

Kidney Disease and Multiple Myeloma

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Summary

Kidney injury is a common complication of multiple myeloma and other plasma cell dyscrasias, and it is associated with increased mortality. Multiple pathogenic mechanisms can contribute to kidney injury in the patient with myeloma, some of which are the result of nephrotoxic monoclonal Ig and some of which are independent of paraprotein deposition. The pathogenic mechanisms that underlie paraprotein-related kidney disease are increasingly well understood. A novel assay allowing the quantification of free light chains in the serum has aided the diagnosis of new onset disease and allowed for the earlier detection of relapse. Novel myeloma agents have shown considerable promise in reversing renal failure in some patients and improving outcomes. Stem cell transplantation remains a mainstay of management for younger patients with myeloma who are suitable candidates for intensive therapy, whereas the role of new drugs, plasma exchange, and kidney transplantation continues to evolve.

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Introduction

Traditionally among the most refractory and feared malignancies, multiple myeloma and other associated plasma cell disorders are receiving well deserved attention as a result of significant progress in the understanding of basic biology of malignant plasma cells and the availability of more effective and less toxic novel therapies. At the same time, the renal effects of plasma cell disorders are similarly receiving increased attention, because the wide pathologic and clinical spectrum of these diseases is better appreciated and therapeutic options have expanded. Defined by abnormal creatinine clearance, renal insufficiency is present in nearly one half of myeloma patients at presentation and associated with increased mortality. The presence of coexistent kidney disease limits therapeutic options and stem cell transplant eligibility (1,2). In some series, survival is reduced to less than 1 year in patients with myeloma-associated AKI who do not recover renal function, and in fact, the reversibility of myeloma-associated renal injury is more predictive of patient survival than the response to systemic chemotherapy (3,4).

Monoclonal plasma cell disorders include the premalignant monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma, light chain amyloidosis (AL), and multiple myeloma in both its asymptomatic and symptomatic forms (5). The disorders are common, with MGUS affecting up to 3.2% of all individuals over 50 years and multiple myeloma accounting for 13% of all hematologic cancers (6–8). At the time of diagnosis, 37% of patients with myeloma are less than 65 years old, and another 37% of patients are >75 years old; the remaining 26% are between the ages of 65–74 years (8). Given how common plasma cell disorders are, it is clear that nephrologists will encounter these conditions with regularity.

Across the continuum of plasma cell disorders, the underlying plasma cell clones proliferate slowly and share malignant features, such as abnormal cell surface protein expression patterns (9). Most plasma cell clones seen in MGUS and all of those plasma cell clones with active myeloma reveal chromosomal abnormalities, including hyper- or hypodiploidy as well as multiple gene rearrangements. In fact, approximately 80% of multiple myeloma patients have chromosomal abnormalities detected by fluorescence *in situ* hybridization analysis, with the remaining 20% having genetic abnormalities detected by gene expression profiling and special karyotyping, with each resulting in abnormal regulation of intracellular signaling pathways. High-risk chromosomal abnormalities are often present in rapidly proliferating, aggressive disease and typically associated with poorer prognosis (10). Malignant plasma cells enjoy a physiologically dependent relationship with bone marrow stromal cells, extracellular matrix, and cortical bone, which together form a microenvironment that supports myeloma cell proliferation and protects the cells from chemotherapy (11). This review will highlight the syndromes of myeloma-associated kidney injury, the advances in the understanding of the pathogenetic effects of monoclonal Ig, the improved laboratory tests now in widespread use for the detection of monoclonal Ig, and the availability of new renoprotective chemotherapeutic approaches.

Mechanisms of Myeloma and Plasma Cell-Associated Kidney Injury

Reflecting the highly variable composition of Ig, the spectrum of renal disease-associated monoclonal Ig and plasma cell malignancies is remarkably broad and encompasses nearly all nephropathologic entities. The diversity of the abnormal light chains produced by

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different myeloma clones dictates the diversity of the nephropathologic injury that is observed, which is described in more detail below. The mechanisms underlying the renal disease can be logically separated into those mechanisms resulting from monoclonal Ig and those mechanisms in which other factors predominate, recognizing that, in any particular patient, multiple contributing factors may be observed (Table 1). The three most common forms of monoclonal Ig-mediated kidney disease are cast nephropathy, monoclonal Ig deposition disease (MIDD), and AL amyloidosis. (The term myeloma kidney refers to cast nephropathy and should not be used to refer to the entire spectrum of renal failure and myeloma.) Beyond these three forms, GN with active urinary sediment can occur in a membranoproliferative, diffuse proliferative, cryoglobulinemic, or crescentic pattern (12). A minimal change disease or membranous pattern may be observed in patients who present with nephrosis (13,14). Monoclonal Ig can form crystalline inclusions in the proximal tubule accompanied by a classic clinical Fanconi syndrome

or cause mild tubulointerstitial nephritis (15–17). Thrombotic microangiopathy, typically limited to the kidney, can result from Ig-induced endothelial injury as well as systemic chemotherapy or stem cell transplantation used to treat myeloma (18). Monoclonal IgM, which is a much larger molecule than IgG, can produce hyperviscosity-associated renal impairment and additionally form deposits that occlude glomerular capillaries (19). Monoclonal IgA can result in IgA nephropathy or Henoch–Schönlein purpura, although this result is uncommon (20).

