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(CASE REPORT)

Periocular nasociliary lesion with elevated serum IgG4 levels: A case report on the risks of overdiagnosis in IgG4-related disease

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Abstract

Introduction: IgG4-related disease is a systemic fibroinflammatory condition characterized by tumefactive lesions, a lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, in a variable proportion of patients, elevated serum IgG4 levels (1–3). Its clinical spectrum is broad and may involve virtually any organ, including salivary glands, lacrimal glands, orbital tissues, pancreas, biliary tract, kidneys, lungs, lymph nodes, retroperitoneum, skin, and the gastrointestinal tract (1,4). IgG4-related ophthalmic disease represents a particular diagnostic challenge due to its clinical and histopathological overlap with inflammatory, infectious, granulomatous, and even lymphoproliferative conditions (5,6).

Case presentation: We report the case of an 80-year-old male patient with a history of narrow-angle glaucoma and blindness, evaluated for an indurated lesion in the left nasociliary region. Laboratory studies demonstrated a markedly elevated serum IgG4 level of 1,605 (upper reference limit: 0.864), along with significantly increased total IgE. Available autoimmune workup, including ANA, anti-dsDNA, anti-Ro, rheumatoid factor, and VDRL, was negative, and no clinical features suggestive of systemic connective tissue disease were identified on targeted history-taking. The patient had previously received methotrexate, which was discontinued due to intolerance reported as alopecia. Treatment with low-dose prednisolone with a gradual taper and azathioprine as a steroid-sparing immunomodulatory agent was initiated.

Discussion: The case is consistent with a clinical-serological phenotype suggestive of probable IgG4-related ophthalmic disease; however, the absence of orbital imaging, tissue biopsy, quantification of IgG4-positive plasma cells per high-power field, IgG4/IgG ratio, storiform fibrosis, and obliterative phlebitis precludes a definitive diagnosis. Current literature emphasizes that serum IgG4 elevation is non-specific and that IgG4-related ophthalmic disease requires rigorous exclusion of mimickers, including MALT lymphoma, orbital pseudotumor, sarcoidosis, granulomatosis with polyangiitis, mycobacterial or fungal infections, and histiocytic disorders (1,5,6).

Conclusion: This case highlights the importance of a systematic, critical, and multidisciplinary diagnostic approach to periocular lesions associated with elevated serum IgG4. Although serology may raise suspicion for IgG4-related disease, it is insufficient for a definitive diagnosis. Careful exclusion of inflammatory, infectious, and lymphoproliferative mimickers is essential prior to initiating long-term immunosuppressive therapy.

Keywords: Igg4-Related Disease; Igg4-Related Ophthalmic Disease; Orbital Pseudotumor; Narrow-Angle Glaucoma; Blindness; Azathioprine; Prednisolone; Ige

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1. Introduction

IgG4-related disease (IgG4-RD) is a relatively recently recognized systemic fibroinflammatory disorder characterized by tumefactive lesions, dense lymphoplasmacytic infiltrates, IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis, and, in a variable proportion of patients, elevated serum IgG4 levels (1,2). Its recognition as a systemic entity was consolidated following the description of extrapancreatic manifestations in patients with type 1 autoimmune pancreatitis, which allowed the integration of multiple previously distinct conditions into a single clinicopathological spectrum (1,3).

IgG4-RD may involve virtually any organ system. The most frequently affected sites include the pancreas, biliary tract, salivary glands, lacrimal glands, orbital tissues, kidneys, lungs, lymph nodes, retroperitoneum, mesentery, skin, and gastrointestinal tract (1,4,7,16). This multisystem behavior explains its ability to mimic malignancies, infections, vasculitides, granulomatous diseases, connective tissue disorders, and lymphoproliferative conditions (1,5,7).

IgG4-related ophthalmic disease may involve the lacrimal glands, extraocular muscles, orbital nerves, eyelids, orbital soft tissues, and other adnexal structures (5,6). Its diagnosis is particularly challenging due to significant clinical and histopathological overlap with multiple mimicking entities. These include Sjögren's syndrome, sarcoidosis, granulomatosis with polyangiitis, orbital pseudotumor, Kimura disease, xanthogranuloma, Erdheim-Chester disease, Rosai-Dorfman disease, tuberculosis, mucormycosis, and MALT lymphoma (5,6).

