A Case of Systemic Lupus Erythematosus Associated with Longitudinal Extensive Transverse Myelitis, Cerebral Neutrophilic Vasculitis, and Cerebritis

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Abstract

Systemic Lupus erythematosus (SLE) is an autoimmune disease with multiple clinical presentations and manifestations. Here, we report an intriguing case of a 30-year-old female with full-blown SLE, associated with longitudinal extensive transverse myelitis (LETM) on Magnetic Resonance Imaging (MRI) manifested by lower extremity weakness, neurogenic bladder and bowel, and central nervous system (CNS) lupus clinically manifested by changes in mood and behavior as well as neutrophilic vasculitis and cerebritis on pathology. LETM is a rare complication of SLE, however, what makes this case even more intriguing is that it additionally had cerebral lesions consistent with neutrophilic vasculitis and cerebritis, and that it may all have started at least 10 years prior with nonspecific musculoskeletal manifestations subsequently followed by a rash as well as intractable fevers of unknown etiology—much later attributed to her lupus. Although she had a most concerning and dramatic presentation, she, so far, had responded very well to therapy including pulse dose steroids, plasmapheresis, intravenous immunoglobulins (IVIG), cyclophosphamide, and related medications.

Lupus patients with significant neurological involvement may develop longitudinal extensive transverse myelitis (LETM); this association SLE-LETM had been more recognized over the last two decades, perhaps due to more awareness but also to the availability of better neuro-imaging modalities, such as the MRI. The mean time of occurrence of LETM from the diagnosis of SLE is 3 years, and depending on the sources, LETM refers to a lesion that extends over three or more vertebral segments or over four or more vertebral segments. When not associated with SLE, LETM may be due to other inflammatory or non-inflammatory etiologies. Perhaps no other disease entity comes to mind more than neuromyelitis optica (NMO) when it comes to its association with a condition; yet, NMO accounts for only half of adult cases of isolated LETM in adults, as such, unless obvious, working up the underlying cause of LETM itself can be arduous. This case report and literature review raises awareness of LETM in association with SLE, other inflammatory and non-inflammatory conditions, things to consider during the work-up, and the need for a prompt diagnosis and treatment to avoid deplorable consequences.

Case Report

The case is that of a 30-year-old Caucasian female with a 10-year history of polyarthralgias and subjective polyarthritis, who was admitted to the medical service for intermittent but persistent high-grade fever. After the onset of her polyarthralgias, she took Nonsteroidal Anti-inflammatory Drugs (NSAIDs) for about 3 to 4 years on a regular basis as well as a gluten-free diet; she stopped the medication, and she was more or less asymptomatic for 6 years. However, about 10 months prior to admission, she started developing macular erythematous rashes across the chest with intermittent febrile episodes for which she would take acetaminophen. She did not feel the need to formally seek medical attention.
at that time. Yet, 4 to 5 months prior to admission, she again started experiencing daily episodes of fever; as reported by the patient, the longest episode lasted about 40 days. Concomitantly, she started experiencing joint stiffness, and her arthralgias began to reoccur again. She was given a diagnosis of SLE based on inpatient work-up results: elevated ANA (1:640, speckled), +Smith/+dsDNA, +arthritis (reported), hypocomplementemia and +serositis (+minimal pericardial effusion). Prednisone therapy was continued, which had been started on an outpatient basis a few weeks prior for presumed inflammatory syndrome. She was also started on hydroxychloroquine therapy. This led to an initial improvement in her arthralgias and other musculoskeletal issues; however, she developed a more defined macular rash over her upper chest and forehead without frank signs of malar rash. She was also becoming more reserved with mild to moderate psychomotor retardation. This was not very obvious at first. Also, of note, 1 week prior to admission, she was treated with ciprofloxacin for an episode of urinary tract infection, and later reported that 2 days prior to admission, while attempting to get out of bed at night, she had an episode of urinary incontinence. She still later added that she felt significant weakness in her lower extremities and required the help of her boyfriend for transfer to the bathroom and back. Not much was done about this at first since on her day of admission, though febrile, she was ambulating without major difficulties and her weakness was thought to be due to fatigue.

