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MAJOR REVIEW

Scleritis

Narciss Okhravi, PhD, FRCOphth,[1] Bola Odufuwa, FRCOphth,[1] Peter McCluskey, MD, FRCS,[2] and Susan Lightman, PhD, FRCOphth[1]

[1]Department of Clinical Ophthalmology, Institute of Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD, United Kingdom; and [2]Department of Ophthalmology, Royal Prince Alfred Hospital, Missenden Road, Camperdown, New South Wales, 2050, Australia

Abstract. Scleritis is typically a severe painful inflammatory process centered in the sclera that may involve the cornea, adjacent episclera, and underlying uvea; it poses a significant threat to vision. Careful clinical history taking, detailed ocular examination, appropriate investigation for ocular disease with or without underlying systemic disease, and timely intervention with the use of immunosuppressant drugs when necessary, has improved the long-term outcome for patients with this disease. (**Surv Ophthalmol 50**:351–363, 2005.

Key words. autoimmune • episcleritis • infectious • masquerade • necrotizing • nodular • scleritis • scleromalacia

I. Introduction

Scleritis is defined as inflammation of the sclera, and it has a characteristic clinical picture. It is typically a severe painful inflammatory process centered in the sclera that may involve the cornea, adjacent episclera, and underlying uvea; it poses a significant threat to vision. Up to 50% of patients with scleritis have evidence of an underlying systemic disease. Scleritis is usually suspected from the clinical history, and it is confirmed by its characteristic clinical signs. When the posterior sclera is involved, clinical signs may be less obvious and ultrasonography or other imaging studies may be necessary to confirm the diagnosis.

A. OCULAR ANATOMY

In order to understand the pathophysiology of this condition, a review of ocular surface anatomy is required. The sclera is an incomplete shell comprising approximately 90% of the outer coat of the eye; it begins at the limbus and terminates at the optic canal. The sclera is composed of extracellular matrix—collagen, elastin, proteoglycans, the bundles of which run in whorls and loops. The innermost part of the sclera is the lamina fusca, which has many grooves caused by the passage of ciliary vessels and nerves. Anteriorly, the sclera is continuous with the cornea at the corneoscleral junction, and lying just posterior to this, within the sclera, is the canal of Schlemm. Posterior to the canal is the scleral spur, which is triangular with its apex pointing anteriorly and inward and attaching to the ciliary body. The posterior pole of the sclera is weakened and has a sieve-like appearance (lamina cribrosa) where it is perforated by the axons of the optic nerve. Here, the sclera is fused with the dura mater and arachnoid sheaths of the optic nerve, hence explaining the optic

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nerve swelling seen in 43% of eyes with posterior scleritis.[17] The sclera has a rich sensory innervation from the ciliary nerves, which pierce the sclera around the optic nerve. Many short posterior ciliary nerves supply the posterior portions and two long posterior ciliary nerves supply the anterior region. Because the extraocular muscles are inserted into the sclera, the dull ache of scleral inflammation is made worse by ocular movement.[116]

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. There is a vascular plexus of vessels within the conjunctiva and two vascular layers within the episclera, superficial and deep. The sclera itself is avascular, and, therefore, highly dependent on the vascular coats on either side. Anteriorly, the episclera has a rich blood supply from the anterior ciliary arteries, which form a rich plexus deep to the conjunctiva. These vessels form extensive collateral arterial anastomoses with the posterior ciliary arteries at the root of the iris and are normally inconspicuous but become visibly congested in the presence of inflammation.[116] The anterior vascular system is readily visible with the slit-lamp and can be imaged by fluorescein angiography.[127] The superficial episcleral capillary plexus is a radially arranged series of vessels, which anastomose at the limbus with the conjunctival vessels and with the deep plexus. The deep episcleral capillary network is closely applied to the sclera. Posteriorly, four vortex veins drain the choroidal circulation, pierce the sclera posterior to the equator, and join the ophthalmic vein.[116]

B. DIFFERENCE BETWEEN SCLERITIS AND EPISCLERITIS

Scleritis is often confused with episcleritis, which is inflammation confined to the superficial episcleral tissue and does not involve the deep episcleral tissue that overlies the sclera. Episcleritis is a mild non-vision-threatening form of ocular inflammation that is usually idiopathic in nature and is not usually associated with involvement of other ocular structures although adjacent corneal involvement can be seen and the intraocular pressure may be raised. The clinical differentiation of episcleritis and scleritis involves a detailed history and a careful ocular examination to determine which layers of the wall of the eye are involved by inflammation. Differentiation is important at presentation as management, prognosis, and complications are very different for these two diseases and long term studies have shown that very few patients progress from one to develop the other.[107,121]

To sort out the clinical signs it is essential to understand the anatomy of the episclera and sclera, the vascular plexuses contained therein, and to appreciate the examination techniques that allow this determination. The key clinical observations in patients with scleral inflammation involve determining the relationship of the vascular plexuses to each other and the site of maximal vascular involvement, best seen with red-free light on slit-lamp biomicroscopy. In episcleritis, the conjunctival and superficial episcleral vascular plexuses are displaced outward from the sclera and the underlying deep episcleral plexus is uninvolved and flat against normal-thickness scleral tissue. In scleritis all vascular layers may be involved but the maximal involvement is in the deep episcleral plexus, which is displaced outward by edematous swollen sclera. This displacement of the deep episcleral vessels is seen only in patients with scleritis.

