

Ocular Manifestations of Systemic Lupus Erythematosus

Asima Bajwa^{1,2} and Stephen C Foster^{1,2,3*}

¹Massachusetts Eye Research and Surgery Institution (MERSI), 5 Cambridge Center, 8th Floor, Cambridge, MA 02142, USA

²Ocular Immunology and Uveitis Foundation (OIUF), 5 Cambridge Center, 8th Floor, Cambridge, MA 02142, USA

³Harvard Medical School, Boston, MA, USA

*Corresponding author: Stephen C Foster, Massachusetts Eye Research and Surgery Institution (MERSI), 5 Cambridge Center, 8th Floor, Cambridge, MA 02142, USA, Tel: 617 621 6377; Fax: 617 494 1430; E-mail: sfoster@mersi.com

Received date: Dec 20, 2013, Accepted date: Feb 24, 2014, Published date: Feb 28, 2014

Copyright: © 2014 Bajwa, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by production of numerous antibodies that may affect multiple organ systems. Wide variety of systemic features of SLE are attributed to antibodies against the components of cell nuclei. Many of the clinical features, like nephritis and arthritis are due to deposition of immune complexes resulting in tissue damage. Other features of the disease such as hemolytic anemia, thrombocytopenia is due to direct effect of autoantibodies. The ocular manifestations of SLE include lid dermatitis, keratitis, scleritis, secondary Sjogrens syndrome, retinal and choroidal vascular lesions and neuro-ophthalmic lesions. Keratoconjunctivitis sicca is the most common ocular manifestation, but visual morbidity is usually due to retinal and neuro-ophthalmic manifestations of the disease. Ocular involvement may precede systemic onset of the disease. Early recognition of ocular disease by an ophthalmologist may prevent not only the blinding complications of SLE but also alert the clinician to the likely presence of disease activity elsewhere and timely institution of systemic therapy.

Keywords: Systemic lupus erythematosus; Ocular manifestations; Sjogrens syndrome; Glaucoma

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, multisystem disease and is believed to be a complex interplay of genetics, infectious and immunologic factors. It is particularly prevalent in women often with relapsing remitting clinical course. Its history dates back to 1845 when lupus dermatitis was first described by Hebra [1]. Kaposi in 1872 performed the first autopsy on a lupus patient and reported it as a systemic, life threatening illness. Ocular lesions (cotton wool spots, disc hyperemia, white retinal patches) were first reported in 1929 by Bergmeister [2].

The prevalence of SLE varies worldwide and is reported highest in Italy, Spain, Martinique and the UK, 40 per 100,000 in North America [3,4]. African Americans and Hispanics appear to have higher incidence rates. It may affect 1 in 1000 young women in child bearing age with median age of onset between late teens and early 40s [4].

SLE is believed to be a complex interplay of genetics, infectious and immunologic factors with a greater concordance rate of 30-50% in monozygotic twins, association with HLA-DR2, HLA-DR3, HLA-B7, HLA-B8 [5]. Various viruses, drugs and environmental triggers have been implicated to induce molecular mimicry [6]. Classically, antinuclear, anti double stranded DNA, anti single stranded DNA and anti Smith antibodies are implicated in the pathogenesis of SLE, but recent studies suggest that wider than the previously appreciated array of autoantibodies are produced in patients with SLE, including antibodies against annexins, CD 45 cell surface glycoprotein, calreticulin and nucleosomes [7-10].

Ocular manifestations of SLE—seen in one third of patients—can not only be vision threatening but also a marker of systemic disease activity.

Diagnostic Criteria

According to the 1982 revised criteria for systemic lupus erythematosus, a diagnosis of SLE can be made by the serial or simultaneous presentation of at least 4 of the following 11 criteria: malar rash, discoid rash, photosensitivity, oral ulcers, nonerosive arthritis, serositis, renal dysfunction, neurological derangements (i.e., seizures or psychosis), hematologic disorder (i.e., anemia, leukopenia, thrombocytopenia), immunologic disorder (i.e., anti-DNA antibody, anti-Sm antibody, and false positive VDRL testing), and presence of antinuclear antibodies (Table 1).

Although ocular inflammation may be a manifestation of SLE (indeed, may be the initial clinical obvious one), the ocular lesions are not included among the 11 criteria; we believe this is an oversight and believe, further, that inclusion of ocular inflammation among the diagnostic criteria for SLE would enable earlier establishment of the diagnosis and therapeutic intervention in some instances.

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis (nonerosive, two or more peripheral joints)
6. Serositis (pleuritis, pericarditis)
7. Renal disorder (proteinuria, nephritis)
8. Neurologic disorder (seizures, psychosis)

9. Hematologic disorder (hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia)
10. Immunologic disorder (anti-native DNA, anti-Sm, false-positive test for syphilis)
11. Antinuclear antibody (in the absence of drugs associated with "drug-induced" lupus)

Table 1: The 1982 revised criteria for the classification of systemic lupus erythematosus.

Ocular Manifestations

The incidence of ocular involvement varies between 20% to 34% in patients with SLE [11-15].

SLE can affect any part of the eye, adnexae or the visual system fairly commonly. Secondary Sjogren's syndrome is the most common and lupus retinopathy perhaps the most well recognized ocular manifestation of the disease.

In a study of 75 patients, including 26 with antiphospholipid syndrome Ostanek et al. reported, high activity of ocular disease (conjunctiva, iris, uvea, retina, spot, vessels and optical nerve disc involvement), late diagnosis of SLE (retinopathy and conjunctival involvement), arterial hypertension (reduced visual acuity, cornea involvement, vessel involvement), age (reduced visual acuity, cornea involvement, retinopathy), glucose metabolism disorders (changes in optical nerve disc) and presence of anti-double stranded DNA antibodies (retinopathy) as significant factors of the occurrence of eye involvement in our series of SLE patients.

Orbital disease

Rare ocular presentations include orbital masses, periorbital edema, orbital myositis, panniculitis, acute orbital ischemia and infarction. A biopsy is often necessary to confirm the diagnosis. Treatment is with systemic immunosuppression [16,17].

Escudero et al. reported unilateral exophthalmos secondary to orbital pseudotumor in patients with SLE is not only extremely rare but on occasion it can be refractory to conventional pharmacological treatment (glucocorticoids and immunosuppressants). They reported excellent clinical response to Rituximab in unilateral exophthalmos refractory to cyclophosphamide, probably due to the antibody mediated pathogenesis of SLE [18].

Orbital vasculitis leads to irreversible vision loss secondary to elevated intraocular pressure from neovascular glaucoma as well as ischemic optic neuropathy. This has been shown to be caused by nonperfusion of the globe and extraocular muscles [16].

