Chapter 7: Hematologic Disorders and Kidney Disease

Ala Abudayyeh, MD,* and Kevin Finkel, MD, FACP, FASN, FCCM*†

*Division of General Internal Medicine, Section of Nephrology, University of Texas MD Anderson Cancer Center, Houston, Texas; and †UTHealth Science Center at Houston Medical School, Department of Medicine, Division of Renal Diseases and Hypertension, Houston, Texas

MULIPLE MYELOMA

Pathogenesis
Multiple myeloma (MM) is a hematologic malignancy involving the pathologic proliferation of terminally differentiated plasma cells. It is the second most common hematologic malignancy behind non-Hodgkin lymphoma, with an annual incidence of 4–7 cases per 100,000 in the United States. Clinical symptoms are due to osteolysis of the bone, suppression of normal hematopoiesis, and the overproduction of monoclonal immunoglobulins that deposit in organ tissues. Clinical symptoms include bone pain and fractures, anemia, infections, hypercalcemia, edema, heart failure, and renal disease.

Kidney involvement and pathology
More than one-half of patients with MM initially present with varying degrees of AKI. Nearly 20% of patients present with a serum creatinine >2.0 mg/dL, and 10% of patients require dialysis on presentation (1). AKI is associated with higher mortality, but this may be reflective of patients with more advanced disease (2).

The major diseases in the spectrum of myeloma-related kidney disease include cast nephropathy, light chain deposition disease (LCDD), and AL-amyloidosis. Renal biopsy demonstrates the presence of monoclonal light chains on immunofluorescence exam, as well as characteristic ultrastructural features of deposits on electron microscopy. Less common forms of renal injury include light chain–induced Fanconi syndrome, cryoglobulinemia, proliferative glomerulonephritis, heavy chain deposition disease, and immunotactoid glomerulonephritis (Table 1) (3).

Cast nephropathy
Cast nephropathy has been diagnosed in 41% of patients with MM and renal disease (4). Excess light chains precipitate with Tamm–Horsfall protein (THP) secreted by the thick ascending limb of the loop of Henle and produce casts in the distal tubule. Decreased GFR may increase the concentration of light chains in the distal tubule and enhance the formation of casts. Therefore, hypercalcemia, volume depletion, diuretics, and nonsteroidal anti-inflammatory drugs can exacerbate renal injury.

In some cases of AKI associated with MM, cast formation is rare on renal biopsy. Instead, renal injury is attributed to the direct toxic effects of urinary free light chains (FLCs) on proximal tubule cells (5,6). After reabsorption, lysosomal degradation of FLCs can activate the NF-κB pathway leading to oxidative stress with an inflammatory response, apoptosis, and fibrosis. This lesion is characterized histologically by loss of brush border and cell vacuolization and necrosis (7).

The classic presentation is an elderly patient with unexplained renal failure, anemia, and bone pain or fractures. Proteinuria, when quantitatively measured with a 24-hour urine collection, is usually subnephrotic and primarily composed of monoclonal light chains (Bence-Jones proteins). The qualitative measurement of proteinuria using a urine test strip, which mainly detects albumin, is generally minimally reactive.

Most patients with myeloma cast nephropathy are diagnosed without kidney biopsy using serum and urine immunofixation and serum FLC analysis (see Chapter 9). When biopsied, casts are eosin positive, fractured, and waxy in appearance on light microscopy (Figure 1) (8). Multinucleated giant cells may surround casts, and an interstitial

Correspondence: Kevin W. Finkel, MD, FACP, FASN, FCCM, Division of Renal Diseases & Hypertension, UTHealth Science Center at Houston-McGovern Medical School, 6431 Fannin St., Houston, Texas 77030. Email: kevin.w.finkel@uth.tmc.edu

Copyright © 2016 by the American Society of Nephrology
inflammatory infiltrate composed of lymphocytes and monocytes may also be present. Widespread tubular atrophy and interstitial fibrosis eventually develops. Immunofluorescence staining generally demonstrates light chain restriction within the casts, although patterns may be mixed or nondiagnostic as well. Casts have a lattice-like appearance and may contain needle-shaped crystals on electron microscopy. The glomeruli and vessels appear normal, unless LCDD is concurrently present.

