Kidney Involvement in Leukemia and Lymphoma

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Leukemia and lymphoma are hematologic malignancies that can affect any age group. Disease can be aggressive or indolent, often with multiorgan system involvement. Kidney involvement in leukemia and lymphoma can be quite extensive. Acute kidney injury (AKI) is quite prevalent in these patients, with prerenal and acute tubular necrosis being the most common etiologies. However other prerenal, intrinsic, and obstructive etiologies are possible. AKI can be a direct effect of the malignancy, a complication of the malignancy, or the consequence or side effect of chemotherapy. Nephrotic syndrome and glomerulonephritis, often presenting without overt kidney failure, have also been seen in all forms of leukemia and lymphoma. Lastly, the direct effects of the malignancy and complications from the tumor often result in numerous electrolyte disturbances and acid-base disorders, with life-threatening consequences if left untreated.

Key Words: Lymphoma, Leukemia, Acute kidney injury, Nephrotic syndrome, Glomerulonephritis

Introduction

Leukemia and lymphoma are hematologic malignancies derived from bone marrow or lymphoid cells, respectively. Although uncommon, more patients are living longer lives with disease or in remission. Leukemia and lymphoma can involve other organs, including the kidney. Kidney manifestations encompass a broad spectrum of disease: prerenal acute kidney injury (AKI), acute tubular necrosis (ATN), renovascular disease, parenchymal infiltration, obstruction, glomerulopathies, and electrolyte and acid-base abnormalities. Kidney injury may result from the underlying malignancy itself or as a secondary complication of therapy. It may delay treatment, which in turn can affect prognosis and mortality. The overlap of these cancers and the kidney will be discussed.

AKI in Lymphoma and Leukemia

AKI in patients with lymphoma and leukemia is common. A study looking at 349 patients with hematologic malignancy admitted to the intensive care unit demonstrated some form of AKI in 149 patients (43%). Of those patients with AKI, 29% required renal replacement therapy with a mortality rate of 72%.[1] In a study of 1411 intensive care unit patients, the diagnosis of lymphoma or leukemia had the greatest risk for AKI (odds ratio 2.23) relative to other factors, including infection, cirrhosis, and cardiovascular disease. It also had the greatest risk of death (odds ratio 2.31) in all AKI patients.[2] The approach to a patient presenting with AKI in the setting of lymphoma or leukemia must assess prerenal, intrarenal, and postrenal etiologies (Table 1).

Prerenal AKI

Prerenal AKI is the most common kidney injury in lymphoma or leukemia. Volume depletion from poor oral fluid intake (78%), anorexia (64%), early satiety (50%), emesis (23%), and diarrhea (16%) contribute to prerenal AKI.[3] Insensible losses and decreased effective circulating volume can be exacerbated by comorbid conditions such as cirrhosis or heart failure. Medications that affect kidney afferent and efferent tone, including renin-angiotensin blockade, nonsteroidal anti-inflammatory medications, and diuretics used for hypertension, may also contribute. Prerenal AKI is often suspected based on clinical course and history and supported with physical exam and laboratory data. The urine sediment is usually bland, with occasional hyaline casts or cellular elements. Treatment is supportive, with crystalloid expansion and removal of exacerbating factors.

Postrenal AKI

In patients with lymphoma or leukemia, obstruction may result from direct compression or encasement of ureteral outflow by tumor or lymph nodes, retroperitoneal fibrosis, or nephrolithiasis from tumor lysis syndrome.[4,5] Anuric kidney failure should raise the concern for bilateral obstruction, but often with obstructive AKI, urine output is stable. Hematuria and pyuria may be present, and kidney ultrasound should demonstrate hydronephrosis unless collecting system dilatation is prevented by fibrosis. Immediate decompression with nephrostomy tubes may prevent permanent injury.

Intrarenal AKI

Intrarenal causes of kidney injury in hematologic malignancy can be grouped into ischemic and nonischemic ATN, tubulointerstitial disorders, renovascular disorders, and glomerulopathies. Hemodynamically mediated injury (for example, severe volume depletion, heart failure, or sepsis) and drug-induced injury are common

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with hematologic malignancy. However, it is critical to separate these processes from kidney injury directly caused by hematological malignancy because therapy and hopes of improvement of kidney function depend on treatment of the underlying disease. In subsequent sections, we will focus on intrarenal AKI specific to hematologic malignancy.