From a methodological perspective, serum IgG4 elevation should be interpreted as a supportive finding rather than an isolated diagnostic criterion. Histopathology, complemented by immunohistochemistry, remains the diagnostic cornerstone, particularly in ophthalmic disease, where overdiagnosis may lead to inappropriate immunosuppressive therapy or delayed recognition of infectious or malignant conditions (1,5,6). Organ-specific criteria for IgG4-related ophthalmic disease incorporate clinical and imaging features, lymphoplasmacytic infiltrates with fibrosis, an IgG4/IgG ratio ≥40%, increased numbers of IgG4-positive plasma cells per high-power field, and elevated serum IgG4 levels (5). However, even these criteria require strict clinicopathological correlation, as no diagnostic system is infallible in routine practice (5).

We present a case of probable periocular involvement by IgG4-RD in an elderly male patient with a history of narrow-angle glaucoma and blindness, presenting with a left nasociliary indurated lesion, elevated serum IgG4 and markedly increased total IgE, managed with prednisolone and azathioprine after intolerance to methotrexate.

2. Case presentation

An 80-year-old male patient with a history of narrow-angle glaucoma and blindness was evaluated for a left ocular lesion located in the left nasociliary region. His relevant medical history included lacrimal punctal agenesis, with ongoing ophthalmologic surgical planning, and intolerance to methotrexate.

On directed review of systems, the patient denied photosensitivity, oral ulcers, Raynaud phenomenon, arthritis, enthesitis, fever, inflammatory-pattern hair loss, ocular redness, and cutaneous lesions. No systemic symptoms suggestive of connective tissue disease, systemic vasculitis, or active inflammatory musculoskeletal disease were identified.

On physical examination, a left nasociliary periocular lesion was identified, characterized as an indurated, firm mass with a slightly raised, nodular-infiltrative appearance and poorly defined clinical margins, located in the left medial canthal/perinasal region.

No ulceration, fluctuation, discharge, or signs of local superinfection were observed. The overlying skin showed mild erythema with minimal inflammatory changes, without evidence of necrosis or bleeding. The finding was associated with a mild increase in local volume (see Figure 1). Neurological examination revealed no abnormalities.

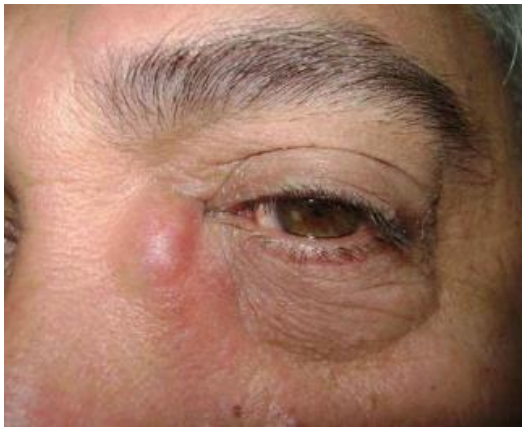

Figure 1 Left nasociliary periocular lesion at the time of initial evaluation. A localized, elevated swelling is observed, with mild erythema and increased volume in the medial canthal region and adjacent perinasal area

Initial laboratory studies demonstrated a negative autoimmune profile, with non-reactive rheumatoid factor, ANA, anti-dsDNA, and anti-Ro antibodies, as well as a non-reactive VDRL. Erythrocyte sedimentation rate (ESR) was mildly elevated, while complement C3 levels were preserved. The complete blood count showed no leukocytosis, renal function was normal, and urinalysis revealed no abnormalities.

Table 1 Initial immunological, inflammatory, and biochemical profile of the patient

Parámetro	**Resultado**
Factor reumatoide	<10
ANA	Negativo
Anti-dsDNA	Negativo
Anti-Ro	Negativo
VDRL	No reactivo
VSG	23 mm/h
C3	109 mg/dL
Hematocrito	39.4%
Hemoglobina	12.6 g/dL
Leucocitos	7410/mm^3
Plaquetas	420.000/mm^3
Creatinina	0.96 mg/dL
Urea	28.8 mg/dL
GOT/AST	12 U/L
GPT/ALT	12 U/L
IgE total	2252 UI/mL
IgG1	10.01 g/L
IgG2	Normal
IgG3	0.576 g/L
IgG4	1.605 g/L
Uroanálisis	Normal

From an immunological perspective, elevated serum IgG4 levels were documented relative to the laboratory reference range, accompanied by markedly increased total IgE and a mild elevation of IgG1. These findings are summarized in Table 1.

Based on the left nasociliary indurated lesion and elevated serum IgG4 levels, IgG4-related disease with probable periocular involvement was considered. The absence of clinical criteria for systemic lupus erythematosus, Sjögren's syndrome, inflammatory arthritis, Raynaud phenomenon, or systemic vasculitis reduced the clinical support for an underlying systemic connective tissue disease based on the available data. However, the lack of biopsy, immunohistochemistry, and orbital imaging limited definitive diagnostic classification.

