

Antiphospholipid Antibodies and Arterial Thrombosis

Case Reports and a Review of the Literature

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● Antiphospholipid antibodies are a relatively heterogeneous mix of immunoglobulins with binding specificities for negatively charged or neutral phospholipids. Currently, the most commonly detected antiphospholipid antibodies include the anticardiolipin antibody, the lupus anticoagulant, and an antibody implicated in false-positive VDRL testing. Recently, a clinical syndrome of vaso-occlusive disorders associated with antiphospholipid antibodies has been identified and may result from immune-mediated disruption of endothelial function. This clinical syndrome encompasses arterial and venous thrombosis, recurrent fetal loss, neurologic dysfunction (eg, migraine, chorea, and encephalopathy), systemic and pulmonary arterial hypertension, and endocardial disease. Although most commonly associated with systemic lupus erythematosus, the antiphospholipid antibody syndrome also has been identified in patients with vaso-occlusive disease without systemic lupus erythematosus. Recently, identification of antiphospholipid antibodies has been facilitated by the development of a more sensitive assay for anticardiolipin antibody. In this article, case histories of three patients with arterial thrombosis and associated anticardiolipin antibodies, including the first associated case of terminal aortic thrombosis, are reviewed and the subject of the antiphospholipid antibody syndrome is discussed.

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Antiphospholipid antibodies have been detected since Wassermann et al¹ used complement fixation in 1906 to detect reagin in the serum of patients with syphilis. The first antigens were saline extracts of liver from fetuses with syphilis, followed by alcohol extracts of various nor-

mal tissues. Pangborn² in 1942 noted that the antigen responsible for reagin reactivity was an acidic phospholipid extracted from a bovine heart muscle, which was subsequently named *cardiolipin*. Following the development of the more specific treponemal immobilization test in 1949, many patients were found who were either transiently or chronically false positive using the VDRL (cardiolipin) antigen. These patients had a higher prevalence of autoimmune disease and other antibodies in their serum.³

Thrombotic complications have long been associated with systemic lupus erythematosus (SLE). The occurrence of thromboembolic events in patients with SLE was first noted by Baehr et al⁴ in 1935, and the association between circulating anticoagulants, false-positive VDRL test results, and SLE was reported by Conley and Hartmann⁵ in 1952. These lupuslike anticoagulants have been found to be antibodies to procoagulant phospholipids, which prolong the activated partial thromboplastin time, thromboplastin (factor III), and properties of viper venom testing. Diagnosis of lupus anticoagulants requires correction of the activated partial thromboplastin time and phospholipid, with care taken to remove platelet debris from samples before testing. In 1963, Bowie et al⁶ first reported four cases of thrombotic complications in patients with both SLE and circulating anticoagulants. This apparent paradox of circulating anticoagulants and thrombosis was initially misinterpreted as a compensatory phenomenon associated with increased thromboplastin generation in these patients with SLE and anticoagulants.

Laurell and Nilsson⁷ demonstrated in 1957 that cardiolipin in syphilitic assays would remove lupus anticoagulant activity, and in 1980, Thiagarajan et al⁸ confirmed the presence of specific antiphospholipid antibodies (APLA) in patients with the lupus anticoagulant. The lupus anticoagulant and the anticardiolipin antibody appear to be similar immunoglobulins with different binding specificities. Inhibition of endothelial prostacyclin secretion by these circulating immunoglobulins was proposed by Carreras et al⁹ to explain the increased thrombotic complications in patients with lupuslike antibodies. Other possible mechanisms suggested to account for excessive

