Case Report / Olgu Sunumu

# Understanding Igg4 Related Orbital Disease: A Rheumatologist's Perspective

## Olgu Romatoloji Pratiğinde IgG4 ilişkili Orbital Hastalı

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**Abstract:**Immunoglobulin G4-related disease (IgG4-RD) is also known as IgG4-related systemic disease, hyper-IgG4 disease, IgG4-related autoimmune disease. It is a multi-organ, fibro-inflammatory condition with tumefactive lesions of unknown etiology and characteristic histopathological features. It can affect all orbital tissues, including the lacrimal glands and extraocular muscles. A 52-year-old female patient, presented with complaints of swelling above her right eye. After undergoing a contrast-enhanced MRI, she had a biopsy. Consequently, the pathological findings were reported as consistent with IgG4-related sclerosing disease. The patient was initially prescribed corticosteroid therapy, followed by methotrexate and azathioprine treatment, which successfully stabilized her condition. Since the disease can affect almost all organs and systems, it is crucial for clinicians to have knowledge about early diagnosis and employ a multidisciplinary approach in patient management.
**Keywords:** IgG4 related disease, IgG4 related orbital disease, IgG4, eye

**Özet:**İmmünoglobulin G4 ile ilişkili hastalık (IgG4-RD), IgG4 ile ilişkili sistemik hastalık, hiper-IgG4 hastalığı, IgG4 ile ilişkili otoimmün hastalık olarak da bilinir. Etiyolojisi bilinmeyen ve karakteristik histopatolojik özelliklere sahip tümefaktif lezyonlarla karakterize, birden fazla organ tutulumu ile seyredebilen, fibroinflamatuar bir durumdur. Lakrimal bezler ve göz dışı kaslar da dahil olmak üzere tüm orbita dokularını etkileyebilir. 52 yaşında kadın hasta, sağ gözünün üstünde şişlik şikayetiyle başvurdu. Kontrastlı MR çektirdikten sonra biyopsi yapıldı. Sonuç olarak patolojik bulguların IgG4'e bağlı sklerozan hastalık ile uyumlu olduğu bildirildi. Hastaya başlangıçta kortikosteroid tedavisi verildi, ardından metotreksat ve azatiyoprin tedavisi uygulandı ve bu tedavi, durumunu başarılı bir şekilde stabilize etti. Klinik pratikte bu hastalık neredeyse tüm organ ve sistemleri etkileyebildiğinden, klinisyenlerin erken tanı konusunda bilgi sahibi olması ve hasta yönetiminde multidisipliner bir yaklaşım benimsemesi büyük önem taşımaktadır.
**Anahtar Kelimeler:**Igg4 İlişkili Hastalık, Göz, Igg4 İlişkili Orbital Hastalık, Igg4

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## 1. Introduction

IgG4-related disease (IgG4-RD) is a rare, multisystemic chronic fibroinflammatory disease that was identified in the 21st century. It is characterized by extensive tissue fibrosis, lymphoplasmacytic cell infiltration, sclerosing inflammation, and the widespread presence of IgG4-positive plasma cells in the tissue(1). IgG4-RD was first described as a distinct entity in 2001. At that time, it was reported to affect specific organs such as the pancreas and biliary system, and was associated with an increase in IgG4 levels in the blood. However, in 2003, Kamisawa et al. demonstrated that this disease progresses with systemic multiorgan involvement(2). The etiology of the disease is not yet clear. It progresses with relapsing-remitting attacks, and, therefore, if these attacks are not controlled with treatment, the disease may cause permanent damage.

The disease may clinically present with endocrine dysfunction, visual impairment, jaundice, and loss of sexual function(3). Many patients present with simultaneous yet unsynchronized multiorgan involvement. The 2019 ACR-EULAR classification criteria, widely accepted for diagnosing the disease, define pathological involvement and evidence of clinical and radiological findings in one of the eleven potentially affected organs. These criteria specify tumor-like formations or organ growth, accompanied by inflammation with lymphoplasmacytic infiltrates(4). In patients who do not meet these diagnostic criteria, organ-specific criteria are utilized, and pathological diagnosis becomes paramount in cases of organ involvement. From the perspective of eye involvement, literature describes that it can affect all orbital tissues, including the lacrimal glands and extraocular muscles. Patients often present with either a well-circumscribed orbital mass or diffuse involvement of the orbital fat tissue(5). The most common form of IgG4-related orbital disease is dacryoadenitis, with reported cases extending to the orbital apex and even involving the cavernous sinus(6).

