Current Approach in Diagnosis and Management of Scleritis

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Introduction

Scleritis is a chronic, painful, and potentially blinding inflammatory disease that is characterized by edema and cellular infiltration of the scleral and episcleral tissues. Because of the potentially devastating ocular complications and possible association with serious systemic disease, the diagnosis of scleritis should not be missed. Scleritis most often presents within 4th–6th decades with a mild preponderance towards women over men (1.6:1)\(^1,2,3\). Scleritis is usually suspected from clinical history, and it is confirmed by its characteristic clinical signs. In a case of posterior scleritis, ultrasonography and other imaging studies may be necessary to confirm the diagnosis.

Anatomic considerations

The function of the sclera is to provide a firm protective coat for the intraocular contents. This coat is resilient enough to allow for variations in the intraocular pressure, firm enough to prevent severe distortion of the contents of the eye on movement or when pressed on by the muscles or external forces.

The bulbar conjunctiva is a thin transparent mucous membrane, the epithelium of which is continuous with the corneal epithelium. Beneath the epithelium lies stroma which is a loosely arranged connective tissue.

Tenon’s capsule is a dense well defined membrane which extends backwards from the limbus to ensheathe the extraocular recti muscles and becomes continuous with the perimysium. It also passes backwards to cover the globe. Posteriorly it becomes inserted into the dural sheath of the optic nerve.

The episclera forms the superficial aspect of the sclera. It is a thin dense, vascularised layer of connective tissue, the fibers of which are continuous with the underlying sclera. The episclera is immobile, when viewed with a slit-lamp microscope. Lamina fusca is the innermost layer of the sclera adjacent to the uvea. In order to reliably differentiate episcleritis and scleritis, an understanding of the anatomy of the vascular plexuses contained within the conjunctiva, episclera, and sclera is essential. The blood supply to this region is enormous, being derived from the anterior ciliary arteries, but with extensive collateral arterial anastomoses to the posterior ciliary arteries at the root of the iris. The anterior system is readily visible with the slit lamp and by anterior segment fluorescein angiography, especially if the eye is inflammed, and its recognition is of vital importance in the differentiation of episcleral and scleral conditions. The separation and displacement of these vascular layers give the most important clinical clues to the site and the severity of the inflammation. On slit lamp examination, three layers of vessels are readily visible. The conjunctival plexus, which is the most superficial layer of vessels, can be moved over the underlying structures. The superficial episcleral capillary plexus is a radially arranged series of vessels lying within the parietal layer of Tenon’s capsule. The vessels in this layer anastomose...
at the limbus with the conjunctival vessels, with other
members of the same plexus, and with the deep plexus.
The deep episcleral capillary network is closely applied
to the sclera in the visceral layer of Tenon's capsule.
The conjunctival and superficial episcleral vessels can
be blanched with 1:1000 epinephrine or 10%
phenylephrine, but the deep vessels are affected slightly.
This is of considerable assistance when attempting to
differentiate deep and superficial scleral inflammation.

**Classification**

In 1976, Watson and Hayreh proposed a clinical
classification of scleritis based upon the anatomic
location of the inflammation and the observed
alterations in the associated vascular structures. This
categorization of disease entities does not infer etiology,
but provides valuable information regarding severity
of inflammation, prognosis, management options, and
association with systemic diseases and with ocular
complications. Few patients progress to a different form
of scleritis from their initial presentation.

Scleritis is defined as anterior or posterior based upon
the location of inflammation, relative to the equator of
the globe. The majority of scleritis is anterior and can
be categorized as non-necrotizing or necrotizing.
Diffuse and nodular scleritis are non-necrotizing and
represent the most common forms of anterior scleritis.
The necrotizing types of anterior scleritis are less
common, but represent a more severe disease entity.\(^1\,\text{,}\,3\) Necrotizing scleritis is classified as either with
inflammation or without inflammation, with the latter
being synonymous with scleromalacia perforans.
Ultrasonographic classification categorizes posterior
scleritis as diffuse or nodular, based upon increased
eye wall thickness or finding of scleral nodule,
respectively.

