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A rare case of a severe ocular complication as an initial presentation of adolescent-onset systemic lupus erythematosus: a case report

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Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease that causes severe complications in multiple organs. Ocular manifestations are critical in patients with SLE because of the vision-threatening risk of such complications. However, severe retinopathy as an initial presentation of SLE is uncommon, even when the severity of SLE is mild, especially in children.

Case presentation: We encountered a 14-year-old female patient with rapidly progressive impairment of her left vision that was determined to be caused by severe retinopathy secondary to SLE. Her other systemic symptoms, including a mild renal disorder, were not severe. The patient showed positivity for anticardiolipin antibody, although she did not have antiphospholipid antibody syndrome. She was initially treated with high-dose methylprednisolone, antiplatelet therapy, and anticoagulation therapy because of the high possibility of vision loss; this was followed by tacrolimus as maintenance therapy. Photocoagulation therapy was also performed to prevent vitreous hemorrhage and retinal detachment. Early diagnosis of SLE based on the rapid deterioration of her vision allowed for early interventions and a good clinical course with recovery of her vision.

Conclusions: Importantly, regardless of the severity of the systemic symptoms in patients with SLE, ocular involvement is critical and requires aggressive treatment.

Key words：children systemic, lupus erythematosus, retinopathy

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that may affect multiple organ systems, including the eye [1]. The male:female ratio is 1:9; thus, SLE overwhelmingly affects women, and the age of onset is also more common in younger women aged 20 to 40 years. Childhood onset accounts for about 20% of all cases of SLE, the percentage estimated as 29% of all cases of rheumatic disease in registered children, followed by juvenile idiopathic arthritis which estimated as 51% [2, 3, 4]. Among the initial symptoms, arthritis and arthralgia occur in about 67% of patients, followed in frequency by skin lesions and fever. SLE is characterized by various clinical manifestations of systemic organs such as the kidneys, nerves, pleura, and pericardium [5]. A meta-analysis of 16 studies was performed to investigate clinical differences between children and adults with SLE, and the authors reported that fever, lymphadenopathy, butterfly rash, ulcers, renal impairment, seizures, hemolytic anemia, and thrombocytopenia were more common in children [6]. Children have more aggressive disease course, and one-third of pediatric patients with SLE have atypical clinical features [7]. Ocular lesions are found in 30% of all patients with SLE [8], and they are more frequent particularly in cases complicated by antiphospholipid antibody syndrome (APS) and

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central nervous system lupus [9, 10, 11]. The incidence of retinal involvement in patients with SLE ranges from 7% to 26% [12]. However, severe retinopathy is very rare, even when the severity of SLE is mild, especially in children. We herein describe a patient whose diagnosis of SLE was triggered by ocular impairment.

Case report

A 14-year-old female patient presented with decreasing left vision. She was diagnosed with left retinal vasculitis with macular edema, and her left best corrected visual acuity (BCVA) had decreased to 0.3. A sub-Tenon steroid injection and betamethasone ophthalmic solution were applied to treat the lesion. Subsequently, however, the patient's left BCVA decreased to 0.1. Furthermore, her antinuclear antibody (ANA) titer increased. These findings led to suspicion of collagen disease, and she was admitted to our institution.

No family history of autoimmune renal disease and other autoimmune diseases. Oliguria, ascites, and edema were absent. Her height was 159.7cm and her weight was 48.7 kg. Physical findings upon admission included a blood pressure of 115/75 mmHg, pulse of 86/min, and body temperature of 37ºC. Her consciousness was clear and her whole-body condition was good. No ulcers were found in the oral cavity. Skin examination showed depilation of the head, butterfly erythema (Figure 1a), and erythema of the finger pulp (Figure 1b). Her BCVA had decreased to 0.09 in the left eye and not changed 1.5 in the right eye, indicating severe damage especially in the left eye. Her bilateral intraocular pressures were normal, and corneal abnormality and iritis were absent. Fundus examination revealed soft leukoplakia (Figure 2a), and fluorescencein angiography (FA) showed retinal arteriovenous vasculitis, strong ischemia in the macular region, no reflux area, and leakage from the blood vessel (Figure 2b). Optical coherence tomography (OCT) revealed marked macular edema (Figure 2c), and Goldmann visual field testing indicated the scotoma in the vicinity of the center. The right fundus was normal. Her chest sounds were clear with no friction rubs or murmurs. Her abdomen was soft without muscle guarding or rebound tenderness. No coldness or ulcerative lesions were present in the peripheral limbs. Dull red spots were observed on the ventral side of the bilateral upper limbs.