Orbital myositis presents with significant pain, proptosis, periorbital swelling, and globe restriction due to which it may be misdiagnosed as bacterial orbital cellulitis. CT and orbital ultrasound are both valuable in demonstrating enlargement of one or multiple extraocular muscles. Creatinine kinase, aldolase, and myoglobin levels are markedly elevated. Inflammation and symptoms typically respond to steroids [17,19].

Lupus erythematosus profundus, also known as panniculitis is a nodular inflammation of adipose tissue. Panniculitis involving orbital structures as the primary presenting symptom of SLE is quite unusual and has only rarely been reported in the literature as orbital inflammatory syndrome [15].

Periorbital edema in the absence of proteinuria or hypoalbuminemia has been only rarely described in association with a flare of SLE that resolved promptly and completely with glucocorticoids. It appears as violaceous swelling with overlying eczematous changes without any skin necrosis. Some cases can resemble chronic blepharitis [20,21].

Eyelids

The eyelids may manifest the inflammatory and scaly lesions of discoid lupus erythematosus which appear as erythematous raised areas with keratotic scaling, more prominent over the lateral third of lower lid (Figure 1). The patients present with recurrent eyelid irritation and redness and, may be mistaken as blepharitis, meibomian gland dysfunction and eczema. Histopathologic features include hyperkeratosis, basal cell vacuolation, perivascularitis and dermal inflammation [22]. A distinct hypertrophic variant of discoid lupus erythematosus involving the conjunctiva has been described [23].

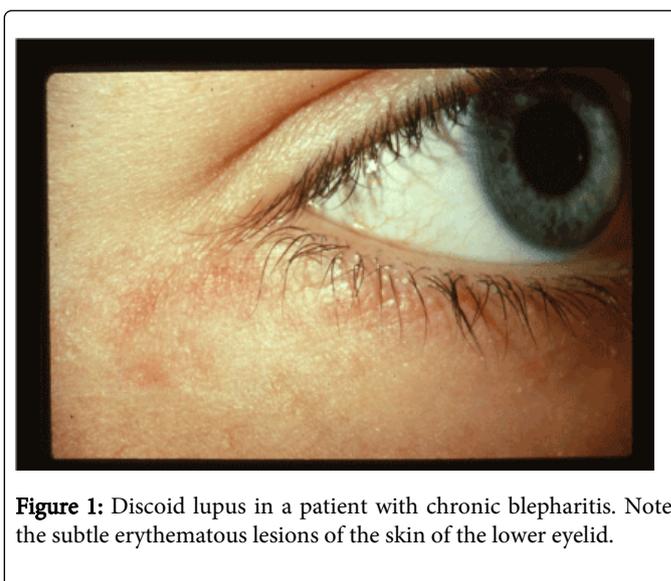


Figure 1: Discoid lupus in a patient with chronic blepharitis. Note the subtle erythematous lesions of the skin of the lower eyelid.

Secondary sjogrens syndrome

Secondary Sjogren's Syndrome or Keratoconjunctivitis sicca (KCS), the most common ocular manifestation of SLE is seen in 20% of patients and is indistinguishable from KCS due to other connective tissue diseases. The hallmark of disease is a decreased production of the aqueous layer of the tear film.

Manoussakis et al. [24] identified 9.2% who had developed Sjogren's syndrome (SS) in their review of 283 SLE patients. The SLE SS group had a lower frequency of renal involvement, lymphadenopathy, and thrombocytopenia but had a higher frequency of Raynaud's phenomenon, anti-Ro antibody, anti-La antibody, and rheumatoid factor. These patients tend to undergo a more benign course with a significantly reduced mortality and need for immunosuppression [25].

Episcleritis and scleritis

Episcleritis (superficial) and scleritis (deeper inflammation of the sclera) are both seen in SLE, and may be the presenting feature of the

disease [26] and scleritis is a reasonably accurate guide to the presence of significant systemic activity. Episcleritis usually presents with mild, if any, irritation, and redness due to injection of the superficial blood vessels (Figure 2). In a review of 100 patients with episcleritis, Akpek and coauthors noted SLE as an underlying disease in 4 of 36 (11%) patients with an identifiable systemic illness. Although episcleritis is generally considered a benign, self-limited disease, a careful review of systems and an ocular examination should still be conducted in patients with episcleritis, so as not to miss an associated ocular or underlying systemic condition [27].

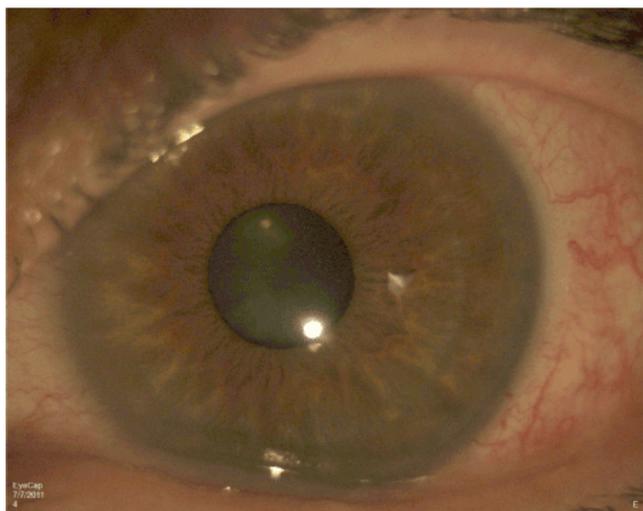


Figure 2: Episcleritis.

Scleritis is much more painful, described as an 'ache' or 'boring' and may be generalized to the whole eye or the side of the face. It may be sight threatening and requires urgent assessment by an ophthalmologist. In anterior scleritis there is redness due to injection of the deeper episcleral vessels which give a violaceous due to the sclera, best appreciated in natural light (Figure 3). In a review of 172 patients with scleritis, we found systemic vasculitic disease present in 82 patients (48%) including 7 with SLE (4%) [28]. Of these seven patients, four manifested with diffuse anterior, two with nodular and one with posterior scleritis. Scleritis in a patient with systemic lupus generally has a good ocular prognosis, because necrotizing scleritis rarely develops in patients with SLE.

Cornea

Corneal changes in SLE are confined primarily to ocular surface epitheliopathy secondary to KCS, and stromal keratitis (rare), peripheral keratitis particularly marginal and segmental [29,30] (Figure 4).

