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IgG4 Disease: Is It or Isn't It?

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Dr. Jones

A 58-year-old woman with a history of presumed, recurrent left idiopathic orbital inflammation (IOI) was evaluated in the emergency room with a 1-day history of right eye injection, photophobia, pain, and decreased vision. The right eye had never been affected previously. Her left eye had chronically poor vision from old IOI-associated posterior uveitis and macular scarring. She had developed severe allergies and asthma approximately 20 years previously that had coincided with the onset of her left IOI. Ten years ago, she had had an extensive evaluation for IOI, including lymph node, sinus, and left lacrimal gland biopsies at another medical facility that had revealed no specific cause for the inflammation. She had taken corticosteroids periodically for her allergies and eyelid swelling with improvement in symptoms and signs. An allergist had attempted allergy desensitization, but the patient had failed this treatment due to development of anaphylaxis.

On our examination, the patient had normal vital signs. Her best-corrected visual acuity was 20/50, right eye, and 20/200, left eye. Color vision using Ishihara plates was 7/11 with the right eye and 0/11 with the left. Both pupils were irregular due to iris synechiae; there was a left relative afferent pupillary defect. Cranial nerve examination was normal. Extraocular movements were full; there was no pain with eye movement. Hertel exophthalmometry was 28 mm on the right and 29 mm on the left, with moderate resistance to retropulsion bilaterally. There was marked upper and lower eyelid edema with yellow plaques on the medial upper eyelid skin (Fig. 1), but palpation revealed no masses. On slit-lamp examination, the right eye had marked conjunctival injection, moderate corneal edema, diffuse punctate epithelial erosions in a stellate pattern that corresponded to endothelial striae, marked anterior chamber non-pigmented cells, and a 1-mm hypopyon. The right fundus appeared normal. The left eye had a clear cornea. There were a few iris synechiae, but no signs of active intraocular inflammation; a posterior chamber intraocular lens was well positioned. Ophthalmoscopy of the left eye revealed peripapillary atrophy and macular fibrosis consistent with resolved posterior segment inflammation.

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In addition, the patient had marked bilateral parotid gland swelling and cervical lymphadenopathy. Computed tomography (CT) of the orbits and neck was performed.

Dr. Srinivasan

Orbital CT demonstrates bilateral proptosis, extraocular muscle enlargement, and stranding of the retrobulbar fat as well as bilateral prominence of the preseptal soft tissues and lacrimal glands without a fluid collection (Fig. 2). There is evidence of pansinusitis with near complete opacification of the frontal, maxillary, ethmoid, and sphenoid sinuses bilaterally. Thickening and sclerosis of the sphenoid sinus walls suggests chronicity. There is thinning of the lamina papyracea on both sides, but there is no extension of sinus disease into the orbits. Evaluation of the soft tissues of the neck (images not shown) demonstrates prominence of the parotid and submandibular glands bilaterally.

Dr. Jones

The patient was admitted to the hospital and evaluated by otolaryngology for pansinusitis. She was treated with intravenous vancomycin and ceftriaxone for possible infectious causes of her orbital and sinus disease. In addition, because of her history of significant vision loss in the left eye and concern for right optic nerve tethering and compression, she also was treated with 1 g of intravenous methylprednisolone per day as well as topical prednisolone drops and erythromycin ophthalmic ointment to both eyes. Chest radiography was negative for hilar lymphadenopathy. Extensive serological testing was unrevealing other than a significant elevation of serum IgG4 (1,330 mg/dL; Table 1).

Despite treatment, on day 2 of admission, the patient's vision decreased to count fingers in the right eye, associated with worsening of color vision, corneal edema, and anterior chamber inflammation and inability to appreciate fundus details on an ophthalmoscopy. Left eye examination findings remained unchanged. There was no change in the pupil examination. Magnetic resonance imaging (MRI) of the orbits and brain was obtained and a biopsy of orbital tissue was performed.

Dr. Srinivasan

Orbital MRI demonstrates bilateral proptosis with anterior displacement of both lacrimal glands, bilateral enlargement of all extraocular muscles including the myotendinous junctions, and enhancement in the retrobulbar fat (Fig. 3). Changes consistent with inflammatory infiltration with enhancement are present in the extraconal space bilaterally. There is orbital apex crowding bilaterally. Compared with the previous CT, there has been an interval increase in the size of both superior ophthalmic veins; however, there is no increase in optic sheath fluid. There is extensive sinonasal inflammation and diffuse opacification of the paranasal sinuses with mucosal thickening and fluid collection. The brain MRI (not shown) revealed that the optic chiasm and the intracranial segments of the optic nerves were unremarkable. Intracranial cisternal structures demonstrated normal contrast enhancement; however, there were multifocal, scattered areas of nonspecific T2 prolongation in the subcortical white matter bilaterally thought to represent chronic small-vessel ischemic disease.

