## **KIDNEY BIOPSY TEACHING CASE**

# **ARF and Cerebral Infarcts in a Young Woman**

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### INDEX WORDS: Anticardiolipin antibodies; antiphospholipid syndrome; renal failure.

W E PRESENT the case of a 22-year-old woman with acute renal failure (ARF) and cerebral infarcts. A renal biopsy allowed specific diagnosis of her underlying disease.

## CASE REPORT

A 22-year-old woman of Indian descent was admitted to our hospital because of severe anemia and renal failure. Three weeks before presentation, she had exertional dyspnea, orthopnea, and generalized weakness, which had worsened progressively thereafter. Additionally, she had progressive complaints of epigastric pains unresponsive to antacids. Two weeks before these complaints she had suffered from an upper respiratory tract infection with an unproductive cough and a sore throat. Her history was otherwise unremarkable, and she had not been taking any medication other than antacids.

On physical examination, blood pressure was 180/120 mm Hg, pulse was regular at 100/min, central venous pressure was not elevated, and body temperature was 36.8°C. The skin and mucous membranes were pale but otherwise normal. Fundoscopy results showed 2 small cotton wool exudates. A third heart sound and a holosystolic apical murmur were heard over the heart. Bilateral crackles were apparent at the lung bases. The liver was enlarged with a tender margin. There was no pitting edema. Physical examination findings were otherwise normal.

Laboratory examination showed an erythrocyte sedimentation rate of 118 mm/h, a hemoglobin level of 4.8 g/dL (48 g/L) with a mean corpuscular volume of 71 fL, a white blood cell count of  $8.3 \times 10^{3}/\mu L (\times 10^{9}/L)$  with a normal differential and a platelet count of  $144 \times 10^{3}/\mu L$  (×10<sup>9</sup>/L). There were no schistocytes. The activated partial thromboplastin time was lenghtened to 60 seconds without correction on dilution with normal donor plasma. Prothrombin time was also abnormal (40.8 seconds). Serum creatinine level was elevated to 3.9 mg/dL (347 µmol/L) corresponding with a calculated creatinine clearance of 14 mL/min (0.23 mL/s). Urine analysis found hematuria (5 to 10 erythrocytes per high-power field) without casts, and proteinuria was 1.68 g/24 h. Liver enzymes, electrolytes, calcium, phophorus, albumin, and glucose levels were normal. Additional laboratory examinations were performed (Table 1).

The chest radiogram showed an enlarged heart, bilateral pleural effusions, and bilateral air space consolidations caused by pulmonary edema. An abdominal ultrasound scan showed normal-sized kidneys without obstruction and engorgement of the liver. An echocardiogram showed left ventricular hypertrophy, mitral valve insufficiency due to a nodular lesion of the anterior leaflet, and a small pericardial effusion. The ejection fraction was 65%, but there was a clear diastolic dysfunction. The electrocardiogram was normal.

It was concluded that the patient was severely overhydrated and hypertensive because of ARF. A treatment was instituted with diuretics intravenously and antihypertensive agents resulting in a lowering of blood pressure to normal levels and the achievement of euvolemia in the course of 3 days. One day after admission, the patient had thrombopenia, which prevented a renal biopsy. A preliminary diagnosis of systemic lupus erythematosus (SLE) was made, in spite of the negative antinuclear antibody titer, on the basis of the coombs positive anemia, the thrombopenia with autoantibodies to thrombocytes, the pericardial effusion, the mitral valve lesion, and the ARF. The patient was then treated with solumedrol (1 g intravenously for 3 days) followed by prednisone orally (60 mg per day) and cyclophosphamide orally (100 mg per day). Renal function did not improve during this treatment. However, 17 days after admission, the platelet count normalized spontaneously, enabling a renal biopsy.

### Renal Biopsy Findings

The specimen received for light microscopy contained a total of 21 glomeruli, showing mesangial expansion and thickening of glomerular capillary walls to varying extent (Fig 1A). In 3 glomeruli, fresh microthrombi were seen. The arteries showed severe wall thickening with "onion skin lesions" and multiple fresh thrombi (Fig 1B). In addition, there was extensive tubular atrophy with almost diffuse interstitial fibrosis. Immunofluorescence was negative, electron-microscopic examination was not performed.

The morphologic diagnosis was thrombotic microangiopathy with severe, chronic lesions. A clinical-pathologic diagnosis of antiphospholipid syndrome (APS) was established.

