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Longitudinally Extensive Transverse Myelitis Associated With Systemic Lupus Erythematosus: A Case Report and Literature Review

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Abstract **Background:** Lupus myelitis is a rare but disastrous complication of systemic lupus erythematosus (SLE). The transverse myelitis (TM) may involve three or more contiguous spinal cord segments and as such is designated longitudinally extensive transverse myelitis (LETM). The neurological presentation may vary based on the location of the pathology and may consist of a combination of sensory and motor deficits. TM could be the presenting feature of SLE or present after 10 years of disease, while SLE was considered to be in remission. **Case presentation:** 26-year-old Black man with history of biopsy proven-lupus nephritis that had progressed to ESRD, presented with sudden onset quadriplegia that resolved upon arrival to the hospital. On exam, the temperature was 101.8°F and the neurological exam was consistent with residual weakness on the left sided-upper and lower extremities. Leukopenia, lymphopenia and thrombocytopenia, along with low complements were noted. Brain MRI was normal however, the spine MRI was suspicious for an epidural process (C2-T4) and intravenous antibiotics were commenced. After five days, neurological improvement was nil and new spine MRI revealed spinal cord edema secondary to myelitis at several spinal cord levels (C2-T4). Laboratory data was consistent with a SLE flare complicated with longitudinal extensive transverse myelitis. Pulse steroids and plasma exchange were initiated. Two weeks after admission, MRI demonstrated resolution of the epidural spinal lesion and marked improvement in spinal cord edema. **Conclusion**: TM can be the presenting feature of SLE or appear later on during the course of their disease. LETM is the most frequently type of TM found among SLE patients. Given the grave nature of the disease, it is of paramount importance that clinical features of TM be promptly recognized among SLE patients, to prevent catastrophic or even life-threatening outcomes.

Keywords: *systemic lupus erythematosus, transverse myelitis, longitudinal extensive transverse myelitis, neuromyelitis optica spectrum disorders, aquaporin 4 antibodies, seronegative NMOSD, autoimmune disease*

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1. Introduction

Lupus myelitis is a very rare but serious complication of systemic lupus erythematosus (SLE). Neurological manifestations are reported in up to 60% of patients with SLE however, these most commonly include stroke syndromes, seizures and peripheral neuropathies [1,2]. Only 1-2% of patients with SLE develop lupus myelitis [3,4]. Transverse myelitis can be complete or partial. In some cases, however, transverse myelitis can present in the form of a longitudinally extensive transverse myelitis (LETM), which is defined as myelitis affecting three or more contiguous segments of the spinal the cord [5]. Hereby, we present a case of LETM that occurred in a patient with SLE diagnosis which manifested as sudden onset quadriplegia.

2. Case Report

A 26-year-old Black man presented to another hospital five years before with anasarca and a maculopapular rash. The patient underwent skin and renal biopsies and the diagnosis of lupus nephritis class IV was confirmed. The patient was initially prescribed hydroxychloroquine and subsequently mycophenolate mofetil which were later discontinued due to adverse effects. The patient's renal function deteriorated and was started on rituximab every 6 months with the last infusion 1 month before presentation. Despite the therapeutic interventions, the patient had

progressed to end-stage-renal disease (ESRD) requiring hemodialysis.

On the morning of presentation, the patient experienced sudden onset paralysis below the neck and severe pain affecting the extremities. While being transported in the ambulance, the neurological symptoms ameliorated. While in the Emergency Department of our Institution, the patient reported that he had neck and shoulder pain for weeks in addition to, pain in the wrists, hands, ankles and feet.

On presentation, the patient was febrile to 101.8°F. The physical exam revealed that the patient had regained strength in all extremities with residual weakness in the left upper and lower extremities. Initial laboratory values were notable for leukopenia, lymphopenia, thrombocytopenia, hypoalbuminemia, transaminitis, uremia, and elevated creatinine. C3 and C4 levels were 15.6mg/dL and 8.0mdg/dL respectively and erythrocyte sedimentation rate (ESR) was 36mm/hr. (Table 1).

