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Recurrent Acute Transverse Myelopathy Associated with Anticardiolipin Antibodies

Adriana Campi, Massimo Filippi, Giancarlo Comi, and Giuseppe Scotti

Summary: In three patients with recurrent episodes of acute transverse myelopathy, spinal MR imaging during each episode showed areas of hyperintensity on proton density- and T2-weighted images with inconsistent contrast enhancement. Cranial MR imaging, laboratory screenings, and CSF analysis showed only increased titers of anticardiolipin antibodies. Although a causative role in neurologic conditions has not been established conclusively, an association between these antibodies and acute transverse myelopathy and its recurrences cannot be ignored.

Recently, much attention has been paid to a possible relationship between antiphospholipid antibodies and such neurologic conditions as transient ischemic attacks, cerebral arterial and venous thrombosis, retinal occlusive disease, migraine headaches, Behçet syndrome, chorea, seizures, Guillain-Barré syndrome, optic neuropathy, and transverse myelopathy (1, 2). Acute transverse myelopathy may be idiopathic or secondary to viral diseases (3), vaccinations (4), acute disseminated encephalomyelitis (5), multiple sclerosis (MS) (6), vascular insults (7), systemic lupus erythematosus (SLE) (8), or spinal arteriovenous malformations (9).

The antiphospholipid antibody syndrome includes the anticardiolipin antibody (ACA) and the lupus anticoagulant antiphospholipid syndromes. These are acquired blood protein defects associated with recurrent venous and arterial thrombosis, repeated abortions, or thrombocytopenia. ACA syndrome is more common than the lupus anticoagulant antiphospholipid syndrome, with a ratio of 5 or 6 to 1 (10). Recurrent transverse myelopathy is uncommon and raises the possibility of SLE, MS, or spinal arteriovenous malformations, since it has been described in these conditions (2, 8, 9, 11-13). The three patients presented here all had similar findings: recurrent acute transverse myelopathy, abnormal spinal magnetic resonance (MR) patterns, and increased ACA values.

Case Reports

Case 1

A 24-year-old woman had back pain, ascending numbness, and weakness of her legs. She had had three similar episodes of myelopathy, once a year from age 24 to 27, in which there was paraparesis and a T-6 sensory level. Our first observation of this patient was during the second episode of acute myelopathy (Fig 1A-C). Serial cranial MR images and a cerebrospinal fluid (CSF) study were normal, and no oligoclonal bands were detected by electrophoresis. Collagen screening tests and antibodies to different pathogens were negative. ACA was increased (IgG, 20 IU/mL; normal values, 0 to 15 IU/mL), lupus anticoagulant antibodies were normal, and circulating immune complexes were increased (9.87 ng/mL; normal values, 0 to 5 ng/mL). There was no evidence of MS or other systemic disease.

Twelve months after her second episode, when steroid therapy was tapered, the cord showed no high signal and atrophy was present (Fig 1D). Thirteen months after the second episode, during this third episode of myelopathy, she again underwent spinal MR imaging (Fig 1E and F). At the final follow-up MR examination, some months after a fourth episode of myelopathy, the enhancement had completely disappeared. In the fourth year from the onset of disease, she experienced a right-sided acute optic neuropathy, which regressed completely after steroid treatment.

Case 2

An 11-year-old girl presented at onset with chorea and 1 year later with an episode of acute optic neuropathy. Symptoms in both episodes responded to steroid treatment. Then, when she was 13 years old, she had two episodes of acute myelopathy. During the first she had paraparesis, sensory loss, and paresis of the left arm. Findings at cranial MR imaging and CSF examination were normal. ACA was increased (IgG, 39 IU/mL; IgM, 31 IU/mL), and there was thrombocytopenia ($70\,000/\text{mm}^3$) and increased circulating immune complexes. Collagen screening tests and antibodies to different pathogens were negative. There was no evidence of MS or other systemic disease.

