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REVIEW ARTICLE

Systemic lupus erythematosus and ocular involvement: an overview

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Abstract

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of undefined etiology and with remarkably heterogeneous clinical features. Virtually any organ system can be affected, including the eye. SLE-related eye involvement can be diagnosed in approximately one-third of the patients and is usually indicative of disease activity. An early diagnosis and the adoption of suitable therapeutic measures are necessary to prevent sight-threatening consequences, especially in patients with juvenile SLE. Periocular lesions, such as eyelid involvement and orbital inflammation, are relatively rare and, in case of orbital masses, may require a biopsy control. Keratoconjunctivitis sicca or secondary Sjögren's syndrome is the most frequent ophthalmic manifestation of SLE. According to its variable severity, lubricating tear drops may be sufficient in mild cases, whereas cyclosporine-A ophthalmic solution, glucocorticoids (GCs), methotrexate, and/or other immunosuppressive drugs may be required in the more severe cases. Partial occlusion of the lacrimal punctum by thermal cautery is rarely applied. Although uncommon, episcleritis and scleritis can sometimes be detected as an initial finding of SLE and reveal themselves as moderate to intense ocular pain, redness, blurred vision, and lacrimation. Unilateral or more often bilateral retinopathy is responsible for visual loss of variable severity and is ascribed to vasculitis of the retinal capillaries and arterioles. In addition to the combined treatment suitable for all patients with active SLE, intravitreal bevacizumab should be considered in cases of severe vaso-occlusive retinopathy and laser photocoagulation in cases of neovascularization. Purtscher-like retinopathy is likely ascribable to the formation of microemboli that results in retinal vascular occlusion and microvascular infarcts. Choroidal disease is characterized by monolateral or bilateral blurred vision. Because of the choroidal effusion, retinal detachment and secondary angle-closure glaucoma may occur. Ischemic optic neuropathy is characterized by acute-onset and progressive binocular visual impairment as a consequence of occlusion of the small vessels of the optic nerves due to immune complex vasculitis. Intravenous GC boluses followed by oral GCs and/or, in case of recurrence, intravenous cyclophosphamide and/or rituximab are commonly employed. Neovascularization can be treated by intravitreal bevacizumab and progression of retinal ischemic areas by retinal laser photocoagulation. Ocular adverse events (AE) have been described following the long-term administration of one or more of the drugs presently used for the treatment of SLE patients. Posterior subcapsular cataracts and secondary open-angle glaucoma are common AE of the prolonged GC administration. The long-term administration of hydroxychloroquine (HCQ) sulfate is well known to be associated with AE, such as vortex keratopathy and in particular the often irreversible and sight-threatening maculopathy. Length of administration > 5 years, > 1000 g total HCQ consumption, > 6.5 mg/kg daily dosing, coexistence of renal disease, and preexisting maculopathy are all considered risk factors for HCQ-induced retinopathy. Ocular AE of additional immunosuppressive and biological agents are still poorly known, given the worldwide more limited experience with their long-term use. A thorough ophthalmological control is strongly recommended at closer intervals for all SLE patients, in step with the total length of exposure to the drugs and the cumulative dose administered.

Keywords Ocular adverse events · Ophthalmic manifestations · Optic neuropathy · Retinopathy · Systemic lupus erythematosus

Abbreviations

AAO	American Academy of Ophthalmology
ACL	Anti-cardiolipin
ACR	American College of Rheumatology
AE	Adverse events

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AG	Amsler grid
ANA	Antinuclear antibodies
APS	Anti-phospholipid antibody syndrome
AVFs	Automated visual fields
BAFF/BLyS	B cell-activating factor/B-lymphocyte stimulator
BILAG	British Isles Lupus Assessment Group
BM	Biomicroscopy
CQ	Chloroquine
CsA	Cyclosporine-A
CT	Computed tomography
ELM	External limiting membrane
FAF	Fundus autofluorescence
FE	Funduscopic examination
FFA	Fundus fluorescein angiography
GCs	Glucocorticoids
HCQ	Hydroxychloroquine
HVF	Humphrey visual field
ICGA	Indocyanine green angiography
IO	Indirect ophthalmoscopy
ION	Ischemic optic neuropathy
LAC	Lupus anticoagulant
mfERG	Multifocal electroretinography
MR	Magnetic resonance
MTX	Methotrexate
OAE	Ocular adverse events
PSRT	Photo-stress recovery time
RPE	Retinal pigment epithelium
SD-OCT	Spectral domain optical coherence tomography
SLE	Systemic lupus erythematosus
SLEDAI	SLE disease activity index
SLICC	Systemic Lupus International Collaborating Clinics
SS	Sjögren's syndrome
VEP	Visual evoked potentials

Introduction and epidemiology

Systemic lupus erythematosus (SLE) is a multisystem, chronic, autoimmune disease that mostly affects women (female/male ratio ranging from 6:1 to 10:1) in their childbearing age [1, 2]. Women of black race or ethnicity have the highest incidence and prevalence. In Europe, the SLE prevalence is estimated to be 39.2 (95% CI 28.5–52.6) cases per 100,000 individuals and the annual incidence rate is 2.0 (0.9–3.8) per 100,000 individuals [3]. Its etiology is still undefined, but variably intertwined factors such as genetic predisposition, environmental stimuli, and an unfailing dysregulation of the immune system are likely to mediate the involvement of several organs, resulting in significant morbidity and mortality [4, 5].

The spectrum of symptoms and signs is largely variable from patient to patient and in the same patient over time, resulting in protean clinical course with different degrees of severity ranging from indolent to fulminant. Because of its heterogeneity, SLE has often been subdivided into subsets and defined as a syndrome rather than a single, well-defined disease condition [6].

At least three different clinical pictures have been recognized, namely (a) chronic active; (b) relapsing–remitting; (c) quiescent, the last state being often the consequence of properly applied therapies. At presentation and throughout its course, SLE can virtually affect any organ system. In addition to obvious constitutional symptoms such as fever, arthralgia, and fatigue, the clinical spectrum includes a variable combination of dermatologic, renal, musculoskeletal, neuropsychiatric, and hematologic manifestations. Cardiac, pulmonary, and gastrointestinal features can also occur, though less frequently.

