Antineutrophil cytoplasmic antibody-positive scleritis: Clinical profile of patients from a tuberculosis-endemic region

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Purpose: To report the clinical profile of a series of antineutrophil cytoplasmic antibody (ANCA)-associated scleritis in Indian population. **Methods:** We conducted a retrospective review of medical records of 33 eyes of 26 consecutive patients with scleritis, who tested positive for either antibody to proteinase 3 [anti-PR3/cytoplasmic antineutrophil cytoplasmic antibody (cANCA)] or myeloperoxidase [anti-MPO/perinuclear anti-neutrophil cytoplasmic antibody (pANCA)] between 2006 and 2015. **Results:** The mean age at presentation was 54.1 (11.1) years and 61.5% of the patients were female. Underlying systemic disorder was found in 46.2% of patients and includes granulomatosis with polyangitis (30.8%) and tuberculosis (15.4%). Necrotizing scleritis (48.5%) was the most common scleritis observed, followed by diffuse anterior scleritis (42.4%). Positive cANCA was found in 65.4% of patients and 34.6% was found positive for pANCA. Four of the six patients with positive Mantoux test were started on anti-tuberculosis treatment (ATT) by pulmonologist. Cyclophosphamide was the most common immunosuppressive and 11.5% of the patients required combination of two immunosuppressives. Seventeen eyes developed cataract and four eyes required patch graft. Female gender was more frequently associated with pANCA-associated scleritis than cANCA ($P = 0.037$). Incidence of necrotizing scleritis was higher in patients with positive cANCA, but this difference was not statistically significant ($P = 0.806$). cANCA-positive patients had statistically significant higher association with systemic rheumatic diseases ($P = 0.021$). **Conclusion:** Necrotizing scleritis is the most common subtype of scleritis in ANCA-positive individuals and even in the absence of systemic involvement. All patients with ANCA positivity should be thoroughly screened to rule out any evidence of tuberculosis, especially in tuberculosis-endemic region before planning aggressive immunomodulatory therapy.

Key words: Antineutrophil cytoplasmic antibody, granulomatosis polyangitis, necrotizing scleritis, scleritis, tuberculosis

Scleritis is a severe painful inflammatory condition characterized by edema and cellular infiltration of the sclera and episclera. If not treated properly and effectively on time, scleritis can cause a significant threat to vision. Scleritis can be a presenting manifestation of a life-threatening systemic autoimmune disease such as rheumatoid arthritis (RA), granulomatosis with polyangitis (Wegener granulomatosis) (GPA), relapsing polychondritis, or microscopic polyarteritis.[1] RA is the most common connective tissue disease and GPA is the most common cause of systemic vasculitis associated with scleritis.[1] Scleritis due to these systemic autoimmune conditions usually runs a more aggressive course and sometimes may be the initial presentation of underlying systemic diseases.[2,3] Timely diagnosis of scleritis and associated systemic cause can save not only the eye but also the life of a patient from certain systemic lethal vasculitides. However, even with the availability of newer diagnostic modalities, the diagnosis of these systemic autoimmune disorders is not always easy and often requires a perfect combination of meticulous history, thorough clinical examination, appropriate laboratory investigations, and multidisciplinary approach.

Antineutrophil cytoplasmic antibody (ANCA) was first reported in 1982 in patients with microscopic polyarteritis.[4] Originally thought to be a response to arboviral infection, ANCA has been found to be an important biomarker in the diagnosis of systemic vasculitis.[5,6] Two specific ANCA patterns have been recognized with indirect immunofluorescence of ethanol-fixed neutrophils – a cytoplasmic diffuse staining pattern [cytoplasmic antineutrophil cytoplasmic antibody (cANCA)] and the perinuclear staining pattern [perinuclear anti-neutrophil cytoplasmic antibodies (pANCA)]. cANCA is seen when antibody detects a neutrophil serine proteinase and has been found to be associated with GPA. pANCA is exhibited when antibodies detect lysosomal enzymes such as myeloperoxidase (MPO) and has been linked to microscopic polyarteritis and renal vasculitis. However, these biomarkers have limited role in monitoring the disease activity and often they are not definitive for systemic vasculitis. For example, the

