Myeloma-related Kidney Disease
Nelson Leung and Samih H. Nasr

Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by the overproduction of monoclonal proteins. The kidney is one 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

Multiple myeloma is a malignant plasma cell disorder that accounts for approximately 10% of all hematologic malignancies. 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). 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. However, because few patients with MGUS (1% per year) will ever progress to MM, only observation is recommended. 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. The incidence is highest in patients with advanced stage disease. 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). 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. 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 ≤ 2.27 mg/dL) and 13 months for those with severe kidney injury (Scr > 2.27 mg/dL). AKI due to hypercalcemia was more likely to reverse. Other positive prognostic factors include lower Scr and (Bence–Jones) proteinuria (< 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. The introduction of novel agents had improved the tolerability and response, but evidence suggests they are not all the same. 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.

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. 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. 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. The most common histological diagnoses for the AKI are myeloma cast nephropathy (MCN) and acute tubular necrosis (ATN). In another study of patients with severe AKI, MCN was the most prevalent, present in 86.6%...
of patients with kidney histology evaluation. 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. Other series have also found myeloma infiltration and pyelonephritis/postinfectious glomerulonephritis, whereas nephrocalcinosis was only noted in 1 series. 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. 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. 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. Because of limitations, this article will focus on kidney diseases that are most commonly seen in patients with MM.

**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. In a study of 34 patients with severe AKI, MCN was present in 86.6% of the 30 patients who had kidney histology evaluated. 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). MCN is a myeloma-defining event. It almost always occurred in the setting of high tumor burden. Most cases of MCN occur in patients with a serum FLC above 100 mg/dL. One study found only 3% of patients with kidney impairment had low tumor load. In this situation, the serum FLC level may be prognostic.

MCN is characterized by tubular obstruction by light-chain casts. 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. 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. 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. Hydrogen peroxide generated by monoclonal FLC has been shown to activate the nuclear factor kappaB (NFκB) pathway to induce monocyte chemotactant protein-1 and interleukin (IL)-6.

Histologically (Fig 1), MCN is characterized by the presence of intratubular light-chain casts in the distal tubules and collecting ducts. 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.

AKI is the most common presentation for MCN. Even in patients with severe kidney failure (SCr > 11.0 mg/dl), only 50% were oliguric. 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. 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.
Other nephrotoxic drugs include intravenous contrast, which 23.5% received before the development of AKI.

MCN usually presents with rapidly progressive AKI. This can occur in a matter of days. Proteinuria in MCN is mainly composed of Bence–Jones protein (monoclonal FLC) and usually contains less than 10% albumin on urine protein electrophoresis. Patients should have elevated FLC levels usually above 70 mg/dL. The patient may present with AKI alone or in combination with other CRAB lesions. Treatment requires elimination of the precipitating agent, correction of hypercalcemia and dehydration, increase of urine flow, and rapid reduction of serum FLC levels by chemotherapy and extracorporeal removal. Two separate studies found that a 50% reduction of serum FLC is the minimum required for kidney recovery. Timing is also essential because the kidney recovery rate decreased the longer it takes to achieve a 60% reduction in serum FLC levels.

