Case Report

Simultaneous Tubular and Glomerular Involvement with Cryoglobulinemic Vasculitis in Multiple Myeloma

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ABSTRACT. Renal manifestations in myeloma are varied. Tubulopathic light chains cause cast nephropathy or proximal tubulopathy, usually associated with tubulointerstitial nephritis. Glomerular involvement includes amyloidosis and monoclonal immunoglobulin deposition diseases. We report a case of multiple myeloma with systemic manifestation of Type-1 cryoglobulinemic vasculitis (skin rash and polyarthritis) and unusual renal manifestation with both tubular and glomerular involvement on renal biopsy along with features of cryoglobulinemic renal vasculitis. Renal biopsy showed light chain cast nephropathy and glomerular involvement. Glomeruli displayed membranoproliferative pattern with monoclonal immunoglobulin deposition disease and features of cryoglobulinemia. Immunofluorescence showed Kappa restriction in the tubular casts and glomerular deposits. Serum light chain assay and immunoelectrophoresis revealed IgG Kappa light chain restriction. The exact mechanism of the varied renal manifestations of multiple myeloma in different patients is not known.

Introduction

Myeloma, the most severe form of plasma cell dyscrasia, constitutes around 1% of all malignant and 10% of all hematologic neoplasms.1 Renal involvement in multiple myeloma is heterogeneous. Approximately 85% of the monoclonal light chains in the plasma cell dyscrasias are nephrotoxic. These light chains may primarily involve tubules as in light chain cast nephropathy, proximal light chain tubulopathy, and monoclonal light chain-mediated tubulointerstitial nephritis. Glomerular involvement may be in the form of amyloidosis or light and/or heavy chain deposition diseases. Simultaneous involvement of both tubules and glomeruli in multiple myeloma is uncommon.2 We report an unusual renal manifestation of multiple myeloma in an elderly patient presenting with both tubular and glomerular involvement on renal biopsy associated with features suggestive of cryoglobulinemic renal vasculitis. We did not come across any such case.
Informed consent was obtained from the patient before presenting the report.

A 63-year-old normotensive man, diabetic for 10 years, was referred to our nephrology outpatient department with complaints of bilateral lower limb neuropathic symptoms and diminution of vision, especially during evening hours. A diagnosis of diabetic nephropathy was considered, and a fundus examination along with urinary quantification of protein was advised.

Investigation showed hemoglobin 8.8 g/dL, total leukocyte count 4200/mm³, blood urea nitrogen 51 mg/dL, serum creatinine 1.6 mg/dL, and serum albumin 3.7 g/dL. Urinary protein was 3+ with 5 red blood cell/hpf and no pus cells. Fundus showed no features of diabetic retinopathy. However, retinitis pigmentosa was detected. The patient was given conservative and supportive treatment.

On one-month follow-up, the patient developed bilateral pedal edema, anorexia, malaise, fatigue, vomiting, and bilateral symmetrical arthralgia, involving both large and small joints. On examination, the patient was conscious, oriented, and afebrile. Pulse rate was 98/min and blood pressure was 200/100 mm Hg. Pallor and bilateral pedal edema were present. He also had multiple joint arthritis with prominence of painful and tender right ankle arthritis. There was a faint erythematous, papular, nonblanchable rash in the lower limbs, dorsum of feet, and around ankles on both sides. Rest of the systemic examination was unremarkable. Investigations at this time revealed normocytic, normochromic anemia with normal iron, ferritin, and total iron binding capacity levels. Erythrocyte sedimentation rate (117 mm in the 1st h) and serum lactate dehydrogenase (745 u/L) levels were high. Serum creatinine had risen to 5.7 mg/dL, while serum protein (5.2 g/dL) and albumin (2.5 g/dL) had decreased. He had proteinuria with urinary protein-creatinine ratio of 7. Ultrasound of the kidneys showed normal right kidney. Left kidney was distorted and shrunken with pelvicalyceal dilation due to previous nephrolithotomy. In view of rapid deterioration of symptoms and progression of renal failure within one month, renal biopsy was performed.

The renal biopsy for light microscopy (LM) and immunofluorescence (IF) was received. Renal biopsy for LM comprised of a single linear core with 11 glomeruli, of which one was globally sclerosed and remainder displayed membranoproliferative pattern with enlargement, lobular accentuation, increase in mesangial matrix along with endocapillary and mesangial proliferation, and segmental neutrophilic exudation. Thickening and focal splitting of the glomerular basement membrane was noted along with subendothelial widening by pale material. The glomerular capillaries were dilated and occluded by hyaline thrombi (Figures 1 and 2). These hyaline thrombi were nonargyrophilic on silver stains and were strongly positive on periodic acid–Schiff stain. The tubules showed mild acute tubular injury and fractured casts associated with neutrophils and occasional giant cell reaction (Figure 3). Interstitium showed moderate mixed inflammatory cell infiltrate. Blood vessels were largely unremarkable. No congophilic deposits were noted.

On IF microscopy, the glomeruli showed positivity for Kappa light chain (2–3+) in the

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Figure 1. Glomerulus displaying enlargement with lobular accentuation (membranoproliferative glomerulonephritis pattern) along with dilated glomerular capillaries which are occluded by hyaline thrombi (PAS, ×40).
Hyaline thrombi on a trichrome stain (MT, ×40).

