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CASE REPORT

IgG4-related ophthalmic disease in association with adult-onset asthma and periocular xanthogranuloma: a case report

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ABSTRACT

A 54-year-old male presented with a three-year history of bilateral upper eyelid and peri-orbital swelling and adult-onset asthma. Histopathology of a left orbital biopsy showed lymphoid follicles with foamy macrophages and Touton giant cells. Clinical, histological and radiological features were consistent with adult-onset asthma and periocular xanthogranuloma. Treatment with rituximab led to a complete clinical and radiological remission. Nine years later, his condition relapsed with a biopsy of the left orbit and lacrimal gland demonstrating features of IgG4-related disease and adult-onset asthma and periocular xanthogranuloma. Immunohistochemistry showed increased numbers of IgG4+ plasma cells (290 per high power field) and an elevated IgG4+/IgG+ plasma cell ratio of 480%. Involvement by both disorders in the orbit and ocular adnexa of a single patient has not previously been reported in the literature, to the best of our knowledge, and suggests a possible aetiologic or pathophysiologic association.

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Adult xanthogranulomatous disease (XG) of the orbit and ocular adnexa comprises a heterogeneous group of rare fibroinflammatory disorders presenting with orbital masses and often xanthelasma-like lesions of the eyelids.[1] There are four distinct subtypes: 1) adult onset xanthogranulomatous disease of the orbit (AOX), 2) adult-onset asthma with peri-ocular xanthogranuloma (AAPOX), 3) necrobiotic xanthogranuloma (NXG), and 4) Erdheim–Chester disease (ECD).[1] AOX is a localised disorder of the peri-ocular soft tissues. AAPOX comprises AOX with additional features of adult-onset asthma, often nasal and paranasal sinus disease and reactive lymphadenopathy.[1] NXG characteristically presents with periorbital subcutaneous skin lesions, which tend to ulcerate, and histological features of necrobiosis with palisading necrosis.[1] ECD can affect the orbit, typically posteriorly, and often has systemic manifestations.[1] It has been found to have activating mutations within the MAPK pathway, in particular, BRAF V600E mutations in more than 60% of the cases.[2] Compared to the other subtypes of adult XG, ECD has a worse prognosis, but this has been improved with treatment with vemurafenib, a BRAF inhibitor.[3] The stereotypical pathological features of XG include an infiltration of foamy xanthomatous macrophages and Touton giant cells.[1]

IgG4-RD is a systemic fibroinflammatory condition, not uncommonly presenting with an ophthalmic tumefactive lesion or lesions, but can affect almost any organ.[4] Diagnosis is made by integration of clinical, radiologic, serologic and histopathological data, with reference to consensus criteria.[5] The term IgG4-related ophthalmic disease (IgG4-ROD) is preferred for ocular adnexal and orbital involvement of IgG4-RD.[4] Histological findings show significant overlap between XG and IgG4-RD: common features include fibrosis; reactive lymphoid follicles; eosinophils; plasma cells; and diffuse infiltrates of T cells.[6] Characteristics specific to IgG4-RD include storiform and/or eosinophilic angiocentric patterns of fibrosis, obliterative venulitis and a consistent IgG4+/IgG+ plasma cell ratio greater than 40%. Xanthoma cells and Touton giant cells do not comprise part of the histological pattern.[6]

Previous reports have revealed an association between the two conditions, but only rarely have both been described in a single patient. For a true dual-diagnosis, one requires pathological confirmation of XG in the orbit plus histological evidence of IgG4-RD in a site other than the orbital tissue involved by the XG inflammation.[6] Herein, the authors present a case of AAPOX complicated by IgG4-ROD. This patient has previously been reported in a published case series prior to the recurrence of disease and development of

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IgG4-RD.[7] Informed consent to publish the photographs was signed by the patient. This research adhered to the tenets of the Declaration of Helsinki.

