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CASE REPORT

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A case of systemic lupus erythematosus presenting transverse myelitis after an episode of meningitis

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Abstract A 27-year-old woman suffering from systemic lupus erythematosus was admitted because she had motor and sensory palsy of the lower extremities, neck stiffness, and a fever. Cerebrospinal fluid study indicated meningitis, and magnetic resonance imaging revealed cord swelling and high signals at Th9–Th12 levels. Antibiotics treatment led to resolution of the meningeal signs. Intravenous cyclophosphamide and prednisolone resulted in a partial recovery from the transverse myelitis neurological disturbance.

Key words Intravenous cyclophosphamide (IVCY) · Systemic lupus erythematosus (SLE) · Transverse myelitis (TM)

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with unknown etiology. Transverse myelitis (TM) is a rare but severe complication of SLE which involves the central nervous system (CNS) lupus.[1–3] The most common clinical symptoms of acute or subacute TM are weakness in the lower extremities that occasionally extends to the upper regions, paraparesis or quadriparesis, paresthesia, and sphincter and sensory disturbances at the thoracic segments levels.[1] The diagnosis of TM is difficult, but a recent report demonstrated that magnetic resonance imaging (MRI) was very useful in assessing the extension and severity of lupus-related TM.[4] Although some hypotheses have been reported,[1,5–12] the pathophysiological mechanism of lupus-related TM is still unclear and an optimal treatment has not been established.

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We describe here the case of a female SLE patient presenting acute TM after an episode of meningitis. The MRI findings were consistent with her neurological abnormalities. Intravenous cyclophosphamide (pulse) therapy (IVCY) partially improved her symptoms.

Case report

A 27-year-old woman was admitted to our hospital on 26 August 2003 suffering numbness of the lower extremities, headache, and intermittent fever of 1 week's duration. She had been diagnosed with SLE according to American Rheumatism Association criteria in 1995. American Rheumatism Association criteria included nonerosive polyarthritis, leukocytopenia, positive antinuclear antibody (ANA), and positive anti-DNA antibody. She was effectively treated with prednisolone (40 mg/day) orally. In June 1996, she was found to have proteinuria, and renal biopsy revealed World Health Organization type V lupus nephritis. After increments of prednisolone (PSL) to 25 mg/day, her PSL dose was maintained at 12 mg/day for 6 years without any clinical and serological recurrence.

In August 2002, she suffered from high fever. Three days later she was admitted to a hospital. Physical examination disclosed nuchal stiffness. Cerebrospinal fluid (CSF) study showed marked pleocytosis (1522/mm^3; polymorphonuclear cells: 1296; mononuclear cells: 226). Anti-DNA antibody was elevated (31 U/ml). On the third day of hospitalization, she had a sudden onset of lumbago and motor and sensory palsy of the bilateral lower extremities. With suspected bacterial meningitis and a SLE flare, she was transferred to our hospital by an ambulance for further evaluation of the disease on 26 August.

On admission, her body temperature was 37.7°C, heart rate 72 beats/min, and blood pressure 154/78 mmHg. General examination revealed anemic conjunctivae, hair loss, coarse crackles at the bilateral lung, and a grade 3 systolic cardiac murmur. Optic fundi, visual acuity, and visual fields were normal. Neurological examination showed complete

