Ocular manifestations of systemic lupus erythematosus

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Ocular manifestations of lupus are fairly common, may be the presenting feature of the disease and can be sight-threatening. Almost any part of the eye and visual pathway can be affected by inflammatory or thrombotic processes. Ocular pain and visual impairment require urgent assessment by an ophthalmologist. Infection should be excluded. Optic neuritis and ischaemic optic neuropathy may be difficult to distinguish. Scleritis and severe retinopathy require systemic immunosuppression but episcleritis, anterior uveitis and dry eyes can usually be managed with local eye drops. Vaso-occlusive disease, particularly in the presence of antiphospholipid antibodies, requires treatment with anticoagulation and proliferative retinopathy is treated with laser therapy. Hydroxychloroquine rarely causes ocular toxicity at doses under 6.5mg/kg/day. When this has occurred, it has been associated with more than 5 years of drug exposure.

KEY WORDS: Lupus, Ocular, Ophthalmic, Retinal, Scleral, Corneal, Optic.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multisystem disease which may affect the eyes and/or visual system in up to a third of patients. These ocular manifestations cause significant morbidity in their own right, but can also be a useful indicator of underlying systemic disease activity. Although early recognition and treatment have led to a reduction in severe ocular complications, ocular involvement in SLE is still a potentially blinding condition.

Methods

In addition to the authors’ personal knowledge of the subject, we performed a comprehensive literature search using PubMed, medline and dialog datastar from 1966 to present using key words lupus, SLE, eye, orbit, conjunctiva, cornea, glaucoma, iridocyclitis, retina, choroid, neuro ophthalmology and treatment. We also mined the bibliographies of the included publications for additional relevant publications. It should be noted that there is a paucity of controlled studies addressing the prevalence and treatment of ophthalmic manifestations of SLE.

Pathophysiology of ocular disease

SLE may cause ocular disease by a number of mechanisms including immune complex deposition and other antibody related mechanisms, vasculitis and thrombosis. Immune complex deposition has been identified in blood vessels of the conjunctiva, retina, choroid, sclera, ciliary body, in the basement membranes of the ciliary body and cornea, in the peripheral nerves of the ciliary body and conjunctiva [1]. Antibody dependent cytotoxicity may cause retinal cell death and demyelination of the optic nerve. Pathogenic circulating antibodies include anti-phospholipid antibodies (APA) and antineuronal antibodies. Similar mechanisms centred on the lacrimal gland may result in secondary Sjögren’s syndrome with consequent dry eyes (keratoconjunctivitis sicca) due to inadequate tear production; this is in marked contrast to most cases of dry eyes in the general population where it is primarily a problem of disturbance of the lipid layer of the tear film resulting in increased tear evaporation.

Ocular manifestations in SLE are fairly common, potentially sight threatening and may be the presenting feature of their disease [4, 5]. SLE may affect almost any part of the eye and visual pathway. Additionally drugs used in the treatment of SLE may cause ocular problems such as cataract or retinopathy. The patient will usually be aware that there is an ‘eye problem’, and will report it to their rheumatologist (or General Practitioner). It is therefore important that the implications of these symptoms are recognized and appropriate help is sought. In general terms, pain (often accompanied by visible inflammation or redness) usually indicates significant external/anterior segment disease, whereas problems with vision (blurring, distortion, double vision usually indicates posterior segment/neuro-ophtalmic disease (Tables 1 and 2). All such complaints warrant urgent referral to an ophthalmologist for more detailed assessment.

External eye disease

Eyelid disease. SLE (and discoid lupus erythematosus) can present with a discoid lupus-type rash over the eyelids. These discrete raised scaly lesions must be distinguished from the much more common chronic blepharitis (inflammation of lid margins). These lesions usually respond well to systemic but not topical anti-inflammatory therapy [6].