It has been hypothesized that because of the rich connective tissue in the cornea, the biomechanical properties of the cornea are especially vulnerable to connective tissue diseases. Corneal biomechanical properties differ in SLE. Yazici et al. used Reichert ocular response analyzer measurements to show that corneal hysteresis and corneal resistance factor were both lower in SLE patients which can lead to an underestimated IOP and development of keratoconus [31].

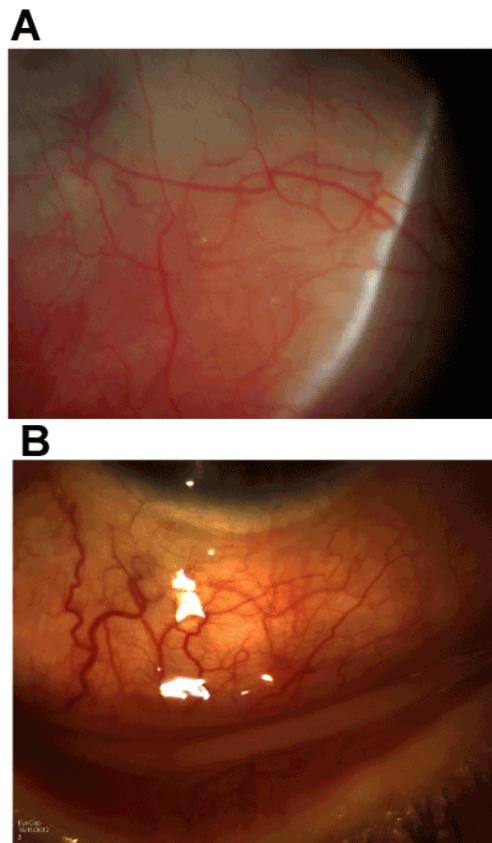


Figure 3: Scleritis.



Figure 4: Peripheral keratitis in a patient with systemic lupus erythematosus. Note the peri limbal, circumferential mid to deep stromal infiltrate in the corneal stroma.

Glaucoma

Angle-closure glaucoma secondary to uveal effusion may be an initial manifestation of SLE. Wisotsky and colleagues reported a case of bilateral pleural and uveal effusions with secondary angle-closure and elevated intraocular pressures. Intraocular pressures were

refractory to anti-glaucoma medications and laser therapy. Drainage of the choroidal effusion via sclerotomies resulted in resolution of the angle closure glaucoma [32].

Retinopathy

Retinal lesions in SLE patients are the most well recognized ocular manifestation and are of critical importance, both visually and prognostically. Presence of active retinal vasculopathy is an extremely accurate guide to the existence of systemic disease activity, occult or overt. Additionally the life-table survival estimates have shown decreased survival in patients with SLE retinopathy, compared to SLE patients without retinopathy. Its prevalence varies from 3% [22] in patients with mild to absent systemic disease to 29% [33] among patients with active disease. In patients on maintenance therapy with chloroquine, Klinkhoff and associates detected retinopathy in 7 of 43 (16%) patients, systemic lupus activity was present in 5 of these 7 patients (71%). The onset of retinopathy may be associated with the exacerbation of systemic SLE [34].

The lesions of lupus retinopathy vary in appearance and are believed to be due to retinal vasculitis. The different manifestations and their complications are shown in Table 2.

1. Cotton-wool spots
2. Retinal hemorrhage: dot, blot, flame-shaped
3. Preretinal hemorrhage
4. Microaneurysms
5. Focal narrowing of retinal vasculature
6. Arterial occlusion with focal deposits
7. Central/branch retinal arterial occlusion with cherry red spot
8. Central/branch venous occlusion
9. Retinal neovascularization
10. Anterior segment ischemia
11. Vitreous hemorrhage
12. Traction retinal detachment
13. Neovascular or hemorrhagic glaucoma
14. Hypertensive changes (arteriolar narrowing, hard exudates, flame hemorrhages, papilledema)
15. Optic disc vasculitis

Table 2: Signs of lupus retinopathy.

A review of 1473 SLE patients from several published series [34] revealed the frequencies of ocular findings shown in Table 3. In a large prospective study of 550 patients designed to examine the relationship of lupus retinopathy to systemic disease, Stafford-Brady and coworkers found that 41 patients (7.5%) exhibited lupus retinopathy. Of these patients, 34 had microangiopathy (cotton-wool spots in 20 patients; hemorrhages in 7; both cotton-wool spots and hemorrhages in 7), and 3 exhibited transient papilledema [35].

Another large series of fluorescein angiograms performed on 50 patients, the study concluded that angiographic changes in SLE are more frequently found in patients with active systemic disease [36]. However, the authors were careful to point out previous reports that emphasized that severe retinal vasculitis may occur without obvious systemic illness [37].

1. Cotton-wool spots 168/1473 (11.4)
2. Retinal hemorrhages 111/1473 (7.5)
3. Arterial narrowing 86/1473 (5.8)
4. Papilledema 13/1473 (0.9)
5. Retinal edema 9/1473 (0.6)
6. Uveitis 6/1473 (0.4)

Table 3: Intraocular findings in patients with systemic lupus erythematosus.

Source: Gold DH, Morris DA, Henkind P (1972) Ocular findings in systemic lupus erythematosus. Br J Ophthalmol 56: 800.

Jeon and Lee reported aggravation of ischemic changes associated with intravitreal bevacizumab in a young patient with SLE retinopathy and macular edema. As bevacizumab is a non-selective VEGF inhibitor, the drug may block not only pathological but also physiological VEGF, which may be essential for maintaining retinal circulation. Risks and benefits of intravitreal anti-VEGF injection in patients with SLE or antiphospholipid syndrome should be carefully considered, particularly when there are underlying vascular changes [38].

Fundoscopic findings shown in Table 2 can be classified into the following closely related categories [34,35,39-44].

Vasculitis

The basic pathological features of SLE are that of inflammation and blood vessel abnormalities, which include band or occlusive vasculopathy, vasculitis, and immune complex deposition [45].

As early as 1932, Goldstein and Wexler demonstrated extensive fibrinoid necrosis of the retinal vessel walls [46]. Perivascular inflammatory infiltrates, immunoglobulin and complement deposits have been demonstrated in the retinal and cerebral blood vessel walls [37], ciliary body, choroid, and conjunctival basement membrane of SLE patients [47].

