



Systemic Lupus Erythematosus Presenting as Acute Posterior Multifocal Placoid Pigment Epitheliopathy - Case Report and Review of the Ocular Manifestations of Systemic Lupus Erythematosus

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Abstract

The ocular manifestations of systemic lupus erythematosus (SLE) are numerous and may be due to complement-activating immune complex deposition causing inflammation or thrombosis, secondary effects of SLE such as hypertension, related diseases such as Sjogren's and Antiphospholipid antibody syndrome, or a combination of these.

Left untreated, these manifestations can result in serious morbidity and rarely, mortality. Here we present the first reported case of systemic lupus erythematosus masquerading as Acute Posterior Multifocal Placoid Pigment Epitheliopathy, a rare chorioretinal disorder. An overview of the numerous ocular manifestations of this disease are presented, as well as recent highlights into the pathophysiology of SLE.

Case Report

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is a rare disease affecting males and females equally in their second to third decade of life. It is thought to be due to an immune driven vascular alteration of the choriocapillaris with a secondary pigment epithelial reaction. More than half are associated with a viral etiology, and up to one-third will have a viral prodrome. Systemic autoimmune diseases such as erythema nodosum, granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN), as well as other inflammatory diseases such as cerebral vasculitis, microvascular nephropathy, scleritis and episcleritis are associated with APMPPE [1,2].

A 35 year-old Caucasian female with a known history of systemic lupus erythematosus presented with a two week history of decreased vision and headaches. She had been previously well with no symptoms of infection. Her visual acuity at presentation was 20/500 right eye and 20/30 left eye, with intraocular pressures of 12 mmHg in both eyes and no afferent pupillary defect. Diffuse anterior scleritis of the right eye was noted following instillation of phenylephrine 10%. Funduscopy revealed bilateral confluent, deep, cream-colored chorioretinal lesions of varying sizes with indistinct borders located mostly between the

arcades (Figure 1). There were 0.5+ cells in the vitreous in both eyes and no haze. Fluorescein angiography showed early hypofluorescence (Figure 2) and late hyperfluorescence (Figure 3) of the lesions. Optic nerve edema was noted on the clinical examination and confirmed with fluorescein angiography, which showed early hyperfluorescence and late staining of the optic nerve (Figure 2 and Figure 3). In the late frames, there was significant background hyperfluorescence and vascular flushing with extravasation of dye (Figure 3). The clinical features and angiography appeared consistent with a diagnosis of APMPPE.

However, there were atypical features including profuse vascular leakage and punctate hyperfluorescence in the temporal macula and around the optic nerve. As well, the fluorescein pooling was



Figure 1: Color photograph of the right eye showing deep chorioretinal lesions of varying sizes becoming confluent, located mostly between the arcades, as well as disc edema.

not typical of APMPPE. A macular OCT showed subretinal fluid (Figure 4). These characteristics, along with the anterior scleritis at presentation, pointed to a possible diagnosis of posterior scleritis.

A blood work panel was significant for an ANA of 2560, and further testing was negative for syphilis, Lyme disease and tuberculosis. An MRI/MRV/MRA of the brain did not reveal vasculitis or any other abnormality. Rapid resolution and visual improvement occurred with oral prednisone therapy

Literature Review

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that preferentially affects women in their childbearing years. African Americans, Hispanics and Asians are at greater risk of developing SLE [3].

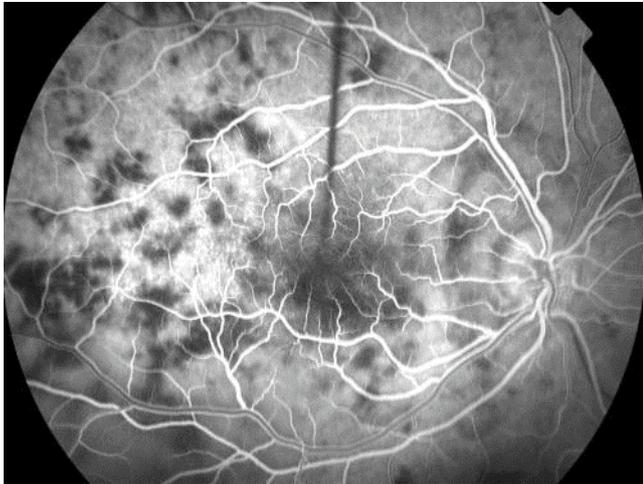


Figure 2: A fluorescein angiogram of the right eye showing early hypofluorescence of the lesions.

