Renal Disease in Hematological Malignancies

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Hematological malignancies can affect the kidneys in different ways. There may be direct invasion by the tumor cells, or the malignancy may act indirectly via immunologically mediated mechanisms. Primary renal lymphoma (PRL) without evidence of extrarenal spread has also been reported. The existence of this entity, however, has been questioned, because the kidneys do not normally contain lymphoid tissue. Renal involvement is rare in leukemias, and in some leukemias, renal dysfunction is usually found during the blastic crisis. Renal infiltration of leukemic cells has been recognized in some patients. In addition, some types of hematological neoplasia are associated with severe hypercalcemia that can lead to nephrocalcinosis. Renal involvement is one of the major manifestations of multiple myeloma (MM) and is an important cause of renal failure in the elderly. Renal failure occurs in more than 50% of MM patients, and is usually caused by the so-called myeloma kidney. Tumor lysis syndrome (TLS) is an oncological emergency characterized by a combination of metabolic disorders observed at the start of treatment of hematological malignancies. TLS may also be associated with the advancement of aggressive lymphomas and leukemias. The syndrome is frequently associated with renal dysfunction. Bone marrow transplantation for treatment of selected hematological neoplasms can be complicated by renal failure resulting from a variety of causes. Early renal injury most often results from infection and its subsequent treatment. Late renal injury after bone marrow transplantation, characterized by a syndrome similar to the hemolytic uremic syndrome, is called bone marrow transplant (BMT) nephropathy. This article reviews the clinical and pathological features of renal injury in hematological malignancies. [Hong Kong J Nephrol 2011;13(1):5–18]

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Renal Involvement in Lymphoma

Primary renal lymphoma (PRL) has been reported in the medical literature, although its occurrence is rare and controversial, the kidney being an extranodal organ [1]. The involvement is typically diffuse, bilateral (75% of cases), and symmetrical. This presentation is similar in both Hodgkin’s lymphoma and non-Hodgkin’s lymphoma, although it occurs more often in the latter. PRL without evidence of extrarenal spread has also been reported [2,3]. The existence of this entity, however, has been questioned, because the kidneys do not normally contain lymphoid tissue [3–6]. It is generally agreed that the criteria for primary extranodal renal lymphoma (PRL) should include the following [3–7]:

1. Renal failure as the initial presentation
2. Enlargement of the kidneys without obstruction or other organ or nodal involvement
3. Absence of other causes of renal failure
4. Diagnosis made by renal biopsy (Figure 1)
5. Rapid improvement of renal function after therapy

Primary renal lymphoma is a rare disease [8], accounting for only 0.7% of all extranodal lymphomas in North America [9] and 0.1% in Japan [10]. A MEDLINE search (1980–2008) revealed only 70 cases in the English-language literature, of which 28 (43%) had bilateral renal involvement [11–26].

Renal involvement in patients with diffuse lymphoma has been reported in 34–62% of cases at autopsy [6]. In one of the largest series, renal parenchymal involvement was identified in 34% of 696 autopsy cases. Of the 142 patients for whom antemortem clinical data were available, lymphomatous infiltration was recognized in only 14% prior to death. In contrast, the reported incidence of renal involvement by lymphoma has ranged between 2.7% and 6.0% based on reviews of computed tomography (CT) scans [27]. In patients with newly diagnosed non-Hodgkin’s lymphoma (NHL), radiological involvement of the genitourinary tract has been reported in as many as 10% of cases [28] (Figure 2). The generally higher frequency of lymphomatous infiltration of the kidney found in autopsy studies reflects the fact that renal involvement is often clinically silent.

Causes and Clinical Presentation

Most patients with lymphomatous infiltration of the kidney have no clinical evidence of renal involvement. When present, renal manifestations are usually nonspecific. They may include flank pain, gross hematuria, abdominal distension, and/or a palpable mass. There may also be ureteric obstruction by the tumor mass and hypertension resulting from renal ischemia due to compression by the tumor. Urine nephropathy, hypercalcemia, sepsis, and volume depletion may be the initial presentations.

Nephrotic syndrome and nephrotic range proteinuria [6,29] may be present. The pathogenesis of paraneoplastic glomerulonephritis remains uncertain, although autoimmune mechanisms and T-lymphocyte dysfunction may be important in this respect [30–32]. Immune-mediated glomerulopathies have been known to be associated with both chronic lymphocytic leukemia and lymphomas [33–36]. Membranoproliferative glomerulonephritis (MPGN) has been the most commonly reported diagnosis, although minimal change disease, focal segmental glomerulosclerosis, membranous glomerulopathy, mesangial proliferative glomerulonephritis, immunoglobulin A nephropathy and monoclonal immunoglobulin deposit diseases have been reported.

