Scleritis: presentations, disease associations and management

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ABSTRACT
Scleritis is a serious inflammatory condition that is often painful, and in severe cases can result in permanent loss of vision. Approximately half the patients affected have no identifiable cause, but 30%–40% have an underlying systemic autoimmune condition. Scleritis may be the initial manifestation of Wegener’s granulomatosis or rheumatoid arthritis, and all patients with scleritis require a thorough systemic evaluation.

Scleritis has a variable presentation and disease course, and may be an acute mononuclear illness, a relapsing remitting process, or take a chronic course. Treatment options include local therapy with subconjunctival steroid injections for non-necrotising scleritis, and systemic anti-inflammatory or immunosuppressive therapy. Biologic agents have been used with success in some refractory cases. Ocular and systemic morbidity is reduced by timely treatment with immunosuppressant medications.

INTRODUCTION
Scleritis is a severe and potentially vision-threatening inflammation affecting the outer coat of the eye that causes disabling eye pain or visual disturbance. Almost 50% of cases are associated with systemic autoimmune disease, such as rheumatoid arthritis (RA) and Wegener’s granulomatosis, where scleritis may be the first manifestation. Accurate detection of scleritis, and the ability to distinguish it from more common eye conditions, such as conjunctivitis or corneal problems, is crucial as it can also lead to diagnosis of other organ-involving vasculitis. Prompt diagnosis and initiation of treatment may also reduce risk of ocular complications and loss of vision.

This article will review the classification system of scleritis and episcleritis and approach to the patient. Important aspects of history and the clinical signs will be reviewed, including important features that can be evaluated without the aid of a slit lamp or other specialised ophthalmology equipment. Management strategies will also be discussed including the role of local and systemic immunosuppressant medications.

CLASSIFICATIONS OF SCLERITIS
The sclera is a tough connective tissue layer that begins at the limbus, where it is continuous with the cornea, and ends at the optic canal. It is avascular, but has a rich supply of sensory nerves. Scleritis is diagnosed based on clinical findings of inflammation affecting the sclera and involvement of the superficial and deep episcleral venous plexuses. The classification system devised by Watson and Heyreh categorises scleritis into anterior and posterior types depending on the anatomical location of the disease. Anterior scleritis is further classified as diffuse, nodular or necrotising. Necrotising scleritis typically is associated with inflammation and a red, painful eye, but in rare cases can present with progressive thinning or melting of the sclera without inflammation, known as scleromalacia perforans.

Posterior scleritis is inflammation of the sclera posterior to the insertion of the rectus muscles and occurs less frequently than anterior scleritis, accounting for 6%–16% of all cases. It can also be classified as diffuse or nodular, and when patients have both anterior and posterior scleritis they are considered as posterior scleritis.

Diffuse anterior scleritis is the most common type seen clinically, accounting for 45%–61% of all cases. Necrotising scleritis is rare, affecting 3.5%–22%. Less than 10% of cases will progress from one anatomical type of scleritis to another. Episcleritis is not synonymous with scleritis, and is caused by inflammation in the episcleral layer of the eye rather than the deeper scleral layer. The distinction is important, as episcleritis is not vision-threatening, rarely causes disabling symptoms, and is less commonly associated with any systemic autoimmune disease. Episcleritis is far more common than scleritis and can be simple or nodular. The clinical features of episcleritis (and its differentiation from scleritis) will be discussed later in this review.

EPIDEMIOLOGY
A large series of 172 patients reported by Sainz de la Maza and Foster, found a mean age at time of onset of 50 years, with age range 11–87 years. There is a female preponderance in western populations, accounting for almost two-thirds of cases. Bilateral inflammation is present in 30%–50% of patients. Scleritis can be self-limited with complete resolution after treatment, or have a chronic course with need for ongoing immunosuppressant treatment.

CAUSES OF SCLERITIS
The incidence of systemic disease in patients with scleritis is reported between 59% and 48%. RA is the most common connective tissue disease seen in association with scleritis and occurs in 10%–33% of patients. These patients usually have a long history of severe, erosive joint disease, although Goldstein et al recently reported that a significant minority of patients presenting with scleritis were eventually found to have RA.

