



Review Article

Exigency of ocular complications of systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is an auto immune connective tissue disease which affects all organs in the body including eye. Ocular manifestations vary with underlying severity of the SLE had been observed in 30% of cases. Ocular complications of SLE are commonly seen in advanced but uncontrolled and patients on irregular treatment. Keratoconjunctivitis sicca is the most common form of ocular complication of SLE, clinically manifests as dry eyes, lack of tear production which can be managed with artificial tear preparations. Clinical severity varies from mild asymptomatic red eyes and acute painful conjunctivitis, retrobulbar pain, orbital cellulitis, retinal artery occlusion and very severe cases leads to blindness which is often irreversible. Scleritis is an inflammatory complication of sclera which is as common as episcleritis in SLE. It can be classified in to anterior scleritis and posterior scleritis. Retinal involvement is a rare devastating complication of SLE. The prevalence of retinal disease in SLE accounts for 10% of cases. Mild forms of retinopathy are usually asymptomatic. In acute cases of SLE, the retinal changes manifests as defects in the visual field, distortion or floaters and sudden loss of vision. Anti-inflammatory agents, corticosteroids, anti-malarials play a major role in the management of long-standing complications of SLE. Immune complex deposition of antibodies against various structures of eye manifest differently. Early suspicion, prompt treatment, periodic monitoring of disease activity, early ophthalmic assessment of fundus, retina will bring down the incidence of SLE associated blindness. Early intervention of immune complex mediated Vasculitis involving eyes will prevent brain stem and central Nervous system (CNS) complications will bring down the mortality.

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1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease (CTD), affects all organs in the body with the production anti nuclear antibodies (ANA). Ocular manifestations of SLE are ranging from asymptomatic nonspecific transient inflammatory episodes of conjunctivitis to acute blindness which are either unnoticed by the patient or misinterpreted by the clinician. The clinician should aware of signs and symptoms of CTDs and their dreadful complications, and should consider CTD as a differential diagnosis with higher priority, whenever they come across patients with multiple complaints like

easy fatigability, persistent fever, photosensitivity, joint pain, throbbing head ache and ocular illness. Most of the patients are often treated inadvertently with over the counter steroidal preparations, further delays the clinical diagnosis of CTD and complicate further. Unless the patient develops symptoms like untractable pain, red eyes (Table 1), visual hallucinations, vision threatening complications most of the cases will not prefer a specialist ophthalmological consultation. In this review, have focussed mainly on, the significance of various life threatening ocular as well as sytemic complications and their clinical presentations.

Ocular manifestations of SLE develop in about 30% cases affect anterior and posterior segments of the eye. Circulating Immune complexes are deposited in the blood vessels cause vasculitis and thrombosis of the conjunctiva,

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retina, choroid, sclera, ciliary body, basement membrane of the ciliary body and corneal nerves resulted in blindness. Ocular complications were significantly correlated well with disease severity and it can be considered as a marker of disease severity in SLE (Table 1).¹

SLE affects the periorbital tissue, ocular adnexa, all segments of eye, retina, optic nerve and the inflammation tends to involve even brain. The most common ocular complication of SLE is keratoconjunctivitis sicca which can be easily visualized with naked eye. Sjogren syndrome (SS) is another auto immune connective tissue disorder which is known to cause dry eyes and dry mouth secondary to involvement of glandular secretion. Anti-cardiolipin (ACA) and anti-phospholipid antibodies (APA) deposited in optic nerve can cause blindness follows optic neuritis and retinal vein occlusion

The ophthalmological examination of SLE should be carried out in all cases at all stages of disease activity and also before and after starting chloroquine for fundus status and also to assess the ocular toxicity. Hence the physician should be more suspicious when the patients presenting with dry eyes, redness, severe pain, head ache, blurring or sudden loss of vision in association with photo sensitive rash. Such complex clinical presentation, should arouse the physician to suspect, either SLE complicating ocular or CNS disease. All those patients should get an emergency ophthalmological consultation. Institution of corticosteroids in high dose can reverse most of the complications in moderate to severe cases. The irreversible visual loss will affect the quality of life of affected individual if not intervened early.

