

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

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Abstract

Introduction: The American College of Rheumatology recognizes 19 main forms of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). Acute confusional states, cerebrovascular disease, peripheral neuropathies and seizure are the most common. We report a rare case of SLE-related myelopathy in teenager girl.

Case report: 16 years-old teenager girl, with no previous health history, presented 8 days before her admission, rapidly progressive flaccid tetra paresis with paresthesia and sphincter disturbance. These symptoms were associated to polyarthritis and facial lupus discoid lesion. Spinal MRI objectified Longitudinal Extensive Transverse Myelitis (LETM) to more than 12 vertebral segments. Cerebrospinal Fluid (CSF) showed normal cytology with mild high protein level (0.8 g/l). Immunologic tests went positive to anti-nuclear and anti-DNA antibodies, with negative anti-aquaporin 4 and anti-MOG antibodies. Several infectious serologies went negative. The diagnosis of acute LETM secondary to NPSLE was established. The patient was treated by bolus methylprednisolone and cyclophosphamide, relayed by oral prednisolone. The course was favorable with clinical and radiological improvement, apart from sequellar spinal atrophy on the MRI.

Discussion: Neuropsychiatric Systemic Lupus Erythematosus (NP SLE) is one of the most challenging forms of SLE, as one-third of patient with NPSLE are primary manifestation of lupus autoimmunity. Lupus myelitis is occurring in 1 to 2% of SLE patients. In above 22% of reported cases, LETM was the revealing syndrome of SLE. Several differential diagnoses cause LETM, and must be eliminated according to clinical peculiarities and adequate para clinical tests (infection, neuromyelitis optica spectrum disorders, Sjogren's syndrome, paraneoplastic syndrome). Early methylprednisolone bolus and cyclophosphamid have shown better prognosis with sensori-motor and sphincter improvement.

Conclusion: LETM may be the initial presentation of NPSLE. The absence of other systemic symptoms makes the diagnosis a real challenge. This went to procession of clinical and biological arguments. Randomized studies should be led, to report clear guidelines concerning therapies and prognosis.

Keywords: Neuropsychiatric Systemic Lupus Erythematosus (NPSLE); Longitudinally Extensive Transverse Myelitis (LETM); Lupus discoid; Neuromyelitis Optica Spectrum Disorders (NMOSD); AQP4 antibody

Introduction

For unknown reason, a roman family living in central France in A.D 600 years, with man named LUPUS (meaning "wolf" in Latin), attributed his name to the disease [1]. Systemic Lupus Erythematosus (SLE) is a worldwide distributed disease, with autoimmune reaction, producing auto-antibodies to nuclear antigens, with complement fixing other complex. The result is multiple asynchronous and incomplete tissues damaging. These conditions make SLE the "disease with multiple faces" and a broad spectrum of clinical manifestation [2]. Its prevalence is estimated to 100-150 per 100.000 people, with sex ratio female: male above 9:1, and a peak incidence between 15 and 40 years-old [3]. The incidence is above 1 to 15 per 100.000 people per year [3] and becomes higher in blacks, Hispanic and Asian patients compared

to Caucasian [4]. Hormonal, genetic and environmental factors contribute in complex interaction, with loss of self-tolerance, but the exact pathogenesis are still unknown. The course of the disease is variable, ranging from mild to fatal. Three forms were described: relapsing-remitting, chronic active and long quiescence [5]. Neuropsychiatric SLE (NPSLE) is one of the most challenging forms of SLE, as one-third of patient with NPSLE are primary manifestation of lupus autoimmunity. The American College of Rheumatology (ACR) recognizes 19 main forms of NPSLE that occur central, peripheral and autonomic nervous system. Acute confusional states, cerebrovascular disease, peripheral neuropathies and seizure are the most common [6]. CSF protein and cell count, oligo-clonal bands, and CNS MRI are traditional biomarkers of NPSLE. We report a case with rare form of NPSLE with central nervous system involvement.

Case Report

A 16 years-old girl teenager, right-handed, with no previous health history, reported eight days before her admission, rapidly progressive weakness of both lower limbs, starting with reduction of walking

perimeter (<50 m), then aggravation of weakness making her bedridden, with extension to both upper limbs.



Figure 1: Butterfly wing erythematous aspect, papilla-macular and moderately squamous rash, without pruritus, localized in photoexposure zones: Nose Bridge, cheeks, upper lip and neckline.

