Fundamentals of Clinical Ophthalmology

Scleritis

Peter McCluskey

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Scleritis

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Scleritis

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Preface to the *Fundamentals of Clinical Ophthalmology* series

This book is part of a series of ophthalmic monographs, written for ophthalmologists in training and general ophthalmologists wishing to update their knowledge in specialised areas. The emphasis of each is to combine clinical experience with the current knowledge of the underlying disease processes.

Each monograph provides an up to date, very clinical and practical approach to the subject so that the reader can readily use the information in everyday clinical practice. There are excellent illustrations throughout each text in order to make it easier to relate the subject matter to the patient.

The inspiration for the series came from the growth in communication and training opportunities for ophthalmologists all over the world and a desire to provide clinical books that we can all use. This aim is well reflected in the international panels of contributors who have so generously contributed their time and expertise.

Susan Lightman

Preface

Scleritis is a rare disease and most ophthalmologists will only see a new patient with scleritis every three to five years. Scleritis is, however, an important diagnosis for the ophthalmologist to make given its severe pain, potential threat to vision, association with systemic disease, and need for systemic immunosuppressive therapy. As well, posterior scleritis has a host of clinical presentations that can be confused with a variety of ocular and neurological diseases.

This book gives the reader a concise overview of the pathogenesis, clinical manifestations, and management of scleritis. It emphasizes the need for a careful clinical assessment to make the diagnosis of scleritis and for selective investigations to determine whether there is an associated systemic disease. A practical guide to medical and surgical treatment of scleritis and its complications completes the book.

The contributors hope that this book will provide the clinician with useful and practical guidelines for the diagnosis and management of patients with scleritis.

Peter McCluskey

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1: Anatomical and biochemical aspects of the sclera

NICK DI GIROLAMO

The sclera (Greek *scleros* meaning hard) is an elastic, opaque, and resilient tissue of the eye. It is an incomplete shell comprising approximately 90% of the outer coat of the eye. It begins at the cornea and terminates at the optic nerve canal posteriorly. It is predominantly composed of collagen and some elastin fibrils and is relatively avascular and acellular. Except for the slow collagen and cell turnover, the normal sclera is essentially inactive. Humans have the largest amount of exposed sclera compared with most other species of primates. In addition, humans are also the only primate species with white sclera.[1] However, the shiny white appearance can take on a yellowish coloration, particularly in older people, because of the deposition of fat. In young children the sclera can sometimes take on a blue appearance, as the uvea, shows through the thin sclera. The sclera's functions include:

- providing a protective outer coat;
- stabilizing intraocular pressure;
- providing attachment sites for muscles.

This role of stabilizing pressure, along with the sclera's tough interwoven collagenous structure, helps maintain internal ocular structures important in normal vision. Scleral thickness varies in different regions of the globe. The anterior sclera closest to the limbus measures approximately 0.8 mm in thickness; at the site of insertion of the rectus muscle it measures 0.3 mm, at the equator 0.4–0.6 mm, and near the optic nerve 1.0 mm.

The foetal human eye develops during week 4 of gestation. The sclera is of neural crest origin and develops from anterior to

posterior. Scleral differentiation begins by week 6, progressing back towards the equator and to the posterior pole by week 12. By week 24, both foetal and adult sclera have identical ultrastructural characteristics.[2]

STRUCTURE

The sclera is composed of three layers:

- the episclera
- the sclera proper
- the lamina fusca.

The episclera is the outermost layer of the sclera, composed of elastic and loose collagenous connective tissue. Anteriorly, it is connected to Tenon's capsule. Posteriorly, it merges with the scleral stroma. The episcleral collagens vary in diameter, are generally smaller and, more often than not, widely spaced compared with those of the scleral stroma. Resident fibroblasts (with some pigmented melanocytes and leukocytes) predominate in this layer, with nutrients supplied to them by a network of capillaries. Like the episclera, the scleral stroma contains scattered resident scleral fibroblasts with spindle-shaped extensions located between collagen fibres which are generally larger in diameter than those found in the episclera. The collagen fibres are interwoven in a complex manner, giving this layer of the sclera greater tensile strength and contributing to its opacity. The scleral stroma is largely an avascular structure nutritionally supplied by episcleral and choroidal vessels. The lamina fusca is the innermost segment of the sclera, lying directly adjacent to the uvea. Collagen bundles are generally smaller in diameter than those found in the scleral stroma. Its brown coloration is due to the presence of melanocytes. These cells are usually located on and below the collagen bundles.

The sclera is relatively poorly vascularized. Its nutritional requirements are modest owing to the slow rate of collagen and cell turnover. Its blood supply is derived from the anterior and posterior ciliary arteries. There are superficial and episcleral capillary plexuses over the anterior sclera derived from the anterior ciliary and conjunctival arteries, which form clinically identifiable layers of vessels and supply the scleral stroma. These plexuses continue posteriorly in a less dense and less identifiable pattern. The short posterior ciliary nerves innervate the posterior sclera,

while the long posterior ciliary nerves supply the remaining sclera. These nerves enter the sclera around the optic nerve.

STRUCTURAL MOLECULES AND CELLS

The make-up of the sclera is predominantly extracellular matrix with resident fibroblasts within. These cells play a vital role in the synthesis and organization of matrix proteins. These matrix components include collagen, elastin, proteoglycans, and glycoproteins. Scleral fibroblasts are also involved in the slow connective tissue turnover that normally occurs in the sclera, although the precise mechanism of matrix degradation and deposition remains to be determined. The matrix-degrading enzymes, called matrix metalloproteinases (MMPs), which are secreted by scleral fibroblasts constitutively and induced by inflammation, are likely to be an important mechanism of scleral connective tissue turnover.[3] Other proteases such as elastases and proteoglycanases are likely to be involved. Although fibroblasts are not abundant in the sclera, their cellular processes are often in close contact with each other. Cultured scleral fibroblasts produce complement components (C1, C2, and C4) and express human leukocyte antigen (HLA),[4] suggesting their potential involvement in immunological diseases of the eye.

Collagens

The most abundant matrix protein of the sclera is collagen. The normal human sclera contains collagens I, III, V, and VI; types IV and VII are absent, and type IV collagen is exclusively found in the basement membrane of blood vessels.[5] The function of type I collagen is its ability to resist tension, whereas type III collagen is considered important in the maintenance of structural integrity of expansible organs such as arteries and lungs.[6] Collagen type V and VI function as anchoring proteins between basement membranes and the adjacent stromal matrix. Collagen type VI resembles a sheath of filaments, surrounding blood vessels and nerves, and separating them from other collagen fibrils. Electron microscopic studies of the sclera have demonstrated that the collagen fibrils exhibit a wide range of diameters (25–230 nm) and are interwoven in an irregular and complex pattern.[7,8] Although the collagens of the outer sclera are of uniform size and arranged in parallel, the

inner scleral layer contains collagen bundles that are irregular and interwoven like a mesh. This elaborate intertwining of collagen bundles functions to give the globe its rigidity and flexibility against changes in intraocular pressure and may be the reason for scleral opacity.[7,9] This arrangement is in contrast to the cornea, with collagen fibrils of uniform diameter (10-30 nm). A similar pattern of collagen staining has been observed in scleral tissue from patients with scleritis (an inflammatory and degenerative disease of the sclera), suggesting that the proteoglycans are the first matrix components degraded in the diseased sclera.[10] This hypothesis is strengthened by recent studies, which have localized matrix metalloproteinase-3 (MMP-3) to fibroblasts and macrophages in tissue derived from patients with scleritis.[3,11,12] This protease is highly active against fibronectin, laminin, and, in particular, proteoglycans such as aggrecan.

Elastin

Elastic fibres are characteristic of tissues that are subjected to multidirectional stretching. They are located in the innermost layer of the sclera, whereas the superficial layers rarely contain elastic fibres.[13] This reflects biological function where a greater amount of collagen is required to resist the tension exerted by the contraction of extraocular muscles. Investigations on normal and glaucomatous human eyes have revealed a similar density of elastin fibres,[14] which correlates with the known durability of this protein. Corroborating evidence was presented by Marshall,[15] who also observed that the density of elastin fibres was greatest adjacent to the scleral fibroblasts, suggesting that these cells too are a potential source of elastin.

Proteoglycans

Proteoglycans (PTGs) consist of a core protein of varying length to which glycoaminoglycan (GAG) chains are covalently attached. GAGs are long-chain, unbranched, linear polymers of repeating sugar units. The varying molecular weight of PTGs is due to the composition of one to hundreds of GAG chains, making these proteins negatively charged. At least four types have been identified in the sclera (dermatan sulfate, chondroitin sulfate, heparin sulfate, and hyaluronic acid).[16] Together they make up a large percentage of the amorphous ground substance of the sclera

and are synthesized by scleral fibroblasts. The amount of each GAG present varies within different regions of the sclera and with age.[17,18] Decorin and biglycan (two related PTGs) have been localized in sections of foetal,[18] and adult human sclera,[19] in close association with collagen fibrils. In addition, the other major PTG detected in the human scleral tissue and scleral fibroblasts is aggrecan (principally a cartilage PTG).[19] PTGs serve several biological functions, which include:

- regulation of hydration;
- maintenance of structural integrity;
- matrix organization, and
- growth regulation (as they can bind certain growth factors).

In vitro, PTGs (such as decorin) have been shown to bind to collagen type I, delaying the lateral assembly of collagen molecules, resulting in thinner diameter fibrils.[20]

A significant loss of GAG composition (particularly dermatan sulfate) occurs in the anterior human sclera with increasing age.[17] This loss is coincident with a decrease in tissue hydration (as GAGs are highly hydrated). However, no such age-related loss of GAGs occurs in the cornea. In pathological conditions, such as in nanophthalmos (a rare disease characterized by small eyes and a thickened sclera), investigators have noted increased levels of GAGs in the sclera of affected individuals.[21] These abnormal levels of GAGs may influence scleral collagen organization and contribute to the pathogenesis of the uveal effusion, which are characteristic of nanophthalmic sclera. In animal models of myopia, investigators have demonstrated a decrease in GAG levels in the posterior pole of vision-deprived compared with control animals.[22,23]

Glycoproteins

Glycoproteins (GPs) are components of the ground substance, which makes up the sclera. Although PTGs are glycosylated proteins owing to their attached sugar moieties, the term glycoprotein is used to describe molecules with an oligosaccharide make-up such as fibronectin. This ubiquitous protein, with binding sites for cells, collagen, GAGs, complement components, and many other macromolecules, plays a vital role in wound healing[24] and in the organization of matrix. It is a high molecular weight protein synthesized by scleral fibroblasts and detected in the sclera. Similarly,

laminin, a multifunctional GP which plays a key role in cell-to-matrix and matrix-to-matrix interactions, is found in the human sclera.[15]

Immunomodulatory factors

Fibroblasts are the predominating resident cells of the sclera. Cultured human scleral fibroblasts are activated by cytokines (proteins involved in modulating an inflammatory response) such as interferon gamma (IFN-γ). They respond by enhancing the expression of human leukocyte antigen (HLA) on their cell surface.[4] Scleral fibroblasts constitutively express complement component C1, but the addition of INF-γ induces the otherwise undetectable levels of complement components C2 and C4.[4] These observations suggest that scleral fibroblasts have the potential to participate in immunological diseases of the eye.

Tumour necrosis factor-alpha (TNF-α), another pro-inflammatory cytokine, has also been found in involved scleral tissue derived from patients with necrotizing scleritis.[3,25] *In vitro*, TNF-α increases the expression of collagenases produced by cultured human scleral fibroblasts.[3] In contrast, exposing human scleral fibroblasts to interleukin-4 (an anti-inflammatory cytokine) resulted in no significant change in the levels of these enzymes, but enhanced the production of the collagenase inhibitor (TIMP-1) (Di Girolamo *et al.*, unpublished data). These data highlight the potential importance of immunomodulatory proteins, such as cytokines, in the pathogenesis of scleral disease.

MATRIX METALLOPROTEINASES AND THE SCLERA

Characteristics of matrix metalloproteinases

A major advance in understanding the process of extracellular matrix (ECM) remodelling came with the identification of collagenolytic activity.[26] The enzyme they described and characterized over 30 years ago was later named interstitial collagenase. In the last decade, at least 17 members of this gene family of enzymes have been cloned in man. MMPs are neutral proteolytic enzymes active against most (if not all) components of

Table 1.1 The matrix metalloproteinase gene family

Enzyme name	MMP number	Substrate(s) cleaved
Interstitial collagenase	MMP-1	Fibrillar collagens
Neutrophil collagenase	MMP-8	Fibrillar collagens
Collagenase-3	MMP-13	Fibrillar collagens
Collagenase-4	MMP-18	Fibrillar collagens
Gelatinase A	MMP-2	Gelatin, collagen IV, V
Gelatinase B	MMP-9	Gelatin, collagen IV, V
Stromelysin-1	MMP-3	FN, VN, LMN, PTGs
Stromelysin-2	MMP-10	FN, VN, LMN, PTGs
Matrilysin	MMP-7	FN, VN, LMN, PTGs
Stromelysin-3	MMP-11	α-1-antitrypsin
Membrane-type-1 MMP	MMP-14	Progelatinase A
Membrane-type-2 MMP	MMP-15	Progelatinase A
Membrane-type-3 MMP	MMP-16	Progelatinase A
Membrane-type-4 MMP	MMP-17	ND
Membrane-type-5 MMP	MMP-21	ND
Macrophage metalloelastase	MMP-12	Elastin
Not determined	MMP-19	ND
Enamelysin	MMP-20	ND

Abbreviations: FN, fibronectin; VN, vitronectin; LMN, laminin; PTGs, proteoglycans; ND, not determined.

the ECM (Table 1.1). These enzymes are generally divided into four subclasses, depending on substrate specificity. The collagenases include:

- interstitial collagenase (MMP-1)
- neutrophil collagenase (MMP-8)
- collagenase-3 (MMP-13).

The gelatinases consist of:

- gelatinase A (MMP-2)
- gelatinase B (MMP-9).

The stromelysins comprise:

- stromelysin-1, -2, -3 (MMP-3, -10, -11)
- matrilysin (MMP-7).

The most recently discovered MMPs include the membrane-associated enzymes, which include membrane-type or MT-1, -2, -3, -4.

The collagenases are the only known enzymes capable of specifically cleaving interstitial collagens of type I, II and III at a single locus on the triple helix, forming characteristic one-quarter and

three-quarters length collagen fragments. The gelatinases (also referred to as the type IV collagenases) preferentially degrade denatured collagens (degraded after the actions of the collagenases) and type IV collagen (the main constituent of basement membranes). The stromelysins have broader substrate specificity, and are capable of digesting a number of ECM glycoproteins, such as laminin, fibronectin, vitronectin, proteoglycans, and other collagen types (Table 1.1). Finally, the MT-MMPs are involved in the activation of other MMPs as well as having proteolytic activity against fibrillar collagens. Despite the overlap in substrate activity between several MMPs, often their pattern of expression is distinct.

The criteria for classification of enzymes as MMPs are:

- The enzymes require intrinsic zinc and extrinsic calcium for full activation.
- They display proteolytic activity against specific substrates such as collagen, gelatin, fibronectin at or near neutral pH.
- Their cDNAs encode for highly conserved sequences, which allow the enzymes to be activated and bind zinc at the active centre of the molecule.
- All members share similar domain structure.
- Enzymatic activity is specifically blocked by naturally occurring inhibitors.

Regulation of matrix metalloproteinases

Transcriptional regulation

Under normal physiological conditions, the process of connective tissue remodelling by MMPs occurs under stringent control. Uncontrolled remodelling generally leads to degradative pathologies, which are usually attributed to a breakdown in the regulatory mechanisms. Regulation of MMPs can occur at the level of gene expression by a variety of inflammatory cytokines, such as TNF-α, IL-1α, transforming growth factor-beta (TGF-β) and platelet derived growth factor (PDGF) (Fig. 1.1), as well as tumour promoters including 12–*O*-tetradecanoylphorbol-13-acetate.[27] In contrast, glucocorticoids and retinoic acid down-regulate induction of MMPs. Similarly, IL-4 and IL-10 have been shown to decrease MMP expression while enhancing the expression of the TIMPs.[28,29]

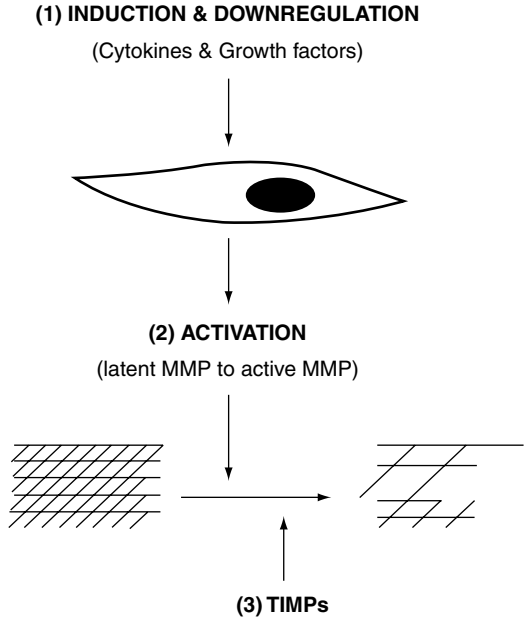


Figure 1.1 Matrix metalloproteinase regulation. MMP regulation generally occurs at several levels including; (1) stimulation or inhibition of expression by cytokines and growth factors, (2) at the level of proenzyme activation, and (3) enzyme inhibition by the TIMPs.

Regulation by activation of the proenzyme

Generally, MMPs are secreted in a zymogen (inactive) form. The only exceptions are neutrophil collagenase (MMP-8) and macrophage metalloelastase (MMP-12) which are stored in the cell's granules awaiting discharge. Thus, the conversion of the latent MMP to the active enzyme requires an additional regulatory step. Upon activation there is a cleavage of the intact MMP, which usually takes place extracellularly. This cleavage takes place at the *N*-terminal end of the MMP molecule and results in the removal of approximately 10 kDa, making the enzyme fully capable of denaturing matrix components. The mechanism of MMP activation is called the "cysteine switch".[30]

Although the *in vitro* system of MMP activation is well characterized, the precise *in vivo* mechanism is yet to be fully elucidated. Human pro-stromelysin-1 and -2 and fibroblast and neutrophil pro-collagenase have identifiable peptide motifs cleavable by plasmin (a serine protease). Hence plasmin is able to convert pro-collagenase

and pro-stromelysin to their active forms. *In vitro* at least, active stromelysin can "superactivate" pro-collagenase by proteolytic attack,[31] as shown in the schematic representation of MMP activation (Fig. 1.2). Also, active collagenase and stromelysin can potentiate the activity of pro-gelatinase B (MMP-9). Pro-gelatinase A (MMP-2) follows a diverse activation pathway from that of pro-collagenase, pro-stromelysin, and pro-gelatinase B. This protease is not activated after digestion with physiological activators of other MMPs such as plasmin.[32] Instead, this enzyme is activated at the cell membrane, where it binds and is proteolytically processed at the cell surface. This membrane-dependent activation mechanism is via a recently cloned member of the MMP family (MT-1 MMP).[33] In addition to the activation by other physiological activators, such as plasmin, trypsin, chymotrypsin, neutrophil elastase, cathepsin G, and MMPs, the serine protease chymase and tryptase derived from mast cells are capable of MMP activation.

Inhibition of matrix metalloproteinases by TIMPs

The activity of MMPs on ECM proteins is dependent on a fine tuned balance between the proteinases and their naturally occurring inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). To date four TIMPs (TIMP-1, -2, -3, -4) have been identified, cloned and characterized. They include TIMP-1, -2, -3, and -4. TIMPs can bind to both latent and active MMPs to form a stable non-covalent but essentially irreversible 1:1 stoichiometric complex. Although TIMPs are soluble secreted inhibitors, TIMP-3 is secreted and found complexed to the ECM, perhaps acting as a localized inhibitor of matrix degradation. In addition to their roles as MMP inhibitors, TIMPs display growth-promoting activities,[34] and are involved in cell apoptosis.[35] MMP and TIMP genes can be coordinately expressed and regulated or expressed independently. For example TGF-β, a cytokine that induces connective tissue deposition by fibroblasts, suppresses collagenase synthesis, while increasing TIMP-1 and gelatinase A expression.[36]

Expression of MMPs in the normal and diseased eye

Subtle disturbances in the MMP-TIMP balance is thought to occur during many physiological processes associated with the

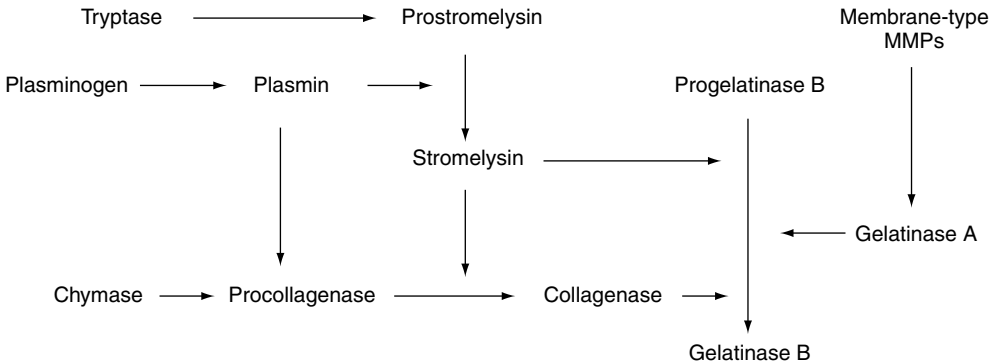


Figure 1.2 Proteinase activation cascade of matrix metalloproteinase. Most MMPs are activated in the extracellular space. Although the *in vivo* mechanism of activation is yet to be determined, *in vitro* they are activated by serine proteases such as plasmin and the mast cell derived proteases chymase and tryptase. In addition, the active forms of several MMPs can "superactivate" the latent forms of other MMPs.

migration of cells and in normal connective tissue remodelling. Many examples in support of such coordinated regulation exist, for example the proteolytic degradation of matrix proteins that occurs during embryogenesis, lung development, bone formation, and wound healing. Maintenance of the enzyme-inhibitor balance thus appears to be important in limiting degradation of matrix proteins in normal physiological processes.

MMP activity has been detected in normal ocular tissue and fluids. Gelatinase A and B have been identified in aqueous humour (AH) samples from both human and bovine eyes.[37,38] Their expression in normal ocular fluid suggests their involvement in the trabecular meshwork connective tissue remodelling and other anterior chamber tissues. Gelatinase activity and membrane-type MMP (MT-MMP) has also been detected in extracts and in normal whole scleral, iris, retinal, vitreous, choroidal, and corneal specimens.[39] As well as localizing MMPs in the eye, TIMPs have been detected in Bruch's membrane,[40] and TIMPs 1-3 in both interphotoreceptor matrix and vitreous,[41] indicating that TIMPs may regulate MMP activity in the normal human eye.

MMPs in necrotizing scleritis

Although there is some evidence that immune complex deposition is involved in the pathogenesis of scleritis, the putative antigen(s) have not yet been identified, and the pathogenesis of scleritis remains essentially unknown. It has been hypothesized that activated scleral fibroblasts and inflammatory cells, such as macrophages, could be responsible for releasing collagenolytic proteases capable of digesting scleral collagens.[42] Using electron microscopy, Young and Watson[43] demonstrated two possible mechanisms of collagen degradation in the scleral stroma in cases of advanced necrotizing scleritis:

- phagocytosis of collagen fibrils by activated stromal fibroblasts and macrophages;
- the solubilization and unravelling of collagen fibrils in the scleral stroma in the absence of infiltrating leukocytes.

The authors concluded that resident stromal fibroblasts were probably the major source of proteolytic enzymes (of unknown class) that caused collagen degradation.

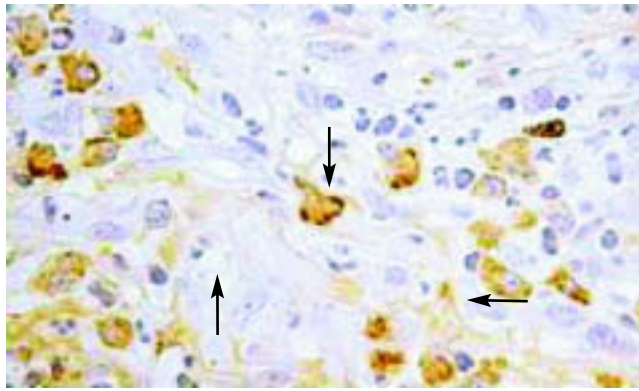
Tissue and cell culture studies have identified and localized

matrix-degrading enzymes of the MMP class,[3] which may be responsible for the extensive connective tissue destruction in this disease.[3,12] These have identified the abundant expression of mRNAs corresponding to the matrix degrading enzymes, stromelysin-1 and gelatinase B in tissue derived from patients with necrotizing scleritis (Fig. 1.3). These enzymes were localized to infiltrating inflammatory cells, such as macrophages, T-lymphocytes, plasma cells, and resident scleral fibroblasts. By contrast, the expression of the MMP inhibitor, TIMP-1, by similar cells was less extensive, suggesting an imbalance between enzyme and inhibitor molecules.

