Scleritis as the harbinger of Granulomatosis with polyangiitis

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A B S T R A C T

Introduction: Ocular and orbital involvement in Granulomatosis with polyangiitis (GPA) is common. GPA can lead to life and sight threatening complications due to necrosis and tissue melting.

Cases: We report four cases presenting with ocular pain and redness for varied durations. One had diminution of vision. All of them had deep sectoral/diffuse congestion with one having scleral thinning. All were diagnosed with anterior necrotizing/non-necrotizing scleritis. One had associated penetrating ulcerative keratitis. Topical steroids and systemic non-steroidal anti-inflammatory drugs were started in all cases and rheumatology consultation was taken. Pertinent investigations were sent, and GPA was diagnosed. Intravenous immunosuppressive regimens and oral steroid were started and significant improvements were seen, preventing untoward complications.

Conclusion: Scleritis could be manifesting feature of GPA so cautious history taking and evaluation is important. Management often requires multidisciplinary care and ocular features could be the reference guidelines to adjust dose of systemic medications of GPA.

1. Introduction

Granulomatosis with polyangiitis (GPA), is a small vessel vasculitis clubbed under anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV), with symptoms and signs of small vessel vasculitis affecting multiple organs leading to necrotizing granulomatous inflammation [1]. GPA is a potentially lethal, multisystemic vasculitis disorder, classically characterized by a triad of necrotizing granuloma of the respiratory system, systemic vasculitis, and necrotizing glomerulonephritis [2]. Ocular and orbital involvement in patients with GPA is not rare, occurring in as high as 30–50% of patients with GPA and may sometimes be the only presenting feature [3–6].

Ocular GPA can either spread from contiguous structures such as the sinuses, or as part of systemic vasculitis. Involvement of the nasolacrimal system and orbital tissues also can occur. The ocular and orbital manifestation can be divided into vasculitis manifestations like episcleritis, scleritis, retinal vasculitis and granulomatous manifestations like orbital pseudotumor [7]. Undiagnosed and untreated cases of ocular GPA have been associated with a high rate of ocular morbidity and blindness. Hence, high index of clinical suspicion is needed for not to miss any case of GPA.

We herein report four cases of GPA with scleritis, who presented to out-patients services of B. P. Koirala Lions Centre for Ophthalmic Studies, where the scleritis was the presenting features of GPA. The collaborative management from the ophthalmologist and rheumatologist successfully saved the scleral melting and other life-threatening complications. Though multiple reports on GPA associated scleritis exist in literature, this is the first report of its kind from Nepal.

This case series has been reported in line with the PROCESS Guide line [8].

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2. Case 1

A 38-year-female presented with recurrent history of left eye nodular episcleritis for 6 months. It was associated with ocular pain and redness with progressive worsening. She also complained of recurrent bouts of epistaxis in the past.

On examination, her best corrected visual acuity (BCVA) was 6/6, N6 & 6/9, N6. There was deep non-blanching sectoral congestion in the

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temporal sclera with peripheral ulcerative keratitis and corneal thinning adjacent to the inflamed sclera with focal necrosis Fig. 1A). The corneal thinning was documented in corneal topography as well. (Fig. 1B). The rest ocular findings were unremarkable. Necrotizing sclero-keratitis was suspected and urgent rheumatology consultation was sought. On further evaluation she tested strongly positive for C-ANCA on immunofluorescence and anti-proteinase-3 (PR3) antibody. She was thus, diagnosed as GPA and started on prednisolone (1 mg/kg) and intravenous injection cyclophosphamide (15 mg/kg) with topical steroids and tear substitutes. The corneal melting halted, thinning was self-sealed via conjunctivilization and scleritis completely resolved (Fig. 1 C). There has been no recurrence in the past 6 months follow-up. She is currently on rituximab maintenance.

3. Case 2

A 41-year-female presented with left ocular pain and redness on & off since a month. It was not associated with diminution of vision but 2 similar episodes had occurred in the past which resolved on its own. She was hypertensive under medication and gives history of completion of anti-tubercular treatment for 6 month 1.5 years back for pulmonary tuberculosis. She was on oral methotrexate 7.5 mg/week for rheumatoid arthritis.

On examination, her BCVA was 6/9, N6 bilaterally. There was deep sectoral scleral congestion with tenderness on the supero-temporal quadrant of left eye (Fig. 2) with normal anterior chamber and fundus.

