Atypical Presentations of Systemic Lupus Erythematosus by Cerebral Venous Thrombosis and Generalized Lymphadenopathy without Antiphospholipid Antibodies: Case Report

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Abstract

Introduction: Atypical presentations of systemic lupus erythematosus (SLE) with features outside of the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria can make the diagnosis of SLE elusive.

Case Presentation: We describe a case of a healthy 31-year old female who presented with syncope preceded by progressive headache, serositis, and generalized lymphadenopathy. CT-head and MR-venogram confirmed a cerebral venous thrombosis (CVT). Subsequent workup revealed high titers of antinuclear (ANA), anti-double stranded DNA (anti-dsDNA), anti-Smith (anti-Sm) antibodies, as well as low complement levels, lymphopenia and neutropenia. Diagnosis of SLE was confirmed by SLICC classification criteria. Antiphospholipid antibodies (APLA) were negative. While in hospital, she sustained a seizure secondary to the CVT.

Conclusion: We discuss considerations for atypical SLE presentations by CVT (without APLA syndrome) and generalized lymphadenopathy, and the nuances of SLE diagnosis using existing classification criteria.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can manifest in a myriad of presentations. To date, its diagnosis relies on classification as per the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, which was a revision to limitations in the 1997 American College of Rheumatology (ACR) criteria aimed at clarifying heterogeneity within initial presentations [1-2]. Despite efforts to broaden current classification criteria to encompass the spectrum of SLE presentations, clinical manifestations falling outside of existing criteria continue to pose a challenge for diagnosticians. Here, we present an atypical first presentation of SLE by cerebral venous thrombosis (CVT) and generalized lymphadenopathy, neither of which fall within current classification criteria in the diagnosis of SLE [1-3].

CVT is a rare form of venous-thromboembolism, accounting for 0.5% of all strokes [4-6]. Though the incidence of thrombosis in SLE is reported at 7.2-12% [7-10], the incidence of CVT in SLE is not well established and has been documented to vary from 0.36% [11] to 7.9% [12-13]. When CVT does occur as a neurocomplication of SLE, it tends to manifest years to decades after diagnosis of SLE [11, 14], possibly related to a developing hypercoagulable state or concomitant antiphospholipid antibody (APLA) syndrome [6]. CVT as the initial presentation of SLE is even more rare, with limited case reports published describing this occurrence [7-10, 13-20]. Out of these documented cases, CVT presentations were mixed, the occurrence of concomitant APLA syndrome was varied, and “classic” clinical SLE manifestations of arthritis, serositis, or other cutaneous features are often secondarily elucidated to the patient’s primary neurological manifestations [7-10, 13-20]. Although the association between CVT and SLE is becoming better understood, it is not currently part of SLICC nor ACR neurological criteria [1-2]. The variability of CVT presentation [5], as demonstrated by these cases, and its rare association with SLE can delay

diagnosis of SLE when CVT is the presenting feature. An ultimate diagnosis of both conditions can prevent severe and irreversible neurological damage, or death.

Generalized lymphadenopathy (>3 lymph node chains) [21] can be seen in patients presenting with a variety of illnesses, particularly in the context of other constitutional symptoms [22]. Though isolated lymphadenopathy can be a frequent finding in SLE, generalized lymphadenopathy is less common and has been linked to higher levels of disease activity [23-24]. The presence of diffuse, generalized lymphadenopathy is non-specific and usually leads to an extensive work up for malignancy and/or infectious causes that can delay diagnosis of SLE [25-27]. Generalized lymphadenopathy is not currently part of SLICC, nor ACR classification criteria [1-2], but should prompt consideration of diagnostic evaluation to differentiate SLE lymphadenopathy from other differential diagnoses with different prognostic outcomes [25].

Case Presentation

A 31-year-old female of African descent presented to hospital after an unwitnessed syncopal episode, preceded by three days of progressive, left-sided, throbbing headaches and visual prodrome. First responders noted involuntary facial movements without a post-ictal phase. The headaches were new, positional in nature (improving with lying down), and not associated with nausea, fever, neurological symptoms nor meningismus.

The patient denied joint pains/swelling, morning stiffness, recent travel nor trauma. She carried no established diagnoses, particularly no venous thromboembolism, hypercoagulable nor autoimmune disorders, and no malignancy. Family history was negative for the aforementioned. She had never used oral contraceptive pills (OCPs). She had two uncomplicated pregnancies (last being over two years ago) with no recurrent miscarriages. Further review of systems (including constitutional symptoms) was negative.

