CHAPTER 16

Antiphospholipid Syndrome

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- An acquired cause of hypercoagulability; 50% of antiphospholipid syndrome (APS) patients have systemic lupus erythematosus (SLE).
- Antiphospholipid syndrome predisposes to both venous and arterial thrombosis. The most common venous thrombosis is deep venous thrombosis; the most common arterial thrombosis is stroke.
- Antiphospholipid syndrome predisposes to miscarriage and other pregnancy morbidity.
- Antiphospholipid syndrome may cause thrombocytopenia.
- Antiphospholipid syndrome is diagnosed by persistent antiphospholipid antibody: lupus anticoagulant; anticardiolipin; and anti–beta 2 glycoprotein I.

Antiphospholipid antibodies (aPL) are autoantibodies directed against negatively charged phospholipid/plasma proteins. The most common plasma protein target is beta 2 glycoprotein I. The three most important antiphospholipid antibodies are the lupus anticoagulant, anticardiolipin, and anti–beta 2 glycoprotein I.

Antiphospholipid syndrome (APS) is one of the most common acquired causes of hypercoagulability. Fifty percent of APS patients have systemic lupus erythematosus (SLE). APS presents in two major ways: thrombosis (venous or arterial) and pregnancy loss. Thrombocytopenia, present in about 20% of cases, can be an important clue.

EPIDEMIOLOGY

Antiphospholipid antibodies (aPL) occur in 1% to 6% of the general population (1). The estimated relative risk of venous thromboembolism with anticardiolipin is 2 and with the lupus anticoagulant is 10 (2). APL also increase the risk of an initial myocardial infarction, initial stroke, recurrent stroke, and death. In patients presenting with a deep venous thrombosis, up to 30% will have the APS. In a person under age 50 with a stroke, up to 46% will have APS.

If APS occurs in a patient without SLE or other connective tissue disease, it is termed *primary APS*. About 8% of primary APS patients later develop SLE (3). In SLE patients, about 30% have anticardiolipin and about 25% have the lupus anticoagulant. The term *secondary APS* is used for SLE patients who have aPL and have had thrombosis or pregnancy losses. The risk of venous thrombosis in a SLE patient with the lupus anticoagulant is 50% by 20 years after diagnosis.

CLINICAL FEATURES

The most common cutaneous finding in APS patients is livedo reticularis, a purplish lacelike reticular pattern, especially apparent on the extremities. Other cutaneous signs include splinter hemorrhages, superficial thrombophlebitis, cutaneous necrosis, digital gangrene, and leg ulcers (4).

Venous thrombosis in APS usually presents as a deep venous thrombosis of the lower extremities. Other possible sites of venous thrombosis include pulmonary emboli, Budd–Chiari syndrome, and dural sinus thrombosis.

The most common site of arterial thrombosis is the brain. Although strokes can occur from in situ thrombosis, about one third of patients with primary APS have cardiac valve vegetations or valve thickening that can lead to emboli. Rarely, a destructive valvulitis occurs requiring valve replacement. Other sites of arterial thrombosis include myocardial infarction, retinal thromboses, renal artery thrombosis, glomerular capillary thrombi, and digital gangrene. Pregnancy losses from APS can occur in the first trimester or as late fetal deaths. Severe placental insufficiency can occur. HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) has been reported in APS, as well, but the true relationship between the HELLP syndrome and APS is unclear.

Some nonthrombotic neurologic presentations of APS include chorea and transverse myelitis.

Approximately 20% of APS patients have thrombocytopenia, usually in the range of 50 to 140,000/mm^3.

TABLE 16-1. CLASSIFICATION CRITERIA FOR ANTIPHOSPHOLIPID SYNDROME (SYDNEY REVISION).

One clinical criterion	
Thrombosis	Arterial or Venous or Vasculopathy
pregnancy morbidity	3 or more first trimester losses or 1 or more late fetal losses or Severely preterm birth due to placental insufficiency
One laboratory criterion: persistent over 3 months	
Lupus anticoagulant or Moderate/high titer IgG or IgM anticardiolipin or Moderate/high titer IgG or IgM anti–beta 2 glycoprotein I	

SOURCE: From Miyakis S, et al. J Thromb Haemost 2006;4:295–306, by permission of *Journal of Thrombosis and Haemostasis*.

Thrombosis can occur even in the presence of thrombocytopenia in APS. Catastrophic APS is a rare presentation with multiorgan thrombi (5). Precipitants of catastrophic APS include infection, surgery, pregnancy, exogenous estrogen, and cessation of anticoagulation. In the evaluation of APS, it is necessary to exclude genetic and acquired causes of hypercoagulability (6). Genetic causes include Factor V Leiden, the G20210A prothrombin mutation, deficiency of antithrombin III, Protein C or Protein S, and hyperhomocysteinemia.

CLASSIFICATION CRITERIA

Classification criteria for APS have been revised multiple times, most recently in 2006 (Table 16-1) (7). Classification requires a clinical criterion (thrombosis or pregnancy morbidity) plus evidence of persistence (present twice over 3 months) of the lupus anticoagulant, medium or high titer IgG/IgM anticardiolipin, or medium-to-high titer IgG/IgM anti–beta 2 glycoprotein I antibodies.

LABORATORY FEATURES

Lupus Anticoagulant

The lupus anticoagulant (LA) is a double misnomer, because only 50% of patients with LA have lupus. Moreover, the LA behaves as a procoagulant in vivo. To confirm the presence of an LA, three criteria are required:

1. A sensitive screening test must show prolongation of the clotting time. A sensitive activated partial thromboplastin time (aPTT) or the dilute Russell viper venom time (dRVVT) is recommended for screening. No single screening test can detect all LAs.