**Light chain deposition disease**

LCDD has been diagnosed at autopsy in 19% of patients with MM and renal disease (4). The renal manifestations are most apparent clinically, whereas light chain deposits within the heart, liver, spleen, and peripheral nervous system may remain asymptomatic. The hallmark of the disease is the development of mesangial nodules from mesangial matrix expansion secondary to the up-regulation of platelet derived growth factor-β and transforming growth factor-β. The nodules can occasionally be confused with the Kimmelstiel-Wilson lesion of diabetic nephropathy.

Clinically, patients present with proteinuria, renal insufficiency, and a nodular sclerosing glomerulopathy. Several retrospective reviews have reported on the clinical characteristics of these patients (9,10). The mean age was 58 years with no significant preference with respect to sex. Marked renal insufficiency was common on presentation, with a median serum creatinine >4 mg/dL, and renal function rapidly declined thereafter. Nephrotic range proteinuria was detected in 26%–40% of patients and correlated with the degree of glomerular involvement. Hypertension and microscopic hematuria were also present in the majority of patients.

Light chain deposition stimulates mesangial and matrix expansion leading to nodule formation. On light microscopy, mesangial nodules are more uniform in distribution and size in LCDD compared with diabetic nephropathy (Figure 2) (8). Irregular thickening and double contours of the glomerular basement membrane may also be present. Eosin-positive deposits may be seen diffusely throughout the tubular basement membranes. Immunofluorescence demonstrates a characteristic linear staining of basement membranes with monotypic

<table>
<thead>
<tr>
<th>Table 1. Kidney manifestations of multiple myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma cast nephropathy</td>
</tr>
<tr>
<td>AL amyloidosis</td>
</tr>
<tr>
<td>Light chain deposition disease</td>
</tr>
<tr>
<td>Heavy chain deposition disease</td>
</tr>
<tr>
<td>Immunotactoid glomerulopathy</td>
</tr>
<tr>
<td>Fibrillary glomerulopathy</td>
</tr>
<tr>
<td>Light chain Fanconi syndrome</td>
</tr>
<tr>
<td>Plasma cell infiltration</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
</tr>
</tbody>
</table>

---

**Figure 1. Pathology of myeloma cast nephropathy.**

(A) Large atypical casts are seen within distal tubular lumina. The casts appear hypereosinophilic with fractured texture and sharp edges. They are associated with giant cell (arrows) and mononuclear cell reaction, acute proximal tubular cell injury, and interstitial inflammation (hematoxylin and eosin, 3,200×). (B) The casts characteristically are periodic acid–Schiff (PAS) negative (3,200×). (C) Myeloma casts almost always stain for just κ or λ light chain. This figure shows bright staining of casts for κ (immunofluorescence, 3,400×). The casts were negative for λ (data not shown). (D) Occasionally, myeloma casts are composed of small rod- or needle-shaped crystals that fill the distal tubular lumina and, as shown, appear highly electron dense on electron microscopy (31,850×). Reprinted from reference 8, with permission of the Elsevier Science and Technology Journals.
light chains, which are most commonly \( \kappa \) restricted. On electron microscopy, granular-powdery deposits are distributed within the mesangium and midportion of the glomerular, tubular, and vessel wall basement membranes.

Therapy of LCDD is directed at the underlying myeloma. Cytotoxic chemotherapy followed by hematopoietic stem cell transplantation (HCT) has met with good success (11,12).

**AL amyloidosis**

AL amyloidosis occurs when pathogenic light chains unfold and deposit as insoluble fibrils extracellularly within tissues. It is found in up to 15% of patients with MM on autopsy (13,14). In 40% of patients with AL amyloidosis, the bone marrow will have >10% plasma cells, although only 10% will meet other criteria for MM (15). Amyloid fibrils may deposit within any organ, but most commonly affect the kidneys, heart, liver, and peripheral nervous system.

Patients often present with fatigue, weight loss, and nephrotic syndrome. The clinical characteristics of patients with biopsy-proven renal amyloidosis were described in a retrospective review of 84 patients at the Mayo Clinic (15). The median age at diagnosis was 61 years, and 62% were male. The median serum creatinine on presentation was 1.1 mg/dL. The majority of patients had nephrotic syndrome (86%) with a median 24-hour protein loss of 7 g/day. RRT was eventually required in 42% of patients, and median survival after starting dialysis was less than 1 year. In general, cardiac involvement occurs in nearly one-third of patients and portends a poor prognosis.

