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Renal Involvement in Hematological Malignancies: from Leukemia to Lymphama

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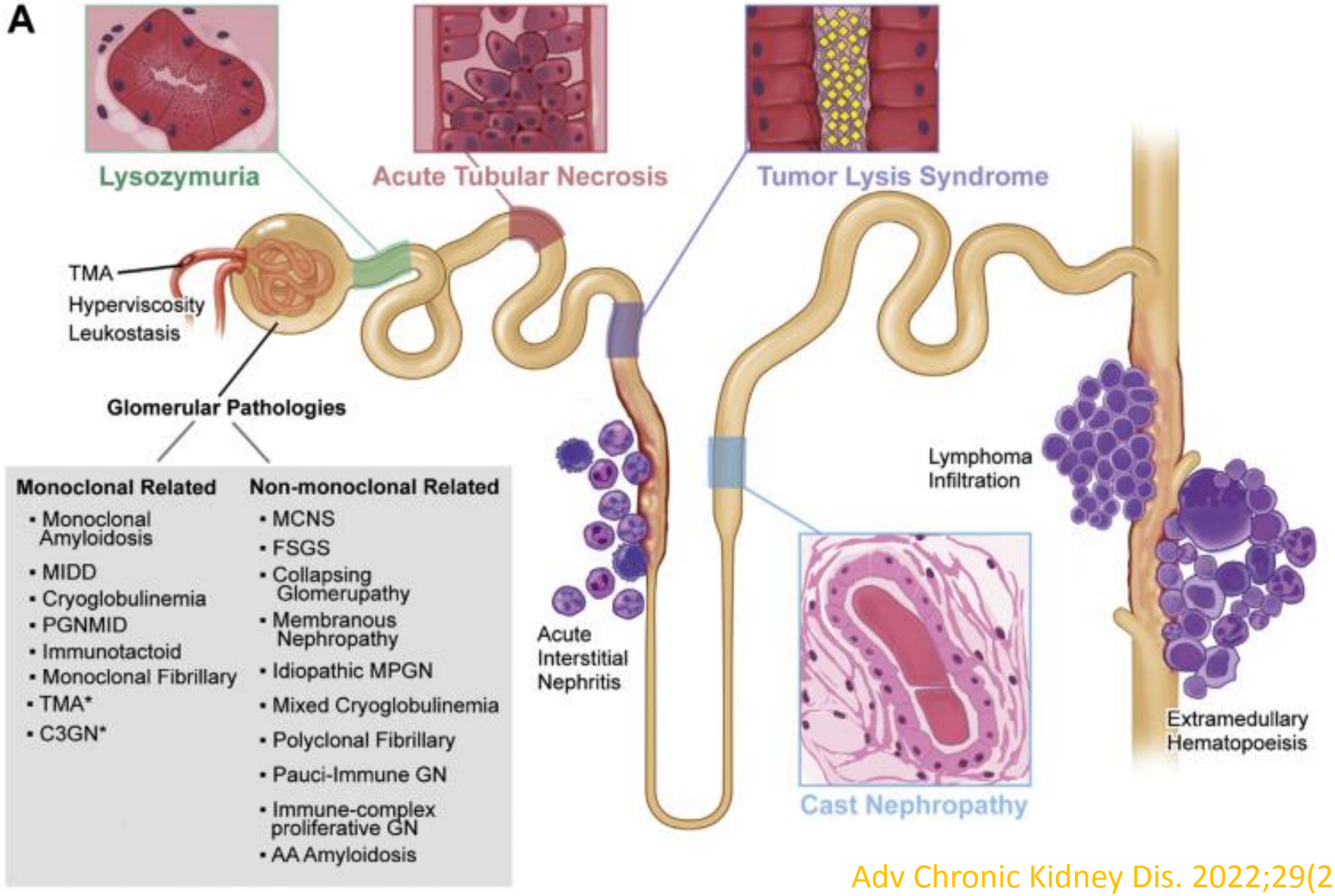
Introduction

- ✓ **Leukemia** and **lymphoma** are 2 of the most common malignancies worldwide.
- ✓ The incidence of leukemia and lymphoma continues to rise.

  (26% increase for leukemia, 45% increase for non-Hodgkin lymphoma (NHL) from 2006 to 2016)
- ✓ Lifetime incidence approximately **1/110 for men** and **1/160 for women**.
- ✓ **Outcomes are overall improving**, likely due to earlier detection and improved treatments.
- ✓ Acute kidney injury (**AKI**) is a common adverse outcome in these patient populations, occurring in **approximately 30-70% of patients**, and is associated with **a lower remission rate** and **higher mortality**.

Introduction

- ✓ We describe **clinical manifestations**, **pathophysiology**, **outcomes**, and **management** of kidney disorders related to hematologic malignancies, from the perspective of the *affected nephron compartment*:
- ✓ Vascular
- ✓ Tubular
- ✓ Interstitial
- ✓ Glomerular



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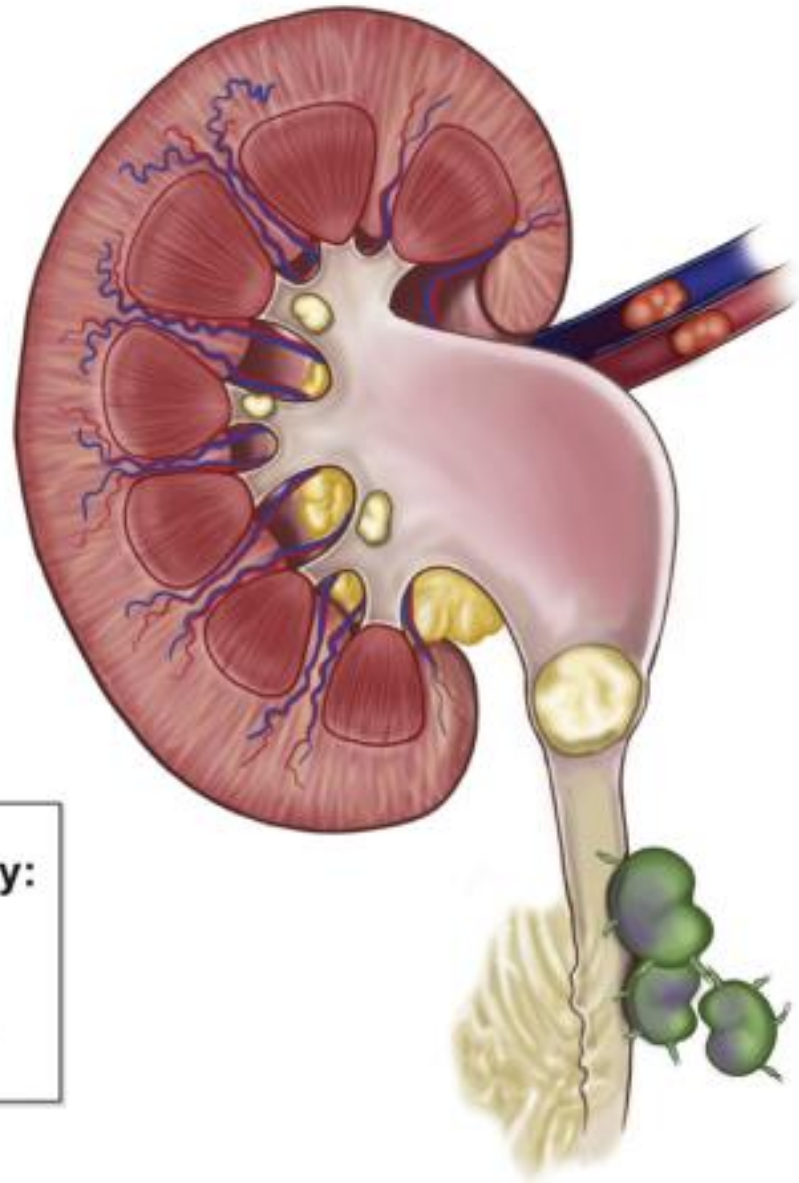


