Optometric Management of Scleritis

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Anterior Segment

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COURSE DESCRIPTION:

This course focuses on the clinical diagnosis and management of scleritis. It covers the clinical features of scleritis as compared to episcleritis and other red eye conditions. Additionally, associated systemic conditions are discussed with relevant medical therapy.
Hello, first off, thanks for joining me for a discussion on scleritis. When we talk about scleritis we need to keep in mind its milder cousin episcleritis which I covered in another presentation, so please refer to the episcleritis presentation for a comprehensive understanding of these two red eye conditions.

Scleral inflammatory disease consists of episcleritis and scleritis. Episcleritis is typically self-limiting or quickly responsive to topical therapies. In contrast, scleritis is a painful, destructive, and potentially blinding disorder that may also involve the cornea, adjacent episclera, and the underlying uveal tract. Scleritis has a striking, highly symptomatic clinical presentation (Fig 1).

Scleritis sometimes occurs in an isolated fashion, without evidence of inflammation in other organs. However, in up to 50% of patients, scleritis is associated with an underlying systemic illness such as rheumatoid arthritis or granulomatosis with polyangiitis (aka Wegener’s Syndrome) [1]. Two-thirds of patients with scleritis require high-dose glucocorticoids or the combination of high-dose glucocorticoids and another immunosuppressive agent to achieve disease control [2].

Before considering the criteria by which the differential diagnosis is reached it is necessary to understand the normal vascular anatomy of the outer coats of the eye. The blood vessels of the episclera are not easily seen in the uninflamed eye, but as soon as the eye becomes congested three quite separate vascular plexuses become readily visible.

1. **Bulbar conjunctival plexus**
   This is the most superficial plexus of fine hair-like interlacing vessels freely moveable over the underlying structures. Overlying the episclera the conjunctival arteries are derived from two sources the anterior ciliary arteries at the limbus, and the palpebral branches of the ophthalmic and lacrimal arteries. When they are inflamed the colour is bright red.

2. **Episcleral plexus**
   The vessels, which are straight and radially arranged, lie in the superficial episclera (parietal layer of Tenon’s capsule) at a depth of about one quarter to one-third of the distance between the surface of the conjunctiva and sclera (Graves, 1937). The visible vessels are mainly veins, accepting the aqueous veins at intervals around the globe.

   These vessels are moveable over the deep layers, although not so easily as the conjunctival vessels. In the anterior episcleral plexus (anterior to the equator and over the muscle) the vessels belong to the anterior ciliary system; while in the posterior episcleral arterial plexus (posterior to the equator) they are derived from the arteries of the oblique muscles, the posterior ciliary arteries, and the vessels of the...
optic nerve sheaths (Hayreh and Baines, 1972). When inflamed, these radially arranged vessels can easily be seen, giving the eye a salmon pink color.

3. Scleral (deep episcleral) plexus
This plexus consists of a rete (criss-cross) of vessels lying within the visceral layer of Tenon's capsule, closely applied to the sclera. At the limbus the superficial and deep episcleral plexuses merge into one another and terminate in the superficial marginal plexuses of the cornea. When congested this layer looks bluish-red in colour and is immobile.

Approximately 90% of scleritis cases involve the anterior portion of the sclera. (Fig 3) Posterior scleritis is defined as involvement of the sclera by inflammation posterior to the insertion of the medial and lateral rectus muscles. Subtypes of both anterior and posterior scleritis are recognized.

