Medical and Research Publications
International Open Access

Case Report **Journal of MAR Ophthalmology (Volume 3 Issue 2)**

Rare Primary Ocular Presentation in PR3-ANCA Associated Vasculitis: Bilateral Acute Trabeculitis with Glaucoma

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Received Date: July 10, 2021

Published date: July 16, 2021

Abstract

Background: A case of ANCA Associated Vasculitis (AAV) presenting with primary bilateral acute trabeculitis and glaucoma.

Case presentation: A 39-year-old male with no significant past medical or family history, presented with bilateral persistent circumcorneal conjunctival congestion and increased intraocular pressure. Ocular examination revealed bilateral normal open-angle glaucoma. An initial diagnosis of herpetic trabeculitis was made, and the patient was treated accordingly. Brief improvement was followed by a relapse of symptoms.

Deep questioning revealed a history of migrating shoulder pain. Various laboratory investigations were requested, and PR3-ANCA levels were found to be elevated. After a tortuous treatment course, only systemic treatment with methotrexate and rituximab was beneficial.

***Conclusion**: Although other ocular symptoms can occur as a primary presentation in ANCA-associated vasculitis, bilateral acute trabeculitis with glaucoma has not been reported in the literature as a presenting feature. A thorough investigation is important in relapsing symptoms as it can indicate underlying systemic disease.*

***Keywords**: ANCA Associated Vasculitis; glaucoma; trabeculitis; granulomatosis with polyangiitis; eosinophilic granulomatosis with polyangiitis; microscopic polyangiitis.*

List of Abbreviations

PR3-ANCA: Proteinase 3 Anti-Neutrophil Cytoplasmic Antibody

IOP: Intra-Ocular Pressure

HSV-1: Herpes Simplex Virus- 1

HSV-2: Herpes Simplex Virus-2

AAV: ANCA Associated Vasculitis

MPO-ANCA: Myeloperoxidase- Anti Neutrophil Cytoplasmic Antibody

ACE: Angiotensin-Converting Enzyme

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

DCVAS: The Diagnostic and Classification Criteria for Primary Systemic Vasculitis

ACR/EULAR: The European League Against Rheumatism

GPA: Granulomatosis with polyangiitis

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are a collection of rare autoimmune diseases that cause small vessel vasculitis.**[**1**]** PR-3 ANCA titers are present in up to 95% of patients with Wegener granulomatosis.**[**2**]** Patients usually present with a triad of acute necrotizing granulomas in the upper respiratory tract, vasculitis of small to medium-sized vessels most prominently in the lungs, and renal disease often glomerulonephritis. Although about 16% of patients with AAV present with inflammatory ocular diseases,**[**3**]** rarely do patients present with bilateral acute trabeculitis

with glaucoma as the primary manifestation of disease. The most common ocular presentations include scleritis, uveitis, and other inflammatory conditions. **[**4**]** Their ocular presentations can range from conjunctivitis and episcleritis to keratitis, scleritis, uveitis, and retinal vasculitis.**[**5**]** Digging into the patient's past medical history and ordering necessary investigations is vital when a patient presents with persistent ocular symptoms that do not resolve with treatment. As with our patient, the ocular symptoms in AAV rarely respond to topical steroids and require systemic immunosuppressive therapy.**[**5**]** We think that this is the first case in the literature in where bilateral acute trabeculitis with glaucoma is the first presentation in a patient with AAV.

Case Report

Informed and written consent was obtained from the patient. A 39-year-old male presented to ophthalmology with bilateral conjunctivitis irresponsive to Prednisolone eye drops, and he was found to have raised intraocular pressure (IOP). The ophthalmologist discontinued the Prednisolone eye drops thinking that it was a steroid response. Upon follow-up, bilateral ocular congestion was worse with a rising IOP, which demanded a referral to another ophthalmologist for a second opinion.

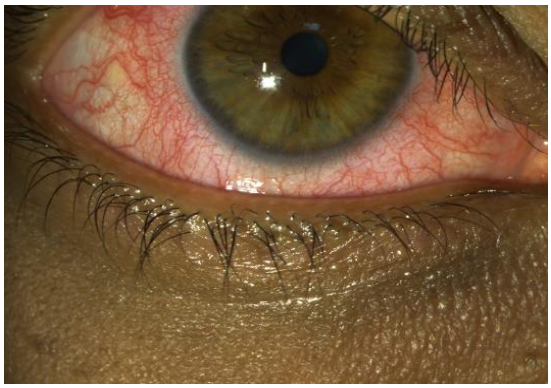

Figure 1: Conjunctival injection in a 39-year-old male with PR3- ANCA associated vasculitis