Systemic/vascular

- Hypovolemia
- Sepsis syndrome
- Vascular thrombosis
- Vasoconstriction (Hypercalcemia/hyperuricemia)
- Cytokine release syndrome
- Cardiac/Liver dysfunction

Obstructive Uropathy:

- Nephrolithiasis
- Lymphadenopathy
- Retroperitoneal Fibrosis

VASCULAR:
Hyperleukocytosis and Leukostasis

Hyperleukocytosis is a clinical syndrome which usually occurs when **WBC >100,000/mL**

- ✓ Most frequently with AML, ALL, and CLL
- ✓ With an associated **mortality of 40%**
- ✓ Hyperleukocytosis may lead to **leukostasis**, **DIC,** and **TLS**

VASCULAR:
Hyperleukocytosis and Leukostasis

Leukostasis (**also called symptomatic hyperleukocytosis**) is a medical emergency:

- ✓ Most commonly in patients with **AML** or **CML in blast crisis**
- ✓ **C**haracterized by an **extremely elevated WBC count** and **symptoms of decreased tissue perfusion**
- ✓ Main clinical symptoms of leukostasis and causes of early death: **CNS** and **lungs involvement**
- ✓ Less common signs or symptoms of leukostasis include:
  - ✓ **myocardial ischemia**
  - ✓ **worsening renal insufficiency**
  - ✓ **priapism, acute limb ischemia**
  - ✓ **bowel infarction**

VASCULAR:
Hyperleukocytosis and Leukostasis

Hyperleukocytosis management:

- ✓ *IV fluids* and *management of hyperuricemia*
- ✓ **Cytoreduction with induction chemotherapy** or **hydroxyurea (if induction therapy not possible)**
- ✓ **In leukostasis: initial leukapheresis in addition to induction chemotherapy or hydroxyurea**

Hydroxyurea, given at a total dose of 50 to 100 mg/kg per day orally, **reduces WBC count by 50 to 80 percent within 24 to 48 hours**. The usual **hydroxyurea dose is 2 to 4 grams orally every 12 hours, which is continued until WBC count is below 50 x 10^9/L (50,000/microL).**

VASCULAR:
Hyperviscosity Syndrome

Hyperviscosity syndrome:

- ✓ In up to 30% of patients with Waldenstrom macroglobulinemia (WMG) and up to 6% of patients with MM.
- ✓ Normal serum viscosity is 1.5 cP (1.7 times higher viscosity than water)
- ✓ **IgM** is more likely to increase viscosity due to its pentameric structure and size
- ✓ **IgM levels >3 g/dL** are associated with hyperviscosity, compared with **10 g/dL for IgG** (except **IgG-3 subtype**, which has a higher tendency to aggregate)
- ✓ The risk of hyperviscosity syndrome increases when **serum viscosity >4 cP**

VASCULAR:
Hyperviscosity Syndrome

Symptoms:

- ✓ *mucosal bleeding*
- ✓ *CNS and ophthalmic changes (headache, vision changes, seizure)*
- ✓ *Priapism*
- ✓ *heart failure*
- ✓ ***AKI likely related to renal hypoperfusion***

✓ **Plasmapheresis** is an important early intervention:

- ✓ effective with WMG given that **IgM is highly intravascular (75-80%)** compared with
- ✓ **IgG (45-65% intravascular)**

VASCULAR:
Cryoglobulinemia

Cryoglobulinemia

- ✓ a hematologic disorder of immunoglobulins that
- ✓ **precipitate** at a **low temperature (below 37 C in vitro**) and
- ✓ associated with **hyperviscosity syndrome**

- ✓ **Type I** makes up 10-15% of cases and refers to **monoclonal disease, usually IgM**.
- ✓ **Type II** is a mixture of **monoclonal IgM (often termed rheumatoid factor),** which binds to the Fc portion of **polyclonal IgG.**
- ✓ **Type III** involves **polyclonal IgM and IgG** interactions.

VASCULAR:
Cryoglobulinemia

Type I

- ✓ Usually a result of **hematologic malignancy**, including CLL, MM, WMG, and HL
- ✓ Precipitation occurs in the **distal extremities** where the coolest temperatures occur
- ✓ **Vascular occlusion** can occur when cryoglobulin concentrations are high (hyperviscosity syndrome)
- ✓ Usually when **serum monoclonal protein is > 4 g/dL**

VASCULAR:
Cryoglobulinemia

Mixed cryoglobulinemias (MCs):

- ✓ **Infection** (most commonly **hepatitis C**) and **autoimmune diseases**
- ✓ **WMG** (most common malignant cause), up to 22% of patients with MC have **B-cell lymphoma**

Vasculitis may occur with MC: cutaneous purpura, livedo reticularis, peripheral neuropathy, and nephropathy.

