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Neuro-ophthalmology Update

IgG4-related ophthalmic disease

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Abstract

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

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

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Introduction

The term inflammatory pseudotumor 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 1800s 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 fibro-inflammatory 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).[1]

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.[1] 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, meningioma 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-

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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.[2] The other 10 cases were comprised of granulomatosis with polyangiitis (3), rheumatoid arthritis (1), giant cell arteritis (1), neurosarcoidosis (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.

Pathophysiology

The pathophysiology of IgG4-related disease is poorly understood. IgG4-related disease seems to sit at an intersection between different inflammatory markers.[3] 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 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 for the initiation of IgG4-related disease. 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.[4] 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 or if it is a mere epiphenomenon.

Diagnosis

The diagnosis of IgG4-related disease is based on a typical clinical scenario, supportive laboratory data, expected radiological characteristics and distinct histopathological and immunohistochemical features. As mentioned previously, 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 (case report).

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.[5] 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.[1] 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.[6] Cerebrospinal fluid (CSF) analysis in patients with IgG4-related disease of the central nervous system may reveal mild to moderate lymphocytic pleocytosis, a non-specific finding. Therefore, the main value of CSF testing in those cases is the exclusion of infection and cancer. Further, it is unclear how sensitive or specific IgG4 measurement in CSF really is.[2]

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.[7] 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.[8]

The histopathology of IgG4-related disease was a specific focus of the international symposium held in Boston, Massachusetts in October 2011 mentioned previously. The authors of those consensus guidelines recognized that although the combination of histopathological features and immunohistochemical 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.[9] 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. The consensus group concluded that the diagnosis of IgG4-related disease requires both, an appropriate histological appearance and increased numbers of IgG4 plasma cells in tissue. 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.

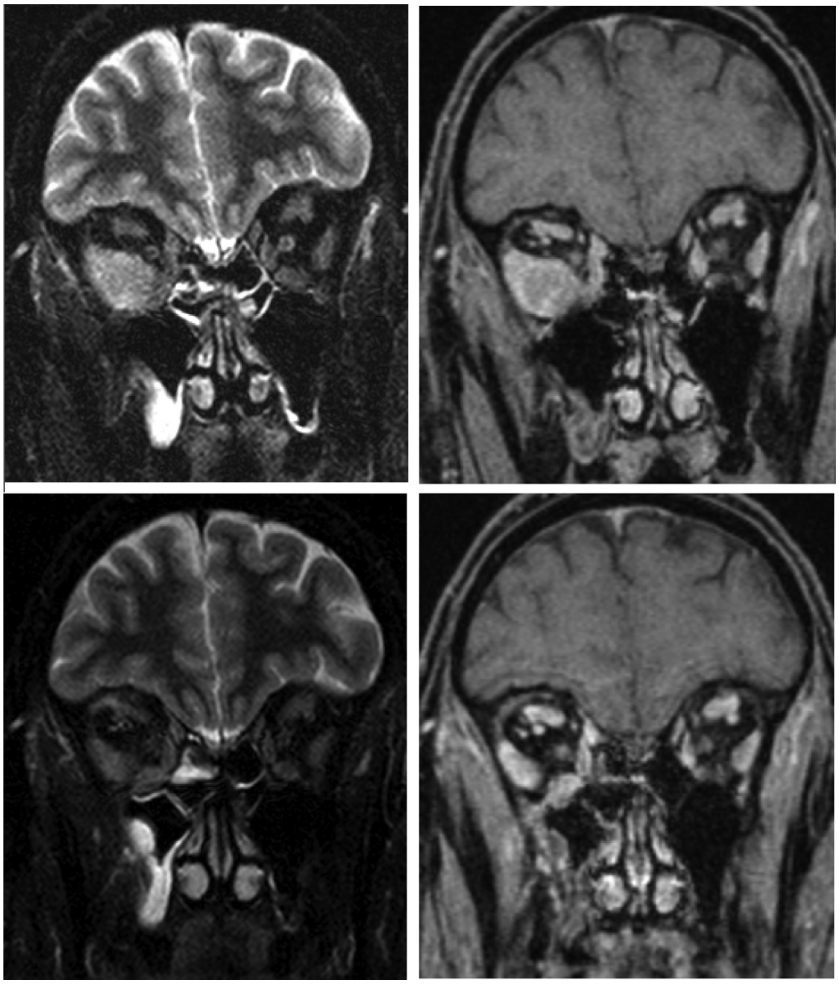

Figure 1. Findings on MRI of orbits on presentation (top row) and 6 months later, after having received steroid treatment (bottom row), on coronal fat saturated T2-weighted (A, C) and gadolinium-enhanced T1-weighted images (B, D), showing enlargement of the right lateral rectus muscle with homogenous attenuation and enhancement with improvement at 6 months. Mucosal thickening of adjacent air sinuses is also appreciated.

