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Original Research Article

Extraocular Disease Association in Patients with Scleritis and Episcleritis-A Cross-Sectional Study at a Tertiary Eye Care Center

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Abstract

Background: Scleritis and episcleritis are inflammatory ocular disorders that may occur as isolated eye diseases or as manifestations of systemic autoimmune, infectious, or local inflammatory conditions. Identification of associated extraocular diseases is clinically important because systemic disease may influence severity, recurrence, treatment response, and visual prognosis.

Objective: To describe the extraocular diseases in patients presenting with scleritis and episcleritis.

Methods: This hospital-based cross-sectional observational study was conducted in the Department of Ophthalmology, Government Medical College, Kottayam, Kerala, India, over 12 months after Institutional Review Board approval. A total of 256 patients clinically diagnosed with episcleritis or scleritis and satisfying the eligibility criteria were included by consecutive sampling. Patients with other anterior segment diseases such as conjunctivitis and anterior uveitis were excluded. All participants underwent detailed history taking, ocular examination, and phenylephrine blanching test, slit-lamp evaluation, posterior segment examination, intraocular pressure measurement, and B-scan ultrasonography when posterior scleritis was suspected. Basic investigations included complete blood count, ESR, CRP, VDRL, rheumatoid factor, chest X-ray, and Mantoux test. Relevant specialty referrals were made for confirmation of systemic or local disease. Data were entered in MS Excel and analysed using SPSS version 16.0. Qualitative variables were expressed as frequency and percentage, and Fisher's exact test was used where applicable.

Results: Among 256 patients, 54 patients (21.1%) had associated extraocular disease, while 202 patients (78.9%) had no identifiable systemic or local association. Rheumatoid arthritis was the most common associated disease, observed in 22 patients (8.6%), followed by tuberculosis in 10 patients (3.9%), ankylosing spondylitis in 8 patients (3.1%), and Wegener's granulomatosis/granulomatosis with polyangiitis in 8 patients (3.1%), and systemic lupus erythematosus in 6 patients (2.3%). The association between type of scleritis/episcleritis and extraocular disease was statistically significant (Fisher's exact test, $p<0.001$). Systemic autoimmune diseases were more frequent in scleritis, particularly non-necrotizing diffuse anterior scleritis and necrotizing anterior scleritis without inflammation, whereas tuberculosis was seen in selected episcleritis/nodular anterior scleritis cases.

Conclusion: Extraocular diseases were present in nearly one-fifth of patients with scleritis and episcleritis. Rheumatoid arthritis was the commonest systemic association. Scleritis, especially severe anterior forms, showed stronger association with autoimmune diseases than episcleritis. Routine systemic evaluation and multidisciplinary referral are essential in patients presenting with scleritis and recurrent or atypical episcleritis.

Keywords: Scleritis; Episcleritis; Clinical profile; Ocular inflammation; Posterior scleritis; Anterior scleritis; Visual acuity; Ocular examination.

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Introduction

Scleritis and episcleritis are important inflammatory disorders affecting the outer coats of the eye and differ considerably in their severity, systemic associations, management, and prognosis. Episcleritis is a relatively benign and self-limiting inflammation involving the episcleral tissue, whereas scleritis is a deeper and potentially vision-threatening inflammatory disease of the sclera that often requires prompt diagnosis and treatment. The distinction between these two entities is clinically important because scleritis is frequently associated with underlying systemic diseases and may serve as

the first manifestation of a serious autoimmune or infectious disorder [1]. Over the years, increasing evidence has demonstrated that scleritis is not merely an isolated ocular disease but often reflects an underlying systemic inflammatory process. Posterior scleritis, although less common than anterior scleritis, is particularly significant because it may be associated with severe visual impairment and may mimic other ocular conditions. Smith J et al. reported that posterior scleritis is frequently associated with systemic diseases and requires a high index of suspicion for accurate diagnosis and timely management [2]. Their findings highlighted the need for detailed systemic evaluation in all patients presenting with scleral inflammation.

The relationship between ocular inflammatory diseases and systemic autoimmune disorders has gained considerable attention in recent decades. Large cohort studies have demonstrated that a significant proportion of patients with scleritis and, to a lesser extent, episcleritis have associated systemic diseases. Promelle V et al. demonstrated patients with scleral inflammatory disease and found that systemic autoimmune disorders were commonly associated with severe forms of scleritis, while episcleritis was more frequently idiopathic [3]. Similarly, Nevares A et al. emphasized that although episcleritis often follows a benign course, recurrent or atypical cases warrant systemic investigation because they may be associated with underlying inflammatory disorders [4].