Worked up for: **monoclonality**, **rheumatoid factor, C3 and C4, BMB**

VASCULAR:
Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA)

- ✓ ***Primary***: hereditary or acquired, with TTP and atypical HUS
- ✓ ***Secondary*** causes: **malignant hypertension, autoimmune disease, drugs, infections, malignancy, and transplant.**

Pathology

- ✓ **typical MPGN pattern** of **intimal thickening** of glomerular capillaries
- ✓ **intracapillary fibrin thrombi**
- ✓ with eventual **"onion-skinning"** (double contours of capillary walls)

VASCULAR:
Thrombotic Microangiopathy

TMA in:

- ✓ WMG (*fibrin-negative monoclonal IgM aggregates or pseudothrombi)*
- ✓ **CLL/monoclonal B-cell lymphocytosis (MBL).**
- ✓ TMA may occur due to *monoclonal gammopathy* either:
  - ✓ via **direct damage of antibodies to the endothelium** or
  - ✓ via **autoantibody-mediated dysregulation of the alternate complement cascade**

VASCULAR:
Thrombotic Microangiopathy

Drug-induced TMA:

- ✓ **Anti VEGF therapy** (bevacizumab)
- ✓ **Highly-selective multi-receptor tyrosine kinase inhibitors** (sunitinib, sorafenib, pazopanib, lenvatinib) (used in RCC and **solid malignancies)**
- ✓ Less well described in multi-receptor tyrosine kinase inhibitors for patients with hematologic malignancy (imatinib, dasatinib).
- ✓ **Proteasome inhibitors** (bortezomib and carfilzomib)
- ✓ **Gemcitabine** and **Mitomycin**

Multi-receptor tyrosine kinase inhibitors is *not usually dose-related* and has *high likelihood of reversibility with discontinuation* and overall favorable kidney outcomes.

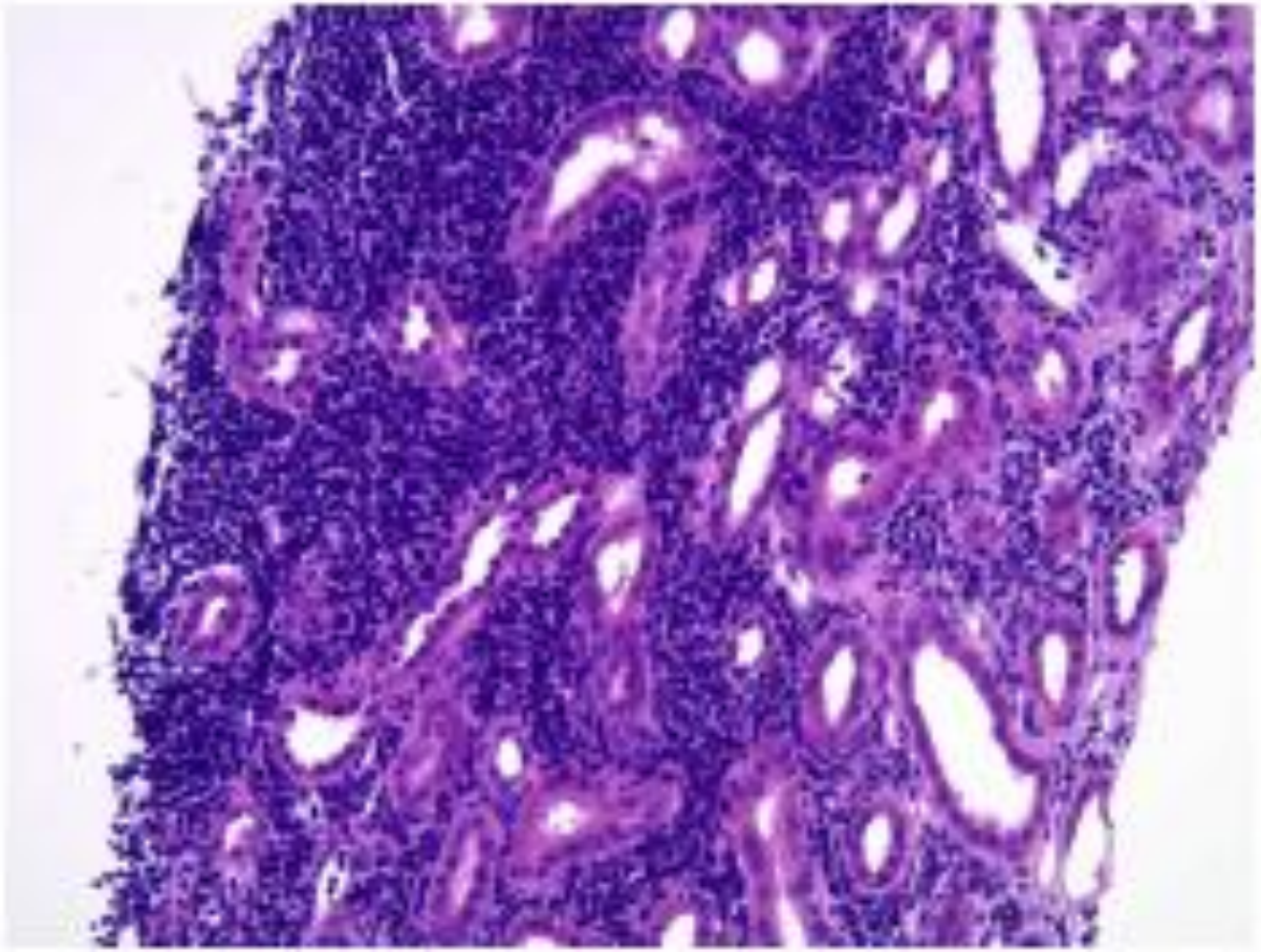
VASCULAR:
Vascular Thrombosis

Patients with *leukemia* are at high risk for ***venous and arterial thromboses:***

- ✓ There is 1 case report of a patient with **APL** who developed anuria after treatment with all-trans retinoic acid (**ATRA**) and was found to have **arterial thrombosis with cortical necrosis on kidney biopsy.**
- ✓ Patients with APL are at high risk for DIC due to thrombin activation by tumor cells
- ✓ **Renal vein thrombosis leading to kidney failure** has been reported in a case of **AML**
- ✓ Controversy regarding prophylactic anticoagulation, given thrombocytopenia-related high bleeding risk.
- ✓ **Constriction of renal vessels due to lymphomatous encasement** has been reported leading to **severe hypertension and kidney failure.**

TUBULOINTERSTITIAL:
Kidney Infiltration

- ✓ Autopsy series have shown that **interstitial kidney infiltration** in hematologic malignancy is **common**:
  - ✓ with involvement in **59-90% of patients with CLL**
  - ✓ **83% with ALL**
  - ✓ **50% with low-grade NHL**
- ✓ **Kidney failure is rare**, regardless of extent of involvement.
- ✓ Infiltration at the subcapsular cortex, corticomedullary junction, and adjacent to the vasa recta
- ✓ AKI may occur due to **intrarenal tubular and vascular compression** and local inflammatory response
- ✓ **Quick reversal of AKI within 2-3 days** reported following treatment
- ✓ **Lymphomatous involvement** should be considered in patients with **nephromegaly** and **AKI** (or **proteinuria**), as this can be the **initial manifestation of lymphoma.**