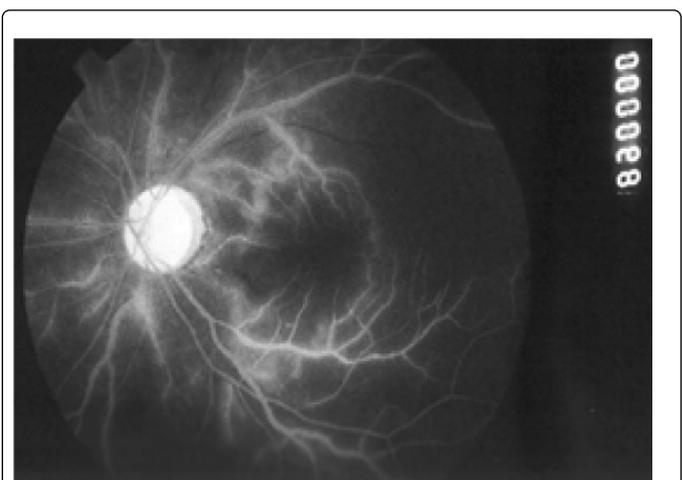


Figure 5: Vasculitis.

Retinal vasculitis may be seen as sheathing on fundoscopy and focal leakage from capillaries and arterioles on fluorescein angiography. It may involve optic nerve vessels as well (Figure 5).

Vaso-occlusion

Microvascular occlusion

Cotton-wool spots, the classic lesions of lupus retinopathy are believed to result from occlusion of the small retinal arterioles, or endarterioles, by infiltrating inflammatory cells. These represent focal areas of ischemia where there is interruption of axoplasmic flow within the nerve fiber layer of the retina, resulting in accumulation of axoplasmic material and swelling of the nerve fiber. The patients may be asymptomatic or have visual loss with macular involvement. On fluorescein angiography, cotton-wool spots correspond to areas of focal nonperfusion. In contrast to retinal nonperfusion from hypertension and diabetes, the ischemia produced in lupus retinopathy is often not as extensive and is not associated with widespread arterial narrowing [43,46].

Arterial occlusion

Central retinal artery occlusion is rare but can cause permanent visual loss due to widespread retinal ischemia. It is characterized by rapid, painless visual loss, a Marcus-Gunn afferent pupil defect, arterial attenuation, macular edema and cherry red spot of fovea. Multifocal branch retinal artery occlusion may also occur in SLE. Sudden visual loss with central retinal artery occlusion in a young patient should prompt the clinician to include SLE and other collagen diseases in the differential diagnosis.

Venous occlusion

Venous occlusion in the form of central or branch retinal vein occlusion is a rare manifestation of lupus retinopathy as lupus retinopathy largely manifests as arteritis, but can be a cause of permanent visual loss [48-50].

Vasodisruption

Various clinical signs may develop due to vasodisruption including microaneurysms, vascular leakage with retinal edema, pre retinal hemorrhage but intraretinal hemorrhages are commonly present. Stafford-Brady and coauthors believe that the presence of retinal hemorrhages is a significant finding because it is associated with a greater risk of mortality [35].

Ischemic sequelae

Severe retinal ischemia from either arterial or venous occlusive disease may result in retinal neovascularization resulting in sight threatening complications of severe ischemia, such as vitreous hemorrhage, traction retinal detachment, and secondary neovascular glaucoma [42,44] (Figure 6).

Hypertensive changes

Hypertensive retinopathy may develop secondary to SLE nephropathy. It is characterized by bilateral retinal arterial narrowing, arteriovenous crossing changes, intraretinal hemorrhages, hard exudates and papilledema. Rarely, multiple areas of choroidal infarction (Elschnig's spots) may appear as localized brown-red areas ophthalmoscopically. These foci show underlying choriocapillaris nonperfusion on fluorescein angiography and may be associated with transudation of subretinal fluid and neurosensory retinal detachment [51-53].

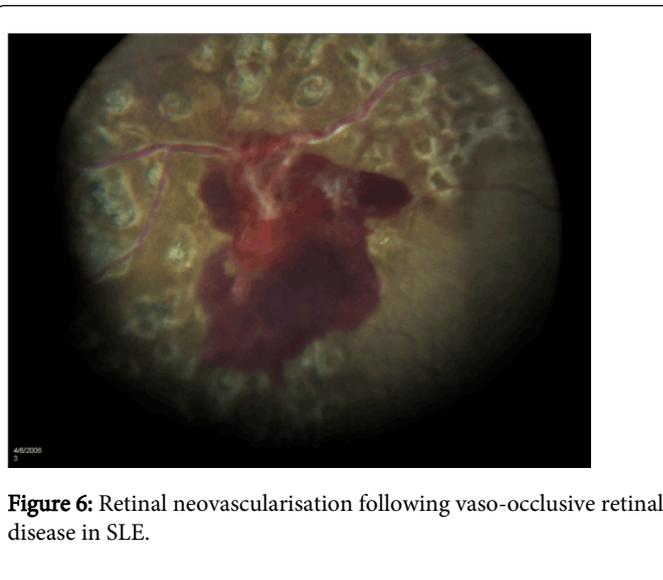


Figure 6: Retinal neovascularisation following vaso-occlusive retinal disease in SLE.

Choroidopathy

Although, less known than retinopathy, lupus choroidopathy may be more common than generally appreciated. It usually serves as a sensitive indicator of lupus activity and is generally indicative of coexistent (although sometimes occult) nephropathy, CNS vasculitis, and other SLE visceral lesions. It has been reported that immunomodulation of the systemic disease can lead to improvement and resolution of the systemic vasculitis as well as the choroidopathy [54].

It presents as single or multiple areas of serous elevation of the retinal pigment epithelium and sensory retina with associated retinal pigment epithelial mottling [55].

In a study of twelve patients with lupus choroidopathy, six manifested with hypertension and nephritis, three with systemic vasculitis, one with central nervous system (CNS) lupus, and one with disseminated intravascular coagulopathy and thrombotic thrombocytopenic purpura. The ocular prognosis for lupus choroidopathy is relatively good when systemic immunosuppressive treatment is given. Eleven of the twelve described patients subsequently experienced resolution or improvement of the choroidopathy [36,41,56-58].

Fluorescein angiography reveals focal areas of fluorescein leakage through the retinal pigment epithelium, with dye pooling under the sensory retina but indocyanine green (ICG) imaging of choroid may give a better clue to choroidal pathology. Studies show that transient early hypofluorescence and late hyperfluorescence are likely to be due to choroidal vascular perfusion delay and subsequent leakage due to increased vascular permeability.

Optic nerve and central nervous system

Ocular motility

It may manifest as extraocular muscle involvement due to brainstem, cranial nerve or direct muscular pathology and is reported in 29% patients [59]. Occasionally disorders of conjugate gaze such as internuclear ophthalmoplegia either unilateral or bilateral and one a

half syndrome (internuclear ophthalmoplegia with ipsilateral horizontal gaze palsy are seen [60-62]. Other reported complications include nystagmus and Miller Fisher syndrome [63]. Sixth nerve palsy is the most common cause of disconjugate gaze defect [64].