In episcleritis the patient's main complaint is often redness, which may also be associated with a feeling of grittiness. This is in contrast to scleral inflammation, where pain is much more prominent along with globe tenderness and redness that may involve the whole eye or just a small localized area. The vascular engorgement of the deep episcleral plexus in scleritis has a characteristic bluish-violet hue, which is not present in patients with episcleritis, in which case the engorgement of the superficial episcleral plexus has a distinct red hue. Episcleritis may be associated with nodules and may overly an area of anterior scleritis. Examination in natural daylight can be extremely useful allowing the detection of these subtle color differences that are often not appreciable using the slit-lamp. Additionally, slit-lamp examination with red-free light and diffuse illumination accentuates visibility of blood vessels and areas of capillary nonperfusion. In addition, the conjunctival and superficial vessels can be blanched with 2.5–10% phenylephrine or 1:1,000 epinephrine while the deep vessels are hardly affected.

II. Immunopathology

Most eyes with scleritis do not come to biopsy or to enucleation. In one study of enucleated eyes, eyes with necrotizing scleritis showed vasculitis with fibrinoid necrosis and neutrophil invasion of the vessel wall in 75%, and vascular immunodeposits were found in 93% in the scleral tissue. In addition, there was a significant increase in the number of inflammatory cells, including T cells of all types and macrophages. HLA-DR expression was dramatically increased.[29] Studies of deep episcleral biopsies from patients with nodular non-nectrotizing scleritis did not show the same findings and vasculitis was not prominent.[9] T cells and macrophages were the major inflammatory cells seen infiltrating the deep episcleral tissue with clusters of B cells in perivascular areas. Increased

HLA-DR expression was seen as well as increased IL-2 receptor expression on the T cells, suggesting an active cell-mediated immune response.[8] Others found neutrophils and granulomatous inflammation in enucleated eyes with necrotizing disease.[99] Antibody deposition was not seen nor was complement found, suggesting that T cells are the effector cell in scleritis rather than immune complex deposition. Plasma cells may be involved through production of matrix metatolloproteinases, which can cause destruction and remodeling,[23] and TNF alpha, a pro-inflammatory cytokine.[24]

III. Classification of Scleral Inflammation

The classification system devised by Watson is accepted as the most clinically useful. It is anatomically based and is detailed in Table 1. Episcleritis is recognizable in the anterior episclera as a diffuse process or less commonly as a nodular form of episcleral inflammation. Posterior episcleritis occurs and has been documented pathologically but is not recognizable as a clinical entity.

Scleritis may involve the anterior sclera, posterior sclera or both.[107] Anterior scleritis is the most common pattern of disease, and it may be diffuse, nodular, or necrotizing in type. Very rarely a necrotizing form of anterior scleritis occurs in the absence of pain and other clinical signs of inflammation in patients with longstanding rheumatoid arthritis and is termed scleromalacia perforans.

Posterior scleritis is defined as involvement of the sclera posterior to the insertion of the rectus muscles and may be difficult to recognize in the absence of good imaging as there may be little in the way of physical signs. Modern B-scan ultrasonography and high-definition orbital magnetic resonance imaging are used to detect posterior scleritis and both diffuse and nodular forms can be identified. Necrotizing posterior scleritis has been reported on histopathological examination of enucleated eyes but cannot be recognized clinically at this time.

TABLE 1

Classification of Scleral Inflammation

Type	Subtypes
Episcleritis	Diffuse
	Nodular
Anterior Scleritis	Diffuse
	Nodular
	Necrotizing
	With inflammation
	Without inflammation
	Scleromalacia perforans
Posterior Scleritis	Diffuse
	Nodular
	Necrotizing (at least on histopathology)

IV. Presentation of Scleritis

Patients with scleritis may present in one of two ways—they may already be known to have an underlying related disorder, such as rheumatoid arthritis, or the scleritis may present de novo in the absence of any known underlying systemic disease.[107] 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, is worse at night often interfering with sleep, and characteristically wakens the patient from sleep early in the morning. Scleritis has a subacute onset and the intensity of the pain may increase over several weeks. The pain is usually severe in nature and often resistant to mild analgesics. The pain can be so severe that it prevents the patient from working and performing their normal activities and of such severity that the patient is investigated and/or treated for other causes of severe headache, such as migraine, giant cell arteritis, tic doloureux, cerebral aneurysm, and tumor. Patients may also be thought to have depression or other psychological disturbance. Some patients with scleritis, however, have no pain or may have little pain because of a partial effect from the use of non-steroidal anti-inflammatory drugs.

The patient with anterior scleritis usually notices redness and tenderness of the globe. There may be photophobia and lacrimation. Patients with posterior scleritis may present with reduced vision with or without pain. Unilateral or bilateral inflammation can occur. Patients may have an underlying systemic disorder but not all do and many remain healthy. Although most scleritis is immune-mediated, it can also be triggered by infection, ocular surgery, malignancy, or drugs. There are different types of scleritis that have differing threats to vision, and, therefore, careful clinical examination is paramount.