Acute renal failure (ARF) due to lymphomatous infiltration of the kidneys is uncommon and is rarely the initial manifestation of lymphoma [14,26,29]. Although
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the precise mechanisms of ARF in this situation are unknown, some interesting structure–function relations are emerging. Loss of renal function seems to be related to both the extent and type of intrarenal tumor infiltration. First, renal involvement has to be bilateral and widespread [2,4,7,11]. Second, ARF is much more strongly associated with the interstitial type than the intraglomerular type of lymphomatous infiltration.

Tornroth et al studied 55 patients with renal lymphoma diagnosed by percutaneous kidney biopsy [37]. The principal indication in 48 (87%) was ARF or nephrotic-range proteinuria. Of the 44 patients with interstitial lymphoma, 39 (88.6%) presented with ARF compared with 5 (45%) among the 11 patients with intraglomerular lymphoma. All but two cases (95%) of the 39 patients with ARF and interstitial lymphoma showed bilateral enlargement of the kidneys. In contrast, none of the patients with ARF and intraglomerular lymphoma exhibited enlarged kidneys, suggesting different mechanisms behind the appearance of ARF in these two groups [33]. Finally and most importantly, in almost all of the patients with ARF due to interstitial lymphoma, renal function, renal size, and histology rapidly improved or returned to normal in response to chemotherapy and/or radiotherapy [7,30].

Treatment

The response of renal failure associated with lymphomatous infiltration of the kidney to chemotherapy and/or radiotherapy is generally good [7,30]. In the series reported by Glicklich et al [22], 14 patients were treated with various chemotherapeutic regimens. Six of them also underwent irradiation limited to the kidneys. Three other patients were treated with kidney irradiation alone. With these various therapeutic modalities, 11 patients achieved a serum creatinine concentration of <176.8 μmol/L after therapy. Improvement of renal function was often dramatic, with serum creatinine concentrations returning to normal 1–4 weeks after institution of therapy. The decrease in kidney size to normal paralleled the improvement in renal function.

Information on the treatment of immunologically mediated glomerulopathies associated with Hodgkin’s lymphoma is usually obtained when the lymphoma is cured [39]. A review of the literature by Korzets and associates, however, yielded 14 patients in whom the course of minimal change nephropathy did not parallel that of the lymphoma [40]. The patients experienced spontaneous remission, but with minimal change in the nephropathy.

When renal replacement therapy is required for established ARF, it is generally well tolerated and complications are rare [41].

RENAL INVOLVEMENT IN LEUKEMIAS

Chronic myelocytic leukemia

The leukemic cells of chronic myelocytic leukemia (CML) are minimally invasive, and their proliferation is largely confined to hematopoietic tissues, primarily the blood, bone marrow, spleen, and liver. During the blastic phase, not only these sites, but also a number of extramedullary tissues, including the kidneys, may show leukemic infiltration [42]. Renal involvement, however, is rare with CML [43,44]. Renal dysfunction is usually found in the blastic crisis of CML. Renal infiltration by leukemic cells has been recognized during autopsy in patients who had renal dysfunction, acute tubular necrosis, and hypercalcemic nephropathy [44] (Figure 3). Few cases of CML associated with nephrotic syndrome have been described; one case of CML was complicated with minimal change nephrotic syndrome and another with proliferative glomerulonephritis [45,46].

Chronic myelomonocytic leukemia

Renal involvement is rare in chronic myelomonocytic leukemia (CMML), which might also be considered a myelodysplastic syndrome. It was found that four of 825 patients with CMML had glomerulopathy, displaying amyloidosis or extracapillary proliferation, but no infiltration of the kidneys by leukemic cells [47]. Only

Figure 3. Leukemic infiltration of the kidney (PAS, 400×).
a few cases of CMML with leukemic cell infiltration of the kidneys have been reported in the world literature [48–50], and among these cases a kidney mass was present in only two [48].

**Chronic lymphocytic leukemia**

At autopsy, up to 90% (range 63–90%) of chronic lymphocytic leukemia (CLL) cases have kidney infiltration [51–54]. Renal failure is rare, however, with only five cases having been reported [55,56]. Despite many potential causes of renal complications, it is obvious that glomerulonephritis has rarely been reported [57], with only about 42 cases recognized [57–61]. The glomerulopathy in these cases most often revealed the presence of CLL. Nephrotic syndrome developed in most patients (36/42) and was associated with renal failure in only one-third. The most common lesion reported seems to be MPGN (35.7%), followed by membranous glomerulonephritis [27,32]. The remaining findings were variable and include minimal change disease, focal segmental glomerulosclerosis, unclassified proliferative glomerulopathy, immunotactoid glomerulonephritis (Figure 4), and amyloidosis. In a review of 17 patients with renal failure and CLL, 14 patients had renal failure unrelated to their CLL. In the remaining three, one had diffuse glomerulonephritis, another had tumor lysis syndrome (TLS) after therapy, and the third had associated autoimmune hemolytic anemia with renal failure [60].

