

Catastrophic Primary Antiphospholipid Antibody Syndrome

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In the years since the antiphospholipid antibody syndrome (APLS) was first described in 1983,¹ significant interest has been generated in this autoimmune disorder, largely because of its association with thrombo-occlusive events in virtually every organ system and the clinical sequelae of these thromboses. In patients with persistent elevation of their antiphospholipid antibody level, the major clinical manifestations of APLS include arterial or venous thrombosis, recurrent fetal loss, and thrombocytopenia. Because of the greater awareness among clinicians of the syndrome, APLS is being diagnosed with increasing frequency despite its diverse signs and symptoms, which can mimic a variety of clinical disorders.

This article reports the case of a 52-year-old woman with gait instability in whom primary APLS marked by recurrent thrombosis was diagnosed. The rapid progression of her disease (including bilateral internuclear ophthalmoplegia, respiratory failure, and gastrointestinal hemorrhage) despite apparently adequate anticoagulation therapy highlights the need for improved strategies in the treatment of APLS.

CASE PRESENTATION

A 52-year-old Haitian woman was admitted to the hospital because of a 1-day history of gait instability. There was no history of a fall, weakness, numbness, paresthesias, headaches, dizziness, loss of consciousness, diplopia, dysphagia, change in vision, chest pain, or palpitations. Medical history was significant for a spontaneous abortion in 1981, a cerebrovascular accident with central loss of vision in 1997, and a right lacunar infarct in the internal capsule with residual left upper extremity paresis in 1998. The patient had been taking aspirin (81 mg) daily since her stroke in 1997 and had no hypertension, diabetes mellitus, or hyperlipidemia. She did not smoke cigarettes or use illicit drugs.

The patient's vital signs were within normal limits. The only significant findings were gait instability, mild left upper extremity monoparesis, left pronator drift, left facial paresis, and mild dysarthria. Her platelet count on admission was $245 \times 10^3/\text{mm}^3$. A computerized tomographic (CT) scan of the head showed evidence of a lacunar infarct in the anterior limb of the right internal capsule.

The history of recurrent strokes in this 52-year-old woman who had no apparent predisposing factors, as well as her prior spontaneous abortion, suggested the presence of a hypercoagulable state (Table 1) or vasculitis. Based on serology, a diagnosis of APLS was made. Pertinent laboratory data are shown in Table 2. Other recently described causes of thrombophilia (eg, protein C and S deficiency, resistance to activated protein C) were not thought to play a role in the patient's condition because of the normal results on laboratory testing; moreover, these alternate causes more commonly are associated with venous thromboembolism (their role in arterial thromboses currently is unresolved). The slightly elevated homocysteine level might have contributed to her disorder, but its precise effect was unquantifiable. The patient was started on anticoagulation therapy using unfractionated heparin.

Magnetic resonance imaging performed 1 day after admission showed an area of hypoattenuation in the pons and medulla, which suggested another infarct.

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Table 1. Hypercoagulable States

Activated protein C resistance
Antiphospholipid antibody syndrome
Antithrombin III deficiency
Dysfibrinogenemia
Hageman factor deficiency
Homocystinuria
Hypercoagulable state of patients taking certain medications (eg, oral contraceptives, heparin)
Plasminogen and plasminogen-activator deficiency
Protein C and S deficiency

Two days after admission, the patient developed bilateral internuclear ophthalmoplegia with worsening dysarthria and left facial palsy, followed within 24 hours by dysphagia and left hypoglossal palsy. A feeding tube was placed to prevent aspiration. Her platelet count remained within normal range, so heparin-induced thrombocytopenia was excluded as a cause of her worsening condition. Anticoagulation was continued and appropriately monitored.

On the fourth day after admission, the patient developed acute respiratory distress and hypoxic respiratory failure. She was tachycardic and tachypneic, and coarse crackles were heard over both lung fields on auscultation. Arterial blood gas analysis showed respiratory alkalosis with hypoxemia. Chest radiography was unremarkable. The patient was intubated and transferred to the medical intensive care unit. A repeat CT scan of the head revealed no intracranial bleeding. A normal ventilation perfusion lung scan essentially ruled out a pulmonary embolus. The patient was given dexamethasone for presumed cerebral edema.

Her clinical course over the next few days included massive upper gastrointestinal hemorrhage and inability to be weaned off ventilator dependence. A tracheostomy was performed, and a gastrostomy feeding tube was placed. The patient subsequently was transferred to a long-term care facility.

DISCUSSION

Etiology and Epidemiology

APLS can be either primary or secondary in nature. Secondary APLS can be caused by certain coexisting disorders (eg, systemic lupus erythematosus, immune thrombocytopenic purpura and other autoimmune disorders, leukemia and other cancers, infections) or by the use of particular drugs (eg, chlorpromazine, procainamide). Estimates of the number of persons in

Table 2. Laboratory Test Results in the Case Patient

Test	Result
Anti-DNA antibodies (quantitative)	Negative (normal result)
Antinuclear antibody panel	Negative (normal result)
aPTT	26.9 sec (normal, 20.9–34.5 sec)
Erythrocyte sedimentation rate	15 mm/h (normal, 0–20 mm/h)
IgG aCL	42.6 µg/mL (normal, < 23 µg/mL)
	41.7 µg/mL* (normal, < 23 µg/mL)
IgM aCL	3.3 µg/mL (normal, < 11 µg/mL)
	2.1 µg/mL* (normal, < 11 µg/mL)
Serum C3 complement	126 µg/mL (normal, 104–187 mg/dL)
Serum C4 complement	37 µg/mL (normal, 21–87 mg/dL)
Serum homocysteine level	12.7 µmol/L (normal, < 9 µmol/L)
Serum protein C activity	115.3% (normal, 73%–139%)
Syphilis screen	Nonreactive (normal result)

aCL= anticardiolipin antibody; aPTT = activated partial thromboplastin time.