With the aim of achieving a better knowledge of the clinical features, adopting consistent methodology requirements, minimizing selection bias, and paying due attention to the evolving immunological criteria, the Systemic Lupus International Collaborating Clinics (SLICC) group has updated the SLE classification criteria developed by the American College of Rheumatology (ACR) in 1982 [7] and revised in 1997 [8]. The SLICC group has provided a classification system that includes 11 clinical criteria plus 6 immunological criteria (Table 1). It is established that a patient has SLE if at least four criteria are satisfied, including at least one clinical criterion and one immunological criterion. Alternatively, the diagnosis of SLE can be accepted if the patient has biopsy-proven nephritis compatible with SLE, associated with antinuclear (ANA) or anti-dsDNA antibodies [9].

Ocular findings in SLE

Ophthalmic manifestations can be detected in approximately one-third of SLE patients, may be present at the outset of the disease or appear during the evolution, can affect any part of the visual system, may sometimes be sight-threatening if not promptly and properly treated, and are usually indicative of disease activity.

Because ocular involvement may remain clinically silent for months, it is essential that all patients with SLE, regardless of whether they are asymptomatic or symptomatic, undergo a careful eye examination. In addition to standard ophthalmic examination (visual acuity, ability to identify different colors, full visual field, proper eye muscle coordination, eye pressure, and eye structures), one or more special tests are often necessary. Although routine and special tests are obviously well known to all ophthalmologists, we have shortly summarized their properties in Table 2 in order to

Table 1 Clinical and immunological criteria used in the systemic lupus international collaborating clinics (SLICC) classification system Modified from Petri et al. [9]

Clinical criteria
1. Acute cutaneous lupus, including
Lupus malar rash (do not count if malar discoid)
Bullous lupus
Toxic epidermal necrolysis variant of SLE
Maculopapular lupus rash
Photosensitive lupus rash in the absence of dermatomyositis
OR subacute cutaneous lupus (non-indurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with post-inflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus, including
Classic discoid rash: localized (above the neck); generalized (above and below the neck)
Hypertrophic (verrucous) lupus; Lupus panniculitis (profundus); mucosal lupus;
Lupus erythematosus tumidus
Chilblains lupus
Discoid lupus/lichen planus overlap
3. Oral ulcers
Palate; buccal; tongue
OR nasal ulcers in the absence of other causes, such as vasculitis, Behcet's disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods
4. Non-scarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
In the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia
5. Synovitis involving two or more joints, characterized by swelling or effusion
OR tenderness in 2 or more joints and at least 30 min of morning stiffness
6. Serositis
Typical pleurisy for more than 1 day OR pleural effusions OR pleural rub
Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography
In the absence of other causes, such as infection, uremia, and Dressler's pericarditis
7. Renal
Urine protein-to-creatinine ratio (or 24-h urine protein) representing 500 mg protein/24 h
OR red blood cell casts
8. Neurological
Seizures; psychosis
Mononeuritis multiplex in the absence of other known causes such as primary vasculitis; myelitis
Peripheral or cranial neuropathy in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
Acute confusional state in the absence of other causes, including toxic/metabolic, uremia, drugs
9. Hemolytic anemia
10. Leukopenia (< 4000/mm^3 at least once)
In the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension
OR Lymphopenia (< 1000/mm^3 at least once) in the absence of other known causes such as corticosteroids, drugs, and infection
11. Thrombocytopenia (< 100,000/mm^3) at least once
In the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura
Immunological criteria
1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range (or twofold the reference range if tested by ELISA)
3. Anti-Sm: the presence of antibody to Sm nuclear antigen
4. Anti-phospholipid antibody positivity as determined by any of the following
(a) Positive test result for lupus anticoagulant
(b) False-positive test result for rapid plasma reagin

Table 1 (continued)

Clinical criteria
(c) Medium- or high-titer anti-cardiolipin antibody level (IgA, IgG, or IgM)
(d) Positive test result for anti-β2-glycoprotein-I (IgA, IgG, or IgM)
5. Low complement
Low C3
Low C4
Low CH50
6. Direct Coombs' test in the absence of hemolytic anemia

Criteria are cumulative and need not be present concurrently. The patient must satisfy at least 4 criteria, including at least one clinical criterion and one immunological criterion **OR** the patient must have biopsy-proven lupus nephritis in the presence of antinuclear antibodies or anti-double-stranded DNA antibodies

allow a better comprehension to all the specialists who take part in the SLE multidisciplinary team.

The importance of the ophthalmic involvement is emphasized by the decision of the British Isles Lupus Assessment Group (BILAG) to improve and update their activity index by including the ophthalmic manifestations among the diverse clinical features of SLE [10].

It is, therefore, somewhat surprising that in certain multicenter cooperative studies the spectrum of eye involvement in SLE patients (with the exception of Sjögren's or sicca syndrome: SS) has been given poor attention. In a detailed description of a very large cohort of unselected, consecutive 1000 patients from 7 European countries, enrolled in the multicenter "Euro-lupus" project, the only mentioned eye manifestation was in fact SS, diagnosed in 5% of the patients at onset and in 16% during evolution. This percentage raised during evolution to 33% in patients with older-onset SLE [4].

The UK Juvenile-Onset SLE Study Group examined a cohort of 232 juvenile-onset SLE patients from 14 centers and of different ethnic distribution, with a median age at diagnosis 12.6 years (interquartile range 10.4–14.5 years). An ophthalmic involvement was detected in only 5 patients (3%), including ocular cataract in 4 patients and retinal change in 1 [11]. Studying a total of 924 patients, 413 of them with juvenile SLE and 511 with adult-onset SLE, Ambrose et al. [12] confirmed that this disease may present at any age and in either gender and that clinical manifestations are similar at all ages. However, incidence and severity differ, in that an aggressive phenotype of disease associated with a worse outcome is usually found in patients with juvenile SLE. In spite of the relatively high number of patients examined, no mention is made of ocular manifestations in any of them. Overall, these data suggest that ocular lesions other than SS are possibly overlooked or mistakenly interpreted as unrelated to SLE when patients are not fully and jointly assessed by experienced clinicians and ophthalmologists.