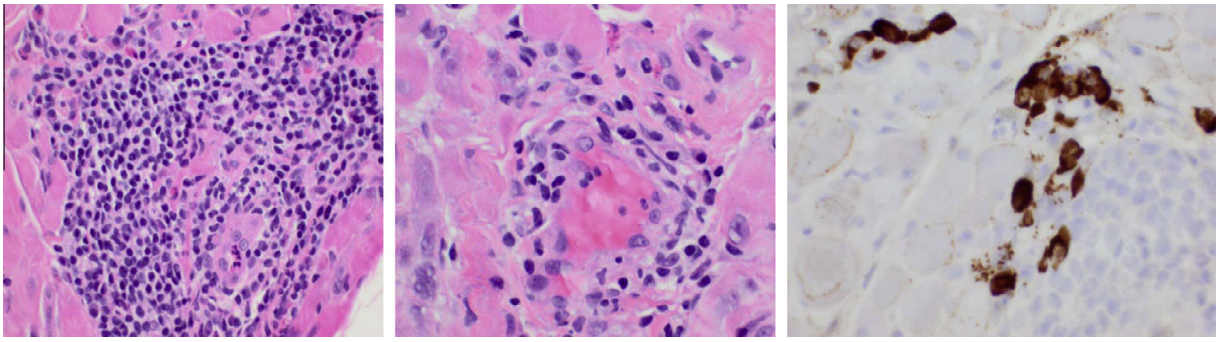

Figure 2. Histologic features of left medial rectus muscle biopsy. Hematoxylin and eosin stain at low (10x magnification) (left) and high power (40× magnification) (middle) demonstrates a perivascular mixed inflammatory infiltrate and venulitis without obliteration. IgG4 immunohistochemical stain (right) demonstrates plasma cells with strong IgG4 expression.

Treatment and prognosis

IgG4-related disease may affect one organ or tissue, spread to contiguous areas, or be multifocal 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.[10] Although the standard first line therapy consists of steroids, there is no uniform recommendation.[11] 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.[10,12] Rituximab has also been demonstrated to be an effective alternative allowing for discontinuation of steroids.[13] 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 immunohistochemical 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.

Conflict of interest

The authors declared that there is no conflict of interest.

Appendix A. Case report

A 43-year-old man was referred to neuro-ophthalmology with diplopia for 15 months. He had initially presented to his ophthalmologist with diplopia and palpebral edema in the right eye 15 months prior. MRI of the orbits then revealed enlargement of the right lateral rectus muscle with homogenous attenuation and enhancement, as well as mucosal thickening of adjacent air sinuses (Fig. 1, top row). He received oral prednisone for 2 weeks with complete resolution of symptoms. However, he developed recurrence of symptoms 2 months later, which resolved again after a second round of oral prednisone. A month later his symptoms returned and he was seen by an orbit specialist, who instituted a longer course of oral steroids. Blood serology for various inflammatory and connective tissue diseases was non-contributory. Repeat MRI 6 months after initial presentation revealed improvement of right lateral rectus enlargement (Fig 2. bottom row). Symptoms resolved once again but recurred a few weeks after stopping treatment. A biopsy of the right lateral rectus muscle showed chronic inflammation. He then underwent fractionated radiation therapy with a dose of 2000 centigray (cGy) to the right orbit only. His diplopia improved but was still present on right gaze. Four months after completing radiation therapy, he developed worsening diplopia and was found to have new limited adduction of the left eye. An MRI of the orbits confirmed enlargement of the left medial rectus (not shown).

Neuro-ophthalmic consultation was completed 15 months after initial presentation. Serum IgG4 level was elevated at 156 mg/dL (4.0–86.0 mg/dL). The first biopsy sample was obtained, but the tissue was deemed not sufficient for repeat testing. Therefore, a second biopsy, this time of the left medial rectus was performed. Microscopic examination of the biopsy showed perivascular mixed inflammatory infiltrate and venulitis without obliteration. Further, IgG4 immunohistochemical stain demonstrated plasma cells with strong IgG4 expression (Fig. 2). A diagnosis of IgG 4-related orbital myositis was made. He then initiated treatment with oral prednisone and mycophenolate mofetil 1,000 mg twice a day. The dose of oral prednisone was gradually decreased and stopped 3 months later. At the 10-month follow-up visit, he still had mild diplopia on certain position of gaze and no new symptoms. Furthermore, the degree of strabismus had improved in a remarkable way.

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