Case Report

Isolated Orbital Involvement of IgG4-Related Disease Mimicking Malignancy

Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a rare, immune-mediated systemic condition that can affect the orbit. In this report, we describe a 76-year-old female patient who experienced a 4-month history of pain in the right orbit and vision loss. Imaging studies revealed a mass occupying the right orbital apex. Although the patient's serum IgG4 level was within normal limits, which complicated the diagnostic process, histopathological evaluation revealed significant tissue infiltration by IgG4-positive plasma cells, confirming the diagnosis of IgG4-RD. Following treatment with azathioprine and methylprednisolone, the lesion regressed; however, the vision loss became permanent. Isolated orbital involvement in IgG4-RD is rare and can mimic neoplasms. Early diagnosis and combination therapy may help prevent disease progression, although complete functional recovery is not always possible.

Keywords: *Immunoglobulin G4-related disease, immunosuppressive treatment, orbit, vision loss*

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a rare, chronic fibroinflammatory condition that is immune-mediated and can affect various organs. Originally described in 2003, this condition often mimics malignancy or infections and may present with either systemic or localized symptoms.

At the International IgG4 consensus symposium held in Boston in October 2011, a standardized nomenclature was proposed. This recommended using the term "IgG4-related disease" (IgG4-RD) alongside the name of the affected organ system.[1]

Recently, IgG4-related ophthalmic disease (IgG4-ROD), which primarily affects the lacrimal glands and orbital tissues, has been identified as a distinct clinical subset.[2,3] Patients may experience symptoms such as double vision (diplopia), protrusion of the eyeball (proptosis), ocular pain, vision loss, or inflammation of the lacrimal gland (dacryoadenitis).

Diagnosis involves a comprehensive assessment that includes clinical presentation, imaging findings, serum IgG4 levels, and characteristic histopathological features. Notably, elevated serum IgG4 levels are not always present; they remain within normal limits in approximately 20%–40% of cases. Radiological evaluations using computed tomography (CT) or magnetic resonance imaging (MRI) may show soft-tissue masses, dural thickening, or perineural infiltration.[4,5]

Histopathological diagnosis relies on three key criteria: dense lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis. To support a diagnosis, at least two of these features must be present, along with an IgG4+/IgG+ plasma cell ratio >40%.[6]

Initial treatment typically involves corticosteroids, which often lead to early clinical improvement. However, due to a high relapse rate, long-term immunosuppressive therapy using agents such as mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, or rituximab may be necessary.[7,8] Surgical intervention should be restricted to diagnostic purposes, while radiotherapy may be considered for localized, refractory cases.

Differential diagnosis must include lymphoma, plasmacytoma, tuberculosis, sarcoidosis, granulomatosis with

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polyangiitis, Tolosa–Hunt syndrome, and idiopathic orbital inflammation. Histopathological features and therapy response are critical for distinguishing IgG4-RD from these other conditions.

In this report, we present a rare case of isolated IgG4-related orbital disease affecting the orbital apex without systemic involvement. This case highlights the crucial role of biopsy in diagnosis and emphasizes that delays in diagnosis can lead to irreversible vision loss.

Case Report

A 76-year-old female patient with a known history of diabetes mellitus and hypertension presented with a 4-month history of the right orbital pain and progressive vision loss. A physical examination revealed complete vision loss in the right eye and restricted lateral gaze.

The patient denied any history of trauma, sinonasal surgery, sinusitis, or tobacco use.

Orbital CT demonstrated a well-defined soft-tissue density mass involving the right orbital apex, optic canal, sphenoid sinus, and pterygopalatine fossa. No additional pathology was detected in the paranasal sinuses [Figure 1].

Orbital MRI showed a contrast enhancing lesion that was isointense on T1-weighted images and hypointense on T2-weighted images [Figure 2].

To exclude malignancy and evaluate for systemic involvement, positron emission tomography-CT was performed. This revealed a hypermetabolic lesion with a maximum standardized uptake value of 5.0, with no evidence of other systemic uptake.

The serum total IgG4 level was 95 mg/dL, which fell within the normal reference range, complicating the diagnosis. However, histopathological findings supported the diagnosis.

The patient underwent endoscopic ethmoidectomy and sphenoidotomy under general anesthesia. Punch biopsies were taken from the fibrotic periorbital tissue. Histopathological examination revealed dense lymphoplasmacytic infiltration and storiform fibrosis, with no evidence of obliterative phlebitis. Immunohistochemical staining showed >50 IgG4-positive plasma cells per high-power field, with an IgG4/IgG ratio of 45% [Figures 3 and 4].

