Antiphospholipid Syndrome: A Review and Update for the Dermatologist

Jonathan E. Blume, MD; Craig C. Miller, MD, PhD

GOAL

To understand antiphospholipid syndrome (APS) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the dermatologic importance of APS.
2. Explain the clinical and laboratory diagnosis of APS.
3. Describe the treatment of APS.

CME Test on page 416.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: November 2006.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Drs. Blume and Miller report no conflict of interest. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest.

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.

Cutis. 2006;78:409-415.

Accepted for publication June 27, 2006.

Dr. Blume is Instructor in Clinical Dermatology, Columbia University College of Physicians and Surgeons, New York, New York. Dr. Miller is Assistant Professor of Clinical Dermatology and Dermatology Residency Program Director, State University of New York at Buffalo School of Medicine.

Reprints: Jonathan E. Blume, MD, Westwood Dermatology and Dermatologic Surgery Group, PA, 390 Old Hook Rd, Westwood, NJ 07675 (e-mail: jeblumemd-derm@yahoo.com).

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 anticardiolipin antibody titer (immunoglogulin [Ig] G >150 anticardiolipin units; reference, high >80 anticardiolipin units) and anti-β_2-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,[1] while the first lupus anticoagulant was described in 1952 by Conley and Hartmann.[2] However, it was not until the 1980s that APS was described by Hughes[3] and Hughes et al,[4] 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.[5] 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.[5] However, it has been shown that patients with infection-related antiphospholipid antibodies may be at increased risk for developing catastrophic APS.[6]

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[7] 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[8] 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[9] 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.[6]

Livedo reticularis is the most common skin finding in APS. In the study by Francès et al,[7] 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[10] 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.[6] Furthermore, a large percentage of cases of Sneddon syndrome (livedo reticularis and cerebrovascular accidents) have been shown to be manifestations of APS.[11-13]

Cutaneous necrosis is another common manifestation of APS and, after livedo reticularis, is likely the most common dermatologic finding.[14-18] Cervera et al[10] 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,[19,20] gangrene,[9] purpura fulminans,[6] acrocyanosis,[8] Raynaud phenomenon,[8] livedoid vasculitis,[21] subungual splinter hemorrhages,[22] venous leg ulcerations,[23] Degos disease-type lesions,[24,25] thrombophlebitis,[9] cutaneous papules and nodules,[26] erythema nodosum,[27] anetoderma,[28,29] and multiple sterile abscesses.[30]

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.[5] 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.[31] The search for APS is suggested in any young patient who develops a stroke.[31] Catastrophic APS occurs when numerous thromboses develop in multiple organs, frequently resulting in death.[5]

