Diagnosis and treatment of IgG4-related ophthalmic disease

ABSTRACT

Purpose: To further characterize the clinical presentation, diagnosis, and current treatment strategies of IgG4-related ophthalmic disease.

Methods: Review and analysis of seven cases orbital inflammatory syndrome found to be biopsy positive for IgG4.

Results: We present seven cases of IgG4-related ophthalmic disease, a previously unknown entity that has only recently been identified as a treatable systemic disorder. Management included surgical excision, systemic steroids, steroid-sparing immunosuppression, and radiotherapy.

Conclusions: These cases illustrate the importance of including IgG4-related ophthalmic disease in the differential diagnosis of periorbital or orbital masses. Prompt recognition of this entity by clinicians can allow for effective treatment with corticosteroids. Treatment with steroid-sparing immune suppressants and radiotherapy has shown promise in chronic or refractory disease, nonetheless tumor excision may ultimately be necessary.

Keywords: IgG4; Immunoglobulin G; Rituximab.

Introduction

Recently, IgG4-related disease has been recognized as a distinct entity, separate from the autoimmune and idiopathic diseases under which it fell.¹ First described in patients with autoimmune pancreatitis, IgG4-related disease represents a spectrum of systemic disease that has manifested in nearly every organ system.¹ The systemic nature of IgG4-related disease is backed by the finding of increased IgG4-positive plasma cells in blind biopsies of symptomatically uninvolved tissues.¹ IgG4 plays a significant role in atopic eczema and bronchial asthma.² Past associations of patients with autoimmune pancreatitis who also had other autoimmune diseases such as primary sclerosing cholangitis, Sjögren syndrome, and retroperitoneal fibrosis are more likely to have been manifestations of a single systemic disease rather than multiple separate autoimmune diseases.¹

IgG4 is the least common of the four subclasses of Immunoglobulin G, with normal levels found to be at 3% to 6% of total IgG.³ Patients with IgG4-related disease can be found to have an elevated level of IgG4 although this may be normal in some patients, especially if treatment with steroids had already begun. Tissue infiltration with IgG4 positive plasma cells is found in almost all patients, with a highly specific histochemical staining pattern.² Common orbital involvement includes the lacrimal glands, extraocular muscles, and IgG4-related orbital inflammation.
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Some processes extend beyond the orbit, such as including part of the course of the trigeminal nerve.3 Initially, a broad differential diagnosis must be maintained. Infectious and malignant etiologies must be ruled out while maintaining a high level of suspicion for IgG4-related disease. Cases previously considered to be idiopathic, or improperly diagnosed as “pseudotumor,” should be re-examined as IgG4 may be found to be positive. The work-up of IgG4-related ophthalmic disease includes physical examination, imaging studies, and serum levels of IgG4. Ultimately, tissue biopsy with pathologic examination showing plasma cells positive for IgG4 is required for diagnosis. We present seven cases along with radiologic and pathologic findings that led to a diagnosis of IgG4-related ophthalmic disease.

**Case Reports**

**Case 1**

A 62-year-old male with rheumatoid arthritis treated with subcutaneous etanercept 25mg twice a week and methotrexate 2.5mg weekly presented with painless proptosis and diplopia that began two weeks prior. Examination showed mild right eye restriction, conjunctival injection, chemosis, and right parotid fullness (Figure 1). Intraocular pressures were 24 in the right eye and 15 in the left eye. Hertel exophthalmometry measured 22mm (right) and 15mm (left). Radiographic imaging showed a mass as described in Figure 1. Histology from a CT-guided fine needle aspiration found a mixed lymphoplasmacytic infiltrate and myositis. A methylprednisolone dose pack generated some improvement of his new symptoms. Ultimately an incisional biopsy with tumor resection via right anterior orbitotomy was performed. Pathology showed IgG4 to be positive (cell concentration not recorded). With incomplete steroid response and total resection unachievable, further immune suppression was discussed in combination with rheumatology. Etenarcept was exchanged for intravenous rituximab 1000mg every two weeks for two doses along with methotrexate 2.5mg weekly and oral prednisone 20mg daily. Rituximab was repeated at 4 months as prednisone was tapered to 2.5mg. Rituximab treatment was then extended to 6 months. The patient did experience another acute exacerbation, which was controlled by increasing prednisone back to 20mg and tapering once symptoms improved. He is currently being maintained on intravenous rituximab 1000mg for two doses two weeks apart.

