REVIEWS

Ocular lesions in systemic lupus erythematosus: An overview

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Abstract

Systemic lupus erythematosus (SLE) is a life-threatening, multisystemic, chronic autoimmune disease. Ocular manifestations of SLE are diverse, affecting any part of the eye. It is a potentially blinding disease with ocular manifestations as the presenting feature. The prevalence of retinal involvement is estimated to be 3% to 29% and it tends to be bilateral and asymmetrical. Retinal signs often concur with the severity of systemic inflammation. Microangiopathy in SLE mimics diabetic and hypertensive retinopathy, moderately severe SLE can have presentation that mimic Purtscher-like retinopathy with a prevalence of 0.14%. Vaso-occlusive disease can either have isolated/ combined, retinal artery or vein occlusion. Associated antiphospholipid antibody also increases the risk of vaso-occlusion. The occurrence of optic neuritis and ischemic optic neuropathy is rare in SLE. Presence of peripheral ulcerative keratitis, and scleral, orbital, retinal, choroidal, and neurological manifestations require immediate systemic therapy. Hydroxychloroquine >6.5 mg/kg for 5 years is associated with high risk of toxicity. Modern imaging techniques like fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) help in diagnosis and monitoring of disease activity.

Keywords: Systemic lupus erythematosus, SLE, ocular lesions, manifestations, retinopathy

Introduction

Systemic lupus erythematosus (SLE) is a chronic life-threatening, autoimmune, complex connective tissue disease with a relapsing and remitting clinical course. It can affect almost any organ system and ocular involvement is noted in one-third of the SLE patients.[1] Presentations are highly variable ranging from indolent to fulminant. Ocular manifestations range from mild to severe manifestations with significant visual morbidity and may also indicate underlying systemic disease activity. Early diagnosis and management can lead to reduction in severe ocular complications. SLE affects both genders and all ethnic groups, and has striking female preponderance.

Tissue damage occurs due to microvascular inflammation, and the production of autoantibodies or immune-complex depositions play a major role in SLE pathogenesis. These changes can occur in kidneys, heart, vessels, central nervous system, skin, lungs, muscles and joints, leading to significant morbidity and mortality.[2] Both innate and adaptive immune responses are involved in SLE. In eyes, immune complex deposition is identified in blood vessels of conjunctiva, retina, choroid, sclera, ciliary body, and basement membrane of cornea and ciliary body.[3] Antibody-dependent cytotoxicity leads to retinal cell death and demyelination of optic nerve.[4]

Incidence

The incidence of SLE ranges between 0.3-31.5 cases per 100 000 individuals per year and has increased in the last 40 years, probably due to recognition of milder cases. Adjusted prevalence rates worldwide are approaching or even exceeding 50-100 per 100,000 adults.[5] Therefore, numerous targets have been identified, which act against TNF- α for the potential management of inflammation.

Ocular manifestations

Ocular manifestations of SLE may affect any part of the

eyes and visual pathways. Drugs used in SLE can also cause ocular complications like cataract and retinopathy. Ocular lesions include discoid lupus type of eyelid rash. The keratoconjunctivitis sicca is the most common ocular manifestation, and orbital involvement like orbital masses, periorbital edema, orbital myosotis, or acute orbital ischemia is rare. Corneal involvement can present as recurrent corneal erosions, filamentary keratitis, corneal ulceration and scarring. Peripheral ulcerative keratitis indicates active SLE disease.[4]

Scleral involvement can manifest as episcleritis, anterior (diffuse, nodular or necrotizing scleritis) and posterior scleritis. Episcleritis and scleritis can be the presenting features of SLE. Episcleritis presents with redness and irritation and it is often self-limiting. Posterior scleritis does not cause redness, however it can cause visual disturbance and pain on movement of the globe.