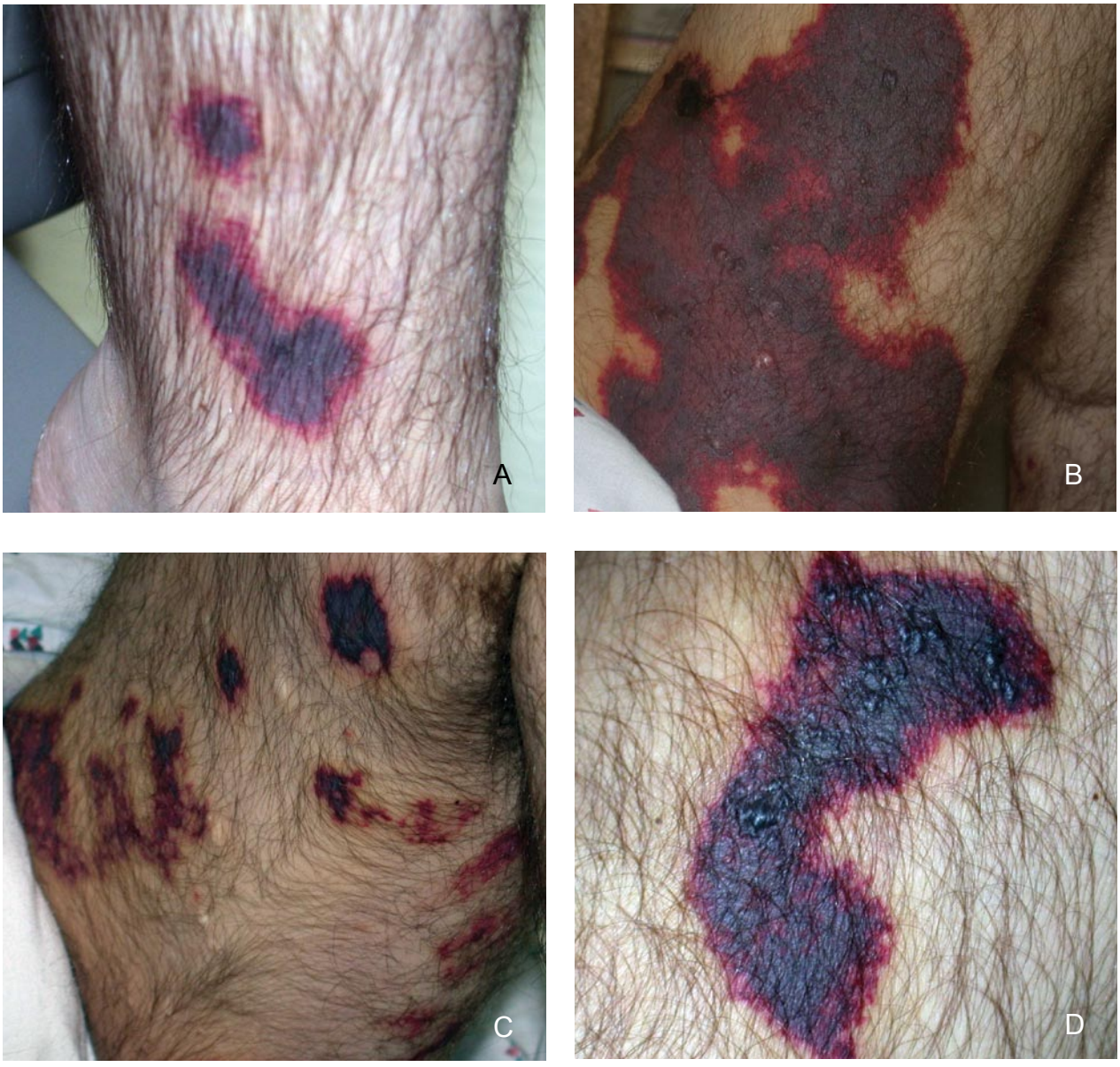

Figure 1. Multiple reticulate necrotic plaques of varying sizes on the ankle (A), anterior thigh (B), medial thigh (C), and leg (D).

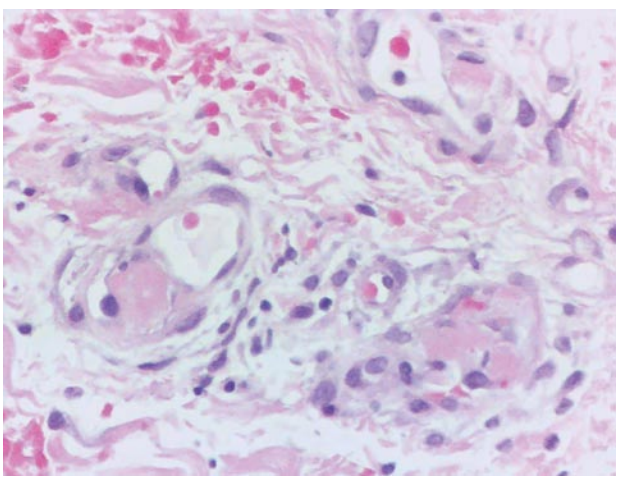

Figure 2. Biopsy from the edge of a purpuric plaque shows fibrin thrombi in the dermal vessels, dermal hemorrhage, and a lack of vasculitis (H&E, original magnification ×40). Photograph courtesy of Dr. Thomas N. Helm.

Table 1.