This was associated to paraesthesia in four limbs with bladder disorders (dysuria) evolving in feverish context. She also reports acute mild diffuse inflammatory arthralgia evolving three days before the admission, with photo sensibility over her face. There was no other extra-neurological functional symptom (ophthalmologic, respiratory, cardiac, digestive), as no infectious focalization sign.

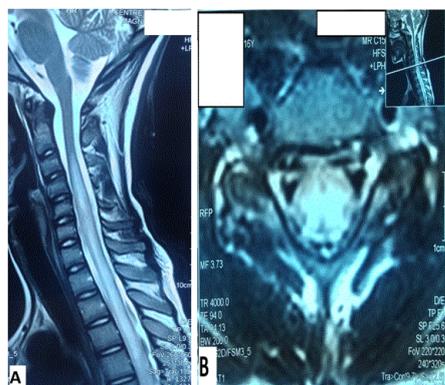


Figure 2: (A) MRI of the spinal cord, in sagittal T2 weighted image, showing enlargement with increased signal intensity extended longitudinally to more than 12 vertebral segments; (B) MRI of the spinal cord, in axial T2 weighted image, showing increased signal intensity extended transversally to more than 50% of the spinal cord large diameter.

General examination found consciousness girl, with supple neck. Her hemodynamic and respiratory parameters were stable. Neurological examination found: flaccid tetra paresis quoted to 1/5 in lower limbs and 2/5 in upper limbs; bilateral Babinski with sensory level at C4. Articulation was sensible with positive squeeze test, but with no effusion. Skin inspection revealed discoid lupus dominating over the face (Figure 1). The clinical syndrome was acute myelopathy associated to fever, polyarthritides and facial discoid lupus in teenager girl.

Spinal cord MRI showed increased signal intensity on T2 and FLAIR weighted images. The signal was extended transversally over more than 50% of the large spinal cord diameter and longitudinally through more than 12 vertebral bodies (Figure 2).

Cerebral MRI was normal. Lumbar puncture was performed. The Cerebrospinal Fluid (CSF) study found no cell, with mild elevated protein (0.88 g/l) without intrathecal I_gG synthesis or oligo clonal bands. Biologic inflammatory syndrome was objectified with elevated erythrocyte sedimentation rate (ESR: 28 mm at first hour), C-reactive protein (CRP=30 mg/l) and gammaglobulinemia.



Figure 3: Control MRI of the spinal cord, in sagittal T2 weighted image, showing the regression of the increased signal intensity, and the dorsal spinal atrophy extended to 5 vertebral segments.

Complete count blood (CCB) was normal. Joints X-ray showed no erosion, and chest one was normal. Multiple serologies were performed and went all negative (Tuberculosis, Epstein-Bar virus, Herpes simplex virus, cytomegalovirus, hepatitis B and C, VIH, syphilis, borreliosis and brucellosis). Plasmatic level for B12 and folic acid were normal, as much as angiotensin converting enzyme, phospho-calcic and cooper level in blood and urine. The salivary gland biopsy study was normal. The anti-AQP4 antibodies were tested by cell based assay in plasma and went negative. Secondary, the anti-MOG antibodies test went negative too. Cortical and retinal waves were normal in latency and amplitude in the Visual Evoked Potential (VEP) study. Immunologic

tests were performed and showed positive anti-nuclear antibody and anti-DNA anti-body whit high titers.

Thus, clinical and biological tests fulfill the 1997 ACR criteria and the diagnosis was acute longitudinally extensive transverse myelitis secondary to systemic lupus erythematosus. Patient was treated by bolus corticosteroid (three days methylprednisolone 1 g/d) and cyclophosphamide (three months 600 mg/m²/month), relayed by oral corticotherapy: prednisolone 1 mg/kg/d for 6 weeks than progressive depression till the lowest effective dose: 10 mg/d, with adjuvant treatment (vitamin D; calcium and potassium supplementation). Evolution was favorable with complete regression of paresis in upper limbs, sphincter disorders and facial discoid lupus. Sequelar spastic paresis quoted to 4/5 of both lower limbs was objectified in the control at month 6, 12 and 18. Controlled ESR, CRP, CCB and anti-DNA antibodies went normal. Control of spinal MRI at moth 6 showed regression of abnormal signal, with longitudinal spinal atrophy from D8 to D12 (Figure 3).