On exam, she was hemodynamically stable with normal vital signs. A thorough cardiovascular and neurological examination revealed no abnormal findings. Fundoscopy revealed no papilledema. There was mild tenderness to end range on right knee flexion but without small joint pains/effusions on an otherwise benign joint exam. Mucocutaneous exam did not reveal any lesions. Multiple enlarged lymph nodes were palpated in the axillary and inguinal regions, bilaterally, that were soft, non-tender, and mobile. Spleen was not enlarged.

Investigations

An urgent CT-head showed a small (6mm) area of hyperdensity adjacent to the left distal transverse sinus (Figure 1). Subsequent CT-venogram revealed non-opacification of the left distal transverse, sigmoid, and sagittal sinuses, with findings confirmed on magnetic resonance (MR)-head (Figure 2) and MR-venogram (Figure 3) indicating presence of a CVT. A CT-chest was negative for pulmonary embolism but showed

evidence of trace pericardial effusion and enlarged axillary nodes (up to 2.5cm). An echocardiogram and continuous cardiac monitoring showed a structurally normal heart in sinus rhythm.

Bloodwork showed anemia and leukopenia (Table 1) with normal renal function, liver enzymes, and cardiac biomarkers. Serum protein electrophoresis (SPEP) and serum free light chains were normal. Serology was negative for HIV, syphilis, hepatitis B and C. Blood cultures showed no growth. Erythrocyte sedimentation rate (ESR) was elevated. Thrombophilia workup was negative, including APLA (Table 2).

Table 1

Hematological Work-Up

Test	Value		Reference Range
Hemoglobin	89	LOW	(115-150 g/L)
White blood cells	3.2	LOW	(4.0-11.0 x 10 ⁹ /L)
Red blood cells	3.35	LOW	(3.50-5.00 x 10 ¹² /L)
Platelets	155		(150-500 x 10 ⁹ /L)
Neutrophils	1.7	LOW	(2.0-7.5 x 10 ⁹ /L)
Lymphocytes	<1.0	LOW	(0.8-3.5 x10 ⁹ /L)
Erythrocyte Sedimentation Rate	61	HIGH	(0-20 mm/hr)
INR	1.0		(0.8-1.2)
aPTT	27		(24-34 seconds)

Table 2		
Thrombophilia Work-Up		
Test	Value	Reference Range
ACA IgG*	<2	0-19 GP-U/mL
ACA IgM*	<1	0-19 GP-U/mL
Lupus Anticoagulant [†]	Negative	
Protein C Activity	0.73	>0.70 U/mL
Protein S Free Ag	0.59	>0.55 U/mL
Antithrombin III	0.89	0.77-1.25 U/ml
Prothrombin 20210G	Not detected	
Factor V Leiden	Not detected	
b2 Glycoprotein IgG [‡]	<5	<20 GP-U/mL
b2 Glycoprotein IgM [‡]	0.6	<20 GP-U/mL
<p>*ACA IgA testing was not performed in this case. Although ACA IgA is listed in the immunological criteria in the SLICC 2012 criteria in the diagnosis of SLE, only ACA IgG and ACA IgM are used in the diagnosis of APLA. As such, only ACA IgM and IgG were performed, for which the tests were conducted twice and both returned negative.</p> <p>† Lupus anticoagulant testing was performed using both an aPTT based-assay and a dilute Russell's viper venom test, which was negative on both assays independently.</p> <p>‡b2 Glycoprotein IgG and IgM testing were performed as an outpatient. b2 Glycoprotein IgA was not performed for similar reasons as above with the decision to ignore ACA IgA testing. Although b2 Glycoprotein IgA is listed in the immunological criteria in the SLICC criteria, only b2 Glycoprotein IgG and IgM are used in the diagnosis of APLA.</p>		

Autoimmune serology (Table 3) displayed high titers of antinuclear (ANA), anti-double stranded DNA (anti-dsDNA), and anti-Smith (anti-Sm) antibodies. C3 complement was low with normal C4. Interestingly, the patient's IgG subclass 4 was elevated but polyclonal. Urinalysis revealed trace protein.

Table 3			
Autoimmune Work-Up			
Test	Value		Reference Range
Anti-Nuclear Antibody	>1:640, speckled	HIGH	>18 years, negative <1:80
<i>ENA Profile</i>			
Anti-dsDNA*	13 IU/ml	HIGH	>9 IU/mL = positive
Anti-Chromatin	>8.0	HIGH	<1.0 AI
Anti-Ribosomal	4.3	HIGH	<1.0 AI
Anti-Smith	>8.0	HIGH	<1.0 AI
Anti-smRNP	>8.0	HIGH	<1.0 AI
Anti-RNP 68	>8.0	HIGH	<1.0 AI
Anti-RNP A	>8.0	HIGH	<1.0 AI
C3	0.85	LOW	0.90-1.80g/L
C4	0.15		0.10-0.40g/L
IgG Subclass 4	0.955, polyclonal	HIGH	
*Anti-dsDNA antibody levels were performed twice and were elevated above the reference range using a mutliflex flow immunoassay test, and was therefore elevated above laboratory reference range on two occasions using a non-ELISA test.			

