MEDICAL COLLEGE OF WISCONSIN

Renal Complications in Hematologic Malignancies

Paul Hanna, MD MSc

Director of Onconephrology

phanna@mcw.edu. @PaulHannaMD

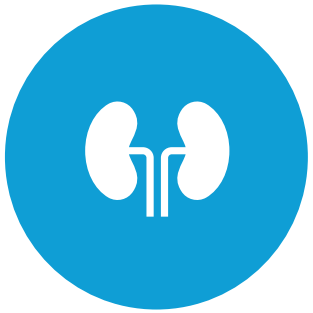
Disclosures

- Glass Health – Deputy Section Editor, Nephrology
- Amgen Pharmaceuticals – Speaker/Consultant

Objectives

Recognize the spectrum of renal complications in hematological malignancies.

Discuss the etiologies of renal insufficiency post HSCT



Evaluate risk factors and pathophysiology for developing renal complications

Implement diagnostic and monitoring strategies essential for prevention and early treatment.

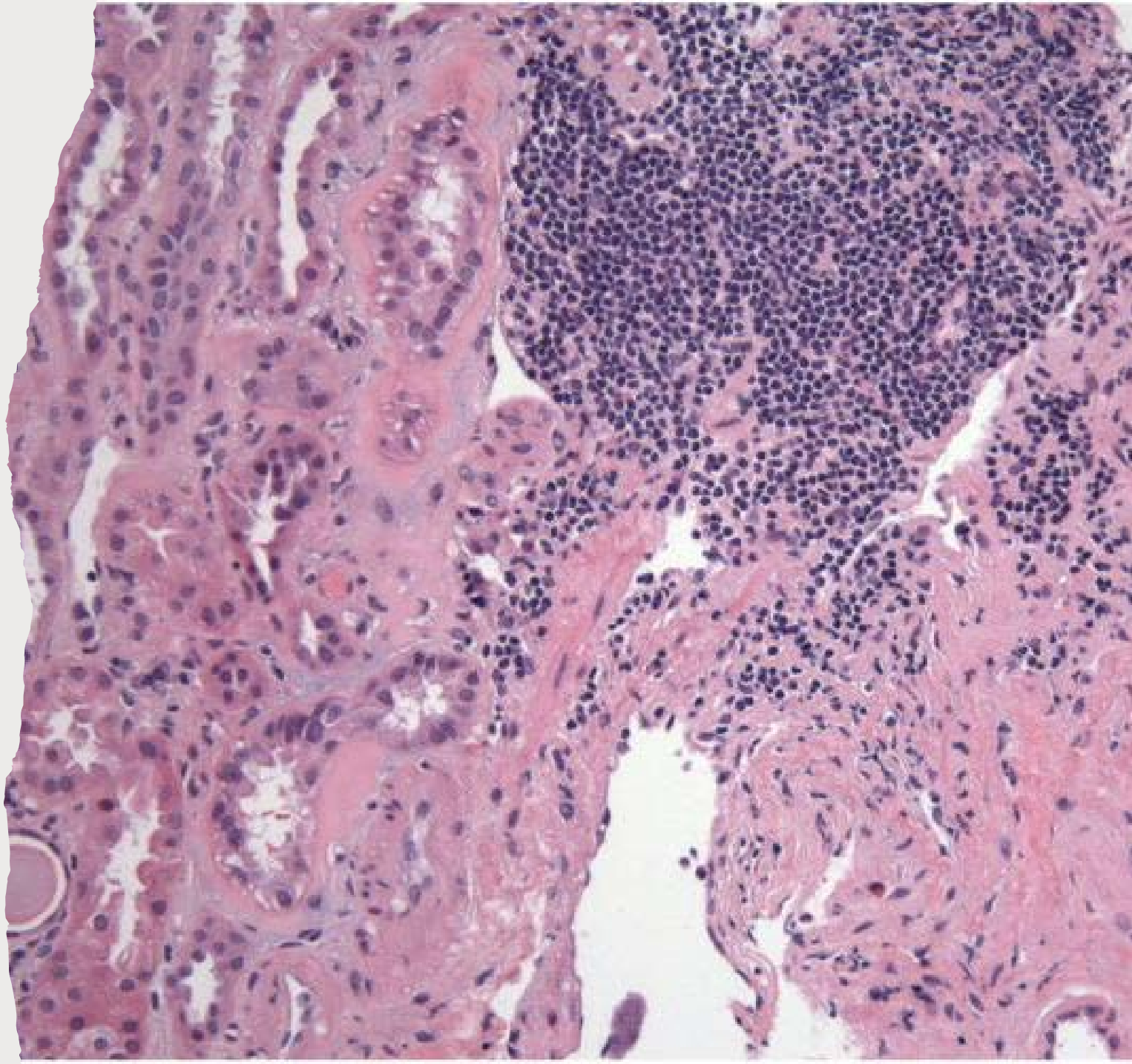
Etiologies of Renal Insufficiency

- Direct infiltration/Hydronephrosis (NHL, AML, MM)
- Thrombosis, aHUS/TTP (rare cause)
- Tumor lysis/ genesis syndromes
- Electrolyte derangements (NHL, AML, MM)
- Nephrotoxic agents
- Post-HSCTcomplications

Case 1

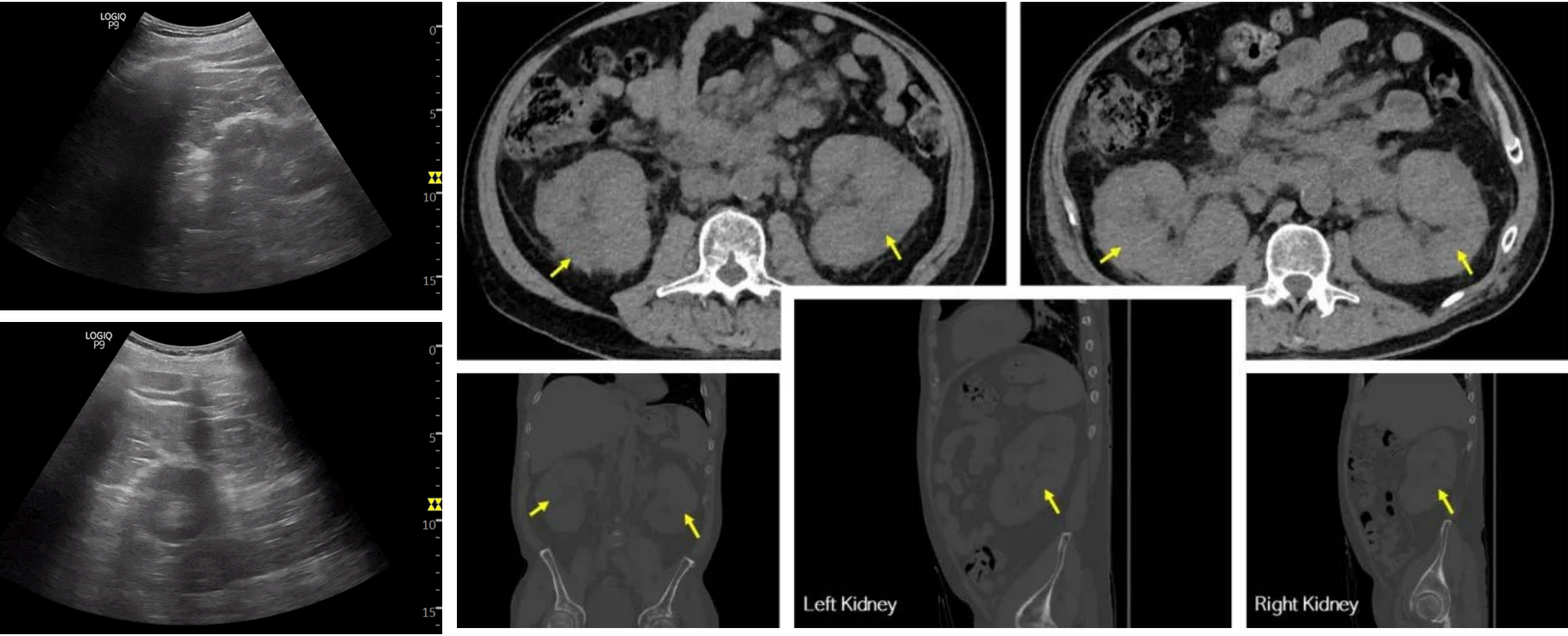
- A 76-year-old man with a history of coronary artery disease, peripheral vascular disease, and diabetes mellitus evaluated of worsening kidney failure. He had developed progressive edema and nephrotic-range proteinuria (19.5 g/day) over two months, with a rising creatinine from 1.3 to 5.0 mg/dL. Serum studies revealed an IgG kappa monoclonal M spike, and bone marrow biopsy showed a lymphoplasmacytic infiltrate with 15% plasma cells.
- Next steps?

Focal infiltration of the parenchyma by small lymphoid cell aggregates



Cohen et al. AJKD 2010

Direct kidney infiltration of lymphoma



Nephropocus.com

Treatment of NHL with Renal Failure

- Treatment of NHL most important
  - Need reduced doses of some medications - Methotrexate, Cytarabine
- Nephrostomy if necessary to address any obstructive components
- IV Hydration
- Alkalinization
- Treat Hyperuricemia with rasburicase
- RRT as indicated

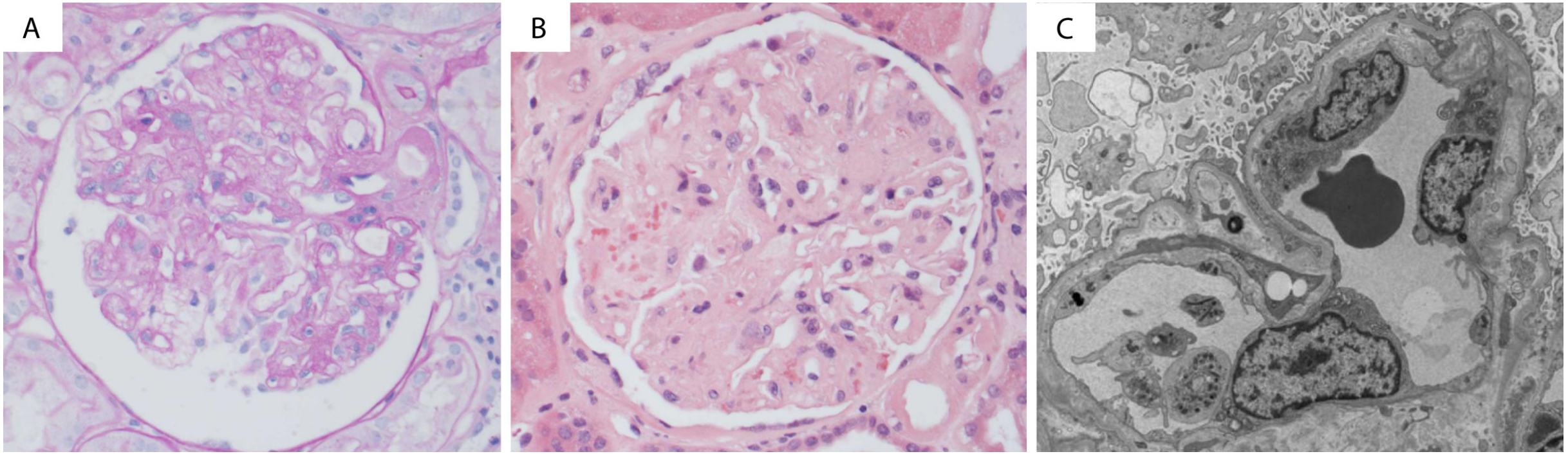
Case 2

- A 67-year old female receives a TKI (dasatinib) for CML. She has no known past medical history. Four weeks into therapy, she has worsening HTN. She is prescribed an anti HTN with no major response. In 2 weeks, she requires 3 anti HTN agents. Urine reveals hematuria and 3+ protein and quantification of 4.5g/g.
- She has normal LDH, normal haptoglobin and no schistocytes on blood smear. C3, C4 are in normal range.

Onconephrologist: This is likely renal limited TMA from the TKI.

Oncologist: But the LDH is normal, and there are no schistocytes in the smear.

