



## Adult Onset Asthma and Periocular Xanthogranuloma: A Difficult Diagnosis

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### Abstract

**Purpose:** This case report describes the presentation, diagnosis, and treatment of adult onset asthma and periocular xanthogranuloma (AAPOX) in a 41 year-old male and highlights the diagnostic and therapeutic challenges of this disease.

**Observations:** The authors report a case of a 41 year-old male with a 12 year history of episodic bilateral upper eyelid edema, and mechanical ptosis of uncertain etiology. He had previously undergone biopsy and failed trials of surgical excision, systemic corticosteroids, methotrexate, and radiation therapy. He was initially diagnosed in 2004 with bilateral idiopathic orbital inflammation by biopsy. Due to concomitant sinus congestion, shortness of breath, and hilar adenopathy on chest x-ray, the patient underwent endoscopic sinus surgery and transbronchial biopsy, which showed vague granulomatous chronic inflammation suggestive of sarcoidosis. Serologic workup was notable for peripheral blood eosinophilia (17%); however, infectious and rheumatologic serologies, including angiotensin converting enzyme (ACE) and antinuclear antibody (ANA), were unremarkable. The patient presented to the Bascom Palmer Eye Institute (BPEI) for evaluation due to recurrence of bilateral lid swelling. He underwent repeat biopsy which disclosed fibrovascular and adipose tissue containing xanthomatous infiltrate of foamy histiocytes without necrosis consistent with xanthogranuloma. The overall presentation was suggestive of AAPOX. The patient was started on methotrexate and long-acting bronchodilators, and at 8-month follow-up the patient reports improved left-sided peripheral vision, and continues to be followed by the Pulmonology, Rheumatology, and Oculoplastics services.

**Conclusion and Importance:** AAPOX is a rare, non-Langerhans histiocytic disorder with characteristic orbital and systemic findings. This patient was followed for 12 years by multiple providers with innumerable work-up, biopsies, and imaging without a definitive diagnosis. This case illustrates the diagnostic challenges and important histopathologic clues in the diagnosis of this rare disease.

**Keywords:** Orbital mass; Eyelid swelling; Asthma; Xanthogranulomatous disease

### Introduction

Adult onset asthma and periocular xanthogranuloma (AAPOX) is a rare, non-Langerhans histiocytic disorder with characteristic orbital and systemic findings. This case report explores the diagnostic and therapeutic challenges of this disorder, and the importance of a multidisciplinary approach in recognizing and treating this disease.

### Case Presentation

A 41 year-old male with a history of diabetes and keratoconus presented to the Bascom Palmer Eye Institute (BPEI) Oculoplastics service due to chronic, intermittent upper eyelid swelling and diplopia in all fields of gaze of uncertain etiology. His symptoms began 12 years prior to presentation with bilateral upper lid swelling. He underwent bilateral anterior orbitotomies with biopsies and was diagnosed with bilateral idiopathic orbital inflammatory disease (IOIS). The patient was only partially responsive to high dose oral steroids and methotrexate, and reported clinical worsening with radiation therapy of 10 fractions for a total of 2000 cGy. Two years later, the patient underwent repeat bilateral upper lid blepharoplasties for surgical debulking and biopsy, and histopathologic examination showed a xanthomatous and chronic inflammatory infiltrate. The diagnosis was unclear at this point, and the patient was continued on oral corticosteroids for presumed IOIS.

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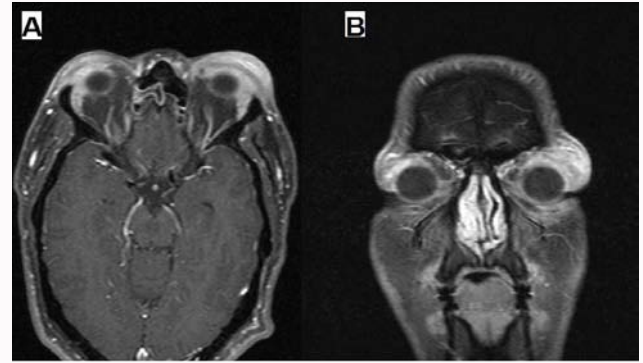
**Figure 1:** Clinical photograph at presentation demonstrating fullness of bilateral upper lids, with a left upper lid palpable soft preseptal mass in the super temporal quadrant. Parotid gland enlargement was notable on the left greater than right.

Concomitant with his ocular symptoms, the patient complained of sinus congestion and shortness of breath, with x-rays showing sinusitis and hilar adenopathy. The patient underwent endoscopic sinus surgery, and transbronchial biopsy revealing vague granulomatous chronic inflammation suggestive of sarcoidosis, thus the patient was diagnosed with sinusitis and pulmonary sarcoidosis.

After 12 years of symptoms, he developed worsening of his eyelid swelling and presented to the BPEI Oculoplastics service. He reported bilateral eyelid enlargement and diplopia that obstructed his visual axis and impacted his activities of daily living. On review of symptoms, he endorsed sinusitis and pulmonary disease, but was otherwise pain free and without evidence of systemic, arthritic, renal, or dermatologic disease. Best corrected visual acuity was 20/30 OD, 20/25 OS, with normal pupils and intraocular pressure. No proptosis was noted, and the patient was orthophoric. External exam revealed fullness of both superotemporal upper lids, with a palpable soft preseptal mass in the left upper lid extending to the superotemporal quadrant into the lacrimal gland (Figure 1). The patient demonstrated limited supraduction OS, and left superior hemifield defect. Parotid gland enlargement was notable on the left greater than right. Anterior segment examination was notable only for bilateral papillary conjunctivitis and the rest of the ocular exam was unremarkable in both eyes.