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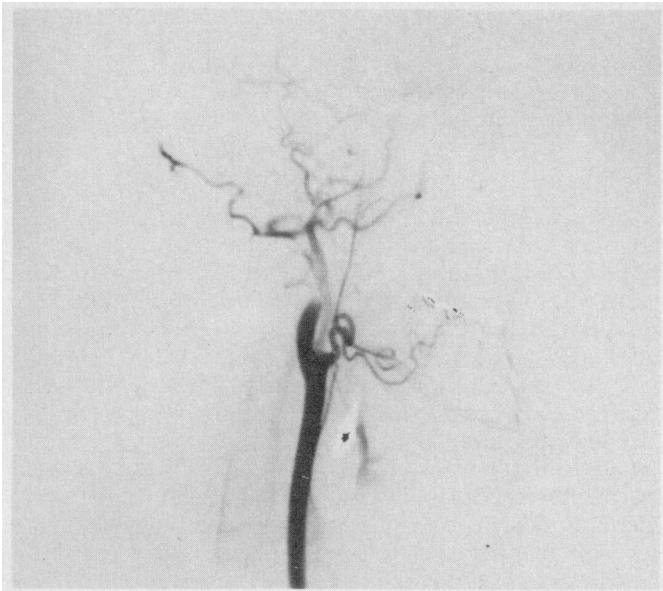


Fig 1.—Case 2. Carotid angiogram demonstrates occlusion of the right internal carotid artery distal to the bifurcation.

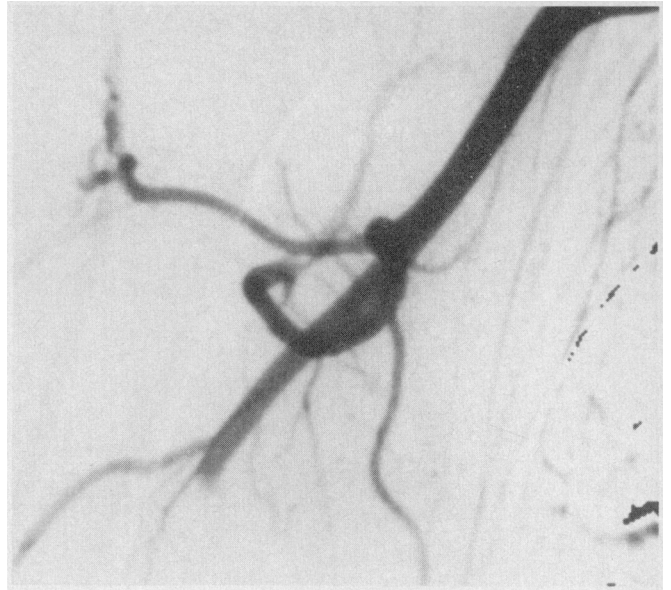


Fig 2.—Case 2. Upper-extremity angiogram reveals occlusion of the right proximal brachial artery.

thrombosis in patients with lupus and APLA include prekallikrein inhibition,¹⁰ tissue factor induction,¹¹ thrombomodulin neutralization,¹² alteration in protein C and S activity,^{13,14} and lowered functional antithrombin III activity.¹⁵

Following the standardization of the anticardiolipin antibody enzyme-linked immunosorbent assay for this APLA in 1985,¹⁶ increasing numbers of patients with thrombotic complications with and without autoimmune diseases tested positively for anticardiolipin antibodies. This report documents the clinical histories and outcomes of three patients presenting to a vascular surgical service with arterial thrombosis and positive APLA. The anticardiolipin antibody test used was a solid phase enzyme immunoassay (EL-ACA, Thera Test Laboratories Inc, Chicago, Ill).

REPORT OF CASES

CASE 1.—A 25-year-old white woman was examined because of the sudden, transient loss of sight in a sector of the right visual field. She had no history of neurologic events, no other known medical illnesses, and no family history of thrombotic or connective tissue disorders. Laboratory studies revealed normal values for proteins C, S, fibrinogen, and antithrombin III; however, she tested positively for the antinuclear antibody, and her erythrocyte sedimentation rate and rheumatoid factor were elevated. There was no clinical evidence of SLE or scleroderma, and the results of her lupus erythematosus cell preparation were negative. Her initial platelet count was $155 \times 10^9/L$, her prothrombin time was 12 seconds, and her partial thromboplastin time was 35 seconds. The results of tests for the anticardiolipin antibody (strong positive IgG, weakly positive IgA, and negative IgM) and the lupus anticoagulant were positive.