Scleritis is the first manifestation of a systemic disease process in 15% of patients, and therefore, all patients without a known cause need general
work-up for autoimmune disease. Wegener’s granulomatosis and relapsing polychondritis are the most frequent diseases discovered subsequent to diagnosis of scleritis. Systemic work-up should include anti neutrophil cytoplasmic antibodies (ANCA), creatinine, urinalysis, anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor and treponemal serology. In some cases, it may take years for the final diagnosis to be known.

Certain ocular characteristics can indicate a higher chance of underlying autoimmune disorders. Patients with necrotising scleritis have highest association with systemic disease (45–95%), compared with posterior scleritis (19–45%). Wegener’s granulomatosis is the systemic vasculitic disease most frequently associated with necrotising scleritis. Almost 90% of patients with conjunctival involvement adjacent to an area of scleritis, such as peripheral ulcerative keratitis (PUK), will be found to have an underlying systemic disease (figure 1).

Other entities that can cause scleritis are ocular infections, and ocular malignancies that may masquerade and present clinically as endogenous inflammatory scleritis. Infectious scleritis is rare, accounting for 4–18% of cases, and can be caused by viruses, including herpes simplex and zoster, bacteria and fungi. Infectious scleritis can develop contiguous to an area of infectious keratitis (figure 2).

Surgically induced necrotising scleritis (SINS) usually has onset within 1 month of ocular surgery, but rarely can develop many years later. Multiple surgeries increase the risk, with three-quarters of patients having two or more surgical procedures prior to onset of SINS. The inflammation tends to remain localised to the area of the surgical wound. About 50%–90% of patients developing SINS will have an underlying systemic autoimmune disease, although this may not be identified until after development of scleritis.

Scleritis has rarely been described with medications including bisphosphonate use, and in association with ocular malignancy.

**Clinical assessment**
Clinical assessment is aimed at confirming the diagnosis and determining the type of scleritis, detecting complications, and identifying the underlying causes or presence of associated systemic disease.

**Episcleritis**
Episcleritis is a mild condition and many patients will present with a red eye and no symptoms of discomfort. Severe pain is not a feature of episcleritis. If discomfort occurs it will be mild and will not disrupt sleep. Mild watering may be present, but symptoms such as sticky discharge or itch suggest an alternative diagnosis, such as conjunctivitis.

**Clinical signs**
Episcleritis can be simple or nodular and frequently involves only one sector of the eye. The redness caused by episcleritis is described as salmon pink, whereas the deeper inflammation seen in scleritis gives the eye a deeper purple hue, and this is best appreciated using natural light. Instillation of phenylephrine 10% drops will result in the episcleral vessels constricting and blanching in episcleritis, but not in scleritis.

**Anterior scleritis**
Anterior scleritis almost always presents with severe pain. This has the character of a headache around the eye and is often severe enough to disrupt sleep. The eye will be tender to touch. The eye is intensely red and photophobia may be a feature. Vision is usually normal.

Rarely, scleritis can present with progressive thinning of the sclera without significant redness or pain. This pattern is predominantly seen in patients with RA, and patients may present having noticed the sclera acquiring a blue-black hue, resulting from the melanocyte-laden choroidal layer of the eye becoming visible through the very thin sclera. This is known as scleromalacia perforans and usually develops in elderly female patients.

Pain may also be absent in patients already on immunosuppressive treatment at the time their symptoms begin.

**Clinical signs**

**Macroscopic examination**
The redness associated with anterior scleritis is intense, and has a ‘violaceous hue’, imparted by the involvement of both the deep and superficial episcleral vascular plexuses. This is seen most readily with natural light and the patient looking in different directions of gaze, or with a direct ophthalmoscope. The scleritis can be diffuse, involving the whole external eye, or sectoral. In some cases, a firm, red, tender nodule will be visible on the sclera. If a blue or dark brown appearance is seen then this is indicative of scleral thinning.

Anterior scleritis is almost always associated with severe pain. The eye will feel tender to palpation, and clinically this is elicited by applying gentle pressure through the eyelids. Uveitis (intraocular inflammation) does not cause a tender eye, and
this can help distinguish the entities without a slit lamp. The pupil reactions will be normal (unlike acute glaucoma) and the cornea will be clear centrally.