Renally limited TMA on kidney biopsy



TMA/aHUS

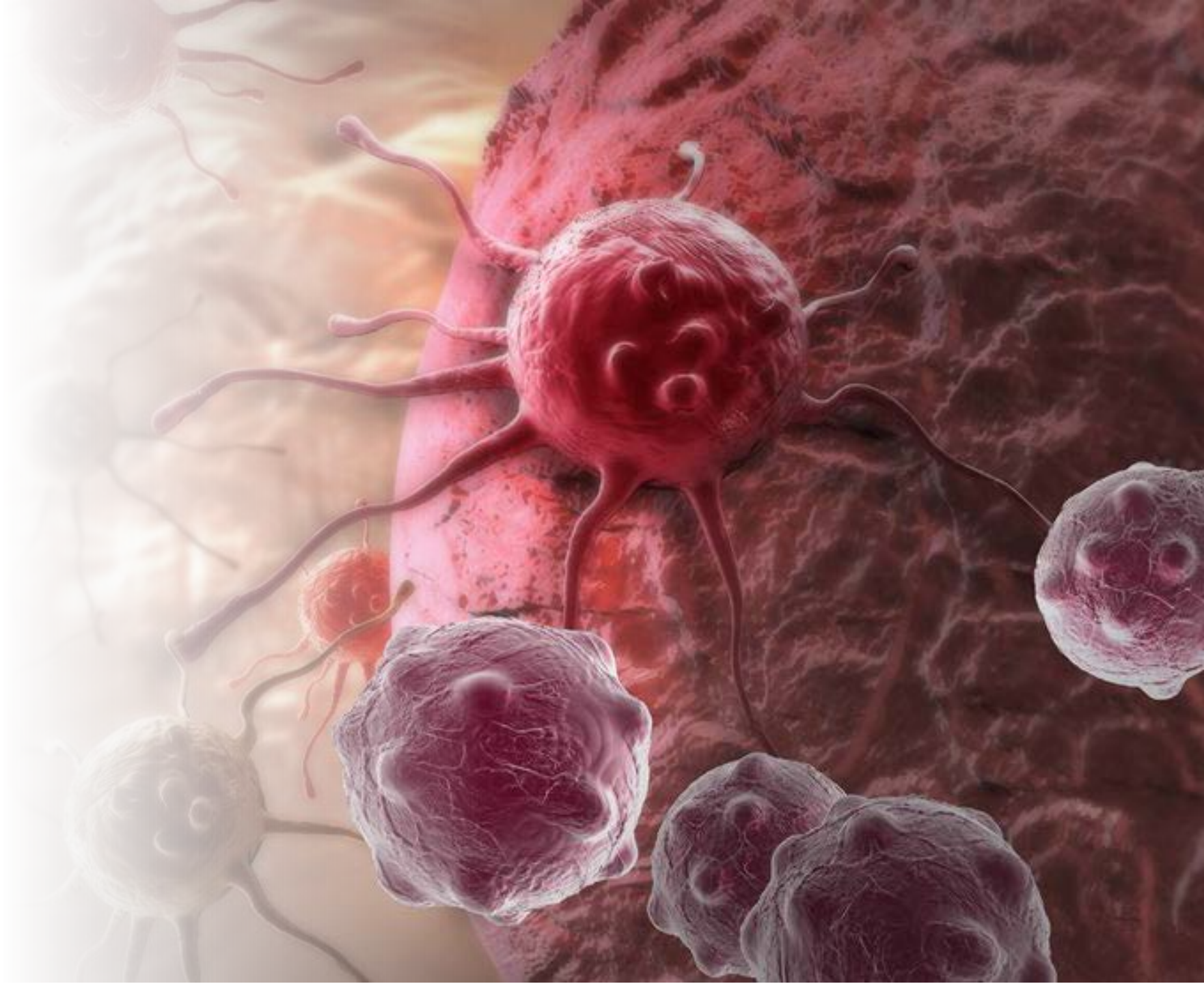


Table 1. Characteristics of Types I and II Cancer Drug–Induced TMA

	Type I Cancer Drug–Induced TMA	Type II Cancer Drug–Induced TMA
	Chemotherapy regimen	Anti-VEGF therapy
Characteristic agent	Mitomycin C and/or gemcitabine	Bevacizumab
Onset	Delayed; usually 6-12 mo after starting therapy	Occurs any time after the initiation of treatment and may be involved after prolonged treatment (1 dose to 29 mo)
Dose effect	Cumulative, dose related	Not dose related
Clinical	Appears to be permanent and irreversible; hematologic manifestations usually present; hypertension, acute renal failure, pulmonary edema, and ARDS are common	High likelihood of recovery after interruption (reversible); hematologic manifestations only in half of pts; hypertension, and varying degrees of proteinuria usually without kidney failure
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable kidney failure	Some evidence for the relative safety of rechallenge (additional data needed)
Pathologic	Arteriolar and glomerular capillary thrombosis	Exclusive glomerular capillary thrombosis
Therapy and prognosis	High incidence of acute mortality (4-month mortality up to 75%) and chronic kidney disease requiring dialysis despite drug discontinuation, steroids, or plasma exchange before rituximab and eculizumab use	Patient and kidney survival rates are excellent after stopping drug in association with antihypertensive drugs

Abbreviations: ARDS, acute respiratory distress syndrome; pts, patients; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor.

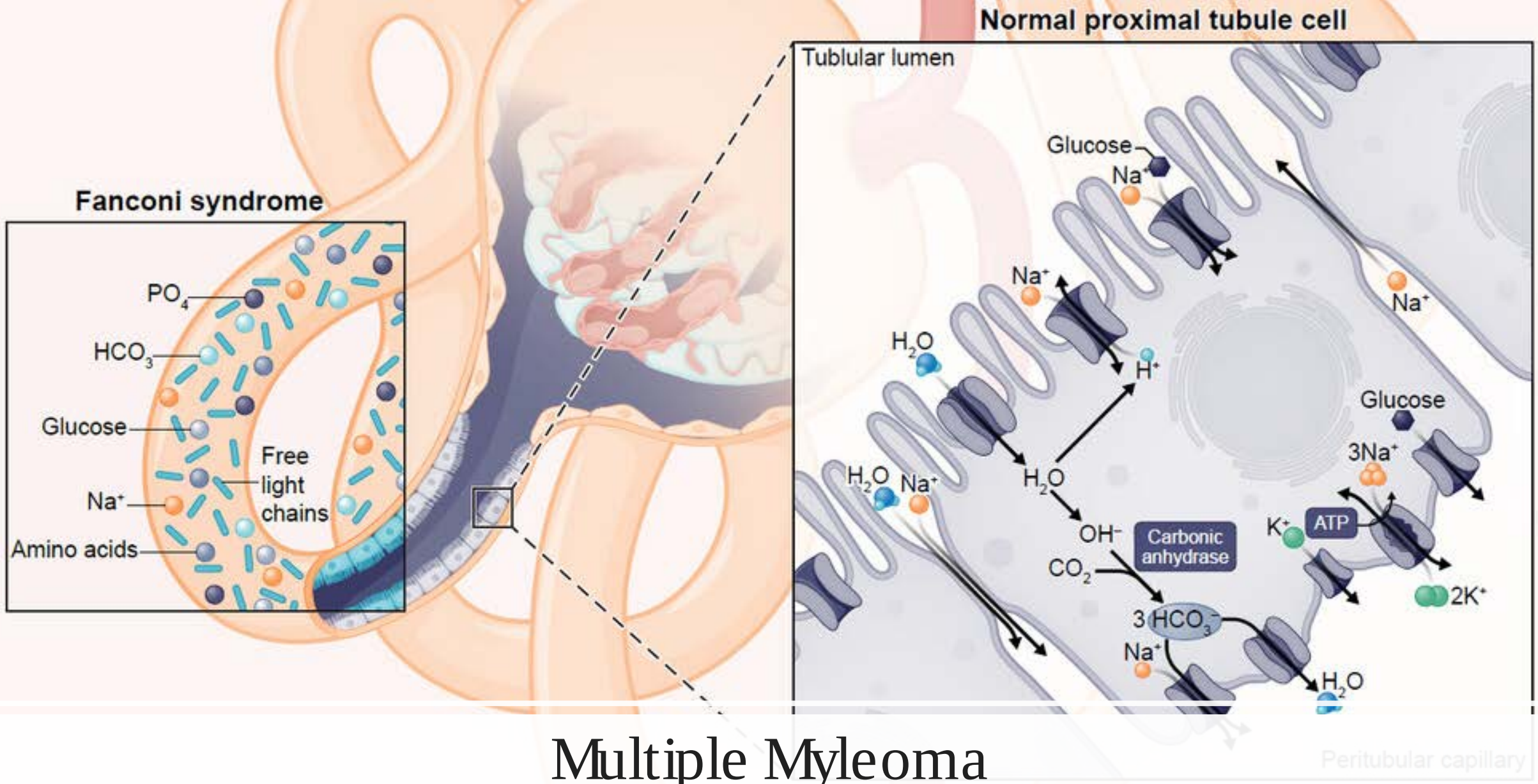
TMA/aHUS

Izzedine, Hassan et al. AJKD, Volume 66, Issue 5, 857 - 868

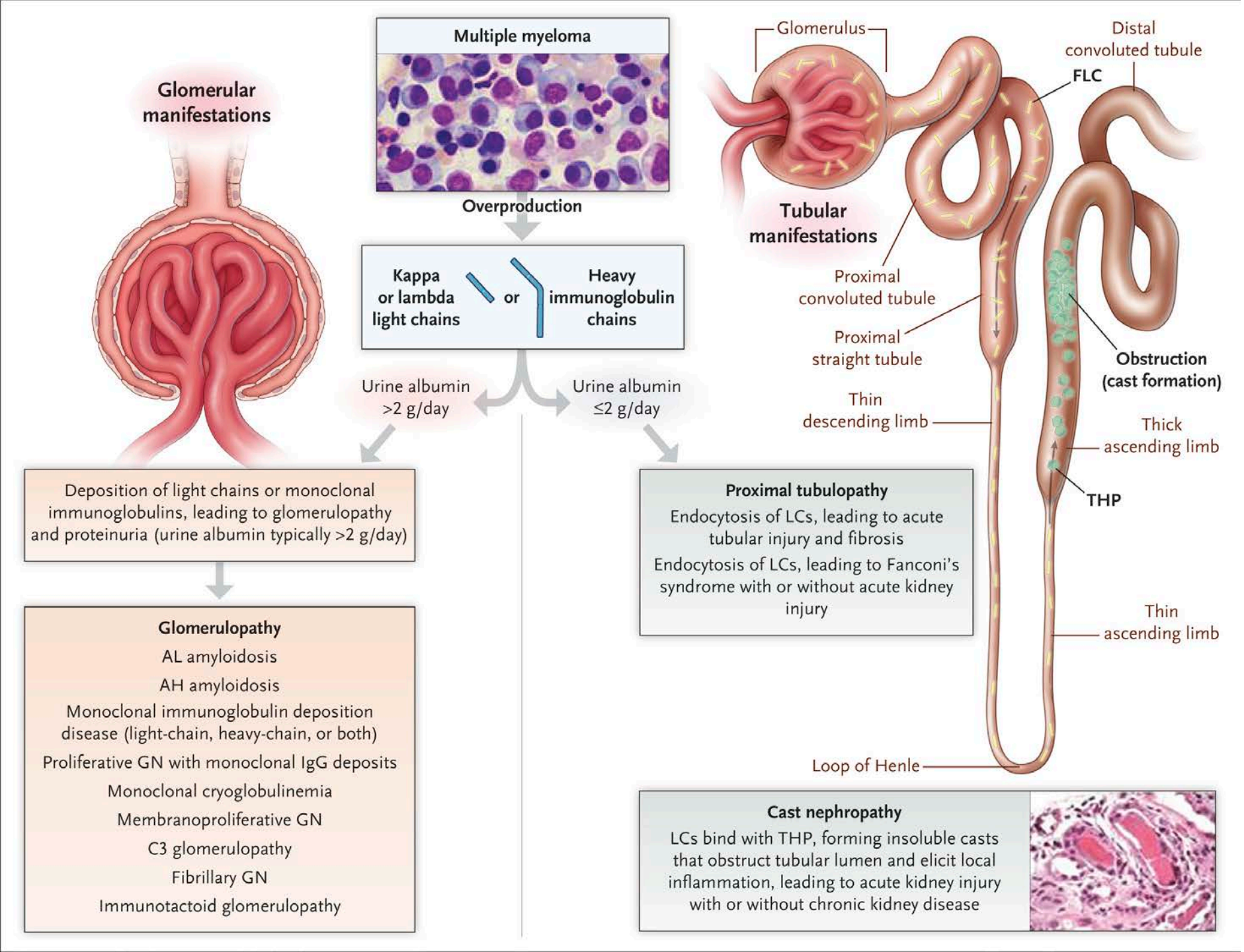
Case 3

- A 65-year-old female with a history of multiple myeloma (MM) presents with progressive weakness, bone pain, and polyuria.
- Laboratory findings reveal normocytic anemia, hypercalcemia, and an elevated serum creatinine level.

- Suggested work-up?



Multiple Myeloma



Rosner et al. NEJM. 2017

Treatment of renal complications in MM

- IV Hydration
- Remove contraindicated medications
- Treat hypercalcemia – Zometa (careful with dosing, more efficacious than pamidronate but could be toxic)
- Treat hyperuricemia
- Kidney Biopsy?
- RRT if needed - may reverse renal insufficiency in some cases
- Treat the MM- bortezomib containing combination (lenalidamide reduced dosing)

Case 4

- A 41-year-old male presented with headache, facial numbness, and fever. Notable findings included third cranial nerve palsy and laboratory abnormalities, including severe hypophosphatemia (0.6 mg/dL), acute kidney injury (creatinine 2.9 mg/dL), hyperuricemia (13.2 mg/dL), elevated LDH (3880 IU/L), leukocytosis (137×10^9/L), and thrombocytopenia (48×10^9/L). Further evaluation with flow cytometry and bone marrow biopsy confirmed a diagnosis of T-cell acute lymphoblastic leukemia (ALL).
- Diagnosis?

Tumor lysis vs. tumor genesis syndromes

- TGS is a potentially life-threatening condition linked to rapidly proliferating neoplastic cells.
- The high metabolic demand of tumor cells causes excessive phosphate uptake, leading to severe hypophosphatemia, which may result in rapid cardiorespiratory collapse.
- Patients with high-burden malignancies, such as leukemias and lymphomas, may present with isolated TGS, isolated tumor lysis syndrome (TLS), or a combined TLS-TGS.

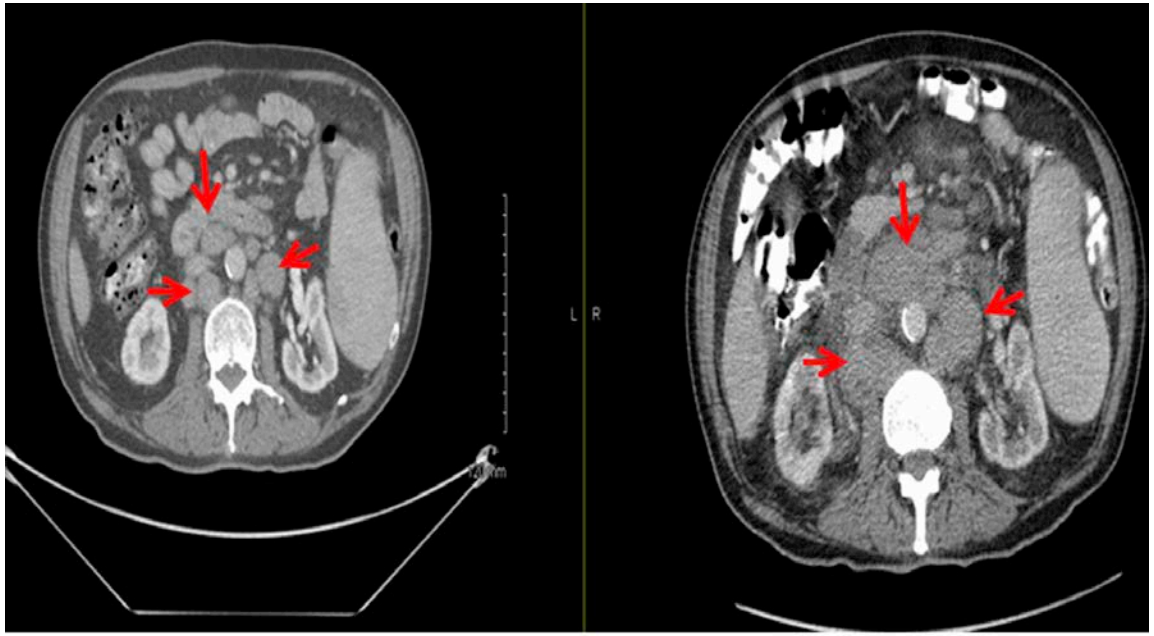


Figure 1:
On the right, significant progression of abdominal/pelvic lymphadenopathy (arrows) on a CT abdomen/pelvis with contrast done at presentation, compared to the scan on the left done approximately 2 months prior.