Dr. Lin

Multiple orbital biopsies of the right lacrimal gland and orbital fat show fibroadipose tissue with areas of fibrosis, xanthogranulomas with Touton giant cells, and lymphoid follicles (Fig. 4A). The lacrimal gland tissue was atrophic without necrosis. Scattered plasma cells were present but did not appear to be prominent within the inflammatory infiltrate.

Immunohistochemical stain for CD138 confirmed the presence of plasma cells, many of which stained positively for IgG, and specific stains for IgG4 revealed an average of 96 IgG4+ plasma cells per high-power field (HPF) (Fig. 4B). The ratio of IgG4+ to IgG+ plasma cells was approximately 0.6 (60%). There was no immunophenotypic evidence of a T-cell or B-cell lymphoproliferative disorder on flow cytometry.

In this case, the tissue samples do not meet tissue-specific histologic criteria for IgG4-RD of the lacrimal gland, as the currently accepted cutoff for IgG4-RD of the lacrimal gland is 100 IgG4+ plasma cells per HPF (1). However, orbital xanthogranulomatous diseases also may demonstrate increased numbers of IgG4+ plasma cells.

Dr. Jones

The clinical history of asthma, sinusitis, lymphadenopathy, salivary gland enlargement, and recurrent orbital inflammation, together with the histologic appearance of the biopsy specimen was consistent with the diagnosis of adult-onset asthma with periocular xanthogranuloma (AAPOX). Accordingly, the patient was treated with intravenous solumedrol for 3 days followed by a prolonged oral prednisone taper. Topical prednisolone acetate and cyclopentolate drops, and erythromycin ophthalmic ointment were continued in the right eye. Antibiotics were transitioned to an oral route for completion of a 10-day course for sinusitis. The patient's eyelid swelling and conjunctival injection responded quickly to the treatment (Fig. 5). Her intraocular inflammation and corneal edema were slower to respond, but her corneal epithelial disease resolved in 4 days and her vision improved to 20/50 in the right eye, whereas the left eye findings stabilized by day 10. She was continued on a 6-week taper of oral prednisone and referred to rheumatology for further workup and treatment.

Final Diagnosis

Adult-onset asthma with periocular xanthogranuloma (AAPOX).

Dr. Jones

In 1993, Jakobiec et al (2) differentiated AAPOX from Erdheim-Chester (E-C) disease and necrobiotic xanthogranuloma, although these disorders fall within a spectrum of xanthogranulomatous disease. These authors presented a series of 6 patients who had orbital swelling and xanthomatous eyelid lesions with histopathologic features that closely mimicked E-C disease (granulomatous inflammation with Touton giant cells). However, the patients with AAPOX did not have the systemic associations of E-C disease or of necrobiotic xanthogranuloma and, therefore, had a better overall prognosis. Similar to our case, their patients presented with swelling and xanthomatous skin lesions of the eyelids

with onset of symptoms temporally associated with the diagnosis of adult-onset asthma. Also similar to our patient, all 6 patients had mostly anterior orbital inflammation, with some having lacrimal gland involvement and enlarged extraocular muscles sparing periorbital nerve connective tissue.

Since the initial description of AAPOX, there have been multiple additional reported cases, all of which describe similar inflammation and characteristic skin plaques; however, unlike most previous reports, our patient had significant active intraocular inflammation with corneal decompensation in one eye and evidence of prior intraocular inflammation in the other eye. There also have been multiple reported cases of IOI associated with uveitis in children (3–7), but IOI only rarely is associated with uveitis in adults (8,9). Based on our review of the PubMed database, we are unaware of previous reports of AAPOX associated with intraocular inflammation.

The relationship of AAPOX and IgG4-RD is worth discussing. There have been multiple cases of AAPOX associated with increased IgG4+ plasma cells in tissue and serum samples (10–12). One publication of 3 patients confirmed a direct link between AAPOX and IgG4-RD, with 2 of 3 reported patients meeting tissue-specific criteria for ocular adnexal IgG4-RD (12). IgG4-RD is a relatively newly discovered disease characterized by chronic sclerosing inflammation and a tissue lymphocytic infiltration of IgG4+ plasma cells often associated with elevation in serum IgG4. Since it was first reported as a systemic condition in 2003, IgG4 cells have been detected in virtually all organs, but particularly the pancreas, liver, kidney, lung, orbit, and thyroid. IgG4-RD causes relapsing and remitting inflammation with tissue-destructive lesions in multiple sites that can lead to organ dysfunction and organ failure (13).