On laboratory examination, mild to moderate proteinuria (0.5 g/day) and hematuria (1+) were noted. The pH was 6.0 in urine and urinary cylinder was (1+). Her peripheral white cell count and red cell count were normal. The platelet ($23.4x10^5$/μl; reference range, $16.7x10^5$ - $36.2x10^5$/ μl) was normal. Her peripheral white cell count was normal. Blood coagulation function test results were normal. The results of most laboratory blood examinations, including measurements of electrolytes, serum creatinine, and blood urea nitrogen, were normal. Total protein (8.5 g/dl; reference range, 6.5-8.2g/dl) was mild heigh, albumin (4.6 g/dl; reference range, 3.6-5.5 g/dl) was normal. The concentrations of aspartate aminotransferase and alanine aminotransferase were normal. The lactate dehydrogenase and creatinine kinase concentrations were also normal. The serum concentrations of fibrinogen (267 mg/dL; reference range, 150–400 mg/dL), fibrin and fibrinogen degradation products (2.2 μg/dL; reference range, 5.0 μg/dL), thrombin–antithrombin III complex (1.0 ng/dL; reference range, 0.0–3.0 ng/dL), and D-dimers (0.6 μg/mL; reference range, 0.0–1.0 μg/mL) were normal. The prothrombin time and activated partial thromboplastin time were also normal, indicating no signs of disseminated intravascular coagulation. Serologic analysis showed an elevated ANA titer (x320; reference range, 0–x40). The anti-double-strand DNA titer (12 IU/L; reference range, 0–12 IU/L) was negative. The anti-single-strand DNA titer (73 IU/L; reference range, 0–25 IU/L) was elevated. Anticardiolipin antibody was identified (42 IU/mL; reference range, 0–10 IU/mL). Anticoagulant and anticardiolipin β_2 glycoprotein I antibodies (2 IU/mL; reference range, 0–10 IU/mL) were negative. Myeloperoxidase antineutrophil cytoplasmic antibodies were negative. The serum complement component C3 activity (73 mg/dL; reference range, 82–145 mg/dL) was low, while the C4 activity (13 mg/dL; reference range, 12–33 mg/dL) and total complement activity (CH50 screening test) (29.1 U/mL; reference range, 24.2–52.8 U/mL) were normal. Circulating immune complexes (1.5 μg/mL; reference range, 0.0–3.0 μg/mL) were also normal. The serum immunoglobulin G (IgG) concentration (2009 mg/dL; reference range, 810–1780 mg/dL) was high. The IgA, IgM, and IgE concentrations were normal. An infectious work-up came back negative for hepatitis B and C. No findings of optic neuritis were observed by short T1 inversion recovery. Ultrasonographic findings

of the renal size and shape were normal, and mass lesions were absent.

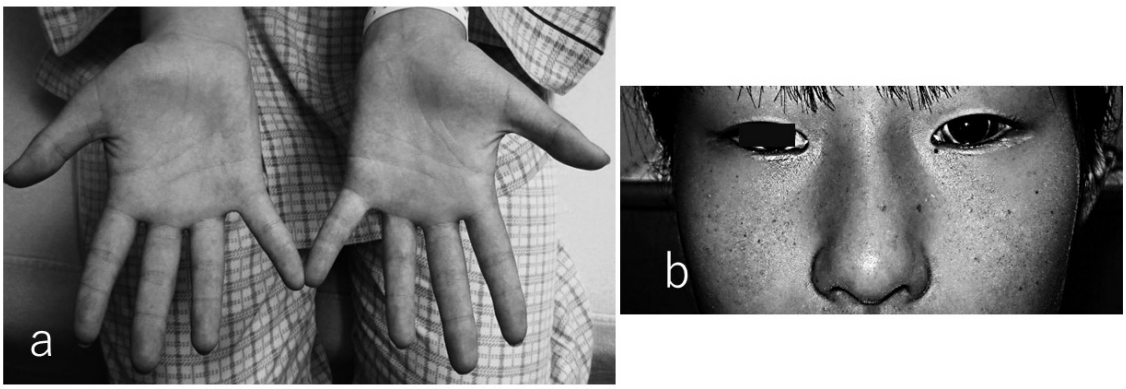

Figure 1 Skin lesions on admission. (a) Erythema of the finger pulp and (b) butterfly erythema were present.

