# A pediatric case of orbital inflammation and sinusitis– the diagnostic boundary between localized ANCA-associated vasculitis and IgG4-related disease

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**Background**

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immunoglobulin G4 (IgG4)-related disease (IgG4-RD) share some clinical and histological features and can have both localized and systemic presentations, including orbital inflammation, rhinosinusitis and OME[1-5]. AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), and are characterized by necrotizing inflammation of small/medium blood vessels[3-4].

In GPA, antibodies directed against proteinase 3 (PR3) are detected more frequently than antibodies against myeloperoxidase (MPO)[4,6]. PR3-antibody-positive GPA is associated with a higher risk of relapse, whereas MPO-antibody-positive GPA is usually less severe, with fewer extrarenal manifestations.[7] Head and neck involvement occurs in approximately 85% of all GPA patients, affecting most frequently the sinonasal region, which can lead to otitis media with effusion (OME)[7,8]. On the other hand, only 30% of patients with GPA present with orbital inflammation[7,9].

IgG4-RD is an immune-mediated condition characterized by fibroinflammatory lesions, histologically defined by lymphoplasmacytic infiltrates with an increase in IgG4-producing plasma cells in the affected organs. The clinical manifestations are varied, as it can potentially affect any organ, with predilection for the salivary and lacrimal glands, orbit, pancreas and biliary tree, lungs, kidneys, aorta, meninges and thyroid. Elevated serum IgG4 is not essential for diagnosis, as 30-50% of histologically confirmed cases have normal levels of serum IgG4[1, 10, 11].

AAV and IgG4-RD share some clinical features, making it difficult to distinguish between them[1,2]. The histologic examination in GPA might mimic IgG4-RD, since the inflammatory infiltrate may be rich in IgG4-positive plasma cells and accompanied by fibrosis and/ or obliterated blood vessels as in IgG4-RD[12]. In the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for IgG4-Related Disease, ANCA positivity was established as an exclusion criterion for IgG4-RD.[1] Nevertheless, some cases of overlapping diagnoses have been described[13,14].

We report a case of orbital inflammation histologically suggestive of IgG4-related disease and sinusitis with histological features suggestive of granulomatosis with polyangiitis, representing a complex diagnostic and therapeutic challenge.

**Case presentation**

An 11-year-old female patient, with no previous relevant personal or family medical history, presented in the emergency department (ED) with bilateral eyelid redness, edema and proptosis, which had started one month earlier. She denied any other symptoms. A diagnosis of cellulitis was assumed, and she was discharged with amoxicillin and clavulanic acid for eight days and prednisolone 1 mg/kg/day for three days. The symptoms partially improved in the first days but worsened again after discontinuing the corticosteroid. She returned to the ED and was referred to the pediatric rheumatology team for further evaluation.

At pediatric rheumatology appointment, etiological work-up was initiated. The investigation showed a normal complete blood count, erythrocyte sedimentation rate of 25 mm/h, and C-reactive protein of 2.5 mg/dL. Liver enzymes, thyroid and renal function, lactate dehydrogenase, creatine kinase, protein electrophoresis, immunoglobulins (IgG, including IgG4, IgM, IgA) and complement levels were normal. Elevated MPO-ANCA by enzyme immunoassay was detected (82.0 U/ml, reference range: positive >5 U/ml), while antinuclear antibodies, anti-dsDNA, anti-SSA, anti-SSB, angiotensin-converting enzyme, and lysozyme were negative/normal. Interferon Gamma Release Assay, VDRL and serologies for Ebstein-Barr virus, Cytomegalovirus, Hepatitis A, B and C virus, *Bartonella henselae*, and *Borrelia burgdorferi* were negative. Urine analyses did not reveal hematuria or proteinuria, and chest CT scan was normal.

Initial magnetic resonance imaging (MRI) revealed infiltration of the superior extraconal orbital fat and bilateral eyelids, predominantly on the right side, suggesting orbital inflammatory disease (Figure 1). Sinus involvement was not reported.

A biopsy showed findings consistent with nonspecific orbital inflammation, namely a mixed inflammatory infiltrate of small interstitial lymphocytes forming aggregates, plasma cells, neutrophils, and eosinophils, with predominant perivascular distribution, without endothelial injury or necrotizing vasculitis. Notably, there was an increased IgG4/IgG ratio (>40%), over 10 IgG4+ cells/ high-power field and obliterative phlebitis, supporting IgG4-RD (Figure 2).

