which is able to determine its specific effector function. The Fc (fragment, crystallisable) receptor is the protein portion that binds antibody, specifically to the Fc region of the antibodies. There are five immunoglobulin isotypes, including IgA, IgD, IgE, IgG, and IgM, which are classified by their differences in their constant region. In general, immunoglobulins facilitate immunity in three ways: binding pathogens to prevent entry into cells, stimulating pathogen removal by activating macrophages and other cells through opsonization (coating), and by activation of immune responses such as the complement cascade.

The isotype produced is dependent on both the type of pathogen encountered and the location in which this immunity is required. The isotypes IgA and to some extent IgM, for example, dominate the mucosal immune system by covering the epithelium of the intestinal, respiratory, and urogenital tracts, and in doing so prevent the adhesion of pathogens such as viruses and bacteria.

IgG is the most common and long-lived immunological isotype in the serum (75%) within which are four different subclasses, IgG1, IgG2, IgG3, and immunoglobulin G4 (IgG4), listed in order of their abundance.

Immunoglobulin G4

Although IgG1, 2 and 3 form 96% of total IgG and are able to activate the complement system, IgG4 accounts for only 4% of total IgG and is inefficient at inducing both Fc receptor-mediated clearance and the complement cascade.[9] Despite this, IgG4 is commonly produced in parallel with IgE in response to allergen[10] and is able to bind with high affinity to house dust mites and grass pollen. In addition, IgG4 is often produced upon long-term exposure to a specific pathogen and there are several examples that suggest that this ensures minimal side effects to persistent activation of the complement pathway.[11] Although inhibition of immune inflammation may be desirable in some instances, such as prolonged exposure to allergens, production of IgG4 can be comparatively undesirable in response to infection.

Immunoglobulin G4 and systemic disease

IgG4-related disease is a recently discovered entity characterised by widespread tissue infiltration by IgG4-positive plasma cells and high serum levels of IgG4.[12,13] It was first reported in relation to autoimmune pancreatitis[14] and later the link with other organs was published, namely the liver,[15] salivary gland[16] and the retroperitoneal space.[17] Now, subtypes of interstitial lung disease[18] and tubulointerstitial nephritis[19] are now also considered part of the IgG4-related disease spectrum.

Evidence linking elevated serum IgG4 to the lacrimal gland enlargement was published in 2004,[20] and the first histological reports of raised IgG4 in orbital tissue biopsies began emerging in 2007[21] with many following in the past 4 years.[22–28] IgG4-associated disease is now recognised as a systemic disease process.[22] Table 2 describes conditions once viewed as unique but which are now recognised by the IgG4-related systemic disease spectrum.[29]

The role of immunoglobulin G4 in IOI

As the name implies, the pathogenesis of IOI has remained elusive. IOI is often a diagnosis of exclusion, clinically and morphologically.[22] Interestingly, in 1993 a subset of IOI was reported to have an association with systemic fibrosclerosis, but the actual link was not

Table 2 Previously idiopathic conditions now thought to be IgG4-related

Previous name	*Target organ(s)*
Mikulicz's disease	Salivary and lacrimal glands
Kuttners tumour	Submandibular glands
Riedel's thyroiditis	Thyroid
Chronic sclerosing aortitis	Aorta
Retroperitoneal fibrosis	Retroperitoneum
Autoimmune pancreatitis	Pancreas
Sclerosing cholangitis	Biliary tree
Orbital pseudotumour	Orbital adnexa
Eosinophilic angiocentric fibrosis	Sinuses and nasal cavities
Multifocal fibrosclerosis	Various organs

found.[30] Eighteen years later with the benefit of modern immunohistochemistry, we now know the link between orbital inflammation and IgG4-related systemic disease.

Morphologically, the IgG4-related lesions of the pancreas and other systemic organs are characterised by a diffuse lymphoplastic infiltrate and an abundance of IgG4+ plasma cells on a background of fibroblasts. IOI encompasses a broad spectrum of histopathological features, but evidence is emerging linking a subtype of IOI with the recently discovered clinical spectrum of IgG4-related systemic disease.