AL amyloid presents as an amorphic hyaline substance within the mesangium, glomerular basement membranes, and vessel walls. Mesangial involvement may be diffuse or nodular. Amyloid stains positive for Congo red and reveals a characteristic apple-green birefringence under polarized light. Immunofluorescence staining reveals the underlying monotypic light chain, which has a \( \lambda : \kappa \) ratio of 6:1. Electron microscopy demonstrates nonbranching randomly oriented 8- to 10-nm fibrils (Figure 3) (8). Amyloid deposits may appear as subepithelial spikes along the basement membrane similar to membranous nephropathy.

Treatment with high-dose melphalan followed by HCT increases hematologic response and overall median survival (16). Improvement in renal function highly correlates with increased survival (17).

**Treatment of cast nephropathy**

**General measures**

Volume resuscitation to assure optimum hemodynamic support and adequate urine output (~3 L/day) are of critical
importance in the initial management. Based on experimental evidence that furosemide promotes intratubular cast formation by increasing sodium delivery to the distal tubule, the use of loop diuretics should be avoided unless there is volume overload. Hypercalcemia should be aggressively treated because it can lead to renal vasoconstriction, volume depletion, and enhanced cast formation. It has been suggested that urinary alkalinization decreases cast formation by reducing the net positive charge of FLCs and the interaction with THP (18). However, there is no clinical data supporting this approach. Given the risk of causing renal calcium precipitation in the setting of hypercalcemia, urinary alkalinization cannot be recommended. Colchicine was shown to reduce cast formation through decreasing THP secretion and binding in rats, but human studies have been disappointing (19,20).

Chemotherapy and stem cell transplantation
The key to treating myeloma cast nephropathy is rapid reduction in FLC concentrations. An early decrease in FLC levels is associated with the highest rate of renal recovery. In severe AKI due to cast nephropathy, a 60% reduction in FLC levels by day 21 after diagnosis is associated with renal recovery in 80% of cases (21). Previous studies with conventional

Figure 3. Pathology of kidney AL amyloidosis. (A) There is extensive global mesangial and segmental glomerular capillary wall deposition of acellular, PAS-negative amyloid deposits. For comparison, the hyaline casts depicted are PAS positive (3,400×). (B) By definition, amyloid deposits should be Congo red positive (i.e., stain red). The figure shows global glomerular and extensive interstitial Congo red-positive amyloid. (3,200×). (C) Congophilic amyloid deposits characteristically show an apple-green birefringence when viewed under polarized light (3,200×). (D) On immunofluorescence, amyloid deposits appear smudgy and only stain for one of the light chains. The figure shows global mesangial and segmental glomerular capillary wall staining for λ (3,400×). Staining for κ was negative (not shown). (E) A distinctive feature of kidney AL amyloidosis is glomerular amyloid spicules, which result from parallel alignment of amyloid fibrils in the subepithelial space perpendicular to the glomerular basement membrane (electron microscopy, 320,000×). (F) On high magnification, amyloid fibrils appear haphazardly oriented and measure between 7 and 12 nm in diameter (electron microscopy, 326,000×). AL, immunoglobulin light chain; PAS, periodic acid–Schiff. Reprinted from reference 8, with permission of the Elsevier Science and Technology Journals.
chemotherapy protocols demonstrated that high-dose dexamethasone rapidly reduced FLCs. Newer, novel agents such as thalidomide and the proteasome inhibitor, bortezomib, also rapidly lower FLC concentrations; this has been referred to as “renoprotective chemotherapy.”

Significant improvement in renal dysfunction has been reported for MM patients treated with bortezomib-based regimens (22–24). Reversal of renal dysfunction with bortezomib may be more frequent and rapid than with other agents, based on observational analysis. No dose adjustment for renal function is necessary for bortezomib.

Thalidomide and lenalidomide are two related chemotherapeutic agents commonly used in the treatment of MM. Lenalidomide dose must be adjusted for renal dysfunction (25). Thalidomide is not dependent on renal function for clearance and does not require dose adjustment for renal function; however, it may predispose to hyperkalemia in the setting of renal failure (26,27). Regimens with thalidomide or lenalidomide have shown superior effectiveness to traditional therapy with alkylating agents in terms of reversing renal dysfunction in MM; these agents may be nearly as effective as bortezomib regimens (28). Their effects are likely due to rapid lowering of serum FLC levels.