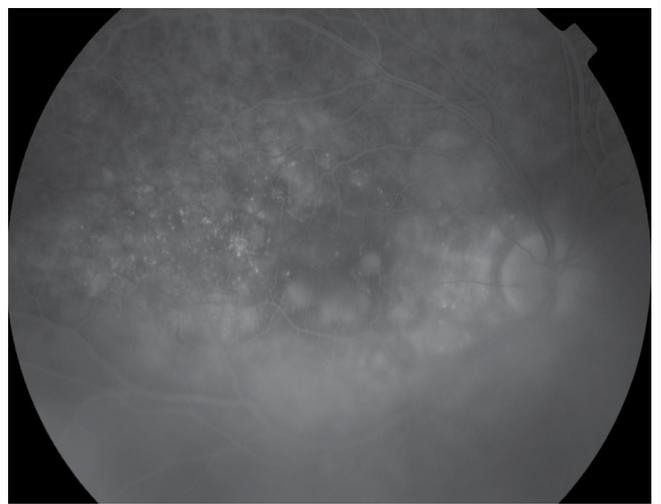


Figure 3: A fluorescein angiogram of the right eye showing late hyperfluorescence of the lesions, as well as significant background hyperfluorescence with vascular flushing and optic nerve staining. Pinpoint areas of leakage in the temporal macula are consistent with posterior scleritis rather than APMPPE.

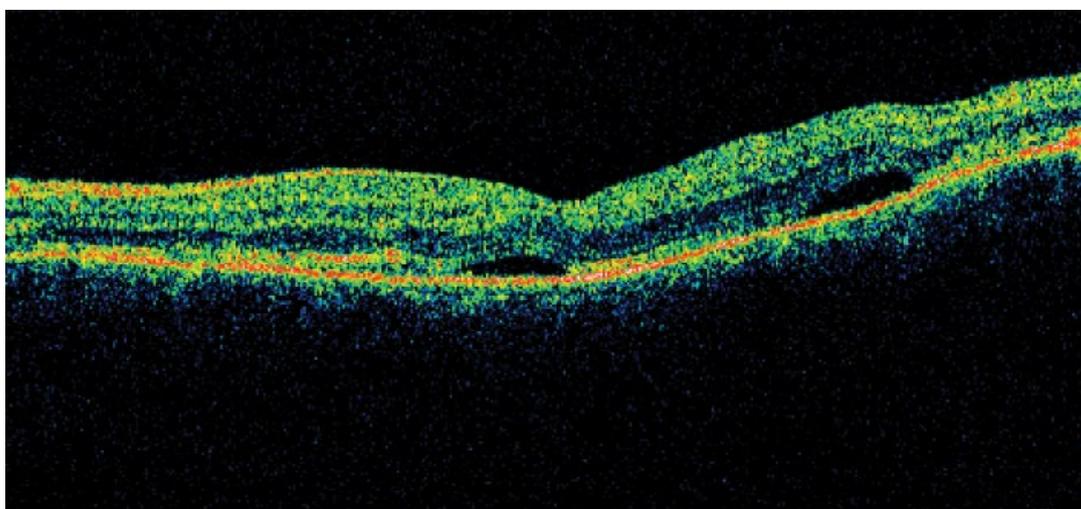
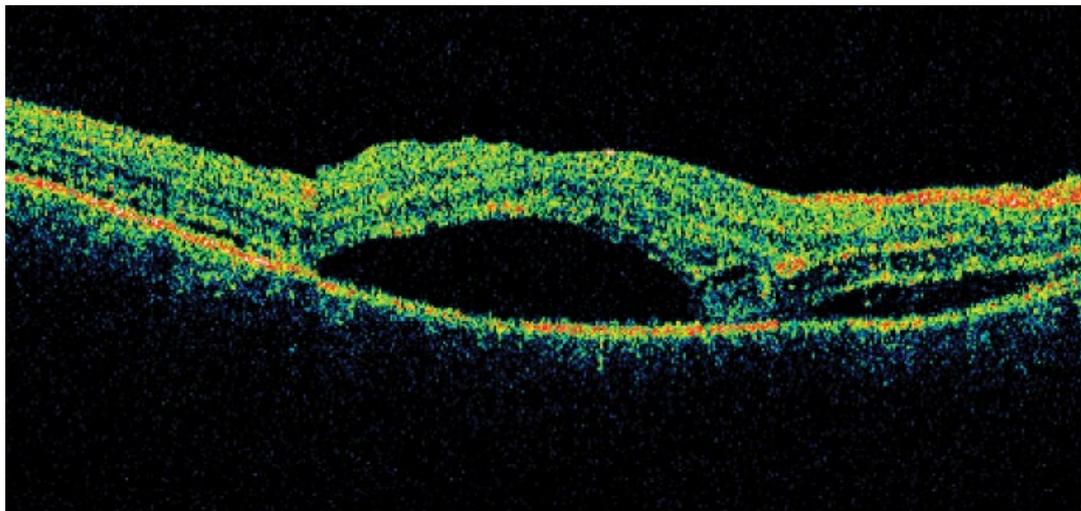