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Gender</th>
<th>Past Medical History</th>
<th>Presenting Feature</th>
<th>Laterality</th>
<th>Orbital Involvement</th>
<th>Treatment</th>
<th>Status</th>
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<tr>
<td>Case 1</td>
<td>62</td>
<td>Male</td>
<td>Rheumatoid arthritis</td>
<td>Proptosis</td>
<td>Unilateral</td>
<td>Diffuse periorbital</td>
<td>Steroids, Rituximab</td>
<td>Medically controlled</td>
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<tr>
<td>Case 2</td>
<td>46</td>
<td>Male</td>
<td>Autoimmune pancreatitis</td>
<td>Proptosis</td>
<td>Bilateral</td>
<td>Diffuse periorbital</td>
<td>Steroids</td>
<td>No recurrence</td>
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<tr>
<td>Case 3</td>
<td>40</td>
<td>Female</td>
<td>None</td>
<td>Proptosis</td>
<td>Bilateral</td>
<td>Lacrimal glands</td>
<td>Steroids</td>
<td>No recurrence</td>
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<tr>
<td>Case 4</td>
<td>60</td>
<td>Male</td>
<td>Asthma</td>
<td>Eyelid mass</td>
<td>Unilateral</td>
<td>Lacrimal gland</td>
<td>Steroids, Excision</td>
<td>No recurrence</td>
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<td>65</td>
<td>Female</td>
<td>None</td>
<td>Eyelid mass</td>
<td>Unilateral</td>
<td>Upper eyelid</td>
<td>Surgical debulking</td>
<td>No recurrence</td>
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<tr>
<td>Case 6</td>
<td>66</td>
<td>Female</td>
<td>Asthma, sinusitis</td>
<td>Eyelid mass</td>
<td>Bilateral</td>
<td>Lacrimal gland</td>
<td>Resuspension</td>
<td>No recurrence</td>
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<tr>
<td>Case 7</td>
<td>4</td>
<td>Male</td>
<td>None</td>
<td>Eyelid mass</td>
<td>Unilateral</td>
<td>Lacrimal gland</td>
<td>Surgical excision</td>
<td>No recurrence</td>
</tr>
</tbody>
</table>

Table 1. Patient characteristics
every six months, oral methotrexate 2.5mg weekly, and oral prednisone 2.5mg daily.

Case 2
A 46-year-old male with history of autoimmune pancreatitis presented with bilateral proptosis for seven years. Mild bilateral restriction was present with Hertels measuring 29mm (right) and 32mm (left). Thyroid studies were within normal limits. CT revealed diffuse bilateral inflammation. Orbital biopsy revealed fibrotic tissue with prominent reactive follicle formation and a chronic inflammatory reaction rich in plasma cells diffusely infiltrating the adipose tissue. IgG4 staining was positive at 75 cells/HPF with an IgG4/IgG ratio of 0.70. Treatment was started with prednisone 60 mg daily with significant improvement. Hertels decreased to 23mm bilaterally with no restriction. Prednisone was tapered over three months without recurrence.

Case 3
A 40-year-old female presented with one year of bilateral proptosis. Hertels measured 23mm (right) and 21mm (left). The lacrimal glands were easily palpable. Laboratory studies revealed IgG4 level of 1428 mg/dL (Ref: <86 mg/dL). CT showed bilateral lacrimal gland enlargement. An orbital biopsy of the right lacrimal gland revealed lymphoplasmacytic infiltrate with germinal center formation. IgG4 staining showed up to 75 cells/HPF. Treatment was started with prednisone 30 mg daily tapered over three months down to 5 mg per day. Lacrimal gland enlargement resolved without recurrence.

Case 4
A 60-year-old male presented with enlargement of a lacrimal gland mass. The mass was biopsied two years prior with pathologic result showing “benign lacrimal gland tissue with focal chronic inflammation”. He was then lost to follow-up until the current presentation. He stated that he had recently developed asthma. A left lacrimal gland mass creating an S-shaped lid deformity was palpated and measured 30mm by 4mm. Hertels measured 15mm (right) and 18mm (left). B-scan ultrasound showed an encapsulated, homogenous mass not impinging on the orbit or muscle cone. A steroid taper (dose unknown) was started with slight improvement. The patient underwent anterior orbitotomy with tumor excision and intraorbital steroid treatment. Biopsy showed dense fibrous tissue, scattered lymphocytic, histiocytic infiltration with some in a follicular arrangement, and scattered eosinophils. IgG4 stain was positive at 50 cells/HPF. IgG4 level drawn three months after biopsy was measured at 57 mg/dL (Ref: 7-89 mg/dL). No recurrence has been noted to date.