Hematopoietic stem cell transplantation is an important and potentially curative therapy in MM; however, patient selection criteria are stringent, and significant renal dysfunction has traditionally excluded patients from transplantation. Recent studies have shown that HCT may be safe and effective in highly selected patients with renal failure (29).

**Extracorporeal removal of free light chains**

Light chains are small-molecular-weight proteins. kappa light chains usually circulate as monomers with a molecular weight of 22.5 kDa, whereas lambda light chains are typically dimeric with a molecular weight of 45 kDa (30). Because of their size, there has been a keen interest in the use of extracorporeal therapy as a means of FLC removal.

### A. Therapeutic plasma exchange (TPE):

Several small trials initially suggested that TPE was effective in rapidly lowering FLC concentrations and improving renal function. However, these studies were small, single center, and underpowered. The largest randomized controlled trial of TPE did not demonstrate any benefit in patients with cast nephropathy (31). This study assessed the benefit of five to seven TPE sessions in 104 patients (30% were dialysis requiring) with presumed cast nephropathy (not all patients had biopsy confirmation). There was no difference in the two groups with respect to the composite outcome of death, dialysis, or reduced renal function at 6 months. This lack of benefit may be related to the volume of distribution of FLCs. Based on their molecular weights, 85% of light chains are confined to the extravascular space (32). Therefore, a traditional 2-hour TPE session would be ineffective in removing significant amounts of FLCs because of the excessive rebound effect. Most of the previous trials were performed prior to the availability of bortezomib-containing regimens. In a recent study of 14 patients with presumed myeloma kidney treated with bortezomib and TPE, 12 had complete or partial renal response by 6 months; however, there were no control patients (33). Although there is still interest in TPE as a therapy for cast nephropathy, its routine use cannot be recommended based on the current evidence.

### B. High cutoff hemodialysis (HCO-HD):

More recently interest has developed for another method of extracorporeal removal of FLCs: HCO-HD. In this technique, a hemofilter with a large pore size (45 kDa) is used for extended periods of time to remove FLCs.

In the largest study of dialysis dependent renal failure secondary to MM, 67 patients were treated with HCO-HD and chemotherapy (34). Only 57% of patients had a renal biopsy, of which 87% had cast nephropathy. Most patients (85%) received combination chemotherapy with dexamethasone and either bortezomib or thalidomide. The median number of HCO-HD sessions was 11, and all patients had extended (>4 hour) treatments. Overall, 63% of the patients became dialysis independent. The factors that predicted renal recovery were the degree of FLC reduction at days 12 and 21 and the time to initiating HCO-HD. Unfortunately, this trial did not have a control group to assess the benefit of HCO-HD compared with renoprotective chemotherapy alone.

It is not known whether HCO-HD offers any additional benefit over current chemotherapeutic regimens. Randomized controlled trials proving the benefit of adding HCO-HD to patients with cast nephropathy treated with current chemotherapy will be necessary before its routine use can be recommended.

**LEUKEMIA AND LYMPHOMA**

The development of kidney disease is common in patients with lymphoma and leukemia. As with all hospitalized patients, those with lymphoma and leukemia are at risk for developing AKI from hypotension, sepsis, or administration of radiocontrast, antifungal, and antibacterial agents. With the presence of cancer, renal injury can also result from chemotherapy, immunosuppressive drugs, hematopoietic stem cell transplantation, or tumor lysis syndrome. Furthermore, patients are at risk for renal syndromes specific to the presence of lymphoma or leukemia including various forms of paraneoplastic glomerulopathies, electrolyte disorders, urinary tract obstruction, lysozymuria, leukostasis, and infiltration of renal parenchyma (Table 2). Several of these manifestations are discussed elsewhere in the Curriculum.

**Lymphomatous infiltration**

**Background**

Renal involvement in lymphoma is often clinically silent so patients can present with slowly progressive CKD attributed to other etiologies. Therefore, a high index of suspicion is needed to make a diagnosis. Patients may present with AKI, but this is rare and is most commonly seen in highly malignant and...
disseminated disease (35–38). Other presentations include proteinuria in both the nephrotic and nonnephrotic range, as well as a variety of glomerular lesions including pauci-immune crescentic glomerulonephritis (39). Patients may also present with flank pain and hematuria.