Anterior scleritis is classified into diffuse, nodular and necrotizing which is further divided into with or without inflammation. (Fig 4)
Diffuse anterior scleritis — Diffuse anterior scleritis is the most common and least severe form of scleritis, accounting for nearly 50% of cases. Most cases respond to relatively mild therapies and do not recur. (Fig 5a)
Nodular anterior scleritis — Nodular anterior scleritis is the second most common form of anterior scleritis, accounting for 20 to 40% of cases. Multiple attacks of scleritis occur in approximately 50% of these patients. (Fig 5b)

Necrotizing anterior scleritis — Necrotizing anterior scleritis is the least common but most dangerous subtype of anterior scleral inflammation. Compared with diffuse or nodular scleritis, this disorder occurs more frequently in women, has an older mean age of onset (average age 66 years), is more often associated with a systemic inflammatory illness, and is more likely to lead to ocular complications. Necrotizing anterior scleritis is further divided into two forms:

Necrotizing anterior scleritis "with inflammation" — This form of necrotizing anterior disease is highly symptomatic, with florid inflammatory features. (Fig 5c)

Scleromalacia perforans — Scleromalacia perforans, also known as necrotizing anterior scleritis "without inflammation", is a rare form of severe scleritis. The majority of these patients have longstanding histories of rheumatoid arthritis, granulomatosis with polyangiitis (aka Wegener’s Syndrome), or some other systemic inflammatory illness. (Fig 5d)

Scleritis is associated with a systemic disease in approximately 50% of cases. The most common association is with rheumatoid arthritis (RA). When scleritis complicates RA, it is generally considered to be a manifestation of rheumatoid vasculitis, heralding the need for an intensification of therapy. A number of other systemic disorders are associated with scleritis; among the primary vasculitides, granulomatosis with polyangiitis (Wegener’s Syndrome) is a much more common cause of scleritis than the other types of vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) such as microscopic polyangiitis and the Churg-Strauss Syndrome.

The distribution of causes of scleritis was evaluated in a review of 97 patients [2]. Rheumatic and infectious diseases accounted for all of the underlying systemic diseases. A rheumatic disease was present in 39%. These included rheumatoid arthritis (18%), vasculitis (7%), inflammatory bowel disease (5%), systemic lupus erythematosus (4%), and relapsing polychondritis (3%). An infectious disease was present in 8%. These included herpes zoster ophthalmicus (5%), herpes simplex (2%), human immunodeficiency virus (2%), and Lyme disease (1%).

Scleritis may first occur after ocular surgery, perhaps initiated by trauma to the sclera [5-7]. The risk may be greater in patients with underlying rheumatic disease [5,6].
Table 1: Systemic Diseases Associated with Scleritis

<table>
<thead>
<tr>
<th>Connective Tissue Diseases</th>
<th>Infections</th>
</tr>
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<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Reactive Arthritis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>Lyme Disease</td>
</tr>
<tr>
<td>Relapsing Polychondritis</td>
<td>Herpes Zoster</td>
</tr>
<tr>
<td></td>
<td>Aspergillus</td>
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</table>

Table 2 shows an introduction to the vasculitides, including the vasculitis affecting the large, medium or small vessels. The most practical way to classify the vasculitides is according to the size of the predominant vessels that are affected. Large-vessel vasculitides involve the aorta and its branches; medium-vessel vasculitides affect medium-size and small arteries of the kidneys, liver, heart, brain, muscles, and GI tract; and small-vessel vasculitides predominantly target capillaries and postcapillary venules. In terms of scleritis, the small vessel vasculitis is highly associated. Just like the ANCA-related Churg-Strauss syndrome. For large vasculitis, the one that we know well is Giant Cell Arteritis or Temporal Arteritis. Vasculitides may be primary or occur secondary to drug treatment, connective tissue diseases, infections, or malignancies. They may involve multiple organs (systemic) or be limited to a single organ. Idiopathic and drug-induced cutaneous vasculitis, giant cell arteritis (GCA), and Wegener granulomatosis (WG) are the vasculitides seen most frequently in North America.