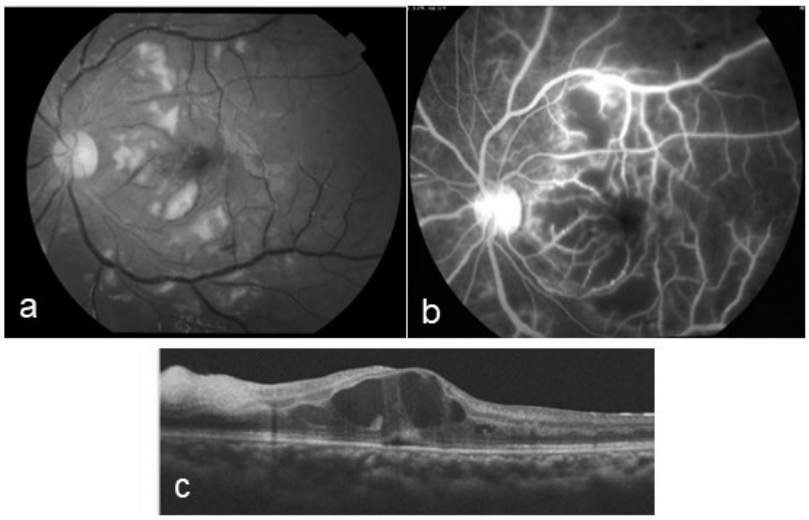

Figure 2 Fundus photograph of the left eye at the first visit. (a) Retinal arteriovenous vasculitis, soft vitiligo, an area of nonperfusion, and macular edema were observed. (b) Fluorescein leakage from the vessel and ischemia in the macular region were seen by fluorescein angiography. (c) Marked macular edema was observed by optical coherence tomography.

The patient met 5 of the 12 SLE diagnostic criteria according to Guidance to diagnosis of SLE in childhood, and the complication of SLE retinopathy was confirmed based on the FA. The patient's total SLE Disease Activity Index score was 16 points (8 for the vision disorder, 2 for the new skin rashes, 2 for hair loss, 2 for low-complement blood disease, and 2 for anti-DNA antibody elevation). In an attempt to decrease the disease activity and prevent visual loss in the left eye, three courses of high-dose methylprednisolone (1000 mg/day) were administered along with oral prednisolone (PSL) at 60 mg/day with a gradual decrease of 10 mg/day every 2 weeks. The gradual decrease in PSL was followed by maintenance therapy with tacrolimus (Tac) at 2 mg/day. Although the patient was negative for lupus anticoagulant and anticardiolipin β_2 glycoprotein I antibodies, we suspected APS based on the presence of anticardiolipin antibody and the severe findings of a thrombotic tendency, stenosis, and infarction in the fundus; therefore, we administered a combination of intravenous heparin sodium solution as an anticoagulant and oral aspirin (300 mg/day) as antiplatelet therapy. After these treatments, the macular edema of the left fundus and retinal arteriovenous vasculitis improved (Figure 3), and the left BCVA recovered from 0.09 to 1.2. The butterfly erythema and erythema of the extremities also improved. The ANA titer decreased

from 320 to x80, and the anti-single-strand DNA antibody decreased from 73 to 16 IU/L. Percutaneous renal biopsy was performed on the 50th day of disease because of the complication of lupus nephritis. Histologic examination of a renal biopsy specimen revealed mild to moderate proliferation of mesangial cells but no thickening of the glomerular capillary walls (Figure 4). Interstitial fibrosis, atrophy or other injury of the tubular cells, and necrosis were absent. Immunofluorescence showed IgG, IgA, IgM, C3, C4, C1q, and fibrinogen reactivity in portions of the mesangium and capillary walls. Electron microscopy revealed nodular deposits in the mesangial and capillary walls. These findings indicated lupus nephritis (histopathologic class II according to the International Society of Nephrology/Renal Pathology Society). She was discharged on the 59th day of disease with PSL, Tac, and an angiotensin receptor antagonist. She continued to undergo follow-up therapy including laser treatment for the non-reflux area in the ocular fundus. The clinical course is summarized in Figure 5.

