

Adult ocular adnexal xanthogranulomatous disease associated with immunoglobulin G4-related disease: an unusual association

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SUMMARY

Adult-onset xanthogranuloma (AOX) and immunoglobulin G4-related disease (IgG4-RD) are uncommon fibrosing conditions that may exhibit localized ocular manifestations and occasionally systemic symptoms. These conditions exhibit overlapping clinical and histological features, suggesting a potential correlation between them, although their exact relationship remains unclear. This paper presents the case of a black male patient exhibiting typical histological indications of both AOX and IgG4-RD. The patient responded positively to corticosteroid treatment.

Key words: IgG4-related disease, adult-onset xanthogranuloma, orbit.

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■ INTRODUCTION

Adult orbital xanthogranulomatous disease (AOXGD) is a group of inflammatory disorders that impact the orbital area (1). This disease can be divided into four subtypes: adult-onset xanthogranuloma (AOX), necrobiotic xanthogranuloma, Erdheim-Chester disease, and adult-onset asthma and periocular xanthogranuloma (1). Among these, the AOX subtype is the least common within the AOXGDs. It is typically a self-limited process, devoid of extraocular involvement, and does not necessitate aggressive treatments (1).

Immunoglobulin G4-related disease (IgG4-RD) is a multisystem condition characterized by swollen or inflammatory lesions (2). It is categorized into four distinct phenotypes to aid in its identification (2). Patients may exhibit pancreato-hepato-biliary symptoms, aortic and retroperitoneal involvement, Mikulicz syndrome, or limited head and neck involvement. The latter often presents with inflammation and orbital fibrosis (2).

Thus, both conditions appear to share fibro-inflammatory mechanisms and some clinical-histological characteristics (3, 4). Despite these similarities, few cases have been reported where both entities are present in the same patient (5). We present a case of a patient with this association, who responded positively to corticosteroids and methotrexate.

■ CASE REPORT

A 47-year-old Brazilian man presented at our outpatient clinic, referred by his ophthalmologist owing to a 4-year history of recurrent, painless, bilateral periorbital swelling. He had no history of systemic manifestations or related illnesses. Physical examination revealed a non-tender bilateral upper lid mass, mild proptosis, and a xanthelasma-like lesion on his eyelids (Figure 1). The remainder of his physical examination was unremarkable. Laboratory tests, including total white blood counts, erythrocyte sedimentation rate, C-reactive protein,

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thyroid function, viral serology, tuberculin skin test, protein electrophoresis, antineutrophil cytoplasmic antibody, antinuclear antibody, C3, C4, and other autoantibodies (anti-SSA, anti-SSB, anti-Sm, anti-DNA, anti-RNP), showed no abnormalities. However, a quantitative serum immunoglobulin G4 (IgG4) level at 4880 mg/dL (normal range: 84-170 mg/dL). Orbital computed tomography imaging indicated bilateral proptosis, increased volume and densification of the periorbital soft tissues, and diffuse bilateral thickening of the lacrimal gland and the superior and lateral rectus muscles (Figure 2). Screening for systemic

involvement was performed with a tomographic study of the chest and abdomen, which showed no changes. Asthma was excluded by spirometry. Positron emission tomography was unavailable.

A biopsy of the left upper eyelid was performed, and the anatomopathological analysis revealed fibroadipose tissue with a moderate lymphoplasmocytic inflammatory infiltrate, scarce eosinophils, and abundant xanthomatous histiocytes in conjunction with Touton-type giant cells (Figure 3). The immunohistochemical examination disclosed extensive regions abundant in foamy histiocytes (CD68-KP1+, CD68-PGM1+), sporadic multinucleated giant

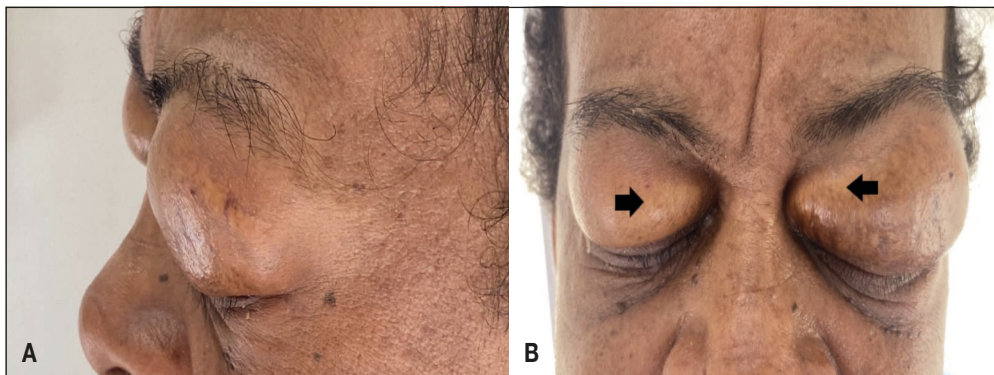


Figure 1 - A) Bilateral upper eyelid mass with mild proptosis; B) a yellowish lesion (black arrows) resembling a xanthelasma.