Table 2: Classification of the Vasculitides

<table>
<thead>
<tr>
<th>Vessel Size</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>Giant Cell Arteritis, Takayasu Arteritis</td>
<td>Ankylosing Spondylitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection (syphilis, tuberculosis)</td>
</tr>
<tr>
<td>Medium</td>
<td>Polyarteritis Nodosa, Kawasaki Disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary CNS Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Small (ANCA-related)</td>
<td>Wegener Granulomatosis, Microscopic Polyangiitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Churg-Strauss Syndrome</td>
<td></td>
</tr>
<tr>
<td>Small (Non-ANCA-related)</td>
<td>Henoch-Schonlein Purpura, Cryoglobulinemic Vasculitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic Cutaneous Vasculitis</td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Connective Tissue Diseases (SLE, RA, Sjogren Syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection (Hepatitis C, HIV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoplasia (Hematological, Solid)</td>
</tr>
</tbody>
</table>

**ANCA: anti-neutrophil cytoplasmic antibodies; SLE: Systemic Lupus Erythematosus; RA: Rheumatoid Arthritis**
Although the ocular complaints and findings are the most prominent disease feature for many patients with scleritis, critical clues to the presence of a systemic inflammatory condition may be present on the general history and physical examination. (Fig 7)

The clinician must question the patient directly through a careful review of systems about constitutional symptoms (such as weight loss, shaking, chills, fever, and vomiting) and other organ system involvement. In addition, the clinician must examine with particular care the skin, joints, ears, nose, mouth, heart, lungs, and peripheral nerves, as these organs are often affected by the types of systemic disorders associated with scleritis.

The precise steps in the pathophysiology of most forms of scleritis are not well defined, largely because most patients do not undergo ocular biopsy or enucleation at a time when active, untreated disease is present. (See Fig 8) One report evaluated conjunctival and scleral biopsies from 25 patients with necrotizing scleritis and five with recurrent non-necrotizing scleritis [8]. The patients with necrotizing scleritis had histopathologic evidence of vasculitis, with fibrinoid necrosis and neutrophil invasion of blood vessel walls and immune complex deposition.

In rheumatoid vasculitis, which is often associated with necrotizing scleritis, immune complex deposition within the vessel wall leads to fibrinoid necrosis, thrombotic occlusion of blood vessels, and the generation of a chronic inflammatory response in the sclera [9]. The scleritis is usually characterized by granulomatous inflammation adjacent to or involving the scleral blood vessels.

The vasculitides are defined by the presence of inflammatory leukocytes in vessel walls with reactive damage to mural structures. Loss of vessel integrity may lead to bleeding. Compromise of the lumen leads to downstream tissue ischemia and necrosis. In general, affected vessels vary in size, type, and location in association with the specific vasculitic disorder. Vasculitis may occur as a primary process or may be secondary to another underlying disease [1]. The exact mechanisms underlying these disorders are unclear. Three different pathogenic models of disease have been advanced to help explain why the lesions of a particular vasculitic syndrome are only found in specific vessels [2]:

● The distribution of the antigen responsible for the vasculitis determines the pattern of vessel involvement.
The recruitment and accumulation of the inflammatory infiltrate is determined by the endothelial cell, including the expression of adhesion or other receptor molecules, the secretion of peptides and hormones, and the specific interaction with inflammatory cells. Some endothelial cells are therefore able to attract inflammatory cells, while others are not.

Non-endothelial structures of the vessel wall are involved in controlling the inflammatory process. In addition to the endothelial cells that provide costimulatory function, other cellular components serve as antigen-presenting cells and contribute pro-inflammatory mediators.

It is likely that elements of each model contribute to the pathogenesis of these diseases. The vasculitides are often serious and sometimes fatal diseases that require prompt recognition and therapy. Symptomatic involvement of affected organs may either occur in isolation or in combination with multiple organs. The distribution of affected organs may suggest a particular vasculitic disorder, but significant overlap is observed.

Fortunately, available treatments are helpful, particularly in the acute phase. However, during maintenance therapy with glucocorticoids and immunosuppressive agents, the adverse effects of drugs and superimposed infections may assume increasing importance. Mortality data suggest that, while early deaths in vasculitis are due to the active disease, late deaths may be due to the complications of therapy [3].

