Steroid-resistant nephrotic syndrome secondary to primary focal segmental glomerulosclerosis and smoldering multiple myeloma

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We present a patient with steroid-resistant nephrotic syndrome due to focal segmental glomerulosclerosis along with smoldering multiple myeloma. While investigating the cause of proteinuria, a monoclonal gammopathy with a negative kidney biopsy for myeloma-related pathology was discovered.

CASE REPORT

A 62-year-old man with systemic hypertension for at least 1 year on amlodipine 5 mg daily presented with frothy urine for 3 months. He weighed 76 kg, with no recent changes. His blood pressure was 140/80 mm Hg. Urinalysis disclosed a 4+ proteinuria with no erythrocytes or leucocytes. He had a serum creatinine of 0.8 mg/dL, serum albumin of 3.2 g/dL, and total cholesterol of 283 mg/dL. His 24-hour urine protein was 4.3 g. His fasting blood sugar, postprandial blood sugar, anti-streptolysin titer, C3/C4 complement, and β -2 microglobulin levels were all within normal limits. Tests for hepatitis B surface antigen, antineutrophil cytoplasmic antibody, antinuclear antibodies, human immunodeficiency virus 1 and 2, and hepatitis C virus antibodies were all negative. Renal ultrasonography revealed normal-sized kidneys with no masses or stones and normal renal echogenicity. His serum protein electrophoresis showed a monoclonal band in the gamma region measuring 1.5 g/dL. Serum immunofixation studies showed immunoglobulin G kappa monoclonal protein. The patient's serum free light chain ratio (kappa/lambda ratio) was 6.1.

Light microscopy of the kidney biopsy revealed segmental areas of mesangial collapse in most glomeruli (*Figure 1*) with some global glomerulosclerosis (*Figure 2*). No light chain deposition, clusters of plasma cells, or amyloid deposits were observed. Tubules had evidence of acute tubular necrosis but no tubular casts. Immunofluorescence microscopy did not reveal any significant deposits of immunoglobulin G, immunoglobulin M, immunoglobulin A, complement 3, or complement C1q fibrin, kappa, or lambda. Electron microscopy revealed effacement of foot processes, and no fibrils or deposits were noted (*Figure 1*). A diagnosis of focal segmental glomerulosclerosis (FSGS) not otherwise specified was made. Bone marrow aspirate showed 8% to 10% plasma cells, and bone marrow biopsy showed 15% plasma cells with kappa light chain restriction. The patient had

Figure 1. Light micrograph of a single glomerulus with the lower half showing a sclerotic process and the upper half showing relatively preserved architecture; tubules show some evidence of acute tubular necrosis.

Figure 2. Light micrograph of a sclerotic glomerulus and acute tubular necrosis.

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Table 1. Timeline of therapy and corresponding pertinent laboratory values

Time	Free kappa (mg/L)	Free lambda (mg/L)	Kappa/lambda ratio	M-band (g/dL)	Urine protein (mg/24 h)
On presentation (11/22/2011)	86.6	14.2	6.1	1.5	4340
On prednisone (2/21/2012)	16.6	7.9	2.1	0.3	4800
After cyclophosphamide and prednisone (8/8/2012)	29.7	7.7	3.9	0.6	2027
On prednisone (2/24/2013)	67.6	7.2	9.3	1	3456
On maintenance cyclophosphamide and dexamethasone (3/24/2013)	54.1	9.3	5.8	1.1	380

a calcium level of 9.1 mg/dL and a hemoglobin of 14.9 g/dL. His skeletal survey did not show any lytic lesions. A magnetic resonance imaging skeletogram was also negative.

The patient was started on oral prednisone 1 mg/kg in addition to his angiotensin receptor blocker and angiotensin-converting enzyme inhibitor. Three months later, his proteinuria had not decreased, whereas there was a reduction in his free light chains and a monoclonal protein spike. Since the patient was still having severe proteinuria, cyclophosphamide (1 g intravenously every month) was started, and the prednisone was tapered to 5 mg/day. After 6 months of treatment with cyclophosphamide and low-dose prednisone, the patient's proteinuria and serum monoclonal protein were lower. Cyclophosphamide was stopped and the low-dose prednisone continued. His serum free kappa light chain as well as his 24-hour proteinuria increased within a matter of weeks (*Table 1*). At that time dexamethasone (20 mg by mouth weekly) and cyclophosphamide (1 g every 8 weeks) were begun, and both the free light chains and proteinuria responded to this treatment.

DISCUSSION

In most patients with plasma cell disorder, the renal lesion is paraprotein related (1). The most common paraprotein-associated lesions are myeloma cast nephropathy, monoclonal immunoglobulin deposition disease, and amyloidosis. In such cases the treatment for the renal lesion is to treat the underlying cause, i.e., myeloma. The most common non-paraprotein-associated lesions seen on renal biopsy are acute tubular necrosis, hypertensive arteriosclerosis, and diabetic nephropathy (1). These have been attributed to a variety of causes: hypercalcemia, drug toxicity (e.g., nonsteroidal anti-inflammatory drugs), contrast exposure, and other coexisting illnesses such as diabetes mellitus and hypertension. The well-established connection of FSGS with myeloma is pamidronate; it is used to treat hypercalcemia due to bone lesions, including lytic lesions as seen in myeloma. Exposure to pamidronate has been described to cause a characteristic collapsing variety of FSGS (2). The absence of any myeloma-related renal pathology, the presence of glomerulosclerosis, and a negative etiological workup for proteinuria pointed towards an idiopathic FSGS in our patient. However, some may still argue that the two processes are in fact related (3).

It has been reported that patients with smoldering multiple myeloma (SMM) will progress to symptomatic myeloma or amyloidosis at an approximate rate of 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% to 2% per year for the following 10 years (4). Risk factors for progression include a high serum monoclonal protein level, a high proportion of plasma cells in the bone marrow, and a high serum free light chain ratio (5). Currently, the consensus is to treat SMM only if there is evidence of progression of the monoclonal gammopathy (6).

Steroids were an appealing treatment choice in our patient since they are the first line of therapy for idiopathic nephrotic syndrome as well as effective in suppressing myeloma. The plan was to treat the patient's proteinuria/FSGS with steroids and monitor his SMM. However, after 3 months of steroids, the patient showed deterioration in his proteinuria but with evidence of improvement in his SMM parameters, i.e., a lower level of serum monoclonal protein and free light chains. This reinforced our belief that the patient's nephrotic syndrome and monoclonal gammopathy were not related in a causative fashion. When the patient's proteinuria failed to respond to 3 months of steroids, cyclophosphamide was picked as the immunosuppression agent. Even though cyclosporine is, arguably, the preferred agent for steroid-resistant FSGS, we chose cyclophosphamide due to its long track record in myeloma treatment (7, 8). After 6 months of monthly cyclophosphamide, the patient had evidence of relapse of his primary FSGS on stopping the agent. Again, cyclophosphamide was used on a bimonthly basis as a maintenance regimen in preference to other immunosuppressants like cyclosporine or mycophenolate mofetil. Use of cyclophosphamide clearly improved the patient's monoclonal gammopathy.

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