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Original Article

Clinical Spectrum of Anterior Scleritis at a Tertiary Eye Care Centre of Western India

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ABSTRACT

Introduction: Anterior scleritis can be the first sign of an underlying life-threatening systemic disease, can be lethally blinding and its management can be challenging. Thus, it is important to study the clinical spectrum of the disease to aid in early diagnosis and timely management.

Objective: To evaluate the clinical spectrum of anterior scleritis (AS) at a tertiary care centre of Western India and to study the importance of its systemic association.

Methodology: This analytical cross-sectional (prospective) study was carried out at a tertiary eye care centre of Western India between 2021 February to 2023 January after institutional ethical clearance. A total of 45 eyes of 37 patients were included in the study using convenience sampling.

Result: The mean age of presentation was 43.41 ± 14.20 years. The mean follow-up duration was 6.00 ± 5.92 months. Bilateral AS occurred in 21.6% patients and was found to be more common in females (75%). The most common subtype of AS was non-necrotising AS in 35/37 (94.6%) patients. Non-necrotising diffuse AS was more common in females (p=0.047). Systemic association was present in 11/37 (29.73%) patients and rheumatoid arthritis (RA) was the most common systemic condition. Methotrexate was the most common immunosuppressive used in 18.91% patients. The mean time period for recurrence of AS was 3.53 ± 1.35 months. Recurrence was seen in 40.5% patients and was more common in patients with diffuse AS and patients with RA.

Conclusion: The RA is an important cause of AS in India and knowledge of the systemic association of AS may enable early diagnosis and timely management of the condition to decrease morbidity and mortality.

Key words: Anterior scleritis; rheumatoid arthritis; systemic association.

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INTRODUCTION

Scleritis is a painful inflammation of the sclera, characterised by engorgement of conjunctival, superficial, and deep episcleral vessels. It is a potentially blinding inflammatory disease and may be the first sign of a life threatening systemic autoimmune disease. Hence, a detailed medical history and a thorough systemic examination are critical in these patients. Scleritis is classified as either anterior or posterior, of which anterior scleritis (AS) is the most common form of scleral inflammation. AS can be either necrotising or non-necrotising scleritis. Non-necrotising scleritis is further classified as either nodular or diffuse. Necrotising scleritis can present with inflammation or without inflammation (scleromalacia perforans) (Watson et al., 1968; Dutta Majumdar et al., 2020). The AS remains a therapeutic challenge for an ophthalmologist due to its varied differentials, refractory nature to the standard treatment protocol, systemic association and visually debilitating complications (Sainz de La Maza et al., 2012; Patnaik et al., 2020). In 15% of cases, it is the presenting manifestation of a collagen vascular disorder and may precede additional symptoms by one to several months. By far, rheumatoid arthritis (RA) is the most common systemic association with AS, followed by Wegener's Granulomatosis (WG) (Pavesio et al., 2001). The first choice of therapy in non-necrotising AS is a combination of systemic non-steroidal anti-inflammatory drugs (NSAIDs) with topical corticosteroids, whereas in refractory AS and necrotising AS, additional systemic immunosuppression may be needed. There is limited literature published specifically on AS and its subtypes from India. Moreover, there is no study to date reporting the clinical profile of AS from western India**.** The present study aimed to evaluate the clinical spectrum of AS, its treatment modalities, the complications encountered during the follow-up and the systemic association of AS amongst the patients presenting to a tertiary care centre of western India.

METHODOLOGY

This analytical cross-sectional (prospective) study was carried out at a tertiary eye care centre of Western India, the M and J Institute of Ophthalmology, Asarwa, Ahmedabad, Gujarat during the period between 2021 February to 2023 January. The study was approved by the Institutional review board (Reference number: 14/2021) of the hospital and adhered to the declaration of Helsinki. Patients were included in the study by convenience sampling method. An informed consent was obtained from all patients included in the study. All the patients included in the study were examined by a single ophthalmologist either in the out-patient clinic or in the emergency room. The diagnosis of AS was based on the history and clinical examination suggesting oedema of the episcleral and scleral tissues accompanied by engorgement of deep and superficial episcleral plexuses. Deeper episcleral congestion was confirmed by the blanching of vessels with topical 10% Phenylephrine, a useful test to differentiate between episcleritis and scleritis. Phenylephrine blanches the superficial conjunctival vascular plexus so that the deeper episcleral vascular plexuses can be differentiated and their relationship to the sclera determined (Watson et al., 1968). Other sub-types of scleritis including posterior scleritis and infective scleritis, diagnosed microbiologically and