Detailed neurological exam encountered intact sensation and grossly normal motor function except for the left-hand muscles. See Table 2. MRI of the brain was performed, which showed no abnormalities.

MRI of the entire spine was obtained and demonstrated a high T2 signal ventral to the spinal cord spanning from C2-T4 representing an epidural process. See Figure 1. The differential diagnosis included an epidural abscess or an epidural hemorrhage. Risks and benefits of a lumbar puncture were explained to the patient who declined the procedure. Pancultures were obtained. Given the fact that the patient was febrile, leukocytopenic and had received rituximab within the last six months, broad spectrum antibiotics were administered for the suspected epidural abscess. 24 hours after the initiation of antibiotics, patient noted improvement in left upper extremity strength however, continued to have neck and shoulder pain. The serological test for detection of Aquaporin-4 antibodies returned negative, as well as the tests for human immunodeficiency virus (HIV), Lyme Disease and rapid plasma reagin (RPR) serology. Double stranded-deoxyribonucleic acid (dsDNA) levels resulted at 1000 IU/dL (normal ≤30IU/dL). Anti-Smith (anti-Sm) and anti-Sm/RNP Antibodies were not detected.

The patient continued to have febrile episodes and a repeat MRI total spine was obtained five days later demonstrating decreasing epidural signal however, significant spinal cord T2 signal was demonstrated, suggestive of edema secondary to myelitis at several spinal cord levels. See Figure 2.

At this point, the differential diagnosis included myelitis likely secondary to a severe lupus flare. The laboratory values revealed which were highly suggestive of a lupus flare and the antibiotics were discontinued. Pulse steroids and plasma exchange were initiated. The patient received a total of five plasmapheresis sessions on non-dialysis days for a total of five days.

Patient reported resolution of neck pain, shoulder pain and improvement in the left upper extremity weakness with near complete restoration of strength except for fine motor skills when compared to the initial presentation. MRI spine imaging, on day 15 of admission, demonstrated resolution of the epidural spinal lesion and marked improvement in spinal cord edema and the patient was discharged with close rheumatology and neurology follow-up.