It is important for the clinician to understand the basic mechanisms thought to underlie the three most common entities. In cast nephropathy, filtered monoclonal light chain forms intratubular casts and crystals that obstruct distal renal tubules, sometimes quite suddenly, and can simultaneously incite an accompany tubulointerstitial nephritis as obstructed tubules rupture (18) (see Figure 1). In MIDD, filtered monoclonal Igs, in any of its many forms (intact or fragmented, light or heavy chains, or both), deposit along glomerular or tubular basement membranes

Table 1. Mechanisms of renal failure in plasma cell dyscrasias: Ig-dependent and -independent

| Mechanism | Details |
|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ig-dependent mechanisms | |
| Cast nephropathy (known traditionally as myeloma kidney) | Risk factors include light chain myeloma with >10 g/d monoclonal Ig excretion, volume depletion, sepsis, medications (see below); Ig deposition is primarily in the tubules |
| Monoclonal Ig deposition disease | Systemic syndrome may be present; Ig deposition can be in the tubules or glomeruli but generally not both |
| Light chain amyloidosis (AL) | Often associated with nephrotic-range albuminuria and λ -light chains; systemic syndrome may be present, and amyloid deposition is primarily in the glomeruli |
| GN | Membranoproliferative, diffuse proliferative, crescentic, cryoglobulinemic all recognized |
| Tubulointerstitial nephritis | May also result from non-Ig mechanisms |
| Minimal change disease | Albuminuria is typically present in addition to light chain proteinuria |
| Membranous glomerulopathy | Associated with IgA myeloma |
| Henoch–Schönlein purpura/IgA nephropathy | |
| Immunotactoid glomerulopathy (and possibly fibrillary GN) | Rare conditions; the association between fibrillary disease and paraproteins is uncertain |
| Intracapillary monoclonal deposits of IgM thrombi | Associated with Waldenström's macroglobulinemia |
| Thrombotic microangiopathy (TMA) | Paraprotein causes endothelial injury with resulting TMA |
| Hyperviscosity syndrome | More common in cases of IgA, IgG3, or IgM myeloma |
| Ig-independent mechanisms | |
| Volume depletion | Can cause prerenal azotemia and acute tubular necrosis and/or contribute to cast nephropathy |
| Sepsis | Can cause AKI directly or contribute to cast nephropathy |
| Hypercalcemia | Uric acid or phosphate nephropathy |
| Tumor lysis syndrome | Zoledronate: rare cause of acute renal failure |
| Medication toxicity | Pamidronate: rare cause of collapsing focal and segmental glomerulosclerosis |
| | Nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, loop diuretics, or iodinated contrast may precipitate cast nephropathy |
| Direct parenchymal invasion by plasma cells | Rare cause; associated with advanced or aggressive myeloma |
| Pyelonephritis | Rare cause; multifactorial from immunodeficiency and deficient Ig and chemotherapy from myeloma |

(21) (see Figure 2). On light microscopy, glomerular and tubular basement membranes appear thickened by precipitates, which appear dense and granular on electron microscopy (22). Monoclonal Ig can cause glomerular nodules resembling the Kimmelstiel–Wilson lesion of diabetic nephropathy and result in similarly high-grade proteinuria. In AL amyloidosis, monoclonal light chains and other proteins interact to form a β -pleated sheet in the glomeruli and tubules (see Figure 3). Tubular basement membrane thickness is normal, but the Congo red stain is positive. Organized, nonbranching, 7- to 10-nm amyloid fibrils are seen on electron microscopy. In each of these cases, which are discussed in more detail below, the absorption and processing of monoclonal Ig in the proximal tubule incite profibrotic mechanisms that contribute to interstitial damage and renal impairment. A recent biopsy series revealed monoclonal Ig-related lesions in 73% of 190 patients biopsied and monoclonal Ig-independent issues in 25% of patients (21). As in previous series, myeloma cast nephropathy (33%), MIDD (22%), and amyloidosis (21%) were the most common lesions observed.

Myelomas that produce only light chains account for 40%–60% of severe myeloma-associated kidney injury, reflecting the nephrotoxicity of filtered light chain (5). In fact, it was the unusual solubility properties of myeloma-associated light chains that led to their original identification more than 150 years ago, as Bence–Jones Proteins, in a patient with light chain proteinuria. Nonsecretory myeloma is rarely associated with kidney injury. The balance of the cases result from the most common type of myeloma, in which intact monoclonal Ig is secreted along with a small amount of accompanying monoclonal light chain. Some degree of renal impairment is observed at some point in the natural history of nearly all cases of myeloma; 70% of patients who secrete more than 10 g/d light chain will develop renal failure, whereas those patients with the rare IgD form of myeloma seem to develop renal impairment 100% of the time in some series (2). Nephrologists who evaluate patients with CKD should bear in mind that, on occasion, patients will develop MIDD as a result of a small plasma cell clone, which produces (23) monoclonal Ig with nephrotoxicity that far exceeds its content in plasma (24).

