Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 2
CASE REPORT
Pages:244-251

Rare coexistence of adult-onset asthma with periocular xanthogranuloma and immunoglobulin G4-related disease

Erişkin başlangıçlı astım ve perioküler ksantogranülomun IgG4 ilişkili hastalıkla birlikte görüldüğü nadir bir olgu

Meryem ALTIN EKİN[1]
Semih GÜLLE[2]
Banu LEBE[3]

[1] Department of Ophthalmology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[2]Department of Rheumatology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[3] Department of Pathology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

Immunoglobulin G4-related disease
Received: 18.07.2025
Accepted: 28.09.2025
DOI: 10.18614/dehm.1745719

Corresponding author
Meryem ALTIN EKİN
ORCID ID: 0000-0002-0395-7700
meryem.altinekin@deu.edu.tr

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 2
CASE REPORT
Pages:244-251

ABSTRACT
Immuoglobulin G4 (IgG4)-related disease (IgG4-RD) is a systemic fibroinflammatory condition affecting multiple organs, including the orbit. Adult-onset asthma with periocular xanthogranuloma (AAPOX) is a rare subtype that may share histopathological and immunological features with IgG4-RD. We report a 61-year-old man with a history of asthma and pancreatitis who presented with recurrent bilateral eyelid swelling and ptosis. Elevated serum IgG4 levels and dense IgG4-positive plasma cell infiltration in the orbital tissue supported the diagnosis of IgG4-RD with overlapping AAPOX features. The patient showed an initial response to corticosteroids, and early rituximab therapy contributed to sustained remission, despite a transient relapse during tapering. During follow-up, an incidental intramucosal carcinoma arising in a sigmoid colon polyp was detected. This case highlights the rare coexistence of AAPOX and IgG4-RD, emphasizing the importance of comprehensive systemic evaluation and malignancy screening in patients with atypical or relapsing presentations.
KEYWORDS
Asthma, eyelid swelling, IgG4-related disease, periocular xanthogranuloma, rituximab

ÖZ
IgG4 ilişkili hastalık (IgG4-RH), orbita dahil olmak üzere birçok organı tutabilen sistemik bir fibroenflamatuar hastalıktır. Perioküler ksantogranülom ile birlikte erişkin başlangıçlı astım (AAPOX), IgG4-RH ile histopatolojik ve immünolojik benzerlikler gösterebilen nadir bir alt tiptir. Bu yazıda, astım ve pankreatit öyküsü bulunan, tekrarlayıcı bilateral göz kapağı ödemi ve pitoz ile başvuran 61 yaşında bir erkek olgu sunulmaktadır. Serum IgG4 düzeylerinin yüksek olması ve orbital dokuda yoğun IgG4 pozitif plazma hücresi infiltrasyonu, AAPOX özellikleriyle örtüşen IgG4-RH tanısını desteklemiştir. Hasta, sistemik kortikosteroid tedavisine başlangıçta yanıt vermiş; doz azaltımı sırasında geçici bir nüks yaşanmasına rağmen, erken dönemde başlanan rituksimab tedavisi ile kalıcı remisyon sağlanmıştır. İzlem sırasında, sigmoid kolondaki bir polipten gelişen intramukozal karsinom tesadüfen saptanmıştır. Bu olgu, AAPOX ve IgG4-RH'nin nadir birlikte görülmesini ortaya koymakta; atipik veya nüks eden olgularda kapsamlı sistemik değerlendirme ve malignite taramasının gerekliliğine dikkat çekmektedir.

ANAHTAR KELİMELER
Astım, göz kapağı şişliği, IgG4 ilişkili hastalık, perioküler ksantogranülom, rituksimab

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 2
CASE REPORT
Pages:244-251

Immuoglobulin G4 (IgG4)-related disease (IgG4-RD) is a systemic fibroinflammatory disorder characterized by tumefactive lesions, dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells, storiform fibrosis, and often elevated serum IgG4 levels (1). Since its initial recognition in autoimmune pancreatitis, the disease has been shown to affect nearly any organ, including the orbit. Orbital IgG4-RD commonly presents with lacrimal gland enlargement, periorbital swelling, or extraocular muscle involvement (1). Recent epidemiological studies estimate the prevalence of IgG4-RD to be approximately 0.28–1.0 per 100,000 individuals, highlighting its rarity on a global scale (1).

Adult-onset asthma and periocular xanthogranuloma (AAPOX) is a rare subtype of adult-onset xanthogranulomatous disease, typically associated with asthma and chronic rhinosinusitis. Although AAPOX and IgG4-RD are distinct entities, emerging evidence suggests potential overlap of their histopathological and immunological features (2–6).