Although a variety of cancers can metastasize to the kidneys and invade the parenchyma, the most common malignancies to do so are lymphomas and leukemia. The true incidence of renal involvement is unknown because it is usually a silent disease and only occasionally causes renal impairment. Autopsy studies suggest renal involvement occurs in 90% of patients with lymphoma, whereas radiographic evidence is significantly lower.

The cause of impaired renal function from lymphomatous infiltration is poorly understood. Based on biopsy series, patients who present with AKI have predominantly bilateral interstitial infiltration of the kidneys with lymphoma cells and uniformly have increased renal size on radiographic imaging (40). These findings suggest that increased interstitial pressure results in reduced intrarenal blood flow with subsequent renal tubular injury. Patients who present with proteinuria, on the other hand, often have intraglomerular infiltration with lymphoma (40). It is not known how proteinuria develops in these cases, but the local release of permeability factors and cytokines has been suggested (41,42).

Diagnosis
The diagnosis of lymphomatous infiltration is necessarily one of exclusion because more common explanations are often present. Renal ultrasonography or computed tomography (CT) scan may reveal diffusely enlarged kidneys sometimes with multiple focal lesions (Figure 4) (43). However, many times, radiology will be unrevealing. In a study of 668 consecutive patients with lymphoproliferative disease who underwent diagnostic imaging with a CT scan, only 3% with non-Hodgkin lymphoma were found to have kidney abnormalities (44). Both diffuse enlargement and solitary lesions were detected. This discrepancy between radiologic and autopsy/histopathologic results may due to the fact that renal involvement is often indolent and only detectable in histopathologic examination (Figure 5) (43). Due to increased metabolic activity within lymphomatous deposits, positron emission tomography may be a more sensitive imaging technique (45). Although definitive diagnosis depends on renal biopsy, this procedure often is impossible because of contraindications. In such cases, the following criteria support the diagnosis of kidney disease due to lymphomatous infiltration: 1) renal enlargement without obstruction; 2) absence of other causes of kidney disease; and 3) rapid improvement of kidney function after radiotherapy or systemic chemotherapy.

Treatment
The treatment of lymphomatous involvement of the kidney is directed at the underlying malignancy. There are numerous case reports of improvement in renal function after initiation of antitumor therapy. In indolent malignant disease that is usually treated by observation alone, kidney involvement is an indication for starting systemic therapy.

Leukemic infiltration
Background
Leukemia cells can infiltrate any organ, and the kidneys are the most frequent extramedullary site of infiltration. Autopsy studies reveal that 60%–90% of patients have renal involvement (46). On biopsy, cells are usually located in the renal interstitium, although occasional glomerular lesions are noted (47). Increased interstitial pressure leads to vascular and tubular compression and subsequent tubular injury. Occasional nodular lesions are found, but this is more common with lymphoma.
Clinical Features
Leukemic infiltration of the kidneys is often an indolent and clinically silent disease. Most often it is incidentally noted after autopsy or by detection of renal enlargement on ultrasound or CT scan. Although uncommon, many cases of AKI attributable to leukemic infiltration have been described (48–50). Patients may also experience hematuria or proteinuria. Occasionally renal enlargement is accompanied by flank pain or fullness. There are also reports of patients with chronic lymphocytic leukemia who develop AKI from leukemic infiltration and are infected with polyomavirus (BK) (51). Urine from patients demonstrates viral inclusions in tubular cells (“decoy” cells) and blood is positive for BK viral DNA. Therefore, in leukemia patients with AKI considered due to leukemic infiltration, evidence for coexisting BK virus infection should be sought.

Diagnosis
The diagnosis of leukemia infiltration as a cause of AKI requires a high level of vigilance because it is often clinically silent, and leukemic patients usually have multiple alternative explanations for renal injury. A presumptive diagnosis can be made if there is no other obvious cause of AKI, bilateral renal enlargement is demonstrated radiographically, and there is prompt improvement in renal function after chemotherapy. Screening for leukemic infiltration with radiographic imaging is not revealing. In a study of 668 consecutive patients with lymphoproliferative disease who underwent diagnostic imaging with a CT scan, only 5% with leukemia were found to have kidney abnormalities (45). As with lymphoma, this discrepancy between radiologic and autopsy/histopathologic results may be due to the fact that renal involvement is often indolent and only detectable during histopathologic examination.

