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A case of neuropsychiatric lupus in a patient presenting with sepsis

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Abstract

Systemic Lupus Erythematosus (SLE) refers to an autoimmune condition of multifactorial origin. While SLE most commonly causes constitutional symptoms, complications involving the cardiorenal and nervous systems may also occur. The case presented in this report is of a 34-year-old female with a history of hypertension and iron deficiency anemia who presented to the Emergency Department with a cough. The patient was found to have pneumonia with sepsis on presentation to the ED, and was started on azithromycin and ceftriaxone. During this time frame, the patient developed pleural and pericardial effusion along with bilateral lymphadenopathy. Evaluation of both the effusions and lymphadenopathy with a thoracentesis and lymph node biopsy respectively were unremarkable. An autoimmune workup was initiated, revealing positive ANA and double-stranded DNA antibodies. This workup, along with the patient's symptoms, led to a diagnosis of SLE. While the patient was still admitted, she had 2 episodes of new-onset, witnessed seizures along with proteinuria. An MRI of the brain also showed an unwitnessed stroke. The patient was placed on aspirin, statin, and Keppra to become clinically stable for further workup. While prognosis for SLE has improved due to various factors, the possibility of mortality becomes elevated with active infections or kidney or central nervous system disease. The message conveyed in this case emphasizes the need for prompt work-up and subsequent therapy to reduce the possibility of complications associated with SLE such as Neuropsychiatric Lupus (NPSLE).

Keywords: Neuropsychiatric lupus; SLE; Autoimmune; Sepsis; Stroke.

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that can cause a range of symptoms and affect multiple organ systems. While fatigue, fever, arthritis, arthralgias, and skin lesions serve as the most common symptoms of SLE, life-threatening cardiac, renal, and neurologic symptoms may also manifest. In terms of etiology, the exact cause remains unknown; however, SLE is thought to be influenced by various environmental, hormonal, and genetic factors, with more than 100 different gene loci mutations that could cause the more common polygenic SLE, and more than 30 different gene mutation possibilities that could cause monogenic SLE phenotype. Furthermore, the underlying cause for most SLE symptoms can also vary, ranging from antibody and immune complex

formation, to cell-mediated inflammation, cytokine-mediated mechanisms, or pathogenic autoantibodies such as seen in Neuropsychiatric Lupus (NPSLE) [1]. These autoantibodies and proinflammatory cytokines can then lead to a range of neurologic manifestations, including vascular occlusion, neuronal damage, and blood-brain barrier dysfunction amongst others. In this specific report, the patient presented with pneumonia and sepsis, and on further work up, was found to have SLE with both neurological and renal manifestations [2].

Case presentation

A 34-year-old African American female with a history of hypertension and anemia presented to the Emergency Department (ED) with a chief complaint of persistent cough. This patient had presented to ED 1 week prior to this admission with a cough as well, with an EKG demonstrating sinus tachycardia and a chest x-ray showing bibasilar densities consistent with atelectasis (Figure 1). The patient was diagnosed with community-acquired pneumonia and was discharged on doxycycline from the ED by an emergency physician. However, the patient presented now with diarrhea for 2 days along with chills and fatigue in addition to her cough.

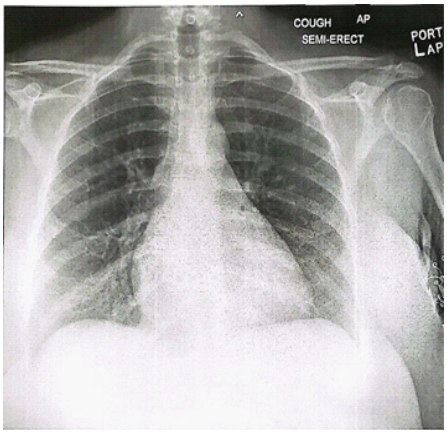

Figure 1: Chest x-ray of the patient 1-week prior shows bibasilar densities consistent with atelectasis and infiltrates. No pleural effusion or acute bony abnormality is identified on imaging.