Renal parenchyma infiltrated by lymphoma. Immunohistochemical staining showed strong CD20 positivity, with aberrant CD5 expression as well as Lef1 staining, supporting the diagnosis of CLL/SLL

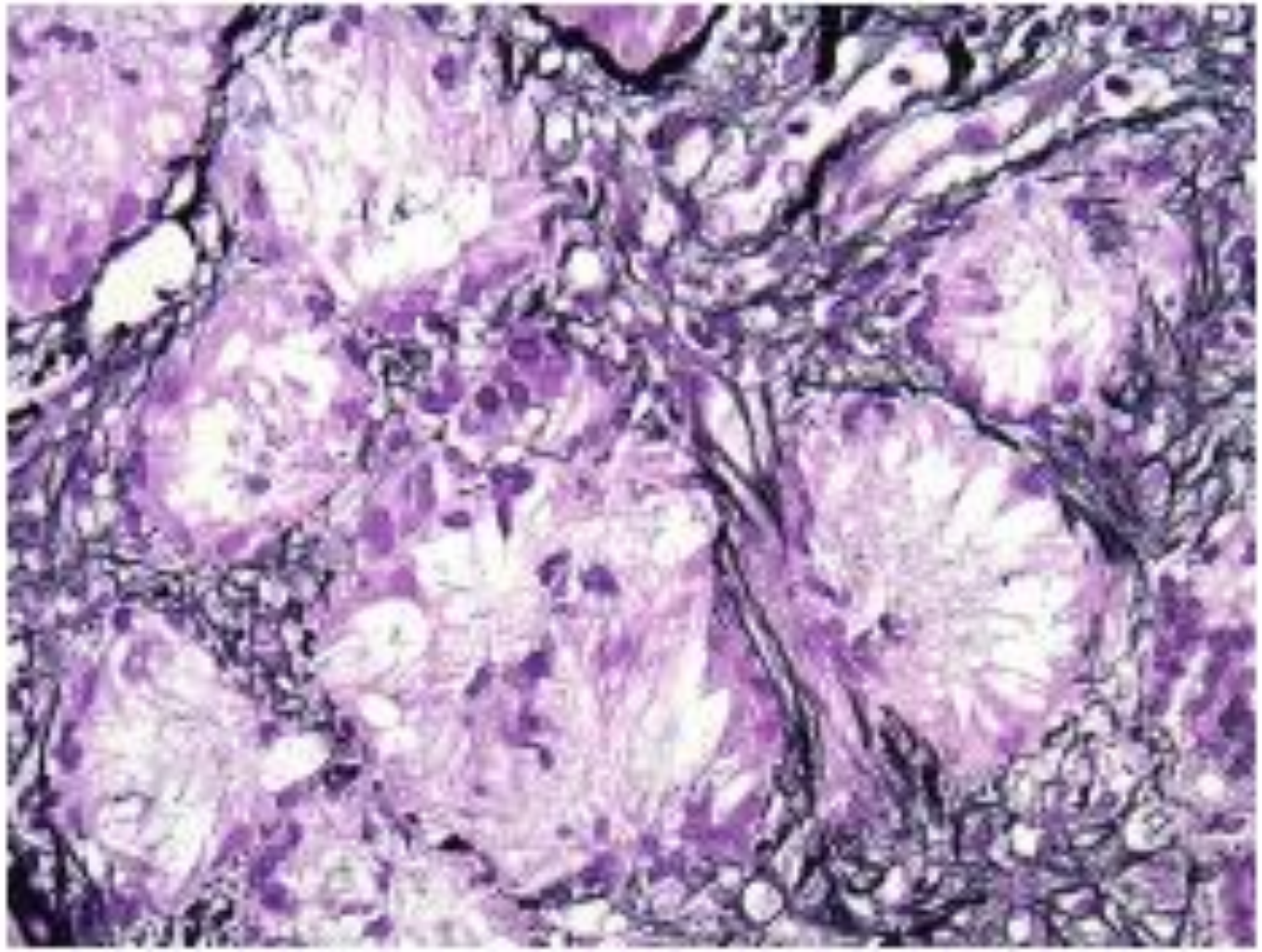
TUBULOINTERSTITIAL:
Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an *oncologic emergency* that is caused by massive tumor cell lysis with the **release of large amounts of potassium, phosphate, and nucleic acids** into the systemic circulation.

- ✓ Catabolism of the nucleic acids to uric acid leads to ***hyperuricemia and AKI:***
  - ✓ **Precipitation of uric acid in the renal tubules**
  - ✓ **Renal vasoconstriction**
  - ✓ **Impaired autoregulation**
  - ✓ **Decreased renal flow**
  - ✓ **Oxidation** and **inflammation**

  Hyperphosphatemia with **calcium phosphate deposition in the renal tubules** can also cause AKI.

- ✓ High concentrations of both uric acid and phosphate potentiate increases risk of AKI.



Urate crystals (dissolved out during processing) surrounded by giant cell reaction in the renal medulla.

TUBULOINTERSTITIAL:
Tumor Lysis Syndrome

- ✓ TLS is a catastrophic outcome in patients with hematologic malignancy, with a **mortality rate of 21%** in a recent cohort, and defined with **at least 2 of the following laboratory criteria**, according to the Cairo Bishop classification:
- ✓ potassium > 6 mEq/L, phosphorus > 4.5 mg/dL, uric acid > 8 mg/dL, and calcium < 7 mg/dL or 25% change in baseline of any 2 criteria.
- ✓ **Clinical TLS** requires end-organ damage, including creatinine level **1.5x upper limit of normal**, **cardiac arrhythmia**, or **seizure**.
- ✓ Malignancies at high risk of causing TLS include acute leukemia **(ALL, AML) with hyperleukocytosis, lymphomas with bulky tumor and high LDH, diffuse large B cell lymphoma (DLBCL),**, and **CLL receiving venetoclax or targeted therapies**.