Radi, Suhaib et al. Canadian Journal of Diabetes, Volume 43

Other lyte derangments?

Hyperphosphatemia

- Seen in Tumor Lysis Syndrome (TLS) due to massive tumor cell breakdown and phosphate release

Hyperkalemia

- Common in TLS due to tumor cell lysis and potassium release
- Can lead to cardiac arrhythmias

Hypokalemia

- Can occur from chemotherapy-induced renal losses or diarrhea

Hyperuricemia

- From purine breakdown during cell lysis (TLS)
- May contribute to acute kidney injury

Hypocalcemia

- Secondary to hyperphosphatemia (calcium-phosphate precipitation) in TLS
- Can cause tetany, seizures, and cardiac arrhythmias

Hypercalcemia

- More common in hematologic malignancies with bone involvement (e.g., multiple myeloma, adult T-cell leukemia/lymphoma)
- Due to osteolysis, PTHrP secretion, or vitamin D-mediated effects

Metabolic Acidosis

- Lactic acidosis from high tumor metabolic activity
- Renal failure due to TLS-related nephropathy

Hyponatremia

- SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion) in leukemias and lymphomas

Case 5

A 56-y old female with CLL presents with a serum potassium of 8mmol/L. Her kidney function is normal with a serum creatinine of 0.9mg/dl and BUN is 10mg/dl. Her cell count is 400 and mostly lymphocytes. Her platelets are 90 and hemoglobin 9g/dl

Would you ask your onconephrologist to perform hemodialysis?

pseudo-

Table 1. Spurious Electrolyte Disorders

Spurious Electrolyte Disorder	Associated Conditions		Confirmatory Testing
Pseudohyponatremia	*Hyperproteinemia* 1. Plasma cell disorders • Multiple myeloma • Solitary plasmacytoma • AL amyloidosis • Light chain deposition disease • Heavy chain deposition disease • POEMS syndrome • Castleman disease	3. Medications • Intravenous immunoglobulin *Hypertriglyceridemia* • Hemophagocytic lymphohistiocytosis • L-asparaginase • All trans-retinoic acid *Hypercholesterolemia (lipoprotein X)* • Extrahepatic biliary obstruction	Whole blood sodium (direct ISE)
Pseudohyperkalemia	• Essential thrombocytosis • Chronic myelogenous leukemia • Acute myelogenous leukemia		Compare serum and plasma potassium, whole blood potassium (direct ISE)
Reverse pseudohyperkalemia	• Chronic lymphocytic leukemia • Pneumatic specimen tube transport		Carefully carrying the blood specimen to the laboratory, whole blood potassium (direct ISE)
Pseudohypokalemia	• Acute myelomonocytic leukemia		Compare serum and plasma potassium
Pseudohyperbicarbonatemia	• Monoclonal gammopathies		Calculated bicarbonate from blood gas
Pseudohypobicarbonatemia	• Severe hypertriglyceridemia • Waldenstrom macroglobulinemia		Similar to pseudohypobicarbonatemia
Spurious decreased serum anion gap	• Hypoalbuminemia • IgG paraprotein		Correct for hypoalbuminemia, evaluate for paraproteins
Spurious increased serum anion gap	• IgA paraprotein		Evaluate for paraproteins
Pseudohypophosphatemia	• Mannitol • Acute leukemia • Paraproteinemia		Dilution with normal saline, using a protein-free filtrate, or treatment of the sample with trichloroacetic acid or sulfosalicylate
Pseudohyperphosphatemia	• IgG or IgM paraprotein		Similar to pseudohypophosphatemia

Abbreviations: AL, amyloid light chain; ISE, ion selective electrode; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes.

Chowdhury R et al, AJKD 2023

CLL and the Potassium

Most common electrolyte disorder encountered in CLL patients is pseudohyperkalemia.

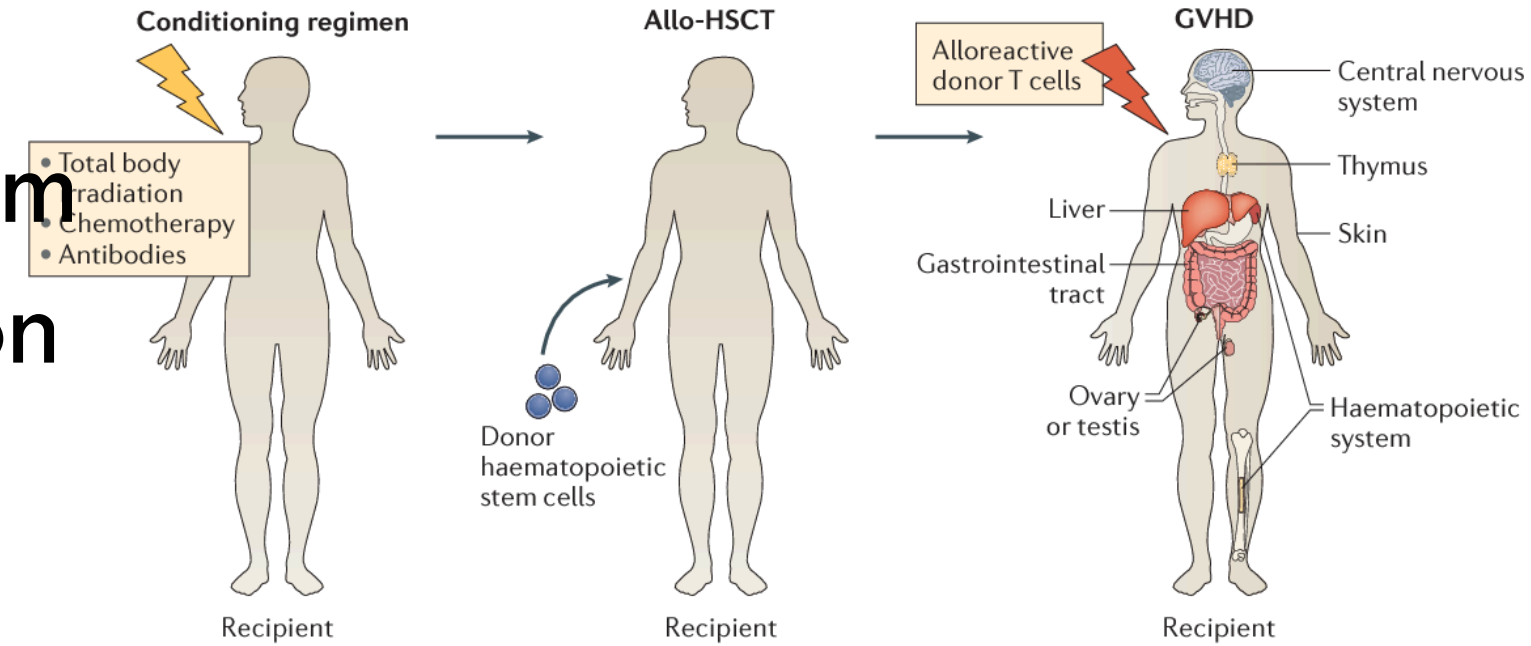
Potassium tends to stay predominantly in the intracellular compartment. Leakage of potassium from the intracellular compartment at the time of collection due to hemolysis, cell fragility or heparin-induced damage can lead to spurious elevation of measured potassium levels, which is known as pseudohyperkalemia.

High platelets and leukocytosis—lead to an artifactually elevated serum potassium level or spurious hyperkalemia

Below a white blood cell count of 50×10^9 cells/L, the median estimated percentage of a patient's potassium being elevated 1.7%, but was considerably higher, at 8.1%, when the white blood cell count was $\geq 100 \times 10^9$/L.

Katkish et al, *Minn Med* 2015
Wanchoo et al, *CKJ 2018*

Renal complications post Allogenic Hematopoietic Stem Cell Transplantation (Allo-HSCT)



https://www.nature.com/articles/nrc.2018.10

Acute Kidney Injury: Epidemiology

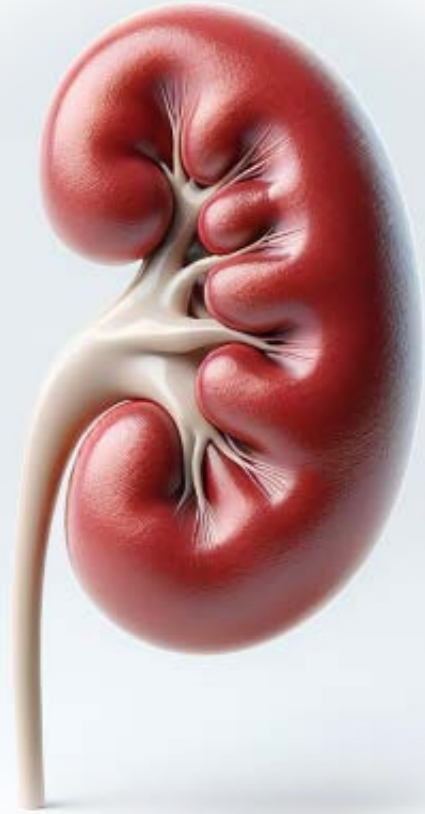
- 1989: Zager et al. Retrospectively analyzed 272 patients with HSCT.
  - 53% of patients developed AKI and 24% required RRT after HSCT.
  - BMT transplant requiring RRT had mortality of 84%

- 2002: Parikh et al. 2002: 88 patients who received HSCT at the University of Colorado.
  - Allogenic Transplant + Myeloablative strategy associated with an incidence of ~92% of AKI.
  - Allogenic + myeloablative group had a 4x increase in the need for RRT vs nonmyeloablative group.
  - RRT once gain conferred a mortality of ~82.6%
  - Autologous transplants have incidence of AKI ~20%.

Zager RA. Acute Renal Failure Following Bone Marrow Transplantation: A Retrospective Study of 272 Patients. American Journal of Kidney Diseases. 1989;13(3):210-216.
Parikh CR. Renal dysfunction in allogeneic hematopoietic cell transplantation. Kidney International. 2002;62(2):566-573.

Acute Kidney Injury: Epidemiology

- 2020: meta-analysis by Kanduri et al. 36 cohort studies with a total of 5144 patients undergoing HCT
  - Incidence of AKI and severe AKI was 55% and 8.3%, respectively.
- Key points:
  - Incidence of AKI post HSCT likely around ~50%
  - Onset of AKI can be as late as ~100 days post-transplant.
  - Allogenic HSCT+ myeloablative strategy has the highest risk of AKI, ~73%
  - AKI post HSCT requiring RRT confers a mortality between 60-80%



Kanduri SR. Incidence and mortality of acute kidney injury in patients undergoing hematopoietic stem cell transplantation: a systematic review and meta-analysis. *QJM: An International Journal of Medicine*. 2020;113(9):621-632.

Acute Kidney Injury: Risk Factors

Pre-Transplant Creatinine/CKD

Allogenic + myeloablative strategy

- CNI/cyclophos use

Volume depletion

Nephrotoxic Therapy

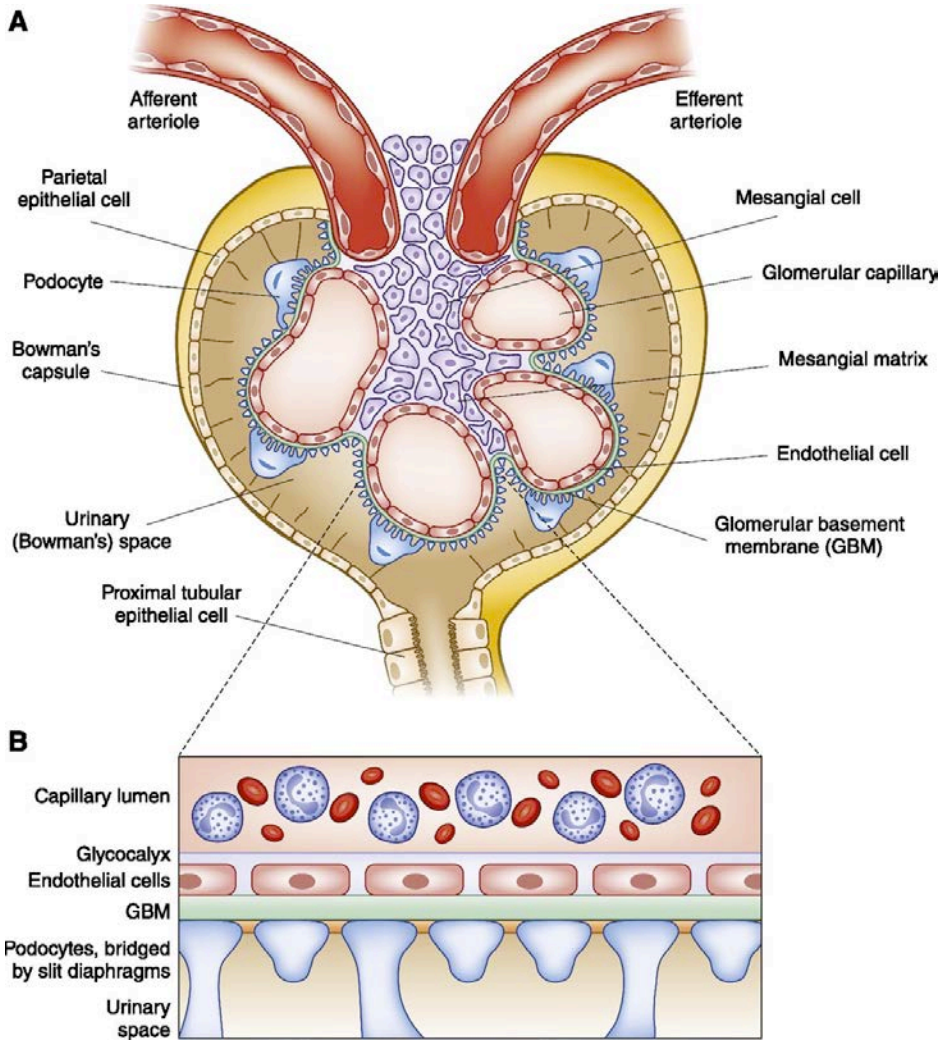
- Ampho, vanc, cidofovir

GVHD

Sepsis

Hingorani S. Renal Complications of Hematopoietic-Cell Transplantation. *New England Journal of Medicine*. 2016

