THE NEPHROLOGY TRAINING PROGRAM AT UNIVERSITY OF CINCINNATI MEDICAL CENTER

The Nephrology Training Program at UCMC has been in existence since July 1972. A total of 66 fellows have thus far received their training and are pursuing careers evenly split between academic medicine and the private practice of clinical nephrology. Currently, the program is a 2-yr program, with an additional third year for individuals desiring to pursue laboratory or clinical investigation. Each year, between two and three additional fellows are accepted into the program. The clinical programs are founded on a busy nephrology consultation service and inpatient combined nephrology and medicine ward service, as well as an inpatient combined nephrology and surgical transplant service. Approximately 500 new consultations are seen by the nephrology consultation service and between 50 to 60 transplants are performed annually. There are several free-standing satellite dialysis facilities that are staffed by the Division of Nephrology and Hypertension faculty. A computerized data base that extends retrospectively to 1976 is a major tool for pursuing clinical and outcome analyses in the ESRD population. Fellows are expected to participate in ongoing research activities within the division or to pursue an independent project under close supervision by one of the faculty. Divisional research interests include hypertension and its genetics, cellular and molecular studies of epithelial transport particularly related to acid-base metabolism, clinical transplantation and protocols in newer immunosuppressive agents, immunobiology of transplantation and tolerance, and vascular disease and clotting abnormalities in systemic lupus erythematosus and ESRD. An active and ongoing collaboration exists with various basic science departments, as well as the Division of Pediatric Nephrology at Children’s Hospital.

Catastrophic Secondary Antiphospholipid Syndrome With Concomitant Antithrombin III Deficiency

V. Ram Peddi and Kotagal S. Kant

ABSTRACT

The association between thrombotic events and primary or secondary antiphospholipid/anticardiolipin syndrome is now well recognized. A spectrum of renal involvement ranging from glomerular thrombosis to renal infarction has been described. A case of systemic lupus erythematosus with immunoglobulin G and M antiphospholipid/anticardiolipin antibodies is reported. The patient developed catastrophic thrombosis in multiple organs, and glomerular thrombosis was documented by renal biopsy. The patient had an acquired antithrombin III deficiency, and the combination of secondary antiphospholipid syndrome with accompanying antithrombin III deficiency predisposed to thrombosis. Several mechanisms by which antiphospholipid/anticardiolipin antibodies cause thrombosis have been proposed and are briefly reviewed.

Key Words: Anticardiolipin, antithrombin, thrombosis, infarction, kidney

We report a patient with systemic lupus erythematosus (SLE) with antiphospholipid antibodies (APA), absent lupus anticoagulant (LA), and antithrombin III (AT III) deficiency who developed thrombotic events in multiple organs including the kidney. We review the pathophysiology of this disorder.

CASE REPORT

A 38-yr-old white woman was admitted from the medical clinic to the University of Cincinnati Medical Center in December 1993 with nausea, vomiting, and abdominal pain. She was seen in the clinic with a 1-yr history of generalized arthralgia and an erythematous rash. Investigations in the clinic were significant for a positive antinuclear antibodies in a 1:320 titer, positive antidualle-stranded DNA, and low complements.
Her abdominal pain was constant, dull, and nonradiating and was not associated with dysuria or hematuria. She also had blurring of vision in both eyes of 2-wk duration.

Past medical history was significant for carcinoma of the cervix with conization in 1985 and a recent negative Pap smear. Epilepsy was diagnosed 18 yr ago with the last seizure over 10 yr ago. Fibrocystic breast disease with a negative mammogram was seen in November 1993. She also had an appendectomy and tubal ligation in 1992. There was no history of miscarriages. The patient's only medication was Dilphenyl Hydantoin.

On physical examination, she was afebrile with a pulse of 88 beats per minute and her blood pressure was 110/80 mm Hg. She had facial edema, acrocyanosis, and livedo reticularis on the forearm and both lower extremities. Her lungs were clear at the initial evaluation, and her heart sounds were normal with no murmurs. The abdomen was diffusely tender; there was no guarding or rebound, and bowel sounds were normal.