As detailed in Table 1, myeloma-associated renal failure may also result from Ig-independent mechanisms. These mechanisms include hypercalcemia, uric acid nephropathy, volume depletion, sepsis, rhabdomyolysis, nonsteroidal anti-inflammatory drugs, and renin-angiotensin system inhibitors (25,26). Rarely, pyelonephritis or direct renal parenchymal invasion by plasma cells may be present. The amino bisphosphonate zoledronate has been rarely associated with AKI in myeloma patients, and its pharmacologic cousin pamidronate has been associated with collapsing FSGS (27,28). Given that bisphosphonates play a very important role in the control of bony disease in myeloma and the management of hypercalcemia, their cautious use should continue despite these reports, with pamidronic acid being often preferred in the setting of renal dysfunction and dose-reduced zoledronic acid also being helpful. Uncertainties about bisphosphonates that should be addressed by future clinical trials include the dose and duration of use, particularly in patients with advanced CKD or dialysis dependence who may

experience a higher risk of adynamic bone disease and other complications as a result of reduced renal clearance of the drugs.

Much progress has been made in elucidating the molecular events that lead to monoclonal Ig-mediated kidney injury, which have been the subject of a recent review (29). Light chains are filtered at the glomerulus and undergo clathrin-dependent endocytosis by the megalin/cubilin receptor system. Some of these light chains are resistant to chemical degradation and accumulate as precipitates that interfere with proximal tubule function (30,31). Light chains that are degraded induce proinflammatory cytokines, such as monocyte chemoattractant protein-1 and IL-6 and -8 (32,33). These light chains also seem to catalyze the production of reactive oxygen species, which in turn, results in inflammatory cell infiltration, matrix deposition, and fibrosis, and it may contribute to epithelial–mesenchymal transformation of renal tubular epithelial cells (34). Both the mitogen-activated kinase and NF- κ B pathways mediate the proinflammatory cascade (32,33).

The diverse patterns of nephropathologic injury seen in patients with myeloma reflect the diversity of the abnormal light chains that are present. In a classic experiment, Solomon *et al.* (35) injected light chains from 40 patients with myeloma or amyloidosis into mice and found that light chains from myeloma patients with renal dysfunction were significantly more likely to deposit in the mice kidneys than light chains from myeloma patients with normal renal function. Furthermore, light chains from human patients with cast nephropathy, MIDD, or amyloidosis recapitulated similar patterns of injury in the mouse kidneys (35). Cast nephropathy results when abnormal light chains with a strong affinity for Tamm–Horsfall protein form casts that, in turn, obstruct renal tubules, leading to rupture and secondary interstitial inflammation. In contrast, the MIDD pattern of injury results from sometimes fragmented or abnormally large light chains, generally of the κ -type subtype 1, 3, or 4, which as a result of atypical glycosylation or amino acid patterns misfold, become insoluble and precipitate (36). Ig amyloid deposition is most commonly associated with λ -light chains, particularly the λ -6 subtype (37). These light chains undergo endocytosis at the glomerulus and are delivered to lysosomes. The amyloid β -pleated sheet forms as a result of electrostatic interactions between heparan sulfate proteoglycan, serum amyloid P, and permissive amino acids within the variable region of amyloidogenic light chains (38). Light chains that cause MIDD seem to induce a fibroblast phenotype in glomerular mesangial cells, which in turn, leads to matrix deposition (39). Unfortunately, this detailed knowledge of the molecular characteristics of pathogenic monoclonal Ig has not translated into valid clinical tests, and thus, the risk of kidney injury in a particular patient with myeloma cannot be predicted by analyzing the monoclonal Ig in question. Promising new areas of investigation include the analysis of urinary exosomes from patients with paraprotein-related kidney disease (40).

Detection of Monoclonal Ig

Understanding the strengths and weaknesses of the laboratory tests used to detect monoclonal Ig in serum

and urine is critical for physicians who care for patients with multiple myeloma. The gold standard for the diagnosis has been protein electrophoresis, an inexpensive test that unfortunately has poor sensitivity for free light chains and cannot always differentiate polyclonal from monoclonal light chain expansion. Immunofixation has much greater sensitivity than electrophoresis but is a qualitative test, and thus, it has limited usefulness in the monitoring of light chain myeloma progression and response to treatment (5,41). The newest test for monoclonal Ig detection is the free light chain (FLC) immunoassay, which uses polyclonal antibodies to κ and λ in a highly precise nephelometric assay that can detect monomers and dimers of κ and λ at concentration $<2\text{--}4$ mg/L, regardless of whether intact monoclonal Ig is also present (42). Physicians who wish to use the serum FLC assay to diagnose new disease must bear in mind that it does not detect clonality but rather, suggests it through abnormalities in the κ to λ ratio. Because light chains are cleared by the kidney, both κ and λ will be increased proportionately when renal function is decreased, but the ratio of κ to λ typically remains in the normal range. Similarly, the ratio will remain normal in the patient with inflammatory disease, such as lupus, in which there is a polyclonal expansion of light chains. In dialysis-dependent patients, the FLC assay remains useful for diagnosing myeloma as long as an expanded reference range is used to reflect the enhanced retention of κ relative to λ when glomerular filtration is reduced (43). The FLC assay is useful, in part because of its increased diagnostic sensitivity: a substantial portion of patients with MIDD, amyloid, or nonsecretory myeloma, in whom no monoclonal Ig has been detected using conventional testing, will have abnormal serum κ to λ ratios by the serum FLC assay (41,44). In these newly diagnosed patients, high serum FLC levels are associated with an elevated risk of kidney injury (45). In addition, the role of the serum FLC assay in the diagnosis of new disease and the short half-lives of κ and λ make the assay invaluable in following patients with known myeloma to both assess response to treatment and detect early relapse.