Upon the patient's current ED presentation, work up including vitals, an EKG, chest x-ray, and basic blood work including a CMP, CBC, prothrombin time, INR, lactate, and PTT were done (Tables 1-3). A PCR COVID/Flu/RSV panel was also ordered. Further history from the patient revealed that her appetite was decreased; however, she was able to drink 6 bottles of 16 ounce waters daily. She also denied having symptoms of chest pain or shortness of breath. At the time of admission from the ED, after initial work up, patient was determined to be septic. She was immediately given a 30 ml/kg fluid bolus and antibiotics azithromycin and ceftriaxone were started. Her initial work up showed a normal WBC count and lactate levels, and her vitals showed a blood pressure within normal range. SARS COV-2, Flu A, Flu B, and RSV were all negative. However, the patient was having a fever of 103˚F, a pulse of 133, and respirations of 22. Also, EKG demonstrated sinus tachycardia, while her chest x-ray demonstrated bibasilar pneumonias with bilateral pleural effusions (Figure 2). For further treatment and workup, the patient was admitted into the hospital with an initial diagnosis of pneumonia with sepsis.

Tables 1-3: Labs ordered upon patient's ED admission, including a CMP, CBC, prothrombin time, INR, lactate, PTT, and PCR COVID, Flu, and RSV panel.

CBC	
WBC	6.00
RBC	3.41
Hemoglobin	8.4
Hematocrit	25.7
MCV	75.4
MCH	24.6
MCHC	32.6
RDW	15.5
MPV	9.0
Platelets	202

PROTIME-INR	
Prothrombin Time	15.2
INR	1.18
COVID/FLU/RSV BY PCR	
SARS COV-2	Negative
Flu A	Negative
Flu B	Negative
RSV	Negative
Lactic Acid, Plasma	
Lactate	1.37
APTT	Normal
PTT	32.0

CMP	
Sodium	129
Potassium	4.1
Chloride	98
CO_2	25
Glucose	107
BUN	11
Creatinine	0.62
Calcium	8.1
Total Protein	8.5
Albumin	2.8
ALT	33
AST	127
Alkaline Phosphatase	33
Total Bilirubin	0.7
Anion Gap	10
BUN/Creatinine Ratio	18
Albumin/Globulin Ratio	0.5
GFR CKD-EPI	>60

From day 1 of hospital admission, the patient revealed that she was also having back pain, joint pain, and myalgias. On physical exam, bilateral rales were auscultated, and lymphadenopathy in the axilla, cervical lymph nodes, and submandibular lymph nodes were palpated. At this point, a pneumonia PCR panel and blood cultures were ordered followed by a pulmonology consult, who expressed concern due to the patient's combination of fevers, myalgias, and cough. She was encouraged to do incentive spirometry, and for wheezing and shortness of breath, PRN DuoNeb was prescribed for every 4 hours along with BiPAP for respiratory distress. Also, imaging from the patient's ED visit 1 week ago was referenced, where a CT angiogram that was done had demonstrated small pericardial effusion but ruled out PE. A decision was made to order a lymph node biopsy and to repeat the CTA at this visit due to the patient's shortness of breath and elevated D-dimer levels. This updated CTA showed extensive adenopathy in the submandibular and supraclavicular regions along with the axilla, cardiomegaly, a small pericardial effusion, and no PE (Figure 3).

On day 1, an echocardiogram was also ordered due to the patient's bilateral pleural and pericardial effusion, and a stool sample and GI panel were ordered to identify the cause of the patient's diarrhea. Interventional radiology was also consulted to perform a thoracentesis, and autoimmune disease workup involving cyclic citrullinated peptide, rheumatoid factor, and ANA was initiated as it was on the differentials. By the end of the day, the echo result came back indicating a LVEF of 65-70%, with mild concentric left ventricular hypertrophy and other parameters unremarkable. On day 2, the HIV and TSH levels or-

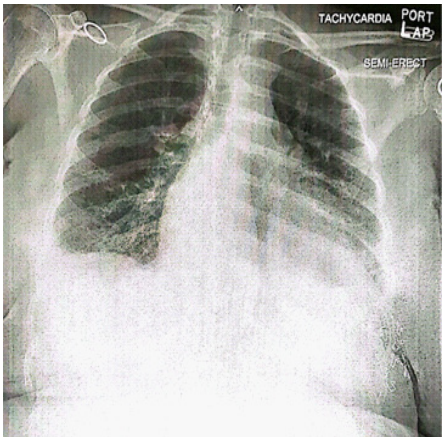

Figure 2: Chest x-ray of the patient at this specific ED visit shows bibasilar pneumonias, small bilateral pleural effusions, and cardiomegaly.