SLE retinopathy

Prevalence of retinal involvement in SLE is estimated to be 3% to 29%.[6] SLE retinopathy is a potential blinding ocular disease, which tends to be bilateral and asymmetrical. It indicates that systemic disease is inadequately controlled. SLE retinopathy may occur due to the disease itself, secondary to the renal involvement or due to the drug toxicity. The retinal signs are often parallel to the severity of systemic inflammation. The SLE renal involvement leads to secondary hypertension, eventually affecting retina and choroid with signs of arteriolar attenuation, arteriovenous crossing changes, cotton wool spots and disc edema.

SLE retinopathy can be further classified into three types namely mild, moderate and severe. Mild lupus retinopathy may be asymptomatic, whereas the moderate and severe lupus retinopathy cases have profound retinal involvement.

Microangiopathy may often mimic hypertensive retinopathy or diabetic retinopathy. Presentation includes cotton wool spots, perivascular hard exudates, retinal hemorrhages, arteriolar narrowing with capillary dilations and venous tortuosity. The cotton-wool spots, the most common finding, can be isolated or may be surrounded by hemorrhage. Additional small, discrete spots may also be seen alone or in areas of retinal edema and infarction.[9] They usually have good visual prognosis and reverts upon controlling the blood pressure and blood sugar.

More severe disease presents with decrease in visual acuity, visual field defects, distortion and floaters. Moderately severe type can present with focal/ general arteriolar constriction, venous tortuosity, and Purtscher-like retinopathy. The Purtscher-like retinopathy may be attributed to the microemboli formation, which results in arteriolar pre-capillary occlusion and microvascular infracts. The visual prognosis is usually poor, despite prompt treatment. Prevalence of central nervous system lupus is highly significant among Purtscher-like retinopathy. In a study by Chan et al., high SLE disease activity index >20 was noted in patients with Purtscher-like retinopathy. Overall prevalence of Purtscher-like retinopathy was 0.14%.[7]

Severe lupus retinopathy includes vasculitis (Fig.1), vaso-occlusive retinopathy, and proliferative retinopathy. The vaso-occlusive retinopathy is common end point of vasculitis. It includes central retinal artery occlusion, branch retinal artery occlusion, central retinal vein occlusion and branch retinal vein occlusion (either isolated or combined, unilateral or bilateral).[5]The vein occlusion is noted in nearly 63.3% of the patients with SLE retinopathy. The association of antiphospholipid antibody syndrome raises the risk of retinal and central nervous system occlusion by 4 times.[7]

Proliferative retinopathy is seen in 72% of SLE cases.[3] The spectrum of presentations includes neovascularisation (occur in 72% of eyes), vitreous haemorrhage (Fig. 2), retinal traction and retinal detachment. Pseudoretintis pigmentosa and pigmentary changes are rare manifestations. A study from Nepal has reported the renal involvement in 59.3% cases and central nervous system in 11%. Among lupus nephropathy cases, 27.3% had central nervous system involvement.[8] Viral retinitis secondary to cytomegalovirus, herpes simplex, or varicella zoster is reported in patients who had immunosuppression due to treatment regimen, and it is one of the most dreadful ocular complications.[3]

SLE choroidopathy is an underdiagnosed cause of visual morbidity. It serves as a sensitive indicator for disease activity. It can present as single or multiple areas of serous or exudative retinal detachment; the choroidal effusions can lead to secondary angle closure glaucoma. Choroidal ischemia presents as hypopigmented subretinal patchy lesion and choroidal neovascular membrane.[5] Sobrin et al. have described lupus choroidopathy with multiple areas of subretinal fluid and pigment epithelial detachments. The fundus may be left with a mottled appearance to the pigmented epithelium upon resolution of the fluid.

