Case Report

Life-threatening thrombosis 18 years after first presentation of primary antiphospholipid antibody syndrome

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Keywords: antiphospholipid syndrome; aortic thrombosis; β2 glycoprotein 1 antibodies; renal failure

Case

A 46-year-old woman presented at our renal unit for investigation of renal impairment. Of note in her past medical history, she had had several toes amputated while in her late twenties due to digital ischaemia. Investigations at that time had revealed a thrombotic stenosis of the left popliteal artery and occlusion of the anterior and posterior tibial vessels. She subsequently underwent successful arterial bypass grafting. Laboratory testing had revealed a positive anti-nuclear antibody (titre 1/160) but nothing else of note. There were no other clinical features to support a diagnosis of systemic lupus erythematosus (SLE). Empirical steroid therapy was given for a period and she was placed on long-term warfarin anticoagulation treatment.

Some 18 years later this woman returned to our unit, having been entirely asymptomatic in the intervening period. She had been non-specifically unwell for about 1 month before admission, complaining of lethargy and malaise with some associated nausea and vomiting. Initial clinical examination revealed that she was hypertensive, with a blood pressure of 200/100 mmHg, and was manifestly fluid overloaded with significant peripheral oedema and bilateral pleural effusions. Loud renal bruits were audible bilaterally and were noted to be best heard posteriorly. Examination of the lower limbs revealed evidence of vascular insufficiency, with no pulses palpable on the left and only a femoral pulse palpable on the right. A radio-femoral delay was noted. The left foot appeared mottled with evidence of previous amputations.

Initial laboratory investigations showed a serum creatinine level of 150 µmol/l, which rose progressively to 320 µmol/l. The urine sediment was persistently bland, with only trace protein on dipstick and a few granular casts on microscopy. Full blood count showed a microcytic anaemia with a haemoglobin level of 7.4 g% and an mean corpuscular volume (MCV) of 64. Subsequent haemoglobin electrophoresis confirmed the presence of alpha thalassemia trait. A marked thrombocytopenia was also present with a platelet count of 14×10⁹/l. Bone marrow aspiration showed increased megakaryocyte numbers, suggesting increased platelet consumption or peripheral destruction. Autoantibody testing demonstrated a weakly positive anti-nuclear antibody (ANA) with a titre of 1:80. Antibodies against double-stranded DNA were absent. Rheumatoid factor was negative, as were antibodies against extractable nuclear antigens. Complement studies were normal.

In view of the history of previous arterial thrombosis, anti-phospholipid antibodies were sought and proved to be positive for IgG (titre 38.0; normal <12) but negative for IgM. A lupus anticoagulant was also detected (ratio of 2:1). Antibodies were also present and directed against the platelet antigen β2 glycoprotein 1 (titre 19.3; normal <12.4). Other anti-platelet auto-antibodies, including anti-CD36, were not detected.

A chest radiograph showed cardiomegaly and confirmed the presence of bilateral pleural effusions. There was no evidence of rib notching. Renal imaging by ultrasound demonstrated normal sized kidneys measuring 10 cm bilaterally. There was no evidence of obstruction. On Doppler examination of the renal vessels, however, no arterial signal was obtainable and the venous signal was present only in systole.

In view of the clinical evidence of lower limb vascular insufficiency, arteriography was performed via the femoral route. This showed a complete occlusion of the abdominal aorta above the level of the renal arteries and below the coeliac axis (see Figure 1). An extensive collateral circulation involving the intercostal and epigastric arteries was also present, suggesting either...
abdomen did not show any extrinsic compression of the aorta.

Balloon dilatation of the abdominal aorta was performed, which resulted in recovery of renal function and the patient becoming dialysis-independent. A significant stenosis remained, however, with a pressure gradient of 120 mmHg (Figure 2). Definitive treatment was by aortic endarterectomy, which was uncomplicated. Splenectomy was performed concomitantly for treatment of resistant autoimmune thrombocytopenia.

Discussion

The antiphospholipid syndrome (APS) is a clinical entity characterized by the presence of antibodies directed against negatively charged phospholipids or against neo-epitopes created by plasma proteins bound to anionic phospholipids. These may be detected as lupus anticoagulants, as antibodies directed against phospholipids such as cardiolipin, or may give rise to false positive syphilis testing. The disease may occur in isolation (primary APS) or in association with SLE, other auto-immune diseases, certain infections and drugs (secondary APS). Clinical manifestations include recurrent arterial or venous thrombosis, recurrent foetal loss, neurological dysfunction and thrombocytopenia [1]. There are no agreed diagnostic criteria for the condition, but diagnosis is usually made based on the finding of antiphospholipid antibodies in association with the above clinical features.

Renal manifestations of APS have received scant attention in the past, yet the kidney has been increasingly recognized as a major target organ of the disease. Kant et al. found that in patients with SLE, the presence of a lupus anticoagulant correlated strongly with the finding of glomerular capillary thrombosis on examination of renal histology [2]. Capillary thrombosis was associated with a more rapid evolution to glomerular sclerosis.

Intra-renal vascular lesions occurring in the absence of glomerulonephritis have been well described previously [3,4]. They may give rise to severe or malignant hypertension. These lesions are seen in both primary and secondary APS. Recurrence in renal allografts has also been reported [5]. Thrombosis of the renal artery trunk is rare. Patients with a circulating lupus anticoagulant may also be at an increased risk of renal vein thrombosis [6], although this is more usually attributed to a co-existing nephrotic syndrome.

Antiphospholipid antibodies are also prevalent among the haemodialysis population and may be associated with an increased risk of vascular access thrombosis [7].

The pathogenesis of the hypercoagulable state in APS is unclear. It may be due to increased platelet activation or disturbed regulation of coagulation. The thrombocytopenia seen in APS is auto-immune in origin and is thought to be due to anti-platelet activity of a subset of antibodies. Platelet-bound

that the occlusion was long standing or had developed secondary to a pre-existing thrombotic stenosis. It became apparent, in retrospect, that this woman’s ‘renal bruits’ were in fact due to increased flow in lower intercostal collateral vessels. CT imaging of the

Fig. 1. Aortogram demonstrating thrombotic occlusion of the supra-renal aorta with retrograde filling via markedly dilated intercostal vessels.

Fig. 2. Post angioplasty. Collateral vessels are now less prominent. Persistent pressure gradient of 120 mmHg across the stenosed segment of the abdominal aorta.
Thrombosis 18 years after antiphospholipid syndrome

$\beta_2$ glycoprotein 1 has been suggested as a possible target [8].

The cornerstone of treatment is lifelong warfarin anticoagulation, with recent studies favouring high intensity therapy (target INR > 3.0) [9]. Aspirin may confer a small additional benefit when used in combination with warfarin, but is of little value when used alone. Immunosuppressive therapy is of limited value.

Acute renal failure due to aortic thrombosis in APS has been reported only once previously [10]. Although our patient had a very rare site of thrombosis, the temporal association between cessation of anticoagulation and the presentation, together with her earlier episode of arterial thrombosis, highlights the importance of lifelong anticoagulation in such patients.

References


Received for publication: 17.10.00
Accepted in revised form: 17.11.00