Classically, the vasculitic syndromes have been categorized by the predominant sizes of the blood vessels and types of vessels most commonly affected among patients with the disorder [4,5]. The presence or absence of anti-neutrophil cytoplasmic antibodies (ANCA) has been added to proposed classification criteria [6,7]. Table 3 summarizes the demographic characteristics of 807 patients with vasculitis.

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>% with disorder</th>
<th>Mean age at onset</th>
<th>% Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyarteritis Nodosa</td>
<td>15</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)</td>
<td>3</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (Wegener’s)</td>
<td>10</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td>12</td>
<td>47</td>
<td>54</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura (IgA vasculitis)</td>
<td>10</td>
<td>17</td>
<td>46</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>26</td>
<td>69</td>
<td>75</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>8</td>
<td>26</td>
<td>86</td>
</tr>
<tr>
<td>Other vasculitis, type unspecified</td>
<td>16</td>
<td>44</td>
<td>55</td>
</tr>
</tbody>
</table>


One quick note is that scleritis is associated with Wegener’s Syndrome. We have 10% of vasculitis disorder, with a mean age of 45, and affecting about 37% are females. Another one of our interest, in terms of a true emergency, is Giant Cell Arteritis, which as you can see is 26% of the vasculitis, age of onset is much older (69), and tends to affect more females (75%). These are very interesting statistics.

**Small vessel vasculitis**

Eosinophilic granulomatosis with polyangiitis — EGPA, also called Churg-Strauss syndrome, and allergic granulomatosis and angiitis, is a vasculitis of the medium and small-sized muscular arteries and is often
found with vascular and extravascular granulomatosis. The vasculitis classically involves the arteries of the lung and skin, but it may be generalized.

Granulomatosis with polyangiitis (Wegener’s Syndrome) — GPA, is a systemic vasculitis of the medium and small arteries, as well as the venules and arterioles. It typically produces granulomatous inflammation of the upper and lower respiratory tracts and necrotizing, pauci-immune glomerulonephritis in the kidneys. GPA is usually associated with ANCA.

Microscopic polyangiitis—Microscopic polyangiitis or polyarteritis is a vasculitis that primarily affects capillaries, venules, or arterioles. Involvement of medium- and small-sized arteries may also be present. This disorder is thought by some investigators to represent part of a clinical spectrum that includes GPA, since both are associated with the presence of ANCA and similar histologic changes outside the respiratory tract.

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause that can affect the skin, joints, kidneys, lungs, nervous system, serous membranes, and/or other organs of the body. Immunologic abnormalities, especially the production of a number of antinuclear antibodies (ANA), are another prominent feature of the disease. The clinical course of SLE is variable and may be characterized by periods of remissions and of chronic or acute relapses. Women, especially in their 20s and 30s, are affected more frequently than men.

Patients with SLE are subject to myriad symptoms, complaints, and inflammatory involvement that can affect virtually every organ [1,2]. The most common pattern is a mixture of constitutional complaints with skin, musculoskeletal, mild hematologic, and serologic involvement [1]. However, some patients have predominately hematologic, renal, or central nervous system manifestations. The pattern that dominates during the first few years of illness tends to prevail subsequently [3,4]. See Fig. 9 for a summary of symptoms commonly experienced by patients with SLE.

Anterior scleritis is usually readily apparent to both the patient and clinician and can be diagnosed and classified based upon its clinical features. By comparison, posterior scleritis is often less apparent and has variable clinical manifestations that may overlap with other clinical entities, such as inflammatory orbital "pseudotumor" [3,4].

Scleritis is usually associated with a severe, constant boring pain that worsens at night or in the early morning hours and radiates to the face and periorbital region. The extraocular muscles insert into the sclera, which explains why ocular movements exacerbate the pain associated with scleral inflammation. The pain generally limits activity and often prevents sleep. Additional symptoms include headache, watering of the eye, ocular redness, and photophobia.
The essential sign of scleritis is edema, usually accompanied by violaceous discoloration of the globe and tenderness. All vascular layers of the sclera may be involved, but the maximal involvement is in the deep episcleral vascular plexus, which is displaced outward by the edematous, swollen sclera. On slit-lamp examination, there is profound dilation of the deep episcleral vascular plexus. With the use of 10% phenylephrine, as you may have seen in my episcleritis web CE presentation, the episcleral vessels tend to constrict with episcleritis, and we get minimal constriction with scleral vessels. This is why 2.5% or 10% phenylephrine may be used to differentiate between the two closely-related entities.

