Neurol Med Chir (Tokyo) 38, 34~39, 1998

Superior Sagittal Sinus Thrombosis Associated with Primary Antiphospholipid Syndrome

—Case Report—

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Abstract

A 36-year-old female with a history of recurrent pregnancy loss experienced sudden onset of disturbance in consciousness, with right hemiparesis and total aphasia. Computed tomography revealed a massive hemorrhage in the left frontal lobe, and angiography showed occlusion of the anterior two-thirds of the superior sagittal sinus. Laboratory investigations detected the presence of lupus anticoagulant, elevation of the anticardiolipin β_2-glycoprotein I complex antibody level, and a decreased protein S activity level. There were no underlying conditions, such as connective tissue disorders, malignancies, infectious diseases, and drug-induced disorders, so the diagnosis was primary antiphospholipid syndrome. Primary antiphospholipid syndrome should be considered in the evaluation of patients with "idiopathic" or "primary" sinus and cerebral venous thrombosis.

Key words: antiphospholipid syndrome, thrombosis, superior sagittal sinus, cerebrovascular disorder

Introduction

Antiphospholipid syndrome is characterized by clinical features which include arteriovenous thrombosis, recurrent pregnancy loss, thrombocytopenia, and the presence of antiphospholipid antibodies including anticardiolipin antibody (aCL) and lupus anticoagulant (LA).[9,11] Antiphospholipid syndrome was first observed in a patient with systemic lupus erythematosus,[11] but has also been observed in patients with other connective tissue disorders, as well as with infections or drug-induced disorders.[9] Antiphospholipid syndrome in the absence of such underlying conditions has been observed, and is defined as primary antiphospholipid syndrome.[1,3] Antiphospholipid syndrome has been associated with juvenile cerebral infarction and transient ischemic attack.[2,15] The deep veins of the lower extremities are commonly involved in venous thrombosis of antiphospholipid syndrome,[13] but sinus and cerebral venous thrombosis are rare with only eight cases reported.[12,14,18,22,23] We report a case of superior sagittal sinus thrombosis associated with primary antiphospholipid syndrome.

Case Report

A 36-year-old female suddenly lost consciousness with vomiting, and was admitted to our hospital on March 9, 1995. Nine days earlier, she had delivered a child prematurely after 9 months of pregnancy. The pregnancy was accompanied by a placental dysfunction syndrome, and the newborn had a hemolytic disease associated with an incompatible blood-type pregnancy. She had previously experienced two spontaneous abortions, one stillbirth, and two other incompatible blood-type pregnancies. She had received a blood transfusion under a diagnosis of idiopathic thrombocytopenia at the age of 12 years. On admission, she was stuporous with total aphasia

Received June 12, 1997; Accepted October 14, 1997

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Table 1 Results of routine coagulative investigation on admission

Test	Normal range	Mar. 9, 1995
White blood cell ($\times 10^3$/mm^3)	4.0–9.0	12.9
Red blood cell ($\times 10^6$/mm^3)	3.8–4.8	3.77
Hemoglobin (g/dl)	12.0–16.0	10.4
Hematocrit (%)	34–42	33.8
Platelet ($\times 10^3$/mm^3)	130–400	172
Bleeding time (min)	≤5	4.5
Prothrombin time (%)	70–100	100
APTT (sec)	20–40	34.4
Fibrinogen (mg/dl)	200–400	393
Hepaplastin test (%)	≥70	120
Thrombin time (%)	≥70	100
FDP (μg/ml)	≤10	10
Antithrombin III (%)	≥70	70
Factor XIII (%)	≥70	121
Coagulation time (min)	5–15	9.5

APTT: activated partial thromboplastin time, FDP: fibrin degradation products.

