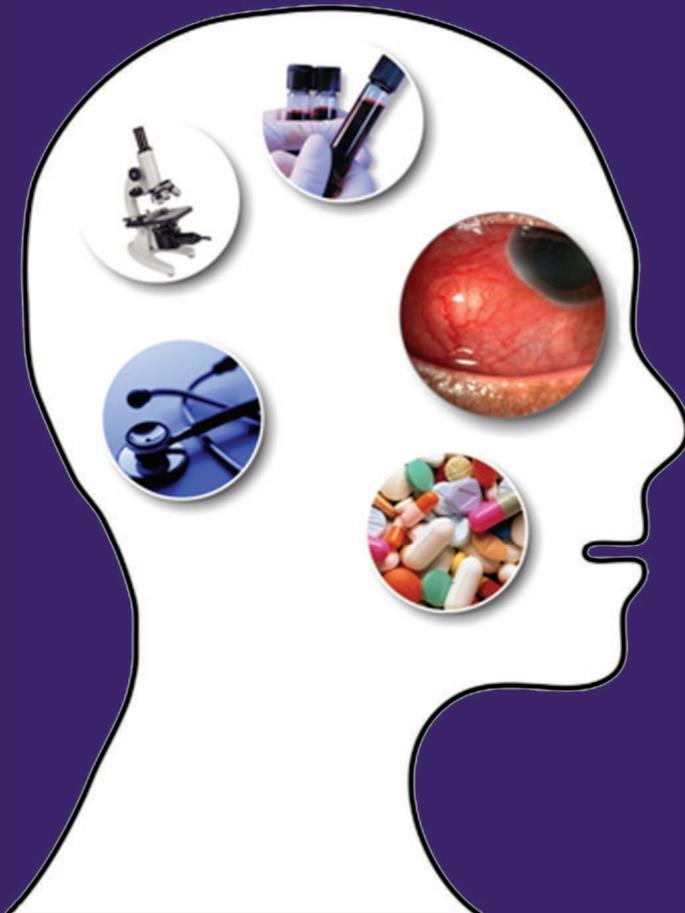


AIOS, CME SERIES (No. 29)



# Scleral inflammations: An update



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# Sclearal inflammations: An update



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# Foreword

Scleral inflammations are common occurrence in general ophthalmology practice. One cannot effort to ignore any form of sclera inflammation.

Dr. Jyotirmay Biswas has vast experience in Uveitis and scleritis, has made very good attempt in crafting the CME Series on Scleral inflammations. While going through each chapter, one can understand the need to have clarity about the disease process, symptomatology and clinical presentation of Scleral inflammations. Dr. Biswas has brought out the clinical features excellently, for easy understanding and diagnosing various scleral inflammations.

Investigations to find out the aetiology and underlying systemic conditions, at times life threatening, is very essential and this was nicely elucidated in this CME series. Management in terms of etiologic factors infections & foreign body can be straight forward, however, most scleral inflammations needs good knowledge of anti-inflammatory and anti-metabolic agents. This aspect is very well covered. Overall, this CME series on Scleral inflammations has turned out to be a very useful exercise. We appreciate the efforts of Dr. Biswas for this master piece.

Dr. Ajit Babu Majji, as Chairman Academic and Research Committee, did a commendable job, in bringing out very useful CME series, one after the other.



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## Preface

Uveitis is a very common clinical presentation in ophthalmic practice. One needs to have good knowledge about the ocular as well as systemic etiologies of uveitis, to deal effectively with patients presenting with uveitis. Scleral inflammations, both infective & non-infective, are much more challenging. Dr. Jyotirmay Biswas, who is expert in the field, was chosen to handle the task of bringing out a CME series on Scleral Inflammations.

This CME series was crafted very well by Dr. Biswas. He has made the clinical presentations of different forms of Scleral inflammations very simple, so that every Ophthalmologist can diagnose. Good knowledge of systemic diseases causing sclera inflammations as well as investigations is vital. While going through the chapters, one will understand very well about it. Dr. Biswas has given good guidelines for management of sclera inflammations, so that, every Ophthalmologist can follow-up a patient. As Dr. Biswas correctly pointed out, one should know, when we are dealing with the infective etiology, as for most sclera inflammations treatment is either steroids or immunosuppression, but for infective etiology, steroids are contra indicated.

Hope this CME series on sclera inflammations, helps you all to a great extent, in your day to day practice.



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# Section I

## Anatomical perspective

The term sclera is derived from Greek word “scleros” meaning “hard”. Sclera is an opaque, elastic, and resilient tissue of the eye. It can be compared to an incomplete shell comprising approximately 90% (five-sixths) of the outer coat of the eye. Anteriorly it begins at the limbus and terminates at the optic nerve canal posteriorly.

The human sclera is white in color. In children, a bluish hue is observed because of the extremely thin sclera which allows the visibility of underlying choroid. In older age the sclera may appear slightly yellowish because of the deposition of fat. Human sclera is thickest near the optic nerve, where it is approximately 1 mm in thickness and thinnest at the insertion of extra ocular muscles (0.3 mm).

**Human beings are the only primates with white sclera.**

The episclera is the thin densely vascularized layer of connective tissue overlying the sclera and situated below the tenon’s capsule. Apart from the vessels and unmyelinated nerve fibers, it contains bundles of collagen. Anteriorly episclera blends with subconjunctival tissues and tenon’s capsule 1 to 3 mm behind the limbus. It becomes very thin and indistinct posterior to the equator. Scleritis is always accompanied by an overlying episcleritis. On the other hand, episcleritis per se is very rarely associated with scleritis.

Ultrastructurally, sclera is composed of collagen bundles, elastic fibers, fibroblasts and ground substances. These ground substances are proteoglycans and glycoproteins. Collagen bundles in sclera are of varying sizes and are irregularly arranged – the reason why sclera is not transparent like cornea. The scleral fibroblasts play an important role in synthesis and organization of collagen, proteoglycans and glycoproteins.

The episclera receives its blood supply from the anterior ciliary arteries, anterior to the insertions of the rectus muscles and the long and short posterior ciliary arteries. Scleral stroma is relatively avascular and receives its blood supply mainly from the episcleral vascular bed and, to some extent from the underlying choroidal vasculature. The sclera contains numerous channels or passages through which the arteries, veins and nerves pass. These channels or passages are known as emissary canals.

- Sclera is a relatively avascular structure except for some vessels that pass through the emissary canals.
- The low vascularity of sclera can be explained by the low metabolic demand of the tissue because of the slow turnover rate of its collagen and cells.
- Scleritis occurs more commonly anterior to the equator because of the more abundant anterior vascular supply.

The circulation overlying the sclera can be divided into three vascular layers.<sup>1,2</sup> The location, configuration of vessels and their clinical significance is tabulated in Table-I and shown in the Fig. I.

**Table I**

| Vascular plexuses                    | Locations  | Vessels   | Mobility of vessels       | Colour (when inflamed) | Clinical importance   |
|--------------------------------------|--|---|---------------------------|------------------------|---|
| <b>Conjunctival plexus</b>           | Most superficial                                 | Arteries are tortuous and veins are straight.   | Freely mobile             | Bright red             | Congested in conjunctivitis. Blanches with topical vasoconstrictor.   |
| <b>Superficial episcleral plexus</b> | Lies at the level of Tenon's capsule             | Vessels are straight with radial configuration. | Mobile over deeper layers | Salmon pink            | Congested in episcleritis. Blanches with topical vasoconstrictor.     |
| <b>Deep vascular plexus</b>          | Lies deep to the Tenon's capsule and over sclera | Vessels are arranged in criss-cross pattern.    | Immobile                  | Violeaceous            | Congested in scleritis. Does not blanch with topical vasoconstrictor. |

Sclera is richly supplied with nerves. The posterior ciliary nerves enter the sclera near the optic nerve. The anterior part of sclera is mainly innervated by the two long posterior ciliary nerves and posterior part receives nerve supply from numerous short posterior ciliary nerves. Direct damage to or the stretch of these nerves is the cause for severe pain in scleritis.<sup>3</sup> And because of the insertion of the extra ocular muscles in sclera, the eye movement increases the intensity of pain in scleral inflammation.

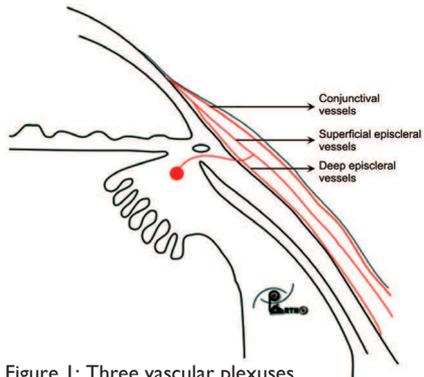


Figure I: Three vascular plexuses

## Section 2

### Classification of scleral inflammation and Episcleritis

The classification system proposed by Watson and Hayreh is widely accepted.<sup>3</sup> Broadly scleral inflammations can be divided into the episcleritis and scleritis. Both episcleritis and scleritis are recurrent inflammation. Though episcleritis is a benign, self-limiting disease, scleritis almost always requires systemic therapy. Scleritis can be divided into anterior and posterior scleritis. Anterior scleritis has been classified into four subgroups: diffuse, nodular, necrotizing with inflammation and necrotizing without inflammation. Necrotizing scleritis without inflammation is also called scleromalacia perforans. The outline of scleral inflammations has been summarized in figure 2.