Given the presence of orbital inflammation, possibly related to IgG4-RD, but with positive MPO-ANCA suggesting AAV, the patient was treated with prednisolone at 0.5 mg/kg/day for three months, resulting in clinical improvement. During gradual tapering, there was a relapse at 12.5 mg/day of prednisolone, and it was decided to start rituximab (375mg/m2 weekly, for 4 weeks). After the second administration of rituximab, there was a new attempt of slow tapering of

prednisolone, until a new relapse at 7.5 mg/day, with recurrent orbital inflammation. During this period, the patient had also occasional episodes of epistaxis and rhinorrhea.
Facing the relapse after rituximab, a second MRI was performed (Figure 3), including orbital and para-nasal sinuses, which revealed rhinosinusitis. MPO-ANCA remained positive (101.5 U/ml, reference range: positive >5.0 U/ml).

On otorhinolaryngology consultation, otoscopy showed OME in the left ear, and audiological testing demonstrated mild conductive hearing loss.
A rhinoscopy was performed and biopsies of the nasal sept mucosa (Figure 4) revealed moderate lymphoplasmacytic inflammatory infiltrate with multiple scattered multinucleated giant cells, without granuloma formation nor necrobiosis. Venules were permeated by inflammatory infiltrate without definite destruction of elastic lamina. These findings are suggestive of GPA.

The patient was started on mycophenolate mofetil (MMF), with a target dose of 600 mg/m2 twice daily and completed 3 days of intravenous methylprednisolone at 30 mg/kg, followed by oral prednisolone 1 mg/kg/day for 4 weeks, with a tapering regimen thereafter.
The patient has been on MMF for the last 14 months, tapering prednisolone slowly, currently at 0.06 mg/kg/day. There was no recurrence of eyelid erythema, edema, proptosis nor nasal congestion.

**Discussion and Conclusions**

GPA and IgG4-RD head and neck phenotype represent a difficult differential diagnosis. Regarding our case, the patient fulfilled the ACR/EULAR classification criteria for GPA [5 points: nasal involvement (+3), giant cells on biopsy (+2), inflammation of the nasal sinuses on imaging (+1), positive anti-MPO (-1)].[2] With the exception of ANCA positivity, she would also have met the criteria for IgG4-RD [20 points: dense lymphocytic infiltrate and obliterative phlebitis (+6), IgG4+/IgG+ ratio: 41–70% and the IgG4+ cells/hpf: ≥10 (+14)][1].

Chang *et al.* reported 43 cases of GPA and found 8 patients whose biopsies revealed increased IgG4+ cells and a IgG4+/IgG+ ratio greater 40%. Interestingly, all 8 biopsies were obtained from head and/or neck regions, specifically from the sinonasal (n=4) and orbital/periorbital (n=4) areas, suggesting that IgG4+ cells occur more frequently in GPA cases involving head and neck region[12],

On the other hand, Martín-Nares *et al.* reported 25 cases of IgG4-RD, who were tested for ANCA by indirect immunofluorescence, 14 showing ANCA positivity[15]. These patients presented more commonly a systemic phenotype, lymph node and kidney involvement, and none belonged to the pancreato-hepatobiliary phenotype[15]. Among this cohort, only four patients had positive MPO-ANCA by ELISA, 2 of them with orbital involvement. Martín-Nares *et al.* hypothesize that some patients might have ANCA antibodies due to B-cell stimulation, without necessarily a concomitant AAV[15].

Furthermore, there are several case reports describing patients fulfilling diagnostic criteria for both IgG4-RD and AAV, suggesting a possible overlap syndrome. [13,14]

Even if GPA is strongly associated with PR3-ANCA, 5 to 30% might have MPO-ANCA. [7] Baca *et al.* reported 16 cases of pediatric GPA misdiagnosed initially as idiopathic orbital inflammation and noted that localized GPA was more frequently MPO-ANCA positive and PR3-ANCA negative compared to systemic GPA[16].

We report a pediatric case with an orbital biopsy suggestive of Ig4-RD disease, however with ANCA positivity and GPA histologic features on the nasal biopsy. The possible overlap between IgG4-RD and AAV has important implications for therapeutic decision-making.

Regarding treatment, in cases of organ/life-threatening GPA, including retro-orbital involvement, EULAR recommends glucocorticoids combined with rituximab or cyclophosphamide to induce remission, with rituximab preferred in relapsing disease[6]. Both have demonstrated efficacy in trials involving new-onset and relapsing patients[18]. However, cyclophosphamide is associated with significant long-term toxicities, including infertility, malignancy, and bone marrow disorders[18,19]. Although MMF has shown non-inferior remission induction, there's a higher relapse rate, which limits its use to patients who are intolerant or contraindicated for rituximab or cyclophosphamide[6,20].

In our patient, glucocorticoids alone were first initiated as there was a strong suspect of IgG4-RD at that time, which are very effective in this condition[1]. In fact, in the 2019 ACR/EULAR classification criteria for IgG4-RD no objective response to GC, such as prednisolone at a minimum of 40 mg/day (~0.6 mg/kg/day) or equivalent, for a period of 4 weeks, constitutes an exclusion criterion.[1] As the patient had a relapse during the afterwards tapering of prednisolone, rituximab was started, considering that it is recommended both in AAV, as previously discussed, and in IgG4-RD, being effective in inducing remission, preventing and treating disease flares[21, 22].