Case Presentation

A 54-year-old male presented in 2010 with a three-year history of worsening bilateral upper eyelid swelling (Figure 1A). His past medical history was significant for asthma from the age of 52, intermittent symptoms of nasal obstruction and obstructive sleep apnoea. On examination, he had bilateral upper lid ptosis and swelling, skin lesions consistent with xanthelasmata, and palpable masses in the anterior superior orbits. At presentation an orbital MRI scan confirmed bilateral preseptal soft tissue thickening. There were no intraconal masses or infiltration. Biopsy of the left lid lesion revealed foamy histiocytes. A deeper orbital adipose biopsy showed a xanthomatous infiltrate, Touton giant cells (Figure 2A) and reactive lymphoid follicles. No necrotising xanthogranulomas were noted. Immunohistochemistry demonstrated 70 IgG4+ plasma cells per high power field and an IgG4+/IgG+ ratio of 82%. Flow cytometry analysis of the deeper biopsy was negative for B- and T-cell clonality. The clinical and histological features were consistent with a diagnosis of AAPOX. The patient was managed with methotrexate (10 mg per week, increasing to 25 mg weekly over 3 months) and oral prednisolone (initially 25 mg daily) with only moderate response. In May 2011, he was commenced on single agent rituximab induction and maintenance treatment (375 mg/m^2 weekly for 4 weeks, followed by 3 monthly infusions for 2 years), with a dramatic clinical and radiological improvement (Figure 1B). He experienced no side effects to rituximab and was monitored with biannual ophthalmology review and serial orbital imaging.

Nine years after the initial presentation, and six years after treatment with rituximab, the patient's disease relapsed manifesting with swelling of the upper eyelids (Figure 1C). On examination, he displayed increased proptosis. Serum IgG4 was 12.10 g/L (normal 0.03–2.01 g/L), eosinophils 0.6 x 10^9/L (normal 0–0.5 x10^9/L), LDL-cholesterol was 3.8 mmol/L and total cholesterol/HDL ratio was 5.3. All other laboratory tests, including serum paraprotein, anti-DNA autoantibodies and anti-neutrophil cytoplasmic antibodies, were within normal limits. Biopsies of the left orbit and lacrimal gland showed fibroadipose tissue with multiple nodules of lymphoid tissue (Figure 2B), including reactive follicles, and a localised infiltrate of xanthoma cells and Touton giant cells (Figure 2E). Immunohistochemistry demonstrated 290 IgG4+ plasma cells per high power field (Figure 2C,D) and an IgG4+/IgG+ ratio of 480%. Flow cytometry analysis confirmed no abnormal clone of lymphoid cells. MRI of the orbits showed patchy infiltration and enhancement in bilateral periorbital soft tissues and lacrimal glands. CT chest demonstrated irregular ground glass nodules in the periphery of both lower lobes and mild mediastinal and hilar lymphadenopathy. FDG-PET/CT scan confirmed moderately avid symmetrical mediastinal and bilateral hilar lymph nodes, which were not biopsied. In addition, two small subcentimetre nodules in the right lung were shown to be mildly FDG avid. No significant FDG avidity was found elsewhere.

This patient demonstrated features of both AAPOX of the left orbit, with elevated numbers of IgG4+ plasma cells, and subsequently AAPOX and IgG4-RD involving the left orbit and bilateral lacrimal glands. Our case also fulfils consensus criteria for the diagnosis of IgG4-RD in the 2019 biopsy, with a total of 37 inclusion points (20 points required for diagnosis) comprised of 4 for dense lymphocytic infiltrate, 16 for immunostaining features, 11 for serum IgG4 more than 5x normal levels and 6 for bilateral lacrimal gland involvement.[5] Treatment commenced in January 2020 with rituximab induction and maintenance therapy (375 mg/m^2 weekly for 4 weeks, followed by monthly infusions). The patient has tolerated the treatment without significant complication after six months of follow-up.

Discussion

Adult XG disease and IgG4-RD are fibro-inflammatory conditions involving the orbit and ocular adnexa. Caution, however, should be heeded in concluding that a patient has both conditions.[8] Our authors have previously demonstrated that patients with XG often have significant numbers of IgG4+ plasma cells on histopathology.[6] This alone, however, does not fulfill the new three-step IgG4-RD classification criteria by the American College of Rheumatology and European League Against Rheumatism.[5] In this manner, despite our patient's first biopsy showing a plasma cell IgG4+/IgG+ ratio over 40% and elevated numbers of IgG4+ plasma cells, the presence of Touton giant cells, foamy histiocytes and clinical features of xanthelasmata, indicates the initial condition is most consistent with AAPOX and would not meet the entry criteria for IgG4-RD.[5] Other overlap cases in the literature similarly feature XG of the orbit with increased numbers of IgG4+ plasma cells, but not fulfilling the new IgG4-RD