The majority of reports in the literature emanate from Japan. In 2008, a group from Okayama reviewed 112 cases with ocular adnexal lymphoproliferative disorders between 1990 and 2006.[23] In all, 78 were orbital and 34 involved the conjunctiva. The histology was revisited with murine monoclonal antibody testing against human IgG4. Twenty-one of 112 (19%) patients had identifiable IgG4-related disease, classified as >10 IgG4-positive plasma cells per tissue section. All patients had orbital lesions but there was no conjunctival involvement. Three lesions were 'orbital' but no further details are reported but are presumed to be extra-lacrimal as 17 had lacrimal gland involvement (12 having bilateral involvement). Of this group, 13 patients had blood samples stored and 10 (77%) had raised serum IgG4. However, the authors highlighted the majority of these samples were collected after treatment was commenced, a factor known to decrease serum levels.[31] No details are reported but 'most had abnormally high serum IgG4 levels even in remission'. One criticism of this paper is the definition used for tissue-positive IgG4 levels.[28] Most papers require at least 30 cells per high-power field, but for this analysis >10 was considered significant. In defence, this paper was the first large review conducted and predated a consensus on histological definition.

A 2009 single-case report described fibroinflammatory changes in the facial tissue planes with extension in to the orbit with preferential involvement of the periorbital membrane.[28] Tissue IgG4 levels were >35 cells per high-power field. Interestingly, separating this case from most of the other reports, the lacrimal gland was completely devoid of sclerosing inflammation. The patient died from cardiac arrhythmia before serum could be collected for IgG4 analysis.[28]

In 2010, a review of nine cases of benign lymphoproliferative lesions of the ocular adnexa was published.[26] It included three men and six women aged 21–95 (mean 45) years. Bilateral lacrimal gland masses were found in seven cases (78%) and orbital extension in four of these. The remaining two cases were a unilateral conjunctival lesion and a unilateral lacrimal lesion with orbital extension. Immunohistochemical staining for IgG4 showed five cases (56%) were IgG4 negative and four cases (44%) were IgG4 positive (defined as >10 IgG4+ plasma cells in a high-power field, and ratio of IgG4+ plasma cells to CD138+ plasma cells was >40%). Echoing results of previous studies and these cases showed marked plasmacytic infiltration, dense fibrosis, lymphoid follicle formation, and destruction/atrophy of the glandular tissue. One patient also exhibited raised tissue IgG4 in the lung and the liver tissue biopsied. The remaining three IgG4+ patients and the five patients who were ocular adnexal IgG4 negative had no systemic manifestation consistent with IgG4-related disease and had negative IgG4 tissue biopsies elsewhere (lung, liver) where sampled. Again, this study could be criticised for employing a low threshold for classifying tissue as IgG4 positive (10 cells per high-power field).

At the time a contemporary review stated 'although a direct correlation with systemic disease cannot be made with orbital inflammatory pseudotumour, the rapid response of inflammation to corticosteroids and other immunosuppressive agents supports this theory'.[32]

More data from 2010 looked at tissue IgG4 levels in a range of orbital inflammatory conditions to try to uncover which other disease subtypes may be IgG4 related.[27] A total of 18 cases were histologically examined but no serum samples were available. Cases consisted of mild non-specific dacryoadenitis ($n=10$), IOI (4), necrobiotic xanthogranuloma (2), xanthogranuloma (1), and fungal infection (1). The dacryoadenitis subgroup, the orbital condition most commonly found to exhibit IgG4 dysfunction, showed raised IgG4 levels in only one case (10%). However, the only xanthogranuloma case and one of the two necrobiotic xanthogranulomas revealed diagnostically elevated IgG4 cells. This case series highlights that other orbital sites may be involved and represents the first detection of IgG4-related disease in granulomatous orbital inflammation. Having discovered another possible link with IgG4 and xanthogranuloma, the authors concluded that

'it is not yet clear what type(s) of orbital inflammatory disease other than sclerosing dacryoadenitis might be caused by abnormalities in IgG4'.[27]