2. Orbital cellulitis in SLE

Orbital complications are relatively rare in SLE. It commonly affects the skin over periorbital region, orbit, underlying extra ocular muscles, subcutaneous fat and the vessels supplying the structures of orbit. Histopathological findings are similar to SLE lesions of skin and other organ systems, suggestive of vasculitis, myositis, and panniculitis. The affected individuals commonly develop sudden onset of severe orbital pain, edematous swelling and blurring of vision and clinically presenting with proptosis, enophthalmos, chemosis. The extraocular movements are also restricted. The clinical presentation may closely resemble orbital cellulitis which may mislead the physician, to refer the case for surgical intervention.

Vascular involvement associated Ischemic complications are common, which usually follows after an acute episode of orbital vasculitis. It causes non-perfusion of the globe and extraocular muscles. In severe cases, irreversible loss vision secondary to ischemic injury to the optic nerve, and high intraocular pressure resulting from neovascular glaucoma are common.² SLE associated orbital myositis also can mimic orbital cellulitis. The involvement of extra ocular

muscles can be non-invasively visualized with the help of computerized tomography (CT) and orbital ultrasound. The markers of muscle enzymes creatinine kinase (CK) and aldolase levels are markedly elevated.

The patients with discoid lupus erythematosus (DLE) often develop localized sub cutaneous inflammatory swellings termed as “lupus erythematosus panniculitis” affects the orbit. They commonly present as tender deep subcutaneous nodules involving proximal extremities, trunk, the face, and scalp. Histopathology reveals perivascular lymphocytic infiltrate involving dermis and subcutaneous tissue. This condition responds dramatically to steroid therapy. Enophthalmos is a rare event develop in CTD as result of underlying fat atrophy.³

3. Facial erythema (periorbital) in LE

Acute SLE cases commonly present with facial erythema and diffuse swelling overperiorbital region.(Figure 1) The Neonates born to subacute cutaneous lupus erythematosus mother with positive titres ANA and anti Ro antibodies will develop neonatal LE lesions will which involve the periorbital regions on both sides in addition to facial rash.(Figure 2) The periorbital edema is a sign of renal complications of SLE. The erythematous to violaceous edematous rash commonly labelled as ‘heliotrope rash’, is a sign of dermatomyositis (DM), an auto immune CTD commonly present in association with SLE in overlap syndrome.(Figure 3) Juvenile dermatomyositis is also a common CTD, and the affected children will develop diffuse infiltration and generalized poikiloderma like lesions everywhere. The classical lesions of DM Gottron’s papules involve the dorsum of hands with erythematous violaceous papules and plaques sparing the knuckles. Localized periorbital swelling with diffuse edema of the eyelids are also tend to occur in juvenile cases of dermatomyositis. Localized form of scleroderma can affect the orbit and fore head with its classical form called ‘en coup de sabre’ will show linear atrophic scarring of scalp and forehead. Morphea, a localized form of scleroderma, involving face will have subcutaneous atrophic lesions and hemifacial atrophy involving face. Systemic sclerosis(SSc) can affect the facial skin, eye lids cause restriction of retraction of eye lid and diffuse fibrotic changes which cause mask like face, also common when it as associated with SLE.

Periorbital edema occurs in 4.8% of cases of systemic and discoid lupus erythematosus. Violaceous swelling with overlying eczematous changes without any skin necrosis is seen occasionally which may resemble chronic blepharitis. Periorbital edema in SLE can be secondary to nephrosis, increased vascular permeability, dermal mucin deposits, and angioedema secondary to C1 esterase deficiency. Treatment options include topical/intradermal/systemic corticosteroids, and antimalarial agents in mild cases.

4. Blepharo- conjunctivitis in SLE

The chronic cutaneous form of lupus erythematosus clinically presents as discoid rash, commonly involves eyelid and other sun exposed areas on the head, face and neck. The classical discoid lupus erythematosus develop over eye lids with characteristic well defined erythematous, scaly plaques with adherent scales restricts the eye opening. When the DLE lesions heal it leads to atrophic scarring and depigmentation. DLE lesions of the eyelid can mimics squamousblepharitis and eczema. Lupus lesions involving eye lids develop blepharoconjunctivitis as a result of inflammation of the Meibomian glands. When the lupus lesions heal, the patients will develop madarosis, lid scarring, and cicatricial ectropion/entropion.