The aim of this study is to draw the attention on the diverse presentations of ophthalmic disease, their prevalence and characteristics at the onset and throughout the evolution of SLE on the basis of the literature review and of our own experience. The results obtained in our large cohort of SLE patients as tertiary referral university center will be the object of a separate paper.

Periocular lesions

Eyelid involvement

Although less frequently than in discoid lupus erythematosus, eyelids can be affected with plaques, erythematosus patches and madarosis, areas of atrophy and scaling, and sometimes dyspigmentation. Lid scarring may eventually ensue. These lesions are commonly associated with the more obvious manifestations occurring on the head, face, neck, and other sun-exposed areas. Topical corticosteroids and oral antimalarial drugs are usually prescribed in these patients [13]. The coexistence of unilateral or bilateral blepharitis may also be detected.

Orbital inflammation

The occurrence of inflammatory pseudo-tumor orbital masses in SLE is an unusual finding that may remain undiagnosed until the patient complains of proptosis, pain, and diplopia as a consequence of myositis with infiltration of the ocular muscles [14]. Rare cases of lupus profundus (panniculitis) with ocular involvement have also been associated with orbital inflammatory syndrome [13] or masquerading as idiopathic orbital vasculitis [15]. In these patients, the exact diagnosis is usually dependent on a biopsy confirmation. In addition to the eyelid application of dexamethasone 0.1% when requested, a general therapy includes the daily

Table 2 Ophthalmic evaluation: the most common routine and special tests

Methods	Definition and properties
Funduscopic examination (FE) and indirect ophthalmoscopy (IO)	FE allows a good inspection of retina, retinal blood vessels, optic disk, macula, fovea, posterior pole and, to a lesser extent, subjacent choroid IO provides an inverted direct image magnified 2–5 times, thus allowing a better view of the fundus and a peripheral viewing of the retina, even when cataracts coexist
Multifocal electroretinography (mfERG)	mfERG measures at the same time, by electrodes embedded into a corneal contact lens, the retinal responses to a light stimulus from over 200 retinal locations within the central 30°. The test is of help in the diagnosis of retinal disorders, to monitor disease progression and to assess retinal toxicity from various drugs
Biomicroscopy (BM)	By the use of a binocular slit-lamp and in conjunction with a biomicroscope, the test provides a stereoscopic magnified view of the anterior and posterior segments of the eye
Humphrey visual field (HVF) automated perimetry	HVF provides information regarding the location of any disease process throughout the visual pathway. In the majority of instances, 10-2 tests are performed measuring 10° temporally and nasally (68 points). Useful for macula, retinal and neuro-ophthalmic conditions, and advanced glaucoma
Spectral domain optical coherence tomography (SD-OCT)	By using light to capture micrometer-resolution, SD-OCT provides three-dimensional images of the eye's anterior segment and from within the retina. Due to its cross-sectional properties, it is used to assess axonal integrity in glaucoma, macular degeneration, and macular edema. Following proper engineering, it is also employed to diagnose retinal microvasculature pathology
Fundus autofluorescence (FAF)	FAF is a noninvasive retinal imaging technique that provides a density map of lipofuscin in the retinal pigment epithelium. It makes use of different imaging systems such as fundus camera, confocal scanning laser ophthalmoscope, or wide-field imaging device. FAF provides functional information about retinal cells and can therefore be applied for almost any fundus disorder, being often able to detect abnormalities unrevealed by FE, FAG, or SD-OCT
Amsler grid (AG)	AG is a grid of horizontal and vertical lines used to monitor the patient's central visual field. It is applied in the detection of visual disturbances caused by changes in the retina, such as macular degeneration, epiretinal membrane, and optic nerve diseases
Color vision testing	The test allows to check the patient's type of color vision deficiency and its severity. There are several ways of performing the test. Among them, the well-known Ishihara plates consist of 38 different pseudo-isochromatic plates, each of them hiding a number or lines behind colorful dots
Fundus fluorescein angiography (FFA)	FFA is a largely used technique to assess the circulation of the retina and choroid. It is based on the administration (intravenously or orally) of a fluorescent dye. The fluorescence emitted after illumination of the retina with blue light is photographed, and a series of black-and-white or digital photographs of the retina are taken before and after the fluorescein reaches the retinal circulation. In pathologic conditions, the angiogram may show either hyper-fluorescence or hypo-fluorescence
Indocyanine green angiography (ICGA)	ICG is a water-soluble dye that, being protein-bound after intravenous injection, is characterized by low diffusion through the small fenestrations of the choriocapillaris. ICGA is therefore particularly suitable in the imaging analysis of choroidal circulation. The fluorescence is usually detected by a scanning laser ophthalmoscope, but with the new technologies it is even possible to achieve FAG and ICG images at the same time. ICG is applied for the diagnosis of several conditions, including choroidal neovascularization, pigment epithelial detachment and polypoid choroidal vasculopathy

administration of intravenous cyclophosphamide (1–2 mg/kg body weight) and glucocorticoids (GCs, 1 mg/kg body weight) with progressive tapering, often associated with oral acetazolamide (500 mg daily).

Dry eye or keratoconjunctivitis sicca

It is the most common ocular manifestation of SLE that can be detected in approximately one-third of SLE patients [16, 17]. In the most typical cases, keratoconjunctivitis sicca or secondary SS can be diagnosed. In patients without secondary SS, the dry eye severity has been found to be directly related to anti-dsDNA titers and low C3 levels, though not to C4, erythrocyte sedimentation rate, and ANA [18].

Clinical features may be of variable severity, ranging from mild redness and sandy eyes with foreign body feeling to painful corneal ulceration and filamentary keratitis. The increased production of inflammatory cytokines usually results in chronic conjunctivitis. On slit-lamp examination, an abnormal tear film and lesions of different types can be detected, including corneal epitheliopathy, corneal erosions, scarring and ulcerative keratitis, with variable visual loss and potentially sight-threatening consequences [19].

The decreased tear production in patients not using tear substitution for at least 1 day is obviously confirmed by the Schirmer test and corneal fluorescein staining. Additional methods include biomicroscopy (BM), tear film breakup time, rose bengal vital dye, corneal sensitivity test, spectral domain optical coherence tomography (SD-OCT), and tear osmolarity measurement, although no gold standard has been established. Anti-SSA/Ro and/or anti-SSB/La antibodies can be found in the large majority of these patients.