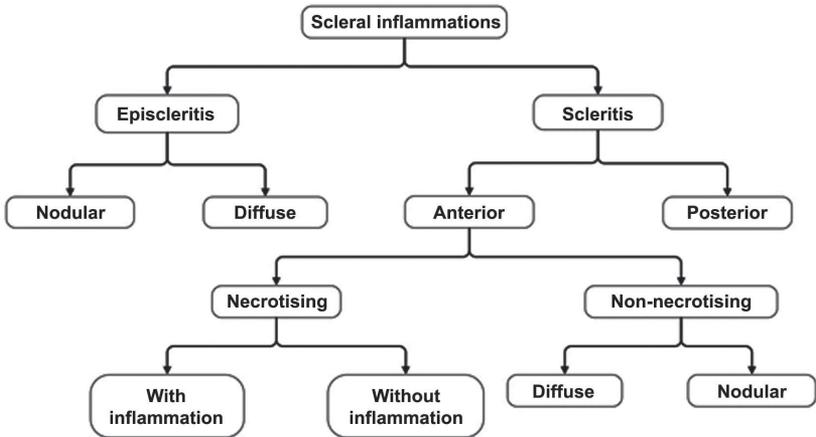


Figure 2: Outline of scleral inflammations

Since sclera is mainly dependent on episclera providing a response to an inflammatory stimulus, scleritis is almost always accompanied with overlying episcleritis. However episcleritis is usually not associated with scleritis.

Episcleritis can be differentiated from the scleritis on certain clinical features. The distinguishing features between episcleritis and scleritis are highlighted in table 2.

**Table 2**

| <b>Episcleritis</b>  | <b>Scleritis</b>  |
|--|---|
| Usually redness, irritation are the main presenting symptoms   | Severe excruciating pain, which deteriorates at night and often wakes up the patient from sleep, is the main symptom. |
| Nil or minimal tenderness  | Moderate to severe tenderness   |
| Congested vessels are bright red in color and vessels can be moved easily with the help of cotton bud. | Congested vessels are purple red in color and vessels cannot be moved easily with cotton bud.                         |
| Blanching of vessels occurs with 10% phenylephrine   | Blanching of vessels does not occur with 10% phenylephrine  |

## Episcleritis

Episcleritis was first called “subconjunctivitis” by von Graefe, then subsequently “Hot eyes” by Hutchinson. The name “episcleritis” was first used by Fuchs, who described the condition as “episcleritis periodica fugax” in 1895.

Episcleritis is seen more frequently in young to middle-aged women. The chief complaint of patients with episcleritis is usually ocular redness with or without irritation. The redness typically persists for 24-72 hours and then resolves spontaneously. Rarely, patients may experience more severe redness and mild pain. Episcleritis occurs most commonly in the exposed zone of the eye and is generally recurrent in nature. More than one-third of patients have bilateral disease.

Half of the episcleritis cases are idiopathic in nature. Systemic diseases associated with episcleritis are rheumatoid arthritis, relapsing polychondritis, Cogan’ syndrome, polyarteritis nodosa etc.<sup>4</sup> The majority of patients with episcleritis recover completely and have no residual changes. However, episcleritis can sometimes be associated with corneal involvement, uveitis, and glaucoma.

Careful examination with slit lamp and meticulous history is usually sufficient for the diagnosis of episcleritis. Episcleritis is diagnosed clinically by the presence of inflamed episcleral vessels, which typically radiate from the limbus, have a salmon pink color in natural sunlight, can be moved over the deeper sclera with a cotton tipped applicator and will blanch with topical phenylephrine 10%.<sup>3</sup>

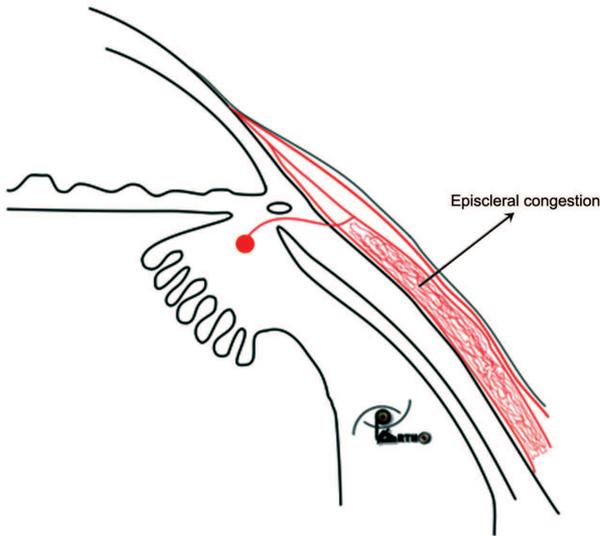


Figure 3: Episcleritis

Episcleritis is classified as diffuse or nodular. A localized mobile nodule develops in nodular episcleritis. (Figure 3)

### **Treatment of episcleritis:**

Usually episcleritis is a self-limiting, benign inflammation, whether treated or not, it will resolve in 10 to 21 days. If the condition is recurrent, medications such as topical nonsteroidal anti-inflammatory drugs (NSAIDs) like flurbiprofen, bromofenac and nepafenac or topical weaker corticosteroid like loteprednol, fluomethalone are often required to control this milder variety of scleral inflammation. However, prolonged use of topical corticosteroid should be avoided because of its potential side effects. It should be kept in mind that though simple episcleritis resolves spontaneously and rapidly, resolution of nodular episcleritis is much slower and may require oral medications. Systemic medications like oral NSAID and very rarely oral corticosteroids are required in the treatment of indolent episcleritis.<sup>5,6</sup>

Nodular episcleritis resolves slowly, responds slowly to topical therapy and often may require systemic medications

## Section 3

### Scleritis

Scleritis is a severe inflammation of the scleral tissue. This painful inflammatory condition is characterized by edema and cellular infiltration of the sclera and episclera. If not treated properly and well in time, it can cause a significant threat to vision.

Scleritis affects women more often than men, with a peak incidence in the fifth decade. It frequently starts in one eye and becomes bilateral in more than half of the cases.<sup>7</sup> Bilaterality is more commonly encountered in scleritis associated with systemic rheumatic disorders.

#### **Causes of scleritis:**

The causes of scleritis can be broadly divided into following categories

**Idiopathic:** Most of the time scleral inflammation starts with disturbances in equilibrium of scleral specific antigens towards collagen or glycosaminoglycan, the ground substances of sclera. These autoimmune reactions are usually idiopathic and mostly mediated by type IV delayed type of hypersensitivity reaction.

**Systemic rheumatic diseases or collagen vascular disorders:** Half of patients with scleritis have evidence of an underlying systemic disease. Scleritis can be a presenting manifestation of a life-threatening systemic autoimmune disease. Rheumatoid arthritis is the most common systemic condition associated with scleritis. The incidence of rheumatoid arthritis in patients with scleritis ranges from 10 to 33%.<sup>4,7</sup> Scleral inflammations in such systemic rheumatic disorders are mostly due to vascular involvement which results from deposition of circulating immune complexes in superficial and deeper episcleral vessels.

**Infectious:** Endogenous spread of microorganisms can give rise to scleral infections. Neurotropic viruses like Herpes viruses can invade the scleral nerves and causes scleral inflammation. Infectious scleritis has been discussed under a separate section of this book.

**Surgery induced scleritis (SINS):** SINS was first described in 1976 by Arensten et al.<sup>14</sup> SINS is a rare but serious complication of ocular surgery. It has been reported with most types of ocular surgeries. SINS typically occurs after surgery as intense scleral inflammation associated with necrosis near the site of scleral incision. This dreaded variety of post-surgical scleral

inflammation is commonly associated with peripheral ulcerative keratitis. The condition has a poor prognosis with chances of scleral perforation and therefore early diagnosis and rapid management is very essential.

### Systemic association of scleritis<sup>4,7,10,11,12,13</sup>

Rheumatoid arthritis.  
Relapsing polychondritis,  
Systemic lupus erythematosus and antiphospholipid syndrome  
Wegener's granulomatosis  
Polyarteritis nodosa  
Cogan syndrome  
Juvenile idiopathic arthritis  
Ankylosing spondylitis  
Ulcerative colitis  
Polymyositis  
Sarcoidosis

### Drug induced scleritis

The following drugs have been reported to cause scleral inflammations:

1. **Bisphosphonates/diphosphonates** are potent inhibitors of osteoclasts, prevent the loss of bone mass, and used to treat osteoporosis and similar diseases. Examples include alendronate, risedronate, zoledronic acid medronate
2. **Erlotinib hydrochloride** is a drug used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer. It is a reversible tyrosine kinase inhibitor.
3. **Procainamide Antiarrhythmic Agents**  
These drugs have been reported to cause scleritis and episcleritis but the incidence is so low, they can still be prescribed safely in people with ocular inflammatory disease.

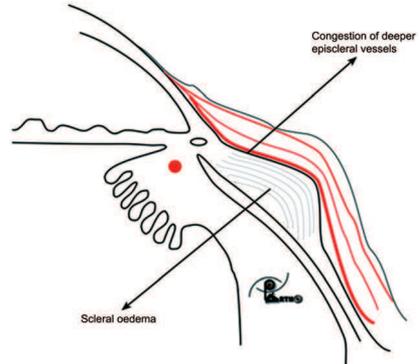
Most of these drug induced scleral inflammations can be managed with NSAIDs and discontinuation of the drug.

### Diagnosis of scleritis:

Diagnosis of scleritis is almost always clinical; however when the posterior sclera is involved, clinical signs may be less obvious, and imaging studies are required to confirm the diagnosis. Patients with anterior scleritis presents with redness and pain. The onset is usually gradual, extending over several

days. Ocular pain is severe and typically dull and boring (piercing) in nature, exacerbated by eye movement, and occasionally may worsen at night and waken the patient from sleep. The pain often radiates to the ear, scalp, face, temple and jaw.

The sine qua non of scleritis is the presence of scleral edema and congestion of the deep episcleral plexus (figure 4). Slit-lamp examination using red-free light is extremely helpful in determining the pattern and depth of episcleral vascular congestion and engorgement.



There is tenderness of the globe. In scleritis, the sclera assumes a violaceous hue in natural sunlight.

Figure 4: Scleritis is characterized by the presence of scleral edema and congestion of the deep episcleral plexus

It is very important to examine patients in daylight with the unaided eye to note the subtle color differences of the vessels. Also inflamed scleral vessels have a crisscross pattern. They are adherent to the sclera and can't be moved with a cotton-tipped applicator. Engorged scleral vessels cannot be blanched with 10% phenylephrine, whereas phenylephrine easily blanches engorged vessels in the superficial episcleral and conjunctival plexuses.