We report a rare case of a 61-year-old man with asthma and prior pancreatitis who developed recurrent eyelid swelling and was diagnosed with IgG4-related disease with overlapping AAPOX features. This case highlights the rare coexistence of these two entities and supports a potential link between them.

Case presentation

A 61-year-old man was admitted to our hospital with complaints of swelling and drooping of both eyelids. The patient had no history of smoking, alcohol consumption, or family history of allergic disease or malignancy. His medical history included bronchial asthma diagnosed 17 years ago, for which he had been receiving long-term treatment with budesonide/formoterol, albuterol, and montelukast sodium. Fourteen years earlier, he had been treated for focal pancreatitis. He also reported a long-standing history of intermittent nasal obstruction and rhinosinusitis, which had been managed with triamcinolone acetonide nasal spray. Ten years before the current presentation, the patient had undergone bilateral ptosis surgery due to eyelid swelling and drooping. Histopathological analysis of the excised upper eyelid tissue at that time revealed a xanthogranulomatous infiltrate composed of foamy histiocytes, Touton giant cells, and dense lymphoid aggregates, consistent with periorbital xanthogranuloma.

In the current ophthalmological examination, bilateral upper eyelid ptosis was noted, being more pronounced on the right side, along with yellowish xanthogranuloma-like skin lesions and periorbital swelling involving both upper and lower eyelids (Figure 1). The best-corrected visual acuity was 5/10 in both eyes. Orbital magnetic resonance imaging (MRI) revealed inflammatory changes with contrast enhancement in the bilateral preseptal and postseptal spaces, involving the extraocular muscles, right retrobulbar fat, and optic nerve sheath (Figure 2). Laboratory investigations showed a markedly elevated serum IgG4 level of 978 mg/dL (normal range: <135 mg/dL). A repeat biopsy from the right upper eyelid demonstrated a dense inflammatory infiltrate consisting of CD68-positive histiocytes, some of which were multinucleated, intermixed with polyclonal plasma cells (kappa and lambda light chain-positive) and CD3/CD20-positive lymphocytes (Figure 3). Immunohistochemistry revealed that more than 40% of IgG-positive plasma cells were IgG4-positive.

These findings were consistent with IgG4-RD based on the 2019 classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR). The patient was diagnosed with IgG4-related disease involving the orbit and systemic corticosteroid therapy was initiated with prednisolone at 40 mg/day. Two weeks later, rituximab was initiated at a dose of 500 mg weekly for four doses, and prednisolone was gradually tapered thereafter. When the dose of prednisolone reached 4 mg/day, the patient experienced a recurrence of symptoms, prompting an increase in the corticosteroid dose to 16 mg/day. Following this adjustment, a marked clinical improvement was observed. The patient did not experience any significant adverse effects during corticosteroid or rituximab therapy. Minor transient weight gain and mild insomnia were observed during the initial high-dose corticosteroid phase, but no adverse effects related to rituximab infusion were reported. The patient remains under follow-up and treatment continues without any subsequent disease relapse (Figure 4).

During follow-up, fluorodeoxyglucose 18F–positron emission tomography/computed tomography (FDG-PET/CT)

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 2
CASE REPORT
Pages:244-251

imaging revealed focally increased FDG uptake in an intraluminal polypoid lesion in the sigmoid colon. However, colonoscopy and subsequent polypectomy could only be performed 6 months later due to the patient's irregular follow-up. Histopathological analysis confirmed intramucosal carcinoma arising in a tubulovillous adenoma. In addition to colonoscopy, the patient underwent chest CT and abdominal ultrasound as part of a systemic evaluation. No additional malignancies were detected.



Figure 1. Initial clinical photographs showing bilateral periorbital swelling, ptosis (more prominent on the right side), and yellowish xanthogranulomatous eyelid lesions: (a) frontal view, (b) right lateral view, and (c) left lateral view.

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 2
CASE REPORT
Pages:244-251



Figure 2. Axial (A) and coronal (B) orbital MRI showing bilateral preseptal and postseptal inflammation with involvement of extraocular muscles, retrobulbar fat, and optic nerve sheath.

