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...
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 normalized 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 withacenocoumarol was initiated.

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.
**DISCUSSION**

APS is a prothrombotic autoimmune disease with a significant heterogeneity in clinical manifestations. At least, one clinical and one laboratory criterion 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 [3]. 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 2) [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.

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**ETHICAL APPROVAL**

No ethical approval was required.

**CONSENT**

Informed consent was signed by the patient.
GUARANTOR
Stathis Tsiakas.

REFERENCES
1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
2. Sciascia S, Amigo MC, Roccatello D, Khamashta M. Diagnosing antiphospholipid syndrome: ‘extra-criteria’ manifestations and technical advances. Nat Rev Rheumatol 2017;13:548–60.
3. Devreese KMJ, Ortel TL, Pengo V, de Laat B. Subcommittee on lupus anticoagulant/antiphospholipid antibodies. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost 2018;16:809–13. doi: 10.1111/jth.13976 Epub 2018 Mar 13. PMID: 29532986.
4. Alchi B, Griffiths M, Jayne D. What nephrologists need to know about antiphospholipid syndrome. Nephrol Dial Transplant 2010;25:3147–54.
5. Goodship TH, Cook HT, Fakhouri F, Fervenza FC, Fremeaux-Bacchi V, Kavanagh D, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “kidney disease: improving global outcomes” (KDIGO) controversies conference. Kidney Int 2017;91:539–51.
6. Brocklebank V, Wood KM, Kavanagh D. Thrombotic microangiopathy and the kidney. Clin J Am Soc Nephrol 2018;13:300–17.
7. Tenedios F, Erkan D, Lockshin MD. Cardiac manifestations in the antiphospholipid syndrome. Rheum Dis Clin North Am 2006;32:491–507.
8. Shan Y, Wang P, Liu J. Antiphospholipid syndrome combined with acute coronary syndrome: case report. Medicine 2018;97:e13613.
9. Tektonidou MG, Andreoli L. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019;78:1296–304.
10. Pengo V, Ruffatti A, Legnani C, Testa S, Fierro T, Marongiu F, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood 2011;118:4714–8.