patients with follow-up less than three months were excluded from the study. The patients with AS were categorised into three distinct subgroups: anterior diffuse, anterior nodular, and anterior necrotising (with or without inflammation) according to the classification by Watson and Hayreh. The following data were recorded for each patient: demographic information including age and gender, symptoms at presentation, laterality of AS, best corrected visual acuity (BCVA) at presentation, and at the end of the follow-up, detailed ocular examination including anterior segment slit lamp bio-microscopy, posterior segment (90D examination and indirect ophthalmoscopy), ultrasonography, and intraocular pressure (IOP), specific laboratory results or diagnostic investigations, associated systemic disease, the management given and time taken for the resolution of the inflammation and secondary ocular complications if any. Diminished visual acuity was defined as loss of visual acuity of two or more Snellen lines at the end of the follow-up. Glaucoma was defined as IOP consistently more than 21 mm Hg by applanation tonometry with disc and/or visual field changes, requiring antiglaucoma therapy. Resolution was defined as lack of symptom with resolution of clinically detectable episcleral and scleral congestion and surrounding scleral oedema on slit lamp evaluation. Recurrence of the AS was defined as the reappearance of scleral inflammation during the follow-up period. Laboratory tests performed in all the patients included routine haemogram, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), rheumatoid factor (RF), antistreptolysin antibody (ASO), antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) screening to rule out suspected autoimmune disease such as vasculitis; and Mantoux test and Quantiferon for *Mycobacterium tuberculosis* (TB) infection. High resolution computed tomography, serum angiotensin converting enzyme and human leucocyte antigen B-27 were the tests carried out in selected cases as per the advice of the physician. All patients were evaluated by a physician and rheumatologist was consulted to rule out associated collagen vascular disease as well as for immunosuppression therapy.

All patients with AS were initially managed with systemic NSAIDs (Indomethacin 25mg three times a day OR Ibuprofen 400 mg three times a day OR Celecoxib 100 mg twice daily) and adjunctive topical steroids (Prednisolone acetate 1% started 4-6 times a day) in a gradually tapering dose for at least two weeks, depending on the clinical response. If the non-necrotising scleritis was not controlled by two weeks, oral corticosteroids (Tablet Prednisolone 1mg/kg/day) were started. Oral corticosteroids were started as the first line of management, along with topical steroids and oral NSAIDs in cases of necrotising AS. For patients who responded to oral corticosteroids, dosage was continued until clinical resolution of the AS was seen. Then gradually, they were tapered and immunosuppressive agents like oral Methotrexate (MTX) and Cyclophosphamide in coordination with a rheumatologist, were started for steroid sparing therapy, if needed. In cases with systemic autoimmune disease, immunosuppression was considered according to the advice of the rheumatologist. Antitubercular therapy (ATT) was given by a pulmonologist in cases diagnosed as systemic tuberculosis. A follow-up period of minimum

three months was maintained.

The data were tabulated in Microsoft Excel spreadsheet and analysed using Statistical Package for Social Sciences (SPSS) software version 21 (SPSS Inc., Chicago, USA). Comparisons of the characteristics of patients in the different subgroups and correlations between the data analysed were done using Chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULT

The demographic details of the patients are tabulated (Table 1).

