

Lupus nephritis and antiphospholipid syndrome

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Nefrología 2008; 28 (5) 555-558

CASE REPORT

A 47-year-old female was referred to the nephrology outpatient clinic in January 2007 for follow-up of lupus nephritis. Her history started at 17 years of age, when she was diagnosed thrombocytopenic purpura that, after 6 months of ineffective corticosteroid treatment, led to splenectomy, the pathological study of which showed a preserved architecture. Arteries showed a reduced lumen due to intimal hyperplasia (fig. 1).

On September 1979 (at 19 years of age), the patient was admitted to internal medicine after experiencing joint pain, fever, edema, and erythematous lesions in the face and being diagnosed systemic lupus erythematosus (SLE). Clinical findings included nephrotic syndrome with sediment changes and serum creatinine levels of 1.9 mg/dL, and cardiological study revealed mitral valve prolapse. Renal biopsy was performed. The core contained 12 big, lobulated glomeruli with an irregularly distributed, diffuse mesangial proliferation, nuclei in karyorrhexis, occasional intracapillary thrombi, and thickened «wire loop» capillary walls. No changes were seen in small arteries (fig. 2). Direct immunofluorescence showed the presence of subendothelial and mesangial deposits of IgG, C3, C1q, IgM, and IgA (fig. 3).

Diagnosis: Class IV lupus nephritis.

Treatment was started with corticosteroids and azathioprine, leading to normalization of renal function and negativization of immune activity. Proteinuria of 2 g/24 h persisted. As early as in November 1981 (when patient was 21), high blood pressure values were found.

In December 1981, in her first pregnancy, she had a spontaneous abortion after two months of amenorrhea.

In September 1982 (at 22 years of age), immunosuppression was withheld during her second pregnancy, that arrived to term. She had arterial hypertension in her eighth month of pregnancy.

Just after delivery in May 1983, the patient showed a worsening of her condition with arterial hypertension and proteinuria of 3 g/24 h. Treatment with corticosteroids and azathioprine was restarted and resolved patient symptoms and proteinuria. Patient showed a normal renal function and a negative immunological study, but arterial hypertension persisted.

In September 1985 (at 25 years of age) she started to experience seizures. A CT scan of the brain revealed multiple ischemic lesions. One month later, she suffered a second lupus outbreak consisting of fever, joint and skin involvement, recurrence of proteinuria with normal renal function and immune activity. Immunosuppressive treatment was increased, and the condition remitted. Azathioprine was discontinued in 1990 and corticosteroids were temporarily suspended in January 1991, but have been continued to date with fluctuating doses.

In 1996, when she was 36, the patient underwent surgery for a fusiform aneurysm in the right carotid artery.

In 2000, the patient experienced a stroke with left hemiplegia from which she recovered completely.

From 1999 to 2006m arterial hypertension persisted and a progressive, slow renal function impairment occurred to creatinine levels of 1.8 mg/dL in 2006, with negative proteinuria. She was then referred to nephrology under low-dose corticosteroid treatment. Among tests performed, special mention should be made of an immunological study with negative ANA and positive IgG anticardiolipin antibodies subsequently confirmed in several measurements, as well as low C4 and C3 in the lower normal limit. An echocardiogram showed mitral valve thickening with calcification of the free margins of both leaflets and involvement of the subvalvular apparatus suggesting a typical Libman-Sacks lesion with mild to moderate mitral insufficiency. Abdominal ultrasound showed a nodule in the upper pole of the right kidney, 2 cm in