The scleral matrix consists of approximately 70–80% collagen by weight, predominantly composed of type I collagen, with smaller amounts of collagen types II and III. Elastic fibres strengthen the collagen with PTGs completing the microstructure of the sclera. Although the MMPs localized in these studies have limited activity against interstitial collagens, these proteinases possess elastinolytic activity.[44] The triple helix of native fibrillar collagens can only be cleaved by the collagenases (MMP-1, -8, -13). It has however been reported that gelatinase B can degrade the α2 chain of type I and the α1 chain of type II collagen.[45] Furthermore, stromelysin is active against type III collagen[46] and aggrecan (a major PTG component of the sclera). In this capacity, MMPs derived from resident or inflammatory cells may play a crucial role in the scleral connective tissue destruction, which occurs in necrotizing scleritis.

Figure 1.3 (Pages 14–15) Expression of matrix metalloproteinases, their inhibitors, and tumour necrosis factor-alpha in necrotizing scleritis tissue. Scleritis tissue (a–f) was sectioned and analysed by *in situ* hybridization (a & b) using a stromelysin-1 (a), a TIMP-1 (b) antisense, and a stromelysin-1 sense (inset b) digoxigenin-labelled riboprobe. Messenger RNA hybridization signal denoted by the blue cytoplasmic staining was more abundant for stromelysin-1 than for TIMP-1, particularly in large macrophage-like cells (arrows). Scleritis tissue was also analysed imunohistochemically (c–f) using specific antibodies. The red staining denotes positive immunoreactivity (c & d), and the brown reactivity is specific staining (e & f). Stromelysin-1 (c) protein was detected in connective tissue fibroblasts as well as in macrophage-like cells. Gelatinase B (d) was detected in resident scleral fibroblasts, perivascular leukocytes, and vascular endothelial cells. The proinflammatory cytokine TNF-α (e) (a potent modulator of MMP expression) was localized in scleritis tissue, predominantly in IgG positive plasma cells (f). Arrows (in e & f) identify the same cell in contiguous tissue sections. (Original magnification × 640)

(a)



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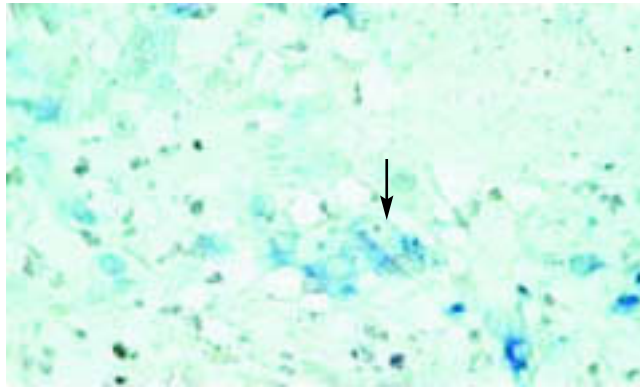

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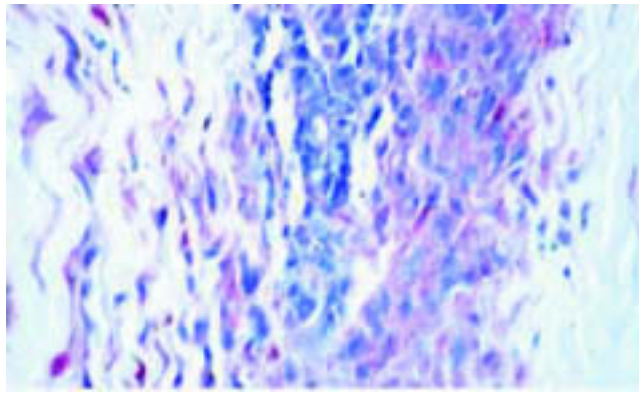

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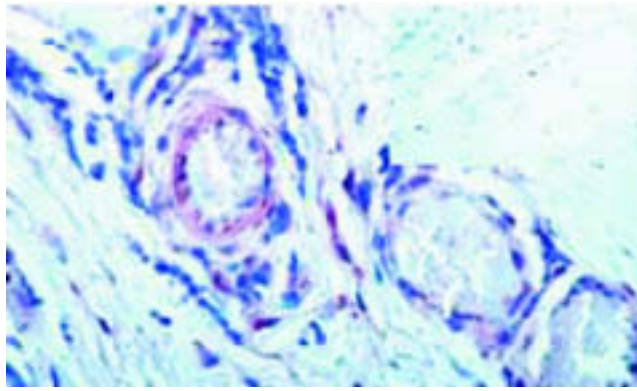

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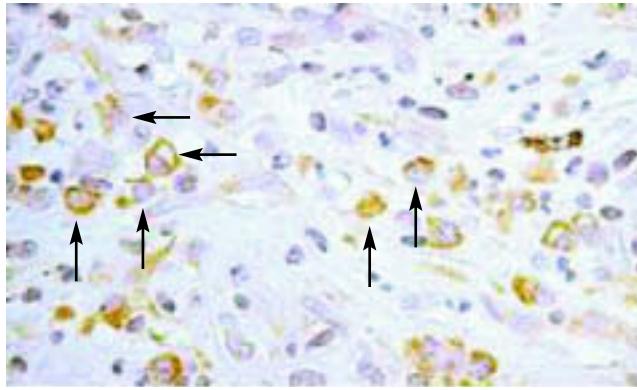

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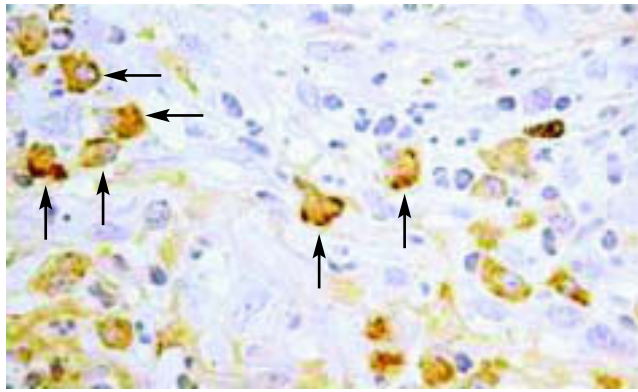

Transcriptional regulation is an important mechanism by which MMP activity is modulated, in particular via the effects of cytokines and growth factors. Recently the pro-inflammatory cytokine TNFα has been successfully localized to plasma cells in scleritis tissue.[3,25] TNFα is a potent enhancer of MMP expression, stimulating the production of these enzymes in leukocytes and in stromal fibroblasts. The observation that TIMP-1 expression was less abundant may be explained by the fact that TNFα is less effective at inducing TIMP-1 than MMPs.[47]

Large numbers of mast cells have been detected in sclera involved by necrotizing scleritis.[48,49] MMPs are secreted in an inactive form and require cleavage to become active against matrix components. It is well established that mast cell-derived proteases, namely chymase and tryptase, are potent activators of pro-stromelysin *in vitro*.[50] There is close proximity of tryptase positive mast cells to stromelysin and gelatinase B expressing leukocytes and scleral fibroblasts.[48] It is likely that mast cell-derived tryptase activates pro-stromelysin, leading to a proteinase cascade similar to the one depicted in Fig. 1.2.

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2: Classification of scleral inflammation

PETER WATSON

Scleral disease has been described sporadically in the older literature, usually in association with rheumatic disease, syphilis or tuberculosis. Galileo was possibly the most famous sufferer of scleral disease.[1] He certainly suffered from severe bouts of arthritis that were aggravated by the cold and wet weather from the age of 35 years. He had intermittent eye trouble throughout his life and became totally blind at the age of 74 years from what was probably a destructive scleritis complicated by keratitis and secondary glaucoma. So much is now known about the disease and how to treat it that history should not be allowed to repeat itself but, even now, similar problems are seen from time to time.

Although scleral inflammation is only seen in 1 in every 6000 new patients, the consequence of an incorrect diagnosis or inappropriate treatment can be blindness. It is therefore important that all ophthalmologists are aware of what constitutes serious disease needing urgent treatment, and what can safely be left alone possibly without any treatment at all. This is relatively easy when the inflammation affects the anterior sclera, but is much more difficult when the posterior segment is involved. Many of those with posterior scleritis have no associated anterior scleritis and indeed some have no physical signs, and yet these are the patients who can go blind extremely rapidly.[2]

It may seem a daunting prospect to distinguish between the various forms of scleral disease; however, the symptoms are usually suggestive and almost always all the physical signs can be elicited by a properly performed, careful ocular examination.[3]

CLASSIFICATION

Inflammation of the sclera is classified by its location and severity using the system devised by Watson.[4] This classification is

detailed in Box 2.1. Both episcleritis and scleritis are recurrent disorders. Recurrences are often triggered by simple factors such as a viral infection or even stress. However, long-term studies have revealed that it is exceptional for one type of scleritis or episcleritis to recur in a different form.[5] As it is vital not to undertreat serious disease or overtreat benign disease, it is important to identify the exact condition when the patient first presents. The most important differentiation is between episcleritis and scleritis, because episcleritis rarely requires treatment (although it is usually given) and scleral disease almost always requires systemic therapy.

DIFFUSE AND NODULAR EPISCLERITIS

Episcleritis can be diffuse or nodular and may affect both the anterior and posterior segment of the eye. As the name implies only episcleral tissue is involved in the inflammatory process, although the conjunctival vessels and the vessels lying directly on the scleral surface become dilated as a result of the inflammatory process (Fig. 2.1). It is known from fluorescein angiographic studies that the inflamed appearance results from leakage and extravasation of fluid from blood vessels in the inflamed area.[6] The reason for this dramatic and sometimes severe inflammation is unclear, nor is it known why the inflammatory process remains localized in some individuals resulting in nodular episcleritis, whereas in others all the episcleral vessels of one or both eyes are

Box 2.1 Classification of inflammation of the sclera

Episclera

- *Episcleritis*
  - Diffuse
  - Nodular

Sclera

- *Scleritis – anterior*
  - Diffuse
  - Nodular
  - Necrotizing
    - with inflammation
    - without inflammation
    - scleromalacia perforans
- *Scleritis – posterior*
  - Diffuse nodular necrotizing

Figure 2.1 Diffuse episcleritis associated with ocular rosacea.

dilated and involved by the inflammatory process resulting in diffuse episcleritis.

Careful slit lamp examination is required to make the diagnosis of anterior episcleritis. The crucial observation is whether or not there is any underlying scleral swelling, as episcleral oedema can be seen in patients with either episcleritis or scleritis.[3] Scleral oedema can usually be detected through eye observation using the very fine beam at high magnification and the red-free (green) light of the slit lamp. If the sclera underlying the inflamed episclera cannot be easily visualized then phenylephrine (or other vasoconstrictor) will blanche the superficial vessels. The area of the episcleral oedema in the inflamed area will appear yellow in red-free light – an appearance rarely seen in scleritis.

Posterior episcleritis probably exists but is difficult to detect even with good modern ultrasonography. This is not necessarily because the ultrasound technique is poor but, as the episcleral tissue is extremely thin over the posterior pole, the inflammation produces very little oedema. The "T" sign, seen with β scan ultrasonography detects movement of the episclera away from the scleral surface. This sign can be observed whenever there is posterior episcleral inflammation, and is seen mostly in patients with posterior scleritis as there is always overlying posterior episcleral inflammation in patients with posterior scleritis.

DIFFUSE AND NODULAR ANTERIOR SCLERITIS

In diffuse and nodular scleritis the degree of inflammation of both sclera and its overlying episclera and conjunctiva is very

much more severe than that seen in episcleritis. As the scleral tissue becomes stretched, the nerves are stimulated and, as a consequence, severe pain accompanies the inflammation. This pain is referred to the face and temple, unlike the discomfort of episcleritis, which is confined to the eye alone.

Whereas there is little to choose in the degree of severity between the diffuse and nodular episcleritis, this is not true of scleral disease. Diffuse scleritis presents with severe pain, referred largely to brow and jaw, and marked oedema of both the episcleral and scleral tissue (Fig. 2.2). Provided that it is treated quickly and intensively, the condition can be brought under control within 48 hours. Nodular disease, whether single or multiple, follows a much more prolonged course (Fig. 2.3). The nodule may persist even when the disease has been fully controlled and there is no

Figure 2.2 Diffuse anterior scleritis.

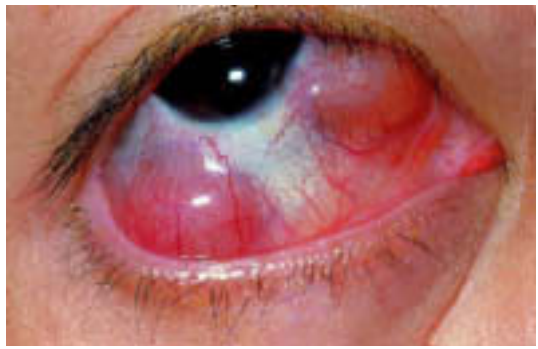

Figure 2.3 Nodular anterior scleritis.

active inflammation. This makes the decision of how much and how long to continue treatment much more difficult. Systemic disease is much more commonly associated with nodular disease than diffuse anterior scleritis.[5]

NECROTIZING SCLERITIS WITH INFLAMMATION

This is the most destructive form of scleral disease and is a serious threat to vision and the integrity of the globe (Fig. 2.4).[7] It is therefore essential to identify this pattern of scleral inflammation by careful slit lamp examination of the sclera.

Although the onset of necrotizing scleritis is almost always rapid and the pain intense, there are a few patients who present with an inflamed eye without much pain. Such patients are often taking low-dose systemic corticosteroid therapy for an associated disease such as rheumatoid arthritis. Destruction of the sclera in patients with necrotizing scleritis takes place within the deeper layers of the sclera, and so the necrotizing nature of the condition can easily be missed. This makes close inspection of the vasculature with or without fluorescein angiography essential to distinguishing between the more benign forms of scleritis and the necrotizing disease. The blood within the vascular networks overlying the necrotic area becomes static, even though the vessel contains blood and is dilated.[3] As a consequence there is no perfusion of blood through the episclera in this region. If this stasis is not

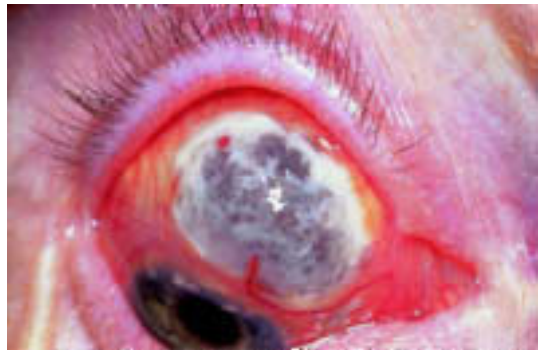

Figure 2.4 Severe necrotizing anterior scleritis.

noticed and the causative inflammation is not suppressed, necrosis occurs, and this may rapidly lead to loss of tissue not only in the sclera but also in the overlying conjunctiva and episclera. These changes occur whether there is a nodule present or not. However, if a nodule is necrotic the destruction is usually well within the substance of the tissue and not at its surface. Nodules become filled with fluid and heal as fibrous scar tissue. Tissue that has been destroyed and has ulcerated is replaced by fibrous tissue in due course. This may result in the sclera becoming variably thin or translucent. However, the eye will remain intact unless the intraocular pressure rises rapidly so that it is rarely necessary to support the underlying choroid.

NECROTIZING SCLERITIS WITHOUT INFLAMMATION (*SCLEROMALACIA PERFORANS*)

This unusual condition occurs virtually exclusively in elderly, usually female, patients with longstanding destructive and inactive rheumatoid arthritis. It is extremely rare. The eye is not painful. Either the patient or their attendant notices that the white eye has changed colour from porcelain white to yellow. The yellow spots are necrotic areas of sclera and represent a sequestrum of scleral tissue. Progression can be inhibited if the disorder is treated early, but those regions that already contain necrotic sclera cannot be influenced by treatment. Over time the necrotic area will be resorbed, leaving the bare choroid exposed, covered only by a thin film of fibrous tissue. These areas of exposed choroid are readily visible on examination and appear blue/black in colour. Unless the intraocular pressure rises this will not be harmful and no treatment is necessary.

POSTERIOR SCLERITIS

Posterior scleritis is a very much underdiagnosed condition. The use of β scan ultrasonography confirms that posterior scleritis is far commoner than previously thought and, because of the lack of visible physical signs and the proximity of the inflammation to the macula, retina and optic nerve, it is potentially devastating.[2] Undiagnosed and untreated posterior scleritis of whatever type can rapidly lead to blindness.

DIFFUSE AND NODULAR POSTERIOR SCLERITIS

The exact diagnosis depends almost entirely on the ultrasonographic appearances (Fig. 2.5). Physical signs such as choroidal folds, disc oedema, choroid effusions, and retinal detachments are not a guide to the type of posterior scleritis, and, commonly there are no physical signs other than decreased vision. Attention is drawn to the possibility of this disease by deterioration of vision and by pain, which is not always a prominent feature. Fortunately the ultrasonographic signs in these patients are characteristic and allow the diagnosis of posterior scleritis to be made.[2] Diffuse posterior scleritis, if detected adjacent to the disc or macula, must be treated extremely vigorously and at once, if the vision is not to be affected permanently. Scleral nodules on the other hand can often be enormous without apparently affecting vision at all.

POSTERIOR NECROTIZING SCLERITIS

Necrotizing scleritis involving the posterior sclera is seen occasionally by vitroretinal surgeons when a scleral plomb becomes infected following surgery.[8] The necrotizing nature of the scleritis is readily apparent at surgery; however, thus far it has not been possible to make this diagnosis by ultrasonography.

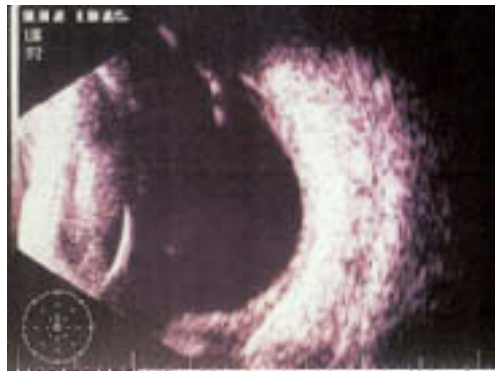

Figure 2.5 β scan ultrasound showing a peripheral uveal effusion in a patient with posterior scleritis.

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3: Pathology of scleritis

PHILIP LUTHERT

The receipt of scleritis specimens is a relatively uncommon event for most surgical ophthalmic pathologists. Such specimens may come in the form of small biopsies, enucleations or, rarely, exenterations. Often, the diagnosis is not in doubt; the patient may, for instance, have a longstanding history of rheumatoid arthritis with a typical clinical picture. On other occasions, pathology may provide critical diagnostic information. An unexpected infectious organism may be identified or malignant disease uncovered. Handling of scleritis specimens requires little out of the ordinary although, as with any inflammatory process, if there is any possibility of an infectious aetiology, material should be sent for microbiology as well as histopathology. From a research perspective, scleritis specimens offer an important opportunity to study pathogenesis, both from the perspective of aetiology and, in the case of autoimmunity, disease mechanism.

Classification of scleritis has already been considered (Chapter 2). From a histopathological point of view the same issues apply, i.e. site, aetiology, and, in particular, the presence or absence of necrosis and the presence or absence of granulomatous inflammation. For the purposes of this chapter a largely aetiological approach will be taken.

Although in the majority of cases it is possible to identify a local or systemic cause for the scleritis, an idiopathic group remains. The histopathology of a group of such cases has been described by Rao.[1] The features described included small foci of scleral necrosis with chronic non-granulomatous inflammation with lymphoid follicles. Most, if not all, cases of idiopathic scleritis are likely to represent ocular directed autoimmunity, and will considered as such.

AUTOIMMUNE DISEASE

Systemic autoimmune disease is a common finding in patients with scleritis,[2] and scleral and episcleral tissues appear to be particularly at risk in a wide range of autoimmune disorders. Why this should be the case is not clear. It is possible that everyday exposure to irritants and pathogens provokes minor episodes of inflammation that in some way prime the autoimmune-mediated inflammation. The following description includes details of histology of some cases where precise information concerning aetiology was not provided, but it has been assumed that the cases were of autoimmune aetiology.

The detailed pathogenesis of this heterogeneous group of conditions remains uncertain although it is agreed that autoimmunity plays an important role. Immune complex deposition may be a feature[1–3] and, interestingly, one case of scleritis following treatment with a mouse monoclonal antibody has been reported.[4] Immune complex formation has also been described in at least one pathological report.[5] In conditions such as relapsing polychondritis, autoantibodies, in this instance to type II collagen, may have a role to play. It has been proposed that the presence of higher levels of complement C1 in the anterior sclera may explain the increased incidence of immune complex disease-associated scleritis at the front of the eye.[6]

Necrotizing and non-necrotizing vasculitis (especially arteritis) have been seen in some cases.[2,7] The early involvement of sclera adjacent to anterior and posterior ciliary vessels has been used to support the notion that vasculitis is an important component in the pathogenesis of scleritis,[8] but non-vasculitic inflammatory diseases, such as multiple sclerosis, are also characterized by perivascular pathology. In addition, in many cases vasculitis is not found and, although this may to a degree reflect problems with sampling, it seems probable that vasculitis is not a universal finding. Interestingly, other vascular changes, in the absence of inflammation, vasculitic or otherwise, have been reported. These include vascular closure,[9] which might be anticipated to lead to ischaemic necrosis in the absence of vasculitis.

There has been relatively little analysis of the detailed phenotype of the inflammatory cell infiltrate. In one study of two cases there was a predominance of CD4 positive T cells with clusters of B cells in a perivascular location.[10] In this study no evidence of vasculitis was seen. Relatively few of the T cells appeared activated as

assessed by the level of IL-2 receptor expression. A predominance of T helper cells was also seen in a study of 30 scleritis patients.[2] *In vitro* studies have shown the potential of scleral fibroblasts and inflammatory cells to release matrix metalloproteinases, which would be expected to play an important role in the degradation of scleral collagen.[11] Dissolution of scleral collagen certainly develops with time and is likely to be the consequence of the sustained release of a variety of proteases from inflammatory cells. One ultrastructural study has interestingly shown that there is loss of proteoglycan from scleral collagen prior to its destruction.[12]

Rheumatoid arthritis

The prototypical autoimmune scleritis is that seen in rheumatoid arthritis. As with other autoimmune conditions, rheumatoid scleritis may be seen in isolation or in association with other ocular manifestations. In active rheumatoid arthritis, simple episcleritis may be seen. There is little reason to biopsy such lesions, but histopathologically they consist of little more than perivascular lymphocyte-rich, non-granulomatous inflammation associated with oedema formation. Classically, in nodular rheumatoid episcleritis, or more commonly, scleritis, the histological appearances are those of subcutaneous rheumatoid nodules. At low power, the affected sclera is seen to be thickened with expansion by inflammatory cells and associated destruction of collagen (Fig. 3.1a–c). There is often a sharp line of demarcation between

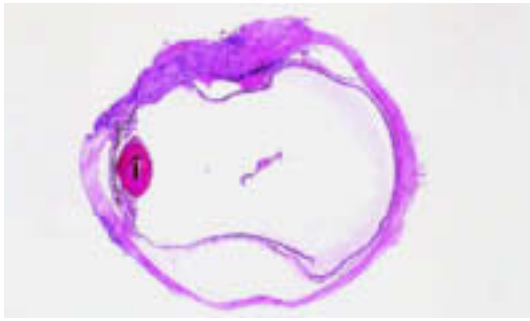

Figure 3.1a Low power image of whole mount section of an eye with marked thickening of the sclera from the limbus back to the equator on one side. Note a small amount of eosinophilic material just under the retina; evidence of a genuine retinal detachment at this point. (Haematoxylin and eosin; magnification × 0.8)

Figure 3.1b Low power image of a whole mount of a different case with intense inflammation of the anterior sclera (staining blue), on both sides of the specimen. (Haematoxylin and eosin; magnification × 1.8)

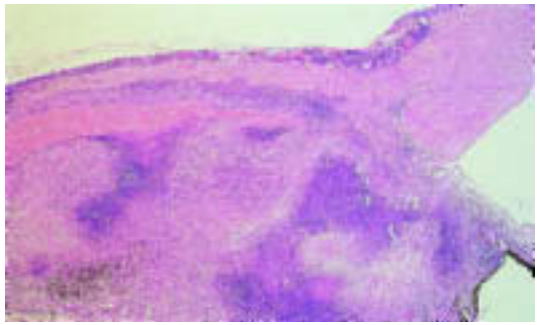

Figure 3.1c Photomicrograph of a further case with the anterior chamber angle and a little iris on the right and extensive thickening of the inner sclera with inflammation extending into the ciliary body. Note a linear band of inflammation running through the sclera parallel to the surface. (Haematoxylin and eosin; magnification × 6.5)

normal and destroyed collagen (Fig. 3.2). The rheumatoid inflammatory nodules comprise a central necrotic, fibrin-rich region surrounded by histiocytes, typically arranged in a palisading pattern (Fig. 3.3 and 3.4). External to this is a zone of chronic non-granulomatous inflammation. This configuration is not specific for rheumatoid disease and may be seen in many other conditions. Similarly, there are no particular features of scleral disease in rheumatoid arthritis that distinguish it from changes elsewhere in the body.