It is very important to examine patients in daylight with the unaided eye to note the subtle color differences of the vessels.

### Grading of scleritis:

Many authors have tried to devise a standardized grading system for clinical evaluation as well as severity of the inflammation and response to treatment. Based on the common clinical signs of scleritis, McCluskey and Wakefield proposed a scoring system for the extent and severity of the disease.<sup>14</sup> However, their grading system has taken more account of clinical course and response to treatment rather than clinical activity, specifically severity of the disease. Sen *et al* proposed a grading system based on their cross-sectional interobserver agreement study on National Eye Institute's digital photo archive. The high resolution photographs were taken after application of 10% phenylephrine and scleral inflammation was graded as follows:<sup>15</sup>

| <b>Grading</b> | <b>Description</b>  |
|----------------|---|
| 0              | No scleral inflammation with complete blanching of vessels  |
| 0.5            | Trace inflammation with minimally dilated deep episcleral vessels   |
| 1              | Mild scleral inflammation with diffuse mild dilatation of deep episcleral vessels   |
| 2              | Moderate scleral inflammation with tortuous and engorged deep episcleral vessels  |
| 3              | Severe scleral inflammation with diffuse significant redness of sclera and obscuration of deep episcleral vessels with edema and erythema |
| 4              | Necrotizing scleritis with or without uveal show  |

### **Complications of scleritis:**

Despite of rapid and effective treatment scleritis can have various complications, some of which can give rise to significant ocular morbidity.<sup>17</sup> The complications are summarized below:

- Scleral thinning
- Staphyloma formations
- Corneal thinning
- Scleral rupture/perforations
- Glaucoma
- Uveitis
- Phthisis bulbi
- Cataract

## Section 4

### Anterior scleritis

Anterior scleritis is the most common form of scleral inflammation. As discussed in section 2, anterior scleritis can be broadly divided into non-necrotizing scleritis and necrotizing scleritis. Non-necrotizing scleritis is the most common form of anterior scleritis, which can be further divided into nodular and diffuse varieties. The relative frequency of occurrences of various subtypes of scleritis in various large series has been summarized in table.<sup>3</sup>

| Subtypes of scleritis                                 | Reported frequency |
|---|--------------------|
| Diffuse scleritis                                     | 40-83%             |
| Nodular scleritis                                     | 16-44%             |
| Necrotizing scleritis (with and without inflammation) | 6-15%              |

### Non-necrotizing scleritis: nodular & diffuse scleritis

Diffuse scleritis denotes diffuse involvement of scleral inflammation which is characterized by congestion of deeper episcleral plexuses and scleral oedema (figure 5 & 6). Often it starts with sectoral congestion to involve the entire sclera. The patients complain of photophobia and excruciating pain, which often wakes them up from sleep. There is almost always tenderness of the globe of varying degree. Signs of uveal tract inflammation in the form of anterior chamber reaction can be observed in some patients. Corneal involvement e.g. corneal infiltrates, peripheral corneal ulcerations, thinning of peripheral cornea are also seen in such patients. Raised intraocular pressure can occur from spread of the inflammation to the underlying trabecular meshwork.



Figure 5: Non-necrotizing scleritis: diffuse variety



Figure 6: Non-necrotizing scleritis: diffuse variety (note the deeper episcleral vessels involvement)

Nodular anterior scleritis is characterized by a localized area of scleral edema and congestion of the scleral vessels. The scleral nodule is deep red to purple in color, immobile, tender on palpation and separated from the overlying episcleral tissue, which is elevated by the nodule (figure 7). The lack of necrosis within the nodule and the localization of inflammation within the borders of the nodule differentiate this form from necrotizing anterior scleritis with inflammation. All of the vascular layers overlying the nodule are displaced forward. Sometimes, multiple nodules may be present.<sup>7, 8,9,10</sup>

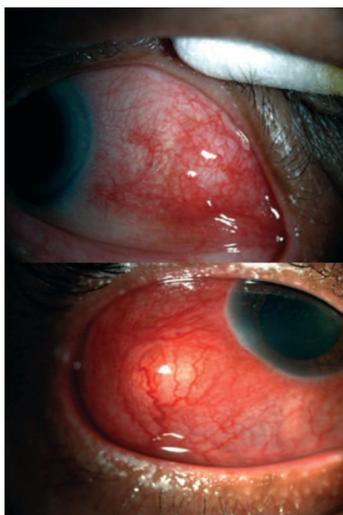


Figure 7: Non-necrotizing scleritis: Nodular variety

## **Necrotizing anterior scleritis with inflammation**

It is the most severe of all the types and carries a potential threat to visual loss. It is often seen in patients with rheumatoid arthritis. The condition is bilateral in 60% of cases. The patient presents with severe pain and tenderness out of proportion to inflammatory signs. Examination reveals white, avascular areas of localized scleral edema and congestion, the edges of these lesions are more inflamed than the center (Figure 8). Gradually underlying uveal tissue becomes visible as the sclera becomes thin and translucent. The condition has been found to be due to vasculitides secondary to immune complex deposition and results in shut down of the episcleral vascular bed. Because of the ectasia of the sclera, staphylomas are frequently seen. If not treated, the necrotizing scleritis may spread to the equator and circumferentially and can involve the entire globe.<sup>17,18</sup>

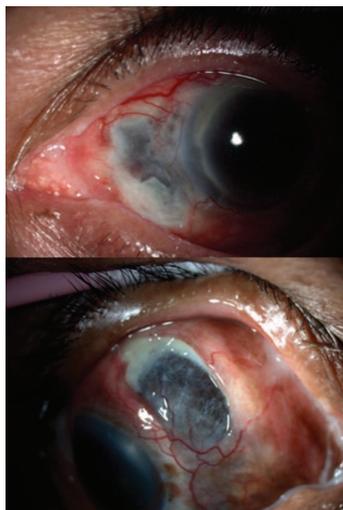


Figure 8: Necrotizing anterior scleritis with inflammation (Note the white, avascular areas)

## Necrotizing anterior scleritis without inflammation (Scleromalacia perforans)

Van der Hoeve first used the term scleromalacia perforans in 1934 to describe this variety of scleritis. Necrotizing anterior scleritis without signs of inflammation occurs predominantly in patients with long-standing rheumatoid arthritis. Though rare, the condition is vision threatening. The condition is characterized by minimal signs of inflammation and absence of pain. In early phase of the disease, patient may present with blurred vision because of astigmatism due to thinning and distortion of the globe.

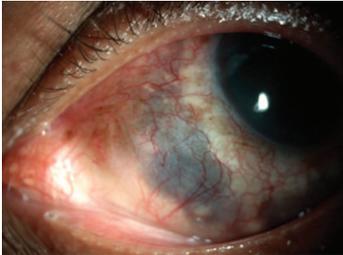


Figure 9: Necrotizing anterior scleritis without inflammation

As the disease progresses, the sclera progressively thins and the underlying dark uveal tissue becomes visible (figure 9). Staphylomas can develop during the course of scleral thinning. Peripheral corneal thinning is often seen, though direct corneal involvement is rare. Spontaneous perforation is rare but these eyes are prone to rupture with minimal trauma because of the extreme thinning of sclera.<sup>17,18</sup>

### **Scleromalacia perforans**

Minimal or nil signs of inflammations  
No pain unlike other subtypes of scleritis.  
Most commonly associated with rheumatoid arthritis.

# Section 5

## Posterior scleritis

“Posterior scleritis must be one of the most under diagnosed treatable conditions in ophthalmology, partly because its manifestations are so protean and partly because the diagnosis is rarely considered.”

*Peter Watson*

---

Posterior scleritis is defined as an inflammation of the sclera, posterior to the ora serrata. Posterior scleritis accounts for 2-12% of all scleritis cases. However actual number of incidence of this clinical entity is always underestimated because of the lack of diagnosis and vivid presentation of posterior scleritis.

### **Clinical Presentations:**

Patients with posterior scleritis present with pain, tenderness, proptosis, visual loss, and occasionally restricted motility, macular or paramacular edema choroidal folds, exudative retinal detachment, papilledema, and angle-closure glaucoma secondary to choroidal thickening. Severe scleral inflammation of posterior segment can rarely manifest as proptosis or diplopia. Many a times the posterior scleral thickening leads to altered refractive status – decrease in myopia or increase in hypermetropia and often misdiagnosed as refractive error. Posterior scleritis may occur in association with anterior scleritis or may be isolated.<sup>19</sup> Posterior scleritis, with anterior scleritis is relatively easy to diagnose.

The fundus picture of posterior scleritis is varying and confusing. Few common presentations are:

- Circumscribed mass or swelling at the posterior pole (figure 10)
- Chorioretinal folds, retinal striae with nil or minimal sub retinal fluid (SRF) (figure 11)
- Optic nerve head involvement with peripapillary SRF (figure 12)
- Exudative retinal detachment (figure 11)
- Choroidal detachment

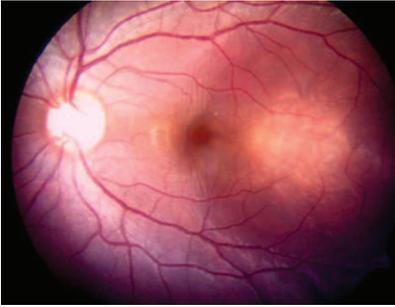


Figure 10: Posterior scleritis : presenting as a circumscribed mass at posterior pole

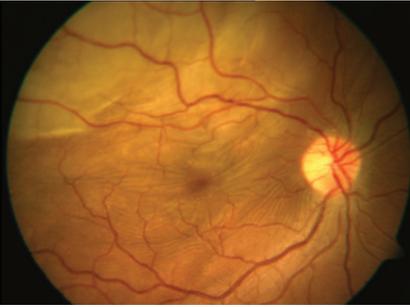


Figure 11: Posterior scleritis : presenting with exudative retinal detachment, chorioretinal folds and retinal striae

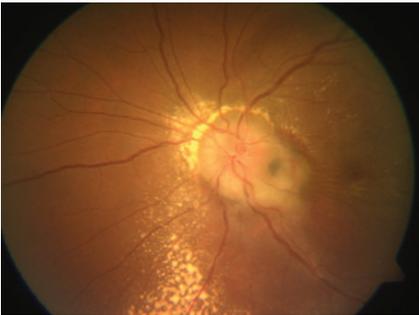


Figure 12: Posterior scleritis: involvement of optic nerve head with peripapillary SRF

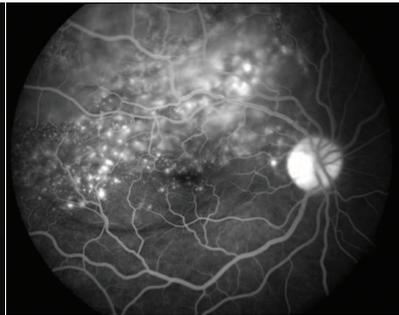


Figure 13: Fundus fluorescein angiogram of fundus shown in figure 11. Note the pin head leaks.

