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Unilateral CRAO as the presenting clinical sign of systemic lupus erythematosus

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ABSTRACT

Purpose: This report describes the case of unilateral central retinal artery occlusion (CRAO) as a patient's presenting clinical sign of systemic lupus erythematosus (SLE).

Observations: Though the patient knew of her SLE diagnosis through incidental abnormal lab work, she never pursued treatment because she never exhibited signs of the disease. Despite her asymptomatic course, she presented with a sudden and severe thrombotic event that left her with no light perception in her affected eye. Laboratory work-up was consistent with SLE and anti-phospholipid syndrome (APS).

Conclusions and importance: This case draws attention to the possibility of CRAO as a presenting sign of SLE, rather than a sequela of active disease. Awareness of this risk may play a factor in future discussions between patients and their rheumatologists when considering initiation of treatment at the time of diagnosis.

1. Introduction

Systemic lupus erythematosus (SLE) is known to have various ophthalmologic manifestations. One of these is vascular occlusions due to either pro-thrombotic states or deposition of immune complexes. These devastating cases are typically associated with active and severe disease. This manuscript describes the case of a 41-year-old woman without previous systemic or ocular manifestations of SLE, whose presenting sign was unilateral central retinal artery occlusion resulting in no light perception vision. Laboratory work-up was consistent with SLE as well as anti-phospholipid syndrome (APS). The patient was diagnosed with SLE years prior from incidental lab abnormalities and followed with a rheumatologist. Yet, no treatment had been initiated due to her asymptomatic state. Other cases of retinal vascular occlusions in patients with mild, untreated SLE have been reported, however, this is the only case, to our knowledge, of the process happening in a patient with no other outward signs. Awareness of such cases may add to the discussion that ophthalmologists and rheumatologists have with their patients when considering treatment options for SLE.

2. Case

A 41-year-old African American woman with a history of asymptomatic systemic lupus erythematosus (SLE), not currently on treatment, presented with acute, painless loss of vision in her right eye. The patient reported waking up that morning unable to see anything out of her right eye. The vision loss was not accompanied by head or eye pain. A review of systems was negative except for intermittent headaches over the past few days which were relieved by ibuprofen. She had no significant past ophthalmologic history and no family history of coagulopathies. Her social history was non-contributory. Three years ago, the patient was diagnosed with SLE by Systemic Lupus International Collaborating Clinics (SLICC) criteria.[1] At the time, she had symptoms of fatigue and mild joint pain. A false positive Rapid Plasma Reagin (RPR) test prompted the work-up for SLE.[2] It showed positive Anti-Nuclear Antibodies (ANA) and Anti-Smith (*Anti*-Sm) antibodies, low C4, leukopenia, and thrombocytopenia, supporting the diagnosis. In agreement with her rheumatologist, the patient did not pursue medical treatment, as she was asymptomatic.

Inpatient ophthalmologic examination showed anisocoria with right pupil dilated to 6mm and unreactive to light, although it retained consensual constriction through the normal left pupil. Right eye visual

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acuity was no light perception (NLP) with projection. Examination of the right fundus showed optic disc edema and diffuse pallor with a cherry red spot [Fig. 1]. Altogether these findings were suggestive of a central retinal artery occlusion (CRAO). Intraocular pressures and extraocular motions were normal. Examination of the left eye was unremarkable without a disc at risk.

The patient's young age and relative lack of risk factors other than her history of untreated lupus pointed to the likelihood that her CRAO was secondary to her SLE. Nevertheless, it was important to consider other hypercoagulable, inflammatory, and infectious etiologies as well.

Laboratory tests were notable for a hemoglobin of 9.4 g/dl, and a platelet count of 464 $\times$ 10^3/μl. The Erythrocyte Sedimentation Rate (ESR) was elevated at 123 mm/hour and C-Reactive Protein (CRP) was high at 24.04 mg/L. Blood lipid profiles showed slightly elevated cholesterol (206 mg/dl) and low-density lipoprotein (134 mg/dl). Antithrombin III activity was low (76%), and Factor VIII activity was high (299%). Antiphospholipid antibodies, including lupus anticoagulant and *anti*-cardiolipin (IgM 28), were positive. Beta-2 glycoprotein IgG and IgM, Protein C, and Protein S levels were normal. Factor V was demonstrated to be wild type.