Diffuse anterior scleritis is associated with widespread ocular erythema and scleral edema but no nodules or areas of necrosis, as can be seen in Figure 10 above. Only a small number of patients with diffuse anterior scleritis have disease that progresses to more aggressive forms.

Table 4: Features of the ocular exam differentiating between Scleritis and Episcleritis

<table>
<thead>
<tr>
<th>Examination</th>
<th>Episcleritis</th>
<th>Scleritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>In daylight</td>
<td>Salmon pink</td>
<td>Purple/grey choroid</td>
</tr>
<tr>
<td>Slit-lamp (red-free)</td>
<td>Yellow patch</td>
<td>Scleral edema, vessels, avascular patches</td>
</tr>
<tr>
<td>10% phenylephrine</td>
<td>More constriction</td>
<td>Minimal constriction</td>
</tr>
</tbody>
</table>

Nodular anterior scleritis (Fig 11) presents with localized areas of firm, tender edema associated with intense dilation of the deep episcleral vessels. With treatment, the pain and scleral tenderness resolve rapidly; however, the nodules may persist for months.

Necrotizing anterior scleritis (Fig 12) — Symptoms of necrotizing anterior scleritis with inflammation include severe ocular and periorbital pain that steadily worsens to excruciating levels over days or weeks. The pain is boring in quality, and usually worse in the early morning hours. Physical examination reveals scleral edema with intense vasodilation of the deep episcleral plexus and superficial vessels. With advanced disease, slit lamp examination reveals obvious blood vessel closure associated with thinning of the sclera and a bluish discoloration, representing the underlying choroid visible through thinned scleral tissue.

Patients with this form of scleritis may also develop concurrent corneal ulceration and inflammation as a manifestation of peripheral ulcerative keratitis (PUK) as shown in Figure 12.

Scleromalacia perforans (Fig 13), commonly bilateral, is characterized by a remarkable lack of symptoms, particularly an absence of pain. The absence of pain results from the necrosis of pain fibers. Patients may notice a change in color of their sclera because of scleral thinning. They may also experience a decrease in vision caused by a change in the shape of the eyeball and an alteration of corneal curvature (an acquired astigmatism). Examination reveals thinning and atrophy of the episclera and loss of the normal episcleral vasculature. The anterior sclera develops localized tissue infarctions that have a yellowish-white color often referred to as “marbleized.” Spontaneous perforation of the globe is rare, but reported.
Symptoms of posterior scleritis may include variable amounts of pain, often severe, that is difficult to localize. Diplopia and pain upon eye movement are common. In addition, these patients may have reduced vision due to compression of the retina or optic nerve.

When posterior scleritis occurs in association with anterior scleritis, the eye is red. However, when posterior scleritis occurs in isolation, the eye is white. In this setting, the examiner may observe inflammation of parts of the posterior sclera only at extremes of the patient’s gaze.

Signs of posterior scleritis include exudative retinal detachment, annular choroidal detachment, optic disc edema, retinal folds, choroidal folds, retinal vasculitis, posterior uveitis, and glaucoma. Posterior scleritis was diagnosed based on the typical T sign on B-scan ultrasonography examination, in association with suggestive clinical findings on fundus examination. (Fig 14)

Because of the delays inherent in diagnosing an inflammatory process focused behind the eye and the proximity of posterior scleral inflammation to sensitive ocular tissues (ie, the retina and optic nerve), posterior scleritis usually requires the types of intensive immunosuppressive therapy used in necrotizing anterior scleritis.