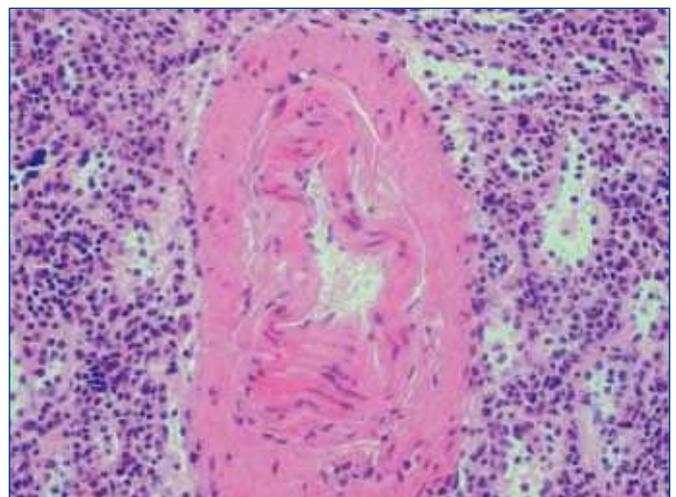


Figure 1.

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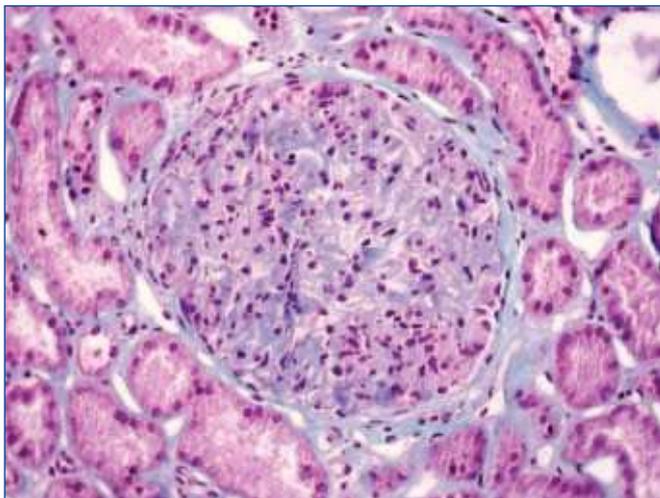


Figure 2.

diameter, and an aneurysmal dilation in the infrarenal aorta 3.5 cm in diameter. The patient was assessed by the urology department, and partial nephrectomy was decided in August 2007.

Histological study of tumor-free parenchyma showed a great number of glomeruli with lesions superimposable to those of the first biopsy: mesangial proliferation and capillary wall thickening (fig. 4). Immunofluorescence could not be performed because the specimen was fixed in formalin. Immunohistochemistry for C4d showed the presence of subendothelial wall deposits (fig. 5). There was a subcapsular area of cortical atrophy, with areas of tubular thyroidization and

pseudocystic glomeruli. Arteries of medium and small size showed occlusive lesions caused by myointimal cell proliferation. These cells were positive for actin using indirect immunoperoxidase techniques (fig. 6).

The tumor causing partial nephrectomy was a benign tumor consisting of actin-positive epithelial and stromal elements.

Diagnosis: Class IV lupus nephritis. Nephropathy associated to antiphospholipid syndrome. Mixed epithelial and stromal renal tumor.

DISCUSSION

The APS may appear isolated, in which case it is called primary APS, or associated to other diseases, the most common of which is SLE. Antiphospholipid antibodies are known to recognize free phospholipids and/or those bound to membrane proteins. The best known of these proteins is β 2-glycoprotein I, able to act at different levels in the coagulation, complement, and vascular endothelium cascade. Detection of IgG and/or IgM anticardiolipin antibodies is actually the demonstration of antibodies against a phospholipid- β 2-glycoprotein I complex.^{1,2}

A number of pathological lesions which are characteristic but not exclusive of both primary and secondary APS and which have been generically called APS-associated nephropathy have been reported.³

The case of a patient affected of SLE in whom the main clinical events occurring over time were primarily caused by the associated APS is reported here. That was the case of the thrombocytopenia that led to splenectomy and miscarriage after