Immunologic tests indicated a positive ANA speckled pattern (>1:320) and positive *anti*-Sm antibodies. Levels of rheumatoid factor were elevated at 20 IU/ml. Complement proteins, C3 (136 mg/dl) and C4 (11 mg/dl), were within normal limits. Other tests, including antibody tests for syphilis, HIV, and Bartonella, and PCR tests for Epstein-Barr Virus were negative.

Further testing, including MRI of the brain and orbits, CTA of the head and neck, transthoracic echocardiogram, and a lumbar puncture all showed no abnormalities.

Two days after her initial presentation, the patient also underwent a Fundus Fluorescein Angiogram (FFA) which showed severe delay and limitation in arterial filling, indicative of diffuse retinal and choroidal ischemia [Fig. 2].

After being seen by rheumatology and hematology teams, the patient was given a dose of 1 g methylprednisolone IV inpatient, which was subsequently stopped due to concern that infection had not been completely ruled out. She was discharged on 20 mg prednisone PO with sulfamethoxazole-trimethoprim for Pneumocystis jirovecii prophylaxis and enoxaparin bridge to daily warfarin for anticoagulation.

On follow up with rheumatology at 12 weeks post-admission, lupus anticoagulant and *anti*-cardiolipin IgM remained elevated, confirming a concurrent diagnosis of antiphospholipid syndrome.[3] She is currently being maintained on 50 mg daily prednisone PO and has continued on warfarin for anticoagulation with plans to transition to apixaban. After careful discussion of available disease modifying anti-rheumatic drugs (DMARDs), the patient was placed on 200 mg of weekly subcutaneous belimumab.

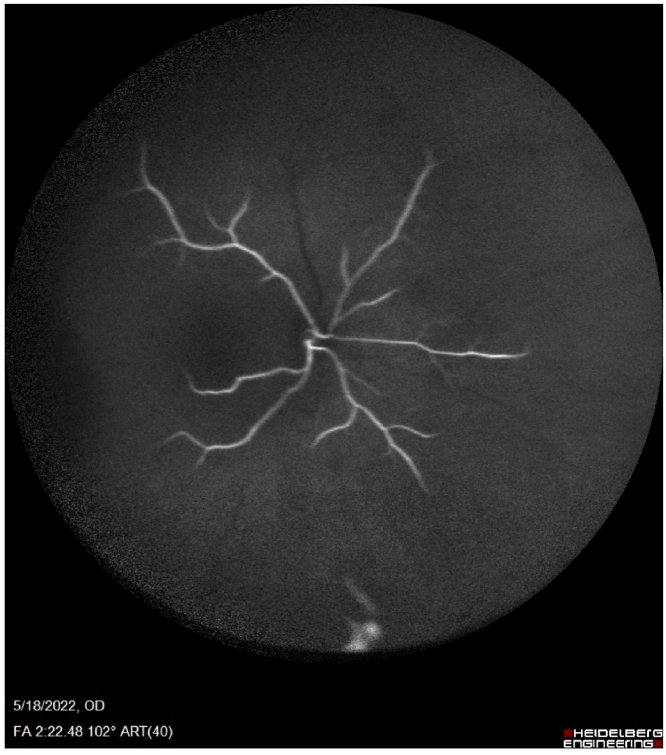

Fig. 2. Fluorescein angiography showing severely delayed filling at 2 minutes.

3. Background

Systemic Lupus Erythematosus (SLE) is an autoimmune disease involving both innate and adaptive immunity. It affects neurologic, cardiac, orthopedic, pulmonary, renal, and dermatologic systems, among others.[4] Similarly, SLE can affect almost every part of the eye, ranging from keratoconjunctivitis sicca to orbital myositis to optic neuritis.[5] The disease's impact on the retina, including large vessel ischemia, is well known. Occlusions may occur due to either thrombosis from co-occurring antiphospholipid syndrome or immune complex deposition with subsequent inflammatory response in the vessels.[4,6]

Typically, signs of retinopathy and large vessel occlusions have been associated with active and severe SLE.[7] However, a review of the indexed literature between 2012 and 2022 found at a least 11 cases in which a CRAO, CRVO, BRAO, or some combination of these were a patient's primary presenting sign of SLE [Table 1]. Five of these cases reported signs of SLE within the preceding six months which were quite mild, such as skin changes and oral ulcers [Table 2].[8–12] Of the