Figure 4: Macular OCT showing subretinal fluid in the right eye (Top) and left eye (bottom).

While the diagnostic criteria for SLE by the American College of Rheumatology from 1997 are still being used, the Systemic Lupus International Collaborating Clinics (SLICC) group recently revised the criteria in 2012 to now include seventeen clinical or laboratory criteria. Diagnosis requires at least 4 criteria, including at least one clinical criterion and one immunologic criterion, or a positive biopsy-proven lupus nephritis in the presence of antinuclear antibodies or anti-double-stranded DNA antibodies [4]. Patients can also be classified as “probable SLE patients” if they do not fulfill the classification criteria, or for those with other SLE manifestations not included in the classification criteria. The revised criteria are as follows:

- Clinical criteria
 1. Acute cutaneous lupus, including: lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash (in the absence of dermatomyositis), or subacute cutaneous lupus.
 2. Chronic cutaneous lupus, including: classic discoid rash, hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chillblains lupus and discoid lupus/lichen planus overlap.
 3. Oral ulcers 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. Nonscarring alopecia in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia.
 5. Synovitis involving 2 or more joints, characterized by swelling or effusion or tenderness in 2 or more joints and at least 30 minutes of morning stiffness.
 6. Serositis
 7. Renal: Urine protein–to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours OR red blood cell casts
 8. Neurologic: 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 ($< 4,000/\text{mm}^3$ at least once) (in the absence of other known causes such as Felty’s syndrome, drugs, and portal hypertension), OR lymphopenia ($< 1,000/\text{mm}^3$ at least once) (in the absence of other known causes such as corticosteroids, drugs, and infection).
 11. Thrombocytopenia ($100,000/\text{mm}^3$) at least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura
- Immunologic criteria
 1. ANA level above laboratory reference range
 2. Anti-dsDNA antibody level above laboratory reference range (or 2-fold the reference range if tested by ELISA)
 3. Anti-Sm: presence of antibody to Sm nuclear antigen
 4. Antiphospholipid antibody positivity as determined by any of the following: positive test result for lupus anticoagulant, false-positive test result for rapid plasma regain, medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM), positive test result for anti-2-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

The ocular manifestations of SLE are numerous and diverse. The pathophysiology of ocular manifestations of SLE are also varied and somewhat controversial. They may be due to complement-activating immune complex deposition causing inflammation or thrombosis, secondary effects of SLE such as hypertension, related diseases such as Sjogren’s and Antiphospholipid antibody syndrome, or a combination of these [5-9].

The ocular manifestations of SLE can be the initial presentation and if misdiagnosed or left untreated, can result in serious morbidity and even mortality. Therefore, prompt diagnosis and treatment is required.

