The eye in rheumatology

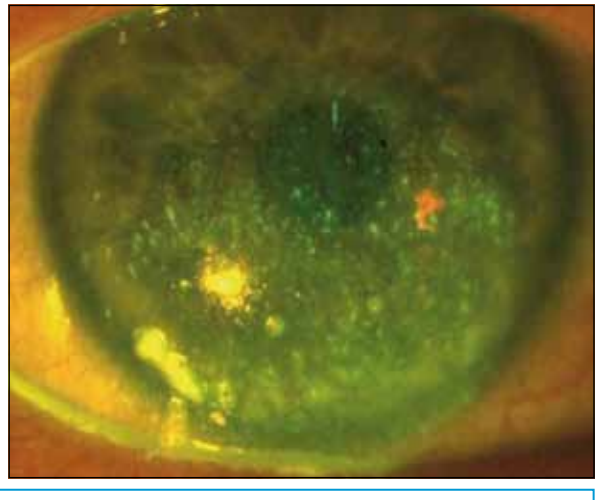
Rheumatic conditions affect a wide variety of tissues, including the eye, and can cause significant visual loss. Early diagnosis coupled with appropriate management, using immunosuppression where necessary, can significantly improve the outcome. This article reviews the most common manifestations seen in clinical practice.

Rheumatic conditions affect a wide variety of tissues and the eye is no exception. This article focuses on the common ocular manifestations of familiar rheumatological diseases in the eye. Early detection of ocular disease is important, as it can reduce the risk of the development of irreversible visual loss.

Dry eye

The tear film is a balanced composite consisting of three layers – lipid, aqueous and mucin. Imbalances in these constituents in conjunction with reduced secretion and increased evaporation of the tear film can result in the development of dry eyes (Taylor et al, 2011) (*Figure 1*). Sjögren's syndrome is a common cause of dry eye in rheumatology and is mediated by an autoimmune T-cell infiltration and destruction of exocrine glands. These patients may also have dry mouth (xerostomia) which is associated with the presence of anti-Ro and anti-La antibodies (Harley et al, 1986; Nguyen and Peck, 2009). Primary Sjögren's syndrome is aqueous deficient dry eye with the presence of anti-Ro and anti-La, and secondary Sjögren's syndrome is symptoms and signs of the primary condition plus concurrent autoimmune rheumatological disease (Lemp et al, 2007). Dry eye is also present in 92% of patients with rheumatoid arthritis (Lemp, 2005), but is not associated with the severity of disease. Patients with systemic lupus erythematosus, Wegener's granulomatosis, polyarteritis nodosa and graft *vs* host disease are also susceptible to developing dry eye, and the pathophysiology behind these conditions is similar (Taylor et al, 2011).

Figure 1. Dry eye stained with 2% fluorescein dye, showing an abnormal tear film together with multiple punctate epithelial erosions which are stained green by the dye.

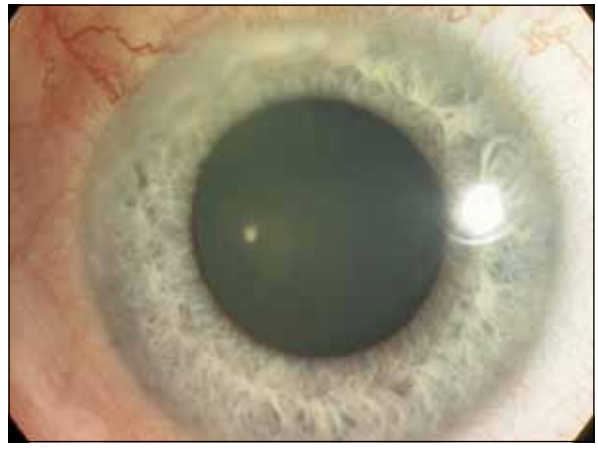


Mild symptoms which do not affect vision can be treated with topical ocular lubrication. If these treatments fail to improve symptoms in the mild–moderate stages and if there are signs of 'severe' features, refer to an ophthalmologist as persistent untreated dry eye can result in permanent corneal damage in the form of ulceration, structural inflammatory changes in the conjunctiva and new vessel formation onto the cornea.

