



Posterior scleritis with anti-neutrophil cytoplasmic antibody-associated vasculitis utilizing rituximab therapy to maintain remission: A case report

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ABSTRACT

Purpose: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a necrotizing vasculitis syndrome characterized by the destruction of small vessels, leading to various organ disorders. Here, we report a case of posterior scleritis with AAV successfully treated with prednisolone and rituximab (RTX) combination therapy.

Observations: A 69-year-old female suffered from ocular pain and redness in her left eye for 2.5 years. She had been diagnosed with idiopathic otitis media before a year. At her initial visit, scleral injection with nodular elevated scleral lesions, vitreous haze, and serous retinal detachment (SRD) in the inferior periphery were observed in the left eye. Enhanced computed tomography revealed the enhancement and thickening of the left sclera. The results of laboratory analysis were positive for myeloperoxidase ANCA. Accordingly, she was diagnosed with AAV. Owing to the exacerbation of vitreous haze and SRD, topical treatment and steroid pulse therapy were initiated. Following therapy, anterior and posterior scleritis improved, and additional RTX was administered to maintain the remission. Following treatment, the patient has maintained remission with 10 mg/day prednisolone to date.

Conclusions and importance: We encountered a case of posterior scleritis with AAV in which inflammatory manifestations subsided with RTX and glucocorticoid combination therapy. RTX administration likely contributed to the maintenance of remission.

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a necrotizing vasculitis syndrome characterized by the destruction of small vessels, leading to the dysfunction of various organs, such as the ear, nose, throat, eye, respiratory tract, kidney, skin, and nervous system.¹ Typical ocular complications include scleritis, episcleritis, orbital inflammation, lacrimal duct stenosis, and uveitis.²

Rituximab (RTX) is a chimeric monoclonal antibody against B-cell-specific CD20. RTX has recently been recommended for the treatment of granulomatosis with polyangiitis (GPA) in patients who are resistant to or intolerant of cyclophosphamide (CYC).^{3,4}

Posterior scleritis is an uncommon form of scleral inflammation and often extends to optic disc edema, exudative retinal detachment, and choroidal detachment. Here, we report a case of posterior scleritis with AAV successfully treated with prednisolone (PSL) and RTX combination therapy.

2. Case report

A 69-year-old female patient suffered from ocular pain and redness in her left eye (OS) for 2.5 years, and she noted decreased visual acuity OS 1.5 years previously. She had been treated with topical betamethasone several times only when she had symptoms. At her visit to an eye clinic, scleral injection was detected and she was treated with topical

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Abbreviations

ANCA	anti-neutrophil cytoplasmic antibody
AAV	ANCA-associated vasculitis
PSL	prednisolone
RTX	rituximab
SRD	serous retinal detachment
GPA	granulomatosis with polyangiitis
BCVA	best-corrected visual acuity
CME	cystoid macular edema
AZA	azathioprine
UBM	ultrasound biomicroscopy
STTA	sub-tenon injection of triamcinolone acetamide
RA	rheumatoid arthritis
PR3-ANCA	protein-3 ANCA
MPO-ANCA	myeloperoxidase ANCA
GC	glucocorticoid
CYC	cyclophosphamide
CHCC	Chapel Hill Consensus Conference

examination revealed 1+ vitreous haze, a yellowish elevated lesion at the superotemporal periphery, and serous retinal detachment (SRD) at the inferotemporal periphery OS (Fig. 2a). Optical coherence tomography (OCT) revealed cystoid macular edema and retinal pigment epithelium (RPE) undulations OS (Fig. 2b). There were no abnormal findings, except mild superficial punctate keratopathy OD. Ultrasound biomicroscopy revealed enlargement of the supraciliary space OS (Fig. 2c), and B-mode ultrasonography revealed the thickening and flattening of the posterior coats OS (Fig. 2d).

Laboratory analysis revealed high titers of antinuclear antibody (ANA) (1:160) and the CRP level was as high as 0.4 mg/dl. The results were positive for myeloperoxidase ANCA (MPO-ANCA) and negative for proteinase 3 ANCA (PR3-ANCA) (Table 1). Others results were not significant.

Computed tomography (CT) revealed high brightness of the soft tissue enhanced by the contrast agent in the left orbit and inferior retinal detachment OS (Fig. 3a–b). Magnetic resonance imaging (MRI) revealed enlargement of the supraciliary space and retinal detachment OS (Fig. 4).

