Onconephrology: Core Curriculum 2023

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Onconephrology focuses on management of kidney disease in cancer, which manifests itself in a variety of clinical syndromes, including acute kidney injury, chronic kidney disease, hypertension, proteinuria, and electrolyte disorders. Many of these syndromes result from cancer treatments including chemotherapy, immunotherapy, chimeric antigen receptor T cells, and stem cell transplant. Others are due to kidney-specific effects of the cancer, as seen with monoclonal gammopathy or glomerular diseases associated with malignancy. Further, cancer risk itself is heightened in patients with kidney disease, particularly kidney transplant recipients, and their care requires specific considerations. In this installment of AJKD's Core Curriculum in Nephrology, we review these and other core concepts in onconephrology, using a case-based approach to highlight clinical decision making.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Despite therapeutic strides such as targeted therapies and immunotherapy, patients with cancer may experience drug nephrotoxicity and end-organ damage from underlying malignancy. When involving the kidney, acute kidney injury (AKI), chronic kidney disease (CKD), electrolyte and acid-base disorders, proteinuria, and hypertension may result. In this installment of *AJKD*'s Core Curriculum in Nephrology, we will use clinical cases to illustrate evaluation and management of kidney disease in patients with solid tumors and hematological malignancies. We will also highlight other important topics within onconephrology including cancer in recipients of kidney transplants.

The Scope and Impact of Kidney Disorders in the Cancer Patients

Cancer patients develop a myriad of kidney disorders, with AKI being a frequent reason for nephrology consultation. Depending on the etiology, proteinuria and/or hypertension may accompany AKI, and some anticancer agents induce isolated hypertension or proteinuria. Multiple myeloma and RCC are the most common malignancies associated with AKI.

Workup of AKI in cancer patients follows the usual schema of determining prerenal, kidney-intrinsic, or postrenal causes. Certain etiologies of AKI are much more common with specific cancers, such as obstructive uropathy from bladder cancer, prostate cancer, and cervical cancer. Multiple risk factors for AKI may be present in the same patient. For example, Burkitt lymphoma may result in AKI from tumor lysis syndrome or from ureteral compression due to retroperitoneal lymphadenopathy. Cancer patients with AKI have a higher mortality risk, greater hospital lengths of stay, and inferior cancer outcomes. They may also face decisions about dialysis or pain management with reduced glomerular filtration rate (GFR), decisions similar to those encountered by patients with kidney disease not related to cancer. These basics of kidney-specific palliative care are reviewed in the recent Core Curriculum noted in the Additional Readings. Finally, AKI may result in CKD, highlighting the fact that as cancer survivors live longer, they also experience the burden of kidney complications.

Additional Readings

- Gelfand SL, Scherer JS, Koncicki HM. Kidney supportive care: core curriculum 2020. *Am J Kidney Dis.* 2020;75(5):793-806. doi:10.1053/j.ajkd.2019.10.016 ★ESSENTIAL READING
- Kitchlu A, McArthur E, Amir E, et al. Acute kidney injury in patients receiving systemic treatment for cancer: a population-based cohort study. *J Natl Cancer Inst.* 2019;111(7):727-736. https://doi.org/10.1093/jnci/djy167

Measurement of Kidney Function in Cancer Patients

Case 1: *A 42-year-old man with diabetes mellitus and gout undergoes a radical inguinal orchiectomy for left testicular stage IIa seminoma. Adjuvant curative-intent etoposide and cisplatin are the planned chemotherapy. The cisplatin dosing will be at 100% unless a creatinine clearance (CL_{cr}) of <60 mL/min necessitates a 25% dose reduction. On cycle 1, day 1, the patient's weight is 77 kg, and his height is 57 inches. He reports recent corticosteroid dosing for a now-resolved gout flare. The laboratory results are notable for a serum creatinine (Scr) of 1.4 mg/dL, which is at baseline. The oncologist calls you to ask which test best reflects this patient's kidney function.*

Question 1: Which of the following tests is the best answer for the oncologist's question?