The serum FLC assay is not without its drawbacks. The interpretation of κ - and λ -values in the urine can be difficult, because renal light chain handling influences urinary concentration and has confounded attempts to define a normal urinary range (46). In cases in which FLCs are present in extremely high concentrations, the assay may result in paradoxically normal results, because the detecting antibodies become saturated by the abnormal light chains (47). Clinical laboratories who offer the FLC assay should have procedures in place for the appropriate dilution and retesting of specimens when antigen excess is suspected. The optimal cost-effective combinations of the various tests for monoclonal Ig remain to be determined, and at this point, the serum FLC assay seems to complement conventional immunofixation and electrophoretic techniques rather than replace them (48).

Clinical Approach to Myeloma and Kidney Disease

The initial symptoms of myeloma are sometimes subtle and can include weight loss, malaise, fatigue, and bone pain. Similarly, the symptoms of progressive CKD are

nonspecific, and thus, primary care physicians, nephrologists, and hematologists/oncologists should consider plasma cell dyscrasia as an underlying explanation for patients with a wide variety of presenting complaints. The occasional patient will present with a fulminant syndrome of dialysis-dependent AKI or other symptoms resulting from severe hypercalcemia and dehydration (typically these patients have underlying myeloma cast nephropathy). Most patients are older than 60 years, with a minority of patients less than 40 years old and the occasional patient who presents in late teens or 20s (49). Anemia is a hallmark of the disease and is present in 75% of patients; thus, patients presenting with renal dysfunction and anemia should be screened for paraprotein disease. Patients with amyloidosis or MIDD may present with systemic symptoms and signs, including gastrointestinal bleeding, elevated alkaline phosphatase, heart failure, cardiac arrhythmias, and periorbital purpura (50). The BP may be a helpful differentiating feature, because patients with amyloid frequently have hypotension with or without orthostasis, typically as a result of coexistent myocardial amyloid, whereas those patients with MIDD and renal disease typically have hypertension. The prognosis of these syndromes is highly variable. Even patients with severe renal complications, such as nephrotic syndrome or dialysis dependence, can remain stable for prolonged periods of time if the myeloma responds to therapy.

The assessment of urinary protein excretion is essential to the evaluation of the patient with possible paraprotein-mediated kidney disease. Urine dipsticks detect albumin alone and are notoriously unreliable for cationic myeloma paraprotein, but both a spot and 24-hour urine sent to the chemistry laboratory for a test of total protein will be abnormal when paraproteins are present. A low microalbumin to creatinine ratio coincident with a high total protein to creatinine ratio in a spot urine specimen is highly suggestive of light chain proteinuria and should be confirmed with specific tests as described below (tubular proteinuria would also explain this gap, but the total protein in these cases rarely exceeds 1 g protein per 1 g creatinine). Nephrotic-range albuminuria is most consistent with amyloidosis or glomerular involvement by MIDD. Except in rare cases of GN mediated by monoclonal Ig, the urinary sediment is typically bland, although microscopic hematuria may be present in a minority of patients (50). Myeloma cannot be excluded on the basis of urine studies alone, and thus, additional testing is always required if the index of suspicion is high.

A remarkable number of interesting laboratory abnormalities might be present, some of which are epiphenomenon resulting from interference by the paraprotein with routine clinical tests. The globulin fraction may be high or low. Hyponatremia, hypercalcemia, hypo- or hyperphosphatemia, renal tubular acidosis with or without evidence of the Fanconi syndrome, low HDL cholesterol, and nephrogenic diabetes insipidus have all been described (51). Renal imaging is often nonspecific, although the kidneys may be large on ultrasound in patients with amyloid or plasma cell infiltration.