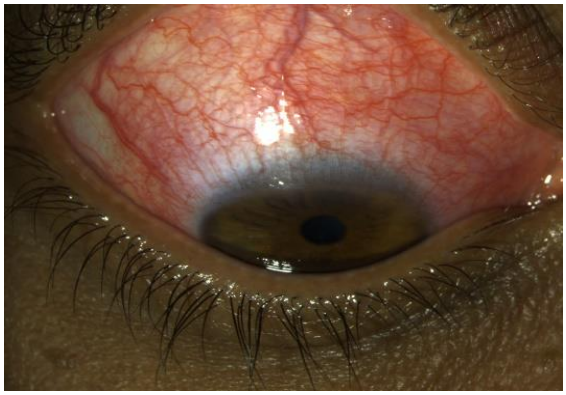

Figure 2: Conjunctival injection

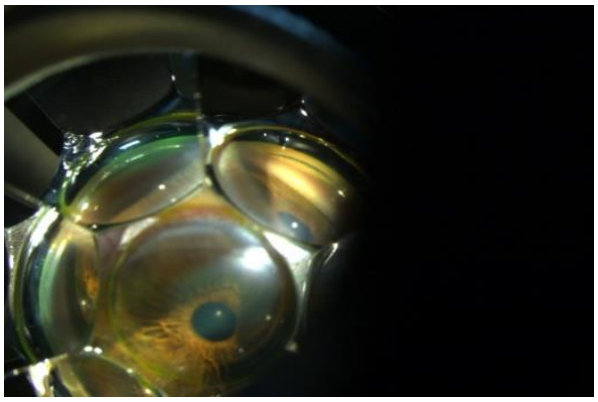

Figure 3: Right eye Gonioscopy with open angle glaucoma

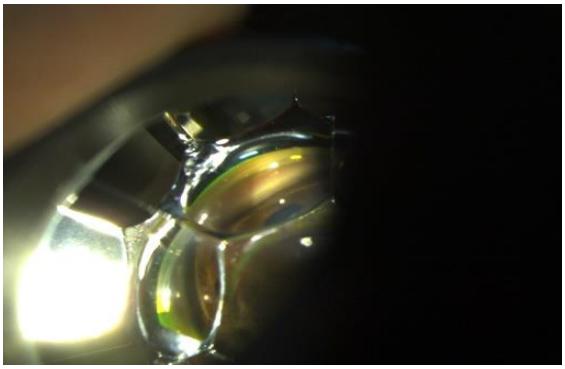

Figure 4: Left eye Gonioscopy with open angle glaucoma

On examination, bilateral marked bulbar conjunctival and circum-ciliary congestion was noted. On very careful examination, there was a mild flare in both eyes and occasional cells were seen floating in the anterior chamber, there were no keratic precipitates. His IOP was 36 mmHg in the right eye and 30 mmHg in the left eye with applanation tonometry. Gonioscopy showed bilateral normal angle, which was open grade 4, the scleral spur was visible (**Image 3,4**). Cornea, pupil size, shape and reactions were normal in both eyes. The crystalline lens was clear and there was no abnormality in the ocular adnexa, no pre-auricular lymphadenopathy and corneal sensations were normal. On dilated fundus examination, there was no evidence of pars planitis, vasculitis, chorioretinitis, or any posterior segment past or present inflammation. Scanning laser ophthalmoscopy of optic nerve and macular Optical Coherence Tomography (OCT) were within normal limits in both eyes. Visual fields 24-2 were within normal limits.

There were no associated signs, symptoms, or systemic medical complaints. Past medical history, family history, surgical, and social history were all insignificant. Initially, a diagnosis of bilateral acute trabeculitis with glaucoma, possibly due to herpetic infection was made.

Investigations

Laboratory tests including full blood count, C-Reactive protein, and Herpes simplex virus (HSV) 1 and 2 IgG and IgM were sent to confirm the diagnosis of herpetic infection. The patient had mild eosinophilia (10%). A few days earlier, the patient presented to his rheumatologist complaining of left shoulder pain and laboratory tests were ordered including rheumatoid factor, Anti-cyclic citrullinated peptide, and Anti-Nuclear Antibody, all of which were normal. IgG and IgM for both HSV-1 and HSV-2 were reported to be within normal limits. Upon follow-up with the ophthalmologist, further investigations were requested including PR3-ANCA, MPO-ANCA, and angiotensin-converting enzyme (ACE). His PR3-ANCA levels were high at 779.4 AU/ml (the normal range is <12).

Differential diagnosis

A final diagnosis of AAV was made. Arrival at this final diagnosis would not have been possible without repetitive and deep questioning about past medical history in the follow-up sessions. The patient gave a history of left shoulder pain for which he was treated with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) by another physician. Few days after stopping the NSAIDs, the patient developed similar pain in the right shoulder which was alleviated by taking NSAIDs again for few days. In the light of this history, the ophthalmologist reviewed again the investigations ordered by the rheumatologist. The missing tests of c-ANCA and ACE were ordered and a diagnosis of PR3-ANCA associated vasculitis was made. Past medical history was crucial to arrive at the final diagnosis, especially because the patient's family history and past medical history were insignificant. The patient did not complain of any other symptoms upon review of systems. Detailed questioning about past medical history was required to arrive at the final diagnosis.