Given the patient's history of methotrexate intolerance, treatment with prednisolone 10 mg/day was initiated, followed by a gradual taper, in combination with azathioprine 100 mg/day as an immunomodulatory and steroid-sparing strategy. Clinical and laboratory follow-up was planned, including complete blood count, renal function tests, liver transaminases, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate.

At three months of follow-up, clinical improvement was observed, with reduction in both the size and induration of the left nasociliary lesion, and no development of new cutaneous lesions, lymphadenopathy, or systemic symptoms. No hematologic, hepatic, or renal adverse effects related to treatment were documented. The favorable clinical course is shown in Figure 2.

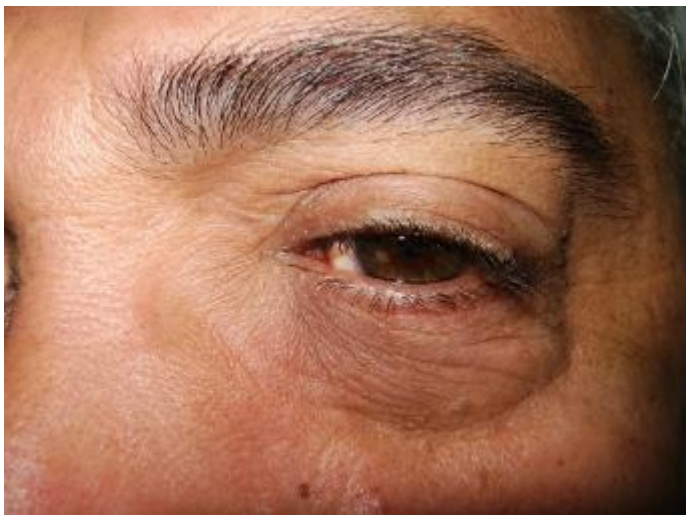

Figure 2 Clinical evolution at three months after initiation of prednisolone and azathioprine. A reduction in the volume and clinical induration of the nasociliary lesion is observed, with no evident cutaneous inflammatory signs

3. Discussion

This case describes an 80-year-old male patient presenting with a left nasociliary indurated lesion, elevated serum IgG4, and markedly increased total IgE, in the absence of clinical or serological evidence suggestive of systemic lupus erythematosus, Sjögren's syndrome, inflammatory arthritis, Raynaud phenomenon, or systemic vasculitis. The clinical context supported a presumptive diagnosis of IgG4-related disease with probable periocular involvement; however, definitive diagnosis cannot be established due to the lack of histopathological confirmation.

IgG4-related disease (IgG4-RD) is characterized by a fibroinflammatory process with a tendency to form tumefactive lesions that may mimic neoplasms (1,2). It can involve virtually any organ, with synchronous or metachronous manifestations, requiring a thorough systemic evaluation at diagnosis and during follow-up (1,4). In this patient, physical examination and available laboratory data did not demonstrate renal, pulmonary, cutaneous, lymph node, hepatic, or urinary tract involvement. Serum creatinine and urinalysis were normal, and no adenopathy, skin lesions, respiratory symptoms, or relevant abdominal findings were reported.

Elevated serum IgG4 is compatible with IgG4-RD but is not a specific diagnostic marker (1,5,6). Recent literature emphasizes that diagnosis should not rely solely on serum IgG4 levels or the presence of IgG4-positive plasma cells, as a variety of inflammatory, infectious, granulomatous, and lymphoproliferative disorders may show similar findings

(1,5,7). Therefore, in this case, the IgG4 level of 1,605 above the laboratory reference range should be interpreted as a supportive, but non-confirmatory, finding. The markedly elevated total IgE is an additional relevant observation. IgG4-RD has been associated with type 2 immune responses and allergic manifestations in a subset of patients (1,13).

IgG4-related ophthalmic disease may affect the lacrimal glands, extraocular muscles, orbital soft tissues, eyelids, and orbital nerves (5). In the present case, the indurated nasociliary lesion suggests periocular or adnexal involvement; however, precise anatomical characterization requires dedicated ophthalmologic assessment and orbital imaging. The documented lacrimal punctal agenesis is an independent ophthalmologic condition under surgical evaluation and should not be attributed to IgG4-RD without specific evidence.

Organ-specific diagnostic criteria for IgG4-related ophthalmic disease include imaging or clinical enlargement of lacrimal glands, trigeminal nerve involvement, extraocular muscle enlargement, or orbital masses; lymphoplasmacytic infiltrates with fibrosis; an IgG4/IgG ratio ≥40%; at least 50 IgG4-positive plasma cells per high-power field; and elevated serum IgG4 levels (5). Revised criteria for IgG4-RD classify disease as definite, probable, or possible depending on the combination of clinical, serological, and histopathological domains (5).