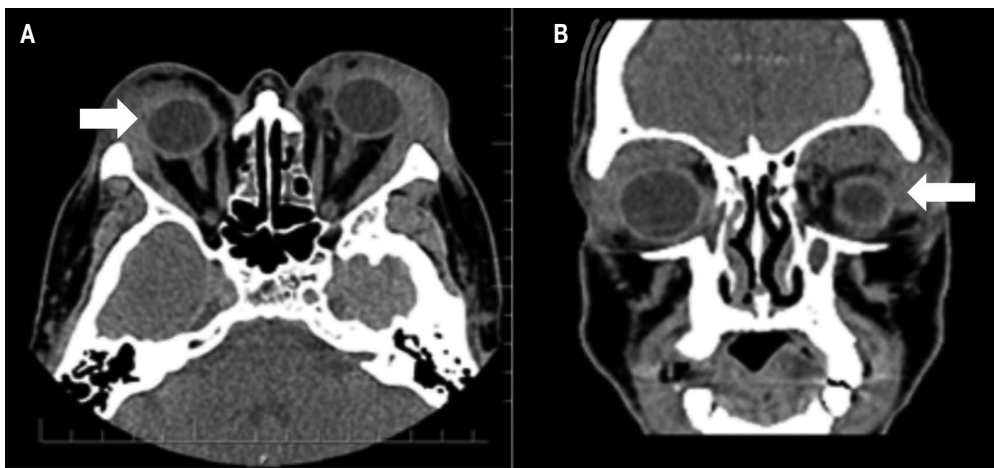


Figure 2 - Computed tomography on the axial (A) and the coronal (B) slices showed a bilateral proptosis with increased volume and densification of the periorbital soft tissues with bilateral involvement of the upper eyelids.

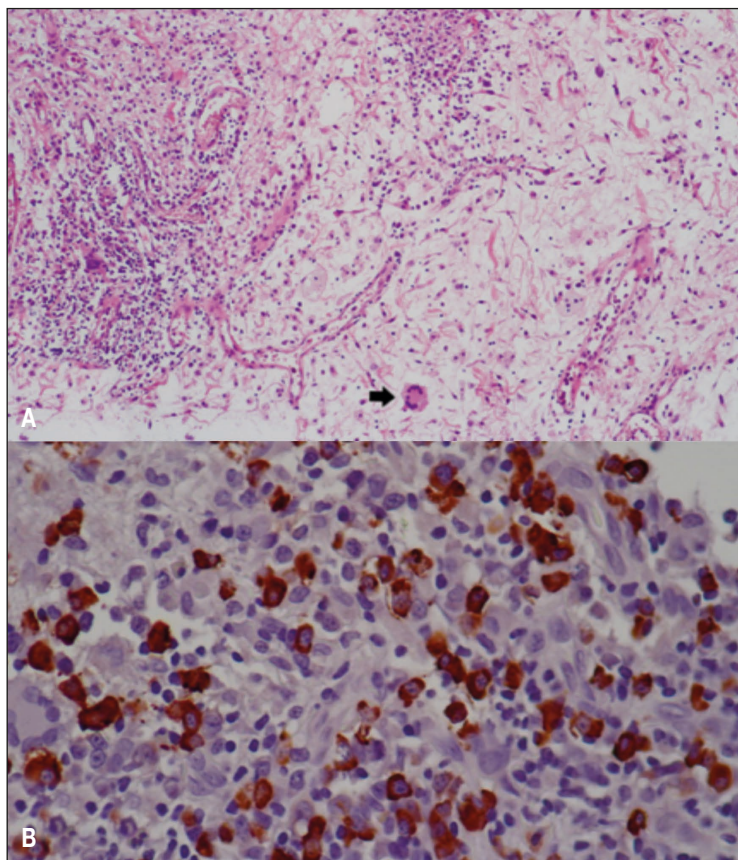


Figure 3 - A) Left upper eyelid biopsy shows fibroadipose tissue displaying moderate lymphoplasmacytic inflammatory infiltrate with frequent xanthomatous histiocytes associated with Touton-type giant cells (black arrow) (hematoxylin and eosin stain, $\times 4$); B) a revised immunohistochemical study demonstrated an increase of immunoglobulin G4+ plasma cells, immunoglobulin G4/immunoglobulin G ratio $>40\%$ (hematoxylin and eosin stain, $\times 40$).