Peripheral ulcerative keratitis

This can be caused by a spectrum of rheumatological diseases from rheumatoid arthritis, Wegener's granulomatosis and other forms of vasculitides such as relapsing chondritis and polyarteritis nodosa. T-cell-mediated inflammation precipitates an inflammatory response, resulting in the release of cytokines and collagenases leading to peripheral corneal thinning and eventual perforation (*Figure 2*) (Dana et al, 2000). Patients present with decreased visual acuity associated with ocular pain and redness. Treatment consists of ocular lubricants to prevent corneal desiccation, antibiotics to treat a potential infective cause and effective systemic immunosuppression.

Figure 2. Peripheral ulcerative keratitis, illustrated by a superior corneal gutter and associated infiltrate, in a patient with Wegener's granulomatosis.



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Episcleritis and scleritis

Episcleritis is a benign self-limiting condition resulting from inflammation of the episclera (*Figure 3*). Unlike scleritis, episcleritis does not result in visual disturbance or significant complications and is usually short lived (Jabs et al, 2009). An easy way to discriminate between episcleritis and more serious scleritis is that superficial episcleral vessels blanch upon application of 10% topical phenylephrine. Episcleritis can be associated with systemic disease, but there is usually no need for investigation or treatment, although recurrent episodes can be associated with raised serum levels of uric acid.

Scleritis is a severe inflammation of the deeper structures of this fibroelastic coat which poses a significant threat to vision. It is associated with systemic rheumatological disease in up to 50% of patients, and may be the first presentation (Okhravi et al, 2005). Anterior scleritis is typified by the symptoms of a deep boring ocular pain which radiates to the brow and other facial structures and can rouse the patient from sleep. The eye is red and exquisitely tender on gentle palpation (Singh et al, 2011). Raised nodules may also form (*Figure 4*). Posterior scleritis affects the posterior aspect of the eye, and is more commonly associated with sight-threatening complications. The eye may be white on inspection, but ultrasonography can indicate posterior scleral thickening.

Necrotizing scleritis is an ophthalmic emergency and is particularly associated with Wegener's granulomatosis. Untreated, the scleral necrosis leads to eventual perforation and exposure of the intraocular contents. Necrotizing scleritis without inflammation – scleromalacia perforans – can occur in association with rheumatoid arthritis, but is now extremely rare. Simple non-necrotizing scleritis can be treated with systemic non-steroidal anti-inflammatory agents, but other types require systemic immunosuppression.

Uveitis

Anterior uveitis is most commonly found in patients with patients who are HLA-B27 positive, and may therefore occur in association with other HLA-B27-related diseases, such as ankylosing spondylitis (*Figure 5*). Anterior uveitis may be the first presentation of ankylosing spondylitis, and may precede the irreversible changes to the sacroiliac joints that can occur later in disease, allowing for early detection and the institution of appropriate management (Huerta-Sil et al, 2006; Gugleimi et al, 2009; Hooper et al, 2011).

Behçet's disease is a systemic inflammatory condition characteristically associated with oro-genital ulceration, arthritis and uveitis. The insidious progression and visually destructive course warrant urgent systemic treatment in patients who present with uveitis affecting the posterior segment. Patients present with decreased vision and/or blurred vision, ocular pain and photophobia. A hypopyon may be present and the retina may reveal patches of retinitis and occlusive retinovascular disease.

Sarcoidosis is a granulomatous inflammatory disorder which is common in patients of Afro-Caribbean origin. It affects many organ systems. Diagnosis can be made on the basis of signs and symptoms, raised serum angiotensin-converting enzyme level and a chest X-ray to exclude the presence of bilateral hilar lymphadenopathy (Birnbaum et al, 2011). Uveitis in these patients spans from anterior to posterior. The presence of dense white precipitates seen on the corneal endothelium are sometimes described as 'mutton-fat' precipitates and are pathognomonic of sarcoid. The retina is said to have a characteristic appearance of 'candlewax drippings' caused by inflammation around the retinal veins.

