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Recurrence of Transverse Myelitis After Long Term Neurological Recovery Associated with Antiphospholipid Antibodies in a Patient with Systemic Lupus Erythematosus : A Case Report

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A 44-year-old female Taiwanese developed T5 transverse myelitis (TM) in 1984, eight years before the diagnosis of systemic lupus erythematosus (SLE). She responded very well to prednisolone and azathioprine administration and had complete neurological recovery. In August 1997, a relapse of TM at vicinal level, T6, occurred. Magnetic resonance image of the spinal cord revealed long segment involvement from T4 to T8. High titer of antiphospholipid antibodies and various serological markers of lupus activity were found to correlate with this relapse of TM. She responded very well to methylprednisolone pulse therapy with nearly complete neurological recovery. Follow-up examination of magnetic resonance imaging, 4 months after relapse, revealed much improvement. Here we report this rare condition in a woman with SLE, who suffered relapse of TM 13 years after a previous episode with complete neurological recovery. A sequential change of antiphospholipid antibodies correlated with LE activities was also presented. (J Rehab Med Assoc ROC 1999; 27(4): 227 – 234)

Key words: transverse myelitis, SLE, pulse therapy, antiphospholipid antibodies

INTRODUCTION

Neurological involvement occurs in about 50% of the patients with systemic lupus erythematosus (SLE), but transverse myelitis (TM) is a rather rare complication of SLE [1-8]. The neurological symptoms of TM have an acute onset and evolution of neurological deficits occurs within just a few hours [2,7,9,10]. The usual manifestations are: numbness, paresthesia and weakness of the legs, fever, interscapular, low back or abdominal pain and impaired sphincter control [9,11,12]. Cerebrospinal fluid (CSF) protein is usually elevated and glucose is decreased, both of these are accompanied by a pleocytosis [11]. Although TM is usually a late complication, it can also be an initial manifestation of SLE [2-4,9,11,13-17]. TM in SLE is usually associated with a poor prognosis [5,7,9,18]. Lately, the early use of intravenous pulse methylprednisolone

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and/or cyclophosphamide has seemed to improve the neurological outcome [8,9,12,18,19]. In this report, we describe a SLE patient who had a recurrence of TM after more than 13 years of complete neurological recovery.

CASE REPORT

A 44-year-old female Taiwanese developed easy bruising, purpura and menorrhagia in 1981. Idiopathic thrombocytopenic purpura (ITP) was the diagnosis given after a series of laboratory examinations which included a normal bone marrow aspiration, a negative antinuclear antibody test and a normal complement level. She responded well to prednisolone 30mg qd. However, nonadherence to medication regimen resulted in a recurrence of ITP. She had paresthesia at the midthoracic level in February 1984. Two weeks later, she had dysuria and urinary retention, and the following day experienced weakness in both lower limbs, which continued to progress resulting in her being bed-ridden within 4 days. She was admitted to National Taiwan University Hospital where myelopathy at the T5 level and ITP were noted. Neurological examination revealed a sensory level of T5, i.e. decreased pin-prick and vibration sensation being more severe on the right side and relative preserved light touch sensation, and muscle power 3/5 over the right lower limb and 1-2/5 over the left side. There was hyperreflexia over both lower extremities, absent superficial abdominal reflexes and bilateral plantar flexor responses. There were urinary retention with a full sensation and a positive bulbocavernosus reflex. Evoked potential (EP) examinations including visual (VEP), brainstem auditory (ABEP) and somatosensory (SSEP) were all normal. Cystometry revealed detrusor hyperreflexic neurogenic bladder. Also noted were: a positive VDRL test and a weak positive antinuclear antibody (ANA), speckle type 80x, an increased IgM, and a low C3, 46 mg/dl. The LE cell preparation and the anti ENA (Sm, RNP) were negative. The CSF examination and myelogram were not performed because of a bleeding tendency in the patient. The computed tomography (CT) of the thoracic spinal cord was non-informative. She responded very well to prednisolone 50mg qd and azathioprine 50mg bid. The thrombocytopenia, paresis and paresthesia resolved gradually and she had complete neurological recovery by May 1984. No residual bladder problem remained. She was followed up in our outpatient clinic that included a gradual tapering of steroid and azathioprine.