In addition to the sclera, other ocular tissues may be involved in scleral inflammatory disease:
Cornea — Chronic inflammation at the limbus can result in collagenolysis, epithelial ulceration, and the rapid development of peripheral ulcerative keratitis (PUK). In severe cases of PUK, the syndrome of "corneal melt" may lead swiftly to irreversible loss of vision in the eye [10].

Uveal tract — Anterior uveitis occurs in up to 40% of eyes involved by scleritis and may lead to additional management considerations, for instance, the use of glucocorticoid eye drops. This is thought to be primarily a form of "spillover" inflammation, rather than a primary involvement of the uveal tract.

Posterior segment — Posterior scleritis may be associated with vitritis, cystoid macular edema, and exudative retinal detachment.
Lens — Cataract formation is related to the severity of the scleritis. It primarily occurs in necrotizing scleritis, affecting approximately 20% of such patients. The incidence of cataract is much lower (less than 5%) with other subtypes of scleritis. Glucocorticoid therapy may be a contributor to cataract formation.

Selected investigations should be guided by findings from the history and general physical examination. Both routine and specialized serologic assays are important in the evaluation of patients with scleritis. (Table 5)

The following routine tests are useful in excluding systemic disease:

- **Complete blood count** — Patients with systemic inflammatory conditions frequently have abnormalities of the white blood cell count, platelet count, or hematocrit.
- **Serum chemistry profile** — This should include creatinine, blood urea nitrogen, electrolytes, albumin, total protein, and aminotransferases.
- **Urinalysis with microscopy** — Urinalysis with microscopic examination of the urine sediment is essential to excluding glomerulonephritis, a common occurrence in some of the systemic diseases associated with scleritis, particularly granulomatosis with polyangiitis (Wegener’s) and systemic lupus erythematosus.
- **Acute phase reactants** — Patients with scleritis associated with a systemic illness are likely to have extremely high acute phase reactants. Both the erythrocyte sedimentation rate and serum C-reactive protein should be checked. These markers may also be useful in following responses to therapy and in detecting disease flares.

**Blood tests targeted to specific systemic inflammatory diseases associated with scleritis include:**

- **Rheumatoid factor** — A positive rheumatoid factor assay is a nonspecific result, but extremely high titers of rheumatoid factor are usually found in the setting of rheumatoid vasculitis.
- **Antibodies to cyclic citrullinated peptides** — Antibodies to cyclic citrullinated peptides (anti-CCP antibodies) have a high specificity for rheumatoid arthritis.
- **Antineutrophil cytoplasmic antibodies** — Antineutrophil cytoplasmic antibody (ANCA) assays are positive in most patients with granulomatosis with polyangiitis (Wegener’s) or microscopic polyangiitis and in a smaller proportion of patients with the Churg-Strauss syndrome. Patients with inflammatory bowel disease may also have ANCA.

If an immunofluorescence assay for ANCA is positive in either a cytoplasmic or perinuclear pattern (ie, C-ANCA or P-ANCA), then further investigation through specific enzyme immunoassays is important. Among the vasculitides, only antibodies to proteinase-3 for (C-ANCA) or myeloperoxidase (one of a variety of P-ANCAs) have specific associations with granulomatosis with polyangiitis (Wegener’s), microscopic polyangiitis, and the Churg-Strauss syndrome. Patients with inflammatory bowel disease typically have P-ANCAs that are directed against non-myeloperoxidase antigens, assays for which are not widely clinically available.
Antinuclear antibody testing – Antinuclear antibody (ANA) testing is useful for the exclusion of connective tissue diseases related to systemic lupus erythematosus. A strongly positive ANA assay should be followed by a rheumatology consultation and possibly by additional serologic testing to determine the specific disease responsible for the ANA positivity. The additional testing may include serum complement levels (C3, C4), antibodies to double-stranded DNA, and antibodies to the Ro, La, Sm, or RNP antigens.