Autoimmune diseases constitute the most important group of extraocular diseases associated with scleritis. Rheumatoid arthritis is recognized as the most frequent systemic association and may account for a substantial proportion of cases. In addition, systemic vasculitic disorders such as granulomatosis with polyangiitis and connective tissue diseases such as systemic lupus erythematosus contribute significantly to the burden of scleral inflammation.

Rheumatoid arthritis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis were among the most common systemic diseases identified in patients with scleritis and were associated with more severe ocular manifestations [5]. Noninfectious autoimmune scleritis is strongly linked to systemic immune-mediated diseases and often requires multidisciplinary management involving ophthalmologists and rheumatologists [6].

Infectious diseases also play an important role in the etiology of scleral inflammation, particularly in developing countries. Tuberculosis remains a significant cause of ocular inflammatory disease and may present as episcleritis, scleritis, or posterior segment inflammation. Ocular tuberculosis should be considered in endemic regions, especially in patients presenting with recurrent or atypical ocular inflammation [7]. Failure to recognize infectious causes may result in delayed diagnosis and inappropriate treatment. Recent studies continue to reinforce the importance of identifying extraocular diseases in patients with scleral inflammation. It had been found that systemic diseases remain highly prevalent among patients with scleritis and significantly influence disease severity, recurrence, and treatment outcomes [8]. Early recognition of these associated conditions enables timely referral, appropriate systemic investigations, and initiation of targeted therapy, thereby reducing ocular morbidity and improving overall patient outcomes.

In view of the substantial association between scleral inflammatory diseases and systemic disorders, the present study was undertaken to describe the extraocular diseases in patients presenting with scleritis and episcleritis at a tertiary care center and to evaluate the pattern of systemic disease associations among different clinical subtypes.

Material and Methods

This hospital-based cross-sectional observational study was conducted in the Department of Ophthalmology, Government Medical College, Kottayam, Kerala, India, over a period of 12 months following approval from the Institutional Review Board [IRB Approval No. and Date: 194/2023, 12/06/2023]. The study included all consecutive patients presenting to the ophthalmology outpatient department who were clinically diagnosed with episcleritis or scleritis and fulfilled the eligibility criteria. Patients with other anterior segment inflammatory conditions such as conjunctivitis and anterior uveitis were excluded from the study.

A total of 256 patients who met the inclusion criteria were enrolled using consecutive sampling after obtaining informed written consent. Detailed demographic and clinical information, including age, sex, duration of symptoms, ocular complaints, previous treatment history, and history suggestive of systemic diseases, was recorded using a structured proforma.

All participants underwent a comprehensive ophthalmic evaluation that included assessment of best corrected visual acuity using Snellen's chart, external ocular examination, slit-lamp biomicroscopy, measurement of intraocular pressure using Goldmann applanation tonometry, and posterior segment examination using a Volk 90D lens and indirect ophthalmoscopy with a Volk 20D lens.

Phenylephrine eye drops were instilled and the eyes were re-examined after 20 minutes to differentiate

episcleral from scleral vascular involvement. Patients presenting with sectoral or diffuse redness associated with mild-to-moderate ocular discomfort and blanching of superficial vessels were diagnosed as episcleritis, whereas patients with severe deep ocular pain, violaceous scleral congestion, scleral edema, nodules, tenderness, visual impairment, or associated posterior segment findings were diagnosed as scleritis. Cases with clinical suspicion of posterior scleritis underwent B-scan ultrasonography, and the diagnosis was confirmed by the presence of increased scleral thickness, scleral nodules, fluid in the sub-Tenon's space producing the characteristic "T-sign," or separation of Tenon's capsule from the sclera. Particular emphasis was placed on identifying associated extraocular diseases. All patients underwent detailed local examination to detect potential infective foci including sinusitis, tonsillitis, pharyngitis, gingivitis, dental caries, ear infections, and orbital or periorbital infections. Systemic examination of the respiratory, cardiovascular, gastrointestinal, genitourinary, and musculoskeletal systems was performed. Laboratory investigations included complete blood count, differential leukocyte count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, Venereal Disease Research Laboratory (VDRL) test, chest radiography, and Mantoux testing. Based on clinical findings and preliminary investigations, patients were referred to appropriate specialties including Rheumatology, General Medicine, Respiratory Medicine, Cardiology, ENT, and Dental departments for confirmation and management of suspected systemic diseases such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, granulomatosis with polyangiitis, and tuberculosis. Data were entered into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) software version 16.0. Qualitative variables were expressed as frequencies and percentages. The association between clinical diagnosis and extraocular diseases was assessed using Fisher's exact test, and a p value less than 0.05 was considered statistically significant.