Visual pathway

Optic nerve may be implicated in different forms; papilledema rarely associated with visual loss, optic neuritis associated with visual loss and painful ocular movements, ischemic optic neuropathy (ION) associated with painless visual deterioration. Optic neuritis is typically unilateral and is caused by vasculitic ischemic injury to optic nerve resulting in eventual axonal necrosis [66,67]. Early diagnosis and prompt treatment with high-dose corticosteroids is associated with better visual outcomes [67,68].

Optic neuropathy on the other hand is usually bilateral except in antiphospholipid syndrome and is caused by focal capillary thrombosis resulting in altitudinal or arcuate field defect. Treatment for lupus optic neuropathy includes intravenous high-dose corticosteroids followed by an extended oral taper [69]. Some studies have shown success with other immunosuppressive agents such as cyclophosphamide, cyclosporine, methotrexate, and azathioprine [70,71]. Heparinization may also be critical in such patients [72].

Inflammation of optic chiasm, retrochiasm tracts and visual cortex may also develop. Visual pathway inflammation may cause visual disturbance, visual field defect or even blindness.

Cerebral involvement may cause visual hallucinations and field loss [73]. Histopathology of optic nerve shows two types of nervous tissue involvement: microangiopathy resulting in focal demyelination, axonal damage and optic nerve infarcts [73-75] or inflammation of the nervous tissues. Transverse myelitis is present in more than half of patients with lupus optic neuropathy [76]. Other rare manifestations include pseudotumor cerebri [77] and neuromyelitis optica, a form of multiple sclerosis characterized by spinal cord demyelination and optic atrophy [78]. Aquaporin-4 antibody positivity has been reported to have important clinical implications in patients with neuromyelitis optica as it is associated with a relapsing course of myelitis and optic neuritis and can lead to blindness and immobility quickly if not treated [79].

Ophthalmic disease and the role of anti-phospholipid antibodies

The presence of anti-phospholipid antibodies (APA) is associated with both retinal and CNS vaso-occlusive disease in SLE [80,81]. 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, quinidine 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 ophthalmic 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.

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. Irreversible vision loss secondary to a drug-induced maculopathy has been well documented in the literature. Factors associated with high risk of developing maculopathy include greater than 5-7 years of therapy, greater than a cumulative dose of 1000 g of hydroxychloroquin, 460 g of chloroquin, impairment of liver or kidney function, obesity, age greater than 65, and preexisting retinopathy. The American Academy of Ophthalmology recommends a baseline-dilated eye exam on all patients starting hydroxychloroquin followed by annual exams starting at 5 years after initiating therapy. A Humphrey 10-2 automated visual field test, multi-focal electroretinogram, spectral domain optical coherence tomography, and fundus autofluorescence should be performed at each of these visits. Discontinuation of the drug should be recommended at the earliest sign of toxicity [82-84]. Candidly, baseline multifocal ERG testing is advised, with subsequent reassessment every other year.

Therapeutic options

Immunosuppressive therapy is the core of treatment for both systemic and ocular lupus. The option of management is dependent on the organ involved and on the severity of the lesions. When only arthritis or serositis is present, nonsteroidal anti-inflammatory agents may be sufficient to control the disease. Currently, the acceptable dose of hydroxychloroquin is 400 mg/day and that of chloroquin is 250 mg/day (except for individuals of short stature for whom doses should be determined by ideal body weight).

SLE is well known to be extremely responsive to systemic steroids but these are usually reserved for hematologic, renal and CNS involvement. An intravenous high dose steroid (solumedrol infusion) is recommended for retinal vasculitis as an emergency vision saving treatment. In many instances patients need maintenance therapy with split dose oral corticosteroids.

Long-term steroid-sparing maintenance therapy may necessitate the use of systemic immunosuppressive agents such as cyclophosphamide or azathioprine [6,85,86]. Mycophenolate mofetil has been found to be effective and safe for the treatment of patients with chronic uveitis, at least one study has reported that MMF alone may be insufficient for the control of SLE-associated ocular inflammatory disease [87].

Tacrolimus, a calcineurin inhibitor, has been recognized for its immunosuppressive properties and widely used to prevent kidney rejection in transplantation surgery. Tacrolimus demonstrated effectiveness in the treatment of lupus nephritis and non-SLE chronic uveitis [88].

Recently, belimumab, a fully human recombinant immunoglobulin G (IgG)1 monoclonal antibody to soluble B-lymphocyte stimulator

(BLyS), has been approved on the basis of two major trials. On the contrary, the disappointing results of rituximab in lupus nephritis provided a clinical and mechanistic counterpoint in SLE. Still, major limitations in the LUpus Nephritis Assessment with Rituximab (LUNAR) trial, positive subset analysis and new open studies and registries continue to provide hope for and major insights into the use of B-cell depletion [89].

In a few, severe, recalcitrant cases, pulsed sequential plasmapheresis and intravenous cyclophosphamide in the treatment of severe visual loss due to retinal vasculitis in patients with SLE and has been demonstrated to restore vision in these desperate situations [90].

Over the past decade earlier diagnosis and improved treatment of lupus nephritis has resulted in substantial improvement of renal function and patient survival. Despite these advances, 10-15 % of SLE patients with lupus nephritis progress to end-stage renal disease, requiring dialysis or renal transplantation [91].

A recent retrospective analysis of 900 patients, of whom 95 had SLE, an overall 85% 5-year survival and 43% progression-free survival was seen with stem cell transplantation. Approximately 30% of patients in all disease subgroups had a complete response, often durable despite full immune reconstitution [92].

Allogeneic mesenchymal stem cell transplantation (MSCT) resulted in the induction of clinical remission and improvement in organ dysfunction in drug-resistant SLE patients. No transplantation-related adverse event was observed in this study by Wang et al. [93].

In order to prevent ischemic complications of lupus retinopathy, laser photocoagulation in cases of severe vaso-occlusive disease may be successful. Panretinal photocoagulation may lead to anterior segment ischemia, mandating careful management. Complete systemic control of SLE is advised prior to laser treatment. Vitreoretinal surgery may be indicated for patients with vitreous hemorrhage or traction retinal detachment [94].