### Ancillary investigations:

**Fundus fluorescein angiogram:** Fundus fluorescein angiogram though aid in diagnosis of posterior scleritis, the findings of the angiogram is not specific for this clinical entity. Angiogram in a case of posterior scleritis with sub retinal fluid shows pinhead leak in early phases and leakage of dyes in late phases of angiogram (figure 13). Similar pattern of angiogram can also be encountered in Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, punctate inner choroidopathy, choroidal malignant melanoma and various other conditions. However it is helpful in cases with sub retinal fluid in posterior pole, allowing one to differentiate multifocal leak central serous chorioretinopathy from posterior scleritis. The treatments of these conditions are paradoxical – while in the former one needs to avoid steroid, the latter responds well to oral steroid. However in posterior scleritis presenting with choroidal folds, scleral mass does not show any leakage of dye and fundus fluorescein angiogram in such cases are of limited value.

## Ultrasonography:

Ultrasonography B-Scan of eye is considered as one of the most helpful ancillary investigation in diagnosis of posterior scleritis. Ultrasonography in a case of posterior scleritis shows thickening of the posterior coats of the eye and retrobulbar oedema (figure 14). Widening of the subtenon space with T-sign is often observed in cases with posterior scleritis.

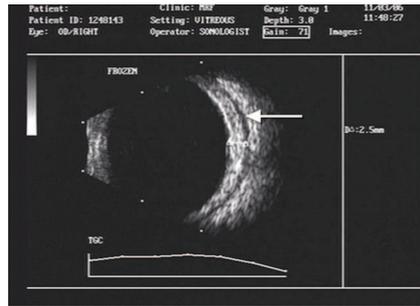


Figure 14: Ultrasound B scan in a case of posterior scleritis

**Computed tomography and magnetic resonance imaging:** These modalities of investigations, though rarely used for the diagnosis, can aid in the diagnosis in difficult situations. An infiltration of extraocular muscles in the region of the posterior scleritis may lead to retraction of the lower lid in the upper gaze.<sup>19,20</sup>

## Differential diagnosis of posterior scleritis:

The following conditions commonly mimic posterior scleritis<sup>7,19,20</sup>

- Malignant melanoma of choroid
- Metastasis to choroid
- Choroidal haemangioma
- Uveal effusion syndrome
- Vogt-Koyanagi-Harada syndrome
- Central serous chorioretinopathy
- Cystoid macular oedema

The differential diagnoses of these clinical conditions are discussed in the table below:

| <b>Parameters of differentiation</b>                 | <b>Posterior scleritis</b>  | <b>Malignant melanoma of choroid</b>  | <b>Metastasis to choroid</b>                           | <b>Choroidal haemangioma</b>   |
|--|---|---|--|--|
| Age  | Middle age, can occur in young                                    | Old age group   | Middle aged and older group                            | Middle aged and older group  |
| Laterality   | Unilateral  | Unilateral  | Unilateral   | Unilateral   |
| Pain   | Moderate to severe  | Rare  | Rare   | Rare   |
| External appearance                                  | Can present with anterior scleritis                               | Can present with dilated episcleral vessels   | Normal   | Normal   |
| Inflammation in anterior chamber & anterior vitreous | Seen  | No  | No   | No   |
| Posterior pole mass                                  | Greyish orange coloured, associated with choroidal/retinal striae | Dark pigmented elevated ovoid mass lesion, can be amelanotic  | Yellowish white mass, no choroidal/retinal striae seen | Well defined red-orange, slightly elevated dome shaped lesion usually located at the posterior pole. Sometimes associated with SRF |
| Fundus fluorescein angiogram                         | Multiple pin head leak which gradually show pooling of dyes       | Mottled hyperfluorescence in the early phase with increased staining of the mass lesion in the late phase of the angiogram. Larger melanomas may show double circulation – simultaneous filling up of the normal retinal vessels and the tumor vessels. | Multiple small leaks                                   | Early stippled hyperfluorescence with late leakage of the dye and staining of the tumor.   |
| Ultrasonography                                      | Thickening of the posterior sclera, retrobulbar oedema            | Choroidal mass with low internal reflectivity and choroidal excavation  | Moderately high reflectivity                           | High internal reflectivity   |

| <b>Parameters of differentiation</b>                 | <b>Uveal effusion syndrome</b>       | <b>Vogt-Koyanagi-Harada syndrome</b>                                      | <b>Central serous chorioretinopathy</b>                          | <b>Cystoid macular oedema</b>                 |
|--|--------------------------------------|---|--|---|
| Age  | Middle aged                          | 20-50 years   | 30-50 years  | Middle to older age                           |
| Laterality   | Bilateral                            | Bilateral   | Unilateral   | Unilateral                                    |
| Pain   | Minimal                              | No  | No   | No  |
| External appearance                                  | Congestion                           | Ciliary congestion  | Normal   | Normal  |
| Inflammation in anterior chamber & anterior vitreous | Can be seen                          | Present   | No   | No  |
| Clinical findings in posterior pole                  |                                      |   |  |   |
| Fundus fluorescein angiogram                         |                                      | Multiple pin head leaks which gradually enlarges and show placoid pooling | Usually single leak which shows ink blot or smoke stack pattern. | Shows characteristic flower petal appearance. |
| Ultrasonography                                      | Choroidal detachment with thickening | Shows choroidal thickening  | Not contributory   | Not contributory                              |

## Section 6

### Infectious scleral inflammation

Scleritis with purulent exudates or infiltrates should raise the suspicion of an infectious etiology. Formations of granulomas or fistulas, painful nodules, conjunctival and scleral ulcers are often seen in infectious scleral inflammations. Infectious scleritis accounts for 5-10 % of all cases of scleritis.<sup>21,22</sup>

One must be careful while treating the infectious scleritis, as diagnosis of such cases are difficult and presentations are same as immune mediated scleritis. While oral steroid and Immunosuppressives are known to cause rapid resolution of immune mediated scleritis, it worsens or deteriorates infectious scleritis.

#### Common causative organisms:

Most of the literature reported *Pseudomonas aeruginosa* as the most common cause of infectious scleritis, though many of the cases were post-surgical most commonly after pterygium excisions. Endogenous spread of bacteria, fungi<sup>23</sup> (*Aspergillus*), viruses (Herpes simplex or H. zoster) or parasites (*Toxocara*, *Toxoplasma*, *Onchocerca*) are reported to cause infective scleritis. Also infections of adjacent tissues like the conjunctiva; cornea may involve the sclera by contiguous spread. In chronic cases, possibility of a foreign body must be ruled out.

#### Tips to diagnose a case of infectious scleritis (figure 15,16)

- Scleritis with purulent exudates or infiltrates
- Scleritis associated with scleral or conjunctival ulcers.
- Scleritis associated with visible pus points or scleral abscesses
- Scleritis associated with hypopyon

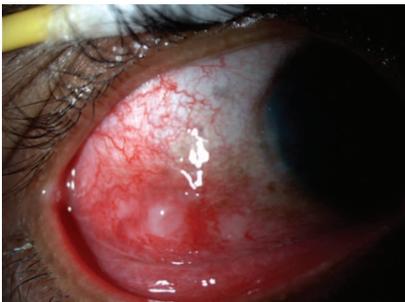


Figure 15: Infectious scleritis with puspoint



Figure 16: Infectious scleritis: presentation with scleral abscess

Infectious scleritis has been reported to occur more commonly in sclera damaged by injury or surgical trauma. It can occur in patients with scleritis due to systemic rheumatic diseases as a superadded infection following prolonged immunosuppressive therapy. Infectious scleritis has been reported most commonly after pterygium excision. Adjuvant therapies like mitomycin C and beta radiation have shown to increase the risks of infection. *Pseudomonas aeruginosa* has been reported to be the most common pathogen in such cases.

### **Spread of infection from adjacent structures:**

Corneal infections or conjunctival infections<sup>25</sup> can spread to the adjacent sclera and cause Sclerokeratitis. Bacterial infections of cornea are most common to spread, but infections by virus, fungus and parasite too. Patients on long-term immunosuppressant or patients with acquired immune deficiency syndrome are more prone to fulminant form of such Sclerokeratitis.