When the histology is focal, the picture of nodular scleritis

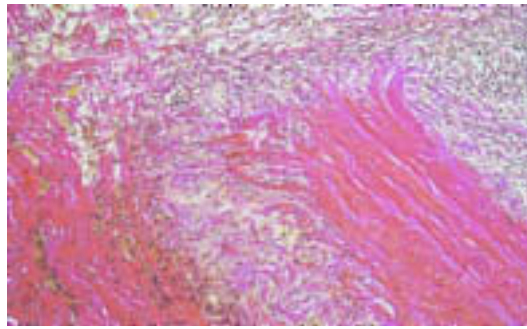

Figure 3.2 Bundles of scleral collagen stained pink/orange clearly demarcated from inflammatory cell infiltrate. (Haematoxylin van Gieson; magnification × 33)

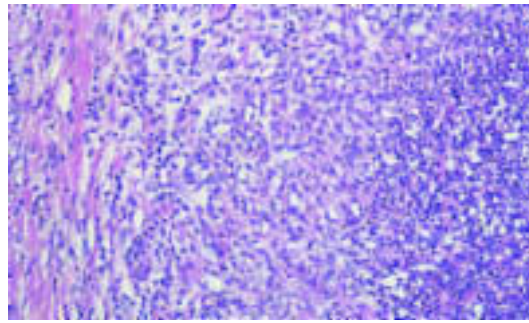

Figure 3.3 Light micrograph of the inflammatory cell infiltrate in a case of rheumatoid scleritis. There is an area of destruction with much nuclear debris on the right, and a zone with epithelioid cells in the centre. This is separated by a thin layer containing lymphocytes from surviving bundles of scleral collagen on the extreme left. (Haematoxylin and eosin; magnification × 66)

results, but from a histological point of view the changes are essentially the same in diffuse (or brawny) scleritis. The disease may evolve in a variety of ways. There may be extension in continuity, say from anterior to posterior, or multiple focal lesions of different ages may be seen. Recurrent focal lesions often develop adjacent to older, resolved lesions. Resolution with scarring ultimately takes place and, if the damage to the scleral collagen is sufficiently severe, scleral thinning or a staphyloma is seen.

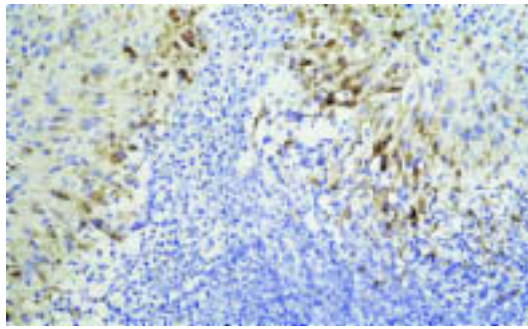

Figure 3.4 Light micrograph from case shown in Figure 3.3 where the epithelioid cells (macrophages) have been labelled in brown with an antibody to CD68. (Magnification × 66)

Wegener's granulomatosis

Wegener's granulomatosis may affect the eye in isolation in its localized form or as part of systemic disease. Similarly, scleritis may be the only ocular manifestation or it may be seen with orbital, conjunctival, uveal, or retinal inflammation. In a review of 44 cases of Wegener's granulomatosis, 19 had ocular involvement, six had orbital disease, and three had episcleritis and scleritis. In the Mayo clinic series of 140 biopsy proven cases, 15 of the 40 individuals with ocular involvement had episcleritis or scleritis. Diffuse and nodular disease, with and without necrosis, was described.

Histologically, Wegener's granulomatosis may present a major diagnostic challenge. The triad of necrosis, vasculitis and granulomatous inflammation is always sought for but is often not present.[13–15] Indeed there are occasions when all that is initially seen, in cases that later turn out to be classical Wegener's granulomatosis, is a completely non-specific, chronic non-granulomatous inflammatory cell infiltrate (Fig. 3.5). It is therefore important that clinician and pathologist maintain a high index of suspicion for this devastating potentially fatal, yet treatable, condition. The increasing use of antineutrophil cytoplasmic antibody (ANCA) serology is clarifying views as to the breadth of histopathology seen in Wegener's granulomatosis.[16] A single case of propylthiouracil-induced vasculitis associated with ANCA causing scleritis has been reported.[17]

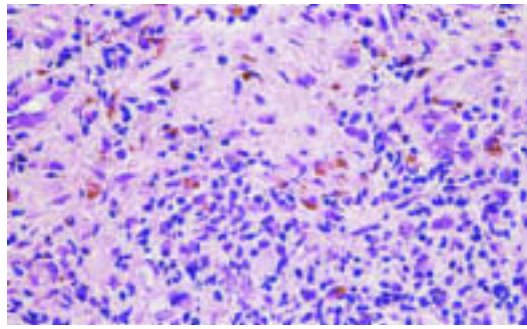

Figure 3.5 Light micrograph of chronic non-granulomatous inflammation in a patient with Wegener's granulomatosis but without the classical features. The pigment is haemosiderin secondary to haemorrhage related to a previous biopsy. (Haematoxylin and eosin; magnification × 130)

Autoimmunity and infection

Patients with coccidiomycosis and erythema nodosum may have scleritis, presumably due to an immune reaction rather than to local infection. A similar immune-mediated response to infection has been seen with leprosy,[18] where histology showed non-granulomatous chronic inflammation of the sclera.

Autoimmunity and other systemic diseases

The range of systemic conditions associated with autoimmune-mediated scleritis is wide and, in general, there are no specific features that characterize individual disorders. Patients with systemic lupus erythematosus and spondyloarthropathies have a more benign clinical course than those with other connective tissue disorders, and patients with the latter usually fare better than those with Wegener's granulomatosis.[19] Posterior scleritis has been reported in a patient with biopsy-proven sarcoid involvement of the parotid gland.[20]

INFECTIOUS CAUSES

Infection can lead to scleritis in many different contexts. It may arise as part of a systemic infection or complicate infection elsewhere in the eye or in the orbit; it may follow surgery, particularly

for cataract, glaucoma or pterygium, or accidental trauma. Following trabeculectomy, mitomycin C toxicity as well as infection can be responsible.[21] Scleral biopsy may be of value in identifying the aetiological agent.[22]

Viral infections

Herpes zoster varicella is the most widely reported viral cause of scleritis and usually arises in association with keratitis and iridocyclitis. Focal or diffuse scleral involvement may be seen at the early vesicular stage and focal nodules may form 2–3 months later.[23]

Bacterial infections

In a large survey of patients with tuberculosis, 1.4% had ocular manifestations and 9% of these had scleritis.[24] The histopathology of tuberculous scleritis has not been specifically addressed although scleral destruction is seen (Fig. 3.6). Scleritis is a rare manifestation of syphilis,[25] as is nocardia.[26]

Fungal infections

Aspergillus scleritis has been reported in a patient where scleral biopsy was required to make the diagnosis,[27] and classical hyphae

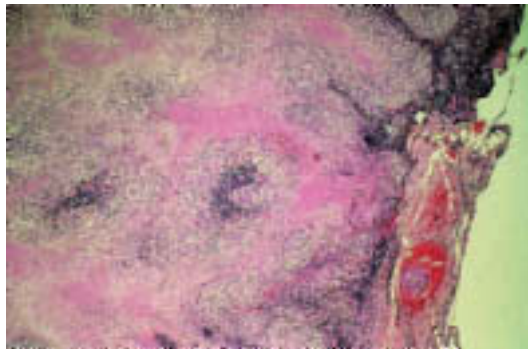

Figure 3.6 Light micrograph showing scleral involvement in a case of tuberculosis. The sclera is expanded by an extensive inflammatory cell infiltrate. A small amount of choroid is present on the right hand side of the figure. (Haematoxylin and eosin; magnification × 6.5 approx.)

can be demonstrated with a Grocott stain (Fig. 3.7). In an instance of postoperative scleritis following cataract extraction *Rizopus* species were identified.[28] In a case of posterior scleritis following pterygium surgery, histology of a scleral biopsy specimen disclosed numerous fungal hyphae that, on culture, proved to be *Pseudallescheria boydii*.[29]

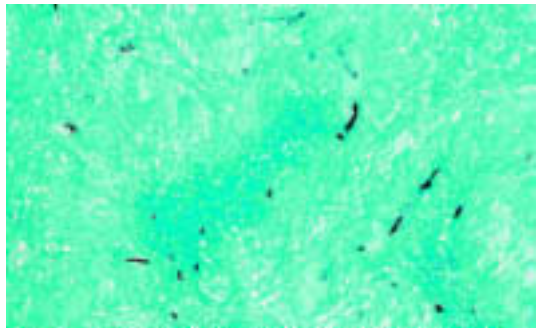

Figure 3.7 Light micrograph of Aspergillus infection affecting the orbit and sclera. Note the black-staining organisms. (Grocott's methanamine silver stain; magnification × 50 approx.)

Protozoal and parasitic infections

Acanthamoeba keratitis may extend to the adjacent sclera and form scleritic nodules. Usually the clinical context is such that the diagnosis is clear prior to biopsy for histology or culture, and the appropriate special stains for acanthamoebae can be carried out. They may be visible in PAS or under UV light following staining with Calcofluor white. Immunohistochemistry is, however, probably the most sensitive, although not entirely specific, special stain. Acanthamoeba cysts may be associated with relatively little inflammation, a chronic non-granulomatous inflammatory cell infiltrate or granulomatous inflammation.[30] In other cases, organisms may be restricted to the cornea but the associated inflammation leads to damage of the adjacent sclera.[31]

Toxoplasma may also cause scleritis in association with retinochoroiditis. However, in a pathological study of three cases,[32] organisms were found in the retina but not the sclera.

Onchocerciasis may cause scleritis, amongst its ocular manifestations. Scleritis caused by intraocular infection is discussed below.

METABOLIC CAUSES

Gout can cause scleritis in association with conjunctivitis, episcleritis, tendonitis, and iridocyclitis. Histology of the scleritis does not appear to have been reported but at other sites intranuclear crystals of uric acid have been seen.[33] The histopathology of porphyria-associated scleritis[34] also is not known.

ADJACENT INFLAMMATION

Intraocular tumour and inflammation

Retinoblastoma, melanoma, and choroidal metastases can provoke a sometimes dramatic scleral reaction, usually in response to massive necrosis of the intraocular tumour. Macroscopically, the sclera and episcleral tissues may have a gelatinous quality that can be mistaken for extraocular extension. The activated fibroblasts may have marked nuclear pleomorphism, which may add to the confusion. Similarly, intraocular inflammation from infection or VKH[35] may involve scleral tissues.

Rarely, tumour may metastasize directly to the sclera and episcleral tissues[36] and more recently, low grade B cell lymphoma (extranodal marginal zone lymphoma) has been described mimicking scleritis.[37] As the authors comment, if biopsy-proven scleritis fails to respond to therapy, the possibility of lymphoma should be considered. Locally invasive squamous carcinoma may also present as scleritis.[38]

Orbital inflammation

Involvement of the sclera by an orbital inflammatory process is not uncommon and in general the orbital disease predominates and no diagnostic difficulties arise. Orbital cellulitis and non-infectious causes of orbital inflammation, including idiopathic chronic inflammation of the orbit, are well-recognized causes. Rarer conditions, such as Rosai–Dorfman disease and necrobiotic xanthogranuloma, have also been described. Three of 15 patients

with lymphomatoid granulomatosis had scleritis[39] and a further case of scleritis in this condition has been reported.[40]

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4: Episcleritis

ANTHONY JH HALL

Episcleritis is an acute, recurrent, benign inflammatory condition of the loose connective tissue lying superficial to the sclera. It has been recognized for more than a century and a number of recent studies have provided information about its clinical features, aetiology, and management.

Episcleritis is overwhelmingly a disease of adults with a broad age range at presentation; childhood involvement is distinctly uncommon.[1–3] The sex distribution varies between published series but those series that describe an association with rheumatic diseases tend to have a female preponderance. Episcleritis is uncommon and the exact incidence of episcleritis is difficult to know but, of 9600 new referrals to two eye departments in Glasgow between 1966 and 1974, only eight (0.08%) were due to scleral inflammation.[4] In the same paper of 4210 patients with rheumatoid arthritis, only 0.17% had episcleritis at any stage of their disease. Diffuse episcleritis is more common than nodular episcleritis (78:16 in one series).[5] Episcleritis is far commoner than the series in the medical literature would suggest. The majority of patients with episcleritis have mild evanescent disease that usually does not require ophthalmological intervention and treatment.[6]

CLINICAL FEATURES

The onset of episcleritis is usually acute and associated with discomfort rather than severe pain as the presenting symptom. The pain is usually mild discomfort and localized to the eye, rather than boring in nature and associated with severe headache as is typical of scleritis. Some episodes of episcleritis may be entirely pain free. There may be associated foreign body sensation and epiphora.

The hallmark signs of episcleritis are oedema and inflammation of the episclera and injection and dilatation of the episcleral blood vessels. The sclera and subtarsal conjunctiva are not involved but the conjunctiva overlying the inflamed area is always affected. There is no scleral swelling or necrosis and the intraocular structures are typically not involved. Unless there is other coexistent ocular pathology the visual acuity is normal. Episcleritis is divided into diffuse and nodular types (see Chapter 2).

In diffuse episcleritis (Fig. 4.1) there is diffuse swelling and oedema of a sector of the episclera in around two-thirds of patients or of the whole eye in around one-third of patients. In diffuse episcleritis the redness varies in intensity, but is always red or pink (rather than the bluish, brawny red colour seen in diffuse scleritis), and the episcleral vessels, although engorged, retain their characteristic radial orientation.[2] The best way of appreciating the colour of episcleritis and in particular differentiating it from scleritis is not to use the slit lamp but to examine the eye using natural light or an incandescent lamp. The eye is generally not tender to touch.

In nodular episcleritis (Fig. 4.2), the oedema and infiltration is localized to one part of the globe. A raised nodule forms within the episcleral tissue. It is bright red to pink in colour and often has overlying or surrounding vascular irregularity. The nodule may be tender to touch and is usually mobile. There is generally only one nodule at any one time and the nodules do not undergo necrosis.

Careful slit lamp examination of the episclera, sclera, and the blood vessels is essential to differentiate episcleritis from scleritis. In patients with episcleritis there is oedema of the episclera and dilatation of the conjunctival vessels. There is no oedema of the

Figure 4.1 Diffuse episcleritis.

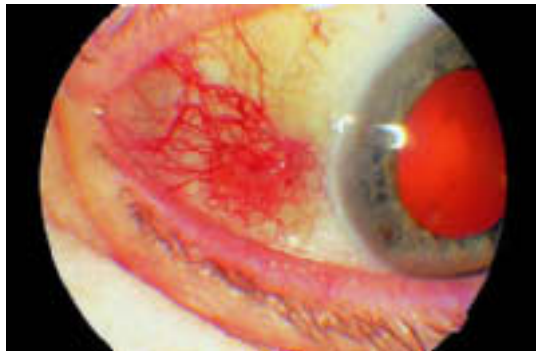

Figure 4.2 Nodular episcleritis.

underlying sclera. The lack of scleral involvement is often easiest to appreciate using red-free light and after blanching the superficial conjunctival vessels with phenylephrine 10%.

After an attack of episcleritis the eye returns completely to normal, but after repeated attacks over a long period of time there may be some mild scleral thinning.

DISEASE ASSOCIATIONS OF EPISCLERITIS

Systemic associations

Episcleritis has been associated with a large number and variety of underlying diseases. There is wide divergence in the incidence and relevance of systemic diseases associated with episcleritis among the series and case reports in the literature with series from rheumatology centres and ophthalmology centres and tertiary referral centres having a higher incidence of systemic disease associations than other series.[1,2,7] The commoner systemic conditions associated with episcleritis are detailed in Box 4.1.

There are a large number of small series and case reports that confirm these relatively common disease associations of episcleritis and, additionally, there are a number of isolated descriptions of other much rarer associations, such as IgA nephropathy, Lyme disease and drug reaction to pamidronate.[8–10]

Episcleritis is rarely severe in children and is uncommonly reported in the literature. In a recent retrospective series from a group of tertiary paediatric ophthalmology centres, episcleritis was

Box 4.1 Recognized systemic disease associations of episcleritis

Atopy
Rheumatoid arthritis
Spondyloarthritis and other seronegative arthritis
Inflammatory bowel disease
Systemic lupus erythematosus
Relapsing polychondritis
Gout

associated with a diverse range of rheumatological diseases.[3] Additionally, recurrent episcleritis in children and adults is associated with gout and hyperuricaemia secondary to renal failure (Fig. 4.3).

Ocular associations

Acne rosacea is the commonest ocular disease associated with episcleritis and is typically seen in patients with eyelid and corneal involvement.[11] The ocular disease often precedes skin involvement. Episcleritis is also frequently seen as part of the spectrum of atopic keratoconjunctivitis and in patients with sicca syndromes.[1] Episcleritis occurs as part of the normal healing response following surgery involving the conjunctiva.

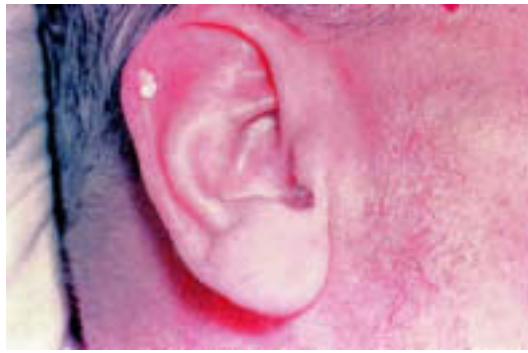

Figure 4.3 Gouty tophus involving the ear in a patient with renal failure, severe hyperuricaemia and recurrent episcleritis.

INVESTIGATIONS

In general, extensive investigation is not required in patients with episcleritis. While a broad range of underlying diseases is possible in episcleritis, the number of common underlying diseases is low (see Box 4.1). Where indicated clinically, a small number of serological tests looking for rheumatoid arthritis or systemic lupus erythematosus may be useful.

Anterior segment fluorescein angiography in episcleritis reveals a normal vascular pattern but the flow rate is generally faster than normal and the whole transit of dye may be completed within two to three seconds.[12] Anterior segment fluorescein angiography is rarely needed clinically in the diagnosis or management of episcleritis. High definition anterior segment ultrasound may also have a role in differentiating episcleritis from scleritis but is rarely necessary clinically.

HISTOPATHOLOGY

Biopsy and histological examination of tissue from patients with nodular and diffuse episcleritis is only indicated in persistent or atypical cases. It is not useful in determining the underlying disease. Histologically a chronic, non-granulomatous inflammatory infiltrate of lymphocytes and plasma cells along with oedema is usually found in the episcleral tissue (Fig. 4.4). Rarely a chronic granulomatous inflammatory infiltrate may be seen.[13]

TREATMENT

Episcleritis is a self-limiting, benign disease that frequently does not require any treatment. If the symptoms are severe or prolonged enough to warrant treatment, topical steroids generally provide rapid symptomatic relief and have proven benefit over topical non-steroidal anti-inflammatory treatment and topical lubricants.[14] Systemic treatment with oral non-steroidal anti-inflammatory drugs such as cyclo-oxygenase inhibitors, may be required for episcleritis and may carry less morbidity than long-term topical steroids. In general any systemic disease should be treated on its merits and the episcleritis treated as necessary. Any local ocular disease, such as acne rosacea, atopy, or

Figure 4.4 Chronic inflammatory infiltrate in an episcleral biopsy from a patient with episcleritis.

keratoconjunctivitis sicca that may be causing or contributing to the episcleritis, should be treated aggressively.

COMPLICATIONS

Involvement of other ocular structures is rare in patients with episcleritis. Episcleral inflammation adjacent to the cornea can be accompanied by mild peripheral corneal infiltrate or oedema, and the peripheral cornea can be left thinned or vascularized. Recurrent attacks of episcleritis over many years can result in some mild scleral thinning, which is of no consequence to the integrity of the eye.

The most frequent complications seen in patients with episcleritis are related to the use of long-term topical corticosteroids. Cataract, ocular hypertension, and steroid-induced glaucoma are not uncommon. Topical corticosteroids may also induce herpetic keratitis. These treatment-related complications are the commonest causes of visual loss in patients with episcleritis.

COURSE AND PROGNOSIS

Episcleritis is a mild, non-vision-threatening inflammation of the episclera that may recur over irregular intervals for many years. It is important to recognize its benign nature and not to induce vision-threatening complications by overtreating episodes of episcleritis.

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5: Anterior scleritis

PAUL A LATKANY and DOUGLAS A JABS

Scleritis is an uncommon disease. Although no epidemiological studies have estimated the prevalence of scleritis, cross-sectional studies have suggested that approximately 1% of patients with rheumatoid arthritis will develop scleral disease. The estimated prevalence of rheumatoid arthritis in the population is approximately 1%, and rheumatoid arthritis-associated scleritis accounts for 10–33% of all scleritis, suggesting that the prevalence of scleritis in the general population is between three and ten per 10 000.[1–3]

Anterior scleritis is the most common form of scleritis and is substantially more common than posterior scleritis.[4–6] Anterior scleritis may occur at any age but typically affects middle-aged and older adults. It is more frequent in women than men. There is no known racial predilection and no recognized immunogenetic marker for the disease. Anterior scleritis may be diffuse, nodular or necrotizing in nature and careful clinical examination allows the clinician to determine the type of scleritis. It is uncommon for anterior scleritis to change its clinical type. The classification of scleritis is discussed in Chapter 2. Two large published series have estimated that diffuse anterior scleritis and nodular anterior scleritis account for 78–85% of patients with scleritis.[5,6] The range of estimates of the different subtypes of scleritis is reported in Table 5.1.

Anterior scleritis may be an isolated ocular inflammatory condition or may be associated with an underlying infection or

Table 5.1 Frequency of anterior scleritis subtypes

Subtype of scleritis	Reported frequency (%)
Diffuse anterior	40–60
Nodular anterior	21–45
Necrotizing	14–23

systemic autoimmune disease. Approximately 8% of patients with anterior scleritis will have an associated infectious disorder, 40–50% an associated systemic immune-mediated disorder, and approximately 50% will have isolated ocular inflammation.[4–6] Necrotizing anterior scleritis is more likely to be associated with a systemic autoimmune disease.[4]

CLINICAL FEATURES

Symptoms

The hallmark symptom of scleritis is pain and this is overwhelmingly the commonest clinical presentation of patients with anterior scleritis. The pain is dull, aching, and boring in nature and is centred in the eye and orbit. It typically radiates to involve the scalp, ear, jaw, and teeth. The onset is over days to weeks. The pain characteristically worsens at night and wakens the patient from sleep in the early hours of the morning. The pain is usually sufficient to limit the patient's activities. The severity of the pain increases with the severity of the scleritis, and in severe necrotizing disease may be extreme, incapacitating, and described as the worst pain the patient has ever experienced. In patients with systemic diseases such as rheumatoid arthritis, who are taking regular anti-inflammatory therapy, such as non-steroid anti-inflammatory drugs, low-dose prednisolone or methotrexate, the pain may be masked to a great extent, and patients with severe scleritis may have little or no pain. Patients may also complain of redness and tenderness of the globe, photophobia, and epiphora.

Signs

The essential signs of anterior scleritis are scleral oedema and intense dilatation of the deep episcleral vascular plexus as a result of inflammation centred in the sclera. There is always overlying episcleral oedema and inflammation in patients with scleritis; however, on clinical examination, the episclera and overlying conjunctiva are bowed forward by the underlying scleral oedema. Scleral oedema may be difficult to detect and can be inferred from outward displacement of the overlying episcleral vessels.[6] Examination of the eye using the green (red-free) light beam on the slit lamp helps to determine the level of maximum inflammation and

vascular dilatation. Blanching of the overlying conjunctival vessels with a weak solution of phenylephrine can also determine the amount of episcleral and scleral inflammation.