**Classification of scleritis**

1. **Anterior scleritis**
   a) Diffuse
   b) Nodular
   c) Necrotizing
      i) With inflammation
      ii) Without inflammation (scleromalacia perforans)

II. **Posterior scleritis**
   a) Diffuse
   b) Nodular

Scleritis may be classified etiologically, although it is
most often idiopathic or associated with a systemic
disease, scleritis can also be post surgical or related to
an infectious process. In one study, 25–57% of scleritis
cases were associated with a known systemic condition\(^1\,\text{,}\,2\,\text{,}\,3\). In the Watson and Hayreh series,
connective tissue disorders were present in 15% of
the patients, of which rheumatoid arthritis constituted
10%. In another series with a higher proportion of
necrotizing scleritis cases, half of the patients had an
associated systemic connective tissue or vasculitic
disease\(^3\). Necrotizing scleritis has the highest
association with systemic illness and represents the
most frequent type of scleritis that is the first
manifestation of a systemic condition.\(^1\,\text{,}\,3\). Approximately
two-thirds of patients with scleromalacia perforans have
an associated systemic condition\(^1\), most commonly
longstanding rheumatoid arthritis (47%)\(^3\). Diffuse
scleritis appears to be the most benign form with the
lowest prevalence of associated systemic illness.
Systemic conditions associated with scleritis are shown
in table 1. Vasculitis is a proposed common factor in
the pathogenesis of both scleritis and the systemic
autoimmune disorders. Scleritis may occur following
ocular trauma. Surgically induced necrotizing scleritis
(SINS) can occur after any type of ocular surgery with
scleral manipulation, including cataract surgery,
strabismus surgery, filtering blebs, pterygium surgery,
and operations for retinal detachments. Many
organisms have been reported as possible causes of
scleritis and these are shown in table 2.

<table>
<thead>
<tr>
<th>Systemic diseases associated with scleritis</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Wegener's granulomatosis</td>
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<td>Inflammatory bowel disease:</td>
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<td>Ulcerative colitis and Crohn's disease</td>
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<td>Relapsing polychondritis</td>
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<td>Systemic lupus erythematosism</td>
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<td>Polyarteritis nodosa</td>
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<tr>
<td>Giant cell arteritis</td>
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<td>Behçet's disease</td>
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<td>Polymyalgia rheumatica</td>
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<td>Reiter's syndrome</td>
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<td>Raynaud's disease</td>
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<tr>
<td>IgA nephropathy</td>
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<td>Ankylosing spondylitis</td>
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Infectious scleritis

**Table-2 Infectious scleritis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Organisms</th>
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<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td>Pseudomonas, Proteus mirabilis, Staphylococcus epidermidis, Streptococcus pneumoniae</td>
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<tr>
<td><strong>Viral</strong></td>
<td>Herpes zoster, Herpes simplex, Mumps</td>
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<tr>
<td><strong>Granulomatous</strong></td>
<td>Mycobacterium tuberculosis, Mycobacterium chelonae, Mycobacterium leprae, Syphilis</td>
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<tr>
<td><strong>Fungal</strong></td>
<td>Aspergillus, Pseudallescheria boydii, Sporotrichosis</td>
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<tr>
<td><strong>Parasitic</strong></td>
<td>Acanthamoeba, Toxocariasis, Toxoplasmosis, Onchocerciasis</td>
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**Histopathology**

Previous pathologic studies were based upon tissue obtained from enucleated eyes with advanced disease. Scleral biopsies have rarely been performed because of the high rate of associated complications. The pathologic findings of scleritis are classified as (1) rheumatoid and rheumatoid-like necrotizing scleritis, (2) idiopathic necrotizing scleritis, (3) post infectious scleral inflammation, and (4) sarcoidal inflammation.

The typical feature of rheumatoid or rheumatoid-like scleritis is central scleral necrosis with a distinct surrounding zone of granulomatous inflammation. Inflammatory cell infiltration with polymorphonuclear leukocytes, histiocytes, and lymphocytes within the episcleral tissue and suprachoroidal area, the presence of an associated necrotizing vasculitis, and scleral fibre necrosis between the pars plana and limbus are other notable findings in rheumatoid scleritis.

In scleritis following a previous herpes zoster ophthalmicus infection, histologic findings usually include scleral necrosis, an associated vasculitis, and surrounding zonal granulomatous inflammation, primarily in the anterior sclera. The inflammation can be non-granulomatous and focal. Although the scleritis is suspected to be an immune-mediated response to the prior infection, the presence of a reactive proliferation of granulation tissue distinguishes this form from the rheumatoid type. In infectious scleritis, the presence of microabscesses with or without histologic identification of a pathogen can be a distinguishing factor.