Although other primary ocular presentations do occur in AAV, there were no reports of bilateral ocular trabeculitis with glaucoma as an initial presentation. The patient had no uveitis, scleritis, or peripheral ulcerative keratitis which are some of the common ocular presentations in AAV.**[**4**]** It was thought initially that the rising IOP was a response to topical steroids. But stopping the topical steroids had no improvement, which made the ophthalmologist consider a different diagnosis. In fact, after increasing the doses of topical steroids and adding systemic steroids the IOP was finally controlled. The typical presentation of acute trabeculitis and glaucoma pointed towards an infectious etiology such as a

herpetic infection. However, negative HSV laboratory results, responsiveness to topical medication, and the bilateral nature of the disease hinted at a systematic pathology.

Treatment

Before the final diagnosis, the patient was treated with Prednisolone 1% eye drops twice daily for 15 days. There was a brief period of improvement followed by relapse and raised IOP. For a suspected Herpetic infection, the patient has treated with Famciclovir 250 mg thrice daily for 7 days, Prednisolone 1% eye drops 2 per hour in both eyes, dorzolamide hydrochloride-timolol maleate eye drops twice daily in both eyes, Brimonidine eye drops thrice daily in both eyes, Acetazolamide tablet 250 mg 4 times daily and Slow-K (slow-release potassium) 600 mg 1 tablet daily. Upon follow-up, considerable improvement was noted. The patient was asked to stop Acetazolamide and potassium tablets and to reduce the Prednisolone 1% eye drops frequency to 3 hourly. After four days, with relapsing symptoms, he has prescribed Etoricoxib tablets 60 mg twice daily for 2 days followed by 60 mg once daily for 5 days. He has also given Prednisolone 1% eye drops 2 hourly, Nepafenac 4 times daily, continue dorzolamide hydrochloride-timolol maleate and Brimonidine eye drops.

Following the final diagnosis of AAV, the patient was also treated by his rheumatologist with Methotrexate injection 15 mg weekly, Rituximab intravenous injection, Prednisolone 40 mg per day, and Folic acid 5 mg weekly. The IOP was still high at 36 mmHg in right and 38 mmHg in the left eye. Thinking that the rising IOP is a response to topical steroids, Prednisolone was replaced with Loteprednol, and he was given Bimatoprost eye drops at bedtime with Acetazolamide 250 mg thrice daily. After a week, the patient was advised to reduce the Loteprednol and stop in another 6 days. IOP settled to normal in both eyes.

By that time, the patient was on Loteprednol, dorzolamide hydrochloride-timolol maleate, and Brimonidine eye drops, with no topical steroids for the last 10 days. The patient was on Prednisolone tablet 20 mg once daily with systemic treatment from the rheumatologist. The patient was advised to stop Acetazolamide. Topical treatment was slowly withdrawn according to the IOP and findings. As the patient progressed with the systemic treatment, the patient's symptoms resolved, Brimonidine and Nepafenac were discontinued.

Outcome and follow-up

The patient was treated and followed up by his ophthalmologist from the time of his presentation on 09/02/2019 till 07/12/2019. By March 2019, the patient was already on methotrexate injection 15 mg weekly and has received the first infusion of Rituximab. On 11/05/2019, the patient was asymptomatic with normal IOP. The patient was given Loteprednol eye drops for his intermittent conjunctivitis.

On 13/07/2019, IOP was 14 mmHg in right and 15 mmHg in the left eye. The patient was on prednisolone 5 mg and 2.5 mg every other day along with methotrexate weekly. Four cycles of Rituximab were done. On 14/09/2019, his PR3-ANCA levels were noted to be increased to 366.3 AU/ml. On 05/10/2019, IOP was 13 mmHg in both eyes. From this visit and further, he was receiving systemic immunosuppression only.

On 23/11/2019, C-ANCA levels decreased to 46.5 AU/ml. He was reviewed on 07/12/2019, and no ocular symptoms were found except mild dry eyes due to excess screen time. The patient was advised to continue the systemic treatment and ocular lubricants in the form of Hypromellose eye drops.

In April 2020, the patient developed microscopic hematuria and was asked to stop Prednisone. He was given hydroxychloroquine twice daily and Mycophenolic acid 1gm twice daily.

Patient's Perspective

"After completing almost 30 tests, I was found to be ANCA positive Vasculitis which required treatment in coordination with a rheumatologist. With all efforts and distinctive medication including a combination of various drugs (as I understand I was not responding to traditional medication), this was controlled fairly in good time. I am continuing with treatment; it is now controlled with no significant inflammation and pressure increase in the eyes. I would like to thank my doctor for liaising with other specialist doctors."