The treatment of keratoconjunctivitis sicca is related to its severity. Lubricating tear drops are the most obvious remedy, with preference for a medium-viscosity carbomer-containing ophthalmic gel. Cyclosporine-A (CsA) ophthalmic emulsion 0.05%, instilled twice daily in each eye in patients with bilateral dry eye disease and a symptom score of ≥ 2 on the ocular discomfort scale [20], have also been used, resulting in remarkable improvement in both signs and symptoms of dry eye as well as in improved visual function after 6 months of treatment [21]. Systemic immunosuppressive agents such as GCs, methotrexate (MTX), CsA, and infliximab, singly or variably combined, may be necessary for the treatment of severe and recalcitrant cases [22].

In the more advanced cases, it is common to use "punctal plugs" which may be temporary or permanent. An alternative approach is to use thermal cautery with a sterile tip, with the aim of reducing the lacrimal punctum to < 0.5 mm [23]. This can be extended to total permanent occlusion. In very severe cases where there is corneal breakdown, tarsorrhaphy may be considered. The role of biological drugs and topical immunomodulators such as tacrolimus, tofacitinib, and IL-1 receptor inhibitor has not been clearly defined, and their use should therefore be allowed under controlled experimental conditions [24]. However, in a prospective double-blind randomized study, topical tacrolimus was found to be effective in improving tear stability and ocular surface status in patients with dry eye syndrome [25, 26].

Anterior segment

Corneal involvement

In addition to keratoconjunctivitis sicca, corneal involvement can present as initial or later manifestation of SLE and under different clinical features, including corneal erosions, often recurring, punctate epithelial loss, corneal stromal infiltration, bilateral transient keratoendothelitis, and more rarely peripheral ulcerative keratitis [27–29]. The patient frequently complains of painful eye, hyper-lacrimation, and blurred vision. Topical and systemic GC treatment and systemic antimalarial drugs are commonly employed in these patients with fairly good results.

No significant association between keratoconus and SLE was found in a retrospective observational case–control study [30].

Episcleritis and scleritis

Although relatively uncommon, episcleritis and scleritis can be the initial findings and precede other manifestations of SLE, their occurrence being usually indicative of active disease. Patients with episcleritis complain of moderate ocular pain and redness often associated with lacrimation, but the process is usually mild and self-limiting. No specific treatment is therefore required, except for the possible use of eye drops of vasoconstrictors such as phenylephrine [16].

SLE-related scleritis is often underdiagnosed but may be clinically much more painful and vision-threatening, if not properly treated. The patient may be awakened at night by the severity of the pain that extends from the eye to the corresponding side of the face and jaw. It is more frequently unilateral, and, according to its characteristics, it can be classified as anterior or posterior. Anterior scleritis can be diffuse or nodular, the latter type being more frequently necrotizing. Depending on the pathological features, anterior necrotizing scleritis can be defined as vaso-occlusive, granulomatous, or scleromalacia [31]. Posterior scleritis, on the other hand, is non-necrotizing and clinically characterized by blurred vision, refractory changes, and diplopia [28].

The scleral changes of the anterior segment can be visualized by SD-OCT. In patients with diffuse anterior scleritis,

the sclera appears edematous and deeply infiltrated with inflammatory cells. By the same technique, non-necrotizing nodular scleritis reveals that the nodules contain extracellular fluid and that the collagen fibers are separated and distinct, in the absence of tissue necrosis. On the contrary, SD-OCT of necrotizing nodular scleritis shows hyper-reflectivity of the scleral nodule, whose deep layers appear liquid and interspersed with blood vessels [30].

Although B-scan ultrasonography is most commonly employed in diagnostic imaging of scleritis, computed tomography (CT) and magnetic resonance (MR) imaging have also been shown to be of diagnostic usefulness [31]. Scleral enhancement, scleral thickening, and focal periscleral cellulitis are usually detected by MR during the active phase, but reliable diagnostic features can also be drawn from the use of CT in patients with posterior scleritis.

Because scleral disease suggests that SLE is in the active phase, its treatment requires the same systemic approach (including GCs and immunosuppressive drugs) that is employed in all situations of active SLE.

Conjunctivitis and anterior uveitis

Each of these pathologies is rarely diagnosed alone, being more often associated with scleritis or posterior phlogosis [16]. Allergic conjunctival disease (including allergic conjunctivitis, atopic keratoconjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis) is infrequently diagnosed in SLE patients. Compared with the controls, people with SLE are not at an increased risk of IgE-mediated/associated allergic disorders [32], including patients with an allergic family history [33]. Conversely, in a population-based case–control study, a significant relationship was described between atopic diseases and the risk of SLE, with obvious prevalence for females [34]. The reasons for these opposing results are not clear: in addition to the immunological similarities and differences between SLE and various allergic diseases, a change in the environmental factors contributing to allergy has also been suggested [35].

An interesting study on the association between SLE and uveitis [36] reports that the prevalence of SLE in patients with uveitis ranges from 0.1 to 4.8%. After reviewing data relative to over 53,000 patients included in 63 studies from 30 countries, the prevalence of SLE as a cause of uveitis was estimated to be 0.47% (95% CI 0.41–0.53%). SLE should therefore be considered a rare cause of uveitis, and routine ANA, given its low positive predictive value for SLE, does not seem to be justified in all patients with uveitis [36].

Since conjunctivitis and anterior uveitis, as stated above, are usually associated with scleritis or posterior inflammation, their therapy may require from nonsteroidal anti-inflammatory drugs to GCs and other immunosuppressive agents, depending on their severity.

Posterior segment

Retinopathy

Retinal involvement, that in terms of frequency comes soon after secondary SS, has been found to range from 3 to 29% of SLE patients, depending on the population studied and the activity phase of the disease [37]. Its prevalence is generally much less frequent now, due to better overall systemic control. Clinically, unilateral or more often bilateral visual loss of variable severity is reported. Microangiopathy is the most common finding. On ophthalmological examination and fundus fluorescein angiography (FFA), pathological features may include sheathed or tortuous retinal vessels, edema of the papilla, hemorrhagic or cotton-wool spots, and less frequently retinal detachment, optic atrophy, and hard exudates. Multiple large vessel branch retinal artery occlusions, including bilateral central retinal artery occlusion with choroidopathy complications, can sometimes be observed [38]. The appearance and extent of retinopathy are directly related to SLE disease activity index (SLEDAI) scores and are more frequently detected in patients with renal failure and/or central nervous system involvement such as chorea, epilepsy and convulsions [39].