Idiopathic necrotizing scleritis is characterized by chronic, non-granulomatous inflammation and diffuse lymphocytic infiltration of the anterior sclera, episclera, and uvea. The presence of newly formed vascular channels and focal granulation tissue with fibroblasts, lymphocytes, and histiocytes in idiopathic scleritis may be suggestive of a delayed type of hypersensitivity.

**Clinical Presentation of Scleritis**

The clinical presentation of scleritis depends upon the anatomic site involved and extent of inflammation. The characteristic feature of scleritis is the severe pain that may involve the eye and orbit and radiates to involve the ear, scalp, face, and jaw. Scleritic pain is typically dull and boring in nature, exacerbated by eye movement. It is worse at night often interfering with sleep, and characteristically wakes the patient from sleep early in the morning. The pain is usually severe in nature and resistant to mild analgesic.

Scleritis typically has a gradual onset of redness with increasing inflammation over several days. In contrast to the brighter redness of episcleritis, scleritis is usually a darker violaceous-red hue due to the depth of the congested vascular plexus.

The patient with anterior scleritis usually notices redness and tenderness of the globe. There may be photophobia and lacrimation. Patient with posterior scleritis may present with reduced vision with or without pain. Patients may have features of an underlying systemic disorder.
Physical examination: ocular signs

The key clinical observations in patients with scleral inflammation involve determining the relationship of the vascular plexuses to each other and the site of maximum vascular involvement best seen with red-free light on slit-lamp biomicroscope. Deep discoloration, extent of scleral edema, and areas of increased transparency are best appreciated in natural day light.

A hallmark finding that distinguishes scleritis from episcleritis is the presence of scleral edema. Edematous sclera can bow forward, displacing the deep episcleral vascular plexus and exacerbating deep vascular congestion. To assess the degree of scleral involvement, blanching the superficial conjunctival and episcleral vasculature with topical 10% phenylephrine can improve visualization of the underlying tissue. Further examination using a red-free filter is instrumental in evaluating the vascular architecture, areas of avascularity, and cellular infiltration of the episclera. The anatomic location of the inflammation and typical alterations in the vessels form the basis of the classification of the vascular layers overlying the nodule are displaced forward.

Diffuse anterior scleritis: It is the most benign and most common form of scleritis characterized by diffuse involvement of anterior sclera by oedema and dilatation of deep episcleral vascular plexus. These changes lead to distortion of the normal vascular pattern which remains as permanent marker of past scleral inflammation. The swollen sclera loses its normal appearance and takes on a dusky hue which is much more obvious when viewed in daylight (Fig. 1). The globe is usually tender to touch.

Nodular anterior scleritis: Nodular anterior scleritis can present with single or multiple scleral nodules. Typically, the nodule is a darker hue of red, separate from the overlying episclera, immobile, and tender to palpation. These features distinguish this form of scleritis from nodular episcleritis. The lack of necrosis within the nodule and the containment of inflammation within the borders of the nodules differentiate this form from necrotizing anterior scleritis with inflammation. All of the vascular layers overlying the nodule are displaced forward (Fig. 2).

Necrotizing scleritis with inflammation: Necrotizing scleritis, the most severe form of scleritis is a serious threat to vision and integrity of the eye. Aching pain, particularly in head, is usually the predominant feature. The scleral involvement is characterized by severe vasculitis and there are visible areas of capillary non perfusion on clinical examination. Ischemia subsequently leads to scleral infarction and necrosis. The edges of the affected area is usually far more inflammed than its centre where destructive changes are occurring.

Thinning of the sclera with increased visualization of the underlying uveal tissue may result in a bluish-grey hue to the sclera. If any form of necrotizing scleritis remains untreated then tissue loss occurs, producing...
milky white areas of necrotic sclera, episclera, and conjunctiva. With time this dead tissue is absorbed, leaving areas of dark choroid covered only by a thin layer of atrophic conjunctiva (Fig. 3).

**Scleromalacia perforans:** Scleromalacia perforans does not produce the acute signs of necrotizing scleritis, may present with blurred vision from high astigmatism due scleral thinning leading to loss of scleral rigidity. The sclera may appear porcelain-like, as the vascularity diminishes. Necrotic sclera can slough or become sequestered. With severe scleral thinning, increased visualization of the dark underlying uvea may occur. Due to decreased scleral vascularity attributed to arteriolar vaso-occlusion, large abnormal vessels may cross and surround the areas of affected region (Fig. 4).