A urinalysis revealed ++ proteinuria and trace blood. Microscopic examination of the spun urine showed three red blood cells per high-power field, granular casts, and one red blood cell cast. An ophthalmology consultation was obtained, and she was reported as having choroidal infiltrates with exudate and overlying retinal detachment consistent with lupus chorioidopathy and lupus-associated uveitis.

LABORATORY EVALUATION

The following laboratory values were obtained (normal values in parenthesis): sodium, 134 mEq/L; potassium, 3.9 mEq/L; chloride, 101 mEq/L; bicarbonate, 26 mEq/L; BUN, 16 mEq/L; creatinine, 0.8 mg/dL; glucose, 107 mg/dL; albumin, 2.4 g/dL; aspartate aminotransferase, 24 U/L; alkaline phosphatase, 8 U/L; alanine aminotransferase, 24 U/L; albumin, 2.4 g/dL; bilirubin, 0.42 mg/dL. A 24-h urine contained 4.19 g of protein. A complete blood count demonstrated a hemoglobin of 14.5 g/dL, hematocrit, 43.1%, white blood cell count, 14,700; and platelet count, 154,000. Prothrombin time was 10.3 s (10.7 to 13.3), APTT was 19 s (25 to 35), dilute VVT was 40.6 s (34.4 to 43.2), bleeding time was 7 min (<9.5), fibrinogen level was 437 mg/dL (150 to 400), d-dimer was 1 (<1). Functional AT III was 47% of normal, antifibrinogen AT III was 58% of normal, repeat functional AT III was 43% of normal, repeat antigenic AT III was 64% of normal (80 to 120), protein C antigen was 96% of normal (70 to 150), protein C function was 65% of normal (80 to 140), protein S antigen total was 82% of normal (75 to 183), and protein S antigen free was 97% of normal (63 to 162). Also, antinuclear antibody was a positive 1:320 titer, and antithrombin DNA (blood) was 36.3% (1 to 25). An ANA screen revealed the following: SM, negative; RNP, positive; SCL-70, negative. C3 was 36 mg/dL, C4, <8 mg/dL, antinuclear antibodies (ACA) immunoglobulins G (IgG), 67 GPL units (<23) and IgM, 21 MPL units (<11); RPR, nonreactive; chest x-ray showed a small, left-sided pleural effusion.

RENAL BIOPSY

The specimen was divided for light microscopy, immunofluorescence, and electron microscopic studies. The sample for light microscopy was stained with hematoxylin and eosin, Jones, Lendrum, and Trichrome stains. The sample had 18 glomeruli on both light microscopy and immunofluorescence specimens.

On light microscopy, 1 of the 18 glomeruli showed a segmental proliferation of mesangial cells with increased neutrophils in the capillary loops. The remaining glomeruli showed a segmental increase in mesangial matrix and mesangial deposits. One glomerulus showed the entire tuft to be occluded by thrombotic material (Figure 1) in the absence of inflammation. Arteries and arterioles were normal. By immunofluorescence, there were extensive mesangial and granular capillary loop deposits staining for IgG, IgA, IgM, C3, and fibrin.

By electron microscopy, the vast majority of deposits were in the mesangium. Glomerular basement membrane thickening of an irregular nature was noted. Subendothelial deposits were seen in the immediate vicinity of the mesangium and not elsewhere along the capillary wall. There were no subepithelial deposits, and variable foot process effacement was noted.