V. Signs

The signs of scleritis depend on the location of the scleritis and its severity.[107] The hallmark signs of scleral inflammation are the development of scleral edema and dilatation or closure of the deep episcleral vascular plexus. Each pattern of scleritis has physical signs that allow its recognition and are described below.

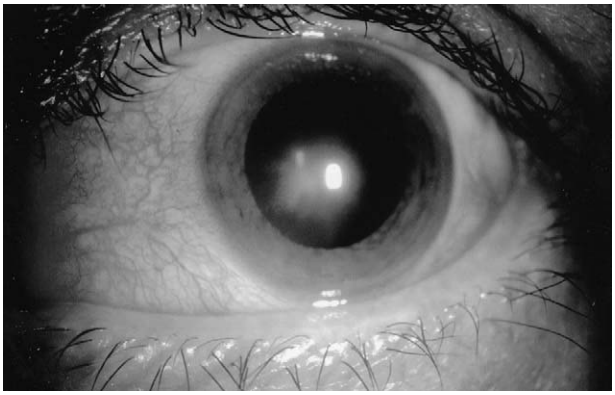

Fig. 1. Diffuse anterior scleritis. Note dilated blood vessels persist despite instillation of phenylephrine drops (pupil is dilated). The reflex on the cornea is as a result of flash photography and does not represent keratitis.

A. ANTERIOR SCLERITIS

Anterior scleritis is the most common form of scleral inflammation and is characterized by diffuse involvement of the anterior sclera by edema and dilation of the deep episcleral vascular plexus (Fig. 1). It can be localized to a patch of the sclera or may involve the entire anterior sclera. The patient may be photophobic and the globe is usually tender to touch, which may be extremely so. Signs of corneal infiltrates, thinning, or stromal keratitis may be present with corneal ulceration much less common than with necrotizing disease.[105] The underlying trabecular meshwork can be involved (trabeculitis) with resultant raised intraocular pressure also occurring due to the raised episcleral venous pressure.[130] In isolated anterior scleritis, no posterior segment signs are seen and ultrasound shows no thickening of the posterior coats of the eye.

Nodular anterior scleritis is characterized by a more localized area of scleral edema such that distinct nodules result. They may be single or multiple and can become quite prominent and tender to palpation (Fig. 2). There is no evidence of capillary closure or non-perfusion and no evidence of scleral necrosis.

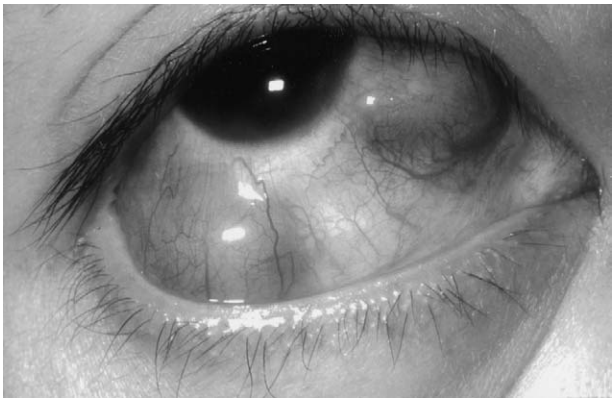

Fig. 2. Nodular scleritis. Note large nodule and rest of sclera is uninvolved.

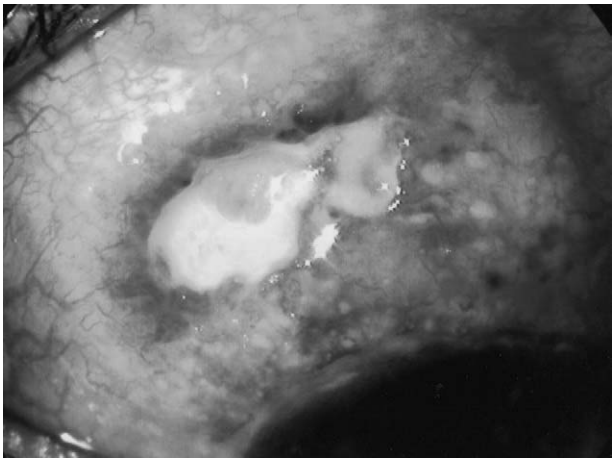

Fig. 3. Necrotizing anterior scleritis. Note large area where sclera is ulcerated and overlying conjunctiva and episclera are missing.

B. NECROTIZING ANTERIOR SCLERITIS

Necrotizing anterior scleritis is the most severe form of scleritis and is a serious threat to vision and the integrity of the eye.[121] There is usually severe pain and extreme scleral tenderness. The scleral involvement is characterized by severe vasculitis and closure of the episcleral vascular bed such that there are visible areas of capillary non-perfusion on clinical examination, and infarction and necrosis of the involved sclera (Fig. 3). Necrosis of the sclera can be subtle or profound, localized, or generalized, and progress rapidly to expose the choroid. There is commonly spread of inflammation that involves the cornea, ciliary body, and trabecular meshwork, resulting in keratitis, anterior uveitis, and elevated intraocular pressure, which may lead to staphyloma formation, although this latter finding may be witnessed without coexistent raised intraocular pressure.[107] Although the necrosis may be seen anteriorly its exact extent may be difficult to visualize or detect using ultrasound as this only detects scleral thickening.