Optical coherence tomography (OCT) has no characteristic

Fig. 1: Fundus montage showing vasculitis, perivascular exudates and retinal hemorrhages

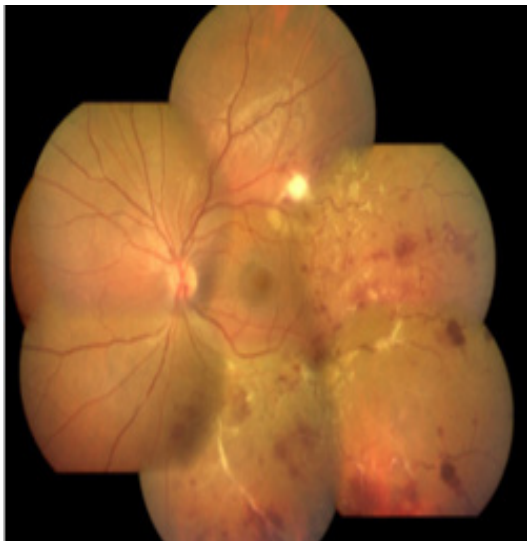


Fig. 2: Fundus montage showing severe SLE retinopathy in right eye with neovascularisation

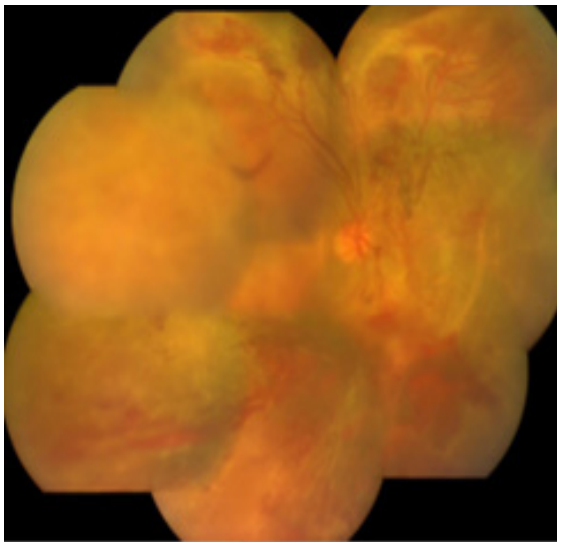
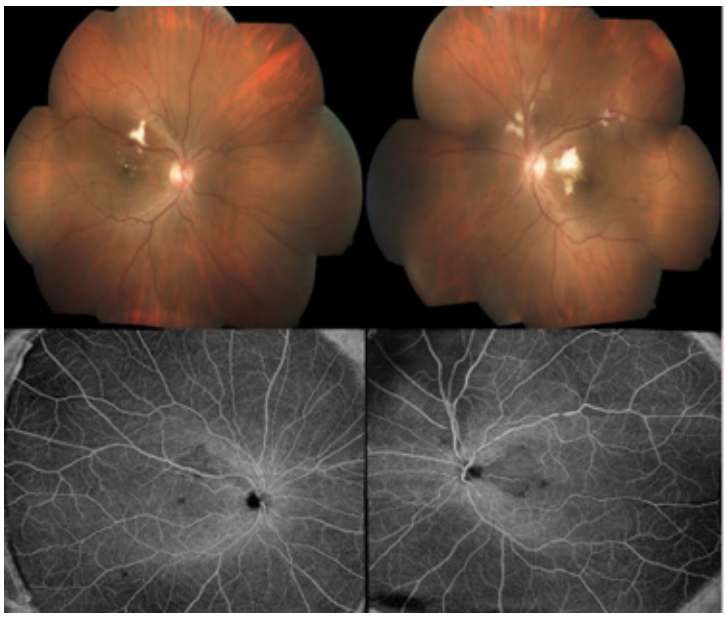


Fig. 3: Color fundus photographs showing corresponding retinal vasculitis and cotton wool exudates in both the eyes

