Antiphospholipid syndrome (APS) is a hypercoagulable disorder that results in vascular thrombosis. The symptoms are numerous and depend on the size and location of the vessels involved. Patients with this condition can have significant morbidity and occasionally mortality. It is important for dermatologists to be knowledgeable about APS because a large percentage of patients with this condition will present with dermatologic manifestations. If diagnosed and treated early, patients can be spared the consequences of this serious disease.

**Case Report**

A 41-year-old man was referred to our dermatology clinic because of a 3-day history of a widespread painful eruption. The patient had no significant past medical history and denied fevers, chills, nausea, vomiting, abdominal pain, chest pain, and shortness of breath. The patient’s vital signs were stable. A full skin examination revealed multiple reticulate, purpuric, and...
necrotic plaques on all 4 extremities (Figure 1). The affected areas varied in size from 1 cm to greater than 10 cm in length, and some had overlying vesiculation. The trunk was relatively spared.

Two punch biopsies from the left thigh showed fibrin thrombi in the dermal vessels, ischemic necrosis of the overlying epidermis, dermal hemorrhage, and no evidence of vasculitis (Figure 2). The patient's antiphospholipid antibody titer (immunoglobulin [Ig] G >150 antiphospholipid units; reference, high >80 antiphospholipid units) and anti-β2-glycoprotein I antibody titer (IgG 53 U/mL; reference, normal <10 U/mL) were both very elevated and remained significantly elevated when tested 6 weeks later. A complete blood count with differential, comprehensive metabolic profile, urinalysis, blood cultures, coagulation studies, dilute Russell viper venom test, protein C and S activity levels, cryoglobulin levels, serum protein electrophoresis, rheumatoid factor, and antinuclear antibody screen were all within reference range or negative.

The patient was diagnosed with primary antiphospholipid syndrome (APS) and referred to rheumatology for treatment. He was subsequently placed on enoxaparin sodium (a low molecular weight heparin) and has not developed any skin lesions or other symptoms of APS for more than 1 year after beginning treatment. His skin lesions were treated with local wound care (mupirocin and nonadhesive dressing) and healed with minimal scarring over 2 to 3 months.

Comment

APS is a relatively new disease entity. The first antiphospholipid antibody was described in patients with syphilis in 1906, while the first lupus anticoagulant was described in 1952 by Conley and Hartmann. However, it was not until the 1980s that APS was described by Hughes and Hughes et al, the first to note the association between antiphospholipid antibodies and hypercoagulability.

APS is divided into primary and secondary categories. Primary APS occurs in the absence of any other disease, whereas secondary APS is associated with autoimmune disease or another condition. Systemic lupus erythematosus is by far the most common condition seen with secondary APS. Antiphospholipid antibodies also can be seen in association with infections, medications, and cancers; these antibodies usually are IgM antibodies, present at low levels, often only transiently elevated, and usually do not lead to APS. However, it has been shown that patients with infection-related antiphospholipid antibodies may be at increased risk for developing catastrophic APS.

Dermatologic symptoms are common in APS and often can be the first or only signs of the disease. In a study of 200 patients with APS, Francès et al reported that 49% of the patients had dermatologic findings and more than 30% of the patients presented with skin complaints. In a study of 39 patients with APS, Diógenes et al reported that 16 patients (41%) had a dermatologic symptom as the main complaint. In a study of 295 patients with circulating lupus anticoagulant, Alegre et al reported that nearly one quarter of the patients displayed cutaneous manifestations. Finally, in a study of 100 patients with infection-related APS, 36% of patients developed skin findings.

Livedo reticularis is the most common skin finding in APS. In the study by Francès et al, livedo reticularis was the most frequent dermatologic symptom occurring in slightly more than one quarter of cases. In a study of 1000 patients with APS, Cervera et al reported that livedo reticularis was found in just more than 24% of patients and was the presenting sign in 20.4% of patients. In the study of 100 patients with infection-related APS, 16% of patients developed livedo reticularis. Furthermore, a large percentage of cases of Sneddon syndrome (livedo reticularis and cerebrovascular accidents) have been shown to be manifestations of APS.

