Steroid-responsive focal segmental glomerulosclerosis in primary antiphospholipid syndrome with successful pregnancy outcome

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Introduction

Antiphospholipid syndrome (APS) is a clinico-pathological syndrome characterized by the association of venous and/or arterial thrombo-embolic events, pregnancy morbidity and the presence of circulating antiphospholipid (APL) antibodies, namely lupus anticoagulant (LA) and/or anticardiolipin antibodies (ACLs). The diagnosis of definite APS is made when the patient fulfils one clinical (thrombosis or pregnancy morbidity) and one laboratory (APL or LA) criterion [1]. APS may be primary or secondary to various autoimmune diseases: systemic lupus erythematosus (SLE), rheumatoid arthritis and systemic sclerosis. The commonly described renal involvement in APS includes renal artery stenosis and/or thrombosis, renal infarction, renal vein thrombosis and thrombotic microangiopathy [2]. In the last few years, glomerular involvement has been documented [3,4]. We report a case of primary APS with nephritic syndrome due to focal segmental glomerulosclerosis (FSGS), and a successful pregnancy outcome.

Case

A 31-year-old female was referred 4 years previously by the obstetrician to the renal clinic in the 8th week of her third pregnancy for evaluation of proteinuria.

She had been hypertensive for the last 10 years on regular treatment with amlodipine. At that time, no investigations had been done to elucidate its cause. She was married 8 years previously and conceived a year later. However, she had a missed abortion at 6 weeks. A subsequent pregnancy a year later also resulted in a first trimester abortion. Since there was a rash on her extremities, she was referred to the rheumatology clinic. There was no history of fever, joint pains, oral ulcers or pedal oedema. The rash was diagnosed to be livedo reticularis. Antinuclear antibodies (ANAs) and anti-double-stranded DNA were negative. C3 and C4 levels were normal. ACLs (IgG 49.5 GPL U/ml, IgM 38.5 MPL U/ml) and LA were positive. Other significant past history included rheumatic chorea 15 years previously. She was also diagnosed to have hypothyroidism 8 years previously and was on thyroxine 50 μg/day. The thyroid function tests were normal. Based on the above findings, she was diagnosed by the rheumatologist to have primary APS and was prescribed aspirin 75 mg/day. Subsequently she was on regular follow-up with the rheumatologist and instructed to report immediately when pregnant. A year later, she became pregnant. Injection of heparin 5000 IU twice a day subcutaneously was initiated at 6 weeks of pregnancy and continued together with aspirin 75 mg/day throughout her pregnancy.

On examination in the renal clinic, there was no pallor or pedal oedema. Blood pressure was 140/100 mmHg. There was extensive livedo reticularis on both the forearms and lower extremities. Fundus examination was normal. Blood urea was 47 mg%, creatinine 1.2 mg%, urine 3+ albumin, 4–5 red blood cells (RBCs), 2–3 white blood cells (WBCs) and RBC casts. Urine protein excretion was 1.3 g/24 h. Screen for Down syndrome was negative and ultrasonography did not reveal any fetal abnormalities. Ultrasonography of maternal kidneys was normal. Antihypertensive treatment included amlodipine 10 mg/day.

As the pregnancy progressed, her requirement for antihypertensives increased. Amlodipine was increased to 10 mg twice daily, and aldomet 250 mg four times daily was added. She was admitted at 32 weeks gestation for intrauterine growth retardation, oligohydramnios and uncontrolled blood pressure. Blood urea was 57 mg% and serum creatinine was 1.5 mg%;
haemogram and liver function tests were normal. Her 24 h urine excretion was 4 g. Fundus examination was normal. The day after admission, the patient complained of severe abdominal pain. She was taken for an emergency caesarian section for suspected abruptio placenta. A female child weighing 1.4 kg with an Apgar score of 9/10 was born. There was no evidence of abruptio placenta. Post-operatively, her blood pressure settled after 72 h and was controlled with amlodipine 10 mg twice daily and atenolol 50 mg twice daily. There was primary lactation failure. The child was given nursery care for a week and then discharged. The subsequent course was uneventful and development of the child was normal. Post-partum ramipril 5 mg/day and irbesartan 150 mg/day were added.

