

Membranoproliferative Glomerulonephritis in a Postpartum Woman With Sickle Cell Disease

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Keywords.

membranoproliferative
glomerulonephritis, sickle
cell anemia, pregnancy,
preeclampsia

Renal insufficiency occurs in a considerable proportion of patients with sickle cell disease. Common advanced glomerular lesions include focal segmental glomerulosclerosis and nonimmune membranoproliferative glomerulonephritis. Due to the paucity of data supporting an immune-mediated pathophysiology, anti-inflammatory and immunosuppressive therapies have not been successfully evaluated in such patients. We present a case of membranoproliferative glomerulonephritis in a postpartum patient with sickle cell disease, where treatment with steroids was helpful.

IJKD 2011;5:63-5
www.ijkd.org

INTRODUCTION

Renal insufficiency occurs in a considerable proportion of patients with sickle cell disease (SSD). The spectrum of renal lesions is diverse, progressive, and mostly resilient to management. Tubular disorders are quite common, such as hematuria secondary to papillary necrosis, renal tubular acidosis, and the loss of concentrating ability. Common advanced glomerular lesions include focal segmental glomerulosclerosis (FSGS) and nonimmune membranoproliferative glomerulonephritis (MPGN). Due to the paucity of data supporting an immune-mediated pathophysiology, anti-inflammatory and immunosuppressive therapies have not been successfully evaluated in such patients. We present a case of MPGN in a postpartum patient with SSD, where treatment with steroids was helpful.

CASE REPORT

A 31-year-old postpartum African-American woman with SSD was referred to us by her primary care physician for management of proteinuria and kidney failure. The patient was 9 days postpartum following a cesarean section delivery of her 3rd child. Thirteen years prior (at the age of 18), she had undergone a kidney biopsy for nephrotic syndrome, which had shown mild hypertrophy of glomerular tuft and mesangial expansion. No immune deposits had been noted. The nephrotic syndrome was

transient and resolved spontaneously. Over the past years, her serum creatinine remained steady (serum creatinine, 1.3 mg/dL to 1.5 mg/dL), associated with mild proteinuria (< 1 g/d). Through her first 2 pregnancies, she only developed mild-to-moderate hypertension with some worsening of proteinuria. During the course of the 3rd pregnancy, she developed progressive nephrotic-range proteinuria along with a rising serum creatinine (increasing from 1.5 mg/dL in the 2nd trimester to 3.9 mg/dL by the 3rd trimester). The proteinuria peaked from 4.5 g/d to 18.5 g/d near term.

Clinically, the acute kidney failure, proteinuria, and uncontrolled hypertension were attributed to preeclampsia. She delivered by cesarean section at term. At the time of delivery, the serum creatinine and proteinuria were 3.9 mg/dL and 22 g/d, respectively. The patient was lost to follow-up immediately postdelivery and was seen on the 9th postpartum day by her primary care physician.

At the time of her presentation, proteinuria was quantified to be at 19 g/d and serum creatinine at 4.9 mg/dL. Other pertinent laboratory values included: hemoglobin, 7.1 g/dL; hematocrit, 20.6%; blood urea nitrogen, 28 mg/dL; and albumin, 1.5 mg/dL. The fractional excretion of sodium and urea were 4.8% and 60%, respectively. The patient received blood transfusions for severe anemia. Renal ultrasonography showed symmetrical kidneys

measuring 11 cm in length. Urine microscopy performed by the nephrologist revealed nephrotic sediments. Serologic workup including anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, anti-double-stranded DNA, perinuclear anti-neutrophil cytoplasmic antibody, hepatitis B and C, cryoglobulin, and complements were within reference range. An human immunodeficiency virus screen was previously negative. A magnetic resonance venography (MRV) of renal veins was negative for thrombosis.

Initial management included blood pressure control with labetalol, enalapril, valsartan, and furosemide. Despite achieving good blood pressure control, the proteinuria did not improve and the serum creatinine continued to worsen. A kidney biopsy was performed 2 weeks postpartum. The biopsy findings were consistent with MPGN without evidence of immune deposition on immunofluorescence and electron microscopy (Figure 1). Three of the 23 glomeruli seen in the biopsy showed crescentic features (Figure 1). No preeclamptic changes were noted.

The patient's serum creatinine reached 6.2 mg/dL 2 weeks postpartum. Conservative management seemed to be ineffective; no spontaneous recovery was noted and dialysis requirement was imminent. Since the clinical course was similar to a rapidly progressive glomerulonephritis (RPGN), we started her on intravenous methylprednisolone, 1g daily, for 3 consecutive days. The serum creatinine immediately started to improve (Figure 2) and decreased to 5.1 mg/dL by the 3rd day. Encouraged by the outcomes, she was continued on prednisone,

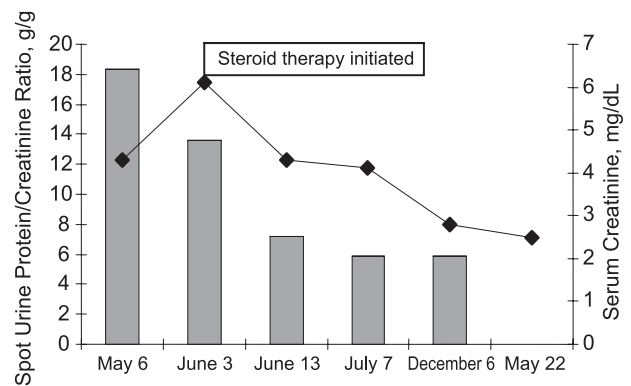


Figure 2. Trend in serum creatinine (square bullets) and proteinuria (solid bars) before and after initiation of steroid therapy.