HOSPITAL COURSE

Our patient fulfilled the criteria for the diagnosis of SLE and antiphospholipid syndrome. The admitting symptoms were thought to be due to bowel ischemia. In view of her ophthalmologic findings, she was started on IV methylprednisolone, 2 mg/kg per day, and aspirin, 81 mg/day, with dramatic improvement of her symptoms. A renal biopsy was performed at this stage, and a few hours later (before the biopsy results were available), the patient developed dysphasia and right-sided weakness. A computed tomographic scan of the head was normal, and there was no epileptiform activity on electroencephalogram. A magnetic resonance image showed a left temporal and frontal ischemic infarction and a smaller right frontal infarction. A cerebral angiogram showed left middle cerebral artery occlusion. There was no embolic source evident on echocardiography. Methylprednisolone was continued, and the patient received a single dose of 1 g of IV cyclophosphamide. Anticoagulation with heparin was initiated but had to be discontinued because of thrombocytopenia and pulmonary hemorrhage diagnosed by bronchoscopy. She had recurrence of abdominal pain, and a computed tomographic scan of the abdomen showed a large, wedge-shaped defect at the lateral aspect of the right kidney, consistent with a renal infarction. She continued to have a good urine
output in excess of 1.5 L/24 h and remained normotensive; her BUN and creatinine remained in the normal range and were 13 mEq/L and 0.8 mg/dL, respectively, at the time of the diagnosis of the renal infarction. She was anticoagulated with low-molecular-weight dextran and started on warfarin. Her dysphasia and weakness gradually improved, but she was left with a residual weakness and was discharged to a nursing home after about 35 days of hospital stay. She was seen in the outpatient clinic 1 month after discharge, and she continues to have some residual dysphasia and right-sided weakness. She had a BUN of 12 mEq/L and a creatinine of 0.8 mg/dL; a 24-h urine contained 1.428 g of protein. Her urine sediment was unremarkable. ACA levels were IgG, 13 GPL (<23), and IgM, 2 MPL (<11). A repeat functional AT III level while she was on warfarin was 141% of normal, and antigenic AT III was 123% of normal (normal, 80 to 120).

**DISCUSSION**

The association between APA and recurrent thrombotic events in patients with SLE and the primary antiphospholipid syndrome is well recognized (1–7). It is now evident that a subset of these patients with APA develop catastrophic thrombotic illness. These patients may present with a combination of cardiac, renal, pulmonary, or cerebral dysfunction, often accompanied by skin lesions (Table 1), and have detectable LA, ACA, or both. In a review of 10 documented cases of catastrophic antiphospholipid syndrome by Asherson (2), these patients had clinical evidence of multiple organ involvement with renal dysfunction, accompanied by hypertension in 70% of patients.

<table>
<thead>
<tr>
<th>Skin</th>
<th>Livedo reticularis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acrocyanosis</td>
</tr>
<tr>
<td></td>
<td>Digital infarctions</td>
</tr>
<tr>
<td>Renal</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td></td>
<td>Renal infarctions</td>
</tr>
<tr>
<td></td>
<td>Glomerular thrombosis (on biopsy)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>ARDS</td>
</tr>
<tr>
<td>CNS</td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Behavioral changes</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular events</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Vasculopathy of retinal vessels</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Malignant hypertension</td>
</tr>
<tr>
<td></td>
<td>Congestive cardiac failure</td>
</tr>
<tr>
<td>Others</td>
<td>Hepatic thrombosis and infarction</td>
</tr>
<tr>
<td></td>
<td>Bowel ischemia/infarction</td>
</tr>
<tr>
<td></td>
<td>Adrenal infarction</td>
</tr>
<tr>
<td></td>
<td>Fetal loss</td>
</tr>
</tbody>
</table>

*ARDS, adult respiratory distress syndrome; CNS, central nervous system.*

Central nervous system symptoms predominated, and there was histopathologic evidence of multiple large-or small-vessel occlusions. ACA were measured in 8 of 10 patients and were positive in all 8 patients in high titers, with the IgG isotype predominating. Similarly,
LA was measured in 7 of the 10 patients and was positive. Greisman et al. (3) reported a patient with SLE and antiphospholipid syndrome with hepatic necrosis and anuric renal failure. The patient had positive ACA in high titer, but LA was absent, as in our patient. There is usually a high mortality rate, in the region of 40%, in these patients with catastrophic antiphospholipid syndrome (1,2).