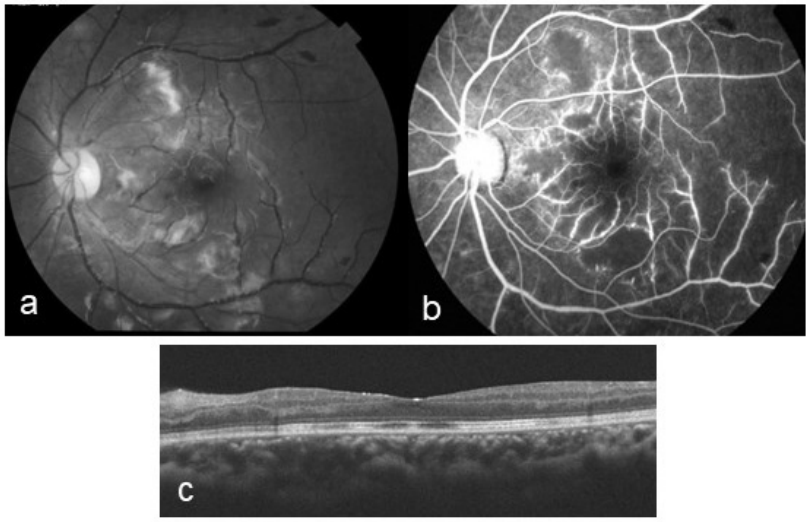

Figure 3 Fundus photograph of the left eye on day 32 of admission. (a) The retinal arteriovenous vasculitis had improved. The soft vitiligo, the nonperfused area, and macular edema had also improved, but were still present. (b) Fluorescein leakage from the vessel in the macular region had decreased on fluorescein angiography, and (c) no macular edema was present on optical coherence tomography.

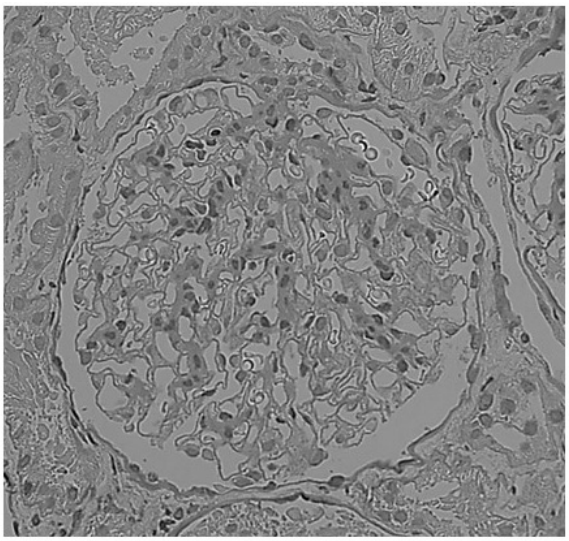

Figure 4 Histologic findings of the renal specimen. Diffuse mild mesangial cell proliferation in the glomeruli and the lack of thickening of the glomerular basement membrane indicated the presence of diffuse proliferative lupus nephritis (International Society of Nephrology/Renal Pathology Society class II) (periodic acid-Schiff stain, ×400).