Note that upon her arrival to the emergency department on this admission, she was started on intravenous antibiotics as there was an initial concern of urosepsis with her temperature up to 104° F. However, her infectious work-up, including complete metabolic panel, urinalysis, and initial labs as well as chest x-ray, were unremarkable. She had no leukocytosis or bandemia, and immunosuppression was continued as mentioned above.

However, 5 days after admission, she complained of urinary incontinence consistent with overflow as well as a new episode of a fall in the bathroom due to weakness.

Figure 1 A 30-year-old woman with history of systemic lupus erythematosus and new spinal cord lesions. Axial FLAIR (A) of the brain reveals an irregular lesion within the right basal ganglia surrounded by extensive T2 hyperintensity and expansion of the right basal ganglia extending to the right temporal lobe, with related mass effect on the right frontal horn and lateral ventricle. Also, visible is T2 hyperintensity of the left striate body (B). Axial T1 of the brain prior to (C) and following (D) gadolinium administration reveals irregular ring enhancement of the margins of the lesion. Axial FLAIR of the brain at 6-month follow-up (E) reveals almost complete resolution of the right basal ganglia lesion with some residual gliosis primarily involving the caudate head.
of her legs, though she had been working with physical therapy all along. Given her new symptoms, the medical team completed a neurology exam and requested a neurology consultation as well. Her exam revealed evidence of decreased motor strength in the lower extremities; the upper extremity strength was intact—so were her cranial nerve exam and sensation throughout. She had some hyper-reflexia noted at the level of the triceps. An urgent MRI of the brain and spine revealed evidence of multifocal brain lesions with large right basal ganglia ring enhancing lesion (Fig. 1). She was also found to have a lesion in the spinal cord spanning over multiple vertebrae; this was consistent with longitudinal extensive transverse myelitis (Fig. 2). As for her brain lesion, an extensive infectious disease work-up was undertaken with multiple viral, bacterial, and fungal cultures and polymerase chain reactions ordered. A little later, a brain biopsy showed findings of cerebral neutrophilic vasculitis and lesions consistent with lupus cerebritis (Fig. 3). Her final diagnosis was, therefore, systemic lupus erythematosus associated with longitudinal extensive transverse myelitis.

Given the extent of disease and no initial improvement in her condition (she essentially became paraplegic after her second fall) on the therapy at the time, she was emergently given pulse dose methylprednisolone 1000 mg IV daily for 3 days, initiated on cyclophosphamide monthly dosing, four cycles of plasmapheresis, and 2 cycles of intravenous immunoglobulins (IVIG). Also, out of an abundance of precaution, the infectious disease service recommended continuing her antimicrobials—including vancomycin, imipenem (later discontinued due to concern of lowering seizure threshold),

Figure 2 A 30-year-old woman with history of systemic lupus erythematosus and new lower extremity weakness. Sagittal T2 (A) and sagittal STIR (B) of the cervical spinal cord reveal T2 hyperintense intramedullary lesions scattered within the cervical cord with mild cord expansion. The most dominant lesion is diffuse and spans the C2-C3 level. Also present are T2 hyperintense intramedullary lesions with mild cord expansion in the thoracic spinal cord (C), visible at C8-T1 and at T5-T6 in this image. Sagittal T2 of the cervical spinal cord at 6 month follow-up (D) reveals almost complete resolution of the previously seen lesions with some residual mild T2 hyperintensity of the spinal cord at C2 without cord expansion.
acyclovir, and antifungals, the latter of which she was on long time after the other ones were discontinued. Her corticosteroids were later switched to an oral tapering regimen. She was continued on her hydroxychloroquine and placed on various supplementary agents, such as atovaquone for pneumocystis jiroveci prophylaxis, calcium and vitamin D as indicated, and deep venous thrombosis as well as gastrointestinal prophylaxis as indicated. A repeat MRI, done about 3 weeks after onset of her acute neurological issues, showed stable to mildly improving lesions (Figs. 1C and D) and 6 months later, almost complete resolution of the right basal ganglia lesion (Fig. 1E), as well as that of the previously seen T2 hyperintense intramedullary lesions (Fig. 2D). Clinically, she started improving slowly, was hemodynamically stable, afebrile, and without any stool incontinence, though her Foley catheter remained in place. For this reason, she was deemed appropriate for a transfer to inpatient subacute rehabilitation.

