Renal Dysfunction in Leukemia and Lymphoma

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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.

AKI in Lymphoma and Leukemia

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. The urine sediment is usually bland, with occasional hyaline casts or cellular elements. Treatment is supportive, with crystalloid expansion and removal of exacerbating factors.

Post renal 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. 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.

Intra renal AKI

Intrarenal causes of kidney injury in hematologic malignancy can be grouped into ischemic and nonischemic ATN, tubulointerstitial disorders, renovascular disorders, and glomerulopathies. 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. Examination of the urine sediment is critical, is often underutilized.

- 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.

Acute Tubular Necrosis

ATN is the most common cause of intrinsic AKI in lymphoma and leukemia.

Lysozyme-induced tubular necrosis occurs in patients with hematologic malignancies. Lysozyme is freely filtered by the glomerulus and then reabsorbed by the proximal tubule cells. It can present as nephritic-range proteinuria leading to a pseudonephrotic syndrome. When suspected, the protein can be measured with serum and urine protein electrophoresis revealing increased g globulin levels; this can be confirmed with immunofixation to exclude monoclonal paraproteins. 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. 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. Prevention of tumor lysis syndrome with adequate hydration or direct xanthine oxidase inhibitors such as allopurinol or febuxostat is ideal.

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. Kidney dysfunction varies from asymptomatic to severe and requiring renal replacement therapy. The rate of infiltration parallels the stage and grade of disease. The prevalence of kidney infiltration at the time of autopsy 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 patients with lymphoma, kidney infiltration was present in 34% of patients with Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL). However clinical 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. Infiltration is bilateral in nature, and kidney enlargement is usually uniform. Kidney biopsy is often useful in these patients to know the extent and location of infiltration which tends to influence prognosis. Improvement of kidney function depends on treatment of the underlying disease. Regression and improvement in kidney function should be prompt (ie, occurring sometime within 2-3 days of therapy).

Glomerular Disease with Hematologic Malignancies

Acute Lymphoblastic Leukemia

Proteinuria in ALL is usually pseudonephrotic syndrome, associated with lysozymuria. However, in children, nephrotic syndrome may portend a future diagnosis of ALL. It is unclear whether nephrotic syndrome is an early manifestation of ALL or whether immunosuppressive treatment causes proliferation of an abnormal WBC clone. MCD has been diagnosed during induction chemotherapy for known ALL, suggesting that an immune cell dysregulation is common between the 2 disease entities.

Acute Myeloid Leukemia

Proteinuria in AML can also be related to lysozymuria. Biopsies from patients with nephritic-range proteinuria, in the absence of lysozymuria, have identified FSGS, MCD, mesangioproliferative glomerulonephritis, and membranoproliferative glomerulonephritis (MPGN). Studies of subclinical immune complexes in kidneys of patients with AML have identified antigens related to oncornaviruses, suggesting a possible viral-related etiology to the immune-mediated glomerular lesions.

Chronic Lymphoid Leukemia

CLL infiltrates the kidney interstitium of approximately 90% of patients at the time of autopsy; however, clinical kidney disease is uncommon. Although many glomerular lesions have been reported, MPGN is the most common, followed by membranous. CLL is characterized by aberrant proliferation of a monoclonal B-cell clone, and it is the deposition of the monoclonal immune complexes in the glomerulus that is thought to be pathologic. CLL is also associated with various autoimmune disorders, and this association may predispose patients to cryoglobulin production and subsequent immune complex deposition.

Chronic Myeloid Leukemia

Glomerular disease associated with CML is rare. Cases of MPGN, membranous nephropathy, and MCD associated with CML have been reported. Glomerular injury in CML has occurred in blast crisis and the chronic phase of malignancy, making an association with disease state difficult.

Hodgkins Lymphoma

The most common glomerular lesion associated with HL is MCD, although FSGS has also been reported. Amyloidosis (AA amyloid) has been described in HL; however, the prevalence has decreased with improved treatment.Anti-glomerular basement membrane disease, which occurs with a frequency several-fold higher than in patients without malignancy, and pauciimmune crescentic GN have been reported.42 The development of a glomerulopathy in HL is likely secondary to abnormal cytokine production and secretion by affected T-cells. This leads to alterations in glomerular permeability and thereby proteinuria. In particular, Reed Sternberg cells express vascular endothelial growth factor-25 and transforming growth factor (TGF)-b126, cytokines linked to the pathogenesis of FSGS.