In October 1991, for the first time, she developed Coombs positive hemolytic anemia. The diagnostic criteria of SLE was fulfilled since May 1992 when she developed multiple arthritis. She was unable to taper off steroid because of a flare up of LE activity. During the course of follow-up, the followings were noted: a gradual increase in ANA titer, a decrease in the serum C3 and C4 level, recurrent episodes of finger and elbow arthritis and Coombs positive hemolytic anemia. However, each episode responded to an adjustment of steroid dosage.

On August 1, 1997, she developed fingertip cyanosis, malaise, sleepiness and slowness in motion. However, there was no laboratory evidence of any LE activity flare up. Intermittent fever was noted later. On August 30 she developed urinary retention, constipation, abdominal pain, hypoesthesia below T6 and weakness of both lower limbs. Urinary catheterization in the emergency room yielded 1800-ml urine. Neurological examination revealed a sensory level of T6 with more impairment over the left side i.e. reduced pinprick, thermal and vibration sensations. There was an absence of the superficial abdominal reflexes and increased deep tendon reflexes. Muscle power was mildly decreased, 4/5. Laboratory examinations revealed Coombs positive hemolytic anemia, 2+ VDRL test, ANA 1:2560x with a speckled pattern, low C3, 55 mg/dl and C4, 5.5 mg/dl and positive Anti-ENA, including Sm, RNP and SSA. SSEP with median nerve stimulation was normal. Scalp SEP on peroneal nerve stimulation revealed decreased amplitude with normal latency. VEP and ABEP studies were normal. The anticardiolipin antibody test was positive, i.e. IgG titer 23.5 u/ml and IgM titer >100 u/ml, both with normal <7 u/ml. The urodynamic study revealed areflexic neurogenic bladder. Magnetic resonance imaging (MRI) of the spinal cord revealed abnormal signal intensity on both T_1- and T_2-weighted images around the level of T4 to T8, which showed abnormal enhancement with Gadolinium-DTPA (Fig 1). Axial T_2-weighted image at the correlate thoracic cord showed an increase of signal intensity in the cord more on the right side. Urinary tract infection with E. Coli was treated with antibiotics. Pulse

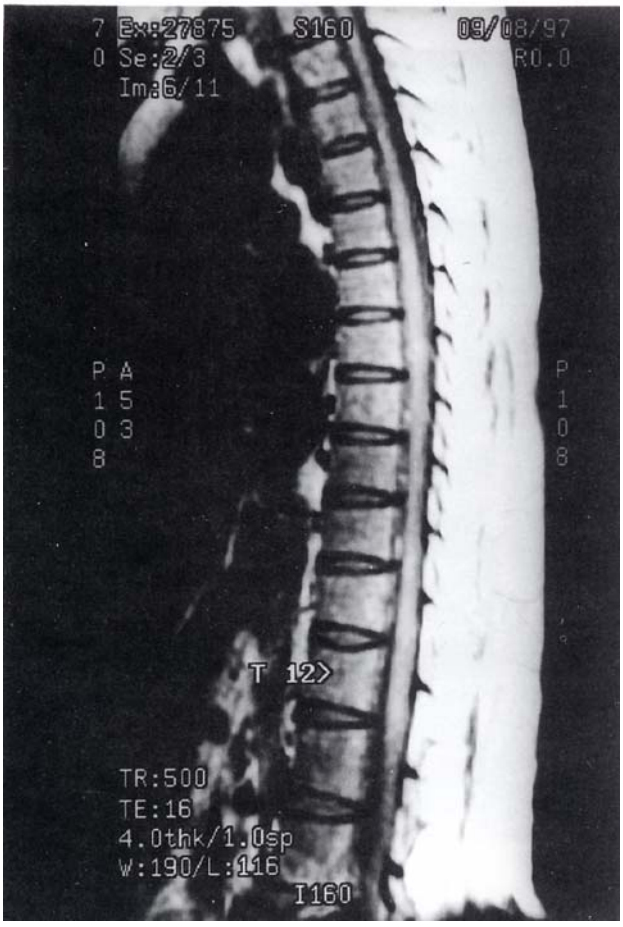

Fig. 1 Sagittal plain T_1-weighted image revealed slight enlargement and irregular outline of the thoracic cord with relatively heterogeneous signal intensity around the T4 to T8.

