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Review Article

Ocular findings in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease. Ocular complications occur in up to one-third of patients with SLE. The ocular findings may represent the initial manifestation of the disease and may lead to severe ocular morbidity and loss of vision. Early diagnosis and prompt management of patients with SLE are mandatory and require collaboration between the ophthalmologist and the rheumatologist.

Keywords: SLE, Autoimmune, Ocular complications

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Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease. The eye is frequently involved in SLE.[1] The disease may cause ocular involvement by several mechanisms including immune complex deposition in the basement membrane of endothelial cells of the small blood vessels.[1] Ocular complications have been reported in up to one-third of patients with SLE.[2] Ocular manifestations of SLE may be due to the disease or may be due to the complications of systemic or topical therapy.[3] Unlike other autoimmune diseases, which may have a predilection for either anterior or posterior segment of the eye, SLE may affect any structure of the eye and adnexa.[3] The ocular findings in SLE are important because they may be the initial manifestation of the disease.[3]

The diagnosis of SLE is clinical and is based on the presence of 4 of the 11 features listed by the American College of Rheumatology classification criteria.[4] The presence of four criteria makes the diagnosis of SLE, serially or simultaneously, during the course of the disease. The revised criteria include: (1) malar rash, (2) discoid rash, (3) skin photosensitivity, (4) oral ulcers, (5) nonerosive arthritis, (6) serositis, (7) renal involvement, (8) neurological disorder, (9) hematologic disorder, (10) immunologic disorder, and (11) positive antinuclear antibodies.[4] The presence of 4 of these 11 criteria confirms the diagnosis of SLE and yields a sensitivity of 85% and a specificity of 95% for SLE.[5] The main purpose of this paper was to present the clinical findings and complications of therapy in patients with SLE.

Ocular involvement in SLE is variable affecting various parts of the eye and the visual pathway and may be sight threatening. Table 1 shows the ocular manifestations of SLE.

Orbital and external eye disease

Orbital involvement is a rare manifestation of SLE. Clinical presentation may be in the form of proptosis, enophthalmos, orbital pain, blurred vision, chemosis, and restriction of extraocular motility.[6,7] Limitation of ocular motility may result from orbital vasculitis and/or orbital myositis.[8,9] Orbital vasculitis may lead to nonperfusion of the globe and extraocular muscles leading to restriction of extraocular movements. Orbital myositis secondary to SLE may be misdiagnosed as

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Table 1. Ocular involvement in systemic lupus erythematosus.

Structure	Clinical findings
Orbital and external eye disease	Discoid lupus-type rash over the eyelids Panniculitis Orbital masses Periorbital edema Orbital myositis Orbital vasculitis, acute orbital ischemia and infarction
Conjunctival involvement	Conjunctivitis
Corneal involvement	Dry eye syndrome Recurrent corneal erosions Peripheral corneal infiltrates Peripheral ulcerative keratitis Interstitial keratitis Endotheliitis Keratoconus
Sclera and Episclera	Scleritis Episcleritis
Uveal involvement	Anterior uveitis
Retinal involvement	Lupus retinopathy (cotton wool spots, intraretinal hemorrhages, and vascular tortuosity) Retinal hard exudates Retinal vasculitis Retinal artery and/or vein occlusion Arteriolar narrowing and arteriovenous crossing changes Macular pigmentary mottling Retinal scarring Macular infarction
Choroidal involvement	Central serous chorioretinopathy
Neuro-ophthalmic findings	*Optic nerve involvement* Optic neuritis Ischemic optic neuropathy Papilledema *Central nervous system vasculitis* Internuclear ophthalmoplegia Nystagmus Cranial nerve palsies Homonymous hemianopia

bacterial orbital cellulitis. CT scan of the orbit or diagnostic ultrasound may reveal enlargement of the extraocular muscles in these cases.[6] Treatment of orbital disease is with systemic immunosuppressant drugs. Discoid lupus erythematosus (DLE) is a chronic cutaneous lupus erythematosus without internal organ involvement.[10] SLE and DLE can present with a discoid lupus-type rash over the eyelids. These discrete raised scaly lesions may be confused with chronic blepharitis. Treatment of these lesions is usually with systemic anti-inflammatory drugs.[1] Eyelid involvement was reported also in cases of cutaneous lupus erythematosus.[9] Lupus panniculitis is a rare skin condition, which predominantly affects the deep dermis and subcutaneous fat in young to middle-aged women. It may occur independently or in association with DLE or SLE. Clinically, these lesions appear as nodules or hardened subcutaneous plaques which are often adherent to the overlying skin. After healing, they may undergo atrophy and residual scarring. These nodules and plaques are usually located on the forehead, cheeks, extremities, and buttocks. They have occasionally been reported to affect the orbit.[11] The main treatment option for orbital and external eye disease is systemic hydroxychloroquine therapy. In cases of failure of antimalarials, immunosuppressive medications can be considered.[12] Several agents have been reported to be successfully used for DLE including azathioprine, dapsone, methotrexate, cyclophosphamide, thalidomide, retinoids, and interferon alpha-2. Corticosteroids are mainly used in patients with orbital inflammatory syndrome to control the severe inflammation or associated with hydroxychloroquine therapy at the beginning of the treatment.[12]

