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Case report

Bilateral simultaneous Central Retinal Artery Occlusion (CRAO) in a patient with Systemic Lupus Erythematosus (SLE)

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ABSTRACT

Purpose: The objective of the study is to report a rare case of severe vaso-occlusive retinopathy with bilateral simultaneous Central Retinal Artery Occlusion (CRAO) in a patient with Systemic Lupus Erythematosus (SLE).

Observations: A female patient aged 22 years, presented with a sudden onset of painless diminution of vision in both eyes for three weeks. She had systemic features of SLE for six months at the time of the study. A diagnosis of bilateral CRAO was made after an examination of the fundus and by ruling out other causes of severe vaso-occlusion based on clinical and angiogram findings. Her antiphospholipid antibody (APLA) levels were normal. The visual prognosis was poor even after treatment with intravenous steroids and panretinal photocoagulation.

Conclusion and importance: This case highlights the importance of bilateral CRAO as an initial presentation of severe systemic disease. This case demonstrates that despite apparent normal APLA levels, a state of hypercoagulability can exist in SLE patients. In addition, it demonstrates that severe vaso-occlusive complications such as CRAO, which results in blindness, can also develop in a patient with apparently well-controlled SLE. Therefore, it is important to take cognizance of this sight-threatening complication in SLE patients at initial presentation. A holistic approach to management, both systemic and ocular, is required to prevent sight-threatening complications from vaso-occlusion. Early and aggressive intervention can be beneficial in the prevention of severe visual loss.

1. Introduction

SLE is an autoimmune multisystem disorder characterized by dysregulation of the immune system, formation of immune complexes, and complement system activation. It is characterized by musculoskeletal, skin, renal and ocular manifestations. Retinal vaso-occlusive disease is seen in several systemic diseases such as SLE, rheumatoid arthritis, giant cell arteritis, Wegener's granulomatosis, polyarteritis nodosa and Behçet's disease. SLE, most commonly, presents as retinopathy with microangiopathy manifesting as cotton-wool spots and intra-retinal hemorrhages.[1] Severe vaso-occlusive retinopathy such as retinal arterial and venous occlusions as initial manifestation is rare in SLE cases.[2] Very few case reports exist about CRAO presenting an ocular manifestation of SLE. It is unusual for SLE to present with vaso-occlusion in the absence of any obvious hypercoagulable state. A literature review for similar presentation in PubMed, ScienceDirect and Scopus databases provided three reported cases, suggesting this could be a rare occurrence and thus of interest to the broader Ophthalmic community.

2. Case report

A South Indian female aged 22 years, with no pre-morbidities, presented with fever, generalized weakness, fatigue and painless oral ulcers for the past 6 months. She also complained of sudden, painless diminution of vision in both eyes for 3 weeks. The decrease in vision occurred simultaneously in both eyes, and was noticed by her when she woke up in the morning. There were no preceding episodes of transient blurring of vision. There was no ocular redness, discharge, pain or periorbital swelling. She was married with no significant obstetric history. There was no previous history suggestive of an arterial or venous thrombotic event in the patient. A systemic examination showed hypotension with tachycardia, malar rash and multiple oral ulcers. Upon admission, an ocular examination revealed visual acuity of finger counting at 1 m bilaterally, with no restriction of extraocular movements. The pupillary reaction was sluggish, while the rest of the anterior segment examination was normal. On Fundus examination, there was bilateral pallor of the optic disc (OS > OD) with multiple confluent peripapillary cotton-

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wool spots (OD > OS, more nasally to the disc). Severe arteriolar attenuation with box-carring of arteries and veins was present. There were numerous scattered large and small dot and blot hemorrhages in the posterior pole and midperiphery. Hard exudates in clusters were seen just inferior to the fovea in the right eye (OD). Diffuse retinal whitening along with cherry-red spot at the macula was present. This fundus picture was suggestive of a vaso-occlusive retinopathy with bilateral Central Retinal Artery Occlusion (CRAO) with a duration of more than 48 hours (Fig. 1a and b).