SLE is a worldwide distributed autoimmune disease that affects 5 million people [7]. The exact pathogenesis of SLE remain unknown, but complex multifactorial interaction are suspected: when patient obtains critical dose of susceptibility genes and get exposed to complex environmental factors within infection, ultraviolet light, drugs, chemicals, hormones, stress; these conditions lead to antigen alteration to more immunogenic forms, with exposure to high quantities of apoptotic cells, molecular mimicry, auto-antigen epitope spreading. The T-cells become abnormal too and get activated with fewer antigens, more reactive, resistant to apoptosis with abnormal receptor engagement. This context results in increased B cells and thus in pathogenic auto-antibody and immune complexes formation. The reticulo-endothelial system fail in cleaning immune complexes, become more permissive to auto-antibodies, which cause damages in targeted tissue including central, peripheral and autonomic system [8,9]. Lupus myelitis is one of the rare presentation of SLE, occurring

in 1 to 2% of patients, thus few patients have been documented worldwide [10]. The usual clinical presentation evolves in less than 4 weeks, and involves limbs bilaterally with both sensor and motor deficits remarked below the spinal level and sphincter disturbances. Once the clinical syndrome of acute myelopathy is evoked, the spinal MRI become crucial, with two sensitive sequences: T2 weighted image (normal at the onset, or showing increasing signal or spine enlargement), and intravenous gadolinium administration in T1-weighted image (showing gado enhancement). The MRI defines two forms: the most described one in NPSLE is acute transverse myelitis with the extension of the lesion transversally to more than 50% of the spine; On the other hand, Longitudinally Extensive Transverse Myelitis (LETM) is more exceptional, especially as revealing form of SLE. The MRI definition of LETM adds a second criterion: the longitudinally extension of the lesion to more than 3 vertebral segments. The first case series was reported by Tellez-Zenteno and Al in 2001 [11]. In above 22% of reported cases, LETM was the revealing syndrome of SLE [12]. In front of LETM MRI defined case, the survey follows an explorative strategy recommended by expert including: WBC, PT,PTT, CRP, liver and kidney test, serology hepatitis B, C, HIV, anti-AQP4, CSF study, cerebral MRI. The second phase tests depend on the clinical context. According to test results, LETM etiologies are devised to three groups: infectious, auto-immune and paraneoplastic [13-17]. In our case, auto-immune etiology was suspected by the synchronous multisystem involvement (polyarthritits, lupus discoid, LETM, fever) and the positivity of auto-antibodies (AAN, Anti-DNA). Thus, referring to ACR and SLICC criteria, we had enough argument to retain the systemic lupus erythematosus (Table 1). CSF study in NPSLE usually reveals lymphocytic pleocytosis with high protein level. The contribution of positive anti-phospholipids antibodies (aPL) to more frequent and severe neurological involvement is now well established [13]. aPL were negative in our case, explaining in part the good prognosis under treatment.

Clinical criteria
1. Acute cutaneous lupus including:
• Lupus malar rash (do not count if malar discoid)
• Bullous lupus
• Toxic epidermal necrolysis variant of systemic lupus erythematosus (SLE)
• Maculopapular lupus rash
• Photosensitive lupus rash
in the absence of dermatomyositis
• or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus including:
• Classical discoid rash
• Localized (abovethe neck)
• Generalized (above and below the neck)
• Hypertrophic (verrucous) lupus
• Lupus panniculitis (profundus)

• Mucosal lupus
• Lupus erythematosus tumidus
• Chillblains lupus
• Discoid lupus/lichen planus overlap
3. Oral ulcers:
• Palate
• Buccal
• Tongue
• Or nasal ulcers
in the absence of other causes, such as vasculitis, Behcets, infection (herpes),inflammatory bowel disease, reactive arthritis, and acidic foods
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia
5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness.
6. Serositis:
• Typical pleurisy for more than 1 day
• Or pleural effusions
• Or pleural rub
• Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
• Or pericardial effusion
• Or pericardial rub
• Or pericarditis by EKG
in the absence of other causes, such as infection, uremia, and Dressler's pericarditis
7. Renal:
• Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein/24 hr or
• Red blood cell casts
8. Neurologic
• Seizures
• Psychosis
• Mononeuritis multiplex
in the absence of other known causes such as primary vasculitis
• Myelitis
• Peripheral or cranial neuropathy
in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
• Acute confusional state
in the absence of other causes, including toxic-metabolic, uremia, drugs
9. Hemolytic anemia

