Systemic Lupus Erythematosus Related Transverse Myelitis Presenting Longitudinal Involvement of the Spinal Cord

Yu-ko Kimura Kato, Yoshihiko Seino, Yoshiyuki Hirayama, Takumi Aramaki, Hiroshi Yamaguchi*, Hiroyuki Amano** and Teruo Takano

Abstract

Lupus-related transverse myelitis is a rare but serious complication. A 25-year-old Japanese woman with systemic lupus erythematosus (SLE) was admitted because of numbness of the face and left upper extremity, headache, and intermittent fever. Six days later, she developed tetraplegia. MRI of the spinal cord showed longitudinal high intensity signals from medulla oblongata to C5, and from Th12 to conus medullaris on T2-weighted image. These MRI findings were consistent with acute catastrophic neurological abnormalities. Despite administration of the combination of methylprednisolone and cyclophosphamide pulse therapies, as well as plasmapheresis, her condition did not improve. Any vasculopathy in addition to the autoimmune pathogenesis, and narrow therapeutic window may relate to the present refractory case.

(Internal Medicine 41: 156-160, 2002)

Key words: systemic lupus erythematosus, transverse myelitis, magnetic resonance imaging, magnetic resonance angiography, steroid pulse therapy, cyclophosphamide pulse therapy, plasmapheresis

Case Report

A 25-year-old Japanese woman was admitted because of numbness of the face and left upper extremity, headache, and intermittent fever from 2 weeks previously. Nine years earlier, she was hospitalized for autoimmune hepatitis with laboratory findings of elevated antinuclear antibody (ANA) >x640 (speckled, peripheral, homogeneous type), immune complex (anti-Clq antibody method) 67.7 |igu/ml (normal range <34.5), immune complex (anti-C3d antibody method) 12.6 |igu/ml (normal range <8.5), and a decreased level of CH50 21.7 IU/ml (normal range 32-44). Liver biopsy revealed perilobular necrosis, giant hepatocyte and lymphocyte infiltration around the necrosis area, which were consistent with fulminant hepatitis. She was treated with plasmapheresis three times and improved completely. Eight years earlier, she had been diagnosed as SLE on the basis of positive ANA >x640 (speckled, peripheral, homogeneous type), positive anti-ds-DNA antibody 32 U/ml (normal range <10), positive LE cell, thrombocytopenia, and clinical symptoms of arthralgia and malar rash. She was treated with prednisolone, and the symptoms were resolved completely. She was subsequently maintained with combination therapy of azathioprine 50 mg twice a day and prednisolone 15 mg per day.
Her present symptoms of numbness of the right side of her face and left upper extremity developed two weeks before admission. She was ambulatory when admitted to Nippon Medical School hospital. Her consciousness was clear and vital signs were: body temperature 37.2°C, blood pressure 146/76 mmHg, heart rate 84/min, respiratory rate 18/min. Neurological examinations of the cranial nerves revealed only diminished facial sensation on the right side of her face. Muscle strength was remarkably decreased at both upper extremities; grasping power was 2.5 kg on right hand and 3.5 kg on left hand. Sensory examinations revealed diminished pain sense in the L3 to S2 area on both sides. Deep tendon reflexes were normal and symmetric, and Babinski reflex was negative at the time of admission.

Blood cell counts, liver and renal function were all within normal range. Laboratory examinations showed elevated CRP (3.8 mg/dl), ANA >x640 (speckled, peripheral, homogeneous type) and anti SS-A antibody 200.8 U/ml. Anti-DNA antibody (RIA) and anti-ds DNA antibody were within the normal range, however C3 50 mg/dl (50–95), C4 15 mg/dl (15–40), and CH50

Figure 1. A–C; Lumbar MRI 3 days after admission showed high intensity signals from Th12 to conus medullaris on T2-weighted image, which were not enhanced by gadolinium. These findings were compatible with all sensorial palsy of right lower limb, bladder and rectal dysfunction, and lower extremities paralysis.
20.0 mg/dl (20.0–45.0) were slightly low. Immune complex was <1.5 μg/ml (anti-C1q antibody method, <3.0), 10.3 μg/ml (anti-C3d antibody method, <13). TAT (5.0 μg/l), PIC (2.0 μg/ml), D-dimer (4.2 μg/ml), and FDP (15.6 μg/ml) were all elevated, and suggested secondary fibrinolysis accompanied with accelerated coagulation cascade. APTT was normal, and cardiolipin IgG antibody, anti-cardiolipin-β2GPI antibody and lupus anticoagulant (PNP, APTT method) were also within normal range. Electroencephalogram showed burst of 2.5 Hz, which was a nonspecific finding in CNS lupus. CT scan of the brain showed atrophy in the anterior lobe.