The sustained reduction of serum FLC levels requires effective chemotherapy. The choice of chemotherapy depends on whether the disease is newly diagnosed or relapsed. In chemotherapy naive patients, agents that are not renally cleared or metabolized should be given preference (bortezomib and thalidomide). Pomalidomide and carfilzomib were recently approved for use in relapse MM. Neither undergoes significant kidney metabolism or clearance, but experience in kidney failure patients is scant. High-dose steroids may have benefits in addition to its antimyeloma activity. Extracorporeal light-chain removal is controversial. Three randomized trials on the use of plasmapheresis have produced mixed results with the largest one being negative; however, serum FLC was not used as a marker of response in any of the trials and kidney biopsy was not used to confirm the diagnosis in the largest study. A report found high rates of kidney recovery when plasmapheresis was combined with...
a bortezomib-based therapy, but others have found nearly as high rates of recovery with bortezomib-based therapy alone.\textsuperscript{30,40} Others have used the use of high-cutoff (HCO) dialyzers for the removal of FLC. These dialyzers have molecular cutoffs as high as 45 kD.\textsuperscript{41} Promising results were demonstrated in a pilot study in patients who were able to complete the HCO dialyzer treatment.\textsuperscript{42} As a result, 2 randomized trials are being conducted to investigate the use of the HCO dialyzer in MCN. Two compounds have shown promising results in animal studies. The first is pituitary adenylate cyclase-activating polypeptide, a 38-amino-acid peptide that has immunomodulatory effects in addition to other effects.\textsuperscript{43} It has been found to attenuate tubular cell injury as a result of monoclonal FLC. The second is a cyclized peptide constructed from the CD3 binding region of FLCs with high affinity toward THP. This cyclized peptide competitively blocks the binding of monoclonal FLC to THP.\textsuperscript{49} In a rescue experiment, it has shown to be effective up to 4 hours after infusion of the FLC at preventing the development of AKI due to MCN.

**AL Amyloidosis**

AL amyloidosis is a rapidly fatal systemic disease characterized by the extracellular deposition of congophilic fibrils in soft tissues.\textsuperscript{45} It is the most common glomerular lesion in patients with MM.\textsuperscript{4,12} These fibrils are composed of monoclonal immunoglobulin or its components. Monoclonal immunoglobulin light-chain fibrils are called AL whereas monoclonal heavy-chain fibrils are AH and those containing the intact immunoglobulin are represented by ALH.\textsuperscript{44} AL is the most common subtype, representing over 95% of the cases. For the purpose of this paper, AL amyloidosis will represent all 3 subtypes. AL amyloidosis is found in 5% to 15% of patients with MM during autopsy.\textsuperscript{14-16} Forty percent have greater than 10% plasma cells in their bone marrow, but only 9.5% will meet the other criteria for MM.\textsuperscript{45} The median age of patients with AL amyloidosis is 64 years, and 69% are male.

Although AL amyloidosis is a systemic disease, kidney involvement is quite common. Nearly half of all AL amyloidosis patients present with abnormal SCr, and 73% have proteinuria with 28% having nephrotic syndrome.\textsuperscript{45} Median proteinuria is 5.8 g/day, and 70% of the urinary protein is made up of albumin.\textsuperscript{46} On the other hand, patients with vascular limited AL amyloidosis present with kidney insufficiency but little (<1 g/day) or no proteinuria.\textsuperscript{46} Rare patients may also present with nephrogenic diabetes insipidus.\textsuperscript{45} Patients who present with kidney manifestation are at risk for progression to ESRD. In a study of 145 patients, 41.6% of patients who presented with kidney manifestations required renal replacement therapy vs 4.9% of those who did not.\textsuperscript{47} Median survival from the start of dialysis is 10.4 months. Although the kidney can be the only organ involved, often patients present with other systemic symptoms. The coexistence of congestive heart failure, orthostatic hypotension, peripheral neuropathy, diarrhea, macroglossia, and easy bruisability should prompt further testing for amyloidosis.

Amyloid appears as amorphous periodic acid–Schiff negative and silver-negative deposits on the kidney biopsy, which can be nodular in appearance at times (Fig 2). The most common kidney compartment affected by amyloid deposits is the vessel walls, but deposits can be found in the glomeruli and tubular interstitium.\textsuperscript{44} On silver stain, feathery spicules are sometimes visible on the glomerular basement membranes (GBMs). An apple-green birefringence should be elicited by polarized light after staining with Congo red (Fig 2). For AL, the deposits should stain for just a single light chain on IF. For ALH, a single heavy chain would also stain positive whereas only the heavy chain will stain in AH. Randomly arranged fibrils with a diameter of 7 to 12 nm should be identified on EM (Fig 2). Because treatment is very different for other types (familial, secondary [AA], etc) of amyloidosis, accurate typing is essential.\textsuperscript{44} The use of laser microdissection followed by mass spectrometry has been very useful in cases in which the IF is equivocal or negative. Differences in the spectra ratio of immunoglobulin to serum amyloid P to apolipoprotein E may someday allow laser microdissection followed by mass spectrometry to distinguish amyloid fibrils from immunotactoid and fibrillar fibrils.\textsuperscript{48}

