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Case Report

Nodular Scleritis as Isolated Symptom of IgG4-Related Disease, Mimicking as Conjunctival Lymphoma: A Case Report

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Keywords

Immunoglobulin G4-related disease · Antineutrophil cytoplasmic antibody-associated vasculitis · Rituximab · Scleritis · Immunoglobulin G4-related disease overlap syndrome

Abstract

Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a systemic, immune-mediated disorder marked by the infiltration of IgG4-positive plasma cells and fibrosis in affected organs. This report presents a rare case of a patient with isolated nodular scleritis as an IgG4-RD (in a more precise way antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [AAV] and IgG4-RD overlap syndrome). ***Case Presentation:*** A 51-year-old woman was referred with the presumed diagnosis of conjunctival lymphoma due to a painful, salmon-colored lesion in the superior conjunctiva of the right eye. A biopsy of the conjunctiva showed a lymphoplasmacytic infiltrate with multiple IgG4-positive cells (>200 cells/high power field), elevated IgG4/IgG ratio of 66% and fibrotic tissue without obvious vasculitis, confirming the diagnosis of IgG4-related disease (IgG4-RD). ANCAs directly against myeloperoxidase were also positive, suggesting AAV. Given that the clinical signs align with both disease entities, it was concluded that the case fits in its restricted sense the newly described overlap syndrome. The scleritis was successfully treated with a tapering dose of corticosteroids and rituximab. ***Conclusion:*** This case illustrates a rare presentation of scleritis as an IgG4-RD (in a more precise way AAV and IgG4-RD overlap syndrome) and demonstrates that rituximab and low dose of corticosteroids can lead to remission.

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic, immune-mediated disorder marked by the infiltration of IgG4-positive plasma cells and fibrosis in affected organs, with the lacrimal gland being typically involved in ophthalmologic cases [1]. This report presents a rare case of a patient with isolated nodular scleritis – mimicking conjunctival lymphoma (due to the characteristic "salmon patch"-like lesion, though admittedly less typical because of the accompanying pain) – as the initial symptom of IgG4-RD. Additionally, it describes the second case of IgG4-RD-related scleritis successfully treated with combination of corticosteroids and rituximab. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543084).

Case Report

A 51-year-old woman was referred to our department with a painful, salmon-colored lesion in the superior conjunctiva of the right eye. Previously, the patient presented twice (5 years and 2 months before this presentation) with a marginal keratitis, resolving after 1-month treatment with dexamethasone and antibiotic drops. At a follow-up examination 1 month after the second episode, biomicroscopy revealed a red, hard, swollen conjunctival nodule. She was referred with the presumed diagnosis of conjunctival lymphoma.

The patient experienced pain in her right eye and orbit for the past month. She had no systemic comorbidities and was taking systemic nonsteroidal inflammatory drugs (ibuprofen 400 mg twice a day) for the pain, as well as anti-allergic eye drops (cromoglycate twice a day). Her best-corrected visual acuity was 9/10 in both eyes. Anterior segment evaluation revealed a salmon-colored lesion with no signs of anterior uveitis (shown in Fig. 1). A B-scan ultrasonography showed no T-sign (fluid accumulation between optic nerve and sclera) or other indications of posterior scleritis. Fundoscopy revealed a normal posterior segment. Serology revealed highly elevated IgG4 levels 2.653 g/L (reference value 0.080–1.400 g/L). Antineutrophil cytoplasmic antibodies (ANCAs) directly against myeloperoxidase (MPO) were positive (14 U/mL, reference value <5 U/mL). A biopsy of the conjunctiva revealed active follicular inflammation with IgG4-positive cells (>200 cells/high power field; magnification ×20), an elevated IgG4/IgG ratio of 66% and fibrotic tissue without obvious vasculitis, and no monoclonality of B cells (also shown in Fig. 1). Positron emission tomography-CT (PET-CT) showed FDG (fluorodeoxyglucose) uptake in the ascending aorta, in the pleura, the right sacroiliac joint, and a limited colitis. An MRI of brain/orbit was normal, except for an enlarged right lacrimal gland (also shown in Fig. 1). Given that the clinical signs align with IgG4-RD and antineutrophil cytoplasmic antibody-associated vasculitis (AAV), it was concluded that the case fits the newly described overlap syndrome.