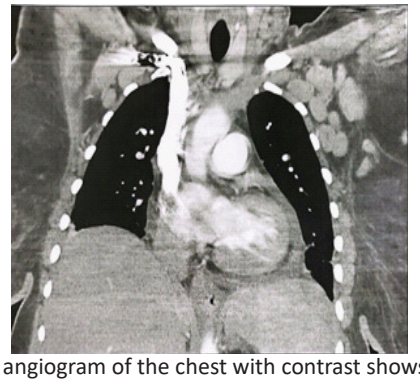

Figure 3: CT angiogram of the chest with contrast shows extensive adenopathy in the neck and axilla, cardiomegaly with small pericardial effusion, and moderate bilateral pleural effusions. Minimal reticulonodular changes suggesting superimposed pneumonitis is seen as well.

dered in the ED came back negative and normal respectively. Furthermore, patient's stool sample was OBT negative. Patient was advised to continue her antibiotic regimen based on her blood culture and pneumonia PCR results; however, a repeat blood culture sample came back negative, resulting in cessation of antibiotics after 5 days. On day 3, the patient's stool PCR also came back negative, and further management of her diarrhea with loperamide was continued. Based on the patient's CTA results, oncology was consulted on day 3 for evaluation to further investigate the etiology of the patient's symptoms. They agreed with a lymph node biopsy, and also suggested a CT of the abdomen to assess for splenomegaly and intra-abdominal adenopathy. On day 4, results for the core needle biopsy of the lymph node came back not showing any malignancies, including lymphomas or leukemias. Thoracentesis that had yielded about 700 mL of clear, yellow, pleural fluid also came back as transudative, unremarkable for any pathology on cytology. The confirmatory CT of the abdomen and pelvis with contrast that was ordered demonstrated bilateral pleural effusions with diffuse adenopathy of neoplastic or reactive nature. However, after a few days, the results for the full autoimmune workup ordered on day 1 came back. This workup was negative for RF and anti-CCP, but positive for ANA, double-stranded DNA, and anti-smooth antibodies as well as for reduced C3 and C4 levels. By this time, the patient's condition had been steadily improving; however, she then experienced bilateral upper and lower extremity weakness on day 4, with no focal neurological deficits. An MRI of the thoracic and lumbar spines were ordered, revealing no acute changes and multilevel spondylotic changes respectively. Neurosurgery was consulted regarding her back pain and leg weakness; however, no epidural collection or significant stenosis was appreciated on MRI. By day 5, the patient's weakness had resolved, and she was walking again. On day 6 of admission, patient developed generalized weakness, and later in the day, had a new-onset, witnessed seizure resulting in altered mental status, weakness, and a postictal state for 15 minutes. A CT scan of the head without contrast was ordered and showed a normal brain parenchyma for age with no apparent abnormalities. A consult for neurology was placed, and she was started on aspirin by the neurologist and a statin by the primary care team due to increased risk of recurrent strokes. On day 7, an MRI of the brain without contrast was ordered, showing the presence of unwitnessed bilateral infarcts (Figure 4). Physical exam of the patient yielded no focal neurological deficits, and an EEG ordered by the neurologist also came back negative for seizure-like activity. With both lupus and vasculitides still on the differentials, a lumbar puncture was also ordered to evaluate for CSF cell count, glucose, protein, and a meningitis/encephalitis panel, which were all negative.

Rheumatology was consulted with details regarding the patient's autoimmune work-up, and a diagnosis of lupus was made with an appropriate treatment plan made to address this. However, the patient had another witnessed seizure and had to spend a few more days in the hospital. Keppra was initiated on a twice a day regimen along with steroids and hydroxychloroquine. Furthermore, new labs drawn on the patient revealed new-onset proteinuria with an elevated urine albumin/creatinine ratio. Nephrology was consulted, and she was made NPO.