Treatment of AL amyloidosis has made tremendous advances in the past decade. High-dose melphalan followed by autologous stem cell transplantation and melphalan and dexamethasone have increased hematologic response rates to nearly 70% and improved median survival from 18 months to over 5 years.\textsuperscript{49-51} Bortezomib-based therapy has also been used with success.\textsuperscript{52,53} Clinical trials are ongoing comparing bortezomib-based therapy to standard therapy. The kidney is actually quite important in the treatment of AL amyloidosis. Because patients generally die of organ failure rather than bone marrow failure, organ response is the ultimate goal of therapy. Kidney response is highly correlated with the hematologic response and is predictive of OS.\textsuperscript{54,55} Kidney transplantation has been used in conjunction with chemotherapy or autologous stem cell transplantation. In patients without significant cardiac involvement or MM, this can be a good option.\textsuperscript{56}

**MIDD**

MIDD represents a group of kidney diseases that includes light-chain deposition disease (LCDD), light heavy-chain deposition disease (LHCDD), and heavy-chain deposition disease (HCDD).\textsuperscript{57} It is characterized by amorphous to granular deposition of monoclonal...
immunoglobulin or its components. The most common MIDD is LCDD. In autopsy studies of patients with MM, MIDD is seen in 5% of MM patients, approximately half the incidence of AL amyloidosis. Unlike AL amyloidosis, MIDD usually only affects the kidney, but systemic involvement has been reported in the lungs, heart, liver, and other soft tissue. MM is diagnosed in 59% to 65% of cases, whereas 3% of cases are due to CLL. The rest had been described as idiopathic. However, a recent study by Nasr and colleagues found an abnormal serum FLC ratio in 100% of the patients. Thus, the patients that do not meet criteria for MM or CLL are better classified as MGRS than idiopathic.

On light microscopy, the most recognizable histological lesion of MIDD is nodular mesangial sclerosis, present in two thirds of cases. These nodules are PAS and silver positive and show less variation in size compared with Kimmelstiel–Wilson nodules. Mesangial sclerosis without nodules, membranoproliferative features, and even crescents have been described. It is on IF where the distinguishing features are seen. Monoclonal light chains, heavy chains, or entire immunoglobulin can be seen staining in linear pattern diffusely along the GBM and tubular basement membranes (TBMs) and in a weblike pattern along vessel walls. Mesangial staining can be seen, but it is less consistent than TBM or GBM staining. C3 staining may also be detected in LCHDD and HCDD. On EM, the electron-dense deposits appear haphazardly oriented and measure between 7 and 12 nm in diameter.

In LCDD, there is a predilection for kappa over lambda light chains. Approximately 75% of the reported cases are from kappa clones. Within the kappa light chains, V_{κ1} seems to be most common. The over-representation...
of kappa light chain in MIDD may be found in its tertiary and quaternary structure. Structural analyses show that a β edge can be formed in the CDR2 loop of kappa light chains as a result of a conserved cis-proline at position 8. This proline is in the trans position in lambda light chains and it is often followed by another trans-proline at position 9. Exposure of the β edge allows for spontaneous aggregation of kappa light chains into oligomers that elongate into a fibril. These fibrils do not bind serum amyloid P or Congo red like amyloid fibrils; therefore, they do not have amyloid characteristics. These oligomers may form the deposits that are seen in MIDD.