A key issue in this case is the need to exclude mimickers. IgG4-related ophthalmic disease shares features with infectious, inflammatory, granulomatous, and neoplastic conditions (5,6). Bakshi et al. demonstrated that non-IgG4-related diseases may also exhibit elevated serum IgG4, fibrosis, dense lymphoplasmacytic infiltrates, increased IgG4-positive cells, and even elevated IgG4/IgG ratios, underscoring the risk of misdiagnosis when relying on isolated serological or histological features (5). Differential diagnoses include tuberculosis, mucormycosis, vasculitis, orbital pseudotumor, sarcoidosis, Kimura disease, Rosai-Dorfman disease, inflammatory dermoid cysts, and MALT lymphoma (5).

Similarly, ocular adnexal literature shows that IgG4-RD may clinically mimic ocular lymphoma. Karamchandani et al. reported cases initially suspected as lymphoma in which IgG4-related disease was identified only after appropriate immunohistochemical evaluation, highlighting the importance of IgG/IgG4 staining in the presence of plasmacytic infiltrates and sclerosis (6).

Therefore, in the context of a persistent indurated nasociliary lesion, particularly in a patient with significant ophthalmologic history, biopsy should be strongly considered when anatomically feasible and when the diagnostic benefit outweighs procedural risk.

Regarding treatment, systemic glucocorticoids remain the first-line therapy for IgG4-RD, particularly in early inflammatory stages (1,3,8,10). However, relapse rates and cumulative steroid toxicity have led to increased use of steroid-sparing agents such as azathioprine, methotrexate, and mycophenolate mofetil, although the supporting evidence for these agents is less robust compared with glucocorticoids or rituximab in refractory disease (8,10,16).

In this case, methotrexate was previously discontinued due to intolerance. The use of prednisolone 10 mg/day with a gradual taper, combined with azathioprine 100 mg/day, represents an immunomodulatory and steroid-sparing strategy. This approach requires close clinical and laboratory monitoring, including complete blood count, liver enzymes, renal function, urinalysis, and inflammatory markers, as implemented in the follow-up plan.

Rituximab has been reported as an effective option in refractory, relapsing, or steroid-dependent IgG4-RD (8,10,16). However, in this case, there is no evidence of refractoriness, progressive multiorgan involvement, or histopathological confirmation to support its indication at this stage.

Given the multisystem nature of IgG4-RD, evaluation of potential additional organ involvement is recommended based on symptoms, physical examination, laboratory findings, and imaging (1,4,7,9,16). In this patient, normal renal function and urinalysis reduce the likelihood of clinically evident renal involvement, although subclinical disease cannot be excluded. No respiratory symptoms, lymphadenopathy, or abdominal findings were documented, and the absence of lymphadenopathy is particularly relevant given its potential occurrence in IgG4-RD and its ability to mimic hematologic malignancies (7).

Limitations

Although clinical improvement was documented at three months, this assessment was based on clinical evaluation and photographic documentation, without standardized lesion measurements, activity scoring systems, comparative orbital imaging, or histopathological confirmation.

4. Conclusion

We report an 80-year-old male patient with a history of narrow-angle glaucoma and blindness, presenting with a left nasociliary indurated lesion, elevated serum IgG4 levels, and markedly increased total IgE, without clinical or serological evidence of systemic connective tissue disease. The patient was managed with a tapering regimen of prednisolone following intolerance to methotrexate, in combination with azathioprine.

The case is compatible with probable IgG4-related disease with periocular involvement. However, definitive diagnosis requires correlation with orbital imaging and histopathological evaluation, particularly given the broad spectrum of mimickers of IgG4-related ophthalmic disease. From a scientific perspective, the main strength of this case lies in its diagnostic reasoning and in highlighting the need to avoid both underdiagnosis and overdiagnosis of IgG4-related disease in periocular lesions. The principal methodological recommendation is not to classify such cases as definitive disease in the absence of sufficient tissue-based or imaging criteria.

Compliance with ethical standards

Disclosure of conflict of interest

The authors report no conflicts of interest for this article

Statement of informed consent

Informed consent was obtained from the patient for the publication of this case report and any accompanying clinical information. The patient was fully informed about the purpose of the report, the measures taken to protect confidentiality and anonymity, and the voluntary nature of participation. The patient provided written authorization prior to the preparation and submission of this manuscript.

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