Adult Onset Xanthogranuloma Associated with IgG4-related Disease

Dear Editor,

Adult xanthogranulomatous disease (AXG) is a spectrum of inflammatory diseases occurring in the orbital adnexa and has four distinct subtypes. Adult onset xanthogranuloma (AOX) subtype is the least common form and is usually self-limiting without extra-ocular involvement. IgG4-related disease (IgG4-RD) is a systemic disorder that virtually includes all exocrine organs, with ophthalmic manifestation commonly presenting as orbital fibro-inflammation. AXG and systemic IgG4-RD appear to share common clinical, histological and radiological features [1]. Despite the assumed association, reports on simultaneous occurrence of AOX and IgG4-RD are scarce [2-4]. We present a patient with dual diagnosis of AOX and systemic IgG4-RD, which had an undulating course and was atypical of AOX in its pure form. In addition, this is the first report of such an occurrence in a Chinese subject.

A 61-year-old Chinese male presented to our clinic with 1-year history of progressive development of diffuse yellowish lesions over bilateral swollen eyelids. His medical history was significant for reactive follicular parotid hyperplasia, which had been resected. Family history was unremarkable. Examination revealed visual acuity of 0.8 bilaterally and eyelid swelling (Fig. 1A) without proptosis or diplopia. Serum thyroid function test, thyroid antibodies and fasting lipids were within normal limits. Magnetic resonance imaging showed left upper eyelid soft tissue swelling associated with lacrimal gland enlargement and orbital muscle swelling (Fig. 1B). The mass was subsequently biopsied via anterior orbitotomy together with intralesional triamcinolone injection. Histology revealed aggregates of foamy histiocytes and scattered Touton giant cells set in a fibrous stroma, consistent with xanthogranuloma (Fig. 1C, 1D). Whole-body positron emission tomography did not show evidence of hypermetabolic signals. The swelling responded to courses of high-dose oral prednisolone (1 mg/kg). With rituximab treatment, the patient’s condition improved significantly (Fig. 1E). Informed consent has been obtained from patient for treatment and publication.

Fig. 1. (A) Xanthelesmatous lesions and swelling involving bilateral eye lids. (B) Magnetic resonance imaging showed enhancement of soft tissue density in superior and lateral aspects of the left globe in the preseptal region (red arrow). (C) Histology showing diffuse infiltrate and nodular aggregates of foamy histiocytes in biopsy (>400). (D) Histology showing Touton type giant cells with histiocytic infiltration consistent with diagnosis of xanthogranulomatous disease (>400). (E) Resolution of xanthelesmatous lesions and reduced swelling after treatment with rituximab. Informed consent has been obtained from patient for treatment and publication.
but recurred shortly after discontinuation. Six years after initial presentation the subject was diagnosed with autoimmune pancreatitis presenting with gastric outlet obstruction. IgG4 serology was highly elevated at 513 mg/dL (>13.5 mg/dL), meeting the criteria for possible systemic IgG4-RD. Orbital involvement of IgG4-RD was suspected. Slides from previous lid biopsy were stained with IgG4 but were negative. The patient’s eye condition was treated with additional courses of prednisolone and later changed to azathioprine as a sparing agent. Because of suboptimal efficacy, two courses of rituximab were prescribed and resulted in interval reduction in size of periorcular swelling (Fig. 1E) and serum IgG4 level.

AXG is a rare disease characterized by presence of class II non-Langerhans histiocytosis, foamy macrophages and Touton giant cells. Four clinical subtypes exist: AOX, adult-onset asthma and periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma and Erdheim-Chester disease. IgG4-RD is a systemic fibro-inflammatory disease with hallmark features of lymphoplasmacytic infiltration of IgG4-positive plasma cells and storiform fibrosis. AXG tends to present with xanthelasmatous lesions within the eyelid and anterior orbit, with the exception of Erdheim-Chester disease, where involvement is more posterior. Orbital IgG4-RD commonly presents as orbital pseudotumor, dacryoadenitis, orbital myositis and scleritis whilst eyelid involvement is rare. Common histological features in both forms include fibrosis, lymphoid follicles and increased IgG4 plasma cells and eosinophils [1]. Fat necrosis and Touton giant cells are only present in AXG, while an IgG4/IgG ratio >40% is typical in IgG4-RD. Notably, IgG4 plasma cells lack specificity in IgG4-RD and are increased in other granulomatous conditions, creating difficulty in differentiation between the two entities. Elevated serum IgG4 also supports IgG4-RD diagnosis but is only present in 60% of cases.

Our patient is the first reported case of confirmed concurrent diagnosis of AOX subtype and IgG4-RD. Previous reports only demonstrated simultaneous diagnosis with AAPOX and necrobiotic xanthogranuloma subtypes [2-4]. AXG typically follows a benign course without systemic involvement. Its undulant nature and association with IgG4-RD in this case are unknown. Earlier case series on AAPOX associated with systemic IgG4-RD have indicated the need for long-term immunosuppression or biologics for disease control [2]. This helped determine treatment regime for simultaneous AOX and IgG4-RD in our case.

The close relationship between AOX and IgG4-RD is diagnostically challenging. Differentiating AXG from ocular IgG4-RD is important as development of lymphoma is a well-recognized complication in the latter [5]. The authors believe that the incidence is probably underestimated due to underreporting and difficult diagnosis, as both diseases responded to immunosuppression, steroid-sparing agents and biologics. In this report, we also showed that involvement of both diseases is possible in Chinese subjects.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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