

Lupus myelopathy

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A 35 year-old right-handed woman presented in April 2016 with an upper respiratory tract infection and recent fatigue. No rash or joint symptoms were reported. Her father was Ghanaian and her mother was white British. The patient had travelled to Ghana within the last year. She had given birth to her second child in November 2015. Her only previous medical history was asymptomatic left bundle branch block, discovered during her first pregnancy in 2014. Laboratory investigations revealed a raised ESR (>100 mm/hr), with a normal CRP and positive ANA (1:640).

In May she developed night sweats and then re-presented with abrupt-onset lower limb weakness, urinary retention and reduced perineal sensation.

On examination, she had a flaccid paraparesis (power 2/5 in the lower limbs). Reflexes were symmetrically brisk and the plantar extensor. There was no clear sensory level and sensation was preserved throughout the lower limbs. MRI of the spine was normal. She was anaemic (Hb 84) and neutropenic (0.7×10^9 /L), serum ACE was 48, and dsDNA, RNP and Ro antibodies were positive. HIV, hepatitis B and C, and syphilis serology was negative. Complement levels were low (C3 84), but lupus anticoagulant and antiphospholipid antibodies (APL) were negative. She was given two courses of G-CSF. (Granulocyte – Colony Stimulating Factor), which may also have pro-Th2 and anti-inflammatory properties. A chest radiograph showed groundglass opacification within the left and middle zones.

Her CSF was acellular, with an elevated protein (3790mg / L) and glucose 2.7 mmol/L (plasma glucose 4.7 mmol/l). An echocardiogram revealed a left ventricular ejection fraction of 35-40%. MRI spine performed two days after the LP and three weeks after the first MRI now revealed leptomeningeal enhancement, most pronounced in the lower spinal cord and conus medullaris.

A preliminary diagnosis was made of transverse myelitis secondary to systemic lupus erythematosus (SLE). Other possibilities were ischaemic myelopathy, and myeloradiculitis due to lymphoma or tuberculosis. PET CT revealed metabolically avid nodal disease above and below the diaphragm with involvement of the spleen and the bone marrow. Three bone marrow biopsies were unrevealing and repeated lymph node biopsies showed only B-cells, reactive lymphadenitis and no acid-fast bacilli.

High dose methylprednisolone was given, followed by high dose oral steroids, to which there was no response. She remained an inpatient and two months after being admitted, developed right-sided facial weakness and became encephalopathic. Cyclophosphamide treatment was delayed due to the patient becoming pyrexial and concerns about this being a lupus-mimic caused by tuberculosis.

An MRI brain showed multiple new foci of restricted diffusion in the right cerebellar white matter and bilaterally in the striatocapsular regions, suggesting an evolving vascular process. A brain biopsy revealed minor blood vessel inflammatory changes, deemed insufficient to diagnose vasculitis. There was no evidence of lymphoma. The classical histopathological studies have consistently found the principle CNS changes to be small vessel infarction in the cerebral cortex and brainstem as a result of vasculopathy. Changes are predominantly related to small blood vessels, with evidence of necrosis of the blood vessel wall, extravasation of fibrin and red blood cells, together with endothelial cell proliferation, hypertrophy and the appearance of fibrin thrombi. Although vasculitis may account for peripheral neuropathy in SLE, it is only rarely encountered complication of cerebral lupus [1]

Ten weeks into the presentation, in July, there was a deterioration of consciousness from GCS 15 to 9. Anti-tuberculosis therapy was instigated to cover possible mycobacterial infection. Hydroxychloroquine and IV cyclophosphamide were given to treat presumptive SLE. She also received two rounds of plasma exchange and a single dose of rituximab (1000 mg), when cyclophosphamide rendered her neutropenic and could not be continued. The patient subsequently returned to ITU with chest sepsis. Concern grew about the effect that immunosuppressive agents might be having on the heart and monitoring of cardiac enzymes and echocardiography was instigated. After two further rounds of cyclophosphamide, gradual improvement was noted in the patient's awareness, cognition and degree of disability. Blood results revealed a decrease in dsDNA levels and a lower ESR (see Figures 2 and 3). She was discharged to her local hospital in January 2017 for rehabilitation assessment.

Discussion

CNS lupus describes the neurological manifestations of SLE, which occur in 24% of patients.[2] Common presentations include encephalopathy and seizures, but myelopathy resulting from abrupt vaso-occlusive events is recognised.[3] This patient presented with non-specific symptoms, but the laboratory investigations suggested an underlying autoimmune condition. When she developed acute paraparesis, she fulfilled 4 of the required Systemic Lupus International Collaborating Clinics (SLICC) criteria for lupus diagnosis (anti-nuclear antibody positive, a neurological disorder (albeit not seizures), anaemia

and neutropenia.[4] A raised ESR (>100 mm/ hr) is also compatible with lupus vasculitis, as are antibodies against dsDNA and low complement levels.[5,6]

The progression to encephalopathy despite steroid therapy raised doubts over the initial diagnosis, but eventual response to cyclophosphamide further supports the diagnosis of CNS lupus. Although the brain biopsy was non-confirmatory, the likely diagnosis was a micro-vasculopathy, characterised by inflammation of venous and arterial walls.[7] MRI eventually showed multiple foci of restricted diffusion in the spinal cord. Myelopathy is a rare complication of SLE and occurs in around 1-2% of cases.[8]

Analysis of 105 cases of SLE patients who presented with transverse myelitis as an initial manifestation or within five years from diagnosis was conducted by Kovacs et al.[9] Most patients present with a detectable sensory deficit at thoracic level, which was not the case here. APL antibodies in patients with transverse myelitis and SLE were more common than in the overall SLE patient population (64% as compared with 48%). This might be important for understanding the mechanism behind spinal cord microvasculopathy, however our patient was negative for APL antibodies.

