Myeloma-related Kidney Disease

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Multiple myeloma is a malignant plasma cell disorder characterized by the overproduction of monoclonal proteins. The kidney is 1 of the major target organs of multiple myeloma. Most often, this is the result of the monoclonal proteins, which can injure the kidney via several mechanisms. In some cases, direct invasion by myeloma cells and/or bone marrow cells can also result in kidney injury. A kidney biopsy can help distinguish the various myeloma-related kidney diseases and aid in the treatment plan.

Key Words: Kidney, Multiple myeloma, Amyloidosis, MIDD, Cast nephropathy

Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 10% of all hematologic malignancies.[1] It is characterized by the presence of a serum monoclonal spike (M-spike) of more than 3 g/dL or more than 10% clonal plasma cells in the bone marrow and at least 1 of the myeloma defining events such as CRAB (hyperCalcemia, Renal impairment, Anemia and Bone lesions).[2] Patients meeting the M-spike or bone marrow plasma cell requirement but not having CRAB are classified as having smoldering MM. Monoclonal gammopathy of undetermined significance (MGUS) is reserved for those patients with less than 3 g/dL of M-spike and less than 10% bone marrow plasma cells with no myeloma defining events. It is now recognized that MM is almost always preceded by a period of MGUS.[3] However, because few patients with MGUS (1% per year) will ever progress to MM, only observation is recommended.[4] Patients with a higher serum M-spike, an abnormal serum free light chain (FLC) ratio, or non-immunoglobulin G (IgG) monoclonal immunoglobulin are at a greater risk for progression.

The kidney is a major target organ in MM. Up to 40% of patients will develop kidney impairment and 10% to 15% will require dialysis.[5] The incidence is highest in patients with advanced stage disease.[6] Kidney impairment has a significant effect on the overall survival (OS) of these patients. A study from Spain found that patients with acute kidney injury (AKI) had a median OS of 8.6 months whereas patients who never developed AKI had a median OS of 34.5 months ($P < 0.001$).[6] It is interesting to note that the poor prognosis was reversible if their kidney function was restored. Median OS increased to 28.3 months in patients who recovered their kidney function vs 3.8 months in those who had irreversible kidney failure.[6] Results were similar from the Nordic Myeloma Study Group, in which patients with normal creatinine had a median OS of 36 months vs 18 months in patients with moderate kidney injury (serum creatinine [SCr] $>$ 1.48 mg/dL but $\leq$ 2.27 mg/dL) and 13 months for those with severe kidney injury (SCr $>$ 2.27 mg/dL).[7] AKI due to hypercalcemia was more likely to reverse.[6,7] Other positive prognostic factors include lower SCr and (Bence–Jones) proteinuria less than 1 g/day. Although some of the survival differences can be explained by the severity of the MM, patients with AKI appeared to be less responsive and tolerant to certain chemotherapies.[6,7] The introduction of novel agents had improved the tolerability and response, but evidence suggests they are not all the same.[8] A retrospective review of 133 consecutive patients with kidney impairment treated with thalidomide, lenalidomide, and bortezomib found that kidney recovery was more likely in the bortezomib-treated patients in the multivariate analysis.[9] In the randomized Phase III HOVON-65/GMMG-HD4 trial, a subgroup analysis found a significant survival advantage in the renally impaired patients treated with bortezomib, doxorubicin, and dexamethasone vs vincristine, doxorubicin, and dexamethasone.[10] What is important to note is that both treatment arms had a significantly poorer 6-month survival as compared with patients with normal kidney function. The improvement in OS did not appear in the bortezomib-treated patient until after 6 months, suggesting that not all of the adverse effects of AKI were completely reversed with bortezomib.

Different kidney pathologies have different clinical presentations, implications for treatment, and prognosis in MM.[11] Therefore, it is important to try to identify the kidney disease when evaluating a MM patient with kidney impairment. The most recent International Myeloma Working Group consensus defines kidney impairment as an acute decompensation of kidney function that results in a SCr of more than 2.0 mg/dL, but a confirmation of the kidney histology is currently not required.[5] The most common histological diagnoses for the AKI are myeloma cast nephropathy (MCN) and acute tubular necrosis (ATN).[12] In another study of patients with severe AKI, MCN was the most prevalent, present in 86.6%

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of patients with kidney histology evaluation.[13] In autopsy studies, MCN along with immunoglobulin light-chain (AL) amyloidosis and monoclonal immunoglobulin deposition disease (MIDD) are the most common kidney diseases in MM.[14] Other series have also found myeloma infiltration and pyelonephritis/postinfectious glomerulonephritis, whereas nephrocalcinosis was only noted in 1 series.[15-17] It is important to realize that nonparaprotein-related kidney disease can also occur in patients with MM. In the largest biopsy series to date with 190 patients, nonparaprotein-related kidney disease was found in 25% of the biopsies.[17] Another important point is that MM is not required for the development of kidney disease. Kidney lesions in man can be replicated in mice just by injection of Bence–Jones protein.[18] Except for myeloma infiltration, the kidney disease is propagated by the monoclonal proteins. The term monoclonal gammopathy of renal significance (MGRS) was recently introduced to classify B-cell and plasma cell disorders that do not qualify for MM but are responsible for a kidney disease.[19] Because of limitations, this article will focus on kidney diseases that are most commonly seen in patients with MM.