Few reported examples are:

- *Pseudomonas aeruginosa*<sup>24</sup>
- *Staphylococcus aureus*<sup>25,26</sup>
- *Streptococcus pneumoniae*<sup>27</sup>
- *Mycobacterium chelonae*<sup>27</sup>
- *Herpes simplex*<sup>28</sup>
- *Herpes zoster*<sup>29</sup>
- *Aspergillus*<sup>23,30</sup>
- *Acanthamoeba*<sup>31,32</sup>

### **Infectious Scleritis after surgical intervention:**

#### **Post scleral buckling surgery:**

Scleral infections associated with scleral buckle can be seen and the clinical presentations are varying. The patients complain of varying degree of redness, pain and discomfort. Scleral abscess, purulent discharge, conjunctival granulomas can be seen. Though rare, “bloody tears” or haemolacria can be seen in some patients.<sup>34</sup> Extrusion of buckle, endophthalmitis can occur. The most common organisms causing scleral buckle infection are coagulase positive and coagulase negative Staphylococci species.<sup>33,35</sup>

#### **Post-ptyerygium excision:**

Scleral infections after pterygium excision are usually associated with the application of mitomycin-C or  $\beta$ -irradiation.<sup>36,37</sup> However, infective scleritis was reported following bare sclera technique without these adjunctive therapies also.<sup>38,39</sup> *Pseudomonas aeruginosa* is the most common organism found in infectious scleritis following pterygium excision.

## Herpetic scleritis

Though rare, the sclera can be involved in primary varicella zoster and in herpes zoster ophthalmicus and is usually associated with some form of corneal involvement. Involvement of the vessels with ischemia is common. Scleritis and episcleritis occur in 8% of the cases with herpes zoster ophthalmicus.<sup>29</sup> Association of viruses in infectious scleritis has been reported by various authors. Most of the time, herpetic scleritis is unilateral, acute in presentation with moderate-to-severe pain and associated uveitis or keratitis. Scleral biopsy is a helpful tool for diagnosis in such cases and they responds well to oral acyclovir therapy.<sup>40</sup> Scleral infection in herpes simplex is rare and most of the times associated with milder inflammation of the perilimbal sclera.

## Syphilitic scleritis

Syphilitic scleritis is rare and usually inflammation is restricted to episclera in such patients. Often they are associated with interstitial keratitis. Though the exact pathogenesis of syphilitic scleritis is not clear, the positive serological tests in patients, response to anti-microbial therapy, and absence of collagen vascular diseases indicates direct role of spirochete.

## Mycobacterial scleritis

Mycobacterium tuberculosis related scleritis is thought to be due to hypersensitivity reaction to mycobacterial protein rather than direct role of the microorganism. Most of the time, such scleral inflammation is of anterior nodular variety.<sup>41,42</sup> Often multiple scleral nodules are seen.

## Fungal scleritis: (figure 17)

Fungal infectious scleritis are devastating cause of infectious scleritis. They are most difficult to diagnose because of their varied clinical picture and most of the time lead to loss of the eye in spite of all treatment. The reported incidence of fungal scleritis varies; 11 to 38 % of total infectious scleritis cases.<sup>43,44</sup>

Case series from India on infectious scleritis showed relatively higher

incidences of fungal involvement which can be attributed to the hot and humid climate and higher prevalence of fungal spores in the environment.<sup>44,45</sup>

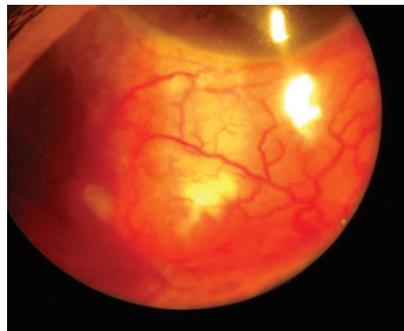


Figure 17: Fungal scleritis (candida)

Like other infectious scleritis, the treatment of fungal scleritis is frustrating and requires rapid and aggressive multidrug fungal therapy. Voriconazole, an azole antifungal, is a promising therapy in patients refractory to standard antifungal agents. The topical and oral voriconazole is often used with capsosungin as both the drugs have synergistic activity and may be useful in severe form of fungal scleral infections. However, poor penetration of antifungals into the tightly bound collagen fibers of the scleral layer, allows fungi to remain in the intrascleral lamellae for a long time even after extensive antifungal therapy. Most of the diagnosis is delayed and lead to poor visual outcome. Scleral biopsy is required to confirm the diagnosis in such cases.

### **Treatment of infectious scleritis:**

Treatment of infectious scleritis is frustrating and cumbersome. Microbial invasion of the sclera is difficult to treat and eradicate, because of the poor penetration of various antimicrobial agents into avascular sclera. Combinations of topical and oral anti-microbial therapy along with surgical debridement are found to be effective in such cases. Most of the time diagnosis is delayed and patients are started on oral and topical steroid thinking of scleritis due to autoimmune or idiopathic reasons. Use of corticosteroids can lead to deeper penetration of the microorganism and detrimental outcome. Corticosteroids, given before adequate control of infection, in an infectious scleritis worsen the condition by inhibiting release of lysosomal enzyme. Debridement and sclerectomy, debulking necrotic tissue facilitates access of antimicrobial agents in such cases and is found to be useful. It is very important to surgically explore the scleral abscess that does not respond to antimicrobial therapy. However because of the recurrent nature of infections most of the cases in literature had been reported to have poor visual outcome.

#### **Treatment of infectious scleritis: tidbits**

- Differentiating infectious scleritis from non-infectious scleritis is of paramount importance because corticosteroid therapy and immunosuppressive therapy (used in noninfectious autoimmune scleritis) are contraindicated in active infections.
- Prior to microbiological determination of the causative organism and its antibiotic sensitivity spectrum, vancomycin or cephalosporins in combination with aminoglycosides usually are chosen.
- Any foreign body, if present, may need to be removed before the infection can be brought under control.

## Section 7

### Systemic diseases associated with scleral inflammation

The discussion on all the systemic diseases associated with scleral inflammation is beyond the scope of this chapter. We have tried to limit the discussion to few most common systemic rheumatic diseases/ collagen vascular disorders.

#### **Rheumatoid arthritis:**

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting about 1 percent of the population worldwide. It has a wide spectrum of disease manifestations and extra-articular involvement involving most organ systems is not uncommon. Women are affected three times more than men, mostly aged 40 to 60. There is some genetic predisposition conferred in a handful of specific HLA-DQ and HLA-DR alleles. Morning stiffness of the joints is the hallmark of the disease and probably the most widely noted presenting symptom.

#### **Rheumatoid arthritis : Quickie**

Symmetrical arthritis involving hand joints  
Early morning stiffness of the joints  
Characteristic skin nodules  
Characteristics joint deformities (figure 18)  
Rheumatoid factor, though not diagnostic, helpful.  
X-ray of joints

Episcleritis can be seen in 5% of patients with RA. RA is the most common systemic association of scleritis. 17 to 33% of all patients with scleritis have RA and 0.2 to 6.3% of patients with RA have scleritis.<sup>4</sup> Patients with scleritis associated with RA more commonly have bilateral scleritis than patients with scleritis due to other systemic rheumatic diseases. Diffuse anterior scleritis is the most common subtype of scleral inflammation seen in patients with rheumatoid arthritis.



Figure 18: Joint deformities in rheumatoid arthritis

Scleromalacia perforans is a very rare type of scleritis that is due to obliterative endarteritis of the scleral vessels. It is seen exclusively in patients with longstanding rheumatoid arthritis. It is clinically silent and pain-free, and is becoming extremely rare with improved treatment for rheumatoid arthritis.<sup>4,46,47,48</sup>

**Wegener’s granulomatosis:**

Wegener’s granulomatosis (WG) typically involves small to medium sized vessels. It is characterized by formation of necrotizing granulomas within blood vessels. Anybody at any age can be affected.

| <b>Wegener’s granulomatosis: Quickie</b>   |
|--|
| Epistaxis, sinusitis<br>Hemoptysis<br>Hematuria<br>Cytoplasmic antineutrophil cytoplasmic antibody (ANCA) test |

Eye problems develop in about half of patients with Wegener’s granulomatosis. In 10% to 15% patients, ocular involvement may be the initial presentation of the disease. The orbit is most often involved, usually with resultant proptosis. This is the only systemic inflammatory disease that may present with proptosis, which is due to infiltration of the orbit with granulomatous tissue. Orbital inflammation or cellulitis can occur from extensive sinus involvement or secondary purulent sinusitis and in such cases; bony erosion of the ethmoid and nasal bones is common. Orbital involvement often results in compressive optic neuropathy and ophthalmoplegia.

Scleritis is common in patients with WG and sometimes it can be the presenting manifestation. Scleritis in WG is severe and can lead to permanent blindness. Scleritis, which is of necrotizing variety, often associated with peripheral corneal changes and indicates severe systemic involvement and the need for more aggressive immunosuppressive therapy.<sup>4,49,50</sup>

The antineutrophil cytoplasmic antibody (ANCA) test has been very helpful in the diagnosis of WG. The sensitivity of cANCA’s have been reported as high as 85-96% in patients with widespread Wegener’s granulomatosis. However, a positive ANCA should not be considered as sole definitive test for the diagnosis of WG and thorough systemic evaluation for systemic vasculitides under a rheumatologist is essential prior to initiation of any immunosuppressive therapy.<sup>50</sup>

### **Relapsing polychondritis:**

Relapsing polychondritis is an idiopathic small vessel vasculitides which predominantly affects cartilaginous structures of body namely, pinnacle of ear, nasal cartilage etc. Some of these patients have other coexisting connective tissue disorders.

| <b>Relapsing polychondritis: Quickie</b>  |
|---|
| Acute painful swelling of one or both pinnae.<br>Hoarseness of voice, cough, stridor or expiratory wheeze because of the involvement of tracheobronchial cartilage. |

Episcleritis and scleritis are frequently seen in patients of relapsing polychondritis.

### **Systemic lupus erythematosus:**

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder in which individuals produce self-directed antibodies. These antibodies cause widespread tissue and cell destruction by misdirected inflammatory response via the formation of immune complexes. Women, mostly in the childbearing years are four times more commonly affected than men.

| <b>Systemic lupus erythematosus: Quickie</b>   |  |
|--|--|
| Photosensitivity<br>Malar rash (characteristic butterfly pattern) figure 19<br>Non-erosive peripheral arthritis.<br>Pericarditis<br>Pleuritis<br>Antinuclear antibody test, though not specific, is a useful screening test<br>Raised anti-DsDNA |  |

Figure 19: Butterfly rashes in a patient of Systemic lupus erythematosus

Scleritis is seen in 5% of patients with SLE. Sometimes scleritis can be the initial presentation of SLE.