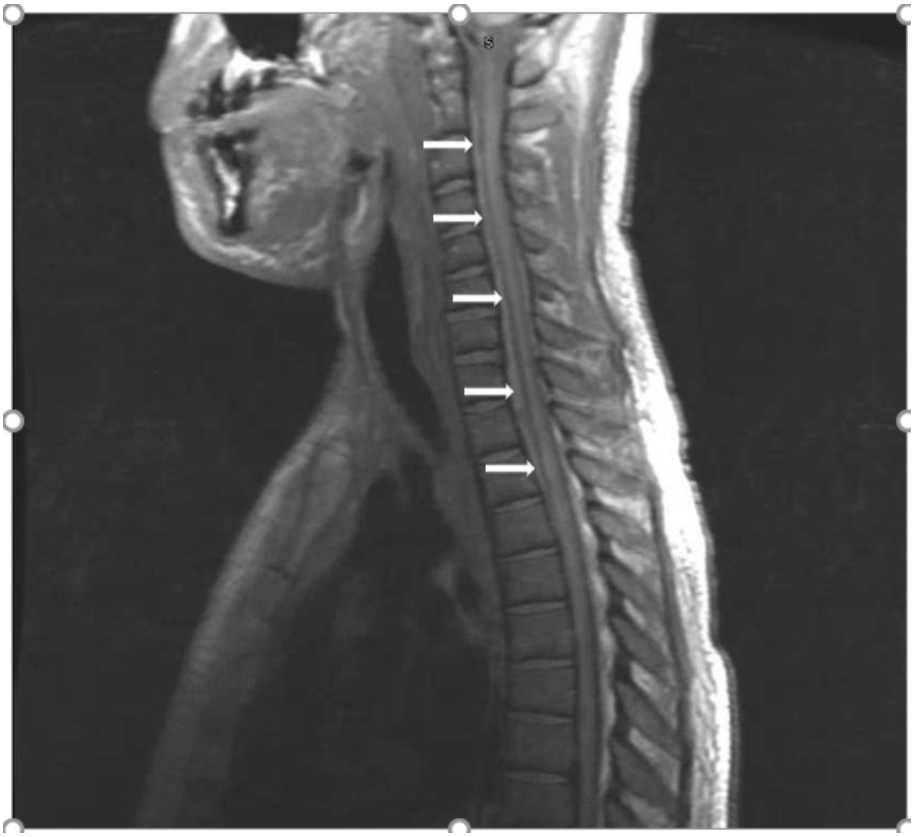

Figure 1. MRI Cervical and Thoracic Spine Sagittal

Subtle intermediate T1 signal ventrally in the spinal canal extending from C2 to T4 (Solid white arrows).

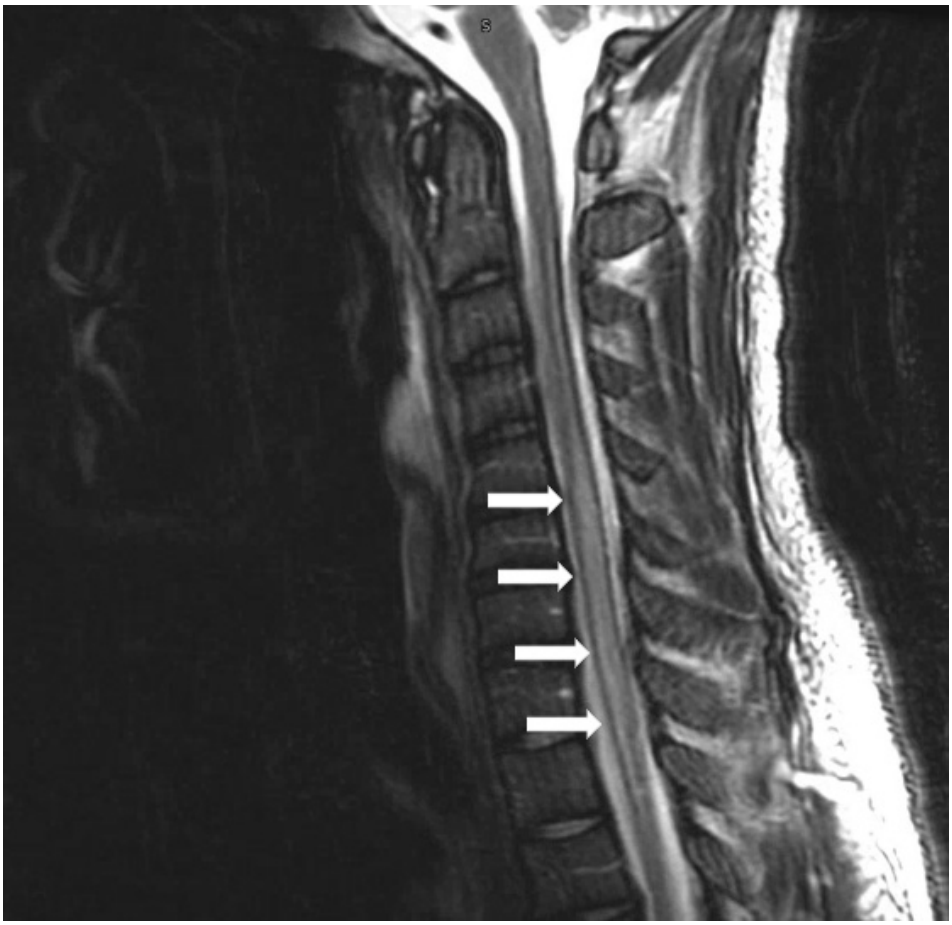

Figure 2. MRI cervical and thoracic spine Sagittal T2

Spinal cord edema spanning levels C2-T2 spinal levels suggestive of longitudinally extensive transverse myelitis. Interval improvement of anterior epidural lesion.