TUBULOINTERSTITIAL:
Tumor Lysis Syndrome

TLS most often occurs **after the initiation of cytotoxic therapy** in patients with:

- ✓ Clinically aggressive and highly aggressive lymphomas (particularly the **Burkitt subtype**) and
- ✓ **T-cell acute lymphoblastic leukemia (ALL)**

However, it can occur **spontaneously** and with **other tumor types** that have:

- ✓ **High proliferative rate**
- ✓ **Large tumor burden**
- ✓ **High sensitivity to cytotoxic therapy**

TUBULOINTERSTITIAL:
Tumor Lysis Syndrome

Prophylaxis

Hydration

- ✓ For all patients at high or intermediate risk of TLS, we recommend aggressive fluid hydration (**2 to 3 L/m^2 daily**) to achieve a **urine output of at least 80 to 100 mL/m^2 per hour**. If there is no evidence of acute obstructive uropathy and/or hypovolemia, a **loop diuretic may be used** to maintain the urine output, if necessary.
- ✓ There is **no evidence that urinary alkalinization is of benefit**, and there are potential harms, **especially when phosphate levels are elevated**. IV administration of sodium bicarbonate should not be used in the absence of metabolic acidosis.

TUBULOINTERSTITIAL:
Tumor Lysis Syndrome

Prophylaxis

Hypouricemic agents — Hypouricemic agents include **allopurinol**, **rasburicase**, and **febuxostat**.

Rasburicase:

- ✓ Should generally **not** be given to individuals with **G6PD deficiency** due to the risk of severe hemolysis
- ✓ **Use in High-risk** patients for TLS
- ✓ **A single dose of rasburicase (0.2 mg/kg) rather than multiple-day therapy**
- ✓ Blood samples for uric acid should be collected in a pre-chilled tube, immediately placed on ice, and the assay completed within four hours, if possible.

TUBULOINTERSTITIAL:
Tumor Lysis Syndrome

Prophylaxis

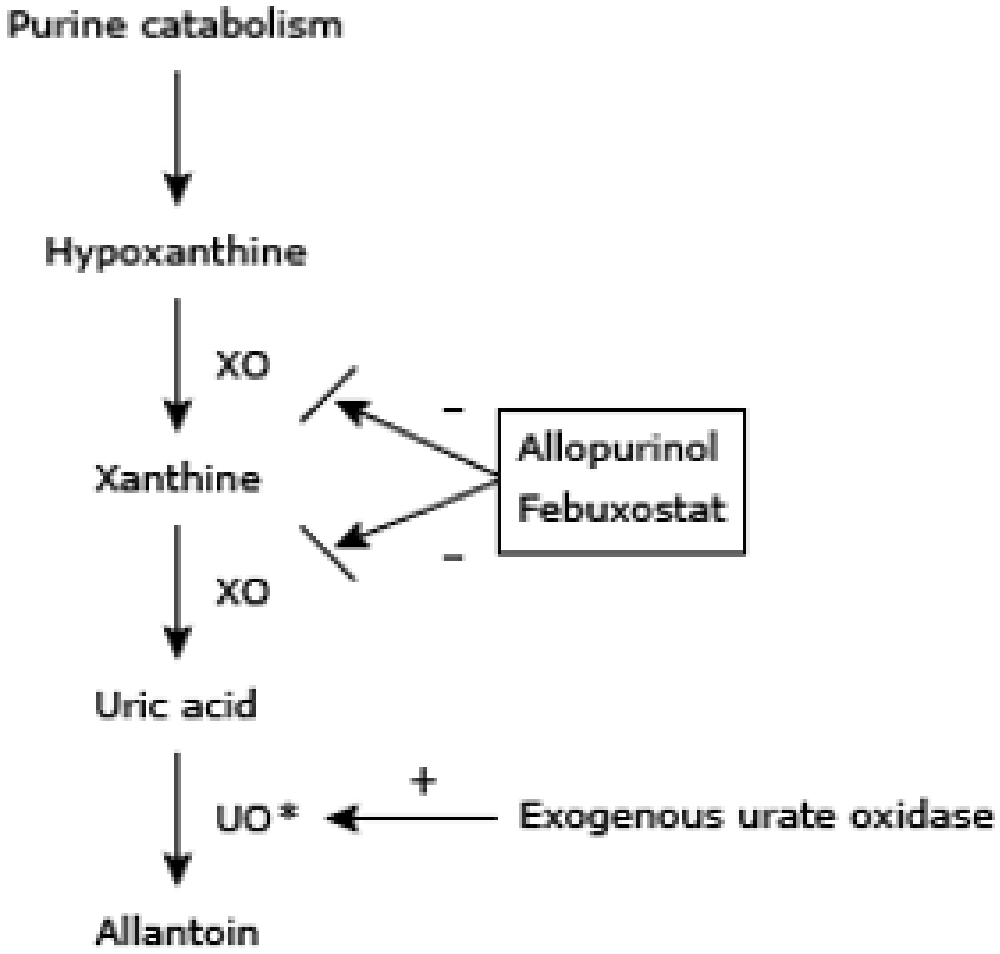
Allopurinol:

- ✓ For patients with **intermediate risk for TLS** and
- ✓ **Uric acid level <8 mg/dL**

Febuxostat:

- ✓ We *should not use febuxostat* as an alternative to allopurinol to prevent TLS in patients at intermediate to high risk for TLS.
- ✓ **Febuxostat** may be used judiciously in patients with hyperuricemia **who cannot tolerate allopurinol in a setting in which rasburicase is not available or contraindicated.**

Endogenous production of uric acid



TUBULOINTERSTITIAL:
Tumor Lysis Syndrome

Patients at high risk for TLS should receive *intensive supportive care* with:

- ✓ Continuous cardiac monitoring
- ✓ Close monitoring of urine output and fluid balance, and
- ✓ Frequent serial measurement of electrolytes, creatinine, and uric acid (four to six hours after the initial administration of chemotherapy, and every 6 to 12 hours thereafter)

Indications for renal replacement therapy include:

- ✓ •**Severe oliguria or anuria**
- ✓ •**Persistent hyperkalemia**
- ✓ •**Hyperphosphatemia-induced symptomatic hypocalcemia**
- ✓ •**A calcium-phosphate product ≥70 mg^2/dL^2**

Management of electrolyte abnormalities in tumor lysis syndrome

Abnormality	Management recommendation
Hyperphosphatemia	
Moderate, ≥2.1 mmol/L (6.5 mg/dL)	Restrict phosphate intake (avoid IV and oral phosphate; limit dietary sources)
	Phosphate binders:
	Calcium acetate[¤] Adult: 2 to 3 tabs (1334 to 2668 mg) with each meal; or
	Calcium carbonate[*] Adult: 1 to 2 grams with each meal; Pediatric: 30 to 40 mg/kg with each meal; or
	Sevelamer[¶] Adult: 800 to 1600 mg with each meal; Pediatric: 40 to 54 mg/kg with each meal; or
	Lanthanum carbonate Adult: 500 to 1000 mg with each meal[Δ]; or
	Aluminum hydroxide Adult: 300 to 600 mg with each meal; Pediatric: 12.5 to 37.5 mg/kg four times daily with meals; (avoid use in patients with renal insufficiency)
Severe	Dialysis, CAVH, CVVH, CAVHD, or CVVHD
Hypocalcemia, total serum calcium ≤1.75 mmol/L (7 mg/dL) or ionized calcium ≤0.8 mmol/L (3.2 mg/dL)	
Asymptomatic	No therapy
Symptomatic	Calcium gluconate administered slowly with ECG monitoring; patients with acute hypocalcemia and hyperphosphatemia should not be treated with calcium until the hyperphosphatemia is corrected (unless they have tetany or a cardiac arrhythmia from hypocalcemia)
	Calcium gluconate[◇] Adult: 1 gram (10 mL of 10 percent solution); Pediatric: 50 to 100 mg/kg. Slow IV infusion (maximum 50 to 100 mg per minute) in large vein. May be repeated after 5 to 10 minutes if symptoms or ECG changes persist.