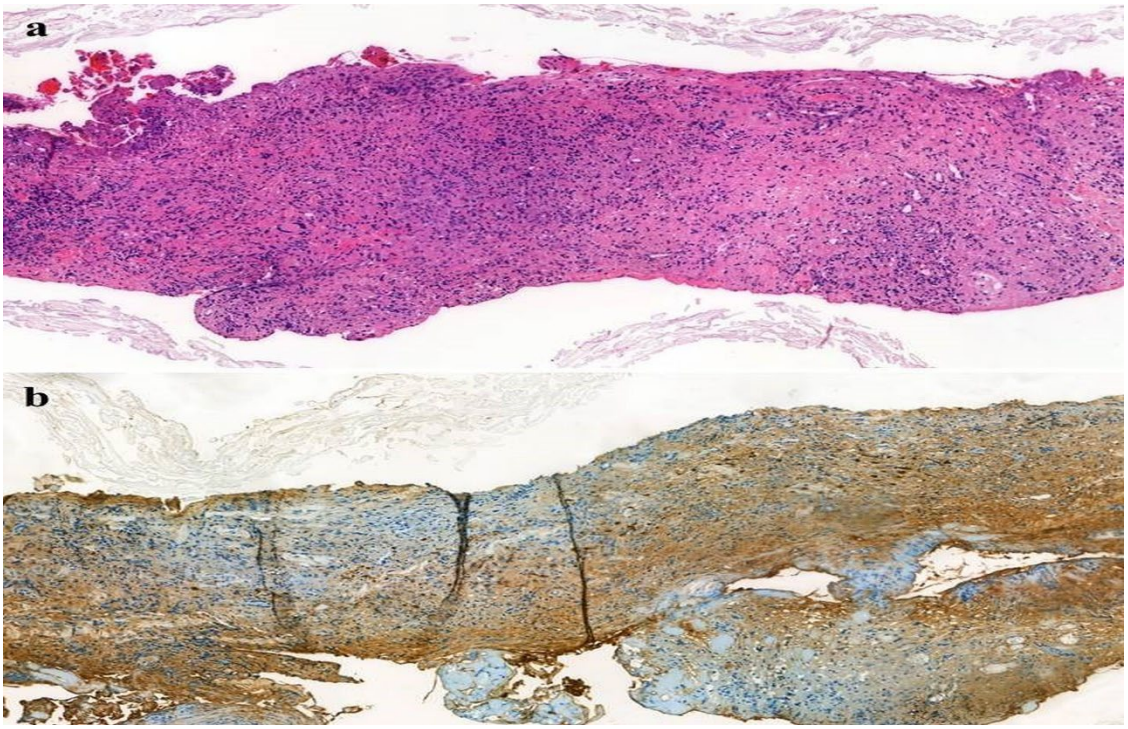


Figure 3. (a) H&E staining shows dense chronic inflammation with lymphocytes, polyclonal plasma cells, and histiocytes in a fibrotic stroma. (b) Immunohistochemistry highlights numerous IgG4-positive plasma cells, comprising over 40% of IgG-positive cells.

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 2
CASE REPORT
Pages:244-251



Figure 4. Clinical photograph showing marked resolution of periorbital swelling and eyelid lesions after steroid and rituximab therapy.

Discussion

Since its recognition in 2003 as a distinct clinicopathologic entity, IgG4-RD has attracted growing interest due to its complex pathogenesis, variable clinical manifestations, and multisystem involvement. Initially described in autoimmune pancreatitis, the term has expanded to include fibroinflammatory disorders characterized by tumefactive lesions, storiform fibrosis, and IgG4-rich plasma cell infiltration, potentially affecting nearly any organ, including the orbit (1–6).

Among the rare orbital presentations, AAPOX is a poorly understood subtype of adult-onset xanthogranulomatous disease. It typically presents with periocular swelling and xanthomatous skin changes and may precede or accompany asthma (2,3). Histologically, AAPOX features lipid-laden histiocytes, giant cells, and variable IgG4-positive plasma cell infiltration and has been linked to systemic atopic findings such as chronic rhinosinusitis, nasal polyps, and eosinophilia (4–6).

The diagnosis of IgG4-RD in our case is strongly supported by the 2019 ACR/EULAR classification criteria, which include an entry criterion, exclusion criteria, and a weighted scoring system (7). Our patient met the entry criterion with orbital involvement and had no exclusion factors. Key scoring items included a dense lymphoplasmacytic infiltrate with >40% IgG4+/IgG+ plasma cells (+13), elevated serum IgG4 (978 mg/dL; +11), and characteristic orbital MRI findings (+6), yielding a total score well above the 20-point threshold. The clinical, radiological, serological, and histopathological findings are highly consistent with IgG4-RD and align closely with the current international consensus (7). Only a few studies have suggested a potential link between xanthogranulomatous inflammation and IgG4-RD (2–6). Singh et al. described a patient who initially presented with bilateral xanthelasmas and subsequently developed an inflammatory orbital syndrome characterized by proptosis and ptosis (8). Histopathological examination of the biopsy revealed a xanthomatous inflammatory infiltrate with a high density of IgG4-positive plasma cells. The IgG4/IgG ratio was calculated at 80%, meeting the histological criteria for IgG4-related ophthalmic disease (8). In a separate report, Mudhar et al. described two cases of orbital necrobiotic xanthogranuloma with elevated serum IgG4 levels, one of which showed systemic involvement (9). Similarly, Verdijk et al. conducted a retrospective study