Juvenile idiopathic arthritis causes an acute anterior uveitis in children and can be classified into various subtypes (Petty et al, 2004) (*Figure 6*). Of these, oligoarthri-

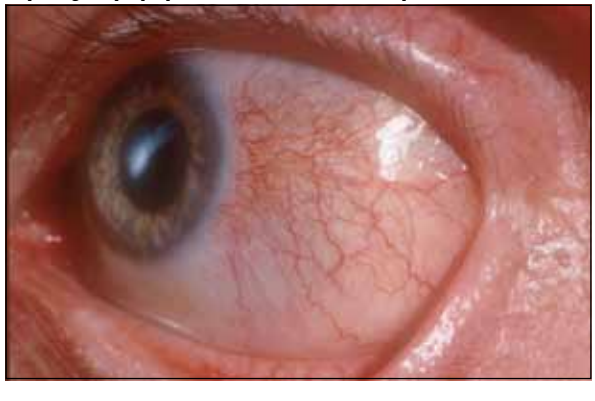


Figure 3. Episcleritis, showing superficial temporal redness of the left eye. Episcleritis is not serious and is usually self-limiting, requiring only symptomatic treatment with topical lubricants.

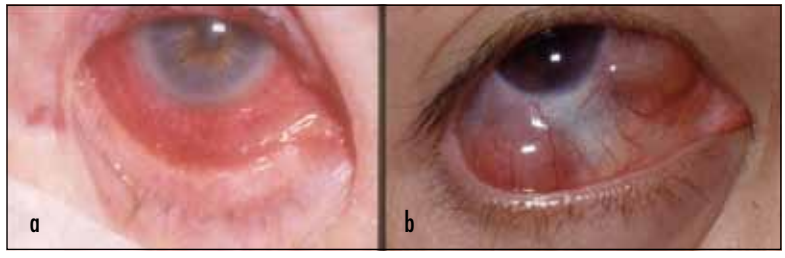


Figure 4. a. Diffuse and (b) nodular anterior scleritis. The eye is 'beefy red' and tender to the touch. Characteristically, the patient is woken from sleep by pain.

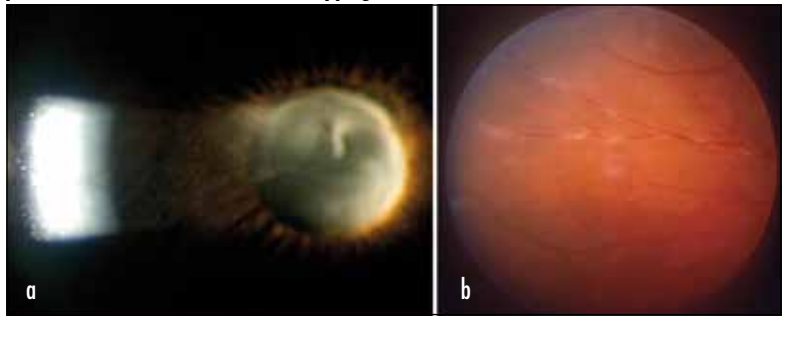


Figure 5. a. Anterior uveitis, with cells in the anterior chamber and fibrin at the pupil margin. b. Retinal periphlebitis in sarcoidosis. When more severe, this can form a pattern reminiscent of candlewax drippings, but this is less common.

tis with a positive antinuclear antibody titre is most strongly correlated with the development of uveitis (Grassi et al, 2007). The clinical problem is that, in contrast to other conditions, the anterior uveitis of juvenile idiopathic arthritis is asymptomatic in up to 90% of cases (Grassi et al, 2007), so children may present late with irreversible visual loss. Visual loss occurs as a result of cataract formation, glaucoma, amblyopia and corneal changes such as band keratopathy (Thorne et al, 2007). As the majority of the ocular signs and symptoms are occult, children diagnosed with juvenile idiopathic arthritis need to be referred for ophthalmology screening (ideally within 6 weeks of juvenile idiopathic arthritis diagnosis) to exclude uveitis and prevent the development of such complications (Hooper et al, 2011).