Hyperkalemia[§]	
Moderate and asymptomatic, ≥6.0 mmol/L	Avoid IV and oral potassium
	ECG and cardiac rhythm monitoring
	Sodium polystyrene sulfonate[¥] Adult: 15 to 30 grams orally; Pediatric: 1 gram/kg orally. Onset 1 to 2 hours. Repeat every 4 to 6 hours up to four times daily as needed based on repeat serum K+ level.
Severe (>7.0 mmol/L) and/or symptomatic	**Same as above, plus:**
	To stabilize cardiac membranes:
	For patients with ECG changes (widening of the QRS complex or loss of p-waves but not peaked t-waves alone), *give calcium gluconate by slow IV infusion* to prevent life-threatening arrhythmias:
	Calcium gluconate Adult: 1 gram (10 mL of 10 percent solution); Pediatric: 50 to 100 mg/kg. Slow IV infusion (maximum 50 to 100 mg per minute) in large vein. May be repeated after 5 to 10 minutes if ECG changes persist.
	To temporarily shift potassium into cells:
	Give IV insulin and dextrose:
	IV insulin and dextrose Adult: regular insulin (10 units) IV plus 100 mL of a 50 percent dextrose solution (D50) IV; Pediatric: regular insulin (0.1 unit/kg) IV, plus 25 percent dextrose solution (D25) 0.5 gram/kg (2 mL/kg of D25) IV over thirty minutes. May be repeated after thirty to sixty minutes. Monitor fingerstick glucose closely.
	Sodium bicarbonate can be given to induce influx of potassium into cells if patient is acidemic. Sodium bicarbonate and calcium solutions should not be administered through the same line due to incompatibility.
	Sodium bicarbonate Adult: 45 to 50 mEq; Pediatric: 1 to 2 mEq/kg. Slow IV infusion over five to ten minutes.
	Beta 2 agonist inhalation: Albuterol per nebulisation or metered dose inhaler
	Albuterol Adult: 10 to 20 mg in 4 mL saline nebulized over 20 minutes or 10 to 20 puffs per metered dose inhaler over 10 to 20 minutes; Pediatric: 0.1 to 0.3 mg/kg per nebulisation.
	Dialysis

TUBULOINTERSTITIAL:
Extramedullary Hematopoiesis

- ✓ The **kidney** is the **fourth most common site for extramedullary hematopoiesis:**
  - ✓ Most often in patients with **primary myelofibrosis**
  - ✓ Followed by chronic myelomonocytic leukemia **(CMML)**
- ✓ kidney biopsy typically shows **trilineage interstitial infiltrate:** erythroid, myeloid, and megakaryocyte cells
- ✓ Proposed mechanisms of kidney injury include:
  - ✓ **Renal hypoperfusion due a Page-like effect** on the renal capsule
  - ✓ **Intratubular obstruction**
  - ✓ **Obstructive uropathy** due to extrinsic ureteral compression.

TUBULOINTERSTITIAL:
Light-Chain Cast Nephropathy

- ✓ **light-chain cast nephropathy (LCCN)**:
  - ✓ Associated with **MM (a myeloma-defining illness)**
  - ✓ Other hematologic malignancies associated with LCCN: **WMG, CLL, and marginal zone lymphoma**
  - ✓ High suspicion for LCCN in the setting of **AKI and monoclonal proteinuria**

TUBULOINTERSTITIAL:
Granulomatous Interstitial Nephritis

Granulomatous interstitial nephritis has been reported in patients with **CLL/SLL**:

- ✓ associated with **kidney failure and leukocyturia**
- ✓ with kidney biopsy showing **nonnecrotizing granulomas with giant cells** and
- ✓ associated **leukemic infiltrate**

✓ Proposed mechanisms of kidney injury include arteriolar and tubular compression by leukemic cells leading to *ischemia and obstruction.*

TUBULOINTERSTITIAL:
Lysozymuria

- ✓ **Lysozymes** are lytic bactericidal enzymes produced by *monocytes*, **freely filtered by the glomerulus** and **reabsorbed by proximal tubular cells**.
- ✓ Lysozymuria can occur when lysozyme production in patients with acute and chronic leukemia of monocytic lineage exceeds tubular reabsorption, leading to a **tubular overflow** into the urine.
- ✓ This can present as **nephrotic-range proteinuria and AKI from tubular injury**:
  - ✓ clinically appearing as a **pseudonephrotic syndrome**
  - ✓ as well as **urinary potassium and magnesium wasting**, and
  - ✓ **proximal tubulopathy**
- ✓ *Kidney biopsy* may show **vacuolization of the renal tubular epithelium with eosinophilic droplets** that **stain for antilysozyme antibody**.

POSTRENAL:
Obstructive Uropathy

- ✓ Obstructive uropathy has been reported in **7% of patients with lymphoma**, usually due to **ureteral obstruction resulting in hydronephrosis**, mainly due to lymphomatous compression.
- ✓ Anuric kidney failure should raise suspicion for bilateral ureteral obstruction.
- ✓ **Retroperitoneal fibrosis** is an important cause of obstructive uropathy, *with 50% of patients developing AKI, usually due to bilateral hydronephrosis.*
- ✓ Approximately **8% of patients with RPF have underlying malignancy**.
- ✓ **NHL** is the **most common** hematologic malignancy to cause RPF, due to a sclerotic response to retroperitoneal tumor; it has also been reported with **CMML**.

