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Case Report

CASE REPORT

Case of an unusual diagnosis of primary antiphospholipid syndrome with multiple clinical complications

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Abstract

Antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by the presence of antiphospholipid antibodies in association with thrombotic events and/or obstetric complications. Renal involvement is not infrequent in both primary and secondary APS. Kidney manifestations comprise a wide range of clinical features, including hypertension, major renal vessel thrombosis or microvascular endothelial injury, also described as APS nephropathy. In the absence of a thrombotic event, clinical manifestations of APS are often non-specific. We recently encountered a case of primary APS in a young male with newly diagnosed hypertension and renal impairment. The diagnosis of APS was initially suspected by his kidney biopsy findings, when electron microscopy examination showed the features of chronic microangiopathy, and was later confirmed by a triple positive antiphospholipid antibody profile and multiple organ involvement.

INTRODUCTION

Antiphospholipid syndrome (APS) is an acquired hypercoagulable disease defined by the presence of consistently elevated antiphospholipid antibodies (aPL). It is an established cause of vascular thrombosis and recurrent pregnancy morbidity, affecting predominantly young and middle-aged adults [1]. Moreover, a variety of clinical features related to aPL antibodies (renal microangiopathy, heart valve disease, skin ulcers, thrombocytopenia and neurological disorders) may develop in patients with overt APS or appear as initial presentation, occasionally preceding a thrombotic event [2]. Herein, we describe a case of primary APS in a young man presenting with new-onset hypertension and renal impairment.

CASE REPORT

A 25-year-old man was referred to our department for further evaluation of recently diagnosed kidney disease. Five weeks earlier, grade 2 hypertension was incidentally found during physical examination for an upper respiratory tract infection and additional investigation revealed renal impairment with a creatinine level of 132.6 μmol/l (normal: 61.9-106.1 μmol/l) and subnephrotic proteinuria 2.5 g/day (normal: <150 mg/day). A kidney biopsy performed at a regional hospital showed ischemic glomerular lesions in the absence of immune-complex deposition and he was discharged on antihypertensive medication.

Upon presentation to our department, physical examination was unremarkable, except for a grade 3/6 systolic heart

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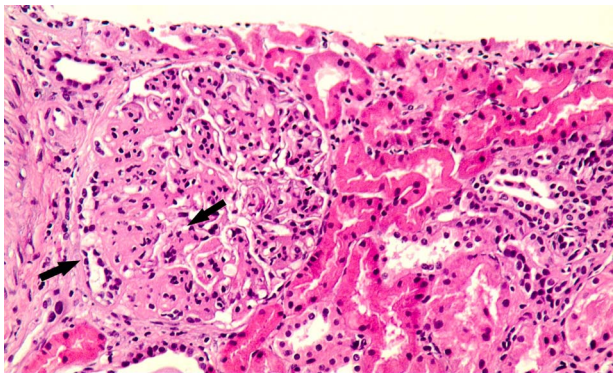

Figure 1: Focal segmental glomerulosclerosis and mild mesangial expansion by light microscopy. (Courtesy of G. Liapis—Pathology Department, Laiko Hospital, Athens, Greece).

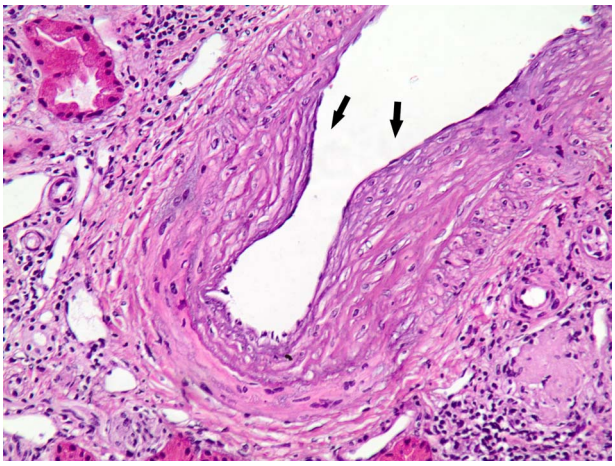

Figure 2: Severe intimal thickening of an interlobular artery by light microscopy. (Courtesy of G. Liapis—Pathology Department, Laiko Hospital, Athens, Greece).

murmur. He reported intermittent episodes of headache and blurred vision over the past year. His family history was remarkable for autoimmune disorders; his mother had systemic lupus erythematosus (SLE) and his sister Hashimoto's disease.