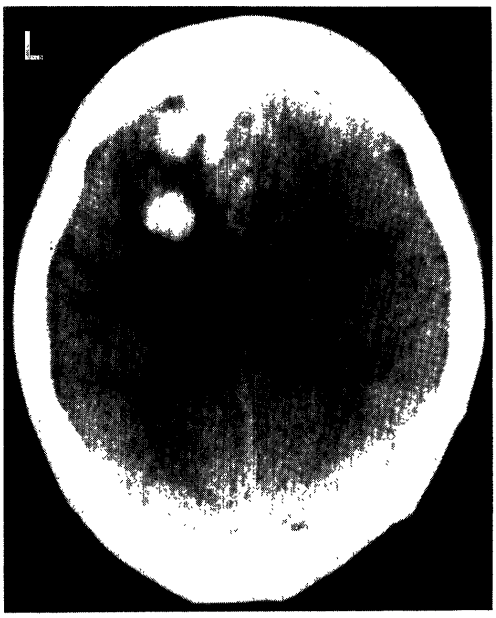

Fig. 1 Computed tomography scan on admission showing a large hypodense area and other patchy hyperdense areas in the left frontal lobe with severe mass effect.

and right hemiparesis accompanied by exaggerated deep tendon reflexes. Physical examination found no abnormalities except a body temperature of 38.0°C. Blood cell count, biochemical examination, and routine coagulative investigation revealed no abnormal findings except for leukocytosis and mild anemia (Table 1).

Computed tomography (CT) revealed an irregular heterogeneous high density area with a perifocal

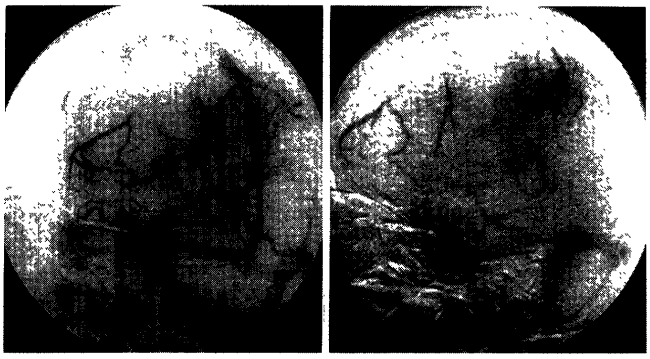

Fig. 2 Left carotid angiograms, venous phase, oblique view (*left*) indicating occlusion of the anterior two-thirds of the superior sagittal sinus, and lateral view (*right*) showing blood stasis in the left frontal veins.

low density area in the left frontal lobe, and the midline was shifted to the right (Fig. 1). Left carotid angiography showed a round shift of both anterior cerebral arteries to the right. In the venous phase, the anterior two-thirds of the superior sagittal sinus could not be identified, and blood stasis was observed in the left frontal veins (Fig. 2). Right carotid angiography revealed that the blood circulating in the right cerebral hemisphere was draining into the superficial middle cerebral vein and the vein of Labbé. Prednisolone, mannitol, and an anticonvulsant were administered. Eight hours after admission, she became comatose, and external decompression was performed. Reflection of the dura revealed several spotty hemorrhages on the swelling brain surface. Palpation showed the bridging veins draining into the superior sagittal sinus were stiff suggesting thrombosis. Blood reserves for perioperative transfusion could not be used, because a serological study showed the indirect Coomb's test result was positive, and irregular agglutinins including anti-RhE, Rhc, and Le^a antibody were detected. The direct Coomb's test result was negative. Her postoperative course was good, and by the 14th day after the surgery, she was able to engage in simple conversations. Angiography performed 5 months after the onset revealed recanalization of the superior sagittal sinus.

The results of further serological and coagulative investigation are presented in Table 2. After the onset throughout her clinical course, the LA test result had been positive, and the aCL to β_2-glycoprotein I complex (aCL β_2-GPI) level had increased. The antinuclear antibody test result was positive one month after the onset, but by one year was negative. The lupus erythematosus test and anti-Sm antibody test results were negative. Anti-double strand-deox-

