How to approach myelitis in systemic lupus erythematosus: A commentary

Xiang-Yang Li, Hai-Bing Xiao, Pearl Pai

Department of Nephrology and Neurology, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China; Department of Medicine, The University of Hong Kong – Queen Mary Hospital, Pokfulam Road, Hong Kong, China.

Abstract

Systemic lupus erythematosus (SLE) can affect the nervous system at multiple levels, among which SLE-associated transverse myelitis is an infrequent but potentially severe complication affecting around 1% of SLE population. To assist a timely diagnosis and optimal outcome, the clinical and radiological features, differential diagnosis (particularly with other central nervous system inflammatory demyelinating disorders), current therapeutic approach and the prognosis of SLE-associated myelitis are presented based on recent data and progress.

Keywords: Systemic lupus erythematosus; myelitis; transverse myelitis; diagnosis, therapy; prognosis

INTRODUCTION

Acute transverse myelitis (ATM) comprises a heterogeneous group of inflammatory spinal cord disorders characterized by acute or subacute motor, sensory and autonomic dysfunction. The term was first used in 1948 in its current connotation to describe paraparesis with a thoracic sensory level in a patient with postinfectious myelitis. It is now known that “transverse” here is meant to stress the characteristic spinal sensory level rather than pathologically or radiologically cross-sectional spinal cord injury. As always, ATM is ascribed as “idiopathic” when a causal factor is apparently missing; or as “secondary” disease when induced by pathogenic invasion, or occurs as a part of a CNS demyelinating disease, or of a systemic inflammatory disease (SID).

Systemic lupus erythematosus (SLE), among SIDs, can affect the nervous system at multiple levels. SLE-associated myelopathy, one of the 12 CNS neuropsychiatric systemic lupus erythematosus (NPSLE) syndromes, defines neurological deficits resulting from spinal cord impairment attributable to the pathogenesis of SLE. Since spinal cord compression or infarction (due to anterior spinal cord artery thrombosis) are uncommon conditions of lupus, myelitis is the prototype of myelopathy in SLE. According to the literatures of the 1990s, SLE-associated acute transverse myelitis (SLE-ATM) is a severe but uncommon complication of lupus with a prevalence of around 1 to 2%. Based upon pooled analysis of 17 studies published after year 2000, Unterman et al. reported a incidence of 0.9% ATM among 5057 SLE patients, and the frequency ranged 0.4 to 2.1% in cohorts of more than 200 (282 to 1695) cases. In addition to lupus, other SIDs that can give rise to ATM include Sjögren syndrome, sarcoidosis, ankylosing spondylitis, antiphospholipid syndrome, Behçet disease, mixed connective disease, rheumatoid arthritis and systemic sclerosis. Given a higher prevalence of lupus in the general population and a smaller literature volume of acute myelitis related with non-lupus SIDs, SLE is held to be the commonest condition underlying SID-associated ATM.

THE COMMON CLINICAL PRESENTATION OF ATM?

Clinical presentations of myelitis arise from the parenchymal impairment and/or interruption in the descending and ascending spinal tracts. The clinical phenotype and severity of ATM are compatible with the scope and extent of damages in the transverse and longitudinal planes of the spinal cord. ATM typically presents with...
acute or subacute development of neurological deficits characterized by motor, sensory, and autonomic dysfunctions. Motor symptoms include progressing paraparesis or quadriplegia corresponding to the level of the spinal lesion. The initial flaccidity is often followed by spasticity and hyperreflexia if the white matter/corticospinal tract is involved. In the case of spinal gray matter/lower motor neuron injury, the paraparesis develops more rapidly and has a high probability to progress to persistent flaccidity and hyporeflexia. Common sensory disturbances encompass dysesthesia, paresthesia and pain. Most patients have a sensory level. Autonomic symptoms involve increased urinary urgency, bladder and bowel incontinence, difficulty or inability to void, incomplete evacuation with bowel constipation, and sexual dysfunction.

HOW IS ATM CLASSIFIED CLINICALLY?