The median age of presentation ranged from 51 to 57 years. Roughly two thirds of the patients were male. Proteinuria was present in almost all patients. The median proteinuria was 2.7 to 4.1 g/day with approximately 40% of patients with nephrotic-range proteinuria. Patients with HCDD appeared to have a higher degree of proteinuria. Microscopic hematuria was common (62%), but gross hematuria was rare (3%). Kidney insufficiency was also nearly universal, with an average SCr of 3.8 mg/dL. ESRD was reached by 39% to 57% of patients. Median OS varied from 13 months in 1 study of LCHDD to 90 months. Kidney histology, presence of MM, and presence of lytic bone lesion were factors that influenced OS.

In patients who have MM or CLL with MIDD, the treatment should be based on the standard treatment for each disease. In patients with MGRS (≤10% bone marrow plasma cells), treatment with cytotoxic therapy is still necessary because MIDD will result in ESRD. In

Figure 3. Pathology of kidney MIDD. (A) The glomerulus shows nodular mesangial sclerosis, which is seen in close to two thirds of cases of MIDD. The nodules are paucicellular and stain PAS positive. They show less variation in size than what is seen in diabetic glomerulosclerosis (PAS, ×200). (B) Frequently, there is prominent thickening of arterial walls by PAS-positive deposits, which surround the myocytes of the outer media (PAS, ×400). (C and D) In this case of light-chain deposition disease kappa type, immunofluorescence shows diffuse linear glomerular and tubular basement membranes staining for kappa (C) with negative staining for lambda (D) (×100 for C and D). (E and F) The diagnostic ultrastructural finding in MIDD is finely granular electron-dense deposits involving the inner aspect of the glomerular basement membranes (E) and the outer aspect of the tubular basement membranes (F) (electron microscopy, ×6000 for F and ×4800 for F). Abbreviations: MIDD, monoclonal immunoglobulin deposition disease; PAS, periodic acid–Schiff.

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1 study, the patient survival at 5 years was 71% whereas kidney survival was only 40%. The authors believed that inadequate treatment of the MGRS was the reason for the high rate of ESRD. However, because these patients do not have a malignant condition, minimizing chemotherapy-related toxicity is as important as efficacy. Because of its ability to inhibit NFκB, bortezomib-based therapies have been used in the treatment of patients with LCDD.68,69 However, severe adverse effects have been reported with several patients, and efforts should be made to use the least toxic schedule and route.70 Autologous stem cell transplantation either alone or after induction in LCDD has also produced good results.69,71-74 Kidney transplantation in MIDD should be reserved for those patients who had a complete response to therapy because the recurrence rate in patients not in complete response is near 80%.75

Light-Chain Fanconi Syndrome

Light-chain Fanconi syndrome (LCFS) is a rare condition characterized by proximal tubular toxicity resulting from crystalline deposition from a monoclonal light chain. This is closely related to crystal-storing histiocytosis, in which crystals are found in the cytoplasm of histiocytes in the bone marrow and other organs. Similar to crystal-storing histiocytosis, nearly 90% of the clones in Fanconi syndrome are kappa restricted, and Vκ1 seems to be the most common.76,77 Nearly half of the patients have a diagnosis of MM. Other diagnoses include WM, CLL, smoldering MM, and MGRS.

The median age of these patients was 57 years, and 58% were male. Patients generally present with proteinuria (usually not high grade) and kidney insufficiency. In addition to proteinuria and kidney insufficiency, patients often present with glycosuria, bone pain, osteomalacia, and fatigue. Electrolyte abnormalities including hypouricemia (66%), hypophosphatemia (50%), and hypokalemia (44%) were noted in most patients.76 It is important to note that as the kidney function declines, the electrolyte abnormalities resolve. Aminoaciduria (100%) is the most common urinary abnormality, followed by glycosuria (~100%) and phosphaturia (43%). In cases in which glycosuria or phosphaturia is absent but aminoaciduria is present, an incomplete Fanconi syndrome is diagnosed. Distal tubular dysfunction including distal renal tubular acidosis and nephrogenic diabetes insipidus can rarely occur with the proximal tubular dysfunction.78-80 The mechanism for this is not well understood, and other disease processes may be involved.78

