Probable pediatric IgG4-related orbital disease presenting as a lacrimal gland mass

Doença orbitária pediátrica relacionada à IgG4 apresentando-se como massa em glândula lacrimal

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How to cite:
Gomes BC, Souza JR, Baptista GM, Balbi GG, Matos AM. Probable pediatric IgG4-related orbital disease presenting as a lacrimal gland mass. Rev Bras Oftalmol. 2026;85:e0106.

doi:
https://doi.org/10.37039/1982.8551.20260106

Keywords:
Orbit; Inflammation; Lacrimal apparatus; Child; Immunoglobulin G4-related disease

Descritores:
Órbita; Inflamação; Aparelho lacrimal; Criança; Doença relacionada a imunoglobulina G4

Received on:
February 5, 2026

Accepted on:
September 6, 2026

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Conflict of interest:
no conflict of interest.

Financial support:
no financial support for this work.

Data availability statement:
the data that support the findings of this study are not openly available but are available from the corresponding author upon reasonable request.

Associate Editor:
Renato Wendell Ferreira Damasceno, Universidade Estadual de Ciências da Saúde de Alagoas, Maceió, AL, Brazil; https://orcid.org/0000-0002-9380-0335

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ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition characterized by tumefactive lesions, lymphoplasmacytic infiltration, and fibrosis. Orbital involvement is uncommon in children and may mimic infectious dacryoadenitis, idiopathic orbital inflammation, and lymphoproliferative disorders. We report the case of a 13-year-old girl with four days of left periorbital swelling and pain, associated with lacrimal gland enlargement on imaging. Biopsy showed fibrosis, dense lymphoplasmacytic infiltration, and reactive lymphoid aggregates. Immunohistochemistry demonstrated mixed B- and T-cell populations, polyclonal kappa/lambda plasma cells, and up to 31 IgG4-positive plasma cells per high-power field, with an IgG4/IgG ratio of 30%. Serum IgG4 was 76 mg/dL. Although the patient did not fulfill classical adult-based serological and histopathological criteria for definite IgG4-RD, the clinical, radiological, histopathological, and therapeutic-response findings supported a presumptive diagnosis of probable pediatric IgG4-related orbital disease. This case highlights the importance of orbital biopsy, exclusion of differential diagnoses, and cautious interpretation of adult diagnostic criteria in pediatric patients.

RESUMO

A doença relacionada à imunoglobulina G4 (IgG4-RD) é uma condição fibroinflamatória imunomediada, caracterizada por lesões tumefativas, infiltrado linfoplasmocitário e fibrose. O acometimento orbitário é incomum em crianças e pode simular dacrioadenite infecciosa, inflamação orbitária idiopática e doenças linfoproliferativas. Relata-se o caso de uma paciente de 13 anos com edema e dor periorbitária à esquerda há 4 dias, associada a aumento da glândula lacrimal em exames de imagem. A biópsia demonstrou fibrose, infiltrado linfoplasmocitário denso e agregados linfoides reativos. A imuno-histoquímica evidenciou populações mistas de linfócitos B e T, plasmócitos policlonais kappa/lambda e até 31 plasmócitos IgG4-positivos por campo de grande aumento, com relação IgG4/IgG de 30%. O IgG4 sérico foi de 76 mg/dL. Embora a paciente não preenchesse critérios séricos e histopatológicos clássicos para diagnóstico definitivo em adultos, o conjunto clínico, radiológico, histopatológico e evolutivo sustentou o diagnóstico presuntivo de doença orbitária pediátrica provavelmente relacionada à IgG4. O caso ressalta a importância da biópsia orbitária, da exclusão de diagnósticos diferenciais e da interpretação cautelosa dos critérios diagnósticos adultos em pacientes pediátricos.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory disorder characterized by tumefactive lesions, dense lymphoplasmacytic infiltration, variable fibrosis, and tissue infiltration by IgG4-positive plasma cells.[1,2] It may affect a single organ or occur as a systemic condition, with potential involvement of the pancreas, biliary tract, salivary glands, lacrimal glands, lymph nodes, retroperitoneum, lungs, thyroid, kidneys, and other organs.[1,2]