C. SCLEROMALACIA PERFORANS

Scleromalacia perforans is now a very rare form of necrotizing anterior scleritis that is the result of an obliterative arteritis involving the deep episcleral vascular plexus.[70,90,107] It does not produce the acute clinical signs of necrotizing scleritis described above but is asymptomatic or presents with blurred vision from high astigmatism due to scleral thinning leading to loss of scleral rigidity. The sclera is parchment white, avascular, and thin. There may be exposure of the choroid and staphyloma formation if the

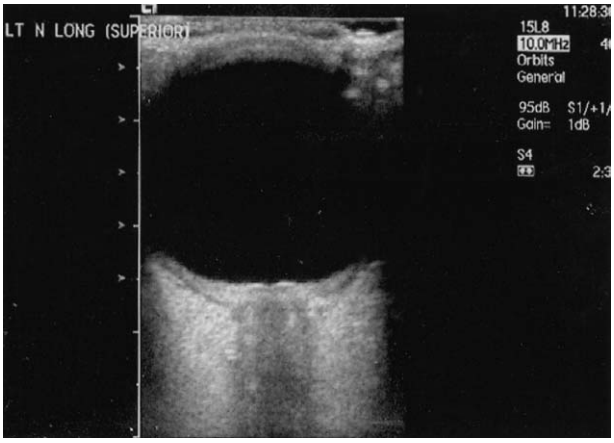

Fig. 4. B-scan ultrasound demonstrating posterior scleritis. Note localized thickened area indicating area of posterior scleral swelling.

intraocular pressure is elevated. There may be sequestra of infarcted sclera surrounded by areas of thinning scleral tissue. There is no corneal involvement except for limited peripheral corneal thinning.

D. POSTERIOR SCLERITIS

Diffuse and nodular forms of posterior scleritis can be delineated from the clinical signs or with the use of imaging studies such as B-scan ultrasonography and magnetic resonance imaging (Fig. 4). The clinical presentation of posterior scleritis depends on the location, extent, and severity of involvement of the posterior sclera.[77] Posterior scleritis may occur in association with anterior scleritis or may be isolated. In either case the pain is typical except in the rare cases of scleromalacia perforans when the necrosis is painless. In patients with associated anterior scleritis, the eye is red. When it occurs in isolation, the eye may be white, but sometimes inflamed posterior sclera can be visualized coming from behind the eye in the extremes of gaze. Ultrasound remains the key to diagnosis with which the thickened posterior coat of the eye (usually greater than 2 mm) can be identified. The posterior segment may appear normal or there can be a variety of signs, such as chorioretinal granulomas, serous retinal detachment, and optic nerve swelling with or without cotton-wool spots.[4] Large serous retinal detachments can be associated with shallowing of the anterior chamber, and secondary angle-closure glaucoma from ciliary body rotation secondary to uveal effusion.[96]

E. UVEITIS IN EYES WITH SCLERITIS

All types of scleritis can be associated with uveitis which may be mild or severe.[101] Anterior uveitis occurs in up to 40% of eyes with scleritis[101] and is more common with more severe scleritis, most often seen in association with necrotizing disease.[107] It is important to be sure that it does not signify an associated endophthalmitis when seen with scleral necrosis.[89]

VI. Demographic Data

Patients with scleritis are predominantly middle-aged and Caucasian with a mean age at onset of 49 years.[77] Female patients comprise 71% of all patients with scleritis[45] and 65% of patients with posterior scleritis.[77] In 30% of patients, posterior scleritis occurred before the age of 40 years. Interestingly, in a small series of patients from the West Indies a preponderance of male patients was seen with posterior scleritis, who also tend to be much younger (mean age 19 years) at presentation.[17] Patients with posterior scleritis greater than the age of 50 years have been shown to have a greater risk of having an associated systemic disease, associated visual loss, and were more likely to require systemic immunosuppressive agents to control their disease.[77]

VII. Classification by Etiology

The incidence of systemic disease in patients with scleritis is reported as 39–50%.[45,77,104] There is no known HLA association.[49] It is useful to note that the association of posterior scleritis with anterior scleritis is much more likely to occur in a patient in whom there is an underlying systemic disease.[77]

A. AUTOIMMUNE SYSTEMIC ASSOCIATIONS

A large number of connective-tissue disorders are associated with scleral disease but the most common is rheumatoid arthritis. Wegener granulomatosis is the most common vasculitis associated with scleritis. Other systemic diseases associated less commonly include relapsing polychondritis, inflammatory bowel disease, systemic lupus erythematosus, and polyarteritis nodosa. A large number of these systemic associations are diagnosed at the outset either because of known preexisting disease or following careful history taking and clinical examination.[38] Equally, as scleritis can be the presenting feature of systemic disease it is important to exclude multisystem disease at presentation, in which case control of the systemic disease is of great importance and has the beneficial effect of also controlling the ocular inflammation.[30,38] The importance of an occult systemic autoimmune disease should not be underestimated in patients with scleritis. The spectrum of systemic investigations varies among clinicians and reflects the reported rates of associations with systemic disease. The most common systemic associations of scleritis are detailed in Table 2. Other less

