Proliferative glomerulonephritis and primary antiphospholipid syndrome

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ABSTRACT

Little is known regarding the association of primary antiphospholipid syndrome (APLS) and proliferative glomerulonephritis (GN). We describe a biopsy-documented case with primary APLS and proliferative GN with no evidence of thrombotic microangiopathy (TMA), and in the absence of other manifestations of systemic lupus erythematosus (SLE). She presented initially with left popliteal deep venous thrombosis and nephrotic syndrome. Her first pregnancy at the age of 26 years resulted in intra-uterine fetal death at term. Two subsequent pregnancies ended up with miscarriages at 3 and 4 months of gestation. Urinalysis revealed glomerular red blood cells of 1.0000.000/ml and granular cast; proteinuria of 13.4 grams/24 hours, which was non-selective; hemoglobin 12 gm/dl, normal white blood cell and platelets; serum albumin 2.6 gm/dl; anti-nuclear antibody (ANA) and anti DNA were negative and complement levels normal. Lupus anticoagulant was positive leading to a diagnosis of primary APLS. The biopsy findings were consistent with membranoproliferative GN. She continued to have steroid-resistant proteinuria, but stable renal function after a 12-year follow up period. She had 2 pregnancies during this period and was delivered at term using caesarian section. She received heparin during the pregnancies. Later she developed hypertension easily controlled by atenolol. This case provides evidence that primary APLS can be associated with proliferative GN due to immune deposits and not only TMA as previously reported, and in the complete absence of SLE. Performing more renal biopsies in this group of patients may disclose a greater prevalence of proliferative GN and may help in devising a rationale for treatment.

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There have been several recent reports regarding the renal involvement with primary antiphospholipid syndrome (APLS).[1-5] The primary presentations of renal involvement in these patients are a very variable ranging from asymptomatic mild proteinuria within normal renal function to acute renal failure with heavy proteinuria and often severe hypertension.[5] In most of these cases, the histological pattern resembles thrombotic microangiopathy (TMA) with intraglomerular and renal vascular thrombosis. Little is known of the association of primary APLS with proliferative glomerulonephritis (GN). We describe in this paper, a biopsy-proven case with primary APLS associated with proliferative GN and in the absence of any other manifestations of systemic lupus erythematosus (SLE).

Case Report. A 35-year-old Saudi lady, who was referred to our center in 1986 with left popliteal deep venous thrombosis and nephrotic syndrome. Her first pregnancy at the age of 26 years resulted in intra-uterine fetal death at term. Two subsequent

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pregnancies ended up with miscarriages at 3 and 4 months of gestation. She has a history of recurrent rash over the chins of the legs for several years. Systemic examination was unremarkable except for bilateral non-pitting edema. Laboratory data revealed the following: normal serum urea, creatinine and creatinine clearance. Urinalysis revealed glomerular RBs of 1.0000.000/ml and granular cast; proteinuria of 13.4 grams/24 hours, which was non-selective; hemoglobin 12 gm/dl, normal white blood cell and platelets; serum albumin 2.6 gm/dl; anti-nuclear antibody (ANA) and anti DNA were negative and complement levels normal. Hepatitis B surface antigen was negative, venereal disease research laboratory (VDRL) was positive and fluorescent treponemal antibody (FTA) was negative, lupus anticoagulant (by coagulation assay) was positive and immunoglobulin A (IgA) anti-cardiolipin (ACL) was positive (42 u/ml); IgM negative (using enzyme-linked immunosorbent assay) leading to a diagnosis of primary APLS. Abdominal ultrasonography showed normal size, and the shape of both kidney and the result of the abdominal CT scan showed no evidence of renal vein thrombosis. A renal biopsy was performed. The tissue included 12 glomeruli; on light microscopy all showed considerable increase in the mesangial matrix and associated mesangial hypercellularity. The peripheral glomerular capillaries were thickened, and the capillary lumina were reduced in size. With silver staining, the capillary basement membrane showed duplication in some segments (**Figure 1**). There was minimal tubular atrophy, but no interstitial disease. The vessels showed no abnormality. By immunofluorescence there was a strong staining of the glomerular capillary wall with anti-sera to IgG, IgM, and C3. The biopsy findings were consistent with membranoproliferative GN. Few days after the biopsy, she developed a pulmonary embolus and was heparinized and later put on warfarin. She was started on prednisolone 60 mg/day with no obvious improvement in her proteinuria, and thus, the prednisolone was tapered off and stopped. Over the last 10 years, she continued to have heavy proteinuria, but with normal renal function. She had 2 pregnancies during this period and was delivered at term using caesarian section. She received heparin during the pregnancies. Later she developed hypertension easily controlled by atenolol.