Following a second relapse, and as the suspicion of GPA or an overlap syndrome increased, mycophenolate mofetil (MMF) was initiated as a steroid-sparing immunosuppressive agent due

to concerns regarding the potential long-term adverse effects of cyclophosphamide, particularly in a female adolescent.

Refractory courses and frequent relapses are described in orbital masses. Holle *et al.* reported over 40% of relapses and high rates of visual impairment and definitive blindness[23]. Localized head-and-neck GPA may exist, over the years, without systemic involvement[24].

This case highlights the diagnostic complexity of distinguishing between IgG4-RD and AAV, raises the possibility of an overlap syndrome and emphasizes the importance of a multidisciplinary approach to diagnosis and treatment.

## Tables and Figures

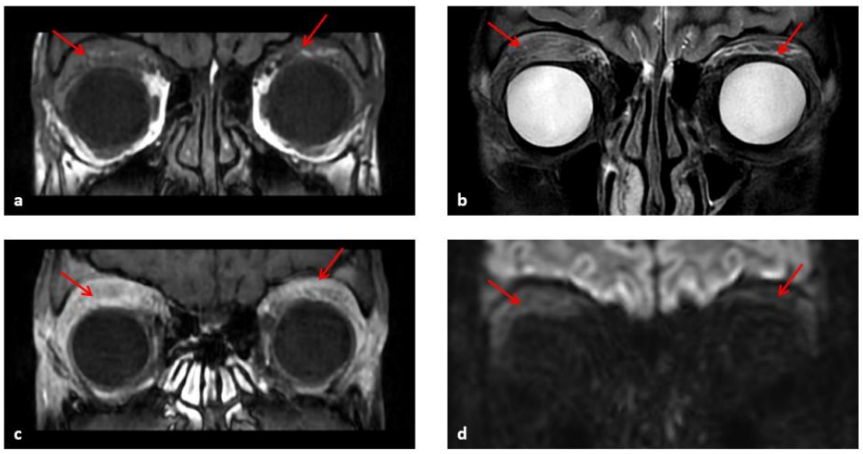


**Figure 1** – Coronal images in T1 weighting (a), T2 STIR (b), T1 FS after gadolinium (c), and diffusion (d). Infiltration and enlargement of the bilateral superior extraconal fat, predominantly on the right (arrows), by tissue isointense on T1 (a), slightly hyperintense on T2 (b), without diffusion restriction (d), and with signal enhancement after contrast (c).

