Antiphospholipid Syndrome in Systemic Lupus Erythematosus

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The antiphospholipid syndrome, which may occur in a primary form,1 is increasingly recognized as a complication of systemic lupus erythematosus.2,3 Indeed, it is likely that many examples of what has been termed in the past lupus vasculopathy or lupus vasculitis4 were in fact examples of antiphospholipid syndrome, because most were described in the era before widespread recognition of the syndrome as a complication of lupus. The following case is an apt example of this entity, both clinically and morphologically.

CASE HISTORY

The patient was a 32-yr-old white woman with a 2-yr history of lupus, presenting initially with articular manifestations and mild malar rash, with positive antinuclear antibodies and elevated double-stranded DNA antibodies but without renal abnormalities. History revealed a normal term pregnancy at age 20, followed by three spontaneous abortions during the subsequent 6 yr. There was also an ill-defined episode of “phlebitis” in one leg 5 yr previously, resolving without specific treatment. She responded promptly to low-dosage steroid therapy. However, on routine follow-up at 2 yr, she was found hypertensive (170/105 mmHg) with moderate leg edema. Evaluation revealed a frank nephrotic syndrome with proteinuria of 5.2 g/24 h, marked hematuria (200,000 red blood cells/ml), serum creatinine (SCr) of 180 μmol/L, hemoglobin of 10.4 g/dl, elevated DNA, and low C3 and C4. Despite the evidence for a thrombotic microangiopathy, standard coagulation studies were normal and platelets were minimally reduced at 130,000 mm3.

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Because of the findings on renal biopsy, further testing was performed and she was found to have both a lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) of IgG type in high titer (40 GPL units, the normal in our laboratory being ≤10 GPL units), with anti–β2-glycoprotein 1 (B2GP-1) antibodies as well. Despite the evidence for a thrombotic microangiopathy, standard coagulation studies were normal and platelets were minimally reduced at 130,000 mm3.

REFERENCES

Her renal biopsy revealed active class IV-G lupus nephritis, with fairly uniform glomerular endocapillary proliferation, definite “wire loops,” and occasional crescents. There was widespread tubular atrophy and interstitial fibrosis with a diffuse interstitial infiltrate. The vascular lesions, however, were the most impressive part of the biopsy. Numerous arteries showed intimal lesions varying from clear subendothelial swelling to cellular fibrinoid hyperplasia (Figure 1). Associated with these lesions was variable thrombus formation, from mural plaques to near-complete occlusion, with one artery showing an organized, partially re-canalized thrombus. In addition, one artery showed fibrinoid necrosis of myocytes in the media (Figure 1A). Despite the widespread arterial/arteriolar lesions, only one small glomerular thrombus was seen, although several glomeruli seemed somewhat ischemic (Figure 1B). The overall complex of vascular lesions qualified as a thrombotic microangiopathy; no venous lesions were recognized. Because the biopsy did not extend to the capsule, a frequent feature of antiphospholipid syndrome nephropathy (APSN), focal cortical atrophy,
which is most pronounced in the subcapsular region, could not be identified.

Immunofluorescence studies revealed bright glomerular mesangial and irregular coarsely granular capillary staining for IgG, C3, and C1q, with lesser amounts of IgM and IgA. Arteries and arterioles showed widespread staining of the media for IgG, IgM, and C3, with some C1q. There was widespread intimal and focal medial staining for fibrinogen, some in apparent thrombi. Electron microscopy was not performed.

DISCUSSION

This patient had a history typical of primary antiphospholipid syndrome, fortunately fairly mild in that she had three spontaneous abortions plus an episode of “phlebitis” likely related to venous thrombosis. She was ultimately tested and found to have circulating aCL and LA antibodies. In its more severe form, antiphospholipid syndrome may include arterial thrombi, particularly cerebral, and venous thrombi, which may be complicated by pulmonary emboli and even pulmonary hypertension. Cerebral vascular events are frequent and may lead to neurologic deficits, seizures, or simply diminished intellectual function. In lupus, even in patients without frank cerebral infarcts, antiphospholipid antibodies and neuropsychiatric manifestations are strongly linked. It is interesting that there is also an association in lupus between antiphospholipid antibodies and mitral valve nodules and mitral regurgitation.