This patient was diagnosed with AAV in consultation with a rheumatologist and categorized as GPA on the basis of the Watts classification.⁵

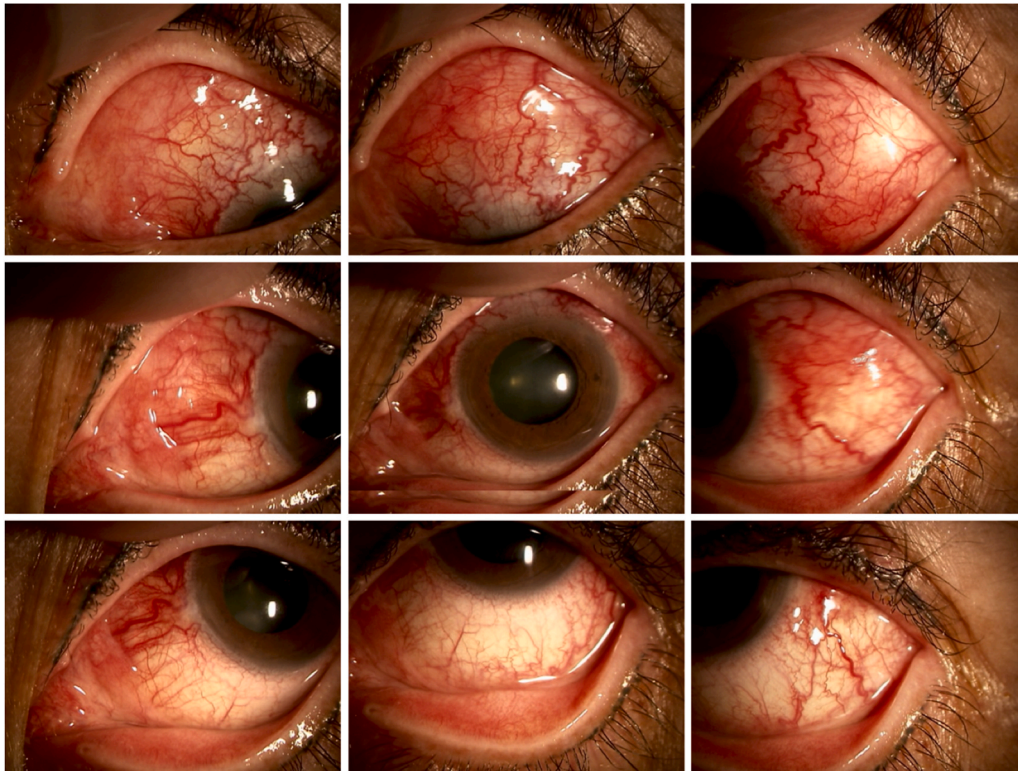


Fig. 1. Slit-lamp photographs of the left eye at the initial visit. Scleral injection and nodular elevated lesion in the upper sclera were observed.

betamethasone for two months. There was no improvement, and she was thus referred to our hospital. She had been diagnosed with otitis media of unknown etiology before a year, and her family history was unremarkable.

At her initial visit to our hospital, the best-corrected visual acuity (BCVA) was 0.9 in the right eye (OD) and 0.7 OS. Intraocular pressure was within the normal range in both eyes. Slit-lamp examination showed the injection of the sclera and conjunctiva, 1+ flare, 1+ cells of anterior chamber inflammation with fine keratic precipitates, and nodular-elevated lesion in the upper sclera OS (Fig. 1). Fundus

She was treated with topical betamethasone for three weeks after her initial visit. However, BCVA decreased to 0.15 and anterior chamber inflammation and vitreous haze OS exacerbated. OCT revealed the aggravation of SRD and RPE undulations OS. Therefore, she was treated with steroid pulse therapy, and her ocular findings improved (Fig. 5). Three weeks after the treatment, RTX was additionally administered at a dose of 500 mg/week for 4 weeks to maintain the remission. As the injection of the sclera and conjunctiva, vitreous haze, and SRD were resolved, PSL dose was gradually tapered. However, 3 months after the initial treatment when the PSL dose was tapered to 12.5 mg/day, SRD