International Consensus Statement—Criteria for Antiphospholipid Syndrome*†[34-36]

Clinical Criteria
Vascular thrombosis (≥1 episodes of arterial, venous, or small-vessel thrombosis)
Complications of pregnancy (fetal loss at 10 wk of gestation or later without apparent fetal abnormalities; ≥1 premature births of neonates without apparent fetal abnormalities at or before 34 wk of gestation; ≥3 consecutive unexplained spontaneous abortions at ≤10 wk of gestation)
Laboratory Criteria
Anticardiolipin antibodies, immunoglobulin (Ig) G or IgM of moderate or high titer, on ≥2 occasions at least 6 wk apart
Lupus anticoagulant antibodies on ≥2 occasions at least 6 wk apart

*Diagnosis of antiphospholipid syndrome requires at least 1 clinical and 1 laboratory criterion.
†Although not included in the official criteria, anti-β_2-glycoprotein I antibodies (IgG and IgM titers) also should be obtained.

Cardiac valvular vegetations with resultant emboli are not uncommon in patients with APS.[32] Hematologic findings include thrombocytopenia, hemolytic anemia, and thrombotic microangiopathies (eg, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura).[5] Obstetric complications are common and are among the diagnostic criteria for APS (Table 1).[33] 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.[37] However, this rate drops to between 15% and 35% with appropriate therapy (ie, low dose aspirin and low molecular weight heparin).[38] In addition, antiphospholipid antibodies have been shown to be responsible for 15% of patients with 3 or more consecutive fetal losses.[39]

According to the proposed criteria, the diagnosis of APS requires at least 1 clinical and 1 laboratory criterion (Table 1).[34] The clinical criteria include a documented episode of vascular thrombosis (arterial, venous, or small vessel) 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.[34] Anticardiolipin antibodies are a more sensitive test for APS, while positive tests for lupus anticoagulant are more specific.[5] In addition, although not included in the official criteria, it also is important to obtain anti-β_2-glycoprotein I antibodies, as these are felt to be very important in the pathophysiology of APS.[34-36]

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.[40] Later findings include organization and recanalization of thrombi, vascular proliferation, and hemosiderin deposition. Although a perivascular lymphocytic infiltrate may be seen, vasculitis is absent.[40]

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-β_2-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.[41] At least 2 coagulation tests should be conducted and need to be negative in order to rule

Table 2.

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

APS Specific
Lupus anticoagulant
Anticardiolipin antibody titer
Anti-β_2-glycoprotein I antibody titer
Other Coagulopathies (if clinically indicated)
Cryoglobulin levels
Cryofibrinogen levels
Protein C activity
Protein S activity
Factor V Leiden mutation testing
Other (if clinically indicated)
Complete blood count
Peripheral blood smear
Blood cultures
Coagulation studies
Antinuclear antibodies
Rheumatoid factor
Fibrin split products
Skin biopsy

out the presence of lupus anticoagulant antibodies.[42] 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 anticardiolipin and anti-β_2-glycoprotein I antibodies.[43,44] 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.[5] 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, phosphatidylserine, phosphatidylethanolamine) are still under development and not routinely obtained.[45,46]

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.[47] Also, anticardiolipin and lupus anticoagulant antibodies have been found in 5% and 8% of healthy blood donors, respectively.[48,49]

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 β_2-glycoprotein I is felt to be a natural anticoagulant.[5]

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

secondary to APS.[50] 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.[50] Hydroxychloroquine and steroids have no role in APS, unless it is secondary to an underlying systemic disease (eg, systemic lupus erythematosus).[51] Finally, intravenous immunoglobulin may have a role in severe recalcitrant APS, APS associated with severe thrombocytopenia, and cases of catastrophic APS.[52-54]

