Case Report

Focal Segmental Glomerulosclerosis Associated Seronegative Antiphospholipid Syndrome

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Introduction

Secondary Focal Segmental Glomerulosclerosis (FSGS) from thrombotic microangiopathies including Antiphospholipid Antibody Syndrome (APS), is well documented. We present a case with clinical features of APS but consistently negative serologies, suggesting ‘Seronegative APS (SNAPS)’. The patient was evaluated at the Division of Nephrology, University of Connecticut Health Center for progressive Chronic Kidney Disease (CKD). A renal biopsy exhibited thrombotic microangiopathy and associated FSGS.

Systemic thrombophilia can be primary or secondary and has an extensive list of differential diagnoses. Distinct clinical features and serologic markers characterize a particular etiology. Antiphospholipid Syndrome (APS) is the most common acquired thrombophilia. Serologic evidence of APS is the presence of commonly recognized antibodies to phospholipids in this syndrome i.e. anticardiolipin (aCL) antibodies, Lupus Anticoagulant (LA) and β2-glycoprotein 1 (β2GPI) antibodies. Rarely a patient with classic clinical features of APS does not exhibit any of the above antibodies, suggesting ‘Seronegative APS (SNAPS)’.

Case Report

Clinical history

A 37-year-old African American female was seen in our nephrology department with history of multiple pregnancy losses (G6P2), deep venous thrombosis, chronic uncontrolled hypertension, cardiomyopathy, stable angina, recurrent strokes and Raynaud’s phenomenon with acro-osteolysis.

In 1992 she presented with gangrene of eight fingers and a great toe. After extensive inconclusive workup it was considered to be secondary to severe Raynaud’s phenomenon associated with undifferentiated connective tissue disorder. She required surgical debridement and received steroids, cyclophosphamide (for suspected vasculitis), warfarin, heparin and tissue plasminogen activator infusion during hospitalization. Later on she underwent bilateral upper extremity sympathectomy. The patient was continued on warfarin there onwards. She had two ischemic strokes, in 1995 and 1997 and completely recovered from the resultant left sided weakness and aphasia. She lost 4 pregnancies in the second and third trimesters (Table 1). Placental examination of the last pregnancy revealed extensive placental infarcts (25-30%) and decidual vasculopathy (Figure 1). She was successfully anticoagulated with heparin during the last two pregnancies, which resulted in viable births at term. She now has two healthy children of ages 4 and 7 years. The patient’s family history is notably insignificant. She is chronically anticoagulated with warfarin since 1992. Although noncompliant in the past, she appears to be more compliant with her medications over recent years. Her INR is consistently between 2 & 4. No new events are reported for the last five years.

The patient was referred to us for progressive CKD and proteinuria (Figure 2). On physical examination, she was a well-built healthy looking individual without any significant findings. A blood pressure was 148/100 mmHg. Her medications included coumadin, valsartan, hydralazine, prednisone, norvasc, aspirin, isosorbide and furosemide. Pertinent recent laboratory values at the time of initial visit are; serum creatinine 3.8 mg/dl, BUN 29 mg/dl, Hb 10.3 g/dl and albumin 2.7 g/dl. A spot urine protein-to-creatinine ratio was 5.0 g/g and urine microscopy was bland. Renal ultrasound was unremarkable. The patient has been extensively worked up for a possible autoimmune etiology of the thrombophilia over the last two decades. A review of the results showed consistently positive ANA, anti Ro and anti La antibodies and negative LA, aCL and β2GPI antibodies. The patient never had any features of lupus or Sjogren’s syndrome. We repeated the serologic evaluation along with a detailed hypercoagulable work-up. The results were similar to before, except one interesting finding. This time patient was also checked for Plasminogen Activator Inhibitor (PAI) gene polymorphism. This showed PAI gene locus 4G/5G polymorphism. This gene polymorphism has been associated with hypercoagulopathy

Table 1: Details of the pregnancies.

