Primary Antiphospholipid Syndrome: Indications for Long-Term Anticoagulation

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Primary antiphospholipid syndrome, defined as the presence of antiphospholipid antibodies with recurrent thrombosis in patients who have no clinical or serologic features of systemic lupus erythematosus, is now a medically recognizable and treatable disorder.1 The syndrome is associated with a high incidence of recurrent arterial and venous occlusions, with cerebrovascular thrombi occurring second in frequency only to deep vein thrombi.2 Current recommendations are to screen for antiphospholipid antibodies in all patients younger than 45 years (even those with risk factors for thromboses) who have had a thrombotic event, as well as in patients who have clinical features of systemic lupus erythematosus or who have had more than two miscarriages.3 The case presented here illustrates the challenge and importance of recognizing primary antiphospholipid syndrome in a family practice.

Case Report
The patient was a 37-year-old, obese woman who had non-insulin-dependent diabetes mellitus and hypertension and who smoked marijuana and tobacco (one pack per day for 4 years). She developed sudden left arm pain and neck numbness the day of admission.

Several months earlier she had an episode of word-finding difficulty lasting less than 24 hours; her speech was normal on examination several days later. At that time a nonenhanced computed axial tomography (CT) scan of her head showed a small, low-density region in the left frontal white matter that was nonspecific and less conspicuous on magnetic resonance imaging a few days later. One month later a repeat CT scan with contrast medium showed that the lesion had resolved.

She had mild dyspepsia; otherwise, her medical history was unremarkable. There was no history of miscarriages, rashes, or arthralgias. After one normal pregnancy she had a bilateral tubal ligation, and she was not taking oral contraceptives. Her medications were famotidine, lisinopril, glyburide, and daily aspirin.

Her physical examination was remarkable for weakness of her left-hand grip, mild dysphagia and slurred speech, and no lower extremity edema or calf tenderness. Her blood pressure was 120/90 mmHg, and blood glucose was 226 mg/dL. A CT scan of her head without contrast medium showed an old infarct in the left parietal lobe, but no cerebral hemorrhage. The prothrombin time, partial thromboplastin time, and complete blood count were within normal limits. Her total cholesterol was 135 mg/dL, and results of antinuclear antibody testing and a serologic test for syphilis were negative. Findings on echocardiogram and carotid Doppler studies were normal. The lower extremity Doppler on the right showed decreased venous capacity suggestive of deep vein thrombosis, which could not be confirmed clinically. She was prescribed intravenous heparin and warfarin. On hospital day 3 a repeat CT scan showed a small acute infarct in the right parietal lobe, but no other changes were noted. On hospital day 11 warfarin was discontinued, and she was discharged to an inpatient rehabilitation unit. She stopped smoking tobacco and marijuana.

During the next 4 weeks her deficits resolved with inpatient and then outpatient rehabilitation. Seven weeks after her right parietal infarct, however, she began having intermittent symptoms of right arm and neck numbness lasting less than 2 minutes, causing her to drop objects from her right hand. When she came to her family physician’s office, her neurologic examination was unremarkable except for a slight drift of her left arm. Her neurologist ordered electromyographic studies of the right upper extremity and cervical magnetic resonance imaging. Findings from both tests were normal, and a repeat CT scan of her head showed no change.

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Further laboratory studies were ordered by her family physician. Thyroid-stimulating hormone, antithrombin III, and protein C and S levels were within normal limits. The glycohemoglobin was 8.8 percent; however, the anticardiolipin immunoglobulin (Ig)M and IgG antibodies were positive by standardized enzyme-linked immunoabsorbent assay (IgM = 11 MPL U/mL [IgM less than 11 MPL U/mL is normal], IgG = 29 GPL U/mL [IgG less than 23 GPL U/mL is normal]*). Based on these results and her history of a cerebrovascular accident, her condition was diagnosed as primary antiphospholipid syndrome, and warfarin therapy was prescribed. She continued with warfarin therapy for 8 months, maintaining an international normalized ratio (INR) of 3 to 3.5. Interestingly, her symptoms of intermittent right arm and neck numbness resolved, and she developed no further symptoms.

Discussion
The incidence of elevated anticardiolipin antibodies (ACLAs) in patients younger than the age of 50 years who have had their first transient ischemic attack or stroke could be as high as 32 percent according to a retrospective study by Czlonkowska et al. They found 16 of 49 patients who had their first transient ischemic attack or stroke when they were younger than 50 years old were ACLA positive. Only 2 of the 16 ACLA-positive patients had clinical or serological evidence of systemic lupus erythematosus. No differences in clinical characteristics or frequency of stroke risk factors were found between the ACLA-negative and the ACLA-positive groups. Multiple risk factors for an ischemic stroke should not preclude screening for ACLAs in a young patient with symptoms, as exemplified by our case in which the patient abused tobacco and had hypertension and diabetes for risk factors.