As mentioned above, the symptoms and signs of ATM are in keeping with the profundity of the spinal cord injury. ATM is clinically classified into the acute complete transverse myelitis (ACTM) and acute partial transverse myelitis (APTM), or into gray matter or white matter myelitis. ACTM refers to paralyzing moderate or severe symmetrical loss of function distal to a spinal level; APTM describes incomplete or patchy involvement of one or more spinal segments with mild to moderate weakness, asymmetric sensory symptoms and occasional autonomic involvement. A gray matter myelitis is characterized by acute deteriorating flaccid paralysis associated with anterior horn cell injury; the white matter myelitis features upper-motor neuron spasticity and hyperreflexia with less severity and slower progression of paralysis. Either classifications may assist differential diagnosis, clinical decision and prognosis prediction.

HOW IS ATM CLASSIFIED RADIOLOGICALLY?

MRI examination of the spinal cord is clinically critical to the diagnosis and classification of ATM. The MRI appearance of ATM without contrast reveals a high intensity lesion on T2-weighted image. Gadolinium contrast enhances the display of tissue inflammation on T1-signal image. Radiographically, ATM is classified as “short” transverse myelitis (STM) if the spinal cord injury on MRI spans 1 to 2 vertebral segments; or as longitudinally extensive transverse myelitis (LETM), if the spinal cord MRI lesion extends at least 3 vertebral segments. Upon reviewing of the published literature concerning MR imaging of lupus myelitis, our previous investigation found that 71.4% (45/63) SLE-ATM had a longitudinal form of myelitis (defined as spanning 4 or more vertebral bodies on MRI), while the rest (28.6%, 18/63) spanned 3 or less vertebral bodies. It is noteworthy that MRI findings may not always be present at the onset of SLE-ATM. There were 4 patients with delayed MRI anomalies in this study.

HOW TO APPROACH AN INITIAL DIAGNOSIS OF SLE-ATM?

A diagnosis of SLE-ATM is established only when myelitis occurs in the context of SLE and other secondary causes are excluded. To facilitate the diagnosis of lupus, the 2012 SLICC (Systemic Lupus International Collaborating Clinics) classification criterion and 1997 ACR (American Rheumatism Association) criterion can be used in combination, the two criteria is complementary to each other in terms of diagnostic sensitivity (SLICC) and specificity (1997 ACR). It is notable that ATM can be the first presentation of SLE and may happen in the absence of active lupus. Our aforementioned pooled analysis, based upon the published case series or cases, showed 21% (12/58) of SLE-associated ATM patients had acute myelitis as the initial symptom of SLE (though publication bias of unusual or severer disease could not be ruled out). Moreover, 64.8% (61/94) ATM attacks occurred in the background of moderate to high disease activity, the other 35.2% (33/94) came forth at low activity of SLE (SLEDAI≤4). In addition to presenting symptoms, past history, imaging study, routine serum and cerebral spinal fluid (CSF) tests, panels of infectious, rheumatological and neoplastic disorders are essential to distinguish SLE-ATM from other secondary myelitis. An algorithm facilitating the diagnosis and differential diagnosis of SLE-ATM is proposed in Figure 1.

THE USEFULNESS OF CSF TEST IN SLE-ATM?

Aside from MRI, the CSF analysis of pleocytosis/elevated protein and increased Immunoglobulin G (IgG) index are established testings of spinal cord inflammation. But as in many other inflammatory myelopathy, CSF abnormality in terms of pleocytosis/elevated protein level in SLE-ATM has limited sensitivity and specificity and shows variable rate of positivity.
Noticeably, in a 10-year prospective study, West et al. documented an elevated IgG-index in 60% (30/50) of neuropsychiatric lupus erythematosus (NPLE) hospital patients; and CSF oligoclonal band (OCB) was detected in 48% (24/50) of this cohort (including 3 SLE-ATM patients).  

**HOW TO DIFFERENTIATE SLE-ATM WITH OTHER CNS INFLAMMATORY DEMYELINATING DISORDER (IDDs)?**

At present, the pathogenesis of SLE-ATM is thought to be related with autoantibodies, cytokines and chemokines, vasculopathy or vasculitis, and other factors. Although the pathophysiology of SLE-ATM or other CNS-IDDs remain elusive, growing evidences reveal they are induced by diverse routes via distinct pathological pathways, are thus regarded as disparate entities bearing overlapping clinical symptoms. In practice, therefore, a challenging but indispensable step is to discriminate SLE-ATM from other CNS demyelinating diseases, namely multiple sclerosis (MS), neuromyelitis optica spectrum disease (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated encephalomyelitis (MOG-EM), and acute disseminated encephalomyelitis (ADEM), in which acute myelitis may represent a part of the disease. A detailed discussion of differential diagnosis between these entities is beyond the scope of this article, while a number of recent advances concerning the mechanism and traits of these entities deserve to be mentioned.