TABLE 2

The Most Common Systemic Associations of Scleritis

Disease	Key Points	Key Scleritis References
Rheumatoid arthritis (RA)	**Features:** symmetrical arthritis including hands, skin nodules, anaemia, pericarditis, fibrosing alveolitis, peripheral neuropathy **Frequency:** 17–33% of all patients with scleritis have RA; 0.2–6.3% of patients with RA have scleritis **Helpful investigations:** Rheumatoid factor positive in 60–80% of RA patients; Joint X-rays with osteopenia and erosions	48,60,78,105
Wegener's granulomatosis	**Features:** Epistaxis, sinusitis, haemoptysis. Ocular involvement in 50%; May involve orbit but necrotizing scleritis in 79% with peripheral ulcerative keratitis (50%) **Helpful investigations:** Serum c-ANCA is highly specific; Tissue biopsy shows vasculitis and necrotizing granuloma	3,29,52,68,79,103
Relapsing polychondritis	**Features:** Pain or swelling of ear pinnae, tracheal inflammation (in 25% with hoarse voice, cough, stridor, expiratory wheeze), collapsed nasal bridge, hearing loss, cardiac valve dysfunction, polyarthritis **Helpful investigations:** Raised ESR, 30% of patients have co-existing autoimmune disease, biopsy of auricular cartilage	68,91
Systemic lupus erythematosus	**Features:** Malar rash, skin photosensitivity, peripheral arthritis, pleuritis, pericarditis, seizures **Helpful investigations:** ANA positive or extractable nuclear antigen (Ro) positive; high Anti-ds DNA title (present in 30–50%), proteinuria or casts, anaemia, leucopenia or thrombocytopenia	60,68
Polyarteritis nodosa	**Features:** Scleritis, ulcerative keratitis, uveitis, retinal vasculitis, pseudotumour, myalgia, weight loss, fever, arthralgia, purpura, livedo reticularis, neuropathy, hypertension, nephropathy **Helpful investigations:** Multiple aneurysms of either the mesenteric, hepatic, or renal systems on angiography; Muscle or sural nerve biopsy may be definitive	60,68

common associations with a range of other conditions have also been reported, including juvenile rheumatoid arthritis,[1] systemic vasculitis,[1,6,36] Vogt-Koyanagi-Harada disease,[1,57,126] sarcoidosis,[39,99] ankylosing spondylitis,[53] lymphoma,[25,42,77] temporal arteritis,[1,129] carcinoma of the lung,[133] Takayasu disease,[47] and Cogan syndrome.[111]

B. INFECTIOUS CAUSES OF SCLERITIS

Infectious scleritis can be viral, bacterial, fungal, and parasitic. It is uncommon particularly in the absence of infectious keratitis. The mechanism of inflammation in many infections is thought to be partly or wholly immune mediated. Many organisms have been reported as possible causes of scleritis and these are detailed in Table 3. Infections occur in tissue compromised by disease or trauma—both iatrogenic and accidental.

In a large series of 97 patients with scleritis over a 12-year period, 7.5% had an infectious disease and the most common infection was herpes zoster ophthalmicus.[77] Pyogenic infections of the sclera are often difficult to manage and eradicate because of the poor antimicrobial penetration into the avascular necrotic sclera, but improved success has been achieved with surgical intervention in addition to antimicrobial therapy,[7,98] or a combination of parenteral antimicrobials.[40]

A common risk factor for infectious scleritis is a history of pterygium surgery with adjunctive mitomycin C administration or beta irradiation.[80–82] Late scleral radionecrosis has been found to occur in 4.5% of cases where beta irradiation has been used post pterygium surgery to prevent recurrence.[69] Both mitomycin C and beta irradiation have been associated with calcific plaque formation and scleral necrosis, which may occur several months to years after surgery. This may lead to defects in the overlying conjunctiva, which allows access to pathogens. Once the sclera is invaded, the infection is extremely difficult to eradicate. *Pseudomonas aeruginosa* is the most common pathogen reported.[40,81]

Fungal scleritis may remain undiagnosed for months and a scleral biopsy is recommended in cases of progressive scleritis where infection is suspected. Bernauer et al have reported three cases of *Aspergillus* scleritis in which a combination of surgical and medical intervention was needed both for establishing the diagnosis and for successful management.[7] A similar outcome was reported following a case of *Scedosporium*

TABLE 3

Infectious Causes of Scleritis

Type of Organism	Specific Organism / Disease	Key Points	References
Bacteria	TB	Now rare	12,85,95,119
	Mycobacterium chelonae	Two cases post retinal detachment surgery	73,97
	Leprosy	Incidence as high as 5%	16,22,93
	Syphilis	Most common bacterial cause accounting for 2% of cases	19,128
	Haemophilus influenzae	Nodular abscesses	118
	Pseudomonas aeruginosa	Poor prognosis	40,81,84,97,106
	Staphylococcus spp	Following surgery or beta-irradiation	69,80–82
	Streptococcus spp	Following beta irradiation and streptococcal pharyngitis	37
	Borrelia	Lyme disease	11,58
	Corynebacterium	Following trabeculectomy	18
	Serratia	Post chemotherapy	43
	Nocardia	Usually associated with trauma	14,21,56,117
Fungi	Aspergillus	Following trauma or surgery	100
Virus	Ebstein Barr	Necrotizing scleritis	32
	Coxackie B5	Prolonged systemic upset	34
	Varicella zoster	8% incidence of scleritis in patients with HZO	5,67,74,86,125,131
Amoeba	Acanthomoeba	Associated with keratitis	26,33,44,65
Parasite	Toxoplasma	Associated with retinochoroiditis	108,114