Fig. 2. Diffuse scleral congestion in the left eye.
findings. A diagnosis of left eye non necrotizing anterior scleritis was made. She was initially suspected of scleral tuberculosis but the present investigations were negative for tuberculosis. But she had history of nasal crusts and tachypnoea and on investigation, she had sinusitis on imaging, sensorineural hearing loss and tested positive for P-ANCA and the anti MPO on ELISA was negative. Her methotrexate dose was escalated to 15 mg/week and oral corticosteroid (1 mg/kg) was added on tapering dose. The scleritis came under control and the patient is doing well over the past 6 months.

4. Case 3

A 52-year-old female presented with excruciating ocular pain and redness in left eye for 15 days with normal vision. There was no significant systemic history, except for being treated as case of rheumatoid arthritis with oral sulfasalazine 500mg/daily.

On examination, her BCVA was 6/6, N6 in both eyes. There was diffuse scleral congestion in left eye with a nodule on the superior-temporal aspect (Fig. 3). Anterior and posterior segment evaluation was within normal limits. A diagnosis of left eye anterior non-necrotizing nodular scleritis was made and was investigated for tuberculosis, which came to be negative. Despite treatment with topical & systemic steroids, her ocular pain aggravated and scleral nodule did not resolve and instead developed ocular hypertension. Rheumatology consultation was sought, on further evaluation she was diagnosed as GPA (C-ANCA positive and anti-PR3 positive). She was immediately started on oral prednisolone (1 mg/kg) and injection cyclophosphamide (15 mg/kg) along with anti-glucoma agent. She showed dramatic improvement after treatment with no recurrences in the past 6 months. She completed her 6 cycles of cyclophosphamide at monthly interval and is currently on rituximab maintenance.

5. Case 4

A 71-year-old female with hypertension presented with dull aching pain in right eye for 2 weeks. She had past history of left eye superior-temporal branch retinal vein occlusion (STBRVO) due to hypertension and was treated with sectoral lasers.

The right eye pain was associated with redness, and decreased vision. On ocular evaluation, she had 6/18, N10 in right eye and 6/6, N10 in left eye and had bilateral pseudophakia. There was a nodular scleral mass in the superior-temporal quadrant (Fig. 4 A) with surrounding scleral thinning associated with anterior chamber reactions (cells 2+, flare 1+). Examination of the right eye revealed inferior exudative retinal detachment (Fig. 4 B) with peripapillary edema. The ghost vessels and laser marks in left eye superior-temporal quadrant were documented (Fig. 4 C). She was diagnosed as the case of right eye recurrent non-necrotizing anterior and posterior scleritis with left eye old STBRVO status post sectoral laser.

On repeated query, she gave a history of decreased hearing in the right side with nasal intonation of her voice for the last 2 months. Rheumatological consultation was sought and on evaluation she had pan sinusitis, bilateral sensorineural hearing loss. Her C-ANCA was positive on immunofluorescence analysis, however, anti PR3 antibodies were negative. She was diagnosed as GPA, and was started on oral methotrexate 15 mg/week, oral corticosteroids (1 mg/kg/day). Within a month, her scleral nodule resolved, retinal detachment was absent and the change in voice improved (see Table 1).

6. Discussion

GPA is rare with a global annual incidence estimate of 6.7 cases per million [10]. GPA is an uncommon diagnosis in Nepal; however case reports from the region suggest that GPA is being more frequently recognized [11,12]. The eye symptoms are very variable, and in up to 27% they are the first sign of undiagnosed GPA [13]. Herein, we report four vivid cases like nodular, diffuse, necrotizing, non-necrotizing anterior scleritis and posterior scleritis presenting as the first manifestations of GPA.

Ocular manifestations of GPA may occur as contiguous granulomatous sinusitis or as a result of focal vasculitis. Contiguous granulomatous sinus disease may manifest as nasolacrimal duct obstruction, proptosis and involvement of the ocular muscles or the optic nerve. Focal vasculitis manifests as conjunctivitis, episcleritis, scleritis, conneoscleral ulceration, uveitis and vasculitis of retina [7]. Similar to other systemic immune mediated disease such as relapsing polychondritis necrotizing scleritis leading to perforation of sclera and loss of sight are the most dreaded ocular complications [14,15].

Scleritis is reported to be the third most common oculare manifestation of GPA [6,16,17]. Scleritis may be nodular, diffuse or necrotizing. Scleritis in patients with GPA are often bilateral, diffuse and stubbornly recurrent [18]. GPA is rarely associated with posterior scleritis. GPA associated scleritis tend to be more severe than those associated with other etiologies [19]. The necrotizing scleritis can herald a systemic vasculitis in GPA. Necrotizing scleritis is potentially vision threatening if not treated adequately or promptly. It is often associated with ocular complications secondary to occlusive vasculitis [16,19,20]. Thus the inflamed area of the sclera in necrotizing scleritis becomes avascular and ischemic that can lead to globe perforations requiring enucleation.