**Slit lamp biomicroscopy**

Slit lamp examination will show congestion of the blood vessels and oedema of the sclera and episclera which causes displacement of the superficial and deep edges of the slit lamp beam forward. Phenylephrine 10% can be instilled if there is any diagnostic confusion about whether the patient has scleritis or episcleritis. If the patient has anterior scleritis, the redness will persist.

The peripheral cornea can become involved in scleritis, and this is indicative of severe disease. Clinical findings include peripheral corneal infiltrates, which will appear as small white lesions, and corneal thinning and ulceration. These patients have a higher chance of underlying systemic vasculitis, such as Wegener’s granulomatosis, and of vision loss.

Necrotising scleritis is also a sign of severe vision-threatening disease. Visible areas of capillary non-perfusion may be seen as a pale patch of yellow in the sclera surrounded by dilated vessels which will centrifugally expand (figure 2). The ischaemic sclera will become necrotic and then thinned, leading to a blue appearance of the affected sclera (figure 3). In extreme cases, the eye can perforate, particularly following mild trauma.

Uveitis (intraocular inflammation) can accompany anterior scleritis. At the slit lamp, this will be seen as cells or flare within the anterior chamber, or cells within the vitreous cavity. Patients with uveitis will be more likely to complain of blurred vision, photophobia and new onset of floaters, in addition to the features previously mentioned. Intraocular inflammation is graded according to the Standardisation of Uveitis Nomenclature criteria.

**Posterior scleritis**

Posterior scleritis poses more of a diagnostic challenge as clinical presentation is varied. Pain is a feature in about half the patients, and one-third will have associated anterior scleritis. Blurred vision is common. The posterior sclera is thickened and inflamed, and this can cause a refractive shift as the focal point of the retina moves more anteriorly. The swollen choroid can develop folds within it and the patient may complain of distortion (figure 4).

A mild ptosis may be present, and some patients experience pain on eye movements as the muscles insert into inflamed sclera. If there is associated uveitis, the patient will also complain of photophobia and may notice floaters.

**Figure 3** Scleral thinning following chronic scleritis in a poorly compliant patient. This figure is only reproduced in colour in the online version.

**Figure 4** Residual choroidal folds following right idiopathic posterior scleritis. This figure is only reproduced in colour in the online version.

**Clinical signs**

**Macroscopic examination**

The patient will usually have reduced Snellen visual acuity. Other external eye signs that may be present are a mild ptosis and redness. The redness may be subtle and may only be noticed in extremes of gaze, or can be completely absent.

**Slit lamp biomicroscopy**

The physical examination will be entirely normal in approximately one-fifth of patients. The anterior segment may show signs of inflammation, such as anterior scleritis or uveitis. In one series, 12% had elevated intraocular pressure. The anterior chamber may be shallower on the affected side due to swelling and rotation of the ciliary body.

Examination of the posterior pole may reveal a mildly swollen, hyperaemic optic nerve. However, the optic nerve function will be normal and the patient will have normal pupil responses to light, intact colour vision and visual fields. This distinguishes the nerve swelling from other causes such as optic neuritis or an ischaemic optic neuropathy.

Exudative retinal detachments are seen in 25%, most commonly over the macular region. Nodular posterior scleritis is uncommon, but if present will present as a pale solid mass in the posterior segment. This can mimic other pathologies including amelanotic melanoma of the choroid. Other posterior segment findings include choroidal folds and choroidal effusions.

B scan ultrasonography is an extremely useful adjunctive investigation to use in posterior scleritis, as this confirms presence of scleral thickening and demonstrates any scleral nodules. A ‘T sign’ is often present, where fluid is seen in Tenon’s capsule behind the swollen sclera and surrounding the optic nerve. CT or MRI scans will also demonstrate scleral thickening and confirm a diagnosis of posterior scleritis, although CT scanning has the disadvantage of radiation exposure.

**TREATMENT**

There are three important considerations before deciding on treatment for ocular inflammation. First, are there troublesome symptoms or vision-threatening complications? Is there any concurrent systemic disease that requires treatment? Have infections or conditions that masquerade as endogenous inflammation (such as malignancy) been ruled out? The first two questions determine necessity and urgency of treatment, whereas the last question addresses the safety of treatment. Treatment of infectious or masquerade scleritis is directed towards the specific cause, and will not be discussed further here.
Non-steroidal anti-inflammatory medication

Mild forms of scleritis respond to oral non-steroidal anti-inflammatory medication (NSAIDs), but topical treatment is not effective. An overall response rate of 30%–92% has been reported for diffuse and nodular anterior scleritis. More aggressive types (particularly necrotising and posterior scleritis) require systemic steroid treatment, and often require other immunosuppressant therapy.