The two most common infective causes are varicella zoster and Treponemal infection.

prolificans corneoscleritis.[59] However, despite this approach the eye may still be lost to recurrent infection and intractable pain.[46] A case report of *Sporothrix schenckii* scleritis following trauma with a wood chip failed to respond to topical miconazole and topical amphotericin as well as intravenous amphotericin but had a good response to saturated solution of potassium iodide 10–24 drops orally three times a day for 10 days.[15]

C. MASQUERADE

Intraocular tumors such as melanomas may mimic posterior scleritis but can also be associated with it. Rarely conjunctival tumors and lymphoma can mimic scleritis and secondary malignant deposits can cause severe scleral inflammation.[10,25,42,55,66,71,83,92,132–134] Dorey et al described two patients in whom the initial presentation of lymphoma was misdiagnosed as scleritis.[25] The symptoms and signs did not respond to non-steroidal anti-inflammatory drugs or to steroid treatment and further opinion was sought. Lymphoma is an important diagnosis to exclude in this circumstance. Biopsy should be considered when the pain is atypical for scleritis and the mass is salmon pink, elevated, and solid. Patients with orbital lymphoma need referral for formal staging of their disease before radiotherapy. Posterior scleritis may present as a mass lesion and some of these eyes have been enucleated erroneously.[28] The presence of high internal reflectivity and a retrobulbar echo-lucent area which represents oedema in the tenons capsule on B scan should alert the examiner to the probability of posterior scleritis.[13,28]

D. SURGICALLY INDUCED SCLERITIS

Surgically induced necrotizing scleritis (SINS) can occur after a variety of procedures, most commonly after cataract surgery particularly when a limbal incision is used with an extracapsular approach.[88] Interestingly of the patients who develop SINS, 75% of patients have undergone two or more surgical procedures prior to onset of the disease.[88] Mean time to presentation from surgery has been reported as 9 months[92] with a range from 2 weeks to 6 months reported by others.[102] Patients who have SINS need careful systemic investigation as up to 90% of patients in one study were later diagnosed with autoimmune vasculitic disease which required immunosuppression therapy.[102]

Surgically induced diffuse scleritis (SIDS) is less well recognized, Scott reported 21 cases, representing 3.1% of patients who had had planned extracapsular cataract surgery with intraocular lens implantation.[109] Scleritis was diagnosed clinically on the basis of pain—usually sufficient to prevent or wake patient from sleep; red eye with violaceous hue adjacent to the operative wound with associated photophobia and blurred vision. They found the mean age of patients with SIDS to be significantly younger than the mean of all cataract patients. Treatment was aimed at relief of pain and control of inflammation. Local steroid treatment was ineffective and most of

the patients responded to systemic non-steroidal anti-inflammatory drugs.

E. OTHER CAUSES OF SCLERITIS

Trauma, in some cases self-inflicted, has been reported as a cause of nodular scleritis.[54,123] Rare associated systemic diseases such as congenital erythropoietic porphyria and graft-verus-host disease following allogenic bone marrow transplantation have also been reported.[54,123] Drug-induced causes include scleritis following pamidronate disodium.[31] Thurairajan et al reported a patient who suffered of polyarthopathy orbital myositis and posterior scleritis 10 days after receiving Fluvirin. Fluvirin is an inactivated influenza vaccine consisting of purified haemagglutinin and neuraminidase surface antigen in aqueous suspension.[120]

VIII. Investigation of Patients With Scleritis

Blood tests for diagnosis of inflammation and systemic disease are commonly used in the investigation of these patients. In any acute presentation it is important to obtain an assessment of the patients' blood pressure, renal function (including urine analysis) and the acute phase response (normochromic normocytic anaemia, raised neutrophils platelets, Erythrocyte sedimentation rate, C-reactive protein and plasma viscosity, reduced serum albumin) in order to get an idea of the degree of systemic involvement and aid the formulation of the immediate management plan. These along with evaluation of full blood count, urea, creatinine and electrolytes, rheumatoid factor, anti-nuclear antibodies, anticytoplasmic antibodies, form the core investigations. Additional tests are requested as determined by the history and clinical examination.

Ultrasonography, fluorescein angiography or other imaging studies may be required in some patients with scleritis to confirm the diagnosis. The following ultrasonographic changes can all be seen in posterior scleritis: scleral and choroidal thickening, scleral nodules, fluid in Tenons capsule, optic disk swelling, distended optic nerve sheath, and retinal detachment.