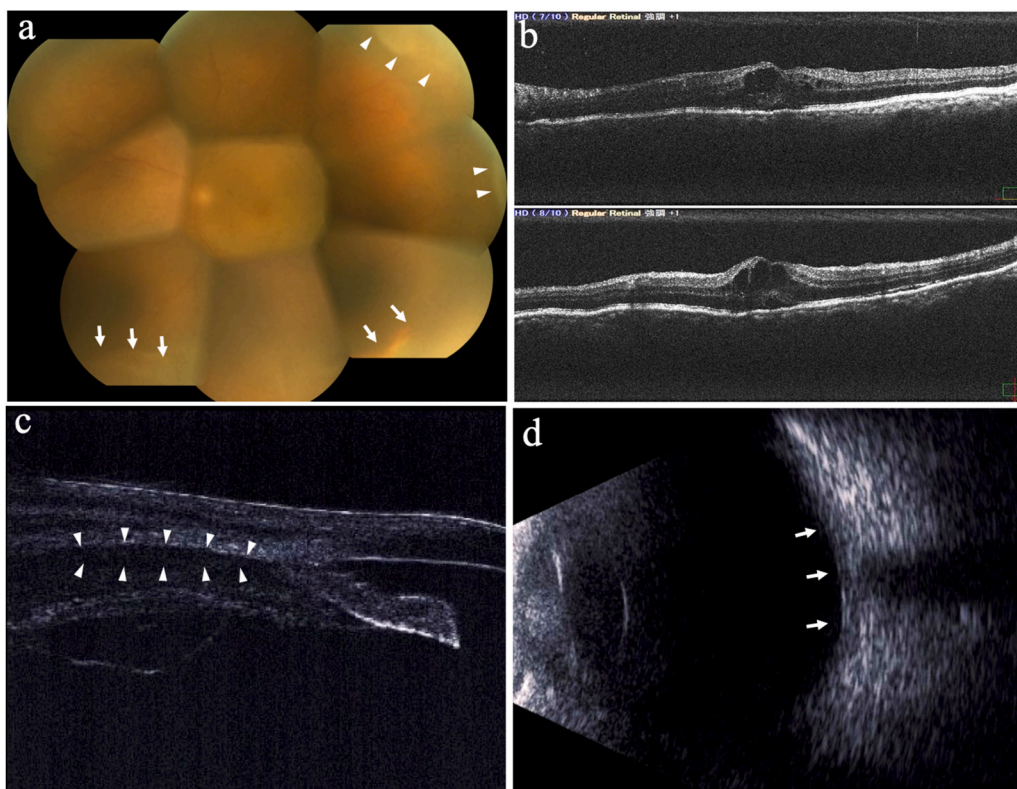


Fig. 2. Ocular findings of the left eye at the initial visit. **a.** Fundus examination: 1+ vitreous haze, yellowish elevated lesion (white arrowheads), and serous retinal detachment (white arrows) were observed. **b.** Optical coherence tomography: Cystoid macular edema and retinal pigment epithelium undulations were observed. **c.** Ultrasound biomicroscopy: Enlargement of the supraciliary space (white arrowheads) was observed. **d.** B-mode ultrasonography: Thickening and flattening of the posterior coats (white arrows) were observed.

Table 1
Blood test results at the initial visit.

Items	Result	Reference Range	Unit
WBC	7.2	3.3–8.6	$\times 10^3/\mu\text{L}$
PR3-ANCA	< 20	< 20	RU/ml
MPO-ANCA	124.2	< 20	RU/ml
RF	29.6	< 15	IU/ml
Antinuclear antibody	$\times 160$	Negative	
CRP	0.40	0.00–0.14	mg/dl
ESR 1 Hour	7		mm
ESR 2 Hour	15		mm

WBC, white blood cell; PR3-ANCA, proteinase 3 anti-neutrophil cytoplasmic antibodies; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibodies; RF, rheumatoid factor; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

was observed in the macula OS (Fig. 6). Therefore, PSL dose was increased to 30 mg/day along with the administration of azathioprine and subtenon injection of 40 mg of triamcinolone acetonide OS. In response to these additional treatments, SRD disappeared OS. Fourteen months after the initial treatment, BCVA increased to 0.5 OS. Although focal thinning and vasodilatation of the sclera persisted (Fig. 7a) and epiretinal membrane developed (Fig. 7b and c), the scleral injection, peripheral yellowish lesions, and SRD disappeared OS. No recurrence has been noted to date, and the patient is currently receiving 10 mg/day of PSL.