**MULTIPLE SCLEROSIS**

MS is a CNS-limited, autoreactive lymphocyte-mediated inflammatory disorder that can affect the cerebrum, brain stem/cerebellum, spinal cord and optic nerve in isolation or in an accumulative progressive manner. It is the most common demyelinating/dysmyelinating disease in western countries. MS frequently manifests as a relapsing-remitting clinical course, and disease deterioration...
is considered slow in most cases. Optic neuritis (ON) in MS is typically unilateral and the MRI lesions of the brain, brainstem and spinal cord are characterized by dissemination in space and time. Acute myelitis in MS is most often STM (<3 vertebral segments). SLE distinguishes itself from MS by positive serology (e.g., ANA, anti-dsDNA, anti-Sm and hypocomplementemia), multiorgan involvement, and frequent LETM if spinal cord is affected. ON is rare in SLE and is typically bilateral when present. In MS, serum ANA is usually negative or low in titer (≤1:160), and the anti-phospholipid antibodies (aPL) are generally absent. Although OCB in CSF alone is not diagnostic of MS, the positivity rate is around 85-95%, significantly higher than in SLE (indicated above). One of the clinical challenges is the coexistence of SLE and MS in a single patient. But the overlap is rare and the two entities commonly occur one after another rather than concurrently with intervals ranging from 2 to 16 years.

**NEUROMYELITIS OPTICA SPECTRUM DISEASE**

NMOSD is a comparatively severe CNS demyelinating disease frequently affecting optic nerves, spinal cord, as well as brain. Considering a prevalence of around 5 to 100 per million, this disorder is clinically commoner than SLE-ATM (estimated by 1% incidence of 200 to 1500 per million of SLE in the general population). NMOSD usually presents with unilateral ON, or rapidly sequential ON, ATM, or area postrema syndrome. Serum aquaporin-4 (AQP4) IgG antibody plays a direct pathogenic role and acts as the serological hallmark of NMOSD; and its serum AQP4-IgG is confirmed in a patient with NMOSD. When serum AQP4-IgG is confirmed in a patient with NMOSD, it is invariably ascribed to NMOSD.

**MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED ENCEPHALOMYELITIS**

MOG is a member of the immunoglobulin superfamily and is expressed solely at the surface of myelin sheath and oligodendrocyte membrane in the CNS. MOG-EM defines a CNS demyelinating impairment directly associated with MOG-Ab-related inflammatory injury. It may show one or more symptoms of ON, ATM, brainstem/brain encephalitis, or ADEM-like syndrome. High serum MOG-Ab (predominantly MOG-IgG) titer is associated with disease activity and relapse, a persistent MOG-Ab seropositivity predicts future recurrence. The diagnosis of MOG-EM is based upon a positive serum MOG-IgG, evidence of CNS demyelination and exclusion of alternative diagnoses. Thereupon, it is invariably necessary to test MOG-IgG in the setting of CNS demyelinating syndrome. Clinically, optic nerve is frequently affected in MOG-EM and is often bilateral. Isolated ATM was found to be the initial presentation in 53.7% (29/54) of MOG-Ab related ATM (MOG-ATM) patients, and LETM is common (72.3%) in MOG-ATM which is comparable to that in AQP4-IgG myelitis (82.4%). And accumulating evidence showed some of the MOG-Ab positive ON or MOG-EM had multiphasic and relapsing-remitting disease course that were highly responsive to steroid therapy, but were susceptible to recurrence on steroid reduction or discontinuation.
Although CBA has improved the sensitivity and specificity of MOG-IgG determination, intricately, a high prevalence (69%) of seropositive MOG-IgG (≥1:160) was documented in 210 pediatric patients with initial diagnoses of ADEM, AQP4-IgG negative NMOSD, or MS. While the overall specificity of MOG-Ab was 98.5%; the overall sensitivity of MOG-Ab in MS was 5.1%, 36.4% in ADEM, and 26.9% in AQP4-IgG negative NMOSD (reviewed in Peschl et al.30). The detection of MOG-IgG in seropositive NMOSD is uncommon, ranging from 1.3% (1/75) to 2.0% (1/51), that fell within the range of MOG-Ab positive rate in disease or healthy controls (1.2-3.4%). And MOG-IgG can also be detected in serum of SLE population. Probstel et al. found in their retrospective cohort that 8% (14/174) of SLE patients had seropositive MOG-IgG, of which 12 were positive at baseline, 6 patients had persistent seropositivity, and 2 cases developed MOG-Ab during follow-up period. Interestingly, only 2 of these 14 cases demonstrated neurological impairments: 1 had asymptomatic MRI lesions in the brainstem and brain, the other had seizure with cerebral imaging abnormality. The effect that MOG-IgG exerted on these 14 lupus patients remained arguable, but the finding of Probstel and colleagues did propose the key questions: under what condition is MOG-IgG pathogenic? How to interpret MOG-IgG positivity in diverse clinical settings? One presumption is that MOG-IgG is not neurotoxic until it enters the CNS. Yet neuropathological studies of MOG-IgG positive CNS lesions frequently showed features of MS pattern II, which is inadequate to effectively discriminating MOG-EM with MS, NMOSD, or LETM. Attempts have been made in this respect. Dubey et al. communicated, based upon the data of Mayo Clinic from 2000 to 2017, that as compared with AQP4-IgG myelitis, the MRI of MOG-myelitis had a higher rate of T2-signal abnormality that confined to the gray matter (sagittal line and axial H sign, 29% v.s., 8%, P=0.002), and had a significantly lower rate of gadolinium enhancement (26% v.s., 78%, P<0.001). More recently, a 32-year-old postpartum SLE patient was diagnosed MOG-ATM on the basis of positive MOG-IgG (with a serum titer of 1:20; normal, <1:20) and non-enhancing LETM on MRI, seronegative AQP4-IgG, negative CSF OCB and IgG index. The patient had radiological improvement after administration of methylprednisolone pulse, plasma exchange, and sequential prednisone and azathioprine, but she was still paraplegic at 8 months after onset.38 We think the diagnosis of MOG-ATM in this case was debatable in light of a marginal MOG-IgG titer and, above all, clinical unresponsiveness despite negative MOG-IgG after intensive immunosuppression, including pulse steroid, that is non-characteristic of MOG-ATM. A practical way, the authors of this article would recommend, is to reduce or eliminate serum MOG-IgG when feasible by applying immunosuppression in the presence of neurological damage or a clinical high risk settings (e.g., persistent high MOG-IgG titer and/or diagnostic uncertainty).

**ACUTE DISSEMINATED ENCEPHALOMYELITIS**

Despite inadequately understood pathogenesis, ADEM is known to be an autoimmune demyelinating disorder of the central nervous system commonly triggered by viral infection, and to a lesser extent, after vaccination among genetically susceptible patients. It usually occurs among children and the disease course is typically monophasic, yet multiphasic and adult-onset phenotypes are occasionally seen. ADEM is an infrequent disease with no specific biomarker, and it exhibits substantial overlaps with MS, NMO, or MOG-EM in terms of clinical presentation and neuroimaging, therefore, the diagnosis of ADEM is largely exclusive. Around 20-24% of ADEM cases had spinal cord involvement which were predominantly longitudinal myelitis (extending >3 vertebral segments). To assist differentiation between SLE-ATM and ADEM, the latter generally occurs after viral infection and typically affects children, less than 1/4 of cases have spinal cord involvement. SLE-ATM is characterized by adult-onset, female predominance, and systemic involvement with positive serum auto-antibodies. MRI image of the brain can sometimes be referenced for their discrimination. Lupus cerebral involvement, when present, is characterized by small focal white matter lesions and cortical atrophy (resulting from small vessel disease), but about 43% of cases also had diffuse white matter abnormalities.43 While in ADEM, brain MRI typically shows ill-defined and large white matter lesions; though uncommon, solitary or multiple small lesions had also been reported in this disorder.

**HOW TO APPROACH THE MANAGEMENT OF SLE-ATM?**

SLE-ATM is generally an organ- or life-
threatening complication of lupus. Given the low prevalence of the disease, high-grade evidence to guide its treatment is limited. The managements commonly aim at (1) suppressing the inflammatory process to minimize spinal cord damage in acute phase; and (2) preventing disease progression and optimizing organ function and (3) improving overall long term survival.