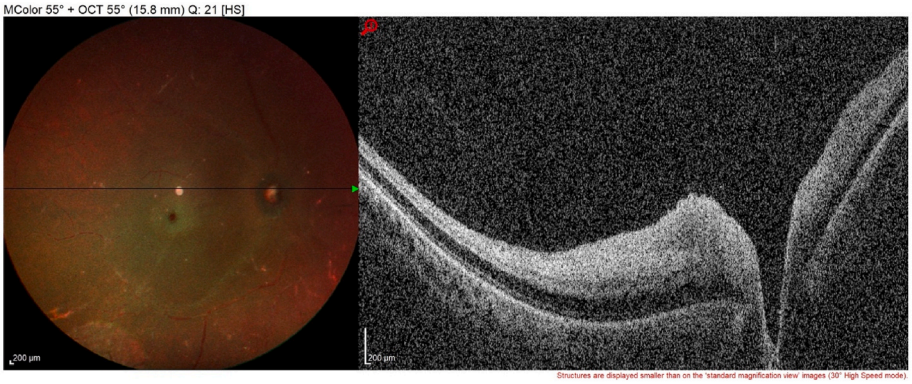

Fig. 1. Fundus photo of right eye showing cherry red spot and thready arteries. Corresponding OCT macula showing hyperreflectivity of the inner retina. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Summary of literature review showing patient characteristics.

Source	Age (years) Sex	Race	Event	Antiphospholipid Syndrome (APS) Present?	Initial Vision	Final Vision
Zhang et. al.	31 F	East Asian (Chinese)	Unilateral BRAO	Yes	OS: 20/50	OS: 20/20
Narang et. al.	19 F	Southeast Asian (Indian)	Bilateral CRAO/CRVO	No	OD: HM OS: LP	OD: HM OS: 20/100
Chandran et. al.	22 F	Southeast Asian (Indian)	Bilateral CRAO	No	OD: CF OS: CF	–
Ish et. al.	52 M	Southeast Asian (Indian)	Bilateral CRAO	No	OD: NLP OS: NLP	OD: NLP OS: NLP
Moreno et. al.	14 M	Hispanic	Unilateral CRAO/CRVO	No	OS: LP	OS: LP
Akhlaghi et. al.	29 F	Middle Eastern (Iranian)	Bilateral CRVO & CRAO/BRVO	No	OD: NLP OS: NLP	OD: NLP OS: NLP
Bawankar et. al.	14 F	Southeast Asian (Indian)	Unilateral CRAO/CRVO	No	OS: HM	–
Parchand et. al.	16 F	Southeast Asian (Indian)	Unilateral CRAO/CRVO	No	OS: LP	–
Hua et. al.	20 F	African American	Bilateral CRAO	No	OD: CF OS: CF	OD: 20/800 OS: 20/400
Hwang et. al.	18 F	East Asian (Korean)	Unilateral CRAO/CRVO	Yes	OD: HM	–
Zou et. al.	42 F	East Asian (Chinese)	Bilateral CRAO	No	OD: HM OS: HM	OD: HM OS: HM

HM: Hand-motion; LP: Light perception; NLP: No light perception; CF: Counting fingers.

Table 2
Summary of literature review showing which SLICC criteria were met by each patient.

Source	SLICC Clinical Criteria Met	SLICC Immunologic Criteria Met
Zhang et. al.	• Chronic cutaneous lupus • Non-scarring alopecia • Arthritis • Anemia • Thrombocytopenia	• ANA • *Anti*-DNA antibodies • *Anti*-Sm antibodies
Narang et. al.	• Chronic cutaneous lupus • Arthritis	• ANA • *Anti*-DNA antibodies • Low C4
Chandran et. al.	• Acute cutaneous lupus • Oral ulcers • Renal (proteinuria) • Neurologic • Leukopenia	• ANA • *Anti*-Sm antibodies • Low C3, C4
Ish et. al.	• Acute cutaneous lupus • Oral ulcers • Anemia	• ANA • *Anti*-Sm antibodies
Moreno et. al.	• Serositis • Renal (proteinuria) • Thrombocytopenia	• ANA • Antiphospholipid antibody
Akhlaghi et. al.	• Arthritis • Serositis • Anemia • Leukopenia	• ANA • *Anti*-Sm antibodies
Bawankar et. al.	• Acute cutaneous lupus • Renal • Leukopenia	• ANA • *Anti*-DNA antibodies • Antiphospholipid antibody • Low C3, C4
Parchand et. al.	• Oral ulcers • Non-scarring alopecia • Arthritis • Leukopenia	• ANA • Low C4
Hua et. al.	• Arthritis • Renal (mild proteinuria) • Anemia	• ANA • Ant-Sm antibodies • Direct Coombs test
Hwang et. al.	• Acute cutaneous lupus • Serositis • Renal (proteinuria)	• ANA • *Anti*-DNA antibodies • Low C3, C4 • Antiphospholipid antibody
Zou et. al.	• Oral ulcers • Non-scarring alopecia • Arthritis • Renal (proteinuria)	• ANA • Low C3, C4