Acute Kidney Injury: The usual suspects



- Pre-Renal
  - Low EABV
    - Volume depletion (mucositis, 5FU/Mel)
    - CHF
    - Cirrhosis
  - CNI
  - Diuretic Use
  - Contrast

Structures of the glomerulus. Kitcheng et al. 2016. CJASN

Pre-Renal AKI: HSCT Related

Comparison Between Spitzer and Maiolino Criteria for Engraftment Syndrome Diagnosis

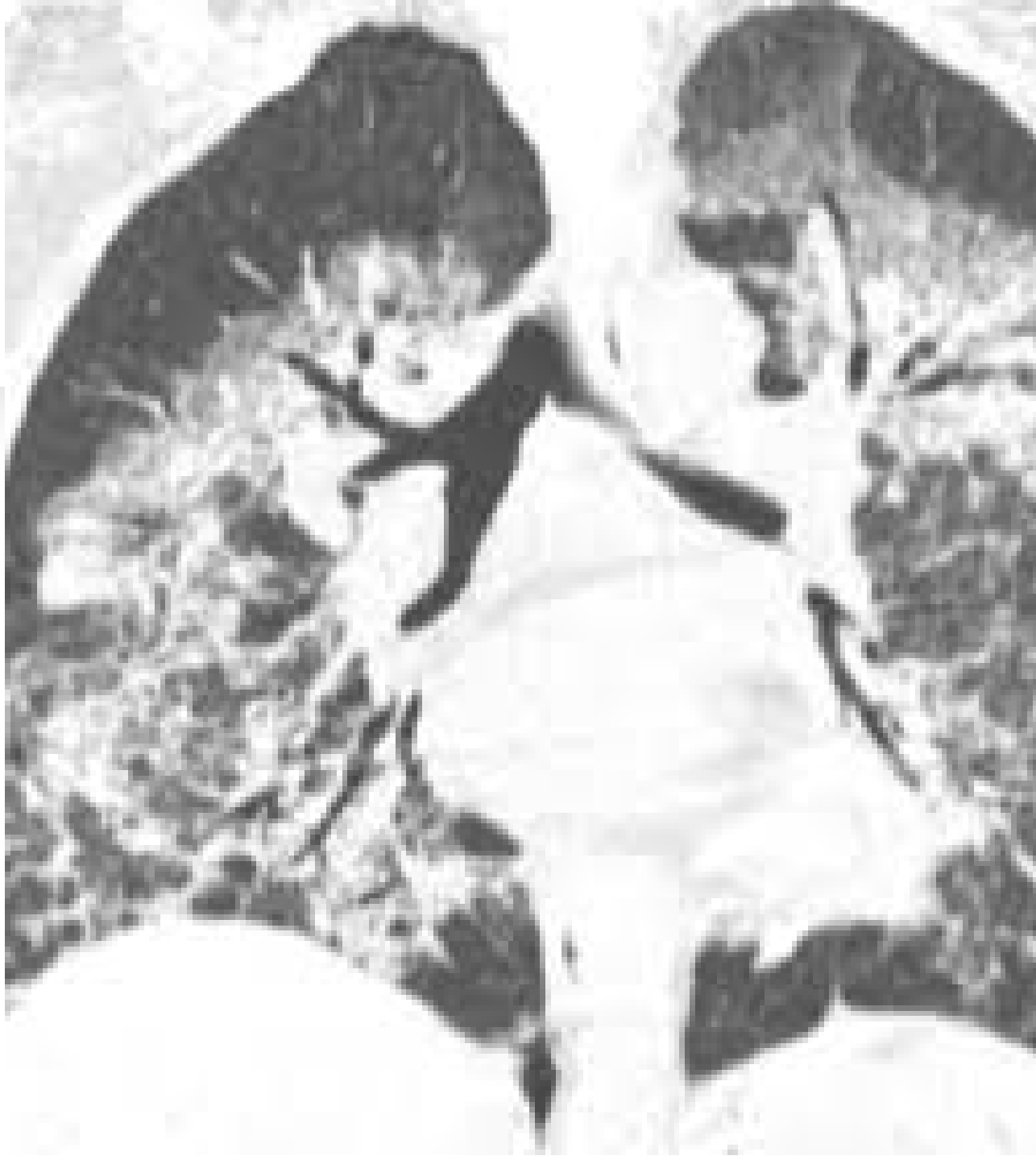
	Spitzer Criteria[a]	Maiolino Criteria[b,c]
Major criteria	1. Non-infectious fever, body temperature ≥ 38.3°C 2. Erythematous skin rash involving > 25% of body surface area; excluding drug allergy 3. Non-cardiogenic pulmonary edema and hypoxia	Non-infectious fever
Minor criteria	1. Hepatic dysfunction (either bilirubin≥ 2 mg/dL or transaminase levels ≥ 2 times normal) 2. Renal insufficiency (serum creatinine ≥ 2 times baseline) 3. Weight gain ≥ 2.5% of baseline body weight 4. Transient encephalopathy unexplainable by other causes.	1. Skin rash 2. Pulmonary infiltrates 3. Diarrhea
Timing to myeloid recovery	Within 4 days of absolute neutrophil count > 500	Within 24 hours of the presence of neutrophil

- Acute Engraftment Syndrome/ peri-engraftment respiratory distress syndrome (PERDS)
  - Occurs ~12 days post-transplant. (Irazabal et al. AJH 2011)
  - Attributed to rapid neutrophil increase and release of IL-2, TNF, IL-6, IL-8
  - 2011: Irazabal et al. incidence of AKI in Engraftment Syndrome to be as high as 93.1% in AL Amyloid patients s/p Autologous HSCT.
  - Association with POEMS
  - In all other disease ~26%.

Engraftment syndrome criteria. Poonsombudlert et al. JHSW 2020

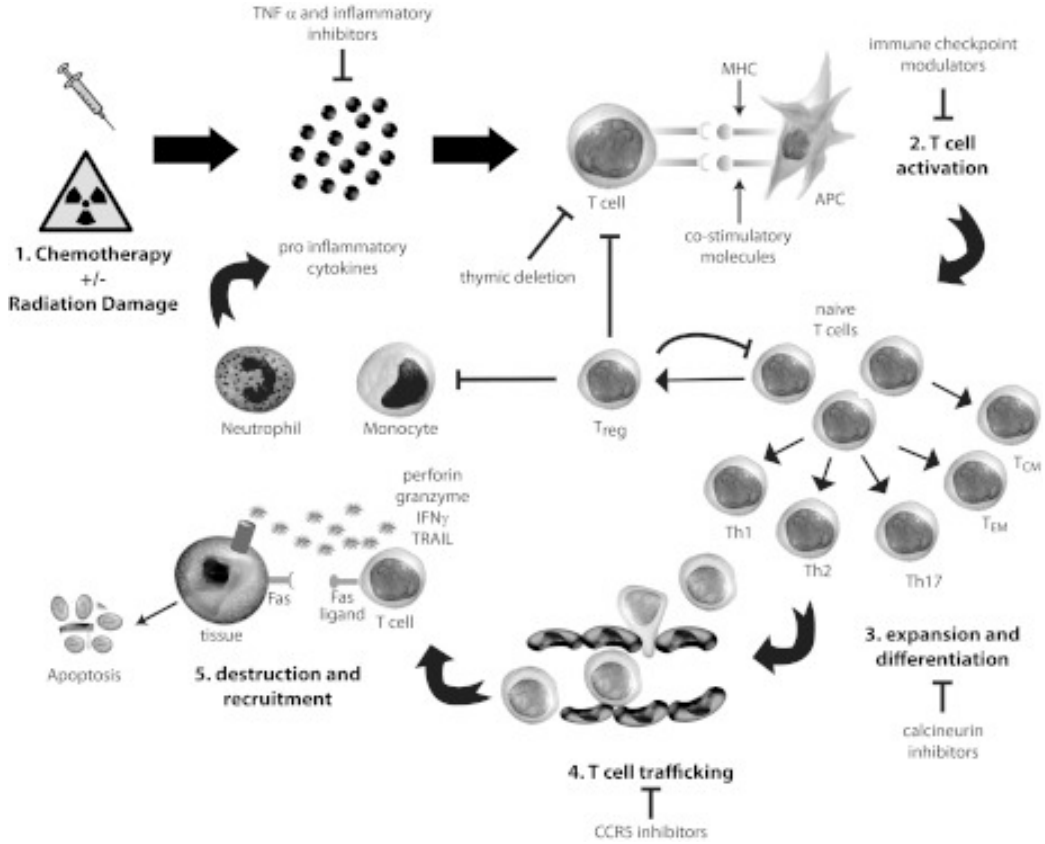
Pre-Renal AKI: HSCT Related

- Acute Engraftment Syndrome/PERDS
  - Management
    - Methylprednisolone 1mg/kg q12 with pred taper over weeks to months.
    - No clear data that steroids improve renal function (it did not uniformly prevent acute renal failure in this study by Irazebel).
  - One possibility is that because not all patients met criteria for ES



Pre-Renal AKI: HSCT Related

- GVHD – T cell mediated!
  - Occurs in Allogenic HSCT
  - Maculopapular rash, diarrhea, hepatitis
  - Occurs in 40-60% of HSCT patients.
  - Acute GVHD usually before 100 days post tx.
  - PPX: MTX, MMF, Cytoxan, CNI, Thymo, Campath
  - AKI partly believed to be from volume depletion.

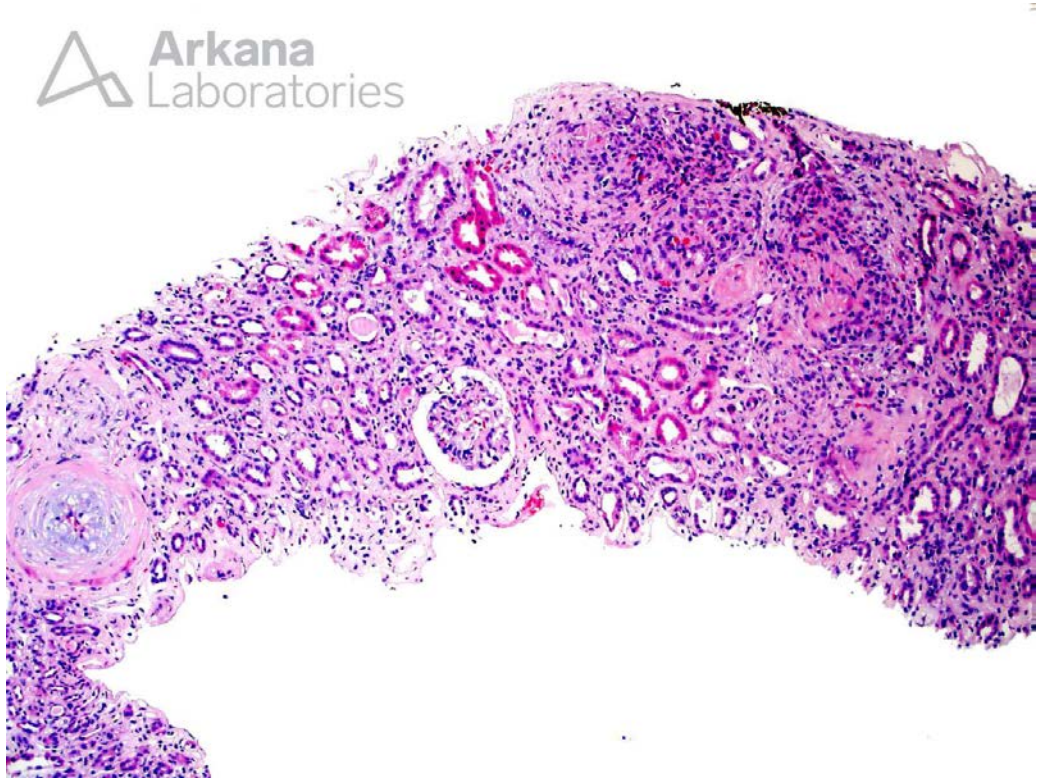


Mechanism of GVHD. Sung et al. Stem Cell Translational. 2012

Sung AD, Concise Review: Acute Graft-Versus-Host Disease: Immunobiology, Prevention, and Treatment. Stem Cells Translational Medicine. 2012;2(1):25-32.

Pre-Renal AKI: HSCT Related

- GVHD in the Kidney?
  - No formal renal histological criteria
  - 2009 Changsirikulchai et al reported: GVHD grades II to IV were associated with an increased risk of TMA in the kidney at autopsy.
  - More recently, Wall et al on their retrospective review of 124 pts with grade 3/4 GVHD found that 67.7% subjects met criteria for TA-TMA and patients that were refractory to steroids.
  - TMA
    - Advanced GVHD associated with TMA, especially when refractory to steroids.
  - Treatment
    - Steroids: 1st line
    - Thymo, Tac, MTOR, MMF antibody therapy against CD or Interleukins, lacking efficacy.



Sung AD. Concise Review: Acute Graft-Versus-Host Disease: Immunobiology, Prevention, and Treatment. Stem Cells Translational Medicine. 2012;2(1):25-32. doi:10.5966/sctm.2012-0115
Changsirikulchai S. Renal Thrombotic Microangiopathy after Hematopoietic Cell Transplant: Role of GVHD in Pathogenesis. Clinical Journal of the American Society of Nephrology. 2009;4(2)

Case 6

A 51-year-old woman with acute myeloblastic leukemia underwent myeloablative therapy followed by allogenic stem cell transplantation. After 9 days, she complains of right upper quadrant pain and develops jaundice. Urine output decreases over 24 hours to 400 mL.