With regard to uveitis, there have been 5 cases of IgG4-RD reported in the literature in which uveitis was a feature (14–18). One of the patients presented as bilateral anterior uveitis in a patient with tubulointerstitial nephritis, and the diagnosis of IgG4-RD made by kidney biopsy (14). The other 4 were characterized by severe uveitis, 3 of which initially presented as scleritis, but without orbital signs or sinus disease (15–18). Three of the cases in which a tissue diagnosis of IgG4-RD could be made were refractory to treatment and required enucleation for alleviation of symptoms (17,18).

Despite the recognition of the IgG4-RD as a specific disease, there is still controversy as to the diagnostic criteria. Although orbital xanthogranulomatous diseases may demonstrate increased numbers of IgG4+ plasma cells, and some authors have even suggested that a xanthogranulomatous variant of IgG4-sclerosing disease exists (10–12,19,20), our patient met the comprehensive criteria for definitive IgG4-RD: tissue specimens with more than 10 IgG4+ plasma cells per HPF with a ratio of IgG4+ to IgG+ plasma cells of greater than 40%, and elevated serum IgG4 concentration higher than 1.35 mg/L (21). However, by tissue-specific criteria, our patient “only” had 96 IgG4+ cells per HPF and, thus, did not reach the lacrimal gland tissue-specific diagnostic criteria of 100 IgG4+ cells per HPF. This raises the question indicated by the title of this case report: is this or is not this a case of IgG4-RD? Just as AAPOX falls on a spectrum of xanthogranulomatous disease, IgG4-RD is likely also

a spectrum, and the lacrimal gland-specific cutoff of 100 IgG4+ cells per HPF is somewhat arbitrary.

Given the fact that of IgG4-RD refractory uveitis may require enucleation for pain management, we chose to treat our patient as if she did have IgG4-RD, although she did not meet the tissue-specific diagnostic criteria. However, the treatment for AAPOX in the absence of IgG4-RD would not have been different from the treatment she did receive. The major importance of understanding her diagnosis of AAPOX lies in predicting her prognosis. Patients on the E-C or necrobiotic xanthogranuloma spectrum of xanthogranulomatous disease have a poorer overall outcome than patients with AAPOX. Our patient's rheumatologist performed a full-body workup that was negative, transitioned her to methotrexate, and slowly tapered the prednisone. To date, she has remained clinically stable and inflammation free.

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FIG. 1.
Initial appearance of the patient shows bilateral upper eyelid swelling, proptosis and conjunctival injection.

FIG. 2. Noncontrast, axial computed tomography demonstrates bilateral proptosis, enlarged extraocular muscles, anterior and posterior orbital inflammation, and bilateral ethmoid sinusitis.

FIG. 3. Postcontrast T1 axial (**A**) and coronal (**B**) magnetic resonance imaging with fat suppression reveals hypertrophy of the extraocular muscles with involvement of the myotendinous junctions. There also is enhancement of the right optic nerve sheath, and of the retroorbital fat in both orbits and enlargement of the superior ophthalmic veins (*arrows*).

FIG. 4.

Orbital biopsy specimens. **A.** The tissue appears sclerotic with xanthogranuloma and multiple Touton giant cells (*arrows*) (hematoxylin and eosin, $\times 23.6$). **B.** Immunoglobulin 4 (IgG4)–stained section of lymphoplasmacytic inflammatory infiltrate shows IgG4-positive plasma cells (brown) (immunostain, $\times 20$).

FIG. 5. Following treatment, there is resolution of eyelid swelling, proptosis, and conjunctival injection.

TABLE 1

Results of hematologic tests

WBC	6.5 thousand/μL
RPR	Nonreactive
FTABS	Nonreactive
ACE	32 μ L
Lysozyme	<0.70 μ g/mL
C3	118 mg/dL
C4	19 mg/dL
IgG4	1330 mg/dL
TSH	1.63 uIU/mL
Free T4	1 ng/dL
Anti-TPO	0.4 IU/mL
C-ANCA	<1:20
RF	14 IU/mL
SSA	4 AU/mL
SSB	0 AU/mL
DSDNA	Not detected
Smith (ENA)	1 AU/mL
ANA	Not detected

ACE, angiotensin converting enzyme; ANA, antinuclear antibody; ANCA, antineutrophilic cytoplasmic antibody; DSDNA, double-stranded DNA; ENA, extractable nuclear antibody; FTABS, fluorescent treponemal antibody absorption; IgG4, immunoglobulin G4; RPR, rapid plasma region; RF, rheumatoid factor; TSH, thyroid-stimulating hormone; TPO, thyroid peroxidase; WBC, white blood cell.