When the orbit and ocular adnexa are involved, the condition is termed IgG4-related ophthalmic disease or IgG4-related orbital disease (IgG4-ROD).[3,4] The lacrimal gland is one of the most frequently affected ophthalmic structures, although extraocular muscles, trigeminal nerve branches, orbital fat, eyelids, optic nerve sheath, lacrimal sac, cavernous sinus, and intracranial structures may also be involved.[3-6] In adults, diagnosis is based on the integration of clinical-radiological findings, serum IgG4 levels, and histopathological criteria.[1,3,4] However, pediatric IgG4-RD remains poorly characterized, and children may present with normal serum IgG4 levels or incomplete histopathological criteria.[7,8]

This report describes a pediatric lacrimal gland mass with clinical, radiological, and immunohistochemical findings suggestive of probable IgG4-ROD. The case is relevant because it illustrates the diagnostic uncertainty that may occur when adult-derived criteria are applied to children, particularly in the absence of elevated serum IgG4. This case report was approved by the Research Ethics Committee of the Hospital Universitário da Universidade Federal de Juiz de Fora (UFJF) (CAAE: 85902824.8.0000.5133; approval date: March 24, 2025). Written informed consent for publication of the clinical data and images was obtained from the patient's legal guardian.

CASE REPORT

A previously healthy 13-year-old girl presented with left periorbital swelling and mild ocular pain for four days. Ophthalmological examination revealed a palpable mass in the left lacrimal gland region, mild local hyperemia, warmth over the lesion, and a tense upper eyelid. Extraocular motility was preserved, and there was no proptosis, diplopia, or visual complaint. Pain was limited to local palpation (Figure 1A).

Orbital computed tomography demonstrated enlargement of the left lacrimal gland with homogeneous contrast enhancement. Laboratory tests showed leukocytosis and elevated erythrocyte sedimentation rate. Orbital magnetic resonance imaging showed diffuse involvement of the left lacrimal gland, predominantly in the superolateral orbit, with isointense thickening on T1- and T2-weighted sequences and homogeneous gadolinium enhancement. (Figure 2). Serum IgG4 was 76 mg/dL, below the usual cutoff adopted in adult diagnostic criteria.

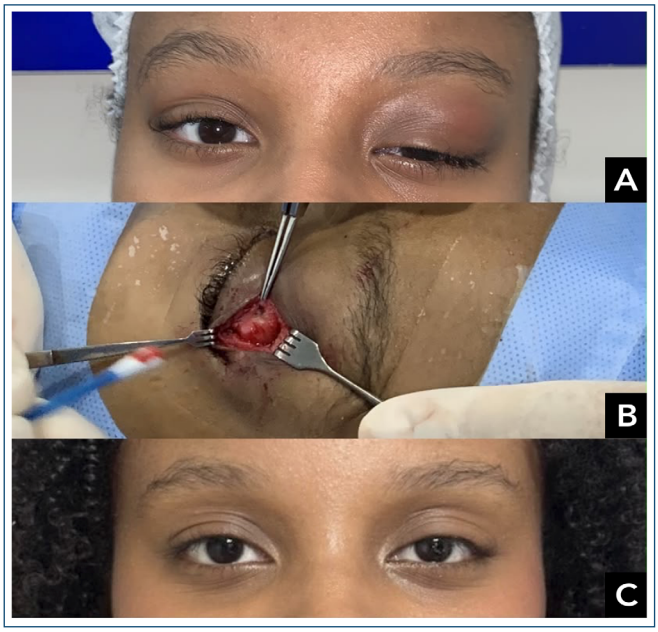


Figure 1. (A) Preoperative lesion in the left lacrimal gland region; (B) lacrimal gland biopsy; (C): postoperative recovery.