flaccid paraplegia. Deep tendon reflexes of lower extremities were absent and all-modality sensory disturbance was below Th12 level. Babinski reflex was bilaterally negative. Sphincter tone of both bowel and bladder was diminished. Laboratory findings were as follows: erythrocyte sedimentation rate, 28 mm/h; white blood cell count, 9700/mm^3 (91.3% neutrophils, 6.4% lymphocytes, 2.0% monocytes, 0.2% eosinophils, 0.1% basophils); hemoglobin level, 9.3 mg/dl on blood cell count. Serological examinations showed elevated C-reactive protein (4.2 mg/dl), positive ANA (×2560 [speckled]), anti-DNA antibody (43 U/ml), anti-RNP antibody (×16), anti SS-A antibody (×8), and hypocomplementenemia (CH_{50} < 10 U/ml, C3 35 mg/dl, C4 5 mg/dl). Thrombin–antithrombin III complex (9.3 ng/ml), plasmin-α2–plasmin inhibitor complex (1.7 μg/ml), and D-dimer (12.26 μg/ml) were all elevated. Prothrombin time and activated partial thromboplastin time were normal, and lupus anticoaglant and anticardiolipin-β2GPI antibody were also negative. Cerebrospinal fluid analysis showed pleocytosis (884/mm^3; polymorphonuclear cells: 644; mononuclear cells: 240), elevated protein (475 mg/dl), and decreased glucose concentration (18 mg/dl). Herpes simplex virus and herpes zoster virus were not found by polymerase chain reaction in CSF. Cytokines in CSF were elevated (interleukin [IL]-6: 60 000 pg/ml; IL-8: 9630 pg/ml; interferon-α: 62.4 IU/ml). IgG index was normal.

Electrocardiogram findings were normal. Chest radiographs showed cardiomegaly and pulmonary congestion. Arterial blood gas showed hypoxemia (PCO_2 30.8 torr, PO_2 53.8 torr, $SatO_2$ 90.2%). The cultures of blood, CSF, sputum, and urine all showed negative results.

A transthoracic cardiac ultrasonographic study showed diffuse hypokinesis of the left ventricle and a moderate mitral regurgitation. A transesophageal cardiac ultrasonographic study showed no vegetation. Computed tomography scan and MRI of the brain, without enhancement, did not show any abnormality. Magnetic resonance imaging of the spinal cord revealed a swollen portion from the Th9 to Th12 level, the signals of which were iso on the T1-weighted image and high on the T2-weighted image (Fig. 1a), respectively. The same level was enhanced by gadolinium on T1-weighted image (Fig. 1b).

Meningeal signs diminished after treatment with antibiotics on the 7th hospitalized day but other neurological disorders and serological activity of SLE remained. Therefore, we diagnosed the patient as having lupus-related transverse myelitis that developed after bacterial meningitis. After methylprednisolone pulse (1 g/day) therapy for 3 days, 80 mg/day of intravenous prednisolone was administered. Pulmonary congestion disappeared immediately after using diuretics.

On the 19th day of hospitalization, fever and headache diminished and the level of serum anti-DNA antibody and CSF abnormality decreased, but the patient's neurological findings did not improve. We thus instituted intravenous cyclophosphamide therapy (IVCY) (500 mg/day, once a month) in addition to oral PSL (60 mg/day). About 1 week after the first IVCY, her sensation in the lower extremities recovered slightly. She began to notice a very weak touch if we grasped her lower limbs strongly for several seconds. She could also recognize passive motions of her ankle joints. However, motor dysfunction and vesicorectal disorder did not improve. Magnetic resonance imaging findings on the 57th day of hospitalization showed that the swelling of the spinal cord and the enhancement by gadolinium decreased (Fig. 2a,b).