5. Dry eyes in SLE

SLE patients when they developed dryness and irritation of the eye, which can be the clinical sign of Sjogren's (SS) syndrome. Keratoconjunctivitis sicca is the most common form of ocular complication of SLE, clinically manifests as dry eyes, lack of tear production which can be managed with artificial tear preparations, (Table 2) those patients with keratoconjunctivitis sicca, in the Raynaud's phenomenon (RP) have mild disease course of SLE with reduced mortality. Other clinical findings are symblepharon formation, forniceal foreshortening, and exposure keratopathy which affects the vision. Histopathological examination of cornea and conjunctiva shows loss of goblet cells, keratinization of the conjunctival epithelium, monocellular infiltration, and granuloma formation in the substantia propria. Immunopathology shows immune complex deposition within the epithelial basement membrane with an increased number of CD4+ and CD8+ T cells, B cells, and macrophages.

6. Red eyes or episcleritis in SLE

Episcleritis was reported in 2.4% of SLE cases. Young females are most commonly affected. The clinical features consist of red eyes, dull ache and excessive tearing. Childhood cases are rare. It needs only symptomatic treatment with topical/systemic nonsteroidal anti-inflammatory drug.

Scleritis is an inflammatory complication of sclera which can be classified in to anterior scleritis and posterior scleritis. Anterior scleritis of sclera shows tender nodular or diffuse infiltrate characterized by scleral nodules, red eye with severe pain. On examination the sclera appears violaceous as a result of injected deep episcleral vessels. Necrotizing anterior scleritis causes scleral thinning of the eye and the deep structures appear dark due to easy visualization of the underlying uveal tissue. [Figures 4 and 5].

Posterior scleritis may not show redness of eyes but presents with severe pain, blurred vision, limited eye

movements, and proptosis. Blurred vision is the most alarming sign as it occurs due to exudative retinal detachment, macular distortion due to a large scleral mass, and cystoid macular edema. The natural course of episcleritis vary with underlying disease severity of SLE hence it can be considered as a sign of disease activity, requires systemic therapy.

7. Retinal complications in SLE

Retinal involvement is a rare devastating complication of SLE. The prevalence of retinal disease in SLE accounts for 10% of cases. Mild forms of retinopathy are usually asymptomatic. In acute cases of SLE, the retinal changes manifests as defects in the visual field, distortion or floaters and sudden loss of vision. (Table 2) Urgent ophthalmic intervention is needed. As the severity of signs and symptoms of retinal complications runs a parallel course with SLE disease activity. Persistence of inflammation in spite of various therapeutic corticosteroid and immunosuppressive agents indicates inadequate disease control SLE. The presence of anti-phospholipid antibodies (APA) is a poor prognostic sign of SLE as there is a severe retinopathy and vascular occlusions.⁴

The ophthalmic examination of mild cases of lupus retinopathy shows cottonwool spots, perivascular hard exudates, retinal hemorrhages and the presence of tortuous blood vessels. (Figures 6 and 7) There is a focal or generalized arteriolar constriction and venous tortuosity observed in moderate to severe cases of SLE. (Figure 8) All the features may mimic hypertensive retinopathy and diabetic retinopathy. If the patient has concomitant systemic hypertension and diabetes in addition to lupus, monitoring the retinal changes during treatment will be a challenging task.

Most severe cases of lupus retinopathy associated with sudden onset of retinal arteriolar occlusion and infarction of retina are collectively labeled as "vaso- occlusive retinopathy" or retinal vasculitis. (Figure 9) Similarly, vitreous hemorrhage, retinal traction and retinal detachment secondary to proliferative retinopathy is encountered in around 72% of cases. Occlusion of large vessels (central and branch retinal vein occlusions, central and branch retinal arteriole occlusions) are more frequent in those SLE patients with positive anti phospholipid antibody. Fundus fluorescein angiogram will be helpful in diagnosing the retinopathy.

The involvement of choroidal structures may show features suggestive of pseudo-retinitis pigmentosa and exudative retinal detachments. As a result of immune suppressive therapy with cytotoxic agents or corticosteroids in high dose, prolonged course, the SLE cases complication lupus retinopathy are more prone to develop viral infections of the retina. The common organisms encountered in causing retinal infections are herpes simplex, varicella zoster virus and cytomegalovirus, causes retinal necrosis.