**RENAL INVOLVEMENT IN MULTIPLE MYELOMA**

Renal involvement, one of the major manifestations of multiple myeloma (MM), is an important cause of renal failure in the elderly. Renal failure occurs in more than 50% of MM patients [62,63] and is usually caused by a myeloma kidney (discussed below). The degree of renal failure is generally moderate and reversible in up to 50% of patients, particularly when it is related to such precipitating factors as hypercalcemia [64]. When renal failure is present, MM has a poor prognosis [65]. Despite its frequency and poor prognostic significance, few reports deal with the outcome of patients with MM and impaired renal function. Renal diseases associated with MM include the following:

1. Light-chain deposition disease (LCDD)
2. Myeloma kidney
3. Acute renal failure
4. Renal tubular dysfunction
5. Hypercalcemia and radiocontrast agents’ effect
6. Plasma cell infiltration (Figure 5)

**Light-chain deposition disease**

Most of the renal diseases in MM are related to overproduction of monoclonal immunoglobulin light chains. The risk for renal dysfunction increases with the amount of light chains excreted. The risk increases from 7% in patients who excrete < 0.005 g/day to 39% in those who excrete > 2 g/day [65,66]. Serum or urinary protein electrophoresis is no longer recommended, because of its limited sensitivity [67].

In contrast to amyloidosis, the deposits in approximately 80% of patients with LCDD are composed of kappa rather than lambda light chains. The deposits are also granular in nature, do not form fibrils or beta-pleated sheets, do not bind Congo red stain or thioflavin T, and are not associated with amyloid P protein. In amyloidosis the fibrils are usually derived from the variable region of the light chains, whereas in LCDD it is usually the constant region of the immunoglobulin light chain that is deposited. This may explain the far brighter...
immunofluorescent staining for light chains found in LCDD than of those found in amyloidosis.

The pathogenesis of the glomerulosclerosis in LCDD is not entirely clear, but mesangial cells from patients with LCDD produce transforming growth factor-β, which acts as an autacoid and promotes these cells to produce matrix proteins, such as type IV collagen, laminin, and fibronectin. Patients with LCDD are generally >45 years of age. Many such patients develop frank myeloma, and others clearly have a lymphoplasmacytic B cell disease such as lymphoma or Waldenström macroglobulinemia. Even in such patients without an overt plasma cell dyscrasia, it is the excessive production of abnormal monoclonal light chains that produce the disease.

As with amyloidosis, the clinical features vary with the location and extent of organ deposition of the monoclonal protein. Patients typically have cardiac, neural, hepatic, and renal involvement; but other organs such as the skin, spleen, thyroid, adrenal, and gastrointestinal tract may be involved. Patients with renal involvement usually have significant glomerular involvement, and thus present with proteinuria. The nephrotic syndrome appears in as many as one-half of these patients, often accompanied by hypertension and renal insufficiency. Some patients have greater tubulointerstitial involvement and less proteinuria, along with renal insufficiency.

The prognosis for patients with LCDD is uncertain, but appears to be better than that for amyloidosis. As with amyloidosis, death is often attributed to cardiac disease and heart failure or infectious complications [68]. In a large series of 63 patients, 65% of the patients developed myeloma [69]. Of the total 63 patients, 36 developed uremia and 37 died. Predictors of worse renal outcome included increased age and elevated serum creatinine at presentation. Predictors of worse patient survival included increased age, occurrence of frank myeloma, and extrarenal deposition of light chains. Although there are few data on dialysis and transplantation in LCDD, patients appear to fare as well as those with amyloidosis. Recurrences within the renal transplant have been reported. One trial of seven patients with LCDD who received renal transplants found recurrences in five of seven within a mean time of <1 year [70]. Thus, suppression of the abnormal paraprotein-producing cell clone is crucial prior to renal transplantation.