## Clinical Course

Three days after the biopsy procedure, the patient had generalized seizures. Multiple cerebral infarcts were seen on

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Table 1. Results of Additional Laboratory Tests

Variable	Value		
Antiplatelet antibodies: Immunoelectrophoresis	Positive		
aCL			
lgG	Positive* (titer 1:200)		
IgM	Negative		
Antinuclear antibodies	Negative		
Extractable nuclear antigen (ENA)	Negative		
Anti-double-stranded DNA	Negative		
Anti-GBM	Negative		
ANCA: ELISA	Negative		
C1q (iE/mL)	97 (normal range, 81-128)		
C3 (mg/mL)	0.78 (normal range, 0.9-1.8)		
C4 (mg/mL)	0.059 (normal range, 0.15-0.40)		
Lupus anticoagulant	Positive		
Coombs test	Positive		
Hepatitis B/C	Negative		
HIV	Negative		
Cryoglobulins	Negative		

Abbreviations: GBM, glomerular basement membrane; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus.

\*The IgG aCL antibodies were present at high levels on 2 occasions with an interval of 2 months.

magnetic resonance imaging of the brain. This provided additional confirmation of our clinicopathologic diagnosis. Appropriate therapy with oral anticoagulation (international normalized ratio >3), steroids (prednisone 30 mg twice a day), and plasmapheresis (10 sessions of  $1.8 \times \text{plasma}$ volume/session) was instituted. After initiation of this treatment, our patient made a remarkable recovery. Her hematologic abnormalities and her mitral valve lesion resolved completely. Also, her neurologic condition resolved without sequelae, enabling the withdrawal of all antiepileptic drugs and permitting her to continue her university education. Finally, her kidney function improved to a value of approximately 60 mL/min (1.00 mL/s; serum creatinine, 1.6 mg/dL [144  $\mu$ mol/L]). This was much better than was initially expected on the basis of the severe chronic lesions in the biopsy.

#### DISCUSSION

The antiphospholipid syndrome is characterized by recurrent arterial and venous thrombosis or recurrent fetal loss in the presence of a lupus anticoagulant, an elevated titer of anticardiolipin (aCL) antibodies, or both.<sup>1-3</sup> Other characteristics of this syndrome are summarized in Table 2. The diagnosis of APS in our patient was established on the basis of renal thrombotic microangiopathy, multiple cerebral infarcts, the presence of aCL antibodies, a positive lupus anticoagulant, thrombocytopenia, autoimmune hemolytic anemia, and the mitral valve lesion.

The obvious prerequisite for a diagnosis of APS is the presence of antiphospholipid antibodies. Although these autoantibodies are associated with thrombosis, they can also be found in healthy individuals. Prevalences of either immunoglobulin G (IgG) or IgM aCL antibodies of 2% to 12% have been described with an increase of antibody titers with increasing age.<sup>13,14</sup> These antibodies are found more frequently in patients with SLE, where prevalences of up to 44% have been described.<sup>15</sup> They are also found in association with other autoimmune disorders (eg, rheumatoid arthritis), certain infections (eg, human immunodeficiency virus), and certain drugs (eg, phenothiazines).<sup>16,17</sup> An APS secondary to SLE is much more common than a primary APS without any underlying autoimmune disorder. In our patient, the renal biopsy findings and, more specifically, the negative immunofluorescence were essential in establishing a diagnosis of primary APS.

Only a small minority of patients with APS presents with a catastrophic syndrome characterized by widespread vascular occlusions affecting multiple organs such as the lungs, heart, brain, kidney, liver, adrenal glands, and gastrointestinal tract. The smaller vessels in these organs are predominantly affected, and this catastrophic syndrome often results in death.<sup>18</sup> There are no data on the incidence of this severe complication.

The pathophysiology of thrombosis in APS is incompletely understood. Whereas lupus anticoagulants are able to prolong lipid-dependent coagulation tests, such as the prothrombin time and the partial thromboplastin time in vitro, by interfering with the phospholipid component of the prothrombin activator complex, they have procoagulant effects in vivo. aCL antibodies can be of different immunoglobulin classes, including IgG, IgA, and IgM. IgG aCLs are associated with a greater risk of thrombosis than other immunoglobulin classes. The risk of thrombosis is also associated with the IgG antibody titer.<sup>19-21</sup> The etiology of thrombosis in patients with antiphospholipid antibodies is incompletely understood. It has been proposed that their procoagulant effects in vivo are related to endothelial cell

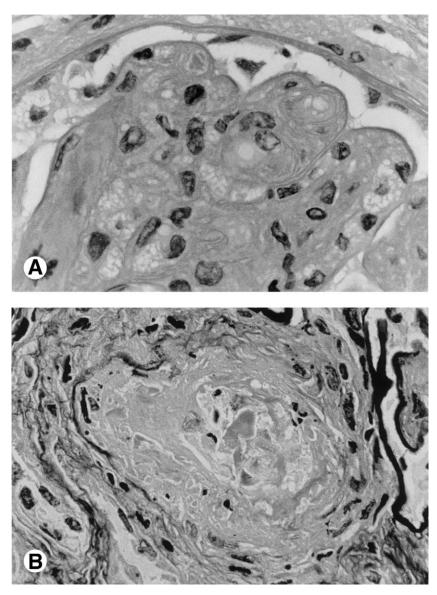


Fig 1. (A) Segment of a glomerulus shows expansion of mesangial area and laminar thickening of glomerular capillary walls with microthrombi. (B) An artery with severe wall thickening owing to concentric fibrosis. The lumen contains a fresh thrombus (Ag, original magnification  $\times$ 100).