In this case report, we discuss a female patient with IgG4-related orbital disease (IgG4-ROD), who presented at our rheumatology outpatient clinic exhibiting redness and swelling of the right eye.

## 2. Case Report

A 52-year-old female patient, with no known prior diseases and not on regular medication, presented at an external center with complaints of swelling above her right eye and redness in the right eye, persisting for two months. She was prescribed symptomatic eye drops; however, her symptoms did not improve with this treatment. Afterward, the patient underwent a contrast-enhanced orbital magnetic resonance imaging (MRI). The MRI showed lacrimal gland enlargement in the right orbital upper outer quadrant, along with involvement of the lateral rectus muscle. Inflammatory processes in the lacrimal gland were also noted. (figure 1) After the MRI, a biopsy was taken from the involved area of the patient's right eye, and the sample was sent for pathological analysis. The pathology report indicated lacrimal gland islets with intense inflammation, characterized by plasma cells against a notably sclerotic background with a storiform pattern in some areas. Additionally, cellular infiltration was observed in the immunophenotypic examination and tested positive for IgG4. Consequently, the findings were reported as consistent with IgG4-related sclerosing disease. The patient was subsequently referred to our rheumatology outpatient clinic to assess for potential systemic involvement related to her eye condition. Upon arrival, she reported no history of arthralgia or arthritis. Physical examination revealed swelling above the right eye and redness in the right eye. (figure 2) Laboratory tests were conducted. The results were as follows: anti-nuclear antibody (ANA) was negative, C-reactive protein (CRP) was 8.68 mg/L (normal range: 0-5 mg/L), and the erythrocyte sedimentation rate (ESR) was 37 mm/h (normal range: 0-20 mm/h). Tests for rheumatoid factor (RF), anti cyclic citrullinated peptide (CCP), and antineutrophil cytoplasmic antibodies (ANCA) were all negative. Additionally, a subgroup study of IgG levels was performed. The IgG4 level was 0.502 mg/mL (0.03-2.01 mg/mL), and total IgG was 13.7 g/L (7.67-15.9 g/L). A positron emission tomography-computed

tomography scan was performed on the patient to assess for systemic involvement. No abnormalities indicative of systemic IgG4 RD were detected. Subsequently, the patient was prescribed corticosteroid therapy at a dosage of 1 mg/kg for IgG4-ROD and continued this treatment for approximately one month. Following the corticosteroid treatment, muscle pains developed, prompting a titration of the treatment. When the swelling in the patient's eye did not respond to corticosteroids, methotrexate at a dose of 15 mg per week was initiated as an immunosuppressive treatment. Subsequently, when the patient developed mucositis from the methotrexate, the medication was discontinued. The patient was then started on azathioprine during subsequent follow-up. After the corticosteroid treatment was titrated, maintenance therapy continued at 4 mg/day. During follow-up, the treatment elicited a positive response and significant reduction in the patient's eye swelling was observed. In the MRI conducted seven months after the initial scan, the borders of the previously observed infraorbital lesions on the right side were indistinguishable. (figure 3) The patient has been treated with azathioprine and corticosteroids for six months and is under the joint care of rheumatology and ophthalmology clinics. Significant shrinkage of the mass above the right eye and resolution of the redness have been observed. (figure 4)

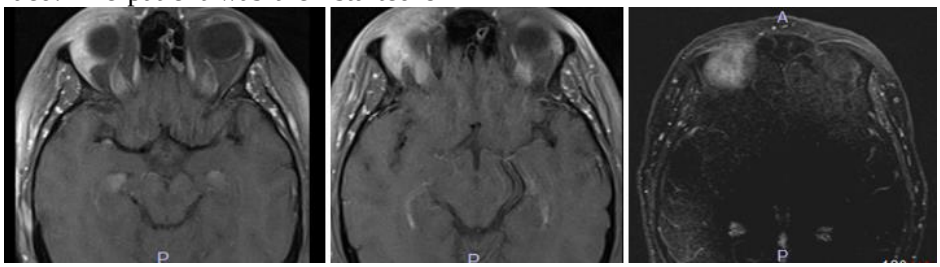

**Figure 1.** MRI images of our patient revealing inflammatory processes and lacrimal gland enlargement along with involvement of the lateral rectus muscle.