The antiphospholipid syndrome, as its name implies, is caused by antibodies to normally occurring phospholipids. In fact, these antibodies do not recognize anionic phospholipids directly but rather plasma proteins bound to anionic surfaces. Of these, B2GP-I and prothrombin are the best studied. The most used and best characterized clinically are aCL, but antibodies other phospholipids, notably phosphatidylserine, also exist. The antibodies, measured by ELISA, are usually IgG or IgM, the former more associated with venous thrombosis and pulmonary emboli, the latter with cerebrovascular accidents. Recent studies suggest that anti-phosphatidylserine/prothrombin antibodies and anti-B2GP-I antibodies may show the best correlations with thrombosis in lupus. Antibodies to prothrombin alone seem to be as good or better than aCL, but not as good as anti-phosphatidylserine/prothrombin antibodies in direct

Figure 1. (A) Artery in antiphospholipid syndrome–lupus. An interlobular artery showing marked clear subendothelial swelling with a small mural thrombus. The medium shows fibrinoid necrosis in places clearly involving individual myocytes (arrows). The glomerulus shows diffuse endocapillary proliferation with evident “wire loops.” (B) Arteries in antiphospholipid syndrome–lupus. An artery (center right) shows mild subendothelial swelling in its lower branch, whereas the upper branch reveals near-total occlusion by a thrombus. An arteriole (arrow) shows marked fibrous intimal hyperplasia, and, in consequence, its glomerulus, although showing mild diffuse proliferation, is clearly ischemic. Magnification, ×350 (Masson trichrome stain).
tients showing that LA is a better predictor of antiphospholipid syndrome than aCL. This is consistent with APSN being statistically associated with LA but not with aCL. LA was present in all patients with primary antiphospholipid syndrome and 30% of patients with lupus. We found that APSN was statistically associated with LA but not with aCL. This is consistent with an analysis of studies totaling 5102 patients showing that LA is a better predictor of risk for thrombosis than aCL.

The pathogenesis of thrombosis in antiphospholipid syndrome is not entirely clear and may differ among patients. It has been proposed that the stable trimolecular complexes formed on the binding of anti–B2GP-I and anti–prothrombin antibodies to anionic phospholipids at the phospholipid surface; these interactions may interfere with proper assembly of the prothrombinase complex, inhibit the formation of thrombin in the coagulation cascade (Figure 2), and/or alternately hamper inactivation of factor Va (Figure 3).

Antiphospholipid syndrome in lupus is not infrequent. We found that 24 (22.4%) of 107 lupus patients who underwent biopsy had an associated antiphospholipid syndrome, corresponding to the experience of other groups. Similarly, the antiphospholipid syndrome frequently precedes the diagnosis of lupus, often by a decade or more. In fact, a recent report indicated that positivity for antinucleosome antibodies at the time of diagnosis of antiphospholipid syndrome may help predict subsequent development of lupus. In our patient, the history of spontaneous abortions suggests that antiphospholipid syndrome may have antedated the lupus by 8 to 10 yr. The reverse question, what percentage of cases of antiphospholipid syndrome are associated with lupus, is not clearly answered. It should be remembered that antiphospholipid syndrome was, in fact, first defined in the setting of lupus and only later as a primary entity. It is clear that lupus is by far the most frequently associated condition. A casual review of four recent series suggests that lupus-associated antiphospholipid syndrome is actually more common than primary antiphospholipid syndrome.

Antiphospholipid syndrome may also occur with any class of lupus nephritis. Importantly, there is no association between the class of lupus nephritis and antiphospholipid syndrome or with activity or chronicity scores. There is also no correlation between antiphospholipid antibody titers and anti-DNA antibody or serum complement levels. However, patients with lupus-antiphospholipid syndrome are more frequently hypertensive (60%) than those with lupus nephritis only (28%). In our series, two aspects of antiphospholipid syndrome were particularly associated with the development of APSN: History of arterial thrombi (odds ratio 8.0) and history of obstetric complications (odds ratio 6.3), as in the patient in this study. The SCr was higher in patients who had lupus with APSN than in those without (median 100 versus 77 μmol/L; P = 0.0007) and consistent with this had a greater amount of interstitial fibrosis. It stands to reason that patients with a greater frequency of hypertension (generally at substantial levels), higher SCr, and more extensive interstitial fibrosis should have a worse renal prognosis. Although our study had too short a follow-up (median 22 mo) to demonstrate this, a long-term Italian study with a mean follow up of 173 ± 100 mo showed a strong association between antiphospholipid antibodies and development of chronic renal insufficiency.

Present therapy for the thrombotic aspects of the antiphospholipid syndrome—lupus complex is anticoagulation with Coumadin or similar agents. Standard steroid and immunosuppressive therapy seem to have little effect on antibody levels. However, a new mode of treatment recently reported showed marked and durable reduction of not only aCL but also anti–double-stranded DNA antibodies by immunoabsorption therapy in 11 patients. Another novel approach with promising results has been treatment of antiphospholipid syndrome in lupus by autologous hematopoietic stem cell transplantation. Whether patients who have lupus with antiphospholipid antibodies but no symptoms relatable to antiphospholipid syndrome should be treated is not clear.

**DISCLOSURES**

None.

**REFERENCES**


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