damage by antibody binding to endothelial phospholipids, reduced prostacyclin release by these damaged endothelial cells, or alterations in platelet function.<sup>4,22</sup>

The histologic picture of a renal biopsy in APS consists of a thrombotic microangiopathy of the arteries, arterioles, and glomerular microvasculature. Other characteristics include fibrous intimal hyperplasia of arterioles and interlobular arteries with onion skin lesions of the vascular wall. There also is often severe narrowing of the vascular lumen and irregularly distributed focal cortical tubulointerstitial atrophy predominantly involving the subcapsular renal cortex. The distinction between primary APS and APS secondary to SLE can be made on the basis of the immunofluorescence, which is characteristically negative in primary APS.<sup>11,12</sup> In general, the morphologic finding of thrombotic microangiopathy has a broad differential diagnosis. This includes APS, malignant hypertension, diarrheapositive classic hemolytic uremic syndrome (HUS), including familial and drug-induced forms, and following radiation. Thus, proper diagnosis requires careful evaluation and integration of morphologic, clinical, and serologic data. It has been advocated that the distinction between APS and the HUS can generally be made

Table 2.	Criteria	for the	Classification	of APS
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Clinical criteria Vascular thrombosis
One or more clinical episodes of arterial, venous, or small-vessel thrombosis, occurring within any tissue or organ
Complications of pregnancy
One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation; or
One or more premature births of morphologically normal neonates at or before the 34th week of gestation; or
Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
Laboratory criteria
aCL antibodies
aCL IgG or IgM antibodies present at moderate or high levels in the blood on 2 or more occasions at least 6 weeks
apart
Lupus anticoagulant antibodies
Lupus anticoagulant antibodies detected in the blood on 2 or more occasions at least 6 weeks apart

NOTE. A diagnosis of definite APS requires the presence of at least 1 of the clinical criteria and at least 1 of the laboratory criteria.

on the basis of the renal biopsy. Microthrombi in HUS are most often restricted to the smaller vessels and the glomeruli. Second, there is normally no fibrous intimal hyperplasia or focal cortical atrophy.11 Malignant hypertension, however, cannot be distinguished from APS on the basis of a biopsy. However, both HUS and malignant hypertension have distinguishing clinical features. Our patient had neither schistocytes in a peripheral blood smear, nor grade III or IV abnormalities on fundoscopy. A diagnosis of primary APS was made on the basis of the negative immunofluorescence, despite the fact that a diagnosis of antinuclear antibody-negative SLE was suggested by multiple clinical and laboratory features of this case. However, the patient did not fulfill the revised American Rheumatology Association criteria for a diagnosis of SLE.23

The treatment of APS remains empirical because of the absence of therapeutic clinical trials in this disorder and is directed at coagulation and immune mechanisms. Venous and arterial thromboses in this condition are effectively prevented by intensive oral anticoagulation with an international normalized ratio greater than 3.24,25 Oral anticoagulation is also the cornerstone of the treatment of thrombotic complications in this disorder.<sup>24,25</sup> Corticosteroids and cytotoxic drugs may be considered in patients unresponsive to antithrombotic therapy, although there is little evidence that these drugs alter the course of the hypercoagulable state.<sup>7,26</sup> Severe organ complications such as ARF are often treated with adjunctive plasmapheresis, which induces a prompt reduction of antiphospholipid antibody titers.<sup>18</sup>

In 1 series of 12 patients with ARF, complete recovery of renal function occurred only in the 2 patients treated with plasmapheresis.<sup>27</sup> In catastrophic APS, patients treated with adjunctive plasmapheresis or intravenous immunoglobulin had the highest survival rate (70%).<sup>18,28</sup>

APS is a severe and potentially life-threatening condition that can be either primary or secondary to SLE. The differential diagnosis of primary APS with renal involvement includes SLE with secondary APS, HUS, and malignant hypertension. A kidney biopsy is an important aid in the resolution of this differential diagnosis. Early and appropriate treatment determines clinical outcome in patients with APS. The prognosis of such patients is, therefore, dependent on early recognition of this diagnosis in patients with antiphospolipid antibodies.