However, proteinuria persisted at ~1.5 g/day and renal function continued to remain deranged with serum creatinine of 1.6 mg%. The serum total protein was 6.5 g%, albumin 3.2 g% and cholesterol 260 mg%. Hence, a year later, kidney biopsy was performed. It showed eight glomeruli. Two glomeruli showed global sclerosis, while two showed segmental sclerosis involving the hilar and parahilar region. The rest of the glomeruli showed a mild increase in mesangial cellularity and focal capsular adhesion. There was patchy tubular atrophy and interstitial fibrosis. The blood vessels showed mild to moderate medial and subintimal thickening. There was no evidence of thrombotic microangiopathy. On silver methenamine staining, glomerular basement membranes were normal. The Congo red stain was negative for amyloid. Immunofluorescence showed focal mesangial deposits of IgM and C3, with absence of IgG and IgA. On electron microscopy, there were no dense deposits. The morphological diagnosis was compatible with FSGS. Doppler sonography of the renal arteries did not show any evidence of renal artery stenosis. Oral prednisolone was started at a dose of 70 mg/day. After 8 weeks of therapy, proteinuria decreased to 0.4 g/day. Subsequently, prednisolone was gradually tapered and then continued at a dose of 5 mg/day. Serum creatinine reduced to 1.4 mg%. Over the last 21 months, she has remained oedema free, without any relapse of proteinuria. The livedo reticularis reduced considerably, but continued to persist. At last follow-up, she was cushingoid, but oedema free. Routine urine analysis showed no proteinuria or cells, with a 24 h protein excretion of 350 mg. ACL titres were within normal limits (4.8 GPL U/ml). LA continued to remain positive. Medications included prednisolone 5 mg/day, low dose aspirin, ramipril 7.5 mg/day, irbesartan 150 mg/day, amlodipine 10 mg/day and atenolol 50 mg/day.

Discussion

Primary APS is diagnosed when there is absence of associated autoimmune disease. A follow-up period of 5 years has been recommended as autoimmune diseases such as SLE may develop within 5 years [5]. In our patient, ANA was persistently negative and renal biopsy showed the absence of IgG and IgA. Also there was a long follow-up of 7 years during which no autoimmune disease developed, which confirms the diagnosis of primary APS. In the early reports, renal involvement in APS consisted mainly of thrombosis of large renal vessels or microangiopathy [2]. Recently, Fakhouri et al. in their study of 29 cases of primary APS found that glomerulonephritis was relatively frequent and represented almost a third of all renal biopsies in primary APS [4]. They described a spectrum of glomerular changes including membranous glomerulopathy, mesangial C3 nephropathy, minimal change disease, FSGS, membranoproliferative glomerulonephritis and pauci-immune vasculitis. So far, membranous glomerulopathy has been the most commonly described glomerular pathology: a total of seven cases [4,6,7]. However, to the best of our knowledge, there is only one definite case of FSGS reported to date, besides another case of pauci-immune vasculitis/FSGS [4]. Both these cases also had livedo reticularis similar to our case. In our patient, the arterioles showed mild to moderate medial and subintimal thickening. This is similar to the finding by Nochy et al., who in a detailed study of 16 cases of primary APS found that arteriosclerosis and fibrous intimai hyperplasia (FIH) were the most common vascular pathologies, followed by thrombotic microangiopathy and organizing intraluminal thrombus [8]. Differentiating the vascular lesion of primary APS from nephrosclerosis is often difficult. The two features which might help are: (i) the thickened arterial intima is more cellular in primary APS, while it is densely collagenous in nephrosclerosis; and (ii) there is less medial fibrosis and degeneration in primary APS.

The treatment regimen of primary APS with renal involvement (PAPSN) has been mainly empirical due to the rarity of cases. Hamidou et al. found disappearance of proteinuria and normalization of renal function with the use of aspirin and captopril in a patient with renal thrombotic microangiopathy and primary APS [9]. Korkmaz et al. found that immunosuppressive therapy comprising steroids and cyclophosphamide along with warfarin and angiotensin-converting enzyme (ACE) inhibitors successfully reduced proteinuria in four cases of PAPSN [10]. Our patient was started on low dose aspirin initially. Heparin was administered throughout pregnancy, with a successful pregnancy outcome. Since there was primary lactation failure, we could safely initiate ACE inhibitors and angiotensin II receptor blocker (ARB) post-partum. Although blood pressure was controlled satisfactorily, there was no respite in proteinuria, which continued to persist, along with mild derangement of renal function. Hence, renal biopsy was performed to determine the exact renal pathology. Following the biopsy report of FSGS, steroid therapy was given. Although proteinuria was in the subnephrotic range, steroids were started because there was hypoalbuminaemia and hypercholesterolaemia with impairment of renal function. There was a satisfactory response after
6 weeks. Subsequently, the dose was tapered but not stopped completely; a dose of 5 mg/day was continued along with low dose aspirin, ACEI and ARB. She has been in remission for the last 2 years. Apart from Cushingoid facies, there were no other side effects.

In conclusion, we report a case of PAPSNI in the form of FSGS. She had a successful pregnancy outcome and the proteinuria responded successfully to steroid therapy.

Conflict of interest statement. None declared.

References


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