During the first episode of myelopathy, the patient was initially admitted to another hospital but after 20 days was transferred to our hospital, where she underwent spinal MR imaging (Fig 2A-C). The upper thoracic spinal cord (T-1 to T-5) was enlarged and showed an abnormal signal, without enhancement. After steroid therapy, all symptoms regressed.

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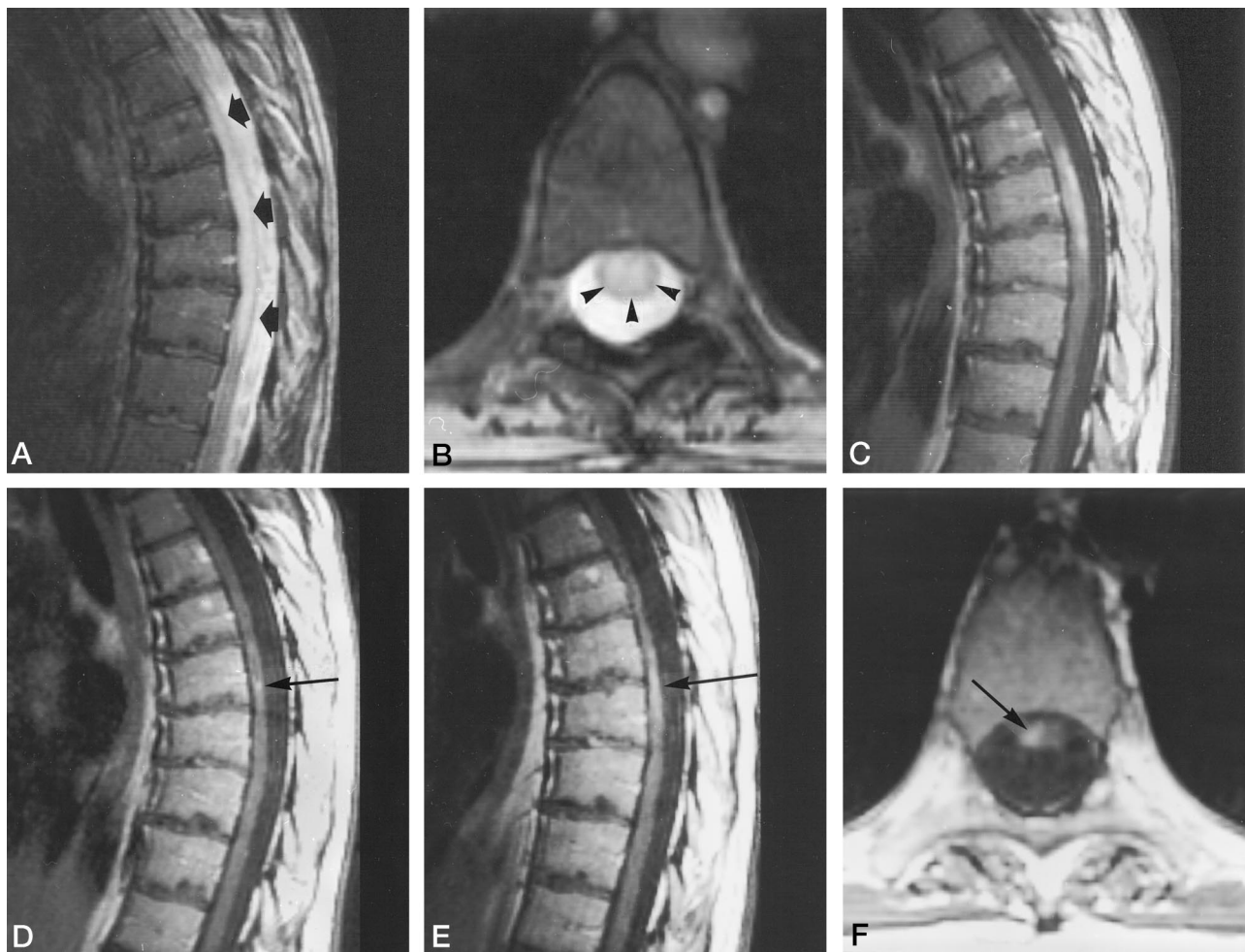


FIG 1. Case 1: 24-year-old woman with antiphospholipid antibody syndrome.