Steroids

Systemic steroids

High doses of oral prednisone (1 mg/kg/day) are commenced to achieve quiescence of disease, and then therapy will be slowly tapered until cessation or a maintenance dose is achieved. Most scleritis are very steroid-sensitive, but rebound of inflammation may occur during the taper. Patients who relapse on doses higher than 7.5–10 mg prednisone per day should be considered for adjunctive immunosuppressive therapy.

Loading treatment with intravenous methylprednisolone can be considered for severe necrotising scleritis or scleritis associated with PUK before switching to oral therapy.

Local steroids

Topical steroids are useful for episcleritis, or concomitant anterior uveitis, but do not penetrate the sclera adequately to treat scleritis.

Recent studies have demonstrated that subconjunctival triamcinolone injections can be effective in controlling inflammation in non-necrotising anterior scleritis. Local therapy has the significant advantage of avoiding systemic side effects, and can be performed simply in a clinic scenario under topical anaesthetic.

Injections do need to be repeated for chronic scleritis as the effect wears off at between 18 weeks and 116 months. There are potential ocular side effects, such as promoting cataract formation, and causing transient elevation of intraocular pressure in approximately 5%–16%.

This generally responds to medical therapy with topical glaucoma medications. The largest series reported to date is from Albini and Zamir, who treated 38 eyes of 35 patients and found 96% had complete resolution of scleritis with average time to recurrence as 116 months.

Roufas et al reported their experience of treating 12 patients who had failed systemic treatment with 25 subconjunctival triamcinolone injections. Complete resolution of symptoms and signs of scleral inflammation occurred after 25 of the 25 injections administered.

Choosing local or systemic steroids

There are no absolute rules for when local steroids are preferable to systemic, however, certain factors influence the decision. In children, local steroids carry certain disadvantages, including the need for a general anaesthetic for administration, and hence, systemic immunosuppression is preferable. Intraocular pressure can be difficult to measure in small children due to cooperation, meaning it is harder to monitor steroid-induced rise in intraocular pressure, and children are also far more susceptible to this complication developing. Cataract management is also more problematic in children.

Local steroid therapy is also avoided in necrotising scleritis, as there have been very rare case reports in the 1970s of scleral melt and perforation developing following steroid injections. It is difficult to be certain that this was a true medication-induced side effect rather than a manifestation of the underlying disease process, however, most clinicians use systemic therapy when treating this patient group.

Second-line medications

Second-line immunosuppressant medications are added when there is difficulty weaning the steroid dose below 10 mg prednisone daily, particularly in cases that persist for more than 3 months. Approximately 26% of patients will need additional immunosuppression treatment. In cases of necrotising scleritis, a second-line agent will be added from the time of diagnosis.

Many agents have been used, including methotrexate, azathioprine, mycophenolate and cyclophosphamide. Severe scleritis is often treated with a combination of steroid and cyclophosphamide. In 1984, Foster et al reported results from 34 patients with RA and necrotising scleritis, or PUK, who either received treatment with steroids or NSAIDs (‘conventional therapy’) or cytotoxic immunosuppression. Nine patients (55%) of the conventional therapy group died of a vascular-related event within 10 years, and in 76% the ocular inflammatory process progressed. The immunosuppression group had a significantly improved prognosis, with only one of 17 patients dying within 10 years (6%), and no patients experienced progression of ocular disease.

Biologic agents

Evidence for use of biologic agents in scleritis is still based on small case series. The efficacy of tumour necrosis factor (TNF) blockers in treatment of RA has been well established, however, active scleritis complicating RA may not respond despite a beneficial effect on joint inflammation. In a retrospective study by Smith et al, six patients receiving etanercept had control of arthritis, but only two had improvement in scleritis, while three patients actually developed scleritis after commencement of etanercept. A greater efficacy of infliximab in comparison with etanercept has been found in several series.