Table 1: Causes of red eye in SLE

Frequency	SLE Associated Ocular Diseases
Common	Dry eye (kerato-conjunctivitis sicca)
Less common	Episcleritis, Scleritis, Conjunctivitis (non-infective)
Rare	Keratitis (other than kerato-conjunctivitis sicca) ,Anterior uveitis

Table 2: Ocular Manifestations of SLE

Parts of eye	SLE ocular manifestations
Anterior segment	Severe kerato-conjunctivitis sicca
Lens	Cataract (secondary to inflammation and/or corticosteroids)
Vitreous	Vitreous haemorrhage (secondary to proliferative retinopathy)
Retina	Severe vaso-occlusive retinopathy, Central retinal vein occlusion (CRVO), Branch retinal vein occlusion (BRVO), Central retinal arteriole occlusion (CRAO), Branch retinal arteriole occlusion (BRAO), Exudative retinal detachment Toxic maculopathy (secondary to anti-malarial treatment).
Choroid	Lupus choroidopathy, Choroidal effusion, Choroidal infarction, Choroidal neovascular membranes.
Neurophthalmic	Optic neuritis, Anterior ischaemic optic neuropathy, Posterior ischaemic optic neuropathy, Optic chiasmopathy, Cortical infarcts.

8. Choroidal changes in SLE

Lupus choroidopathy with exudative retinal detachment is a rare ocular manifestation of SLE. Its occurrence may coincide with CNS vasculitis and nephropathy may present with uncontrolled blood pressure. The choroidal changes are made out clearly by using indocyanine green to evaluate choroidal vascular and tissue inflammation. The fluorescein angiography used as a diagnostic tool in the evaluation of optic nerve inflammation, retinal vascular disease, retinal ischemia, and macular oedema. The pathogenesis of choroidal involvement in SLE is multifactorial. The presence of uncontrolled hypertension, immune complex deposition in the capillaries, antibodies formed against retinal pigment epithelium are the possible factors responsible for the choroidal changes.

9. Optic Neuritis in SLE

Optic neuritis and ischemic optic neuropathy are the rare manifestations of SLE. Impairment of visual acuity is may be worsened more than 20/200. Visual recovery is possible at an early stage, but the recovery takes longer time. SLE induced optic neuritis should be differentiated from idiopathic optic neuritis, which is a primary inflammatory demyelinating disorder of optic nerve, whereas SLE induced optic neuritis cases will have ischemia associated demyelination of optic nerve and axonal necrosis.

Optic neuritis, induced acute loss of vision can be presented with 'altitudinal visual field defect' with or without the oedema of the optic disc. Occasionally focal thrombotic event in the ciliary vasculature can worsen the underlying scenario. High-dose corticosteroids and treatment with immunosuppressive agents such as cyclophosphamide, cyclosporine, methotrexate, and azathioprine tried with

variable success rates.

10. Brain stem/ Neural complications of SLE

Eye movement abnormalities are common in SLE seen in 29% of cases. They can occur as a result of ischemic microvascular disease affecting brainstem, or palsy of sixth cranial nerve which is responsible for the dis-conjugate gaze abnormalities. Visual hallucinations as a result of retro-chiasmal involvement and internuclear ophthalmoplegia also responsible. The other findings are visual field defects, nystagmus, and cortical blindness. The coexistence of antiphospholipid antibodies correlates well with the development of idiopathic intracranial hypertension in the presence of SLE and disease severity.

11. Management of ocular complications in SLE⁵

Ocular complications are mostly unpredictable, and clinical severity vary with underlying disease activity, genetic susceptibility and various predisposing conditions. Acute disease exacerbation with severe throbbing pain and blindness can occur in asymptomatic mild form of disease or those on irregular treatment. Treatment of ocular manifestations is similar to management of SLE. Topical artificial tear liquids, anti-bacterial agents and adequate eye protection should be advised in all cases. Mild cases can be managed with topical or oral nonsteroidal anti-inflammatory drugs, corticosteroids, antimalarial agents, immunomodulatory, and biologic agents. If there is a severe vision threatening complications like severe orbital inflammation, scleritis, retinal vasculitis, choroiditis, and optic neuritis systemic therapy should be considered. The goal of treatment is to suppress immune activity, specifically decreasing the level of autoantibodies.