IX. Management of Patients With Scleritis

Patients with scleritis need to have the type and extent of their disease diagnosed, the complications present detected and any underlying systemic or local cause defined. The aim of treatment is to remove or treat the cause where possible but in the majority is to control the inflammatory process to relieve the pain and thereby reduce the damage to the eye.[75]

A. MEDICAL THERAPY

Patients with posterior or necrotizing scleritis need much more intensive and urgent therapy than those presenting with anterior non-necrotizing disease. Any scleritis that is associated with a systemic disease also usually requires more aggressive immunosuppressive therapy.[77]

1. Cyclo-oxygenase Inhibitors (Cox Inhibitors)

Non-necrotizing scleritis often readily responds to systemic non-steroidal anti-inflammatory drugs.[45] Both non-selective cox inhibitors (e.g., flurbiprofen, indomethacin, and to a lesser extent ibuprofen) and the more selective cox-2 inhibitors have been used successfully to treat this condition, although to date scant data have been published regarding the use of the selective cox-2 inhibitors in the treatment of scleritis. Gastrointestinal side effects are prominent and patients should be warned of the possibility of gastric irritation and bleeding especially with the non-selective cox inhibitors. Photosensitivity skin rashes, renal and hepatic toxicity, and drug interactions are all important considerations.

2. Corticosteroids

Corticosteroids are usually reserved for patients who do not respond to cox-inhibitors or those with posterior or necrotizing disease.[45,77,129] Both systemic administration and orbital floor and subconjunctival injections have been successful although local steroid injections are less commonly used.[135] Systemic corticosteroids may be administered orally or intravenously at high doses to induce disease remission. A starting dose of 1 mg/kg/day is standard with weekly reduction by 20–25 mg/week until a dose of 40 mg/day is reached. After this dose is reached, the rate of reduction is individualized, according to the clinical findings and patients' response, but is in the order of 5 mg /week until cessation or an acceptable maintenance dose is reached.[77,129] Intravenous methylprednisolone is primarily used when a rapid control of the inflammatory response is required, for example, threatened scleral or corneal perforation in necrotizing scleritis.[76]

All patients should be warned of steroid-induced side effects. These are dependant on the dose, frequency, route of administration, and duration of treatment and are more frequently seen in the elderly, diabetics, hypoalbuminaemic states, psychiatric patients, and in pregnancy. They should be used with caution in patients with gastrointestinal disease or bleeding disorders as should non-steroidal drugs.[72] Using the lowest possible dose for the shortest possible time has the best chance of minimizing side effects and with combination therapy; it is no

longer necessary or acceptable for patients to remain on high doses of corticosteroids. Patients who relapse at doses of prednisolone >7.5–10 mg per day should be considered for adjunctive immunosuppressive therapy with a second-line agent that includes cyclosporin,[35,124] mycophenolate,[63,110] methotrexate,[112] and anti-TNF blockers.[115] Patients with Wegener's granulomatosis may require cyclosphosphamide[61] or mycophenolate,[62] and chlorambucil is rarely used today. These patients should be referred to a specialist scleritis clinic for further management.

B. COMPLICATIONS

Scleritis has a wide range of possible complications and these depend on the location of the inflammation as well as its severity and duration (Table 4).

C. SURGERY

There are several indications for surgical intervention in patients with scleritis, but any surgical intervention is uncommon. Rarely, patients require a formal biopsy of the episclera and superficial sclera to exclude a neoplastic or infective cause for their scleritis. Also, emergency or elective tissue grafting is rarely required for tectonic globe support or to repair a perforation. Patients may also develop cataract or glaucoma that requires surgical treatment. Cataract may be secondary to intraocular inflammation and/or steroid use either topically or systemically. Raised intraocular pressure can occur with an associated trabeculitis, shallowing of the anterior chamber, or as a steroid response. Glaucoma is uncommon but develops when permanent damage to the trabecular meshwork has occurred even though the scleritis is quiescent.

1. Episcleral and Scleral Diagnostic Biopsy

In most patients with scleritis, it is clinically apparent that the patient has endogenous scleral inflammation. Patients who present with atypical clinical features such as conjunctival erosions or irregularity, a corneal perforation without severe corneal involvement, a poor response to appropriate anti inflammatory therapy or a past history of ocular surface or periocular actinic neoplasia may have carcinomatous involvement of the episclera and sclera that masquerades as inflammatory scleritis.[71] Episcleral biopsy is necessary to make the diagnosis when there is clinical doubt but this is rare. Lymphoma has also been reported presenting with episcleral masses mimicking scleritis.[25]

Other patients including those with a past history of ocular surgery, such as pterygium surgery or retinal detachment surgery, ocular radiotherapy, or topical antimetabolite therapy to the globe, may develop infective scleritis. The presentation may be long delayed after the original treatment and there may be minimal signs suggesting an infective cause. When an infectious agent is considered likely, biopsy is essential to confirm the diagnosis and infective agent.[41,87] Small corneal perforations may be treated with a bandage lens or glued initially[113] while the inflammatory process is brought under control with high-dose corticosteroids and other agents when necessary. Elective surgery can then be performed at a time when the scleritis is quiescent.

