Immunoglobulin G4–Related Disease Involving the Sclera

To the Editor:

Immunoglobulin G4–related disease (IgG4-RD) recently has been recognized as a new disease characterized by diffuse or focal organ enlargement, with mass-forming or nodular/thickened lesions in various organs. Numerous tissues can be affected either synchronously or metachronously, the most frequent of which are the pancreas, salivary or lacrimal glands, lymph nodes, kidneys, and retroperitoneum.[1]

The ophthalmic manifestations of IgG4-RD are common and reported in the lacrimal gland and duct, extraocular muscles, orbital soft tissues, and sclera, as well as the cranial nerves and their branches.[2]

Ohno et al.[3] presented 1 case of IgG4-related disease involving the sclera. This patient then developed retinal detachment. With a preliminary diagnosis of choroidal tumor, enucleation of the eyeball was performed. Not many reports of patients with scleritis in the setting of IgG4-RD are available..[2–7] We present a new case of IgG4-related disease involving the sclera.

A 75 year-old man came to consultation for right retinal detachment secondary to a presumptive diagnosis of choroidal tumor. At the time of examination, the patient had bilateral ptosis, decreased visual acuity accompanied by a diplopia of 4 months' duration, and hearing loss. In interconsultation with another ophthalmologist, a choroidal tumor is ruled out, and a case of scleritis and anterior uveitis is confirmed.

The slit-lamp ophthalmologic examination reveals intense scleral injection with retinal detachment and preserved ocular motility. A binocular indirect ophthalmoscopy does not show any evidence of mass effect, but an ocular echography demonstrates a choroid enlargement compatible with posterior scleritis and retinal detachment.

Retinal detachment accompanied by diffuse choroidal thickening and right retro-ocular alteration of brightness is confirmed by orbital computed tomography (CT) (Figs. 1 and 2) and nuclear magnetic resonance spectroscopy. A metabolic increase in diffuse projection of the right eyeball and diffuse thickening of the walls is visualized by 2-[^{18}F]-fluoro 2-deoxy-D-glucose positron emission tomography/CT.

Mild retroconal obliteration of fat planes and multiple enlarged lymph nodes in mediastinum and pulmonary hilar lymph nodes were observed. A biopsy of the mediastinal lymph node disclosed reactive follicular hyperplasia.

There was neither eosinophilia nor hyperimmunoglobulinemia, and the tests for serum angiotensin-converting enzyme, myeloperoxidase–anti–neutrophil cytoplasmic antibodies (ANCAs), and PR3-ANCA were all negative.

Serologic tests revealed normal serum IgG (868mg/dL; reference range, 700–1600 mg/dL), and first IgG4 serum levels were normal, but after diluting the material to avoid a prozone effect, the result was 1868 mg/dL (reference range, 110–1560 mg/dL). Immunostaining for IgG4 of mediastinal lymph nodes showed immunoreactivity for IgG4 in infiltrating lymphocytes and plasma cells (>30 cells/high-power field).

Based on multiple organ involvement and infiltration of IgG4-positive cells in the pathologic findings, we could diagnose an IgG4-related systemic disease. We started immunosuppressive treatments consisting of prednisone 60 mg/d and methotrexate at 15 mg/wk, and the patient's general condition and his hearing improved, and the anterior uveitis and scleritis alleviated. Currently, the patient continues with prednisone 2 mg/d, methotrexate 15 mg/wk, and folic acid 5 mg/wk as part of a 2-year follow-up.

Orbital inflammation is due to a number of causes, either systemic or localized, such as systemic inflammatory disease, neoplasm, congenital malformations, infectious diseases, and trauma, and its classification may be based on histological, anatomical, or temporal characteristics. In 5% to 8% of the patients, there is no discernible cause, even on biopsy, and such patients are regarded as having "idiopathic" orbital inflammation (IOI). One histological subtype of IOI is the sclerosing variant, characterized by the replacement of orbital tissues by dense, fibrous tissue with a sparse inflammatory cell infiltrate. It is now thought that this condition might represent a specific subtype and separate entity.