Lacrimal system disease. Dry eye syndrome (keratoconjunctivitis sicca) is the most common ocular feature of SLE (around a third of patients) and is often associated with secondary Sjögren’s syndrome [7, 8]. Usually, symptoms are relatively mild (irritation, redness) but severe pain and visual loss may occur. A reduced tear film and corneal changes are evident on slit-lamp examination. Tear production can be assessed by the Schirmer test which...
Corneal disease. Although the most common, the changes of dry eye syndrome are not the only corneal manifestation of SLE. Recurrent corneal erosions (large breaks in the corneal epithelium) typically present as a painful watery eye that comes on at waking and improves over the course of the day. Another corneal complication is punctate epithelial loss. This may respond to wakin & high viscosity at night) is preferred. In more severe cases, drainage of tears may be reduced by temporary or permanent occlusion of the puncta.

Orbital disease. Rare ocular presentations include orbital masses, periorbital oedema, orbital myositis, panniculitis, acute orbital ischaemia and infarction are rare presentations of SLE. A biopsy is often necessary to confirm the diagnosis. Treatment is with systemic immunosuppression [9–12].

Anterior segment disease

Corneal disease. Although the most common, the changes of dry eye syndrome are not the only corneal manifestation of SLE. Recurrent corneal erosions (large breaks in the corneal epithelium) typically present as a painful watery eye that comes on at waking and improves over the course of the day. Another corneal presentation is punctate epithelial loss. This may respond to systemic antimalarials suggesting that this may be an autoimmune rather than a dry eye phenomenon [13]. Peripheral ulcerative keratitis is rare and is an ominous marker of the presence of active systemic vasculitis [14]. Acute unilateral corneal stromal infiltration and oedema has been reported and responds rapidly to topical corticosteroid therapy.

Episcleral and scleral disease. Episcleritis (superficial) and scleritis (deeper inflammation of the sclera) are both seen in SLE, and may be the presenting feature of the disease [15]. Episcleritis usually presents with mild, if any, irritation and redness due to measures the wetting of a test strip hung over the lower lid for a period of 5 min.

Milder forms of dry eye can be treated with artificial tear drops. The choice of treatment depends on balancing the disadvantages of frequent instillation required for low viscosity preparations (such as hypromellose) with the blurred vision caused by more viscous preparations (such as liquid paraffin). Often a medium viscosity drop (e.g. a carbomer) or a combination (low viscosity plus a viscosifier) is preferred. In more severe cases, drainage of tears may be reduced by temporary or permanent occlusion of the puncta.

Injection of the superficial blood vessels. Since only the superficial blood vessels are affected, a drop of phenylephrine (e.g. 2.5%) will cause visible blanching of the vessels, so confirming the diagnosis. Episcleritis is usually self-limiting.

Scleritis is much more painful, may be sight threatening and requires urgent assessment by an ophthalmologist. The pain is so severe that it can wake the patient from sleep; it may be described as an ‘ache’ or ‘boring’ and may be generalized to the whole eye or the side of the face. In anterior scleritis there is redness due to injection of the deeper episcleral vessels (which do not blanch on the phenylephrine test); the sclera itself is avascular. The redness may be concealed under the upper lid so it is worth examining this area by lifting the lid, whilst asking the patient to look down. It is usually unilateral and is not associated with discharge. Anterior scleritis may be diffuse or nodular in distribution. Rarely it may result in significant destruction (necrotizing scleritis) leaving an area of scleral thinning (Fig. 1). Posterior scleritis does not cause a red eye (unless it extends anteriorly) but may cause visual problems, with blurring, change in refraction and double vision [16]. Although features may be present on fundoscopy (oedema, choroidal detachments, exudative retinal detachments), the diagnosis is most easily confirmed on B-scan ultrasonography.

Episcleritis does not usually require treatment, although artificial tears may be soothing. Suspected scleritis should be referred to an ophthalmologist. The presence of scleritis may indicate activity of the underlying disease and requires systemic therapy, ranging from non-steroidal anti-inflammatory drugs like flurbiprofen to corticosteroids and other immunosuppressive agents (e.g. cyclophosphamide, azathioprine, methotrexate, ciclosporin or mycophenolate).