Given the long history of two weeks and the fundus photograph findings, the CRAO was treated with 0.5% Timolol eye drops twice daily along with ocular massage. An oral antiplatelet agent (Aspirin 75mg) was added. No other aggressive intervention was attempted. A guarded visual prognosis was explained to the patient and patient's family.

The laboratory tests showed a normal hemoglobin of 11g/dl with a red blood cell count of 4.09×10^6/μl, platelet count 147×10^3/μl and a decreased white cell count of 1900/μl. Erythrocyte Sedimentation Rate (ESR) was 19mm/hour and C-Reactive Protein (CRP) was 8.95mg/L. The blood lipid profile was normal. Renal function and electrolyte testing showed an elevated serum creatinine of 1.49 mg/dl and increased serum potassium of 5.2 mmol/L. Urinalysis revealed grade 2+ (100mg/dl) proteinuria (normal <30 mg/dl) with red blood cell count of 5.40/hpf (reference range 0–3/hpf) with few bacteria. Laboratory investigations to ascertain the possibility of a hypercoagulable state was done. This included antiphospholipid antibodies such as Lupus Anticoagulant (LAC) using the Electromechanical clot detection method and Anti-Cardiolipin (ACA) using Enzyme Immuno Assay (EIA). The antiphospholipid antibody screening test results were negative for IgG anticardiolipin and lupus anticoagulant. The patient's activated partial thromboplastin time (aPTT) was 23.7 seconds (reference range 26.8–41.1 sec), prothrombin time (PT) was 9.5 sec (reference range 9.6–12.5 sec) and INR was 0.85. Anti-Nuclear Antibody (ANA) global profile was strongly positive at a titer of 1:100 (granular nucleolar antibody 3+ and granular cytoplasm 3+). Anti-nRNP and anti-SS-A were a strong positive (3+), while anti-Sm, anti-ds DNA and anti-Ro-52 were a weak positive. Complement testing showed low C_3 and C_4 complement protein levels of 30 mg/dl (reference range 90–180 mg/dl) and 5.6 mg/dl (reference range 10–40 mg/dl) respectively. Other immunological tests such as antineutrophilic cytoplasmic antibodies (ANCA) and rheumatoid factor were negative. The chest X-ray was normal. Other tests included Mantoux test for Tuberculosis, Venereal Disease Research Laboratory Test (VDRL) for Syphilis, ELISA for HIV and Toxo-IgG for toxoplasmosis, which were all negative.

The renal biopsy showed diffuse mesangial proliferative glomerulonephritis, suggesting stage 4 lupus nephritis. A diagnosis of SLE was confirmed according to the revised American College of Rheumatology (ACR) classification criteria, based on the findings of painless oral ulcers, seizure episodes, positive antinuclear antibody, low complement proteins, significant proteinuria and positive renal biopsy.[3] A renal ultrasonography revealed normal kidney size and echogenicity bilaterally. An Electrocardiogram revealed normal sinus rhythm. The echocardiography showed no structural heart abnormality and the ejection fraction was 67%. A carotid doppler ultrasonography demonstrated no significant carotid atherosclerosis or plaques.

During her stay in the hospital, she developed generalized tonic clonic seizures, which required an ICU admission. A lumbar puncture was done to rule out infection. A Magnetic Resonance Imaging (MRI) with a Magnetic Resonance Angiogram (MRA) of the brain showed bilateral atrophy (arrows) of putamen, claustrum, external capsule and thalamus along with attenuated caliber of all the vessels, suggestive of Central Nervous System (CNS) vasculitis (Fig. 2 a, b).

She was given a tablet of Cefepime for impending febrile neutropenia and a steroid injection, hydrocortisone. Levetiracetam and Lorazepam tablets were administered to control the seizures. On account of an extensive extra renal disease, a tablet of mycophenolate mofetil 2g/day was given. She developed steroid induced diabetes mellitus, for which she was started on the tablet, Metformin.