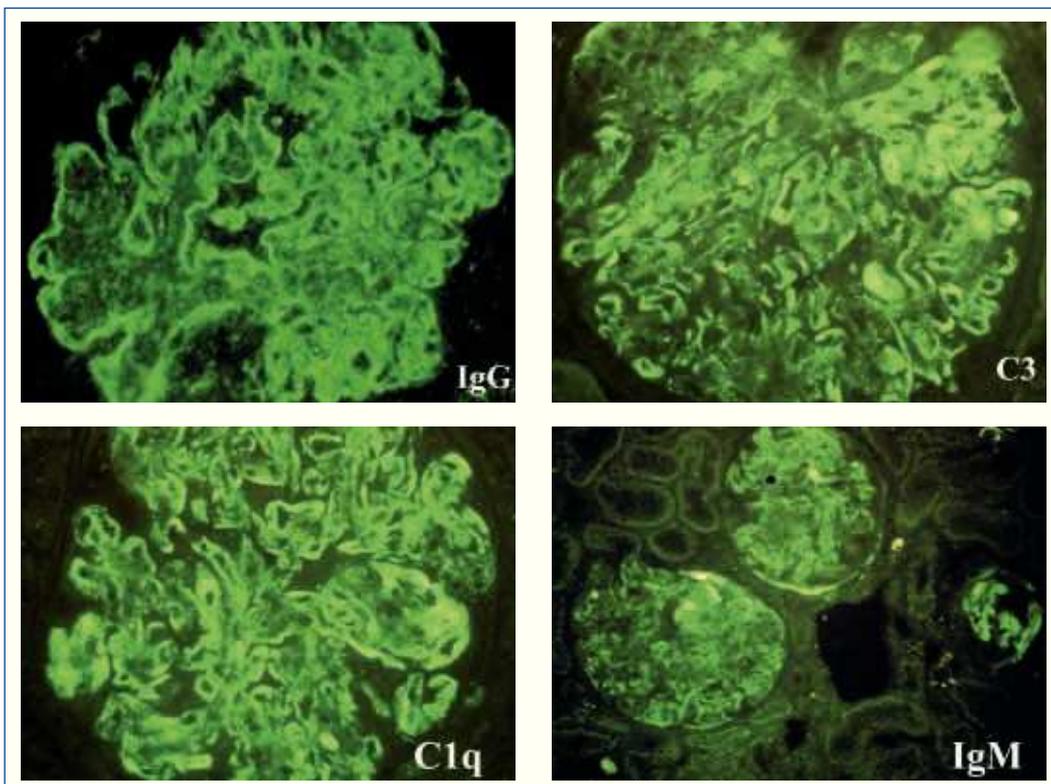


Figure 3.

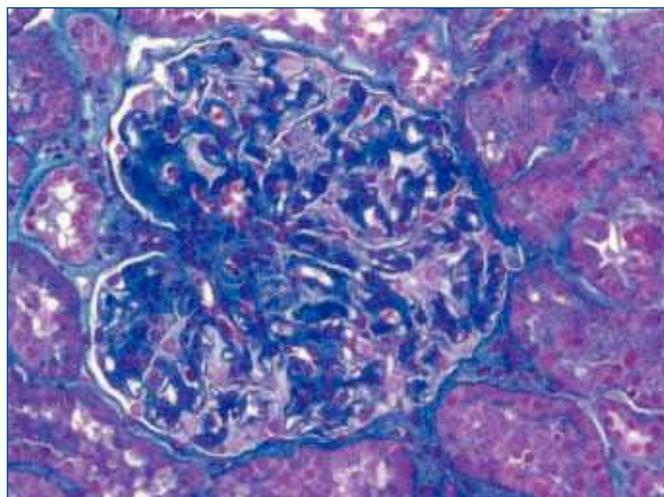


Figure 4.

more the two months of pregnancy. The risk of fetal loss in APS is recognized to be greater from 10 weeks of pregnancy.⁴

Mention should be made of the lack of correlation between the clinical signs and glomerular histological lesions in the last renal tissue sample, the one taken at partial nephrectomy, where a class IV lupus nephritis with some signs of chronicity was still seen, in addition to the already described vascular lesions. This again emphasizes the importance of renal biopsy for staging of lupus involvement.