We believe that the future of immune mediated diseases including SLE may depend on T cell therapy. Although their existence was controversial for some time, it is now absolutely clear that adaptive T regulatory cells (iTreg) develop under a variety of conditions, quite possibly during the normal homeostasis of the gut. For now it is known that iTreg cells play essential roles in immune tolerance and are one of the main barriers to the immune eradication of tumors. Although iTreg cells seem tailored to respond to foreign antigens and neoantigens (such as tumor antigens), it is likely that they are also generated in response to self-antigens and synergize with natural T regulatory (nTreg) cells in the control of autoimmune inflammation [95].

Conclusion

SLE is a chronic, systemic autoimmune disease, particularly prevalent in young women with a propensity for ocular tissues. Eye manifestations in SLE may be sight-threatening and can be an indicator of active systemic disease. Although the eye itself is regarded an 'immune-privileged' organ, systemic lupus erythematosus (SLE) can affect every ocular structure, leading, if left untreated, to significant visual loss or even blindness. When lupus retinopathy or neuro-ophthalmic involvement is detected in a patient, prompt diagnosis and treatment of the underlying systemic autoimmune disease is imperative.

A vigilant ophthalmologist should conduct a thorough search for systemic involvement and refer the patient to the appropriate clinical services. Early recognition of SLE and timely institution of systemic therapy may minimize morbidity and mortality from this disease.

References

1. Hebra F, Kaposi M (1874) On diseases of the skin including the Exanthemata. In: Tay W (Ed). The New Sydenham Society. London.
2. Bergmeister R (1929) Über primäre und miliare Tuberkulose der Retina. *Wien Med Schnschr* 79: 1116-1119.
3. D'Cruz DP, Khamashta MA, Hughes GR (2007) Systemic lupus erythematosus. *Lancet* 369: 587-596.
4. Mills JA (1994) Systemic lupus erythematosus. *N Engl J Med* 330: 1871-1879.
5. Abbas AK, Lichtman AH, Pober JS (1994) Self tolerance and autoimmunity. In: Abbas AK, Lichtman AH, Pober JS (Eds). *Cellular and Molecular Immunology*. (2nd edn) WB Saunders, Philadelphia, p: 384.
6. McClain MT, Heinlen LD, Dennis GJ, Roebuck J, Harley JB, et al. (2005) Early events in lupus humoral autoimmunity suggest initiation through molecular mimicry. *Nat Med* 11: 85-89.
7. Bastian BC (1997) Annexins in cancer and autoimmune diseases. *Cell Mol Life Sci* 53: 554-556.
8. Mamoune A, Saraux A, Delaunay JL, Le Goff P, Youinou P, et al. (1998) Autoantibodies to CD45 in systemic lupus erythematosus. *J Autoimmun* 11: 485-488.
9. Boehm J, Orth T, Van Nguyen P, Söling HD (1994) Systemic lupus erythematosus is associated with increased auto-antibody titers against calreticulin and grp94, but calreticulin is not the Ro/SS-A antigen. *Eur J Clin Invest* 24: 248-257.
10. Van Bruggen MC, Kramers C, Berden JH (1996) Autoimmunity against nucleosomes and lupus nephritis. *Ann Med Interne (Paris)* 147: 485-489.
11. El-Shereef RR, Mohamed AS, Hamdy L (2013) Ocular manifestation of systemic lupus erythematosus. *Rheumatol Int* 33: 1637-1642.
12. Al-Mayouf SM, Al-Hemidan AI (2003) Ocular manifestations of systemic lupus erythematosus in children. *Saudi Med J* 24: 964-966.
13. Gilboe IM, Kvien TK, Uhlig T, Husby G (2001) Sicca symptoms and secondary Sjögren's syndrome in systemic lupus erythematosus: comparison with rheumatoid arthritis and correlation with disease variables. *Ann Rheum Dis* 60: 1103-1109.
14. Ostanek L, Modrzejewska M, Bobrowska-Snarska D, Brzosko M (2007) [Ocular manifestations in patients with systemic lupus erythematosus and antiphospholipid syndrome]. *Pol Arch Med Wewn* 117 Suppl: 18-23.
15. Ohsie LH, Murchison AP, Wojno TH (2012) Lupus erythematosus profundus masquerading as idiopathic orbital inflammatory syndrome. *Orbit* 31: 181-183.
16. Stavrou P, Murray PI, Batta K, Gordon C (2002) Acute ocular ischaemia and orbital inflammation associated with systemic lupus erythematosus. *Br J Ophthalmol* 86: 474-475.
17. Grimson BS, Simons KB (1983) Orbital inflammation, myositis, and systemic lupus erythematosus. *Arch Ophthalmol* 101: 736-738.
18. Escudero González CM, Rodríguez Montero S, Martínez Pérez R, Pastor Mañosa C, Velloso Feijoo ML, et al. (2010) Resistant orbital pseudotumor treated with rituximab in a patient with systemic lupus erythematosus. A case presentation. *Reumatol Clin* 6: 214-216.
19. Serop S, Vianna RN, Claeys M, De Laey JJ (1994) Orbital myositis secondary to systemic lupus erythematosus. *Acta Ophthalmol (Copenh)* 72: 520-523.
20. Jarek MJ, Finger DR, Gillil WR, Giandoni MB (1996) Periorbital edema and mees' lines in systemic lupus erythematosus. *J Clin Rheumatol* 2: 156-159.
21. Gupta T, Beaconsfield M, Rose GE, Verity DH (2012) Discoid lupus erythematosus of the periorbital: clinical dilemmas, diagnostic delays. *Eye (Lond)* 26: 609-612.