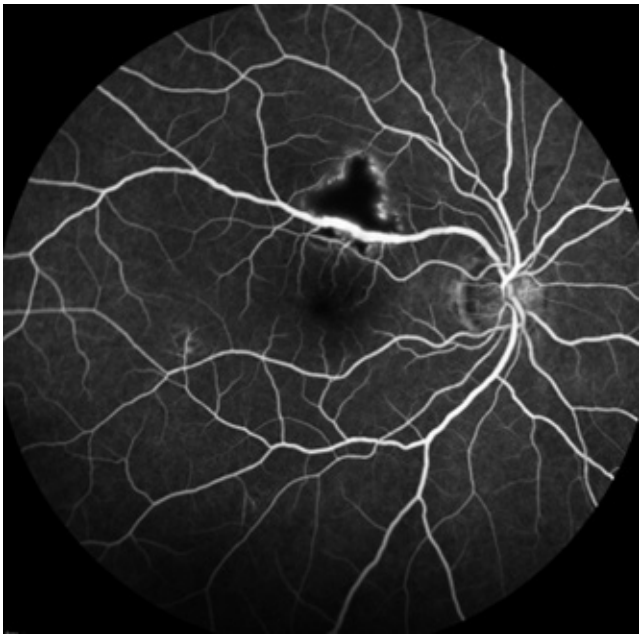


OCTA showing central area of blocked signal intensity corresponding to cotton wool spots. Right eye angiography scan shows distortion of FAZ .

finding for SLE retinopathy. Reduced retinal thickness in long-standing cases occurs due to prolonged ischemia causing atrophy of retinal layers. Optical coherence tomography angiography (OCTA, Fig. 3) is a non-invasive technique for assessing the vascular parameters. Its potential role in early detection of macular ischemia by estimation of superficial capillary plexus density has been published in literature. OCTA can recognize capillary non-perfusion areas, distorted or enlarged foveal avascular zone, and abnormal new vascular network.

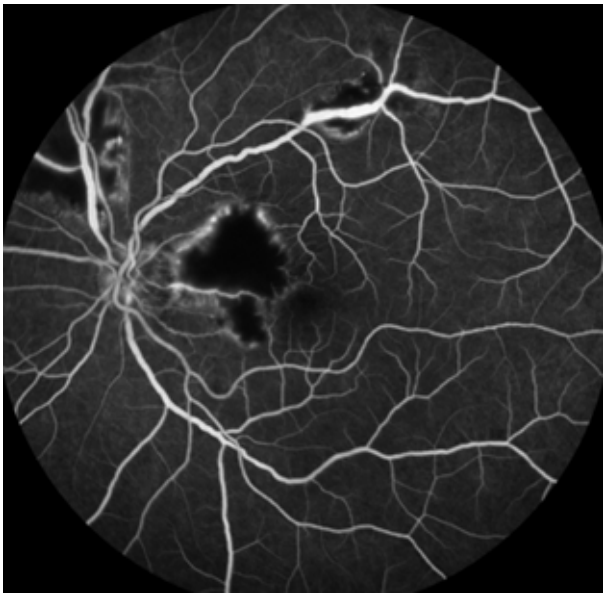
Fluorescein angiography (FFA) is indicated for use in SLE retinopathy (Fig. 4 and Fig. 5). It can help diagnose subclinical cases as well as any secondary complication due to the condition. The classical cotton wool spots in SLE retinopathy occurs due to ischemia causing axoplasmic stasis. Arteriolar

Fig. 4: FFA of right eye showing blocked fluorescence and perivascular staining



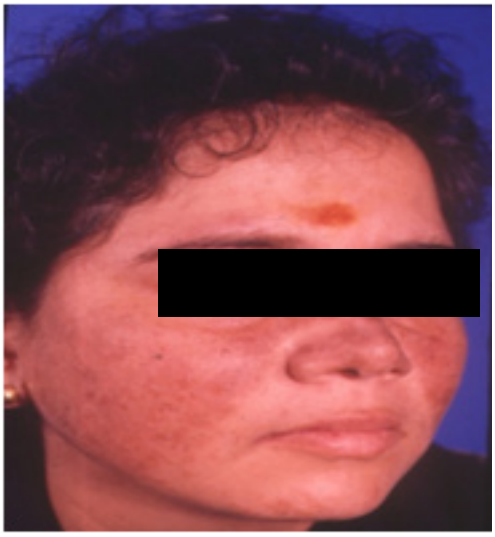
FFA of right eye shows large well demarcated blocked fluorescent along the superotemporal arcade, which is suggestive of cotton wool spots. Hyper fluorescence seen along the capillaries in inferior temporal quadrant. suggestive of staining