(a) Estimated GFR (eGFR)-creatinine
(b) 24-hour urine for CL_{cr}
(c) eGFR-cystatin C and creatinine
(d) eGFR-cystatin C
(e) ^{125}I-Iothalamate urinary clearance

For the answer to this question, see the following text.

Accurately evaluating kidney function in cancer patients is critical in diagnosing kidney disease. GFR remains widely accepted as the best index for kidney function. Creatinine-based measured clearances as well as estimated GFR (eGFR)-creatinine are confounded by factors that affect cancer patients such as cachectic sarcopenia and variable protein intake, which may lead to an overestimation of the actual GFR. Additionally, because tubular secretion contributes to urinary creatinine excretion, drugs such as trimethoprim, which inhibit secretory pathways for creatinine, raise creatinine levels without affecting GFR. Among the cancer drugs, CDK4/6 inhibitors may cause pseudo-AKI by this mechanism.

Cystatin C, which does not undergo tubular secretion, in the general population reflects kidney function more accurately when combined with serum creatinine. The same may be true in the cancer population although some cancers secrete cystatin C and some drugs including corticosteroids may also increase cystatin C levels. Measured GFR also may be considered when clinical uncertainty arises about a patient's kidney function. Inulin clearance is the gold standard for measured GFR, but it is not used in clinical practice. In lieu of inulin, measured clearances of ^{125}I-iothalamate or iohexol are acceptable because they also undergo glomerular filtration without tubular secretion, reabsorption, or metabolism. However, such testing may not be widely available at all hospitals. Thus, accurate GFR assessment in cancer patients needs ongoing study because underdosing of anticancer agents reduces drug efficacy while overdosing increases adverse drug events, including nephrotoxicity.

In case 1, the patient's eGFR-creatinine by the CKD epidemiology equation is 61 mL/min/1.73 m^2, right at the cutoff for cisplatin dose reduction. Further testing would tailor curative intent chemotherapy dosing. Cystatin C measurement may be confounded in this patient by recent corticosteroids, making the values for eGFR-cystatin C and eGFR-creatinine-cystatin C potentially inaccurate. Urinary CL_{cr} and eGFR based on creatinine tends to overestimate GFR because of tubular creatinine secretion. For question 1, the best test to provide the most accurate GFR determination is answer (e), plasma clearance of ^{125}I-iothalamate.

Additional Readings

- Chen DC, Potok OA, Rifkin D, Estrella MM. Advantages, limitations, and clinical considerations in using cystatin c to estimate GFR. *Kidney360*. 2022;3(10):1807-1814. https://doi.org/10.34067/KID.0003202022
- Inker LA, Titan S. Measurement and estimation of GFR for use in clinical practice: core curriculum 2021. *Am J Kidney Dis*. 2021;78(5):736-749. https://doi.org/10.1053/j.ajkd.2021.04.016 ★ESSENTIAL READING
- McMahon BA, Rosner MH. GFR measurement and chemotherapy dosing in patients with kidney disease and cancer. *Kidney360*. 2020;1(2):141-150. https://doi.org/10.34067/KID.0000952019 ★ESSENTIAL READING
- Rosner MH, Perazella MA. Acute kidney injury in the patient with cancer. *Kidney Res Clin Pract*. 2019;38(3):295-308. https://doi.org/10.23876/j.krcp.19.042

Nephrotoxicity of Anticancer Therapy

Case 2: *A 51-year-old woman with RCC with spinal metastases is referred for elevated creatinine levels after initiation of ipilimumab and nivolumab therapy 2 months before. She has a rash for which she applies topical dexamethasone. She takes 400 mg of ibuprofen daily for back pain. The physical examination is notable for scattered erythematous plaques on her left arm. Her creatinine level is at 2.5 mg/dL (preimmunotherapy baseline of 1 mg/dL). Her urinary albumin-creatinine ratio (UACR) is 250 mg/g and urinary protein-creatinine ratio (UPCR) is 0.8. Her urine sediment is bland, and serologies are negative. The kidney ultrasound is unremarkable.*

Question 2: What would be the next best step in your diagnostic approach?