A–C, MR examination during second episode of acute myelopathy, 1 year after the first episode, obtained 12 hours from the onset of this relapse. Sagittal SE T2-weighted image (2200/90/1 [repetition time/echo time/excitations]) (A) shows hyperintense lesion in the cord from T-6 to T-8 (arrows). On axial gradient-echo image (400/18/4; flip angle, 15°) (B), the lesion is located centrally, with involvement of the gray and white matter (arrowheads). Sagittal contrast-enhanced SE T1-weighted image (500/15/3) (C) shows the enhancement is diffuse and more intense along the posterior border of the cord.

D, Follow-up study 12 months after the acute episode, during remission. Sagittal contrast-enhanced SE T1-weighted image (500/15/3) shows a small enhancing area present only at the T-7 segment (arrow).

E and F, MR study during third relapse of the myelopathy, 13 months after the second, obtained 24 hours after onset of initial symptoms. Sagittal (E) and axial (F) contrast-enhanced SE T1-weighted images (500/15/3) show a right-sided small paramedian enhancing area at the T7–8 level (arrows).

After 5 months, she had another relapse, marked clinically only by paraparesis. Spinal MR findings were changed (Fig 2D–F): with focal enhancing areas in both the cervical and thoracic spinal cord (Fig 2G–J). She was treated with steroids and immunosuppressive therapy, and after 2 months again recovered completely. Cervical and thoracic findings improved, although a slight diffuse hyperintensity persisted throughout the upper thoracic spinal cord. Some enhancing and nonenhancing cystic areas persisted in the cervical cord (Fig 2K and L).

Case 3

A 25-year-old woman was examined during the second episode of myelopathy, marked by paraparesis, urinary retention, and a T6–7 sensory level. This episode was clinically similar to the first one from which the patient had completely recovered after steroid treatment. CSF was normal, ACA was increased (IgM, 45 IU/mL; IgG, 11 IU/mL), and circulating immune complexes were increased. Collagen screening tests and antibodies to different pathogens were negative. There was no

evidence of MS or other systemic disease. Cranial MR images showed findings compatible with small-vessel disease. She had multiple small silent lesions that were hyperintense on T2-weighted images, located mainly in the subcortical white matter and corona radiata. Spinal MR imaging showed middle thoracic spinal cord lesions with enhancement and moderate atrophy (Fig 3A and B). After steroid treatment she recovered completely.

Discussion

Acute transverse myelopathy is usually considered a monophasic disease, although recurrences have been described (2, 3, 8, 11, 13). Characterized clinically by acute motor, sensory, and autonomic dysfunction of the spinal cord, acute transverse myelopathy can, however, be complete, with bilateral spinal cord disease, or partial, with unilateral spinal cord disease (14).

