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A Case of Catastrophic Antiphospholipid Syndrome Presented with Diffuse Myelopathy

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Background: Antiphospholipid syndrome (APS) could present numerous clinical features associated with antiphospholipid antibodies. Among them, the symptom complex of predominant microvasculopathy and multiple organ failure is known as 'catastrophic' antiphospholipid syndrome (CAPS) or Asherson's syndrome. Many precipitating factors of CAPS include trauma (either major or minor), malignancies, warfarin withdrawal, "flares" of systemic lupus erythematosus etc. The antiphospholipid antibodies (aPL) mainly effect on the coagulation pathway, however, there are increasing evidences of multifactorial actions of aPL. **Case Report**: A 27-year-old woman presented with dysuria and paraparesis for one day after upper respiratory infection. Neurological examination was compatible to myelopathy at thoracic level. Brain and spinal MRI showed lesions on hypothalamus and diffuse spinal cord. Despite of steroid therapy, probable ischemic cardiomyopathy, livedo reticularis, thrombocytopenia and comatous mental status were developed. She improved partially after plasma exchanges. **Conclusion**: We present a CAPS patient with thrombotic and nonthrombotic manifestations triggered by upper respiratory infection.
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KEY WORDS: Catastrophic antiphospholipid syndrome · Asherson's syndrome · Myelopathy.

Introduction

Antiphospholipid syndrome (APS) is clinically manifested as vascular thrombosis or pregnancy morbidity. Laboratory test should confirm the presence of lupus anticoagulant (LA), anticardiolipin antibody (aCL) or anti-$\beta_2$glycoprotein-I (β_2GPI) antibody. Diagnosis of APS requires at least one of the clinical features and one of the laboratory findings, which are mentioned above.[1] Antiphospholipid antibodies (aPL) are known to cause APS by modulating the cells involved in coagulation pathway and by direct antibody effect on target organs.[2] Recent studies made it clear that the actions of the aPL were multifactorial, and also involved effects on the endothelium and platelets, and possibly on neural tissues and hormonal and complement pathways.[3]

APS can be classified into 'primary' and 'secondary' by underlying etiology. Secondary APS is associated with systemic lupus erythematosus (SLE) and other autoimmune diseases, malignancy, medication and infectious diseases. On the contrary, when APS occurs in patients without clinical or serologic evidence of SLE or other disease, the syndrome is defined as 'primary' APS.[4] Aside from its etiology; the clinical manifestations of APS are divided into two types. Most APS patients present with the so-called 'classic' type as chronic, relatively benign, recurrent thrombotic events involving larger vessels. And some APS patients present with the 'catastrophic' type, which is also described as 'Asherson's Syndrome'.[5] This form starts with acute coagulopathy and multiple organ failure. Through a catastrophic or devastating course, it often ends up the fatality.[6] Catastrophic antiphospholipid syndrome (CAPS) is induced by infection, surgical operation, major or minor trauma, invasive procedures and warfarin withdrawal.[7] We report a CAPS patient presented with diffuse myelopathy triggered by upper respiratory tract infection.

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Case

A 27-year-old unmarried woman with no significant past medical or family history presented with dysuria, paraparesis and hypoesthesia of lower extremities for one day. One week before, she took 3.0 gram of cefazolin and 750 mg of amikacin per a day for mild fever, cough, coryza and sputum. No

preceding skin rash had existed. Blood pressure was 120/70 mmHg, and physical examination revealed neck stiffness. On neurological examination, mental status, mental functions, cranial nerves functions and cerebellar functions were all normal. There was no decreased visual acuity neither visual blurring. Motor and sensory examination revealed MRC G1 on bilateral lower extremities and hypoesthesia below T11 spinal cord level. Knee and ankle jerks were absent. No pathologic reflexes existed. Spinal cord MRI showed diffuse myelopathy in cervical and thoracic spine reaching to the upper medulla (Fig. 1). Routine laboratory tests showed normal results. On CSF study, the results were opening pressure 230 mmCSF, WBC count 2,400/mm^2 (poly 95%), RBC 5,500/mm^2, protein 230 mg/dl, glucose 48 mg/dl and serum glucose 164 mg/dl. Viral markers for Epstein-Barr virus and mycoplasma were negative, as were H & E stain and culture for bacteria as well as AFB stain, culture and PCR for Mycobacterium tuberculosis. Oligoclonal band was absent and IgG index was within normal range. Under the diagnosis of myelitis, IV methylprednisolone started at a dose of 1,000 mg per a day for five days, and IV ceftriazone 4 gram and vancomycin 2 mg per a day injected for two weeks. However, there was no improvement of the neurological findings.