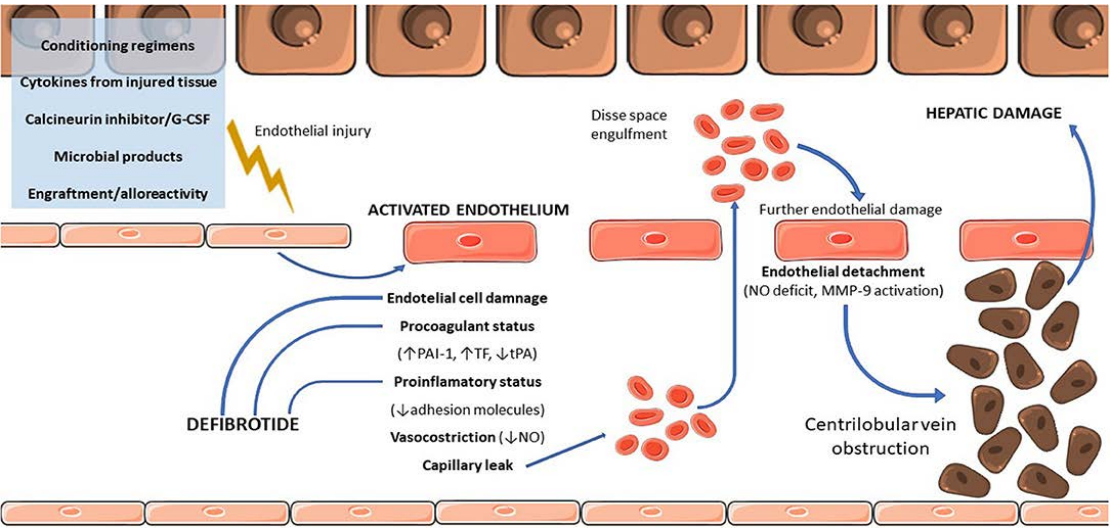
- Physical exam

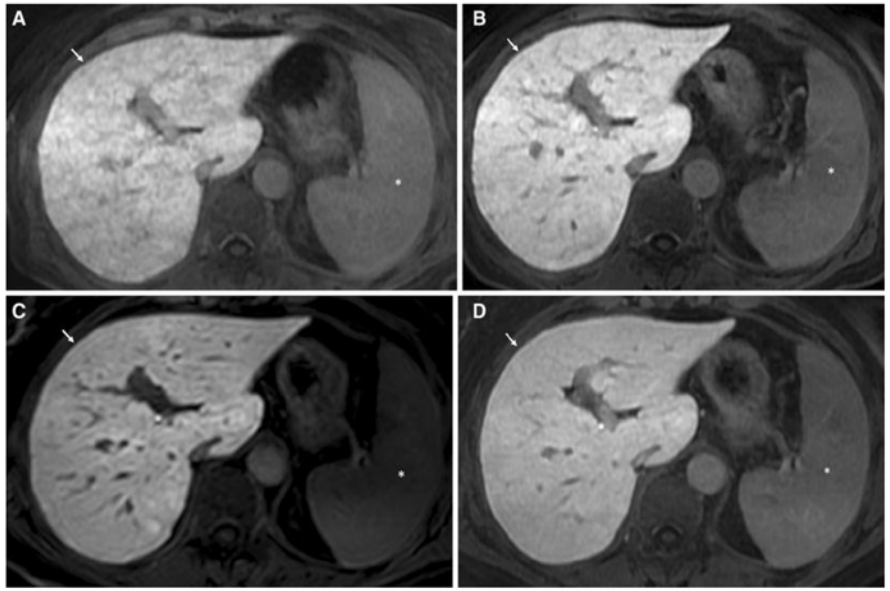
BP, 120/80 mm Hg; temperature, 99°F. Heart and lung examination are normal. Right upper quadrant is tender and 2+ edema is noted.

- Labs/Imaging

U/A 1+ protein with bland urine sediment. Electrolytes are normal with a BUN of 32 mg/dL and creatinine of 2.8 mg/dL. Liver function tests (LFTs): bilirubin, 4.9 mg/dL; alkaline phosphatase, 670 IU. Right upper quadrant ultrasound demonstrates no biliary stones and reversal of flow in the portal vein.

Pre-Renal AKI: HSCT Related





- Marrow Infusion Syndrome
  - Dimethylsulfoxide (DMSO - anti-freezing agent used to cryopreserve cells) exposure causing RBC lysis and pigment nephropathy
  - Pigment can cause renal vasoconstriction and direct pigment nephropathy, cast formation.
- Hepatic Sinusoidal Obstruction Syndrome/SOS (AKA Venooclusive disease/VOD)
  - Common in allogenic transplant, usually within 30 days.
  - Pre transplant myeloablative therapy and radiation cause cytokine release and decrease in glutathione = hepatocellular necrosis, sinusoidal obstruction, portal hypertension.
  - Gemtuzumab and Inotuzumab have been implicated (ALL, AML)
  - Similar physiology and clinical manifestations as Hepatorenal Syndrome.
- Management is generally supportive

Renaghan AD. Acute Kidney Injury and CKD Associated with Hematopoietic Stem Cell Transplantation. *Clinical Journal of the American Society of Nephrology*. 2019;15(2):289-297

Intrinsic Renal Injury: ATN

- Sepsis
  - Guddati et al. reviewed 21,898 HSCT recipients (2000-2008) were 5x more likely to develop sepsis.
  - Mortality significantly higher in allogenic transplants with sepsis (55% than non HSCT patients with sepsis).

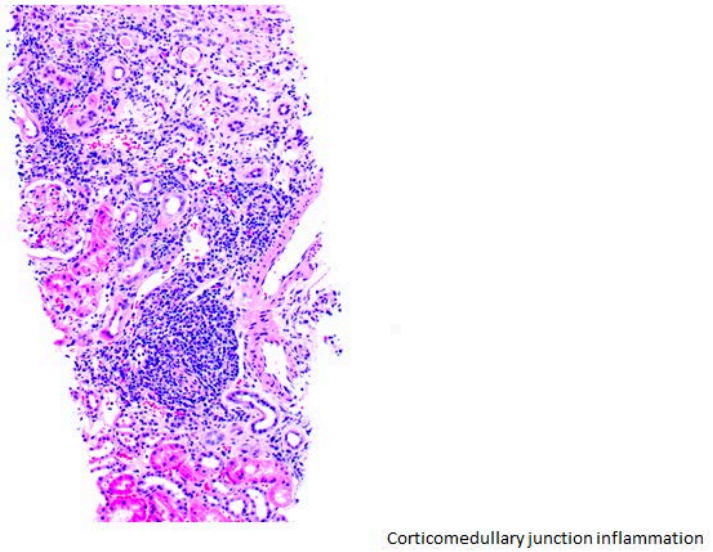
Medications	Comment
Vancomycin/Zosyn	Possible cellular apoptosis and reactive oxidation in tubules w/casts. AIN.
Aminoglycosides	Usually 7-10 days after exposure. Fanconi Syndrome.
Acyclovir	Crystalline tubular injury
Amphotericin	Increased tubular membrane permeability. NDI. Type 1 DRTA

Guddati AK. Trends and outcomes of severe sepsis in hematopoietic stem cell transplant recipients. Journal of Clinical Oncology. 2013;31

Sawaya BP. Amphotericin B nephrotoxicity: the adverse consequences of altered membrane properties. Journal of the American Society of Nephrology. 1995;6(2):154-164.

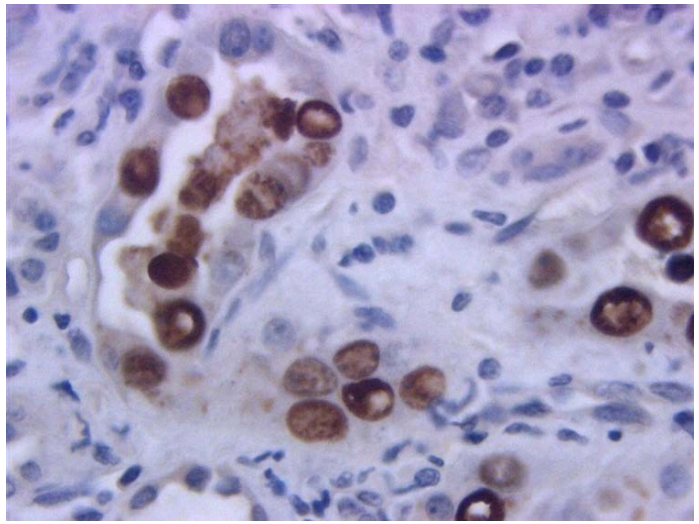
Case 7

A 55 yo M was diagnosed with MDS and received allogenic stem cell transplant. He was treated with cyclosporine, MTX, and campath for GVHD prophylaxis. His course was complicated by steroid resistant GVHD requiring further aggressive immunosuppression. The GVHD did improve but 3 weeks after transplant he developed an AKI, gross hematuria, and 1.2g proteinuria. Imaging did not reveal nephrolithiasis and cystoscopy was also performed, which was unremarkable. Urine microscopy with numerous WBC sheets. Renal biopsy was performed.



Corticomedullary junction inflammation

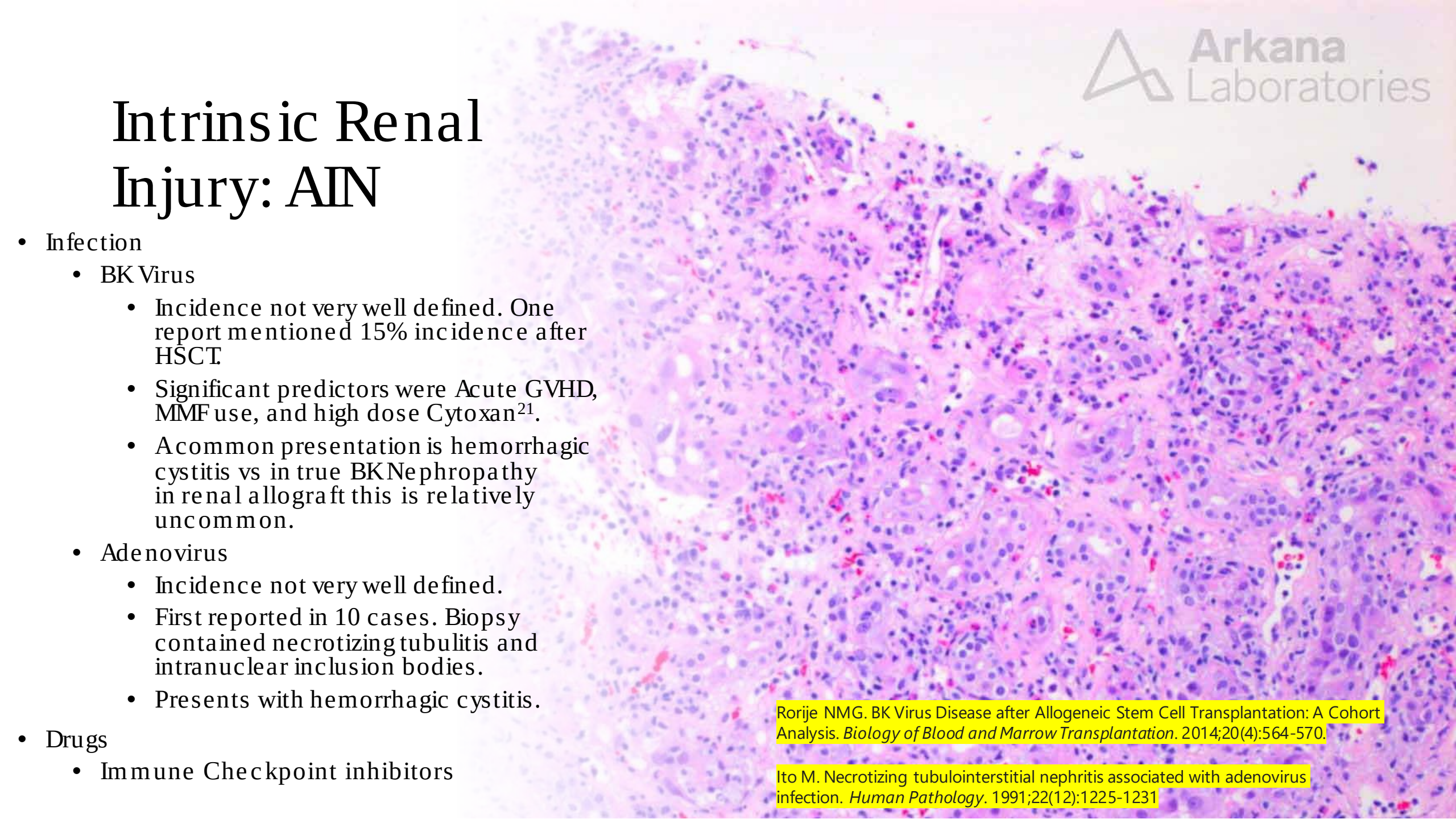
Reproduced from Renal Fellow Network



SV40 T antigen staining. Reproduced from Renal Fellow Network.

Intrinsic Renal Injury: AIN

- Infection
  - BK Virus
    - Incidence not very well defined. One report mentioned 15% incidence after HSCT.
    - Significant predictors were Acute GVHD, MMF use, and high dose Cytoxan[21].
    - A common presentation is hemorrhagic cystitis vs in true BK Nephropathy in renal allograft this is relatively uncommon.
  - Adenovirus
    - Incidence not very well defined.
    - First reported in 10 cases. Biopsy contained necrotizing tubulitis and intranuclear inclusion bodies.
    - Presents with hemorrhagic cystitis.
- Drugs
  - Immune Checkpoint inhibitors



Rorije NMG. BK Virus Disease after Allogeneic Stem Cell Transplantation: A Cohort Analysis. *Biology of Blood and Marrow Transplantation*. 2014;20(4):564-570.

Ito M. Necrotizing tubulointerstitial nephritis associated with adenovirus infection. *Human Pathology*. 1991;22(12):1225-1231

Case 8

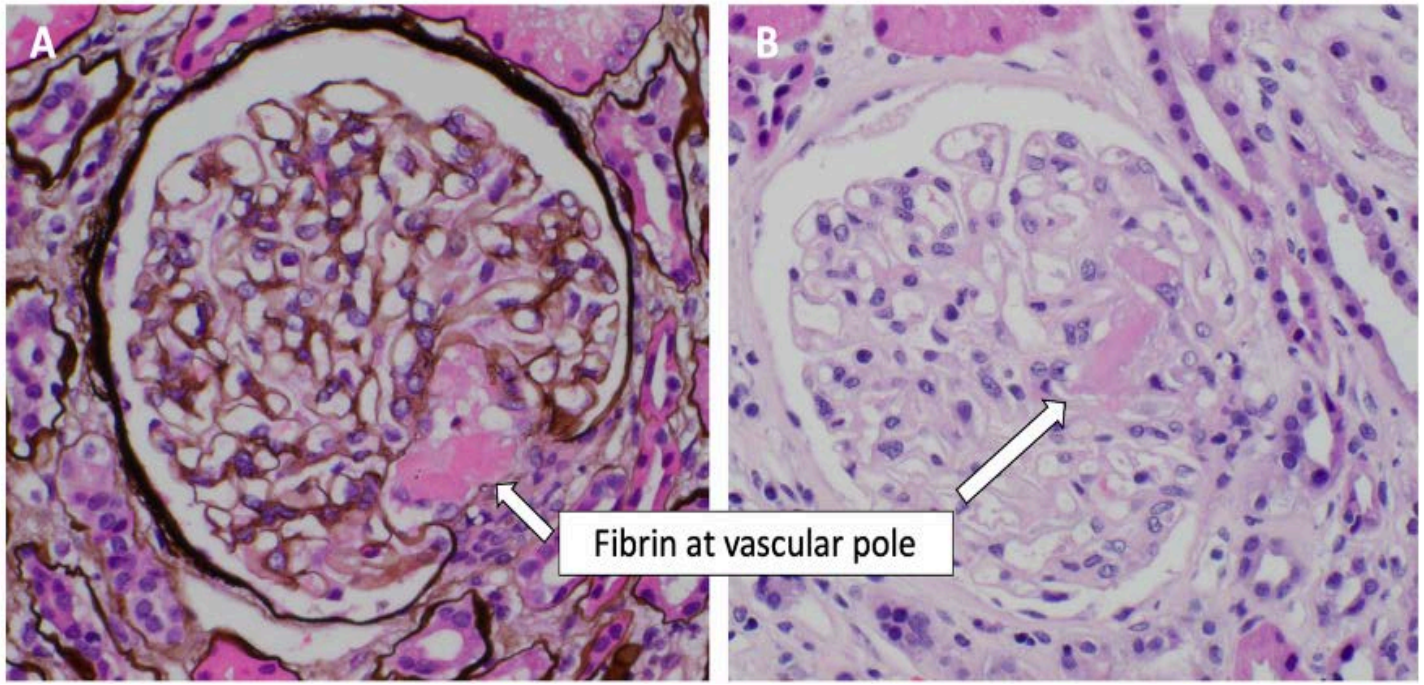
58 yo M with a diagnosis of AML is s/p allogenic myeloablative HSCT. He was felt to be engrafting well, however on day 18 he was persistently hypertensive with a new AKI and proteinuria. His CBC was notable for worsening thrombocytopenia and anemia.