Neurologic events other than strokes and transient ischemic attacks, such as atypical migraines, transient paresthesias, and episodes of mild confusion, have been reported with patients positive for antiphospholipid antibody, and magnetic resonance imaging studies have shown areas of nonspecific increased signal intensity that might increase or decrease with time. Rarely have patients with chorea or transverse myelitis been found to be ACLA positive. Though these neurological findings can be found with elevated ACLAs, the diagnosis of primary antiphospholipid syndrome is made only after a thrombotic event.

Prescribing medication for ACLA-positive patients who have not had a thrombotic event is not recommended unless the titer is highly elevated in a woman who is a primipara, a primiparous patient develops thrombocytopenia or fetal growth retardation (in which case the treatment is aspirin), or a multiparous woman has a history of fetal loss (the recommended treatment is heparin and aspirin). Prednisone should be used in patients with symptoms related to systemic lupus erythematosus, but prescribing corticosteroid therapy, other immunosuppressive drugs, apheresis, or intravenous IgG for patients with primary antiphospholipid syndrome or who are ACLA positive has not been recommended. Furthermore, the importance of elevated ACLAs in someone who has not had a thrombotic event is unknown. Approximately 1 to 2 percent of the normal population is ACLA positive, and ACLAs can be associated with human immunodeficiency virus and other infections, chlorpromazine therapy, and nonlupus collagen vascular disorders.

The risk of recurrent thrombosis (venous or arterial) in patients with primary antiphospholipid syndrome, systemic lupus erythematosus, or lupus-like disease is high and has been noted in the literature since the 1950s. Khamashta et al found a recurrence rate of 69 percent in 6 years of follow-up in patients who were ACLA positive, 42 percent of whom had primary antiphospholipid syndrome. In a group of 75 patients with antiphospholipid antibodies, only 10 of whom had systemic lupus erythematosus, Levine et al reported a recurrence rate of 18.7 percent per year for stroke and 15.2 percent per year for transient ischemic attack. These frequencies are much higher than for the general stroke population, and only one half of the patients had risk factors for stroke (such as hypertension, diabetes, heart disease, hyperlipidemia, or smoking). Furthermore, discontinuation of warfarin therapy is associated with a high recurrence rate. Rivier et al reported that in a group of 23 patients posi-
tive for systemic lupus erythematosus anticoagulant or ACLAs, 43 percent of whom had primary antiphospholipid syndrome, the mean time from discontinuation of warfarin to a recurrent thrombotic event was 20 weeks.

The only treatment found to reduce markedly the recurrence of thrombosis in patients with antiphospholipid antibodies is long-term anticoagulation with high-dose warfarin, maintaining an INR of at least 3.0. The increased risk of hemorrhage with maintaining an INR of greater than 2.9 is outweighed by the decreased risk of recurrent thrombosis. In the study in which Khamashta et al. observed patients for a median of 6 years, the risk of thrombosis recurrence after discontinuing warfarin was 1.3 events per patient year (the highest occurrence was in the first 6 months). Bleeding from warfarin therapy was 0.071 events per patient year and was severe in 0.017 events per patient year. None of the hemorrhagic events was fatal, and most of the patients resumed warfarin therapy without recurrent bleeding. Subcutaneous heparin (15,000 U daily) has not been effective in preventing recurrent thromboses.

The degree of elevation of ACLAs (low, medium, or high elevation) has not been found to be helpful in predicting which patients will have recurrent thromboses. IgM antibodies might be absent in patients with recurrent thromboses, and the levels of ACLAs can actually drop before a thrombotic event. In the case presented here, the IgG level was moderately positive (29 units) and IgM level was in the low positive range (11 units). Recurrent thromboses are more likely to occur in patients with primary antiphospholipid syndrome after withdrawal of warfarin or when warfarin treatment is inadequate (INR < 3.0). No other clinical predictors for recurrent thrombosis in patients with primary antiphospholipid syndrome have consistently been found. Stopping smoking, discontinuing oral contraceptives, and controlling hypertension, diabetes, and hyperlipidemia, however, are recommended in patients with primary antiphospholipid syndrome, because thrombosis could be due to multiple factors.

Conclusion

Young patients (less than 45 years old) with a history of deep vein thrombosis, transient ischemic attacks, stroke, or pulmonary embolism should be screened for antiphospholipid antibodies regardless of risk factors. The recommended secondary prevention for recurrent thromboses in patients who have antiphospholipid antibodies, including those with primary antiphospholipid syndrome, is long-term anticoagulation with warfarin, maintaining an INR of at least 3.0.

References