Results

Extraocular disease was identified in 54 patients, accounting for 21.1% of the study population. The majority of patients, 202 cases (78.9%), had no identifiable systemic or local association. Rheumatoid arthritis was the most common extraocular disease, present in 22 patients (8.6%). Tuberculosis was the second most frequent association, observed in 10 patients (3.9%). Ankylosing spondylitis and Wegener's granulomatosis/granulomatosis with polyangiitis were each seen in 8 patients (3.1%), while systemic lupus erythematosus was present in 6 patients (2.3%). These findings indicate that autoimmune diseases formed the major group of extraocular associations, with rheumatoid arthritis being the leading systemic disease. [Table 1]

Table 1: Distribution of Associated Extraocular Diseases in the Study Population

Associated extraocular disease	Frequency	Percentage
None	202	78.9%
Rheumatoid arthritis	22	8.6%
Systemic lupus erythematosus	6	2.3%
Ankylosing spondylitis	8	3.1%
Wegener's granulomatosis / GPA	8	3.1%
Tuberculosis	10	3.9%
Total	**256**	**100.0%**

When extraocular diseases were grouped by etiology, autoimmune and rheumatological diseases constituted the largest category, affecting 44 patients (17.2%). Infectious disease, represented by tuberculosis, was seen in 10 patients (3.9%).

Thus, among the 54 patients with extraocular disease, autoimmune/rheumatological disorders accounted for 81.5%, while tuberculosis accounted for 18.5%.

This highlights the importance of rheumatological screening in patients with scleritis and selected cases of episcleritis, while also emphasizing the relevance of tuberculosis evaluation in endemic regions. [Table 2]

Table 2: Broad Classification of Extraocular Disease Associations

Disease category	Conditions included	Frequency	Percentage
No associated disease	None detected	202	78.9%
Autoimmune/rheumatological disease	Rheumatoid arthritis, SLE, ankylosing spondylitis, Wegener's granulomatosis/GPA	44	17.2%
Infectious disease	Tuberculosis	10	3.9%
Total		**256**	**100.0%**

The distribution of extraocular disease differed significantly across clinical types of scleritis and episcleritis. Necrotizing anterior scleritis without inflammation showed the strongest association with rheumatoid arthritis, with 6 out of 14 patients (42.9%) affected.

Non-necrotizing diffuse anterior scleritis showed the widest range of autoimmune associations: rheumatoid arthritis in 8 patients (13.3%), SLE in 6 patients (10.0%), ankylosing spondylitis in 8 patients (13.3%), and Wegener's/GPA in 8 patients (13.3%). Posterior scleritis was associated with rheumatoid arthritis in 6 patients (14.6%). Tuberculosis was seen in nodular episcleritis in 7 patients (33.3%) and non-necrotizing nodular anterior scleritis in 3 patients (25.0%). Diffuse episcleritis was largely idiopathic, with 100 out of 102 cases (98.0%) having no associated disease.

The statistically significant p value indicates that extraocular disease association was not uniformly distributed and was more frequent in selected scleritis subtypes. [Table 3]

Table 3: Association of Extraocular Diseases with Type of Scleritis/Episcleritis

Diagnosis	RA	SLE	Ankylosing spondylitis	Wegener's/ GPA	Tuberculosis	None	Total
Nodular episcleritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (33.3%)	14 (66.7%)	21
Diffuse episcleritis	2 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	100 (98.0%)	102
Posterior scleritis	6 (14.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	35 (85.4%)	41
Necrotizing anterior scleritis without inflammation	6 (42.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (57.1%)	14
Non-necrotizing diffuse anterior scleritis	8 (13.3%)	6 (10.0%)	8 (13.3%)	8 (13.3%)	0 (0%)	30 (50.0%)	60
Non-necrotizing nodular anterior scleritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (25.0%)	9 (75.0%)	12
Combined anterior and posterior scleritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (100%)	6
Total	**22 (8.6%)**	**6 (2.3%)**	**8 (3.1%)**	**8 (3.1%)**	**10 (3.9%)**	**202 (78.9%)**	**256**

Fisher's exact test: p<0.001, statistically significant.