**Polyarteritis nodosa:**

Polyarteritis nodosa (PAN) is a necrotizing vasculitis of medium-sized arteries. Inflammation in this disorder is mediated by circulating immune complexes. Essentially all organs can be affected. Men are almost twice as affected as women, usually in the fourth to sixth decades.

| <b>Polyarteritis nodosa : Quickie</b>   |
|---|
| Constitutional symptoms - Fever, weight loss, malaise, arthralgias,<br>Lower extremity nodules and ulcerations,<br>Mononeuritis multiplex,<br>Intestinal angina (postprandial pain caused by the involvement of mesenteric vessels)<br>Perinuclear ANCA |

Scleritis in PAN has similar clinical picture to that seen in WG. Often episcleritis can be the initial presentation of PAN.

## Section 8

### Laboratory investigation in scleritis

Ideally all patients with scleritis should undergo a thorough systemic examination and serological investigation to rule out the presence of any systemic disease. Many a time scleral inflammation can be the initial manifestation of these systemic diseases and many of them can be life-threatening, the systemic evaluation in such patients can be rewarding. In this section we have tried to discuss the laboratory investigations of few systemically important clinical conditions.

#### **Routine blood investigations:**

Routine blood investigations like complete blood count (CBC), erythrocyte sedimentation rate (ESR), should be advised in all patients with scleritis. These blood investigations especially, blood count are of paramount importance, especially when planning for immunosuppressive treatment. Liver function tests, renal function tests, blood glucose levels are usually done to establish baseline normal levels and to monitor response to treatment when the patient is on steroids and immunosuppressives.

#### **Rheumatoid factor:**

Rheumatoid factor is an autoantibody directed against the Fc region of IgG. Rheumatoid factor and IgG join to form immune complexes that contribute to the disease process. Various immunoassays are available for detection of rheumatoid factor. The classic Rose-Waaler test is a hemagglutination test for rheumatoid factor in the serum, which depends on the ability of rheumatoid factor to agglutinate sheep erythrocytes coated with anti-sheep immunoglobulin. The latex agglutination test, in which latex particles coated with human IgG aggregate in the presence of IgM rheumatoid factor is also widely available. These tests identify only the IgM isotype of rheumatoid factor. Enzyme-linked immunosorbent assay (ELISA) can measure IgG, IgA, and IgM rheumatoid factors. It is important to mention here that some forms of rheumatoid arthritis like oligoarticular rheumatoid arthritis may be associated with a negative test for IgM rheumatoid factor but a positive test for IgG rheumatoid factor.<sup>51,52,53</sup>

#### **Antineutrophil cytoplasmic antibody:**

The antineutrophil cytoplasmic antibody (ANCA) test has been very helpful in the diagnosis of WG. Cytoplasmic antineutrophil cytoplasmic antibody (cANCA) is found to be more specific for WG than perinuclear antineutrophil cytoplasmic antibody (pANCA). The sensitivity of cANCAs

have been reported to be as high as 85–96% in patients with widespread Wegener's granulomatosis.<sup>51,52,53</sup>

### **Antinuclear antibodies:**

Antinuclear Antibodies (ANA) is usually the first investigation commonly ordered in case of clinical suspicion of systemic rheumatic diseases or collagen vascular diseases. The antinuclear antibody test is an indirect fluorescence reaction, which is largely dependent on the location of the target antigen. ANA can be considered as an ideal screening test for systemic lupus erythematosus (SLE) because of its simplicity and sensitivity which is approximately 95%.<sup>51,52,53</sup> However the test has low specificity as ANA can be found positive in healthy individuals and in many conditions other than SLE.

### **Diagnosis of SLE:**

Unlike ANA, antibodies to double-stranded DNA (dsDNA) and Anti-Sm (Smith) antibodies are specific for SLE. Anti-ribosomal antibodies are highly specific for the diagnosis of SLE, but they are less sensitive than anti-dsDNA or anti-Sm antibodies.<sup>51,52,53</sup>

### **Diagnosis of tuberculosis:**

Laboratory diagnosis of infectious scleritis due to mycobacterial infections is very difficult. However when suspected clinically, these patients should be investigated thoroughly. Tuberculin skin test or Mantoux test is an intradermal test based on the type IV hypersensitivity reaction for the diagnosis of latent TB. However it is not a definitive test for the diagnosis of tuberculosis and has several limitations like cross reactivity of the antigen used in the test with BCG and environmental nontuberculous mycobacterias, booster effect on repeated injection of PPD leading to false positive results etc.<sup>54</sup> A newer method of diagnosis of tuberculosis known as interferon gamma release assay (IGRA), measures helper T cell stimulated secretion of interferon gamma and are more specific than the tuberculin skin test.<sup>55</sup> Radiological imaging of like chest x-ray and high resolution computerized tomography (HRCT) has been found to be a useful boon in diagnosis of tuberculosis.

### **Diagnosis of sarcoidosis:**

Serum Angiotensin converting enzyme (ACE) and serum lysozyme are the most common parameters used for the laboratory diagnosis of sarcoidosis in common practice. They are measure of macrophage products produced by the sarcoid granulomas. However these tests are not fully specific for the disease and may be raised in various other systemic conditions. Definitive diagnosis of sarcoidosis is made by solid-tissue biopsy showing classic

noncaseating granulomas. Liver is one of the occult sites where sarcoid granuloma can occur and elevated liver enzymes are useful in diagnosis of sarcoidosis. Radiological evidence of bilateral hilar lymphadenopathy is considered as pathognomonic of this clinical entity.<sup>56,57,58</sup>

### **Diagnosis of syphilis:**

Various tests are available for the diagnosis of syphilis. Dark field microscopy provides direct identification of treponema pallidum with compound microscope with a dark field condenser. Serological tests include nontreponomal tests such as Venereal Disease Research Laboratory (VDRL) tests, rapid plasma reagin tests and treponomal tests like fluorescent treponomal antibody absorption FTA-ABS, microhemagglutination – T. pallidum (MHA-TP) assays detect antibodies against treponoma pallidum.

### **Laboratory diagnosis of infectious scleritis:**

Usually specimens from scleritis with ulcerative lesions are collected by scraping with the help of a surgical blade (no 15 blade attached to Bard Parker handle). This procedure can be carried out in outpatient department under topical anaesthesia. However in scleritis with scleral abscesses, nodular scleral nodules with visible pus points the specimens are collected from base of the lesions after dissecting conjunctiva and deroofing of the lesions. Such procedures are better carried out under peribulbar anaesthesia in the operating room and the surgeon must be ready to tackle the accidental inadvertent perforation while collecting the sample.

The sample thus obtained is microscopically examined using Gram's and Giemsa staining methods and potassium hydroxide (KOH) 10% or calcofluor white preparation. Fluorescent microscope is required to examine the slides with calcofluor white preparation. Gram's and Giemsa staining method and potassium hydroxide (KOH) preparation is relatively simple, easy and rapid and often gives useful information for initial of antimicrobial treatment in infectious scleritis. The sample material is also inoculated on various solid and liquid media which facilitate the growth of microorganisms and these include fresh blood agar, chocolate agar, Sabouraud's dextrose agar, non-nutrient agar with an overlay of Escherichia coli, thioglycolate broth and brain heart infusion broth etc.

## Section 9

### Medical Management of scleritis

The primary aim of the treatment of scleral inflammation is to control the inflammatory process to relieve the symptoms and thereby reduce the damage to the eye. However, the effective management of a case of scleral inflammation involves timely diagnosis, prevention of complications and identification of underlying systemic or local cause, if any.

#### Medical management:

Anterior non-necrotizing scleritis readily responds to topical steroid and systemic non-steroidal anti-inflammatory drugs (NSAIDs). Both non-selective COX inhibitors (e.g., flurbiprofen, indomethacin, and to a lesser extent ibuprofen) and the more selective COX-2 inhibitors have been used successfully. Sustained-release indomethacin 75 mg twice a day has been found to be very effective in controlling the inflammation. However, prolonged use of NSAIDs should be avoided in view of their significant side effect on long-term use.<sup>59,60</sup>

Corticosteroids are helpful in patients not responding to COX-inhibitors or those with posterior or necrotizing disease. A starting dose of 1 mg/kg/day is standard with weekly reduction by 10 mg/week until a dose of 40 mg/day is reached. After this dose is reached, the rate of reduction is individualized, according to the clinical findings and patients' response but is in the order of 5 mg/week until cessation or an acceptable maintenance dose is reached.

Intravenous corticosteroids are sometimes needed in patients who need aggressive management of the scleral inflammation for example in cases with threatened scleral or corneal perforation in necrotizing scleritis, which requires a rapid control of the inflammation.<sup>6,7,59,60</sup> The most commonly used drug is methylprednisolone. The usual dosage is 500 mg to 1 gm intravenous infusion with 0.9% normal saline or sodium lactate solution over 30 to 60 minutes daily for 3 consecutive days, followed by high dose of oral corticosteroids. Caution should be taken as intravenous methylprednisolone can cause cardiac arrhythmias and cardiovascular collapse. Intravenous methylprednisolone is usually followed by high dose oral steroid or immunosuppressive agent. (Figure 20)

Periocular application of steroid delivers the drug to the desired site and reduces the chances of side-effects associated with systemically administered corticosteroid. It can be administered by subconjunctival or subtenon route. However the role of periocular steroid in scleritis is controversial.