Lesions described under the term of antiphospholipid syndrome-associated nephropathy are known since the 90s^{11,12} and include acute (thrombotic microangiopathy) and chronic lesions such as myofibroblastic proliferation of the arterial intima causing luminal occlusion and focal cortical atrophy, with tubular and glomerular cystic dilations, areas of tubular atrophy and interstitial fibrosis.^{3,14,15} These lesions are not specific when considered alone, but when they occur combined are characteristic of this nephropathy.

The most striking clinical sign shown by our patient was the presence of large vessel aneurysmal dilations at the carotid artery and abdominal aorta. Such dilations may result from three causes:

1. The vascular risk itself for development of arteriosclerosis and potential aneurysms associated to it, depending on several factors including AHT, dyslipidemia, and chronic steroid treatment.
2. SLE is the autoimmune disease most commonly associated to arteriosclerosis, and the potential associated vasculitis could also lead to development of aneurysms, which could be expected to involve vessels of a smaller size.⁵
3. APS itself may contribute to formation of aneurysmal dilations. Nine cases of primary APS associated to large-vessel aneurysm have been reported in the literature. Antiphospholipid antibodies appear to increase production of metalloproteinase 9 (MMP 9), a protein that acts upon the vascular wall degrading elastin.⁶ Patients with SLE and APS are known to have increased MMP 9 levels, which is correlated to antiphospholipid antibody levels.⁷

QUESTIONS

—Dr. Francisco Rivera (Ciudad Real): *What was the treatment administered following diagnosis of secondary APS? What would be indicated first, antiaggregation or anticoagulation?*

Recent patient arrival to the nephrology department agrees with diagnoses of renal tumor and abdominal aortic aneurysm. She was immediately referred to the urology department, where partial nephrectomy was decided. Patient experienced significant postoperative complications such as abscesses and urinary fistula still pending resolution, which delayed the start of anticoagulant treatment, whose urgency is in addition difficult to justify in a patient with a condition dating back to 30 years. Assessment of the abdominal aortic aneurysm by the vascular surgery department is still pending in a patient whose treatment should be anticoagulation, the only therapeutic option that has been shown to be effective in these cases.²

In patients with anticardiolipin antibodies and no associated thrombotic events, use of low-dose acetylsalicylic acid (ASA) could be considered, but has not been shown to be clearly effective,¹ and only appears to prevent thrombotic events in cases of SLE combined with antimalarials.⁸

—Dr. Isabel García (Málaga): *Was heart disease diagnosed before SLE in this case? And did you consider whether APS could have had an influence on the course of valve disease?*

In our case, heart disease was diagnosed at the same time as SLE. The mitral valve lesion is more common in cases of SLE associated to anticardiolipin,⁹ occurring in up to 76% of patients with primary APS.¹⁰

—Dr. Manuel Praga (Madrid): *Could you give some specific recommendations for management of APS associated to SLE?*

The only effective treatment for APS associated to SLE once thrombotic events and/or abortion have occurred is anticoagulation. No immunosuppressive treatment is helpful. Antiaggregation combined with use of antimalarials may be effective as prophylaxis.

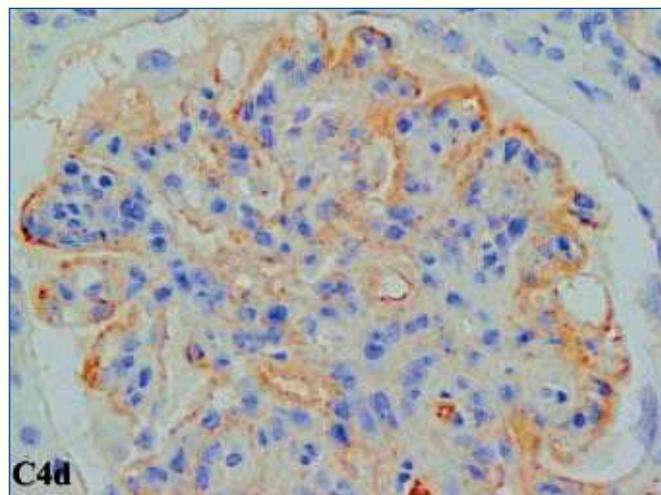


Figure 5.