12. Anti-Malarial agents in ocular LE

Mild asymptomatic SLE cases may not require any aggressive treatment, but monitoring the disease activity should be carried out at every visit. Anti-inflammatory agents, corticosteroids and anti malarial agents like hydroxychloroquine (HCQ), chloroquine are useful in milder forms of disease. The chloroquine and HCQ therapy is relatively safe when compare to all other immunosuppressive agents. HCQ has an added advantage over cytotoxic agents as it curtails future flares and inflammation. Chloroquine induced Irreversible vision loss can occur due to maculopathy, when higher doses for prolonged period of time, or without assessing underlying ocular complications prior to HCQ therapy.

Various predisposing factors for HCQ induced maculopathy are instituting therapy beyond 5–7 years, exceeding the cumulative dose of 1000 g, underlying impairment of liver or kidney function, obesity, elderly aged patients (>65 years), and pre-existing retinopathy. The American Academy of Ophthalmology courtesy should come after legend to figure followed by annual examination starting at 5 years after initiating therapy. In addition to funduscopic or ophthalmoscopic, slit lamp examination if facilities are available, a Humphrey 10–2 automated visual field test along with multi-focal electro Retinogram, spectral domain optical coherence tomography, or fundus auto fluorescence should be performed at each of these visits. Discontinuation of the drug should be recommended at the earliest sign of toxicity and some cases often progress towards retinopathy in spite of withdrawal of HCQ.

13. Corticosteroids and Immunosuppressive Agents in Ocular Complications of LE

Corticosteroids are the mainstay and most effective short-term therapy for SLE. Corticosteroids inhibit both the innate and adaptive immune response by preventing proliferation and inducing apoptosis of T cells, B cells, and macrophages as well as reducing levels of cytokines and prostaglandins. Periocular steroid injections may have a role in unilateral/asymmetric disease; however, they should be used cautiously and avoided in patients with scleritis. Steroid-sparing immunosuppressive agents are used in a large amount of patients following treatment failure or harmful side effects of corticosteroids.

They include methotrexate, azathioprine, mycophenolate mofetil, cyclosporine A, cyclophosphamide, and chlorambucil. They are highly effective during acute flares and/ or they can be combined with corticosteroids.

Those cases who do not respond to corticosteroids and immune suppressive agents or those patients complicated by drugs or those who require long term therapy should be subjected for therapy with biological agents. It targets specific molecules involved in B- and T-cell activation.

Rituximab, a chimeric murine/human anti-CD20 antibody shows successful outcome even in refractory patients.⁶



Fig. 1: Erythematous facial rash of systemic lupus erythematosus with periorbital swelling

Courtesy Dr. Geetharani, (Prof and Head, dept of DVL, Madurai Medical College)



Fig. 2: Neonatal LE with facial LE rash involving face and upper eye lid

Courtesy Dr. Geetharani, Prof and Head, Dept. of DVL, Madurai Medical College



Fig. 3: SLE/Dermatomyositis overlap syndrome with periorbital edema and blepharitis



Fig. 4: Slit-lamp photograph demonstrating diffuse anterior scleritis in a patient with SLE.

Courtesy ref. 1 Neal V. Palejwala, Harpreet S. Walia, and Steven Yeh et al

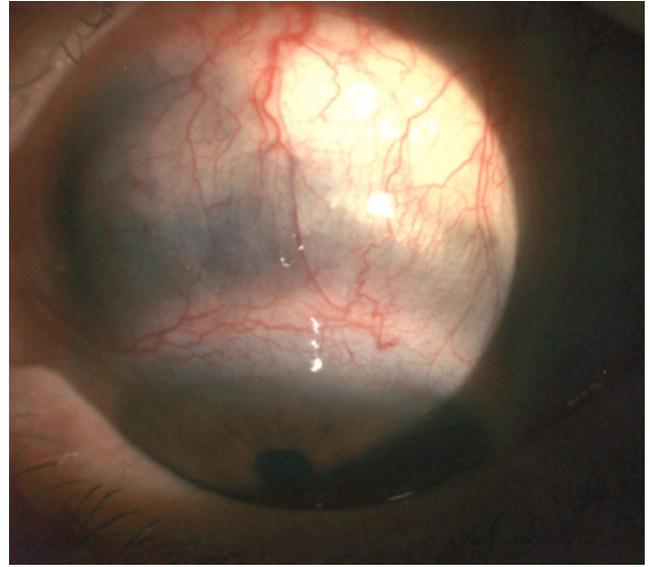


Fig. 5: Necrotizing anterior scleritis resulting in scleral thinning. Areas of scleral thinning appear dark due to visualization of the underlying uveal tissue.