10. Leukopenia (<4000/mm ³ at least once)
in the absence of other known causes such as Felty's, drugs, and portal hypertension
or lymphopenia (< 1000/mm ³ at least once)
in the absence of other known causes such as corticosteroids, drugs and infection
11. Thrombocytopenia (<100.000/mm ³) at least once
in the absence of other known causes such as drugs, portal hypertension, and TTP
Immunological criteria
1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range
3. Anti-Sm
4. Antiphospholipid antibody: any of the following
• Lupus anticoagulant
• False-positive RPR
• Medium or high titer anticardiolipin (IgA, IgG or IgM)
anti-beta2 glycoprotein I (IgA, IgG or IgM)
5. Low complement
• Low C3
• Low C4
• Low CH50
6. Direct Coombs test in the absence of hemolytic anemia

Table 1: 1997 update of the 1982 American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [27] 4 items are necessary for diagnosis, with at least 1 clinical criterion and at least 1 immunological criterion. EKG: electrocardiogram; ANA: antinuclear antibodies; Ig: immunoglobulin; RPR: rapid plasma reagin; TTP: thrombotic thrombocytopenic purpura.

Several differential diagnoses cause LETM, and must be eliminated according to clinical peculiarities and adequate para clinical tests. According to epidemiologic study analyzing articles from 1981 to 2009, done by Bhat and Al, infectious disease remains the main etiology of acute transverse myelitis, and 20 to 24% of all infectious causes are viral (CMV, Hepatitis A virus, HSV, enterovirus) [14]. Viral serologies went negative in our patient. LETM also figures in the core clinical syndrome of neuromyelitis optica spectrum disorders (NMOSD) according to the 2015 guidelines of International Panel of Neuromyelitis Optica Diagnosis (IPND) [15]. In our observation, the patient did not report any specific sign evoking NMOSD: area postrema syndrome, optic neuritis, altitudinal hemianopia, narcolepsy, tonic painful spasm, neuropathic pruritus. Moreover, anti-AQP4 and anti-MOG were negative. There were no additional demyelinating lesion on cerebral MRI, and no optic demyelinating neuritis on VEP study. So she did not fulfill criteria for NMOSD. Transverse myelitis may occur in patients with Sjogren's syndrome (SS) [16]. Also SS may be associated to SLE. In our case, there were no xerostomia or xerophthalmia. Salivary biopsy study was normal, and anti-SSA/SSB antibodies went negative. These were enough arguments to eliminate this association.

Concerning therapy, there have been no randomized controlled studies, due to few number of cases. Therefore, glucocorticoids are usually used as monotherapy, with initial intravenous bolus of methylprednisolone (1 g/d for 3 to 5 days). In severe form or persistent symptom at day 3 or 4 of bolus, immunosuppressant must be delivered, such as cyclophosphamide as first line therapy. This aggressive therapy, once introduced early during the first 2 weeks, have shown better prognosis with sensori-motor and sphincter improvement [18,19]. In our case, methylprednisolone bolus and cyclophosphamide were both used, with clinical and radiological improvement (apart from spinal atrophy and mild para paresis). Other therapies have been used in severe cases with variables responses, such as intravenous immunoglobulin, plasma exchange and rituximab [20-22]. The presence of aPL with thrombosis history impose anticoagulation therapy as curative and prophylactic from recurrent episode.

Prognosis depends on the pathogenesis mechanism behind the SLE related myelopathy. These pathogenesis stay poorly understood. Nevertheless, three hypothesis explain the different course of myelitis in SLE: 1-vascular ranging from perivasculitis to thrombosis; 2-subdural hematoma without vasculopathy; 3- subpial leukomyelopathy defined as peripheral white-matter degeneration at multiple spine levels. The last mechanism seems to be the most common with better

prognosis [23,24]. Apart from these pathogenesis, the course of LETM in NPSLE also depend on the severity of initial neurological presentation, the extent of the spinal cord lesion on MRI and the speediness of adequate therapy. Thus, sphincter disturbance, gray-matter involvement (hyporeflexia and flaccidity) and delayed therapy predict worst outcome [25,26]. Our case presented both clinical signs predicting poor prognosis with MRI extent lesion, however she had favorable course due to prompt and adequate therapy, with the hypothesis of subpial leukomyelopathy rather than other mechanisms [27].

Conclusion

We learn from this case report that LETM may be the first presentation of NPSLE, and the diagnosis in these cases is hardest, and went to procession of clinical and biological arguments. The initial neurologic presentation may be severe, predicting unfavourable outcome. However, an adequate early immune therapy could improve the state. Randomized studies should be led, to report clear guidelines concerning therapies and prognosis.

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