Myelitis in Systemic Lupus Erythematosus: Clinical Features and Approach

Xiang Yang Li¹ and Pearl Pai*¹,²

¹Department of Nephrology, The University of Hong Kong-Shenzhen Hospital, China
²Department of Medicine, The University of Hong Kong - Queen Mary Hospital, China

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*Corresponding author: Pearl Pai, Department of Nephrology, The University of Hong Kong-Shenzhen Hospital, Shenzhen, Guangdong, China

Opinion

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder that can affect any organ tissue during disease process. SLE may influence the nervous system at multiple levels for which it is termed neuropsychiatric systemic lupus erythematosus (NPSLE). SLE associated myelitis is a severe but relative rare complication with a prevalence of around 1% among SLE population [1]. The neurological deficits of SLE associated myelitis comprise motor, sensory and autonomic dysfunctions. Motor symptoms include an acute or subacute paraparesis that can involve the upper extremities, with initial flaccidity followed by spasticity. Most patients have a sensory level. Typical sensory dysfunctions include pain, dysesthesia, paresthesia or sensory loss. Autonomic symptoms comprise bladder and bowel incontinence, difficulty voiding, constipation or incomplete evacuation, and sexual dysfunction. The signs and symptoms depend on the level and the extent of spinal injury.

The term "acute transverse myelitis (ATM)" describes a spinal sensory level rather than a "clear-cut" pathological or radiological lesion. Acute myelitis is categorized according to clinical severity and radiologic extent of the spinal cord lesion. Clinically, acute complete transverse myelitis indicates moderate or severe symmetrical weakness and autonomic dysfunction attributable to a spinal level. Acute partial transverse myelitis refers to mild bilateral or unilateral sensory and/or motor deficit. Under MRI, the myelitis is described as "transverse" if less than 3 vertebral segments are involved; injury ≥ 3 vertebral bodies is ascribed to "longitudinal" myelitis [2]. The diagnosis of SLE-associated myelitis is established when the acute myelitis occurred in the background of SLE and other secondary causes have been excluded. Other major secondary causes include CNS infection (e.g. virus or mycoplasma), other autoimmune disease (e.g. mixed connective tissue disease, Sjögren syndrome) paraneoplastic syndrome, neurosarcoidosis or other multifocal neurological disease (e.g. multiple sclerosis [MS] and neuromyelitis optica [NMO]).

Spinal cord MRI is the investigation of choice to detect acute myelitis in patients present with sensory, motor and autonomic dysfunctions. A typical MRI appearance of acute myelitis is a high intensity lesion on T2-weighted image. Gadolinium contrast administration facilitates detection of inflammatory lesion on T1-weighted MRI. Our group has reviewed the published literature regarding MR imaging of lupus myelitis [3]. Among 63 cases of SLE-associated myelitis, 71.4% of patients (45/63) had longitudinal lesion; whereas 28.6% (18/63) had transverse lesion. The cerebral spinal fluid (CSF) analysis is an established laboratory test to reflect spinal cord inflammation. Pleocytosis and an increased Immunoglobulin G (IgG) index of CSF represent classical inflammatory markers. But CSF abnormality is seen only in about one-half of patients of acute myelitis (with moderate lymphocytosis and an elevated protein level); and the rate of an elevated IgG index (CSF/serum IgG ratio) is even lower (21%) [4].

Further, MRI abnormality may not always correlate with clinical manifestations. In our above-mentioned case series, 4 patients showed delayed MR imaging changes of spinal cord damage. In our above-mentioned case series, there were 4 patients that showed delayed MRI manifestation of spinal cord damage. It is noteworthy that acute transverse myelitis can be the first presentation of SLE. Therefore, it is crucial to identify lupus and other secondary causes in the context of ATM. We use the 2012 Systemic Lupus
International Collaborating Clinics (SLICC) classification criteria and 1997 ACR (American Rheumatism Association) criteria for the diagnosis of SLE. These two classification criteria complement each other in terms of diagnostic accuracy [5]. Around 40-50% of NPSLE occurred in the presence of active SLE. However, lupus-related ATM may happen in the absence of active disease. Our study showed, out of 94 patients of SLE-associated ATM, 61 myelitis (64.8%) occurred in moderate to high disease activity (defined as SLEDI>4 or SLAM>1); but 33 (35.1%) appeared at low disease activity (SLEDI≤4, or SLAM≤1) [3]. The management of SLE-associated ATM has been mainly adopted from treatment of organ-threatening SLE and that of idiopathic inflammatory myelitis.

In the acute phase, treatment is aimed to suppress the inflammatory process and stop disease progression. Longer term goal is aimed to prevent cord damage or loss of function. Intravenous pulse methylprednisolone (0.5 to 1g/day for 3 days) and cyclophosphamide (800 to 1200mg/m2 administered as a single pulse dose) are commonly used as the first line therapy of SLE with major organ involvement [6] and in idiopathic ATM [7]. Glucocorticoids and immunosuppressive therapy are recommended by EULAR for myelitis [8]; addition of cyclophosphamide treatment improves treatment efficacy [8]. Other immunosuppressive agents have also been used in combination with glucocorticoids, which include mycophenolate, azathioprine, intravenous immunoglobulin (IVIG) and rituximab. Rituximab is reported to be effective in both new-onset and refractory myelitis. Positive benefits of plasma exchange (PE) have been documented in patients with NPSLE resistant to other immunosuppressive treatments [9], although its efficacy needs to be further verified in randomized controlled trials. After the induction therapy with high dose intravenous glucocorticoid and immunosuppressive agents, patients invariably need maintenance treatment comprising azathioprine, methotrexate, or mycophenolate in conjunction with low dose steroid. A retrospective study suggests a prolonged tapering-off and long-term maintenance therapy with low-dose steroid reduce disease relapse [10]. Maintenance immunosuppressive treatment is usually recommended for 3 or more years although the optimal duration is yet to be defined in this setting. There is yet no consensus regarding antiaggregation therapy in SLE-associated ATM. Antithrombotic management decisions remain primarily driven by the balance of risks between thrombosis and hemorrhage. The presence of more subtypes and a higher load of anti-phospholipid antibodies predispose to more thrombotic damage [11]. We may consider a target INR of 2.0-3.0 with the use of warfarin in lupus ATM complicated with anti-phospholipid syndrome; we may adopt a higher target INR of 3.1-4.0 where there is a high risk of arterial thrombosis or recurrent thrombosis [12].

At present, limited retrospective studies are available concerning the outcomes and prognosis of ATM on the background of SLE. Partial remission has been reported between 50%-62.5% complete recovery ranged 7.1%-27.8% with diverse observation period [1]. In up to 25%-66.7% of patients, the prognosis is unfavorable (with various degrees of tetraplegia, or paraplegia, sensory loss, sphincter dysfunction). There appears a link between the severity of the motor symptom at onset and poor prognosis. Rate of recurrence was reported between 21%-55% [1]. Earlier administration of effective anti-inflammatory therapy (e.g. glucocorticoids) were associated with better neurological outcome [13]. In summary, ATM is a relative rare association of SLE that often manifests as longitudinal myelitis on MRI. Lupus-related ATM may be the first manifestation of its primary disease and may occur at low disease activity of SLE. The treatment approach includes high dose glucocorticoid and intravenous cyclophosphamide, PE, IVIG, rituximab, and concomitant other immunosuppressive agents. The outcome of lupus associated ATM is variable and recurrent rate is high. Prolonged maintenance therapy with low-dose steroid is recommended to reduce disease relapse.

References