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positive predictive value for a cANCA test has been estimated to be 63%.[7] Thus, using this test alone, there is possibility of wrongly diagnosing GPA in 37% of the patients with a positive cANCA.[7] In addition, there is overlap in clinical presentation of patients with positive ANCA as well as patients negative for ANCA.[8] There is a paucity of literature on ANCA-positive scleritis.[8] In a majority of the studies, cANCA-related scleritis was discussed as a subset of scleritis.[9] To the best of our knowledge, there are no studies from India describing the clinical profile of ANCA-positive scleritis patients. Another study from the same institution in 2003 analyzed nine cases with GPA which included six patients of necrotizing scleritis.[10] This study was undertaken to describe the clinical profile and treatment outcome in patients with ANCA-associated scleritis in India.

Methods

This was a hospital-based retrospective case series that reviewed the files of all consecutive patients with scleritis who were found to be positive for ANCA at a single tertiary eye-care center between January 2006 and December 2015. The study was approved by institutional review board of the hospital and adhered to the tenets of the Declaration of Helsinki. Scleritis was diagnosed clinically on the basis of characteristic ophthalmic symptoms and signs such as excruciating pain with congestion of deeper episcleral vessels, scleral edema and congestion, scleral nodule, and evidence of scleral necrosis, with scleral thinning or defect. Posterior scleritis was diagnosed by fundus examination and B-scan ultrasonography. Scleritis was further categorized into diffuse anterior, nodular, necrotizing, scleromalacia perforans, and posterior scleritis based on the classification proposed by Watson and Hayreh.[11] Patients who tested positive either for antibody to proteinase 3 (anti-PR3) or myeloperoxidase (anti-MPO) and subsequently examined by a rheumatologist for systemic evaluation were included in the study. Patients with insufficient documentation or follow-up of less than 6 months were excluded from the study. In addition, cases with microbiologically proven infective scleritis with specimens obtained by scleral scraping were excluded from the analysis. Information regarding the presenting complaints of the patient, best-corrected visual acuity (BCVA) at the time of presentation and at follow-up, intraocular pressure (IOP), and detailed ocular examination including fundus findings were noted. Laboratory investigations, including routine hemogram, erythrocyte sedimentation rate, serum rheumatoid factor, antinuclear antibodies, human leucocyte antigen B27, tuberculin skin test (TST), and chest-X-ray, were obtained for all the patients in this study. All the patients were examined by an in-house internist before initiating systemic medications. Consultation from a pulmonologist was sought in relevant cases in patients with positive TST, radiological evidence of healed, or active pulmonary tuberculosis. Diminution of vision was defined as a decrease in visual acuity by two Snellen lines, or more and improvement of vision was referred to an increase in visual acuity by two Snellen lines or more after resolution of the scleral inflammation clinically.

Oral corticosteroid was primarily used for the management of scleritis in this study after obtaining clearance from an in-house physician. Additional immunosuppressives were added or immunosuppressives were changed in cases where the scleral inflammation did not respond to the ongoing treatment, change in treatment regimen as suggested by the rheumatologist, and in cases with recurrences. Resolution of scleritis was defined as lack of any pain, resolution of clinically detectable deeper episcleral injection, or scleral edema on objective evaluation. Non-responsive to treatment was defined as persistence of scleral edema with congested and/or engorged deeper episcleral vessels for more than 8 weeks with single immunosuppressive and oral steroid. Additional treatment in the form of intravenous methyl prednisolone or cyclophosphamide was administered in patients with progressive scleral thinning despite treatment with oral corticosteroids or oral immunosuppressive or on recommendation of rheumatologists. Oral medications were tapered and discontinued depending on the response to treatment.

BCVA results were converted to logarithm of the minimal angle of resolution (logMAR) for statistical analysis and are given as logMAR (mean ± standard deviation). The results were considered statistically significant when $P < 0.05$. Data were analyzed using IBM SPSS Statistics, version 20.0 (International Business Machine Corp., Armonk, NY, USA). Paired t-test was used to test the changes in BCVA, and independent-samples t-test was used to compare the subset of cANCA-positive patients with pANCA-positive patients with scleritis.