Within three weeks, her systemic condition improved and she was discharged and a review was scheduled for after two weeks. She was readmitted a week later, with complaints of recurrent seizures. Her antiepileptic medications were changed to Clobazam and Olanzapine. She was discharged after a fortnight and was asked to come in for a review at the medicine outpatient department (OPD) after a month. In the following three weeks, she presented with high grade fever associated with chills. She was diagnosed with a urinary tract infection and was administered I.V. cefaperazone and sulbactam for 14 days. She improved symptomatically, hence, she was discharged and was asked to review her condition after two weeks in the medicine OPD. Two weeks later, she presented with fever and a cough with expectoration. The blood culture showed *Escherichia coli* bacteremia. In light of this, she was administered I.V. Meropenem.

She underwent digital Fundus Fluorescein Angiography (FFA) in the Ophthalmology OPD once her systemic condition improved. The FFA (OU) showed delayed arm to choroid circulation time, delayed arterial filling, delayed arteriovenous transit circulation and extensive capillary non-perfusion areas, with no evidence of neovascularization (Fig. 3a–d). Multiple areas of hypofluorescence suggestive of blocked fluorescence corresponding to the intraretinal hemorrhages on fundus photo were seen (arrows). Diffuse capillary leak (arrowheads) was seen in the peripapillary area as well as in the superotemporal and inferotemporal vascular arcades in both eyes. In view of extensive capillary non-perfusion areas, panretinal photocoagulation was done for both eyes

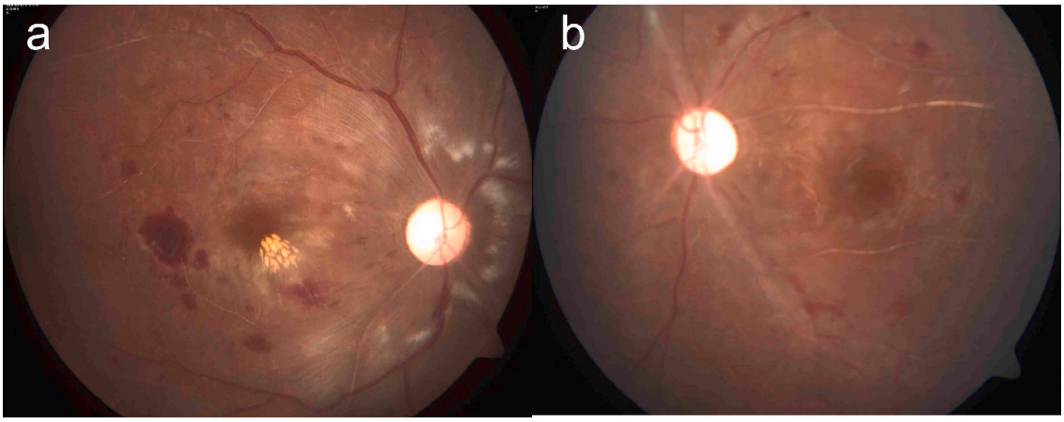

Fig. 1. Fundus photo of both eyes [a-right eye (OD), b-left eye (OS)] showing pallor of the optic disc (OS > OD) with multiple confluent peripapillary cotton-wool spots (OD > OS, more nasally to the disc). Severe arteriolar attenuation with box-carring of arteries and veins, dot and blot hemorrhages and diffuse retinal edema along with cherry-red spot at the macula were also present in both the eyes. These features were typical of bilateral CRAO.