Diagnosis of intrarenal AKI often relies on ancillary tests. Diagnostic imaging, which is involved in staging of hematologic malignancy, may be the first insight into kidney involvement. Computed tomography scan may show renomegaly with diffuse bilateral enlargement pointing to kidney infiltration (Fig 1). Examination of the urine sediment is critical, is often underutilized, and may replace costly laboratory tests. Renal tubular epithelial cells and casts point toward ATN. White cells and white cell casts suggest an underlying malignant infiltration, interstitial nephritis, or severe pyelonephritis. Dysmorphic red cells and red cell casts indicate a glomerulopathy. Biopsy remains the gold standard in diagnosis and can help delineate the aforementioned causes of intrarenal injury. Light microscopy with hematoxylin and eosin staining can elucidate glomerular, tubulointerstitial, or vascular disorders. Immunofluorescence and electron microscopy can provide additional information on glomerular involvement. However, biopsy may be difficult in a patient with hematologic malignancy because of thrombocytopenia and uremia, which increase bleeding risk.

CLINICAL SUMMARY

- Acute kidney injury (AKI) is quite common in patients with hematologic malignancies, contributing to increased morbidity and mortality.
- Diagnosing AKI in patients with hematologic malignancy is similar to other forms of AKI, but certain disease-specific entities (such as lysozyme-induce kidney injury, tumor lysis syndrome, direct kidney infiltration, and hematologic-mediated obstruction) are not uncommon occurrences.
- Acute and chronic leukemias and Hodgkin's and non-Hodgkin's lymphomas are associated with nephrotic syndrome and glomerulonephritis.
- Disorders of potassium, magnesium, phosphate, sodium, and calcium as well as type B lactic acidosis are prevalent in patients with hematologic malignancies.

Acute Tubular Necrosis

ATN is the most common cause of intrinsic AKI in lymphoma and leukemia. In a single-center study, of all patients with hematologic malignancy with AKI, 83% had ATN, with 96% of those patients experiencing sepsis and 88% receiving nephrotoxic medications.[6] The disease-specific etiologies of ATN are discussed below.

Lysozyme-induced tubular necrosis occurs in patients with hematologic malignancies.[7] Lysozyme is a cationic enzyme stored in macrophages and monocytes that may be released to lyse bacterial cell walls. In certain leukemias, clonal expansion increases lysozyme production. Lysozyme is freely filtered by the glomerulus and then reabsorbed by the proximal tubule cells. At high concentrations, as seen in leukemia, lysozyme induces direct tubular damage causing kaliuresis and proteinuria. The high concentrations of urinary lysozyme, exacerbated by proximal tubule injury, which prevents reabsorption, can present as nephritic-range proteinuria leading to a pseudonephrotic syndrome.[7] When suspected, the protein can be measured with serum and urine protein electrophoresis revealing increased γ globulin levels; this can be confirmed with immunofixation to exclude monoclonal paraproteins.[8] Treatment of the underlying malignancy will decrease lysozyme and improve AKI.

Tumor lysis syndrome results from the release of intracellular potassium, phosphate, and nucleic acids from rapidly growing cancer cells. This can be spontaneous or the direct effect of chemotherapy. Purine nucleic acids are converted to xanthine and then to uric acid by xanthine oxidase.[9] At high levels uric acid crystals can precipitate in renal tubules, leading to direct tubular injury. In addition, uric acid is a vasoconstrictor that may exacerbate renal tubular damage, recruit proinflammatory cytokines to the renal interstitium, and delay recovery.[10] Prevention of tumor lysis syndrome with adequate hydration or direct xanthine oxidase inhibitors such as allopurinol or febuxostat is ideal. If uric acid levels increase despite these efforts, rasburicase, a recombinant urate oxidase that converts uric acid to allantoin, can be used.[9]

AKI From Kidney Infiltration

The kidney is the most common extrareticular and extrahematopoietic organ infiltrated by leukemia and lymphoma, with infiltration seen in 60% to 90% of patients with hematologic malignancy.[11] Kidney dysfunction varies from asymptomatic to severe and requiring renal replacement therapy. The rate of infiltration parallels the stage and grade of disease. In a series of 1200 autopsy cases, the prevalence of kidney infiltration was 63% in chronic lymphocytic leukemia (CLL), 54% in acute lymphoblastic leukemia (ALL), 34% in chronic myeloid leukemia (CML), and 33% in acute myeloid leukemia (AML).[12] In a separate autopsy study in 700 patients with lymphoma, kidney infiltration was present in 34% of patients with Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL).[11]

Kidney failure primarily due to lymphomatous or leukemic infiltration is rare. AKI from infiltration is seen in only 1% of cases of all patients with acute leukemias and even less commonly in chronic leukemia and lymphomas.[13] Symptoms and signs that may be associated