![Fig. 4. Scleromalacia Perforans](image)

**Posterior Scleritis:** The presentation of posterior scleritis depends upon the severity, extent, and location of inflammation. The common signs of posterior scleritis are posterior extension of anterior scleritis, a serous or exudative retinal detachment, optic disc edema, circumscribed subretinal mass, choroidal folds, retinal striae, elevated intraocular pressure, and a bullous or annular choroidal detachment ⁹. Extension of scleral inflammation to the adjacent choroid can lead to an overlying serous detachment of the neurosensory retina, which represents the most common sign of posterior scleritis ⁹, ¹⁰. Ultrasound remains the key to diagnosis with which the thickened posterior coat of the eye (usually greater than 2 mm) can be identified (Fig. 5.)

**Surgically induced necrotizing scleritis:** Surgically induced necrotizing scleritis (SINS) can occur after any type of ocular surgery with scleral manipulation, including cataract surgery, strabismus surgery, filtering blebs, pterygium surgery, and operations for retinal detachments ¹¹, ¹², ¹³, ¹⁴. Inflammation is typically localized to the site or adjacent to the site of surgery, but may progress to involve the entire sclera ¹¹, ¹³. Patients who have SINS need careful systemic investigation as 62-90 % of patients in one study were later diagnosed with autoimmune vasculitic disease which required immunosuppressive therapy. ¹¹, ¹², ¹³

**Investigations:**

Because so many patients with scleral disease have systemic disease, a thorough physical examination is essential.

The following routine investigations should be performed:

1. Hemoglobin
2. White blood cell count and differential count
3. Erythrocyte sedimentation rate
4. If connective tissue disease is suspected, full immunologic investigations are undertaken, including levels of immunoglobulins and immunofluorescent studies for autoantibodies (including rheumatoid factor and antinuclear and anti-ds-DNA antibodies); circulating immune complexes are searched for. If Wegener’s granulomatosis or polyarteritis nodosa are suspected, the anti-nuclear cytoplasmic antibody (ANCA) tests should be performed. The C-reactive protein is the best indicator of an active generalized inflammatory response.

5. Serum uric acid
6. Full serologic tests for syphilis
7. X-ray chest

*B-scan ultrasonography* should never be omitted from the examination of patients with scleritis. Now that high-quality ultrasonography has become available, the
The extent and severity of the inflammation can be determined with great accuracy. Many patients who were formerly thought to have only anterior segment disease have been found to have extensive and sight-threatening posterior scleritis as well. It also has become known that many patients with posterior scleritis with few symptoms and signs have much more extensive disease than had previously been considered possible. The hallmark features of posterior scleritis seen with B-scan ultrasonography are helpful in differentiating posterior scleritis from other conditions. B-scan ultrasonography may reveal the characteristic flattening of the posterior aspect of the globe due to retrobulbar edema. Abnormally increased thickening of the posterior ocular coats of the globe >2 mm, optic disc swelling, distension of the optic nerve sheath, retinal detachments, and choroidal detachments can be detected. Fluid can accumulate in the posterior episcleral space and extend around the optic nerve, forming the characteristic “T-sign” on B-scan.

Ultrasound biomicroscopy: This can be valuable for better delineation of scleral thinning and ruling out any malignancy. An underlying squamous cell carcinoma, medulloepithelioma can extend to the sclera.

Complications of Scleritis:

Decreased visual acuity, keratitis, cataract, uveitis, and glaucoma are ocular associations indicating the spread of scleral inflammation to adjacent tissues. Complications are more frequent in severe necrotizing scleritis and posterior scleritis. Due to potential ocular complications related to scleritis, early diagnosis and treatment of scleritis and its associated ocular manifestations are critical.

Vision may be limited due to keratitis, anterior uveitis, cataract, change of refractive status, macular oedema, optic disc oedema, or atrophy, retinal detachment, epiretinal membrane formation, macular cyst or hole, or raised intraocular pressure. Decreased vision occurs most frequently with posterior scleritis (45-84 %), necrotizing scleritis (74-82 %), nodular scleritis (26 %) and least often with diffuse anterior scleritis (9 %).