1 mg/kg/d. Within the next 2 months, the serum creatinine and proteinuria gradually improved and reached 3.3 mg/dL and 8.1 g/d, respectively. She received 70 mg of prednisone per day (1 mg/kg/d) for 4 months. Due to the consistent improvement in creatinine, prednisone was gradually tapered off by the end of the 6th month. The patient's kidney function continued to improve, and approximately 6 months after the last dose of prednisone, her serum creatinine was 2.5 mg/dL. Proteinuria gradually improved, but remained in the nephrotic range (5.5 g/d). Current goal of management was considered to continue aggressive antihypertensive with maximum doses of lisinopril and valsartan.

DISCUSSION

Membranoproliferative glomerulonephritis, commonly seen with hepatitis B, hepatitis C and

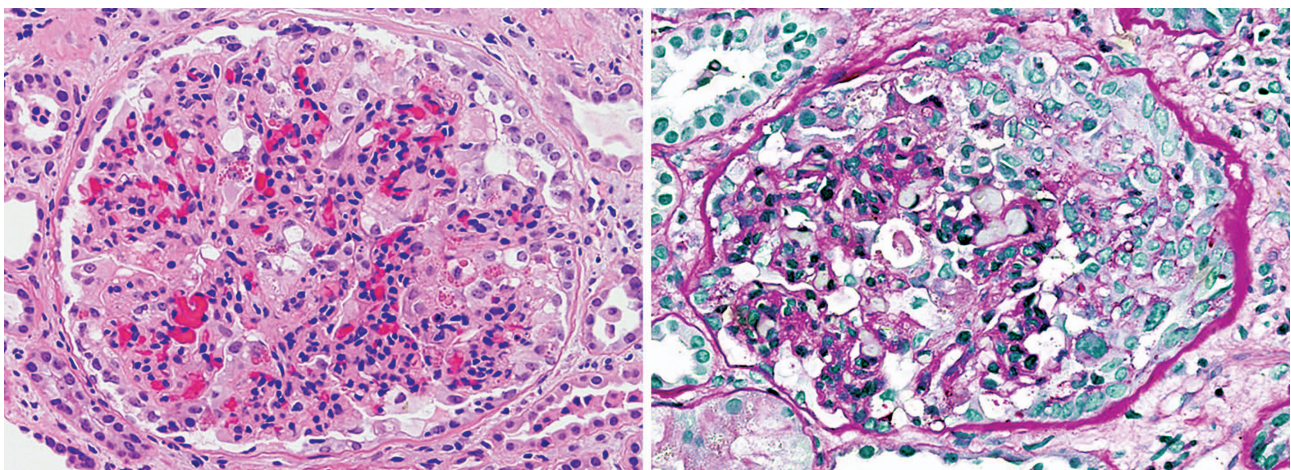


Figure 1. Left, glomerulus with marked diffuse endocapillary hypercellularity and lobular accentuation consistent with membranoproliferative glomerulonephritis (hematoxylin-eosin, × 250). Right, three of the 23 glomeruli present showed cellular crescents (periodic acid-Schiff, × 250).

lupus, is associated by immune complex deposition. However, definite immune complex deposits have been documented in only 12 patients with sickle cell MPGN.^{1,2} In fact, MPGN without immune complex deposits is the 2nd most common advanced glomerular lesion in sickle cell nephropathy (the most common being FSGS). The classic progression of sickle cell nephropathy has been suggested to start with glomerular hypertrophy and medullary interstitial fibrosis, leading to full-blown FSGS with nephrotic syndrome, and eventually, end-stage renal disease.³ The pathogenesis of pauci-immune MPGN is speculated to be due to the fragmentation of erythrocytes within the capillary loops, which are phagocytosed by the mesangial cells.^{4,5} The “active mesangium” then proliferates and lays down new glomerular basement membrane material beneath capillary endothelium, giving a double-contour appearance.^{5,6}

Even though significant data in the literature exists on clinical manifestations of sickle cell nephropathy, exact pathogenic mechanisms governing glomerular lesions and their therapeutic options remain elucidated. There is a National Institute of Health-funded study underway at Emory University in Alabama, United States, to investigate pathogenesis of sickle cell nephropathy. Angiotensin-converting enzyme inhibitors and angiotensin receptor blocker are recommended for targeting proteinuria. However, data on improvement in glomerular filtration rate, filtration fraction or effective plasma flow with these medications is limited.^{3,4,7} Angiotensin-converting enzyme inhibitors and angiotensin receptor blocker combination had minimal impact in this case.

There is scant and inconsistent literature on anti-inflammatory and immunosuppressive therapies in sickle cell nephropathy.^{4,6} Since this case clinically behaved like RPGN with some histological evidence of crescent formation and MPGN, we as decided to assess response to steroids. The clinical diagnosis of RPGN has been classically associated with anti-glomerular basement membrane disease (with linear deposits on immunofluorescence microscopy), immune complex diseases (immunoglobulin A nephropathy, Henoch-Schonlein purpura, MPGN, and membranous glomerulonephritis, causing granular deposits on immunofluorescence microscopy), and pauci-immune disorders (anti-neutrophil cytoplasmic antibody or other

systemic vasculitis or idiopathic RPGN). Treatment recommendations for pauci-immune RPGN include initial steroid treatment with methylprednisolone, 7 mg/kg/d to 15 mg/kg/d, to a maximum of 1 g/d for 3 days, then prednisone, 1 mg/kg/d, for 1 month, gradually tapered over the next 6 to 12 months. Evidence supporting such a treatment is well summarized by Jindal.⁸

We credit acute recovery of our patient to a possibly steroid-sensitive MPGN associated with SSD. Future investigation in this regard may be worthwhile.

CONFLICT OF INTEREST

None declared.

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Received December 2009

Revised July 2010

Accepted September 2010