Bilateral AS was found to be more common in females (75%, p = 0.2459). On clinical examination on the slit lamp biomicroscope, the most common subtype of AS was non-necrotising AS in 35/37 patients (42/45 eyes). Non-necrotising diffuse AS was more common in females (p = 0.047). Amongst the two patients (3 eyes) with necrotising AS, one female patient had bilateral scleromalacia perforans (SP) and one male patient had surgically induced necrotising scleritis (SINS) post cataract surgery. In the present study, posterior segment was found to be within normal limits in all patients. RA Factor was found to be the most common positive laboratory finding (9/37 patients, 27.03%). Mantoux test and Quantiferon TB Gold + test was positive in two (5.4%) patients, while ANA was positive in one (2.7%). The c-ANCA was positive in one patient with both Mantoux and Quantiferon TB Gold + test positive and this patient was subsequently diagnosed as pulmonary TB. Systemic associations were present in 11/37 patients (29.73%) (Table 1). Of these, five patients (45.45%) were previously diagnosed and rest (54.55%) were diagnosed at the centre during the investigations. Out of the 11 patients with a systemic association, AS was the presenting symptom in five (45.45%) patients. Out of these five patients, one was found to have both RA and pulmonary TB and the remaining four patients had associated RA. The topical therapy administered to the study population included corticosteroids (35 patients) and immunomodulator therapy of Cyclosporine (nine patients). Topical corticosteroids included Prednisolone acetate (1%) in 25 patients and Fluorometholone acetate (0.1%) in 10 patients. Systemic therapy given included NSAIDs in 28 patients, corticosteroids in 16 patients and immunosuppression in 10 patients. Ten patients with nodular AS responded to systemic NSAIDs alone without the need for any other systemic agent. The NSAIDs used in the study were systemic Indomethacin tablets (23 patients), Ibuprofen tablets (four patients) and Celecoxib tablets (one patient). One patient who was diagnosed with SINS was given loading dose of intravenous (IV) Methylprednisolone 1 g (15 mg/kg/day) for three days followed by oral steroids. One patient who was diagnosed with SP was also given a loading dose of IV Methylprednisolone 1g for three days with oral steroids added on follow-up, along with IV Cyclophosphamide (500mg IV every two weeks for six weeks). First choice of immunosuppression was MTX followed by Cyclophosphamide. None of the patients previously diagnosed with RA were on systemic immunosuppression. As already published as an isolated case by the authors previously, one patient with AS secondary to pemphigus vulgaris (PV), already on oral Azathioprine (200 mg per day) for PV, needed

opinions of immunologist and dermatologist and intravenous Rituximab (first dose of 1g) was added to the regimen (Bhole PK et al., 2022). Seven patients were given oral MTX (7.5 mg/ week) after consultation with a rheumatologist for associated RA. Three patients of RA were advised oral Cyclophosphamide (1.5 mg/kg/ day). Two of these were already on MTX. ATT was administered to two patients with pulmonary TB, after due consultation with a pulmonologist. Immunosuppression was started after a mean period of six months of completion of ATT in one patient with associated RA after the consultation with the rheumatologist and pulmonologist.

Mean time for resolution of symptoms was 2.00 ± 1.92 months (range: seven days to eight months). Visual acuity improved in 4/5 patients who presented with diminished vision, at the end of the mean follow-up period. All the four

Table 1: Clinical and demographic details of the patients with anterior scleritis enrolled in the study.

Clinical characteristics		Results
Total number of patients		37
Total number of eyes		45
Mean Age of presentation (years)		43.41 ± 14.20 (range:16-65)
Gender	Females	21 (56.8%)
	Males	16 (43.2%)
Laterality	Bilateral	8 /37 (21.6%)
	Unilateral	29/37 (78.4%)
Mean follow up (months)		6 ±5.92 (range: 3-24)
Presenting symptoms	Red eye	33 patients (93%)
	Ocular pain	22 patients (49%)
	Diminished vision	5patients (16%)
Type of Anterior Scleritis (number of eyes)		
Non necrotizing	1. Diffuse	28 (62.22%)
	2. Nodular	14 (31.11%)
Necrotizing	1. Scleromalacia Perforans	2 (4.44%)
	2. SINS	1 (2.22%)
Systemic association		
RA		8 patients (6 Diffuse AS, 1 Nodular AS, 1 SP)
Pulmonary TB		1 patient (Diffuse AS)
RA with pulmonary TB		1 patient (Diffuse AS)
Pemphigus vulgaris		1 patient (diffuse AS)

(SINS- surgically induced necrotizing scleritis, RA- Rheumatoid Arthritis, TB- Tuberculosis)

patients had non-necrotising diffuse AS (three with associated PUK and one with anterior uveitis) and the one with non-improvement of vision had SP. Ocular complications were noted during the follow-up period in 20 (54.05%) patients, with some patients having more than one complication (Table 2).

Scleral thinning was the most common complication found in diffuse AS (p = 0.421) and in patients with RA (p = 0.188). Fifteen (40.5%) patients had recurrence of AS, after a mean period of 3.53 ± 1.35 months, observed during follow-up. All patients presenting with recurrent disease showed signs and symptoms similar to the initial presentation. Recurrence was most commonly observed with patients having non-necrotising diffuse AS (p=0.409) and in patients having RA (p = 0.163) (Table 3).