Results

In all, 40 patients with scleritis who were tested positive for ANCA were seen in our hospital during the study period. Of these 40 patients, 14 patients were excluded due to insufficient documentation and inadequate follow-up. The remaining 33 eyes of 26 patients were included in this analysis. Seventeen patients (65.4%) tested positive for anti-PR3, and anti-MPO was found positive in nine patients (34.6%). All of them were subsequently examined by a rheumatologist. The mean duration of follow-up of this study was 398.2 days (189–769 days).

The mean age of the patients in this study was 54.1 ± 11.1 years (range: 30–77 years). Ten patients (38.5%) were male and 16 (61.5%) were female. Seven patients (26.9%) had bilateral involvement, and in 19 patients (73.1%) scleritis was unilateral. All patients presented with complaints of redness, ocular pain, and diminution of vision. Necrotizing scleritis (16 eyes, 48.5%) was the most common subtype of scleritis observed in this study followed by diffuse anterior non-necrotizing scleritis (14 eyes, 42.4%). Concurrent diffuse anterior scleritis and posterior scleritis were observed in one eye. Isolated cases of posterior scleritis and nodular scleritis were found in one eye each [Table 1]. None of the patients in the current series had scleromalacia perforans. Varying degree of cellular reaction in the anterior chamber was observed in 10 eyes (30.3%) of the patients. Corneal involvement in the form of peripheral keratitis was observed in seven (21.2%) eyes [Fig. 1].

Of nine patients with positive pANCA, none of them had clinical evidence of any systemic disease. Two patients with positive cANCA were found to be simultaneously positive for rheumatoid factor (RF); none of them developed any systemic manifestations of immunological disorders during the follow-up period. Eight (30.7%) patients had GPA as diagnosed by the rheumatologist – six had localized GPA and two patients were diagnosed as generalized GPA.
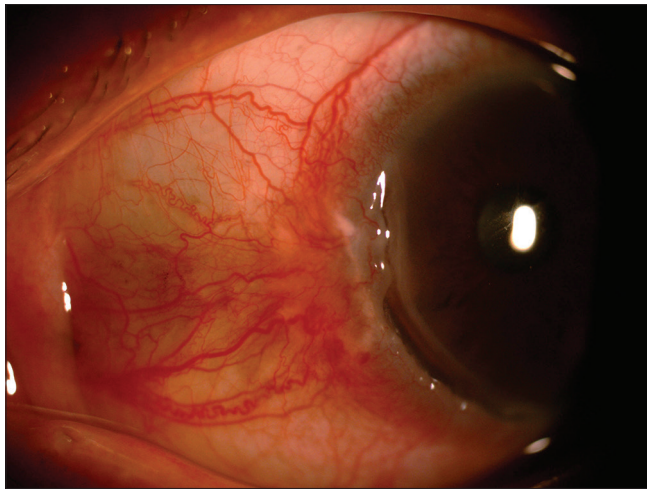
Figure 1: Slit-lamp photograph of a 42-year-old male showing anterior scleritis with peripheral ulcerative keratitis, who tested positive for antibody to proteinase 3 (c-antineutrophil cytoplasmic antibody)

Scleritis was the initial manifestation of the disease in three patients with GPA (24.2%) and 5 (19.2%) had presented with pre-existing systemic diagnosis of GPA. Six patients with ANCA positivity also showed positive Mantoux test (more than 15 mm induration). All these six patients had unilateral involvement – three had necrotizing scleritis, two presented with diffuse anterior scleritis, and one patient had nodular scleritis. A scleral scrapping was obtained in three patients with necrotizing scleritis, and none of them showed any microbiological evidence of *Mycobacterium tuberculosis*. Three of them had radiological evidence of pulmonary tuberculosis, two showed positive result for interferon gamma release assay, and four of the six patients with positive Mantoux test were started on ATT by the chest physician.