Treatment
Treatment is directed by the type of leukemia. Although some patients do not recover, in the majority of cases, renal function does improve as the leukemia responds to systemic treatment.

Lysozymuria
Lysozyme is a cationic protein produced by macrophages and monocytes and released in response to bacterial infection. It is freely filtered by the glomerulus and reabsorbed by the proximal tubule. In certain leukemias, clonal expansion leads to an excessive production of lysozyme and subsequent proximal tubular injury and AKI (52). Damage to the proximal tubule reduces reabsorption and can result in Fanconi syndrome and nephrotic range proteinuria. The presence of lysozymuria can be confirmed by detection of an increased γ globulin level on serum and urine protein electrophoresis with immunofixation negative for monoclonal gammopathy (53). Treatment is directed at the underlying malignancy.

Leukostasis
Patients with myeloid leukemia and exceedingly high white blood cell counts (usually in excess of 100,000 cells/mm³) can develop organ dysfunction due to intravascular aggregation of leukemic cells. The pulmonary and cerebral circulations are the most severely affected, although there are case reports of patients developing AKI (54,55). Leukemic cells occlude the peritubular and glomerular capillaries, thereby reducing GFR. Patients may be oliguric, but their renal function often improves with therapeutic leukopheresis or chemotherapy. Leukostasis is thought to result from the abnormal morphology of blast cells and the hyperviscosity of the serum. It has been described in both acute and chronic leukemia. Treatment is directed at treatment of the malignancy with appropriate chemotherapeutic regimens; in severe cases, therapeutic leukopheresis can rapidly lower cell counts.

CONCLUSION
 Numerous kidney diseases are associated with hematologic malignancies unique to this population (Tables 1 and 2). The most common cause of kidney injury in MM patients is cast nephropathy (myeloma kidney). Rapid reduction of
circulating free light chains with newer “renoprotective chemotherapy” can reverse renal failure in the majority of cases. Although infiltration of the kidneys by leukemia or lymphoma is almost universal histologically, clinical renal disease is uncommon. Given the myriad of potential kidney insults in these patients, a high index of suspicion is necessary to diagnose infiltration as the cause of renal dysfunction.

TAKE HOME POINTS

- Cast nephropathy is the most common cause of renal failure in patients with multiple myeloma.
- Rapid lowering of free light chains with “renoprotective” chemotherapy can reverse renal failure from cast nephropathy in the majority of cases.
- Based on current evidence, extracorporeal removal of free light chains with either therapeutic plasmapheresis or HCO hemodialysis cannot be recommended.
- Leukemic and lymphomatous infiltration of the kidneys is common on autopsy, although it is usually not clinically apparent.
- Enlarged kidneys on imaging and resolution of AKI after therapy with circulating free light chains with monoclonal Ig deposition disease.

REFERENCES


REVIEW QUESTIONS

1. An 80-year-old patient with multiple myeloma presents with serum uric acid of 12.0 mg/dL, serum calcium of 11.0 mg/dL, and a phosphate of 8.1 mg/dL. Serum creatinine is 4.0 mg/dL, and free λ light chains are 3,700 mg/L. Which ONE of the following therapies is contraindicated in this patient?
   a. Urinary alkalinization
   b. Intravenous saline
   c. Rasburicase
   d. Allopurinol

   Answer: a is correct. There is a lack of evidence to support the use of urinary alkalinization to decrease cast formation by reducing the net positive charge of FLCs. In addition, there is an increased risk of renal calcium precipitation with the presence of hypercalcemia.

2. A 57-year-old man with no medical history is diagnosed with chronic lymphocytic leukemia with Richter’s transformation and presents to the emergency room with creatinine of 3.61 mg/dL and white blood cell count of 20,000/mm³. The patient has undergone a renal ultrasound indicating slightly enlarged kidneys 13 cm bilaterally. On examination he was noted to have hepatosplenomegaly. Urinalysis was negative for proteinuria and hematuria. He is planned for chemotherapy pending a renal consult for his rise in creatinine. Which one of the following likely explains his renal injury?
   a. Urinary obstruction related to retroperitoneal lymphadenopathy
   b. Tumor lysis syndrome
   c. Leukemic infiltration of the kidney
   d. Membranoproliferative glomerulonephritis with C3 and monoclonal immunoglobulin deposition

   Answer: c is correct. It is likely leukemic infiltration in the setting of enlarged kidney and hepatosplenomegaly with the lack of other possible etiologies for the patient’s renal dysfunction.