Pathogenesis

Immune-complex deposits have been demonstrated in vessels in the conjunctiva, sclera, retina and choroid of patients with SLE [6,10-13]. One study found that patients with significant immune reactants, most commonly IgG, also had significant disease activity [6]. It is thought that these immune-complex deposits activate the complement pathway which produce C3 and C5, proteins also found in ocular tissue of patients with SLE [12]. These proteins then attract inflammatory cells, resulting in the release of pro-inflammatory cytokines and tissue-damaging enzymes [14]. Histopathological studies of choroidal vessels show necrosis and extravasation of fibrinoid material in the choroid, supporting the theory of a vasculitis secondary to immune-complex deposition [10,11].

These immune-complex deposits may alternatively cause a thrombotic reaction via interactions with platelet and endothelial cell surfaces [6,10,15].

However, the evidence for these two mechanisms is conflicting. One immunopathologic study of active inflamed conjunctiva of SLE patients showed several immune-complex deposits in conjunctival epithelium, stroma and vessel walls including IgA, IgD, IgG, IgM and C4. In this study, the finding of immune-complex deposits at the basement membrane zone was related to the clinical appearance of cicatrizing conjunctivitis. However, there was no evidence of vasculitis or thrombosis [13]. Another older study also failed to show evidence of necrosis and vasculitis in retinal vessels [16].

Interestingly, one study examining the presence of immune-complexes in various biopsy specimens of patients with SLE found that while the conjunctiva had a greater number of antibodies compared to the skin or other mucous membrane, this did not necessarily translate to active disease as many patients were asymptomatic [17].

Recent studies have also pointed to the role of abnormal differentiation of T-helper cells, specifically the role of the proinflammatory Th17 cell in the pathogenesis of SLE [18-20]. The combination of TGF- β and IL-6 leads to differentiation of Th17 cells, which in turn produce IL-17. IL-21 and IL-23 also contribute to the stabilization and proliferation of these cells [21].

The ocular surface provides all of these cytokines and when exposed to inflammatory stimuli or desiccating stress, these cytokines are further up regulated resulting in a vicious cycle [22].

Elevated tear IL-17 levels were found to have a direct correlation with clinical severity of ocular surface disease in patients with systemic inflammatory disease, including SLE. Interestingly, this correlation was not found in patients with ocular surface disease with no systemic inflammatory disease [23].

Related diseases such as antiphospholipid antibody syndrome can also cause thrombosis of ocular vessels, resulting in serious irreversible visual loss. Antiphospholipid antibody has been recognized as a risk factor for severe occlusive SLE retinopathy, and its presence signifies an overall poorer prognosis [7,24,25].

Orbital Manifestations

SLE can involve the lids and periorbital area. It is more frequent in the discoid lupus erythematosus (DLE) variant and has been

well-described in the literature. Presentations include eyelid edema, periorbital edema, plaque-like lesions, erythematous papules, ulcers, telangiectasias, cicatricial changes and madarosis [17,26-64].

The lower lid is most commonly involved and can clinically be mistaken for eczema, blepharitis, squamous cell carcinoma or basal cell carcinoma [26]. As well, squamous cell carcinoma and DLE share many histopathological features including cytologic atypia and infiltrative patterns of squamous proliferation [26,65]. The key features that distinguish DLE from squamous cell carcinoma are perifollicular or periacrosyringeal inflammation, vacuolar basal cell degeneration, and dermal mucin deposition [26,66].

Systemic antimalarial drugs were successfully used to treat these lesions [28,30]. For patients who failed antimalarial drugs, intralesional steroids or thalidomide were found to be beneficial [44,53,63].

Many of the cases described had a delay in diagnosis of up to 25 years, and surgical revision of cicatricial changes such as ectropion and trichiasis were required [61,63,67]. These cases highlight the importance of a biopsy in refractory or unusual periocular skin disease.

Another manifestation of SLE is panniculitis, usually presenting as firm, large subcutaneous nodules on the face and arm [68]. It can rarely affect the orbit, and include symptoms such as lid swelling, proptosis and limited extraocular movements [51,69-73]. Many of these patients improved with antimalarials, but one case resulted in severe orbital melting despite therapy [51,69].

Trochleitis, which presents with swelling and pain in the superonasal orbit that is worse with eye movements, has also been reported as an initial manifestation of SLE. In this particular case, the patient had poor response to conventional treatment consisting of corticosteroid injections, and only experienced relief of symptoms with systemic treatment [74].