All but one patient (96.2%) were treated with oral corticosteroid (1 mg/kg/day in tapering doses) and topical corticosteroid steroid was applied in all eyes. Seventeen patients (65.4%) in the current series required immunosuppressive agents. Cyclophosphamide was the most commonly used immunosuppressives (9 patients, 34.6%) followed by methotrexate (4 patients, 15.4%) and mycophenolate mofetil (3 patients, 11.5%). Three patients who were initially started on oral methotrexate required additional immunosuppressive (mycophenolate mofetil) subsequently to achieve control of scleral inflammation. One patient was advised intravenous pulse cyclophosphamide therapy by the treating rheumatologist. Scleral inflammation in six patients with Mantoux positivity was treated with systemic corticosteroid after clearance from an in-house physician and chest physician; only one of them required additional immunosuppressive (oral methotrexate) subsequently. Oral methotrexate in this patient was added after completion of 4.5 months of ATT after obtaining clearance from the chest physician, and improvement of scleral inflammation was observed with the treatment. Treatment modalities for study patients are shown in Table 2.

Five patients (19.2%), three with necrotizing scleritis (18.8%) and two with diffuse anterior scleritis (14.3%), had multiple

Table 1: Clinical profile of antineutrophil cytoplasmic antibody-associated scleritis

Parameters	Number of patient (Percentage)
Age (years), mean (SD)	54.1 (11.1)
Gender, *n* (%)	
Male	10 (38.5)
Female	16 (61.5)
Laterality, *n* (%)	
Unilateral	19 (73.1)
Bilateral	7 (26.9)
Scleritis subtype (study eye), *n* (%)	
Diffuse anterior scleritis	14 (42.4)
Necrotizing scleritis	16 (48.5)
Nodular scleritis	1 (3)
Posterior scleritis	1 (1)
Diffuse anterior scleritis + posterior scleritis	1 (3)
Laboratory investigation, *n* (%)	
Positive cANCA	17 (65.4)
Positive pANCA	9 (34.6)
RA factor	2 (7.7)
Positive Mantoux test	6 (23)
Proven systemic association, *n* (%)	
GPA	8 (30.8)
Tuberculosis	4 (15.4)
Complications (study eye), *n* (%)	
Cataract	17 (51.5)
Ocular hypertension	7 (21.2)
Phthisis	3 (9.1)
Optic atrophy	1 (3)

SD: Standard deviation; cANCA: Cytoplasmic antineutrophil cytoplasmic antibody; pANCA: Perinuclear anti-neutrophil cytoplasmic antibodies; RA: Rheumatoid arthritis; GPA: Granulomatosis with polyangiitis

Table 2: Treatment modalities for study patients

Treatment modalities	Number (Percentage)
Oral steroid	25 (96.2)
Intravenous pulse corticosteroid	4 (15.4)
IMT	17 (65.4)
Cyclophosphamide	9 (34.6)
Methotrexate	4 (15.4)
Mycophenolate mofetil	3 (11.5)
Combination of 2 IMT	3 (11.5)
Intravenous pulse cyclophosphamide	1 (3.8)
Antitubercular treatment	4 (15.3)

IMT: Immunosuppressives

recurrences during follow-up. Seventeen eyes (51.5%) developed cataract and all of them required surgical intervention. Seven eyes (21.2%) had raised IOP – one required filtration surgery, and the remaining were managed with anti-glaucoma medications. Four eyes (12.1%) required path graft because of extreme thinning of sclera with impending perforation. Vision improved in 23 eyes (69.7%) and was

maintained in 6 eyes (18.2%). Deterioration of vision was noted in four eyes (12.1%) of cANCA-positive patients – three eyes developed phthisis and one eye had optic atrophy. The mean BCVA in pANCA group improved from 0.7 ± 0.8 logMAR at presentation to 0.32 ± 0.68 logMAR at the time of final follow-up, and this difference was statistically significant ($P < 0.0344$). There was improvement in the mean BCVA in cANCA group from 1.1 ± 1.0 logMAR to 0.5 ± 1.1 logMAR, but this difference was not statistically significant ($P = 0.035$).