**Myeloma kidney**

Myeloma kidney should be suspected in older patients who present with unexplained acute or subacute renal failure, normal-sized kidneys on ultrasonography evaluation, bland urinary sediment, negative or trace-positive Albustix test, and a markedly positive sulfosalicylic acid test. Myeloma kidney results when light chains with a predilection for cast formation are delivered to the distal tubule at a critical concentration. Light chains are filtered freely, absorbed by endocytotic receptors, and catabolized in proximal tubular cells [71]. The concentration of light chains reaching the distal tubule depends on the filtrate concentration, and on the capacity of the proximal tubule cells to absorb and catabolize them. Any reduction in the glomerular filtration rate or proximal tubular damage increases distal tubular delivery [72,73]. At a critical concentration, light chains aggregate and co-precipitate with Tamm-Horsfall proteins to form casts that obstruct tubular flow [64] (Figure 6). Hemodialysis has been described as a treatment for this disorder. Other factors that affect cast formation include the following [64,72–74].

1. Distal nephron sodium, chloride, and calcium concentrations
2. Tubular flow rate
3. Presence of furosemide or radiocontrast agents [75]
4. Acidity of the urine
5. Concentration of the carbohydrate content of Tamm-Horsfall glycoprotein [64,67]

The diagnosis is confirmed by demonstrating monoclonal immunoglobulins in the serum or urine and typical intraluminal cast formation observed in a kidney biopsy specimen.

**Renal tubular dysfunction**

In the proximal tubules, there is accumulation of light chains that are resistant to proteolytic degradation. They form intracellular crystals and cause tubular dysfunction. This latter can present as Fanconi’s syndrome, with proximal tubular acidosis, aminoaciduria, hypouricemia, and phosphate wasting that leads to osteomalacia [76]. Proximal cell damage also results in decreased proximal clearance of light chains, thereby promoting cast formation distally [77].

![Figure 6. Close-up of intratubular refractile casts with surrounding syncytial giant cell reaction. Note the chronic tubulointerstitial nephritis and fibrosis, characteristic of myeloma cast nephropathy (PAS, 400×).](image-url)
About 15% of patients with MM are hypercalcemic, with a serum calcium concentration >2.75 mmol/L at diagnosis. Hypercalcemia contributes to renal failure by causing vasoconstriction, inducing hypovolemia through nephrogenic diabetes insipidus, and intratubular calcium deposition [78].

In patients with MM, the incidence of ARF caused by the use of radiocontrast agents ranges from 0.6% to 1.25% [79]. Contrast medium is thought to bind to intratubular proteins, causing them to precipitate and obstruct tubular flow. To prevent contrast nephrotoxicity, patients with MM must be well hydrated, and use of N-acetylcysteine should be considered [79,80].

Plasma cell infiltration of the kidney is seen in MM but is rarely severe enough to cause renal dysfunction [81].

**Therapy of MM**

Although some patients with MM do not require treatment, oncology referral is recommended in all cases (Figure 7). Patients with smoldering (asymptomatic) MM should not undergo treatment, as current research shows that starting active therapy for people with no symptoms does not improve survival [82]. Careful follow-up, however, is recommended. A systematic review by He et al demonstrated a reduction in vertebral compression and time to progression with early systemic treatment for asymptomatic patients, but their study also revealed an increase in acute leukemia in the early-treatment group [83]. An important study by Dimopoulos and associates that evaluated the risk of disease progression in asymptomatic subjects with MM showed that the patients did not benefit from early treatment, and delayed treatment did not affect the efficacy of therapy in terms of survival [84].

**Chemotherapy and bone marrow transplantation**

Initial treatment of MM depends on the patient’s age and co-morbidities. In recent years, high-dose chemotherapy with hematopoietic stem cell transplantation has become the preferred treatment for patients under the age of 65 years. Prior to stem cell transplantation, these patients are given an initial course of induction chemotherapy. The most common induction regimens used today are thalidomide–dexamethasone, bortezomib-based regimens, and lenalidomide–dexamethasone [85].

Autologous stem cell transplantation—transplantation of a patient’s own stem cells after chemotherapy—is the most common type of stem cell transplantation for MM. It is not curative, but does prolong overall survival. Allogeneic stem cell transplantation—transplantation of a healthy person’s stem cells into the affected patient—has the potential for cure, but is available to only a small percentage of patients [86]. Furthermore, there is a 5%–10% treatment-associated mortality rate.

Patients over age 65 years and those with significant concurrent illness often cannot tolerate stem cell transplantation. For these patients, the standard of care has been chemotherapy with melphalan and prednisone. Recent studies among this population [87,88] suggest improved outcomes with new chemotherapy regimens. Treatment with bortezomib, melphalan, and prednisone produced an estimated overall survival of 83% at 30 months [87]; lenalidomide plus low-dose dexamethasone produced 82% survival at 2 years; and melphalan, prednisone, and lenalidomide produced 90% survival at 2 years. In other trials, lenalidomide plus high-dose dexamethasone proved to be superior to high-dose dexamethasone alone as treatment for newly diagnosed MM [88–90]. One study [91] looked at melphalan and prednisone plus thalidomide versus melphalan and prednisone