Thrombotic events in the kidney may involve arterioles, glomerular capillaries, and the renal vein or the renal artery. Kant et al. (4) studied the prevalence and significance of glomerular thrombosis in patients with SLE, who had renal biopsies performed as part of an investigation, irrespective of clinical evidence of renal involvement. One hundred five renal biopsies were performed in 71 patients. On the basis of histology, the biopsies were classified into five groups: (1) normal; (2) predominantly mesangial; (3) predominantly membranous; (4) predominantly proliferative; and (5) sclerosis (Figure 2). Thrombi were seen in 34 biopsies (32.3%). Three of 15 biopsies with predominantly membranous changes and 31 of 63 biopsies with predominantly proliferative (diffuse or focal) glomerulonephritis had glomerular thrombi. No thrombi were detected in biopsies with predominantly mesangial changes. Nine of the total 105 biopsies were in patients with LA, and 7 (78%) of these 9 had glomerular thrombosis. In patients with LA, glomerular thrombosis occurred without evidence of glomerular necrosis (Table 2). Of the total of 71 biopsy patients, 24 had a second renal biopsy performed, 2 to 43 months after the first biopsy, and the degree of glomerulosclerosis in the two biopsies was compared. There was a striking relationship between glomerular thrombosis and a subsequent increase in glomerulosclerosis. It can be concluded that glomerular thrombosis occurs frequently in patients with APA and is a determinant of subsequent glomerulosclerosis. Renal vein thrombosis (5), renal artery occlusions, and renal infarction (6) have also been reported in association with APA.

Table 2. Relationship between the presence of thrombosis and necrosis on renal biopsy and the occurrence of a circulating anticoagulant in patients with SLE

<table>
<thead>
<tr>
<th>Histologic Finding</th>
<th>Circulating Anticoagulant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Present</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Absent</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>96</td>
</tr>
</tbody>
</table>

Adapted from Kant et al. (4).

RELATION BETWEEN LA AND ACA

LA causes the prolongation of activated partial thromboplastin time and the Russel viper venom time. Bowie et al. (7) noted thrombotic events in the presence of LA and suggested that patients with LA were at increased risk of thrombosis. They also noted false-positive VDRL in some of these patients. It was later presumed that these false-positive results were due to the presence of antibodies cross-reacting against cardiolipin, the phospholipid antigen detected in standard tests for syphilis, and a radioimmunoassay to detect ACA was devised (8). Triplett et al. (9) evaluated the incidence of ACA in 100 patients with LA and detected ACA in only 73% of these patients. Their results also indicated that the incidence of thrombosis in patients with either or both of these antibodies is similar.

Figure 2. Light microscopic findings in 105 renal biopsies (B) from 71 patients (P) with SLE. Kant et al. (4).
PATHOPHYSIOLOGY OF THROMBOSIS IN PATIENTS WITH APA

There is at present no agreement on the mechanism(s) associated with APA and thrombosis. Several theories have been proposed. Carreras et al. (10) demonstrated that plasma IgG fraction from a patient with LA decreased prostacyclin production or release from rat aortic endothelial cells, bovine endothelial cells, and human myometrium. This inhibitory effect was abolished in the presence of arachidonic acid. Prostacyclin is a natural potent inhibitor of platelet aggregation. However, no such correlation was seen in a subsequent study with human umbilical vein endothelial cells (11). Abnormalities of endothelium-dependent fibrinolysis have also been suggested as a probable cause of thrombosis. Angles-Cano et al. (12) examined 28 patients with well-documented SLE, and in 24 of these patients, they found a decrease or absence of plasminogen activator activity. Increased von Willebrand factor activity was also demonstrated in these patients. Once again, this hypothesis was not supported in a further study (13) of 11 subjects with LA and a history of thrombosis.

Protein C system is an endothelial membrane-dependent anticoagulant system. Thrombomodulin present on endothelial cells promotes protein C activation. Activated protein C has antithrombotic properties by inactivating factors Va and Villa (Figure 3). It has been demonstrated (14) that thrombomodulin-mediated protein C activation was significantly reduced by LA.