courtesy ref 6. Sivaraj RR, Durrani OM, Denniston AK, Murray PI, Gordon C. Ocular manifestations of systemic lupus erythematosus. *Rheumatology* 2007;46 (12):757–1762

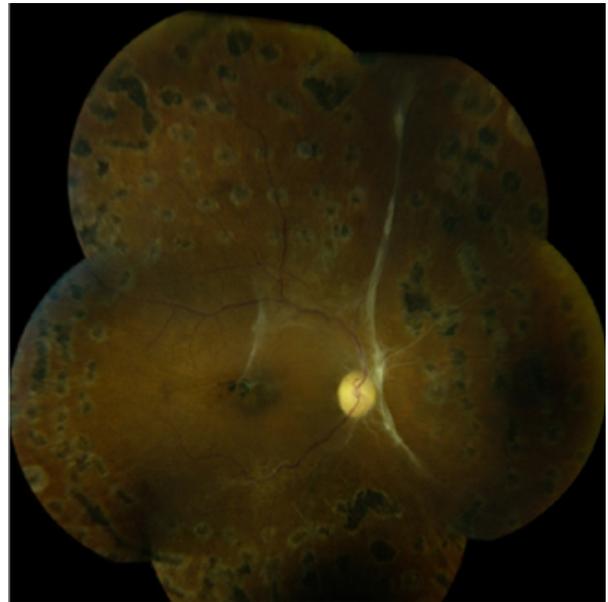


Fig. 6: Funds photograph demonstrating severe retinal vasculitis. Significant ischemia is present which is highlighted by the attenuated and sclerotic vasculature. Panretinal photocoagulation is required to treat ischemic and neovascular complications.

Courtesy ref. 1 Neal V. Palejwala, Harpreet S. Walia, and Steven Yeh et al

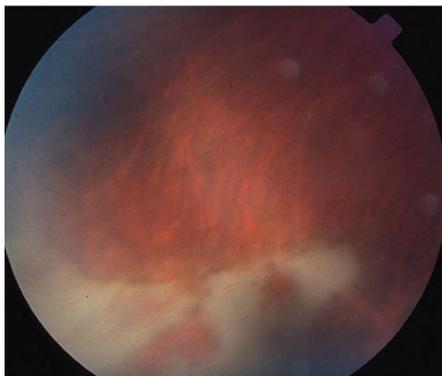


Fig. 7: Acuteretinal necrosis secondary to varicella zoster virus in a patient with SLE.

(Courtesy ref 6. Sivaraj RRet al

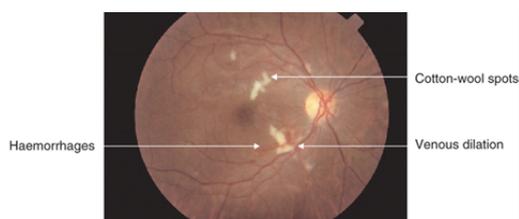


Fig. 8: Acute lupus retinopathy with cottonwool spots, haemorrhages, arterial narrowing, venous dilation and tortuosity.

courtesyref 6. Sivaraj RRet al



Fig. 9: Branchretinal arteriole occlusion in a patient with SLE and antiphospholipidsyndrome.

14. Conclusion

In summary, multi-disciplinary approach is a corner stone in the management of most dreaded ocular complications of SLE. Ocular complications of SLE like 'painless blindness' may be the early presenting sign of SLE, which occur several months in advance before developing photo sensitive rash or proteinuria.⁷ As there is a strong correlation between disease severity of SLE severe ocular complications like choroidopathy, retinopathy, the eye changes are the sensitive markers for disease activity in SLE. The occurrence of redness, retro bulbar pain, blurred vision necessitates ophthalmological intervention at the earliest. The combined advanced diagnostic therapeutic approach of eye complications, at an early stage, along with close communication between the treating physician and consultant ophthalmologist, is critical in the effective management while treating such complex clinical situations.

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17. Conflict of Interest

None.

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