| Years | Status | Complications |
|-------|--------|---------------|
| 1986  | Intrauterine fetal demise at 22 weeks | Placental abruption |
| 1989  | Therapeutic abortion at 8 weeks | Records not available |
| 1995  | Intrauterine fetal demise at 27 ½ weeks | Intrauterine growth retardation, placental infarcts, severe preeclampsia (worsened hypertension and proteinuria). |
| 1997  | Intrauterine fetal demise at 17 weeks | Intrauterine growth retardation, placental infarcts, severe preeclampsia (worsened hypertension and proteinuria). |
| 1998  | Live birth at term with heparin | Preeclampsia (worsening hypertension and proteinuria) |
| 2002  | Live birth at term with heparin | Preeclampsia (worsening hypertension and proteinuria) |

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secondary to high PAI activity. A serum PAI level in this patient, however, was at the lower end of normal values. Due to the unclear significance of PAI gene polymorphism, SNAPS was entertained as the most likely etiology. A percutaneous renal biopsy was performed on February 10, 2006.

**Renal biopsy**

By light microscopy, 31 glomeruli were present. Ten glomeruli were globally sclerosed and obsolete. Two glomeruli were ischemic in appearance, one showing a recent bland thrombus occluding the arteriolar lumen (Figure 3). Three glomeruli show well-developed segmental sclerosis (Figure 4A) one glomerulus showing a capillary luminal thrombus. Sixteen glomeruli showed mild mesangial cellularity with patent capillary loops. Several arterioles showed intimal thickening with fibroplasia without reduplicated elastic lamina (Figure 4B). The tubulointerstitium showed moderate degree of tubular atrophy and interstitial fibrosis.

By immunofluorescence microscopy, 7 glomeruli were found to be present. Three glomeruli were globally sclerosed and showed irregularly distributed peripheral coarse globular fluorescence for IgM and C3. The nonsclerosed glomeruli were negative for IgA, IgG, IgM, kappa light chain, and lambda light chain, C3, C4 and Clq. No segmental lesions were present.

By electron microscopy, 2 nonsclerosed glomeruli were present. Mesangial regions were focally expanded with increased numbers of mesangial cells. Immune complex type dense deposits were absent in mesangial, subendothelial and subepithelial locations. Endothelial cells lined the glomerular capillary basement membranes with no irregular lucent expansion of the subendothelial zone. No mesangiolytic features were appreciated. There were no basement membrane formations internal to the native glomerular basement membranes. The native glomerular basement membranes were unremarkable. The visceral epithelial cells showed approximately 40% foot process effacement and surface pseudo villous transformation.

Based on these findings, arterial vascular and glomerular changes consistent with antiphospholipid syndrome was diagnosed.

**Discussion**

Hughes described APS (Hughes syndrome) in 1983. It is now recognized as the most common acquired thrombophilic disorder. Its cardinal clinical features include a tendency for both arterial and venous thrombosis, recurrent miscarriages and occasional thrombocytopenia [1-3]. Lupus anticoagulant and antibodies to aCL and β2GPI, are the three most commonly detected antibodies and are included in the
diagnostic criteria for APS [4,5]. Anticardiolipin antibodies are present in about 80% of the patients with APS, lupus anticoagulant test is positive in about 20% and both are positive in about 60% of cases [4]. Rarely β2GPI are the sole antibodies detected in patients with APS [4].

Definite APS is defined by the presence of both laboratory and clinical criteria [6]. However recent literature has drawn increasing attention towards a variant with clinico-pathological features consistent with APS, but consistently negative serologic workup. Not surprisingly the term ‘Seronegative APS’ (SNAPS) [7-9] was coined for this entity."

Rare case reports of SNAPS can be found in the literature [7,10]. We present such a patient with classic clinical features of APS namely recurrent thrombosis (venous and arterial) and recurrent abortions, but persistently negative serologic workup.

Diagnosis of FSGS is problematic because the morphologic features are nonspecific and the pattern of focal and segmental sclerosis occurs in a variety of conditions. The glomerular lesions in this case did not meet criteria for the perihilar, cellular, tip and collapsing variants as outlined by the consensus classification for FSGS [11] and defaulted to the NOS category. The biopsy however did include an arteriole with a bland occulsive thrombus (Figure 3) and a peripheral capillary loop with a probable small capillary loop thrombus. These findings were considered correlative with the patient’s thrombophlebitic state and possibly etiologically related to the glomerular and vascular sclerosis lesions present.