therapy of methylprednisolone 1000mg qd for 3 days and then methylprednisolone 40mg bid was started because of the flare-up of LE activity. A Foley catheter was inserted and she was discharged on September 14. She continued to take prednisolone 15mg bid. Ten days later, she was admitted to the rehabilitation ward for bladder training. Neurological examinations demonstrated no obvious muscle weakness of bilateral lower limbs. Hypoesthesia was found below the T6 dermatome. Normal deep tendon reflexes were elicited. Voluntary anal contraction and moderate anal tone were present. Perianal sensation was preserved. The superficial anal reflex and bulbocavernosus reflex were both positive. She could walk independently. A urodynamic study revealed detrusor hyperreflexia with a 200-ml bladder capacity. After bladder training for two weeks, she could void by suprapubic tapping with little residual urine by the time she was discharged. Three months after discharge, MRI of the spinal cord revealed much improvement (Fig 2A, B) and she could void spontaneously.

Her LE activity markers and anticardiolipin antibodies (aCL) were plotted in Fig 3.

DISCUSSION

The patient presented with ITP as an initial manifestation of SLE, nevertheless, there were no other clinical symptoms or serologic markers suggesting this diagnosis. She presented with TM one year and 10 months later. The findings detected for the first time were a weak antinuclear antibody titer, 80x with a speckled pattern, and a false positive syphilis test, VDRL 2+. Still the America College of Rheumatology diagnostic criteria for SLE were not fulfilled. Only by May 1992, ten years after the onset of ITP, the diagnosis of SLE definitely established. Similar cases with delayed diagnosis of SLE have been reported [9,13]. TM is usually a late manifestation of SLE [12], however, several investigators report that TM may be the initial presentation of SLE [3,4,9,11,13-17].

Most cases of LE-related TM occur in females [4,11,19]. The onset of TM is usually acute and its progression is rapid [2,7,9,10]. It is observed that the neurologic deficits typically evolved within a few hours [10], and the progression from initial symptoms to maximum deficits occurred over 12 hours to 1 month [9]. This patient, at her first episode, developed maximal neurologic deficits within 4 days after the onset of numbness. Central nervous system (CNS) involvement in SLE occurs typically at the moment of acute exacerbation of SLE [2]. However, a study reported that 5 of 7 patients with LE-related TM had inactive SLE in other organs [9]. Another study showed that 81% of the CNS symptoms occurred in the absence of other SLE exacerbation [1]. Each time, this patient had SLE exacerbation before the onset of TM.

The presentation symptoms of TM are rather consistent and include impaired sensory and motor functions, abdominal or back pain, loss of sphincter control and fever. Physical examination revealed cord lesion neurological findings such as a sensory level,

