Fatal Cerebral Infarction in an Asymptomatic Young Patient
With Primary Antiphospholipid Syndrome

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An 18-year-old woman with primary antiphospholipid syndrome developed a
major cerebral infarction leading to brain death despite intensive treatment with
steroids, urokinase, glycoel and heparin. Fatal strokes associated with this syn-
drome are rare. A computed tomographic scan of the brain suggested occlusion
of the main trunk of the right middle cerebral artery. The titer of antibodies
against cardiolipin/β₂-glycoprotein I complex in serum was extremely high.
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ANTIPHOSPHOLIPID antibodies (aPL) are
frequently detected in patients with
systemic lupus erythematosus (SLE) or rela-
ted autoimmune diseases. The main clinical
complications associated with the presence
of these antibodies are vascular occlusions,
recurrent fetal loss and thrombocytopenia.
The term “antiphospholipid syndrome” has
been applied to patients characterized by
these pathologic features associated with
increased levels of aPL.¹,² We report here a
young woman with primary antiphospholipid
syndrome who developed major cerebral
infarction leading to brain death. The clinical
significance of aPL and the management of
patients with aPL are also discussed.

CASE REPORT
An 18-year-old woman developed chilblains on her feet in January 1989. Since
her left 4th toe became gangrenous, she underwent amputation of the left 4th toe in
January 1990 at our hospital. Serological tests at that time gave a false-positive sero-
logic test for syphilis, positive antinuclear antibody (ANA) and a positive LE test, but
there were no clinical signs suggestive of connective tissue diseases such as SLE.
Over the next 3 years, she experienced relatively good health without any thrombotic
events until February 24, 1993, when she was readmitted to our hospital because of
a sudden onset of dysarthria and left hemiplegia.
On admission, her blood pressure was
154/76 mmHg, her pulse rate was 60/min and
regular, and her body temperature was 37.1
°C. There were no abnormal physical find-
ings in the heart, lungs or abdomen. She
was not completely alert and had difficulty
in speaking, but was well-oriented and
responded normally to questions and
commands. Conjugate deviation to the right
and right-sided homonymous hemianopsia
were present. Left flaccid hemiparesis with
hypesthesia was observed. The deep tendon
reflexes of the extremities were equal and
normoactive, but Babinski sign was positive
on the left. Hematological examination
showed a mild thrombocytopenia (10.8 × 10⁴

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Japanese Circulation Journal Vol 59, September 1995 641
titer of antibodies to cardiolipin (CL)/β₂-glycoprotein I (β₂-GPI) complex was markedly elevated (>125 U/ml, normal range: <3.5) (optical density at 450 nm was 1.283 in the presence of β₂-GPI and 0.537 in the absence of β₂-GPI) according to the ELISA method developed by Yamasa Shoyu Co. Ltd. Circulating immune complexes (C1q binding assay) were negative. APTT was within the normal range (36.9 sec, normal range: 26.0–38.0 sec). Chest X-ray film and electrocardiogram showed no abnormalities. Echocardiogram did not reveal endocarditis, valvulitis or cardiac thrombus. Plain computed tomographic (CT) scan of the brain taken 2 h after the onset was almost normal except for a focal, low-density area just behind the posterior horn of the right lateral ventricle (Fig. 1A).

The clinical course is shown in Fig. 2. Since her neurological signs suggested cerebral thrombosis, immediately after admission she received steroid pulse therapy, urokinase and heparin. A CT scan of the brain on the second hospital day showed a large, heterogeneous, low-density area in the right cerebral hemisphere which corresponded to the territory of the right middle cerebral artery (MCA) (Fig. 1B). Despite intensive treatment, CT scans of the brain disclosed progressive worsening of the brain edema. On the fourth hospital day, respiratory arrest developed abruptly and artificial respiration was started. On the 6th day, she was diagnosed as brain death based on deep coma, apnea, bilateral dilated pupils, absence of brainstem reflex, a flat electroencephalogram and absence of auditory evoked brainstem response. Plain CT scan of the brain on the 6th day showed a widespread, low-density area in the right half of the brain with marked compression and shift of the lateral ventricles (Fig. 1C). The loss of all cisterns and subarachnoid space suggested cerebral and cerebellar herniation. Despite the absence of brainstem function, she survived for about 6 months while being treated with prednisolone (20 mg/day), catecholaminergic drugs, vasopressin and heparin under the support of artificial ventilation and parenteral hyperalimentation. Plain CT scan of the brain 19 weeks after the onset showed a diffuse, homogenous, low-density area over the whole brain (Fig. 1D).