Three days after admission, she developed motor and sensory palsy of bilateral lower extremities, and acute urinary retention requiring balloon catheter drainage. A lumbar puncture revealed elevated white cell counts 83/mm³, elevated protein concentration 168 mg/dl and lowered glucose level 33 mg/dl. Interleukin-6 (IL-6) in CSF was elevated as high as 13,600 pg/ml. IgG index in CSF was also elevated to 1.9 (normal range <0.70), which indicated polyclonal B cell activation in CNS lupus (3). A gram stain of CSF was negative. CSF cultures were also negative for microorganisms. Oligoclonal band in CSF was also negative. MRI of the brain showed a high intensity spotty signal at the left substantia nigra. MRI of the lumbar spine revealed a longitudinal high intensity signal at the level from Th12 to the conus medullaris (Fig. 1A–C).

According to the laboratory data and MR findings, it was thought her condition was related to SLE related CNS involvement. However, as viral, bacterial and fungal meningitis could not be eliminated from her diagnosis, antibiotic medications (cefpirom, acyclovir and amphotericin B) and methylprednisolone pulse therapy (1,000 mg/day for 3 days) were started from the third hospital day. However, she had worsening of headache, neck pain, and continuous fever in the range of 38–39°C. Four days after admission, the neurological findings were further deteriorated: central facial palsy, bilateral horizontal nystagmus for the right side, absolute sensory disturbance of the left upper extremity, and motor paralysis of bilateral lower extremities. Bilateral patellar tendon reflex had absolutely disappeared and bilateral Babinski’s reflex was positive. Five days later, she became tetraplegic, and showed left-sided medial longitudinal fasciculus syndrome. MRI displayed extension of the high intensity signal in the left thalamus, right pontine, left red nucleus and around these regions (Fig. 2), and gray matter of the spinal cord extending from the medulla oblongata to C5 (Fig. 3A, B), and from Th12 to conus medullaris on T2-weighted images. Gadolinium showed no enhancement and the anterior spinal artery was not occluded. M wave was not induced by nerve conduction velocity study on bilateral tibial nerve, indicating peripheral nerve disturbance in the bilateral lower extremities. On the other hand, bilateral median nerve conduction velocity was relatively within normal limit. She refused further nerve conduction velocity studies. Anti-ganglioside antibody (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, GA1, Gal-C) in CSF was negative.

After methylprednisolone pulse therapy for 3 days, intravenous methylprednisolone 60 mg/day was succeeded. Despite the corticosteroid pulse therapy, she did not have any remission in neurological findings. At the 14th hospital day, although serum immune complex was not elevated, cyclophosphamide pulse therapy using 750 mg/month accompanied by prednisolone (60 mg/day), and synchronized plasmapheresis per week were additionally performed because of her worsening condition. At the end of third cyclophosphamide pulse therapy and ninth plasmapheresis (3 months after the admission), ANA (×160) and anti SS-A antibody (<10 U/ml) were lowered. CH50 42.9 mg/dl, C3 80 mg/dl, C4 34 mg/dl levels were restored. However, her neurological disturbances were hardly improved. At this time, the brain magnetic resonance angiography (MRA) discovered significant stenosis at the right internal carotid artery and diffuse stenotic changes in bilateral cerebral arteries (Fig. 4). Depending on there finding, antiplatelet therapy (ticlopidine) was started.

Four months later, CSF findings including IgG index and IL-6 showed complete resolution of the abnormalities. Although the symptoms and neurological abnormalities were hardly improved, cyclophosphamide pulse therapy and plasmapheresis were terminated because of the complete resolution of CSF abnormalities and improvements in elevated autoantibodies. She continued prednisolone therapy in which the dosage gradu-
SLE with Longitudinal Transverse Myelitis

Figure 3. A, B; Cervical MRI 3 months after admission showed high intensity signal from medulla oblongata to C6 on T2-weighted image, which was the same finding as that assessed 6 days after admission. These abnormal findings were compatible with loss of superficial sensory and motor palsy of the bilateral upper extremities.

ally decreased for each 10% dose every 2 weeks, and antiplatelet medication (ticlopidine) for the suppression of thrombotic and stenotic changes of bilateral cerebral arteries. Even one year after hospitalization, the neurological disturbances were not improved, and she is bedridden, requiring urine catheterization and enema.