Orbital disease

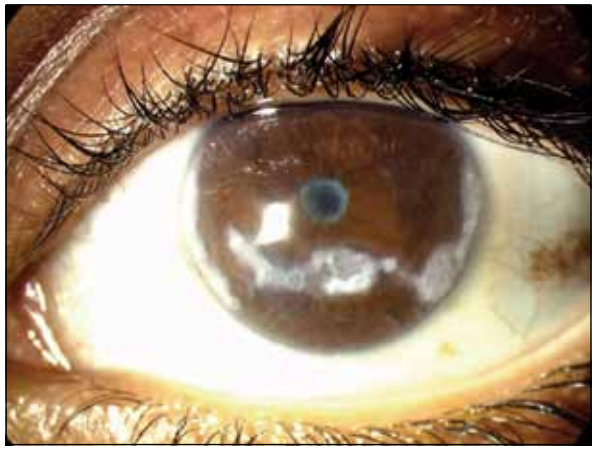
A variety of systemic rheumatological conditions are known to affect the orbital structures, especially Wegener's granulomatosis. In Wegener's granulomatosis, orbital granuloma formation can cause proptosis and compressive optic neuropathy, leading to severe visual loss (Tan et al, 2011). Treatment consists of effective immunosuppression in the form of high-dose corticosteroids and second-line agents, particularly cyclophosphamide or rituximab (Joshi et al, 2011).

Giant cell arteritis

Giant cell arteritis is worthy of separate mention as it can cause a wide spectrum of ocular disease. In this condition, inflammation of the larger arteries commonly occurs affecting the orbit and its surrounding regions. Diagnosis relies mainly on clinical signs and symptoms coupled with biochemical markers of inflammation. Patients usually present with a loss of vision as a result of vasculitic optic neuropathy (*Figure 7*). Jaw claudication associated with temporal tenderness may be described. A 'cherry-red' spot visible at the macula (visible because of the relative pallor of the retina) is caused by a central retinal artery occlusion. Branch retinal artery occlusions may be seen as a localized sector of pallor within the retina.

Although the gold standard for diagnosis, a temporal artery biopsy can provide a false negative result because of the absence of inflammatory changes in sections of the artery (skip lesions). If a biopsy of one side is negative despite clinical signs and symptoms, a biopsy from the opposite side should be taken. It is important not to wait for these investigations but to start high-dose oral steroids immediately in order to protect the second eye from similar pathology.

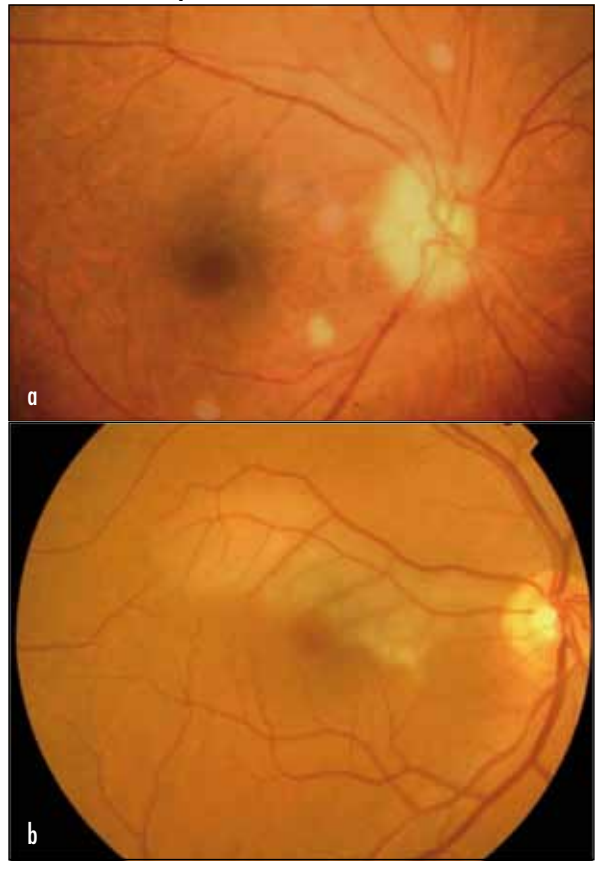
Figure 6. Juvenile idiopathic arthritis with chronic anterior uveitis, evidenced by band keratopathy (calcium deposition in the cornea), extensive posterior synechiae between the pupil and lens, and cataract formation.