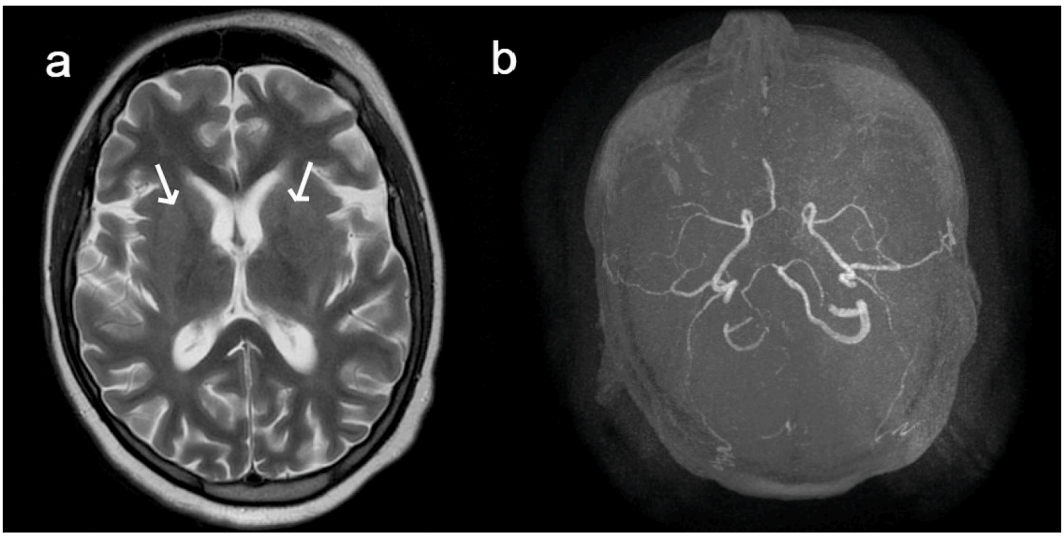

Fig. 2. (a) Magnetic Resonance Imaging (MRI) and (b) Magnetic Resonance Angiogram (MRA) of the brain showing bilateral atrophy (arrows) of basal ganglia and thalamus (a) along with attenuated caliber of all the vessels (b). These features were suggestive of a Central Nervous System Vasculitis.