The most common pattern seen on kidney biopsy is patchy tubular injury. Microcrystals can be seen in flattened or enlarged proximal tubular cells.77 Crystals can be confirmed with toluidine-blue stain. On IF, the crystals should stain for a single light chain. IF on pronase-digested, paraffin-embedded tissue is more sensitive than standard IF on frozen tissue for demonstrating kappa light chain in the crystals (Fig 4).81 Crystals are

![Pathology of light-chain proximal tubulopathy](image)

Figure 4. Pathology of light-chain proximal tubulopathy. (A) Large rod- and rhomboid-shaped hypereosinophilic crystals are seen within proximal tubular cells. (hematoxylin and eosin, ×600). (B) In this patient with smoldering myeloma who has 20% kappa-restricted plasma cells in the bone marrow, the proximal tubular crystals stain strongly for kappa (as shown) with negative lambda (not shown) by immunofluorescence performed on pronase-digested, paraffin-embedded tissue. The intracellular crystals failed to stain for kappa or lambda on standard immunofluorescence on frozen tissue (not shown) (×400). (C) Ultrastructurally, the proximal tubular cells are filled with electron-dense light-chain crystals with rod, rhomboid, or rectangular shapes. The proximal tubule brush border appears preserved (×1850). (D) In this case of light-chain proximal tubulopathy, the proximal tubular cells are loaded with large electron-dense phagolysosomes without crystals (electron microscopy, ×2500).
often rhomboid in shape and are seen in the cytoplasm around lysosomes on EM (Fig 4). Varying degree of tubular atrophy and interstitial fibrosis may be present. Coexistent cast nephropathy can rarely be identified within the same biopsy.

The kidney outcome in LCFS is variable. In 1 series, 5 of 32 patients reached ESRD whereas 8 of 11 did in another series. It is interesting to note that MM was not a risk factor for ESRD. The effectiveness of treatment at preventing ESRD is unclear because most of the reports came from the melphalan and prednisone era. In fact, treatment with alkylation-based therapy was a risk factor for death because many died of treatment-related infections. A recent report described improvement or stabilization of kidney function in 2 patients after treatment with bortezomib-based therapy. Both had a decrease in their serum kappa FLC levels.

The term light-chain proximal tubulopathy has recently appeared in the literature. It is often associated with LCFS; however, the definition has not been uniform. Some use the term to refer to LCFS without crystals whereas others use it when there is light-chain crystal deposition disease but an absence of full or presence of a partial Fanconi syndrome. Some feel they are the same disease whereas others feel they are separate entities. In 1 series, 3.2% of the biopsies associated with a paraprotein-related disease were identified as light-chain proximal tubulopathy. The definition was light-chain restriction in the cytoplasm. Ten of the 13 cases had monoclonal lambda light chains, in which 1 patient with kappa light chains did not have crystals and 2 with lambda chains did. The indications for kidney biopsy in patients without crystals were proteinuria and progressive kidney insufficiency with proteinuria. These patients all exhibited lysosomal or mitochondrial abnormalities along with signs of acute tubular injury such as cytoplasmic swelling or blebbing and flattening or dilatation of tubules and loss of brush border. Eight of the 13 patients were diagnosed with MM. In contrast, only 1 of 190 biopsies of patients with MM was diagnosed with light-chain proximal tubulopathy in another single-center study. More research is clearly needed to define light-chain proximal tubulopathy.