Fig. 5: FFA of left eye showing blocked fluorescence with perivascular staining



FFA of left eye shows multiple blocked hypofluorescent areas suggestive of exudates .There are multiple hyperfluorescent staining areas at the margins of hypofluorescent patchy areas suggestive of capillary leakage.

Fig. 6: A female patient of SLE with malar rash



dilatation noted in this condition is in contrast to the arteriolar attenuation and generalized ischemia prevalent in condition such as diabetes mellitus and hypertension. Focal leakage in capillaries is indicative of subclinical vasculitis in case of no evident clinical presentation. There are a few case reports on arterial occlusion in SLE retinopathy. Such patients present with neovascularization and hyperfluorescent enlarging leak on FFA. SLE does not cause primarily involvement of veins. If FFA is suggestive of venous involvement, any secondary venous occlusion should be kept in differential. Disc staining or leak noted on angiography is suggestive of vasculitis involving the optic nerve blood vessels. This can persist for long, even after the retinopathy is in quiescent stage.

Immunosuppressive treatment can help in resolution of choroidopathy. In immunocompromised state, the choroidal infections like nocardia choroidal abscess, endophthalmitis and tuberculous granuloma have been reported.[10,11] An increase in severity of lupus nephropathy or presence of CNS vasculitis in a patient should prompt evaluation of the choroid. The differential diagnoses for lupus choroidopathy include multifocal central serous chorioretinopathy, hypertensive choroidopathy, Vogt-Koyanagi-Harada disease, and choroidal metastasis.

Neurophthalmic involvement in SLE is rare and occurs in 1% of eyes with SLE. It includes optic neuritis resembling demyelinating disease. More than 50% of patients having persistent central scotoma, progressing optic atrophy, and ischemic optic neuropathy can present with acute onset, progressive binocular visual impairment with altitudinal and arcuate field defects. Oculomotor abnormalities are rare, while sixth nerve palsies are common. The unilateral optic neuropathy associated with antiphospholipid antibody syndrome reflects focal thrombotic event. Pupillary abnormalities like light near dissociation, Horner's syndrome, and Adie's pupil have been described in SLE. The incidence of transient monocular blindness is 11 times more in patients with SLE.[12] The disease can also present with idiopathic benign intracranial hypertension both in children and adults.[13,14]

However, it is believed that 16% of asymptomatic patients having evidence of retinal involvement is an alarmingly high rate for newly diagnosed patients and needs a shift towards incorporating ophthalmic examination as a screening test for all patients diagnosed with SLE.[15]

Ophthalmic manifestations can occur as a complication of SLE treatment. Immunomodulatory treatment is associated with major side effects. Cavernous sinus thrombosis has been reported with high dose of corticosteroid and intravenous cyclophosphamide treatment for lupus nephritis. Hydroxychloroquine (HCQ) can cause vortex keratopathy and irreversible drug-induced bull's eye maculopathy. Retinopathy continues to progress, despite drug cessation. The risk for developing HCQ-induced maculopathy is higher in patients receiving treatment of dosage >6.5 mg/kg for >5 years and with concomitant renal and liver diseases. The American academy of Ophthalmology has recommended conducting a baseline examination within the first year of HCQ use and annual screening for 5 years.[16] Most common side effects related to the use of corticosteroids are steroid-induced cataract, glaucoma and central serous

chorioretinopathy.