For malignancy workup, pap smear and mammogram were negative within 3 years. An abdominal ultrasound demonstrated multiple enlarged inguinal lymph nodes bilaterally. A core needle biopsy of an enlarged axillary lymph node was negative for lymphoproliferative disease; B-cell population was polyclonal without antigenic aberrancy.

During admission, the patient sustained a focal seizure with subsequent CT-head showing a stable CVT without evidence of new pathology nor clot extension. The patient’s seizure workup with enhanced MR-head and electroencephalogram (EEG) were negative for structural lesions, leptomenigeal enhancement, and epileptiform abnormalities.

Differential Diagnosis

Initial differential diagnosis included intracranial pathology (CVT, stroke, hemorrhage), seizure, and syncope. Neuroimaging established a diagnosis of CVT and cardiac evaluation did not suggest cardiac

cause of syncope. Subsequent evaluation ruled out malignancy or infection and pointed in the direction of autoimmune disease. With consensus from the rheumatology team, it was determined that the combination of clinical manifestations (CVT and seizure, serositis from pericardial effusion, lymphopenia, and neutropenia) and positive immunological criteria (positive ANA, anti-dsDNA, anti-Sm, low complement) met SLICC criteria for diagnosis of SLE. In this case, the patient's first manifestation of SLE was through CVT and generalized lymphadenopathy. Relevant hereditary and acquired thrombophilia (specifically APLA) were ruled out.

Treatment

The patient's CVT was initially treated with enoxaparin in hospital (total length of admission was 11 days), then transitioned to apixaban upon discharge. Her seizure was treated initially with phenytoin but switched to levetiracetam due to its interactions with apixaban. She was started on hydroxychloroquine and prednisone for SLE.

Outcome

The patient recovered well in hospital and had no further neurolupus complications. She was discharged with close rheumatology, hematology, and neurology follow-up. At 12 months, she enjoyed symptomatic improvement on hydroxychloroquine and gradually reduced her dose of prednisone, albeit not to zero. She remained on apixaban without complications, as her SLE was still considered active. She continued anti-epileptics for 3 months following discharge, at which point they were discontinued and she remained seizure free. In follow up with her neurology, hematology, and rheumatology teams, the patient did not report any adverse reactions with her medications and was overall satisfied with her treatment plan.

Discussion

The SLICC criteria remains the most reliable classification criteria for adult SLE [1] and was developed to address major limitations in the ACR criteria [2]. Notably, SLICC criteria identified biopsy-proven lupus nephritis as a sole diagnostic criterion in the presence of ANA or anti-dsDNA antibodies, removed the duplication of highly correlated cutaneous criteria, and included a greater number of neurological manifestations [1]. Despite these improvements, many patients present with signs and symptoms that fall outside of classification criteria, potentially delaying diagnosis. Our patient's initial presentation was CVT without APLA syndrome and generalized lymphadenopathy. Neither CVT nor generalized lymphadenopathy is part of SLICC, ACR, nor the new EULAR/ACR criteria [1–3] emphasizing the importance of ongoing diagnostic suspicion and appropriate investigations for atypical presentations.

CVT is rare with an incidence of 1.32/100,000 people [5]; the incidence of CVT in SLE is not well established and has been documented to vary from 0.36% [11] to 7.9% [12–13]. CVT pathophysiology is not well understood but is typically ascribed to a local and/or systemic imbalance between prothrombotic

and thrombolytic processes [5]. Its association with SLE was first described as a neurocomplication from autopsy-proven results of cerebral infarcts in 41 patients with a previous diagnosis of SLE [28]. These results showed greater neurological involvement in Black patients with a worse 10-year-survival-rate [28], suggesting the prognostic importance of CVT in its association in SLE. Though there has been no new evidence to suggest higher associations or worse prognostic outcomes for CVT-associated SLE in Black patients, the pattern described by Gibson and Meyer fits the demographic description of our patient and raises the question of potential ethnic-based risk factors, though these are not well characterized. Common risk factors for CVT in SLE are genetic or acquired prothrombotic disorders, malignancy, infection or underlying inflammatory disorder [6]. Of the prothrombotic disorders, most common associations are with APLA syndrome, G20210A prothrombin polymorphism, and Factor V Leiden [5, 29–34]. CVT is more common in women from OCP use or pregnancy [34], but this was not a factor in our patient. In our case, active SLE was the only risk factor identified.