cells, and dendritic cells (C1a+). There were no indications of neoplasia and no evidence of necrosis. Based on these findings, an initial histologic diagnosis of orbital xanthogranuloma was established.

The immunohistochemical study was revised owing to the elevated serum level of IgG4. The study revealed over 50 IgG4-positive plasma cells per high power field and an IgG4/immunoglobulin G (IgG) plasma cell ratio exceeding 0.4 (Figure 2). According to the 2019 American College of Rheumatology classification criteria for IgG4-RD (6), orbital involvement associated with these histopathological findings and elevated serum IgG4 confirm the diagnosis (25 points). Our patient did not meet

any exclusion criteria. We initiated oral prednisone treatment at a dosage of 1 mg/kg, with gradual weaning over 6 months of follow-up. During prednisone weaning, his ocular edema worsened, and methotrexate was introduced. Currently, he is using methotrexate 10 mg/week without prednisone, without recurrence of his condition.

DISCUSSION

AOX and IgG4-RD exhibit shared demographic, clinical, and histological traits, including fibrosis, lymphoid follicles, elevated IgG4 plasma cells, and eosinophils. Their pathophysiological mechanisms, characterized by the positive regulation of immune responses, inflammation, and fibrosis, may also be similar (7, 8). Our patient demonstrated specific histological findings characteristic of both conditions, marked by a xanthomatous inflammatory infiltrate with Touton cells. The immunohistochemical analysis revealed CD68-positive histiocytes and CD21, CD35, CD1a, and S100-negatives, a pattern typically described in AOX (1). Furthermore, a dense population of IgG4 plasma cells with an IgG4/IgG ratio exceeding 40% was observed.

A few case reports described an association between AOX and IgG4-RD. For instance, Singh *et al.* documented a patient with xanthelasma who developed orbital inflammatory syndrome (5). The histological findings revealed a xanthomatous infiltrate and an IgG4/IgG ratio exceeding 80%, suggesting a link between these two conditions (4). A literature review revealed only two case reports describing the association of AOX and IgG4-RD. The first case featured a patient with an eyelid mass, with histological findings consistent with AOX and IgG4-RD. This patient responded well to corticosteroids (7), mirroring the response of our patient. The second case involved a patient with xanthelasma who developed autoimmune pancreatitis and was treated with corticosteroids and rituximab (9), as shown in Table I (7, 9).

As previously mentioned, both diseases may exhibit orbital and systemic manifestations. In the case of IgG4-RD, ocular char-

Table 1 - Clinical profile of patients with adult-onset xanthogranuloma and immunoglobulin G4-related disease.

Reference	Gender/age	Clinical features	Histopathological findings	Serum IgG4	Treatment	Evolution
Andron et al. (7)	Male/64	Yellow mass on the right upper eyelid	Inflammatory infiltrate of xanthomatous histiocytes. <i>CD68</i> positive, <i>S100</i> and <i>CD1a</i> negatives. IgG4/IgG ratio >80% >10 IgG4 positive plasma cells per hpf	259 mg/dL (normal range: 1-123 mg/dL)	Prednisone 1 mg/kg	Complete response
Leung et al. (9)	Male/61	Yellowish lesions over bilateral eyelids. Autoimmune pancreatitis 6 years after initial presentation	Aggregates of foamy histiocytes and scattered Touton giant cells. IgG4 was negative	519 mg/dL (normal range: 1-123 mg/dL)	Prednisone 1 mg/kg azathioprine rituximab	Complete response after using rituximab
Present case	Male/47	Bilateral upper lid mass, mild proptosis, and xanthelasma-like lesion on his eyelids	Xanthomatous histiocytes <i>CD68</i> positive and <i>CD21</i> , <i>CD35</i> , <i>CD1a</i> , and <i>S100</i> negatives with Touton-type giant cells. IgG4/IgG ratio >40% >50 IgG4 positive plasma cells per hpf	4880 mg/dL (normal range: 84-170 mg/dL)	Prednisone 1 mg/kg methotrexate	Complete response

IgG, immunoglobulin G; IgG4, immunoglobulin G4.

acteristics include orbital pseudotumor, dacryoadenitis, orbital myositis, and scleritis, with eyelid involvement being a rare occurrence. Conversely, AOXGD typically manifests as hardened xanthomatous masses in the eyelids or anterior orbit. However, the Erdheim-Chester subtype is an exception, as its involvement can be more diffuse (10).