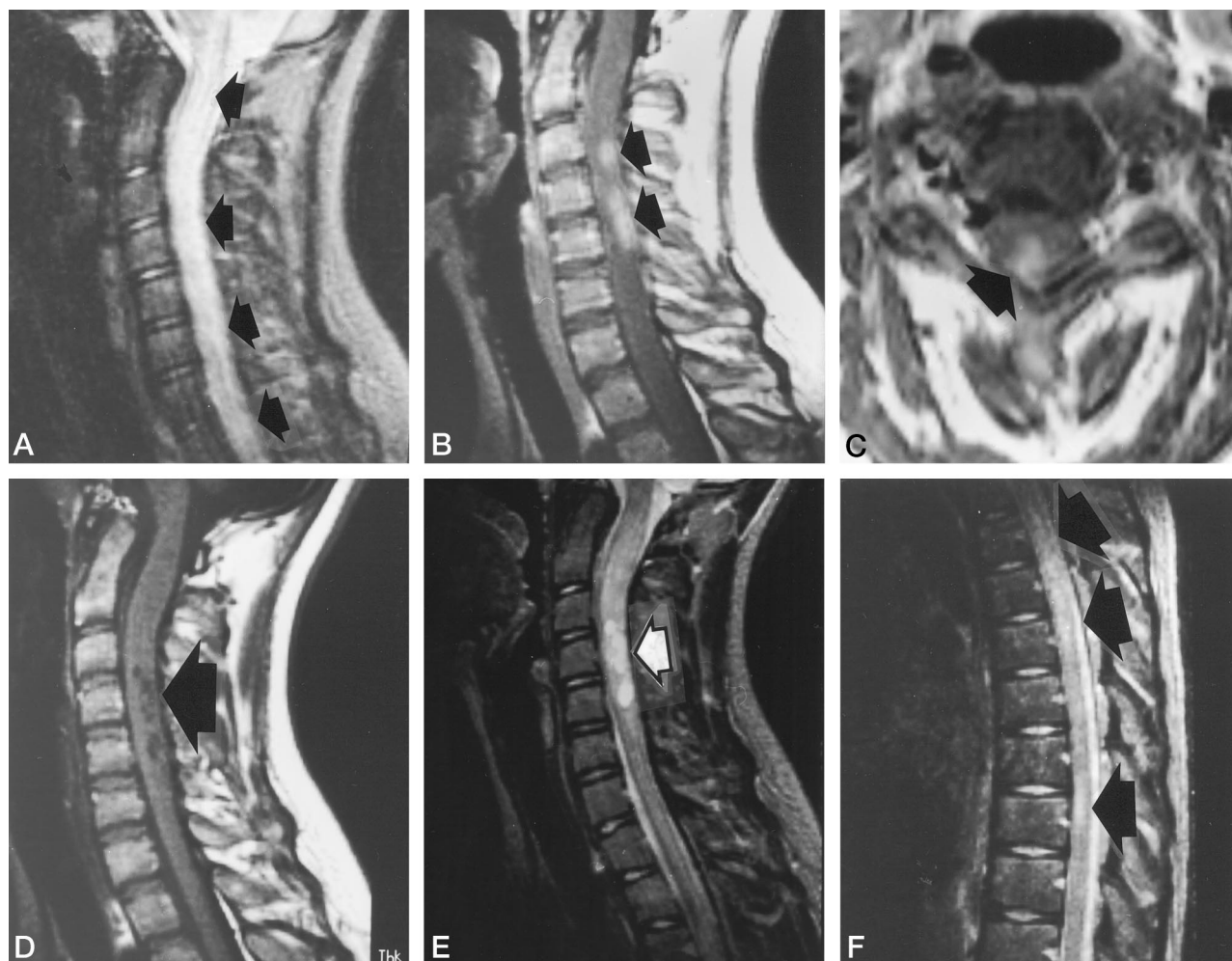


FIG 2. Case 2: 13-year-old girl with antiphospholipid antibody syndrome.

A–C, MR examination during first episode of acute myelopathy, 20 days after onset of symptoms. Sagittal SE T2-weighted image (200/80/1) (A) shows widening of the spinal cord (arrows) with diffuse hyperintense signal from the entire cervical cord to the upper thoracic spinal cord. Sagittal contrast-enhanced cervical SE T1-weighted image (480/15/3) (B) shows nodular focal enhancing lesions (arrows) posteriorly at C-3 and C4–5. Axial contrast-enhanced cervical SE T1-weighted image (650/15/3) (C) at C-4 shows an enhancing area (arrow) in the right median posterior part of the spinal cord, with involvement of the dorsal columns and the posterior gray matter.

D–F, MR study during second episode of myelopathy, 5 months after the first, obtained 24 hours after the onset of paraparesis. Sagittal T1-weighted image (480/15/3) (D) shows appearance of focal cystic lesions (arrows), some of them at C-4 and C-5 levels, which were seen as enhancing areas on first contrast-enhanced MR image (B). Sagittal T2-weighted images (2200/80/1) (E and F) at the cervical segments show the hyperintensity is present above the cystic areas (arrow, E). The cervical cord is enlarged from C-1 to C-6. On F, widening of the upper thoracic spinal cord has regressed, but diffuse hyperintensity is still present (arrows). A focal T-8 hyperintense lesion is detectable.