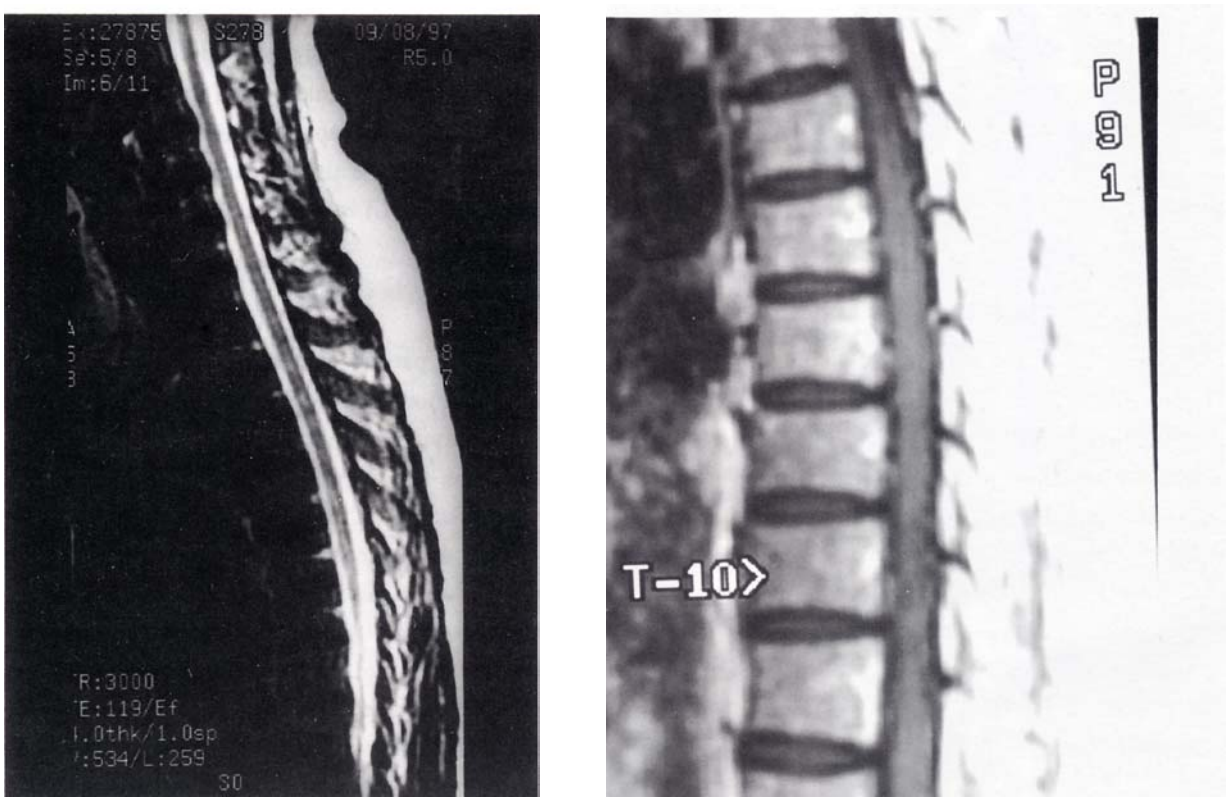

Fig. 2 A, B Sagittal T_2-weighted image, 3 months after discharge, revealed normal signal intensity around the T4 to T8 (A) and contrast-enhanced T_1-weighted image (B) showed disappearance of abnormal enhancement shown in Fig 1 B.

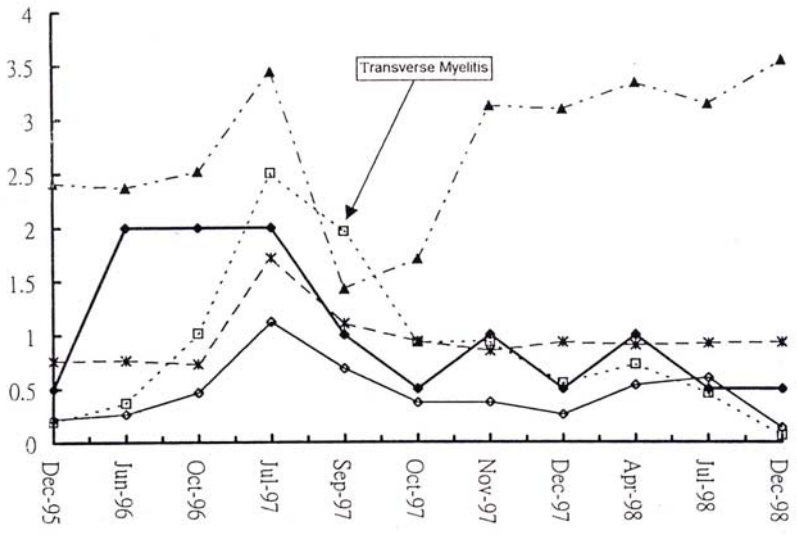

Fig. 3 Sequential changes of various LE activity markers and anticardiolipin antibodies (aCL) titers in this patient, from December 1995 to December 1998.