Japanese Circulation Journal Vol. 59, September 1995
She died of cardiac arrest on August 19, 1993.

Chronological changes in the titers of autoantibodies are shown in Fig. 2. The increased titers of aCL (IgG, IgM) were normalized within a week after beginning steroid therapy. The titers of a-ssDNA, ANA and RPR were also normalized within 1 month. These autoantibodies remained negative or at a low level over the clinical course until her death. The titers of aCL, a-ssDNA, ANA and RPR on admission were almost the same as those at the outpatient clinic. The titer of a-dsDNA remained negative.

DISCUSSION

Our patient was considered to be diagnosed as primary antiphospholipid syndrome, since she had a history of arterial thrombosis (gangrene of the toe) and showed a persistent elevation of aCL titers without apparent clinical features of SLE or lupus-like disease.

Her present stroke was attributed to arterial thrombosis related to aCL, since she had no other risk factors for cerebrovascular disease, and echocardiogram revealed no vegetation or mural thrombus. A CT scan of the brain suggested cerebral infarction due to occlusion of the main trunk of the right MCA or the right internal carotid artery. Levine et al. reported that cerebral angiography revealed large-vessel occlusion or stenosis without changes which might suggest vasculitis in some patients with aPL who presented with cerebral or visual dysfunction. Strokes associated with aPL are often recurrent, multiple and are caused by occlusion of relatively large cerebral arteries, but are rarely fatal. Fatal major cerebral infarction leading to brain death in primary antiphospholipid syndrome has not yet been

Japanese Circulation Journal Vol. 59, September 1995
reported.

aPL can be detected in blood samples not only in SLE and related autoimmune diseases, but also in syphilis and other various infectious diseases. Recent studies showed that aCL associated with autoimmune diseases recognize a novel epitope generated by the interaction of phospholipids and a cofactor, whereas aCL associated with infectious diseases bind to phospholipids directly. This cofactor was identified as \( \beta_2 \)-GPI (apolipoprotein H) by McNeil et al. Matsuura et al. showed that the addition of human cofactor enhanced the aCL titer in SLE and reduced it in syphilis, and suggested that autoimmune-type aCL can be discriminated from infectious-type aCL. In our patient, the aCL titer, expressed in terms of optical density, was markedly increased by the addition of \( \beta_2 \)-GPI, which suggests the existence of autoimmune-type aCL. Recent evidence indicates that \( \beta_2 \)-GPI exerts multiple inhibitory effects on blood coagulation. These findings raise the possibility that aPL interfere with \( \beta_2 \)-GPI function, thereby predisposing the patient to thrombotic diathesis. The titer of antibodies to CL/\( \beta_2 \)-GPI complex is considered to be a more useful predictor of thrombosis than the titer of antibodies to CL itself. The extremely high titer of antibodies to CL/\( \beta_2 \)-GPI complex in our patient may be attributed to the present fetal cerebral infarction.

It is still unclear how to prevent vascular occlusions in primary antiphospholipid syndrome. Our patient had been untreated until the present stroke because she showed low positive aCL levels and had no clinical or laboratory evidence of active connective tissue diseases. Although the aCL level is a useful predictor of vascular thrombosis, an increase from a low to a high positive aCL titer can not be used to predict the onset of thromboembolic events. Our patient also showed no rise in titers of aCL, a-ssDNA, ANA or RPR preceding the present event. It has been recently recommended that asymptomatic patients with sustained high levels of aCL should receive long-term, low-dose aspirin therapy, and patients with one or more episodes of vascular occlusion should receive long-term treatment with oral anticoagulants such as warfarin, even if the other episodes occurred many years previ-ously?

We should recognize that patients with antiphospholipid syndrome, even asymptomatic young patients, may develop fatal strokes, and therefore require strict management and long-term follow-up to prevent serious occlusive vascular complications associated with aPL. Methods for preventing and predicting vascular complications are needed, especially in asymptomatic young patients with this syndrome.

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\textit{Japanese Circulation Journal} Vol. 59, September 1995
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