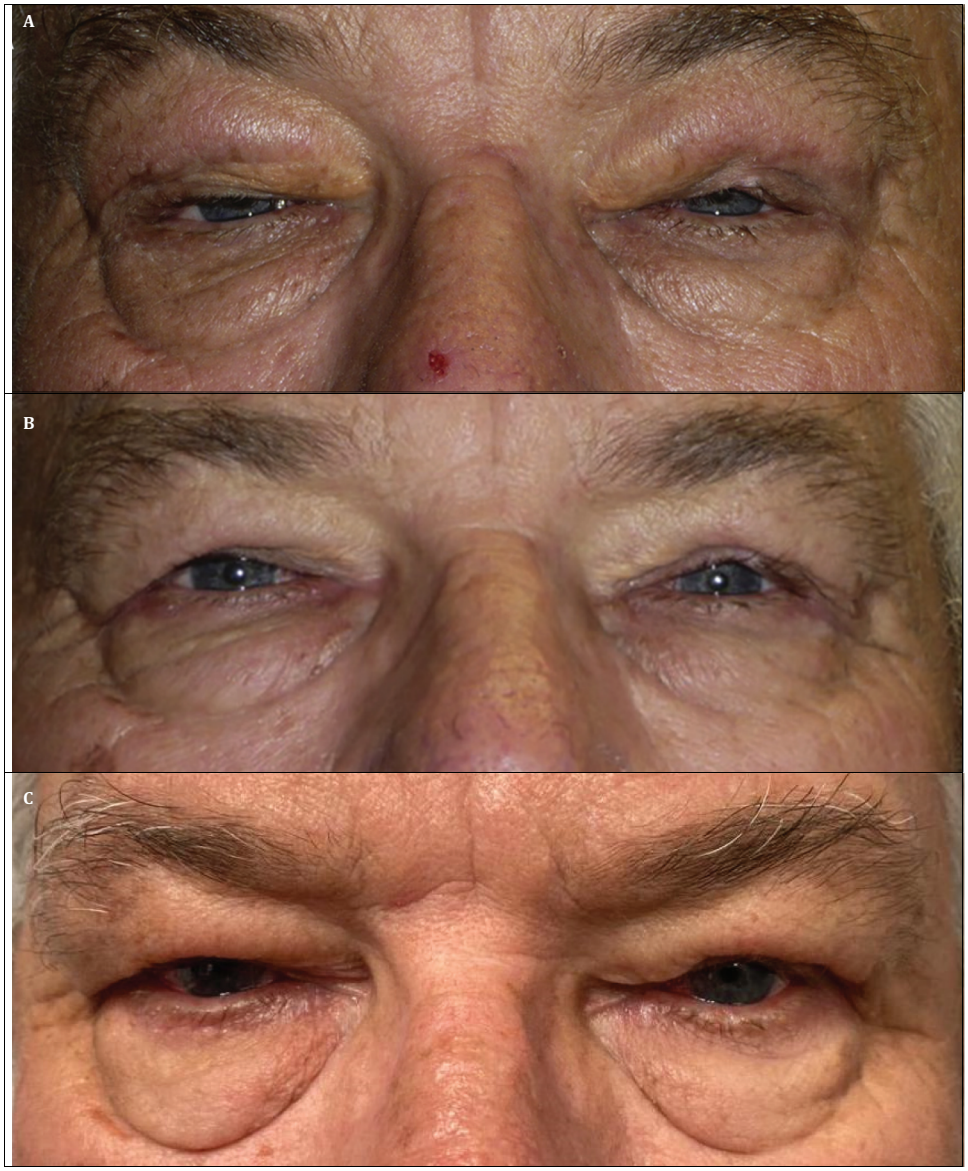

Figure 1. Clinical Images. At presentation in 2010, with adult-onset asthma and periocular xanthogranuloma (AAPOX) (**A**); Early 2013, after completion of treatment with rituximab, displaying significant reduction in periocular swelling and ptosis (**B**); Recurrence of periocular swelling in February 2020 (**C**).