The type of scleral inflammation is determined from the clinical signs found on examination of the sclera.[2,5] Diffuse anterior scleritis (Fig. 5.1) will have diffuse injection of large segments of the anterior sclera. Nodular anterior scleritis (Fig. 5.2) will have nodule formation with focal scleral oedema and swelling. Necrotizing scleritis (Figs 5.3 and 5.4) is characterized by scleral necrosis and areas of capillary non-perfusion. The earliest sign of scleral necrosis is an area of avascular white sclera. Small areas of capillary non-perfusion and closure may be difficult to visualize and require meticulous examination of the episcleral vascular plexuses. In

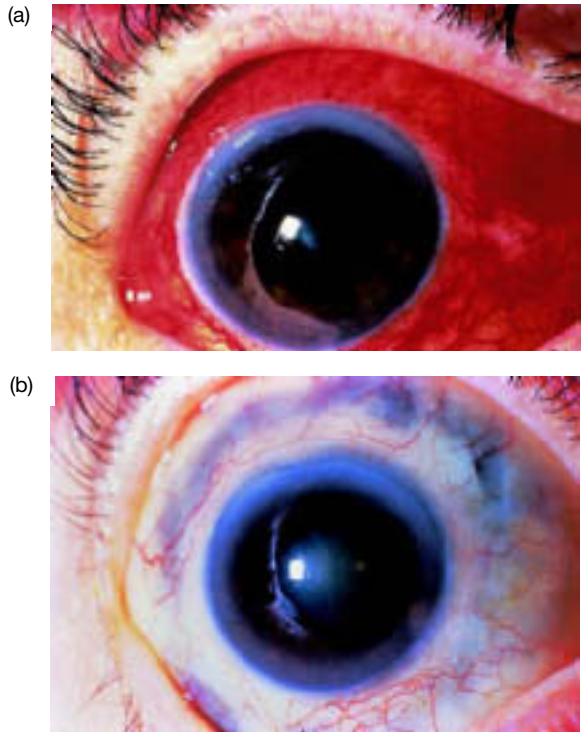


Figure 5.1 Diffuse anterior scleritis in a patient with inflammatory bowel disease. (a) Active scleritis; (b) healed scleritis. (From Jabs DA. Ocular manifestations of the rheumatic diseases. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. Vol. 5. Philadelphia: Lippincott & Wilkins, 1998, pp. 1–39, with permission.)

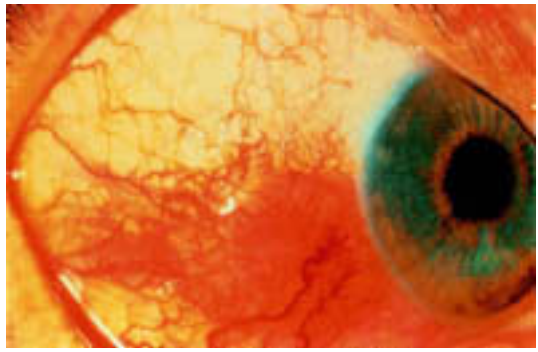
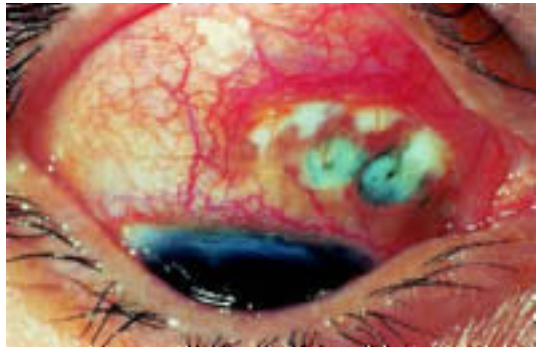


Figure 5.2 Nodular scleritis in a patient with rheumatoid arthritis. (From Jabs DA. Ocular manifestations of the rheumatic diseases. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. Vol. 5. Philadelphia: Lippincott & Wilkins, 1998, pp. 1–39, with permission.)

(a)



(b)

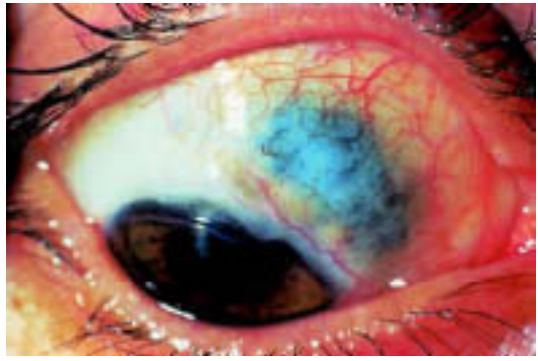
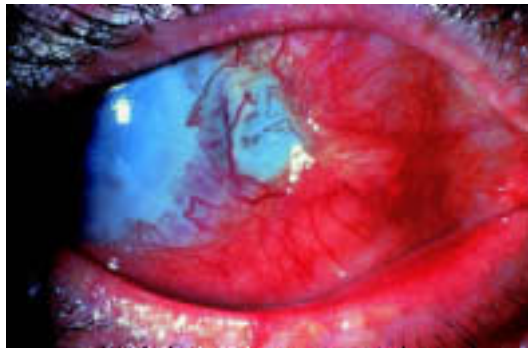


Figure 5.3 Necrotizing scleritis. (a) Active necrotizing scleritis; note the associated peripheral ulcerative keratitis; (b) healed scleritis after cyclophosphamide therapy.

(a)



(b)

Figure 5.4 Interstitial keratitis in a patient with necrotizing scleritis. (a) Scleritis; (b) keratitis.

selected patients anterior segment fluorescein angiography or indocyanine green angiography may be useful investigations to delineate the episcleral vessels. Careful examination of the scleral inflammation for early signs of scleral necrosis is important, as

necrotizing scleritis typically requires more aggressive anti-inflammatory medications than does diffuse anterior or nodular anterior scleritis.

Tenderness of the globe is a useful sign of scleral inflammation and its severity can be used as a guide to the degree of inflammation and its response to treatment. Examination should also assess the eye for complications of anterior scleritis, such as uveitis, corneal involvement, and elevated intraocular pressure. Involvement of the posterior sclera in patients presenting with anterior scleritis is far commoner than previously thought, and a careful clinical assessment for signs of involvement, such as choroidal effusion, serous retinal detachment, macular or optic disc swelling, and subretinal mass lesion, should be performed.[7] Posterior scleritis is discussed in Chapter 6.

ASSOCIATED SYSTEMIC DISORDERS

The immune-mediated diseases most frequently associated with anterior scleritis are rheumatoid arthritis, systemic necrotizing vasculitis, particularly Wegener's granulomatosis, systemic lupus erythematosus, inflammatory bowel disease, and relapsing polychondritis. Systemic autoimmune diseases are present in approximately 40–50% of patients with scleritis.[5,8]

Rheumatoid arthritis

This is the systemic connective tissue disease most commonly associated with scleritis. Approximately 1% of patients with rheumatoid arthritis will develop scleral disease. Of patients with scleritis, 10–33% have been reported to have rheumatoid arthritis.[5,6] Scleritis typically is seen in patients with longstanding rheumatoid arthritis who have extra articular manifestations of rheumatoid arthritis, such as rheumatoid nodules, pulmonary disease, cardiac disease, and rheumatoid vasculitis. Rheumatoid vasculitis most commonly causes peripheral neuropathy or non-healing leg ulcers. Scleritis correlates with more severe rheumatic disease.[3] Necrotizing anterior scleritis correlates with rheumatoid vasculitis and with an increased mortality, largely from systemic vascular disease.[9] Aggressive medical therapy of the vasculitis may improve long-term survival.[9]

Systemic necrotizing vasculitides

Any of the systemic necrotizing vasculitides may be associated with scleritis. The most commonly encountered is Wegener's granulomatosis.[10] Other types of vasculitis that may be associated with scleritis include polyarteritis nodosa, Churg–Strauss angiitis, hypersensitivity vasculitis, giant cell arteritis, and Takayasu's arteritis.[10,11] Some series have reported that nearly 60% of patients with Wegener's granulomatosis have some form of ocular or orbital involvement.[12] In published series of patients with Wegener's granulomatosis, scleritis is either the most common or second most common ocular manifestation.[12] Although any type of scleritis may be seen in patients with systemic vasculitis, necrotizing scleritis often heralds the occurrence of a systemic vasculitis.

Wegener's granulomatosis

Wegener's granulomatosis is classically defined by the occurrence of sinus disease, pulmonary disease, and renal disease.[12] In Wegener's granulomatosis, vasculitis and granulomatous inflammation are present in the sinuses and lungs, and a glomerulitis is present in the kidneys. Limited Wegener's granulomatosis occurs when there is only clinically evident sinus and pulmonary disease. Antineutrophil cytoplasmic antibodies (ANCA) are seen in 90% of patients with active Wegener's granulomatosis and ANCA serology is useful in evaluating patients with scleritis for underlying systemic disease.[13] The ANCA titre may be followed and may decline in patients successfully treated for Wegener's granulomatosis.[14]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystem disorder and generally has been regarded as the prototypic autoimmune disease. The incidence of SLE has been estimated at 5 cases per 100 000 population per year.[15] Systemic lupus erythematosus may affect almost any organ system, and criteria for the diagnosis have been established.[16] The diagnosis remains a clinical one based on a constellation of clinical features and laboratory tests. The most common systemic features of lupus include malar rash; skin lesions, such as discoid lupus; photosensitivity; oral ulcers;

polyarthritis; serositis, such as pleuritis and pericarditis; neurological disease, and lupus nephritis. Less common manifestations include haemolytic anaemia, leukopenia, and thrombocytopenia. A number of serological abnormalities may occur, such as anti-DNA antibodies and anticardiolipin antibodies, with an elevated ANA titre being the most common abnormality.

Scleritis is an uncommon manifestation of lupus, occurring in less than 1% of patients with lupus.[5] However, approximately 5% of patients with scleritis presenting to a tertiary eye-care centre will have systemic lupus erythematosus.[5] Scleritis may be associated with flares of the systemic disease and require aggressive medical therapy for both the ocular and systemic disease.

Inflammatory bowel disease

Inflammatory bowel disease is the general term for two separate disorders, ulcerative colitis and Crohn's disease. *Ulcerative colitis* is an inflammatory disorder of the colonic mucosa, whereas *Crohn's disease* is a focal granulomatous disease involving any part of the gastrointestinal tract. The characteristic clinical features of inflammatory bowel disease are diarrhoea and abdominal pain. A variety of extraintestinal manifestations may be seen in patients with inflammatory bowel disease, including dermatitis, ocular inflammation, and arthritis. The most common ocular manifestation of inflammatory bowel disease is uveitis.[17] Acute anterior uveitis is often seen in patients who have spondylitis or sacroiliitis, and is an HLA-B27-associated disorder. Large series have reported the frequency of ocular manifestation in patients with inflammatory bowel disease at 4–6%, and scleritis is a well-recognized complication of inflammatory bowel disease.[18] Some series have reported a frequency of scleritis as high as 10%.[19] Patients with inflammatory bowel disease and ocular inflammation often have other associated extraintestinal manifestations. Any type of scleritis may be seen in patients with inflammatory bowel disease.

In large series of patients with scleritis, inflammatory bowel disease occurs in approximately 5%.[5] Patients with scleritis and symptoms suggesting inflammatory bowel disease should have appropriate evaluation, including, if necessary, colonoscopy. Because of the low frequency of inflammatory bowel disease in patients with scleritis, patients without abdominal symptoms do not warrant routine gastrointestinal evaluation.

Relapsing polychondritis

Relapsing polychondritis is an uncommon disease characterized by recurrent, widespread, potentially destructive inflammation of cartilage.[20] It appears to be due to an immunological attack on type II cartilage, and patients with relapsing polychondritis have been demonstrated to have cell-mediated immunity and autoantibodies to type II collagen.[21] Type II collagen is not only widespread in cartilage, but also present in the eye. Relapsing polychondritis is diagnosed by the occurrence of appropriate clinical features and confirmed by biopsy, most often of the auricular cartilage. The tissues involved include the ears, nose, joints, cardiovascular system, and laryngotracheal–bronchial tree. Laryngeal involvement occasionally may be fatal from airway collapse. Approximately 10% of patients with relapsing polychondritis will also have a known vasculitis. Although relapsing polychondritis is an uncommon disease, ocular inflammation occurs in nearly 60% of these patients.[22] Scleritis is the most commonly encountered ocular manifestation, and uveitis is the second most common manifestation. In a large series of patients with scleritis, relapsing polychondritis accounts for approximately 5% of these cases.[5] The ocular disease may be treated separately from the underlying disease in some patients but, in others, aggressive medical therapy may be required to control the ocular and associated systemic disease.

ASSOCIATED INFECTIOUS DISORDERS

Infectious causes of scleritis account for approximately 8% of patients with scleritis.[5] Bacteria, mycobacteria, parasites, and viruses may cause scleritis. Herpes viruses are the most common infectious cause of scleritis. Herpes zoster ophthalmicus is the most common cause of infectious scleritis, accounting for approximately 4% of cases of scleritis. Herpes simplex keratitis may have an associated scleritis, although this occurrence is uncommon.[23]

The most common bacterial cause of scleritis is syphilis, accounting for 2% of cases in the series by Watson and Hazleman.[6] Pyogenic bacteria causing scleritis are most often associated with a predisposing factor, such as an associated infectious keratitis, endophthalmitis, ocular trauma, a scleral buckle, and pterygium excision. Patients with scleritis from pyogenic

bacteria often are difficult to diagnose and may require scleral biopsy as well as appropriate cultures.[23]

Infectious scleritis is discussed in Chapter 7.

MANAGEMENT

A thorough ophthalmological and medical history should be performed on every patient with scleritis. A careful ocular examination and physical examination is essential. The onset and duration of symptoms such as pain should be explored. Current medications are important, as anti-inflammatory drugs may mask the pain of scleritis. In the history one should attempt to identify any of the infectious or systemic immune-mediated disorders that might be associated with scleritis. Therefore, one should inquire about previous infections, such as herpes simplex or herpes zoster, and previous ocular surgery. Associated systemic diseases should be inquired after specifically, and a complete review of systems performed. Attention should be paid to symptoms such as fever, weight loss, sinus disease, respiratory problems, gastrointestinal problems, renal problems, arthritis, and cutaneous disease.

The laboratory evaluation of a patient with scleritis is tailored to the individual patient and directed towards identifying associated infections and/or underlying systemic immune-mediated diseases. For patients with scleritis from viruses such as herpes simplex and herpes zoster, the history and physical examination will provide the diagnosis. For scleritis related to syphilis and Lyme disease, serological testing is required. Given the low positive predictive value of Lyme antibody testing in unselected populations, Lyme testing should be reserved for patients who have been exposed to Lyme disease by virtue of residence or travel.[24] The diagnosis of Lyme disease requires a positive serological test plus confirmation on a Western blot assay.[25] For patients with suspected syphilitic disease, obtaining an FTA-Abs, or MHA-TP is necessary, as approximately 30% of patients with ocular syphilis have a negative non-specific test, such as the RPR or VDRL.[26]

The systemic immune-mediated diseases most commonly associated with scleritis include rheumatoid arthritis, systemic necrotizing vasculitis, particularly Wegener's granulomatosis, systemic lupus erythematosus, relapsing polychondritis, and inflammatory bowel disease.[5,6] In most patients the diagnosis can be inferred from the history and physical examination. There is no

point in ordering an undirected, wide-ranging battery of investigations. However, every patient should have a chest X-ray, antineutrophil cytoplasmic antibody (ANCA) testing, serum chemistries and urine analysis to look for evidence of systemic necrotizing vasculitis. As most patients with rheumatoid arthritis and with systemic lupus erythematosus have diagnosed disease before the onset of scleritis, rheumatoid factor and antinuclear antibody (ANA) testing is not necessary in all patients.

Infectious causes of scleritis should be treated with antibiotics appropriate for the offending organism. Isolated ocular disease and disease associated with systemic immune-mediated disorders require treatment with systemic anti-inflammatory medications. Topical corticosteroids are ineffective in the treatment of scleritis.

A detailed account of the investigation and treatment of patients with scleritis can be found in Chapter 9.

COMPLICATIONS OF ANTERIOR SCLERITIS

The anterior segment complications of anterior scleritis include keratitis, uveitis, and glaucoma.[27–29] Cataracts may develop in patients with longstanding inflammation or in patients who require long-term corticosteroid therapy. Posterior segment complications are associated largely with posterior scleritis. Cystoid macular oedema may develop in patients with uveitis associated with anterior scleritis.

Corneal complications of scleritis are either an interstitial keratitis (Fig. 5.4) or peripheral ulcerative keratitis (Fig. 5.3). Interstitial keratitis includes the categories of diffuse stromal keratitis, sclerosing stromal keratitis, and deep keratitis, as defined by Watson and Hazleman.[4] Peripheral ulcerative keratitis is also known as marginal keratitis, marginal corneal ulceration, or limbal guttering, and is most often seen in association with necrotizing scleritis. Up to 20% of patients with diffuse anterior scleritis and 10% of patients with nodular anterior scleritis will have some type of interstitial keratitis. Conversely, nearly 60% of patients with necrotizing scleritis have peripheral ulcerative keratitis. Interstitial keratitis usually responds to treatment of the underlying disease and/or topical corticosteroids, while peripheral ulcerative keratitis requires aggressive systemic therapy with corticosteroids and immunosuppressive drugs. Topical corticosteroids are ineffective and may be harmful in patients with peripheral ulcerative keratitis.

Anterior uveitis occurs in up to 40% of eyes with scleritis.[28] However, examination of pathological specimens reveals that nearly all patients with scleritis have some degree of uveal inflammation. Scleromalacia perforans has clinically evident intraocular inflammation in nearly all cases. The occurrence of uveitis in a patient with scleritis appears to be associated with larger anterior surface area of involvement by the scleritis.[30] In a patient with anterior scleritis treated with an oral NSAID, topical corticosteroids may be of adjunctive value for an associated anterior uveitis.

Elevated intraocular pressure is present in 10–15% of patients with scleritis.[2] Histological studies of enucleated eyes have reported that 40–50% of these eyes will have histological evidence of glaucoma; however, these studies are likely to suffer from bias of ascertainment and overestimate the frequency of glaucoma in patients with scleritis.[31] Elevated intraocular pressure may occur for a variety of reasons, including trabeculitis, ciliochoroidal effusion, peripheral anterior synechiae, and corticosteroid therapy.

Cataracts are reported in approximately 10–15% of patients with scleritis.[5] They may occur as a consequence of uveitis in patients with poorly-controlled longstanding scleritis or more commonly in patients on chronic systemic corticosteroid therapy.

Complications of scleritis are discussed in detail in Chapter 8.

OUTCOME

Anterior scleritis has a variable prognosis and visual outcome. Diffuse and nodular anterior scleritis are less severe forms of scleritis and although commonly recurrent, are uncommonly associated with vision-threatening complications. Necrotizing anterior scleritis is frequently associated with systemic disease and commonly causes significant loss of vision. As up to 50% of patients with anterior scleritis have an associated systemic disease, careful clinical assessment and directed investigations to look for associated systemic disease are essential. Systemic therapy is required to control pain and minimise visual loss.

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6: Posterior scleritis

PETER McCLUSKEY

Posterior scleritis is an uncommon and frequently undiagnosed form of scleritis. It has a wide range of symptoms and signs, is commonly associated with systemic disease and may result in significant visual loss if not recognized and treated appropriately.[1] Until the widespread use of modern B scan ultrasonography, high resolution computerized tomography and magnetic resonance imaging, posterior scleritis was often not recognized. Modern imaging techniques have allowed the rapid and accurate diagnosis of posterior scleritis and have changed long held beliefs regarding its rarity.[2]

Posterior scleritis may occur at any age but most commonly begins in adulthood. It occurs more frequently in women than men. Posterior scleritis may affect both eyes but is most frequently unilateral and recurrent in nature. There is no known racial predilection and no recognized immunogenetic markers for the disease.

DEFINITION

Posterior scleritis is defined as inflammation of the sclera posterior to the ora serrata.[3] Clinically this approximates to a line joining the insertion of the rectus muscles into the sclera. Posterior scleritis may occur in isolation or in association with anterior scleritis. Anterior scleritis may occur in up to 60% of patients with posterior scleritis at some time during the course of their disease.[2]

Posterior scleritis is classified in the same manner as anterior scleritis into diffuse, nodular, and necrotizing forms.[4] In contrast to patients with anterior scleritis where careful clinical examination allows the type of scleritis to be determined, in patients with posterior scleritis, a B scan ultrasound examination is necessary to distinguish between diffuse and nodular disease. It is not possible

at this time to detect necrotizing posterior scleritis reliably with ultrasound; however, this type of scleritis is recognizable clinically and histopathologically.

CLINICAL FEATURES

Symptoms

Pain is the predominant symptom of posterior scleritis and is typically severe, dull, and boring in character and radiates to the face, scalp, and head. Patients may volunteer that it is the worst pain they have ever suffered. The pain may be so severe that it is incapacitating and prevents the patient from undertaking most activities. Pain from scleritis is usually more severe at night and wakes the patient from sleep early in the morning. Patients have often been investigated and treated for a variety of other illnesses such as migraine and tic douloureux prior to the diagnosis of posterior scleritis. They may be taking large doses of analgesics without relief from their pain.

Loss of vision is the other common symptom of patients with posterior scleritis, and this may vary from a minimal to profound decrease in vision. Patients may also complain of photopsias, metamorphopsia, pain on eye movement, and symptoms related to coexistent anterior scleritis such as redness and swelling.

Signs

A wide range of physical signs may be present in patients with posterior scleritis depending on the location, severity, and size of the area involved by inflammation. Serous retinal detachment, swollen optic disc, a discrete subretinal mass lesion, retinal pigment epithelial changes, and peripheral choroidal detachment are each classical presentations of posterior scleritis. There may be other signs such as retinal striae, choroidal folds, macular oedema, elevated intraocular pressure, and angle closure glaucoma from ciliary body rotation in choroidal detachment. Low grade uveitis may also occur in occasional patients. Visual acuity is usually reduced.

This diversity of physical signs means that posterior scleritis needs to be considered in a wide range of clinical situations. It is important to realize that up to 15% of patients may have no physical signs of posterior scleritis.[2] In such patients the diagnosis

is made from the history and with imaging studies of the globe. Table 6.1 details the frequency of some of the common physical signs seen in patients with posterior scleritis.

Serous retinal detachment

A serous retinal detachment is characterized by shifting subretinal fluid and the absence of retinal breaks (Fig. 6.1). In patients with posterior scleritis, the detachment may be localized to the posterior pole or may be extensive, bullous, and involve the peripheral retina. It may be possible to see an ill-defined mass lesion beneath the detachment. The characteristic clinical feature is the shifting of the position of the subretinal fluid with different positions of the patient. The subretinal fluid may be cloudy and

Table 6.1 Signs of posterior scleritis

Physical sign	Number of patients (%)
Associated anterior scleritis	34 (34)
Serous retinal detachment	21 (21
Swollen optic disc	18 (18)
No abnormalities	17 (17)
Subretinal localized granuloma	13 (13)
Elevated intraocular pressure	12 (12)
Choroidal effusion	4 (4)
Uveitis*	2 (2)
Retinal vasculitis	2 (2)
RPE changes	2 (2)

* Uveitis is defined as cells in the anterior chamber, posterior chamber, or both chambers.
NB: Table is taken from reference 2.

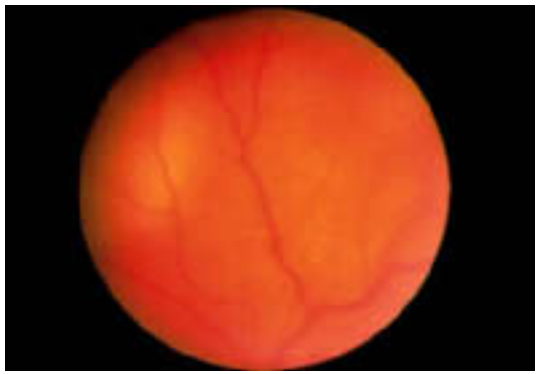

Figure 6.1 Serous retinal detachment and subretinal mass.

the amount of fluid variable. With treatment, the detachment will resolve leaving retinal pigment disturbance and reduced vision if the macula has been involved.

Swollen optic disc

Disc swelling associated with variable loss of visual acuity and field is a common sign of posterior scleritis. There may be associated pain on eye movement, afferent pupil defect, and decreased colour vision. Optic atrophy occurs commonly despite treatment.