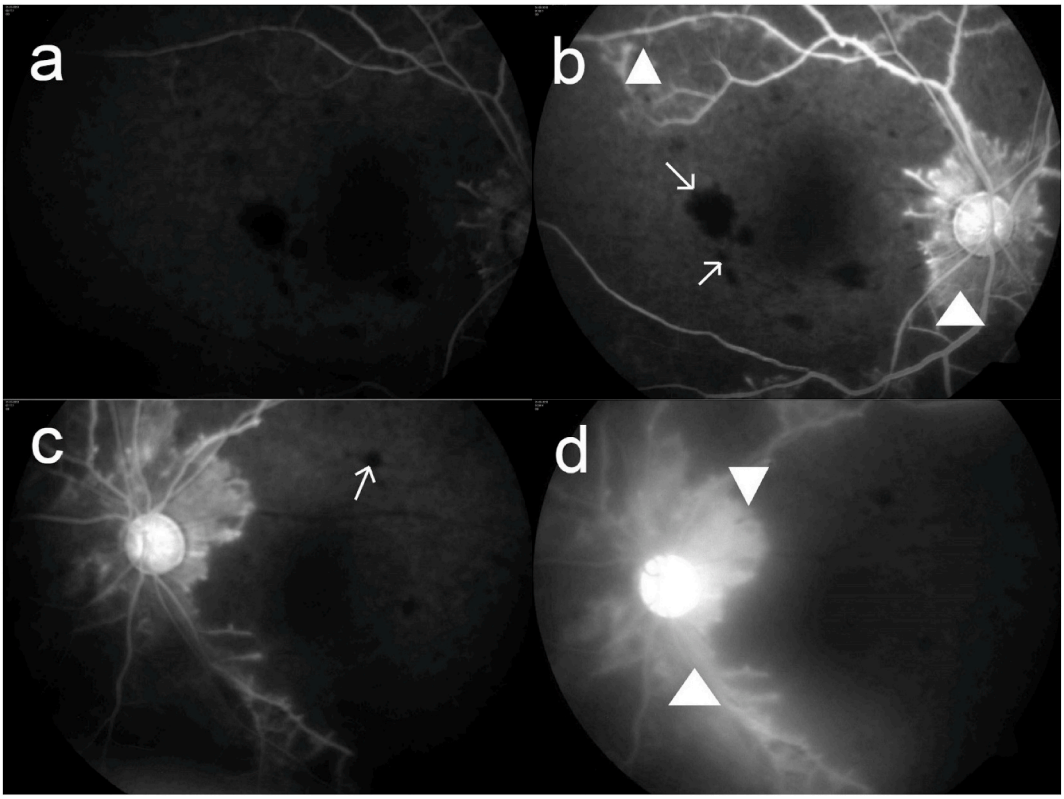

Fig. 3. (a–d): Fundus Fluorescein Angiogram (FFA) of both eyes showing poor perfusion (Right eye-a, b; Left eye-c, d). There is delayed arm to choroid circulation time, delayed arterial filling (right eye at 38 s and left eye at 42 s), delayed arteriovenous transit circulation and extensive capillary non-perfusion areas with no neovascularization in both eyes. Areas of blocked fluorescence (arrows) and diffuse capillary leak around the disc, superotemporal and inferotemporal arcades (arrowheads) are also seen.

under nil visual prognosis. She was discharged, but further monitoring of the patient was not possible due to lack of follow-ups.

3. Discussion

SLE is an autoimmune inflammatory disease affecting multiple organs in our body. In SLE, the thrombotic and inflammatory phenomena affect the eye resulting in keratoconjunctivitis sicca, scleritis, uveitis and ischemic optic neuropathy.[4] Posterior segment manifestations of SLE most commonly includes cotton-wool spots, intraretinal hemorrhages, microaneurysms, hard exudates and vascular abnormalities.[5] The presentation of CRAO initially in SLE is very uncommon.[6] Such a phenomenon occurring in the absence of a hypercoagulable state is even rarer.[7,8]

Retinopathy is one of the most common forms of ocular involvement in SLE patients, present in 2–30% SLE cases. The SLE activity in different

organ systems, such as renal and cerebral, accounts for the retinal involvement. Three forms of retinopathy have been described in SLE patients. The classic variant is characterized by cotton-wool spots with or without intraretinal hemorrhages. The occlusive variant involves arterial and/or venous occlusions (branch or central). The third form of SLE retinopathy is called Proliferative Lupus retinopathy.

The patient had hypotension with tachycardia at the time of examination. This suggested that she was hemodynamically unstable on admission. Although the clinical picture looked like SLE retinopathy with CRAO, other probable causes for the severe vaso-occlusive retinopathy were examined and excluded. Owing to the history, clinical presentation and FFA findings, we also considered differential diagnoses such as Giant Cell Arteritis (GCA), Ocular Ischemic Syndrome (OIS), ophthalmic artery occlusion and sickle cell retinopathy. The patient being in the atypical age group with absence of typical features of GCA such as jaw claudication, headache, absence of temporal artery abnormality on examination with normal ESR and CRP ruled out GCA as being the likely cause for the vaso-occlusive retinopathy. There was no history such as amaurosis fugax, ocular angina and no anterior or posterior segment signs suggestive of Ocular Ischemic Syndrome such as conjunctival and scleral congestion, corneal edema, rubeosis iris or neovascularization in the retina. The retinal veins were not dilated. The carotid doppler was also normal. Although there was a delay in choroidal filling even in the arteriovenous phase of FFA, the absence of other features of OIS made its diagnosis less likely. The patient had a vision of counting fingers and a cherry-red spot was seen on fundoscopy which ruled out the possibility of an ophthalmic artery occlusion and favored a diagnosis of CRAO. The patient was not a known case of sickle cell disease nor was the disease common in the population or geographical area from which the patient hailed. The absence of typical lesions in sickle cell retinopathy such as salmon patch hemorrhages, black sunburst spots and sea fan neovascularization in retina did not favor the diagnosis of sickle cell retinopathy.

The APLA screening for LAC and ACA was normal. There was a higher propensity for vascular occlusions in SLE with increased serum levels of APLA. But in our patient, vaso-occlusive retinopathy developed despite normal APLA. A possible explanation for such presentation can be the sensitivity of these tests in determining the disease. Sciascia et al. have concluded that a combination of lupus anticoagulant (LAC), anti-β (2) glycoprotein 1 (anti- β2 GP1) and anti-phosphatidylserine/prothrombin (aPS/PT) has the best predictive ability to identify the risk of thrombosis.[9] In view of the severity of the disease determined clinically as well as by other diagnostic tests, we can infer that the sensitivity of APLA tests done was not good enough to predict thrombotic tendency in this patient.