CLINICAL SUMMARY

- A large diversity of kidney presentations exists in patients with multiple myeloma.
- Aside from myeloma cast nephropathy and myelomatous infiltration of the kidney, multiple myeloma is not required for the development of kidney disease.
- Acute kidney injury in patients with multiple myeloma is a high-risk feature that requires a thorough evaluation to gain insight into the pathophysiology, prognosis, and treatment.

MCN

MCN, or light-chain cast nephropathy, is the most common cause of kidney disease in MM patients. Autopsy studies found MCN in 32% to 48% of patients who died with a diagnosis of MM.[14-16] In a study of 34 patients with severe AKI, MCN was present in 86.6% of the 30 patients who had kidney histology evaluated.[13] Although it is commonly referred to as myeloma kidney or MCN (Table 1), it can be seen in patients with Waldenström's macroglobulinemia (WM) and chronic lymphocytic leukemia (CLL).[20,21] MCN is a myeloma-defining event. It almost always occurred in the setting of high tumor burden.[5] Most cases of MCN occur in patients with a serum FLC above 100 mg/dL.[22] One study found only 3% of patients with kidney impairment had low tumor load.[23] In this situation, the serum FLC level may be prognostic.[24,25] MCN is more common in light chain only MM and that biopsy proven MCN is extremely rare in patients with less 70 mg/dL of serum FLC.[25,26] Urine FLC excretion may be equally if not more important. Although the median proteinuria is 2.0 g/day in patients with MCN, albumin makes up only 7% of the total protein. Most of the urine protein in these patients is Bence–Jones protein.[27] Another study found that 98% of patients with kidney impairment had significantly elevated levels of urine FLC.[28]

MCN is characterized by tubular obstruction by light-chain casts.[29] These casts form as a result of the binding and subsequent aggregation of monoclonal FLC to Tamm–Horsfall protein (THP). FLCs normally are reabsorbed in the proximal tubule via a receptor-mediated endocytosis after being freely filtered by the glomerulus.[30] In MM, the high FLC concentration overwhelms the capacity of the proximal tubules, thus allowing for large amounts of monoclonal FLC to enter the loop of Henle where THP is produced. Certain amino acid sequences in the CDR3 region of the immunoglobulin FLC are attracted to the carbohydrate moiety of THP.[31] Other factors such as urinary concentration of light chain, THP, sodium chloride, calcium, pH, urine flow rate, and furosemide can also influence the binding and aggregation. The obstructed tubules induce an intense inflammatory response probably through urine leak of FLC into the interstitium.[32] Hydrogen peroxide generated by monoclonal FLC has been shown to activate the nuclear factor kappaB (NFκB) pathway to induce monocyte chemoattractant protein-1 and interleukin (IL)-6.[33]

Histologically (Fig 1), MCN is characterized by the presence of intratubular light-chain casts in the distal tubules and collecting ducts.[26] On immunofluorescence (IF), casts usually stain brightly for a single light chain. Often, they may have a fractured appearance due to the crystalline structure as noted on electron microscopy (EM). Giant cell reaction is commonly seen around the casts as mononuclear cells are recruited in an attempt to remove them. Tubular injury is common. Interstitial inflammation may vary from minimal to intense interstitial nephritis and is probably dependent on the severity and duration of obstruction. In more chronic cases, chronic interstitial nephritis can be seen. MCN can also coexist with other kidney lesions such as MIDD and AL amyloidosis.[34]

AKI is the most common presentation for MCN. Even in patients with severe kidney failure (SCr > 11.0 mg/dl), only 50% were oliguric.[13] The most common trigger for MCN is dehydration. In a study of patients with severe AKI due to MCN in which the average SCr was greater than 11.0 mg/dL, dehydration was the number 1 risk factor present in approximately 65% of patients.[13] It was triggered by hypercalcemia in 38.2% of cases and infection in 26.5%. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the cause in 26.5%. Unfortunately, patients are commonly prescribed or take NSAIDs over the counter for bone pain from compression fractures.