Case 5
A 65-year-old woman presented with an enlarging left upper eyelid mass. Four years earlier, she had undergone debulking of the mass diagnosed as inflammatory pseudotumor with pathology showing leukocytoclastic vasculitis with eosinophils. On presentation, the patient had a 1 x 1.5 cm left medial upper eyelid rubbery mass with medial ptosis (Figure 2). CT showed a 14mm soft tissue mass. Anterior orbital biopsy with debulking was performed. Tissue was gray-white and highly fibrous without a capsule or identifiable levator fibers. Histology revealed eosinophilic angiocentric fibrosis and inflammatory infiltrate with numerous eosinophils. 40 IgG4 positive plasma cells/HPF were seen. IgG4/IgG ratio was increased (0.50), but serum IgG4 levels were within normal limits (value not noted). Through 26 months of follow-up, the patient has remained stable without clinical enlargement of the debulked mass. The patient did not receive oral steroids throughout her course of treatment.

Case 6
A 66-year-old African American female with a past medical history of hypertension, asthma, chronic sinusitis, primary hyperparathyroidism, and multinodular...
goiter presented with a two month history of bilateral upper eyelid swelling. Bilateral lacrimal gland prolapse was evident on external examination. Previous chest x-rays were negative for hilar lymphadentopathy. The patient was brought to the operating room for a planned bilateral lacrimal gland resuspension. A biopsy of the left lacrimal gland was taken, which showed nearly total effacement of the lacrimal architecture by a marked lymphoid infiltration consisting of mature lymphocytes, polyclonal plasma cells, and histiocytes. Lymphoid tissue is composed of B-cells (CD20 positive) separated by bands of fibrous tissue containing T-cells (CD3 positive) and numerous IgG4-positive plasma cells (>50/HPF). The patient is currently being monitored for progression, and is pending rheumatologic evaluation for systemic involvement.

Case 7

A 4-year-old male presented to the emergency department with a right red eye with eyelid involvement, concerning for an orbital cellulitis. Upon examination by the consulting ophthalmologist, the patient was noted to have a reddish-colored mass prolapsing from the right lacrimal gland region along with a right hypoglobus. The patient was admitted for further work-up of the concerning lesion. The patient's mother recalls past episodes over the last couple of years of bilateral upper eyelid masses that subsequently regressed without treatment or physician examination. Magnetic resonance imaging showed marked expansion of the right lacrimal gland with thick enhancement, central cavitation, and indentation of right eye. The patient underwent an anterior orbitotomy, during which a pus-filled abscess was noted and drained. A biopsy of the right lacrimal gland showed marked fibrosis with chronic nongranulomatous inflammation. IgG4 staining was positive at greater than 50 cells/HPF. Post-operatively, the patient showed no signs of infection or lesion recurrence. Rheumatologic examination and laboratory work-up was within normal limits. The patient is currently being monitored for orbital recurrence or systemic involvement without necessitating further treatment.

Discussion

This series highlights the diverse presentation and associated systemic finding in patients with IgG4-related orbital inflammation. The causes of IgG4-related disease are unknown. An association with chronic antigen exposure exists with clinical features of slow progression and weak immune response. Many patients have a history of atopic and immune-mediated diseases as seen in Case 1 with rheumatoid arthritis, Case 4 with recent development of asthma, and Case 6 with asthma, chronic sinusitis, and thyroid disease. Systemic involvement should also be investigated. Case 2 had a history of pancreatic involvement. Patients with orbital involvement should be sent for rheumatologic evaluation once the diagnosis of IgG4-related disease is established.

Middle-aged to elderly men are usually affected in systemic disease; however, orbital involvement has no gender predilection with a lower median age. Our case series follows this trend (Table 1) with four males and three females, and ages ranging from 4 to 66 years of age (average: 49 years of age; median: 60 years of age). Ophthalmic disease commonly presents with painless eyelid swelling or proptosis with or without diplopia. Visual acuity tends not to be impaired. Five of our patients had eyelid masses, and three presented with proptosis. Multiple case series have shown the lacrimal gland to be the most commonly involved site. Four of our patients showed the lacrimal glands to be the primary site of involvement. Both the lacrimal and salivary glands bilaterally can be involved in IgG4-related ophthalmic disease. This constellation of lacrimal and salivary gland involvement had previously been termed Mikulicz disease, which is defined as comprising clinical bilateral, painless, and symmetric swelling of the lacrimal, parotid, and submandibular glands.