Extraocular disease was considerably more common among patients with scleritis than episcleritis.

Among 123 patients with episcleritis, only 9 patients (7.3%) had associated extraocular disease, whereas 114 patients (92.7%) had no detectable association. In contrast, among 133 patients with scleritis, 45 patients (33.8%) had associated extraocular disease. This difference was statistically significant (p<0.001). These findings support the clinical observation that scleritis has a stronger systemic disease association than episcleritis.

Therefore, all patients with scleritis should undergo detailed systemic evaluation, while episcleritis patients should be investigated particularly when disease is recurrent, nodular, atypical, bilateral, or associated with systemic symptoms. [Table 4]

Table 4: Frequency of Extraocular Disease According to Episcleritis and Scleritis Groups

Clinical group	Total patients	Patients with extraocular disease	Percentage with extraocular disease	Patients without disease	Percentage without disease
Episcleritis	123	9	7.3%	114	92.7%
Scleritis	133	45	33.8%	88	66.2%
Total	**256**	**54**	**21.1%**	**202**	**78.9%**

Fisher's exact test: p<0.001, statistically significant.

Discussion

The present study was conducted to describe the spectrum of extraocular diseases associated with episcleritis and scleritis in patients presenting to a tertiary care ophthalmology center. Among the 256 patients included in the study, 21.1% had an

identifiable extraocular disease, whereas 78.9% had no detectable systemic association. Rheumatoid arthritis was the most common associated disease, followed by tuberculosis, ankylosing spondylitis, granulomatosis with polyangiitis, and systemic lupus erythematosus. Furthermore, a statistically significant association was observed between the clinical subtype of scleral inflammation and the presence of systemic disease ($p<0.001$), emphasizing the importance of comprehensive systemic evaluation in these patients.

The concept that episcleritis and scleritis may represent ocular manifestations of systemic disease has been recognized for several decades. Soubrier M highlighted the distinct clinical behavior of these disorders and emphasized that scleritis, unlike episcleritis, is frequently associated with systemic inflammatory diseases and may lead to serious ocular complications if left untreated [1]. Their landmark work established the basis for considering scleritis as a potentially sight-threatening disease requiring detailed systemic assessment.

Posterior scleral involvement has been recognized as an important subtype because of its association with visual morbidity and systemic disease. Smith J et al. evaluated a large series of patients with posterior scleritis and reported that many patients had associated systemic inflammatory disorders and required extensive investigations to establish the underlying etiology [2]. In the present study, posterior scleritis accounted for a substantial proportion of cases and demonstrated a significant association with rheumatoid arthritis. This observation supports previous evidence suggesting that posterior scleral inflammation often reflects underlying systemic immune-mediated pathology.

A large clinical cohort reported by Promelle V et al. demonstrated that systemic diseases are more frequently associated with scleritis than episcleritis and that autoimmune disorders represent the predominant associations [3]. The findings of the present study closely parallel these observations. Among patients with episcleritis, only a small proportion had associated systemic disease, whereas more than one-third of patients with scleritis had an identifiable extraocular disorder. This reinforces the concept that episcleritis is usually a benign, self-limiting condition, while scleritis often reflects a more extensive systemic inflammatory process. Similarly, Nevares A et al. emphasized that recurrent, atypical, or severe episcleritis should prompt clinicians to search for underlying systemic disease, particularly connective tissue disorders and vasculitic conditions [4]. Although most episcleritis cases in the present study were idiopathic, a subset of patients demonstrated associations with tuberculosis and rheumatoid arthritis, highlighting the importance of appropriate clinical evaluation even in apparently benign ocular inflammation.

Among the extraocular diseases identified, rheumatoid arthritis emerged as the most common association, accounting for 8.6% of the total study population. This finding is consistent with previous literature identifying rheumatoid arthritis as the leading systemic disease associated with scleral inflammation. Hsu CS et al. reported that rheumatoid arthritis remains one of the strongest systemic associations of scleritis and is particularly linked to severe forms such as necrotizing anterior scleritis [5]. Chronic immune-mediated vasculitis and collagen destruction associated with rheumatoid arthritis contribute to scleral inflammation and tissue damage. In the present study, rheumatoid arthritis showed a strong association with necrotizing anterior scleritis and posterior scleritis, supporting the observations reported in earlier studies.