A variety of imaging studies may contribute to the assessment of scleritis. Some are important for the diagnosis of systemic diseases associated with scleritis, while others are essential to the full assessment of scleritis itself. (Fig 15) A chest x-ray is performed to exclude infiltrates and nodules that might be associated with vasculitis, sarcoidosis, or infections such as tuberculosis. Abnormal findings on chest x-ray should be defined further with a computed tomography (CT) examination of the lungs.

Imaging to evaluate scleritis — Several types of imaging studies are useful in the evaluation of scleritis:

- Ultrasonography — B-scan ultrasonography can confirm the scleral thickening that is the hallmark of the disease. Imaging of the posterior pole is a critical aspect in the diagnosis of posterior scleritis.
- Cross-sectional imaging — CT and magnetic resonance imaging may be needed to exclude orbital lesions, particularly in cases of granulomatosis with polyangiitis (Wegener’s), which may be complicated by orbital pseudotumors [13].
- On rare occasions, a tissue biopsy is performed for the purpose of diagnosis. The usual indication for episcleral biopsy is for the exclusion of an infiltrative process such as sarcoidosis or a lymphoproliferative disorder. Larger procedures are occasionally required to diagnose the nature of a retrobulbar mass.

Treatment Guidelines

Treatment of scleritis always requires systemic therapy with nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, or other immunosuppressive drugs. In one study, 67% of patients required either high-dose glucocorticoids or the combination of high-dose glucocorticoids and another immunosuppressive agent to control the disease [1].

In some patients, particularly those with peripheral ulcerative keratitis or scleromalacia perforans, surgical intervention is required to preserve vision or prevent globe rupture. Treatment must be individualized according to the severity of the patient’s disease. As an example, patients with either necrotizing anterior scleritis or posterior scleritis require more intensive therapy than those who present with non-necrotizing disease of the anterior [2]. The presence of a systemic inflammatory illness may also dictate an intensive course of therapy, even if the particular subtype of scleritis would normally call for a more benign treatment approach.
It is absolutely essential that scleritis be managed by an ophthalmologist expert in the care of these patients and by a rheumatologist experienced in employing and managing the immunosuppressive therapies required to treat ocular inflammation.

In the absence of systemic disease features that dictate the overall approach to therapy, two major principles guide the treatment of scleritis: The diffuse and nodular subtypes of anterior scleritis (Fig 10 and Fig 11, respectively) have a reasonable likelihood of responding to NSAIDs alone. If the clinician’s sense is that a more aggressive approach is required from the outset, or if NSAIDs fail to control the scleral inflammation, most of these patients respond to high-dose prednisone.

Necrotizing anterior scleritis or posterior scleritis (Fig 12 and Fig 14 [bottom], respectively) are more likely to be associated with permanent ocular complications and should be treated aggressively. Most cases in recent decades have been treated with cyclophosphamide, as well as high-dose glucocorticoids, but concern about the adverse effects of cyclophosphamide and the success of rituximab-based regimens in treating systemic conditions often accompanied by scleritis (such as rheumatoid arthritis and granulomatosis with polyangiitis [Wegener’s]) have made rituximab plus glucocorticoids often the initial treatment of choice.

NSAID therapy is primarily recommended for patients with the diffuse and nodular subtypes of anterior scleritis (Fig 10 and Fig 11). There are few data on which to base the choice of a specific NSAID for the treatment of scleritis. The clinical impression of some investigators is that indomethacin may be more effective than other available NSAIDs [1]. We suggest indomethacin (25 to 75 mg PO three times daily). NSAID treatment should be continued for as long as there is evidence of scleral inflammation. Side effects of NSAIDs and treatment failures may limit the duration of indomethacin use.

Patients with the diffuse and nodular subtypes of anterior scleritis who fail initial NSAID therapy and those with necrotizing anterior scleritis or posterior scleritis (Fig 12 and Fig 14 [bottom]) should be treated with glucocorticoids.

Based upon clinical experience, we suggest initial therapy with prednisone (1 mg/kg per day, up to a maximum daily dose of 80 mg). This regimen is continued for the first four to six weeks of therapy with ongoing assessment of the clinical response. The initial prednisone dose should not be continued beyond six weeks (and usually only four weeks) because of the potential for glucocorticoid-related morbidity. If patients have not demonstrated signs of clinical improvement within four to six weeks, an additional immunosuppressive agent must be considered.