Cutaneous necrosis is another common manifestation of APS and, after livedo reticularis, is likely the most common dermatologic finding. Cervera et al reported that necrotic skin ulcerations were seen in 5.5% of 1000 patients with APS and was the presenting manifestation in 3.9% of patients. It is important that patients be tested for APS whenever they display unexplained necrotic and ulcerative lesions that appear secondary to thrombosis and vascular occlusion.

In addition to livedo reticularis and cutaneous necrosis, other cutaneous manifestations of APS have been reported, including pyoderma gangrenosum, gangrene, purpura fulminans, acrocyanosis, Raynaud phenomenon, livedoid vasculitis, subungal splinter hemorrhages, venous leg ulcerations, Degos disease-type lesions, thrombophlebitis, cutaneous papules and nodules, erythema nodosum, anetoderma, and multiple sterile abscesses. The nondermatologic features of APS are numerous and depend on the size and location of the vessels involved. The most common manifestation of APS is venous thrombosis, particularly lower extremity deep venous thrombosis. Up to one half of patients with venous thrombosis will develop pulmonary emboli. Arterial thromboses occur less often than venous thromboses and can present as strokes and transient ischemic attacks (most common), myocardial infarctions, blindness, and acute renal failure. The search for APS is suggested in any young patient who develops a stroke.
Figure 1. Multiple reticulate necrotic plaques of varying sizes on the ankle (A), anterior thigh (B), medial thigh (C), and leg (D).

Figure 2. Biopsy from the edge of a purpuric plaque shows fibrin thrombi in the dermal vessels, dermal hemorrhage, and a lack of vasculitis (H&E, original magnification ×40). Photograph courtesy of Dr. Thomas N. Helm.
Cardiac valvular vegetations with resultant emboli are not uncommon in patients with APS. Hematologic findings include thrombocytopenia, hemolytic anemia, and thrombotic microangiopathies (eg, hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura). Obstetric complications are common and are among the diagnostic criteria for APS (Table 1). Although the exact incidence of pregnancy loss in women with antiphospholipid antibodies currently is unknown, rates as high as 90% have been reported in untreated patients. However, this rate drops to between 15% and 35% with appropriate therapy (ie, low dose aspirin and low molecular weight heparin). In addition, antiphospholipid antibodies have been shown to be responsible for 15% of patients with 3 or more consecutive fetal losses.

According to the proposed criteria, the diagnosis of APS requires at least 1 clinical and 1 laboratory criterion (Table 1). The clinical criteria include a documented episode of vascular thrombosis (arterial, venous, or small-vessel thrombosis) and complications of pregnancy (eg, recurrent spontaneous abortions at <10 weeks of gestation). The laboratory criteria include the presence of anticardiolipin antibodies and a positive lupus anticoagulant test on 2 or more occasions at least 6 weeks apart. Anticardiolipin antibodies are a more sensitive test for APS, while positive tests for lupus anticoagulant are more specific. In addition, although not included in the official criteria, it also is important to obtain anti-β2-glycoprotein I antibodies, as these are felt to be very important in the pathophysiology of APS.

Although the histopathologic findings of APS are nondiagnostic and do not differ from the findings caused by other thrombotic conditions (eg, monoclonal cryoglobulinemia), histologic confirmation of thrombosis sometimes is helpful. Biopsy of early skin lesions can show dermal edema, hemorrhage, noninflammatory thrombosis of small- and medium-sized vessels, and occasional epidermal necrosis. Later findings include organization and recanalization of thrombi, vascular proliferation, and hemosiderin deposition. Although a perivascular lymphocytic infiltrate may be seen, vasculitis is absent.