Table 2 Results of further serological and coagulative investigation

Test	Normal range	Mar. 30, 1995	May 15, 1995	Aug. 21, 1995	May 15, 1996
Lupus anticoagulant	negative	positive	positive	positive	positive
IgG anticardiolipin antibody	≤1.0	1.2	1.7	2.1	1.1
IgM anticardiolipin antibody	≤1.0	0.9	1.1	1.3	0.8
Anticardiolipin β_2-glycoprotein I complex antibody (U/ml)	≤3.5	24.0	22.5	20.4	7.7
Antinuclear antibody	negative	positive	NA	NA	negative
Lupus erythematosus test	negative	negative	NA	NA	negative
Anti-double strand-DNA IgG antibody (U/ml)	≤10	6	NA	NA	NA
Anti-double strand-DNA IgM antibody (U/ml)	≤10	4	NA	NA	NA
Anti-Sm antibody	negative	negative	NA	NA	NA
Serum complement titer (CH50 U/ml)	30.0–40.0	42.1	NA	NA	NA
Protein C antigen (%)	70–150	110	105	NA	86
Protein C activity (%)	55–140	92	106	NA	85
Protein S antigen (%)	65–135	63	59	NA	67
Protein S activity (%)	60–150	39	43	NA	66
Plasminogen activator inhibitor-I (ng/ml)	≤50	14	28	NA	NA

DNA: deoxyribonucleic acid, Ig: immunoglobulin, NA: not available.

yribonucleic acid immunoglobulin G and M antibody levels were within the normal limits. The protein S activity level was moderately decreased and the protein S antigen level was slightly decreased one month after the onset, but both these levels were normal at one year. Protein C antigen, protein C activity, and plasminogen activator inhibitor-I levels were within the normal limits.

The diagnosis was primary antiphospholipid syndrome followed by superior sagittal sinus thrombosis based on her clinical course and the results of the laboratory investigation. She now takes 81 mg/day of aspirin, and leads a normal daily life.

Discussion

The present patient had two clinical and one serological features among the criteria for antiphospholipid syndrome,[9] superior sagittal sinus thrombosis and recurrent pregnancy loss, and a positive LA test result on more than two occasions, respectively. She had no connective tissue disorders or other identifiable underlying diseases, so the diagnosis was primary antiphospholipid syndrome. Other rare clinical and laboratory findings in cases of antiphospholipid syndrome include hemolytic anemia and a positive direct Coomb's test result.[7] The mechanisms underlying these findings may involve the reaction of antibodies with phospholipids present on the surface of erythrocytes. In the present case, the direct Coomb's test result was negative, and no hemolytic anemia was identified. However, the indirect Coomb's test result was positive, and irregular agglutinins were detected. The patient had experienced three incompatible blood-type pregnancies. These findings might have been related to the blood transfusion she received at the age of 12 years as well as the antiphospholipid antibodies.

The pathogenesis of thrombosis associated with antiphospholipid syndrome is not clearly understood. Recently, antibodies against the β_2-GPI-phospholipid complex,[17,21] prothrombin-phospholipid complex,[4] protein S-phospholipid complex,[20] and activated protein C-phospholipid complex[20] have been detected in the serum of patients with antiphospholipid syndrome. In the present case, aCL β_2-GPI was detected. β_2-GPI is a cofactor which is necessary for the binding of aCL to cardiolipin. The aCL reacts with the β_2-GPI-cardiolipin complex which inhibits the prothrombinase activity of platelets and the generation of factor Xa on the surface of activated platelets in patients with antiphospholipid syndrome.[16,17,19,21] In addition, a slightly decreased protein S antigen level and moderately decreased protein S activity level were detected in the present case. These findings might be related to the presence of antibody against the protein S-phospholipid complex. Protein S has an anticoagulant function by directly binding to factor Va, and this function is independent of activated protein C.[10] Consequently, the superior sagittal sinus thrombosis in the present case might have resulted from the inhibition of the β_2-GPI-cardiolipin complex and protein S by aCL β_2-GPI and anti-protein S-phospholipid complex antibody, respectively.

The majority of cerebrovascular disorders associ-

Table 3 Summary of reported cases of cerebral venous thrombosis associated with antiphospholipid syndrome