Corticosteroids are recommended as the primary treatment for both IgG4-RD and AOXGD, typically yielding a positive therapeutic response, as demonstrated in the current case. In instances of relapse, immunosuppressive agents such as methotrexate may serve as corticosteroid-sparing agents (8, 11). More recently, rituximab has been explored as an initial monotherapy for patients with IgG4-RD and AOXGD, resulting in sustained remission (12). Vemurafenib, tocilizumab, and sirolimus have also exhibited promising results in managing systemic symptoms (13).

CONCLUSIONS

In conclusion, the association between AOX and IgG4-RD is uncommon. Further

research is required to determine whether this association is due to shared pathophysiology, a common cause, or merely a coincidental discovery.

Contributions

All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no potential conflict of interest.

Ethics approval and consent to participate

No ethical committee approval was required by the Department.

Patient consent for publication

The patient's legal guardian's consent was given to share this case for scientific purposes.

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Availability of data and materials

Data and materials are available from the corresponding author.

■ REFERENCES

1. Kerstetter J, Wang J. Adult orbital xanthogranulomatous disease. *Dermatol Clin* 2015; 33: 457-63.
2. Wallace ZS, Zhang Y, Perugino CA, Naden R, Choi HK, Stone JH. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. *Ann Rheum Dis* 2019; 78: 406-12.
3. Burris CKH, Rodriguez ME, Raven ML, Burkat CN, Albert DM. Adult-onset asthma and periocular xanthogranulomas associated with systemic IgG4-related disease. *Am J Ophthalmol Case Rep* 2016; 1: 34-7.
4. London J, Martin A, Soussan M, Badelon I, Gille T, Uzunhan Y, et al. Adult-onset asthma and periocular xanthogranuloma (AAPOX), a rare entity with a strong link to IgG4-related disease. *Medicine* 2015; 94: e1916.
5. Singh K, Rajan K, Eberhart C. Orbital necrobiotic xanthogranuloma associated with systemic IgG4 disease. *Ocul Immunol Inflamm* 2010; 18: 373-8.
6. Wallace ZS, Naden RP, Chari S, Choi H, Della-Torre E, Dicaire JF, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Arthritis Rheumatol* 2020; 72: 7-19.
7. Andron AA, Nair AG, Della Rocca D, Della Rocca RC, Reddy HS. Concomitant adult onset xanthogranuloma and IgG4-related orbital disease: a rare occurrence. *Orbit* 2022; 41: 108-11.
8. Asproudis I, Kanari M, Ntountas I, Ragos V, Goussia A, Batistatou A, et al. Successful treatment with rituximab of IgG4-related disease coexisting with adult-onset asthma and periocular xanthogranuloma. *Rheumatol Int* 2020; 40: 671-7.
9. Leung KCP, Ko P, Ho CHJ, Ko TCS. Adult onset xanthogranuloma associated with IgG4-related disease. *Korean J Ophthalmol* 2018; 32: 424-5.
10. McKelvie P, McNab AA, Hardy T, Rath V. Comparative study of clinical, pathological, radiological, and genetic features of patients with adult ocular adnexal xanthogranulomatous disease, Erdheim-Chester disease, and IgG4-related disease of the orbit/ocular adnexa. *Ophthalmic Plast Reconstr Surg* 2017; 33: 112-9.
11. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012; 366: 539-51.
12. Pomponio G, Olivari D, Mattioli M, Angeletti A, Rossetti G, Goteri G, et al. Sustained clinical response after single course of rituximab as first-line monotherapy in adult-onset asthma and periocular xanthogranulomas syndrome associated with IgG4-related disease. *Medicine* 2018; 97: e11143.
13. Ortiz Salvador JM, Subiabre Ferrer D, Pérez Ferriols A. Adult Xanthogranulomatous Disease of the Orbit: Clinical Presentations, Evaluation, and Management. *Actas Dermosifiliogr* 2017; 108: 400-6.