classification criteria,[9–13] or IgG4-RD associated with foamy cells and giant cells, but not described as Touton type.[4,12,14,15]

Several cases have been reported detailing pathological diagnoses of adult XG of the orbit associated with IgG4-RD of the extra-orbital tissues, including pancreatic (autoimmune pancreatitis type 1),[6,15–19] salivary gland,[20] cheek[20] and parotid gland tissue.[21] Another case described of XG of the orbits with increased IgG4 + plasma cells in the lacrimal glands,[10] yet insufficient biopsy details of these organs were provided to assess its fulfilment of the current IgG4-RD diagnostic criteria. To the best of our knowledge, ours is the only case of adult XG of the orbit complicated by IgG4-RD both involving the orbital tissues. One may speculate that the FDG-avid mediastinal and hilar lymph nodes and pulmonary ground glass changes also represent a systemic manifestation of IgG4-RD in this patient, but no biopsies of these were taken.

AAPOX is rare, most often affecting males between 22 and 74 years of age[1] and presenting with non-destructive lesions of the eyelid or anterior orbit and xanthelasmata.[1] Typically, IgG4-ROD affects men and women equally and has a mean age of onset of 55.5 years (SD 12.9).[22] Each condition is associated with adult-onset asthma [1,23] consistent wth our case. The precise pathogenesis of both