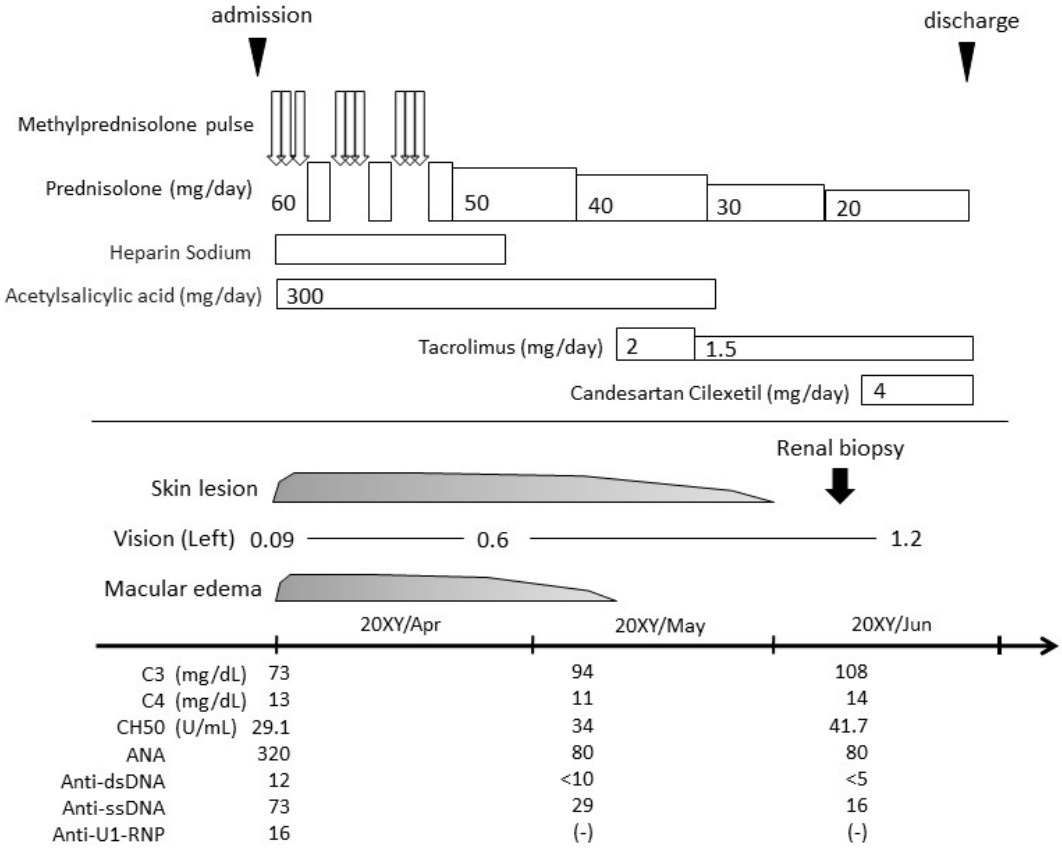

Figure 5 Clinical course.

Discussion

Ocular manifestations of SLE are variable and include abnormalities of the eyelid and ocular adnexa, keratoconjunctivitis sicca, retinal vasculitis, vaso-occlusive disorders, choroidopathy, scleritis and uveitis, and optic neuropathy [8, 13, 14]. SLE retinopathy is characterized by soft vitiligo, retinal vasculitis, vitreous hemorrhage, development of avascular areas, and appearance of new blood vessels [15]; these abnormalities are consistent with the findings in our case. The pathology of SLE retinopathy, as well as the onset mechanism of systemic vasculitis, are attributed to the impairment of the vascular endothelium and basement membrane caused by complement activation and autoantibodies with deposition of antigen–antibody complexes on the blood vessel walls; this results in insufficiency of the peripheral circulation with progression to vascular occlusion. Furthermore, hypercoagulability and high blood viscosity accompanied by the disease activity of SLE promotes thrombus formation and vascular occlusion. APS is well recognized in patients with SLE [11]. The risk factors for progression of SLE retinopathy include complications such as APS, lupus nephritis, and central nervous system lupus [9, 10, 15]. However, no apparent findings indicative of blood hypercoagulability or hyperviscosity were present in our case. Additionally, the patient had no clinical findings or symptoms specific to central nervous lupus, such as convulsions. One prospective study showed that the incidence of renal dysfunction in patients with SLE without retinopathy was 59.3%, but that in patients with retinopathy was 100.0% [15]. In addition, renal involvement in patients with SLE will generally lead to secondary hypertension. When hypertension is prolonged, it usually affects the retina and choroid by inducing retinal arterial narrowing and changes at the arteriovenous crossing. Our patient had the complication of lupus nephritis, but the histopathologic lesions were mild and the patient had no hypertension. However, the presence of hyperphospholipid antibodies indicated the tendency to form thrombi.