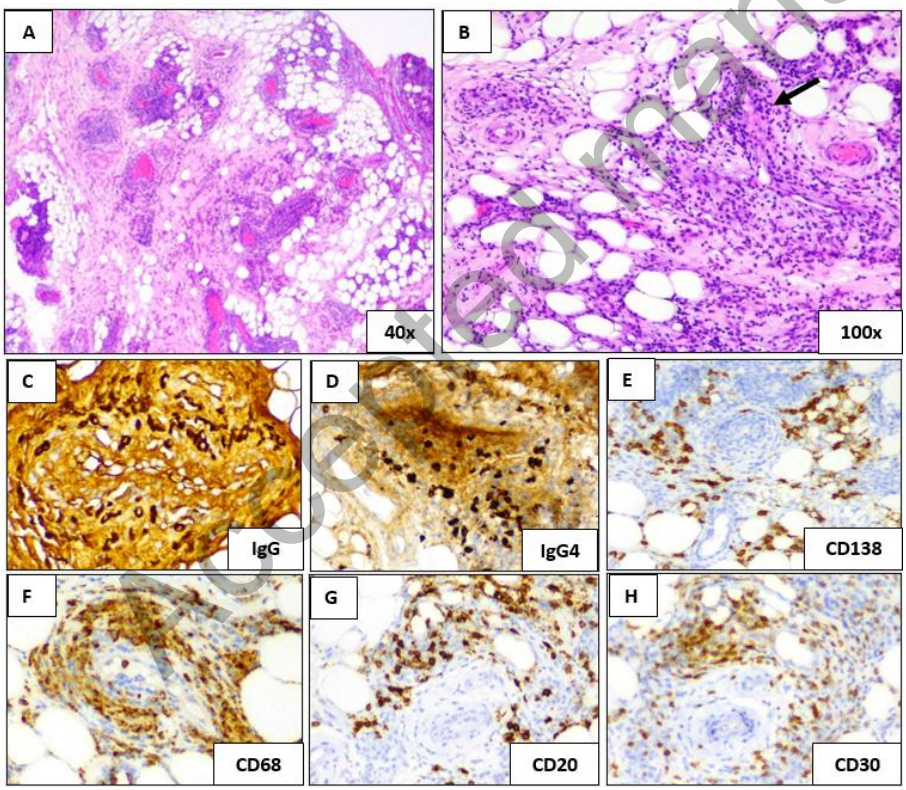


**Figure 2** - **A** (haematoxylin and eosin - H&E) Low power view of orbitary mass showing adipose tissue with interstitial and perivascular inflammatory infiltrate. **B** (H&E) – Obliterative phlebitis (arrow) characterized by dense lymphoplasmacytic infiltrate with > 40% IgG4/IgG plasma cell ratio and IgG4+ plasma cells/high power field > 10, associated with interstitial histiocytes and small lymphocytes, as depicted in the immunohistochemistry panel (**C, D, E, F, G** and **H**).

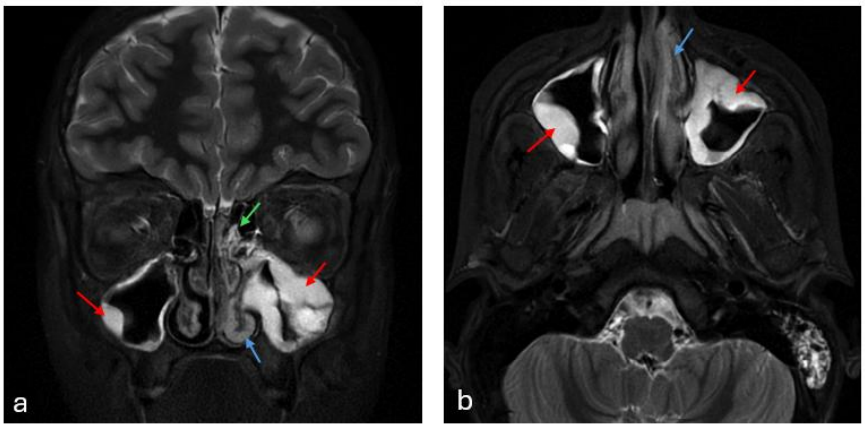


**Figure 3** - T2 STIR coronal and axial images (**a** and **b** respectively). Bilateral maxillary sinus opacification (red arrows), mucosal thickening and partial opacification of the ethmoid sinuses (green arrow) and of the nasal mucosal thickening (blue arrows), suggesting chronic or subacute rhinosinusitis.

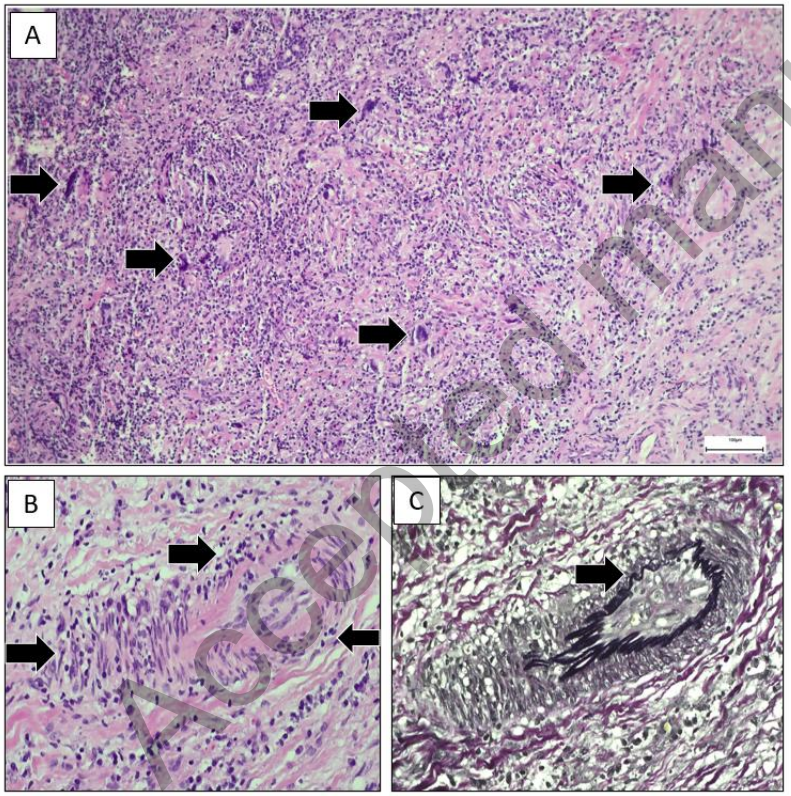


**Figure 4** - **A** (H&E, 50x) Multiple multinucleated giant cells (arrows). **B** (H&E, 200x) – Inflammatory infiltrate permeating the venular wall (arrows). **C** (Verhoeff stain, 200x) - Elastic layer of the same intact venule, highlighted in black (arrow).

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