Figure 2. Presentation, imaging, and pathology of Case 5. Top: External color photograph. Middle: Digitally enhanced image: CT. Bottom: Inflammatory infiltrate with vasculitis (x100) (top left). Early and late infiltrates (x100) (top right). Higher magnification (x200) (bottom left). IgG4-immunostaining (x400) (bottom right).
of unknown etiology for more than three months. Mikulicz syndrome is commonly mistaken for Sjögren Syndrome, the latter also having dry eye and mouth symptoms in addition to serum antibodies against SS type A (Ro) and SS type B (La) antigens. Given the various forms of presentation of IgG4-related ophthalmic disease, the differential diagnosis is broad and includes infectious processes, neoplasm, and inflammatory disease. Hematologic studies should only be used as supporting data, not for absolute diagnosis or to follow disease progression. We recommend that IgG4 levels be drawn as soon as clinical suspicion is raised to establish a baseline prior to treatment, although serum IgG4 levels may be normal in many cases. Possible changes of other activity markers may be seen, such as elevated circulating immune complex (CIC) and soluble interleukin-2 receptor or decreased levels of C3 and C4. Sometimes, Rheumatoid factor may also be elevated. Ultimately, diagnosis requires tissue biopsy. Pathology reveals a fibroinflammatory reaction with tumefactive lesions and dense lymphoplasmacytic infiltration. Storiform fibrosis is commonly seen, although in orbital inflammation, the lesions are usually collagenous. Obliterative phlebitis is another feature commonly seen in other forms of IgG4-related disease outside the orbit. Staining for IgG4 should show greater than 50 IgG4-positive cells/HPF as IgG4-positive plasma cells can be seen in other processes at lower concentrations. This number is not an absolute cut-off, rather it should be used in conjunction with other common histopathologic features as well as the entire clinical picture. Case 4 showed 40 IgG4-positive cells/HPF, with no other co-morbidities and microscopic findings of inflammatory infiltrates, fibrosis, and eosinophilia (another common feature of IgG4-related disease) leading to the final diagnosis. Many IgG4-related diseases are currently misdiagnosed as number of varying processes (or remain in an idiopathic category) as serum IgG-subclass analysis and IgG4 immunostaining of specimens even when biopsied are not performed routinely and the affected organs vary. A neoplastic process can still be present even in the background of IgG4-related disease. Sato et al described a case series of 21 patients with IgG4-related ophthalmic disease, of which 2 had immunoglobulin heavy chain gene rearrangement as well as a high level of IgG4, suggesting B-cell or MALT lymphoma arising from a background of chronic inflammation. Ochoa et al also describe a case of MALT lymphoma arising from a background of Kuttner tumor, which is considered to be an IgG4-related disease. It is of great importance to keep in mind the possibility of malignancy arising from a past of IgG4-related disease even after treatment has been completed. Patients should continue to be monitored after apparent successful treatment of the IgG4-related disease process. Imaging tends to be nonspecific in IgG4-related disease. CT usually reveals intermediate soft-tissue attenuation and low signal intensity is seen on T1- and T2-weighted MRI with homogeneous enhancement because of increased cellularity and fibrosis. Involvement of the lacrimal glands is most commonly noted on imaging studies, which correlates well with clinical findings. Of note, some reported cases do not follow these radiographic generalizations, ultimately requiring biopsy to differentiate IgG4-related disease from other processes. Prompt diagnosis is imperative as improvement with corticosteroids is seen if fibrosis has not already occurred. However,
use of steroids before biopsy should be discouraged as biopsy results may be altered, especially if the IgG4 inflammatory process responds well to steroids. With steroid non-response or recurrence, rituximab has been successfully used, which is thought to deplete B lymphocytes that replenish short-lived IgG4-secreting plasma cells.\textsuperscript{18} Although not used in our patients, radiotherapy has also been successfully employed in cases of sclerosing disease resistant to steroid treatment.\textsuperscript{19,20} Nonetheless, the first line treatment should be complete removal of the mass when possible and whenever symptoms such as diplopia and decreased visual acuity occur. Although orbital disease is more commonly isolated, patients should be referred for medical work-up to rule out systemic involvement. In addition, patients should be monitored for recurrence and malignancy from the background of chronic inflammation. Our case series illustrates the complexity of treatment and the variety of options available. Treatment with steroids or surgical excision are commonly employed, although rituximab may be initiated in refractory cases. Serum IgG4 levels should be drawn before treatment and IgG4 stain performed on biopsies. Continued experience with IgG4-related ophthalmic disease will allow for refinement of treatment methods and promise for understanding its etiology.

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REFERENCES