## Non necrotising scleritis

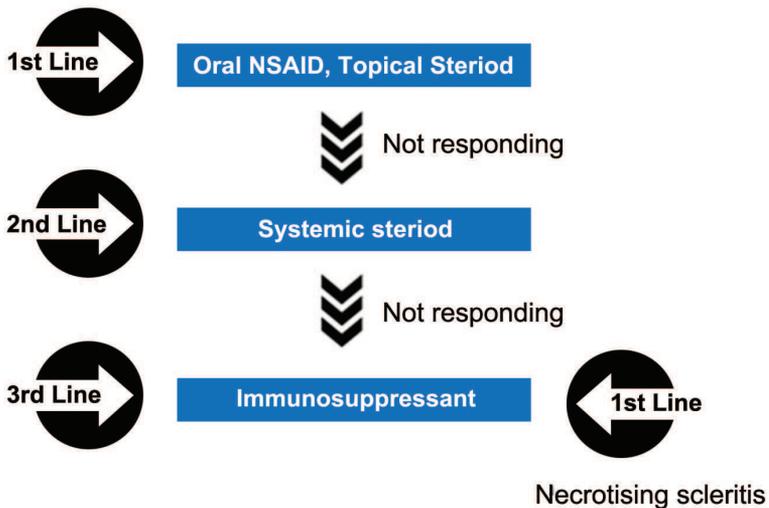


Figure 20: Medical management of scleritis

### CORTICOSTEROID THERAPY: AT A GLANCE

- Choice of route of administration of corticosteroid is governed by the type & site of intraocular inflammation.
- It is mandatory to rule out any infective aetiology before commencement of therapy
- Dosage of the drug is determined on the basis of clinical experience as the degree of inflammation is different in each patient so the treatment has to be individualized with the aim of using minimal effective dose for a minimal time.
- Before starting, a discussion on the various aspects of the corticosteroid therapy including the side effects is crucial.
- All the patients are to be monitored closely at frequent interval to assess the effects of therapy and detect the side effects as early as possible.
- Patient compliance is the most important for effective treatment of scleral inflammation.

Necrotizing scleritis, particularly associated with autoimmune diseases is difficult to treat and almost always requires systemic immunosuppressive therapy, not only for ocular involvement, also for life threatening systemic complications. For example prompt and effective immunosuppression

is required to control the necrotizing scleritis associated with systemic vasculitides like Wegener's granulomatosis because mortality is higher in this group of patients because of the systemic complications. This group of patients also requires a consultation with rheumatologist for their systemic ailments.

| <b>Indications for immunosuppressive therapy in scleral Inflammation</b>  |
|---|
| <ul style="list-style-type: none"><li>• Anterior necrotizing scleritis</li><li>• Posterior scleritis</li><li>• Scleritis associated with a systemic autoimmune disease or collagen vascular disease</li></ul> |

Various immunosuppressants have been tried for treatment of scleritis and these include antimetabolites (methotrexate, azathioprine, and mycophenolate mofetil), alkylating agents (chlorambucil and cyclophosphamide), T-cell inhibitors (cyclosporine and tacrolimus).

Methotrexate is commonly used to treat scleritis not responding to oral corticosteroid and less severe anterior necrotizing scleritis with inflammation. Often the drug is used as a first line treatment in patients in whom oral steroid cannot be started because of systemic ailments. Among steroid sparing immunosuppressives, methotrexate has gained the most widespread usage due to its relatively safe profile. Methotrexate, a folic acid analog, inhibits the enzyme dihydrofolate reductase and thus the production of thymidylate, which is essential for DNA replication. This results in the inhibition of rapidly dividing cells, including leukocytes. The drug is used with or without a short course of oral steroid in tapering dosage. Dosage of methotrexate is 0.1-0.5 mg/kg/week; low dose therapy is started at a dose of 7.5 mg/week and it can be increased up to 25 mg/week. Generally, it is given orally once a week. It has been observed that methotrexate immunosuppressive therapy is moderately effective. The drug takes months to achieve adequate tissue concentration for the therapeutic success. Severe side effects such as hepatotoxicity, cytopenias, and interstitial pneumonia are not uncommon.<sup>59,60,61</sup>

## Methotrexate

**Mechanism of action:** It is a folate analog. It inhibits the enzyme dihydrofolate reductase inhibiting the production of tetrahydrofolate which in turn inhibits formation of thymidylate, leading to inhibition of DNA replication & RNA transcription. It acts both on T & B cells. Methotrexate has little action on resting cells. It is mainly active against rapidly dividing immune cells.

**Dosage:** 0.1-0.5 mg/kg/week; low dose therapy is started at a dose of 7.5 mg/week and it can be increased up to 25 mg/week. Generally given orally once a week.

**Side effects:** Reversible hepatotoxicity, bone marrow suppression, dry cough and interstitial pneumonia

**Monitoring:**

- Complete blood count – monthly
- Liver function test (especially AST & ALT) – every 3-4 weeks

If parameters of the liver function test are elevated to twice the normal, dosage of the drug should be adjusted or stopped.

Azathioprine is another antimetabolite, which is often used as steroid sparing Immunosuppressives. Pasadhika et al have evaluated the use of this drug in scleritis patients. They used oral azathioprine in 27 eyes of 16 patients with scleritis and concluded that the azathioprine, as a steroid sparing immunosuppressive monotherapy, is moderately effective. In their study, sustained control of inflammation was observed in 29.9% of patients after tapering prednisone to less than 5 mg/day in one year.<sup>62</sup>

## Azathioprine

**Mechanism of action:** It is a purine nucleotide analog (competitive inhibitor of purine synthesis), which interferes with adenine and guanine ribonucleotides by suppression of inosinic acid synthesis. This in turn interferes with DNA replication & RNA transcription. Azathioprine is a prodrug which is metabolized in liver and converted to its active form 6-mercaptopurine. It is more effective in preventing proliferation of T cells than B cells. Although, antibody production is unaffected.

**Dosage:** 1.5-2.0 mg/kg/Day; given as single dose or twice a day schedule

**Side effects:** Bone marrow suppression with leucopenia & thrombocytopenia, hepatotoxicity

**Monitoring:**

- Total WBC count & platelet count – every 4 weeks
- Liver function test-every 3 months

If total WBC count falls below 3,500 cells/mm<sup>3</sup> or platelet count falls below 1 lakh/mm<sup>3</sup>, dosage of the drug should be adjusted or stopped.

Mycophenolate mofetil is an immunosuppressive agent that selectively inhibits the proliferation of lymphocytes sparing other proliferating cells. Mycophenolate mofetil has been also used for the management of scleritis. However the drug alone is not sufficient in control of acute scleritis and requires additional immunosuppressants. The drug can be used as maintenance therapy in controlled scleral inflammations.<sup>63</sup>

**Mycophenolate Mofetil**

Mycophenolate Mofetil is derived from the fungus *Penicillium stoloniferum*

**Mechanism of action:** It inhibits purine metabolism. It inhibits the enzyme inosine monophosphate dehydrogenase, which in turn inhibits the synthesis of guanosine thereby affecting the proliferation of B & T lymphocytes. Mycophenolate Mofetil is a prodrug which is metabolized in liver and converted to its active form mycophenolic acid.

**Dosage:** 1000 mg twice a day, available as 250 mg & 500 mg capsules

**Side effects:** Weight loss, gastrointestinal upset and bone marrow suppression. Mycophenolate Mofetil has lower side effects than other antimetabolites because they don't interfere with the salvage pathway of purine synthesis.

**Monitoring:**

- Complete blood count- every month
- Liver function test (specially AST & ALT) every month

Treatment of scleritis associated with necrotizing systemic vasculitis should be prompt and effective. Treatment in such patients should be guided both by the ophthalmic response and control of the underlying disease. Most of the time immunosuppressives are required in such cases. Cyclophosphamide is an effective immunosuppressive drug used in patients with necrotizing scleritis associated with systemic vasculitis like Wegener's granulomatosis, relapsing polychondritis, polyarteritis nodosa etc. Antineutrophil cytoplasmic antibody test is a useful laboratory parameter to monitor therapeutic response in patients with Wegener's granulomatosis. Cyclophosphamide in a dose of 100 mg per day (2 mg/kg/day) orally and tapered monthly, should be the first choice in treating patients with associated potentially lethal

vasculitic diseases. Concomitant administration of prednisone at a dose of 1 mg/kg/day may be needed. Oral corticosteroids can usually be tapered and often discontinued over the first 6–12 weeks of cyclophosphamide therapy.<sup>59,60</sup>

| <b>Cyclophosphamide</b>   |
|---|
| <p><b>Mechanism of action:</b> It is converted to an active metabolite which causes DNA crosslinking leading to DNA miscoding, breaks and defective repair of DNA, causing cell death. Cyclophosphamide inhibits both cellular &amp; humoral immunity.</p>  |
| <p><b>Dosage:</b> oral:1-5mg/kg/day; Pulse doses of intravenous cyclophosphamide 500mg/m<sup>2</sup> can be given once in 4 weeks.</p>  |
| <p><b>Side effects:</b> Haemorrhagic cystitis, carcinoma of urinary bladder, bone marrow suppression, alopecia and sterility.</p>   |
| <p><b>Monitoring:</b> Complete blood count &amp; routine urine analysis initially weekly at the initiation of therapy and then at least every 4 weeks once the dosage is stable. Cyclophosphamide therapy is discontinued/stopped if WBC count is less than 3000/<math>\mu</math>L, platelet count is less than 75,000/<math>\mu</math>L.</p> |

The patient should be instructed to drink copious amounts of fluid to prevent hemorrhagic cystitis. In severe and nonresponsive cases, infusion of 500mg of cyclophosphamide (given over 1 to 2 hours) is often required. Because of potential life threatening complications, it should be administered under the supervision of a rheumatologist.

Biologicals, a group of drugs which are directed mainly against specific cytokines or their receptors, have been tried by various authors with promising results. However most of these agents are not widely used in our country because of their high price and risks of life threatening granulomatous infections. Infliximab, a tumor necrosis factor (TNF)-alpha 1 blocker, has been successfully used for treatment of non-infectious scleritis.<sup>64,65</sup> A case of nodular scleritis, refractory to standard immunosuppressive therapy, has shown promising result with adalimumab.<sup>66</sup> Few cases of scleritis refractory to treatment by Immunosuppressives and TNF alpha 1 blocker showed dramatic responses with rituximab. Rituximab is now a days preferred in scleritis associated with Wegner’s granulomatosis, refractory to standard therapy.<sup>67,68,69</sup> But use of these biologicals require close monitoring for prevention of potential life-threatening side-effects. Various serious side-effects have been reported in some patients.

