IgG4 RELATED OPHTHALMIC DISEASE: AN OVERVIEW

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ABSTRACT

IgG4-related disease is a fibro-inflammatory condition with tendency to form tumors with inflammatory infiltrate and elevation of IgG4 level in serum, which may affect virtually every organ and tissue. It may present as dacryoadenitis, myositis, hypophysitis or pachymeningitis causing cranial neuropathies. The diagnosis of IgG4-related disease is based on a typical clinical scenario, supportive laboratory data, radiological findings and distinct histopathological and immuno-histochemical features. Corticosteroid followed by long-term immunosuppressive therapy is the most commonly attempted treatment.

KEY WORDS

Keywords: IgG4, IgG4-related disease, IgG4 related inflammation, Inflammatory pseudotumor, Orbital syndrome

INTRODUCTION

IgG4-related systemic disease (IgG4-RD) is an inflammatory condition of unknown etiology that has been implicated in pathology affecting the pancreas, salivary glands, gallbladder, thyroid, aorta, and multiple other tissues and organs. The term inflammatory pseudo tumor has been used to describe a heterogeneous group of mass-forming lesions in various anatomic regions and organs characterized by proliferation of fibroblasts and inflammatory infiltrate composed mainly of lymphocytes and plasma cells. The condition has been recognized since the 19th century under various names depending of the organ affected, such as Mikulicz disease, Riedel thyroiditis, lymphoplasmacytic sclerosing pancreatitis or idiopathic hypertrophic pachymeningitis among many others. During the first decade of this century, the discovery of common features among these seemingly disparate conditions was identified allowing the emergence of the fibroinflammatory condition now known as IgG4-related disease. The international symposium on IgG4-related disease held in Boston, Massachusetts in October 2011 with representation of various specialties and countries in its committee, recommended the unifying term of IgG4-related disease followed by the organ or area affected as the preferred nomenclature of this condition (i.e., IgG4-related dacryoadenitis or myositis or pachymeningitis).

The typical characteristics of IgG4-related disease include tendency to form tumors, inflammatory infiltrate with IgG4 rich plasma cells and elevation of IgG4 level in serum. Patients usually present with symptoms related to mass effect or focal deficits caused by the compression of blood vessels or nerves. Of interest in ophthalmology, IgG4-related disease may affect any tissue but often presents as dacryoadenitis, myositis, orbital inflammation, hypophysitis or pachymeningitis causing cranial neuropathies.

The differential diagnosis is broad including inflammatory diseases and vasculitis such as sarcoidosis, granulomatosis with polyangiitis, giant cell arteritis, Behcet’s disease, thyroid eye disease, inflammatory histiocytosis or rheumatoid arthritis; neoplastic diseases such as lymphoma, inflammatory myofibroblastic tumor, neoplastic histiocytosis, meningoipoma or metastasis; and infectious processes such as tuberculosis. Further, there is likely a group of inflammatory conditions grouped in the inflammatory pseudotumor category, which is still today considered idiopathic.

Although IgG4-related disease is thought to comprise a large number of cases previously labeled as idiopathic inflammatory pseudotumor, its exact incidence is unknown. Wallace et al. retrospectively examined 14 cases of pachy-meningitis at their institution over a 25-year span and found that IgG4-related disease accounted for 4 of those cases or 66% of previously labeled as idiopathic cases. The other 10 cases were comprised of granulomatosis with polyangiitis (3), rheumatoid arthritis (1), giant cell arteritis (1), neurosarcoïdosis (1), MALT lymphoma (1), lymphoma (1) and of undifferentiated etiology (2). Furthermore, these findings raise the question if biopsy specimens of cases previously labeled as idiopathic inflammatory pseudotumor, should be reexamined for IgG4-related disease when the original pathological sample is still available or to repeat a biopsy when the current clinical course warrant and previous tissue sample are not sufficient or unavailable.
The pathophysiology of IgG4-related disease is poorly understood. IgG4-related disease seems to sit at an intersection between different inflammatory markers. (4) Many patients have substantial allergic or atopic histories suggesting a modified Th2 response is critical to this condition. IgG4-related disease is most likely driven by an underlying autoimmune mechanism. There is a higher risk for IgG4-related disease in certain genotypes and there is immune complex deposition and increase in regulatory CD25 T cells. No precise triggers have yet been identified. However, molecular mimicry by causing autoimmune reaction to a foreign antigen may be important. Escherichia coli and Helicobacter pylori have been implicated as possible candidates and source of molecular mimicry in IgG4-related pancreatitis. Mast cells have been shown to produce T helper 2 and regulatory T-cell cytokines in tissues affected by this condition suggesting a role in disease pathogenesis.(5) There are four subclasses of IgG, of which IgG4 is the least common (<6%). IgG1-3 can activate all complement, whereas IgG4 cannot. IgG 1, 3 and 4 are effective at opsonization of bacteria. Although IgG4 is increased in tissues and serum in IgG4-related disease, it is unclear if and how it would play a role in the pathophysiology of this condition.