Ocular side effects of antirheumatic medications

The cocktail of medication used in the treatment of rheumatology conditions, such as steroids, non-steroidal anti-inflammatory drugs and disease-modifying anti-rheumatic agents, can lead to increased susceptibility to development of ocular side effects. Steroids are used to help control many rheumatological conditions, but have specific ocular side effects including cataract formation and rises in intraocular pressure. They also have to be used with cau-

Figure 7. Giant cell arteritis can cause several different ocular manifestations. a. Arteritic anterior ischaemic optic neuropathy, indicated by an intensely chalky white swollen optic disc, is the most common ocular complication. b. Branch retinal artery occlusions, showing pale, fluffy ischaemic retina, also occur, as do central retinal artery occlusions.



tion in patients with diabetes as the use of steroids while treating an episode of uveitis can make diabetic management challenging. Bisphosphonates, which are commonly administered together with long-term corticosteroid therapy for osteoprotection, can also cause uveitis.

Hydroxychloroquine is known for its effects on the retina and these can be irreversible (*Figure 8*). The risk of developing retinopathy is greater if the patients are elderly, high doses are prescribed, if patients have comorbid states or pre-existing ocular disease, and if the drug is taken for more than 5 years (Marmor et al, 2011).

In addition patients can become vulnerable to the development of opportunistic infections as a result of iatrogenic immune compromise. Cytomegalovirus can cause an inflammation of the retina (retinitis) and visual loss (*Figure 8*). The retina has a cheese and tomato pizza appearance because of the cotton wool spots in the nerve fibre layer (disruption in the axoplasmic flow indicative of ischaemia), haemorrhage and vasculitis. Herpes simplex and varicella zoster viruses can cause a sudden progressive loss of vision rapidly causing retinal necrosis and irreversible visual loss. Treatment in the form of antivirals should be commenced immediately and an emergency ophthalmology consult should be sought if this is suspected.

Conclusions

The eye is a complex organ which is susceptible to the systemic effects of rheumatology associated disease. The majority of ocular-associated disease is predominantly T and B cell-mediated. In some cases, ocular manifestation of systemic disease can precede the onset of the systemic disease before a diagnosis is made. Basic history taking and examination should include a visual acuity as this can serve as a guide to ocular disease presence or severity. Such patients once identified need to be managed early in close liaison with ophthalmologists and rheumatologists for effective management. **BJHM**

Mr SRJ Taylor is supported by the UK National Institute of Health Research.

Conflict of interest: none.

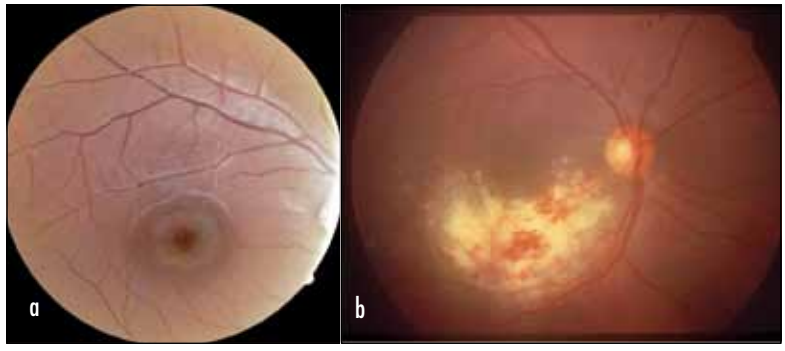


Figure 8. a. The bulls-eye maculopathy seen with hydroxychloroquine toxicity and (b) cytomegalovirus retinitis in an immunocompromised patients being treated for systemic lupus erythematosus.

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KEY POINTS

- Rheumatic conditions are systemic inflammatory processes which affect a wide variety of tissues, including the eye.
- Ocular manifestations may precede the onset of systemic rheumatologic disease and their early identification may assist in making the systemic diagnosis.
- Early identification of characteristic ocular signs and symptoms, together with appropriate management, can prevent the development of significant visual loss.
- Ocular opportunistic infections can occur in response to the systemic immunosuppression used to treat the rheumatic diseases.