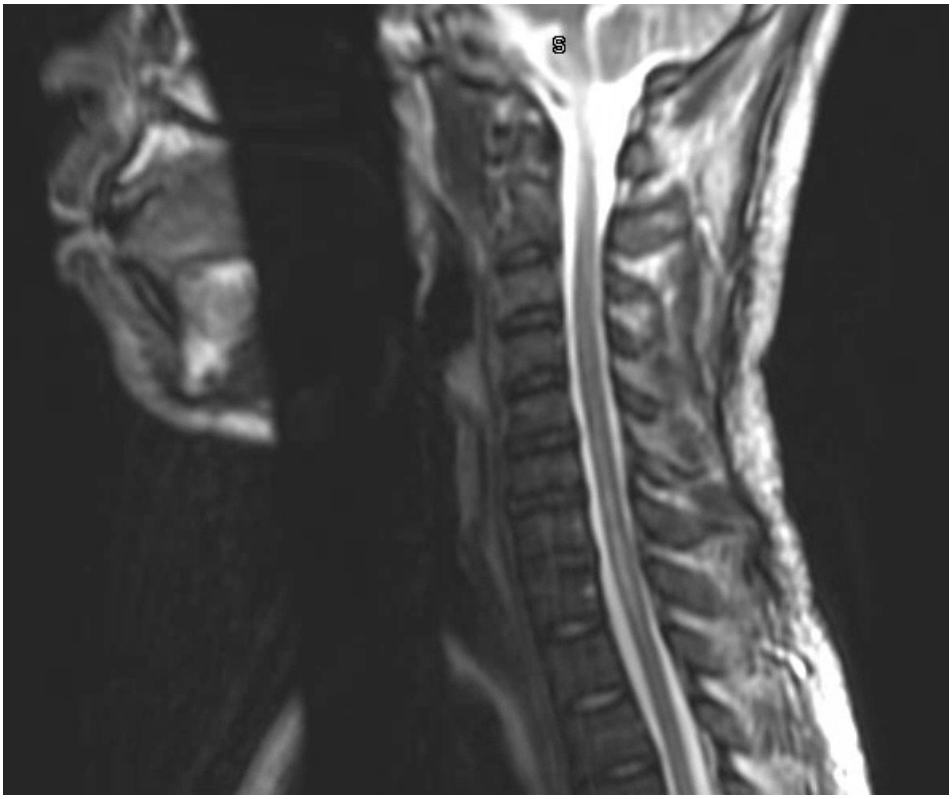

Figure 3. MRI Cervical and thoracic spine sagittal T2

Interval improvement in cord edema from C2-T2 and resolution of ventral epidural lesion.

Table 1. Laboratory data on initial presentation.

Serum	Patient	Reference
Na	132	136-146 (mmol/L)
K	4.5	3.5-5.5 (mmol/L)
Cl	96	98-106(mmol/L)
Glucose	82	70-99(mg/dL)
Blood urea nitrogen	60	6-20(mg/dL)
Creatinine	60.5	0.4-12(mg/dL)
Protein total	3.6	6.0-8.5(g/dL)
Albumin	<1.5	2.8-5.7(g/dL)
Alkaline phosphatase	82	25-125(U/L)
AST	101	10-35(U/L)
ALT	61	0-31(U/L)
Calcium	6.8	8.4-10.3 (mg/dL)
Magnesium	1.8	1.9-27(mg/dL)
Phosphorus	5.1	2.5-5.0(mg/dL)
Total Bilirubin	0.20	0.0-1.2(mg/dL)
Iron	45	50-212(ug/dL)
TIBC	123	200-500(µg/dL)
Ferritin	2842.5	16-294(ng/ml)
C reactive protein	<4.0	0.0-8.0(mg/L)
Hemoglobin	9.4	12.0-16.0(g/dL)
WBC	4.30	4.5-109(cells/mm^3)
Platelets (K/uL)	81	130-400(K/mm^3)
Rapid plasma reagin (RPR)	Non-reactive	Non-reactive
HIV Ag/Ab	Non-reactive	Non-reactive
Bacterial Blood Cultures	No growth-final	No grow-final
Immunoglobulin G	913.3	0.8-7.7(mg/dL)
AQP4 Ig-G	<1.5	<1:5(U/ml)
C3	<15.0	83.0-200(mg/dL)
C4	<8.0	16.0-47.0 (mg/dL)
dsDNA	1000	≤30.0(IU/dL)
Lyme disease, real time PCR	Not detected	Not detected
C2 Complement	<1.3	1.6-3.5(mg/dL)
Sm/RNP antibodies	<1.0	<1.0 Units