β2 Glycoprotein I (β2gp I) is a protein that neutralizes negatively charged macromolecules and thus prevents the unwanted activation of blood coagulation (Figure 3) (15). It also binds to negatively charged phospholipids in the platelet membrane and inhibits adenylate cyclase activity (16). Recent studies (17,18) have shown that APA bind to cardiolipin only in the presence of a cofactor, which has been identified as β2gp I. They speculate that APA interfere with β2gp I function in vivo, predisposing to thrombosis.

Antithrombin III (AT III) is a protease inhibitor synthesized in hepatocytes. It irreversibly neutralizes factors XIIa, Xla, Xa, Xa, and thrombin (Figure 3). Its activity is enhanced by exogenous heparin and in vivo by heparan sulfate present on endothelial cells, which promotes the interaction of AT III with thrombin. AT III deficiency may be inherited as autosomal dominant or may be acquired as a result of liver disease, nephrotic syndrome, oral contraceptive use, or disseminated intravascular coagulation (19). There is only one previous case report (20) of an acquired functional AT III deficiency in a patient with LA who did not fulfill the criteria for the diagnosis of any specific autoimmune disease but who had recurrent thrombosis. This anticoagulant system has received little attention as a mechanism of thrombosis in patients with APA, although it has been shown that monoclonal and polyclonal anti-DNA antibodies from SLE patients bind to heparan sulfate (21,22). This binding interferes with thrombin neutralization and could potentially lead to thrombosis.

The patient we report has SLE with IgG and IgM ACA and absent LA. She developed devastating thrombosis...
in multiple organs—the catastrophic secondary antiphospholipid syndrome. The patient also had a concomitant acquired hypercoagulable state, reflected by a low AT III level when measured on two occasions and a marginally low functional protein C level, at the peak of her illness. AT III deficiency in our patient may be due to the nephrotic syndrome because she had a proteinuria of 4.19 g/24 h when the AT III level was low and a proteinuria of only 1.428 g/24 h when the AT III level was in the normal range. Alternatively, it could be due to disseminated intravascular coagulation, although this is less likely because she had a fibrinogen level of 437 mg/dL (normal, 150 to 400) and a d-dimer of 1 (<1). Inherited AT III deficiency is also less likely because she had a normal AT III level when measured subsequently and also had a lack of a family history of thromboembolism. It is also conceivable that APA bind to or block the heparan sulfate on the endothelial cell, and this consequently results in a decreased heparan sulfate-mediated enhancement of AT III activity. Whatever the cause, clearly, the decreased AT III level was in part responsible for the widespread thrombotic events seen in this patient. It is possible that AT III deficiency is one of the pathogenic mechanisms for thrombosis in patients with catastrophic antiphospholipid syndrome.

It is well recognized that patients with APA may be asymptomatic. We propose that APA causes a disturbance in the anticoagulant homeostatic mechanism(s) at the endothelial level and precipitates clinical disease. Among the mechanisms that are made deficient or dysfunctional by APA are the following: (1) prostacyclin production or release; (2) plasminogen activator activity; (3) thrombomodulin-mediated protein C activation; (4) β2 glycoprotein I function; and (5) AT III activity.

CONCLUSION

We report a case of catastrophic secondary antiphospholipid syndrome with concomitant AT III deficiency. The patient developed thrombotic events in multiple organ systems including the kidney. The mechanism that predisposes patients with APA to thrombosis is unclear. It is possible that APA disturb the integrity of the endothelial cells and make the endothelial surface procoagulant. The treatment of antiphospholipid syndrome is still empirical, and to date, there are no prospective studies of treatment regimens. In the catastrophic syndrome, aspirin, steroids, cytotoxics, anticoagulants, plasmapheresis, and ancrod have been used with varying degrees of success (2). This is the first reported case of AT III deficiency in association with catastrophic antiphospholipid syndrome.

REFERENCES