Other anterior segment complications. Conjunctival inflammation is uncommon. It presents with irritation, redness and may be associated with lid follicles. Anterior uveitis (intraocular inflammation of the anterior part of the eye) seldom occurs in isolation. It is more commonly associated with scleritis or posterior intraocular inflammation. It is rarely of sufficient severity to be associated with a hypopyon.

Posterior segment disease

Retinal disease. Retinal disease affects around 10% of SLE patients, reflecting a reduction in frequency associated with improved control of systemic disease. Mild retinopathy may be asymptomatic but more severe disease may cause loss of vision, field defects, distortion or floaters. Such visual symptoms are therefore an indication for urgent ophthalmic review. The retinal signs often parallel the severity of systemic inflammation, and may indicate inadequate control of the systemic disease [17, 18]. The presence of APA is associated with more severe retinopathy and vascular occlusions [19].

Mild lupus retinopathy consists of cotton-wool spots, perivascular hard exudates, retinal haemorrhages and vascular tortuosity [20] (Figs 2 and 3). Moderately severe cases may also have focal or generalized arteriolar constriction and venous tortuosity.
There are some similarities to both hypertensive retinopathy and diabetic retinopathy; when these conditions occur concurrently, disease monitoring and treatment can be challenging. At the severe end of the spectrum there is occlusion of retinal arterioles and consequent retinal infarction, termed vaso-occlusive retinopathy or ‘retinal vasculitis’ [21, 22]. Proliferative retinopathy may occur in up to 72% of such cases, often with ensuing vitreous haemorrhage, retinal traction and retinal detachment (Figs 4 and 5). Other retinal presentations include large vessel occlusions (central and branch retinal vein occlusions, central and branch retinal arteriole occlusions) that are more common in the presence of APA (Fig. 6), pigmentary changes (pseudo-retinitis pigmentosa) and exudative retinal detachments secondary to choroidal disease. In the immunosuppressed state, rare retinal infections may occur: retinal necrosis due to herpes simplex, varicella zoster (Fig. 7) and cytomegalovirus are all reported.

The mainstay of treatment for significant retinal disease is systemic immunosuppression, but laser therapy and anti-coagulation also have a role. Initial treatment is usually with

**Fig. 2.** Acute lupus retinopathy with cotton wool spots, haemorrhages, arterial narrowing, venous dilation and tortuosity.

**Fig. 3.** Fundus fluorescein angiography of a patient with acute lupus retinopathy demonstrating capillary ‘drop-out’, vessel wall staining and leakage. Phases (i) early, (ii) arteriovenous and (iii) late.

**Fig. 4.** Disc new vessels (proliferative retinopathy) in a patient with lupus vaso-occlusive retinopathy.

**Fig. 5.** New vessels elsewhere (proliferative retinopathy) in a patient with lupus vaso-occlusive retinopathy. Images: (i) suspicious fundal appearance, (ii) new vessels leaking on late phase of fundus fluorescein angiogram, (iii) vessels regressed after laser treatment (photocoagulation).

**Fig. 6.** Branch retinal arteriole occlusion in a patient with SLE and antiphospholipid syndrome.

**Fig. 7.** Acute retinal necrosis secondary to varicella zoster virus in a patient with SLE.
oral corticosteroids (e.g. prednisolone 1 mg/kg/day), but may be preceded by intravenous methylprednisolone (e.g. 500 mg-1 g daily for 3 days). This is then supplemented with, or replaced by, other immunosuppressive agents as part of a steroid-sparing strategy or for resistant disease. In unilateral or asymmetric disease, regional corticosteroid injections are sometimes used in addition.

In the presence of significant vaso-occlusive disease (particularly when APA are present), anti-coagulation and the addition of low dose acetylsalicylic acid may be beneficial. Proliferative retinopathy usually requires treatment with laser (panretinal photocoagulation) akin to the treatment of proliferative diabetic retinopathy [23].