**ATN**

ATN represents a significant portion of MM patients with AKI. Biopsy studies show the prevalence to be between 7.1% and 9.0%. Clinically, it is often difficult to distinguish ATN from MCN. Whereas urinary albumin excretion tends to be lower in MCN (7% vs 25%), there is a great deal of overlap (8%-62% in ATN vs 2%-26% in MCN). In addition, they share common precipitating events. Hydrogen peroxide production by monoclonal promotes redox signaling pathways. Through src kinase, NFkB is activated, which induces IL-6, IL-8, monocyte chemoattractant protein-1, and transforming growth factor-β1. In addition, apoptosis signal-regulatory kinase-1 can be activated directly by monoclonal FLC. These events sensitize the kidney to injury from NSAIDs and dehydration, which are precipitating events for MCN. In addition, MM patients may be more susceptible to kidney injury with iodinated contrast dyes and bisphosphonates. A study of 46 patients who had undergone 80 computerized tomography studies with contrast found that 12 patients had an increase in their SCr of more than 25%. The SCr increased within 48 hours in 4 patients and within 3 to 7 days in 8 patients. Only 1 patient required dialysis. The diagnosis in this study was made clinically, and no kidney biopsy was obtained. Bisphosphonates, which have been shown to be beneficial in MM, do have kidney toxicity as 1 of their adverse effects. Collapsing focal segmental glomerulosclerosis was reported in several MM patients treated with high-dose pamidronate. In addition to focal segmental glomerulosclerosis, AKI from ATN associated with the use of zoledronic acid has been reported in patients with MM in the United States and France. A retrospective study from a single oncology center found that the risk of AKI in MM patients receiving bisphosphonate is higher with zoledronic acid than with ibandronate. This had led the U.S. Food and Drug Administration to issue a warning about zoledronic acid, recommending reduced dosing for kidney function less than 60 mL/minute and caution in patients with dehydration, concomitant use of other nephrotoxic drugs, and in those with MM. On the other hand, a study using the U.S. Food and Drug Administration Adverse Event Reporting System and published cases failed to show a safety signal with any of the bisphosphonates.

**Membranoproliferative Glomerulonephritis**

Membranoproliferative glomerulonephritis (MPGN) were previously thought to be due to infections, autoimmune diseases, and complement dysregulation in type II MPGN, better known as dense deposit disease, but not to monoclonal gammopathy. However, a recent retrospective review found that after excluding hepatitis (B and C) and dense deposit disease, 41% of the cases were associated with a circulating monoclonal protein and deposits in the kidney. Although most cases were classified as MGRS, 21% met criteria for MM. Other diagnoses included WM, CLL, and other lymphomas. Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is another entity that can present in a membranoproliferative pattern. PGNMID has a preference for monoclonal IgG3, which accounts for just over 50% of cases. However, it remains undetermined whether these are the same entity because MM is exceedingly rare in PGNMID. In fact, most of these patients do not have a detectable circulating monoclonal protein. However, MPGN associated with a monoclonal protein and
Immunotactoid Glomerulonephritis

Immunotactoid glomerulonephritis (ITG) is a rare glomerular disease characterized by the deposition of fibrils in the glomerulus (Table 2). However, these fibrils are much larger than amyloid fibrils and do not stain with Congo red. They have a mean diameter of 31 nm with a range of 17 to 52 nm and a hollow center similar to microtubules. Because of their similarity to cryoglobulins, cryoglobulinemia must be ruled out. Unlike the fibrils in amyloidosis and fibrillary glomerulonephritis, which are smaller and randomly arranged, the microtubules in ITG are usually arranged in parallel arrays (Fig 5). Histologically, most cases of ITG show membranoproliferative or membranous patterns of injury with or without endocapillary proliferation, mesangial expansion, and hypercellularity (Fig 5). Hyaline pseudothrombi in the glomerulus and crescents are sometimes seen. IF is usually positive for the entire immunoglobulin, and in contrast to fibrillary glomerulonephritis, it shows light-chain restriction (Fig 5).