Subretinal mass lesion

A localized orange-yellow mass beneath the retina is another hallmark of posterior scleritis and is typically seen in patients with nodular posterior scleritis. The normal choroidal and retinal architecture is preserved over the mass (Fig. 6.1). There are commonly choroidal folds and retinal striae associated with the mass (Fig. 6.2). There may be an overlying serous retinal detachment. If the mass lesion involves the macula or is adjacent to the optic disc, there may be severe visual loss.

Choroidal detachment

Choroidal detachment usually involves the peripheral choroid and ciliary body and may vary from mild and shallow to severe and massive. There can be detachment of the ciliary body, such that the lens–iris diaphragm rotates forward, making the anterior chamber shallow, and resulting in an attack of acute angle closure glaucoma. Ciliochoroidal detachments are smooth dark elevations that allow the ora serrata and peripheral retina to become readily

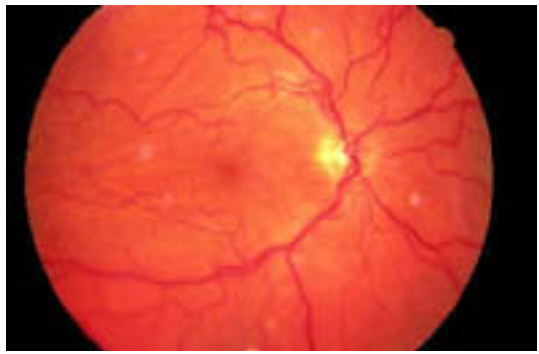

Figure 6.2 Retinal and choroidal folds from severe posterior scleritis.

visualized on fundus examination. Effusions can become so large that they meet in the visual axis. There can be associated serous retinal detachments.

Retinal pigment epithelial changes

The retinal pigment epithelium may be diffusely affected by posterior scleritis and associated choroidal effusion resulting in a subtle leopard skin pattern of pigmentary disturbance (Fig. 6.3). This may be best appreciated during fluorescein angiography. Localized disturbances of the retinal pigment epithelium often involve the macula, and are associated with permanent structural macular changes and reduced visual acuity.

DISEASE ASSOCIATIONS OF POSTERIOR SCLERITIS

Systemic associations

Posterior scleritis can be seen in association with a range of systemic inflammatory diseases, including rheumatoid arthritis, systemic vasculitis, Wegener's granulomatosis, and relapsing polychondritis (Figs 6.4, 6.5).[1,3] This spectrum of disease associations is similar to that seen in anterior scleritis. In a recent large series, about 30% of patients with posterior scleritis had an associated systemic disease.[2] This series also highlighted that posterior scleritis may be the result of ocular involvement by systemic neoplasms,

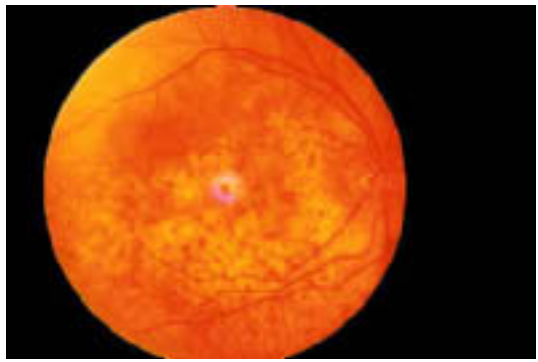

Figure 6.3 Leopard spot pigmentation from posterior scleritis (courtesy of Mr J Kanski).

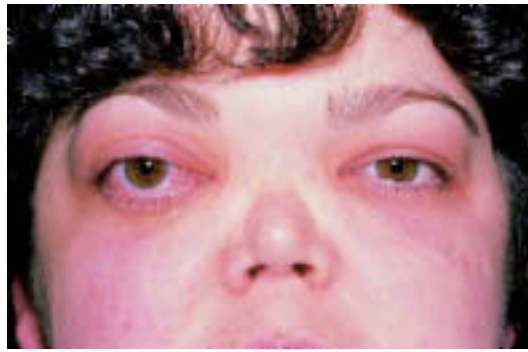

Figure 6.4 Typical facies of Wegener's granulomatosis with nasal collapse. There is active orbital inflammation and scleritis.

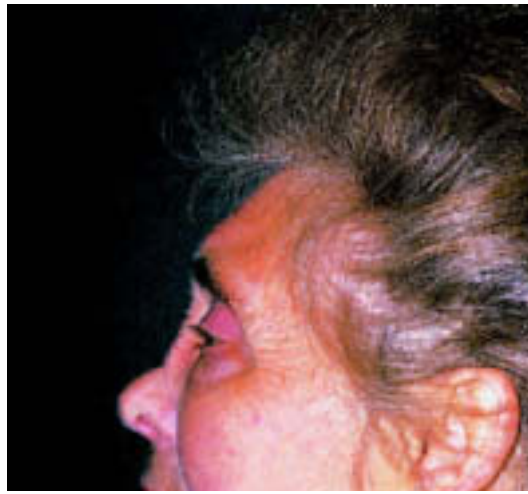

Figure 6.5 Classical facial signs in a patient with relapsing polychondritis.

Table 6.2 Systemic associations seen in patients with scleritis

Systemic disease	Number of patients
Rheumatoid arthritis	5
Systemic vasculitis	4
Wegener's granulomatosis	4
Vogt–Koyanagi–Harada disease	2
Relapsing polychondritis	3
Thyroid disease	2
Sarcoidosis	2
Primary biliary cirrhosis	1
Systemic lupus erythematosus	1
Multiple myeloma	1
Lymphoma	1
Carcinoma of pancreas	1
Ankylosing spondylitis	1
Polyarteritis nodosa	1

NB: Table is taken from reference 2.

such as pancreatic carcinoma, multiple myeloma, and lymphoma. This association has been recognized previously.[5] Table 6.2 details important systemic associations of posterior scleritis.

Ocular associations

Posterior scleritis may result from extension of intraocular inflammation and infection into the posterior sclera. This can occur in severe toxoplasmic retinochoroiditis, in patients with Vogt–Koyanagi–Harada syndrome and when anterior scleritis extends posteriorly.[2,6]

Surgically-induced posterior scleritis can be seen in patients with infected explants following scleral buckling procedures for retinal detachment, and may become necrotizing in type. This form of scleritis is part of the spectrum of surgically-induced necrotizing scleritis first recognized by Watson.[7]

INVESTIGATIONS

Ultrasonography

High quality B mode ultrasonography is the key investigation in patients with suspected posterior scleritis, as it is quick, sensitive and non-invasive, and provides excellent images of the posterior coats of the eye.[1–3] Although unable to differentiate reliably

between choroidal and scleral thickening, ultrasonography is able to demonstrate readily the thickened eye wall that is the hallmark abnormality of posterior scleritis. The absolute upper limit of normal thickness of the posterior eye wall varies, but is generally considered to be 2.1 mm. The eye wall thickening may be diffuse or nodular in type (Figs 6.6, 6.7). Thinning of the posterior eye wall that would reflect necrotizing posterior scleritis cannot be reliably demonstrated with current ultrasound technology.

A number of other abnormalities can be seen by ultrasonography in patients with posterior scleritis; they include fluid within Tenon's capsule, swelling of the optic nerve sheath, swelling of the optic disc, and serous retinal detachment. When there is distension of the posterior sub-Tenon's space around the optic nerve and swelling of the optic nerve sheath, the so-called "T" sign may be visible on scans.

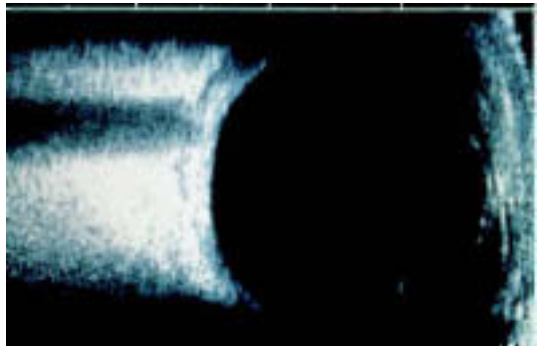

Figure 6.6 B scan showing diffuse posterior scleritis.

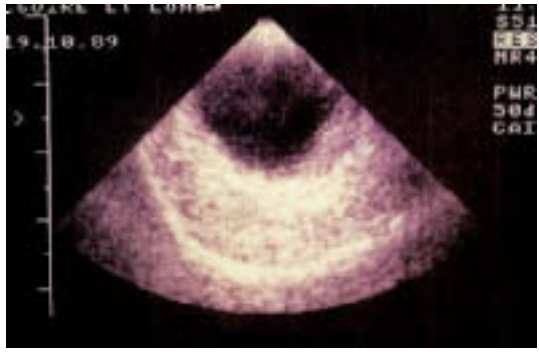

Figure 6.7 B scan showing nodular posterior scleritis.

Computerized tomography

Computerized tomography has revolutionized radiological evaluation of ocular and orbital disease. High definition helical scanning is able to provide excellent images of the orbital contents and bones, and additionally give quite useful images of the eye wall. It can demonstrate large increases in eye wall thickness but is not as sensitive as B scan ultrasonography (Fig. 6.8). Its value lies in excluding other pathology, such as orbital tumours, thyroid eye disease, and sphenoidal sinusitis, and in identifying patients with posterior scleritis that has spread to involve the orbit in the inflammatory process.[3,8]

Magnetic resonance imaging

Magnetic resonance scanning is a relatively new technology that is capable of providing detailed images of the globe and orbit. With high intensity sequences and the use of gadolinium it is possible to differentiate choroidal and scleral thickening (Fig. 6.9). This can be especially useful in the investigation of patients with choroidal detachments.[8,9]

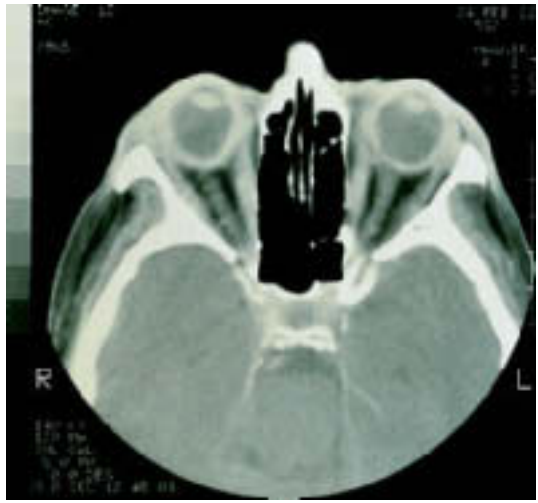

Figure 6.8 CT scan of posterior scleritis.

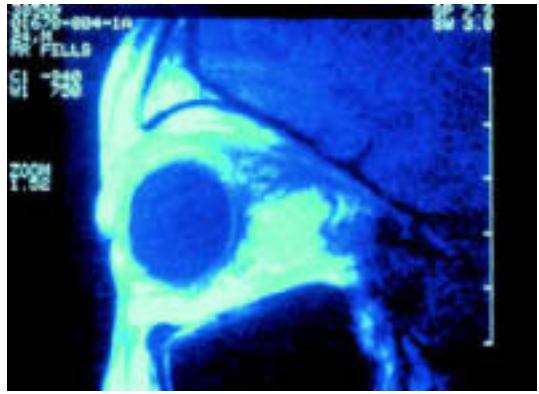

Figure 6.9 MR scan of posterior scleritis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of posterior scleritis is potentially vast given the wide spectrum of symptoms and signs with which it may present. The best way of approaching the differential diagnosis is according to the pattern of presentation of the posterior scleritis.[1–3]

Serous retinal detachment

In patients with bullous retinal detachment it is essential to eliminate rhegmatogenous detachment as the cause. Following this, choroidal melanoma, choroidal metastasis, Vogt–Koyanagi–Harada disease uveal effusion syndrome, and central serous retinopathy need to be considered as possible causes. Diagnosis can be made by a careful history and examination, B scan ultrasonography, and fluorescein angiography.

Swollen optic disc

A swollen optic disc in a patient with possible posterior scleritis needs to be differentiated from posterior uveitis-associated disc swelling and from optic neuritis. Ocular hypotony following intraocular surgery or trauma also should be considered.

Discrete subretinal mass lesion

The major differential diagnosis in patients presenting with a discrete mass lesion is neoplasms. Choroidal melanoma and metastasis to the choroid are the principle tumours, and clinical evaluation combined with B scan ultrasonography are the key steps to differentiate these tumours from posterior scleritis. Choroidal haemangiomas may also cause confusion, and fluorescein angiography combined with B scan ultrasonography should help in the correct diagnosis.

Choroidal detachment

Choroidal detachment often occurs in combination with overlying serous retinal detachment, and the differential diagnosis is similar. When there is choroidal detachment, idiopathic uveal effusion syndrome, nanophthalmos, low flow caroticocavernous fistula, and hypotony from intraocular surgery or trauma need to be considered. Magnetic resonance imaging and B scan ultrasonography are valuable investigations here in these cases.

Acute painful visual loss

In patients presenting with acute painful visual loss, when posterior scleritis is a likely cause, the major differential diagnosis include demyelinating optic neuropathy, sphenoidal sinusitis, orbital tumour, idiopathic orbital inflammatory disease, and thyroid eye disease. Diagnosis can be made following a careful history and examination, B scan ultrasonography, computerized tomography and magnetic resonance imaging.

MANAGEMENT

Patients with posterior scleritis need a careful history, a detailed clinical examination and a thorough review of systems as the first and most important step in management.[10] Based on the results of this clinical assessment, specific investigations can be ordered to exclude likely systemic associations and other disease processes that need to be considered. There is no point in ordering an undirected, wide-ranging battery of investigations. The only

investigations needed in nearly all patients with posterior scleritis are B scan ultrasonography and ANCA serology.

Further details of the investigation and management of patients with scleritis are discussed in Chapter 7.

COMPLICATIONS

The major complication of posterior scleritis is the occurrence of permanent visual loss. This occurs in up to 30% of patients and is usually due to the development of optic atrophy or irreversible macular changes, as a result of posterior scleritis involving these areas of the sclera.

Elevated intraocular pressure and glaucoma are not uncommon in patients with posterior scleritis and may arise from secondary angle closure, as a complication of uveitis, or from the use of corticosteroid therapy.

Anterior scleritis may develop at some time during the course of recurrent posterior scleritis in up to 60% of patients, and result in the development of further significant complications

The complications of scleritis are discussed in detail in Chapter 8.

OUTCOME

Posterior scleritis has a variable prognosis and visual outcome. It is associated with systemic disease in about 30% of cases, recurs in up to 30% of affected patients, and significant visual loss occurs in about 30% of patients. Posterior scleritis is usually unilateral but, in up to 30% of patients, is bilateral.

Given the variable outcome of posterior scleritis and the high rate of association with systemic disease, careful clinical assessment and directed investigations to look for associated systemic disease is necessary. Early treatment is required to minimize visual loss.

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7: Infectious scleritis and surgically-induced scleritis

WOLFGANG BERNAUER

Infectious and surgically-induced scleritis are both very uncommon, and many ophthalmologists will never see this type of inflammation during their professional career. Both types of scleritis are usually associated with ocular surgery, and an eye operation or trauma are important risk factors for the development of infectious scleritis. In surgically-induced scleritis, surgical trauma is the trigger for the disease onset.

The initial clinical presentation of infectious scleritis may be similar to that seen in autoimmune scleritis, and differentiation may be difficult or impossible without laboratory investigation. The recognition of an infectious cause is crucial, as treatment with antimicrobial agents is usually successful, whereas immunosuppressive therapy in isolation will lead to progression of scleral infection.

INFECTIOUS SCLERITIS

Definition

The term infectious scleritis strictly denotes scleral inflammation resulting from invasion of the sclera by replicating micro-organisms; however, in clinical practice, infectious scleritis includes scleral immune reactions that may be observed in association with an infection.

Epidemiology

The incidence of infectious scleritis is not known, but it is estimated that inflammatory scleral disease accounts for 0.08% of

new referrals to an eye department[1] and about 10% of scleritis patients have a history of associated infection.[2] On statistical grounds, this would mean that about 1 in 10 000 new patients seen in an eye department suffers from infectious scleritis.

Aetiology and pathogenesis

All classes of micro-organisms (viruses, bacteria, fungi, and parasites) may cause infectious scleritis (Box 7.1). There are two pathogenic mechanisms involved in the development of infectious scleritis:

- direct invasion of replicating organisms with destruction of the tissue, and
- a spectrum of immune reactions initiated by the infective agent.

It is difficult to determine clinically which mechanism is the major pathogenic one operating in individual patients with infectious scleritis, and therefore therapy usually consists of both anti-infective and anti-inflammatory agents.

Box 7.1 Micro-organisms that cause infectious scleritis

Viruses

- Herpes simplex
- Varicella zoster
- Mumps

Bacteria

- Gram-positive bacteria
- Gram-negative rods
- Mycobacteria
  - *Mycobacterium tuberculosis*
  - *Mycobacterium lepreae*
  - Other mycobacteria
- Spirochetes
  - *Treponema pallidum*
  - *Borrelia burgdorferi*
- Actinomycetes

Fungi

- Filamentous fungi
- Dimorphic fungi

Parasites

- Protozoa
  - Acanthamoeba
  - *Toxoplasma gondii*
- Helminths
  - *Toxocara canis*

The sclera is not normally prone to infection because of its composition, its low metabolic activity, and the protection afforded it by the overlying episclera and conjunctiva; however, if host barriers or defence mechanisms are compromised, bacteria and fungi may infect the sclera. Common predisposing factors for scleral infection include:

- pre-existing corneal infection;
- infectious endophthalmitis;
- tissue devitalization from herpetic infection, corneal exposure, or local radiotherapy;
- recent ocular surgery;
- ocular trauma, or
- debilitating systemic conditions, such as HIV infection, diabetes, or systemic immunosuppression.

Although any infectious agent may cause an inflammatory angiopathy in the sclera by inducing an immune-mediated response in scleral and episcleral blood vessel walls,[3,4] bacteria such as *Pseudomonas*, *Streptococcus*, and *Staphylococcus* spp., herpes viruses, and fungi, such as *Aspergillus* spp. , are typically associated with small vessel vasculitis. Other micro-organisms such as *Treponema pallidum* and *Mycobacterium tuberculosis* usually cause large vessel vasculitis.[3] Vascular damage results from direct invasion of the vessel by the organism, and by embolization, which both result in an inflammatory response and immune complex formation and deposition. The scleritis may then become autoimmune in nature and independent of the presence of the initiating organism.

TYPES OF INFECTIOUS SCLERITIS

Viral scleritis

Direct viral invasion during infection and the host immune response produce this type of scleritis. Viruses that are most frequently associated with scleral inflammation are the herpes varicella zoster virus and the herpes simplex virus.

Herpes zoster

Varicella zoster virus is the most common cause of infectious scleritis. Marsh and Cooper found in their series of 1356 zoster

patients that 37 (3%) had developed scleritis.[5] The scleritis may occur shortly after the onset of acute disease or, more commonly, months or even years after the initial manifestation.

The acute skin manifestations, conjunctivitis and episcleritis, and corneal ulcers in herpes zoster ophthalmicus, are all caused by direct invasion of the virus. In contrast, immune-mediated reactions are predominantly responsible for the development of scleritis, late episcleritis, keratitis, trabeculitis and anterior uveitis. These immune-mediated manifestations typically follow 10–15 days after the onset of the skin lesions. Recurrences may occur at any time and are thought to be independent of the presence of virus. Histopathological examination of the inflamed sclera shows granulomatous changes and inflammatory microangiopathy. Immunohistochemical analysis has not demonstrated the presence of varicella zoster antigen in the affected sclera.[3]

During acute herpes zoster the patient presents with intense pain and episcleritis. Vesicles may form on the conjunctiva and these can involve the episclera, but more commonly a nodular episcleritis develops that resolves over 3–4 weeks.[6] After a variable period of 1–4 months, the patient may present again with nodular or occasionally necrotizing scleritis. Nodular scleritis is the most common type of scleritis seen in zoster ophthalmicus.[2,5] Scleral nodules may take months to resolve and usually leave an area of thinned sclera. Recurrences are common.

Herpes zoster ophthalmicus is usually a straightforward clinical diagnosis. When scleritis occurs months after the onset of a zoster infection, the diagnosis may become more difficult, and a careful history and examination are essential in order not to miss subtle evidence of previous zoster infection, such as nummular corneal infiltrates, reduced corneal sensation, elevated intraocular pressure from trabeculitis and sector iris atrophy. Since scleritis in herpes zoster typically represents an immune-mediated inflammation, histopathological examination of involved scleral tissue is usually non-diagnostic.

Therapy for zoster scleritis is similar to non-infectious scleritis. Cyclo-oxygenase inhibitors such as flurbiprofen, indomethacin, or naproxen are used as initial therapy in non-necrotizing disease. If there is no response, then systemic corticosteroids are used. Systemic antiviral treatment is necessary if there is any active zoster infection and in immunosuppressed patients. Aciclovir 800 mg five times a day or valaciclovir 1000 mg three times a day are needed to control herpes zoster infection. Lower doses of

600–800 mg acyclovir daily may be indicated as long-term therapy in immunosuppressed patients.

Herpes simplex

Herpes simplex virus is a major cause of ocular morbidity and in many developed countries is the commonest infective cause of blindness. Ocular herpes simplex infection most frequently involves the cornea, and is characterized by progressive corneal opacification from recurrent inflammatory episodes.[7] Herpes simplex virus may occasionally also cause scleritis and episcleritis, usually in immunosuppressed patients.[2] Herpetic scleritis may occur at a time of active infection, or it may follow months or years after an episode of herpes simplex virus infection.[3]

The manifestations of primary herpetic disease such as periocular cutaneous involvement, ulcerative blepharitis, acute follicular conjunctivitis, episcleritis, and epithelial keratitis are each caused by direct viral infection, as are the dendritic and geographic ulcers seen in recurrent epithelial disease.[8] In contrast, interstitial stromal keratitis, immune rings, limbal vasculitis, and peripheral ulcerative keratitis represent immune complex hypersensitivity disease, while disciform keratitis is thought to be a delayed hypersensitivity reaction.[3,9] Animal studies suggest that uveitis in acute disease is mediated by infection of tissue by live virus and later by various immune-mediated mechanisms.[10] Some evidence suggests this is also the case in herpes simplex scleritis, as viral particles or herpes simplex antigen have been detected in some patients with herpetic scleritis.[3,6]

Diffuse, nodular, and necrotizing scleritis has been described in association with herpes simplex virus.[2,3] Nodular scleritis is the most frequent and may immediately follow epithelial corneal involvement (Fig. 7.1). In some cases there is prompt resolution of the scleritis on systemic antiviral treatment, but, in others, there is a poor response and anti-inflammatory therapy is required.

Diagnosis of herpes simplex scleritis is based on the clinical findings. Laboratory investigations such as light and electron microscopy, viral culture, polymerase chain reaction (PCR), and immunocytochemistry may be useful to confirm a diagnosis of herpetic scleritis in some patients.

Acute episcleritis is treated with topical acyclovir ointment. Oral aciclovir or valaciclovir is necessary to treat scleritis and uveitis. Judicious use of topical corticosteroids is also necessary. Cyclo-oxygenase inhibitors such as flurbiprofen and indomethacin

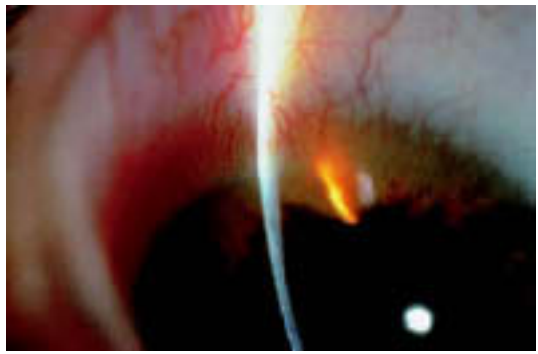

Figure 7.1 Nodular scleritis due to herpes simplex virus in a 37-year-old patient. Epithelial corneal involvement was followed 3 weeks later by limbal swelling and pain.

may also be needed to control pain. Systemic corticosteroids and additional immunosuppressive drugs may be required rarely to treat necrotizing scleritis.

Bacterial scleritis

Bacterial scleritis most commonly occurs following scleral extension of primary corneal infections. A primary bacterial scleritis may follow ocular trauma or surgery to the sclera, or may be a consequence of severe endophthalmitis. The commonest causes of bacterial scleritis are staphylococcus, streptococcus, pseudomonas, and various Enterobacteriaceae species.[11-15]

Normal sclera is not very susceptible to microbial infection and bacterial scleritis is preceded by a breakdown of host defence mechanisms, such as previous primary corneal infection, trauma, and ocular surgery. Operations that involve the sclera, such as pterygium removal with beta irradiation, adjunctive thiotepa, or mitomycin C administration; cataract surgery; trabeculectomy; retinal detachment, and strabismus surgery have been complicated by the development of bacterial scleritis.[11,12,14,17,20,21] Infectious scleritis may be associated with the use of retinal detachment implants used for retinal detachment surgery, and non-absorbable sutures used in strabismus surgery.