Because of the persistent lacrimal gland mass and the nonspecific clinical-radiological presentation, surgical biopsy was performed (Figure 1B). The postoperative course was uneventful, with satisfactory local recovery (Figure 1C). Histopathological analysis showed fibrosis, dense lymphoplasmacytic infiltration, and reactive lymphoid aggregates. Immunohistochemistry demonstrated mixed B-cell (CD20) and T-cell (CD3) populations. Plasma cells showed a mixed kappa/lambda pattern, without evidence of light-chain restriction in the available sample. IgG4 expression was identified in a subset of plasma cells, with up to 31 IgG4-positive plasma cells per high-power field and an IgG4/IgG ratio of 30% (Figure 3).

The findings favored an IgG4-rich fibroinflammatory orbital lesion compatible with probable IgG4-ROD, although the case did not meet criteria for definite IgG4-RD according to adult-based comprehensive criteria. The main differential diagnoses considered were infectious dacryoadenitis, idiopathic orbital inflammation, orbital pseudotumor, Sjögren-related dacryoadenitis, granulomatous inflammatory disease, and ocular adnexal

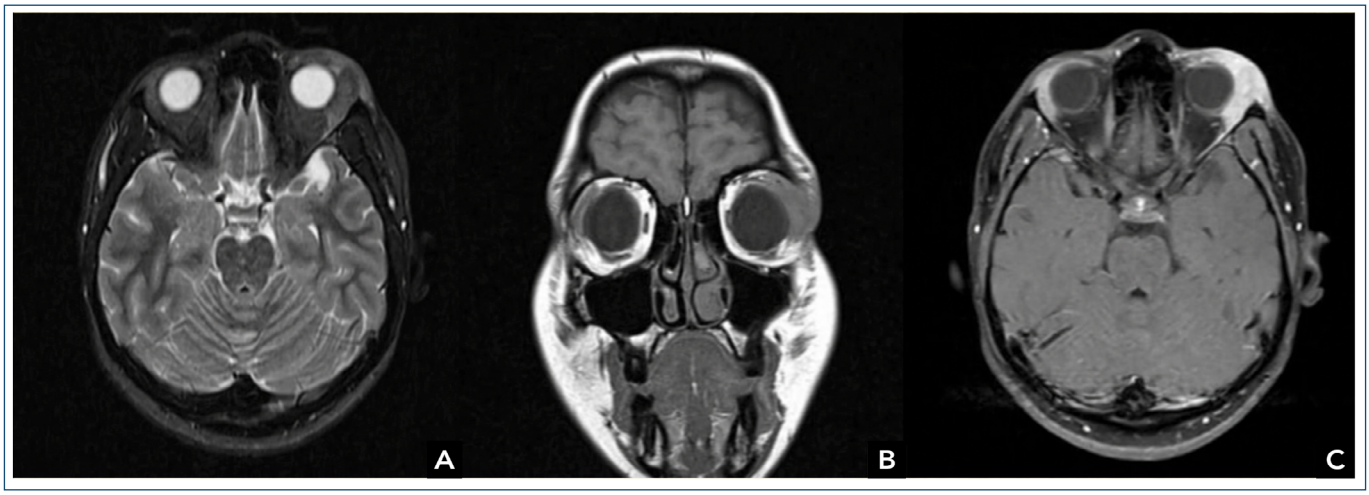


Figure 2. Orbital magnetic resonance imaging: axial STIR sequence showing lacrimal gland involvement (A); coronal T1-weighted sequence showing isointense thickening (B); axial post-contrast T1-weighted fat-suppressed sequence showing homogeneous enhancement (C).