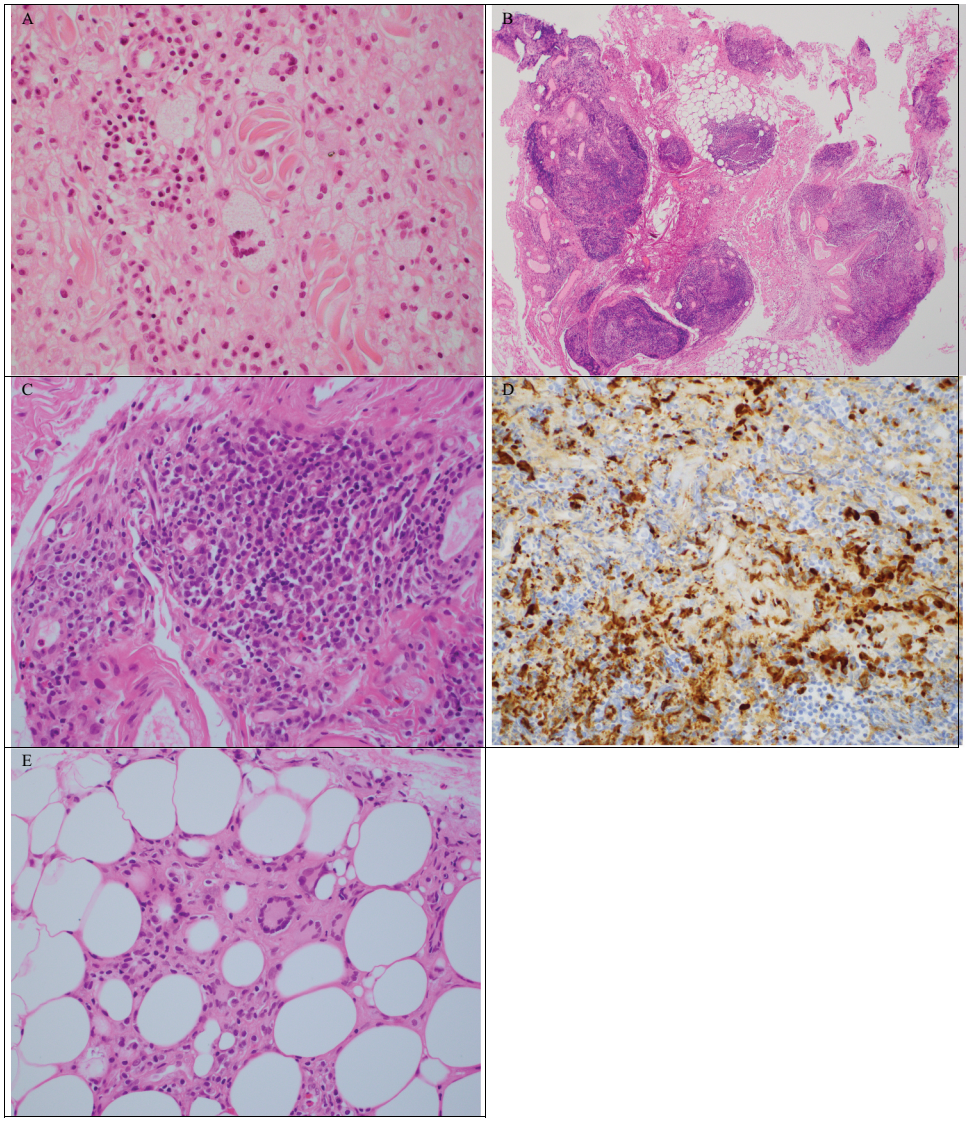

Figure 2. Morphologic and immunohistochemical findings. 2010 orbital biopsy showing numbers of foamy macrophages with Touton giant cells admixed with lymphocytes and plasma cells. Haematoxylin and eosin. Magnification x400 (**A**); 2019 biopsy of orbit showing multiple lymphoid nodules. Haematoxylin and eosin. Magnification x40 (**B**); 2019 biopsy high power showing numerous plasma cells. Haematoxylin and eosin. Magnification x400 (**C**); 2019 biopsy showing numerous IgG4+ plasma cells. Magnification x400 (**D**); 2019 biopsy showing focal xanthogranulomatous inflammation with Touton giant cells. Haematoxylin and eosin. Magnification x400 (**E**).

IgG4-RD and adult XG of the orbit, with the exception of ECD, is unclear. No genetic linkage common to AAPOX and IgG4-RD has yet been identified.[6] Both disorders commonly feature increased IgG4 antibodies – in IgG4-RD it has been suggested that these are not directly pathogenic since levels of the antibody may be normal in approximately 10–30% of patients.[24] In our study, McKelvie et al, 2017[6] we demonstrated that the majority of cases of AAPOX contain IgG4+ plasma cells, which is likely a hallmark of a localised immune reaction without association to IgG4-RD. IgG4+ plasma cells are also found in the orbit in patients with other autoimmune disorders such as Sjogren's syndrome, granulomatosis with polyangiitis (unpublished data) and in lymph nodes of patients with Castleman disease but without features of IgG4-RD.

Some of the mechanisms of disease development of IgG4-RD have newly been elucidated. Oligoclonal expansions of plasmablasts (both IgG4- and non-IgG4-expressing) have been detected in peripheral blood of patients with IgG4-RD.[25] Treatment with rituximab, which depletes B-cells from which these plasmablasts are derived, results in striking clinical improvement.[26] This response to rituximab is also seen in cases of XG[7] and is

consistent with our patient's clinical course. More recently, a clonally expanded population of CD4+ SLAMF7 cytotoxic effector memory T-cells has been causally associated with IgG4-RD.[27–29] It has been suggested that plasmablasts or other activated B-cells play a role in reactivation of these CD4+ cytotoxic T-cells by antigen presentation. This is suggested to induce the B-cells to produce pro-fibrotic cytokines leading to infiltration by innate and adaptive immune cells.[30] However, a specific triggering antigen has not been identified in all patients with IgG4-RD.

Although the medical treatment for adult XG disease of the orbit and IgG4-RD is similar, it is important to distinguish the two disorders as the potential complications differ vastly. IgG4-RD can involve various organs other than orbit and lacrimal gland including pancreas, biliary system, aorta and retroperitoneum, kidney, lung, meninges, salivary glands and thyroid. The potential extraorbital manifestations of adult XG include adult-onset asthma, haematological disorders[1,31] or the association with Erdheim Chester disease.[2] Treatment of IgG4-RD with rituximab may delay the onset of diagnosis of adult XG disease as both respond to this immunomodulatory therapy.

The concurrence of IgG4-RD and adult XG disease described here, and previously, suggests a potential aetiologic or pathophysiologic association. Involvement by both disorders in the orbit and ocular adnexa of a single patient has not before been reported, to our knowledge. This case highlights the significance of obtaining biopsies of orbital inflammatory lesions. Accurate diagnosis of IgG4-ROD and adult XG disease by biopsy is important for the detection of potential systemic involvement or malignant transformation, in order to facilitate early intervention.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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