A mild to moderate anterior uveitis has been observed in 30-42 % of patients with scleritis, most frequently (69 %) with necrotizing scleritis. Almost half of the patients with posterior scleritis have an anterior uveitis. Corneal changes are most frequently seen in patients with necrotizing scleritis including peripheral corneal thinning, stromal keratitis, and peripheral ulcerative keratitis. Patients with scleritis and keratopathy have more chance of being associated with systemic diseases.

During any stage of scleral inflammation, the intraocular pressure may be elevated due to several different mechanisms, such as obstruction of the aqueous outflow channels, elevated episcleral pressure, angle closure, or secondary to a steroid response. Cataract formation may be accelerated by long-standing inflammation or secondary to steroid use. Scleral thinning most commonly occurs in necrotizing scleritis and may progress to staphyloma in the presence of raised intraocular pressure.

Medical management:

The aim of treatment is to treat the cause, to control the inflammatory process and thereby reduce the damage to the eye. Treatment almost always requires systemic therapy. Patients with an associated disease need specific treatment.

○ Treatment of noninfectious scleritis: Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or immunomodulatory drugs are indicated. Topical therapy is routinely insufficient. This treatment must be individualized for the severity of the scleritis, response to treatment, adverse effects, and presence of the associated disease.

Diffuse scleritis or nodular scleritis:

○ The initial therapy consists of an NSAID (eg: Indomethacin 75mg twice daily after meal). In case of therapeutic failure, 2 different NSAIDs should be tried in succession with the first drug. In high-risk patients, consider appropriate gastrointestinal protection with misoprostol or omeprazole.

○ If NSAIDs are not effective or have untoward complications, oral corticosteroids (tab: Prednisolone) at doses of 1 mg/ kg body weight can be substituted. Remission may be maintained with continued NSAIDs.
Periorbital and subconjunctival steroid injections (Inj.Triamcinolone acetonide 40 mg/ml) are also effective in non-necrotizing anterior scleritis (Fig. 6, Fig. 7, Fig. 8). In case of therapeutic failure of corticosteroids, immunosuppressive drugs should be added or substituted. Methotrexate (initial dose-15 mg/week and tapered monthly) can be the first choice, but azathioprine, cyclophosphamide, or cyclosporine may be helpful. Tumor necrosis factor alpha (Tumour necrosis factor (TNF)-alpha) inhibitor infliximab, may be effective, although further investigation is warranted.

**Necrotizing scleritis:**
- Cyclophosphamide(100 mg per day orally and tapered monthly) should be the first choice in treating patients with associated potentially lethal vasculitic diseases, such as Wegener’s granulomatosis or polyarteritis nodosa.
- The initial therapy consists of immunosuppressive drugs that are supplemented with corticosteroids during the first month; the latter is tapered slowly, if possible. Cyclophosphamide is the most effective drug.
- In case of therapeutic failure, another immunomodulatory drug, such as infliximab, may be effective. Other alternatives are daclizumab and rituximab, although their efficacy awaits further study.
- Periocular steroid injections should be applied with great caution in cases of necrotizing scleritis or peripheral ulcerative keratitis. Some authors believe that depot steroids actually may exacerbate necrotizing disease or an underlying infection.
- Pulse intravenous cyclophosphamide with or without pulse intravenous corticosteroids may be required in case of emergencies and may be followed by maintenance therapy.

**Treatment of infectious scleritis:** Systemic treatment with or without topical antimicrobial therapy always is required. Differentiating infectious scleritis from non-infectious scleritis is important because corticosteroid therapy and immunosuppressive therapy (often used in noninfectious autoimmune scleritis) are contraindicated in active infections.

**Surgical care:**
Tectonic surgical procedures rarely may be required to preserve the integrity of the globe.

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**Fig. 6.** Sub-conjuntival triamcinolone acetonide injection in a case of anterior scleritis

**Fig. 7.** Diffuse anterior scleritis before giving subtenon injection of triamcinolone acetonide.

**Fig. 8.** Resolution of diffuse anterior scleritis two days after giving sub-conjuntival injection triamcinolone acetonide.
Consultations

- Rheumatology or internal medicine consultation for associated disease
- Hematology, oncology, or internal medicine consultation for immunosuppressive therapy

Conclusions

Scleritis is highly associated with potentially sight threatening ocular complications and serious systemic diseases. Early diagnosis and treatment of scleritis is important in preventing and diminishing ocular and systemic morbidity. Hence, attempts should be made to achieve excellent long-term prognosis with careful clinical history, detailed ocular examination, and use of immunosuppressant drugs whenever necessary.

References