His urine microscopy revealed 2-3rbc/HPF. Kidney biopsy is planned after platelet transfusion.

LDH 1200

Hapto <10

Peripheral smear with Schistocytes



Fibrin deposition. Reproduced from Renal Fellow Network

Intrinsic Renal Injury: Acute TMA

- Incidence varies 2%-39% post HSCT, mortality as high as 75%.
- Can present with subclinical AKI and lead to CKD.
  - Proteinuria
  - HTN
  - Worsening Anemia
- Diagnostic Criteria
  - >2 Schistocytes/HPF on peripheral smear
  - Increase in serum LDH > baseline. Hapto low.
  - Concurrent renal or neurological dysfunction
  - Negative Coombs
  - Does not always correlate with histological findings.

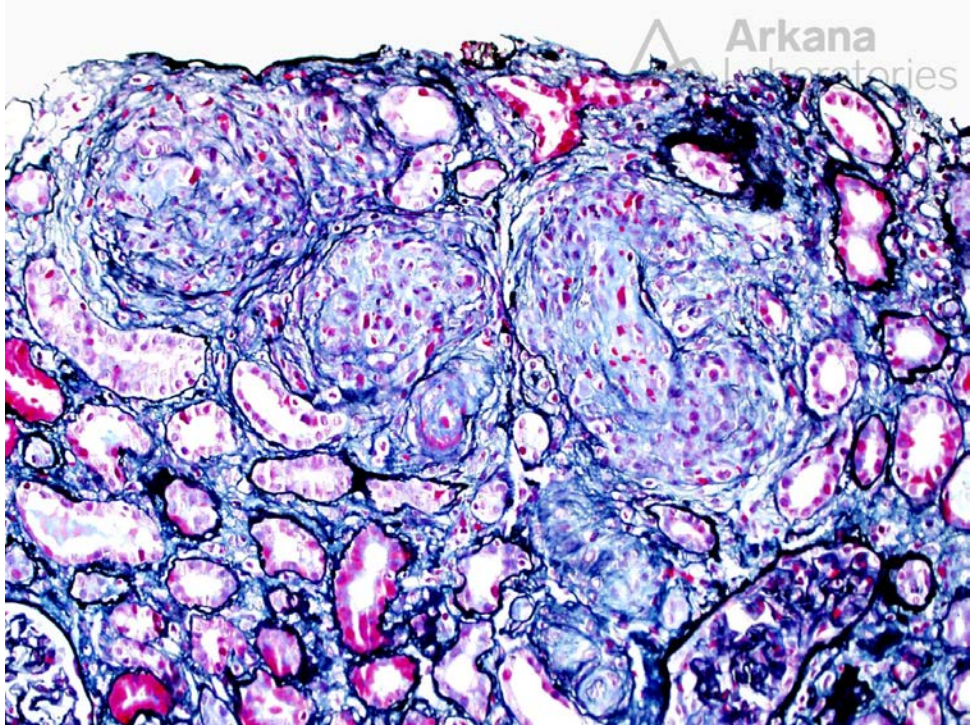
Criteria	COH
Hemolysis	Presence of schistocytes, persistent nucleated RBC's
Thrombocytopenia	Prolonged or progressive thrombocytopenia (platelets <50 ×10^9/L or ≥50% decrease from previous counts)
Liver Function	LDH >2x upper limit of normal
Renal Function	SCr >1.5 × baseline

Changsirikulchai S. Renal Thrombotic Microangiopathy after Hematopoietic Cell Transplant: Role of GVHD in Pathogenesis. Clinical Journal of the American Society of Nephrology. 2009;4(2):345-353.

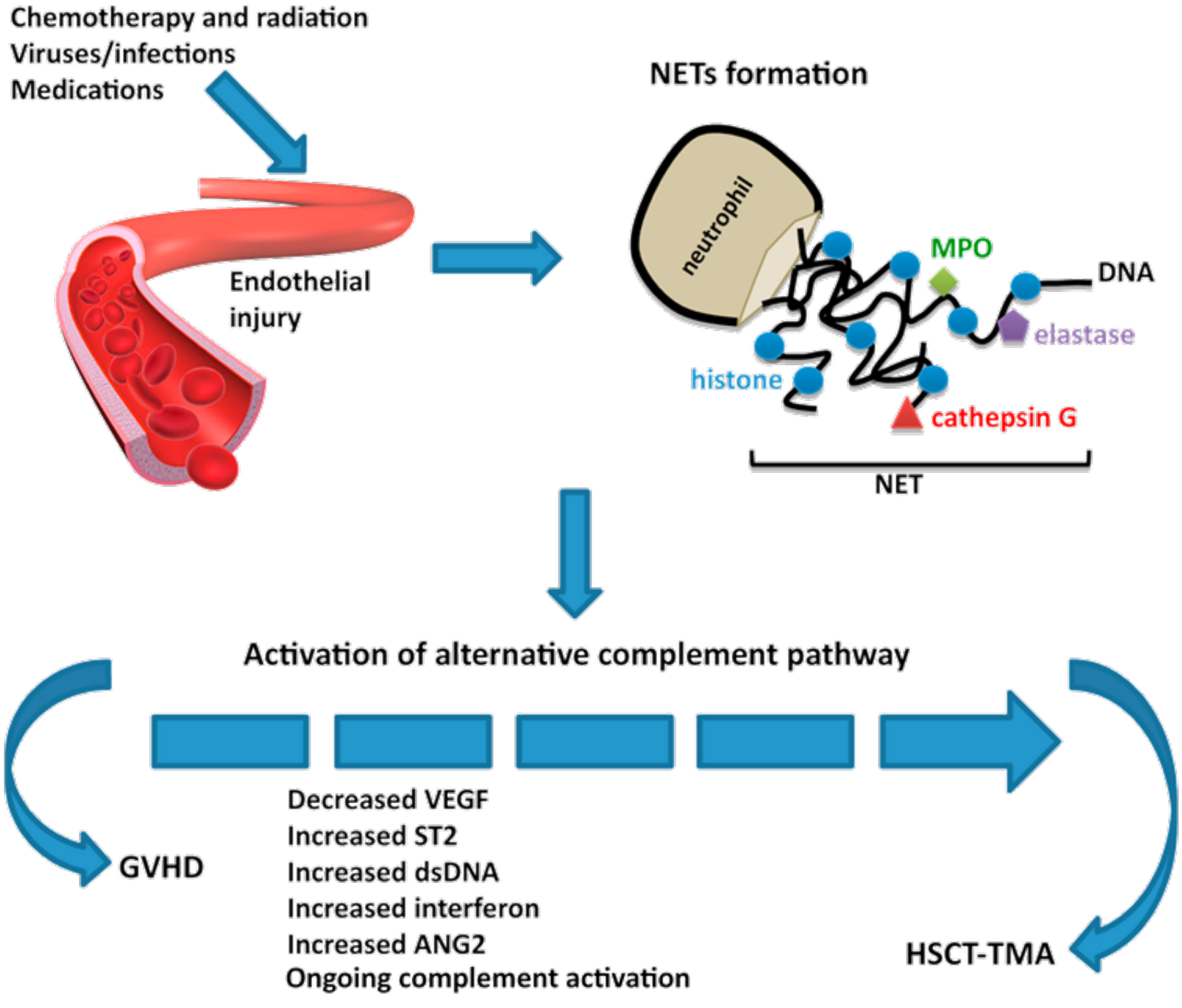
Ho VT. Blood and Marrow Transplant Clinical Trials Network Toxicity Committee Consensus Summary: Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplantation. Biology of Blood and Marrow Transplantation. 2005;11(8):571-575

Intrinsic Renal Injury: Acute TMA

- Causes
  - Complication of HSCT
  - Medications
  - Complication of GVHD?
    - Changsirikulchai et al. Biopsy from 314 patients from 1992-1999 found a correlation between GVHD II-IV
  - Complement Mediated?
    - Alternative pathway mediated Atypical HUS

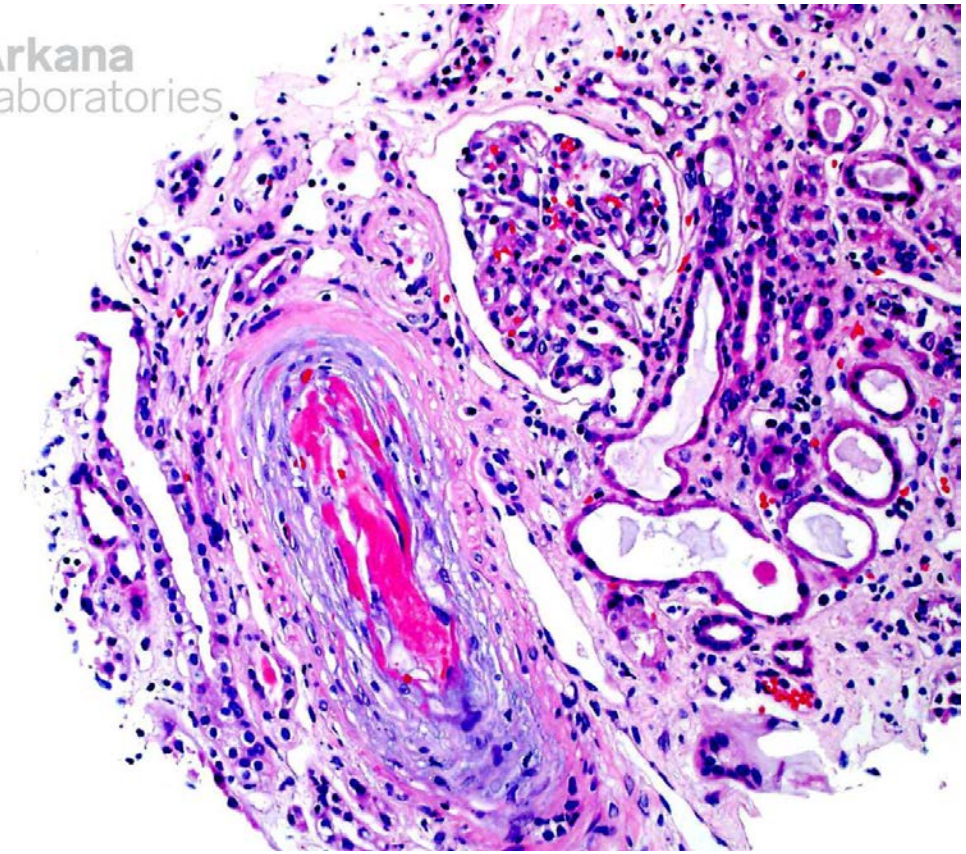


Changsirikulchai S. Renal Thrombotic Microangiopathy after Hematopoietic Cell Transplant: Role of GVHD in Pathogenesis. Clinical Journal of the American Society of Nephrology. 2009;4(2):345-353.



Wanchoo et al AJKD 2018.

Intrinsic Renal Injury: Acute TMA



- Management
  - BP/proteinuria control and Termin stop offending agents
  - al Complement Inhibition? Eculizumab?
    - Jodele et al. Reported 64 pediatric cases of HSCT with high-risk TA-TMA.
      - 66% 1-year survival in treated group vs 16.7% untreated
      - 56% achieved complete remission
      - Only 23% required RRT
      - In survivors median eGFR was 20% lower than pre HSCT.
    - Consider Adams TS, C5B-C9 (MAC) and CFH testing.

Jodele S. Complement blockade for TA-TMA: lessons learned from large pediatric cohort treated with eculizumab. Blood. Published online January 13, 2020.