On the 7th hospital day, CSF showed that opening pressure had fallen to 220 mmCSF, WBC counts to 20/mm^2 (l ympho 95%), RBC to 480/mm^2 and that protein and glucose levels were normalized. Brain MRI showed increased T2 signal intensity at the hypothalamus (Fig. 2). Hemoglobin level was 10.9 g/dl and platelet count was 129,000/ul. ESR was 57 mm/hr. direct and indirect Coombs tests were negative. Activated PTT was normal and VDRL was negative. On routine chemistry test, serum SGOT and SGPT were elevated up to 255/167 IU/l and lactate dehydrogenase (LDH) was 1,810 unit/l with elevated LDH4 fraction. Systolic blood pressure was 80 mmHg. On echocardiography, ejection fraction was 60% and there was no vegetation, or intracardiac thrombi. Sinus tachycardia and nonspecific T-wave abnormality on EKG, as well as elevated levels of cardiac enzymes [Creatine kinase (CK) 232 IU/l, CK-MB 9.95 ng/ml, Troponin-T 0.24 ng/ml], suggested cardiac ischemia.

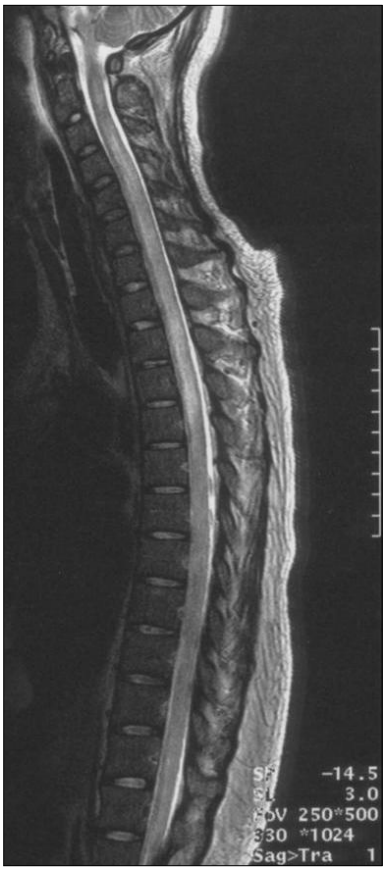

FIGURE 1. Whole spine MRI demonstrates diffuse myelopathy in cervical and thoracic spine reaching to the upper medulla.

On the 28th hospital day, platelet count was decreased to 22,000/ul and purpuric skin eruption with reticular pattern developed on the bilateral lower extremities. Somatic sensory levels ascended to T6 spinal cord level and motor weakness deteriorated to MRC G0 on bilateral lower extremities. On the 30th hospital day, comatose mental status and absent brain stem reflexes were developed. Under the impression of progression to the brain stem, six courses of plasma exchange (50 mL/kg every other day, replaced with serum albumin) were applied. After then, mental status, thrombocytopenia, and skin lesions were improved. However, limited horizontal motions of extraocular muscles ('one and a half syndrome') remained and she could not breathe adequately during sleep, despite voluntary respiration remained intact ('Ondine's curse'). IgG isotype (63.5 GPL), IgM isotype (41.4 MPL) of aCL, and anti-RNP (14.4 AU) were all positive and rheumatic factor was 31.5 IU/ml. ANA was weakly positive. LA and anti-Ro/La were negative. Serum C3 and C4 were decreased.

After oral warfarin and steroid therapy were initiated, brainstem functions were restored but myelopathic sequalae persisted, and there has been no recurrence over 3 years.

Discussion

In this case, differential diagnoses were acute disseminated encephalomyelitis (ADEM), systemic vasculitis involving central nervous system, multiple sclerosis (MS), neuromyelitis optica (NMO), spinal cord infarction, spinal arteriovenos malformation (AVM) and SLE. Patients with ADEM do not develop the thrombocytopenia, livedo reticularis, cardiac and hepatic dysfunctions, which were evident in this case. In systemic vasculitis involving central nervous system, brain lesions must be compatible with multiple infarcts in