Bacterial scleritis may present with one or more scleral abscesses that rapidly involve the overlying conjunctiva and episclera with tissue necrosis and purulent discharge (Figs 7.2, 7.3).

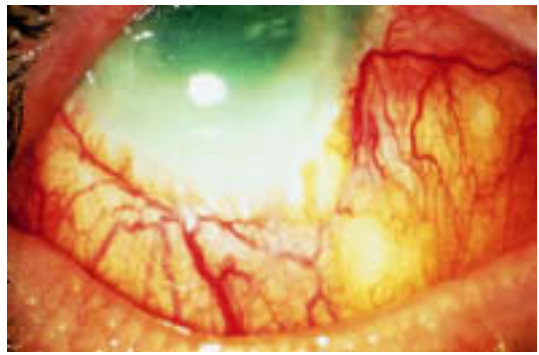

Figure 7.2 *Pseudomonas aeruginosa* scleritis following corneal infection. Note multiple scleral abscesses.

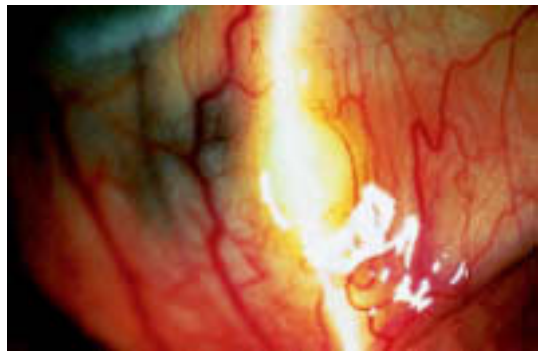

Figure 7.3 Detail of the same eye as shown in Figure 7.2. Note scleral necrosis with suppuration, but without pattern of episcleral nonperfusion as seen in vasculitic autoimmune disorders.

Symptoms include severe pain, lid swelling, proptosis, redness, tearing, and photophobia. Scleral nodules may form at sites clinically remote from the primary site of infection (Fig. 7.3). Severe intraocular inflammation may produce hypopyon, posterior synechia, and cataract. Treatment with corticosteroids alone makes the condition worsen rapidly, and if this occurs in presumed autoimmune nodular scleritis, an infective cause should be suspected. Rarely the posterior sclera may be affected by endogenous infection. Diagnosis is difficult. There is intense pain, reduced vision, proptosis, and lid oedema. The severe posterior scleritis causes exudative retinal detachment, severe uveitis, and

hypopyon. The patient is systemically unwell with fever and preauricular lymphadenopathy.

Accurate microbiological diagnosis in bacterial scleritis is critical. Scrapings for microscopy and culture must be obtained according to the principles outlined for microbial keratitis.[22] Any removed foreign bodies such as sutures and retinal detachment exoplants should be cultured. If there is progression of scleritis despite broad spectrum antibacterial therapy, a scleral biopsy should be obtained for histopathological examination and further microbiological investigations.

Empirical broad spectrum topical and systemic antibiotics, similar to those used to treat microbial keratitis, are the best initial therapy. The appropriate antibiotics are determined by the likely causative bacteria and local antibiotic sensitivity patterns. A typical drug regimen using hourly application of fortified antibiotic drops and intravenous antibiotics, is summarized in Table 7.1. Subconjunctival injections of antibiotics should be avoided or used with caution because their value is doubtful when intensive topical treatment is used, and they may exacerbate necrotizing scleritis.[23] Once the causative bacteria is identified, therapy can be modified according to antibiotic sensitivity results. Topical corticosteroids should not be used initially, but are added after several days of antibiotic therapy, or if there is an inflammatory microangiopathy on histopathology. Corticosteroids should not be used in pseudomonas infection, because they are associated with persistence and progression of infection.[24] Any suture material or scleral explants should be removed. If there is disease progression

Table 7.1 Selection of antibiotic drugs for bacterial scleritis

Micro-organisms	Topical treatment	Systemic treatment
Unknown (initial treatment)	Ciprofloxacin 3 mg/ml or Ofloxacin 3 mg/ml or Ceftazidime 50 mg/ml	Ciprofloxacin 500 mg i.v. b.d. or Ciprofloxacin 750 mg b.d. orally
Pseudomonas	Ceftazidime 50 mg/ml	Ceftazidime 2 g t.d.s. i.v. and Tobramycin 5.0 mg/kg/day
Gram negative bacteria	Ceftazidime 50 mg/ml or Gentamicin/tobramycin 15 mg/ml	Tobramycin 5.0 mg/kg/day
Gram positive cocci	Cefuroxime 50 mg/ml or Vancomycin 50 mg/ml	Flucloxacillin i.v. 2 g 4th hourly

despite adequate medical therapy, surgery such as conjunctival resection with cryotherapy, or lamellar or full-thickness scleral grafts should be considered.[11] Surgery is discussed in detail in Chapter 10. Despite the availability of potent antibiotics and various surgical techniques, the prognosis of bacterial scleritis remains uncertain. Early diagnosis and appropriate management are essential.

Tuberculosis

Tuberculosis has become relatively uncommon, but remains a problem in developing countries, the underprivileged and individuals with HIV infection. Scleral tuberculosis is rare.[25] Tuberculosis may result in two types of ocular lesions:[26]

- infective tuberculosis resulting from invasion of mycobacteria;
- an immune reaction to non-infectious mycobacterial proteins.

There is evidence that both mechanisms cause tuberculous scleritis. Scleritis from direct invasion of mycobacteria is usually due to haematogenous miliary spread of tuberculosis, but may also result from direct extension of lesions in adjacent cornea, conjunctiva, or iris. Immune-mediated scleritis is often associated with interstitial or phlyctenular keratoconjunctivitis and is a type IV hypersensitivity response to mycobacterial cell wall proteins. Biopsy specimens in tuberculous scleritis from invasive mycobacteria show caseating granulomas with multinucleated giant cells and acid-fast bacilli.

Treatment of scleritis involves systemic combination antituberculous therapy with drugs such as isoniazid, rifampicin, pyrazinamide, and ethambutol. Treatment of tuberculosis must be instituted and monitored by infectious disease physicians. There is no role for systemic corticosteroid therapy in the treatment of tuberculous scleritis. Topical therapy with corticosteroids and antibiotics, such as isoniazid, streptomycin, or amikacin may be helpful. Phlyctenulosis is treated with topical steroids.

Leprosy

Mycobacterium leprae infections are uncommon in western societies, but are a major public health problem in parts of Africa, Asia, and Central and South America. Episcleritis and scleritis may be due to direct *Mycobacterium leprae* invasion or may be immune mediated and due to immune-complex deposition.[27] Diffuse and nodular episcleritis is common and is usually found in

the cooler interpalpebral fissure area. Scleritis is less common. It presents with intense pain and tenderness. The inflammation may result in scleral necrosis, ectasia, and staphyloma. Lepromatous lesions may involve other ocular structures and result in lateral thinning or loss of eyebrows, lagophthalmus from facial nerve palsy, keratitis, corneal perineural infiltrates, interstitial keratitis, and anterior uveitis with iris pearls or nodules.

The diagnosis of leprous scleritis is made on the basis of clinical and histopathological findings. Dermatological and ocular findings substantiate the diagnosis, which is confirmed by the finding of a granulomatous inflammation with acid-fast bacilli on scleral biopsy. Treatment consists of combination antibiotic therapy that includes dapsone, clofazimine, rifampicin, and ethionamide.[27]

Other mycobacteria

Mycobacterial infection other than tuberculosis and leprosy is seen increasingly.[28] Keratitis is the principal manifestation of ocular infection by these organisms and *Mycobacterium chelonae* and *Mycobacterium fortuitum* have been identified from patients with keratitis. Scleritis from extension of keratitis into the sclera and after removal of an extruded scleral buckle has been reported.[29,30] The scleral inflammation was characterized by nodular or necrotizing, slowly progressive lesions that developed over several months, and were associated with a mild mucopurulent discharge. The diagnosis is made on the biopsy findings that show acid-fast bacilli. Systemic tuberculosis must be excluded. Therapy consists of tissue debridement in combination with topical and systemic antibiotic therapy. Amikacin or rifampicin can be used as initial treatment and modified according to the results of laboratory antibiotic sensitivity studies.

Syphilis

Episcleritis with limbal chemosis has been described in secondary syphilis.[31] Diffuse or nodular scleritis during secondary syphilis is usually accompanied by anterior uveitis. Scleritis is an uncommon presentation of tertiary syphilis but may be its only clinical manifestation. Typically presenting as nodular scleritis, any form of scleral inflammation can occur.[2] Trans-scleral extension of a ciliary body gumma is a rare condition that causes scleral inflammation and dissolution. In late congenital syphilis, limbal episcleritis may present in the quadrant of active corneal

inflammation during acute interstitial keratitis. Scleritis may occur many years later. Numerous other ocular manifestations have been comprehensively reviewed, and ophthalmologists as well as physicians should be aware that various ocular inflammatory signs may be due to syphilis.[31,32] Syphilis is diagnosed on clinical and serological findings. There is no ideal serological test. Penicillin G is the drug of choice for treating all stages of syphilis.

Lyme disease

Lyme disease is a worldwide tick-borne infection caused by the spirochate *Borrelia burgdorferi*. It is endemic throughout Europe, North America, and Northern Asia. Lyme disease is a multisystem disease with a variable clinical picture. There are many ocular manifestations of Lyme disease including episcleritis and scleritis.[33]

Acute conjunctivitis and episcleritis may occur at the time of erythema migrans skin rash.[33,34] Diffuse scleritis has been associated with late Lyme disease in one case.[3] Lyme disease must be considered in the differential diagnosis of scleritis associated with neuro-ophthalmological symptoms. In the absence of a skin lesion, the diagnosis of Lyme disease is dependent on positive serology. Therapy of Lyme disease remains controversial. For definitive ocular, neuro-ophthalmic, neurological, or cardiac disease, intravenous ceftriaxone is widely used.

Actinomyces

Nocardia organisms are members of the Actinomycetaceae family. They superficially resemble fungi but represent gram-positive, branching pleomorphic rods. *Nocardia* are soil organisms, often found in decaying organic matter. Infection with *Nocardia* spp. has been increasingly recognized in immunocompromised patients.[35] Ocular infections with *Nocardia* have also been reported with orbital disease, conjunctivitis, keratitis, uveitis, endophthalmitis, and scleritis.[60] Nocardial scleritis has been described in association with contaminated scleral buckles after detachment surgery.[36] Necrotizing scleritis with mucopurulent discharge was seen in both cases. Diagnosis of scleral infection by *Nocardia* is established by histological identification and culture. Systemic and topical sulphonamides are the treatment of choice for ocular *Nocardia* infections.

Fungal scleritis

Fungal ocular infections typically occur after corneal trauma. They are much more prevalent in tropical regions than in the western world. Corneal infection not uncommonly spreads to the sclera.[37,38] In contrast, primary fungal scleritis is extremely rare but has been reported after trauma, retinal detachment surgery, treatment of pterygium, cataract surgery, trabeculectomy, and in association with systemic fungal infections.[39-41] Most fungi are saprophytic organisms that cause opportunistic infections. Among them, the filamentous fungi aspergillus, acremonium, and fusarium are the organisms that are most commonly associated with scleral infection.

The clinical manifestations of fungal scleritis are non-specific. This diagnosis should be suspected in cases of relatively slowly progressive scleral inflammation, particularly when there is scleral necrosis without episcleral non-perfusion (Figs 7.4, 7.5). The absence of systemic autoimmune disease, a history of ocular surgery or trauma, and the presence of hypopyon and endophthalmitis are features seen commonly in infective scleral inflammation.

The diagnosis of fungal scleritis is based on the findings at microscopy; however, negative scrapings are frequent. This does not exclude an infection, since the organisms may be present only in the deep stroma. In a series of three cases with aspergillus scleritis, the diagnosis was established only after scleral biopsy.[40] Scleral biopsy should be undertaken in all cases of progressive scleritis when

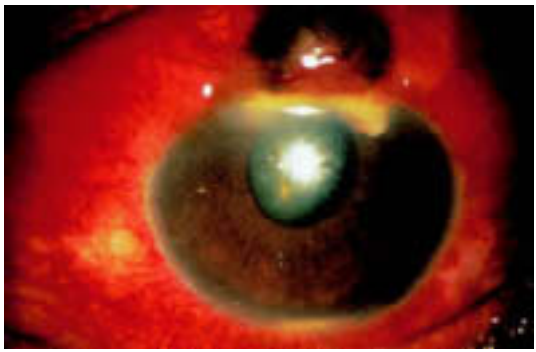

Figure 7.4 Aspergillus fungal scleritis. The left eye of a 54-year-old black man who had undergone trabeculectomy 3 months previously. Note the oval staphyloma at the trabeculectomy site, and the white infiltrate surrounding this lesion and reaching into the limbal cornea.

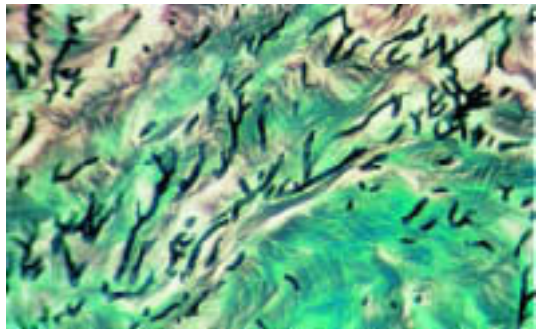

Figure 7.5 Septate fungal hyphae with dichotomous branching in the scleral biopsy specimen from the same patient as in Figure 7.4. Hyphae appear black against green background when specimen is stained with Grocott Gomori methamine silver (× 400).

infection is suspected. The biopsy specimen should be divided for histopathological diagnosis and further microbiological investigations. Detection of mycotic elements on histological examination without a positive culture may be problematic as fungal elements can persist in the sclera after successful medical treatment.[40]

The management of patients with fungal scleritis remains difficult despite the availability of new antifungal agents. There are no clear guidelines for the selection and administration of antifungal antibiotics, since scleral infection is extremely rare and *in vitro* sensitivity data are only of limited value.[42] Topical and systemic antifungal therapy should be administered. Topical econazole 1% may be used as initial therapy for local treatment.[22] Systemic therapy can be started with oral ketoconazole 400–1000 mg/day. For severe infection with filamentous fungi, amphotericin B is the drug of choice.[42] Itraconazole is useful for aspergillus infection.[40] Specialist expertise should be sought for treatment modifications once the organism has been identified. Antifungal therapy alone will not control fungal scleritis and surgical debridement and grafting is usually necessary.[11,40]

Parasite-induced scleritis

Acanthamoeba scleritis

Acanthamoeba species are an uncommon, but important cause of microbial keratitis and may also cause severe scleritis. Important risk factors for the development of amoebic keratitis are

contact lens use associated with contact lens rinsing and soaking solutions that are prepared with non-sterile water and salt tablets, poor hygiene, and swimming whilst wearing lenses.[43] Inflammation of the limbus and sclera is a frequent complication of acanthamoebic keratitis. Scleral inflammation is usually associated with keratitis.[44] Until recently there has been no evidence of direct scleral invasion by acanthamoeba, and scleritis was thought to be a secondary immune reaction to infection.[45] A recent case report has documented organisms in areas of scleral inflammation, and therefore both mechanisms are likely to be involved in the development of acanthamoebic scleritis.[46]

Early signs of acanthamoebic keratitis include punctate keratopathy, pseudodendrites, epithelial infiltrates, diffuse or focal subepithelial infiltrates, and radial keratoneuritis. With progression, ring infiltrates, corneal ulceration, and scleritis may develop. The scleritis usually is diffuse or nodular, but may progress to necrotizing disease. Diagnosis of acanthamoebic keratitis with scleritis is made on the basis of the clinical picture and laboratory investigations. Samples of corneal epithelium and any infiltrated stroma should be taken and smears prepared for staining with Calcofluor and immunocytochemistry. Acanthamoeba can be grown readily on non-nutrient agar seeded with *E. coli*. Corneal biopsies should be considered in cases with negative smears.

Topical therapy with the disinfectant polyhexaminemethylene biguanide (PHMB) is the most effective regimen and may be combined with propamidine or chlorhexidine.[43,47] Pain from scleral inflammation may be treated with oral cyclo-oxygenase inhibitors such as flurbiprofen. The management of the severe associated scleral inflammation may require the use of oral corticosteroids and, rarely, additional immunosuppressive drugs such as cyclosporin. When scleral invasion by amoeba is suspected, systemic anti-amoebic therapy with itraconazole may be a useful adjunct.

Toxoplasma

Toxoplasmic retinochoroiditis may be associated with overlying episcleritis and scleritis as a result of scleral extension of severe toxoplasmosis retinitis and choroiditis.[48]

Helminths

Scleritis due to *Toxocara canis* was recently described.[3] The patient presented with a nodular type of scleritis and intraocular inflammatory signs with a posterior pole granuloma.

SURGICALLY-INDUCED SCLERITIS

Definition

Surgically-induced scleritis describes severe scleral inflammation following ocular surgery.[14,49] The term defines the triggering mechanism for the onset of inflammation rather than a specific type of scleritis. As surgically-induced scleritis is most frequently necrotizing in type, the term surgically-induced necrotizing scleroketatitis (SINS) has been introduced.

Epidemiology

Surgically-induced scleritis is a very rare complication of ocular surgery. The exact incidence is not known, but up to 100 cases have been reported so far.[14,49,50]

Aetiology and pathogenesis

Surgically-induced scleritis has been reported most frequently after cataract extraction, but may also occur following other operations including: strabismus surgery, peripheral iridectomy, trabeculectomies, secondary intraocular lens implantation, trauma repair, keratoplasty, vitrectomy or scleral buckling procedures.[14,49,50] In the majority of these cases, the inflammation was attributed to an immune-mediated response to the surgery. Some cases reported as surgically-induced scleritis represent postoperative infections rather than autoimmune scleritis.

Immunopathological findings in SINS showed neutrophil infiltration and immune complex deposition of the vessel wall.[14] It is likely that the surgical trauma or the temporary ischaemia triggers the onset of this immune-complex response by exposing tissue antigens. In one series of patients with SINS 9 of 10 patients had either Wegener's granulomatosis or rheumatoid arthritis.[14] Other series have also found a large proportion of patients with systemic vasculitis or connective tissue disease.[49]

Clinical presentation

Usually SINS does not occur in the immediate postoperative period, but begins 2 weeks to 6 months later. The onset of inflammation may be long delayed after surgery and SINS has developed

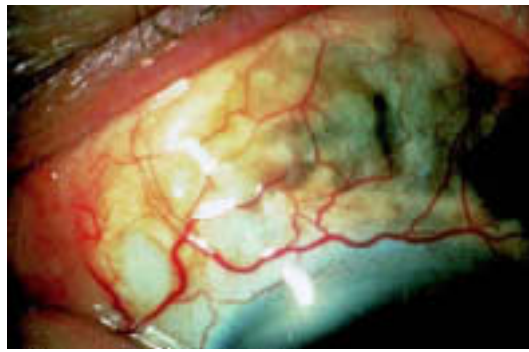

Figure 7.6 Surgically-induced necrotizing sclerokeratitis (SINS). This 70-year-old man with rheumatoid arthritis developed severe corneal and scleral ulcers 2 weeks after uneventful cataract surgery.

40 years after ocular surgery. The clinical features are typical of scleritis and always involves the operative site (Fig. 7.6).[49]

The diagnosis of SINS is a clinical one and can be established after exclusion of postoperative infection. It is important to note that SINS may be the first manifestation of a systemic autoimmune disease and investigations to look for evidence of systemic disease are essential. This is discussed in detail in Chapter 9.

Management

The therapy of SINS follows the principles of treatment for necrotizing autoimmune scleritis described in detail in Chapter 9. Initial treatment of SINS is with high-dose systemic corticosteroids either orally or as intravenous pulse therapy. Maintenance therapy for several months is necessary, and this may require additional immunosuppressive drugs. In cases with extensive necrosis, tectonic grafting may be necessary.

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8: Complications of scleritis

SUSAN LIGHTMAN

Scleritis can have wide ranging complications in the eye and the type of complication seen depends on the location and severity of the scleral inflammation. Most but not all the complications are associated with necrotizing scleral disease and some can have devastating consequences for the eye. It is therefore very important to undertake a thorough ocular examination in patients presenting with scleritis so that these can be identified and appropriate treatment given. Ultrasound is a very useful tool in these patients for identifying posterior segment complications, and rapid assessment of the whole eye is essential. Multiple complications can occur in the same eye. In this chapter, the complications are divided into the effect on various parts of the eye.

SCLERAL THINNING

In some patients with mild diffuse anterior scleritis, there may be no visible evidence when the scleritis has resolved. However in most patients with diffuse or nodular disease, mild scleral thinning occurs (Fig. 8.1) and this can be severe following necrotizing disease (Fig. 8.2). Loss of overlying conjunctiva and episcleral tissue may also occur and, when treated, conjunctival vessels grow in to re-cover the area. Staphyloma formation may occur even in the presence of normal intraocular pressure, particularly if a large area of sclera has been involved (Fig. 8.3). Nodules may take some time to disappear or can leave residual swelling, perhaps because the fluid is very viscous and cannot be easily removed. Only rarely do these require excision.

Figure 8.1 Scleral thinning occurring after non-necrotizing scleral inflammation.

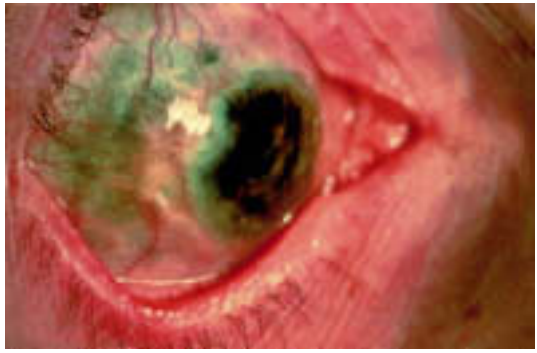

Figure 8.2 Scleral necrosis in necrotizing disease.

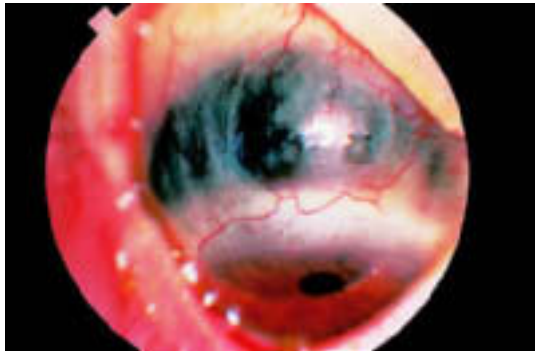

Figure 8.3 Staphyloma formation after necrotizing scleral disease.

ANTERIOR SEGMENT ISCHAEMIA

This rare syndrome can occur with severe, especially necrotizing scleral inflammation that has occurred over 360° although it more usually follows strabismus surgery involving multiple rectus muscles.[1] It occurs because the anterior ciliary arteries pass through the sclera and become involved in the inflammatory process. As they are end arteries, their closure results in ischaemia and this can be demonstrated by anterior segment fluorescein angiography (Fig. 8.4). The syndrome is characterized by cells and heavy flare in the anterior chamber, which often has a greenish appearance. If it is chronic, there is often cataract, and posterior segment examination reveals venous stasis retinopathy. It is essentially untreatable, and control of scleral inflammation to prevent this complication occurring is essential.

CORNEA

Infiltrates in the peripheral cornea adjacent to an area of anterior scleritis (Fig. 8.5) are not uncommon and may be entirely benign, resolving completely on treatment of the scleral inflammation. More severe inflammation, such as with severe diffuse or necrotizing disease, can be associated with adjacent corneal thinning (Fig. 8.6) and, rarely, perforation, which is particularly a feature of the scleritis seen in association with Wegener's disease.[2] Management is by control of the scleral inflammation

Figure 8.4 Fluorescein angiogram showing anterior segment ischaemia.

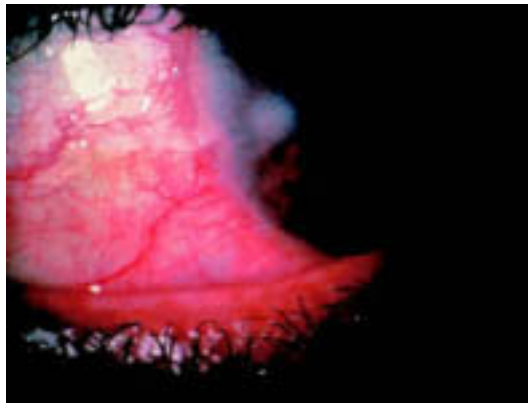

Figure 8.5 Peripheral corneal infiltrate with anterior scleritis.