22. Huey C, Jakobiec FA, Iwamoto T, Kennedy R, Farmer ER, et al. (1983) Discoid lupus erythematosus of the eyelids. *Ophthalmology* 90: 1389-1398.
23. Uy HS, Pineda R 2nd, Shore JW, Polcharoen W, Jakobiec FA, et al. (1999) Hypertrophic discoid lupus erythematosus of the conjunctiva. *Am J Ophthalmol* 127: 604-605.
24. Manoussakis MN, Georgopoulou C, Zintzaras E, Spyropoulou M, Stavropoulou A, et al. (2004) Sjögren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjögren's syndrome. *Arthritis Rheum* 50: 882-891.
25. Xu D, Tian X, Zhang W, Zhang X, Liu B, et al. (2010) Sjogren's syndrome-onset lupus patients have distinctive clinical manifestations and benign prognosis: a case-control study. *Lupus* 19: 197-200.
26. Whaley K, Webb J, McAvoy BA, Hughes GR, Lee P, et al. (1973) Sjogren's syndrome. 2. Clinical associations and immunological phenomena. *Q J Med* 42: 513-548.
27. Akpek EK, Uy HS, Christen W, Gurdal C, Foster CS (1999) Severity of episcleritis and systemic disease association. *Ophthalmology* 106: 729-731.
28. Sainz de la Maza M, Foster CS, Jabbur NS (1995) Scleritis associated with systemic vasculitic diseases. *Ophthalmology* 102: 687-692.
29. Halmay O, Ludwig K (1964) BILATERAL BAND-SHAPED DEEP KERATITIS AND IRIDOCYCLITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS. *Br J Ophthalmol* 48: 558-562.
30. REEVES JA (1965) KERATOPATHY ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS. *Arch Ophthalmol* 74: 159-160.
31. Yazici AT, Kara N, Yüksel K, Altinkaynak H, Baz O, et al. (2011) The biomechanical properties of the cornea in patients with systemic lupus erythematosus. *Eye (Lond)* 25: 1005-1009.
32. Wisotsky BJ, Magat-Gordon CB, Puklin JE (1998) Angle-closure glaucoma as an initial presentation of systemic lupus erythematosus. *Ophthalmology* 105: 1170-1172.
33. Lanham JG, Barrie T, Kohner EM, Hughes GR (1982) SLE retinopathy: evaluation by fluorescein angiography. *Ann Rheum Dis* 41: 473-478.
34. Gold DH, Morris DA, Henkind P (1972) Ocular findings in systemic lupus erythematosus. *Br J Ophthalmol* 56: 800-804.
35. Stafford-Brady FJ, Urowitz MB, Gladman DD, Easterbrook M (1988) Lupus retinopathy. Patterns, associations, and prognosis. *Arthritis Rheum* 31: 1105-1110.
36. Klinkhoff AV, Beattie CW, Chalmers A (1986) Retinopathy in systemic lupus erythematosus: relationship to disease activity. *Arthritis Rheum* 29: 1152-1156.
37. Karpik AG, Schwartz MM, Dickey LE, Streeten BW, Roberts JL (1985) Ocular immune reactants in patients dying with systemic lupus erythematosus. *Clin Immunol Immunopathol* 35: 295-312.
38. Jeon S, Lee WK (2012) Aggravated capillary non-perfusion after intravitreal bevacizumab for macular edema secondary to systemic lupus erythematosus and anti-phospholipid syndrome. *Lupus* 21: 335-337.
39. Bishko F (1972) Retinopathy in systemic lupus erythematosus. A case report and review of the literature. *Arthritis Rheum* 15: 57-63.
40. Coppeto J, Lessell S (1977) Retinopathy in systemic lupus erythematosus. *Arch Ophthalmol* 95: 794-797.
41. Gold D, Feiner L, Henkind P (1977) Retinal arterial occlusive disease in systemic lupus erythematosus. *Arch Ophthalmol* 95: 1580-1585.
42. Jabs DA, Fine SL, Hochberg MC, Newman SA, Heiner GG, et al. (1986) Severe retinal vaso-occlusive disease in systemic lupus erythematosus. *Arch Ophthalmol* 104: 558-563.
43. Dougal MA, Evans LS, McClellan KR, Robinson J (1983) Central retinal artery occlusion in systemic lupus erythematosus. *Ann Ophthalmol* 15: 38-40.
44. Kayazawa F, Honda A (1981) Severe retinal vascular lesions in systemic lupus erythematosus. *Ann Ophthalmol* 13: 1291-1294.
45. Mok CC, Lau CS (2003) Pathogenesis of systemic lupus erythematosus. *J Clin Pathol* 56: 481-490.
46. Goldstein I, Wexler D (1932) Retinal vascular disease in a case of acute lupus erythematosus disseminatus. *Arch Ophthalmol* 8: 852-857.
47. Aronson AJ, Ordoñez NG, Diddie KR, Ernest JT (1979) Immune-complex deposition in the eye in systemic lupus erythematosus. *Arch Intern Med* 139: 1312-1313.
48. Silverman M, Lubeck MJ, Briney WG (1978) Central retinal vein occlusion complicating systemic lupus erythematosus. *Arthritis Rheum* 21: 839-843.
49. Ellis CJ, Hamer DB, Hunt RW, Lever AF, Lever RS, et al. (1964) Medical Investigation of Retinal Vascular Occlusion. *Br Med J* 2: 1093-1098.
50. HARVEY AM, SHULMAN LE, TUMULTY PA, CONLEY CL, SCHOENRICH EH (1954) Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. *Medicine (Baltimore)* 33: 291-437.
51. Steinberg AD, Talal N (1971) The coexistence of Sjögren's syndrome and systemic lupus erythematosus. *Ann Intern Med* 74: 55-61.
52. Hammami H, Streiff E (1973) Changes of retinal vessels in a case of lupus erythematosus disseminatus: development following treatment with immunosuppressive agents. *Ophthalmologica* 166: 16-35.
53. Carpenter MT, O'Boyle JE, Enzenauer RW, Enzenauer RJ, Waterhouse WJ (1994) Choroiditis in systemic lupus erythematosus. *Am J Ophthalmol* 117: 535-536.
54. Nguyen QD, Uy HS, Akpek EK, Harper SL, Zacks DN, et al. (2000) Choroidopathy of systemic lupus erythematosus. *Lupus* 9: 288-298.
55. Jabs DA, Hanneken AM, Schachat AP, Fine SL (1988) Choroidopathy in systemic lupus erythematosus. *Arch Ophthalmol* 106: 230-234.
56. Diddie KR, Aronson AJ, Ernest JT (1977) Chorioretinopathy in a case of systemic lupus erythematosus. *Trans Am Ophthalmol Soc* 75: 122-131.
57. Gass JDM (1968) A fluorescein angiographic study of macular dysfunction secondary to retinal vascular disease: VI. X-ray irradiation, carotid artery occlusion, collagen vascular disease, and vitritis. *Arch Ophthalmol* 80: 606-617.
58. Kinyoun JL, Kalina RE (1986) Visual loss from choroidal ischemia. *Am J Ophthalmol* 101: 650-656.
59. Keane JR (1995) Eye movement abnormalities in systemic lupus erythematosus. *Arch Neurol* 52: 1145-1149.
60. Galindo M, Pablos JL, Gómez-Reino JJ (1998) Internuclear ophthalmoplegia in systemic lupus erythematosus. *Semin Arthritis Rheum* 28: 179-186.
61. Jackson G, Miller M, Littlejohn G, Helme R, King R (1986) Bilateral internuclear ophthalmoplegia in systemic lupus erythematosus. *J Rheumatol* 13: 1161-1162.
62. Yigit A, Bingol A, Mutluer N, Tascilar N (1996) The one-and-a-half syndrome in systemic lupus erythematosus. *J Neuroophthalmol* 16: 274-276.
63. Bingisser R, Speich R, Fontana A, Gmür J, Vogel B, et al. (1994) Lupus erythematosus and Miller-Fisher syndrome. *Arch Neurol* 51: 828-830.
64. West SG (1996) Lupus and the central nervous system. *Curr Opin Rheumatol* 8: 408-414.
65. Read RW, Weiss AH, Sherry DD (1999) Episcleritis in childhood. *Ophthalmology* 106: 2377-2379.
66. Allen IV, Millar JH, Kirk J, Shillington RK (1979) Systemic lupus erythematosus clinically resembling multiple sclerosis and with unusual pathological and ultrastructural features. *J Neurol Neurosurg Psychiatry* 42: 392-401.
67. Lin YC, Wang AG, Yen MY (2009) Systemic lupus erythematosus-associated optic neuritis: clinical experience and literature review. *Acta Ophthalmol* 87: 204-210.
68. Galindo-Rodríguez G, Aviña-Zubieta JA, Pizarro S, Díaz de León V, Saucedo N, et al. (1999) Cyclophosphamide pulse therapy in optic neuritis due to systemic lupus erythematosus: an open trial. *Am J Med* 106: 65-69.
69. Frigui M, Frikha F, Sellemi D, Chouayakh F, Feki J, et al. (2011) Optic neuropathy as a presenting feature of systemic lupus erythematosus: two case reports and literature review. *Lupus* 20: 1214-1218.