There is no standard tapering regimen for scleritis, but regimens similar to the one outlined in Figure 16 are often used. Assuming that a patient begins prednisone at 60 mg/day and remains on this dose for four weeks, the following taper will require a total of 24 weeks to reach a daily dose of 5 mg:

The prednisone dose is tapered by 10 mg each week until a dose of 40 mg/day is reached.
After one week on 40 mg/day, the prednisone dose is tapered by 5 mg each week until the dose reaches 20 mg/day.

After one week on 20 mg/day, the prednisone dose is tapered by 2.5 mg each week until the dose reaches 10 mg/day.

After one week on 10 mg/day, the prednisone dose is tapered by 1 mg every two weeks until the dose reaches 5 mg/day.

The patient should be monitored carefully during the tapering period, watching for signs of recurrent scleritis or the development of inflammatory disease in other organ systems. Sometimes what appears at presentation to be idiopathic scleritis turns out to be the harbinger of a multiorgan system disease. Continuation of the prednisone taper can be considered if the patient has achieved and maintained good disease control. Tapering off prednisone completely should not proceed faster than 1 mg/day decreases every two weeks. Deviations from this regimen are often necessary if patients develop glucocorticoid myopathy or experience disease flares.

Immunosuppressive therapy in addition to glucocorticoids is generally given. There is persistent inflammation after two to three weeks of treatment. There is progression of disease to a more severe variant (for instance, the evolution of diffuse anterior scleritis into the necrotizing subtype). There are no randomized trials in scleritis on which to base the choice of the specific immunosuppressive medication. However, because of the proven effectiveness of both rituximab and cyclophosphamide in patients with granulomatosis with polyangiitis (Wegener’s), the first-line immunosuppressive medication in the treatment of scleritis is typically one of these agents.

Options other than rituximab or cyclophosphamide for patients with milder disease in need of a steroid-sparing agent include cyclosporine, mycophenolate mofetil, and methotrexate. Mycophenolate mofetil has primarily been studied as a steroid-sparing agent, with variable efficacy [4,5], and may also be used as maintenance therapy; methotrexate has been used in a similar fashion.

A response of scleritis to therapy is evidenced initially by resolution of pain, which can be rapid and dramatic. Even for patients with severe disease who require cyclophosphamide and prednisone, a disease response should be evident within two weeks of starting therapy.

Scleritis has a high potential for causing permanent disease-associated morbidity. Some degree of permanent vision loss occurs in approximately 10% of patients with anterior diffuse scleritis, 25% with nodular scleritis, and 75 to 85% with necrotizing scleritis or posterior scleritis [1,18].

Table 6 on the following page summarizes the cardinal features for different subtypes of episcleritis and scleritis for easy comparison and reference. I recommend printing this table and keeping it for your own reference.
Conclusion

The patient with active scleritis is at significant risk for losing sight. Ocular comorbidities are common with scleritis, as are systemic side effects from the treatments. Additionally, scleritis may be a sign of ongoing active inflammation at non-ocular sites, and a sign that the underlying disease process needs more aggressive management. Remember, up to 50% of patients with scleritis have an underlying systemic illness, usually a rheumatic disease. A lab workup is important to help identify underlying systemic disease. Up to 25% of patients may present with ocular symptoms before an underlying systemic cause is diagnosed, so we may be the first health care provider to diagnose the underlying disease.

The treatment of scleritis varies according to disease subtype. A team approach involving the rheumatologist and the ophthalmologist is often required for optimal management of these patients. Usually it is a good idea for a primary eye care provider to have a working relationship with a local rheumatologist and a uveitis specialist, because when it comes to scleritis, most likely we will not be managing the patient long-term, but we should work with the specialist in a co-management situation.

Thank you very much for your attention, and I hope to see you again, soon.

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