Although the diagnostic criteria of myeloma are well recognized and include the presence of a bone marrow plasmacytosis in excess of 10% and a serum monoclonal

protein component in excess of 3 g/dl, it is important to recognize that documented paraprotein-mediated kidney injury or other end organ damage of any degree constitutes myeloma, regardless of these other criteria, and provides a rationale for treatment (5). The clinical nephrologist will see many patients with low levels of monoclonal Ig most consistent with MGUS and mild CKD, which may or may not be related. A kidney biopsy early in the course of CKD can provide a definitive diagnosis and can be particularly useful when the bone marrow biopsy does not provide sufficient rationale for therapy. The availability of more effective and less toxic therapies, as described below, makes a compelling case for more aggressive biopsy investigation of patients with possible paraprotein-mediated kidney disease. Of note, special techniques, such as pronase digestion and immunogold labeling, may be required to detect and characterize monoclonal Ig and amyloid in these patients, and thus, biopsies in patients with suspected paraprotein-related kidney disease should be processed and reviewed in a pathology department with significant expertise in this area (52,53).

Management of AKI from Paraprotein-Mediated Disease

The relative contributions of Ig- and non-Ig-mediated kidney injury are typically unknown in the patient who presents with AKI, because kidney biopsy data are not yet available; thus, various potential mechanisms of kidney injury should be addressed simultaneously. Hemodynamics and intravascular volume should be optimized in an effort to ensure adequate urine output. Oliguric patients may benefit from a trial of volume repletion but should not receive loop diuretics, because they may contribute to paraprotein cast formation (54). Alkalinization of the urine is of uncertain benefit and can theoretically raise the risk of abnormal calcification in the kidney or elsewhere, particularly if hypercalcemia is present. Hypercalcemia should be treated aggressively with intravenous saline and bisphosphonates (dosed for impaired renal function). Hemodialysis is also very effective for lowering serum calcium and should be used in the patient with confusion, cardiac arrhythmias, or other significant complications of hypercalcemia. Rasburicase is remarkably effective but is indicated only in patients with clinically significant tumor lysis syndrome; however, the risk factors are not well understood, although it is rare in myeloma. Allopurinol and hemodialysis may be necessary for patients who are refractory to rasburicase, often as a result of prior administration. Nephrotoxins, such as renin-angiotensin inhibitors, iodinated contrast, and nonsteroidal anti-inflammatory drugs, should be avoided.

Systemic Therapy

Survival from myeloma is improving as a result of the availability of novel therapeutic agents, which also seem to have improved the prognosis for myeloma-associated kidney injury (55). Given the sometimes rapid progression and irreversible nature of monoclonal Ig-mediated kidney disease, chemotherapeutic agents that act rapidly should be administered promptly after diagnosis. Systemic

therapy can extend survival, even in dialysis-dependent patients, some of whom may recover renal function many months after therapy (56). Early reduction in serum FLCs levels is predictive of renal recovery, with a 60% reduction in serum FLCs at day 21 associated with renal recovery in 80% of patients (57).

The reversible, first-in-class proteasome inhibitor bortezomib, a potent boronate peptide small molecule, represents a significant therapeutic step forward in the treatment of paraprotein-related diseases, and it is an important agent with which nephrologists should be familiar. Bortezomib and high-dose dexamethasone have emerged as the most effective therapies for myeloma associated with severe AKI. The efficacy and safety of bortezomib seem unrelated to kidney function, and dose adjustment for GFR is not required (58–60). The drug's rapid onset of action, with a median time to best response of only 30 days in clinical trials, makes it effective for preventing permanent kidney injury (61,62). Bortezomib's mechanism of action relates to interference with protein handling by the ubiquitin proteasome pathway, which in turn, causes apoptosis of malignant plasma cells that synthesize large quantities of Ig (63,64). Bortezomib inhibits the mitogen-activated kinase and NF- κ B pathways, thereby disrupting myeloma–stromal cell interactions, reducing tumoral angiogenesis, and increasing myeloma cell apoptosis (65). By inhibiting these pathways, bortezomib also downregulates the inflammatory state induced by light chain handling in the proximal tubule and therefore, likely reduces the development of renal interstitial fibrosis (66).

Forty percent to fifty percent of patients with myeloma and AKI who respond to bortezomib-based regimens will experience a significant improvement in renal function within a few weeks (60,66–70). Interestingly, the improvement in renal function often precedes significant antiplasma cell effects, an observation that highlights the importance of the drug's anti-inflammatory effects in reversing kidney injury (71). Carfilzomib is an irreversible proteasome inhibitor, which in phase 2 trials, seems to be effective in previously treated populations with relapsed and refractory myeloma; however, in the phase 2 trial by Siegel *et al.* (72), mild to moderate elevations in serum creatinine occurred in 25% of patients, and small numbers of patients experienced more serious episodes of renal failure (72,73). Studies of carfilzomib in renal dysfunction did not show significant changes in the drug's pharmacokinetics, but again, a number of patients in the trial experienced worsening of renal function during treatment, suggesting that the nephrotoxicity of this agent warrants additional study (74).