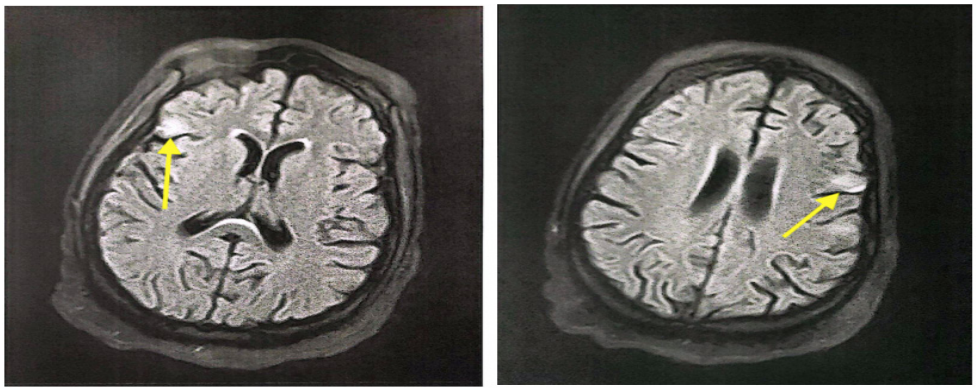

Figure 4: Punctate focus of cortical ischemia in the right posterior frontal lobe seen in image on the left. Focal signal abnormalities are seen in the left frontal and parietal lobes in image on the right.

Urine studies were also ordered, including a urinalysis and urine protein creatinine ratio to establish renal involvement. When the patient was determined to be both clinically and hemodynamically stable, a kidney biopsy was completed to evaluate for possible lupus nephritis. The patient improved significantly with steroids, Keppra, Hydroxychloroquine, aspirin, statin, and from finishing her course of antibiotics. Her shortness of breath, cough, myalgia, arthralgia, and decreased appetite symptoms had all resolved. After a hospital stay spanning more than 2 weeks and a kidney biopsy confirming Lupus Nephritis, the patient was discharged on aspirin, atorvastatin, Keppra, hydroxychloroquine and tapering dose of steroid. She also had multiple outpatient appointments made with a rheumatologist, nephrologist and neurologist to follow-up on her seizures and lupus.

Discussion

The clinical presentation of SLE can vary from patient to patient, including different racial and ethnic groups. An epidemiology update provided by the Georgia and Michigan Lupus Registries found that the incidence and prevalence rates for SLE are highest in African-Americans compared to Caucasians, predominantly affecting women in their childbearing years. The usual presentation of SLE involves having a combination of symptoms affecting multiple systems, including fever, fatigue arthralgia, arthritis, and skin lesions. More significant SLE manifestations involve the deposition of immunoglobulin in the glomeruli, resulting in clinical nephritis, mouth ulcerations associated with the GI tract, atherosclerotic plaques leading to heart disease, and neuropsychiatric manifestations such as described in this case report [3].