These findings confirmed the diagnosis of IgG4-ROD. The patient was referred to the rheumatology department. Given the chronic nature of the disease and the need for long-term immunosuppression, she was started on azathioprine (100 mg/day) and methylprednisolone (8 mg/day). Rituximab was not recommended due to cost considerations and the patient's clinical stability.

At the 3-month follow-up, azathioprine was tapered to 50 mg/day and methylprednisolone to 4 mg/day. The treatment was discontinued after 6 months. Follow-up MRI showed complete resolution of the lesion; however, no improvement in vision loss was noted, which was attributed to irreversible optic nerve damage.

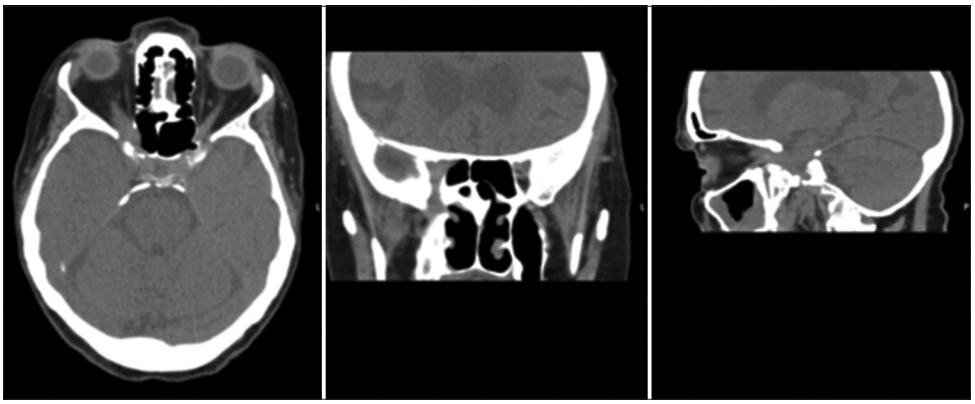


Figure 1: Axial, coronal, and sagittal CT images showing a soft-tissue mass at the right orbital apex involving the optic canal, sphenoid sinus, and pterygopalatine fossa

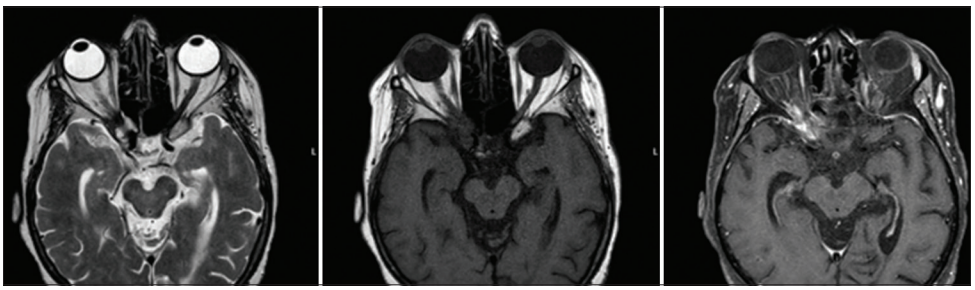


Figure 2: T1- and T2-weighted MRI images showing an enhancing lesion at the right orbital apex

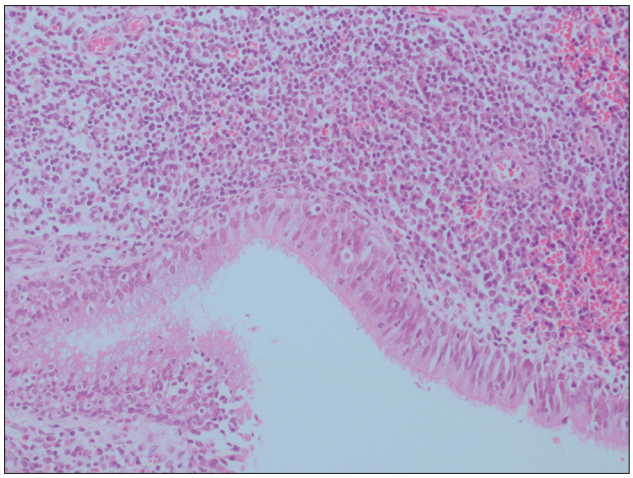


Figure 3: Dense lymphoplasmacytic infiltration with storiform fibrosis (H&E, ×40)