ANA (2560X /unit on scale)
C3 (50 mg/dl /unit on scale)
Platelet (10^5 /μl/unit on scale)
IgG aCL (Optic Density 405nm)
IgM aCL (Optic Density 405nm)

paraparesis, paraplegia or tetraplegia, hyperreflexia and extensor plantar reflex. A midthoracic or low thoracic sensory level is usually present reflecting the most common sites of spinal cord involvement [2,4]. Sometimes noted are unparalleled sensory and motor involvement and unequal level of sensory impairment in both extremities [5]. This patient had T5 myelopathy during the first episode with a more severe weakness over the left side of the lower extremity and a more severe sensory impairment over the right side of the body. There have been some cases with absent deep tendon reflexes [3,9] and this may be associated with a poor outcome. Laboratory investigations usually revealed an elevated erythrocyte sedimentation rate, positive antinuclear and anti-DNA antibodies and hypocomplementemia. CSF examination typically showed increased protein content, pleocytosis and, less consistently, a decreased glucose level. This patient did have the typical clinical presentation and laboratory findings of TM.

Lupus-related TM has to be differentiated from the myelopathy caused by vertebral fractures [6], viral infections [20], tuberculosis, intramedullary tumor [4] and multiple sclerosis [4], especially in some of these conditions associated with increased frequency in patients with SLE. A delay in the diagnosis or an inability to distinguish among these possibilities can mislead to a fatal consequence. An aggressive approach to diagnosis and early appropriate treatment is mandatory. Before the utilization of MRI, the diagnosis of SLE-related TM was one of exclusion and confirmation of diagnosis by CT myelography is neither sensitive nor specific [12]. MRI now is the best of choice for detecting lesions of the spinal cord and it may play a role in monitoring the response to treatment [5,7]. MRI performed during episodes of TM related to SLE may reveal enlargement of the spinal cord and increased signal intensity on T_2WI, and less frequently with contrast enhancement [4]. Improvement or resolution of these findings correlates with clinical improvement. This patient showed the typical MRI findings of lupus-related TM. However, the appearance of TM in a single MRI study is not specific and may be indistinguishable from an intramedullary tumor. Serial MRI is important in making the distinction and provides a measure of specificity not available with a single MRI examination. A rapid onset and prolonged response to steroids in lupus-related TM differentiates it from intramedullary tumor clinically. While serial MRI provide objective evidence of treatment response to a degree and duration greater than expected with a spinal cord neoplasm. It has been reported that MRI finding of the spinal cord in lupus-related TM is normal initially, but show atrophic change lately [21]. Multiple sclerosis was excluded or considered highly unlikely in this patient on the basis of a negative MRI findings of the brain and negative brainstem EP studies, as well as a long segmental, rostrocaudal extent of lesion in the spinal cord on MRI [4].

Three main pathologic findings of TM have been reported [4]. The most common finding is vacuolar degeneration of the peripheral white matter of the spinal cord, with relative sparing of gray matter [12], patchy areas of axonal degeneration and ballooning of myelin sheaths are seen at many levels of the spinal cord. Abnormal signal intensity at the spinal cord may, therefore, be caused by intravacuolar water. The pathophysiology of this vacuolar degeneration includes an autoimmune [22] or ischemia mechanism [11]. The second pathologic finding is spinal cord infarction [11]. The third finding is a compressive myelopathy with hematoma and subsequent necrosis caused by spinal subdural hemorrhage [23], which myelopathy is presumed to be caused by a LE-related coagulopathy or the antiphospholipid syndrome (APS) [24].