Pathological changes reported in SLE-related myelopathy include extensive spinal cord softening occurring at a specific cord level with vascular changes (perivasculitis or even thrombosis); subdural haematomas and peripheral white matter degeneration, called subpial leukomyelopathy. The latter can occur at multiple spinal cord levels and probably explains the changes observed on the MRI spine of this patient. Pathological changes may also be explained by non-vascular injuries due to APL antibodies, white matter degeneration and vascular injuries occurring on the background of immune-complex mediated vasculitis.[10]

Interestingly, the patient showed little initial response to high dose methylprednisolone and cyclophosphamide, which are used together in acute flares, but she did respond to sustained treatment.[11] The use of plasma exchange was in line with recent studies, which suggested efficacy in severe myelopathy, but again in this case did not lead to overt clinical improvement.[12]

It has been suggested that the use of anticoagulation before the onset of myelitis and regardless of the negative APL antibody status, could improve the outcome, owing to the potential role of other antibodies (such as anti-annexin V, anti-oxidised low density lipoprotein antibodies and anti-activated protein C) in arterial and venous brain as well as in the spine. An echocardiogram confirmed cardiac involvement, which is relatively uncommon in SLE.[3] thrombosis in lupus.[13,14,15] This discussion is, however, of pure theoretical value, as myelitis was the first presentation in the case of the patient we present.

Key Points

- 1) CNS lupus should be considered when patients present with myelopathy and satisfy SLICC criteria.
- 2) Lupus-related myelopathy might not respond to cyclophosphamide as rapidly as other neurological manifestations of lupus. This should not discourage clinicians from further treatment as improvement might be noticeable only after weeks or even months. The outcome for the majority of patients who develop lupus myelopathy and survive is severe neurological deficit.

3) Treatment should be initiated as soon as possible, even when there is diagnostic uncertainty, as delay results in extension of CNS involvement and further deficit, provided systemic and CNS infections have been excluded or are concomitantly treated.

4) Cyclophosphamide and methylprednisolone combined therapy have superior efficacy compared with use of methylprednisolone alone, and lupus markers are a useful reflection of therapeutic response.

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References

1. Scolding and Joseph, The neuropathology and pathogenesis of systemic lupus erythematosus, *neuropathology and applied neurobiology* (2002), 28, 173-189.
2. Joseph FG, Lammie GA, Scolding NJ. CNS lupus: a study of 41 patients. *Neurology*. 2007 Aug 14. 69(7):644-54.
3. Honczarenko K, Budzianowska A, Ostanek L. Neurological syndromes in systemic lupus erythematosus and their association with antiphospholipid syndrome. *Neurol Neurochir Pol*. 2008 Nov-Dec. 42(6):513-7.
4. Petri M et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64(8): 2677-2686.
5. Berlit P. Diagnosis and treatment of cerebral vasculitis. *Ther Adv Neurol Disord*. 2010; 3(1): 29-42.
6. Tincani A, Rebaioli C, Taglietti M, Schoenfeld Y. Heart involvement in systemic lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. *Rheumatology* 2006; 45(4): iv8-iv13.
7. Markovic A. Vasculitis and Vasculopathy. *Acta Med Croatica*. 2012; 66(Suppl 1): 19-24.
8. West SG(1994) Neuropsychiatric lupus. *Rheum Dis Clin North Am*. 20:129-158.
9. Kovacs B, Lafferty T, Brent L, DeHoratius R. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. *Ann Rheum Dis* 2000; 59(): 120-124.
10. Andrianakos AA, Duffy J, Suzuki M, Sharp JT. Transverse myelopathy in systemic lupus erythematosus: report of three cases and review of the literature. *Ann Intern Med*. 1975; 83:616-624.
11. Fernandes Moça Trevisani V, Castro AA, Ferreira Neves Neto J, Atallah AN. Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. *Cochrane Database Syst Rev*. 2013 Feb 28. 2:CD002265.
12. Ye Y, Qian J, Gu Y, Chen X, Ye S. Rituximab in the treatment of severe lupus myelopathy. *Clin. Rheumatol*. 30, 981-986 (2011).
13. Satoh A, Suzuki K, Takayama E, Kojima K, Hidaka T, Kawakami M, et al. Detection of anti-annexin IV and V antibodies in patients with antiphospholipid

- syndrome and systemic lupus erythematosus. *J Rheumatol* 1999;26: 1715–20.
14. Cuadrado MJ, Tinahones F, Camps MT, De Ramon E, Gomez-Zumaquero JM, Mujic F, et al. Antiphospholipid, anti- β_2 -glycoprotein-I and anti-oxidized-low-density-lipoprotein antibodies in antiphospholipid syndrome. *Q J Med* 1998;91:619–26.
- 15 Zivelin A, Gitel S, GriYn JH, Xu X, Fernandez JA, Martinowitz U, et al. Extensive venous and arterial thrombosis associated with an inhibitor of activated protein C. *Blood* 1999;94:895–901.