remaining six, accompanying signs at presentation included malar rash in three cases, pleuritis in three, and arthralgias in two.[13–18] Consistent with the demographics of SLE, 9 of the patients were female and ages ranged between 14 and 52 (average 23.4 years).[8–14,16,18] Of the 11 cases, three were East Asian, five were Southeast Asian, one was African American, one was Middle Eastern, and one was Hispanic. Of the types of vascular occlusions, there were four cases each of bilateral CRAO and unilateral combined CRAO/CRVO, two cases of bilateral combined CRAO/CRVO, and one case of unilateral BRAO. Ultimate visual acuity ranged from NLP to 20/100, apart from the unilateral BRAO who achieved 20/20 vision. Overall, patients were treated for SLE with combinations of steroids and disease modifying anti-rheumatic drugs (DMARDs) and had variable course progressions on ophthalmology follow-ups.

4. Discussion

Our patient, a 41-year-old African American female who experienced a unilateral CRAO resulting in NLP vision, seemingly fits in with the population of patients at known risk for retinal complications of SLE. However, her case is particularly poignant as she had no symptoms leading up to this episode to warn of her thrombotic state. Furthermore, she had no signs of SLE on presentation, in contrast to most patients in the literature review who exhibited rashes, ulcers, or pleuritis. She only knew of her SLE status because of an incidental lab finding. She and her rheumatologist had previously had an informed discussion on the risks and benefits of starting treatment and reasonably decided against anti-rheumatic drugs, which come with their own side effects.

The patient is now following closely with a rheumatologist to control her previously quiet inflammatory disorder. She has agreed with rheumatology on initiating the disease modifying drug belimumab. When considering the patient's options for DMARDs, hydroxychloroquine was quickly excluded, given the patient's extensive right eye blindness. Methotrexate was considered as it could help alleviate the patient's principal symptoms of arthralgias and myalgias but was decided against as the drug would not significantly benefit other aspects of her lupus. Azathioprine and mycophenolate were ruled out because of the patient's concern that azathioprine was a previous chemotherapy drug and because of mycophenolate's intense immunosuppressive effects. Therefore, belimumab was chosen as the best option.

Belimumab is currently the only clinically available targeted biologic agent for the treatment of lupus, FDA approved in 2011.[19] It is a human monoclonal antibody that inhibits B lymphocyte stimulator (BlyS), also known as B-cell activating factor (BAFF). BAFF is a member of the Tumor Necrosis Factor family and has been known for decades to be correlated with autoimmunity. Belimumab is indicated for patients with active musculoskeletal or cutaneous disease that is unresponsive to standard therapy with glucocorticoids or other immunosuppressive agents, although its role in cases of lupus nephritis or central nervous system involvement is still under investigation. Some major side effects

include infusion reactions and leukopenia. In view of its good safety profile and efficacy in treating various complications of lupus, belimumab may be considered on a case-by-case approach for patients, such as ours, with SLE unamenable to standard therapies.

The patient was diagnosed with concurrent APS syndrome, supported by the patient's thrombotic event and positive lupus anticoagulant and *anti*-cardiolipin drawn at 12 weeks apart. Cases of APS co-occurring with SLE retinopathy have been previously reported with severe ocular consequences, consistent with our patient's experience.[20] Given this patient's rapid and catastrophic presentation, it is clearly possible for retinal vascular occlusions to occur even in asymptomatic SLE. The ultimate decision to treat SLE without major symptoms resides with the patient and their rheumatologist. This case of severe ocular morbidity in the setting of otherwise asymptomatic SLE may inform discussions between patients and their providers as they consider treatment options.

Patient consent: Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

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

Declaration of competing interest

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