POSTRENAL:
Obstructive Uropathy

- ✓ RPF is **more commonly** associated with the **polyclonal autoimmune IgG4-related disease**.
- ✓ **Rituximab** has been effective in treating RPF related to IgG4-related disease and is used in combination therapy for lymphoma.
- ✓ **Nondilated obstruction** has been rarely reported, whereby **RP fibrosis or mass encases the ureters**, restricting expansion and development of hydroureteronephrosis, with *false-negative imaging*, and relief occurring with percutaneous nephrostomies or other surgical management.
- ✓ Other causes of obstructive uropathy include **uric acid nephrolithiasis**, often related to TLS.
- ✓ **Nephrolithiasis** in patients with hematologic malignancies is seen in **5.5% of patients** (2% symptomatic) with lymphoproliferative and myeloproliferative disorders in 1 study.

SYSTEMIC:
Cytokine Release Syndrome

- ✓ Cytokine release syndrome (CRS) occurs as:
  - ✓ **body's tumor response** in the **treatment** of hematologic malignancies.
  - ✓ Pathogenesis involves **T-cell activation** leading to:
    - ✓ cytokine upregulation (including interferon-gamma, IL-6, and IL-10)
    - ✓ causing endothelial damage
    - ✓ leaky vasculature
    - ✓ activation of complement
  - ✓ **ATRA** differentiates **leukemic blasts into mature myelocytes**, leading to CRS.
- ✓ Pathogenesis of AKI includes:
  - ✓ Decreased kidney perfusion due to vasoconstriction and intravascular volume depletion
  - ✓ Acute tubular necrosis, and
  - ✓ Urinary obstruction

SYSTEMIC:
Cytokine Release Syndrome

Hemophagocytic lymphohistiocytosis (HLH):

- ✓ Can also lead to CRS
- ✓ It is characterized by **dysregulation of cytotoxic T-cells and natural killer cells**
- ✓ *Elevated soluble CD25 level, fever, hyperferritinemia, splenomegaly, and cytopenias*

✓ HLH is associated with hematologic malignancy in 75% of adult cases

✓ **AKI** manifests in up to **62% of patients**

✓ KRT is required in 59% of ICU patients and 8-30% of all comers

✓ Early interventions with **etoposide** and **management/prevention of TLS** may improve kidney and overall survival.

SYSTEMIC:
Cytokine Release Syndrome

CRS is also seen in patients receiving:

- ✓ **Immune checkpoint inhibitor** and
- ✓ Chimeric antigen receptor therapy (**CAR-T**)

✓ AKI has been reported in 5-30% of patients with CRS related to CAR-T therapy, and can be managed with **glucocorticoids** and **tocilizumab (anti-IL-6)** in patients with end-organ failure.

GLOMERULAR DISEASES
WITH HEMATOLOGIC MALIGNANCIES

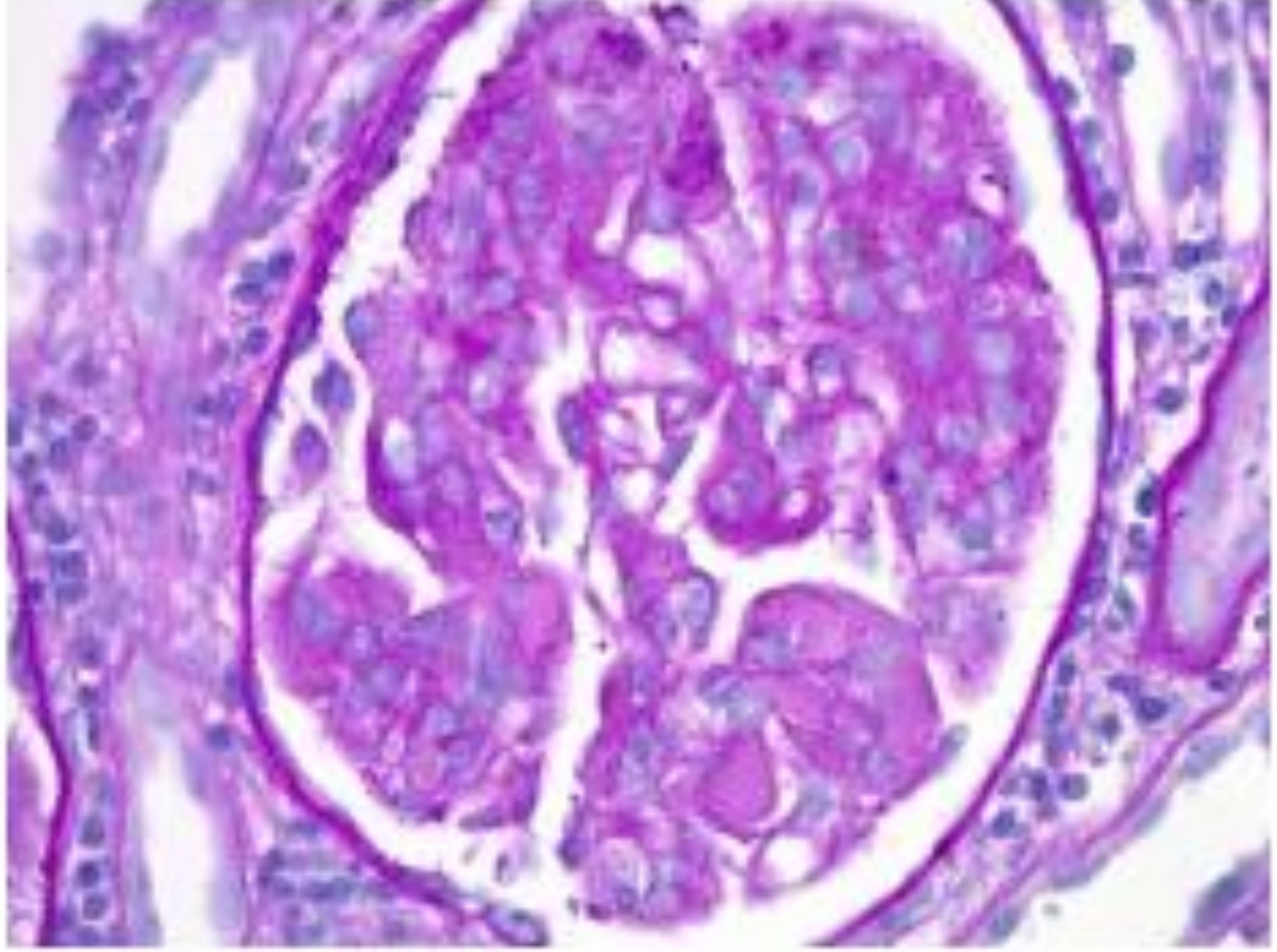
Glomerular diseases have been described across the wide spectrum of hematologic malignancies:

- ✓ These disorders are considered paraneoplastic, and usually with **unclear pathophysiologic basis**, although **occasionally mediated by monoclonal antibodies**.
- ✓ One report demonstrated both **circulating** and **in situ kidney immune complexes**, which included **antibodies against leukemic antigens**.
- ✓ ***Autoimmune dysregulation*** and ***infection-related processes*** are hypothesized to be involved in the pathogenesis of glomerular involvement.