3. Discussion

Posterior scleritis accounts for 2–12% of all scleritis cases,⁶ and it often requires aggressive therapy⁷ because of vision-threatening complications including vitritis, macular edema, and exudative retinal detachment.⁸ Scleritis associated with systemic diseases, such as rheumatoid arthritis, recurrent chondritis, and AAV, is often refractory to treatment. The incidence of scleritis associated with such

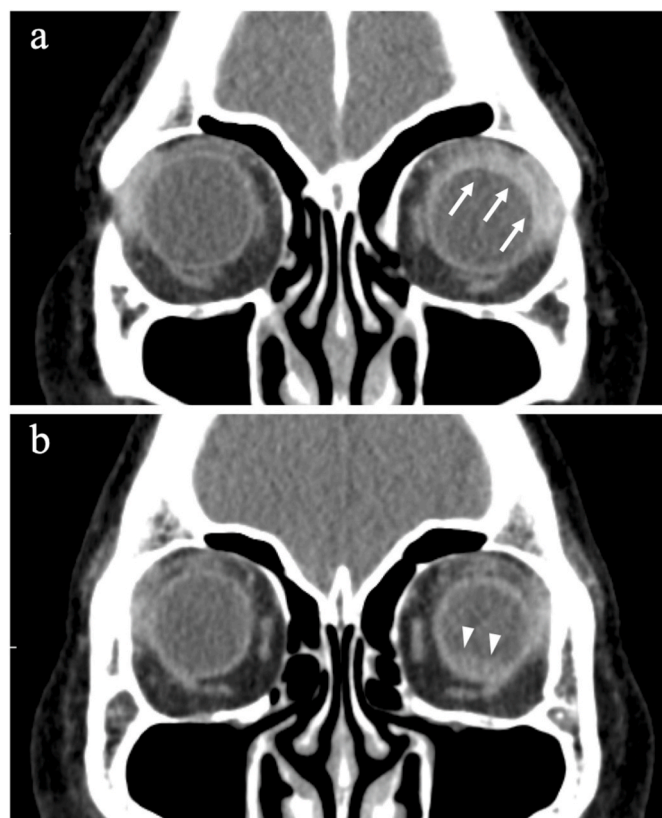


Fig. 3. Enhanced computed tomographic scans at the initial visit. **a.** High brightness of the soft tissue enhanced by the contrast agent in the left orbit (white arrows) was observed. **b.** Retinal detachment in the left eye (white arrowheads) was observed.

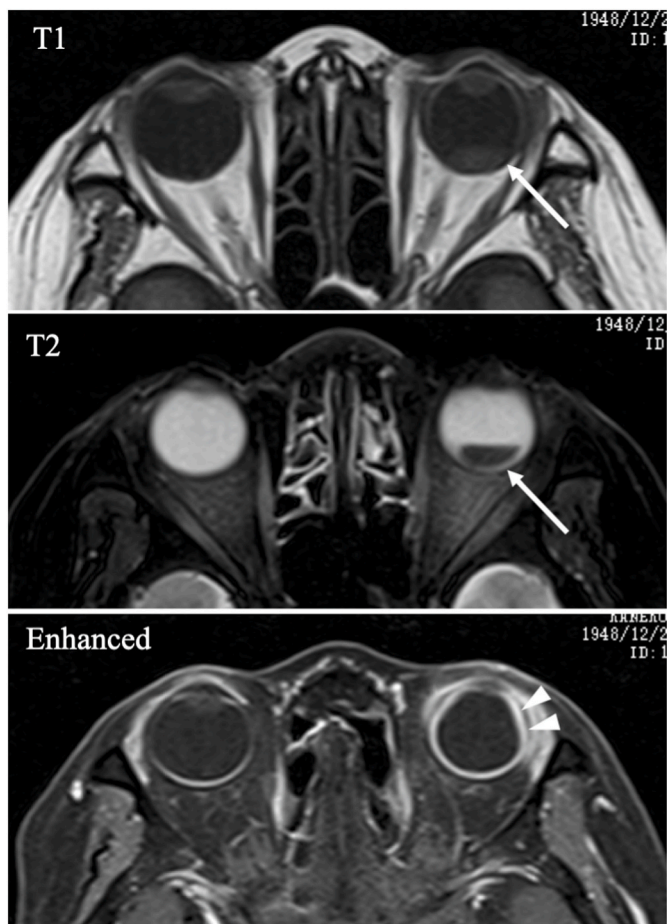


Fig. 4. Magnetic resonance image at the initial visit Retinal detachment in T1 and T2 (white arrows) can be observed. Enhanced magnetic resonance image showed enlargement of the supraciliary space (white arrow heads).