Proteinuria is heavy with ITG, with a median of 11.1 g/day (range 1.4-36 g/day). Microscopic hematuria is common. The median SCr at presentation is 1.5 mg/dL (0.7-3.8 mg/dL). The median age of these patients ranges from 59 to 66 years. There is male predominance ranging from 71.4% to 83.0%. ITG is often associated with a monoclonal gammopathy. In reported series, it is involved with a monoclonal gammopathy in 63% to 86% of cases in contrast to fibrillary glomerulonephritis, which is only involved 15% to 17% of cases. The most common hematologic diagnosis associated with ITG is CLL; in some series, it is up to 44%.

**Table 2. Kidney Diseases of Multiple Myeloma**

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PGNMID recur after kidney transplantation with high frequency.98,99

**Immunotactoid Glomerulonephritis**

In the glomerulus (Table 2). However, these fibrils are much larger than amyloid fibrils and do not stain with Congo red. They have a mean diameter of 31 nm with a range of 17 to 52 nm and a hollow center similar to microtubules. Because of their similarity to cryoglobulins, cryoglobulinemia must be ruled out. Unlike the fibrils in amyloidosis and fibrillary glomerulonephritis, which are smaller and randomly arranged, the microtubules in ITG are usually arranged in parallel arrays (Fig 5). Histologically, most cases of ITG show membranoproliferative or membranous patterns of injury with or without endocapillary proliferation, mesangial expansion, and hypercellularity (Fig 5). Hyaline pseudothrombi in the glomerulus and crescents are sometimes seen. IF is usually positive for the entire immunoglobulin, and in contrast to fibrillary glomerulonephritis, it shows light-chain restriction (Fig 5).

Proteinuria is heavy with ITG, with a median of 11.1 g/day (range 1.4-36 g/day). Microscopic hematuria is common. The median SCr at presentation is 1.5 mg/dL (0.7-3.8 mg/dL). The median age of these patients ranges from 59 to 66 years. There is male predominance ranging from 71.4% to 83.0%. ITG is often associated with a monoclonal gammopathy. In reported series, it is involved with a monoclonal gammopathy in 63% to 86% of cases in contrast to fibrillary glomerulonephritis, which is only involved 15% to 17% of cases. The most common hematologic diagnosis associated with ITG is CLL; in some series, it is up to 44%.

**Figure 5. Pathology of immunotactoid glomerulopathy.** (A) In this case of immunotactoid glomerulopathy and a membranoproliferative pattern of injury, there is global mesangial and glomerular capillary wall deposition of silver-negative immune material. The glomerulus also shows widespread duplication of the glomerular basement membrane, with global mesangial and segmental endocapillary hypercellularity (Jones methenamine silver, ×600). (B) In this case of immunotactoid glomerulopathy with a membranous pattern of injury, there is granular global glomerular capillary wall and mesangial staining for immunoglobulin G (×200). Similar glomerular staining for lambda was seen, with negative staining for kappa (not shown). (C) Electron microscopy shows thickening of the glomerular basement membrane by intramembranous and subepithelial electron-dense deposits that are composed of microtubules (×5000). (D) Electron microscopy from a different case shows mesangial deposits composed of large microtubules with hollow centers, which are organized in parallel arrays (×24,500).
50% of cases. However, ITG can be associated with MM and was found in 12.5% of cases in another series. The rarity of ITG makes it difficult to conduct any clinical trials. Treatments successful in reducing the lymphocyte clones also succeeded in maintaining kidney function and reducing proteinuria.

Myeloma Infiltration

Kidney failure can rarely be due to myeloma infiltration of the kidney. Prevalence varies from 10% to 31% in autopsies series. On biopsy, interstitial infiltration by atypical plasma cells is seen. These cells stain for CD138 and a single light chain corresponding to the monoclonal protein. In a case of a 60-year-old male presenting with AKI, extramedullary hematopoiesis and cast nephropathy were also identified along with myeloma infiltration.

References


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