Table 2: Relation between systemic association of anterior scleritis (AS) and its complications

Complications	Systemic Association of AS				
	None	RA	RA and Pulmonary TB	Pemphigus Vulgaris	Pulmonary TB
None	16	4	0	1	0
Scleral Thinning	5	2	0	0	0
With Staphyloma		1			
PUK	2	1	0	0	0
Scleral Thinning with PUK	1	1	0	0	0
Scleral Melting	2	1	0	0	0
Cataract	0	0	1	0	1
Anterior Uveitis	1	0	0	0	0

Chi square= 8.75; p= 0.188 (RA- Rheumatoid Arthritis, TB- Tuberculosis, PUK- Peripheral ulcerative keratitis)

Table 3: Relation between recurrence of Anterior scleritis (AS) and systemic association and AS subtype

Systemic Association	No. of patients having recurrence (%)	Subtype of anterior scleritis	No. of patients having recurrence (%)
Pemphigus Vulgaris	0	Non-Necrotizing scleritis	
Rheumatoid Arthritis	**7 (46.66)**	☐ Diffuse	10(66.67)
Rheumatoid Arthritis and Pulmonary TB	1 (6.67)	☐ Nodular	04 (26.67)
Pulmonary TB	1 (6.67)	Necrotizing scleritis without inflammation	01 (6.67)
None	6 (40)	SINS	0
Total	15 (100)	Total	15 (100)
Chi square= 5.118; p= 0.163		Chi square=2.883; p=0.409	

DISCUSSION

Anterior scleritis can be the first sign of an underlying life-threatening systemic disease, can be lethally blinding and its management can be challenging. Thus, it is important to study the clinical spectrum of the disease to aid in early diagnosis and timely management. The present study has an advantage of being a prospective study with a uniform study group of patients with non-infectious AS, as compared to earlier reported studies on scleritis (Patnaik et al., 2020; Magesan et al., 2022). Hence, these data may provide a better understanding of the clinical spectrum and profile of AS in a group of patients from a single tertiary care centre of Western India.

The comparison of the present study with similar peer reviewed studies has been tabulated (Table 4).

Table 4: Comparison of clinical and demographic details of the present study with similar previously reported studies.

Study	Present study	Sainz de la Maza et al., 2012	Patnaik G et al.,2020	Magesan et al., 2022	Al Barqi et al., 2015	Keino et al., 2010	Jabs et al., 2000
Type	prospective	retrospective	retrospective	retrospective	retrospective	retrospective	retrospective
Region	Western India	Massachusetts & Spain	India	India	Saudi Arabia	Japan	United States
Number of eyes/ patients	45 eyes/37 patients	500 patients	140 eyes/ 123 patients	107 eyes/96 patients	52 patients	83 patients	97 patients
Entity of scleritis studied	Anterior scleritis	Scleritis (Anterior & Posterior)	Anterior nodular scleritis	Scleritis (Anterior & Posterior)	Scleritis (Anterior & Posterior)	Scleritis (Anterior & Posterior)	Scleritis (Anterior & Posterior)
Mean age (years)	43.41±14.2	53.7	46.8±13.1	46±14	55.3±18.1	51±14	51
Gender preponderance	Female (56.8%)	Female (71%	Females (70.7%)	Female (68%)	Female (58.3%)	Female (55%)	Female (71.1%)
Commonest type of AS	Diffuse AS (62.22%)	Diffuse AS (75%)	-	Diffuse AS (41%)	Diffuse AS (81.8%)	Diffuse AS (69%)	Diffuse AS (59%)
Systemic disease association	29.73% RA	35.8%, RA most common	22%, presumed TB (13%) most common	48%, RA (18%) most common	23.1%, RA most common	29%, rheumatologic disease most common	44% , RA most common
Recurrence	40.54%	15.8%	74.8%	23%	-	-	-

(RA- Rheumatoid Arthritis)

The most common presenting symptom in present study was redness of the eye followed by ocular pain, similar to a study, where redness was reported in 92.6% patients and ocular pain was reported in 69.1% of patients with anterior nodular scleritis (Patnaik et al., 2020). The present study found non-necrotising diffuse AS to be the most common type of AS, comparable to similar studies on scleritis (Keino et al., 2010; Jabs et al., 2000).

The ANCA positivity, as noted in one patient in this study, may be observed in both TB and systemic vasculitic syndromes such as WG. The c-ANCA positivity with Quantiferon TB Gold+ test positivity was noted in one patient, who was subsequently diagnosed as having pulmonary TB in this study. Hence, in countries with a high prevalence of TB, one has to distinguish between these two diseases especially when no sign of extrapulmonary involvement is observed (Sherkat et al., 2011). In a retrospective study done at a tertiary referral centre in Nepal, the most common cause of scleritis was Tuberculosis (Manandhar A., 2016).