autoimmune diseases has been reported to be approximately 20–40%.^{7,9–11} In a previous study, 66% cases of scleritis associated with systemic diseases were refractory and only 6% were mild.¹² AAV can be categorized into three distinct forms, namely GPA (previously known as Wegener's granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome).³

In the present case, although MPO-ANCA was positive, the patient presented no history of allergic diseases, pulmonary and renal abnormalities, or eosinophilia. Moreover, she presented with symptoms such as eye pain, vision loss, otitis media, and episcleritis.

Watts and colleagues proposed an AAV classification algorithm.⁵ This stepwise algorithm incorporated both the American College of Rheumatology (ACR) criteria for EGPA and GPA and the Chapel Hill Consensus Conference (CHCC)³ definition of EGPA, GPA, and MPA. In this case, she was diagnosed with AAV in consultation with a rheumatologist. According to the Watts classification,⁵ her AAV was categorized into GPA based on the findings of otitis media, posterior scleritis, and MPO-ANCA positivity.

Glucocorticoids (GCs) and immunosuppressants were the gold standard for AAV treatment. Although a combination therapy of a GC and an immunosuppressant is effective in the majority of GPA patients, the 2-year relapse rate of GPA is approximately 18–40%.¹³ In Japan, the combination therapy of CYC and GCs has been a gold standard to achieve remission in AAV.¹⁴ However, the frequency of treatment-associated side effects, such as infectious complications, cardiovascular diseases, myelosuppression, malignancy, and infertility,

remains high.^{15–17}

RTX is a cytotoxic monoclonal antibody, which depletes B cells upon CD20 binding. The efficacy of RTX against non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis^{18,19} has been proven, and this drug is now anticipated to be approved for the treatment of other chronic inflammatory conditions^{15,16}. Moreover, RTX has been used to maintain remission in AAV since 2001.^{14,20} In 2011, the European League Against Rheumatism recommended RTX and GC combination therapy as the initial management of GPA. In Japan, RTX was approved for GPA treatment in 2013.¹⁴

In the present case of AAV associated with posterior scleritis, considering the risk of rapid vision loss, RTX and GC combination therapy was administered after consulting a collagen vascular disease specialist. The RTX treatment was considered effective, and the patient successfully maintained remission with a low dose of PSL, although she exhibited mild recurrence once.

The risk of impairment of visual function is much higher in posterior scleritis than anterior scleritis. Therefore, inducing and maintaining the remission is required more in posterior scleritis. Recillas-Gispert et al.²¹ and You et al.²² exhibited the case series of GPA patients with scleritis and revealed the effectiveness of RTX therapy, in which posterior scleritis was involved only one of 8 and one of 9 cases, respectively.

The present case is a rare case report of posterior scleritis associated with AAV providing the detail of clinical course and indicating the benefit of RTX in the management of posterior scleritis associated with AAV.

Based on the present case, RTX may contribute to the maintenance of remission. In addition, taking the various adverse effects of GCs into account, the trend of immune regulation is shifting toward minimizing their use and preferring RTX application.²³ Nonetheless, the detailed mechanism of action of RTX in AAV remains unknown and warrants further research.

4. Conclusion

We encountered a case of posterior scleritis associated with MPO-ANCA-positive AAV, in which inflammatory manifestations subsided following RTX and PSL combination therapy. RTX administration likely contributed to the maintenance of remission in this case.

Patient consent

Institutional review board approval was not required for this case report of a single patient. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. This report does not contain any personal information that could reveal the patient's identity.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Authors' contributions

Xinyu Weng: Data curation, Writing- Original draft preparation, Daiju Iwata: Conceptualization, Writing- Reviewing and Editing, Kenichi Namba: Conceptualization, Supervision.: Writing- Reviewing and Editing, Kayo Suzuki: Data curation, Kazuomi Mizuuchi: Data curation, Hiroyuki Nakamura: Supervision. Tatsuya Atsumi: Supervision. Susumu Ishida: Supervision.