We further compared the subset of cANCA-positive patients with pANCA-positive patients with scleritis [Table 3]. There were no significant differences in mean age and laterality. We found that female gender was more frequently associated with pANCA-associated scleritis than cANCA ($P = 0.037$). There were no differences in the incidence of cataract, secondary hypertension, and anterior uveitis between cANCA- and pANCA-related scleritis. Incidence of necrotizing scleritis was higher in patients with positive cANCA, but this difference was not statistically significant ($P = 0.806$). cANCA-positive patients had statistically significant higher association with systemic rheumatic diseases ($P = 0.021$).

Discussion

ANCA-associated vasculitides are a group of potentially life-threatening systemic necrotizing small-vessel vasculitides. Neutrophils are thought to play a major role in facilitating loss of tolerance to the endogenous antigens recognized by ANCA. Examples of ANCA-associated vasculitides include GPA, microscopic polyangitis, and eosinophilic granulomatosis with polyangitis. GPA is the most common systemic vasculitis associated with scleritis and accounts for half of the cases of vasculitis-associated scleritis[1,2] There is lack of consensus on clinical usefulness of ANCA as serological marker for the diagnosis of systemic vasculitis in patients with scleritis.[12] The literature on ANCA-associated scleritis is sparse. The largest series published to date is by Hoang et al.[8] and included 14 patients of scleritis who tested positive for ANCA. To the best of our knowledge, no such case series on ANCA-associated scleritis patients has been published from a tuberculosis-endemic

region and the current series is also the largest case series on ANCA-associated scleritis published till date.

The mean age of patients and female preponderance in this study was similar to that reported in other previously published series.[8,12] However, the majority of our scleritis cases in ANCA-positive patient were unilateral. This finding in our series can be explained with relatively lower number of definite systemic involvement in our series as bilateral involvement in scleritis is often considered to have relatively higher association with systemic diseases. However, it is unclear why some of the patients do not show any systemic evidence even with positive biomarker for the disease. Initiation of early immunosuppressive therapy for scleritis may have a role in prevention of clinical manifestation of systemic diseases in these patients.[2] Only 46.2% of our patients with ANCA-positive scleritis had a systemic association. This finding of this study was much lower but not diverged from those found in recent literature. In a study by Akpek et al.,[2] 10 patients had a positive ANCA test result without clinical evidence of systemic vasculitis, despite extensive evaluation and a mean follow-up of 1.7 years. Predictive value of ANCA testing in evaluation of systemic vasculitides showed variable results among various populations. In a large retrospective study assessing ANCA positivity in Greek populations, ANCA-associated vasculitis represented 20.5% of positive ANCA results.[13] However, no such population-based study on predictive value of ANCA testing is available from India. Two of our patients had tested positive for both ANCA and RF. Lin et al.[14] reported a patient who tested positive both for ANCA and RF and went on develop RA. However, we did not observe such systemic association in our two patients. A recent study from India by the same authors has shown relatively lower systemic association of systemic rheumatic disease in patients with necrotizing scleritis.[15]

ANCA positivity has been reported in patients with tuberculosis. *M. tuberculosis* is believed to stimulate release of oxygen from the activated neutrophils. Activation of neutrophils has been observed to occur following interaction with phenol glycolipids of the cell wall of *M. tuberculosis*.[16] This may lead to release of lysosomal enzymes from the neutrophils in the initial stages of mycobacterial infection, and autoantibodies against the granular components of those cells can develop. In a study from Mexico, Flores-Suárez et al.[17] found that ANCA were positive in 44.4% of the patients with tuberculosis and high odds ratios for ANCA positivity were observed for patients with tuberculosis when compared with controls. In our study, six patients had positive Mantoux test and four of them received ATT as advocated by the pulmonologist. Conducted in a highly tuberculosis-endemic population, ANCA positivity in our study without any evidence of systemic immunological disorders may have some correlation with the above observations. This finding of the study also warrants ruling out any evidence of tuberculosis in patients with ANCA-associated scleritis from tuberculosis-endemic region as management of such patients usually requires aggressive immunomodulatory therapy often with biologicals.