Discussion

AAV is characterized by small-sized to medium-sized vasculitis and includes granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, and renal-limited ANCA-associated vasculitis. **[**6**]** Predisposing factors include genetic factors, environmental factors, and microbial infections.**[**6**]** Neutrophils are activated by reacting with ANCA in the blood, then they accumulate in the walls of the vessels.**[**6**]** Neutrophils are stimulated to produce pro-inflammatory cytokines and reactive oxygen radicals causing endothelial and tissue injury.**[**2**]** In PR3-ANCA positive vasculitis, granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affect small vessels, including glomerular vessels (as in our patient, suggested by microscopic hematuria).**[**2**]** As for the diagnostic guidelines, The Diagnostic and Classification Criteria for Primary Systemic Vasculitis (DCVAS) and collaborators proposed the ACR/EULAR (The European League Against Rheumatism) 2017 provisional classification criteria for Granulomatosis with polyangiitis (GPA) as shown in **table 1**. **[**7,8**]**

Table 1: The ACR/EULAR 2017 Provisional Classification Criteria for GPA

Items	Score
Score for the ACR/EULAR 2017 provisional classification criteria for GPA	Sum ≥ 5
Bloody nasal discharge, ulcers, crusting or sinonasal congestion	3
Nasal polyps	-4
Hearing loss or reduction	1
Cartilaginous involvement	2
Red or painful eyes	1
C-ANCA or PR3-ANCA	5
Eosinophil count ≥1 (×109/L)	-3
Nodule, mass or cavitation on chest imaging	2
Granuloma on biopsy	3

Conclusion

Our patient had high PR3-ANCA titers which immediately classifies him to have GPA. However, the point of interest in the study is that the first presentation was bilateral trabeculitis with glaucoma. Upon literature search, only one case report was found with a similar presentation by Mete el al.**[**9**]** While their patient had shortness of breath, mild fever, and blurry vision at the time of presentation, our patient seemed healthy with no other complaints. It is a very rare presentation, and the association of this clinical entity with 1Wegener's granulomatosis remains unknown.**[**9**]** As soon as our patient was found to be PR3-ANCA positive, he was referred to rheumatology for treatment according to the guidelines.

Take-home messages

- When there is no other explanation for unresponsive symptoms, systemic diseases should be considered.
- Past medical history is crucial, even if the patient provides a negative past medical history in previous visits, the physician should ask detailed questions in the following visits.

- Although ocular presentation might be involved in AAV, atypical pathological presentations can occur.
- A multidisciplinary approach is vital to ensure the patient's wellbeing.

References

[1] Yates, M. and Watts, R. "ANCA-associated vasculitis". Clin Med 2017; 17(1), pp.60-64. DOI: 10.7861/clinmedicine.17-1-60

[2] Kumar, V. and Robbins, S. "Robbins Basic Pathology, 10th ed".. Philadelphia, USA: Saunders/Elsevier, 2007

[3] Ungprasert P, Crowson C, Cartin-Ceba R, Garrity J, Smith W, Specks U et al. "Clinical characteristics of inflammatory ocular disease in anti-neutrophil cytoplasmic antibody associated vasculitis: a retrospective cohort study". Rheumatology 2017; 56:1763-1770. DOI: 10.1093/rheumatology/kex261

[4] Watkins A, Kempen J, Choi D, Liesegang T, Pujari S, Newcomb C et al. "Ocular disease in patients with ANCA-positive vasculitis". J Ocul Biol Dis Infor 2009; 3:12-19. DOI: 10.1007/s12177-009-9044-4

[5] Pakrou N, Selva D, Leibovitch I. "Wegener's Granulomatosis: Ophthalmic Manifestations and Management". Semin Arthritis Rheum 2006; 35 :284-292. DOI: 10.1016/j.semarthrit.2005.12.003

[6] Al-Hussain T, Hussein M, Conca W, Al Mana H, Akhtar M. "Pathophysiology of ANCA-associated Vasculitis". Adv Anat Pathol 2017; 24 :226-234. DOI: 10.1097/PAP.0000000000000154

[7] Choi C, Park Y, Lee S. "Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in Korea: A Narrative Review". Yonsei Med J 2019; 60:10-21. DOI: 10.3349/ymj.2019.60.1.10.

[8] Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. "Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides". Arthritis Rheum 1997; 40:371-80. DOI: 10.1002/art.1780400222

[9] Mete A, Kimyon S, Saygili O, Pamukcu C, Güngör K. "Bilateral acute angle-closure glaucoma as a first presentation of granulomatosis with polyangiitis (Wegener's)". Arq Bras Oftalmol 2016; 79(5): 336-338. DOI: 10.5935/0004-2749.20160096.