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Review article

# Myelitis in systemic lupus erythematosus

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ABSTRACT

SLE-associated acute transverse myelitis (ATM) is a rare, but potentially severe complication of Systemic lupus erythematosus (SLE), and may lead to significant motor, sensory and autonomic dysfunctions in the central nervous system resulting in marked neurological deficits. It is important to recognize its clinical feature to allow timely diagnosis and management of this condition. In this review, we aimed to provide the reader with the understanding of its clinical presentation and classification, the underlying pathological, MRI (magnetic resonance imaging) appearance, and current status of management, with an emphasis on recent discoveries and advancements.



## 1. Introduction

Systemic lupus erythematosus (SLE) may affect the nervous system at multiple levels. Neuropsychiatric systemic lupus erythematosus (NPSLE) encompasses a spectrum of symptoms and disorders that involve the central or peripheral nervous system during the disease process of SLE. In 1999, the American College of Rheumatology (ACR) developed a nomenclature system containing 19 NPSLE syndromes to facilitate recognition, diagnosis and classification, amongst which "myelopathy" is used to specify injury of the spinal cord [1]. The term "myelopathy" generally describes pathologies such as ischemia, compression, metabolic and inflammatory causes. When the spinal lesion is initiated and caused by inflammation, it is often termed "myelitis", but the two expressions are considered interchangeable in published literatures.

The clinical presentations of myelitis comprise motor, sensory and autonomic dysfunctions. The severity varies according to the extent of spinal lesion and may range from mild extremity numbness, dysesthesia total sensory loss, weakness, paraplegia, and bowel and anal sphincter dysfunction. The term "acute transverse myelitis (ATM)" was first used in 1948 to describe the development of paraparesis with a thoracic sensory level in a patient with pneumonia and postinfectious myelitis [2]. In fact, the word "transverse" bears no relationship to the radiological or pathological lesion, but was solely used to highlight the importance of a spinal sensory level in reaching the diagnosis [3]. By 2002, the International Transverse Myelitis Consortium Working Group produced a set of diagnostic criteria and nosology for ATM and a new classification was proposed and adopted [4]. Based on this classification, ATM is broadly categorized as secondary or idiopathic. The latter can only be established when other disease-associated myelitis has been excluded. When the myelitis is caused by SLE [4], the condition is referred to SLE-associated ATM. This review examined the clinical features, pathological changes, differential diagnosis and therapy in SLE-associated ATM.

## 2. Incidence and prevalence

The overall incidence of transverse myelitis is reportedly between 1 (severe) to 8 (mild) cases per million per year [3], with a bimodal peak between the ages of 10 to 19 years and 30 to 39 years; no gender or familial predisposition has been reported. The reported prevalence of SLE in the population is 200 to 1500 cases per million [5–7]. In Asia, Feng [8] has estimated the prevalence of SLE to be 500–1000 cases per million population. The incidence of SLE is also variable, ranging from 10 to 250 per million per year in North America, South America, Europe and Asia [5,9,10]. Myelitis is a relatively rare complication of SLE [11]. The incidence of ATM among SLE population was mainly based on case serials and was reportedly 1–2% [12,13], documented by literatures prior

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to 2000; and 0.9% [14] to 1.1% [15] according to more recent publications.

## 3. Clinical manifestations and subtypes

TM is characterized by lesions of inflammation within the spinal cord. Its clinical manifestations arise from resultant interruptions of motor, sensory, and autonomic pathways within and passing through the inflamed area. SLE is a systemic inflammatory disorder caused by autoimmune reactions, the pathomechanism of neurological damage of SLE-associated ATM is believed to share same features of its underlying disease [4]. The neurological deficit and clinical symptoms of SLE-associated ATM are not dissimilar to TM of other etiologies. These symptoms include acute or sub-acute paraparesis of the lower extremities, with initial flaccidity followed by spasticity. Most patients have a sensory level. Typical sensory dysfunctions include pain, dysesthesia, and paresthesia. Autonomic symptoms include increased urinary urgency, bladder and bowel incontinence, inability to void, incomplete evacuation with constipation, and sexual dysfunction [16]. The signs and symptoms depend upon the level of spine being involved. ATM can be further divided into two subgroups [17], an acute complete transverse myelitis (ACTM) or acute partial transverse myelitis (APTM). ACTM indicates moderate or severe symmetrical weakness and autonomic dysfunction attributable to a spinal level. APTM describes mild sensory and or motor dysfunction, bilateral or unilateral; when severe deficits are present, marked asymmetry is observed.

ATM may also be categorized as grey matter or white matter myelitis [18]. In the case of grey matter myelitis, conditions may deteriorate rapidly, reaching a clinical nadir within 6 h with no subsequent improvement while white matter myelitis is characterized by the development of upper-motor neuron spasticity and hyperreflexia at the onset but the symptoms were less severe with slower progression.