Renal indices showed a creatinine level of 145.9 µmol/l (normal: 61.9-106.1 µmol/l) and a urine protein level of 1.4 g/day (normal: <150 mg/day). Doppler ultrasonography showed normal-sized kidneys and renal blood flow.

Due to an inconclusive diagnosis, the patient's kidney biopsy specimen was re-evaluated by our renal pathologist. The tissue sample was considered inadequate and we decided to proceed to a second kidney biopsy.

Pre-biopsy evaluation revealed a markedly prolonged activated partial thromboplastin time of 86.9 seconds (normal: 29-40 seconds). Mixing studies performed according to the International Society on Hemostasis and Thrombosis guidelines confirmed the presence of a lupus anticoagulant (LA) [3]. A serologic panel for antiphospholipid antibodies was afterwards requested, which came out strongly positive for anticardiolipin (aCL) antibodies (IgG > 90 GPLU/ml, normal: 0-15 GPLU/ml) and anti-beta2-GP I antibodies (IgG:100 U/ml, normal: 0-9 U/ml). SLE autoantibodies were negative.

The kidney biopsy revealed focal segmental glomerulosclerosis (Fig. 1) and moderate interstitial fibrosis by light microscopy. Severe intimal thickening resulting in a narrowed lumen of an interlobular artery (Fig. 2) was also noticed. Immunofluorescence studies were negative. Notably, electron microscopy (EM) revealed diffuse sub-endothelial edema and glomerular basement membrane reduplications (Fig. 3), findings suggestive of chronic thrombotic microangiopathy (TMA).

A transthoracic echocardiogram showed diffuse mitral valve thickening associated with mitral regurgitation. Small masses on the atrial side of the mitral leaflets were subsequently observed by a transesophageal echocardiography. Fundoscopy detected mild constriction of the retinal arterioles and brain magnetic resonance imaging showed chronic small vessel ischemic lesions in both cerebral hemisphere white matter.

Despite the absence of overt thrombotic events, the patient's 'triple' positive aPL profile (LA, anti-b2-GP I and aCL antibodies) and the presence of renal chronic microangiopathy, heart-valve disease and cerebral microvasculopathy, were strongly indicative of APS. The patient was at high risk for thrombosis and anticoagulation therapy with acenocoumarol was initiated.

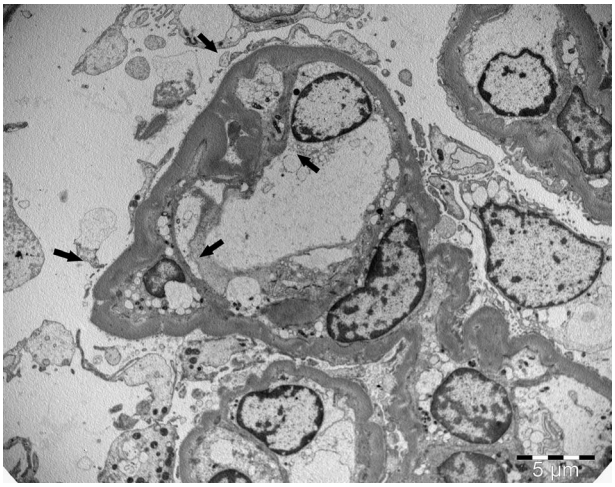

Figure 3: Diffuse subendothelial edema and glomerular basement membrane reduplications by EM. (Courtesy of G. Liapis—Pathology Department, Laiko Hospital, Athens, Greece).

Two weeks later, acenocoumarol was temporarily switched to low-molecular-weight-heparin (LMWH) due to a large thigh hematoma resulting from injury and prolonged prothrombin time (I.N.R.: 10). A few days later, he presented with acute upper abdominal pain, ST-segment depression in II, III and AVF leads on electrocardiogram and elevated troponin T level (1057 pg/ml, normal: <14 pg/ml). Myocardial ischemia was attributed to microvascular thrombosis due to no evidence of coronary artery stenosis on cardiac catheterization. Acenocoumarol was resumed with a target INR of 3-4 in combination with acetylsalicylic acid (100 mg/day).

Antiphospholipid antibodies were repeated at 12 weeks and persisted at the same high levels.

A year later, our patient has not experienced a new thrombotic event. His creatinine and urine protein levels are 129 µmol/l and 0.47 g/day, respectively. Acetylsalicylic acid was discontinued in consultation with the attending hematologist and cardiologist.