The pathogenesis of SLE retinopathy, that has been ascribed to vasculitis of the retinal capillaries and arterioles, may result in local micro-infarction and microembolism and reflects at the ocular level the occurrence of a more extensive and often systemic vascular damage. An important confirmation to this pathogenetic interpretation is the frequent demonstration in these patients of the antibodies that characterize the anti-phospholipid antibody syndrome (APS), namely lupus anticoagulant (LAC), anti-cardiolipin (ACL), and anti-beta-2 glycoprotein-I antibodies, usually of IgG isotype. And it is well known that recurrent infarctions and thromboembolisms are the hallmark of the APS [40].

Because retinopathy mostly occurs in coincidence with the activity phase of SLE, its treatment is based on the typical combination (GCs, hydroxychloroquine [HCQ], and immunosuppressive drugs) that is employed in all severely active SLE patients. In addition, intravitreal bevacizumab should be considered in case of severe vaso-occlusive retinopathy. Laser photocoagulation may be applied when neovascularization secondary to retinal ischemia is diagnosed.

If anti-phospholipid antibodies are detected, the addition of a single or dual anti-platelet therapy (low-dose acetylsalicylic acid and/or clopidogrel), or anti-coagulation with warfarin, or any of the novel oral anticoagulants (apixaban, dabigatran, darexaban, rivaroxaban, and ximelagatran) may be useful. In addition, vitrectomy and retinal photocoagulation are performed to halt neovascularization and prevent aggravation of visual loss.

A rare and peculiar form of retinal involvement is the so-called Purtscher's retinopathy. At variance from the initial description in a post-traumatic condition [41], this type of retinopathy has been diagnosed in a number of non-traumatic disorders including SLE, Still's disease, and cryoglobulinemia: in these conditions, it is more properly designated Purtscher-like retinopathy [42]. Clinically, patients complain of sudden visual loss in one or more often both eyes. Variably localized scotomata may also be detected, whereas the peripheral visual function is commonly spared. Intravenous FFA shows arteriolar occlusion and areas of capillary leakage in the macula of one or both eyes. The key findings are multiple areas of retinal whitening between retinal arterioles and venules (Purtscher flecken) and cotton-wool spots [43]. Less frequent additional findings include optic disk swelling, retinal hemorrhages, pseudo-cherry red spots, and macular edema.

Although multiple pathogenetic mechanisms have been pointed out to account for the occurrence of Purtscher-like retinopathy, the most likely explanation is the formation of microemboli that results in retinal vascular occlusion and microvascular infarcts [43].

In addition to the systemic administration of GCs plus immunosuppressive combination, intraocular therapy includes vitreal injections of bevacizumab (an anti-vasculogenesis biological agent), and subtenon injections of triamcinolone acetonide. Panretinal photocoagulation and pars plana vitrectomy may sometimes be necessary [44].

Choroidal disease

It is a less frequent ocular complication of SLE compared with retinopathy, although it is possibly less rare than commonly believed and usually indicative of lupus activity. Unilateral or bilateral blurred vision is the common presenting sign; in approximately two-thirds of the patients the visual acuity are 20/40 or better [45], more severe visual loss possibly suggesting macular involvement. FFA shows multifocal serous elevations of the sensory retina, associated or not with serous detachments of the retinal pigment epithelium or retinal pigment epitheliopathy. Secondary angle-closure glaucoma with consequent intraocular hypertension may result from the choroidal effusion [46]. The ischemic areas, that appear as subretinal hypo-pigmented patches, are most likely related to choroidal vascular disease, resulting in pigment epithelial damage and serous fluid leakage beneath the retina. These fluorescein angiographic abnormalities differ from those of complete Vogt–Koyanagi–Harada (VKH) disease that usually include focal areas of delayed choroidal perfusion, multifocal pinpoint leakage, areas of placoid hyper-fluorescence, optic nerve staining and pooling in the serous elevations by late phases [47].

Significant serous retinal detachments may be identified on fundoscopy, but SD-OCT is able to detect even very early serous retinal detachments and is valuable in measuring changes over time of intraretinal and subretinal fluid, and the detachment of pigment epithelium [29]. For identifying areas of leakage in active choroidopathy, indocyanine green angiography is a valuable additional tool. It classically reveals focal hypo-fluorescent areas in the early phase with pinpoint areas of hyper-fluorescence appearing in the intermediate and late phases of the angiography sequence [48].

Because choroidopathy is usually indicative of active SLE and may herald the onset of SLE nephropathy [49], treatment is usually with a combination of GCs and immunosuppressive agents. A typical example is the administration of intravenous pulsed methylprednisolone, followed by oral prednisolone, in combination with cyclophosphamide.

Optic neuritis

It is a relatively rare complication of SLE that affects approximately 1% of the patients. Clinically, the patient complains of usually unilateral, severe visual loss and ocular pain that gets worse during the eye movements. In the absence of other unequivocal signs of SLE, this condition may be misdiagnosed as a demyelinating condition such as multiple sclerosis [50]. Progression to optic atrophy may develop in approximately 50% of the patients. It is essential that the GC administration (pulse therapy in the first 3–5 days, followed by oral therapy with progressive tapering) be initiated as early as possible to increase the chances of visual acuity recovery [51].

Ischemic optic neuropathy (ION)

This condition is a sudden loss of vision, due to an ischemic restriction of blood flow with subsequent retinal hypo-perfusion to the optic nerve head (anterior ION) or to the retrobulbar portion of the optic nerve (posterior ION). It can be the presenting feature of SLE, but usually appears during the course of the disease. The patient presents with acute-onset and progressive binocular visual impairment, but ocular pain is usually absent. Ophthalmoscopy may reveal optic disk swelling with mildly blurred margins. Confirmation of the ION may derive from the visual evoked potential, showing reduced amplitude or increased latency. Leakage of dye around both optic disks can be seen by FFA. In addition to the typical serological features of SLE, ACL antibodies and LAC can be detected [52]. The basic underlying mechanism of ION is the occlusion of the small vessels of the optic nerves as a consequence of immune complex vasculitis or, when the corresponding antibodies are detected, a condition of retinal vaso-occlusive disease secondary to APS.