SLE retinopathy is classified into three types:

(1) focal retinal ischemia, (2) retinal vascular occlusive disease, and (3) the proliferative lupus type, depending on the degree of the fundus lesion [16]. In the present case, the patient exhibited the vascular occlusion type, which was mainly caused by vasculitis and retinal arteriovenous occlusion. This resulted in rapid and severe vision deterioration. Hydroxychloroquine is an effective medication for SLE with few side effects [17]. However, usage of hydroxychloroquine should be avoided in case of ocular complication because of the possibility of exacerbating side effects. Steroid therapy is still a key drug in Japan, although clinicians must be alert to its side effects, especially in children [7]. PSL is essential for suppression of vasculitis and minimization of vascular occlusion. Recanalization is reportedly difficult even with steroid pulse therapy in patients with the vascular occlusion type [10, 18]. After the appearance of ocular symptoms, our patient underwent early consultation and intervention including steroid therapy, leading to rapid reduction of the vasculitis and minimization of the obstructive lesions. Methylprednisolone therapy was successful in Indian patients who exhibited a clinical course similar to that of our patient [19]. In our case, photocoagulation therapy was performed early after discharge because the proliferative changes and angiogenesis had resulted in the retinal lesion, causing vitreous hemorrhage in addition, especially in the presence of antiphospholipid antibodies. However, the optimal timing of and criteria for photocoagulation therapy are unclear because vision impairment may still progress after treatment [10, 16, 20]. Especially in children, eye complications such as visual acuity problems deteriorate the quality of school and daily life, leading to restrictions in the scope of the patient's activity. We should consider the patient's age, disease severity, and similar factors in each individual case.

Ocular complications often occur after a certain period of time has passed since the diagnosis of SLE, although they are reportedly correlated with the disease activity and degree of SLE [21, 22]. Even patients with SLE who have no visual symptoms or visible retinal abnormalities have demonstrated abnormal lesions of the fundus by fluorescein angiography. To the best of our knowledge, few cases of visual impairment as the initial symptom of SLE have been reported, especially in children [19, 23]. This suggests that visual impairment is an underlying subclinical condition [9]. It seems difficult to predict the occurrence of ocular symptoms based on a skin rash, dysfunction of other organs, and laboratory test results. However, in a study of the prevalence of clinical and laboratory features in 10 patients with "classic" retinopathy, 60% of patients showed a skin rash, 40% presented with nephritis, and 30% had alopecia and anemia [24]. This emphasizes that high possibility of sudden deterioration of ocular complications even while the SLE disease activity is stable. Because our patient mainly had skin lesions such as butterfly erythema, hair loss, and erythema at the limb extremities with only minor disorders of other organs, the severity of the ocular complications was difficult to predict. With regard to maintenance therapy, immunosuppressant therapy was added in the early stage to alleviate the side effects of steroids over a long period of time. Immunosuppressive agents are selected depending on the patient's disease severity and pathological condition, and cyclophosphamide is considered to be effective for ocular complications [25]. However, few studies have been performed to examine the efficacy of immunosuppressants in detail. In our case, Tac was given because of the severity of the ocular complications and to preserve the patient's fecundity. To the best of our knowledge, however, the efficacy of Tac for ocular manifestations in patients with SLE has not been proven. The use of Tac allowed us to minimize the PSL dosage because of the good lesion response. The patient was followed-up as an outpatient and continued to receive laser treatment.

Conclusion

We encountered a rare case involving sudden visual deterioration, resulting in a diagnosis of SLE. Prediction of the onset of ocular complications in patients with SLE is difficult; however, periodic follow-up is important because ocular complications might influence the patient's prognosis of eye function regardless of the severity of systemic symptoms. Furthermore, suspicion of SLE and early medical intervention are needed when encountering a patient who exhibits rapid deterioration of visual acuity, even if his or her systemic symptoms are mild.

Declarations

Ethics approval and consent to participate

Consent to publish the patient's data, including individual details and photographs, was obtained

from the patient's parents. Tissue staining of the renal specimens was performed with written informed consent from the patient's parents.

Consent for publication

This manuscript has been seen and approved by all authors and is not under consideration for publication elsewhere in a similar form, including in abstract form, in any language.

Availability of data and materials

All data generated during this case report are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YK analyzed and interpreted the patient data regarding the SLE and retinopathy. KS performed the histological examination of the kidney and was a major contributor to the writing of the manuscript. KM, TE, and TM helped to draft the manuscript and acquire renal biopsy for histological images for illustration. MO and KS conceived the idea of the study and did the final proofing of the manuscript. All authors read and approved the final manuscript.

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