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

1. Wassermann A, Neisser A, Bruck C. Eine serodiagnostiche reaktion bei syphilis. *Deutsche Med Wochenschr.* 1906;32: 745-746.
2. Conley CL, Hartmann RC. A haemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. *J Clin Invest.* 1952;31:621-622.
3. Hughes GR. Thrombosis, abortion, cerebral disease and lupus anticoagulant. *Br Med J.* 1983;287:1088-1089.
4. Hughes GR, Harris NN, Gharavi AE. The anticardiolipin syndrome. *J Rheumatol.* 1986;13:486-489.
5. Levine JS, Branch DW, Rauch J. The antiphospholipid antibody syndrome. *N Engl J Med.* 2002;46:752-763.
6. Cervera R, Asherson RA, Acevedo ML, et al. Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. *Ann Rheum Dis.* 2004;63:1312-1317.
7. Francès C, Niang S, Laffitte E, et al. Dermatologic manifestations of the antiphospholipid syndrome: two hundred consecutive cases. *Arthritis Rheum.* 2005;52:1785-1793.
8. Diógenes MJ, Diógenes PC, de Morais Carneiro RM, et al. Cutaneous manifestations associated with antiphospholipid antibodies. *Int J Dermatol.* 2004;43:632-637.
9. Alegre VA, Gastineau DA, Winklemann RK. Skin lesions with circulating lupus anticoagulant. *Br J Dermatol.* 1989;120:419-429.
10. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum.* 2002;46:1019-1027.
11. Sneddon JB. Cerebrovascular lesions and livedo reticularis. *Br J Dermatol.* 1965;77:180-185.
12. Levine SR, Langer SL, Albers JW, et al. Sneddon's syndrome: an antiphospholipid antibody syndrome? *Neurology.* 1988;38:798-800.
13. Kalashnikova LA, Nasonov EL, Stoyanovich LZ, et al. Sneddon's syndrome and the primary antiphospholipid syndrome. *Cerebrovasc Dis.* 1994;4:76-82.
14. Dodd HJ, Sarkany I, O'Shaughnessy D. Widespread cutaneous necrosis associated with the lupus anticoagulant. *Clin Exp Dermatol.* 1985;10:581-586.
15. O'Neill A, Gatenby PA, McGaw B, et al. Widespread cutaneous necrosis associated with cardiolipin antibodies. *J Am Acad Dermatol.* 1990;22(2 pt 2):356-359.
16. Abernethy ML, McGuinn JL, Callen JP. Widespread cutaneous necrosis as the initial manifestation of the antiphospholipid antibody syndrome. *J Rheumatol.* 1995;22:1380-1383.
17. Creamer D, Hunt BJ, Black MM. Widespread cutaneous necrosis occurring in association with the antiphospholipid syndrome: a report of two cases. *Br J Dermatol.* 2000;142:1199-1203.
18. DiFrancesco LM, Burkart P, Hoehn JG. A cutaneous manifestation of antiphospholipid antibody syndrome. *Ann Plast Surg.* 2003;51:517-522.
19. Selva A, Ordi J, Roca M, et al. Pyoderma-gangrenosum-like ulcers associated with lupus anticoagulant. *Dermatology.* 1994;189:182-184.
20. Schlesinger IH, Farber GA. Cutaneous ulcerations resembling pyoderma gangrenosum in the primary antiphospholipid syndrome: a report of two additional cases and review of the literature. *J La State Med Soc.* 1995;147:357-361.
21. Acland KM, Darvay A, Wakelin SH, et al. Livedoid vasculitis: a manifestation of the antiphospholipid syndrome. *Br J Dermatol.* 1999;140:131-135.
22. Asherson RA. Subungual splinter haemorrhages: a new sign of antiphospholipid coagulopathy? *Ann Rheum Dis.* 1990;49:268-271.
23. Fink AM, Kottas-Heldenberg A, Mayer W, et al. Lupus anticoagulant and venous leg ulcerations. *Br J Dermatol.* 2002;146:308-310.
24. Englert HJ, Hawkes CH, Boey ML, et al. Degos' disease: association with anticardiolipin antibodies and the lupus anticoagulant. *Br Med J (Clin Res Ed).* 1984;289:576.
25. Farrell AM, Moss J, Costello C, et al. Benign cutaneous Degos' disease. *Br J Dermatol.* 1998;139:708-712.
26. Ishikawa O, Takahashi A, Tamura A, et al. Cutaneous papules and nodules in the diagnosis of the antiphospholipid syndrome. *Br J Dermatol.* 1999;140:725-729.
27. Nekhlyudov L, Gradzka M, Conti-Kelly AM, et al. Erythema nodosum associated with antiphospholipid antibodies: a report of three cases. *Lupus.* 2000;9:641-645.
28. Romani J, Perez F, Llobet M, et al. Anetoderma associated with antiphospholipid antibodies: a case report and review of the literature. *J Eur Acad Dermatol Venereol.* 2000;15:175-178.