2. Prolongation of the clotting time must be due to an inhibitor (rather than a factor deficiency). This is confirmed by demonstrating that the prolonged clotting time does not correct with a 1:1 or 4:1 mix with normal plasma.

3. Phospholipid dependence of the coagulation test abnormality must be demonstrated. This can be accomplished in several ways, including a platelet neutralization procedure.

Anticardiolipin

Anticardiolipin (aCL) is actually an antibody directed against negatively charged phospholipids bound to beta 2 glycoprotein I. Only medium-to-high titers of the IgG or IgM isotype are accepted for the classification criteria.

Anti–Beta 2 Glycoprotein I

International criteria for anti-beta 2 glycoprotein I (anti-beta 2 GPI) assays do not yet exist. However, multiple valid commercial assays are in use. It is unusual for an APS patient to be negative for both LA and aCL. Thus, anti-beta 2 GPI is rarely necessary to make the diagnosis/classification of APS.

PATHOLOGY

Thrombotic events in APS are bland; that is, in the absence of a coexisting condition, there is no evidence of vasculitis.

PATHOGENESIS

The pathogenesis of APS is complex and multifactorial, reflecting the fact that aPL bind to plasma proteins and to endothelial cells involved in multiple steps in coagulation. APL interfere with the activated Protein C complex and also bind to platelets. They bind to endothelial cells, leading to upregulation of cytokines and tissue factor.

A murine model of APS pregnancy loss has shown that aPL lead to complement activation. Complement deficiency or inhibition of complement activation is protective against pregnancy loss and thrombosis in this model (8). In addition, the benefit of heparin in the animal model is due to its anti-inflammatory effect, not to anticoagulation.

Antiphospholipid syndrome (APS) complications happen to only a minority of patients with aPL. Several features are thought to increase the risk of thrombosis, including the lupus anticoagulant (over aCL), high titers of aCL, persistence of aPLs for longer than 6 months, and comorbid factors including estrogen, thalidomide, nephrotic syndrome, bed rest, surgery, pregnancy, and the postpartum period.

TREATMENT

Asymptomatic Antiphospholipid Antibodies

Patients with aPL but no history of thrombosis or pregnancy loss should avoid medications that might contribute to hypercoagulability, including oral contraceptives and hormone therapy. Other risk factors for hypercoagulability should be minimized. Low dose aspirin can be considered as a prophylactic therapy, but efficacy has not been proven in clinical trials.

Asymptomatic Antiphospholipid Antibodies in Systemic Lupus Erythematosus

In addition to low dose aspirin, hydroxychloroquine can be considered as a possible prophylactic intervention in SLE patients. The benefit of hydroxychloroquine has been confirmed in an animal model and in several observational cohort studies in SLE.

Pregnancy Loss

The preferred regimen to prevent pregnancy loss is prophylactic doses of unfractionated or low-molecular-weight heparin plus low dose aspirin (81 mg) (9). This regimen causes less maternal morbidity (diabetes mellitus, cataracts) and less pregnancy morbidity (preeclampsia, preterm birth) than the older regimens of prednisone and aspirin. Unfortunately, the heparin and aspirin regimen is successful in only 75% of pregnancies. If unsuccessful, there is some scientific rationale to the addition of intravenous immunoglobulin in the next pregnancy.

Thrombosis

The treatment of an acute thrombotic event (thrombolysis and/or heparin) is not changed by knowledge that the patient has an aPL. Because of the high risk of recurrence of thrombosis in APS, a strong case can be made for life-long anticoagulation after a first thrombotic event. If anticoagulation is stopped after 6 months, there is a recurrence rate of 20% or more (10). Although a past retrospective series suggested that an International Normalized Ratio (INR) in the high intensity range (3.0–4.0) was required, two subsequent randomized clinical trials (11,12) have proven that normal intensity anticoagulation (2.0–3.0) is both sufficient and safer in the long term.

The APS patient with thrombosis and thrombocytopenia is of special concern. Thrombocytopenia does not protect the APS patient from thrombosis. Most thrombocytopenia in APS is mild, in the range of 90 to 140,000. Profound thrombocytopenia, however, would greatly increase the risk of bleeding with anticoagulation. The platelet count should be stable at above 50,000 before chronic anticoagulation is begun, and the INR goal would be 2.0 in such a patient.

One clinical trial found no difference in outcome in stroke patients with aPL randomized to aspirin or to warfarin. Stroke patients in this trial had aPL measured at baseline, but were not shown to be persistently positive, a requirement for the classification of APS.

Many experts believe that APS patients with arterial thrombosis should be maintained on both low dose aspirin and warfarin anticoagulation, because platelets are involved in the pathogenesis of arterial thrombi. However, the addition of aspirin does increase the risk of bleeding.

Catastrophic Antiphospholipid Syndrome

Based on analysis of a large case series, catastrophic APS is treated by heparin, plasmapheresis or intravenous immunoglobulin, and high dose methylprednisolone (the latter likely calms the cytokine storm produced by the intense endothelial cell activation) (5). Cyclophosphamide is not recommended as initial therapy because of the increased risk of infection. Mortality of catastrophic APS, even with intensive treatment in major academic centers, remains 50%.

Experimental Treatments

Statins have benefit for APS in animal models and reduce thrombosis in clinical studies of non-APS patients. However, they cannot be used in pregnancy and have not been studied formally in APS.

Rituximab depletes B cells, including B cells that make aPL. However, the period of B-cell depletion is variable, and long-lived plasma cells make aPL survive. Further studies are needed before it can be recommended for APS.

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