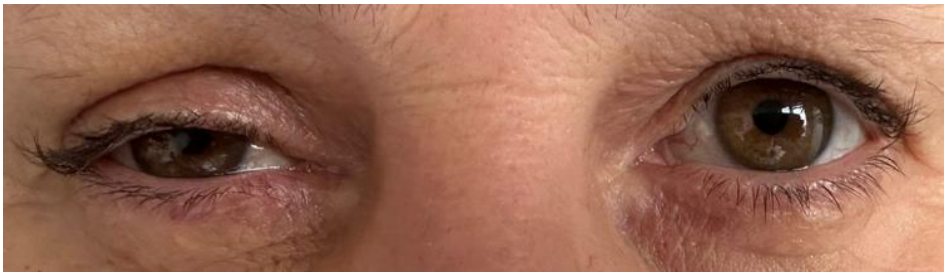

**Figure 2.** Swelling above the right eye.

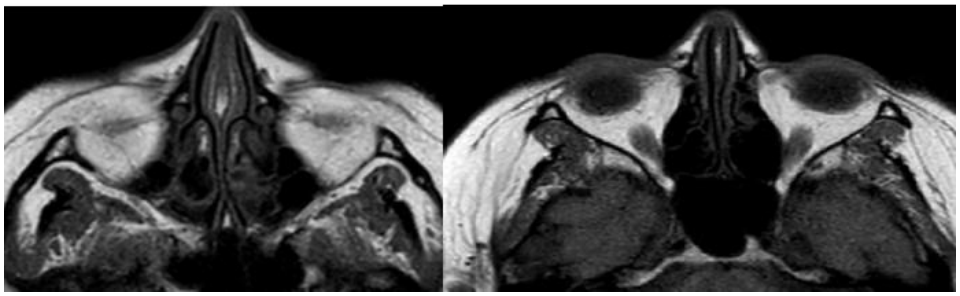

**Figure 3.** MRI revealing the borders of the previously observed infraorbital lesions on the right side were indistinguishable.

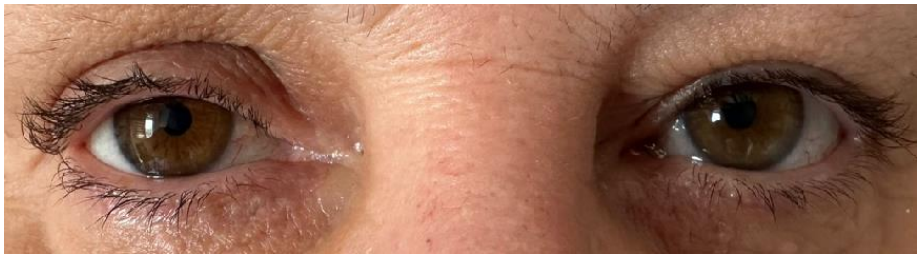

**Figure 4.** Significant shrinkage of the mass above the right eye.

## 3. Discussion

In this case report, we share our experiences with IgG4-ROD through the lens of rheumatology. A review of the literature to date indicates that the prevalence of IgG4-ROD in the context of IgG4-RD ranges from 4% to 34%(6-8). In patients with a multisystemic inflammatory condition, it may lead to ocular complications including uveitis, uveal masses, periorbital swelling, and scleritis. The lacrimal gland is most commonly affected by ophthalmic involvement. This presentation is often accompanied by soft tissue involvement around the orbit, involvement of the extraocular muscles, the trigeminal nerve, and the sclera.

In a multicentric study conducted in France, 25 patients were examined, with 68% exhibiting lacrimal gland involvement(9). Additionally, in this series, 58% of the patients had bilateral eye involvement, which commonly occurred in the presence of dacryoadenitis. In our case, the patient's primary complaint involved swelling around the eyes, with unilateral eye involvement mainly affecting the lacrimal gland. In another case from the United States, a patient had left submandibular gland enlargement associated with the disease(10). However, in our case, there was no lymph node enlargement. In that patient, MRI images showed diffuse enlargement of the lacrimal glands and extraocular muscles, similar to what we observed in our case. For treatment, they first performed surgery and then used oral corticosteroids post-operatively. A dramatic response was achieved with corticosteroids, but in our patient, corticosteroids were not sufficient, and we had to use additional immunosuppressive treatments.

A 42-year-old male patient from the United Kingdom (UK) presented with reduced vision in his right eye. In contrast, our patient did not experience any vision impairment. For the UK patient, clinicians performed a lateral orbitotomy for surgical excision, followed by imaging to assess systemic involvement; this patient did not have any systemic signs, similar to ours. No drug treatment was administered in that case(11). Another case from the UK described in the literature involved a patient with non-lacrimal IgG4-related orbital disease concurrent with IgG4-related mastitis(12). This patient also exhibited swelling and redness around the eye, similar to our case, but the lacrimal gland was not affected. For their patient, clinicians used corticosteroids and performed surgery. However, in our case, we did not perform surgery.