**DIAGNOSIS**

The diagnosis of IgG4-related disease is based on a typical clinical scenario, supportive laboratory data, expected radiological characteristics and distinct histopathological and immune-histochemical features. IgG4-related ophthalmic disease may involve the orbit including lacrimal glands, extraocular muscles or other orbital structures; affect the meninges causing ocular motor cranial nerve palsies or optic neuropathy; and/or extend to adjacent structures such as air sinuses or trigeminal nerve causing additional symptoms.

The serum levels of total IgG and IgG4 are usually elevated in patients with IgG4-related disease and should be checked when the disease is suspected. However, it is increasingly clear that serum concentrations of IgG4 are unreliable as diagnostic marker in this condition. Approximately 20–40% of patients with biopsy-proven IgG4-related disease have normal IgG4 concentrations at the time of diagnosis, even before the institution of therapy.(6) In addition, a proportion of both healthy and disease controls has elevated serum IgG4 levels, although it is uncommon for levels in controls to be more than twice the upper limit of normal. Furthermore, the serum concentration of IgG4 does not correlate with disease activity or response to treatment. Recently, Carruthers et al. estimated that elevation of serum IgG4 concentration had a sensitivity of 90% and specificity of 60% with high negative predictive value of 96% but low positive predictive value of 34% in the diagnosis of IgG4-related disease.(7) Katsura et al. reviewed the radiological features in the head, neck and brain of 17 histopathological confirmed cases of IgG4-related disease, including CT and MRI techniques.(8) The general radiological features found included well defined soft tissues masses showing homogeneous attenuation/signal intensity, which enhanced homogeneously.

Lesions were iso- to hypointense relative to gray matter on T2-weighted imaging. Bones adjacent to the lesions showed remodeling with erosion or sclerosis, but without destruction. Diffuse thickening of the dura mater was also seen. Lacrimal, salivary and pituitary glands were preferentially affected. Perineural spread of cranial nerves, notably the trigeminal nerve, is characteristic, although not pathognomonic. Hardy et al. found enlargement of the infraorbital nerve and canal in patients with both, IgG4-related disease and benign reactive lymphoid hyperplasia, with orbital involvement (9). Although the combination of histopathological features and immune-histochemical stain results can provide strong supportive evidence for the diagnosis of IgG4-related disease, careful correlation with the clinical scenario and imaging characteristics of a particular patient is often required to arrive at a definitive diagnosis.(10) However, while understanding the limitations of pathological studies for the diagnosis of IgG4-related disease, diagnostic biopsy should be pursued as much as possible when encountering patients with this condition.

Idiopathic orbital myositis must be distinguished from Graves’s orbitopathy, which also involves the extraocular muscles and is the most common cause of orbital inflammation. Imaging shows that idiopathic orbital myositis tends to affect one or more of the extraocular muscles in their entirety, from origin to insertion. In contrast, Graves orbitopathy has a predilection for the muscle’s belly. Orbital myositis, as with idiopathic orbital inflammations, can be related to systemic or local inflammatory diseases and infections. Its presentation is variable (unilateral or bilateral and acute or insidious), but diplopia is a common symptom, as is pain with eye movements. Muscle biopsies have revealed infiltrates of plasma cells, lymphocytes, macrophages, and polymorphonuclear cells. Besides IOI and orbital myositis, other considerations in the differential for orbital pseudotumor and lacrimal gland enlargement include granulomatosis with polyangiitis (GPA; Wegener’s granulomatosis) and sarcoidosis. More than
half of GPA patients in some series have either secondary orbital invasion from the nearby ethmoid or maxillary sinuses or de novo involvement of the orbital soft tissue. Granulomatous inflammation with vasculitis and necrosis are key histologic features that distinguish GPA from IgG4-RD. Sarcoidosis, also a disease of unknown etiology, is characterized by non-caseating granulomas.