The mainstay of treatment includes intravenous methylprednisolone boluses and oral GCs. Recurrence during steroid tapering is possible, requiring a combination treatment with GCs and immunosuppressive agents. Monthly courses of intravenous cyclophosphamide administration have also been shown to be an effective therapy for SLE-associated optic neuritis. In refractory patients, a biological treatment with rituximab has been used with positive results [53]. Intravitreal injections of bevacizumab have also been employed to treat neovascularization with properly timed retinal laser photocoagulation to prevent further progression of retinal ischemic areas [54].

At variance from SLE-related ION, idiopathic optic neuritis may have as underlying disease a condition such as multiple sclerosis, neuro-myelitis optica, demyelinating lesions which do not meet the diagnostic criteria for multiple sclerosis, or an unknown cause. Patients with idiopathic optic neuritis have a 30–50% rate of recurring attacks with obvious impairment of the visual acuity, especially when optic neuritis is unilateral and a relatively low corticosteroid daily dosage (equivalent to < 100 mg prednisone) is initially given [55].

Disorders of ocular motility and neuro-ophthalmic manifestations

These abnormalities are usually the consequence of vasculitic and/or vaso-occlusive ischemic events of the nerve and brain, and are obviously of concerted interest for ophthalmologists and neurologists.

In an old study [56], when 53 randomly selected SLE patients were subjected to a thorough neurological examination, electroencephalographic and/or saccadic eye movement and/or brain CT abnormalities were detected in 38 cases (72%), although only 18 of them had clinical evidence of neuro-SLE. These observations indicate that a detailed clinical and instrumental assessment is able to reveal subtle nervous dysfunctions in SLE. In another study, again outdated [57], 33 out of 113 SLE patients were found to have ocular motor abnormalities (29.2%): the most frequent included eye movement limitations, abnormal spontaneous eye movements, abnormal ocular position at rest, and ptosis.

Limited elevation of the adducted eye, ascribable to movement limitations of the superior oblique tendon, is commonly named Brown's syndrome and can mimic a palsy of the inferior oblique muscle, resulting in vertical diplopia on upward and inward gaze. Apart from apparently idiopathic cases, likely due to swelling of the posterior part of the superior oblique tendon, occasional instances of Brown's syndrome have been described in patients with connective tissue diseases, including SLE [58]. In addition to the possibility of spontaneous resolution, a conservative management is initially advisable with the general administration of GCs and/or local GC injections in the region of the trochlea that are commonly followed by a prompt resolution of the diplopia. Surgery with different surgical procedures should be a second line of treatment, with the goal of restoring free ocular rotations [59, 60].

An unusual manifestation of disordered ocular motility in SLE patients is internuclear ophthalmoplegia, with the appearance of diplopia, vertigo, and ataxia [61]. The condition implies a brainstem lesion involving the medial longitudinal fasciculus, resulting in impaired adduction ipsilateral to the lesion and abduction nystagmus contralateral to the lesion [62]. The one-and-a-half syndrome, Miller-Fisher syndrome, Horner's syndrome, abnormal pupillary reflexes, blepharospasm, retrochiasmal disease, transient monocular blindness, and intracranial hypertension have occasionally been reported, sometimes at the debut of the disease [28, 53, 63, 64]. In the majority of instances, GCs are able to induce a positive response, whereas cyclophosphamide, azathioprine, and rituximab are employed as steroid-sparing agents and in refractory cases [63].

Therapy of SLE and ocular adverse events (OAE)

Although no cure of SLE is yet available, its treatment is remarkably improved in the last 20 years. In addition to GCs and HCQ that are given to virtually all SLE patients, several other drugs are employed including azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate, CsA, rituximab, and belimumab in variable combinations, depending on the patient's age, disease activity, refractoriness to initial treatment, damage index, and responder index [65, 66]. In spite of the poor consensus on the most appropriate index for each particular setting, those criteria still maintain their usefulness in the follow-up of patients and the choice of the most suitable therapeutic approach. To monitor SLE patients in clinical practice, quality indicators have been developed with the aim of reducing unwanted variability [67].

The worldwide experience on the long-term administration of one or more of the above mentioned drugs has allowed to establish that they can be burdened by AE affecting several organs, including ocular toxicity whose frequency has probably been underestimated. The observation of these AE has been largely derived from their use as antineoplastic rather than anti-SLE agents [68–70]. Here, we will briefly discuss the treatment-related AE involving the eye, with special emphasis for the better known and more frequently occurring side effects induced by GC and aminoquinolines [16].

GC-related OAE

Although GCs still remain the mainstay of SLE therapy, independently of whether they are initially given as pulse intravenous injections of methylprednisolone (followed by) or directly started as oral prednisone, their long-term administration almost inevitably results in a well-known series of AE such as diabetes, osteoporosis, and fractures and includes ocular manifestations such as posterior subcapsular cataracts and secondary open-angle glaucoma [71].

Although the prevalence of these complications usually ranges from 11 to 15% for cataract and up to 13% for glaucoma [72], obviously the cumulative dose of GCs, the length of their administration, and possibly the patient's genetic predisposition are important contributing factors. Studying a cohort of 170 SLE patients (20% of whom had never undergone eye assessment), who were given a mean daily dose of 5.4 ± 2.4 mg prednisone and a mean cumulative dose of 27.6 ± 20.5 g, cataracts were detected in 29% of the patients at a mean age of 46.5 ± 10 years and glaucoma in 3% of the patients at a mean age of 40.5 ± 16 years [73].