Granulomatosis with polyangiitis and rheumatoid arthritis have been recognized as major systemic diseases associated with severe scleral inflammation. Rademacher J et al. demonstrated that patients with ANCA-associated vasculitis and rheumatoid arthritis frequently develop aggressive forms of scleritis and require systemic immunosuppressive therapy [6]. The occurrence of granulomatosis with polyangiitis in the present study further emphasizes the importance of investigating vasculitic disorders in patients presenting with recurrent or severe scleral inflammation.

Tuberculosis represented the most common infectious association in the present study. Ocular tuberculosis may manifest as episcleritis, anterior scleritis, posterior scleritis, or other inflammatory ocular disorders. Watson PG et al. highlighted the diagnostic challenges associated with ocular tuberculosis and stressed the importance of considering this diagnosis in endemic regions [7]. The association of tuberculosis with nodular episcleritis and nodular anterior scleritis observed in the present study is consistent with previous reports from developing countries where tuberculosis remains a significant public health problem.

The role of autoimmune diseases in the pathogenesis of scleral inflammation has been increasingly recognized. Marin-Acevedo JA et al. reported that noninfectious autoimmune scleritis is strongly associated with systemic rheumatologic disorders and frequently requires collaboration between ophthalmologists and rheumatologists for optimal management [8]. In the present study, non-necrotizing diffuse anterior scleritis demonstrated the widest range of autoimmune associations, including rheumatoid arthritis, systemic lupus

erythematosus, ankylosing spondylitis, and granulomatosis with polyangiitis. These findings support the view that diffuse scleral inflammation often represents an ocular manifestation of systemic immune dysregulation.

Systemic lupus erythematosus was identified in a smaller proportion of patients in the present study Sainz de la Maza M et al., in a population-based cohort study, demonstrated that patients with systemic lupus erythematosus have a significantly increased risk of developing ocular inflammatory disorders, including episcleritis and scleritis [9]. Immune complex deposition and vascular inflammation are believed to play important roles in the pathogenesis of scleral involvement in lupus patients. Early detection of ocular manifestations may therefore facilitate timely diagnosis and management of systemic disease.

Ankylosing spondylitis was another autoimmune condition identified among the study participants. Katz M et al. described ocular inflammation as one of the major extra-articular manifestations of spondyloarthritis and emphasized the need for interdisciplinary management of affected patients [10]. Although uveitis remains the most common ocular manifestation, the occurrence of scleral inflammation in patients with ankylosing spondylitis further broadens the spectrum of ophthalmic involvement associated with this disease.

More recently, Yoshida, A et al. reported that systemic diseases continue to play a major role in the etiology of scleritis and significantly influence disease severity, recurrence, and treatment outcomes [11]. Their findings support the observations of the present study, where systemic associations were significantly more common among patients with scleritis than among those with episcleritis. Likewise, Arruza C et al. and McCluskey PJ et al. demonstrated that detailed systemic evaluation, specialist referral, and long-term follow-up substantially increase the likelihood of identifying associated systemic diseases in patients with scleral inflammation [12,13].

Overall, the findings of the present study reaffirm that scleritis should be considered a potential manifestation of systemic autoimmune or infectious disease. Identification of associated extraocular diseases is crucial because it influences treatment strategies, prognosis, and long-term patient outcomes. Comprehensive systemic evaluation and multidisciplinary collaboration remain essential components of the management of patients presenting with episcleritis and scleritis.

Conclusion

Extraocular diseases were identified in 21.1% of patients presenting with episcleritis and scleritis. Rheumatoid arthritis was the most common systemic association, followed by tuberculosis, ankylosing spondylitis, granulomatosis with polyangiitis, and systemic lupus erythematosus. Scleritis demonstrated significantly stronger systemic associations than episcleritis, particularly necrotizing and diffuse anterior forms. These findings highlight the importance of comprehensive systemic evaluation and multidisciplinary collaboration in the management of patients with scleral and episcleral inflammation. Early recognition of associated autoimmune and infectious diseases can facilitate timely treatment, prevent ocular complications, and improve long-term prognosis.

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