Imaging in SLE retinopathy

Modern imaging techniques like fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT) have helped in diagnosis and monitoring of this disease.

Fundus fluorescein angiography (FFA) helps in identifying subclinical entities like retinal capillary dilation, microaneuryms, capillary non-perfusion areas, hyperfluorescent leak in retinal neovascularisation, and sclerosed and non-perfused vessel occlusions. FFA can also be useful in detecting choroidal pathology to detect delayed choroidal filling, choroidal non-perfusion areas, multifocal subretinal leakage and pooling.[17] In Purtscher-like retinopathy presentation, slower filling of vessels, precapillary occlusion, and moderate mottling of retinal pigment epithelium, per papillary staining are seen.[6]

Indocyanine green angiography (ICGA) can help to identify active choroidopathy, which is not seen on FFA and missed clinically on fundus examination. It helps to detect focal, transient and hypofluorescent areas in the early phase, and spots of choroidal hyperfluorescence in the intermediate to late phase. Interestingly, pinpoint spots of ICG choroidal hyperfluorescence may represent immune deposition in deeper layer of choroidal stroma or Bruch's membrane.[18]

OCT is a non-invasive imaging technique. It is advantageous in active phase of disease in detecting intraretinal and subretinal fluid and pigment epithelial detachment. The qualitative and quantitative analysis of OCT are also beneficial in diagnosis and monitoring of lupus choroidopathy.[19,20] Retinal nerve fiber layer corresponding to cotton wool spots are thicker than that of Purtscher-like flecken.[6]

Diagnosis and assessment of disease activity

The diagnosis of SLE is primarily clinical and based on the presence of four or more of the 11 features listed by the American College of Rheumatology classification criteria (ACR/ ARA).[21,22] The presence of four criteria, serially or simultaneously, indicates a diagnosis of SLE.The revised criteria include: (1) malar rash (Fig. 6) (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. The presence of 4 of these 11 criteria confirms the diagnosis of SLE and has a sensitivity of 85% and a specificity of 95% for SLE.[23]

Patients with SLE retinopathy have lower C3 and C4 concentrations, and have higher levels of ANA and anti-dsDNA, which indicate an antibody-mediated retinal damage pathogenesis.[15] IgG anticardiolipin antibodies (IgG aCL) were detected in 26 of 61 patients (43%). Although IgG aCL were found only in 20/54 (37%) patients without retinopathy, 6/7 (86%) with retinopathy had IgG aCL ($P < 0.05$). Since antiphospholipid antibodies (aPL) are associated with increased risk for retinal and CNS occlusions, aPL should be added to the list of candidates causing lupus retinopathy.[24]

The most widely used disease activity indices of SLE are SLE Disease Activity Index and British Isles Lupus Assessment Group (BILAG) index. Comparison studies suggest both can be used for capturing disease activity and flare in large cohorts. The BILAG 2004 index has the precedence of scoring rare disease manifestations in SLE such as ophthalmic lupus with orbital inflammation, severe keratitis, scleritis, posterior uveitis, retinal vasculitis, retinal or choroidal vaso-occlusive disease, optic neuritis, and anterior ischemic optic neuropathy (all counting as category A features).[25-27] The widely used system for recording the damage in SLE is Systemic Lupus Erythematosus international Collaborating clinics (SLICC) or American College of Rheumatology classification criteria (ACR) damage index. Cataract and retinal changes or atrophy are the ophthalmic features that are scored using this damage index. It is important to differentiate between clinical presentations that indicate disease activity and those resulting from damage. Disease activity and damage might co-exist, and their distinction is important for appropriate treatment.

Treatment

Disease survival and the prognosis for patient with SLE have improved dramatically. Treatment targets include optimum control of systemic inflammation, to decrease the permanent organ damage, reduction in long-term mortality, and decreased corticosteroid-induced damage.

SLE treatment varies depending on the severity of disease and organs involved. Due to multi-organ involvement, collaboration with specialists (ophthalmologists, rheumatologists, nephrologists, dermatologists) is often required for tailored therapy.