It is important to try to identify GC-induced ocular hypertension before it leads to nerve damage and associated visual field loss (i.e., glaucoma). In many cases, it can be controlled with cessation of GCs, where this is possible. Where this is not possible or where intraocular pressure continues to be elevated, a hierarchy of interventions starting with pressure-lowering topical therapy (eye drops), to the addition of systemic therapy (commonly acetazolamide) and glaucoma surgery, may be necessary to protect against visual field loss and even blindness. This is particularly important as the visual loss of glaucoma is irreversible. Thus, SLE patients chronically treated with GCs should be strongly advised, regardless of any visual disturbance, to undergo a yearly eye assessment [74]. These observations emphasize the importance of adopting, whenever possible, steroid-sparing regimens.

At variance from systemically administered GCs that may induce intraocular hypertension after a few months, topical ophthalmic GCs can result in the same side effect after a few weeks of daily administration, the ocular hypertensive response usually being dose-dependent. In this context, a special mention deserves the intravitreal steroid injection and implantation in that, following intravitreal fluocinolone acetonide (Retisert implant) or dexamethasone (Ozurdex implant), over 40% of the patients eventually necessitate glaucoma surgery [75]. However, the incidence of both cataract and raised IOP (≥ 25 mm Hg) is higher in patients receiving the Retisert implant than in those treated with the Ozurdex implant, possibly reflecting the difference in potency of the two corticosteroids and the effect of constant exposure throughout the 30-month lifespan of the first implant [76].

HCQ/chloroquine (CQ) OAE

There exists an overwhelming literature on the potential risks for OAE in patients receiving long-term aminoquinolines. While CQ has been largely abandoned, the long-term administration of HCQ sulfate may be associated with AE such as vortex keratopathy and in particular the dreadful maculopathy. Vortex keratopathy (a complication of several additional drugs, including amiodarone and ibuprofen) is usually mild and reversible. On slit-lamp examination, golden-brown deposits can be seen in the cornea, whereas confocal microscopy may reveal the presence of hyper-reflective, dot-like intracellular inclusions located in the basal epithelial layer and in the stroma, possibly ascribable to phagocytic keratocytes [77]. Obviously, much more important is the irreversible and sight-threatening maculopathy, an insidious condition because initially asymptomatic and usually foreshadowed by the loss of the foveal reflex [78–80].

In spite of the sight-threatening risk, the actual incidence of HCQ retinopathy in large cohorts of patients has been found to be rather low. In a prospective cohort study, 526 Greek patients with rheumatoid arthritis or SLE, treated with HCQ for long periods of time, were submitted to periodic (every 6 months and then yearly) ophthalmologic evaluations that included best-corrected visual acuity, color vision testing, static central VF testing, fundoscopy, mfERG, and FFA. No retinal toxicity was noted in any of the patients given a maximum daily dosage of 6.5 mg/kg during the first 6 years of treatment, and the overall incidence of retinopathy in the patients treated with the mentioned dosages of the drug for a mean of 8.7 years was found to be 0.5% [81].

Other studies, however, indicate that HCQ retinopathy is less rare than commonly believed, high dosages and long duration of use (hence the cumulative exposure) being the most important risk factors for ocular toxicity. In a retrospective case–control study, carried out in a cohort of 2361 patients who were given HCQ for at least 5 years, the overall prevalence of HCQ retinopathy was 7.5%. However, among the patients receiving a daily dose of 4.0–5.0 mg/kg, the prevalence of retinal toxicity was < 2% within the first 10 years and increased to roughly 20% after 20 years of use, especially in those with lupus nephritis and/or concomitantly taking tamoxifen [82].

According to their extent and severity, the toxic effects of HCQ can be distinguished in: (a) early, when patchy parafoveal areas of damage are visible on VF or objective testing; (b) moderate, characterized by a 50–100% thinning of the parafoveal ring on SD-OCT, the retinal pigment epithelium being, however, undamaged; (c) severe, when a bull's-eye

maculopathy is seen on near-infrared reflectance with a confocal scanning laser ophthalmoscope [83]. Fundus examination shows macular pigmentary changes that are responsible for abnormal FAF. In most patients, the external limiting membrane (ELM) and the photoreceptor layer of the fovea are preserved, as detected by SD-OCT.

How do HCQ toxic effects evolve after drug therapy cessation? In favorable cases, retinal regeneration may result in functional visual improvement on static perimetry, whereas FAF either remains stable and may even undergo enlargement in the most severe cases or gradually fades to a pattern of reduced autofluorescence [84]. Obviously, early detection of toxic effects and the prompt discontinuation of the drug can be expected to result in visual improvement of variable extent; conversely, a late diagnosis is usually followed by progression of structural and functional visual deterioration in spite of HCQ discontinuation. It has been observed that patients showing a good preservation of the external limiting membrane (ELM) at the time of initial examination were able to undergo progressive outer retinal remodeling on SD-OCT, partial regeneration of photoreceptors in the areas with ELM preservation and eventually carry a favorable prognosis in terms of restoration of the outer retinal layers [84].

Because maculopathy may be detected rather late by fundus examination, it is advisable not to rely on this procedure for an early diagnosis. Furthermore, given that HCQ is usually prescribed by rheumatologists as a long-term treatment even in patients with limited SLE activity and/or receiving GCs and immunosuppressive agents in addition to HCQ [85], a thorough ophthalmological control (starting with slit-lamp examination) should be strongly recommended at closer intervals, in step with the total length of exposure to the drug and the cumulative dose administered.

To screen for HCQ toxicity, the American Academy of Ophthalmology (AAO) has proposed revised guidelines (2016 revision) [86]. The major concerns stem from the following facts: (a) HCQ toxicity is not treatable; (b) only an early recognition of the damage to the photoreceptors prior to disruption of the retinal pigment epithelium (RPE), and the consequent drug discontinuation can prevent central vision impairment; (c) until advanced stages of photoreceptor damage have been reached, visual acuity may remain normal in the absence of subjective symptomatology, and this may result in underestimation by the patient of the drug potential risks; (d) progression has been detected even after HCQ discontinuation, an event likely due to a slowly developing toxicity of the cells that had been previously exposed to the drug.

According to the AAO statement, HCQ should be given at a maximum daily dose of ≤ 5 mg/kg real weight (rather than ideal weight), and the risk of toxicity is dependent on both daily dose and length of administration. It has been observed that when these doses are fulfilled, the risk of toxicity remains under 1% at 5 years and under 2% up to 10 years, although it can increase to roughly 20% after 20 years. Even so, patients lacking toxicity after 20 years have a low risk (approximately 4%) of developing HCQ retinopathy in the following years. It has also been observed that, along with dose and length of administration, additional risk factors include the coexistence of renal disease (a common complication in SLE) and the consumption of tamoxifen (frequently used in breast cancer patients) [86].