Additional orbital manifestations of SLE include orbital myositis, dacryoadenitis and Tolosa-Hunt Syndrome, characterized by painful ophthalmoplegia due to inflammation of the cavernous sinus or superior orbital fissure. These patients improved on systemic corticosteroids [75-79].

Corneal Manifestations

Keratoconjunctivitis sicca (KCS) is the most common ocular manifestation of SLE. Symptoms include a foreign body sensation, pain, irritation and burning, and can affect up to 60% of patients with SLE [80,81].

Approximately 17.8% of patients with SLE also suffer from Sjogren's syndrome, a chronic autoimmune disorder of the exocrine glands characterized by lymphocytic infiltrates of the affected glands [8,82-84].

Patients with this combination are generally older with more mucosal or arthritic involvement, and less major internal organ involvement than patients with SLE alone. These patients also have a higher prevalence of anti-SSA, anti-SSB and anti-dsDNA antibodies, as well as an increased prevalence of DRB1*0301 [8,82]. These findings indicate that the combination of SLE and Sjogren's may be a separate systemic autoimmune entity with a more favorable prognosis [8,82,83].

Treatment for dry eye symptoms is often chronic and long-term, and can range from the use of artificial tears, oral fatty acids and punctal occlusion, to the use of topical cyclosporine A [85]. One study showed that in vivo blockade of IL-17 in a mouse model significantly reduced the number of Th17 cells, as well as the severity and progression of dry eye [86]. Drugs that target this pathway may play a role in future management of keratoconjunctivitis sicca.

Rare cases of peripheral ulcerative keratitis, corneal stromal keratitis and keratoendothelitis have been reported. They were all generally responsive to corticosteroids and control of the systemic disease [13,87-92].

Refractive surgery is considered a relative contraindication in patients with SLE or other autoimmune diseases due to reports of adverse complications such as corneal haze and stromal melting [93-95]. Two retrospective studies of refractive surgery performed on patients with well-controlled autoimmune systemic disease, including SLE, reported no adverse effects to the cornea [96,97]. In one study of 49 eyes of 26 patients, there were no reports of corneal haze, melting, flap, or interface complications at a mean follow-up time of 19 months [96]. A second study of 42 eyes of 22 patients also found the same result, with a minimum follow-up time of 6 months [96,97]. Despite this, long-term studies are lacking. As well, cases of patients with inactive autoimmune disease suffering from post-operative necrotizing keratitis after undergoing laser eye surgery have been reported in the literature [95].

Conjunctiva and Sclera

SLE can manifest as a chronic blepharoconjunctivitis, cicatrizing conjunctivitis, epibulbar mass, episcleritis and scleritis [13,17,30,44,98-101].

Reported cases of conjunctivitis often had a delay in diagnosis, and similarly to patients with lid manifestations, suffered serious sequelae including symblepharon [17]. These manifestations can also be isolated, as evidenced by a report describing a unilateral, chronic, isolated discoid lupus erythematosus of the conjunctiva [102]. Biopsies were essential in establishing the diagnosis, and in patients with refractory conjunctivitis, are strongly encouraged.

Episcleritis is a generally benign disease that presents with ocular redness without symptoms such as pain or irritation. In some patients with SLE-related episcleritis, the episcleritis can flare along with systemic flares. SLE-related episcleritis can be recurrent or chronic, but will resolve with systemic treatment [17].

Scleritis can be categorized into five categories: diffuse anterior scleritis, nodular anterior scleritis, necrotizing scleritis with inflammation, necrotizing scleritis without inflammation, and posterior scleritis. SLE has been associated with each of these [13,98,103,104]. Symptoms include blurred vision and eye pain. If there is involvement of the anterior sclera, the scleral vessels will be inflamed and patients will present with a red eye. A case of angle-closure glaucoma secondary to posterior scleritis has also been described [105].

Compared to other autoimmune diseases such as granulomatosis with polyangiitis, SLE-related scleritis was found to have a much lower incidence of necrotizing scleritis, and therefore a better prognosis [104]. SLE patients who do present with necrotizing scleritis were found to have significant renal and systemic manifestations [106].