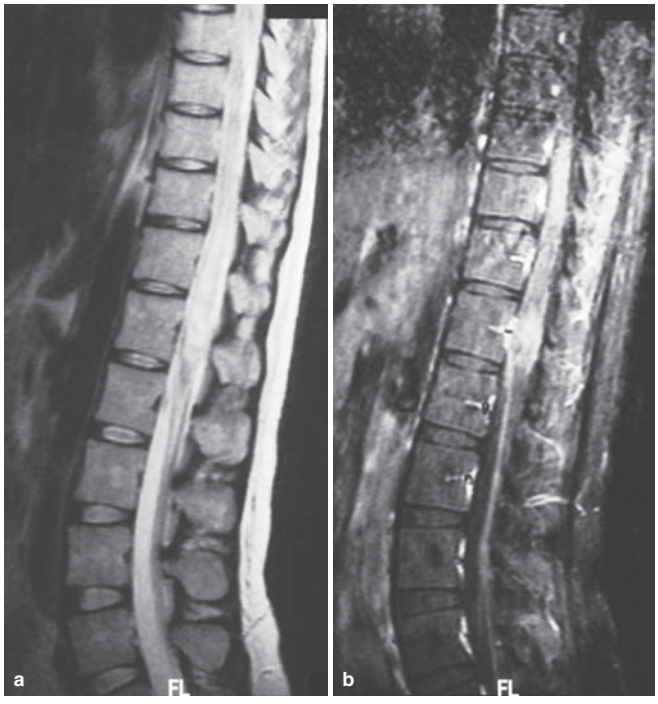

Fig. 1a,b. Sagittal magnetic resonance imaging (MRI) scans of the lumbar spine before intravenous cyclophosphamide (IVCY) treatment. **a** T2-weighted image showed swelling of the spinal cord and high signal intensity at the Th9–Th12 level. **b** T1-weighted gadolinium-enhanced MRI scans of the spinal cord showed marked enhancement at the Th9–Th12 level

The second IVCY had no further effect on her neurological condition and MRI findings. Even 4 months after hospitalization, her neurological disturbance remained the same and she was bedridden, requiring urine catherization. Intrathecal injection of MTX (7.5 mg) and dexamethasone (8 mg) once a week for three times in January 2003 also had no effect on her neurological disturbance.

Discussion

The incidence of TM in SLE has been reported to range from less than 1%[13] to 3.2%.[14] There is no specific diagnostic test for transverse myelitis in SLE. Magnetic resonance imaging is currently the most useful tool for the diagnosis of TM. Kovacs et al.[15] reported that increased signal intensity was found in 39 of 55 (70.9%) SLE-related TM patients, and that those with abnormal MRI findings had unfavorable outcomes. The differential diagnosis of TM in SLE includes intra- and extramedullary tumor, epidural and/or paraspinal abscess complicating disc space infection,

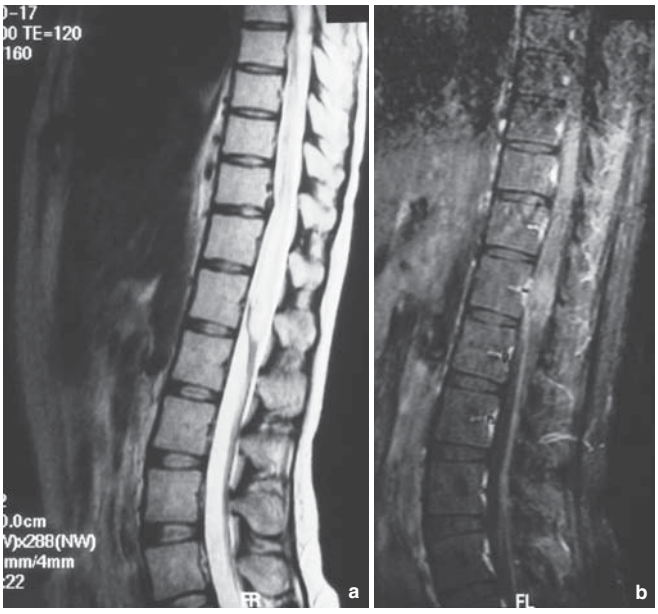

Fig. 2a,b. Sagittal MRI scans of the lumbar spine after the first IVCY treatment. **a** T2-weighted image showed reduction of swelling and the high signal intensity area. **b** T1-weighted gadolinium-enhanced MRI scans of the spinal cord showed reduction of the gadolinium uptake

epidural or subdural hematoma, spinal cord infarction (anterior spinal artery infarction), viral infection, multiple sclerosis, and fractures. Magnetic resonance imaging findings in our case resembled those of intra- and extramedullary tumor, but the sudden onset of clinical symptoms did not accord with the existence of such a tumor. Hematoma could be typically imaged by MRI with a homological change of signal intensity. Spinal cord infarction (anterior spinal artery infarction) also could be distinguished because of the complete motor and sensory disturbance. Resolution of the MRI findings and results of the CSF analysis, as well as normal findings of the brain MRI and clinical course, were all compatible with SLE-related TM.[16–19]

In our case, the patient developed TM 7 years after the onset of SLE. Transverse myelitis has been described as a late complication of SLE,[5] but a contradictory report has also been found.[14] Several reports[10,17–19] suggested that TM appears when SLE is clinically or serologically active. In our case, we considered that transverse myelitis developed when SLE was serologically becoming active.