**Choroidal disease.** Choroidal disease is less common than retinopathy but is probably underdiagnosed as a cause of visual loss in SLE. Angiography of the fundus with fluorescein and indocyanine green often demonstrates disease not detectable on clinical examination. This may include leakage into uni/multifocal retinal detachments and choroidal ischaemia. Other complications include choroidal effusions (which have been reported to cause secondary angle closure [24]), choroidal infarction and choroidal neovascular membranes [25]. In the immunosuppressed state, rare choroidal infections may occur: both a nocardia choroidal abscess [26] and tuberculous granulomas [27] with associated pulmonary disease have been reported.

Treatment is with systemic immunosuppression. However, in some patients, corticosteroids may themselves induce central serous chorioretinopathy, in which case alternative agents should be used [28]. Pulsed methylprednisolone and cyclophosphamide have been reported to be effective in treating bilateral exudative retinal detachment secondary to ischaemic choroidopathy [29].

**Neuro-ophtalmic disease**

**Optic nerve disease.** Optic nerve disease occurs in around 1% of patients with SLE [30–32], and includes optic neuritis and ischaemic optic neuropathy (anterior or posterior). Optic neuritis presents acutely with unilateral loss of vision associated with pain that is worse with eye movements. In the absence of other features of SLE, it can be very difficult to distinguish this from the typical optic neuritis of demyelinating disease [32–34]. However, the prognosis is worse in SLE associated optic neuritis, with more than half having a persistent central scotoma and progressing to optic atrophy. Pathological studies demonstrate infarction of the optic nerve secondary to extensive arteriolar fibrinoid necrosis [35]. Acute optic neuritis may also be bilateral and associated with transverse myelopathy.

In contrast to optic neuritis, optic neuropathy in SLE typically presents with bilateral, acute painless loss of vision associated with an altitudinal or arcuate field defect, with or without optic disc swelling. This is due to occlusion of the small vessels of the optic nerves, which leads to demyelination in mild cases or axonal necrosis in more severe cases. Unilateral optic neuropathy appears to reflect a ‘focal’ thrombotic event and is associated with the presence of APA. Bilateral optic neuropathy that improves with immunosuppressive treatment is suggestive of a more generalised CNS vasculitic pathology [32, 36].

Visual prognosis following optic neuropathy is generally poor, although good outcomes have been reported. Recurrence usually worsens the prognosis. Occasional improvement following early treatment with corticosteroids or pulsed cyclophosphamide have been reported [30, 31], with some patients needing anti-coagulation in addition to immunosuppression.

**Cranial nerve disease and other disorders of ocular motility.** Ocular motor abnormalities are not uncommon in SLE with one series reporting a rate of 29.2% [37]. Diplopia may be transient and indeed is not always present. The motility abnormalities usually arise from vascular or ischaemic events within the brainstem and are frequently associated with both cranial nerve and long tract signs.

Occasionally disorders of conjugate gaze such as internuclear ophthalmoplegia (unilateral [38] or bilateral [39]) and one a half syndrome (internuclear ophthalmoplegia with ipsilateral horizontal gaze palsy [40]) are seen. Other reported complications include nystagmus and Miller Fisher syndrome [41].

**Other neuro-ophtalmic manifestations.** Pupillary abnormalities such as light near dissociation (reduced pupillary light reflex but preserved near reflex), Horner’s syndrome [37], Adie’s pupil and abnormal pupillary reflexes have all been described in SLE. Blepharospasm is also reported and may be troublesome. Retrochiasmal disease can also present with headache, lethargy, dizziness, alterations in memory and consciousness, seizures, other cranial nerve palsies, ataxia, papilloedema, amaurosis fugax (transient monocular blindness), nystagmus, field defects, cortical blindness and coma. Transient monocular blindness was observed 11 times more commonly among patients with SLE than the normal population [42]. Idiopathic intracranial hypertension has been reported in both children and adults with SLE, and may be the presenting feature of the disease [43, 44].

**Ophthalmic disease and the role of anti-phospholipid antibodies**

The presence of APA is associated with vaso-occlusive disease (both retinal and CNS) in SLE [45, 46]. Interestingly retinal vascular occlusions and even a similar retinopathy may also be seen in primary anti-phospholipid syndrome. In general, the presence of APA is linked to focal thrombotic events that may prompt the use of anti-coagulation or low dose aspirin in addition to immunosuppression.

