

Successful Treatment of Central Nervous System Vasculitis Associated with Antiphospholipid Syndrome

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We report a case of severe, non-migraine headache accompanied by multifocal cerebral artery stenosis in a 41-year-old man with antiphospholipid syndrome (APS). He visited the emergency department with a headache that had occurred 2 days prior to presentation. He was administered low-dose aspirin (100 mg) daily after being diagnosed with antiphospholipid syndrome. Magnetic resonance angiography revealed severe multifocal cerebral artery stenosis. We assumed that multiple stenoses of the cerebral blood vessels were caused by APS; hence, we initiated pulse intravenous methylprednisolone therapy. Oral anticoagulation with warfarin was continued. After treatment, the symptoms and stenosis of the cerebral arteries gradually improved. Awareness of central nervous system vasculitis (with non-migraine headaches) caused by APS should be created among clinicians.

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Antiphospholipid syndrome (APS) primarily causes venous, arterial, and small-vessel thrombosis and pregnancy loss.¹ However, the clinical spectrum of the syndrome has widened, and considerable evidence suggests that APS is mediated through inflammatory immune system mechanisms; additionally, APS could be associated with vasculitis.² Although migraine with aura is the most common neurological manifestation of APS, the symptom of non-migraine headache was not considered specific to APS patients.³ Herein, we present a case of the patient who complained of a severe headache with reversible vasculitis attributed to APS.

CASE

A 41-year-old man with a medical history of livedo reticularis at the age of 36 years, diagnosed with APS, presented to the emergency department with a 2-day history of severe headache and vomiting. The patient was administered low-dose aspirin (100 mg) daily. He said

that the headache seemed to be tightening the whole cranium, although he never experienced a thunder-clap headache. He denied any history of head trauma. On admission, his blood pressure and pulse rate were 200/120 mmHg and 118 beats/min, respectively. However, the other vital signs were normal. Physical examination results were unremarkable. His consciousness was clear, and there were no problems with visual function. No fever or neck stiffness was noted.

Initial brain computed tomography (CT) showed no acute hemorrhagic lesions; however, 1 day later, magnetic resonance angiography (MRA) detected luminal irregularity with moderate to severe multifocal stenoses of both the anterior and middle cerebral arteries (Fig. 1A). No abnormal lesions were observed in the brain parenchyma. A complete blood count and basic laboratory findings were within normal limits, except for an elevated erythrocyte sedimentation rate (21 mm/hour, reference range: 0-9 mm/h) and C-reactive protein (0.83 mg/dL, reference range: 0.00-0.49 mg/dL). However, thrombophilia testing revealed increased titers

of anticardiolipin antibodies, which were recorded at 42.2 U/mL (reference range: <15 U/mL). The patient's immunoglobulin G (IgG) anticardiolipin antibody level was initially 393.3 U/mL (reference range: <12.5 U/mL). The lupus anticoagulant test was positive, and anti- β_2 glycoprotein I IgM antibodies were 38.0 units (reference range: 0-20 units) and anti- β_2 glycoprotein I IgG antibodies were 124.1 units (reference range: 0-20 units). The antinuclear antibody test result was positive, with a titer of 1:40; however, the tests for anti-dsDNA and anti-Sm antibodies were negative. The patient did not meet the American College of Rheumatology and Systemic Lupus International Collaborating Clinics diagnostic criteria for systemic lupus erythematosus (SLE). Moreover, cerebrospinal fluid (CSF) analysis revealed a normal white blood cell count (0/mm³) with no red blood cells. The glucose and total protein concentrations in the CSF were 85 mg/dL (blood glucose level: 98 mg/dL) and 46.7 mg/dL, respectively.

During admission, the patient's headache gradually improved. However, his blood pressure was not well controlled despite the administration of calcium channel and angiotensin II receptor blockers. Therefore, secondary hypertension was suspected. Further investigations were conducted. His renin level was 36 microUI/mL (reference range: 1-2.5 microUI/mL) and aldosterone was 236 pg/mL (reference range: 50-194 pg/mL). These results showed that the patient had hyperreninemia with secondary hyperaldosteronism, which

could be due to renovascular disease. The patient underwent contrast-enhanced computed tomography (CT) of the abdomen. Severe focal stenosis (75-90% stenosis) was observed in the proximal part of the right main renal artery. Renal angioplasty with balloon dilation was then performed. After the procedure, the patient's blood pressure was controlled.

We assumed that multiple stenoses of the cerebral blood vessels were caused by APS and initiated pulse intravenous methylprednisolone therapy. Additionally, maintenance immunosuppressive therapy with oral prednisolone was also initiated. In addition, after renal artery stenting, dual antiplatelet therapy and anticoagulation with a vitamin K antagonist (target international normalized ratio=2.0-3.0) were initiated. After 3 months of treatment, the patient's condition improved considerably. Blood pressure was within the normal range, and no headache was reported. MRA showed improvement in stenosis with mild irregularity in both middle cerebral arteries (Fig. 1B). After 9 months, the irregularity was nearly absent (Fig. 1C).