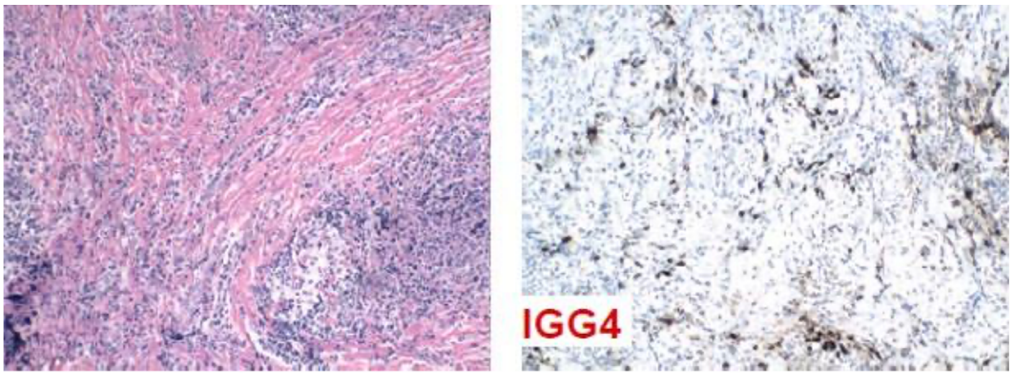


Figure 3. Histology of the left lacrimal gland showing fibrosis, dense lymphoplasmacytic infiltrate, and reactive lymphoid aggregates. Immunohistochemistry demonstrates mixed B-cell (CD20) and T-cell (CD3) populations, polyclonal kappa/lambda plasma cells, and IgG4 expression in a subset of plasma cells, with up to 31 IgG4-positive cells per high-power field and an IgG4/IgG ratio of 30%.

lymphoproliferative disorders. The presence of fibrosis, dense lymphoplasmacytic infiltrate, IgG4-positive plasma cells, preserved mixed B- and T-cell populations, and polyclonal plasma cells made a lymphoproliferative disorder less likely in the available diagnostic context.

The patient was treated with methotrexate 15 mg weekly and folic acid 5 mg three times per week, associated with gradual corticosteroid tapering over three months. Follow-up included rheumatological evaluation, liver and renal function tests, and imaging assessment of the head, neck, thorax, abdomen, and pelvis, with no evidence of extraorbital disease. The clinical course was favorable under immunosuppressive treatment.

DISCUSSION

IgG4-ROD is an important cause of chronic orbital inflammation and may present as focal or diffuse enlargement of orbital adnexal structures.[3-6] In adults, the disease classically manifests with painless eyelid swelling, lacrimal gland enlargement, proptosis, diplopia, extraocular muscle involvement, or infraorbital nerve enlargement.[3-6] Visual impairment is uncommon but may occur in severe cases, especially when orbital apex, optic nerve sheath, or compressive lesions are present.[4]

The present case differs from the typical adult presentation in three main aspects: young age, unilateral acute/subacute presentation, and absence of elevated serum IgG4. Pediatric IgG4-RD is rare and probably underrecognized. In a systematic review of pediatric cases, the median age was 13 years, and orbital involvement was among the most frequent presentations.[7] More recent pediatric reviews emphasize that children may show incomplete serological or histopathological findings and that adult classification or diagnostic criteria may not fully capture the pediatric spectrum.[8,9] Therefore, normal serum IgG4 should not completely exclude the diagnosis in children,

especially when tissue findings and clinical-radiological features are suggestive.

The diagnostic challenge in this case is central. According to the 2020 revised comprehensive diagnostic criteria, definite IgG4-RD requires characteristic organ involvement, serum IgG4 above 135 mg/dL, and pathological findings.[1] Pathological diagnosis requires positivity for at least two of the following: dense lymphocyte/plasma cell infiltration with fibrosis; IgG4/IgG ratio above 40% and more than 10 IgG4-positive plasma cells per high-power field; or typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis.[1] The patient had a characteristic lacrimal gland mass and dense lymphoplasmacytic infiltration with fibrosis, as well as more than 10 IgG4-positive plasma cells per high-power field. However, serum IgG4 was 76 mg/dL, and the IgG4/IgG ratio was 30%, below the classical 40% cutoff. Therefore, the most appropriate interpretation is not a definitive diagnosis, but a probable or presumptive IgG4-related orbital inflammatory disease.