Author (Year)	Age	Sex	Neurological features	CT findings	Cerebral venous thrombosis	Other venous thrombosis	Arterial thrombosis	Associated findings	Treatment
Levine *et al.* (1987)[14]	21	F	headache, dysmetria, 6th cranial nerve palsy, generalized hyperreflexia	partial delta sign	TS	deep vein, pulmonary embolism	—	spontaneous abortion, thrombocytopenia, lupus anticoagulant	steroids, heparin, warfarin
	32	M	headache, 4th cranial nerve palsy, optic disc edema	hyperdensity along torcular, straight, and sagittal sinus	SSS	—	—	thrombocytopenia, lupus anticoagulant	steroids, heparin, warfarin
Vidailhet *et al.* (1990)[22]	31	F	headache, aphasia, agraphia, seizures	frontal hypodensity	SSS, TS	deep vein	—	lupus anticoagulant, systemic lupus erythematosus	steroids, anticoagulants
	52	F	headache, seizures	old cerebral infarction	TS, JV	—	MCA	spontaneous abortion, thrombocytopenia, lupus anticoagulant, systemic lupus erythematosus	steroids, anticoagulants
	24	F	headache, lt hemiplegia, seizures	partial hypodensity and hyperdensity	SSS	—	—	spontaneous abortion, thrombocytopenia, lupus anticoagulant, aCL, systemic lupus erythematosus	steroids, heparin, warfarin
Mokri *et al.* (1993)[18]	49	M	headache, papilledema	normal	TS	—	—	aCL	warfarin, aspirin
Yamaguchi *et al.* (1993)[23]	24	M	consciousness disturbance, aphasia, rt hemiparesis	temporal hyperdensity and hypodensity	vein of Labbé	deep vein, portal vein, inferior vena cava, pulmonary embolism	ICA	thrombocytopenia, lupus anticoagulant, aCL	craniotomy, aspirin
Khoo *et al.* (1995)[12]	51	M	headache, attention and memory deficits, dyscalculia, rt–lt disorientation	normal	SSS, TS, straight sinus	—	—	lupus anticoagulant	steroids, heparin, local urokinase infusion, warfarin
Present case	36	F	consciousness disturbance, aphasia, rt hemiparesis	frontal hyperdensity and hypodensity	SSS	—	—	spontaneous abortion, lupus anticoagulant, aCL β_2-GPI	steroids, craniotomy, aspirin

aCL: anticardiolipin antibody, aCL β_2-GPI: anticardiolipin β_2-glycoprotein I complex antibody, CT: computed tomography, ICA: internal carotid artery, JV: jugular vein, MCA: middle cerebral artery, SSS: superior sagittal sinus, TS: transverse sinus.

ated with antiphospholipid syndrome are occlusive disorders, mainly cerebral infarction and transient ischemic attack, caused by thrombosis or thromboembolism.[2,15] Sinus and cerebral venous thrombosis is relatively rare. The nine reported cases[12,14,18,22,23] (Table 3) showed no specific features in terms of the CT findings and neurological symptoms, like sinus and cerebral venous thrombosis of other etiologies.[5] However, serological studies showed a positive LA test result and/or increased aCL level in all cases. These nine patients, four males and five females, were aged from 21 to 52 years (average 35.6 years). Four of the five females had experienced one or more spontaneous abortions, and sinus and cerebral venous thrombosis occurred during pregnancy or just after delivery in three. Four patients developed other arterial and/or venous thrombosis, and five had thrombocytopenia. Three cases were associated with systemic lupus erythematosus. All nine patients were treated with anticoagulants (heparin and/or warfarin) and/or platelet-activating agent (aspirin), and seven patients with steroids. Craniotomy was performed in two of the three patients under a diagnosis of hemorrhagic infarction. One patient with superior sagittal sinus and transverse sinus thrombosis received a local injection of urokinase. These procedures all yielded good results.

The etiologies of sinus and cerebral venous thrombosis can be divided into infectious and non-infectious types. Various non-infectious etiologies, such as pregnancy, post-partum, oral contraceptives, head injury, tumors, Behçet's disease, nephrotic syndrome, have been reported.[5] However, 10 of 38 cases of sinus and cerebral venous thrombosis had no definite etiology.[5] The presence of aCL or LA was not examined in these cases. Recently, tests for aCL and LA were made in a series of 40 patients with cerebral venous thrombosis, finding aCL or LA in four patients.[6] An increased aCL level was found in three of another series of 40 patients with cerebral venous thrombosis.[8] These reports suggest that some patients with a diagnosis of sinus and cerebral venous thrombosis of unknown etiology may have primary antiphospholipid syndrome. Therefore, primary antiphospholipid syndrome should be considered in the evaluation of patients with sinus and cerebral venous thrombosis of unknown etiology.

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