For the unfamiliar, the laboratory evaluation of APS can be confusing, raising questions on what tests to order and how to interpret them. A practical approach to the laboratory evaluation of the patient with suspected APS is presented in Table 2. This approach can be divided into tests specific for APS, tests to investigate other potential causes of a hypercoagulable state, and tests to identify associated conditions. Laboratory investigations related specifically to APS include the lupus anticoagulant test, anticardiolipin antibody titers, and anti-β2-glycoprotein I antibody titers. Phospholipid-dependent coagulation tests, including the activated partial-thromboplastin time, kaolin clotting time, and dilute Russell viper venom, are used to detect the presence of lupus anticoagulant antibodies. In APS, these coagulation tests are prolonged and fail to correct with the addition of normal plasma, but they do correct with the addition of excess phospholipid or platelets. At least 2 coagulation tests should be conducted and need to be negative in order to rule out APS.
Antiphospholipid Syndrome

The physician only needs to order “lupus anticoagulant,” as most hematology laboratories will then automatically conduct 2 anticoagulant tests.

Enzyme-linked immunosorbent assays (ELISAs) are used to detect and quantify IgM and IgG levels of antcardiolipin and anti-β2-glycoprotein I antibodies. Results often are expressed in terms of low, moderate, and high titers. Moderate or high levels of these antibodies are considered clinically significant and suggestive of APS. Low levels are less specific and can be associated with postinfectious sequelae or can be seen in clinically healthy patients. ELISAs for antibodies against prothrombin, annexin V, and other phospholipids (eg, phosphatidylinerine, phosphatidylethanolamine) are still under development and not routinely obtained.

It should be stressed that the presence of antiphospholipid antibodies alone does not necessarily indicate disease. Up to 5% of healthy control subjects will have antiphospholipid antibodies, and this prevalence increases with age. Also, anticardiolipin and lupus anticoagulant antibodies have been found in 5% and 8% of healthy blood donors, respectively.

The exact mechanism of how antiphospholipid antibodies produce thrombosis is unknown. Theories include activation of endothelial cells, oxidative damage to endothelial cells, and interference with the coagulation cascade. The latter theory seems most plausible given that β2-glycoprotein I is felt to be a natural anticoagulant.

Long-term anticoagulation with coumadin is the treatment of choice for patients with thrombosis.

Table 2.
Recommended Laboratory Workup for a Patient With Suspected Antiphospholipid Syndrome (APS)

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<th>APS Specific</th>
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<tr>
<td>Lupus anticoagulant</td>
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<td>Anticardiolipin antibody titer</td>
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<td>Anti-β2-glycoprotein I antibody titer</td>
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<th>Other Coagulopathies (if clinically indicated)</th>
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<tr>
<td>Cryoglobulin levels</td>
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<td>Cryofibrinogen levels</td>
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<td>Protein C activity</td>
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<td>Protein S activity</td>
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<td>Factor V Leiden mutation testing</td>
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<th>Other (if clinically indicated)</th>
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<td>Complete blood count</td>
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<td>Peripheral blood smear</td>
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<td>Blood cultures</td>
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<td>Coagulation studies</td>
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<td>Rheumatoid factor</td>
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<td>Fibrin split products</td>
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<td>Skin biopsy</td>
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Antiphospholipid Syndrome

secondary to APS. Patients with venous thrombosis should have an International Normalized Ratio (INR) of 2 to 3; patients with arterial thrombosis require more aggressive therapy with an INR of 2.5 to 3.5. Low molecular weight heparin is an alternative to coumadin. Any risk factors for thrombosis (eg, smoking) should be reduced or eliminated. Symptomatic pregnant patients normally are treated with low molecular weight heparin and possibly low dose aspirin. Hydroxychloroquine and steroids have no role in APS, unless it is secondary to an underlying systemic disease (eg, systemic lupus erythematosus). Finally, intravenous immunoglobulin may have a role in severe recalcitrant APS, APS associated with severe thrombocytopenia, and cases of catastrophic APS.

Conclusion

Given that many patients with APS present initially or only with dermatologic manifestations, it is crucial that the dermatologist has a sound working knowledge of this important condition. With timely diagnosis and treatment, patients may be spared significant morbidity and even occasional mortality caused by this serious disease.

REFERENCES


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