TA-MA Therapy

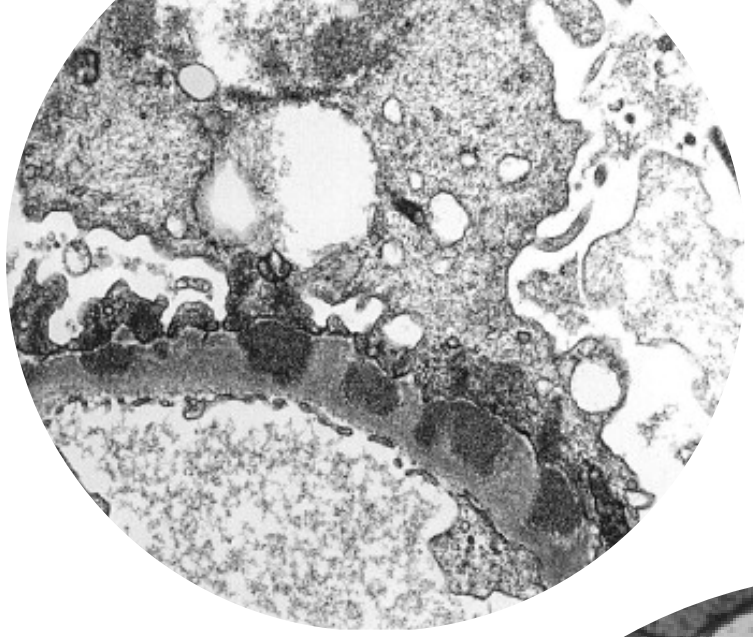
Treatment Modality	No. of Patients in Published Reports	Mechanism	Response Rate	Potential Harmful Effects	Treatment Cost[a]	Ongoing Clinical Trials[b]
Plasmapheresis	162 (adults)	Removal of potential inhibitor/antibody	59%-65%	Bleeding, infections, hypotension, arrhythmias, anemia	4,500-10,000	
Daclizumab	13 (adults)	Anti–IL-2	69%	Skin rash, autoimmune diseases, infections	48,000	
Rituximab	15 (8 adult, 7 pediatric)	Anti-CD20	80%	Infusion reactions, infections, HBV reactivation	23,000	
Defibrotide[c]	16 (11 adult, 5 pediatric)	Antifibrinolytic and thrombotic	67%	Hypotension, diarrhea, bleeding	NA	NCT03384693
Vincristine	16 (13 adult, 3 pediatric)	Antimicrotubular agent, immumomodulator	69%	Constipation, neuropathy	54	
Eculizumab	34 (24 pediatric, 1 adult, & 1 study w/ 9 cases w/ age range of 2-61 y)	C5 inhibitor	67%	Infections, bleeding	140,000	NCT02604420 (adults w/ HSCT-TMA)

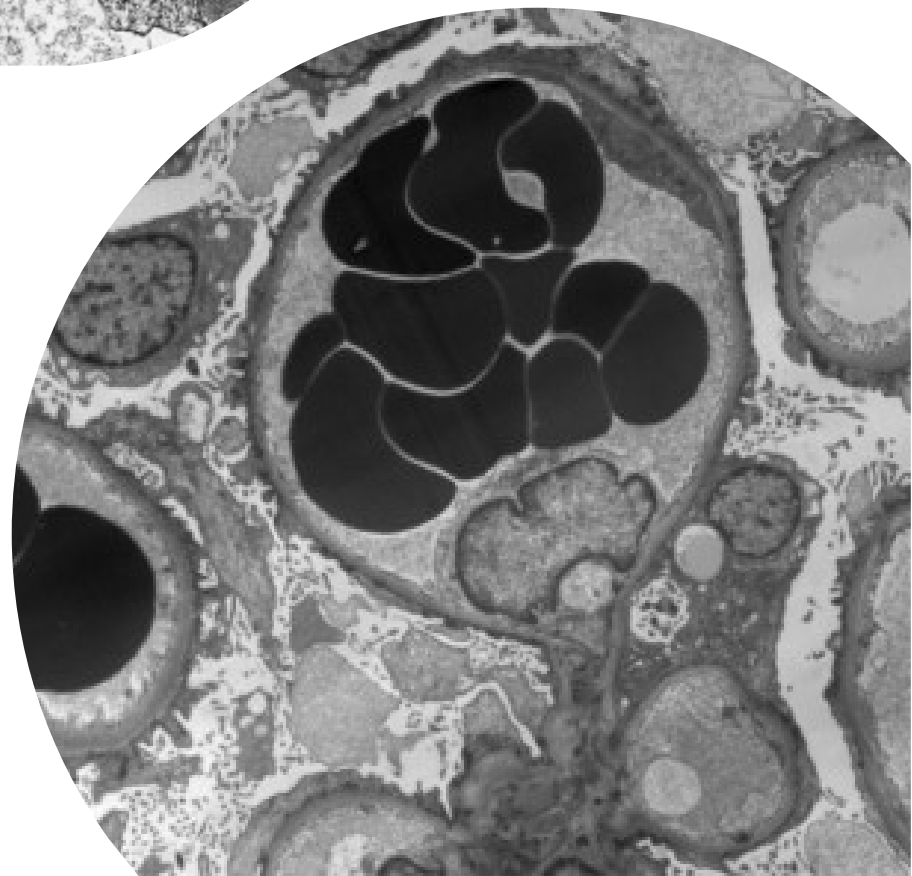
Note: Data for each treatment modality are based on low-quality evidence of case reports and case series only.
Abbreviations; HBV, hepatitis B virus; HSCT-TMA, hematopoietic stem cell transplantation–associated thrombotic microangiopathy; IL, interleukin; NA, not available.
[a]Approximate cost information (US dollars) obtained from pharmacy and blood bank departments.
[b]ClinicalTrials.gov trial number cited when applicable.
[c]Not readily available in the United States, investigational use only.

Wanchoo et al AJKD 2018.

Case 9

- 62 yo F with CLL is s/p allogenic non-myeloablative HSCT with appropriate engraftment 14 months ago. She is referred to outpatient Nephrology by hematology for elevated Cr, 6g of proteinuria, and worsening edema. Urine microscopy was bland and all serologies were negative.

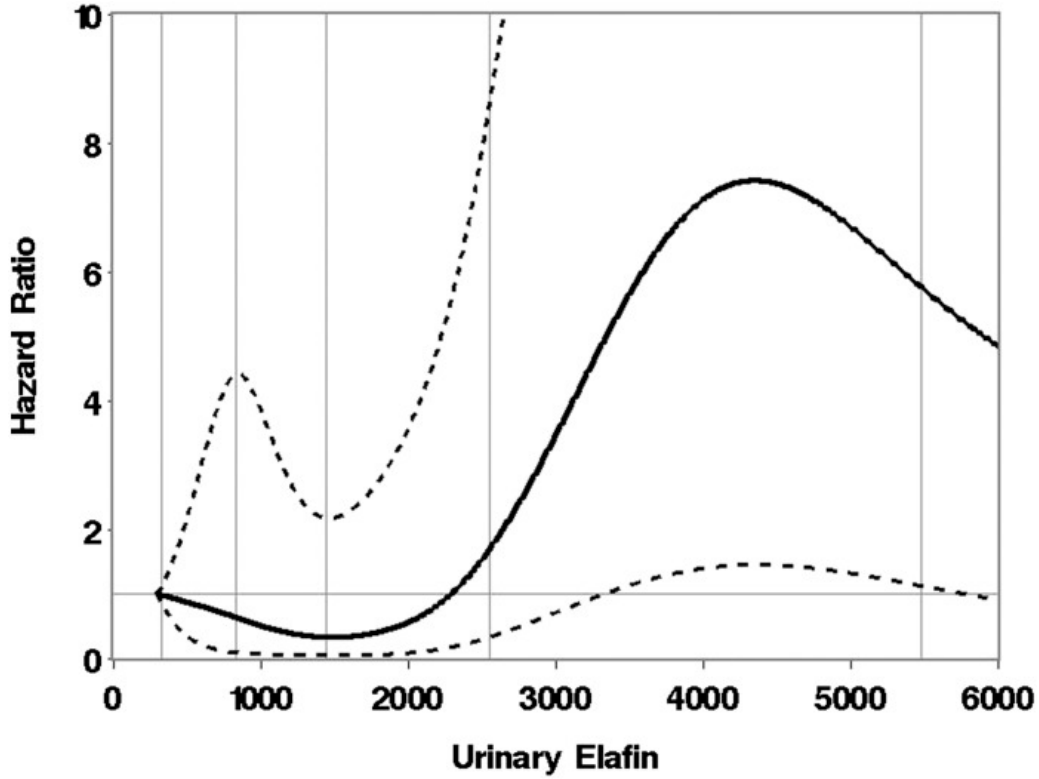




Reproduced from ADJKD Atlas of Renal Pathology.

Intrinsic Renal Injury: GN

- Nephrotic Syndrome
  - Incidence ~1% of AKI relatively rare and Nephrotic Syndrome. More commonly occurs >6 months post HSCT.
  - Nonmyeloablative therapy more commonly associated.
  - GVHD
    - Inflammatory Cytokines such as urinary elafin: a potential plasma biomarker for GVHD
    - Elevated urinary elafin associated with AKI.
    - Elevated urinary elafin associated with micro and macro albuminuria.

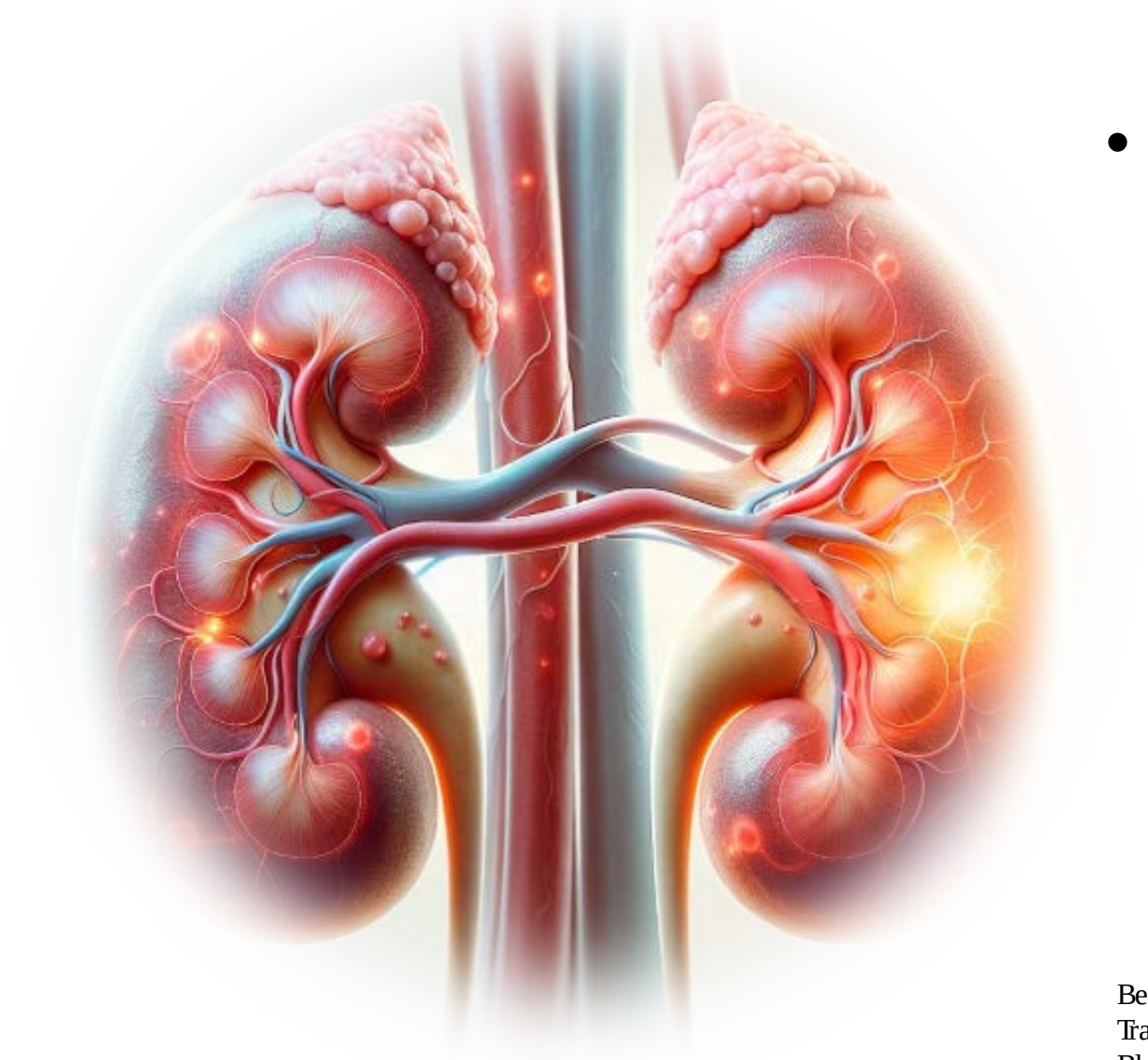


Paczesny S. Elafin Is a Biomarker of Graft-Versus-Host Disease of the Skin. Science Translational Medicine. 2010;2(13).

Hingorani S. Urinary Elafin and Kidney Injury in Hematopoietic Cell Transplant Recipients. Clinical Journal of the American Society of Nephrology. 2014;10(1):12-20.

Beyar-Katz O. Adult Nephrotic Syndrome after Hematopoietic Stem Cell Transplantation: Renal Pathology is the Best Predictor of Response to Therapy. Biology of Blood and Marrow Transplantation. 2016;22(6):975-981.

Intrinsic Renal Injury: GN



- Nephrotic Diseases: Membranous Nephropathy vs Minimal Change
  - In 2016, Beyer-Katz at al from Israel reviewed 116 cases of Nephrotic syndrome post HSCT between 1988-2015 and reported it in BMT
  - Median onset 20.5 months
  - 65.5% had Membranous on biopsy and 19% with MCD
  - Developed concomitant to GVHD
  - MN/MCD a manifestation of GVHD or independent process?

Beyar-Katz, Ofrat et al. Adult Nephrotic Syndrome after Hematopoietic Stem Cell Transplantation: Renal Pathology is the Best Predictor of Response to Therapy Biology of Blood and Marrow Transplantation 22 (6), 975 – 981.

Intrinsic Renal Injury: Nephrotic Syndrome

- Management
  - Membranous Nephropathy
    - Nasr et Al: reported 5 cases treated with rituxan having complete remission.
    - Ratanatharathorn et al. reported 4/8 had complete resolution of GVHD and nephrotic syndrome.
    - Expert opinion: Regardless of PLA2R status and concomitant GVHD, recommend Rituximab.
    - Response can take up to 6 months.