Figure 2 continues on next page.

Spinal MR findings in our patients, were similar to those reported in lupus-related myelitis (7) or in myelopathies of unknown origin (15, 16). On follow-up MR examinations, these lesions can change their pattern from diffuse to focal and cystic areas or even disappear (8). The appearance of cystic necrotic areas was not associated with a poor prognosis or greater disability. Widening of the spinal cord may be prominent during the first episode of acute transverse myelopathy; however, the presence of cord widening and prolonged abnormal signal on MR images was not associated with more severe disability or with a poor prognosis (8, 13, 15, 16). Development of atrophy over time (8, 17), such as in case 1, was, however, associated with only partial recovery of neurologic

functions. Contrast enhancement, always observed during relapses and sometimes also during remissions, was homogeneous and either diffuse or focal.

The antiphospholipid syndromes, lupus anticoagulant and ACA, can both be *secondary*. They have been reported in many conditions, such as SLE or other autoimmune disorders, such as thrombocytopenic purpura, leukemia, cancer, and infections, or in subjects receiving phenytoin, hydralazine, and other drugs. The antiphospholipid antibody syndromes may also be *primary*, and in fact have been found in otherwise healthy subjects (1). ACA syndrome is associated with premature cerebrovascular diseases, migraine, Behçet syndrome, chorea, seizures, and myelitis. Both arterial and venous thrombosis may be