Non-Hodgkins Lymphoma

Glomerular lesions in patients with NHL vary widely and depend on the stage of lymphoma. In contrast to HL, in which glomerular involvement occurs later in the disease without correlation to progression or aggressiveness, glomerulopathies in NHL occur earlier and progress with disease. Proliferative lesions are more common in NHL, compared with HL, and may account for up to 30% of glomerular diseases. MPGN, with or without immune complex deposition, has been reported. Amyloidosis, as with HL, is less common with current chemotherapeutic options, but unlike HL it tends to be the AL amyloid subtype.

With the increased incidence of hematologic malignancy and new therapies that are prolonging survival in patients with leukemia and lymphoma, kidney injury and complications will undoubtedly become more prevalent. Because the differential is broad for AKI in these patients, the nephrologist must be thorough to correctly diagnose the cause of injury. Therapy for AKI, glomerulopathies, or electrolyte disorders is largely supportive, with treatment of the underling malignancy the mainstay.

References

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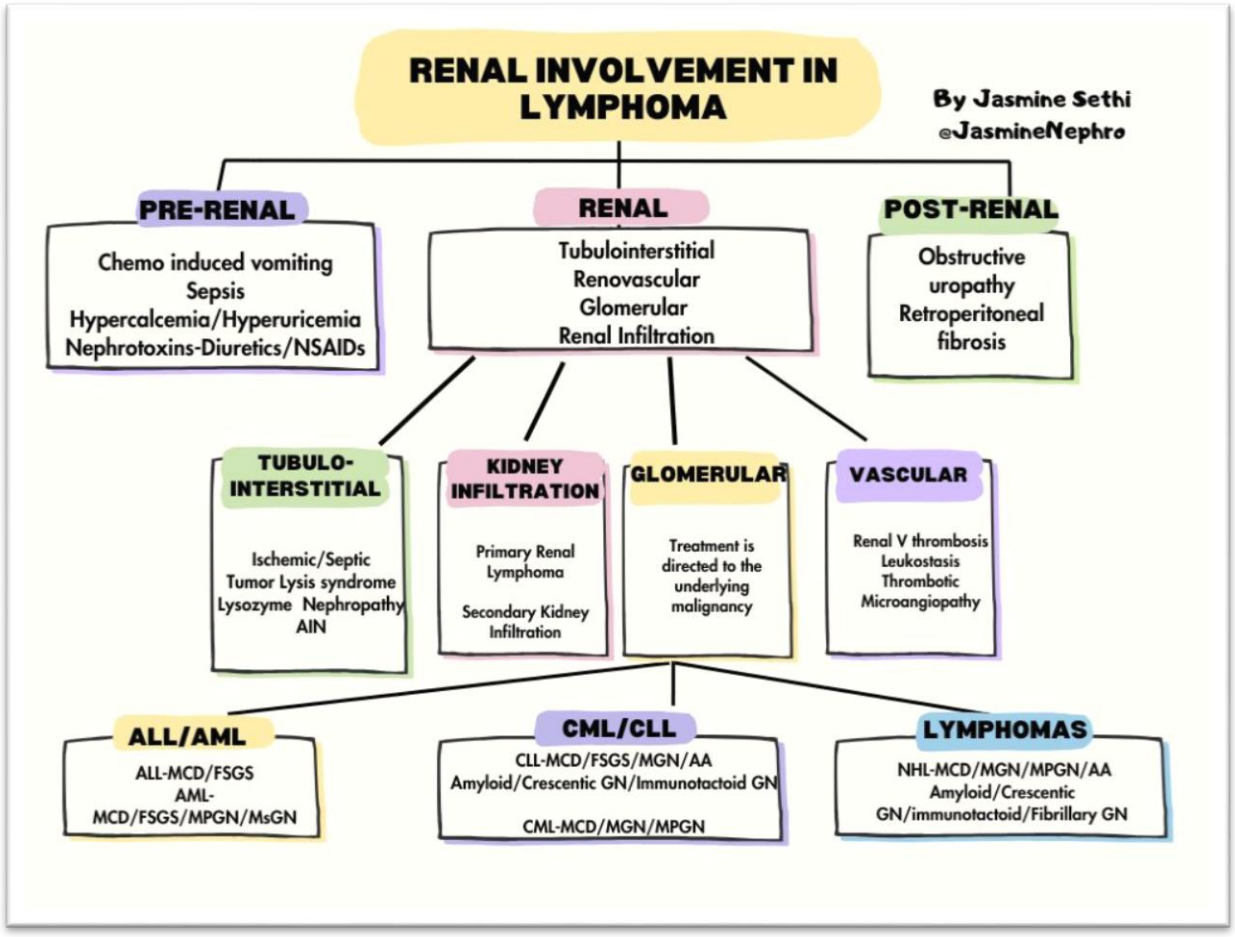

Infographic-Renal Involvement in Lymphoma