*Repeat values obtained after 4 months.

the general population with antiphospholipid antibodies in their blood range from 2%² to 6.5%.³ These antiphospholipid antibodies can cause thrombosis in any vessel or organ in the body.^{4,5}

Pathophysiology

APLS can present clinically in various ways. Typical cardiovascular signs include abnormalities of the cardiac valves (eg, regurgitation, thickening and diminished mobility of the blood, vegetations), myocardial infarction, thrombocytopenia, pulmonary embolism (with infarction), pulmonary hypertension, livedo reticularis, superficial thrombophlebitis, gangrene, ocular ischemia (leading to visual disturbances), and cerebrovascular ischemia. Other common findings include dementia, atypical migraines, seizures, chorea, Guillain-Barré syndrome, acute and subacute renal failure (with proteinuria and an active urine sediment), renal infarction, gastrointestinal hemorrhage, acute abdominal symptoms, esophageal necrosis, adrenal insufficiency, and multiorgan failure.

Cerebral ischemia is the most common arterial thrombotic sign of APLS.^{6–9} A recurrent stroke frequently occurs within a year of the index cerebral ischemic

event.^{10,11} Higher titers of anticardiolipin antibody (aCL) seem to correlate with increased risk for recurrent thrombotic events,¹² although no consensus exists regarding the significance of aCL titers (ie, whether they are low, mid, or high range) in predicting recurrent strokes.⁴ In a prospective study of 81 patients with APLS conducted over a 7-year period, 31% had recurrent ischemic strokes.¹⁰ Patients with aCL IgG titers greater than 100 G phospholipid (GPL) units had a significantly shorter time to recurrence than did those with lower titers (10 to 100 GPL units).¹⁰ Another prospective study of 27 patients with aCL IgG titers greater than 100 GPL units revealed a 96% incidence of recurrent thrombo-occlusive events over a mean 3-year follow-up period.¹³

The hypercoagulable state of patients with antiphospholipid antibodies seems to derive from adverse effects of these autoantibodies on coagulation proteins, platelet activation, and endothelial cell contributions.^{14–16} The proposed specific mechanisms by which aCLs interfere with hemostasis to induce thrombosis include interference with endothelial release of prostacyclin¹⁷ or plasminogen activator,¹⁸ activation of protein C by thrombomodulin, interference with protein S activity,¹⁹ interference with antithrombin III activity,²⁰ interference with prekallikrein activation to kallikrein,²¹ and interaction with platelet membrane phospholipids.²²

Diagnosis

The diagnosis of APLS is based on a combination of pertinent clinical and laboratory findings. Cerebrovascular thrombotic events, especially in young patients (ie, those < 60 years), and recurrent arterial or venous thrombo-occlusive episodes in the absence of an obvious etiology should prompt an investigation for evidence of APLS. Autoantibody testing to detect the presence of 3 types of antibodies in particular can help confirm the presence of APLS.

Lupus anticoagulants. Lupus anticoagulants are antibodies directed against plasma proteins (eg, prothrombin) bound to anionic phospholipids.^{23–25} They block the assembly of the prothrombinase complex, resulting in prolongation of in vitro clotting assays used to determine, for example, activated partial thromboplastin time (aPTT), dilute Russell viper venom time, and kaolin clotting time. The prolongation of aPTT is not corrected by the addition of normal platelet-free plasma.

Anticardiolipin antibodies. aCLs react with phospholipids such as cardiolipin and phosphatidylserine. Although there is a high degree of concordance between the presence of aCLs and the presence of lupus anticoagulants, lupus anticoagulants are a separate popula-

tion of antibodies.^{26–28} The presence of lupus anticoagulants carries a somewhat greater risk for thrombosis.

Antibodies to β_2 glycoprotein 1. Antibodies to β_2 glycoprotein 1, a phospholipid-binding inhibitor of coagulation, are found in many patients with APLS and are the sole antiphospholipid antibodies in approximately 11% of these patients.⁴ Multiple tests to detect these antibodies must be performed if the clinical suspicion of APLS is high, because a single test will detect only 60% to 80% of cases.²⁹

Management

Treatment of patients with APLS generally consists of anticoagulation with heparin, followed by administration of warfarin. Patients with APLS who have a major thrombotic event should receive lifelong anticoagulation with warfarin so they can maintain an international normalized ratio (INR) of 3 or more^{30–32} (but certainly never below 2.6^{33,34}). In patients with APLS who have thrombocytopenia, INRs of 2 to 3 are recommended.

Because some patients with APLS have a baseline prolongation of their aPTT, the usual way of monitoring the anticoagulant effects of heparin is not always reliable. An alternative to this method involves measuring plasma heparin levels by either protamine titration or an automated assay using anti-factor X_a. Another alternative method is to give these patients low-molecular-weight heparin with the dose determined solely by body weight, thus negating the need for laboratory monitoring.

Plasmapheresis is advocated in life-threatening cases of APLS, while the addition of corticosteroids is recommended for patients with platelet counts less than $50 \times 10^3/\text{mm}^3$.³⁵ For pregnant woman, combining aspirin and heparin is the current standard treatment.^{36,37} In cases of recurrent thrombosis, aspirin therapy alone is not effective.³⁸

CONCLUSION

APLS continues to generate considerable clinical and research interest. Further study is needed to delineate the optimal approach(es) to therapy for patients with APLS. Moreover, the accurate identification of subsets of patients with APLS who are at highest risk for developing major thromboses is necessary to institute appropriate preventive measures. **HP**

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