McCarthy et al. reported histomorphologic and immunohistochemical similarities between sclerosing orbital inflammation and retroperitoneal fibrosis, and in fact, sclerosing IOI can be associated with other sclerosing systemic diseases such as retroperitoneal or mediastinal fibrosis, Riedel thyroiditis, or sclerosing cholangitis.[8] Idiopathic orbital inflammation has been found to have several similarities with autoimmune pancreatitis. Both processes mimic neoplasm and are characterized by variable degrees of fibrosis and chronic inflammation.[9] Our patient came to our practice with a preliminary diagnosis of choroidal tumor.

Recent studies have demonstrated that patients with lacrimal gland infiltration and orbital inflammation with IgG4-positive plasma cells tend to have high incidence of bilateral disease, systemic involvement, and more prolonged disease, as opposed to those without IgG4-positive plasma cell infiltrates.[9] Sato et al.[10] reviewed the cases of 112 patients (orbital lesions, n = 78; conjunctival lesions, n = 34) with ocular adnexal lymphoproliferative disorders. Ocular adnexal IgG4-related disease was observed in 21 patients, with 70.6% showing bilateral lacrimal gland involvement. In contrast, the conjunctiva was not involved in any of the patients.

Immunoglobulin G4–related disease has a strong overall tendency to affect

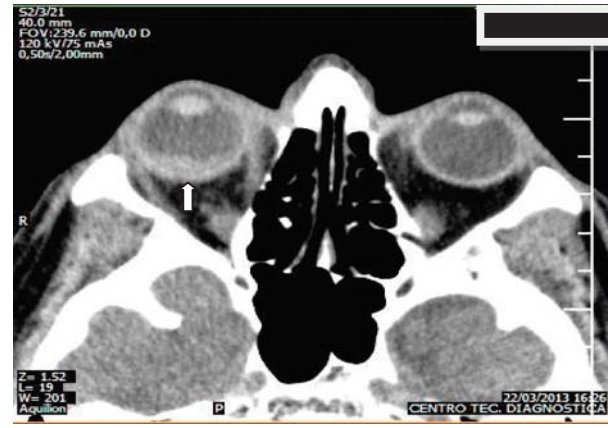

FIGURE 1. Retinal detachment accompanied by diffuse choroidal thickening and right retro-ocular alteration of brightness is confirmed by orbital CT (arrow).

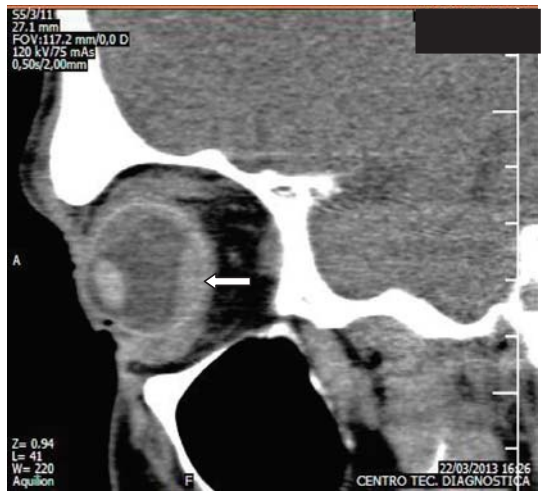

FIGURE 2. Retinal detachment accompanied by diffuse choroidal thickening and right retro-ocular alteration of brightness is confirmed by orbital CT, lateral view (arrow).

men more often than women and to target middle-aged to elderly populations, but the situation appears to be altered in IgG4-related ophthalmic disease (IgG4-ROD). In IgG4-ROD, as well as in other organ involvement of the head and neck, women and men appear to be affected equally by IgG4-ROD.[2]

The signs and symptoms of orbital IgG4-related disease are chronic lid swelling and proptosis, but otherwise there are only mild signs or not signs of inflammation or periocular pain. Ocular motility is restricted mildly if at all, despite the presence of 1 or more enlargements of the large extraocular muscles. There are generally no visual disturbances, although they may occur because of apical orbital lesions.[11]

The histology of orbital IgG4-related disease includes different degrees of lymphoplasmacytic infiltration with dominant sclerosing lesions or reactive lymphoid follicle. Eosinophilic infiltrations are also observed. Obliterative phlebitis is rare in orbital IgG4-related disease.