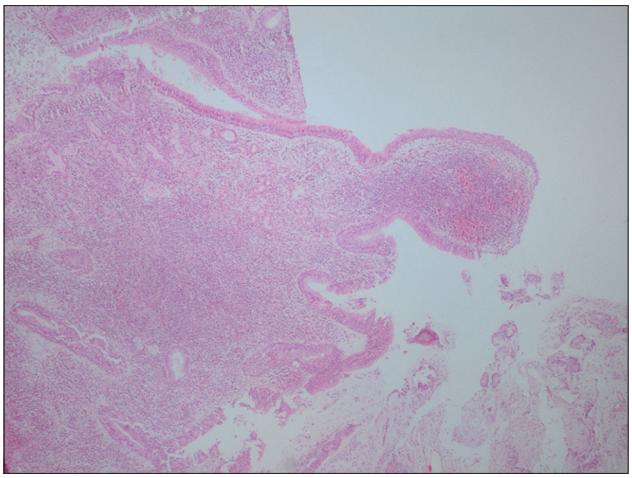


Figure 4: High magnification showing IgG4-positive plasma cells (H&E, ×100)

Discussion

Diagnostic challenge and clinical features

IgG4-RD is a chronic fibroinflammatory syndrome that can affect multiple organs. Based on the pattern of organ involvement, four clinical subtypes have been identified.[9] Head and neck presentations are most commonly categorized as type 3 (involving the lacrimal and salivary glands and orbit) or type 4 (systemic disease). Isolated orbital involvement is a rare manifestation of IgG4-RD and may resemble malignancies, infections, or lymphoproliferative disorders.

In a multicenter study by Goto *et al*., the most frequent symptoms included orbital swelling (85%), diplopia (50%), and visual impairment (25%), with systemic involvement absent in 25% of patients.[2] In our case, the presence of isolated orbital involvement and a normal serum IgG4 level led to a diagnostic delay due to the initial consideration of malignancy. This highlights the critical importance of tissue biopsy, even when serum IgG4 levels are normal.[10]

Histopathological findings and radiologic correlation

Zhang *et al*. emphasized the role of CD4+ cytotoxic T cells in the pathogenesis of IgG4-ROD and proposed that an IgG4/IgG ratio exceeding 40% is a significant diagnostic indicator.[3] Our case showed a histopathologic IgG4/IgG ratio of 45%, consistent with published diagnostic criteria. In addition, the lesion appeared isointense on T1-weighted images and hypointense on T2-weighted images with homogeneous enhancement, in line with previously reported orbital apex IgG4-related lesions.

Therapeutic response and visual loss

In a cohort study involving 573 patients, Gan *et al*. reported that patients with isolated ocular involvement responded better to steroid therapy and exhibited a lower relapse rate compared to those with systemic disease.[11] Our patient demonstrated significant radiologic regression of the lesion; however, irreversible optic nerve damage had already occurred due to the delayed diagnosis. This underscores that anatomical resolution may not always lead to functional recovery.

Fibrosis and ımportance of early ıntervention

The idea that "fibrosis progresses until diagnosis" is supported in our case by both imaging findings (showing dense contrast enhancement) and the histopathologic presence of storiform fibrosis. Therefore, early tissue biopsy is crucial, and normal IgG4 serum levels should not exclude the diagnosis.

Therapeutic options and drug selection

Although there is no universally accepted treatment algorithm, corticosteroids are generally used as first-line therapy. Due to high relapse rates, immunosuppressive agents such as azathioprine, mycophenolate mofetil, methotrexate, and rituximab are often employed as adjunctive treatments. In our case, azathioprine was selected over rituximab due to its lower cost and greater availability. Literature suggests that combined immunosuppressive therapy may reduce the risk of relapse.[8]

Conclusion

IgG4-related orbital disease is a rare immune-mediated condition that can lead to significant complications, such as vision loss, if not diagnosed promptly. In cases involving atypical orbital masses, IgG4-RD should be considered part of the differential diagnosis, and histopathological confirmation should not be delayed, even if serum IgG4 levels are within normal limits.

Early diagnosis and appropriate immunosuppressive therapy can result in the regression of lesions; however, functional recovery may not always be possible, especially when critical structures, such as the optic nerve, are affected. Therefore, a comprehensive evaluation that includes careful

imaging, histopathological confirmation, and immunologic assessment is essential. When necessary, a multidisciplinary approach should be utilized to optimize patient outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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