![Figure 7. Approach to the treatment of newly diagnosed multiple myeloma. ET=eligible for bone marrow transplantation; NET=not eligible for bone marrow transplantation; LD=lenalidomide; TD=thalidomide.](image-url)
versus VAD (vincristine, adriamycin, dexamethasone) induction, followed by high-dose melphalan and autologous stem cell transplantation in patients 65–75 years of age. The complete response rate was significantly better in the melphalan and prednisone plus thalidomide arm than in the melphalan and prednisone arm [91]. Melphalan and prednisone plus thalidomide is now recommended as first-line treatment. Melphalan and prednisone plus lenalidomide have also shown promise [91]. Other studies confirmed the superiority of adding thalidomide for prolonging survival in elderly, newly diagnosed patients with MM. Similar results were obtained with bortezomib [92–94].

Bisphosphonates and erythropoietin

Adjunctive therapy for MM includes radiation therapy to target areas of pain or an impending or existing pathological fracture. Bisphosphonates have a role in the secondary prevention of bony complications in MM, including hypercalcemia, pathological fracture, and spinal cord compression [95–98].

The American Society of Clinical Oncology (ASCO) issued a clinical practice guideline governing bisphosphonate therapy for MM patients who have lytic destruction of bone or a compression fracture of the spine from osteopenia [98]. ASCO recommends intravenous pamidronate, 90 mg delivered over at least 2 hours, or zoledronic acid, 4 mg delivered over at least 15 minutes every 3–4 weeks. Because the risk for osteonecrosis of the jaw is 9.5-fold greater with zoledronic acid than with pamidronate, patients may prefer pamidronate [97].

Zoledronic acid doses should be reduced in patients with preexisting mild to moderate renal impairment (estimated creatinine clearance 30–60 mL/min); the drug is not recommended for use in patients with severe renal impairment [96]. All patients receiving pamidronate or zoledronic acid therapy should be screened every 3–6 months for albuminuria. If unexplained albuminuria (>500 mg/24 hr) is found, ASCO recommends discontinuing the drug until the renal problems resolve [96,98].

Erythropoietin may ameliorate anemia resulting from either MM alone or from chemotherapy. It has been shown to improve quality of life [99,100]. In addition, one study demonstrated a survival advantage with the use of erythropoietin in patients with MM [101].

Treatment of renal complications

Renal failure in MM patients can be acute (reversible) or chronic (irreversible). ARF typically resolves when the calcium and paraprotein levels are brought under control. Treatment of chronic renal failure (CRF) depends on the type of renal failure and may involve dialysis. Hydration (to maintain a urine output of >3 L/day), management of hypercalcemia, and avoidance of nephrotoxins (e.g. intravenous contrast medium, antibiotics) are also key factors. Ludwig et al suggested that bortezomib-based therapy can restore renal function in MM patients with renal failure [102]. Bortezomib, however, has many adverse effects, including neuropathy, hypotension, and thrombocytopenia. Varicella zoster virus activation occurs in 10–60% of patients with MM treated with bortezomib. Antiviral prophylaxis (e.g. acyclovir 400 mg daily) has been found effective for preventing this activation [103]. In addition, the exact timing of bortezomib administration in the treatment plan of MM patients is still evolving through ongoing research.

In an attempt to improve outcomes, direct removal of free light chains (FLCs) by plasma exchange has been studied [104–108]. A randomized controlled trial of 97 MM patients with ARF, however, failed to demonstrate any clinical benefit [107]. In that study, renal biopsies were not reported, serum FLC concentrations were not quantified, and most of the patients were not dialysis-dependent at presentation. Furthermore, plasma exchange does not result in sustained reductions in serum FLC concentrations, as demonstrated by both clinical observations [107] and mathematical modeling [109]. Leung et al demonstrated that patients with cast nephropathy are more likely to recover renal function if a 50% decrease in serum FLC concentrations is achieved [110]. However, they failed to demonstrate any relation between the amount of plasma exchange and the degree of reduction in FLC concentrations or the renal response.

To provide an alternative approach to plasma exchange for direct FLC removal, Hutchison and associates [111] assessed the utility of extended hemodialysis (HD), using a high-cutoff (HCO) dialyzer. Detailed mathematical modeling showed HCO-HD to be far more effective than plasma exchange for FLC removal. In their pilot study, induction chemotherapy in combination with extended treatment by HCO-HD resulted in sustained reductions in serum FLC concentrations in most of their patients. These patients subsequently became independent of dialysis. The authors concluded that with dialysis-dependent ARF secondary to myeloma kidney, patients who undergo uninterrupted chemotherapy and extended HCO-HD are more likely to sustain reductions in serum FLC concentrations and to recover independent renal function. Resolution of cast nephropathy by HCO-HD has been also supported by the report of Basnayake and colleagues [112].