Figure 8.6 Corneal thinning adjacent to necrotizing scleritis.

with systemic immunosuppression, usually steroids and cyclophosphamide, and the gutter becomes shallower as it is filled in with granulation tissue from the bottom. When perforation has occurred, the hole may be sealed by iris or require sealing – ideally with glue if it is small enough.[3] Tectonic corneal grafts to seal larger perforations are occasionally required,[4] but rapid control of the scleritis with immunosuppressive therapy is essential or the graft sutures will not hold in the inflamed/necrotic sclera.

Central thinning or perforation is more likely to be due to drying from reduced tear secretion/dry eyes, often seen in patients with rheumatoid arthritis[5] rather than scleral inflammation; attention to the ocular environment as well as treatment of any

associated infection is very important. Patients may also have unrelated marginal keratitis from staphylococcal lid disease and dellen formation may also occur.

INTRAOCULAR PRESSURE

There are several causes of raised intraocular pressure in patients with scleritis[6] and, in order to undertake the correct management, diagnosis of the cause is very important.

Open angle

A trabeculitis can occur with diffuse anterior scleritis particularly if this is near the limbus. As the scleritis is treated, the trabecular meshwork usually starts to function normally, but occasionally the patient is left with permanent damage and glaucoma follows, even though the scleritis is now quiet. Patients who have had scleritis may coincidentally also get primary open angle glaucoma, which is not associated with it.

Patients with marked episcleral injection and oedema may also have elevated intraocular pressure, which is relieved when the underlying deep episcleral inflammation is treated.[7] Addition of topical steroids to the systemic therapy for the scleritis may expedite resolution.

As with any patient, a steroid response may occur.[8] The clue to this is that the intraocular pressure was normal prior to the initiation of steroid therapy, usually topically but occasionally systemically, and became elevated on treatment. In patients with trabeculitis or raised episcleral pressure, the intraocular pressure is raised before the initiation of steroid therapy.

Closed or narrow angle

In patients with posterior scleritis associated with serous retinal detachment, the lens–iris diaphragm may be rotated/pushed forwards, causing the anterior chamber to become shallow and close the angle, resulting in a rise in intraocular pressure, which can be marked.[9] Ultrasound may be helpful in demonstrating this (Fig. 8.7). YAG laser iridotomy does not help, and the scleral inflammation requires urgent treatment to reduce the effusion. Usually, as the fluid resolves, the angle re-opens and the intraocular

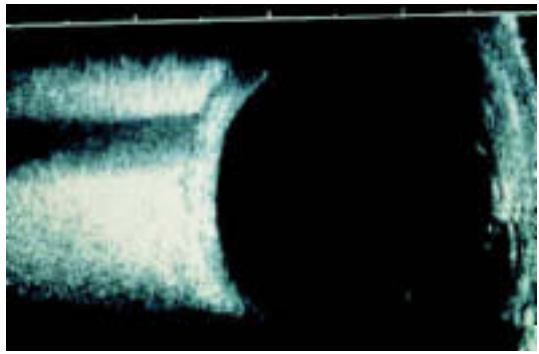

Figure 8.7 Ultrasound showing posterior scleritis with associated shallow annular choroidal detachment involving ciliary body.

pressure will fall as the fluid drains. If there is prolonged shallowing, peripheral anterior synechiae may occur with permanent compromise of the drainage angle.[6] These patients may require trabeculectomy if the pressure cannot be controlled medically.

Occasionally patients with scleritis may have an associated severe uveitis, which can result in posterior synechiae. These may occlude the pupil and there is iris bombé. These patients usually do respond to laser iridotomy, although this is best done with the argon laser first and then the YAG laser to reduce bleeding. A good size hole may result, which will not close.

Low pressure

Patients with a retinal detachment may have a low pressure which responds to reattachment of the retina. This is usually achieved medically, as posterior scleritis may induce a serous retinal detachment, but, just occasionally, a patient may have a rhegmatogenous retinal detachment from vitreous detachment, particularly if there is intraocular inflammation.

Intraocular pressure may drop in any patient with severe ocular inflammation from ciliary body failure. This is usually due to severe posterior segment inflammation, but can occur with severe scleritis over a large area of the ciliary body. As the inflammation is treated, the ciliary body starts to secrete fluid again and the intraocular pressure rises.

UVEITIS

Uveitis is an uncommon association with scleritis[10] but can occur with any type. It is usually mild and anterior, and disappears as the scleritis is brought under control. Posterior synechiae are rare, as are keratitic precipitates or iris nodules. Posterior uveitis is much less common and, when it occurs in the presence of necrotizing scleritis, should trigger the thought of intraocular infection. This is especially important in patients with scleritis following a scleral buckle for retinal detachment (Fig. 8.8), on surgically-induced necrotizing scleritis, when staphylococcal infection is a common initiating factor.

LENS

Cataract is not uncommon in patients with scleritis and is usually posterior subcapsular in type.[11] It can occur in any type but occurs more frequently in those patients with more severe disease, such as the necrotizing type, those with intraocular inflammation, and in patients requiring long courses of systemic corticosteroids. The indications for removal are similar to those for cataract extraction in any patient. Clear corneal phacoemulsification with its small wound size is ideal, and intraocular lens insertion routine. Disease relapse could be triggered by a limbal incision and scleral thinning in areas of previous scleritis has caused problems with wound healing in patients undergoing more conventional extracapsular surgery with large limbal incisions.[12]

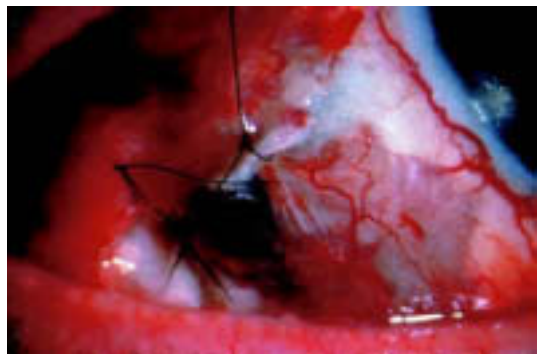

Figure 8.8 Scleritis following scleral buckle.

Necrotizing scleritis can occur after various types of ocular surgery[13] including cataract (Fig. 8.9), retinal detachment (Fig. 8.8), and strabismus procedures. Its aetiology is uncertain and, although some patients have an underlying systemic disorder, most do not. It is very destructive to the eye and treatment with high-dose steroids is urgently required.

Many patients develop posterior subcapsular thickening following cataract surgery. This is most likely to be related to the younger age of the patients as in the uveitic population.[14] YAG capsulotomy is carried out in the usual way.

POSTERIOR SCLERITIS

The complications of posterior scleritis[15] depend on the main area of disease and the structures involved. In many ways posterior segment involvement itself is a complication of scleritis, as it can have very serious sequelae for the eye. Posterior scleritis can cause a localized granuloma that involves the overlying choroid and sclera, serous detachment of the retina which can be localized or total, and optic nerve infiltration (Fig. 8.10) causing severe visual loss. It is also associated with other complications such as uveitis, glaucoma, and cataract, as detailed above. Posterior scleritis is discussed in detail in Chapter 6.

When systemic treatment is initiated, the serous retinal detachment usually settles quickly but, occasionally, residual detachment may occur, which may reflect a failure to absorb very viscous fluid or organization of the fluid such that it cannot be absorbed.

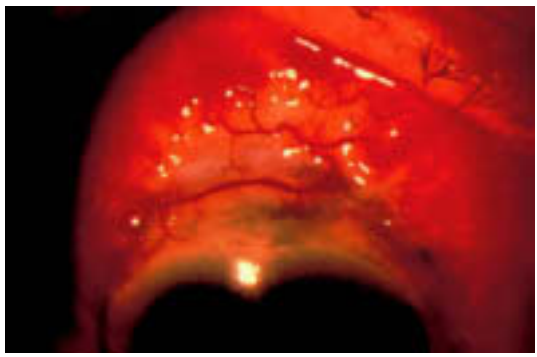

Figure 8.9 Surgically-induced necrotizing scleritis following cataract extraction.

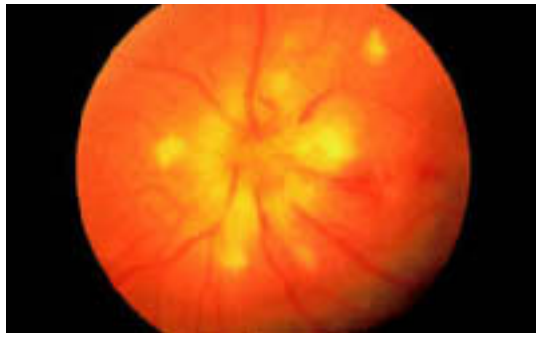

Figure 8.10 Optic nerve involvement in posterior scleritis.

PHTHISIS

This can occur when the eye has received a serious insult of any type. Eyes affected by severe scleritis, usually involving the posterior segment and with intraocular inflammation, may become phthisical after the inflammation has subsided. The phthisical eye is usually pain free. Hypotonic eyes, such as those with intractable retinal detachments or ciliary body failure, may be chronically painful, as can eyes with inflammation that does not respond to treatment.

MASQUERADE SYNDROMES

Posterior scleritis with a localized choroidal granuloma and overlying serous detachment must be distinguished from choroidal melanoma, which can resemble it.[16] Pigment changes due to involvement of the retinal pigment epithelium are not uncommon in scleritis and may add to the confusion. Monitoring of the lesions by ultrasound is very important and, if enlargement rather than reduction of size occurs on treatment, review of the diagnosis is essential. Certainly, the appearance of pigment on the scleral surface, rather than thinning of sclera with visualization of underlying choroid, should immediately make one suspect an underlying melanoma with scleral spread.

Metastasis to the choroid[17] may induce a localized inflammatory or pigment response and can usually be distinguished by their yellowish coloration and lack of ultrasound changes associated with scleritis.

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9: Investigation and management of scleritis

DENIS WAKEFIELD and PETER McCLUSKEY

Scleritis varies in severity from a mild self-limiting disease to a severe necrotizing disorder associated with blinding ocular complications. Scleritis is characterized by severe pain and, in non-sight-threatening disease, pain control is one of the major goals of treatment. In up to 50% of patients, there is an associated or systemic disease that has caused the scleritis.

Therapy for scleritis depends on the nature of the disease, the presence of associated or systemic disease, and the ocular complications caused by the scleritis.[1] This chapter will present an overview of the investigation and medical management of patients with scleritis. As in any patient with inflammatory eye disease, the first step in management is a thorough clinical assessment of the patient.

HISTORY AND EXAMINATION

A comprehensive history, detailed review of systems, and a complete ocular and directed physical examination are the basis upon which the patient is managed. There is no substitute for this. The clinical features of the various forms of scleritis are discussed in detail in Chapters 5, 6, and 7. The aims of the history and examination are to determine the location and severity of the scleritis and assess the severity of any threat to vision. Additionally, symptoms and signs usually suggest the presence of an associated or systemic disease, if present. It is important to also look for clinical evidence of other diseases such as diabetes mellitus, osteoperosis, or peptic ulcer that may complicate systemic treatment.

At this time specific consideration should also be given to the possibility of either a microbial or a neoplastic cause for the

scleritis, as the correct diagnosis is usually delayed and may result in considerable ocular morbidity. Infectious scleritis is discussed in detail in Chapter 7. Ocular surface carcinoma may masquerade as an inflammatory scleritis.

INVESTIGATIONS

Clinical assessment of the patient results in the generation of a differential diagnosis of possible causes for the scleritis. An accurate clinical assessment cannot be substituted by ordering a large array of undirected investigations. There is no "standard" battery of tests performed in all patients with scleritis. The investigations outlined in Table 9.1 indicate those commonly performed in the evaluation of a patient presenting with scleritis.[2,3] There may also be some specific ocular differential diagnoses that need consideration. Biopsy or samples for microbial culture may be necessary to exclude infective or neoplastic causes for scleritis. Ultrasonography or imaging studies of the globe may be necessary in some patients with posterior scleritis to confirm scleral thickening.

Systemic associations of scleritis

A large number of aetiological factors have been implicated in the pathogenesis of scleritis. These can be conveniently divided into infectious, autoimmune, rheumatic, traumatic, surgical, infiltrative, and neoplastic (masquerade) disorders.[3–6] Table 9.2 outlines common clinical features of the systemic diseases most frequently associated with scleritis. It should be noted that a large

Table 9.1 Investigations frequently used in patients with scleritis

Investigation	Specific tests
Blood & serological tests	ESR & full blood count Urea, creatinine, electrolytes, glucose, liver function tests, uric acid Rheumatoid factor, antinuclear factor, antineutrophil cytoplasmic antibody (ANCA) Syphilis, hepatitis B, hepatitis C serology
Urine	Microscopy for haematuria and casts
Radiology	Chest X-ray, CT scan orbit, CT scan sinuses, MRI scan orbit, B scan ultrasonography, dual proton bone densitometry

Table 9.2 Clinical features of systemic diseases commonly associated with scleritis

Disease	Clinical features	
Rheumatoid arthritis	Morning joint stiffness Arthritis of hand joints Polyarthritis	Rheumatoid nodules Serum rheumatoid factor Radiographic changes
Wegener's granulomatosis	Nasal, oral, sinus or upper respiratory tract lesions Pulmonary infiltrates Glomerulonephritis	Granulomatous vascular inflammation on biopsy c-ANCA (PR3)
Polyarteritis nodosa	Weight loss Testicular pain or tenderness Myalgias, Mononeuropathy or polyneuropathy Hypertension Elevated urea or creatinine	Hepatitis B virus antigen Arteriographic abnormalities Biopsy of small or medium sized artery containing PMNs p-ANCA (MPO)
Relapsing polychondritis	Tender auricular and nasal cartilage Tracheal and laryngeal pain and collapse Polyarthritis	Raised ESR Systemic vasculitis Serous otitis media Valvular heart disease
Churg–Strauss syndrome	Asthma Eosinophilia >10% History of allergy/atopy Mononeuropathy or polyneuropathy	Pulmonary infiltrates: migratory or transient Paranasal sinus abnormalities Extravascular eosinophils on biopsy p-ANCA (MPO)
Systemic lupus erythematosus	Malar rash Discoid rash Photosensitivity Oral or nasopharyngeal ulcers Arthritis – non-erosive Pleurisy, pericarditis, serositis Proteinuria/casts	Seizures/psychosis Haemolytic anaemia, leukopenia, thrombocytopenia ANA, DNA, Sm antibodies, LE cells, false positive syphilis serology

number of these diseases are diagnosed on the basis of extraocular clinical features, emphasizing the need for careful clinical assessment at the outset. The most common diseases associated with scleritis are rheumatic diseases, particularly rheumatoid arthritis (Fig. 9.1); connective tissue diseases, such as relapsing polychondritis (Fig. 9.2) and systemic lupus erythematosus

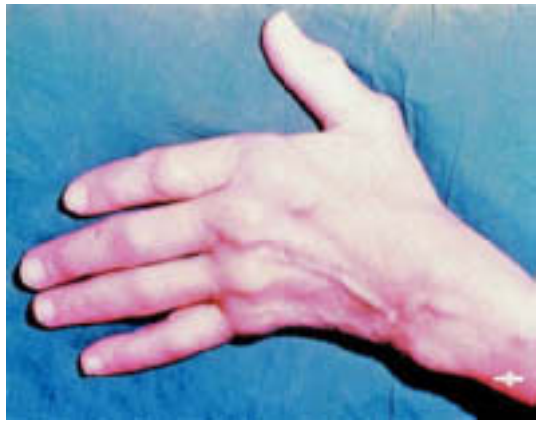

Figure 9.1 Classical hand deformities in a patient with longstanding rheumatoid arthritis. Scleritis typically occurs in patients with longstanding rheumatoid arthritis.

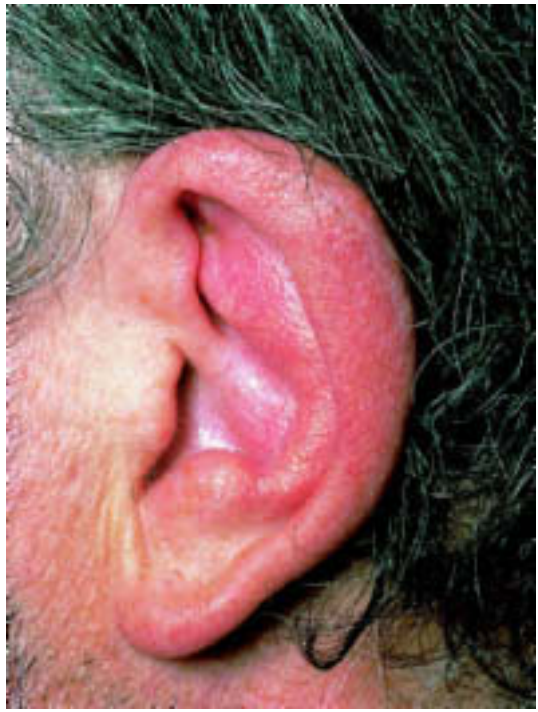

Figure 9.2 Swollen ear cartilage in a patient with relapsing polychondritis.

(Fig. 9.3), and systemic vasculitic diseases such as Wegener's granulomatosis (Fig. 9.4) and polyarteritis nodosa.

While the incidence of scleritis in patients with rheumatoid arthritis is low, varying from 0.15 to 6.3%, rheumatoid arthritis in patients presenting to inflammatory eye disease clinics with scleritis may be up to 30% of all cases.[7] Symptoms and signs related to rheumatoid arthritis usually antedate the onset of scleritis, and it is unusual for scleritis to be the presenting manifestation of rheumatoid arthritis.

In common with patients with rheumatoid arthritis, subjects with SLE with associated scleritis usually have the features of the systemic disease before the onset of their ocular disease. Episcleritis is the commonest form of ocular inflammation seen in patients with SLE, and scleritis is usually diffuse or nodular, rather than necrotizing in type.[8] As with rheumatoid arthritis, the basic underlying immune mechanisms involved in the pathogenesis of SLE are believed to be due to immune complex deposition in the tissue.[1] Both diseases are associated with genetic factors, are more common in women, and involve a complex interaction between the humoral and cell-mediated arms of the immune system.

Systemic vasculitis is well known to be associated with scleritis.[5–9] This complex group of diseases is also believed to be principally due to a type III hypersensitivity immune response, involving deposition of immune complexes, although recent evidence indicates that, as with rheumatoid arthritis and SLE, T cell-mediated

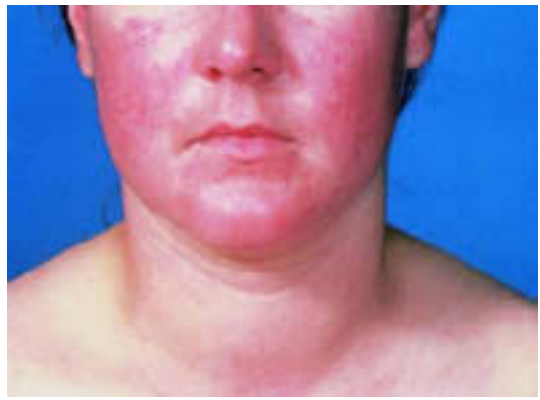

Figure 9.3 Butterfly malar rash in a patient with systemic lupus erythematosus.

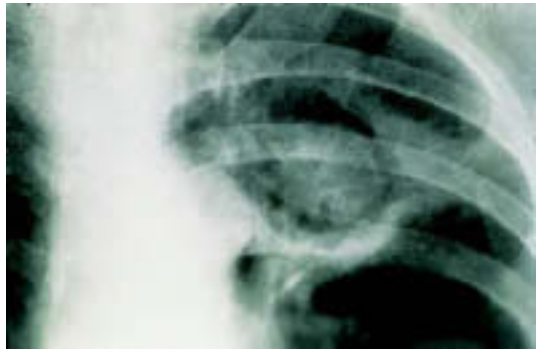

Figure 9.4 Lung abscess and cavitation in a patient with scleritis and systemic Wegener's granulomatosis.

immune responses are also important, particularly in Wegener's granulomatosis.[9,10] Scleritis may be the presenting manifestation of a vasculitic illness, and it is important to assess patients to ensure that they do not have a multisystem disease when they present with ocular symptoms.[1]

Scleritis or episcleritis occurs in up to 50% of patients with relapsing polychondritis and is usually non-necrotizing in type.[10] Other types of inflammatory eye disease, including peripheral ulcerative keratitis, uveitis, and retinal vasculitis may also be seen. As is the case with systemic vasculitis, histological confirmation of relapsing polychondritis may be required to substantiate the diagnosis. The clinical features of auricular and nasal cartilage inflammation, with occasional tracheal involvement, are typical of this disease and are readily recognized in advanced cases.

The treatment of scleritis associated with systemic vasculitis is the treatment of the underlying disease[1] Systemic vasculitis requires systemic immunosuppression to control the disease and such therapy is effective in controlling the associated scleritis. Patients with scleritis associated with systemic vasculitis should be managed jointly by an ophthalmologist and physician experienced in the treatment of such disorders.

TREATMENT

The aims of therapy for scleritis are disease remission or cure as quickly as possible, relief of pain, maintenance of vision, and

minimization of side effects from treatment. The treatment of scleritis involves the use of systemic anti-inflammatory and immunosuppressive drugs, and the drugs used most frequently are briefly discussed below.

Drugs commonly used in the treatment of scleritis

Cyclo-oxygenase inhibitors

Non-necrotizing scleritis often responds to non-steroidal anti-inflammatory drugs and the cyclo-oxygenase inhibitors (cox inhibitors) such as naproxen, ketoprofen, or ibuprofen are by far the most commonly used class of drugs.[11] The new cox-2 inhibitors selectively inhibit the cyclo-oxygenase isoenzyme induced at sites of inflammation without blocking the other isoenzymes present physiologically. Cox-2 inhibitors have not been subjected to clinical trials in patients with scleritis, but anecdotal experience suggests that they are equally effective as non-selective cox inhibitors. Their lack of gastrointestinal side effects is of great benefit to patients.

Experience in the management of patients with rheumatic diseases with non-steroidal anti-inflammatory drugs indicates that they have a considerable spectrum of potentially serious side effects. Patients should be warned of potential side effects, particularly, gastrointestinal side effects and bleeding associated with the use of these medications. Photosensitivity skin rashes, renal toxicity, hepatotoxicity, and the possibility of drug interactions are also important considerations with the use of non-steroidal anti-inflammatory drugs.

Corticosteroids

Patients who do not respond to cyclo-oxygenase inhibitors require systemic therapy with corticosteroids. Orbital floor injections of corticosteroids may be helpful in a small number of patients and occasionally may obviate the use of systemic corticosteroids.

Corticosteroids are the mainstay of therapy for patients with scleritis and the treatment against which other therapies need to be compared in terms of efficacy. A variety of treatment regimens have been developed for the use of corticosteroids in the treatment

of scleritis.[2] Corticosteroids are used orally or intravenously in high doses to induce disease remission.[1,12] The use of high-dose corticosteroid therapy is associated with significant morbidity and steps should be taken at the outset to minimize the potential for corticosteroid-induced side effects.

Oral corticosteroids should be started at a dose of 1 mg/kg per day, which usually equates to 50–80 mg/day in adults. The dose is then tapered by 20–25 mg/week until the dose is reduced to about 40 mg/day. The dose is then tapered by 5mg/week until the steroids are ceased or an acceptable maintenance dose is reached. The therapy must be individualized according to the clinical situation.

High-dose intravenous methylprednisolone has been demonstrated to be both safe and effective in inducing remissions in patients with severe scleritis.[12] It is used most frequently in patients with necrotizing scleritis, especially when there is a threatened scleral or corneal perforation, or rapid control of the inflammatory response is essential. Intravenous methylprednisolone is also useful to control relapses of scleritis. Intravenous methylprednisolone pulse therapy has advantages similar to those of alternate daily oral corticosteroids in decreasing drug side effects associated with this medication.

The side effects associated with high-dose corticosteroid therapy are usually predictable, dependent upon the dosage, frequency, route of administration, and the duration of therapy. Thus short-term therapy with low-dose corticosteroids is well tolerated with few side effects; high-dose corticosteroids given over a long period of time are associated with significant morbidity and occasional mortality.

The major side effects associated with corticosteroids are outlined in Table 9.3. Strategies for decreasing corticosteroid side effects include using the lowest possible dose for the shortest duration and adopting alternate-day dosing if possible. It has been established that alternate-day and intermittent pulse therapy are associated with fewer side effects than daily dose corticosteroids.[13] Other strategies to minimize steroid side effects include:

- encouraging patients to exercise on a regular basis;
- low salt and low fat diets;
- use of calcium supplements and hormone replacement therapy to prevent osteoporosis in postmenopausal women.