## 4. Pathological changes

The pathological hallmark of TM is the presence of local collections of lymphocytes and monocytes, with varying degrees of demyelination, axonal injury, and astroglial and microglial activation within the spinal cord [19]. The pathogenesis of specific disease-associated TM is related to its primary disease [16]. Thus far, our understanding regarding the pathomechanism of NPSLE is limited to the injuries resulting from vasculopathy [20], autoantibodies [21], cytokines and chemokines, and oxidative stress, nitric oxide, and interference with neurotransmission [22–25]. In 1975, a review of autopsy studies regarding the pathological changes in SLE-associated TM revealed various vascular changes within the spinal cord in 11 out of 12 cases. The abnormalities included ischemic necrosis, infarction or malacia in 8 cases, vasculitis without necrotic foci in 2 cases and degenerative lesions within the white matter with adventitia thickening in small arteries in 1 case. Vascular pathologies included perivascular lymphocytic infiltrations, proliferation of connective tissue, thrombi in small arteries and arterioles, and micro-extravasations within the spinal cord parenchyma [26]. The authors suggested that an autoimmunologic process was responsible for the vascular lesions in lupus myelitis. Other researchers demonstrated the presence of thrombosis, fibrinoid arteries, perivasculitis, spinal cord softening and peripheral white-matter degenerations at multiple spinal cord levels [27]. A more recent case report [2014] described the presence of intimal hyperplasia and obliteration of the small arteries and vasculitis (mononuclear cell infiltration and disruption of internal elastic lamina) in the affected case [28]. There are suggestions that the pathological damage in lupus-associated myelitis might be less prominent after intensive immunosuppressive therapy [29].

## 5. Magnetic resonance imaging

MRI is the modality of choice for the investigation of intramedullary lesions of the spinal cord. Both spinal and brain MRI are crucial in excluding spinal cord compression and in differentiating subtypes of acute demyelinating myelitis and other NPSLE disorders.

The detection of inflammatory lesion in the spinal cord can be facilitated by administering intravenous gadolinium on a T1-weighted image. However, the typical MRI appearance of ATM can be seen as a high intensity lesion detectable on a T2-weighted image, indicative of interstitial inflammation.

Under MRI, the affected spinal segments are described as "short" or "transverse" if less than 2–3 vertebral body segments are affected whereas "long" or "extensive" lesions involve more than 3 vertebral bodies. Both multiple sclerosis (MS) and neuromyelitis optica (NMO) may resemble ATM in its presentation. According to Weinshenker BG and co-workers [30], the involvement of more than three vertebral bodies was more common in NMO and helped to differentiate NMO from MS. In 2011, a panel committee of American Academy of Neurology endorsed the classification and recommended >3 vertebral bodies as a standard for the "longer" subtype of TM. Our group has reviewed the published literature regarding the length of spinal cord lesion of SLE-related ATM and MR imaging [31]. Among 63 cases of lupus-associated myelitis with MRI information, 71.4% of patients (45/63) had confirmed longitudinal lesion (more than three vertebral segments) whereas 28.6% (18/63) had transverse lesion (less or equal to three vertebral segments) [31]. Hence, it would appear that the spinal cord injury of SLE-associated ATM is more often longitudinal or extensive.

## 6. Laboratory testings

Besides MRI, the study of cerebral spinal fluid (CSF) is an established tool for detecting spinal cord inflammation. CSF pleocytosis and an increased Immunoglobulin G (IgG) index represent a classic inflammatory marker. Hence, both MRI and CSF studies may be used to ascertain inflammatory myelitis. Serological markers indicative of SLE include antinuclear antibodies (ANA), anti-double-strand antibody (anti-dsDNA), antibodies to extractable nuclear antigen (ENA), anti-Smith antibody (anti-Sm), and antiphospholipid antibodies (aPLs).

It was reported that 40–50% of NPSLE occurred in the presence of generalized disease activity of SLE [32]. It is important to look for activity of SLE by measuring full blood count, urinalysis, Coomb's test, complement profiles of C3, C4, CH50 and auto-antibodies. However, it was observed that SLE-ATM could occur in the absence of other disease activity [13,33]. In a case series of 370 SLE patients, myelitis was associated with a lower SLE Disease Activity Score and European Consensus Lupus Activity Measurement (ECLAM) contrary to other CNS involvement with higher activity score [15].

In our previous study [31], out of 94 patients with SLE-associated ATM and reported disease activities, 61 myelitis (64.8%) occurred during active disease (SLEDI > 4, or SLAM > 1) but 33 (35.1%) occurred during low lupus activity (SLEDI $\leq$ 4, or SLAM $\leq$ 1). It has been reported that SLE patients with ATM are more likely to possess aPLs. Moreover, aPL-induced thrombosis has been proposed as a major pathomechanism in the development of transverse myelitis in SLE [11,34]. According to a large prospective study, all major aPLs (anticardiolipin antibodies, lupus anticoagulant, and β2-glucoprotein-1 inhibitor) and their titers