#### REFERENCES

1. Hughes GRV, Harris NN, Gharavi AE: The anticardiolipin syndrome. J Rheumatol 13:486-489, 1986

2. Hughes GRV: The anticardiolipin syndrome. Clin Exp Rheumatol 3:285-286, 1985

3. Asherson RA, Cervera R, Piette J-C, Shoenfeld Y: The Antiphospholipid Syndrome: History, Definition, Classification, and Differential Diagnosis. Boca Raton, FL, CRC Press, 1996, pp 3-12

4. Triplett DA, Brandt JT, Musgrave KA, Orr CA: The relationship between lupus anticoagulants and antibodies to phospholipid. JAMA 259:550-554, 1988

5. Asherson RA: A "primary" antiphospholipid syndrome? J Rheumatol 15:1742-1746, 1988

6. Alarcón-Segovia D, Sanchez-Guerrero J: Primary antiphospholipid syndrome. J Rheumatol 16:482-488, 1989

7. Asherson RA, Khamashta MA, Ordi-Ros J, et al: The "primary" antiphospholipid ayndrome: Major clinical and serological features. Medicine (Baltimore) 68:366-374, 1989

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8. Piette JC: Diagnostic and classification criteria for the antiphospholipid/cofactors syndrome: A "mission impossible"? Lupus 5:354-363, 1996

9. Amigo MC, Garcia-Torres R, Robles M, Bochicchio T, Reyes PA: Renal involvement in primary antiphospholipid syndrome. J Rheumatol 19:1181-1185, 1992

10. D'Agati V, Kunis C, Williams G, Appel GB: Anticardiolipin antibody and renal disease. A report of three cases. J Am Soc Nephrol 1:777-784, 1990

11. Nochy D, Daugas E, Droz D, et al: The intrarenal vascular lesions associated with primary antiphospholipid syndrome. J Am Soc Nephrol 10:507-518, 1999

12. Hughson MD, Nadasdy T, McCarty GA, Sholer C, Min KW, Silva F: Renal thrombotic microangiopathy in patients with systemic lupus erythematosus and the antiphospholipid syndrome. Am J Kidney Dis 20:150-158, 1992

13. Fields RA, Toubbeh H, Searles RP, Bankhurst AD: The prevalence of anticardiolipin antibodies in a healthy elderly population and its association with antinuclear antibodies. J Rheumatol 16:623-625, 1989

14. Vila P, Hernandez MC, Lopez-Fernandez MF, Batlle J: Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. Thromb Haemost 72:209-213, 1994

15. Love PE, Santoro SA: Antiphospholipid antibodies: Anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. Ann Intern Med 112:682-698, 1990

16. McNeil HP, Chesterman CN, Krilis SA: Immunology and clinical importance of antiphospholipid antibodies. Adv Immunol 49:193-280, 1991

17. Triplett DA: Many faces of lupus anticoagulants. Lupus 7:18-22, 1998

18. Asherson RA, Cervera R, Piette JC, et al: Catastrophic antiphospholipid syndrome: Clinical and laboratory features of 50 patients. Medicine (Baltimore) 77:195-207, 1998

19. Alarcón-Segovia D, Delezé M, Oria CV, et al: An-

tiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus: A prospective analysis of 500 consecutive patients. Medicine (Baltimore) 68: 353-365, 1989

20. Vaarala O, Manttari M, Manninen V, et al: Anticardiolipin antibodies and risk of myocardial infarction in a prospective cohort of middle-aged men. Circulation 91:23-27, 1995

21. Finazzi G, Brancaccio V, Moia M, et al: Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: A four-year prospective study from the Italian Registry. Am J Med 100:530-536, 1996

22. Carreras LO, Defreyn G, Machin SF: Arterial thrombosis, intrauterine death and lupus anticoagulant: Detection of immunoglobulin interfering with prostacyclin production. Lancet 1:244-246, 1981

23. Piette JC, Wechsler B, Frances C, Godeau P: Systemic lupus erythematosus and the antiphospholipid syndrome: Reflections about the relevance of ARA criteria. J Rheumatol 19:1835-1837, 1992

24. Derksen RHWM, De Groot PHG, Kater L, Nieuwenhuis HK: Patients with antiphospholipid antibodies and venous thrombosis should receive long-term anticoagulant treatment. Ann Rheum Dis 52:689-692, 1993

25. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR: The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 332:993-997, 1995

26. Joseph RE, Valeri A, Radhakrishnan J, et al: Anticardiolipin antibody (ACLN) levels in lupus nefritis: Effects of immunosuppression (abstract). J Am Soc Nephrol 8:89A, 1997

27. Kincaid-Smith P, Fairly KF, Kloss M: Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy-related renal failure. Q J Med 258:795-815, 1998

28. Triplett DA, Asherson RA: Pathophysiology of the catastrophic antiphospholipid syndrome (CAPS). Am J Hematol 65:154-159, 2000