Recently, Doctor et al published a series of 10 patients’ refractory to other immunosuppressive treatment who received treatment with infliximab. They found favourable response in 90%, and 60% were able to cease all other immunosuppression. The average time to clinical response was 13 weeks.

The role for other biologic agents is still evolving. There are case reports and small series describing efficacy of rituximab in scleritis. Recently, Taylor et al have reported on 10 patients with Wegener’s granulomatosis refractory to other treatment, including three with scleritis, who had complete response to two doses of rituximab.

Surgical management of inflammatory complications

Surgery in scleritis patients can either be required acutely, to restore the integrity of the globe when scleral melt and perforation has occurred or is impending, or as delayed intervention for visual rehabilitation.

Medical treatment of the underlying scleritis is the mainstay of scleritis management, as control of inflammation will prevent further melting and perforation. If perforation does occur, a graft is performed as an emergency procedure. Graft materials used most commonly are sclera or cornea. All necrotic tissue is removed first, as this removes the source of lytic enzymes that propagate further melting. Visual outcomes are generally very poor for eyes that experience scleral or corneal perforation through melting.

Cataract formation is the most common indication for rehabilitative surgery in a patient with scleritis. Long-term requirement for prednisone will accelerate cataract formation, and this will be further compounded if local steroid injections are used, or if the patient also develops a degree of intraocular inflammation. The role of cataract extraction has occurred or is impending, or as delayed intervention for visual rehabilitation.
inflammation. The important principle of surgery in these patients is that the eye must be quiet on stable dose of immunosuppressant medications for at least 3 months before contemplating surgery. Even routine surgery in an eye with no prior history of scleritis or uveitis will result in some inflammation, and this response will be exaggerated in patients with ocular inflammation. These patients require increased immunosuppression in the perioperative period, starting at least 5 days before surgery, and meticulous follow-up. A scleral or corneal melt may still develop despite these measures.11

**VISUAL PROGNOSIS**

Series reported from tertiary uveitis centres demonstrate that scleritis can be associated with serious ocular morbidity and vision loss, in addition to the often disabling symptoms. Sainz de la Maza et al reported that 57% of patients with scleritis lost more than two lines of snellen visual acuity, with median follow-up of 15 months.2 Early treatment of posterior scleritis limited visual loss, but McCluskey et al found that almost one-third of patients still lost more than two lines of vision.15

Necrotising scleritis and peripheral corneal involvement have been shown by several authors to be poor prognostic factors. Patients with Wegener’s granulomatosis have a higher likelihood of necrotising scleritis, visual loss and development of PUK than patients with idiopathic scleritis or scleritis occurring in association with other autoimmune diseases.2 Hoang and Lim identified a similarly severe disease course in ANCA-positive patients with scleritis, and these patients had more ocular complications (86% vs 31%) including keratopathy and vision loss.33 These patients are more likely to have undiagnosed primary vasculitic disease.

**CONCLUSION**

Patients with scleritis can present with disease that ranges from mild to vision threatening. There is a strong correlation between scleritis and systemic autoimmune disease, and the eye problems will be the first manifestation of multisystem disease in almost 20% of patients. This means that all patients presenting with ‘idiopathic’ scleritis must be investigated for underlying disease. Necrotising scleritis and PUK are more frequent in potentially life-threatening diseases, such as Wegener’s granulomatosis, and ocular and systemic morbidity is reduced by timely treatment with immunosuppressant medications.

### Key references


### MULTI-CHOICE QUESTIONS

1. Local steroid injections are an appropriate management choice for necrotising anterior scleritis, true or false?
2. Posterior scleritis can be present in an eye with a normal eye examination, true or false?
3. Rheumatoid arthritis is the most common systemic disease association found with scleritis, true or false?
4. Scleritis can be induced by some medications, true or false?
5. Posterior scleritis is the most common form encountered in clinical practice, true or false?

### Competing interests

None.

**Provenance and peer review** Commissioned; externally peer reviewed.

**REFERENCES**


ANSWERS

1. FALSE, there is a risk of further scleral melting, and local injections should only be used in non-necrotising disease.

2. TRUE

3. TRUE

4. TRUE, for example bisphosphonates.

5. FALSE, diffuse anterior scleritis is most common.
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