Table 2. Neurological Findings

Neurological Exam	On the field	Initial findings by Neurology	On discharge
Mental status	Alert & oriented	Alert & oriented x 3	Unchanged
Cognition	N/A	Intact	Unchanged
Visual field	N/A	Intact	Unchanged
Sensory	N/A	Decreased pinprick & temperature sensations on the palmar aspect of the left 1st digit. Proprioception and vibrations intact. All modalities intact in all other extremities.	Unchanged
Motor	Complete paresis of all extremities	5(-), flexion/extension, on left 1st & 2nd digits. Decreased grip, left hand 5/5 in all other extremities.	Residual impairment of fine motor movement on left hand, otherwise 5/5 in all extremities
Pain	N/A	Pain present at the posterior neck and upper back	Improved
Reflexes	N/A	Brisk in the right biceps 2(+) in the brachioradialis and triceps bilaterally 1(+) patellar and 0 ankle	2(+) in the biceps, brachioradialis and triceps bilaterally, 1(+) in the patellar and mute in the ankles
Gait	Complete paresis in all extremities.	Apprehensive gait	Deferred by patient

3. Discussion

Systemic Lupus Erythematosus is an auto-immune condition that affects 20-30 for every 100,000 adults in the United States [6]. SLE is a disease that is known to have protean manifestations and the initial manifestation of SLE can affect any of the various organs of the body. The usual clinical presentation of SLE include constitutional symptoms, skin and mucous membrane involvement, arthritis, nephritis, pleuritis, pericarditis, Raynaud's phenomenon and neurological manifestation to name a few [7,8,9,10,11]. Neurological manifestations of SLE most commonly involve stroke syndromes, seizures and peripheral neuropathies [1,2]. Lupus Myelitis is a very rare manifestation of SLE and is seen in 1-2% of SLE patients [3,4]. In most cases of lupus, patients have ongoing lupus symptomology that

precedes transverse myelitis (TM) but in 23% of patients as per one review, TM could be the initial presentation of lupus [12]. Moreover, up to half of patients with TM suffer a recurrence of the disease process after resolution [13]. However, when myelitis does occur, imaging shows that it is usually longitudinal as compared to complete transverse at a certain spinal level [14].

If three or more contiguous spinal levels are involved, the condition is termed as longitudinally extensive transverse myelitis (LETM). A review study found that from 1966-2008, 22 cases of LETM had been reported in the literature [12]. The same review found that 77% of patients presenting with LETM were females [12]. Since then, a review published in 2014 found 6 additional cases reported in the literature [15].

The pathophysiology of myelitis in SLE can be attributed to an array of mechanisms. Autopsy demonstrated various vascular changes in 11 out of 12 cases of SLE associated with TM. The findings included ischemic necrosis, infarction, malacia and degenerative changes within the white matter [16]. These changes were attributed to auto-immune vasculitis. An association between SLE TM and antiphospholipid antibodies (aPL) have been demonstrated in some studies [13,17]. Another study found that among patients who were diagnosed with LETM secondary to SLE, 50% were positive for aPL as compared to 24% who did not develop myelitis [18]. Other mechanisms that might have been involved in TM occurring in SLE include vascular thrombosis, hematomas, abscesses, or demyelinating disorders of the spinal cord [18,19,20].