Considering the presence of an ocular involvement in the absence of systemic manifestations as a quiet disease is a common misconception. Ocular manifestation, particularly necrotizing scleritis, points towards significant morbidity and mortality unless prompt and appropriate evaluation and treatment is introduced [21].

With the exception of certain instances of anterior segment inflammation, the ocular involvement does not respond to topical agents, but instead to systemic anti-inflammatory and immunosuppressive therapy and it held true among our cases too [22]. Severe untreated GPA carries a high mortality rate of greater than 90%. Historically these patients had a mean survival time of 5 months from diagnosis and was virtually considered fatal [23]. Since the inclusion of newer armamentarium like cyclophosphamide and CD20 antibody agents such as rituximab for remission induction, the survival rates have improved in the last two decades. Immunosuppressive therapy has led to significant improvement of GPA prognosis over the past few years and biological treatment is now prominent in GPA treatment procedures. The current 5 years survival rates trends between 74 and 79% [24-27], and the mortality is still 2.5 times higher than the general population. Apart from mortality, GPA is notorious for its frequent relapses but B cell depleting agents like rituximab has brought down the relapse rate significantly [28].
The visual prognosis is generally good when treated appropriately and promptly with systemic immunotherapy and depends on severity and chronicity of the eye disease. With multidisciplinary care, we were able to save vision of all of the four patients. In long standing case or those that are inadequately treated or those with delay in diagnosis, vision loss is a potential event that may be seen in 8–37% of patients [5, 6]. Though there is a remarkable association between scleritis and disease activity, timely diagnosis and the effective treatment prevented the vision loss.

Multispecialty team work is necessary for the early diagnosis and treatment of this life and vision threatening disease. Good collaboration of the ophthalmologist with rheumatologist plays a cardinal role in the diagnostics, monitoring of the diseases course, or adverse effects of the medication and preventing from the lethal threat to life and sight in cases of GPA.

### 7. Conclusion

Scleritis in patients with GPA is a known manifestation and may be the only presenting feature of this potentially fatal, organ and sight-threatening disease. However, the rarity of this disease and its protean clinical presentation may lead to delayed diagnosis or misdiagnosis. A high index of suspicion along with multidisciplinary cohesion is required for diagnosis and management. Further robust studies in the region may help implicate the importance of early detection and management with favorable outcomes.

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**Fig. 4.** Nodular scleral mass in the superior-temporal quadrant of the left eye with surrounding scleral thinning (A) and ultrasound showing inferior exudative retinal detachment. The fundus photo of left eye with ghost vessels present in supero-temporal quadrant (C).

**Table 1.** Clinical summary of the cases.

| Particulars       | Case 1                          | Case 2                          | Case 3                        | Case 4                        |
|-------------------|---------------------------------|---------------------------------|-------------------------------|-------------------------------|
| Demographics      | 38 years, Female                | 41 years, Female                | 52 years, Female              | 71 years, Female              |
| Past history      | None                            | RA on methotrexate              | RA on sulfasalazine           | LE STBRVO                     |
| Laterality        | LE                              | LE                              | LE                            | RE                            |
| VA (affected)     | 6/9, N6                         | 6/9, N6                         | 6/9, N6                       | 6/18, N10                     |
| Findings          | Deep sectoral congestion, PUK   | Deep sectoral congestion, tenderness | Diffuse scleral congestion | Nodular scleral mass         |
| Diagnosis         | Sclero Keratitis                | Anterior scleritis              | Anterior scleritis            | Anterior and posterior scleritis |
| Investigations    | c-ANCA +                        | p-ANCA +                        | c-ANCA +                      | c-ANCA +                      |
|                   | anti-PR3 +                      | anti-MPO -                      | anti PR3 +                    | anti PR3 -                    |
| Treatments        | Corticosteroid                  | Methotrexate                    | Corticosteroid                | Methotrexate                  |
|                   | Cyclophosphamide                | Corticosteroid                  | Cyclophosphamide              | Corticosteroid                |
|                   | Rituximab                       |                                 |                               |                               |
Ethical approval

Ethical approval from the Institutional Review Committee of Institute has been obtained to proceed with the current publication.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

‘This case series has been reported in line with the PROCESS Guideline’.

Author contribution

Ranju Kharel Sitaula and Saket Jha made substantial contributions to management of the case, conception and design of the manuscript, acquisition of data, analysis and interpretation of data; they have been involved in drafting the manuscript and revising it critically for important intellectual content. Himang Man Singh Maskey and Santosh Chaudhary made substantial contributions to interpretation of data and they have been involved in drafting the manuscript and revising it critically for important intellectual content.

Registration of research studies

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Declaration of competing interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104908.

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