Ocular surface disease

Both the major and accessory lacrimal gland may be involved in patients with SLE.[13] Mononuclear cellular infiltrate of the lacrimal glands may lead to decrease in lacrimal fluid. Keratoconjunctivitis sicca is a common ocular feature of SLE. Keratoconjunctivitis sicca leads to upregulation of inflammatory cytokines causing chronic conjunctivitis[13] It tends to be mild but in rare cases it may lead to conjunctival scarring and shrinkage.[14] The prevalence of keratoconjunctivitis sicca among patients with SLE is approximately 25%.[2,15] The symptoms range from mild irritation, foreign body sensation and redness to severe pain due to corneal ulcer and filamentary keratitis. Significant visual impairment may occur due to corneal epithelial defects, corneal ulceration, vascularization and scarring. Treatment of dry eyes associated with SLE is usually through frequent instillation of lubricating eyedrops. Severe cases may require temporary or permanent punctual occlusion. Some cases may benefit from topical tacrolimus as it decreases the inflammatory cellular infiltrate of the lacrimal glands.[16]

Corneal involvement

In addition to dry eye syndrome SLE can be associated with other corneal manifestations such as recurrent corneal erosion, peripheral corneal infiltration, ulcerative Keratitis,[17] interstitial keratitis,[18] and endotheliitis.[19] Immune complexes may deposit in the basement membrane of the endothelial cells of the limbal blood vessels which may lead to release of chemotactic cytokines and may cause peripheral corneal infiltrates. Accordingly, corneal infiltrates can be treated with topical steroids with rapid response.[1] In addition, several autoimmune diseases such as SLE may be associated with keratoconus and this may point to the role of the immune system in the pathogenesis of keratoconus.[20]

Sclera and Episclera and Uveal involvement

Scleritis may occur in SLE, and may be the presenting feature of the disease.[3] The incidence of SLE in patients with scleritis is about 1%.[21,22] Scleritis in patients with SLE may present as anterior diffuse scleritis or anterior nodular scleritis. Necrotizing scleritis in patients with SLE is rare but may lead to significant scleral thinning.[22] Posterior scleritis is also rarely seen in patients with SLE.[23] Episcleritis may be also seen in SLE with milder symptoms and redness due to injection of the superficial blood vessels.[24,25]

Episcleritis is usually self-limiting disease which does not require treatment. Topical non-steroidal or steroidal eyedrops may be required in severe cases. On the other hand,

scleritis may indicate activity of the underlying systemic disease which necessitates systemic therapy.

Nongranulomatous anterior uveitis is rare but may occur in patients with SLE. Adjacent scleral inflammation may also lead to mild uveitis.[1] The prevalence of SLE in patients with uveitis varies from 0.1% to 4.8%.[25] Anterior uveitis in patients with SLE is usually mild but may rarely lead to diminution of vision and hypopyon formation.[26] The inflammation of the anterior segment usually improves with the use of systemic immunosuppressive therapy.[27]

Retinal and choroidal involvement

Retinal disease in patients with SLE ranges from mild asymptomatic lupus retinopathy to severe blinding disease and occurs in about 10% of SLE patients.[1] The most frequent retinal findings include cotton wool spots, retinal hemorrhages, and vascular tortuosity.[28,29] Other reported posterior segment changes include retinal hard exudates, retinal vasculitis[30,31], retinal artery and/or vein occlusion[32], arteriolar narrowing, arteriovenous crossing changes, macular pigmentary mottling, retinal scarring[25], and macular infarction.[33]

Lupus choroidopathy and central serous chorioretinopathy have been reported[34,35]. The posterior segment findings particularly the retinal signs often reflect the severity of systemic inflammation, and may indicate inadequate control of the systemic disease.[25,36] There are several treatment options for lupus retinopathy including systemic steroids, anticoagulants and laser retinal photocoagulation in cases of ischemic retinopathy.

Table 2. Ocular complications of systemic therapy.