29. Bilen N, Bayramgurler D, Sikar A, et al. Anetoderma associated with antiphospholipid syndrome and systemic lupus erythematosus. *Lupus*. 2003;12:714-716.
30. Lee SC, Kim DH, Won YH. Multiple sterile abscesses in antiphospholipid antibody syndrome. *Cutis*. 2001;68: 283-286.
31. Asherson RA, Khamashta MA, Ordi-Ros J, et al. The "primary" antiphospholipid syndrome: major clinical and serological features. *Medicine (Baltimore)*. 1989;68:366-374.
32. Vianna JL, Khamashta MA, Ordi-Ros J, et al. Comparison of the primary and secondary antiphospholipid syndrome: a European multicenter study of 114 patients. *Am J Med*. 1994;96:3-9.
33. Carp HJ. Antiphospholipid syndrome in pregnancy. *Curr Opin Obstet Gynecol*. 2004;16:129-135.
34. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum*. 1999;42:1309-1311.
35. Bas de Laat H, Derksen RH, de Groot PG. β_2-glycoprotein I, the playmaker of the antiphospholipid syndrome. *Clin Immunol*. 2004;112:161-168.
36. Obermoser G, Bitterlich W, Kunz F, et al. Clinical significance of anticardiolipin and anti-β_2-glycoprotein I antibodies. *Int Arch Allergy Immunol*. 2004;135:148-153.
37. Rai RS, Clifford K, Cohen H, et al. High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. *Hum Reprod*. 1995;10:3301-3304.
38. Clowse ME, Magder LS, Witter F, et al. Early risk factors for pregnancy loss in lupus. *Obstet Gynecol*. 2006;107: 293-299.
39. Wisloff F, Crowther M. Evidence-based treatment of the antiphospholipid syndrome: I. pregnancy failure. *Thromb Res*. 2004;114:75-81.
40. Weeden, ed. *Skin Pathology*. 2nd ed. Philadelphia, Pa: Churchill Livingstone; 2002.
41. Brandt JT, Triplett DA, Alving B, et al. Criteria for the diagnosis of lupus anticoagulant: an update. *Thromb Haemost*. 1995;74:1185-1190.
42. Brandt JT, Barna LK, Triplett DA. Laboratory identification of lupus anticoagulants: results of the second international workshop for identification of lupus anticoagulants on behalf of the subcommittee on lupus anticoagulants/antiphospholipid antibodies of the ISTH. *Thromb Haemost*. 1995;74:1597-1603.
43. Greaves M, Cohen H, Machin SJ, et al. Guidelines on the investigation and management of the antiphospholipid syndrome. *Br J Hematol*. 2000;109:704-715.
44. Passam FH, Krilis SA. Laboratory tests for the antiphospholipid syndrome: current concepts. *Pathology*. 2004;36: 129-138.
45. McIntyre JA, Wagenknecht DR. Anti-phosphatidylethanolamine (aPE) antibodies: a survey. *J Autoimmun*. 2000;15:185-193.
46. Pierangeli SS, Harris EN. Clinical laboratory testing for antiphospholipid syndrome. *Clin Chim Act*. 2005;357:17-33.
47. Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun*. 2000;15:145-151.
48. Vila P, Hernandez MC, Lopez-Fernandez MF, et al. Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. *Thromb Haemost*. 1994;72:209-213.
49. Shi W, Krilis SA, Chong BH, et al. Prevalence of lupus anticoagulant in a healthy population: lack of correlation with anticardiolipin antibodies. *Aust N Z J Med*. 1990;20:231-236.
50. Triplett DA. Lupus anticoagulants: diagnosis and management. *Curr Hematol Rep*. 2003;2:271-272.
51. Petri M. Hydroxychloroquine use in the Baltimore Lupus Cohort: effects on lipids, glucose and thrombosis. *Lupus*. 1996;5(suppl 1):S16-S22.
52. Sherer Y, Levy Y, Shoenfeld Y. Intravenous immunoglobulin therapy of antiphospholipid syndrome. *Rheumatol*. 2000;39:421-426.
53. Asherson RA, Cervera R. Catastrophic antiphospholipid syndrome. *Curr Rheumatol Rep*. 2003;5:395-400.
54. Horn HC, Grau K, Junker P. IVIG treatment for progressive stroke in primary antiphospholipid antibody syndrome. *Lupus*. 2004;13:478-480.