DISCUSSION

A wide variety of clinical manifestations associated with APS has been reported. Although venous or arterial thrombosis and fetal loss are the most typical clinical manifestations of APS, it is a multisystem disease;

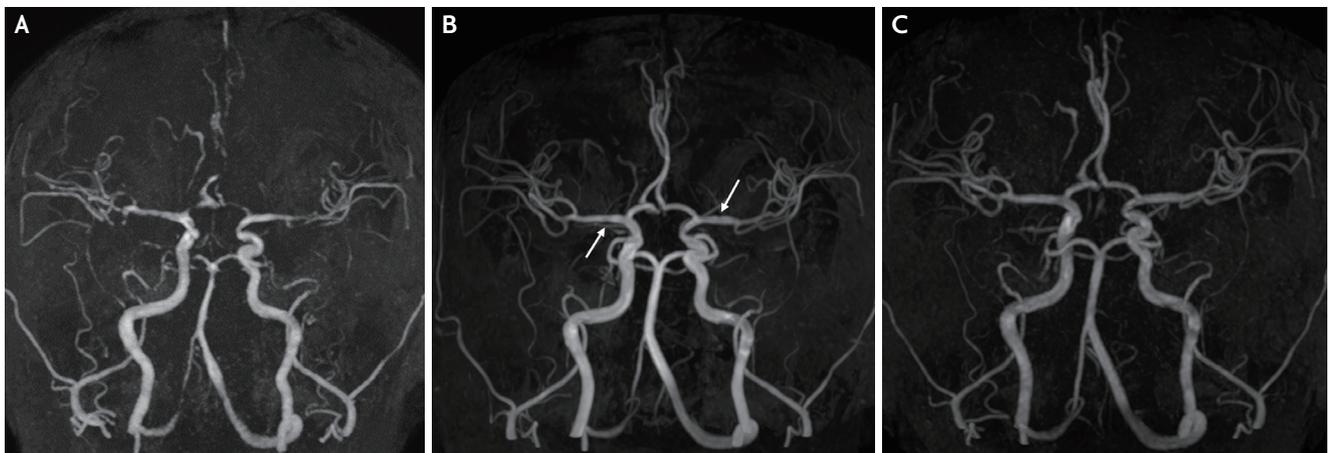


FIG. 1. Central nervous system vasculitis associated with antiphospholipid syndrome. (A) Initial magnetic resonance angiography showed segmental weak flow with multifocal stenosis of both anterior cerebral arteries, both middle cerebral arteries, and right posterior cerebral artery. (B) After 3 months, an improved state of intracranial arterial stenosis is noted, however irregularity of both middle cerebral arteries (M1 segment) remained (arrows). (C) After 9 months, all intracranial arteries are nearly patent.

vascular inflammation may rarely be a component of APS. The pathogenesis of thrombosis in APS is not entirely understood yet; the interactions between antiphospholipid antibodies and antigenic components of the phospholipid complex are essential in mediating the pathologic prothrombotic phenotype.⁴ Subsequent endothelial cell activation and damage contribute to the vascular inflammation of APS.⁵ Differentiating between APS-associated vasculitis and thrombosis may be essential to determine appropriate immunosuppressive or anticoagulant therapy.

Until now, non-migraine headache was not considered a characteristic symptom of APS. However, the chief complaint of our patient was a non-pulsatile headache without aura. These points differ from those of typical migraines. It was not an archetypal thunder-clap, suggesting reversible cerebral vasoconstriction syndrome (RCVS). In addition, RCVS is more prevalent in women, and our patient was not taking any drugs known to cause RCVS. Therefore, we ruled out the possibility of RCVS diagnosis.

Central nervous system (CNS) vasculitis is a rare cause of headache. In our patient, brain MRA showed multifocal stenosis that improved after 3 months of immunotherapy with methylprednisolone. This suggests that multifocal cerebral artery stenosis is an inflammation related to the immune system rather than thrombosis. Therefore, we assumed that the possibility of CNS vasculitis due to APS was high.

Uncontrolled hypertension in this patient may have contributed to the headache. Abdomen CT revealed renal artery stenosis, and the etiology of the patient's elevated blood pressure was thought to be renovascular in origin. The exact mechanism underlying renal artery stenosis in APS patients remains unclear. APS is predominantly a thrombotic condition, although there is now enough evidence to suggest that antiphospholipid antibodies also play a role in the accelerated atherosclerosis observed in some patients. Currently, the best treatment for these patients is anticoagulant therapy and optimal blood pressure control.⁶ We performed immunotherapy with methylprednisolone, dual antiplatelet therapy, and anticoagulation. Headache and uncontrolled hypertension improved dramatically after 3 months.

Our case demonstrated that CNS vasculitis due to

APS can be observed in patients without evidence of vasculitis, such as SLE. It also showed that thrombotic manifestations of APS and vascular inflammation symptoms can occur together in a patient. In other words, as mentioned above, APS is a systemic immune-mediated disease.

To date, most neurological symptoms, such as stroke or transient ischemic attack by APS, have been attributed to thrombotic conditions. However, this case demonstrates that CNS vasculitis caused by APS can be successfully treated with immunotherapy. When patients identified with antiphospholipid antibodies or diagnosed with APS develop headache, the possibility of CNS vasculitis should be considered, and evaluation of cerebral blood vessels should be warranted.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 2110-124-1264). The IRB waived the need for informed consent.

Availability of Data and Material

Due to the nature of this case report, patient did not agree for his data to be shared publicly, so supporting data is not available.

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Conflicts of Interest

No potential conflicts of interest relevant to this article was reported.

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