Central nervous system lupus often emerges as aseptic meningitis, so we first suspected that meningitis in our patient might be caused by SLE. However, there has been no report of SLE presenting TM associated with aseptic meningitis. Improvement of severe inflammation, indicated by severe elevation of both cell counts and cytokine levels (IL-6 >60000 and IL-8 >9000) by antibiotics therapy strongly suggest that bacterial infection was the cause of the meningitis. We deduced that the patient developed lupus-related TM after an episode of bacterial meningitis. Several reports[20–22] pointed out the possibility that TM of rheumatic diseases including SLE might be caused by an autoimmune response following a viral infection. Ijichi et al.[21] speculated that activated T cells with varicella zoster virus infection induced cytokines to produce T-cell hypersensitivity, leading to the development of TM in association with human T-cell lymphotropic virus-I. Furthermore, other reports suggested that high levels of circulating antibodies may cause acute TM by immune complex deposition, as shown in a patient with TM followed by hepatitis B booster immunization.[23] Bacterial infection in the CNS might be involved in the pathogenesis of acute TM in our case as well.

However, the pathogenesis of TM remains unclear. The most common pathological changes of the spinal cord include ischemia caused by vascular thrombosis or necrotizing arteritis, peripheral white matter degeneration, often at multiple spinal cord levels, and cord compression by subdural hematoma.[1,6–8] Some previous reports[5,9–12] suggested that vasculitis mediated by the immune complex may not be the sole mechanism of TM in SLE, since TM occurred without the evidence of complement activation.

A strong association between TM and antiphospholipid antibodies was also reported.[24] Schantz et al.[17] speculated the possibility that antiphospholipid antibodies might develop chronic and longitudinal cord atrophy. In contrast, other reports[14,18] did not support this observation. Anti-SS-A antibodies were also reported to be associated with TM. Elizabeth and Stering[25] reported 11 cases of TM associated with rheumatic disease, and 8 of these including 4 SLE patients had anti-SS-A antibodies. However, many previous reports did not describe anti-SS-A antibodies. In our case, anticardiolipin β2GPI antibody and lupus anticoagulant were negative while anti-SS-A antibody was positive. Further evaluations are needed concerning the role of antiphospholipid antibodies or anti-SS-A antibodies in the pathogenesis of TM in SLE.

The outcome of lupus-related TM is generally unfavorable.[7,10,26–28] Guidelines for its treatment have not been established. Early and aggressive treatment with high-dose mPSL, alone[11,29,30] or in combination with IVCY, showed an improved outcome.[16,31] Kovacs et al.[15] concluded that treatment with mPSL pulse followed by IVCY seemed to be most effective; however, the disease activity of SLE was not related to the outcome. Plasmapheresis has been successfully performed in some previous reports.[12,14,15,19] A new therapy, intrathecal injection of MTX and dexamethasone, has been reported to be effective in two series of cases.[32,33] However, we could not achieve efficacy in our case, and further investigation is necessary for this therapeutic option.

In our case, IVCY therapy seemed partially effective. We attempted to compare our patient with others who were treated with IVCY therapy.[10,14–16,31,34] Among 24 patients, 8 (33%) had complete or partial improvement. Thus, we think that early combined therapy with IVCY and steroids is a better option in the acute phase of severe TM.

In conclusion, we presented a rare case of lupus-related TM after an episode of bacterial meningitis, which might be involved in the pathogenesis of acute TM. Intravenous cyclophosphamide therapy in combination with steroids was partially effective in alleviating sensory disturbance.

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