2. Tectonic Grafting

Tissue replacement in patients with scleritis may rarely be necessary acutely when there is either corneal or scleral perforation. Management in such patients must be individualized as there is a wide range

TABLE 4

Complications of Scleritis

Complications	Comments
Scleral thinning	Can be severe following necrotizing disease
Corneal thinning and perforation	Peripheral corneal perforation is a particular feature of Wegener granulomatosis
	Central perforation more likely to be due to dry eyes associated with rheumatoid arthritis
Glaucoma	Open angle secondary to trabeculitis or raised episcleral venous pressure
	Narrow angle secondary to massive serous retinal detachment
	Secondary to posterior synechiae leading to iris bombe
Hypotony	Secondary to serous or rhegmatogenous retinal detachment
Uveitis	Uncommon—usually mild and anterior
Cataract	More common in severe and necrotizing scleritis long-term systemic steroid treatment
Posterior segment	Serous retinal detachment (localized or total retinal detachment)
	Choroidal folds and optic nerve involvement
Anterior segment ischemia	Rare—can follow 360-degree severe necrotizing anterior scleritis
Phthisis	Following severe scleritis

of clinical presentations. Most frequently the patient presents with florid, uncontrolled necrotizing anterior scleritis and keratitis with either a corneal or scleral perforation. Corneal perforations are dealt with on their merits. In most patients it is possible to use conservative therapy with contact lenses and tissue adhesive[64,87] until the scleritis is controlled with aggressive immunosuppressive therapy. The cornea can then be repaired definitively. In some patients lamellar or perforating keratoplasty is necessary in an inflamed eye. Such grafts will only survive if the scleritis is controlled with medical therapy.[122] Scleral perforations are less common and similar principles of management are used. Lamellar corneal grafts are the easiest tissue to graft but are the most likely to be damaged by severe scleral inflammation. Donor sclera is more difficult to use but extremely robust. A variety of other tissues, such as fascia lata, dura, and pericardium, has been used for tectonic scleral support.[27,50] Occasionally patients may develop late-onset scleral thinning or staphyloma formation that requires scleral grafting to deal with high-grade astigmatism or the threat of scleral rupture. Donor sclera, lamellar corneal tissue or fascia lata[51] is suitable in such patients.

3. Cataract Surgery

Cataract formation has been reported at an incidence of 17% in eyes with scleritis in a group of patients followed up over a period of 11 years.[107] Cataract usually develops some time after the onset of scleritis and is related to both the scleritis and corticosteroid therapy. Cataract surgery is safe in these patients, providing the inflammation is quiescent and has been in remission for at least 3 months. Corneal approach phacoemulsification seems the logical technique for cataract surgery as it avoids the sclera and preserves the conjunctiva and its vascular plexuses.

4. Glaucoma Surgery

The incidence of glaucoma over an 11-year period has been reported as high as 13% in patients with scleritis.[107] Elevated intraocular pressure and glaucoma in patients with scleritis needs careful evaluation to determine the mechanism producing the elevated pressure. Angle-closure glaucoma is typically the result of ciliary body rotation rather than pupil block and therefore will not respond to peripheral iridotomy. Chronic angle closure may result in widespread peripheral anterior synechiae and permanent angle closure requiring surgical intervention.

Patients with severe scleritis can develop significant trabecular damage and subsequent open-angle glaucoma that requires surgery for pressure control. Trabeculectomy is the best initial surgical procedure, but may be technically difficult or impossible due to scleral thinning and those patients require a tube drainage procedure. Anti-metabolites may be needed in high-risk patients and specialist advice should be taken as to the choice of agent.

X. Outcome

The aims of treatment are to control inflammation, eliminate pain, and reduce the occurrences of complications and also to treat any associated systemic disease. It is also important to adequately treat scleritis patients because systemic disease in this group has an associated increased mortality in patients presenting with scleritis.[2,30] Loss of vision is much more common in eyes with posterior scleritis and has been noted in 30% of patients who in one study lost 2 or more lines of Snellen acuity despite optimal treatment.[70] Most patients with posterior scleritis who lose vision have secondary macular changes or optic atrophy.[70] Those with severe disease often have multiple causes for visual loss, such as retinal pigment epithelium changes at the macula, or epiretinal membrane formation, macular edema, cataract, and/or retinal detachment. The presence of peripheral keratopathy in eyes with scleritis is also associated with a poor ocular and systemic prognosis. It is reported that early treatment controlled posterior scleral inflammation and limited visual loss.[2]

XI. Conclusion

Scleritis is an ocular disease that may be difficult to diagnose and manage. However, with informed and adequate care the long-term prognosis can be excellent both for the patient and the eye and every attempt should be made to achieve this with careful clinical history taking, detailed ocular examination, and the use of immunosuppressant drugs when necessary.

Method of Literature Search

This article was prepared using the National Library of Medicine database 1975–2004 using the following search words: *scleritis* or *ocular* or *eye* or *episcleritis* or *scleral*, and one of the following: *necrotising, systemic, immunosuppression, infectious, sclerokeratitis, corneoscleritis, acanthamoeba, zoster, varicella, Borrelia, leprosy, mycobacterium, aspergillus, buckle, polyarteritis nodosa, sarcoidosis, anticytoplasmic, vasculitic, granulomatosis, rheumatic, arthritis, scleromalacia, transplantation, surgery, metastatic, carcinoma, tumour, malignant, beta irradiation, pterygium, necrosis.*

Additional sources included textbooks such as those referenced below. Manual searches based upon articles cited in the texts of other articles. Only those

articles in peer-reviewed journals were included. In the case of non-English articles, abstracts were used wherever possible.

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Reprint address: Professor Susan Lightman, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD, UK.