In terms of why an autoimmune workup was done for this patient, her symptoms along with her epidemiological picture raised suspicion for SLE. Antinuclear Antibody (ANA) titers were ordered for this patient, as the presence of this is highly characteristic of the autoimmune nature of SLE. While ANA is sensitive for SLE, it is non-specific; as a result, anti-dsDNA and anti-Sm antibodies were also ordered to establish a diagnosis. Finally, the EULAR criteria can be used to establish the diagnosis of SLE in this patient. With a positive ANA titer, and both a total score of ≥10 and ≥1 clinical criterion, the patient was able to be diagnosed with SLE using the EULAR criteria method. Clinical criterion scored for this patient included the presence of seizures [4], pericardial effusion, joint involvement, proteinuria, low complement proteins, and SLE-specific antibodies [5]. This case emphasizes the need to recognize the importance of early rheumatological workup and appropriate symptom management in patients presenting with fever, cough, shortness of breath, myalgia, and arthralgia. Rheumatological workup should also be considered in multisystem involvement such as rheumatological symptoms, pleural effusion in the respiratory system, pericardial effusion in the cardiovascular system, proteinuria due to renal involvement and later neurological manifestations. Neurological complications associated with SLE include strokes, seizures and altered mental status amongst others. A review of studies addressing neuropsychiatric symptoms in the context of SLE found that CNS symptoms are the second most common cause of mortality in SLE only to lupus nephritis. Furthermore, cognitive dysfunction can occur in up to 50% of these patients, involving acute confusional states and psychosis. For mortality associated with NPSLE, 8-15% of these cases are directly associated with stroke, emphasizing the need for low-dose anti-platelet therapy to address underlying risk factors. A separate case control study examined patients younger than 50 with a cerebrovascular accident in the setting of SLE. Results indicated that 37% of these patients experienced a hemorrhagic CVA within their 1st year of SLE diagnosis, while 25% of patients experienced an ischemic CVE by their 5th year of CVE diagnosis [6]. Current recommendations for stroke prevention involve focusing on controlling disease activity by the early administration of corticosteroids, hydroxychloroquine to control disease activity, anticoagulation for primary prevention of thrombosis, and/or immunosuppressants when necessary. The use of statins is also indicated for SLE patients to reduce progression of atherosclerosis and the incidence of CVA [7,8]. The main challenge presented in this case was the presence of sepsis on admission with low suspicion of SLE on day 1. While work up was ordered on day 1 and 2, it can take a few days to get results back for rheumatological tests from the labs. A second challenge was determining whether the new-onset seizures and stroke were actually related to the patient's newly diagnosed SLE or if they were unrelated events. A neurology consult was placed for the seizures due to a concern for epilepsy, and despite an unremarkable neurological exam, an MRI was ordered due to the patient's altered mental status and stroke concerns. However, once the patient's workup was complete, her treatment plan became clear: to treat her sepsis, address the underlying cause of her neurologic symptoms, and to prevent recurrent strokes. While the initial management of this patient involved doxycycline monotherapy, her sepsis was addressed using both azithromycin and ceftriaxone empirical therapy to cover multiple pathogens, including possible atypical causes of community-acquired pneumonia. After the patient's first witnessed seizure, an EEG was done that did not show any abnormal waveforms. As seizures can be an early manifestation of SLE, neuroimaging with MRI and CSF analysis can aid in diagnosis. Both were used in this case to help work towards a diagnosis of NPSLE. In terms of seizure management, Anti-Epileptic Drug (AED) therapy is not necessary for a single episode; However, AED is recommended for use in the case of recurrent seizures, MRI structural abnormalities, and impaired awareness associated with seizures. In the case of this patient, 750 mg of Keppra BID was initiated until patient follow up with a neurologist due to the MRI structural abnormality from her bilateral cortical infarcts and her impaired awareness after seizures [9]. The patient was also placed on an aspirin, statin, steroids, and Plaquenil to both control her lupus and reduce the possibility of stroke as described above. By her discharge date, the patient reported improvement in her symptoms, especially after starting the steroids and Plaquenil. Generally speaking, this case supports much of the existing literature on this topic. It also corroborated our beliefs that not only is prompt diagnosis needed to improve patient outcomes in NPSLE, but also how important it is to consider SLE in general as a cause of symptoms related to organ dysfunction, especially after keeping in mind the epidemiology and non-specific nature of this autoimmune disease.

Conclusion

The case in this report served as a clinical example of how neuropsychiatric lupus can manifest as seizures and stroke associated with a diagnosis of systemic lupus erythematosus. Key takeaways from this case emphasize the need for prompt action to address sepsis before end-organ damage as well as the importance of autoimmune workup in the setting of multiple system involvement with non-specific symptoms. This workup is especially important since SLE in particular is known to affect multiple different organ systems. Based on our clinical experience, we recommend prompt NPSLE evaluation in a patient with a suspected seizure and/or stroke with either a sus-

picion for or established diagnosis of SLE. This can be done by evaluating antibody and complement levels, urine studies for proteinuria and by completing an MRI to evaluate for infarcts. Furthermore, beginning both anti-epileptic and disease modifying therapy in addition to aspirin and a statin can decrease morbidity and mortality from recurrent strokes.

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