Table 9.3 Commonly used drugs for treating scleritis and their side effects

Drug	Major adverse effects	Monitoring
Cyclo-oxygenase inhibitors	Peptic ulceration, fluid retention, renal failure, papillary necrosis, interstitial nephritis, hepatitis, bleeding	Clinical assessment, urinalysis Renal and liver function tests 3 monthly
Corticosteroids	Weight gain, bruising, fluid retention, hypertension, diabetes, osteoporosis, acne Muscle weakness, growth retardation (children), infections Psychological disturbances	Blood glucose, urinalysis monthly Blood pressure monthly Bone densitometry
Cyclophosphamide	Cystitis, neoplasms, infections, infertility, alopecia, pneumonitis	Blood count and urinalysis monthly after initial weekly tests
Azathioprine	Nausea, oncogenicity cytopenias, hepatitis	Blood count 1–2 weekly initially, then 1–3 monthly Liver function tests 1–3 monthly
Cyclosporin	Renal impairment, hypertension, tremor, hirsutism, gingivitis, lymphoma	Blood count, serum creatinine, blood pressure weekly, then 2–4 weekly on maintenance dose
Methotrexate	Hepatic fibrosis, nausea, cytopenias, pneumonitis, mouth ulcers	Blood count and liver function tests second weekly, then 1–3 monthly
Mycophenolate	GIT upset and bleeding, lymphoma, infections	Blood count, serum creatinine, blood pressure weekly, then 2–4 weekly on maintenance dose

Patients should be monitored for hypertension, and increased blood sugar and lipid levels. In addition the potential for drug interactions should be kept in mind.

It is well known that some patients are more susceptible to corticosteroid side effects than others. Such individuals include those who:

- are elderly;
- have diabetes or hypo-albuminaemia (associated with nephrotic syndrome or chronic liver disease);
- have a history of gastrointestinal disease, bleeding disorders, or psychological illness, or
- are pregnant.

The risk of osteoporosis should always be kept in mind when corticosteroids are prescribed. Patients who are at greater risk of developing steroid-induced osteoporosis include those who:

- have a past history of fracture and osteoporosis;
- have a family history of osteoporosis;
- are postmenopausal;
- are smokers, or
- have a debilitating systemic disease, especially rheumatoid arthritis.

The bisphosphonates should be considered for patients with osteoporosis who are already receiving calcium, vitamin D, and hormone replacement therapy, and who are on a regular programme of weight-bearing exercises. There is good evidence that alendronate and etidronate are effective in steroid-induced osteoporosis.

Finally, the use of steroid-sparing agents to minimize steroid side effects is commonly adopted. Drugs used in this regard include: azathioprine, methotrexate, cyclosporin, cyclophosphamide, and mycophenolate.

Immunosuppressive therapy

Immunosuppressive therapy is indicated in patients who have severe scleritis, which is not controlled with the use of high-dose oral or intravenous corticosteroids. A large number of drugs have been shown to be effective in the treatment of scleritis. These medications include cyclophosphamide, azathioprine, chlorambucil, methotrexate, cyclosporin, and mycophenolate.[14,15]

Azathioprine is often used as an adjunct to corticosteroid therapy. Clinically, this medication is less effective than other drugs in controlling severe scleritis, probably related to genetic differences in the patient's ability to metabolize azathioprine by the enzyme thiopurine methyltransferase.

Cyclosporin and *mycophenolate* have been shown to be effective particularly in those patients with severe scleritis, who have failed other forms of immunosuppressive therapy.[14] Mycophenolate appears to be of similar efficacy to cyclosporin with a more acceptable side effect profile.

Methotrexate, as a result of its lesser potential to cause oncogenic complications following long-term use, has become increasingly popular in the treatment of scleritis, particularly in younger patients for whom the long-term risks of malignancy and infertility, seen with drugs such as cyclophosphamide and chlorambucil, are important considerations.

Cyclophosphamide has been used extensively in the treatment of systemic vasculitis. Similarly, it has been found to be effective in the treatment of severe scleritis, either orally or as intravenous pulse therapy. Cyclophosphamide is usually reserved for patients with severe scleritis that has relapsed with other forms of immunosuppressive therapy or where therapy with other drugs is likely to cause severe side effects. Cyclophosphamide is particularly useful in older patients where other drugs have been found unsuitable. The drug should always be given as a single morning dosage (1–3 mg/kg per day) or as monthly intravenous pulse therapy. Prehydration is critical and it is important that patients be encouraged to drink at least 3 litres of fluid per day to minimize the potential side effect of haemorrhagic cystitis. The long-term complications with the use of alkylating agents, such as cyclophosphamide and chlorambucil, has led to a reconsideration of their use in patients with non-life-threatening diseases. Despite this, cyclophosphamide remains one of the most effective forms of therapy for severe scleritis. When required, the dosage should be kept to a minimum, as should the duration of therapy. Careful long-term follow-up for oncogenic side effects should be planned.

The side effects and profile of drugs commonly used to treat scleritis are summarized in Table 9.3. Patients receiving immunosuppressive therapy are at increased risk of infection, especially pulmonary infection. Thus all patients should be encouraged to stop smoking, avoid others with infections, and remain up to date with their immunizations, including influenza and pneumococcal vaccination. Patients receiving immunosuppression should not be given live vaccines (e.g. for BCG, polio, yellow fever).

Other therapy

Several other forms of therapy have been used to treat small numbers of patients with scleritis, usually when it is associated with systemic disease. These therapies include plasma exchange, intravenous immunoglobulin, tacrolimus, and rapamycin. Until comparative data on efficacy is available, these forms of therapy remain anecdotal or experimental.

Principles of treatment

It is useful to divide the treatment of scleritis into several phases.

Pretreatment evaluation

A careful pretreatment assessment will avoid the many pitfalls encountered in the management of patients with scleritis. There are three issues of crucial importance in the pretreatment evaluation of patients:

- the exclusion of latent infection and assessment of infection risk;
- careful evaluation for the presence of coexisting local and systemic disease, and
- consideration of the potential for drug side effects and drug interactions.

Table 9.4 outlines a recommended pretreatment evaluation for patients with scleritis requiring systemic immunosuppressive therapy.

Remission induction therapy

A number of different treatment regimens have been used to induce disease remission. Such treatment is usually planned in conjunction with an assessment of the need to treat associated systemic disease. Corticosteroids are the mainstay of therapy for patients with scleritis. In patients in whom scleritis is not adequately controlled with high doses of corticosteroids, additional immunosuppressive treatment is required. High-dose immunosuppressive therapy may be associated with serious complications, and physicians experienced in such treatment should manage this treatment.

In most patients with non-necrotizing scleritis, initial therapy usually involves the use of a single agent such as a cyclo-oxygenase inhibitor, high-dose oral corticosteroids, or pulse therapy with methylprednisolone. In patients with necrotizing scleritis, therapy with high-dose oral corticosteroids, pulse therapy with methylprednisolone or combination therapy (corticosteroids and another agent such as methotrexate, cyclosporin, mycophenolate, or cyclophosphamide) is necessary.

As scleritis comes under control, pain diminishes rapidly, together with objective improvement in the signs of scleral inflammation. In scleral necrosis, blood flow improves in the episcleral plexuses, and the areas of necrosis stop increasing in size. The time course for resolution of signs is variable. Scleral tenderness improves over days; scleral injection and the beginning of healing in areas of scleral necrosis occurs over several

Table 9.4 Pretreatment assessment and prevention of side effects in patients with scleritis

Drug	Pretreatment assessment	Prevention of side effects
Cyclo-oxygenase inhibitors	History of allergy to aspirin, bleeding disorder, peptic ulceration, asthma, renal or heart disease	Medication to be taken on full stomach or avoided Consider cox-2 inhibitors
Corticosteroids	Glucose, urea creatinine and electrolytes, fasting glucose level, uric acid, lipids, chest X-ray, blood pressure History or family history of osteoporosis, especially in postmenopausal women Psychological assessment for anxiety/depression Exclude active infection, Mantoux test if BCG negative	Restrict caloric intake Exercise, sunlight, high-calcium diet. Oestrogen replacement therapy Consider bisphosphonate therapy Avoidance of infections No live vaccines Treat raised blood pressure and glucose Psychological support
Cytotoxics	Blood count, platelets, ESR, urinalysis, urea, creatinine, electrolytes, liver function tests, chest X-ray, exclude active infection, Mantoux test if BCG negative Consider fertility status Exclude malignant or premalignant disease, cervical smear	Adequate fluid intake, diuresis and Mesna with alkylating agents Hormone replacement therapy Consider fertility status 6-monthly check for evidence of malignancy No live vaccines

weeks; resolution of scleral nodules may take months. Scleral thinning becomes apparent as resolution of the other signs occurs. The induction phase of therapy requires from 2 to 8 weeks, depending on the severity of the scleritis and the clinical response to treatment. The next step is to begin to decrease the dosage of corticosteroids and consider appropriate maintenance therapy.

Maintenance therapy

The aim of maintenance therapy is to consolidate improvement in inflammation achieved with induction therapy and to minimize ocular and systemic complications associated with the longer term use of corticosteroids and other immunosuppressive drugs.

In patients treated with cyclo-oxygenase inhibitors, the dose may be reduced to lower levels, but treatment is continued for 6–12 weeks before consideration is given to stopping treatment.

Corticosteroids remain the most frequently used drug for maintenance therapy in patients with scleritis. Clinical experience suggests that long-term low-dose use of corticosteroids (less than 10–15 mg per day) is safe and associated with tolerable side effects. Despite this, patients should be carefully monitored for complications such as osteoporosis, hypertension, diabetes mellitus, vascular disease, and infections. Patients who need corticosteroids to control scleritis usually need a minimum of 3–4 months treatment before consideration should be given to stopping therapy. Patients who develop significant steroid-related side effects require the introduction of a second agent.

Patients on combination therapy for scleritis usually need ongoing treatment for a minimum of 6 months before consideration can be given to stopping treatment.

Cessation of therapy

Once the decision is made to stop therapy, if the patient is taking a single drug such as oral corticosteroid, it can be progressively tapered over 4–6 weeks and stopped. If the patient is on combination drug therapy, the drugs are stopped one at a time after each has been reduced to low dosage levels. As patients most frequently have corticosteroid-related side effects, this drug is often stopped first.

The patient is then followed for disease relapse and monitored for late-onset complications from the scleritis or its treatment.

Relapse therapy

Relapses of scleritis are common as therapy for an episode of scleritis is being reduced. There is usually return of pain and signs of inflammation in patients with anterior scleritis while, in patients with posterior scleritis, there may be only pain or reduction in vision.

Patients who have previously responded to a particular treatment regimen should have this treatment restarted at disease remission induction levels. If this approach fails, a new drug should be used or a combination therapy with additional immunosuppressive drugs considered. The commonest scenario involves scleritis relapse at unacceptably high doses of corticosteroids, or corticosteroid-induced side effects preventing the use of a sufficient dose of corticosteroids to control the scleritis; relapse therapy usually involves the introduction of second-line agents.

The choice of additional immunosuppressive agent depends on the age, associated disease, and laboratory findings in individual

cases. For example, in young patients, less than 30 years of age, alkylating agents should be avoided if possible. In such cases the choice of therapy lies between methotrexate, cyclosporin, azathioprine, or mycophenolate. In patients with mild disease, low-dose azathioprine or methotrexate may be effective. In patients with more severe disease high-dose methotrexate, cyclosporin, or mycophenolate should be considered. If this therapy fails, the use of an alkylating agent such as cyclophosphamide, either as an oral or intravenous regimen, can be considered. In adult patients with scleritis, in whom the risk of infertility is not such an important issue, cyclophosphamide can be used in severe disease; in patients with systemic vasculitis, this drug should be considered early in the treatment regimen. Caution should be exercised in older men with prostate hypertrophy and urinary obstruction when cyclophosphamide is used, as this may cause haemorrhagic cystitis. Cyclophosphamide is the most effective agent in the treatment of severe scleritis, especially when associated with systemic vasculitis such as Wegener's granulomatosis and polyarteritis nodosa.

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10: Surgical management of scleritis

MARK J ELDER

Surgery is not usually necessary during the management of patients with scleritis. In a consecutive series of 290 patients with all types of scleritis, only 4.5% required either cataract surgery, a glaucoma procedure, or penetrating keratoplasty, and another 5.9% required a scleral patch graft for impending or actual ocular perforation.[1] This gives a total surgical intervention rate of 10.3%. All patients requiring patch grafting had necrotizing scleritis, and this subtype of scleritis made up 19% of the entire series of 290 patients. This series is the only one that allows us a calculation of the prevalence of surgical intervention.

INDICATIONS FOR SURGERY

Surgery may be required to establish a diagnosis, to treat actual or impending ocular perforation, and as an adjunct to ensuring sterilization of microbial scleritis.

Diagnostic

Scleral biopsy

Scleral biopsy is potentially hazardous in patients with active scleritis, as it may result in perforation at the site of biopsy.[2] This is especially true for inflammatory causes of scleritis. Biopsy may be necessary to establish the diagnosis in patients with infectious scleritis, or when there is a suspicion of a masquerade syndrome and malignant disease must be excluded.[3] As scleral biopsy specimens are usually small fragments of tissue, it is essential to discuss the handling requirements of biopsy specimens with the

laboratory preoperatively, to ensure that the tissue is collected and prepared correctly.

Therapeutic

Necrotizing scleritis may result in actual or impending perforation of sclera, limbus, or peripheral cornea (Fig. 10.1). There are a number of materials that have been used for patch grafting and these will be discussed in turn.

Scleral grafts

The earliest scleral grafts were performed in 1962 in dogs, when sclera from a fresh enucleated eye was successfully transplanted to the sclera of live dogs.[4] The grafted tissue remained viable for at least 7 months without demonstrable change in structure histologically, and no graft loss occurred in 32 experiments. These outcomes were the same whether the surgery was an onlay graft or full-thickness scleral replacement.

In scleritis, a scleral or limbal deficit can be replaced by donor sclera, which has been banked either as frozen, glycerine-preserved or alcohol-preserved tissue (Figs 10.2, 10.3, 10.4). Publications before the widespread use of systemic immunosuppressive agents document that the donor sclera was at significant risk of being either rejected by the host or involved in the necrotic scleritic process.[5–8]

In a series of 15 grafts in 12 eyes of 12 patients who had donor sclera grafting for scleral necrosis, 10 of the 12 patients had systemic autoimmune disease and eight patients were treated with

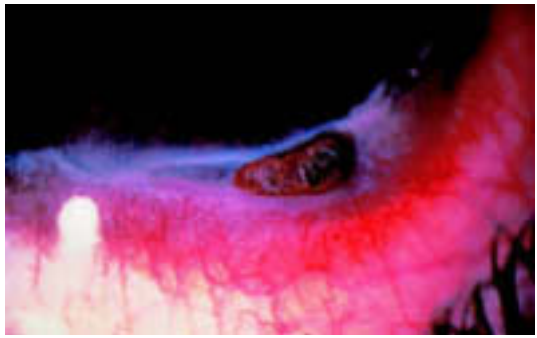

Figure 10.1 Peripheral corneal perforation in patient with scleritis and associated keratitis.

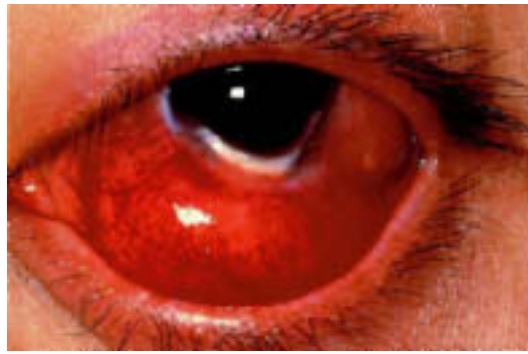

Figure 10.2 Patient with relapsing polychondritis and severe nodular scleritis with keratopathy from globe exposure due to a huge scleral nodule.

Figure 10.3 Operative view of exposed scleral nodule.

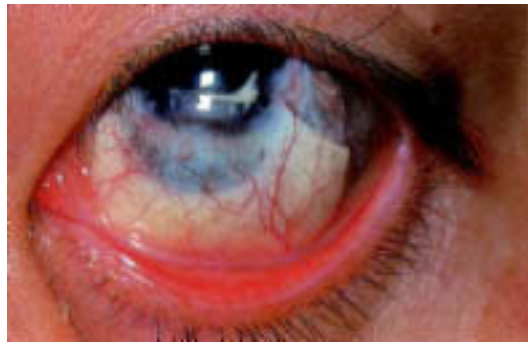

Figure 10.4 Postoperative view showing lamella corneal graft and scleral graft to cover scleral and corneal deficit.

immunosuppressive therapy, such as cyclophosphamide, methotrexate, or penicillamine.[9] In the patients who received chemotherapy, all scleral grafts were stable over the long term except for two: one developed microbial keratitis and subsequent endophthalmitis and the other developed necrosis of the graft within 10 months of the cessation of chemotherapy. This last patient was regrafted and stayed on chemotherapy, and this resulted in a stable graft for the subsequent 35 month follow-up. Four patients were not initially treated with chemotherapy and two developed early graft necrosis at 2 weeks and 7 weeks postoperatively. Both patients had active disease as demonstrated by biopsy. Two patients without chemotherapy had a good outcome from the scleral grafting, and biopsy had showed no evidence of active vasculitis.

Based on this study, it is clear that, if there is any evidence of active disease, then donor sclera will only survive if the patient is adequately immunosuppressed and the scleritis controlled. If the disease remains active or the therapy is inadequate, the donor grafts may melt. If patients with clinically inactive scleritis need scleral grafts to stabilize the ectatic sclera, aggressive systemic immunosuppression is not needed prior to surgery. The excised scleral tissue should be examined histologically to determine whether there is any disease activity. If there is histological evidence of active vasculitis in the excised episclera or sclera, systemic immunosuppression is indicated. The other option is not to use sclera as the patch material if the patient has contraindications to the use of systemic immunosuppressive therapy.

Autogenous periosteum

There are four cases in the literature where the sclera has been reinforced with autogenous periosteum in necrotizing scleritis.[10,11] Two of these cases were situations where donor sclera had been used as the primary patch graft, but had melted away. Subsequent periosteal grafting was successful in all cases.

Autologous periosteum is harvested from the anterior tibial crest of the leg by making a vertical skin incision starting 8 cm below the anterior tibial tuberosity and dissecting the muscles from the periosteum, which is then incised and removed with a periosteal elevator and scissors. The wound is closed in two layers.[10]

The host scleral bed is prepared by reflecting the conjunctiva from the thinned area, performing a lamellar dissection of the thinned scleral or limbal tissues, and suturing the graft with

interrupted 8/0 or 9/0 nylon sutures. The tissue is then covered with conjunctiva if possible.

By using the patient's own periosteum, there is no graft rejection and periosteum will not be involved in the scleral inflammatory process. When periosteum is transplanted it does not induce the laying down of bone in its new location. Extensive work with keratoprostheses reinforced with periosteum has shown good ocular acceptance with excellent long-term follow-up.[12] There is no need for systemic immunosuppression following periosteal grafting from the graft point of view.

Fascia lata

Fascia lata was first used in 1955 to seal a perforation from necrotizing scleritis.[13] The outcome was favourable, although the patient required several procedures because of melting around the edge of the graft. During the last procedure, the patient died on the table. The histology therefore became available for the preceding graft performed several months previously. There was good vascularization and incorporation of the fascia lata into the ocular tissues. Others have also successfully used fascia lata in patients with progressive necrotizing scleritis.[14–17]

Fascia lata is harvested as an autograft from the lateral aspect of the distal third of the thigh. The conjunctiva is carefully reflected from the thinned/perforated area. The fascia is overlaid and secured with sutures. The fascia should be larger than the area to be grafted to allow good healing of the grafted fascia. The conjunctiva is replaced over the graft.

Other scleral patch materials

A pedicle graft of conjunctiva and tarsal plate has been successfully used to patch necrotic sclera and, because the rotation flap has its own vascular supply, healing is rapid.[18] Scleral reinforcement with a homograft of aorta, from which the adventitia and intima have been removed, has been used, as has Gore-Tex mesh.[19,20]

SURGICAL MANAGEMENT OF MICROBIAL SCLERITIS

Infective scleritis is a rare condition often associated with unusual circumstances such as radionecrosis. Biopsy may be required to establish the diagnosis and identify the pathogen.

Surgery may be necessary to debride necrotic sclera and to manage impending or actual ocular perforation. Patch material is usually donor sclera or donor cornea and, as the primary underlying pathology is usually not autoimmune, systemic immunosuppression is not usually needed. This topic is discussed in detail in Chapter 7.

Cataract surgery in patients with scleritis

Cataracts develop relatively frequently in patients with scleritis owing to the high doses and long duration of corticosteroid therapy, the older age group of many patients, and the occasional extension of inflammation to involve the interior of the eye. There is no evidence in the literature to guide surgical decision-making in patients with scleritis requiring cataract surgery.

The indications for cataract surgery are similar to those in other patients. Patients with a past history of scleritis may have high degrees of astigmatism induced by scleral thinning and necrosis. There may be induced irregular corneal astigmatism from scleritis associated keratitis. These changes may significantly limit vision following surgery. Scleral nodules and other posterior segment abnormalities from posterior scleritis may prevent accurate axial length measurements from being obtained. These issues need to be considered by the surgeon and patient preoperatively.

Clear corneal phacoemulsification and intraocular lens implantation is the optimum surgical technique to use, as it avoids thinned or damaged sclera that may have a compromised blood supply impeding healing. Surgical trauma to the sclera may also induce a relapse of scleritis. The peripheral cornea is, however, commonly involved in scleritis and this can lead to difficulties with wound construction during surgery.

Cataract surgery should only be undertaken in eyes where the scleritis has been in remission for a minimum of 3 months. In patients with severe scleritis, there should be at least 6 months of inactive scleritis. There is no consensus on the need for perioperative corticosteroid cover at the time of surgery. If patients are on maintenance immunosuppressive therapy at the time of proposed cataract surgery, many surgeons would use additional corticosteroids in an identical manner to that used for cataract surgery in eyes with severe uveitis. In eyes with a past history of episodes of scleritis, who are not on treatment and who have had inactive disease for many months or years, some surgeons would

use a single dose of intravenous methylprednisolone at the time of surgery. Others would use no corticosteroid cover.

Glaucoma surgery in patients with scleritis

Glaucoma surgery is rarely necessary in patients with scleritis, as the common mechanisms that result in elevated intraocular pressure are usually short lived. Closed angle glaucoma is the commonest mechanism that leads to acute glaucoma, and usually occurs in patients with posterior scleritis who develop ciliary body rotation and secondary angle closure from ciliochoroidal detachment. This responds to medical therapy for the scleritis. Rarely patients can develop pupil block and iris bombé resulting in angle closure from severe uveitis complicating scleritis. Multiple YAG laser peripheral iridotomies are needed to relieve the angle obstruction.

Severe scleritis can induce severe trabeculitis and resultant increased intraocular pressure (Fig. 10.5). This is usually transient and settles with treatment for the scleritis, but, occasionally, patients develop significant glaucoma that cannot be controlled medically. The other common mechanism of increased intraocular pressure or glaucoma with an open angle is corticosteroid-induced pressure elevation. This rarely becomes a problem requiring a surgical solution. Other factors, such as elevated episcleral venous pressure, may also contribute to the glaucoma. Laser trabeculoplasty is not a useful procedure in patients with scleritis. A trabeculectomy enhanced with peroperative 5-fluorouracil is probably the safest surgical option in such patients. It may be

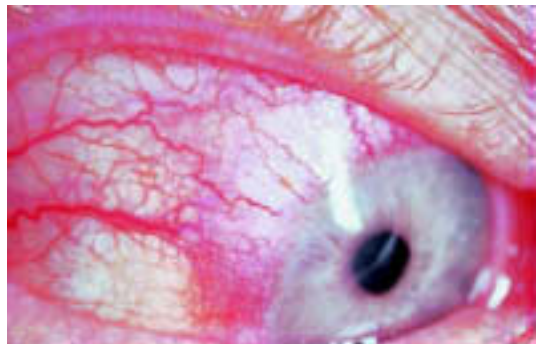

Figure 10.5 Diffuse anterior scleritis with “limbitis”. Elevated intraocular pressure was present due to inflammation of the trabecular meshwork.

difficult to dissect adequate conjunctival flaps in patients who have had severe scleritis, and an individualized approach to surgery is necessary. Perioperative cover with corticosteroids should be considered using the same guidelines as for cataract surgery in patients with scleritis.

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Index

Page numbers in **bold** type refer to figures; those in *italics* refer to tables or boxed material.

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