In rehabilitation, she stayed for about 2 months and continued improving, though she had to be transiently transferred to the medical intensive care unit for an episode of urosepsis that improved with intravenous antibiotics and indicated management. She afterward did very well and began to regain lower extremity strength and bladder function. She was discharged home with close outpatient follow-up and continued to receive monthly cyclophosphamide and a dose of leuprolide 10 days prior to the infusion. On her last visit, she completed her 6-month course of cyclophosphamide, still on low dose prednisone, hydroxychloroquine, as well as other supplementary agents. She recovered her lower extremity function (now able to ambulate 2 to 3 miles without cane or help) and is now neurologically, subjectively, objectively, and overall ready to resume work as a teacher.

Pathology
The pathological specimen consisted of multiple scant fragments of tan to focally brown soft tissue ranging in size from 0.3 to 0.7 cm in greatest dimensions. Microscopic examination revealed extensive foci of perivascular and parenchymal neutrophilic infiltrates, consistent with neutrophilic vasculitis and cerebritis (Figs. 3A and B). Multiple vessels demonstrated fibrinoid necrosis of the vascular wall and microthrombi due to extensive neutrophilic vasculitis (Fig. 3C). The infectious process was ruled out by negative

![Figure 3](https://www.nyuhjdbulletin.org)
special stains and microbiological cultures for bacterial, viral, and fungal organisms.

Discussion

Systemic lupus erythematosus is an autoimmune disease known to have multisystem complications, including renal, hematological, and neurological among others. In the case of our patient, she mostly had a neurological involvement as later confirmed by pathology (lupus cerebritis) and imaging (LETM). Indeed, her neurological symptoms spanned the spectrum of flattened affect and abulia likely as a result of her frontal lobe involvement to urinary incontinence, falls, and paraplegia, ultimately—as a result in part to the extensive spinal involvement. This association is being increasingly recognized. In 1999, Deodhar and colleagues published a case that they thought was the first of its kind. However, more cases, though rare, have been reported. In fact, Espinosa and coworkers conducted a recent literature review spanning about 4 decades leading to 2008 and identified 22 similar cases; since then, at least one more case was reported by White and colleagues. However, what makes our case diagnostically intriguing and therapeutically challenging was the ring-enhancing lesions seen on MRI as well as the simmering and protracted nature of how her symptoms presented. The mean time of occurrence from the initial diagnosis had been reported to be about 3 years, which makes one wonder if, after all, hers has not been about 10 years in the making, even if a formal diagnosis of SLE wasn’t formalized until her admission.

Most sources describe LETM as a rare and serious inflammatory process that expands over more than three vertebrae, though some have described it as more than four. LETM is also known as longitudinally extensive spinal cord lesions (LESCls) or long cord lesions (LCLs) and tend to be idiopathic but may have inflammatory or non-inflammatory etiologies. It had been widely described in conjunction with neuromyelitis optica (NMO); however, as rightly pointed out by Trebst and colleagues, it’s rather part of its diagnostic criteria and may be its initial or limited form, and NMO accounts for only half of adult cases of isolated LETM in adults. Indeed, LETM and LETM-like lesions have been described in conjunction with various pathological states, including inflammatory-autoimmune and non-inflammatory pathologies. Some of the inflammatory diseases states reported are Sjogren’s syndrome (SS), neurosarcoid, Devic’s disease, or SLE as in our case. The other causes are neurologic (multiple sclerosis and acute disseminated encephalomyelitis, for example), traumatic, infectious (such as human T-lymphotropic virus-1, HIV, tuberculosis, and syphilis), vascular (acute spinal cord infarction), nutritional deficiencies (copper and Vitamin B12, for example), and paraneoplastic causes—those who have collapsing response mediator protein 5 (CRMP5) also known as CV2 in particular; amphinysin-IgG, which is known to be commonly associated with small cell lung cancer and breast cancer, had reportedly been detected in the sera of patients with rapidly progressive myelopathy and LETM on imaging. As such, one may only be able to speculate its underlying pathophysiology at this point. The role of antiphospholipids and microthrombi had been raised in SLE, for example; however, when viewing its association with the various disease processes enumerated above, in the end, it may be due to the underlying pathological state. More work remains to be done to further elucidate this.