## Section 10

### Surgical management of scleritis

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Tectonic surgical procedures rarely may be required to preserve the integrity of the globe. Patch grafts might need to be performed along with systemic immunosuppression in cases of extensive scleral melts and uveal show. Van der Hoeve was the first person to recommend surgical intervention in the form of mucous membrane graft for necrotizing scleritis in 1934.<sup>70</sup>

Preoperative evaluation of these patients includes documentation of extent of scleral thinning and melt and the amount of active inflammation. Control of inflammation prior to surgical intervention is the norm except in certain emergency situations. Clinical diagnosis of any systemic condition and prompt immunosuppressive medications in the preoperative period go a long way in stabilizing the globe and maintaining vision in these eyes. Similarly, in the case of infectious scleritis, a detailed microbiological work up and initiation of appropriate medication are important to control the infection. In such cases better surgical results can be obtained, if surgery is performed after proper control of infection.<sup>70</sup> However it is sometimes difficult to wait till the infection is adequately controlled and most of the times tissue damage continues to occur because of the secondary inflammation even after the infections is controlled.

The most commonly used graft material is donor sclera, which has been banked either as frozen, glycerin preserved or alcohol-preserved tissue. Various other materials, both natural and synthetic materials, have been used in scleral tectonic graft procedures. The table summarizes the use of various materials used in scleral patch graft.

| Donor sclera preservation  | Method of preservation   | Maximum period of preservation | Optimal temperature for storage |
|----------------------------|--|--------------------------------|---------------------------------|
| Frozen sclera              | Tissue stored in antibiotic solution and frozen.                     | 3 months                       | -20 degree c                    |
| Glycerin-dehydrated sclera | Donor tissue is preserved in glycerine, which dehydrates the sclera. | 1 year                         | Room temperature                |
| Alcohol-fixed sclera       | Donor tissue is preserved in absolute ethanol                        | 1 year                         | Room temperature                |

### Grafts used in surgical management of scleritis

- Fascia lata<sup>71,72</sup>
- Periosteum<sup>73,74</sup>
- Aortic Tissue<sup>70</sup>
- Polytetrafluoroethylene<sup>75</sup>
- Dura mater<sup>76</sup>
- Split thickness dermis<sup>77</sup>
- Processed pericardium<sup>78,79</sup>
- Conjunctiva–Muller muscle flap<sup>80</sup>

Usually scleral patch graft can be done under local anesthesia with or without intravenous sedation or under general anaesthesia depending on patient age, severity of melt/impending perforation,

### **Surgical steps:** (figure 21, 22, 23, 24, 25, 26, 27, 28)

Preparation of the surgical space by careful and meticulous dissection of conjunctiva, Tenon's capsule and episcleral tissue is most important. Determine the extent of necrotic sclera and debride or excise all unhealthy tissue to reach a clear healthy margin. During debridement or excision adequate care needs to be taken to avoid inadvertent globe perforation. All necrotic tissue should be removed from the surgical bed as any resident necrotic tissue can act as stimulus for postoperative inflammation and can cause melting of the graft. Once the surgical bed is ready for grafting, the size of the defect is measured and a similar sized graft is placed and sutured with interrupted 10-0 nylon or the sclera can be stuck with the fibrin based glue. Advantages of tissue adhesives are reduction of surgery time, avoidance of suture related complications etc. It is important to cover the scleral graft with conjunctiva which can again be sutured over the graft or stuck to the graft with tissue adhesive (fibrin glue) as it ensures proper vascularization and epithelialization of the graft. Amniotic membrane is sometimes used in combination with the scleral grafts in case the residual conjunctiva is too scarred or there is a large conjunctival defect. Amniotic membrane is known

to harbor anti-inflammatory, antiproteolytic, and antimicrobial properties and acts as a good basement membrane, for the conjunctival epithelium to grow and cover the scleral graft.

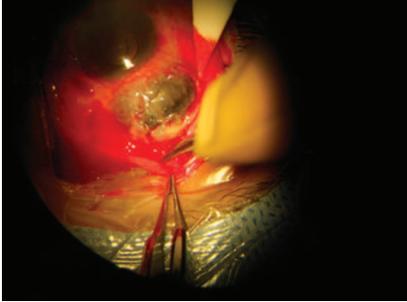


Figure 21: Conjunctival and tenons dissected over the staphylomatous area to expose area of melt

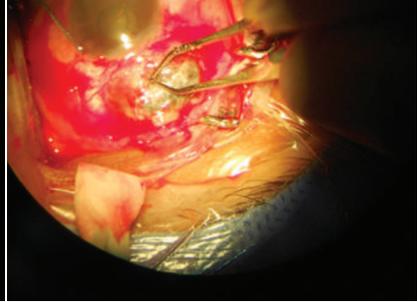


Figure 22: Cautery/diathermy to be applied to shrink staphyloma after a paracentesis to reduce intra ocular pressure

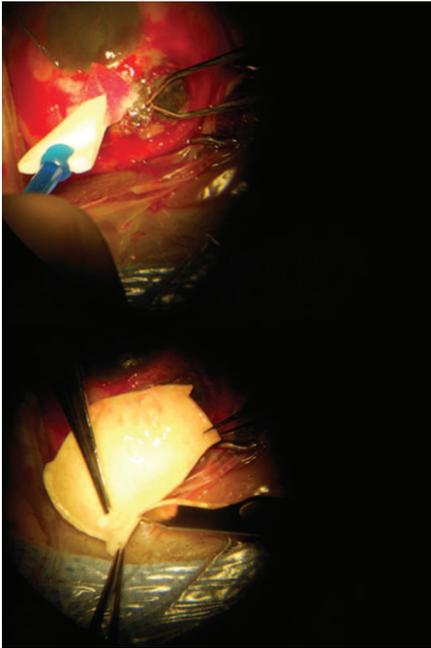


Figure 23: Sclera prepared

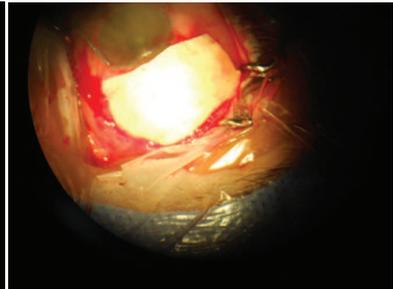


Figure 24: Sclera stuck with fibrin glue (Baxter Inc)

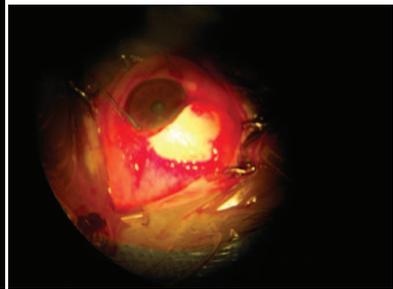


Figure 25: Conjunctiva mobilised to cover but since there was shortage of tissue. Conjunctiva anchored with sutures

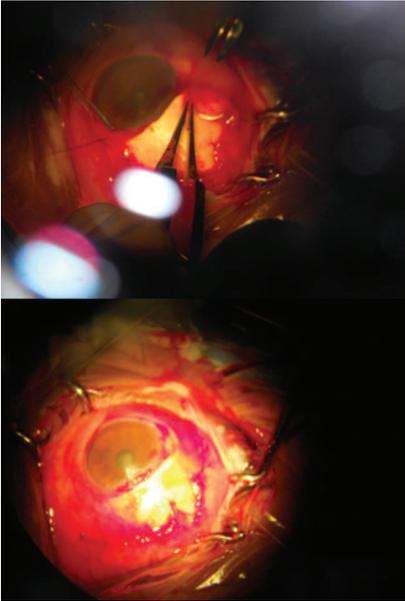


Figure 26: Aminiotic membrane placed over sclera and under conjunctiva to cover exposed sclera

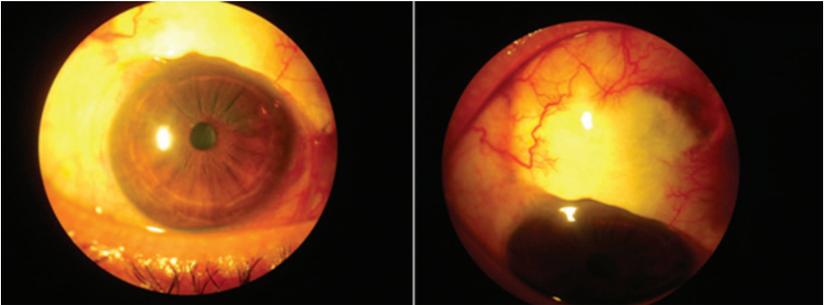


Figure 27: Post surgery: Eye quiet, scleral graft taken up well. 2 months post surgery: Small area superiorly yet to epithelize

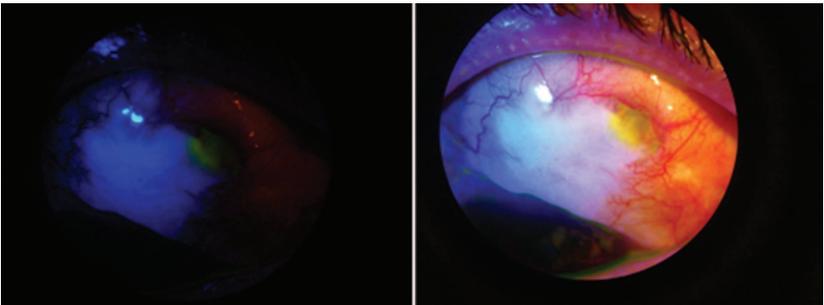


Figure 28: 2 months post patch graft: Small area of scleral graft yet to epithelize. Eye quiet

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