The results of the carotid duplex examination were normal, and a cerebral angiogram failed to demonstrate extracranial occlusive disease or evidence of intracranial vasculitis. The transesophageal echocardiogram revealed a mass in the left atrium near the mitral valve that was thought to be consistent with a myxoma. The preoperative diagnosis was an atrial myxoma, yet, during thoracotomy, a large intra-atrial thrombus was found and removed. A therapeutic postoperative regimen of warfarin sodium was begun, but after 5 months, the patient again experienced a transient episode of visual loss. A second echocardiogram

was obtained and showed no recurrence of the thrombus. Aspirin therapy was substituted for warfarin. She did well for the next 5 months, but then had a first trimester spontaneous abortion. At this writing, she is asymptomatic and continues aspirin therapy.

CASE 2.—A 26-year-old woman was seen for evaluation of thigh and buttock claudication. The patient had suffered a right hemispheric stroke 4 months before admission, and a cerebral arteriogram revealed an occluded right internal carotid and right brachial artery (Figs 1 and 2). The angiogram showed no evidence of aortitis. A transesophageal echocardiogram revealed a small residual ventriculoseptal defect from a repair done at age 22 months, and no intracardiac thrombus was seen. The results of tests for erythrocyte sedimentation rate, antinuclear antibody, and lupus erythematosus preparation were normal; however, the results of her IgG anticardiolipin antibody test were moderately positive, and she was given aspirin and warfarin sodium. A mild residual upper and lower extremity weakness persisted, and an ambulatory rehabilitation program was initiated. In the ensuing 3 months, her walking improved, but she developed claudication that progressed from left calf pain at five blocks to bilateral buttock cramping after walking one half block.

Her surgical history included a ventricular septal defect repair at age 22 months and a left femoral thrombectomy with vein patch angioplasty 3 years before admission. She denied having diabetes, myocardial infarction, hyperlipidemia, or hypertension, although she had a 10-year history of migrainelike headaches. She denied the use of tobacco, alcohol, oral contraceptives, or illegal drugs, and was taking warfarin, ranitidine hydrochloride and aspirin on admission. She had no family history of autoimmune disease or premature atherosclerosis.

On physical examination, she was an alert, normotensive white woman without a facial rash or masklike facies. She had strong and symmetric carotid pulses without temporal artery tenderness. A holosystolic cardiac murmur was heard, while her abdomen was without masses, tenderness, or bruits. The results of an extremity examination revealed nonpalpable right brachial, ulnar, and radial pulse and decreased left leg strength. Palpable pulses were absent in both lower extremities, with ankle-brachial indexes less than 0.3 bilaterally. Laboratory values on admission included a hemoglobin of 134 g/L, platelet count of $185 \times 10^9/L$, prothrombin time of 17 seconds, partial thromboplastin time of 27 seconds, fibrinogen of 2.55 g/L, and normal renal and hepatic profiles. Her erythrocyte sedimentation rate was 19 mm/h, and the results of tests for anti-double-stranded DNA, antiribonu-



Fig 3. — Case 2. A translumbar aortogram reveals terminal aortic occlusion.

cleoprotein, lupus erythematosus preparation, and rheumatoid factor were negative. The results of her protein C and S levels as well as her antithrombin III levels were normal. The results of the tests for anticardiolipin antibody were positive (IgG positive and IgM negative), and the results of tests for lupus anticoagulant and VDRL were negative.

A translumbar aortogram revealed occlusion of her infrarenal aorta (Fig 3), and aortobifemoral grafting was performed with normalization of distal pulses. The patient did well after the surgical procedure and was to continue aspirin and warfarin sodium therapy at discharge.

CASE 3. — A 36-year-old white woman with SLE was examined for complaints of recurrent right-foot ischemia. She had a history of lower extremity Raynaud's phenomenon and had been treated with prednisone, cyclophosphamide, nifedipine, and Bier's Block anesthesia with transient symptomatic relief. Two months before admission, she had undergone a short-segment right tibial to tibial bypass for rest pain resulting from focal tibial vessel occlusion, and had been given warfarin sodium after surgery. She returned with recurrent rest pain.

Her medical history was significant for SLE of 18 years' duration. She did not have hypertension, diabetes, stroke, myocardial infarction, or hyperlipidemia. She denied the use of tobacco, oral contraceptives, or illegal drugs. She had no family history of premature atherosclerosis or autoimmune disease.