3. A 74-year-old man with chronic myelomonocytic leukemia with a long-standing history of hypertension and hyperlipidemia is seen in the clinic. Peripheral blood monocyte count is >1,000/mm³, and splenomegaly is noted. His creatinine has started to rise in the last 6 months to 2.0 mg/dL from a baseline of 1.3 mg/dL. Urinalysis indicated 3+ protein and 3+ glucose. His labs included the following: white blood cells, 50,000/mm³; hemoglobin, 9.0 g/dL; platelets, 60,000/mm³; serum potassium, 3.0 mEq/L; calcium, 8.0 mg/dL; phosphorus, 1.8 mg/dL; serum glucose, 80 mg/dL. Renal ultrasound showed normal size kidneys and no hydrenephrosis. Which ONE of the following is the likely cause of this patient’s renal dysfunction?
   a. Infiltrative disease secondary to underlying leukemia
   b. Membranous glomerulopathy secondary to neoplasm
   c. Renal vein thrombosis
   d. Lysozyme-induced kidney injury

   Answer: d is correct. Lysozyme-induced kidney injury has been underdiagnosed and underrecognized. Uncontrolled production of lysozyme secondary to underlying malignancy predisposes the patient to the damage to the proximal tubule reduces reabsorption of electrolytes and can result in Fanconi syndrome and nephrotic range proteinuria. A clue to Fanconi syndrome is glycosuria with normal serum glucose level. On electron microscopy, the kidney biopsies have shown an increase in number and size of lysosomes in the proximal tubules.

4. A 56-year-old woman with a history of diabetes and hypertension (HTN) presented to the hospital with AKI, calcium of 12.0 mg/dL, hemoglobin of 10.0 g/dL, and serum albumin of 3.5 g/dL. Urinalysis revealed a specific gravity 1.015 with trace protein on dipstick examination and occasional granular cast on microscopic examination. Renal ultrasonography revealed normal-sized kidneys without hydrenephrosis. Creatinine was noted to be at 5 mg/dL, and blood urea nitrogen was 82 mg/dL with a normal baseline 6 months ago. Because there was a high suspicion for multiple myeloma, the patient had a serum free light chain (FLC) assay to determine monoclonality, and the free serum λ light chains were 1,500 mg/L. Which of the following treatments is indicated for AKI due to cast nephropathy?
   a. Chemotherapy
   b. Hemodialysis using dialyzers that have a high-molecular-weight cutoff
   c. Plasma exchange therapy
   d. All of the above

   Answer: a is correct. Based on the current evidence, performing plasma exchange and high cutoff hemodialysis to treat cast nephropathy cannot be recommended. Significant and rapid reductions in FLC concentrations using “reno-protective chemotherapy” have been shown of benefit in preserving renal function.

5. A 63-year-old man with a medical history of well-controlled diabetes and hypertension presents with a creatinine of 2.0 mg/dL, weight loss, fatigue, edema, and worsening peripheral neuropathy. He was noted to have a serum albumin level of 3.0 g/dL, and spot urine protein to creatinine ratio of 2 g, with no red blood cells in the urinalysis. Liver function studies were normal. He had a negative skeletal survey, and a bone marrow biopsy showed normal cellularity with 1% plasma cells. Serum protein electrophoresis indicated IgA λ M-protein. Due to the possibility of amyloidosis, the patient underwent a kidney biopsy which showed a mesangial area expanded by amyloid fibrils. If the patient had AL-type
amyloidosis, what is the most appropriate intervention(s) that would improve overall survival?

a. Chemotherapy to reduce monoclonal protein overproduction
b. Plasma exchange to reduce circulating FLC levels
c. High-dose melphalan followed by autologous hematopoietic stem cell transplant
d. Hemodialysis using dialyzers with high-molecular-weight cutoff
e. Chemotherapy plus extracorporeal removal of the Ig FLC

Answer: c is correct. Based on retrospective studies, patients with AL amyloidosis whom underwent stem cell transplant have been shown to have improved overall survival and improved quality of life compared with those undergoing chemotherapy alone. There is no role for plasma exchange or hemodialysis with a high cutoff filter in the treatment of amyloidosis.