70. Myers TD, Smith JR, Wertheim MS, Egan RA, Shults WT, et al. (2004) Use of corticosteroid sparing systemic immunosuppression for treatment of corticosteroid dependent optic neuritis not associated with demyelinating disease. *Br J Ophthalmol* 88: 673-680.
71. Rosenbaum JT, Simpson J, Neuwelt CM (1997) Successful treatment of optic neuropathy in association with systemic lupus erythematosus using intravenous cyclophosphamide. *Br J Ophthalmol* 81: 130-132.
72. Foster CS. Ocular Manifestations of Systemic Lupus Erythematosus.
73. Hackett ER, Martinez RD, Larson PF, Paddison RM (1974) Optic neuritis in systemic lupus erythematosus. *Arch Neurol* 31: 9-11.
74. April RS, Vansonnenberg E (1976) A case of neuromyelitis optica (Devic's syndrome) in systemic lupus erythematosus. *Clinicopathologic report and review of the literature. Neurology* 26: 1066-1070.
75. Kinney EL, Berdoff RL, Rao NS, Fox LM (1979) Devic's syndrome and systemic lupus erythematosus: a case report with necropsy. *Arch Neurol* 36: 643-644.
76. Shepherd DI, Downie AW, Best PV (1974) Systemic lupus erythematosus and multiple sclerosis. *Trans Am Neurol Assoc* 99: 173-176.
77. Carlow TJ, Glaser JS (1974) Pseudotumor cerebri syndrome in systemic lupus erythematosus. *JAMA* 228: 197-200.
78. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG (2007) The spectrum of neuromyelitis optica. *Lancet Neurol* 6: 805-815.
79. Weinshenker BG, Wingerchuk DM, Vukusic S, Linbo L, Pittock SJ, et al. (2006) Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol* 59: 566-569.
80. Ravelli A, Di Fuccia G, Caporali R, Malvezzi F, Montecucco C, et al. (1993) Severe retinopathy in systemic lupus erythematosus associated with IgG anticardiolipin antibodies. *Acta Paediatr* 82: 624-626.
81. Asherson RA, Merry P, Acheson JF, Harris EN, Hughes GR (1989) Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus erythematosus and the 'primary' antiphospholipid syndrome. *Ann Rheum Dis* 48: 358-361.
82. Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF; American Academy of Ophthalmology (2011) Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 118: 415-422.
83. HOBBS HE, SORSBY A, FREEDMAN A (1959) Retinopathy following chloroquine therapy. *Lancet* 2: 478-480.
84. Marmor MF, Carr RE, Easterbrook M, Farjo AA, Mieler WF, et al. (2002) Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology* 109: 1377-1382.
85. Felson DT, Anderson J (1984) Evidence for the superiority of immunosuppressive drugs and prednisone over prednisone alone in lupus nephritis. Results of a pooled analysis. *N Engl J Med* 311: 1528-1533.
86. Steinberg AD (1985) Management of systemic lupus erythematosus. In: Kelly WN, Harris ED, Ruddy S (Eds). *Textbook of Rheumatology*. (2nd edn), WB Saunders, Philadelphia, p: 1130.
87. Baltatzis S, Tufail F, Yu EN, Vredevelde CM, Foster CS (2003) Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders. *Ophthalmology* 110: 1061-1065.
88. Hogan AC, McAvoy CE, Dick AD, Lee RW (2007) Long-term efficacy and tolerance of tacrolimus for the treatment of uveitis. *Ophthalmology* 114: 1000-1006.
89. Coca A, Sanz I (2012) Updates on B-cell immunotherapies for systemic lupus erythematosus and Sjogren's syndrome. *Curr Opin Rheumatol* 24: 451-456.
90. Papadaki TG, Zacharopoulos IP, Papaliodis G, Iaccheri B, Fiore T, et al. (2006) Plasmapheresis for lupus retinal vasculitis. *Arch Ophthalmol* 124: 1654-1656.
91. Norby GE, Lerang K, Holdaas H, Gran JT, Strøm EH, et al. (2010) [Lupus-nephritis--diagnosis and treatment]. *Tidsskr Nor Laegeforen* 130: 1140-1144.
92. Tyndall A (2011) Successes and failures of stem cell transplantation in autoimmune diseases. *Hematology Am Soc Hematol Educ Program* 2011: 280-284.
93. Wang D, Zhang H, Liang J, Li X, Feng X, et al. (2012) Allogeneic mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus: 4 years experience. *Cell Transplant*.
94. Read RW, Chong LP, Rao NA (2000) Occlusive retinal vasculitis associated with systemic lupus erythematosus. *Arch Ophthalmol* 118: 588-589.
95. Curotto de Lafaille MA1, Lafaille JJ (2009) Natural and adaptive foxp3+ regulatory T cells: more of the same or a division of labor? *Immunity* 30: 626-635.

This article was originally published in a special issue, entitled: "**Systemic Lupus Erythematosus**", Edited by Kaihong Su, University of Nebraska Medical Center, USA