Anticardiolipin antibodies have been reported in as many as 65% of adult patients with SLE [25,26] and have been associated with TM recently. A case report described that a 45-year-old woman developed TM over a 1-year period, who had high serum titers of IgM aCL, a pathogenic role for these antibodies [27]. In a prospective study of 500 SLE patients, 4 cases of them with TM were reported to be aCL positive [28]. In determining the relationship of neurological manifestations to aCL, except for TM, which was associated with IgM aCL, it was found no other significant association between neurological manifestations of SLE and these antibodies [28]. Another study also reported that 12 SLE patients complicated with TM and 10 of them had positive aCL [24]. However, a contradictory opinion that it is difficult to confirm whether antiphospholipid antibodies (APA) have a role in the pathogenetic mechanism of TM in patients

with SLE had been reported [5]. From Fig. 1, LE activation and elevation of aCL preceded the second episode of TM in this patient. So LE activity and aCL contributed to the recurrence of TM.

Vasculitis is a prominent feature in the spinal cord on postmortem examination and steroids may act to suppress the vasculitic process [3,18]. LE-related TM is treated by intravenous corticosteroid pulse therapy within the first few days after onset of symptoms [3,9,10]. Other immunosuppressive agents, such as cyclophosphamide and azathioprine, and antimalaria agents, such as hydroxychloroquine, have also been advocated to administrate [3,4,19]. In SLE, the occurrence of TM is strongly associated with the presence of elevated levels of APA, so if thrombotic events have occurred, it is recommended to add anticoagulation therapy in addition to established immunosuppressive treatment [7]. Early aggressive therapy should be used in SLE patients with TM because if treatment is delayed or inadequate, the prognosis is extremely poor with permanent disability and death [8,12,24]. The outcome of LE-related TM is generally poor. The mortality rate ranges from 30% to 50% [5,11,18]. Till now, only few cases recovered either full or partial neurological function ranging from 15.4% [11] to 26.9% [18]. Lately, the early use of steroid pulse therapy and/or cyclophosphamide has been associated with a better prognosis [8,9,12,18,19]. Since the number of cases reported is small, our result will needs further investigation.

Bladder dysfunction was common in TM [29]. It is commented that paraplegia with loss of sphincter control is the only consistent neurological finding [10]. Urodynamic studies in most cases revealed detrusor hyperreflexia [3,19]. Urinary symptoms began simultaneously with or shortly after the neurological insult [26]. In a study, all of the patients with TM who had acute urinary retention were initially treated with an indwelling catheter or intermittent catheterization [29], and some patients began to void within one to six weeks; it is found that a normal voiding pattern resumed once recovery was complete [29]. As reported elsewhere, our patient suffered acute urinary retention in the beginning of both episodes of TM. An indwelling catheter was used initially and she could void spontaneously at last after bladder training.

This patient had complete and nearly complete neurological recovery after the first and second episodes of TM, respectively. Recurrent LE-related TM has been reported [4,6,9,16,19,21]. The level of neurologic deficits may be similar [4,9] or different [4,19,21]. The recurrence usually occurs within 2 years [19]. It was quite unusual that this patient had a recurrence after more than 13 years of complete neurological recovery.

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全身性紅斑性狼瘡伴有抗磷脂抗體及橫斷性脊髓炎經長期神經恢復後再發：病例報告

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一位 44 歲台灣女性在 1984 年發生 T5 橫斷性脊髓炎，八年後診斷出患有全身性紅斑性狼瘡。其病況對投予的藥物 prednisolone 及 azathioprine 反應良好，並獲得神經完全恢復。1997 年 8 月，在鄰近的 T6 到 T8 胸髓段又發生病變，高濃度抗磷脂抗體與多項血清狼瘡活性檢查顯示與該次橫斷性脊髓炎復發有關， methylprednisolone 脈衝式治療再次對其病情之療效良好，其神經功能幾乎完全恢復，復發四個月後的核磁共振檢查顯示脊髓有明顯改善。由於全身性紅斑性狼瘡併發橫斷性脊髓炎在神經功能完全恢復後十三年再發極爲罕見，因此提出報告，同時檢測其抗磷脂抗體之變化。(中華復健醫誌 1999; 27(4): 227 - 234)

關鍵詞：橫斷性脊髓炎(transverse myelitis)，全身性紅斑性狼瘡(SLE)，脈衝式治療(pulse therapy)，抗磷脂抗體(antiphospholipid antibodies)

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