CVT presentations are variable, with the most common symptoms being isolated headache, intracranial hypertension syndrome, encephalopathy, or seizures and, albeit less commonly, stroke syndromes [34–35]. A significant number of patients present only with headache [36], often described as severe, generalized, persistent, and progressive [7–10, 13–17, 37]. Of reported cases of CVT as the initial presentation of SLE, complaints of persistent headache were frequently noted up to 73.3–95% of the time [7, 13]. Other neurological findings including seizures (20–75%) [7, 13], visual field defects (40%) [13], altered level of consciousness (26.7–57.5%) [7, 13], nausea and/or vomiting (20–82.5%) [7, 13], focal weakness (52.5%) [7], and papilledema [7, 9, 17] presented in variable frequencies [7–10, 13–17]. Our patient presented with similar complaints of progressive, throbbing headaches and visual prodrome. It is difficult to distinguish if this patient's seizure was a complication from her CVT or a neurological complication of her SLE.

Given the variable headache description and non-specificity of CVT symptomatology, diagnosis relies on accurate neuroimaging with MR-venogram being the diagnostic image of choice [6], as was done in this case. The transverse and super sagittal sinuses are more commonly affected [13–14]. One previous study noted that one sinus was involved in 73.3% of cases, and more than one sinus in 26.7% of cases [13]. Our case demonstrated involvement of 3 sinuses (transverse, sigmoid, sagittal). There is presently no documented correlation between extent of CVT and degree of SLE disease activity.

Generalized lymphadenopathy is a common presentation and triggers a broad differential diagnosis that includes infection, malignancy, and autoimmune disorders [21–23]. It is not specific for autoimmune disorders and can distract from the diagnosis of SLE [22–26, 38]. SLE patients with generalized lymphadenopathy often display constitutional symptoms (fever, fatigue, weight loss, night sweats), have higher incidences of hepatomegaly and splenomegaly, and high anti-dsDNA or low complement levels [22]. The latter two were present in our patient. These associations suggest that the presence of SLE lymphadenopathy indicates a more active state of inflammatory disease [22–23].

SLE is associated with an increased risk of developing hematological malignancy [22]. It is good practice to perform a lymph node biopsy with flow cytometric analysis for lymphadenopathy even when SLE is confirmed. Needle-core biopsy is an effective and important step to differentiate SLE lymphadenopathy from infectious causes such as HIV, Castleman's disease, tuberculosis, or brucellosis, and non-infectious causes such as sarcoidosis, lymphoma, Kikuchi-Fujimoto disease, or other connective tissue diseases with different prognostic outcomes. Our patient underwent a core needle biopsy and pathology was negative for lymphoproliferative disease. In combination with negative malignancy and infection workup, her lymphadenopathy was ascribed to SLE lymphadenopathy.

This case highlights the variability of SLE presentation and the importance of understanding the individual patient's SLE manifestations to appropriately diagnose and manage this disease. This case features only a specific constellation of atypical symptoms and does not address all diagnostic pathways of variable presentations leading to a diagnosis of SLE; however, this case does emphasize the importance of a more cognizant approach to atypical presentations of SLE. Furthermore, our case highlights the non-specific presentation of CVT, but the importance of investigating for underlying autoimmune and/or thrombophilia related causes.

Declarations

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Author Contributions:

XSW was involved in the assessment and management of this patient as a member of the general internal medicine team, and responsible for the writing of this manuscript. DK was responsible for overseeing this patient's care as most responsible physician of the general internal medicine team, and was involved in the writing and editing of this manuscript. PB was involved in editing the manuscript. WM was responsible for curating and interpreting this patient's radiographic investigations, and in editing this manuscript.

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Figures

Figure 1

Unenhanced CT Head on initial presentation. Initial unenhanced CT head performed on patient’s presentation to the emergency room. A 6mm area of hyperdensity was noted adjacent to the left transverse sinus (red circle); otherwise negative for acute ischemia, hemorrhage nor intracranial mass.

Figure 2

MRI (FLAIR) Head confirms CVT. Subsequent workup with unenhanced MRI head (FLAIR) shows hypointensity of the left transverse sinus (red circle) as compared to normal hyperintensity of the right transverse sinus; indicating a filling defect consistent with a dural sinus thrombosis.

Figure 3

MRI Venogram delineates involvement of three cerebral sinuses. MRI venogram (Left: Coronal; Right: Axial) demonstrating non-visualization/filling defects of the left transverse and sagittal sinuses (red circle), as compared to normal enhancement of the right venous sinus system, indicative of an occlusive dural venous sinus thrombus in the left transverse sinus.

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