Other novel agents seeing increased use in patients with myeloma include thalidomide and its potent derivative, lenalidomide. These agents have complex mechanisms of action that include the interruption of myeloma cell growth and disruption of myeloma and bone marrow stromal cell interactions (75,76). Lenalidomide needs to be used with caution in the setting of CKD, and dose reduction is mandatory, because the drug is renally cleared. Despite this information, myelosuppression and other adverse events are more common in this setting (76–78). Nonetheless, it is not directly nephrotoxic, and therefore, a low dose (*e.g.*, 5–10 mg/d) can be used. Although thalidomide pharmacokinetics, like bortezomib pharmacokinetics, are relatively

unaffected by renal dysfunction, hyperkalemia has been reported (79,80). Thalidomide can be used at doses of typically 50–100 mg daily as tolerated, with encouraging activity combined with other agents (81). For example, high-dose dexamethasone regimens combined with lenalidomide or thalidomide act rapidly and have beneficial effects on paraprotein-mediated renal impairment similar to the effects of bortezomib-based regimens, while helping to preserve stem cell transplantation options (82,83). The risks of venous thromboembolic disease are increased with these agents, except for bortezomib, and enhanced surveillance for this complication is prudent, particularly if there are other risk factors for venous thromboembolism present, such as nephrosis, hypoalbuminemia, or concomitant erythropoietin use. The empirical use of anticoagulation should be considered in those patients at highest risk.

Stem Cell Transplantation

Despite the availability of new therapeutic agents, stem cell transplantation (SCT) remains a cornerstone of myeloma therapy for younger patients who qualify, although questions regarding its optimal timing remain and research is ongoing in this regard (84). Select patients with Ig amyloid and MIDD can also be successfully treated with autologous SCT, although patients with significant systemic involvement experience unacceptable treatment-related mortality and thus, are not candidates for this approach. Patient selection has been suggested as an explanation for the apparent advantage of SCT over standard therapy (85,86). Allogeneic SCT is potentially curative for small numbers of patients because of a mild graft-versus-myeloma effect, but its use remains experimental in this setting (87). Recent work in this area has focused on the feasibility of reduced intensity conditioning to lower the treatment-related mortality, preserve antimyeloma activity, and limit graft-versus-host disease.

Patients with myeloma-associated renal failure face an unfortunate double jeopardy, in that renal failure, one of myeloma's worst complications, may prevent them from qualifying for SCT, one of the disease's most effective treatments (88). Randomized trials of SCT for myeloma have excluded patients with serum creatinine in excess of 2.3 mg/dl, and thus, the benefits of SCT in this population are uncertain (89). A limited number of US centers will perform autologous SCT in patients with renal failure, including dialysis-dependent patients, but toxicity is increased, despite the deployment of reduced dose conditioning (89). Severe renal impairment is generally a contraindication to allogeneic SCT, although small numbers of patients with dialysis-dependent end stage kidney failure and myeloma have successfully received simultaneous kidney and allogeneic SCT from an HLA identical sibling; in some cases, they have achieved complete remissions. If chimerization is complete, these patients do not require immunosuppressive therapy, because the transplanted bone marrow does not reject a kidney from the same donor (90).

Plasmapheresis and Other Extracorporeal Techniques to Remove Light Chains

Nephrologists and blood bank physicians are frequently asked to consider plasmapheresis as a therapeutic option in

patients presenting with severe AKI and active multiple myeloma, often on the assumption that the kidney injury is primarily mediated by Ig-mediated mechanisms such as myeloma casts. Evidence in favor of plasma exchange in this setting is limited to uncontrolled, retrospective case series, and its rationale has been questioned because of the high volume of distribution of light chains and IgG that results in rapid plasma refill within a few hours after each pheresis session (91,92). The largest clinical trial involving 90 patients showed no benefit to plasma exchange (93). In this trial, 40% of patients in the control group recovered, confirming that chemotherapy alone can be successful in many cases and/or suggesting that some of the enrolled patients had non-Ig-mediated kidney injury that recovered independent of reductions in monoclonal Ig. An attempt in Europe to conduct a larger randomized controlled trial (the Myeloma Renal Impairment Trial [MERIT]) was limited by low patient enrollment. Hyperviscosity syndrome, seen on occasion in patients with IgA or IgG3 myeloma, remains a clear indication for plasma exchange.

Despite uncertainties about plasma exchange, interest in adjunctive techniques to facilitate light chain clearance remains high, because renal outcomes are improved in patients who experience a rapid decline in light chain levels (57). One such approach involves the use of extended dialysis sessions for patients with myeloma cast nephropathy using a dialyzer cartridge with pores of sufficient size to allow the removal of light chains. Pooling data from multiple centers, Hutchison *et al.* (57,94) showed that nearly three quarters of dialysis-dependent patients receiving this therapy recover renal function and that this recovery is predicted by the degree of light chain reduction and a shorter time between presentation and initiation of light chain-removing dialysis (94). Randomized controlled trials of this technique are underway both in Europe (European Trial of Free Light Chain Removal [EULITE]; controlled clinical trials ISRCTN45967602) and France (studies in patients with multiple myeloma and renal failure due to cast nephropathy [MYRE]; ClinicalTrials.gov NCT01208818). Limited experience suggests that continuous venovenous hemofiltration may also be helpful (95).