The three major histopathological features associated with IgG4-related disease are: (1) dense lymphoplasmacytic infiltrate (with predominance of T lymphocytes); (2) fibrosis, arranged at least focally in a storiform pattern (spiral or whorled appearance); and (3) obliterative phlebitis. In most instances, two of the three major histological features are required for diagnosis. Other characteristic histopathological features are phlebitis without obliteration of the lumen and increased numbers of eosinophils. In addition, IgG4 immunostaining is strongly recommended because it is a simple and highly reproducible test that provides strong confirmatory evidence for the diagnosis. An IgG4/IgG plasma cell ratio of >40% is considered a powerful tool supporting the diagnosis of IgG4-related disease. However, elevated levels of tissue IgG4 may also be seen in other conditions such as lymphoma, Rosai-Dorfman disease and rheumatoid arthritis.

**TABLE 1: Preferred nomenclature for involvement of orbital tissues in IgG4 related disease.**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Terminology Preferred</th>
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<tbody>
<tr>
<td>Lacrimal Gland</td>
<td>IgG4 related Dacryoadenitis</td>
</tr>
<tr>
<td>Orbital soft tissue</td>
<td>IgG4 related orbital inflammation</td>
</tr>
<tr>
<td>Extraocular muscle</td>
<td>IgG4 related orbital myositis</td>
</tr>
<tr>
<td>Orbit with involvement of multiple anatomic structures</td>
<td>IgG4 related pan-orbital inflammation</td>
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Figure 1. Clinicopathologic features of IgG4-RD. A. IgG4-related dacryoadenitis presenting as an upper lid swelling in a 55-year-old woman. B. Computed tomography scan in a 7-year-old boy showing a homogenous and diffuse orbital mass. C. Fibrosis with a dense lymphoplasmacytic infiltrate and lymphoid follicles (hematoxylin-eosin stain, original magnification ×40). D. Immunoglobulin G4 dacryoadenitis showing fibrosis and lymphoplasmacytic inflammatory infiltrate (hematoxylin-eosin stain, original magnification ×40). E. Aggregates of plasma cells (hematoxylin-eosin stain, original magnification ×400) and F. IgG4-positive plasma cells

**TREATMENT AND PROGNOSIS**

IgG4-related disease may affect one organ or tissue, spread to contiguous areas, or bimultifocal and even systemic. The clinical course of the disease is variable, although usually slowly progressive and chronic; it may experience
spontaneous remission at least temporarily, or have complete response to treatment (11) Although the standard first line therapy consists of steroids, there is no uniform recommendation (12) Indeed, an early and robust positive response to oral or parenteral steroids is characteristic in this condition, much so that the lack of response to steroids questions the diagnosis. However, their effect may not last, requiring the addition of other treatments. Further, the use of other immunosuppressant medications is recommended to prevent adverse effects of chronic use of steroids. Mycophenolate mofetil (MMF) is an immunosuppressive agent with favorable toxicity profile reported to work in IgG4 and other inflammatory eye diseases. (11,13) Rituximab has also been demonstrated to be an effective alternative allowing for discontinuation of steroids. (14) Other immunosuppressant agents used include methotrexate, azathioprine and cyclophosphamide. The role of radiotherapy is uncertain, although may play a role in localized disease such as unilateral orbital involvement. Surgical resection is of limited value and not recommended.

**CONCLUSIONS**

IgG4-related disease is a fibro-inflammatory condition recently recognized as a common form of inflammatory pseudotumor disorders in virtually every organ or tissue in the body. It is likely of autoimmune mechanism and has a variable but usually progressive clinical course. It has a tendency to form tumors with lymphocytic inflammatory infiltrate rich in IgG4 plasma cells with fibrosis and elevation of IgG4 in serum. The diagnosis is based on clinical presentation with characteristic appearance on MRI, elevated serum IgG4 level and distinctive features on histopathological and immuno-histochemical studies. Most accepted treatment nowadays consists of steroids initially with an expected robust response, followed by the use of long-term immunosuppressive therapy. IgG4-related disease should always be considered by the clinician suspecting an inflammatory condition, because although it may be an uncommon disease, it is likely under diagnosed.

**REFERENCES**