Structure	Clinical Findings
Chronic treatment with *hydroxychloroquine*	Poliosis Cataract Extraocular muscle palsy Anterior uveitis Toxic maculopathy Optic neuritis Cornea verticillata
Systemic steroids	Elevation of intraocular pressure Cataract

Neuro-ophthalmic findings

Optic nerve involvement in patients with SLE may be in the form of optic neuritis, ischemic optic neuropathy and papilledema, and it occurs in around 1 % of SLE patients.[1,37,38] Improvement of optic neuropathy may occur following early treatment with corticosteroids or pulsed cyclophosphamide therapy.[37]In addition to optic nerve involvement, central nervous system vasculitis affecting the brainstem in patients with SLE may lead to cranial nerve involvement and diplopia. Ocular motility disorders may occur in up to 29% of patients with SLE.[38] Internuclear ophthalmoplegia and nystagmus may also occur. Postchiasmal vasculitis of the visual pathway may lead to infarcts that may lead to homonymous hemianopia.[39]

Ocular complications of systemic therapy

The aim of treatment of patients with SLE is to suppress the immune activity in order to induce and maintain remission of the disease and prevent relapses. Treatment options for SLE include nonsteroidal antiinflammatory drugs, corticosteroids, antimalarials, immunomodulatory, and biologic agents.[27] Chronic treatment with hydroxychloroquine may induce systemic and ocular adverse events. Systemic adverse reactions affect the gastrointestinal, nervous and skeletal muscular systems and skin. Ocular adverse reactions include photophobia, cornea verticillata, poliosis, cataract, extraocular muscle palsy, anterior uveitis, toxic maculopathy and optic neuritis [40] (Table 2).

The most concerning side effect is retinal toxicity. Melanin bearing cells in the posterior segment including the retinal pigment epithelium may act as sink for the accumulation of hydroxychloroquine which appears to bind to melanophores. The accumulation of hydroxychloroquine may lead to the toxicity of the photoreceptors. The incidence of toxic retinopathy varies from 0% to 4% .[41] Patients at high risk for the development of hydroxychloroquine maculopathy [41,42] are those with daily dose more than 6.5 mg/kg ideal body, duration of use of more than 5 years, cumulative use of 1000 g

Table 3. Protocol for Assessment of Hydroxychloroquine (Plaquenil®) Toxicity.

Date of examination:	_____	
Date of initiation of therapy:	_____	
Total cumulative dose:	_____	
Diagnosis:	_____	
	_____	
	_____	
Investigations:	Right eye	Left eye
1. Visual acuity (corrected)	_____	_____
2. Funduscopy	_____	_____
3. Visual fields 10-2 (Fovea, OU)	_____	_____
4. Multifocal electroretinogram (ERG)	_____	_____
5. OCT (Macula)	_____	_____
6. Fundus photograph	_____	_____
7. Fundus autofluorescence	_____	_____
Risk factors:		
1. Duration > 5 years	Yes _____	No _____
2. Daily dose >6.5 mg/kg/day of ideal weight	Yes _____	No _____
3. Renal or Hepatic disease	Yes _____	No _____
4. Age >60 years	Yes _____	No _____
5. Pre-existing macular disease	Yes _____	No _____

(total), kidney or liver disorders, pre-existing retinal disease or maculopathy and elderly people. In the early stages of retinal toxicity, most patients are asymptomatic. Patients may later complain of difficult reading, impaired color vision, and the central or paracentral scotoma. A protocol for the follow-up and assessment of hydroxychloroquine toxicity is shown in Table 3.

The fundus may appear completely normal even after development of the central scotoma. The earliest signs of toxicity are stippling of the retinal pigment epithelium at the macula, irregular pigmentary changes and loss of the foveal light reflex.[41] The progression of retinal toxicity may lead to the development of bull's eye maculopathy in which an irregular central zone of pigmentation becomes surrounded by an annular zone of depigmentation of the retinal pigment epithelium. Recommendations for the screening of hydroxychloroquine maculopathy include subjective and objective tests. The objective tests include visual acuity testing for distance and near reading, slit lamp examination (for corneal involvement), fundus examination, automated central perimetry (10-2) and fundus photography. The objective tests include optical coherence tomography of the macula, fundus autofluorescence and multifocal ERG.[41,42] All patients using chloroquine and its derivatives must be followed up and documented since the beginning of therapy for early detection of adverse effects. Systemic steroids which may be used for treatment of SLE, may lead to elevation of intraocular pressure, cataract and secondary infections of the eye.

Conclusion

The eye manifestations in SLE are variable. The eye findings may be the presenting sign of the systemic disease. In addition, these findings may serve as an indicator of active systemic disease. Careful assessment by the ophthalmologist is mandatory to prevent sight-threatening complications. Early recognition of drug induced toxicity may reduce ocular morbidity associated with this disease. SLE is a multisystem disease which requires the collaboration between the rheumatologist and the ophthalmologist to provide adequate treatment and prevent complications.

Conflict of interest

Financial/proprietary interests: The authors do not have any financial and proprietary interests in this study.

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