A tapering regimen of corticosteroids (start dose of 32 mg prednisolone) was implemented, along with two doses of rituximab (1 g each, administered intravenously with 2 weeks interval) and sulfamethoxazole and trimethoprim as pneumocystis jirovecii pneumonia prophylaxis. Thirteen months after starting rituximab, PET-CT showed resolution of FDG uptake in the ascending aorta and sequelae in pleura, with no new inflammatory foci. After 2 years, there was a limited B-cell repopulation (0.023×10^9/L). Consequently, an additional third dose of rituximab (500 mg, intravenously) was administered. Corticosteroids were completely discontinued after 3 years. Throughout the entire follow-up period, no systemic involvement or recurrence of scleritis were observed.

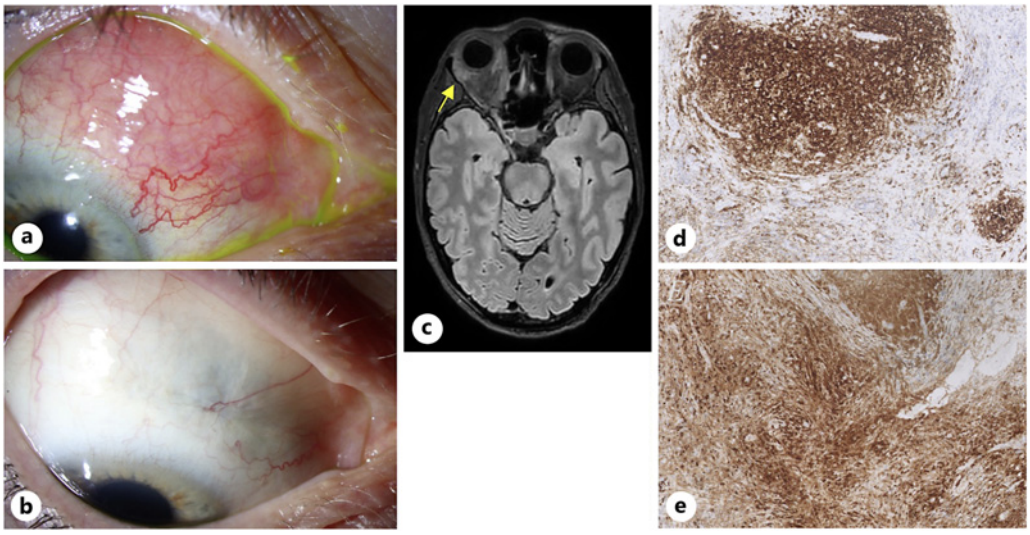

Fig. 1. a Clinical picture at presentation of the salmon-colored lesion in the superior conjunctiva of the right eye. **b** Thirty-three months after treatment (combination of corticosteroids and rituximab) clinical picture of the thinned conjunctiva, resolution of swelling and redness. **c** MRI, T1-weighted image, showing right lacrimal gland enlargement. Histopathological findings: CD20 immunostaining (initial magnification ×5) (**d**) and IgG4 immunostaining (initial magnification ×5) (**e**).

Discussion

There are limited reports of scleritis as a presenting symptom of IgG4-RD, and only 2 cases of isolated scleritis in young patients (20 and 17 years old) have been documented [1–3]. IgG4-RD is a systemic immune-mediated fibroinflammatory disorder and can affect nearly any organ [4]. Suggestive organ involvement includes submandibular gland swelling, parotidomegaly, orbital pseudotumor, Mikulicz's disease, Riedel's thyroiditis, dacryoadenitis, sialadenitis, lymphadenopathy, pachymeningitis, hypophysitis, autoimmune pancreatitis, sclerosing cholangitis, tubulointerstitial nephritis, membranous glomerulonephritis, retroperitoneal fibrosis, mediastinal fibrosis, periaortitis, inflammatory aortic aneurysm, skin involvement, and interstitial lung disease [5]. The orbit is the sixth most frequently involved site, affected in approximately 3.6–12.5% of cases, with the lacrimal gland being particularly susceptible but includes also the extraocular muscles, orbital soft tissues, sclera, and local nerves [4, 6, 7].