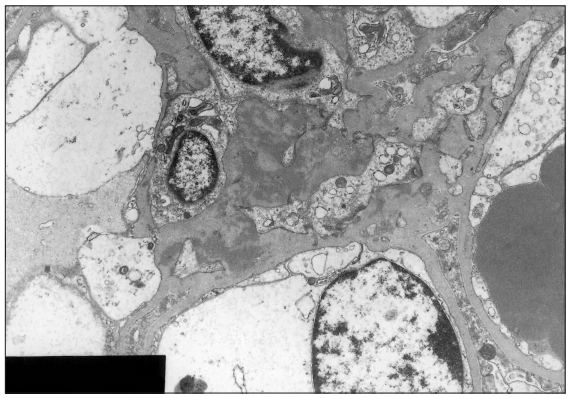

Figure 1 - Electron photomicrograph showing increased mesangial matrix with irregular electron dense deposits and the basement membrane. (Hematoxylin & Eosin x 4000).

Discussion. Queered et al[6] studied prospectively the prevalence of antiphospholipid antibodies in primary chronic GN (n=57), and found that only 9% of these had positive antiphospholipid antibodies (APLA). They concluded that there is a low prevalence of antiphospholipid antibodies in primary chronic glomerulonephritides and that this low incidence of antiphospholipid (APL) in primary GN suggests that APLA probably does not play the major pathogenic role in primary chronic GN. However, 3 lupus anticoagulant and anticardiolipin positive patients in their group of primary GN, had clinical and serological manifestations (positive ANA) suggesting SLE, but without fulfilling the American Rheumatological Association criteria for the diagnosis of SLE. Therefore, they proposed that APLA positivity in a patient with clinical and histological diagnosis of primary GN, should suggest the diagnosis of SLE or SLE-like disease even when a causal sporadic association between chronic GN and APL antibodies cannot be excluded.[6] Based on our finding, we propose that there is a possible pathogenetic association between the different forms of GN and APLS. One may speculate that the APLA may behave as a marker for a hitherto unknown marker or as yet undiscovered the factor that is triggering an immune complex disease. In our case, the mechanism of injury is probably related to an immune complex deposition injury that occurred in the absence of overt SLE. The only long term follow up will provide answers whether this patient will continue to develop classical SLE although the 12 year follow up in one of the patients seems to negate this possibility. It seems that evolution of primary APLS into SLE is uncommon. In one report, only 3 out of 80 patients with APLS developed overt SLE after a mean period of 6.5 years.[7] Interestingly, none of our patients have shown thrombotic microangiopathy on histology. This is different from all previously reported cases of primary APLS and renal involvement in whom TMA has been observed.[1-5] However, it was recently

observed that as with other manifestations of APLS, there is no predictable association between the APLA antibodies and the renal disease.[8]

In view of the small number of our cases and the heterogeneous spectrum of the renal involvement, it would be difficult to compare their prognosis with that of reported cases of APLS and TMA only. There have been scattered reports of GN in association with APLS,[9] but most reports of renal involvement consisted mainly of thrombotic vascular complications. Saracino et al[10] reviewed 270 consecutive renal biopsies carried out at their center and identified only 5 cases associated with primary APLS (1.8%) and of those 4 were associated with vascular lesions and immunofluorescence was positive in only 2 patients.

In conclusion, our 3 cases provide evidence that primary APLS, in the complete absence of other features of SLE, can be associated with significant proliferative GN and not only TMA as has been previously reported. In view of the small number of cases, we have to be cautious in drawing conclusion regarding prognostic aspects and therapeutic implications in these patients. We propose that urine microscopy and renal function should be carefully monitored in patients with primary APLS, and that renal biopsies be more readily performed in these patients. This may disclose a greater prevalence of proliferative GN and may help to propose a rationale for treatment and pathogenesis.

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