Vaso-occlusive processes including thrombophilia leading to FSGS has been reported [12]. A kidney biopsy study of inherited thrombophilia [13] has documented associated vascular fibrointimal fibrosis and focal segmental and global glomerulosclerosis with accompanying tubular atrophy and interstitial fibrosis with associated clinical rise in serum creatinine and proteinuria. Similar features would seem likely to also occur in the acquired thrombophlebitic state of antiphospholipid syndrome.

Probable mechanism as proposed in the study of inherited thrombophilia [11] involves small chronic thrombotic events within the renal vasculature followed by repair that lead to vascular and glomerular scarring on the basis of localized thrombotic microangiopathy with resultant fibrointimal arterial vascular scarring and glomerular capillary wall remodeling and sclerosis. Clinically the process would lead to gradual and progressive decline in renal function. In later stages with progressive nephron loss, adaptive changes of uninovlved remnant nephrons would further add to the already existing morphologic focal segmental glomerulosclerosis.

A review of the literature revealed limited information on SNAPS [1]. Therapeutic approaches do not seem to differ from primary APS and data on prognosis does not exist. Hughes et al. described three possibilities for the seronegativity. Firstly, the diagnosis may be wrong, the patient had a different coagulopathy. Secondly, it may be a “laboratory” problem; conventional testing failing to pick up cases with antibodies directed against different phospholipids or protein cofactors. Thirdly, it is conceivable that previously positive antiphospholipid tests have now reverted to negative [1].

We explored the first possibility with extensive workup to look for a different coagulopathy. Some of the finding are elaborated here; (a) The patient was persistently positive for ANA since 1995, but had no other features for systemic lupus erythematosus or lupus nephritis (anti-dsDNA and complements were consistently within normal range, no immune deposits were noted in the renal biopsy) (b) AntiRo and Antila were positive but no clinical features for Sjogren’s syndrome were noted (c) The presence of Plasminogen Activator Inhibitor (PAI) 4G/5G gene polymorphism in this case is perplexing. Although ill defined, this particular gene polymorphism has been linked with higher serum PAI level (causing hypofibrinolysis) leading to arteriovenous thromboembolic disease and complicated pregnancies [14-17]. However, in this patient, a serum PAI level was <2 u/ml (normal 0.0-22 u/ml), rendering this etiology less plausible. Research in future may elaborate the exact role of PAI gene polymorphism in thromboembolic disease. Interestingly, a case of SNAPS associated with high serum PAI level has been reported in the literature, however the authors were unable to hypothesize a link [18], (d) An undifferentiated connective tissue disorder is another possibility. However, even though the patient had serologic evidence of a possible undifferentiated connective tissue disorder (positive ANA, Anti Ro and Anti La) she lacked any feature unrelated to a pure thromboembolic phenomenon (assuming Raynaud’s phenomenon is secondary). Hence, even though, a diagnosis of SNAPS may not explain the coincidental presence of the above antibodies and gene polymorphism, it, clearly justifies her clinical presentation.

The second possibility would require testing for any other phospholipid antibody known to us today. This approach is not supported in the literature. Bertolaccini and colleagues compared three groups of SLE patients; first with clinical feature of APS and negative serologies, second without any clinical features or positive serologies for APS and third with clinical feature and positive serologies for APS. All groups were checked for the ‘other phospholipid antibodies’ such as phosphatidylserine, phosphatidylcholine, phosphatidylinositol, phosphatic acid and phosphatidylethanolamine. No significant difference was noted [19]. This study suggested that screening by multiple antiphospholipid tests does not increase the diagnostic yield in APS. This seemed to be true in this case since we checked antibodies against phosphatidylethanolamine and phosphatidylinositol, which were negative.

The third possibility requires repeated testing for the common serologies [4,5]. There is no consensus on the number of times and the intervening duration between these tests. Our patient had serologic tests performed numerous times over more than two decades with consistently negative results during acute episodes as well as during quiescence.

Due to the lack of knowledge of an exact serologic fingerprint of APS, the diagnosis of SNAPS can be challenging. Current recommendations suggest checking the common serologic markers. The persistent absence of these antibodies with classic clinical features, suggests SNAPS. Extensive workup, however, may be required to rule out other possible etiologies.

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