Tumor Lysis Syndrome and the Kidney

Tumor lysis syndrome (TLS) is an oncological emergency characterized by a combination of metabolic disorders observed at the start of cancer treatment, or with the advancement of an aggressive malignancy. The syndrome is frequently associated with renal dysfunction, cardiac and skeletal manifestations, and gastrointestinal sequelae. TLS occurs with malignancies that are highly
proliferative and have large tumor burdens, such as lymphomas and leukemias [113–118]. Metabolic abnormalities include hyperphosphatemia, hyperkalemia, hyperuricemia, and/or hypocalcemia. Renal dysfunction usually accompanies TLS. Often, hyperuricemia (generally, a uric acid level ≥ 476 μmol/L) is a hallmark finding of TLS [113,116–118]. Adverse sequelae of TLS can precipitate life-threatening events, and if left untreated can lead to death.

The prevalence of TLS varies among the hematological malignancies, and treatment-sensitive tumors, such as acute lymphocytic leukemia and Burkitt’s lymphoma, are associated with higher frequencies of TLS [114,115]. In studies on patients with intermediate- or high-grade NHL, abnormal laboratory results were more dramatic than the symptomatic clinical syndrome itself [113–115]. Silent laboratory evidence of TLS was seen in 70% of children undergoing induction chemotherapy, whereas significant symptomatic TLS occurred in only 3% [117]. As advances are made in the treatment of hematological malignancies, the incidence of TLS may increase [119].

**Metabolic abnormalities and consequences**

Hyperkalemia may appear 6–72 hours after the initiation of chemotherapy [113–115] and is the most serious manifestation of TLS. Hyperkalemia must be corrected rapidly before potentially lethal ventricular arrhythmias occur.

Hyperphosphatemia usually develops 24–48 hours following initiation of chemotherapy [113–115,119]. Calcium phosphate can precipitate when the solubility product of calcium and phosphate is exceeded, possibly leading to hypocalcemia. Muscle cramps, tetany, cardiac arrhythmias, and seizures can result.

In patients with myeloproliferative diseases or hematopoietic malignancies, nucleic acids are catabolized as a result of increased turnover of malignant cell populations. This results in an increase in purine metabolism, leading to hyperuricemia [118], which is usually apparent 48–72 hours following initiation of treatment [113,114]. As a consequence of the hyperuricemia, renal insufficiency develops when urine becomes supersaturated with uric acid, and crystals of uric acid form in the renal tubules and distal collecting system [115,120]. Despite management of metabolic abnormalities to reduce the risk of renal failure, 25% of children with advanced-stage Burkitt’s lymphoma and B-cell acute lymphoblastic leukemia still experience ARF secondary to severe hyperuricemia at the onset of chemotherapy [111,117]. In patients with TLS, the high uric acid load and hyperphosphatemia may overwhelm the ability of the nephron to autoregulate. The resultant decline in tubular flow may precipitate uric acid, leading to uric acid nephropathy. A urine uric acid/creatinine ratio of ≥ 1.0 is suggestive of uric acid nephropathy, whereas a ratio of < 0.60–0.75 suggests renal failure of another etiology [113,114,121].

Patients with hematological malignancies are at increased risk of ARF from etiologies other than TLS. Acute tubular necrosis should always be considered in the differential diagnosis. Patients at risk of TLS are also susceptible to other forms of renal injury, owing to prolonged periods of hypotension or to exposure to nephrotoxic agents, such as antimicrobial agents, chemotherapy, or contrast media. In addition to the risk of nephrocalcinosis, damaged tubule cells may slough off into the lumens, resulting in obstructed nephron flow. These events further amplify the injury resulting from TLS-associated ARF [113,121]. Pathology studies demonstrate deposits of uric acid in the distal renal tubular lumens, causing intrarenal hydrenephrosis. Uric acid crystals also can be seen in tubular epithelial cells and the medullary microcirculation [113,114].

**Prevention and treatment**

The principles of management should address three critical areas: hydration, metabolic abnormalities, and supportive treatment of renal failure.

**Hydration**

Aggressive intravenous hydration not only helps correct electrolyte disturbances by diluting extracellular fluid, it increases intravascular volume. Increased volume enhances renal tubular flow, the glomerular filtration rate, and urine volume. Ideally, intravenous hydration with normal saline should begin 2 days prior to, and continue 2–3 days after, chemotherapy in high-risk patients [113–115,122].