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 2
CASE REPORT
Pages:244-251

reviewing confirmed cases of orbital xanthogranuloma, including the re-examination of archived tissue samples (10). Among the 16 clinically evaluated cases, approximately 50% met the histopathologic criteria for IgG4-RD; however, only two patients exhibited features suggestive of systemic disease. Notably, serum IgG4 levels were not assessed in this cohort, limiting the ability to establish a definitive diagnosis of IgG4-RD. The authors concluded that, although histological features of IgG4-RD may be present in xanthogranulomatous lesions, systemic IgG4-RD is rarely implicated (10).

IgG4-RD is well recognized for its potential to involve multiple organ systems, often metachronously, and with overlapping histopathological features. Although the initial disease descriptions focused on type 1 autoimmune pancreatitis, subsequent studies have demonstrated that IgG4-RD can affect virtually any organ, including the lacrimal and salivary glands, orbit, pancreas, biliary tract, kidneys, lungs, meninges, and retroperitoneum (1,11). This multisystemic nature underscores the importance of a thorough systemic evaluation in patients with localized IgG4-RD manifestations. In our case, the patient's history of focal pancreatitis more than a decade earlier, in the absence of other known etiologies, may have constituted an early manifestation of IgG4-RD. The subsequent development of orbital involvement, followed by the incidental detection of intramucosal colon carcinoma during the systemic workup, raises important considerations. While the association between IgG4-RD and malignancy remains controversial, several studies have reported an increased risk of synchronous or metachronous cancers (1,11). Thus, the patient's clinical course may reflect the multisystemic progression of IgG4-RD and the need for vigilant malignancy screening, particularly in atypical or relapsing cases.

We still do not fully understand why AAPOX and IgG4-related disease occur together (2–6). Both conditions involve ongoing inflammation with infiltration by IgG4-positive plasma cells, eosinophils, and CD68-positive histiocytes, suggesting that they share certain immune features. Interestingly, elevated serum IgG4 levels and a high number of IgG4-positive cells in AAPOX lesions have led some researchers to suggest that AAPOX may be a localized variant of IgG4-related disease rather than a completely separate condition. A likely immunological mechanism involves a Th2-biased response, characterized by increased expression of cytokines such as IL-4, IL-5, and IL-13, which promote IgG4 class switching and eosinophilic inflammation (12). The frequent association of AAPOX with conditions like asthma and chronic rhinosinusitis adds further weight to the role of this Th2-driven pathway. Another possible contributor is regulatory T-cell activity, which has been found to be elevated in IgG4-RD and may enhance IgG4 production through IL-10 and TGF-β signaling (11). In addition, macrophage activation and chronic lipid exposure in xanthogranulomatous tissue may sustain antigenic stimulation and promote a microenvironment favoring IgG4 responses (13). Although further studies are needed, these mechanisms support the hypothesis of a shared immunopathogenesis between AAPOX and IgG4-RD.

The optimal management of AAPOX associated with IgG4-RD remains undefined due to its rarity; however, treatment generally follows IgG4-RD protocols. Systemic corticosteroids are the mainstay of first-line therapy and typically induce a rapid clinical response, particularly in orbital involvement (14). Nonetheless, relapse upon tapering is common. Immunosuppressive agents such as azathioprine or methotrexate have been used as steroid-sparing options, though with variable efficacy (14). Rituximab, a monoclonal anti-CD20 antibody, has emerged as a highly effective alternative in relapsing or steroid-refractory IgG4-RD, inducing sustained remission in many cases (15). Our patient responded well to initial corticosteroid therapy. Considering the risk of relapse, rituximab was introduced early in the treatment course to help maintain long-term disease control. A mild recurrence occurred during steroid tapering, but symptoms improved promptly after a dose adjustment. Since then, the patient has remained stable without further relapses. The patient's clinical progress suggests that therapies targeting B cells can help treat orbital IgG4-related disease, even in cases of uncommon types like AAPOX. While new biologic treatments focusing on Th2 pathways or B-cell signaling are being studied, we still do not know how well they work for this group.