Diagnosing IgG4-RD requires a comprehensive evaluation that includes systematic work-up of clinical findings, radiology, histopathology, and serology. Histopathology is crucial in diagnosing IgG4-RD, typically revealing dense lymphoplasmacytic infiltrates composed of T cells, B cells, eosinophils, and plasma cells, sometimes with germinal centers; fibrosis, often in a storiform pattern; and phlebitis, which may be obliterative or non-obliterative; however, around the eye and in the lacrimal gland these two last criteria are rarely present and not obligatory for the diagnosis. The ratio of IgG4/IgG and the number of IgG4-positive plasma cells are highly elevated and the standard for diagnosis varies per organ. Elevated serum IgG4 levels occur in 55–97% of cases; however, they should not be considered specific to IgG4-RD, as this can also be found in various other conditions, including other autoimmune diseases, malignancies, and infections [4, 8].

Given the elevated IgG4/IgG ratio of 66%, the high count of IgG4 cells per high power field (>200), the presence of periaortitis and the absence of granulomatous vasculitis, the diagnose of IgG4-RD was made. The positive MPO-ANCAs and the initial symptom of scleritis (the sclera is particularly susceptible to being affected by granulomatosis because of its high collagen content) suggest also AAV [9]. Recently, an overlap is shown between IgG4-RD and AAV,

concluding to a new overlap syndrome [5]. Given that the clinical signs align with both disease entities, it was concluded that this case fits the newly described combined syndrome. This report presents, to our knowledge, the first case report of a patient with an isolated nodular scleritis that fits the AAV and IgG4-RD overlap syndrome [10]. Scleritis is described in one other case report, combined with left exophthalmos due to lacrimal gland enlargement, as an initial symptom of the AAV and IgG4-RD overlap syndrome. Different to our case, in this case report ANCAs directed against proteinase 3 (PR3-ANCA) were positive, which aligns with multiple retrospective studies, where AAV scleritis is more frequent in PR3-ANCA-associated vasculitis comparing to MPO-ANCA-associated vasculitis [10–12]. As in our case, effective treatment was obtained with a tapering of prednisone and a few doses of rituximab (in our case a total of three doses, compared to two doses in the case report of Della-Torre et al. [10]).

Rituximab, an anti-CD20 monoclonal antibody, has emerged as a promising treatment for IgG4-RD, effective in inducing remission and managing disease flares [6, 13, 14]. In a retrospective clinical study by Wu et al. [6], 5 cases of IgG4-RD with biopsy-confirmed orbital inflammatory syndrome showed significant improvement 2 months after starting rituximab treatment, with 3 cases achieving complete clinical resolution and 2 cases achieving partial resolution. Additionally, a case report described improvement in a 17-year-old patient with refractory IgG4-RD scleritis despite steroids and immunosuppressants, upon adding rituximab to prednisone treatment [3]. Rituximab effectively induces remission and prevents relapses in AAV, including cases with ocular manifestations [11, 15]. Danlos et al. [5] suggest a therapeutic approach such as rituximab to be an effective option in both IgG4-RD and AAV. Initial treatment for IgG4-RD typically involves corticosteroids like prednisolone, starting at doses of 30–40 mg per day. While corticosteroids initially demonstrate strong efficacy, their ability to control inflammation diminishes as the dosage is tapered to lower levels. Our case highlights the importance of recognizing AAV and IgG4-RD overlap syndrome in nodular scleritis and demonstrates that rituximab can achieve remission. This is particularly beneficial in middle-aged patients, as in our case, who often have comorbidities that contraindicate long-term glucocorticosteroid use.

Statement of Ethics

This study protocol was reviewed and approved by EC Research UZ/KULeuven, Approval No. S69449. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.D. reviewed medical record, wrote original draft of case report, searched literature and revised intellectual content. G.M., D.B., and R.V.G. critically revised the manuscript and intellectual content. All authors contributed to the revision and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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