**Control of electrolyte disturbances**

- **Hyperkalemia:** The major goals when treating acute hyperkalemia are cardiac membrane stabilization, intracellular shift of potassium, and reduction of the total potassium load. Acute treatment modalities include intravenous infusion of glucose plus insulin to promote redistribution of potassium from the extracellular space to the intracellular space, and intravenous calcium gluconate as cardioprotection for potassium levels > 6.5 mmol/L or for those with electrocardiographic alterations. Intravenous hydration with alkaline fluid can also increase intracellular uptake of potassium. Potassium-wasting diuretics must be employed with caution, as they may worsen renal precipitation in the volume-contracted patient [122]. Long-term therapy such as oral potassium-exchange resins should be given immediately, because of the transient effectiveness of acute treatment modalities. If these measures fail to control serum potassium, hemodialysis should be initiated promptly. Dialysis prevents irreversible renal failure and other life-threatening complications. Indications for dialysis include persistent hyperkalemia or hyperphosphatemia.
Bone marrow transplantation (BMT) is an effective treatment for a variety of hematological neoplasms. However, despite treatment, volume overload, uremia, symptomatic hypocalemia, and hyperuricemia [122]. Hemodialysis is preferred over peritoneal dialysis or continuous venovenous hemofiltration (CVVH), because of better phosphate, potassium, and uric acid clearance rates [122,123]. CVVH has been used and is effective in correcting electrolyte abnormalities and fluid overload [121–124]. Because hyperkalemia can recur after dialysis is initiated and because of the high phosphate burden in some patients with TLS, electrolyte levels must be monitored frequently and dialysis repeated as needed.

- **Hyperphosphatemia/hypocalcemia:** Hyperphosphatemia is managed with oral phosphate binders and the same intravenous solutions of glucose plus insulin used for control of hyperkalemia. Hyperphosphatemia may lead to hypocalcemia, which usually resolves as phosphate levels are corrected. In some cases, depressed serum 1,25-dihydroxycholecalciferol levels contribute to hypocalcemia. Administration of calcitriol may correct the calcium levels [125]. To avoid metastatic calcifications, however, such therapy should not be undertaken until serum phosphate levels have normalized.

- **Hyperuricemia:** The standard treatment for hyperuricemia consists of allopurinol, urinary alkalinization, and hydration. Allopurinol blocks uric acid formation by inhibiting the enzyme xanthine oxidase [126,127]. Patients at high risk for TLS still need to excrete preexisting uric acid, which is not affected by allopurinol. Consequently, a drug that has rapid, highly potent uricolytic properties, reduces metabolic morbidity, and can be conveniently integrated with the initiation of a chemotherapy regimen would be helpful in this situation. Rasburicase is a recombinant form of urate oxidase enzyme available for this purpose [128–131]. A study in healthy adult male volunteers established that single daily intravenous doses of rasburicase were well tolerated and led to a dramatic decrease in plasma uric acid levels [128]. A multicenter Phase II trial of rasburicase in pediatric patients with leukemia and lymphoma (n = 131) demonstrated that 100% of patients achieved uric acid control with rasburicase at a dose of 0.2 mg/kg, despite concomitant intensive chemotherapy [129]. Goldman et al. presented a report demonstrating the efficacy of rasburicase compared with allopurinol in reducing uric acid levels in children with leukemia or lymphoma at high risk for developing TLS [132].

**RENAL INVOLVEMENT IN BONE MARROW TRANSPLANTATION**

Bone marrow transplantation (BMT) is an effective treatment for a variety of hematological neoplasms. However, side effects in the kidneys have been frequently reported. Early during the course of BMT, renal complications often result from infection and its treatment. Acute tubular necrosis may arise as a direct consequence of sepsis, hypotension, or therapy with a variety of nephrotoxic drugs [133]. A frequent, life-threatening allo-BMT complication is ARF requiring dialysis. Some degree of acute renal insufficiency developed in ≥40% of allo-BMT patients [134]. Patients are also at higher risk of BMT nephropathy, a disorder similar to hemolytic uremic syndrome (HUS), which usually occurs during the chronic phase after transplantation [134–136]. Allergic interstitial nephritis may evolve from antibiotics or allopurinol. Cyclosporine, used early after transplantation to prevent graft-versus-host-disease (GVHD), is another agent capable of producing acute or chronic nephrotoxicity [136]. The etiology of BMT-associated renal failure is thus multifactorial. Risk factors, in addition to cyclosporine, include veno-occlusive disease, age, aminoglycosides, combined use of amphotericin B and cyclosporine, amphotericin B alone, elevated pre-transplant serum creatinine, radiation dose, and GVHD [137–143].