The International Panel for NMO Diagnosis redefined the International Consensus Diagnostic Criteria for NMOSD in 2015 [20]. NMOSD is classified in 3 groups: 1) NMOSD with AQP4 antibody (AQP4-IgG) or seropositive NMOSD, 2) NMOSD without AQP4IgG, and 3) NMOSD with unknown AQP4-IgG [6]. Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status are as follows:

Acute optic neuritis which requires a normal brain MRI or only nonspecific white matter lesions or optic neuritis by MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm [20].

Acute myelitis by MRI extending over three contiguous segments (LETM) or three contiguous segments of focal spinal cord atrophy in patients with prior history compatible with acute myelitis [20].

Area postrema syndrome, demonstrating dorsal medulla/area postrema lesions by MRI and lastly, Acute brain stem syndrome: requires associated peri-ependymal brain stem lesions [20].

Our patient had normal brain MRI findings, therefore the possibility of this presentation being seronegative NMOSD is not supported.

Longitudinal myelitis can present in association with various other conditions. Autoimmune diseases such as Sjögren's syndrome, sarcoidosis, myasthenia gravis, inflammatory bowel disease and aPL. Among the infectious etiologies that can present with TM include cytomegalovirus, Epstein-Barr Virus, HIV, varicella zoster virus and mycobacterium tuberculosis [3,4,5,6].

Obtaining and MRI of brain and the spine is an essential step in patients with neurological presentations. Signal enhancement of three or more contiguous vertebral levels on MRI is enough to diagnose LETM. A study demonstrates that in SLE myelitis, MRI imaging demonstrates that significantly more patients (71.4%) have longitudinal lesions as compared to transverse lesion (28.6%) [21]. MRI findings might also include spinal cord diameter increase which was demonstrated in our case and was interpreted as cord edema. Diagnostic work up should include bloodwork for NMO-IgG/AQP4 antibodies and additional rheumatological workup including C3, C4, dsDNA and infectious workup.

Management of myelitis is depends on the underlying etiology. In cases of TM occurring during a SLE flare, the treatment is centered at suppressing the acute inflammatory process. First line treatment includes high dose pulse steroids and disease modifying agents, usually cyclophosphamide and others such as mycophenolate mofetil, azathioprine, rituximab or intravenous immunoglobulin [13,19,21,22,23]. In severe refractory auto-immune conditions, plasma exchange can be used to remove antibodies, cytokines and complement products [23]. In our case the patient had recently received rituximab and treatment was started with high dose methylprednisolone along with plasmapheresis.

The prognosis for acute TM can be simplified by the rule of one third, whereby one third of the population recovers with minimal residual neurological deficits, one third develop moderate disability and the final one third develops severe neurological disability [25]. In contrast, other researchers found that TM associated with SLE, tends to have adverse outcomes in up to 66.7% of the patients [26]. More than ten years of SLE duration, the severity of the initial neurological presentation (paraplegia) and the lack of cyclophosphamide use were associated with unfavorable neurological outcomes at six months and at follow-up [26].

4. Conclusion

TM can be the presenting feature of SLE or appear later on during the course of their disease. There is a female predominance and TM tends to affect patients who had a SLE disease duration of longer than 10 years and was considered to be in remission. LETM is the most frequently type of TM found among SLE patients and work-up directed to exclude other etiologies must be pursued including seronegative NMOSD, Sjögren's syndrome and a number of infectious causes. Given the grave nature of the disease, it is of paramount importance that clinical features of TM be promptly recognized among SLE patients, laboratory and imaging diagnosis be swiftly made, and treatment be immediately administered to prevent catastrophic or even life-threatening outcomes, knowing that one third of the patients will go on to develop severe neurological disabilities.

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