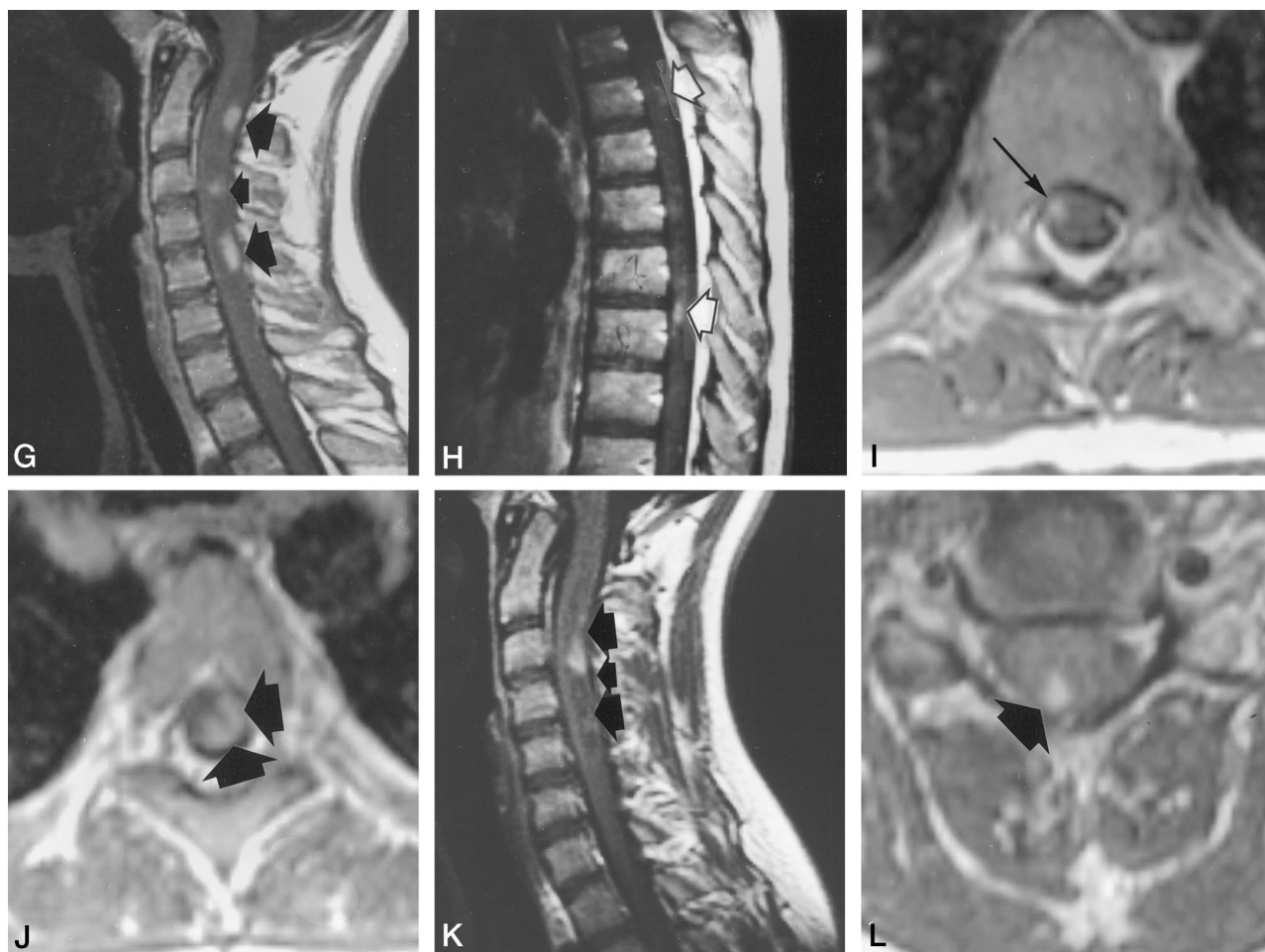


FIGURE 2 CONTINUED.

G, Sagittal contrast-enhanced T1-weighted image (480/15/3) shows a new C-2 oval enhancing lesion and a decrease in size of the C-4 enhancing lesion (arrows).

Sagittal (H) and axial (I) contrast-enhanced T1-weighted images (465/15/3 and 580/15/2, respectively). On H, the focal T-8 lesion is partially enhancing (lower arrow) while another small posterior enhancing area is present at the T-4 level (upper arrow). On I, the enhancing T-8 area is on the right anterior superficial side, involving the ventral columns. The T-4 enhancing area is seen better on an axial section (J), where the enhancement involves the central and left lateral cord, including the ventral, lateral, and posterior columns and gray matter.

K-L, MR study during a period of remission, 2 months after the second relapse of the acute transverse myelopathy and after steroid and immunosuppressive treatment. Sagittal contrast-enhanced T1-weighted image (480/15/3) (K) shows nodular enhancement only at C2-3 and C3-4 posteriorly. At the remaining levels there is central hypointensity. On axial contrast-enhanced T1-weighted image (650/15/3) (L) at C3-4, the enhancing area is still right posterior and paramedian, mainly involving the white matter.

associated with ACA. Arterial thrombotic sites are many, including the coronary arteries, cerebral arteries, distal and proximal aorta (1), spinal arterial system (17), and subclavian, mesenteric, and peripheral arteries (18). Venous thrombotic events can involve deep veins of the arms and legs, intracranial dural sinuses, cerebral and retinal veins (1), pulmonary vein, inferior vena cava, and hepatic (19, 20), portal, or renal veins (1).

In our patients with relapsing transverse myelopathy, the main concerns were the nature and pathogenesis of the spinal cord lesions. Several mechanisms of action have been proposed by which ACA could induce thrombosis. ACA has an affinity for phospholipids and may interfere with the activity of several components of the normal hemostasis system, which depends on phospholipids. ACA can interact with

endothelial release of prostacyclin or with activation of cofactors of hemostasis, such as protein C or protein S; they can interfere with antithrombin activity or with platelet membrane phospholipids (inducing platelet activation), with endothelial plasminogen activator release, or with activation of prekallikrein to kallikrein (1).