**BMT nephropathy**

The term BMT nephropathy was used by Cohen et al to describe this characteristic renal syndrome [138]. An incidence ranging from 0.6% to 13.0% has been noted in adult patients undergoing BMT [138–140]. Children appear to develop the lesion more commonly, with a reported incidence as high as 45% [141]. The pathological features of BMT nephropathy are distinct [144–148]. It is characterized by prominent mesangiolysis and focal aneurysmal capillary dilatation. The endothelial cells are swollen, and the subendothelial space is considerably widened. The glomerular basement membrane appears duplicated. Focal fibrin thrombi may be identified in the capillary loops (Figure 8). Electron microscopy reveals endothelial injury. The subendothelial space is greatly expanded and filled with loose, amorphous, granular material consistent with fibrin and newly laid basement membrane material (Figure 9).

Two clinical patterns of BMT nephropathy may be observed.

- **Acute BMT nephropathy** characteristically presents with an HUS-like picture. Features include microangiopathic hemolytic anemia, thrombocytopenia, elevated lactate dehydrogenase, and severe hypertension with or without congestive heart failure. Renal manifestations include a rapid decline in renal function, significant proteinuria, and microscopic hematuria with or without cellular casts [135,136].

- **Chronic BMT nephropathy** has features that differ from those of the acute syndrome. Hypertension is only mild to moderate. Hemolytic anemia is typically less severe and may be transient [138,139].
All patients, however, tend to have anemia that is out of proportion to the level of azotemia [138]. A slower decline in renal function, as gauged by the slope of the reciprocal of serum creatinine versus time is characteristic [138–140]. In most of these patients, a biphasic pattern of the deterioration of renal function is seen. During the first 12–24 months after BMT, renal function deteriorates steadily. After this phase, it appears to stabilize over time, but with no recovery [141–143]. Proteinuria, usually >1 g per 24 hours, and microscopic hematuria with or without casts are also present. Infection has been noted to precipitate acute exacerbations of this syndrome [143,144,146].

**Treatment of BMT nephropathy**

Once established, BMT nephropathy is largely unresponsive to all treatment except supportive measures. Because the acute form of BMT nephropathy has some features of HUS, plasmapheresis has been utilized in its treatment. However, the results are generally disappointing [149]. Reduction of the cyclosporine dose or even discontinuation of the drug has been tried in patients who develop BMT nephropathy [150]. The vascular toxicity of cyclosporine has been thought to play a role in the progression of the disease, although it is unlikely to be the causative agent. There is no definitive proof that discontinuing the drug is beneficial.

Radiation nephropathy can be avoided if the shielded area covers one-third of the renal volume [151–153]. Renal shielding during post-BMT irradiation is now common, but its protective effect is not fully recognized. Lawton et al reported that the rate of BMT-associated HUS is reduced from 26% to 6% with a decreased radiation dose [151,154].

**Strategies to control the incidence and severity of acute GVHD and veno-occlusive disease**

Supportive therapy is important and includes blood pressure control to diastolic values of <90 mmHg, transfusion of blood products, diuretics, and recombinant erythropoietin for anemia. These measures appear to slow the progression of renal insufficiency [142]. A small number of patients progress to end-stage renal disease and require maintenance hemodialysis [142]. Transplantation of a kidney from the bone marrow donor to the patient with BMT nephropathy and end-stage renal disease is an interesting possibility. Because the donor marrow presumably has reconstituted the patient’s immune system, the kidney theoretically would be well tolerated. Successful kidney transplantation using this technique has been reported [155,156].

**SUMMARY**

Malignant lymphomas can affect the kidneys in many ways. They may precipitate ARF via ureteral or reno-vascular obstruction or by direct renal parenchymal infiltration. They may also insult renal function via paraneoplastic mechanisms. Renal leukemic infiltration is usually associated with extramedullary leukemic involvement elsewhere. The presence of renal leukemic infiltration does not commonly cause renal dysfunction, although a few cases of renal failure have been reported.

It is necessary to look for potential renal impairment in MM patients. Cast nephropathy with renal failure can be aggravated by volume depletion, hypercalcemia, infection, administration of nephrotoxic agents, and proteinuria. Rapid reduction or removal of light chains by
aggressive chemotherapy, extended HCO-HD, and/or plasmapheresis may prevent irreversible renal failure.

Tumor lysis syndrome is frequently associated with hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, which may lead to serious complications, including acute renal injury.

Bone marrow transplantation is a major therapeutic modality for malignant and hematological disorders. The procedure, however, is associated with high morbidity and mortality rates, including acute kidney injury and BMT nephropathy. Recognizing the factors that may cause or aggravate these problems, such as nephrotoxic drugs, irradiation, and GVHD, may save the kidneys from serious damage.

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