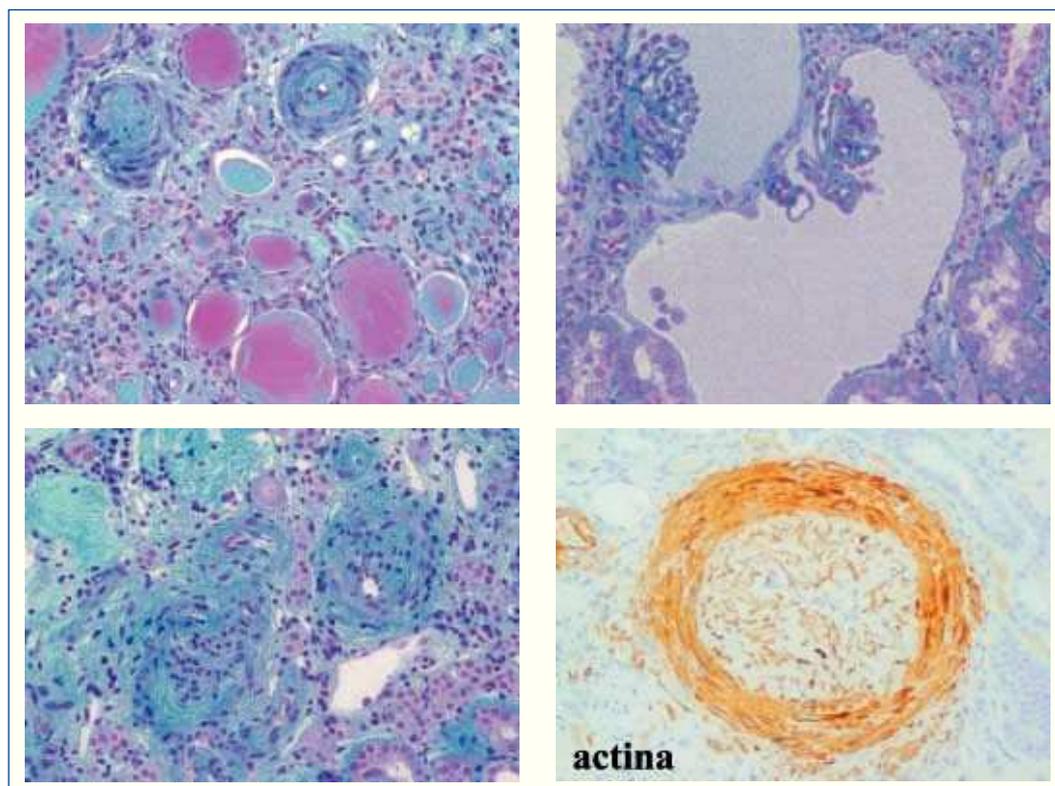


Figure 6.

—Dr. Carlos Quereda (Madrid): *Have lupus patients with APS nephropathy an additional risk of chronic renal failure as compared to patients with no APS?*

Our patient had been losing renal function with no clear signs of lupus activity, which was probably related to a greater extent to vascular damage from APS, found in the last histological sample. An additional risk for development of chronic renal failure may therefore exist in patients with lupus nephropathy and SLE.

—Dr. Frutos (Málaga): *Even considering the low prevalence of the association of APS and arterial aneurysms, in what circumstances would prior screening for this association would be recommended before starting preventive treatment with anticoagulation?*

Only 9 cases of primary APS associated to arterial aneurysm have been reported, and prior screening was not considered because of such low prevalence. It should be reminded that SLE diagnosis and follow-up require a battery of tests, such as abdominal ultrasound, that may be of help for diagnosis.

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