Intensive, individualized immunosuppressive therapy at induction is essential to achieve rapid anti-inflammatory effect and organ protection. Intravenous pulse methylprednisolone (0.25 to 1 g/day for 1-3 days) and cyclophosphamide are established therapy for organ-threatening SLE (including NPSLE). In addition, other immunosuppressive agents or modalities, in conjunction with glucocorticoids, have also been used during induction. These treatments include mycophenolate mofetil, intravenous immunoglobulin (IVIG), rituximab, and plasma exchange (PE). Mycophenolate is known as an alternative to cyclophosphamide for induction and/or maintenance therapy. IVIG is shown to be beneficial in chronic inflammatory demyelinating polyneuropathy and Guillain-Barré syndrome occurring in the context of SLE and other rheumatic diseases, but there is a lack of high-quality evidence of such benefit accrued in lupus myelopathy. PE has been shown to produce better outcome when used with pulse steroid in idiopathic transverse myelitis and is often used as a salvage treatment in SLE with severe organ injury. The use of rituximab in combination with pulse methylprednisolone has been reported as effective in a small group of new onset SLE-ATM patients (4 out of 6), with complete response at 12 months. The same combination has been also effective in the management of NPSLE refractory to intensive immunosuppressive treatment, but the effectiveness of rituximab in SLE-ATM needs further validation. The maintenance treatment of SLE-ATM is intended to consolidate remission and to achieve the lowest possible disease activity while minimizing drug toxicity. The maintenance therapy typically includes low dose steroid plus hydroxychloroquine and another immunosuppressive agents, such as mycophenolate, azathioprine or methotrexate. The authors of this article would recommend the duration for maintenance therapy of 3 or more years though the optimal term has not been agreed upon. There is currently no consensus regarding anticoagulation therapy in SLE-associated ATM. Antithrombotic therapy is warranted in the presence of anti-phospholipid syndrome, or in patients with more aPL subtypes or a higher load of aPL. According to emergent evidence, warfarin is preferable to direct oral anticoagulants (DOACs), especially among patients carrying high thrombotic risks (triple positivity of aPL and/or arterial thrombosis).

**WHAT IS THE PROGNOSIS OF SLE-ATM?**

At present, there are limited retrospective reports with reference to the outcomes and prognosis of SLE-associated ATM. Complete recovery reportedly ranged between 7.1% and 66.7% with various onset severity and diverse observation period; partial remission was between 50% and 62.5%. The prognosis was unfavorable in up to 25% to 66.7% of patients (with various degrees of motor, sensory, or autonomic dysfunction). A higher severity of motor symptom at disease onset has been associated with poor prognosis. Earlier administration of effective anti-inflammatory therapy (e.g., glucocorticoids) is observed to be associated with better neurological outcome.

The recurrence rate of SLE-ATM was considered high ranging between 21% to 55%. A single-center study by Ahn et al. showed that a long taper and long-term maintenance treatment with low-dose steroid reduced disease relapse.

Data from a newly published multicentral retrospective study containing 60 SLE-ATM Latin American patients suggested hypoglycorrhachia, hypocomplementemia, aPL positivity were the prognostic factors of disease relapse at 1 year; administration of 6 or more cycles of intravenous cyclophosphamide was associated with delayed recurrence. But it is noteworthy, despite good short-term functional outcome could be achieved upon existing regimen, there might be increased long-term mortality mainly resulted from sepsis or serious infection. Due to the lower incidence of SLE-ATM, multicentral cohorts or even national registries are needed to sort out predictive factors and therapeutic principles of the disease.

**CONCLUSION**

ATM is a relative rare but potentially life-threatening condition associated with SLE. SLE-ATM often manifests as LETM on MRI; it may present as the first manifestation of lupus and sometimes occurs at low disease activity. A diagnosis of lupus-ATM is established only after myelitis is attributable to lupus, and other secondary ATM and CNS inflammatory demyelinating disease are excluded. The induction therapy favors intensive combined
immunosuppressive therapy on an individualized level followed by stable maintenance therapy of appropriate strength and duration. The outcome of SLE-ATM is variable and the recurrent rate is relatively high. In managing complex immune diseases, we need to pay great attention on how to control the disease activities while minimizing the potential serious treatment-related adverse reaction and complications.

DISCLOSURE
Conflict of Interest: None

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