(a) Check anti-M-type phospholipase A_2 receptor antibody (anti-PLA_2R-Abs) levels
(b) Perform a kidney biopsy
(c) Recheck the laboratory values 1 week after stopping immunotherapy and ibuprofen
(d) Obtain a computed tomography (CT) scan of the abdomen

For the answer to this question, see the following text.

The patient has AKI on immune checkpoint inhibitor (ICI) treatment while taking daily nonsteroidal anti-inflammatory drugs (NSAIDs). Stopping all therapies and rechecking the laboratory values is clinically reasonable but will not reveal cause-specific AKI. With the recent negative ultrasound, a CT scan of the abdomen is unlikely to reveal diagnostic findings for AKI. Anti-PLA_2R-Abs are associated with membranous nephropathy (MN). In this patient, UPCR > UACR suggests tubular proteinuria, making glomerulonephritis unlikely.

Drug-related nephrotoxicity frequently complicates cancer treatment. In this patient, the use of NSAIDs and combination ICIs along with the rash (a known immune-related adverse event of ICI treatment) makes either acute

tubular necrosis (ATN) or acute tubulointerstitial nephritis (AIN) possible diagnoses. For question 2, only answer (b), kidney biopsy, can definitively distinguish between the 2 diagnoses.

Traditional chemotherapeutics, targeted agents, and immunotherapy are necessary cancer therapeutics but may cause glomerular and/or tubular/tubulointerstitial patterns of kidney injury (Fig 1). We will discuss types and mechanisms of kidney adverse events as well as strategies for their prevention and treatment with these drugs (Tables 1 and 2).

Conventional Cytotoxic Chemotherapies

Platinum-based Chemotherapy

Cisplatin, carboplatin, and oxaliplatin are first-, second-, and third-generation platinum-based drugs, respectively, that are used in lung, gastrointestinal, and genitourinary malignancies, among others. These structurally different agents cross-link DNA, distorting the DNA helix and inducing cell death. Kidney effects include dose-dependent nonoliguric AKI from ATN, affecting up to 30% of patients on cisplatin, particularly with single-cycle dosing of >60 mg/m^2 or cumulative-cycle dosing of >300 mg/m^2. Drug cessation usually resolves ATN. AKI risk is highest with cisplatin, followed by carboplatin and oxaliplatin. Besides AKI, hypomagnesemia, Fanconi syndrome, distal renal tubular acidosis, thrombotic microangiopathy (TMA), and hyponatremia from salt wasting syndrome have been well-described with cisplatin, but rarely with carboplatin or oxaliplatin.

Prevention of platinum drug nephrotoxicity starts with volume expansion. Cisplatin enters proximal tubule epithelial cells (PTECs) via transporters, including organic cation transporter-2 whose expression is upregulated by hypomagnesemia. Limited data suggest that magnesium repletion may counteract cisplatin nephrotoxicity. Forced saline diuresis with mannitol has been proposed, but studies have shown conflicting results. Infused cisplatin is protein unbound and dialyzable but becomes irreversibly protein bound within 24 hours. Cisplatin clearance via hemodialysis for toxicity avoidance would only be effective in the early postinfusion period. Otherwise, hemodialysis for cisplatin-associated AKI is determined by usual clinical indications.

Ifosfamide

Ifosfamide is an alkylating agent used against pediatric and adult sarcomas, testicular cancer, and other conditions, whose nephrotoxic metabolite chloroacetaldehyde causes ATN and Fanconi syndrome, particularly with concurrent cisplatin use. Nephrogenic diabetes insipidus has also been described. Kidney biopsy commonly