Before starting therapy, a thorough baseline examination is recommended with the aim of excluding an underlying maculopathy, a condition that would possibly enhance the toxic effect of HCQ and affect the results of screening techniques. The screening should be performed after 5 years and then repeated yearly in patients given the recommended doses of HCQ and lacking major risk factors. An earlier examination is, however, strongly advised for high-risk patients, namely those already mentioned who have been treated with higher doses of HCQ for long periods of time, and/or with renal function impairment and/or taking the anti-estrogen tamoxifen [86].

While patients should be primarily screened by automated central visual fields (VF) plus SD-OCT, multifocal electroretinography (mfERG) is useful to objectively confirm the presence of field loss and fundus autofluorescence (FAF) can provide an early topographic view of photoreceptor damage in parafoveal or extra-macular areas [86].

Although the AAO guidelines published in 2011 have been frequently neglected or overlooked [87, 88], it is hoped that the 2016 revision of the recommendations on screening for HCQ retinopathy may receive a much wider adherence.

MTX-related OAE

At variance from the well-known liver, lung and gastrointestinal toxicity, ocular AE by MTX have been seldom reported. Progressive cotton-wool spots have been detected in both eyes by fundus examination in a woman with rheumatoid arthritis under MTX treatment for 11 years. Laboratory examinations revealed severe pancytopenia [89]. This observation suggests that MTX can also induce ischemic retinal complications, and this finding should raise the suspect of bone marrow suppression and pancytopenia. Additional ocular toxicity includes photophobia and epiphora [90].

Cyclophosphamide-related OAE

Compared with the major and much more frequent adverse reactions such as marrow, gastrointestinal, gonadal, and bladder toxicities, and less often pulmonary fibrosis, OAE of cyclophosphamide are rather unusual and mostly consist of dry eye and increased intraocular pressure [90].

CsA-related OAE

In addition to dreadful renal toxicity and usually mild anemia, increase in bilirubin and transaminase levels, hirsutism, and gingival hyperplasia, visual acuity changes [91] have also been described. Reported hallucinations [92] should obviously be ascribable to neurotoxicity rather than to ocular toxicity

OAE of additional immunosuppressive and biological agents

To the best of our knowledge, no remarkable side effects involving the eye have been reported so far for azathioprine, mycophenolate mofetil, tacrolimus, and leflunomide. The same can be said for the two biological agents most frequently used in the treatment of SLE, namely rituximab, a chimeric anti-CD20 monoclonal antibody, and belimumab, a fully human monoclonal antibody against the B cell-activating factor/B-lymphocyte stimulator (BAFF/BLyS). In addition, an increasing number of biological immunosuppressive compounds and drugs that can modulate innate immunity, B cells or T cells are under study in controlled trials or preliminary assessment [93–95]. Among them, the disappointing or uncertain results obtained with epratuzumab, a monoclonal antibody that targets CD22 [96], and with atacicept, a fusion protein that blocks BAFF/BLyS and a proliferation inducing ligand [97] on the one hand, and the more promising results achieved with blisibimod, an inhibitor of BAFF/BLyS [98] and with anifrolumab, an anti-interferon-α receptor monoclonal antibody [99] on the other, should be mentioned.

For all these immunosuppressive and immunomodulating agents, no information concerning their potential ocular toxicity is at the moment available.

Conclusions

As stated above, the ocular involvement may sometimes be the presenting manifestation of SLE that should always be kept in mind when considering the differential diagnosis of several retinal vascular and neuro-ophthalmic conditions [16, 29]. In particular, the occurrence of retinal vasculitis (that may initially be asymptomatic), necrotizing scleritis, and peripheral ulcerative keratitis should prompt the ophthalmologist to look for extra-ocular abnormalities and to seek for rheumatologic and immunological advice. It is therefore suggested that at diagnosis, all SLE patients should undergo a thorough ophthalmic examination, including external inspection, visual acuity, pupillary reaction, ocular motility, confrontation field testing, and direct ophthalmoscopy with fluorescein staining. The frequency of subsequent controls should be established on an individual basis according to the extent of ocular involvement, degree of disease activity, and type and dose of the drugs prescribed [28, 29].

Although an early diagnosis of retinal vasculitis is an important goal in order to avoid an irreversible damage and achieve a favorable outcome, this is not an easy task given that the symptomatology may often remain vague and non-specific for weeks or months. It is, therefore, strongly recommended that patients with even limited signs of retinal vasculitis be closely monitored both clinically and by FFA. In addition, a suitable therapeutic regimen should also be initiated in order to prevent an irreversible damage to the visual function. The appearance of retinal signs often portends a relapse of the underlying vasculitis, and this should again require a multidisciplinary approach to the patient [17, 19, 29].

Not only ophthalmologists, but also internists, immunologists, and rheumatologists should be aware of the ocular manifestations of SLE for at least two reasons: first, because they can represent (as already mentioned above) the initial features of the disease; second, because a delayed diagnosis and the consequent late beginning of a suitable treatment may result in sight-threatening consequences. On the other hand, SLE patients under chronic therapy with GCs and/or HCQ, which can potentially result in OAE, should be strongly invited to adhere to recommendations for eye monitoring, according to the AAO statement [86]. Whether biological therapies and targeted drugs under development might also be burdened with ophthalmologic side effects will be established on the basis of future prospective studies.

To meet the large majority of the diagnostic and therapeutic problems that may arise throughout the course of an extremely heterogeneous condition such as SLE, tertiary referral centers should be organized as SLE multidisciplinary teams including medical specialists with advanced education and clinical training in specific areas of medicine, such as internal medicine, clinical immunology, rheumatology, nephrology, dermatology, ophthalmology, neurology, psychiatry, and gynecology.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

Ethical approval Since no personal data are reported, in accordance with the policy of the University of Bari submission to a research ethics committee or institutional review board is not required.

Informed consent The manuscript is a review of the literature; informed consent is not applicable.

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