Disease	Glomerular	Tubular	Interstitial	Vascular	Systemic
AML	MCNS, FSGS, MPGN, MesPGN	Lysozymuria (monocytic), TLS		Hyperleukocytosis, leukostasis, DIC (APL), venous thrombosis	CRS (APL after ATRA)
CML	MCNS, MN, proliferative RPGN	Lysozymuria (monocytic)	EMH (CMML)		Retroperitoneal fibrosis
MDS/MPN	MCNS, MN, MesPGN, FSGS, amyloidosis			TMA, intracapillary hematopoietic cells	
ALL	MCNS, FSGS	TLS	Kidney infiltration	Hyperleukocytosis, leukostasis	

Disease	Glomerular	Tubular	Interstitial	Vascular	Systemic
MBL/CLL	**Monoclonal related**: Immunotactoid GN, cryoglobulinemic GN, PGNMID, AL amyloidosis **Possibly monoclonal related:** C3GN, TMA **Not monoclonal related:** Idiopathic MPGN, polyclonal fibrillary GN, pauci-immune GN, MCNS, MN	TLS, LCCN	Kidney infiltration, granulomatous interstitial nephritis	TMA, hyperleukocytosis, leukostasis, DIC	
HL	MCNS, FSGS, **AA amyloidosis**, **anti-GBM**, pauci-immune GN				

Disease	Glomerular	Tubular	Interstitial	Vascular	Systemic
NHL	**Monoclonal related:** Monoclonal fibrillary GN, immunotactoid GN, monoclonal amyloid **Not monoclonal related:** MPGN, MesPGN, MCNS, FSGS	LCCN (marginal zone), TLS	Kidney infiltration	TMA (with HLH)	HLH, retroperitoneal fibrosis
WMG	**Monoclonal related:** Intracapillary monoclonal deposit disease, cryo-GN, immunotactoid GN, PGNMID, MIDD **Possibly monoclonal related:** TMA, C3GN **Not monoclonal related:** Immune-complex proliferative GN	LCCN	Kidney infiltration	Vascular amyloid, cryoglobulinemic vasculitis (MC), hyperviscosity	



Membranoproliferative pattern of glomerulonephritis with large intraluminal “cryo plugs.” In this case, these deposits were found to be IgG2 and kappa restricted and there was a cryoglobulinemic substructure to the deposits consistent with a type 1 cryo GN.

Pathology	Antineoplastic Therapy
TLS	Venetoclax, anti-CD20 (rituximab, obinutuzumab, ofatumumab), cyclin-dependent kinase inhibitors (dinaciclib, flavopiridol)
TMA	Bevacizumab, proteasome inhibitors (bortezomib, carfilzomib, ixazomib), multitarget/VEGF-inhibiting tyrosine kinase inhibitors (axitinib, lenvatinib, pazopanib, sorafenib, sunitinib), mitomycin C, gemcitabine
FSGS	mTOR inhibitors (sirolimus, everolimus)
Proteinuria (unspecified)	BCR/ABL tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib)
Cryoglobulinemic GN	Bevacizumab
Interstitial nephritis	Immune checkpoint inhibitors, pemetrexed, intravesicular BCG vaccine
Acute tubular necrosis	Cisplatin, oxaliplatin, carboplatin, ifosfamide, pemetrexed
Obstructive uropathy	Cyclophosphamide

Electrolyte and Acid-Base Disorders Seen in Hematologic Malignancies

Electrolyte or Acid Base Disturbance	Etiologies	Important Points
Hypokalemia[6,7]	- GI losses - Kaliuresis Metabolic alkalosis Hypomagnesemia Tubular dysfunction (lysozymuria,* tubulotoxic medications) - Cellular uptake High metabolic activity of tumor cells Hematopoietic growth factors	- Most prevalent electrolyte abnormality seen in leukemias and lymphomas.
Pseudohypokalemia[9]	- Potassium influx into tumor cells occurring in blood samples stored at room temperature for a prolonged period of time	- Occurs in leukemias with very high white cell count (>100,000/μl) - Avoided by rapidly separating the cells from the sample or storing it at 4°C
Pseudohyperkalemia[10]	- Potassium efflux from activated platelets and cell lysis during clot formation in the un-heparinized serum sample†	- Occurs with extreme leukocytosis particularly with associated severe thrombocytosis. - Serum potassium exceeds the "true" plasma value by more than 0.3 mEq/L - Plasma or whole blood assays using heparinized tubes resolves the issue
Reverse pseudohyperkalemia[9,10]	- Fragile CLL white blood cells are hypothesized to be sensitive to the heparin - Potassium efflux from cell lysis occurring in heparinized plasma tubes†	- Occurs in CLL patients with high white cell count - Plasma potassium concentrations are falsely elevated as compared to the "true" serum values - Phenomenon accentuated when a pneumatic tube transport system is used[11] - Arterial blood samples (less mechanical stressors associated with blood draw) and ice placement can resolve this issue
Hypercalcemia[12]	- Mediated via activated vitamin D through activation of 1 α-hydroxylase by tumor-associated macrophage - Local osteolysis implicated in some malignancy lymphomas[13] - PTHrP-mediated hypercalcemia reported with Richter's transformation[14] and some T-cell lymphomas[12,15]	- Occurs in 5% and 15% of HL and NHL patients, respectively - Associated with advanced disease and worse clinical outcomes[16] - Corticosteroid therapy most effective for vitamin D-mediated hypercalcemia
Hypophosphatemia[17]	- GI losses and poor dietary intake - Phosphaturia - Intracellular phosphate shifts	- Tumor genesis syndrome describes acute hypophosphatemia associated with rapid tumor growth[18]
Type B lactic acidosis[19]	- Thiamine deficiency with increased lactate production - Liver and kidney dysfunction with impaired lactate metabolism	- Occurs in hematologic malignancies in general and lymphoma predominantly - Ominous sign with grim prognosis

CLINICAL SUMMARY

- Acute kidney injury, chronic kidney disease, and electrolyte abnormalities are common in patients with hematological malignancies.
- All nephron compartments may be affected, including vasculature, glomerulus, and tubulointerstitium.
- Kidney involvement is ubiquitous in patients with hematologic malignancies, and each malignancy presents a unique clinical challenge.
- Prompt recognition of kidney involvement may lead to improved patient outcomes.


THANK YOU