GPA remains an important and common cause of necrotizing scleritis. Sainz de la Maza et al.[3] reported 78% of necrotizing scleritis and 14% of diffuse anterior scleritis in patients with GPA. Gu et al.[18] reported that 86% of their patients with GPA

Table 3: Comparison of subsets of cANCA-positive patients with pANCA-positive scleritis patients

	pANCA (n=9), n (%)	cANCA (n=17), n (%)	P
Age	56.6±10.2	52.76±11.6	0.406
Gender y female	8 (88.9)	8 (47.1)	0.037
Bilateral	2 (22.2)	5 (29.4)	0.694
Diffuse anterior scleritis	5 (45.5)	9 (40.9)	0.803
Necrotizing scleritis	5 (45.5)	11 (50)	0.806
Anterior uveitis	3 (27.3)	7 (31.8)	0.788
Corneal involvement	1 (9.1)	6 (27.3)	0.228
Systemic rheumatic disease	0 (0.0)	8 (47.1)	0.021
Cataract	7 (63.6)	10 (45.5)	0.325
Glaucoma	3 (27.3)	4 (18.2)	0.547

cANCA: cytoplasmic antineutrophil cytoplasmic antibody; pANCA: perinuclear anti-neutrophil cytoplasmic antibodies

had necrotizing scleritis. Again, Hoang *et al.*[8] reported 71% of anterior diffuse scleritis and 14% of necrotizing scleritis in their series of ANCA-positive scleritis patients. Although most of the common subtypes of scleritis in this study were necrotizing scleritis, our series did not observe a great difference between necrotizing scleritis (48.5%) and diffuse anterior scleritis (42.4%) cases. Scleritis was the initial manifestation of GPA in three patients (11.5%) in this study. Scleritis as initial manifestation of underlying systemic autoimmune conditions has been widely reported in literature. In addition, in agreement with previous studies, a significant number of patients with ANCA-positive scleritis do not manifest any systemic involvement until late in the course of disease.

In spite of lower systemic association in this study, we had relatively large number of necrotizing scleritis and despite therapy with immunosuppressive, often combination of immunosuppressives, four eyes (12.1%) had poor visual outcome and three of them developed phthisis. It has been reported that even in the absence of systemic disease, scleritis in patients with ANCA-associated scleritis is difficult to control and requires aggressive immunosuppressive therapy.[2] Another major cause for relatively poor visual outcome in our series was lack of usage of biologicals. Activation of granulomatous systemic disease, especially tuberculosis, is a major concern for use of biologicals in treatment of uveitis in tuberculosis-endemic region such as India, and our series demonstrated that extreme care has to be taken before initiating treatment with biologicals even in condition like ANCA-positive scleritis.

More than half of the eyes (51.5%) in this study developed cataract and 21.2% of the patients developed ocular hypertension. These findings in our study can be attributed to the increased use of topical and oral steroid. The retrospective nature of the case series is a major limitation. Findings such as relative higher number of necrotizing scleritis in our study can also be explained with the referral pattern to our hospital. Our institution is a tertiary care referral center, and as such, there is the potential for bias toward those patients with more unusual or difficult-to-control diseases. Also, being conducted in an eye care setup, detailed evaluation of the systemic involvement in ANCA-positive patients was beyond the scope of our study and may bear the lacunae of correlating the exact association of these cases with systemic involvement. However, from our study a distinct clinical pattern of ANCA-positive scleritis in Indian patients has emerged. Although it will be inappropriate to draw conclusion on association of ANCA positivity with mycobacterial infections based on such a small sample, further studies with a larger sample would be able to make more accurate correlation. Despite this, we believe our work provides a useful evidence for ANCA-associated scleritis.

Conclusion

To conclude, ANCA-associated scleritis should be thoroughly investigated through a multidisciplinary approach to rule out other systemic etiologies including tuberculosis especially in patients from tuberculosis-endemic region like India before initiating aggressive systemic immunomodulatory therapy.

Conflicts of interest

There are no conflicts of interest.

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