Figure 4. Brain MRA 3 months after admission showed diffuse stenotic changes in bilateral middle cerebral arteries and anterior cerebral arteries.

Discussion

Neuropsychiatric manifestations are present in about 60% of patients of SLE, however transverse myelitis is an uncommon but life threatening complication, and the prevalence has been estimated to be approximately 3% (4). Acute transverse myelitis usually presents as an early stage complication of SLE. The mean time interval between the diagnosis of SLE and the occurrence of acute transverse myelitis is reported to be 38 months (5). The time interval between the onset of neurological symptoms and maximum neurological deficits ranges from hours to months, but is usually less than 24 hours. Ropper et al found three types of the disease onset: a smoothly progressive onset with ascending neurological symptoms; a subacute gradually developing type; and a hyperacute, catastrophic-onset type. Of these, the hyperacute catastrophic-onset with the development of total neurological deficit within 12 hours especially followed by the development of tetraplegia and bladder and rectal dysfunction had the worst predicted prognosis (6).

Spinal cord involvement of this disorder occurs commonly at the cervical level and the mid to lower thoracic level, and most often extends four vertebrae in length (2, 4–8). MRI is the most sensitive method to assess the severity and extension of this disorder. MRI findings in the present case showed spinal lesion from the level of medulla oblongata extended to C6, and Th12 to conus medullaris, which were clearly visualized as a longitudinal high intensity signal on T2-weighted image, and was not enhanced by gadolinium. Similar findings are also observed in viral myelitis, intoxication or multiple sclerosis. Based on her long history of SLE, and clinical symptoms, and the lack of findings of microorganism infection, no intoxica-
tion to penicillins and no oligoclonal band in CSF, these findings were considered to be compatible with previous reports of SLE-related transverse myelitis (4–9). Symptoms and physiological findings in the present case; urinary and rectal dysfunction, facial nerve palsy, medial longitudinal fascicular syndrome, numbness of the left limb and bilateral upper extremities, deficiency of all sensation of right limb, and tetraplegia were relatively compatible with the visualized longitudinal spinal lesions of this disorder on MRI assessments. Although the lumbar lesion on MRI disappeared after intensive treatments, her rectum and bladder dysfunction and paralysis of bilateral lower extremities could not be improved. Irreversible peripheral neuropathy and persistent of damage in the upper motor neuron (damage of cervical spinal cord) may be associated with limitation of improvement.

The present case did not respond to the intensive medical treatments which consisted of corticosteroid pulse therapy, cyclophosphamide pulse therapy, and synchronized plasmapheresis. Several reports have demonstrated clinical efficacy of the cyclophosphamide pulse therapy (9), steroid therapy, and synchronized plasmapheresis (10). Due to the rarity of this disorder, no prospective randomized investigations are available to evaluate these therapies, and the efficacy of synchronized plasmapheresis also remains uncertain. Recent reports have described that early aggressive therapy using the combination of corticosteroid and cyclophosphamide or azathioprine is associated with satisfactory outcome (4, 11). In 14 patients with this disorder, Kovacs et al compared the therapeutic effectiveness of the three therapeutic modalities or combinations: corticosteroid pulse therapy, cyclophosphamide pulse therapy and plasmapheresis (12). They reported that patients receiving corticosteroid pulse therapy alone or those receiving combination of corticosteroid pulse therapy and cyclophosphamide pulse therapy showed better recovery compared to those receiving all three combinations (60%, 40%, 0%). In their analysis, more aggressive treatment was not necessarily associated with better outcome.

Lack of response to the intensive treatments in the present case may be due to the relatively narrow therapeutic window in the case of acute onset (8). Magnetic resonance angiographic findings of diffuse stenotic lesions in cerebral arteries and laboratory data presenting secondary fibrinolysis accompanied with accelerated coagulation cascade suggested that any vasculopathy in addition to the autoimmune pathogenesis may have been related to the acute development of longitudinal transverse myelitis in the present refractory case.

References