The endothelial cells are sensitive to both hemodynamic and humoral factors that can trigger the secretion of endothelium-derived substances that influence vessel tone and structure. This process involves cell growth, cell migration, and extracellular matrix modulation (21). Antiphospholipid antibodies might also interfere with vascular remodeling, which could well explain the pathologic findings.

In a clinical and pathologic study on neurologic diseases associated with antiphospholipid antibodies,



FIG 3. Case 3: 25-year-old woman with antiphospholipid antibodies syndrome. MR examination was done 3 days after the initial symptoms of this second relapse of myelopathy, 1 year after the first episode.

A, Sagittal SE T2-weighted image (2200/80/1) shows hyperintense focal lesion at T-5 and elongated lesion at T-7 to T-9 (arrowheads). Some atrophy of the cord is evident.

B, Sagittal contrast-enhanced SE T1-weighted image (480/15/3) shows enhancement is present anteriorly at T-7 to T-8 (arrows).

Levine et al (22) reported cerebral infarcts in the anterior and posterior circulation with 70% of the angiograms abnormal for large-artery stenosis. Pathologic material revealed large or medium-sized vessels occluded by thrombi without evidence of vasculitis. Other reports from cerebral biopsy specimens showed a noninflammatory vasculopathy involving the small and medium-sized vessels with luminal occlusion (23) or endothelial hyperplasia. Most vascular occlusions appeared to be intracranial (22, 23).

Some authors have stated that the upper and midthoracic spinal cord regions are at high risk for vascular insufficiency, since they have few major arterial suppliers and the anterior spinal artery is very thin (24); however, even if the anterior spinal axis is discontinuous, particularly at the thoracic level, there are no important arterial hemodynamic consequences secondary to that configuration (25). All our patients had thoracic lesions whose location was not always compatible with arterial infarcts, probably except for case 1, in whom the T6–8 lesion was in the center of the cord. However, this location is seen in both arterial and venous infarcts (26). The locations of the lesions in the other patients suggested venous involvement with venular thrombosis or venous focal congestion (27). In view of the number of transmedullary anastomoses and the triplication of the longitudinal system, there is a tendency for engorgement or stagnation in the thoracic cord. Moreover, some routine dissection studies have shown that thoracic radicular veins could become thrombotic or fibrotic (28). This further supports the concept that the weak vascular-

ization of the thoracic cord may be related to its venous rather than to its arterial arrangement (25).

There is a significant association between CNS involvement in SLE and the presence of antiphospholipid antibodies (lupus anticoagulant and/or ACA) (29–31). In SLE, these antibodies are associated with the development of transverse myelopathy and ocular vasocclusive phenomena (2, 23, 32). Like SLE patients (2), two of our patients (cases 1 and 2) had acute episodes of optic neuropathy. The pattern of visual loss in both was atypical for primary demyelinating optic neuritis: there was no associated pain on ocular movements and MR images of optic nerves obtained with fat-saturated sequences and after administration of contrast material were normal during the acute phase.

Transverse myelopathy is uncommon as a first manifestation of SLE (8, 33, 34). Moreover, previous studies have shown ACA in different neurologic diseases but rarely in MS (35). We could postulate a diagnosis of SLE or MS for our patients, but they did not entirely meet all the diagnostic criteria for SLE (36) or for definite MS (37). We diagnosed primary antiphospholipid syndrome according to the criteria established by Harris (38), but it is still not clear whether antiphospholipid antibodies are related to the pathologic condition or are merely a result of abnormal immunologic status. These antibodies might in fact be considered consequences not causes of a disease involving immunoregulatory dysfunction.

Conclusion

Our patients, with elevated ACA values, had recurrent episodes of acute myelopathy with the following spinal MR patterns: widening of the cord with signal abnormalities, elongated morphology of lesions extending to multiple segments and frequently to a thoracic location, enhancement during relapses, and development of atrophy over time. It is still uncertain whether ACA is causative in acute transverse myelopathy and its recurrences or simply an epiphenomenon of endothelial injury, which can arise in many abnormal clinical conditions.

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