In the case of this patient, her Aquaporin-4, also known as NMO-IgG, was negative, and this would go along with the report that SLE and SS associated with systemic autoimmune disease and uncomplicated by NMO were seronegative for the biomarker as opposed to observing NMO-IgG seropositivity only in some patients with SLE and SS who had NMO or NMO spectrum disorders. Also, a recent published article suggests that the AQP4-Ab-negative patients were younger than those with AQP-4 Ab (37.74 Vs 45.3 of mean age year at LETM, respectively), more likely to present with a classic Devic phenotype, and more likely to have conus involvement and early urinary retention.

The outcome depends on whether it is inflammatory LETM with good prognosis. As it appears to be the case of this patient so far; however, LETM as a whole has poor prognosis with only about 14% of patients in a systematic review recovering completely. Poor prognostic factors reported include antiphospholipid antibodies (her IgM was positive at 29 but then normalized close to 3 months later) and hyperacute presentation. Nonetheless, according to a recent publication, in multiple sclerosis patients, it is the Expanded Disability Status Scale (EDSS) at nadir in patients with LETM that was associated with the final outcome and extension of the myelitis with risk of recurrence, and that recurrence was not associated with worse outcome.

At this point, the evaluation of a patient with LETM essentially relies on the MRI of the brain and spinal cord where a hyperintense lesions are seen on T2-weighted images associated with rheumatological work-up (vasculitis in particular), CSF analysis as well as more specific antibodies, such as NMO-IgG, soluble IL-2R, anti-ENA antibodies, and onconeural antibodies; novel inflammatory markers, such as IL-6 or other proteins in their signaling pathways, may represent markers of disease severity and potential therapeutic targets. A more recent publication by researchers in Spain also suggest that the inflammatory LETM includes a relatively homogenous group of patients with an overrepresentation of the HLA-DRB1*13 genotype, and checking it as part of the work-up may be considered. For those willing to follow a more standardized diagnostic approach, that of Habek and colleagues may be used (Fig. 4).

Management of LETM should be tailored to the underly-
ing process. In the case of our patient, she received pulse dose steroids, IVIG, plasmapheresis, cyclophosphamide, and hydroxychloroquine—all with the necessary prophylactic measures, including osteoporosis prevention with calcium and vitamin D initially, gastrointestinal and deep venous thrombosis prophylaxis, ulcer precautions, as well as upgrade to a higher level of care as her situation was initially deteriorating.

This case highlights a rare presentation of SLE, in association with concomitant cerebral and spinal lesions. This association needs to be kept in mind and the clinical suspicion high in these types of patients. Furthermore, as many have already reported, it goes without saying that a prompt diagnosis is paramount, and every effort should be made to initiate an aggressive and pragmatic immune-modulatory regimen for the patient once it is clear that it is inflammatory in nature and that an infectious process can reasonably be ruled out. “Throwing the book at” the patient, as was the case here, may be the way to go to avoid ongoing irreparable damage. The importance of an

Figure 4 Suggested diagnostic algorithm for patients with LETM. (Dashed arrow designates possible but unlikely diagnosis). LETM: Longitudinal extensive transverse myelitis, VEP: visual evoked potentials, OCB: oligoclonal bands, EMNG: Electromyoneurography, MS: multiple sclerosis, ADEM: acute disseminated encephalomyelitis. (Adapted from Acta Neurol Belg. 2012;112:39-43, with permission from authors).
interdisciplinary approach and close follow-up in managing such a patient cannot be overemphasized.

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**Disclosure Statement**

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