On examination, she was normotensive with symmetrically strong brachial and radial pulses. She had no cervical bruits, and the results of cardiopulmonary and abdominal examinations were normal. She had symmetric and strong femoral and popliteal pulses, with palpable left posterior tibial and dorsalis pedis pulses. She had a cyanotic right foot with no audible right pedal pulses. She had evidence of polyarthritis and a peripheral neuropathy.

Her laboratory data demonstrated a hemoglobin of 121 g/L, hematocrit of 0.35, a platelet count of $351 \times 10^9/L$, a prothrombin time of 12.6 seconds, and a partial thromboplastin time of 30 seconds. She had a normal renal and hepatic profile, and normal antithrombin III and protein C and S levels. Her sedimentation rate was elevated at 83 mm/h, and the results of tests for lupus erythematosus cell preparation and IgM and IgG anticardiolipin antibodies were positive. Results of the lupus anticoagulant and VDRL testing were negative.

An angiogram confirmed occlusion of her tibial bypass. Thrombolytic therapy was used to recanalize her tibial vein graft, which appeared diffusely sclerotic angiographically. A popliteal

to posterior tibial bypass with reversed saphenous vein was performed. Anticoagulation with heparin sodium was continued after the surgical procedure, and she was discharged with a regimen of nifedipine, warfarin, enteric-coated aspirin, and prednisone. The graft was patent 2 years later.

COMMENT

Antiphospholipid antibodies are acquired autoantibodies (IgG, IgM, and IgA) that are often found in patients with SLE and other autoimmune disorders. Various names have been given to these antibodies, including the lupus anticoagulant, the anticardiolipin antibody, and the antibody responsible for the false-positive syphilis (VDRL) test. The lupus anticoagulant derives its name from its ability to prevent the formation of the prothrombin activator complex required for converting prothrombin to thrombin, resulting in prolongation of the activated partial thromboplastin time and Russell's viper time. Cardiolipin is the phospholipid antigen used in screening tests for syphilis, and thus arises the correlation between anticardiolipin antibodies and false-positive VDRL tests. Although a recent study demonstrated separation of lupus anticoagulant and anticardiolipin activity,¹⁷ little evidence exists to confirm these as distinct antibodies,^{18,19} and they might be best characterized as having different specificities with overlapping reactivities.

Studies of APLA have reported wide ranges in their prevalence. In patients with SLE, the prevalence of anticardiolipin antibody is 21% to 63%, and the prevalence of the lupus anticoagulant is 6% to 73%.^{19,20-24} In normal young adults, the prevalence of anticardiolipin antibodies ranges from 0% to 7.5%.^{18,20} Patients with APLA are more likely to be female (in a 4:1 ratio) and younger if they have SLE than patients with non-SLE disorders.^{25,26} In patients with non-SLE disorders, the prevalence of APLA ranges from 4% to 87%,¹⁸ and includes elderly patients and patients with acute infections, arthritis (both osteo and rheumatoid), syphilis, scleroderma, systemic lupus erythematosus, drug-induced (chlorpromazine) lupus, Guillain-Barré syndrome, and patients infected with the human immunodeficiency virus.²⁷⁻³¹ The apparent increase in the prevalence of APLA syndrome is partially related to improved assays for the detection of anticardiolipin antibody. The use of enzyme-linked immunosorbent assays or solid-phase radioimmunoassay techniques, introduced in 1983,³² has made the detection of anticardiolipin antibody the most specific and the most sensitive of the tests for APLA syndrome.

Although originally described in patients with bleeding disorders, APLA such as the lupus anticoagulant are rarely related to hemorrhage. Much more germane is the risk of both arterial and venous thrombosis and abortion in patients with APLA. The etiology of these clinical events may involve one of several mechanisms. Adherence of the antibody to lipid to the platelet surface may initiate platelet aggregation and attachment,³³ or it may inhibit endothelial cell production of the vasodilator prostacyclin.³⁴ Defects in fibrinolysis may result from a decrease in plasminogen activator release or from diminished protein C, thrombomodulin, or antithrombin III activity in patients with APLA syndrome.^{10-15,35} Although several studies have suggested that high antibody titer and specific antibody isotype (IgG and IgA) may be associated with an increased risk of thrombosis,^{36,37} no firm consensus on this subject has been reached.