Out of the 11 patients with a systemic association, AS was the presenting symptom in five (13.51%) patients in present study. This was comparable to a study done in two tertiary care centres in Turkey by Erkanli et al. where scleritis was the presenting symptom in 11% of patients (Erknali et al., 2010). Although associated systemic diseases are frequent among patients with scleritis, majority of them are previously diagnosed (Akpek et al., 2004). However, 54.45% patients with systemic disease in the present study were diagnosed during the investigations. In present study, association with RA (24.3%) was higher than a retrospective study of patients of scleritis with systemic disease by Akpek et al. (15.2%) and the study done by Watson and Hayreh in a special scleritis clinic (10%). Necrotising scleritis is associated with an increased risk of complications and one patient with SP, diagnosed to have RA in the present study had non improvement of visual acuity even after treatment in present study (Dutta Majumdar et al., 2020). The SP, a rare, silent but severe form of AS, occurring predominantly in elderly women with severe, long-standing RA requires early diagnosis and timely management to avoid sight threatening and life-threatening complications (Yangzes et al., 2019). Systemic vasculitis is less likely than other rheumatic diseases to have been previously diagnosed. There was no case of systemic vasculitis found in present study. But it is a potentially life-threatening disorder and it should be considered in the diagnostic evaluation of patients with AS (Akpek et al., 2004).

In the present study, the use of systemic NSAIDs was found to be higher than a study on scleritis in American population (Jabs et al., 2000). The use of systemic steroids in the present study was similar to that reported by Jabs et al. and lesser than that found in a study in Saudi Arabian population (Al Barqi et al., 2015). The most common systemic immunosuppressive agent used in present study was MTX, similar to a study on Indian population and another study reported from Japan (Patnaik et al., 2020; Keino et al., 2010). The common usage of MTX could be due to its lower side effects, lower cost and once a week dose. According to previous research, Mycophenolate mofetil may be an effective corticosteroid sparing agent in treating inflammatory eye disease (Daniel et al., 2010). However, in the present study, it was not prescribed in any of the patients, due to the higher cost of Mycophenolate mofetil. According to the Systemic Immunosuppressive

Therapy for Eye Diseases (SITE) Cohort Study, MTX, and Cyclosporine were equally effective in controlling scleritis after one year of treatment (58.3% and 52.8%, respectively) (Kempen et al., 2008; Tanaka et al., 2018). In the study by Patnaik et al., patients treated with MTX alone required additional or alternate immunosuppressives, similar to the present study where Cyclophosphamide was added in two patients of RA on MTX. Hence, a proper communication and collaboration between the ophthalmologist, physician/ pulmonologist, rheumatologist, immunologist, and dermatologist was found to be vital to the diagnosis and management of AS.

Ocular complications (43.24%) were found to be similar to the large cohort study on scleritis where 45% patients developed ocular complications (Sainz de la Maza et al., 2012). In the study by Sainz de la Maza et al., necrotising scleritis was more frequently associated with ocular complications, occurring in 91.7% of patients with necrotising scleritis, in contrast to the present study where 77.77% complications were seen in diffuse scleritis. This could be the lesser number of patients with necrotising scleritis in the present study. The most common complication in the present study was scleral thinning (27%), in contrast to a study on scleritis in Japanese population, where glaucoma was the most common complication and the study reported in India where cataract was the most common complication (Patnaik et al., 2020; Keino et al., 2010) In two separate studies by Yang et al. and Tanaka et al., the incidence of anterior uveitis in AS was 24% and 41.2% respectively. However, present study showed anterior uveitis in only 2.7% of patients. PUK was seen in 8.1% of present patients and was in coherence with the study by Sainz de la Maza et al. which reported it to be 7.4%.

The present study has several limitations, as it was performed on a small sample size with a limited follow-up period at a tertiary care centre, which is a referral centre for severe cases and these cases may not represent the entire disease spectrum of anterior scleritis.

CONCLUSION

Rheumatoid arthritis is a common systemic association of anterior scleritis. Recurrences are more common, especially when associated with RA, even after adequate treatment with immunosuppressive agents, which should direct the clinician to maintain a periodic follow-up of such patients. Early diagnosis and management of anterior scleritis with the knowledge of its systemic associations can decrease ocular and systemic morbidity and mortality. A multidisciplinary and team approach to this disease having a multifactorial aetiology and a variety of systemic associations is essential for a desirable outcome.

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