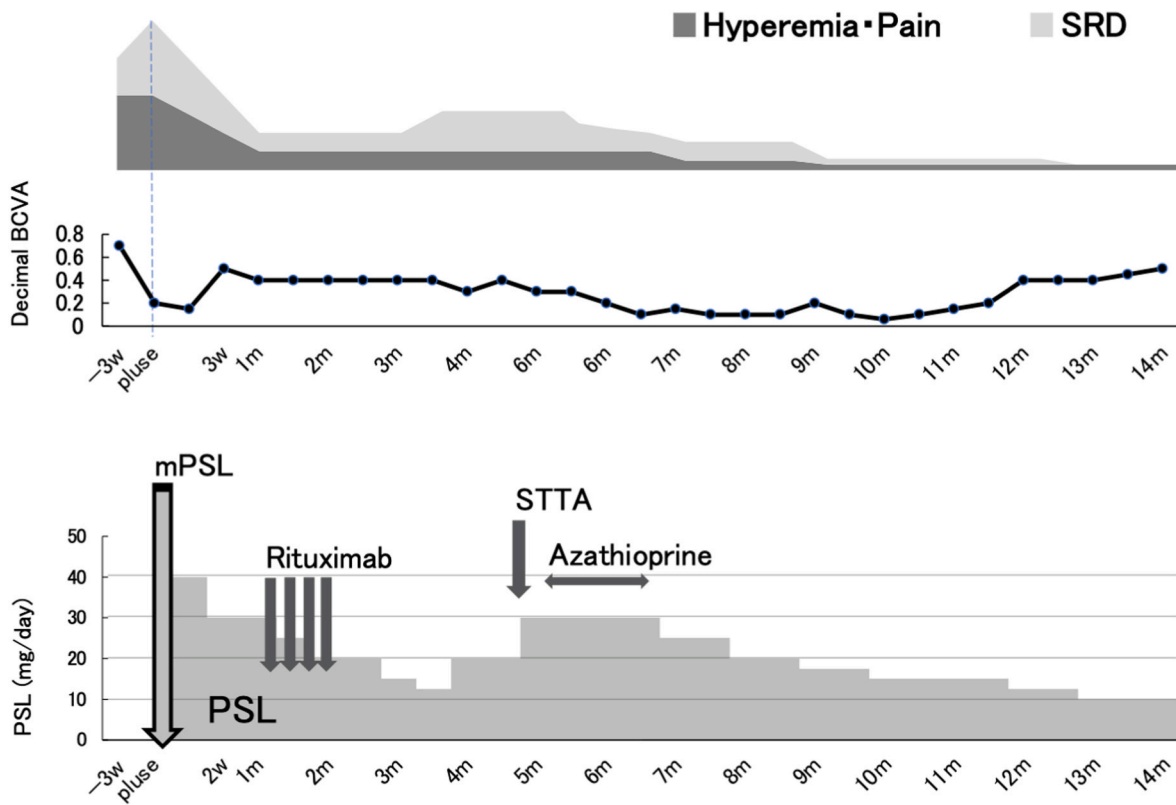


Fig. 5. Clinical course Three weeks after the initial visit, methylprednisolone (mPSL) pulse therapy (1g/day × 3) was initiated, followed by rituximab (0.5g/week × 4) administration. Three months after the treatment, when serous retinal detachment (SRD) appeared in the macular area, prednisolone (PSL) dose was increased along with the administration of oral azathioprine and subtenon triamcinolone acetonide (STTA) (40mg). In response to these treatments, SRD disappeared, and the remission has been maintained to date.