Unlike episcleritis, the course of scleritis can be severe with significant visual loss if left untreated. While patients with idiopathic scleritis may respond well to oral non-steroidal anti-inflammatory drugs, patients with concurrent systemic disease often require systemic immunosuppression including systemic corticosteroids, methotrexate, TNF-inhibitors or cyclophosphamide. The prognosis is good with prompt therapy [98,103,104,106].

Uvea and Retina

The reported prevalence of SLE in patients with uveitis varies from 0.1% to 4.8% [107-111]. One retrospective study found that SLE accounted for 3.3% of anterior uveitis, 7.9% of posterior uveitis cases, and 9.1% of panuveitis cases [108]. In another prospective study examining patients with anterior uveitis, SLE was found to affect only 1.2% [109]. It is important to note that these numbers are inherently biased as the cohorts analyzed represented patients specifically referred to a tertiary care center for further management, and did not include patients seen by primary care eye providers.

Anterior uveitic manifestations of SLE present as pain, eye redness, photophobia and blurred vision. They can be bilateral and severe, and can at times include hypopyon [109,111,112].

SLE retinopathy was previously reported to affect up to 28% of

patients [113], but more recent studies show a rate closer to 10-15% [114-116]. Findings are similar to vascular diseases such as diabetic retinopathy and hypertensive retinopathy, but with a better visual prognosis [114]. Signs include microaneurysms, hemorrhages, hard exudates, retinal edema, retinal ischemia and cotton-wool spots [15,117].

Immune-complexes have been well documented in retinal vessels, supporting the hypothesis that SLE retinopathy is primarily due to an inflammatory mechanism [13,16,118]. As well, SLE retinopathy appears to improve with systemic immunosuppression [5]. However, one study suggested that accelerated atherosclerosis due to the combination of hypertension, corticosteroid use and dyslipidemia in SLE may also play a role in SLE retinopathy [5].

Despite the excellent visual prognosis and generally asymptomatic nature, SLE retinopathy has been associated both with disease activity, and a decreased survival rate [114-116,119,120]. One study found that patients with SLE retinopathy had higher levels of serum creatinine, higher disease activity as measured by the SLE Disease Activity Index (SLEDAI), and a higher incidence of CNS lupus as compared to SLE patients without retinopathy [116].

SLE retinopathy can also present as a more rare, severe vaso-occlusive variant. Contrary to the more favorable prognosis of SLE retinopathy, this variant can result in severe and permanent visual loss from ischemia, neovascularization causing a vitreous hemorrhage or tractional retinal detachment [7]. Presentations include a Purtscher-like retinopathy, central retinal artery occlusions, cilioretinal artery occlusions, retinal vein occlusions, or combinations of these [7,121-130]. One study found that SLE was considered an independent risk factor for the development of vein occlusions, with a reported 3.46 times higher incidence than in controls [131]. The prognosis for these patients depends on the amount of retinal ischemia, but is generally poor [121-126,130].

CNS lupus appears to have a strong association with severe occlusive retinopathy, with one study finding the incidence to be more than 50% [7].

Additional retinal presentations, in addition to our patient with pseudo-APMPPE, include an exudative macular edema with frosted branch periphelbitis similar to CMV retinitis [132], and pseudoretinitis pigmentosa-like picture with bilateral retinal pigment epithelium changes [133]. These patients resolved markedly on corticosteroids.

Treatment is focused mainly on treatment of the systemic disease and includes systemic corticosteroids and immune-modulating therapy [134]. Patients who present with vein occlusions or severe vaso-occlusive disease should undergo screening for antiphospholipid antibody syndrome [24,135,136]. In patients with antiphospholipid antibody syndrome and concurrent SLE, there is often a role for systemic anticoagulation both in preventing further thrombotic events, which can happen in as little as one week, and in possibly treating the retinal occlusions and improving vision [92,121,123,135].

For cases of retinal neovascularization due to ischemia, treatments such as laser and surgery may be warranted, though they are not always successful in regaining or maintaining vision [7].

Lupus choroidopathy is a rare entity characterized by macular serous detachment, RPE detachments and RPE changes, and exudative retinal detachments which can be large and bullous [137,138].