The clinical disorders in which APLA have been reported are varied and include recurrent midterm miscarriage, pulmonary hypertension, endocardial disease, thrombocytopenia, avascular necrosis, transverse myelitis, migraine, chorea, Guillain-Barré syndrome, seizures, livedo reticularis, chronic leg ulcers, arterial thrombosis (cerebral, coronary, retinal, and peripheral), and venous thrombosis (recurrent iliofemoral deep vein thrombosis, renal vein, vena cava, and retinal vein). Patients who test positive for both lupus anticoagulant and APLA have a ninefold increased risk of arteriovenous thrombosis. The first patient had many of the classic stigmata of APLA syndrome, including unexplained thromboses, neurologic dysfunction, thrombocytopenia, and spontaneous abortion. She had evidence of an ill-defined autoimmune disease, and thus would be considered to have secondary APLA syndrome. The second patient had no evidence of SLE or other autoimmune disorders, and would be classified as having primary APLA syndrome. The most common site of thrombosis in patients with non-SLE APLA syndrome is in the cerebral vessels, often resulting in neurologic dysfunction and stroke.³⁸ As in the first two patients described, the diagnosis should be suspected from a history of thrombotic complications in patients without atherosclerotic risk factors such as age, hypertension, and smoking, and should be confirmed with a test for anticardiolipin antibody and lupus anticoagulant.

The association of thrombosis with the lupus anticoagulant in patients with SLE was first described in 1963.⁶ Of patients with SLE and anticardiolipin antibody, as in the third patient in this series, almost one third will have thrombotic events, while in patients with SLE and thrombosis, almost two thirds will test positively for the anticardiolipin antibody.¹⁸ Again, the cerebral circulation is most commonly affected,³⁸ with sporadic reports of axillary, retinal, digital, and mesenteric thrombosis.³⁹⁻⁴¹ Peripheral arterial disease in patients with SLE who are antiphospholipid antibody-negative is rare, occurring in fewer than 1.5% of patients.⁴² Therefore, patients with SLE who manifest symptoms of extremity hypoperfusion, as in the third patient described, should be tested using the lupus anticoagulant and the anticardiolipin antibody enzyme-linked immunosorbent assay. Antibody titers have been shown to fall during active thrombosis, making exclusion of the diagnosis difficult during the acute phase.⁴³ Antibody titers should be rechecked in 4 to 6 weeks to confirm or exclude the diagnosis.

The treatment of patients with APLA is determined by the presence of an associated autoimmune disorder and/or thrombotic events. In asymptomatic cases detected with screening studies, no treatment is recommended. In patients with an associated autoimmune disease (eg, SLE) and clinical manifestations of APLA syndrome (eg, fetal wastage, arteriovenous thrombosis), appropriate immunosuppression and long-term anticoagulation are necessary to prevent recurrent thrombosis. In patients without an autoimmune disease and manifesting clinical evidence of APLA, long-term anticoagulation is also recommended. In one study, discontinuation of oral anticoagulation resulted in recurrent thrombosis,⁴⁴ leading some authors to recommend either indefinite anticoagulation or treatment until the results of APLA tests were negative.⁴⁵

In summary, antiphospholipid antibodies are a group of heterogeneous autoantibodies frequently associated

with autoimmune disease and thrombotic events. Their presence may be suspected after finding a false-positive syphilis test result, the lupus anticoagulant, an elevated partial thromboplastin time, or thrombocytopenia. The diagnosis is best confirmed with the enzyme-linked immunosorbent assay or solid phase anticardiolipin test, with treatment designed to control the autoimmune disease and prevent recurrent thromboembolism.

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Surgical Anatomy Question

Q The inferior epigastric artery (IEA), a branch of the internal iliac artery, enters the rectus sheath at the semicircular fold (of Douglas). [True or False?]

A [False] The IEA is a branch of the external iliac artery and does enter the rectus sheath at the arcuate line.
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THE EDITOR