In conclusion, this case report highlights how rare it is to see AAPOX and IgG4-related disease together and shows why it is important to think about both conditions when a patient presents with orbital xanthogranulomatous inflammation. Careful examination of tissue samples,

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 2
CASE REPORT
Pages:244-251

especially for IgG4-positive cells, is key to making the correct diagnosis and deciding on the best treatment. Our patient's favorable response to rituximab supports the effectiveness of B-cell depletion in managing relapsing IgG4-related disease. Furthermore, this case contributes to the limited literature suggesting a possible shared pathogenesis between AAPOX and IgG4-RD. It highlights the importance of early recognition to identify systemic involvement and initiate timely therapy.

Informed Consent

This case report was previously submitted as an e-poster to the 59th National Congress of Ophthalmology organized by the Turkish Ophthalmological Association.

Authorship contribution

Study conception and design: M.A.E.; data collection: M.A.E., S.G.; clinical evaluation and patient management: M.A.E., S.G.; histopathological evaluation: B.L.; analysis and interpretation of results: M.A.E., S.G., B.L.; draft manuscript preparation: M.A.E. All authors reviewed the results and approved the final version of the article.

Funding

No funding was received for this study.

Conflict of interest statement

The authors declare no conflict of interest.

References

1. Al-Mujaini A, Al-Khabori M, Shenoy K, Wali U. Immunoglobulin G4-Related Disease: An Update. Oman Med . 2018 Mar;33(2):97–103.
2. Sahu AK, Tripathy SR, Parida MK, Patnaik SS, Das BK. Adult-Onset Asthma With Periocular Xanthogranuloma (AAPOX) Associated With IgG4 Related Disorder: A Case Report and Review of Current Literature. Cureu. 2025 Apr;17(4):e82617.
3. Green M, Daly MK, Laver NM, Lefebvre DR. Adult-onset asthma and periocular xanthogranuloma – A rare infiltrative disease of the orbit and eyelid. American Journal of Ophthalmology Case Reports. 2021;22:101043.
4. London J, Martin A, Soussan M, Badelon I, Gille T, Uzunhan Y, et al. Adult Onset Asthma and Periocular Xanthogranuloma (AAPOX), a Rare Entity With a Strong Link to IgG4 Related Disease: An Observational Case Report Study. Medicine (Baltimore) 2015;94(43):e1916.
5. Asproudis I, Kanari M, Ntountas I, Ragos V, Goussia A, Batistatou A, et al. Successful treatment with rituximab of IgG4 related disease coexisting with adult onset asthma and periocular xanthogranuloma. Rheumatology Internationa. 2020 Apr;40(4):671-677.
6. Burris CKH, Rodriguez ME, Raven ML, Burkat CN, Albert DM. Adult onset asthma and periocular xanthogranulomas associated with systemic IgG4-related disease. American Journal of Ophthalmology Case Reports. 2016 Apr;1:34–37.
7. Wallace ZS, Naden RP, Chari S, Choi H, Della-Torre E, Dicaire JF, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. Arthritis Rheumatol. 2020;72(1):7–19.
8. Singh K, Rajan KD, Eberhart C. Orbital necrobiotic xanthogranuloma associated with systemic IgG4 disease. Ocul Immunol Inflamm. 2010;18(5):373–378.
9. Mudhar HS, Bhatt R, Sandramouli S. Xanthogranuloma tous variant of immunoglobulin G4 sclerosing disease presenting as ptosis, proptosis and eyelid skin plaques. Int Ophthalmol. 2011;31(3):245–248.
10. Verdijk RM, Heidari P, Verschooten R, van Daele PL, Simonsz HJ, Paridaens D. Raised numbers of IgG4-positive plasma cells are a common histopathological finding in orbital xanthogranulomatous disease. Orbit. 2014;33(1):17–22.
11. Zen Y, Nakanuma Y. IgG4-related disease: A cross-sectional study of 114 cases. Am J Surg Pathol. 2010;34(12):1812–1819.
12. Della-Torre E, Lanzillotta M, Doglioni C. Immunology of IgG4-related disease. Clin Exp Immunol.2015;181(2):191–206.
13. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. Mod Rheumato. 2021;31(3):529–533.
14. Stone JH, Khosroshahi A, Deshpande V, Chan JKC, Heathcote JG, Aalberse R, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum. 2012 Oct;64(10):3061–3067.
15. Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis. 2015;74(6):1171–1177