One report detailing the indocyanine green angiography findings of lupus choroidopathy found that there were four main findings: focal, transient hypofluorescent areas in the very early phase indicating a choroidal filling delay, fuzziness of large choroidal vessels with late diffuse zonal choroidal hyperfluorescence indicating choroidal vascular leakage; poorly-defined areas of choroidal hypofluorescence visible up to the late phase indicating vascular obstruction; and focal cluster of pinpoint spots of choroidal hyperfluorescence visible from the intermediate to late phase. The first three are nonspecific and can be found in many other choroidal diseases, but the finding of focal

pinpoint spots of hyperfluorescence in the intermediate to late phase may represent immune deposits specific to lupus choroidopathy [139].

Lupus choroidopathy has a strong association with disease activity, with one study finding that 100% of cases of reported lupus choroidopathy had evidence of active systemic vascular disease, 64% had nephropathy and 36% had CNS lupus vasculitis [137].

Left untreated, permanent retinal pigment epithelial damage can result in permanent severe visual loss. For this reason, aggressive control of SLE with immunosuppressive therapy is the initial treatment [11]. While most patients will have good resolution of their symptoms, many patients will suffer from persistent areas of choroidal leakage despite adequate immunosuppression and inactive systemic disease. In these cases, plasmapheresis, focal laser and PDT and surgery have all been used successfully [11,137,140-142].

A rare case of punctate inner choroidopathy (PIC) was recently reported in a patient with SLE. On subsequent general exam, this patient was found to have renal impairment [143].

Neuro-ophthalmic Manifestations

Neuro-ophthalmic manifestations of SLE are uncommon, and a recent review estimated the prevalence to be 1.6% in children and 3.6% in adults [144].

Optic neuropathy caused by SLE is well-recognized in the literature and represents approximately 1% of SLE patients [145-150]. It can present as an optic neuritis with symptoms of decreased vision, dyschromatopsia, pain with extraocular movements or orbital pain, and scotoma [145]. It can further present as neuromyelitis optica, with optic neuritis that is often bilateral, and transverse myelitis [9,144]. Optic chiasmitis causing a junctional scotoma and ischemic optic neuropathy due to SLE have also been reported in the literature [144,151,152].

Optic neuropathy is generally associated with active disease and responds dramatically to corticosteroids, indicating an ischemic pathogenesis that in turn, causes demyelination [144]. Since recurrences can occur with corticosteroid taper, some authors advocate the use of concurrent immunosuppressives such as cyclophosphamide [146,153].

Eye movement restrictions causing diplopia have also been reported. Causes include cranial nerve palsies, internuclear ophthalmoplegia causing an ipsilateral adduction deficit, and Brown's syndrome where the superior oblique tendon becomes inflamed and restricted. Similarly to optic neuropathy, there is often dramatic improvement with systemic corticosteroids [154-164].

SLE-associated intracranial hypertension is characterized by headaches, blurry vision, and papilledema [165-168]. One study found abnormalities of the choroid plexus on MRI, which may indicate micro-occlusion of arachnoid villi [169,170]. In addition, many patients were found to have concurrent antiphospholipid antibody syndrome, and some suffered subsequent cerebral venous sinus thrombosis [171]. Almost all patients were found to have systemic active disease, and treatment mainly involved the use systemic corticosteroids with a slow taper due to the high rate of recurrence, plasmapheresis and immunomodulating therapy [168,170]. As well, treatment for the high intracranial pressure was also required and involved the use of acetazolamide, mannitol and in cases of sinus thrombosis, anticoagulation or surgical intervention [168,170].

Conclusion

The ocular manifestations of SLE are varied and numerous. This is the first reported case of SLE presenting as APMPPE. As with other ocular manifestations of SLE, the disease resolved markedly with corticosteroids. It is important to note that while the ocular manifestations of SLE are rare, they are often misdiagnosed. In addition, they can present as the initial manifestation, with systemic disease expressing itself years later. This highlights the importance

of maintaining clinical suspicion and initiating appropriate investigations, including biopsies and serological analysis, in cases of ocular disease refractory to conventional treatment.

Treatment for these manifestations mainly consists of systemic immunosuppressive therapy. However, as the mechanism and pathophysiology of SLE continues to be elucidated, targeted therapy may play a greater role in its management.

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