Some case reports have suggested CNS involvement in patients with significant retinal vascular lesions, while others have found no link between SLE retinopathy and CNS vasculitis due to SLE.[10,11] However, CNS involvement occurred simultaneously in those with retinal lesions in 73% of the cases.[12] In our patient, the presence of a significant cerebral vasculitis was associated with the severity of occlusive retinopathy due to SLE.

The percentage of patients with severe visual loss in the course of SLE with posterior segment involvement is high. Au et al. have reported visual loss in 80% cases and neovascularization in 40% cases of SLE retinopathy.[6] SLE treatment modalities are diverse and includes anti-malarial agents, steroids, immunosuppression, antiplatelets, hormonal therapy, plasmapheresis and I.V. immunoglobulin. Since the ocular complications of SLE are usually associated with disease activity in other organ systems, aggressive control of the systemic disease process may lead to resolution of ocular complications. There is no clear consensus on medical treatment of retinal vaso-occlusion in SLE. Anticoagulants or antiplatelets are usually recommended. It remains unclear whether steroids and immunosuppressants play a role in preventing thrombotic complications. In the present case, systemic steroid (intravenous hydrocortisone) and immunosuppressive drug (mycophenolate mofetil) failed to stop the worsening of the visual symptom, although her systemic status showed improvement. This could be due to the late presentation of the CRAO which delayed initiating treatment against SLE. Thus, it is important to recognize visual loss developing as a result of vaso-occlusive complications such as CRAO in SLE patients and initiate treatment at the earliest. The vision loss in this patient occurred simultaneously in both eyes, making it difficult for any treatment to salvage the vision in one eye. In view of severe irreversible visual loss, we recommend that the three specific APLA tests; LAC, anti-β2GP1 and aPS/PT should be done simultaneously in all SLE patients presenting with vaso-occlusive retinopathy.

Few case reports have been published previously concerning the occurrence of CRAO in SLE patients. Zou et al. published a similar report in 2012 of a 42-year-old Chinese female with negative APLA who presented with sudden bilateral vision loss. The vision recovery was poor despite treatment with systemic steroids and immunosuppressants.[7] Hua et al. reported bilateral simultaneous CRAO in a 20-year woman with newly diagnosed SLE and who also had a normal APLA panel. The visual prognosis was poor despite treatment with steroids and anticoagulation.[8] Combined vaso-occlusive retinopathies in the form of central retinal artery and vein occlusions are very rare. Akhlaghi M et al. reported a 29-year-old female with SLE who simultaneously presented with bilateral CRVO and CRAO/BRAO in the presence of normal levels of APLA during the clinical flare stage of SLE.[13]

In summary, this patient with SLE, had most of the features fitting the diagnosis of Central Retinal Artery Occlusion (CRAO). Some of the clinical findings such as the co-existing disease in other renal and CNS vascular beds, nasal disc perfusion in one eye (OD) and fundus angiogram findings such as delay in choroidal filling and extent of capillary non-perfusion areas would warrant a thorough search for another entity such as an ophthalmic artery occlusion, ocular ischemic syndrome and arteritic ischemic optic neuropathy. Thus, it is very important to perform a detailed history and clinical examination along with the laboratory and supporting ancillary investigations to reach a diagnosis as soon as possible. This is imperative as most of these conditions result in irreversible vision loss.

4. Conclusion

A thorough ocular and systemic evaluation is essential in patients presenting with severe vaso-occlusive retinopathy. Severe form of retinopathy in SLE is usually unilateral and associated with a hypercoagulable state.[5] This case highlighted that in patients with CRAO, SLE must be considered as a possibility, since the retinal vaso-occlusive disease may manifest as the primary symptom in SLE patients and also occur despite normal APLA levels.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

Nil.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2020.100833.

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