A 2011 review looked for the presence of IgG4 in historical orbital histology specimens.[22] The samples were biopsied from patients with presumed IOI between 1993 and 2006 with the aim to exclude lymphoma. The histology was reviewed and tested for IgG4 immunostaining. Of the 21 patients tested, 11 (53%) had increased IgG4-positive cells (>10 per high-power field/ 0.55 mm^2). A retrospective review of the medical history of this group revealed that the patients had earlier/later diagnoses of asthma (five patients), idiopathic pancreatitis (one patient), inflammatory liver pseudotumour (one), and cirrhotic cholangitis (one); conditions now accepted to have an IgG4 component.[29] Three of the 11 tissue-IgG4-positive patients also had stored serum samples analysed. Two of the 3 (67%) had raised serum IgG4. Comparing the raised IgG4 cohort with the non-raised, the IgG4 group had histology showing a higher incidence of follicular hyperplasia, background fibrosis, plasma cells, and the presence of eosinophils. Clinically this IgG4 category had a unique clinical constellation of signs consisting: eyelid swelling, bilateral orbital involvement, systemic involvement, and more prolonged disease. In total, 45% had a history of asthma, but raised serum IgG4 was present in 3 of 11. The authors postulate that 'these observations offer strong evidence that this group represents a distinct group with orbital manifestations of what is now known as IgG4-associated systemic disease' and go on to declare 'these patients warrant the separation of orbital manifestation of IgG4 systemic disease from the inflammatory orbital pseudotumour category'.[22]

In summary, ocular adnexal IgG4-related disease mainly affects the lacrimal gland but can be unilateral or bilateral.[26] However, other sites can be involved namely the periorbital septum[28] and xanthogranulomatous changes in the anterior orbit.[27] IgG4 implication is more likely in the presence of systemic manifestations consistent with IgG4 involvement, for example, pancreatitis, hepatic inflammatory pseudotumours, nephritis, interstitial lung disease, retroperitoneal fibrosis, and Hashimotos thyroiditis.[33]

IgG4 and lymphoma

Evidence is starting to emerge that lymphomas can arise on a background of IgG4-related chronic inflammation but as yet no causal relationship between ocular adnexal lymphomas and IgG4-positive plasma cells has been established.

Ochoa *et al*[34] reported a case of MALT lymphoma emerging among a background of Küttner's tumour, which is now considered to be an IgG4-related disease.[16] In a 2008 series of 17 cases of ocular adnexal IgG4 disease, 2 cases were detected with immunoglobulin heavy-chain gene rearrangement with Southern blot hybridisation. At first diagnosis, these patients were labelled as MALT lymphoma (1993–2006) but retrospectively (2008) both were noted to also exhibit elevated serum and tissue IgG4. Three lacrimal gland lymphomas were borne out of a series of IgG4-postive patients; two extranodal marginal, and one follicular.[24] Another report describes a multifocal (lacrimal gland and pelvis) MALT lymphoma in a 75-year-old man which secreted IgG4. Serum IgG4 levels normalised following systemic chemotherapy and corticosteroids.[35]

Features suggesting a predisposition are emerging from the current evidence. Most orbital lymphomas derive from the lacrimal gland following inflammatory processes characterised by hypercellular lymphoid masses.[36] The lacrimal gland has its own intrinsic intralobular lymphoplasmacytic architecture with lymphatics.[36] Sequential biopsies throughout the inflammatory process show increasing collagenisation but the densely cellular follicular organisation is still preserved,[37] helping to explain the potential of lacrimal lesions to evolve into lymphoma. In contrast, IgG4-positive sclerosing pancreatitis is dominantly a fibrotic change without lymphoid follicles and this condition is not noted for spawning lymphomas.[25] The afollicular pathology of sclerosing pancreatitis is similar to IgG4-positive disease of the orbit seen outside the lacrimal gland where tissue is devoid of a standing population of inflammatory cells and lacks lymphatic channels.[36]

Lymphomas emanating from the dura have also shown a possible link to IgG4-related diseases. Of 18 cases tested for a IgG4 component, 5 primary dural marginal zone lymphomas and 1 epidural tumour showed high tissue levels IgG4 that were light-chain restricted and clonal on PCR.[38]

All reports to date involve B-cell lymphoma but conversely, a report of T-Cell lymphoma arising in IgG4-related sclerosing cholangitis was published in 2010.[39] The authors note that IgG4-related disease is 'an inflammatory disorder characterised by not only extensive IgG4-positive plasma cell but also T-lymphocyte infiltration'.[39]

Additional disease entities are being discovered to have an IgG4 link. Idiopathic cervical fibrosis, a rare tumefactive inflammatory sclerosing lesion involving the soft tissues of the head and neck,[40] was postulated in 2010. Four cases were reported to demonstrate elevated tissue IgG4 levels although serum samples were not available for analysis. Histological analysis of the soft tissue lesion from one of these four patients revealed features indicating supervening marginal zone

lymphoma (small lymphoid cells exhibiting kappa light-chain restriction and clonal immunoglobulin gene rearrangement). The adjacent lymph node also showed classical Hodgkin lymphoma.[40]