Serologic workup was notable for peripheral blood eosinophilia (17%); however, infectious and rheumatologic serologies, including ACE and ANA, were unremarkable. Contact B-scan and diagnostic A-scan were not consistent with IOIS nor with orbital sarcoidosis, demonstrating a well-circumscribed, irregular, variably reflective, soft tissue lesion in the superior/anterior left orbit involving the levator muscle and extending superotemporally over the orbital rim. MRI showed diffuse sinus disease, extraocular muscle enlargement, and contrast-enhancing superotemporal eyelids and lacrimal gland/orbital masses, left greater than right without fat stranding (Figure 2).

Given the patient's chronic disease and unclear clinical picture, the decision was made for a third incision biopsy of the left orbital lesion to evaluate for IgG4 and xanthogranulomatous-related disease. Flow cytometry revealed no immunophenotypically abnormal B or T-cell populations. Histopathologic exam revealed xanthogranuloma with fibrovascular and adipose tissue with foci of skeletal muscle containing xanthomatous infiltrate of foamy histiocytes without



**Figure 2:** Axial (A) and Coronal (B) T1 magnetic resonance imaging with contrast and fat suppression showing diffuse sinus disease, extraocular muscle enlargement, and contrast-enhancing superotemporal eyelids and lacrimal gland / orbital masses, left greater than right without fat stranding.

necrosis. The lesion stained positive for CD68, CD3, and CD20; and stained variably positive for CD8 and CD4 (Figure 3). Due to the lack of plasma cell infiltration, IgG4 was not stained for on histopathologic exam, and was not tested in the serum.

The differential diagnoses included adult onset xanthogranulomatous disease, IgG4-related disease, eosinophilic granuloma, Kimura's disease, and Mikulicz's syndrome. However, based on the patient's clinical presentation, histopathologic analysis, and associated systemic disease, the overall presentation was suggestive of AAPOX. The patient was started on methotrexate and long-acting bronchodilators, and at 8-month follow-up, the patient reported significant resolution of the left orbital lesion, improved left-sided peripheral vision, and continues to be followed by the Pulmonology, Rheumatology, and Oculoplastics services (Figure 4).

## Discussion

Adult onset xanthogranulomatous (AOX) disease is an uncommon spectrum of non-Langerhans histiocytic disorders characterized by the presence of foamy non-Langerhans histiocytes, Touton giant cells, and varying degrees of fibrosis [1,2]. Non-Langerhans histiocytic disorders are often associated with other systemic manifestations, which allow sub classification into four syndromes: Adult onset xanthogranuloma (AOX), necrobiotic xanthogranuloma (NBX), Erdheim-Chester disease (ECD), and adult onset asthma and periocular xanthogranuloma (AAPOX). First reported in 1993 [2], AAPOX remains an uncommon entity with fewer than 50 cases reported in the English literature to date [1,3-12]. The clinical and histologic features in this case are consistent with AAPOX.

AAPOX is characterized by periocular xanthogranuloma with asthma. Patients are often observed with systemic lymphadenopathy, salivary gland enlargement, and cases of elevated IgG serum levels are reported [1,8]. In the largest review of published reports to date, pooled data analysis of 21 AAPOX cases revealed mean age at diagnosis of 46 years (SD 13, range 22-74) and no gender preference [1]. Patients typically had periocular skin manifestations, preseptal, and anterior orbital involvement, and evidence of immune dysfunction including asthma, lymphadenopathy, paraproteinemia, and B cell lymphoid aggregates on histology [1]. These systemic characteristics of AAPOX overlap with those of IgG4-related ophthalmic disease, and it has been suggested that AAPOX may be associated with IgG4-related disease [8]. AAPOX has not been a reported cause of mortality [1].

Empiric treatment modalities include surgical excision, corticosteroids, chemotherapeutic agents, and radiation with varying effectiveness. In Sivak's case series of 8 AAPOX patients [1], surgery alone was effective in 75% (6 of 8), corticosteroids were useful in 100% (2 of 2), and cyclosporine (T cell suppression) and cyclophosphamide (B cell suppression) were also found to be beneficial. In a review of the literature, cases reporting management with cyclophosphamide, melphalan, chlorambucil, vincristine, vinblastine, interferon, etoposide, methotrexate [3], etanercept, gammaglobulin, clofazimine, and doxorubicine have also been reported. Given the apparent B cell dysfunction demonstrated in patients with AAPOX, there may be rationale for systemic B cell suppression [4].

This patient demonstrated the typical signs of AAPOX with submandibular and hilar lymphadenopathy, parotid gland enlargement, asthma, and preseptal and anterior orbital involvement. However, his diagnosis was delayed for 12 years from presentation, due in part to biopsy results thought to be consistent with IOIS. IOIS and AAPOX share histologically similar features, such as an inflammatory cell infiltrate with predominance of mature lymphocytes admixed with plasma cells, eosinophils and macrophages [13]. Thus, upon receiving biopsy results consistent with IOIS, it is still important to consider AAPOX within the differential diagnosis, most notably when systemic symptoms are present, as was the case in this patient. Interestingly, B cell lymphoid aggregates were not noted on this patient's histology, which may be related with his long-term treatment with systemic corticosteroids. Additionally, our patient further demonstrates the uncertainty of radiation therapy and reinforces the use of methotrexate in treating AAPOX.

## Conclusion

This patient was followed for 12 years by multiple providers with innumerable work-up, biopsies, and imaging without a definitive diagnosis. The rarity of AAPOX and other AOX clinical presentations precludes prospective investigation and meta-analysis for therapeutic studies. This case presentation of AAPOX adds incremental knowledge to our collective understanding of this uncommon entity, and demonstrates the diagnostic challenges, important histopathologic tools, and potential treatment modalities used particularly in the case of rare diseases with difficult diagnoses.

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