Mesangium, along capillary walls, and in the hyaline thrombi. The tubular casts also showed Kappa light chain restriction with very faint lambda (0–1+) staining (Figure 4). There were faint granular mesangial and hyaline deposits of C3 (1+). IgG, IgM, IgA, and C1q were negative.

In view of these kidney biopsy findings, the patient was investigated on the lines of monoclonal gammopathy and for cryoglobulinemia. Bone marrow aspiration was done which was consistent with plasma cell proliferative disorder. Complements were normal (C3 119 mg/dL, C4 58.7 mg/dL). Tests for hepatitis B and C and HIV were negative. Serum cryoglobulins evaluated once were not detected. ANA, ANCA, and anti-GBM antibodies were negative. Rheumatoid factor done was negative, serum electrophoresis showed M-band in the gamma region (0.74 g/dL) which on immunofixation was of IgG Kappa type. Serum Kappa-free light chain levels were markedly elevated (2660 mg/L) with a Kappa/Lambda ratio of 83. Serum beta-2 microglobulin level was also elevated (6.74 mg/dL).

Fluorescence in situ hybridization analysis on enriched plasma cells showed deletion of 13q14.3 in 15% of the cells (cutoff for normal individuals is 3%).

Discussion

The morphologic manifestations of myeloma in kidney vary, depending on the renal compart-

Figure 3. Membranoproliferative pattern in the glomeruli along with fractured cast in the tubule (H and E, ×20)

Figure 4. (a) Kappa (2–3+) in the mesangium, along capillary walls, and in hyaline thrombi, (b) Kappa 2–3+ in the casts, and (c) negative for lambda.
ments targeted by the nephrotoxic light or heavy chains, but cast nephropathy remains the most common histological presentation in patients with myeloma. Membranoproliferative pattern of glomerular involvement may be seen in different conditions, including immune complex or complement-mediated injury, autoimmune diseases, chronic infections, such as hepatitis C and sometimes in monoclonal gammon-amyloidosis. Renal involvement by cryoglobulinemic vasculitis is rare and can also manifest as membranoproliferative pattern of glomerular involvement with the presence of vascular thrombi. Regarding type I cryoglobulinemic vasculitis, patients are characterized by more frequent cutaneous involvement in almost half of the patients and a lower frequency of glomerulonephritis than in mixed cryoglobulinemic vasculitis. Our case is unique in that there was a concurrent presence of light chain cast nephropathy in addition to glomerular light chain deposition manifesting morphologically as membranoproliferative pattern along with features of cryoglobulinemic vasculitis.

Physiologic properties of abnormal light chains are thought to determine which pattern of renal injury occurs in a particular patient of multiple myeloma. Light chains have different local effects within the kidney. Light Chains involved in cast nephropathy are referred to as tubulopathic as they affect the tubules while sparing the glomeruli where as those causing amyloidosis and light chain deposition diseases (LCDDs) have been termed glomerulopathic light chains because they interact with mesangial cells within glomeruli and alter mesangial homeostasis. Despite the rationality of the above theories, light chain pathophysiology appears to be more complex. Reported cases of cast nephropathy combined with LCDD and cases of amyloidosis combined with LCDD exist. Cast nephropathy occurring with amyloidosis has also been described. Our case demonstrates an unusual interplay of these light chains leading to heterogeneous morphology, which is a rare manifestation of the disease.

A possibility of proliferative glomerulonephritis with monoclonal immunoglobulin deposits could also be considered on morphology; however, on IF, IgG was negative. The patient was diabetic for 10 years and had peripheral neuropathic symptoms; however, renal biopsy did not reveal any features suggestive of a diabetic nephropathy.

In view of Kappa monoclonal gammopathy along with typical light microscopic features of cryoglobulinemic vasculitis on renal biopsy and strong clinical pointers such as vasculitic rash and arthritis, a possibility of cryoglobulinemic vasculitis should be considered, despite the fact that cryoglobulins were negative in this patient. False-negative result is a common drawback of test for cryoglobulins, the reason being multifactorial ranging from improper handling or storage of the sample to patient factors like lipemia.

This patient highlights the importance of performing a renal biopsy in patients of multiple myeloma which can reveal coexisting pathologies. Our patient, who was put on steroids (as kidney biopsy was deferred in view of distorted and shrunken left kidney), showed improvement in his renal function and serum creatinine decreased from 5.6 mg/dL to 2.2 mg/dL. It seems that there might have been improvement in the cryoglobulinemic vasculitis part of renal pathogenesis. Cryoglobulinemic vasculitis represents crossroads among autoimmune and lymphoproliferative disorders. Even if the steroids may not hamper much of the lymphoid proliferation but is expected to decrease the autoimmune nature of such immune deposits.

The detection of retinitis pigmentosa in this patient may be an incidental finding or may have some relation with the basic disease; the reason is however not clear.

We conclude the presence of unique combinations of both glomerular and tubular involvement in patients of multiple myeloma. Unknown host factors as well as disease-related factors may be responsible for the varied renal presentations in these patients. More studies are required to study the exact mechanism of variation in morphological patterns of a single disease in different patients.
Conflict of interest: None declared.

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