Ocular manifestations in SLE play a role as a marker for systemic disease activity, indicating the need for escalation

of systemic treatment. Dual approach ensuring the optimized systemic control of SLE can manage the residual features with best therapeutics. If there are no systemic manifestations, ocular surface and anterior segment disease can be treated with standard topical therapy.

Treatment for SLE includes non-steroidal anti-inflammatory drugs, corticosteroids, anti-malarial drugs and immunosuppressive drugs. Corticosteroid is the mainstay for acute treatment in ocular SLE. They are fast acting and effective for short-term use. However, corticosteroid-sparing agents should be considered for long-term therapy. In patients with mild disease, NSAIDs and antimalarials like chloroquine and hydroxychloroquine (HCQ) are the preferred treatments. The presence of corneal PUK, scleral, orbital, retinal, choroidal or neurological manifestations usually requires systemic therapy.[28] Variety of immunosuppressive agents like methotrexate, mycophenolate mofetil, cyclosporine A, azathioprine, chlorambucil and cyclophosphamide have demonstrated efficacy in treating ocular SLE.

Intravenous (IV) cyclophosphamide has been beneficial, in severe cases such as lupus nephritis, central nervous system lupus and vasculitis.[29] Long-term immunosuppression can result in various serious side effects like bone marrow suppression, hepatotoxicity and risk of infection, and various opportunistic infections of retina and choroid.

Recently, several biologic agents targeting specific components of the immune system are being used for the treatment of SLE. Belimumab in most trial patients with musculoskeletal and mucocutaneous disease manifestations had shown to reduce disease activity and flare-up. However, they lack any role in managing lupus nephritis and severe non-renal lupus. Observational data suggested that rituximab and mycophenolate can dramatically limit the need of corticosteroids.[30] Other biologic agents that have completed early phase human trials are sifalimumab, rontalizumab, sirukumab, abatacept and N-acetylcysteine. TNF-α exerts deleterious tissue-damaging effects mainly through its pro-inflammatory activities and beneficial effects by dampening aggressive autoimmune responses. Soforo et al. concluded that patients treated with TNF blockers, especially those with positive ANA, should be closely monitored for development of SLE.[31]

Although systemic medication is required to treat the underlying disease, the ocular manifestations of SLE may require additional local therapy. In kerato-conjunctivitis sicca, ocular manifestations can be treated with artificial tears, punctal plugs and topical cyclosporine. FFA-guided targeted laser photocoagulation has been advocated for the treatment of vaso-occlusive lupus retinopathy. Combined intravitreal bevacizumab and intravitreal dexamethasone have promising results in the management of lupus retinopathy with macular edema. Vitrectomy can also be performed in proliferative retinopathy with vitreous hemorrhage or tractional retinal detachment resulting from ocular ischemia.[32] Anterior uveitis can be treated with topical corticosteroids.

Conclusion

SLE is chronic life-threatening, multisystem connective tissues disease. A high clinical suspicion for SLE is required for early recognition and diagnosis of disease. Eye manifestations can be the first presenting feature of the disease and if undetected, sight and life-threatening complications can occur. Reduction in visual acuity and pain needs urgent evaluation by an ophthalmologist. Treatment of ophthalmic involvement in collaboration with a lupus specialist is the key to reduce ocular morbidities. The presence of corneal peripheral ulcerative keratitis, and scleral, orbital, retinal, choroidal manifestations often requires systemic therapy. Course of SLE is highly relapsing and remitting, assessment of disease activity with accepted activity index helps in monitoring and can provide basis for therapeutic intervention. Many new therapeutic advances including biologic agents are being evaluated in the present years. However, ideal guidelines for treating SLE have not been established. Further research is needed to understand the pathogenesis of this disease and formulate ideal therapy.

Competing interests

The authors declare that they have no competing interests.

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