In summary, there is mounting evidence suggesting that B-cell lymphomas can supervene on a background of chronic inflammation similar to that recently documented for IgG4-related disease of the ocular adnexa.[23] Also, IgG4-producing cells by themselves might be neoplastic.[41] But are these cases lymphoma complicating IgG4 disease or *de novo* lymphoma? A 2010 review found 9% (10 or 114 cases) of marginal B-cell lymphoma contain IgG4-positive infiltrate. The paper suggests that 'IgG4-positive plasma cells with sclerosing and reactive follicles are specific inflammatory lesions within ocular adnexal marginal zone B-cell lymphomas' and likely 'correlate with a systemic condition that induces unique serum abnormalities (including raised IgG4)'.[42]

Treatment of IOI

An excellent review of treatment was described by Gordon[1] therefore will not be discussed here in detail. 'The mainstay of therapy for IOI is corticosteroids'[43] but response to steroids should not be used to make the diagnosis. Treatment response is often rapid (24–48 h) on initial therapy usually ranging 60–100 mg daily. However, response is 'often excellent but unsustained'.[29] A slow taper of prednisolone over several weeks to months is recommended. Anecdotal reports suggest pulsed intravenous methylprednisolone is beneficial in patients with more aggressive disease but should be reserved for those patients with rapid progression of symptoms, visual loss, or disease refractory to oral prednisolone.[43] However, treatment response is often poor. A retrospective study of 32 patients found a modest response to a 60-mg daily dose of prednisolone. Only 37% of patients achieved cure, but 78% of patients had an initial response but with a 52% recurrence rate.[44] Another retrospective study showed 80–100 mg of prednisolone was effective in 31% of patients.[45]

Radiotherapy has demonstrated modest efficacy in several small studies and should be considered for patients who are steroid resistant or are unable to tolerate corticosteroids.[43] A study of 10 patients receiving radiotherapy at a dose of 2500–3000 cGy over 10 days showed clinical benefit.[46] Whereas, another study reported response in 15 of 21 patients with a dose of 1000–2000 rads over 10–15 days.[47] Finally, Orcutt *et al*[48] showed a 75% treatment effect using 2500 cGy over 15 days.

Steroid sparing therapy with agents such as cyclophosphamide, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil and more recently, infliximab also show useful clinical effect.[1,43]

Treatment of specific IgG4-related disease

Does the discovery of an IgG4 link in a subtype of IOI change management? In addition to the cardinal features of IgG4 disease, a raised serum IgG4 (>135 mg/dl) and local tissue IgG4 plasma cell infiltration, the disease is characterised by a marked response to corticosteroid.[49] This response is even greater for gastrointestinal disease.[49] However, this observation is not reinforced with prospective randomized control data. As orbital involvement is very recent, no clinical trials addressing orbital outcomes exists currently.

With regard to pancreatic disease, early initial response to corticosteroids is usually dramatic, especially if the treatment is commenced early in the disease process.[49] Fibrosis and sclerosis are usually the result of long-term inflammatory processes and these features are common in non-IgG4-related disease (diseases that are often refractory to treatment and cause irreversible histological change). However, an anecdotal report from the Japan documents the surprising reversal of fibrotic and/or sclerotic lesions if IgG4 has a role in causation.[49] The question of prednisolone dosing is still to be answered but studies are underway in the gastrointestinal field. The only dose-related prospective study to date showed clinical improvement with initial therapy of 0.6 mg/kg per day tapering by 10% every 2 weeks to a maintenance a dose of 10 mg/day for 3 months. Detailed treatment outcomes are not discussed in the paper although the authors do state that 30–40% of patients relapse after 3 months so clinician-tailored long-term maintenance of 5–10 mg/day may be indicated.[49]

Radiotherapy is commonly used to treat IOI but no reports of specific IgG4-related ocular adnexal disease treated with radiotherapy, successfully or otherwise, have been reported to date.

No data on the use of immunosuppressant or immunomodulatory therapy for IgG4-related disease have been published at present.

Conflict of interest

The authors declare no conflict of interest.

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