**Ophthalmic disease in drug induced lupus**

Ocular complications are rare in drug-induced lupus, although retinal vasculitis and occlusive disease have been reported in hydralazine and procainamide induced lupus syndrome.

**Ophthalmic disease as a side-effect of treatment**

The agents used in the treatment of SLE can themselves cause significant opthalmic morbidity. Corticosteroids are commonly used in SLE and may cause cataract formation. Although steroid induced glaucoma does occur with patients taking oral corticosteroid, it is more frequent in those patients using topical corticosteroids. The introduction of other immunosuppressive agents in steroid-sparing regimes has resulted in reduced corticosteroid exposure for most patients.

Other immunosuppressive agents are usually more costly, have their own side-effects and need careful monitoring. Overwhelming septic cavernous sinus thrombosis has been reported after a combination of high dose steroid and intravenous cyclophosphamide therapy for lupus nephritis [47].

The aminoquinolones, chloroquine and, to a lesser extent, hydroxychloroquine can cause reversible visually insignificant changes in the cornea (vortex keratopathy) and, more importantly, an irreversible sight-threatening maculopathy. Initial changes are subtle (loss of foveal reflex and a fine granular appearance) and often asymptomatic, but can progress to a ‘bull’s eye’ maculopathy and even generalized atrophy of the retina and optic nerve [48]. This retinopathy may continue to progress despite cessation of the drug. Although both drugs can cause identical changes the risks are much lower with hydroxychloroquine, particularly at recommended doses of up to 6.5 mg/kg/day [49, 50]. Below this level, hydroxychloroquine, toxicity is extremely rare. One prospective cohort study of 400 patients receiving long-term hydroxychloroquine of up to 6.5 mg/kg/day
found only two patients to be affected, in both cases only after more than 6 years of treatment [51]. Indeed Lee [52] estimated that at these recommended levels there have been only 20 affected cases in over a million patients receiving the drug; all 20 cases had been taking the drug for over 5 years.

In the UK, the Royal College of Ophthalmologists (in conjunction with representatives from the Royal College of Physicians, the British Society of Rheumatology and the British Association of Dermatologists) have advised that the prescribing rheumatologist should carry out the baseline assessment of lean body weight (if overweight), renal and liver function, asking about any visual impairment which is not corrected by glasses and testing reading vision [49]. Any apparent visual impairment or eye disease should be first confirmed by an optometrist, and then referred on to the local ophthalmologist before starting treatment. If visual problems occur once treatment has started, patients should be advised to stop treatment, attend their optometrist and seek advice from the prescribing physician who would refer on to the ophthalmologist. Annual evaluation should be by the prescribing rheumatologist and includes enquiry about visual symptoms and measuring reading acuity [49]. In the USA, screening by an ophthalmologist is recommended for those patients on hydroxychloroquine who are at higher risk: dose >6.5 mg/kg/day, duration of treatment >5 years, renal or hepatic disease, pre-existing retinal disease or age >60 years [50].

Chloroquine has a less clear safety profile and should be avoided where possible. All patients taking chloroquine should have regular ophthalmic examination according to locally arranged protocol.

Conclusion
Eye manifestations in SLE may be sight-threatening and can be an indicator of active systemic disease. Significant ocular pain or reduction of vision are serious symptoms requiring urgent assessment by an ophthalmologist. The serious ocular manifestations of SLE (such as scleritis and lupus retinopathy) generally require systemic immunosuppression. Future research will hopefully provide more evidence on which to base treatment choice. Early recognition by the rheumatologist, prompt assessment by the ophthalmologist and coordinated treatment strategies are key to reducing the ocular morbidity associated with this disease.

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Rheumatology key messages
- Ocular pain and visual impairment require urgent assessment by ophthalmologist.
- Scleritis and lupus retinopathy usually require systemic immunosuppression.
- Anti-phospholipid antibodies may cause vaso-occlusive disease affecting the retina.

References