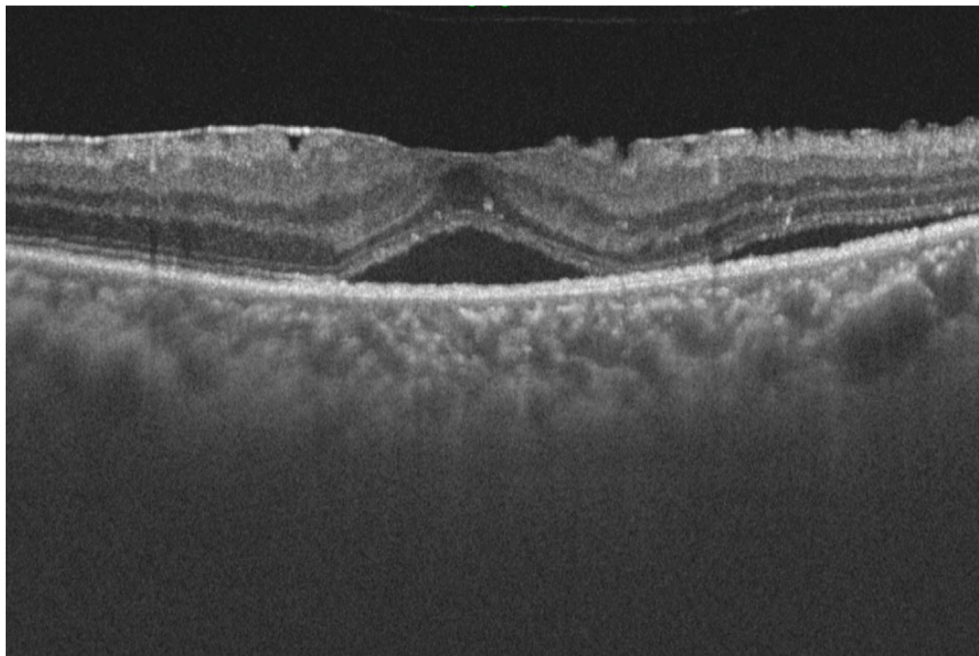


Fig. 6. Optical coherence tomographic scan of the left eye three months after the initial treatment Serous retinal detachment in the macula of the left eye was observed.

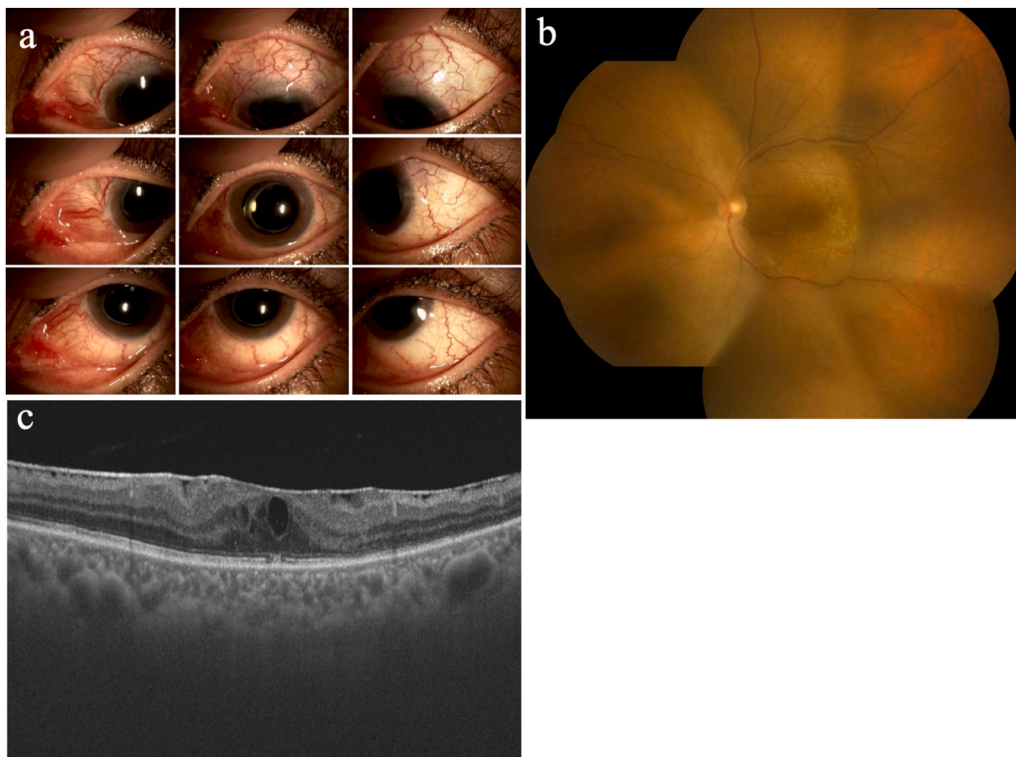


Fig. 7. Ocular findings of the left eye 14 months after the initial treatment. **a.** Slit-lamp photographs: Focal thinning of the sclera and remaining scleral vasodilatation were observed. **b.** Fundus examination: Elevated lesions and serous retinal detachment (SRD) disappeared. **c.** Optical coherence tomography: SRD in the macula disappeared, and the epiretinal membrane developed.

Declaration of competing interest

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