This distinction is important for scientific accuracy and directly addresses the main limitation of the case. The IgG4/IgG ratio has a diagnostic value, but cutoff values vary according to organ, sample quality, inflammatory background, and fibrosis.[10] A ratio of 30% is not sufficient to fulfill standard criteria, but it increases the probability of IgG4-RD when associated with compatible clinical-radiological findings, IgG4-positive plasma cell density, fibrosis, exclusion of mimickers, and treatment response.[1,10] In pediatric patients, this interpretation must be particularly cautious, because the frequency and diagnostic weight of classic histological findings are less well established than in adults.[7-9]

The main differential diagnoses include idiopathic orbital inflammation, infectious dacryoadenitis, Sjögren-related dacryoadenitis, granulomatous diseases, and ocular adnexal lymphoma.[3,5,11] Idiopathic orbital inflammation can present acutely with pain and swelling, often overlapping clinically with the initial findings in this case. Infectious dacryoadenitis may also present with local warmth, hyperemia, leukocytosis, and pain, but persistence of a mass-like lesion and the histopathological pattern favored a noninfectious fibroinflammatory process. Ocular adnexal lymphoma is a particularly important differential diagnosis because IgG4-positive plasma cells may be seen in lymphomas, and IgG4-producing MALT lymphoma can mimic IgG4-RD.[11] In this patient, the mixed B- and T-cell populations and polyclonal kappa/lambda plasma cells argued against a clonal lymphoproliferative process in the available sample.

Treatment of IgG4-RD generally begins with systemic glucocorticoids when there is active symptomatic disease, risk of organ damage, or relevant functional impairment.[12] However, relapse after steroid tapering is common, and steroid-sparing immunosuppressive agents, including methotrexate, azathioprine, mycophenolate mofetil, and rituximab, may be considered in recurrent, persistent, or steroid-dependent disease.[9,12] Pediatric evidence remains limited, but available reviews suggest that glucocorticoids are frequently used as first-line therapy and that steroid-sparing agents may be required in a relevant proportion of children.[7,9] The favorable clinical course after methotrexate and corticosteroid tapering in this patient supports the inflammatory and immune-mediated nature of the lesion, although therapeutic response alone should not be used as definitive diagnostic proof.

This report has limitations. First, the patient did not meet adult-based serological criteria for definite IgG4-RD. Second, the IgG4/IgG ratio was borderline and below the classical diagnostic threshold. Third, histological review by an additional reference pathologist was not available. For these reasons, the terminology "probable" or "presumptive" IgG4-ROD is more appropriate than "confirmed" IgG4-RD. Nevertheless, the case remains clinically relevant because it demonstrates the diagnostic complexity of pediatric IgG4-rich orbital inflammation and reinforces the need for biopsy, careful exclusion of mimickers, systemic evaluation, and long-term follow-up. These diagnostic challenges are consistent with broader discussions regarding the limitations of current IgG4-RD classification frameworks and with clinicopathological observations of IgG4-rich lesions in pediatric head and neck disease.[13,14]

In conclusion, pediatric IgG4-ROD may present as a unilateral lacrimal gland mass with normal serum IgG4 and incomplete adult diagnostic criteria. In such cases, diagnosis should be based on cautious integration of clinical, imaging, histopathological, immunohistochemical, and follow-up findings. Recognition of this entity is important to guide appropriate immunosuppressive therapy and avoid misclassification as infection, idiopathic orbital inflammation, or lymphoproliferative disease.

AUTHORS' CONTRIBUTION

Matos AM and Balbi GG contributed to the conceptualization of the study, formal analysis of the findings, drafting of the manuscript, and critical review and editing of its content. Gomes BC, Baptista GM, and Souza JR contributed to the investigation, formal analysis of the findings,

preparation of the figures, drafting of the manuscript, and critical review and editing of its content. All authors approved the final version of the manuscript and are accountable for all aspects of the work, including ensuring its accuracy and integrity.

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