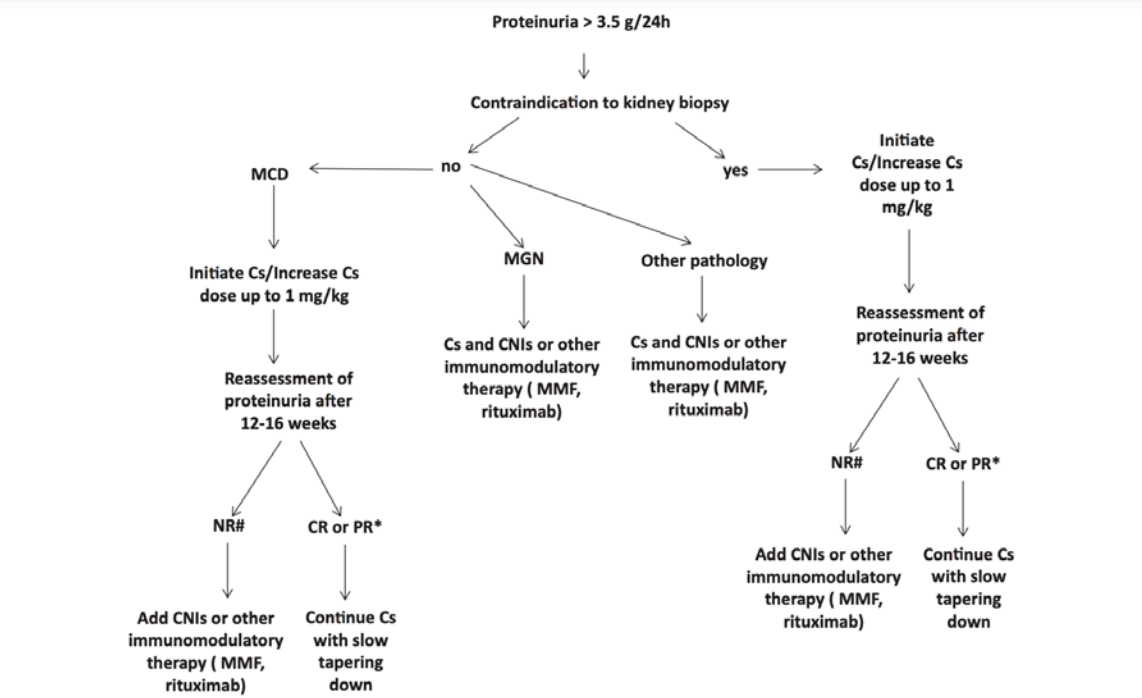


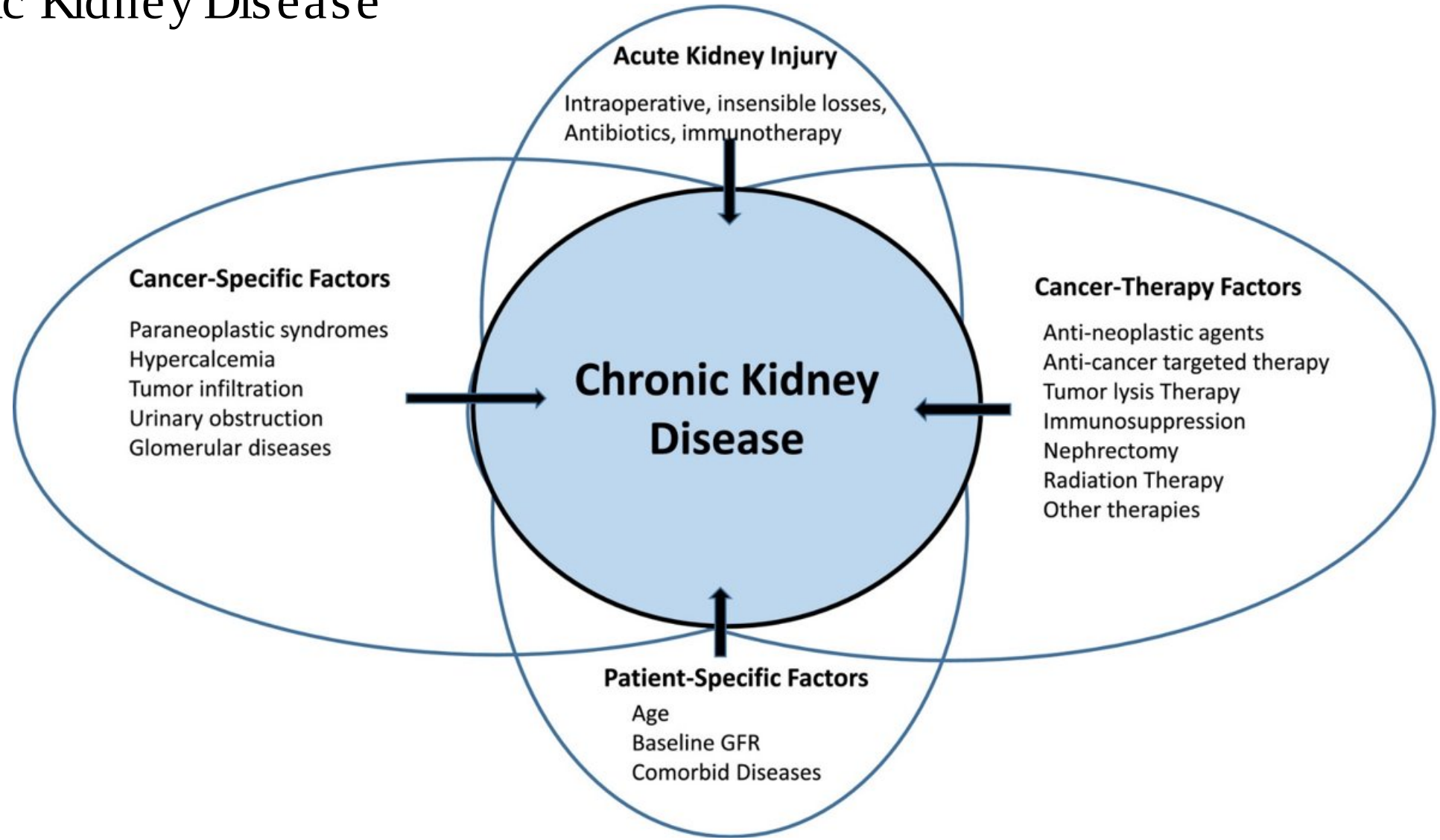
Figure 2. Management of NS after HSCT. Cs indicates corticosteroid; CNIs, calcineurin inhibitors; MMF, mycophenolate mofetil; NR#, no reduction in proteinuria level; CR or PR*, complete response defined as a reduction in proteinuria levels <. 5 g/day, and partial response defined as a reduction in proteinuria > 50% relative to baseline values.

  - Minimal Change Disease
    - Expert opinion similar to above. Steroids + Rituxan or CNI.

Nasr SH. Membranous Nephropathy With Extensive Tubular Basement Membrane Deposits Following Allogeneic Hematopoietic Cell Transplant: A Report of 5 Cases. American Journal of Kidney Diseases, 2021.

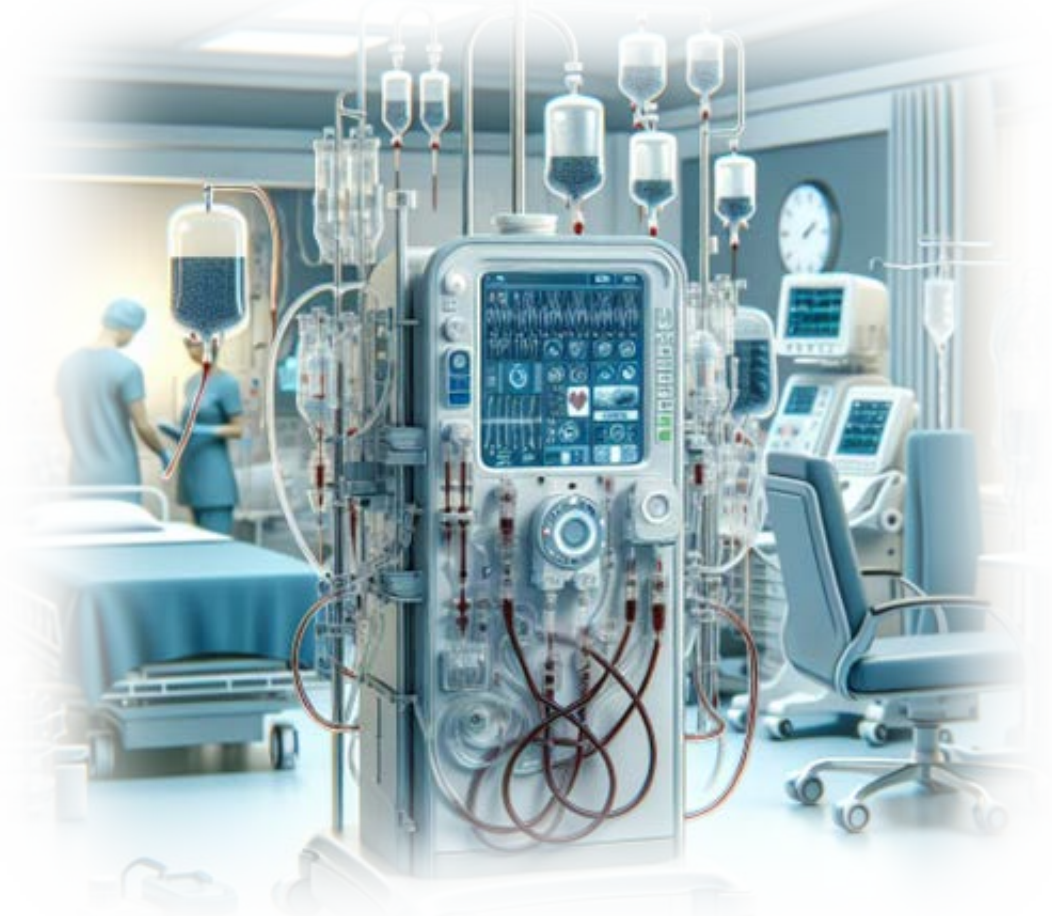
Ratanatharathorn V. Treatment of chronic graft-versus-host disease with anti-CD20 chimeric monoclonal antibody. Biology of Blood and Marrow Transplantation. 2003;9(8)

Chronic Kidney Disease



HSCT and CKD. Rosner, Jhaveri, Perazella CA: A Cancer Journal for Clinicians, 2020

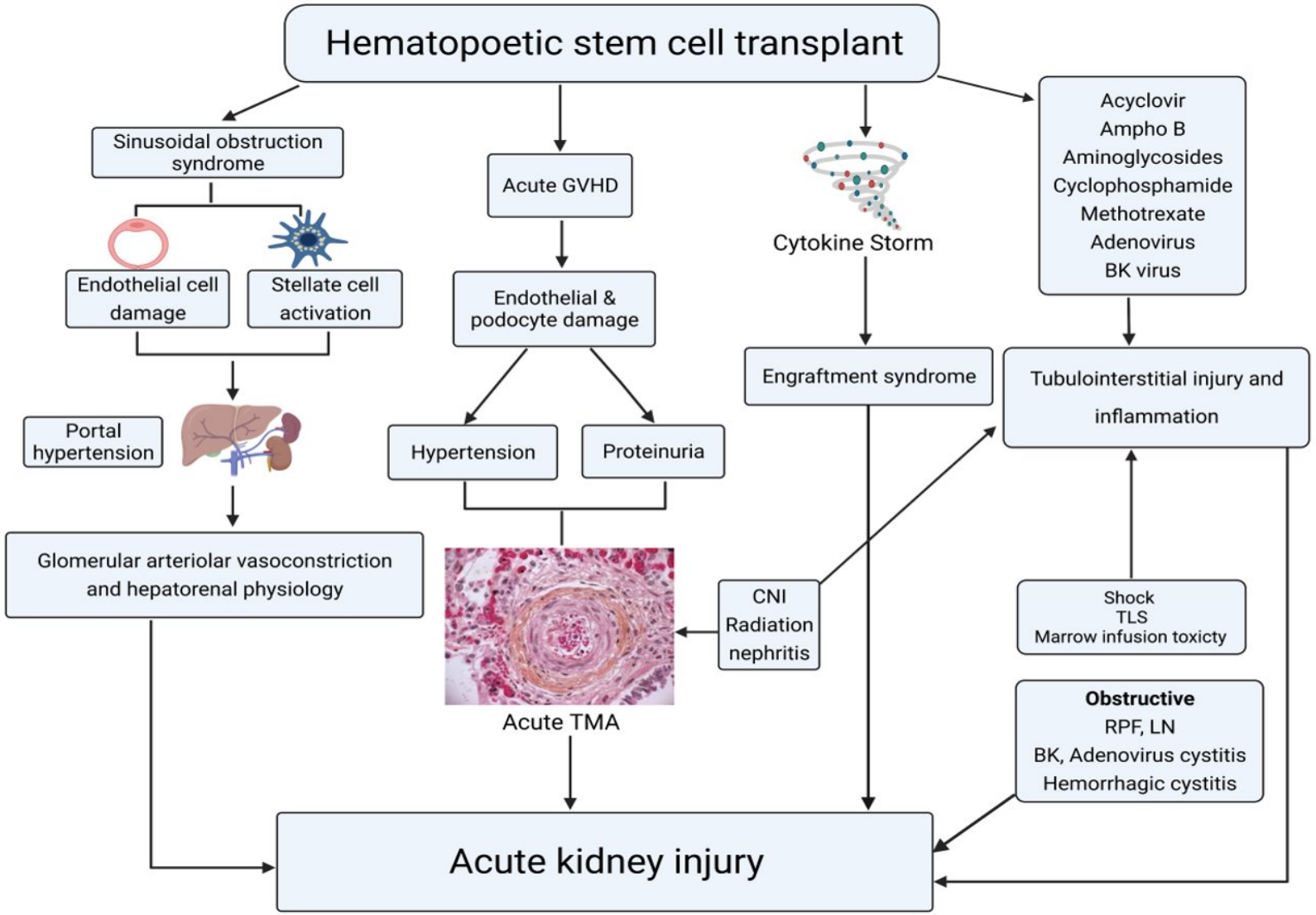
Renal Replacement Therapy



- HSCT requiring RRT has mortality of 60-80%
- Transplant?
  - Koenecke et al reported 67,578 allogenic HCT recipients with 15 undergoing renal transplant.
  - 5-year survival was 100%. 2-year incidence of graft failure was 20%. Overall good prognosis.
  - Combined HSCT and Kidney Transplant?
    - Stanford's clinical trial reported 56 patients receiving HSCT and KT from same donor.
    - 14 year follow up: no rejection. Maintenance IS were stopped in 80% of patients that were fully matched.
  - In patients with advanced CKD after HSCT, KT should be considered if primary disease in remission.

Koenecke C. Solid Organ Transplantation After Allogeneic Hematopoietic Stem Cell Transplantation: A Retrospective, Multicenter Study of the EBMT. American Journal of Transplantation. 2010;10(8)
Issa F. The Fourth International Workshop on Clinical Transplant Tolerance. American Journal of Transplantation. 2020;21(1):21-31.

Summary of renal complications post HSCT



Causes of AKI in HSCT. Gupta et al, CJASN 2022

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MASSACHUSETTS GENERAL HOSPITAL

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ONCONEPHROLOGY GROUP

Dana-Farber Cancer Institute

UNIVERSITY OF TORONTO

MEDICAL COLLEGE OF WISCONSIN

Thank you!

Paul Hanna, MD MSc

Director of Onconephrology

phanna@mcw.edu. 𝕏@PaulHannaMD