Kidney Transplantation

On occasion, patients with myeloma-associated renal failure achieve a sustained remission of myeloma but remain dialysis-dependent, and thus, kidney transplantation is contemplated. The risks of kidney transplant in this population include recurrent myeloma (possibly more likely as a result of the effects of immunosuppression), monoclonal Ig-mediated graft dysfunction, and infection. Early severe allograft dysfunction has been reported as a result of a monoclonal Ig necrotizing GN, and more subacute forms of graft deterioration are frequent in patients whose native kidney disease was MIDD (96,97). If the original lesion was cast nephropathy, the risk of kidney graft recurrence seems low if the myeloma remains in remission (98). Recently, Naina *et al.* (99) studied the outcomes of kidney transplant recipients and MGUS; 2 of 23 patients with pretransplant MGUS developed smoldering myeloma, and 2 patients developed another post-transplant lymphoproliferative disease over a mean

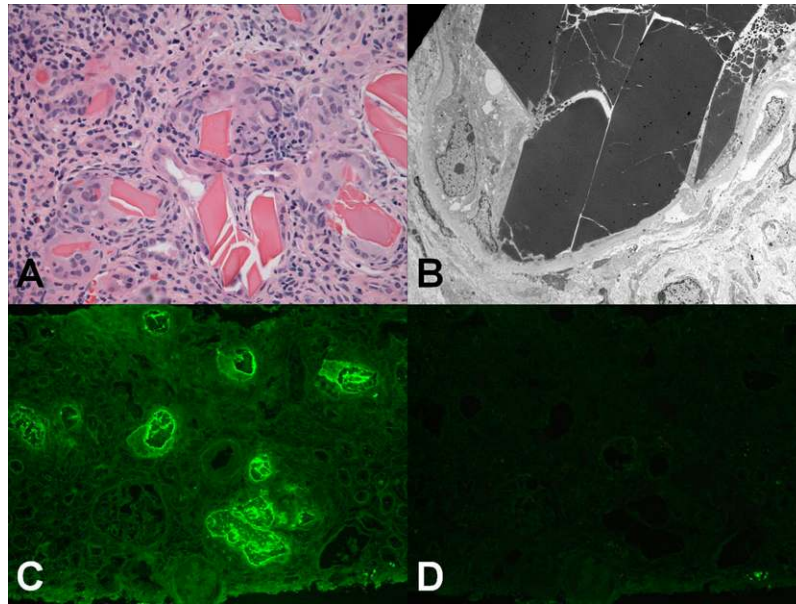


Figure 1. | Light chain cast nephropathy (also known as myeloma kidney). (A) The tubules contain eosinophilic proteinaceous casts that have a crystalline and broken appearance. Notice the prominent inflammatory reaction with foreign body type multinucleated giant cells in close proximity to the cast material (hematoxylin and eosin-stained section). (B) The electron microscopy shows the characteristic electron-dense cast material inside a tubule. The conditions in the tubule have facilitated the organization of the light chain into a supramolecular crystal-like structure. (C) The immunofluorescence microscopy with fluoresceinated anti- λ -antibodies shows strong staining of the cast for this light chain. Notice the high background staining of the tissue for the λ -light chain, a reflection of the higher plasma and hence, tissue concentration of this protein. (D) The staining of the casts for κ -light chains is negative. Also, the staining of the background for this light chain is significantly weaker than for λ -light chains.

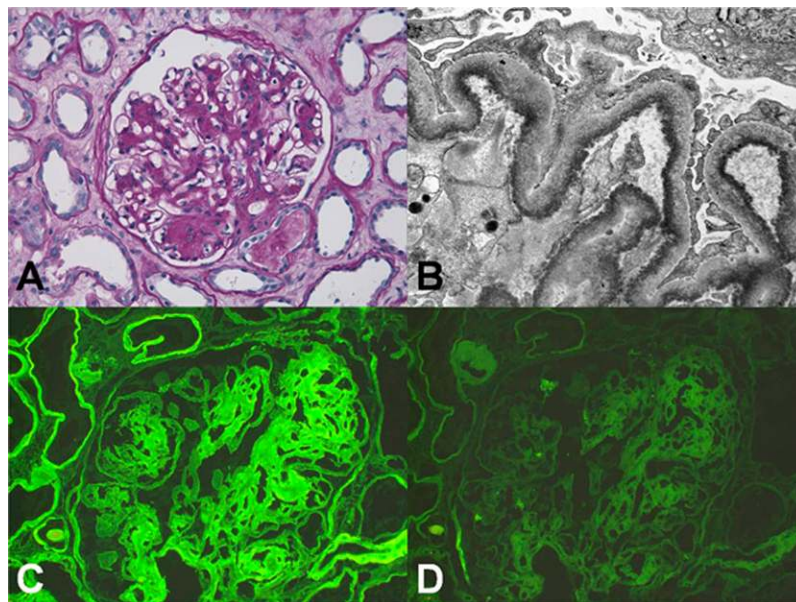


Figure 2. | Systemic κ -light chain deposition disease. (A) The glomerulus reveals a distinctive nodular appearance caused by expansion of the mesangial matrix in response to the deposition of the paraprotein (periodic acid–Schiff-stained section). Notice the thickening of the tubular basement membranes and prominent interstitial fibrosis. (B) The electron microscopy shows characteristic confluent and fine granular Randall-type dense deposits along the inner aspect of the wrinkled glomerular basement membranes. The endothelium has been damaged by this process and is missing from this segment of the capillary loop. (C) By immunofluorescence microscopy with fluoresceinated anti- κ -antibodies, all basement membranes and the mesangial nodules show strong staining for this light chain. (D) The staining of the basement membranes and the mesangial nodules for λ -light chains is significantly weaker and near background. The staining for all heavy chains is likewise negative (not shown).