Tissue biopsy remains the gold standard for diagnosing IgG4-ROD. Diagnostic criteria include the presence of more than 10 IgG4-positive cells per high-power field, typical storiform fibrosis, and obliterative phlebitis. Additionally, the ratio of IgG4-positive cells to IgG-positive plasma cells must exceed 40%(13). A limitation of these pathological findings is that storiform fibrosis is relatively rare(14). In some cases documented in the literature, a diagnosis of probable IgG4-ROD is made when the ratio of IgG4-positive cells to IgG-positive cells is below 40%. In our case, sporadic areas of storiform fibrosis were observed, and the number of IgG4-positive cells reached as high as 110 in some areas. The IgG4 to IgG cell ratio was 60%. Based on

these findings, our case was classified as definite IgG4-ROD.

Accurate diagnosis of IgG4-ROD using imaging is essential for optimal clinical management and appropriate treatment adaptation. Nevertheless, IgG4-ROD presents structural imaging features similar to other causes of orbital inflammation, making accurate diagnosis challenging(15). Although infraorbital nerve infiltration is a highly suggestive indicator of IgG4-ROD, its sensitivity is low(16). Diffusion-weighted imaging (DWI) has demonstrated promising results in diagnosing orbital lesions, effectively distinguishing between benign and malignant lesions(17). Clinicians should carefully evaluate to distinguish other causes of orbital inflammation from IgG4-ROD to ensure proper treatment.

The primary treatment for IgG4-ROD is systemic corticosteroids. The literature recommends initiating treatment at a dosage of 0.6 mg/kg and reducing the dose by 10% every two weeks(18). The initial response to steroid treatment shows a remission rate of 90%. However, relapse occurs in approximately 30% of cases when the steroid dosage is reduced or discontinued(19). However, myopathy developed in our patient following steroid treatment, prompting an adjustment to a lower maintenance dose. In cases of steroid resistance or relapse, the literature reports alternative agents such as methotrexate, azathioprine, and mycophenolate mofetil. It has been reported that anti-CD20 therapy can be effectively used as a third-line treatment(20). In the literature concerning conventional disease modifying antirheumatic drugs (DMARDs), methotrexate and azathioprine are frequently reported as first-line treatments following steroids. However, the efficacy of azathioprine remains controversial, as it is reported to be effective in only a small percentage of patients(19). However, after observing side effects from methotrexate and muscle pain associated with steroids, we incorporated azathioprine into our treatment regimen. We continue to monitor our patient's progress with this therapy, noting both clinical and radiological improvements.

In cases diagnosed with IgG4-ROD, a high incidence of systemic IgG4-related disease is observed. According to the literature, systemic involvement is reported in 14% of cases with unilateral eye involvement and 79% of cases with bilateral eye involvement(21). In such cases, the most common sites of extraocular involvement are the salivary glands and lymph nodes. Given the frequency of extraocular manifestations, thorough investigation for systemic involvement is strongly recommended. The primary reason our patient was referred by her ophthalmologist was to assess for systemic involvement. Consequently, our nuclear medicine imaging did not reveal any pathology indicative of systemic disease.

A relationship between IgG4-ROD and lymphoma has been noted in the literature. For this reason, long-term follow-up is recommended for these patients. We manage our patient's care in a multidisciplinary approach, involving both ophthalmology and rheumatology, to monitor for any potential developments(22, 23).

## 4. Conclusion

Given that IgG4-ROD is both rare and a relatively recent topic, clinicians often find it challenging to diagnose and formulate treatment plans, especially when patients present with atypical manifestations such as ocular masses, uveitis, scleritis, and conjunctival infiltration. This entity should be considered in every patient presenting with chronic, recurrent, and multisystemic fibro-inflammatory diseases. Corticosteroids are the initial step in treatment, and depending on the patient's clinical presentation, immunosuppressives may also be utilized. Long-term multidisciplinary follow-up is essential to monitor for potential complications.

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**Ethics**

**Informed Consent:** The authors declared that informed consent form was signed by the patient.
**Copyright Transfer Form:** Copyright Transfer Form was signed by the authors.
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**Authorship Contributions:** Surgical and Medical Practices: DBG. Concept: DBG, RM. Design: DBG. Data Collection or Processing: DBG. Analysis or Interpretation: DBG, RM. Literature Search: DBG. Writing: DBG.

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