Histological assessment is essential in differentiating igG4-RD from other conditions that often involve orbital structures with nonspecific presentations, such as proptosis or palpable lesions that may also be present bilaterally.

Because serum IgG subclass analysis and IgG4 immunostaining of specimen are not performed routinely, and the affected organs vary, IgG4 is often misdiagnosed as granulomatosis with polyangiitis, sarcoidosis, neoplasia, lymphoma, infection, or Sjögren syndrome,

Idiopathic orbital inflammations and idiopathic orbital myositis have unknown etiology but involve inflammation. They are characterized by sudden onset of orbital inflammation, periocular pain, swelling and redness of the eyelids, proptosis, ptosis, and ocular motility restrictions. These differ from the signs and symptoms of orbital IgG4-related disease. However, some cases of IOIs have atypical signs and symptoms; that is, they lack acute onset and inflammatory signs; in such cases, biopsy specimens are needed to differentiate IOI from IgG4-related disease. Idiopathic orbital inflammations show lymphoplasmacytic infiltration and fibrosis with few IgG4-positive plasma cells.[12]

Ocular adnexal marginal zone B-cell lymphomas make up the majority of lymphomas arising from the ocular adnexa. They are characterized histologically by the presence of reactive follicles in up to 64% of cases, sclerosis in up to 20% of cases, and plasma cells in up to 35% of cases. These histological characteristics are similar to those of orbital IgG4-related disease. In addition, 9% of patients with ocular adnexal marginal zone B-cell lymphomas have infiltration of IgG4-positive plasma cells and elevated serum level of IgG4. Ocular adnexal lymphomas are reported to arise in IgG4-related sclerosing dacryoadenitis, indicating a possible link between the 2 conditions. However, the causal relationship between lymphomas and IgG4-related disease remains unclear.

Anti–neutrophil cytoplasmic antibody–related vasculitis often infiltrates in ocular adnexal lesion. The symptoms of patients with orbital lesions include periocular pain, which can differentiate these patients from those with orbital IgG4-related disease. However, the histology may be similar to that of IgG4-related disease. The presence of granulomatous lesions, vasculitis, and neutrophilic microabscesses are consistent with granulomatosis with polyangiitis. Thus, ANCA-related vasculitis may not only include nonspecific inflammatory lesions but also have abundant IgG4-positive plasma cells.[11]

Sarcoidosis involves orbital structures in 10% to 50% of patients. Two recent reviews found that, like in IgG4-RD, the lacrimal gland was the most commonly involved orbital structure in sarcoidosis with common presentations including a palpable mass, eyelid swelling, and proptosis.[13,14]

In conclusion, this is a new report of a case of IgG4-related disease involving the sclera. Because the eyelids, lacrimal glands, and orbit are frequently involved, ophthalmologists play an important role in providing diagnosis and offering easily accessible sites for biopsy.

Alberto Christian Ortiz, MD
Rheumatology Section
Cullen Hospital
Santa Fe, Argentina
albertoortiz_4@hotmail.com

Jesica Gallo, MD
Rheumatology Section
Cullen Hospital
Santa Fe, Argentina

Noelia Paira, MD
Ophthalmologist
Nosti Hospital
Rafaela
Santa Fe, Argentina

Sergio Paira, MD
Rheumatology Section
Cullen Hospital
Santa Fe, Argentina

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