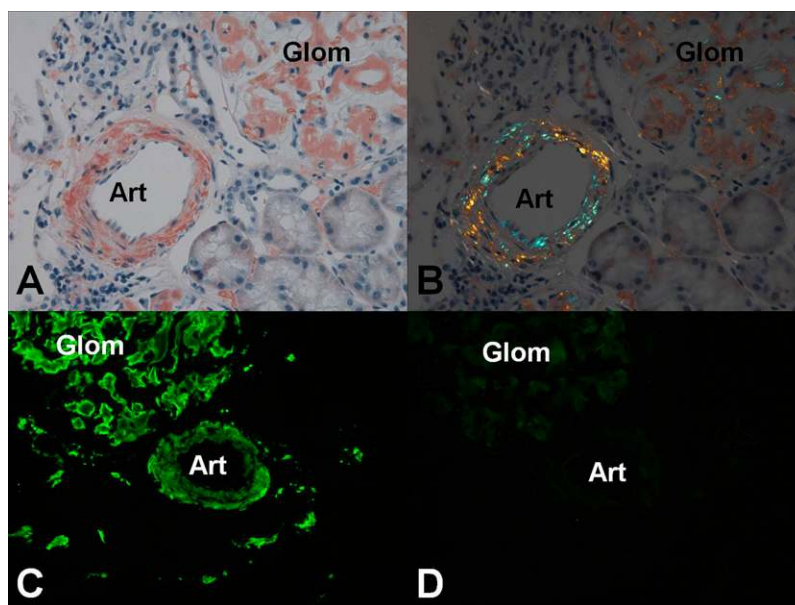


Figure 3. | Light chain amyloid (AL) with λ -light chain specificity, with involvement of glomeruli (Glom) and arteries (Art). (A) The Congo red stain reveals orange-red deposits expanding the mesangium and infiltrating the peripheral capillary walls of the Glom and the Art. (B) Amyloid deposits show characteristic apple-green birefringence when viewed under polarized light. Only those amyloid aggregates with fibrils in a particular stage of orientation show green birefringence at any given position of the polarizing filters. As one rotates the slide on the microscope stage, green birefringence of the amyloid deposits with fibrils at the various angles of orientation within the tissue will be revealed. (C) Immunofluorescence microscopy with fluoresceinated anti- λ -antibodies shows strong staining of the coarse and confluent amyloid deposits in the Glom and the wall of the Art. (D) The reactivity of the amyloid is negative for κ -light chains as revealed with the fluoresceinated anti- κ -light chain reagent.

follow-up of 8.5 years. None of the patients who developed MGUS post-transplant developed myeloma, but 2 patients developed post-transplant lymphoproliferative disease decades after transplantation (99).

For a patient with myeloma to be considered for kidney transplant, most centers require that patients be in treatment-free remission for at least 3–5 years. Occasionally, patients with MIDD or amyloid may be kidney transplant candidates after complete hematologic response is achieved, regardless of whether SCT was performed (100). There is little published information about smoldering myeloma, although most centers are reluctant to proceed. Transplantation can proceed for most patients with MGUS if the cause of renal failure is unrelated to MGUS and monoclonal Ig levels are stable and low. Pretransplant counseling should address the risk, which seems low, that immunosuppression will accelerate the premalignant condition (98). The treatment of post-transplant paraprotein disease is beyond the scope of this article, but both bortezomib and lenalidomide have been used successfully.

Conclusion

Nephrotoxic monoclonal Ig can cause kidney injury through a remarkably diverse set of mechanisms, and thus, nephrologists and other clinicians should have a low threshold to test appropriate patients for paraproteins. Wider use of kidney biopsy to identify monoclonal Ig-mediated kidney disease may be indicated, because therapeutic options for paraprotein-mediated diseases have improved. The serum FLC assay is a sensitive biomarker

useful as an adjunctive diagnostic tool for monitoring response to therapy of many paraprotein diseases. Bortezomib, lenalidomide, and thalidomide more effectively target plasma cells and their microenvironment and represent exciting therapeutic advances in the field. Autologous SCT is associated with increased risk in patients with advanced renal failure, and thus, its use is limited. Although enthusiasm has waned for the use of plasma exchange to treat paraprotein-associated AKI, new light chain-clearing dialyzers show promise in this regard combined with effective chemotherapy. Kidney transplantation in patients with plasma cell malignancy is typically contraindicated, although the rare patient who has enjoyed a prolonged remission and has stable light chain levels may qualify.

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