Table 1: Table 1: Classification Criteria for Definite APS and CAPS

Updated Classification Criteria for Definite APS*
Clinical criteria
1. Vascular thrombosis: ≥1 episodes of arterial, venous or small-vessel thrombosis
2. Pregnancy morbidity:
a) ≥1 unexplained death of a fetus at or beyond the 10th week of gestation
b) ≥1 premature birth before the 34th week of gestation because of eclampsia, severe pre-eclampsia or placental insufficiency
c) ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation
Laboratory criteria
1. LA present on ≥2 occasions at least 12 weeks apart
2. Anticardiolipin (aCL) antibody (IgG and/or IgM) present in medium or high titer (i.e. >40 GPL or >99th percentile) on ≥2 occasions at least 12 weeks apart
3. Anti-β2-glycoprotein-I antibody (IgG and/or IgM) present in titer > the 99th percentile on ≥2 occasions at least 12 weeks apart
Classification criteria for CAPS**
1. Evidence of involvement of ≥3 organs, systems or tissues
2. Development of manifestations simultaneously or in less than 1 week
3. Confirmation of histopathology of small vessel occlusion in ≥ organ or tissue
4. Laboratory confirmation of the presence of antiphospholipid antibodies (LA, aCL, β2GPI)

*At least, one clinical and one laboratory criterion are required for definite APS.
**All four criteria are required for definite CAPS.

DISCUSSION

APS is a prothrombotic autoimmune disease with a significant heterogeneity in clinical manifestations. At least, one clinical and one laboratory criteria are required for the diagnosis of definite APS (Table 1) [1].

Kidney involvement is common in both primary and SLE-associated APS. Thrombotic lesions may affect any level within the renal vasculature typically resulting in high blood pressure, renal impairment and low-grade proteinuria. Hypertension, occasionally severe to malignant, may be the major presenting feature of APS nephropathy [4]. Notably, in our case, hypertension was an incidental finding, which eventually led to the diagnosis of APS. Considering the absence of overt thrombosis, the diagnosis could have been easily missed with potentially severe complications for the patient.

Kidney biopsy findings raised suspicion for an underlying chronic TMA. The intimal proliferation of the renal arteriole is frequently encountered in active microangiopathies, reflecting a tissue response to endothelial injury [5]. Furthermore, new glomerular basement membrane formation shown by EM examination indicated a chronic stage of TMA. Of note, EM is valuable for identifying chronic lesions of TMA since overt fibrin thrombi are usually absent in these cases [6]. Histologically proven small-vessel thrombosis fulfills the clinical criterion for APS [1].

Besides renal involvement, cardiac manifestations and triple positive aPL profile established the diagnosis of APS and guided our therapeutic decisions. Our patient's mitral valve thickening is a common manifestation of APS, posing an increased risk for stroke and other embolic complications [7]. Acute coronary syndrome is uncommon in young APS patients without traditional risk factors. APS may predispose to accelerated atherosclerosis; however, cases of myocardial infarction due to microthrombosis have been described [8]. Regarding the patient's aPL profile, the presence of more than one antiphospholipid antibody, the high titer and the persistent positivity associate with high risk for thrombosis [9]. Pengo *et al.* showed that even asymptomatic carriers of all three antiphospholipid antibodies had a high incidence of thromboembolic events, raising the question for primary thromboprophylaxis in these subjects [10].

As mentioned above, several of our patient's organs (kidney, brain and heart) had been affected. The chronic or subacute development of the aPL-associated lesions, as well as his good clinical status, distinguished his condition from catastrophic APS (CAPS), an emergent life-threatening condition with poor prognosis. CAPS is suspected when acute multiple-organ thrombosis occurs within a short period of time (<a week) (Table 1) [1].

Management of APS aims to prevent recurrent thrombotic events through long-term use of antithrombotic agents. Vitamin K antagonists (VKAs) remain the mainstay of chronic anticoagulation in non-pregnant APS patients. Our patient experienced an acute coronary syndrome, after VKA was switched to LMWH. Perhaps, overexpression of tissue factor due to recent injury and inadequate therapeutic effect of LMWH in this high-risk patient contributed to his thrombotic event. In APS patients with arterial thrombosis, a target INR of 3–4 or treatment with VKA plus low-dose aspirin may be considered according to EULAR recommendations for the management of APS [9].

In conclusion, APS should be considered in young patients presenting with new-onset hypertension and kidney injury, even in the absence of overt thrombosis.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

FUNDING

No funding.

ETHICAL APPROVAL

No ethical approval was required.

CONSENT

Informed consent was signed by the patient.

GUARANTOR

Stathis Tsiakas.

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