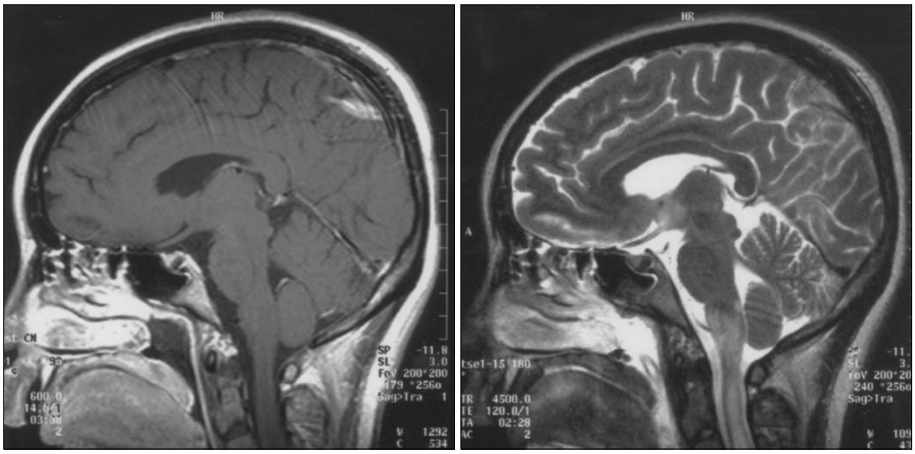

FIGURE 2. Brain MRI demonstrates the increased signal intensity in T2-weighted image, in which there is no contrast enhancement, at the hypothalamus and medulla oblongata.

more than one vascular territory. The MS was less likely because of absent oligoclonal band, normal level of IgG index, multiorgan failure and inconsistent brain and spinal cord lesions on MRI. In this case, optic neuropathy, which is the principal features of NMO, was not evident and systemic symptoms other than brainstem and spinal cord lesions did not compatible with NMO. The diffuse spinal involvement distinguished this patient from spinal infarction or spinal cord AVM, because it did not fit to the vascular territory of the spinal cord. The patient's past medical history, laboratory findings and clinical features did not fulfill the diagnostic criteria of SLE of American Rheumatology Association.[8] Consequently, the diagnosis of this patient was CAPS (Asherson's syndrome) as evidenced by myelopathy, thrombocytopenia, positive aCL, cardiac dysfunction, hepatic dysfunction and livedo reticularis triggered by previous upper respiratory tract infection.

Acute disseminated coagulopathy and vasculopathy associated with aPL are thought to be the major pathophysiology of CAPS. In these patients, clinical findings are acute progressive multiple vascular occlusions involving more than three organs and often results in death.[6] The most frequent predisposing factor is infection; trauma and invasive procedures, anticoagulation problems and tumors follow.[7] Because infection is the most frequent predisposing factor of CAPS, recent studies suggest 'molecular mimicry' theory for infectious triggering of APS. Viral proteins are found to have sequence homology to the GDKU and GDKU2 proteins, which are the major phospholipids binding sites on β_2GPI, and the aPL antibodies are mainly directed to β_2GPI.[9] Then, viral infection may induce pathogenic antiphospholipids and precipitate APS.[10]

The pathogenic mechanisms mediating APS have not yet been completely established. Over the ensuing few years, it became clear that the actions of aPL were multifactorial. The first mechanism of aPL is their effects on the coagulation pathway. Vascular thromboses occurs by the inhibited production of prostacyclin, suppression of protein C pathway and antithrombin III activity, decreased fibrinolysis, activated platelet aggregation and activation of prekallikrein. Regarding thrombotic events, recent studies have emphasized the functions of cells involving coagulation homeostasis. Endothelial cells play a major role in the paradox of the prolongation of coagulation assays in vitro and the association with thrombophilic diathesis in vivo. Experimentally, coagulation is precipitated with damaged, rather than intact, endothelial cells. Endothelial cell apoptosis and thrombotic vasculopathy are induced by activated endothelial cells consisting of cofactors (β_2GPI or prothrombin) of antiphospholipid antibody complex.[11] There is increasing evidence that antithrombin antibodies and anti β_2GPI antibodies may play other important roles in thrombotic events.[12]

The pathogenesis of nonthrombotic events may be the immune-mediated responses such as direct antigen-antibody response, complement-mediated and cytokine-mediated reactions, rather than aPL associated thrombosis.[13,14] Among the nonthrombotic APS events, chorea, transverse myelitis, epilepsy and multiple sclerosis-like syndrome represent the central nervous system involvement. Particularly, direct interaction between aPL and cellular elements of the central nervous system seems to be a more probable mechanism and presence of unrecognized myelin-specific antibody is also suggested in transverse myelitis and multiple sclerosis-like syndrome.[14] Furthermore, transverse myelitis appeared in the viral peptide or anti-β_2GPI antibody -induced APS mice model.[9]

In this case, thrombotic and nonthrombotic mechanisms occurred in one event. This finding suggested that thrombotic and nonthrombotic mechanisms could not be separated each other and more comprehensive pathogenic hypothesis should be considered. This also suggests that while infection may trigger the catastrophic events, it is the underlying genetic,

immunologic and other individual factors of patient background that are much more important in disease progress.

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