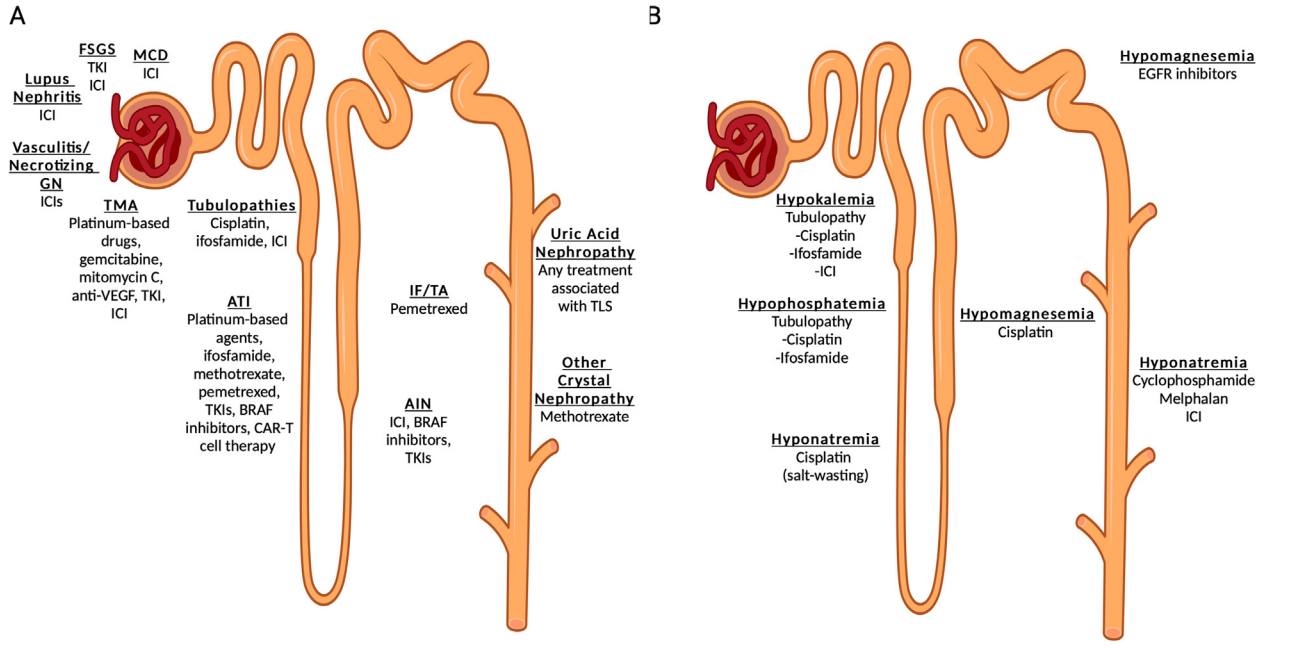

Figure 1. (A) The spectrum of kidney disease seen across the nephron, from glomerulus to collecting duct, due to cytotoxic chemotherapy, targeted therapy, and immunotherapy. (B) The various electrolyte disorders seen in patients with cancer due to effects of cytotoxic chemotherapy, targeted therapy, and immunotherapy across the nephron. Created with Biorender.com. Abbreviations: AIN, acute tubulointerstitial nephritis; ATI, acute tubular injury; BRAF, serine-threonine kinase B-rapidly activated fibrosarcoma; CAR-T, chimeric antigen receptor T cells; EGFR, epidermal growth factor receptor; GN, glomerulonephritis; ICI, immune checkpoint inhibitor; IF/TA, interstitial fibrosis/tubular atrophy; TKIs, tyrosine kinase inhibitors; TLS, tumor lysis syndrome; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor.

Table 1. Cytotoxic Chemotherapy Drugs, Types of Kidney Disease, and When Indicated, Specific Management of Kidney-related Effects

Drug	Type of Kidney AEs	Mechanism of Kidney AEs	Prevention and Treatment
Platinum agents	AKI-ATN (Cis>>Carbo>Oxali), Fanconi syndrome, hyponatremia, hypomagnesemia	ATN: direct tubular toxicity	Volume expansion, magnesium repletion
Ifosfamide	AKI-ATN, hemorrhagic cystitis, NDI	ATN: direct tubular toxicity; hemorrhagic cystitis: bladder injury	Volume expansion/mesna for hemorrhagic cystitis
Cyclophosphamide	Hyponatremia, hemorrhagic cystitis	Hyponatremia: increased tubular reabsorption of water/? ADH secretion; hemorrhagic cystitis: bladder injury by metabolite	Volume expansion/mesna for hemorrhagic cystitis
Bendamustine	AKI-ATN, NDI, Gitelman	ATN: direct tubular toxicity	
Melphalan	AKI, hyponatremia	SIADH	SIADH: drug withdrawal, usual approach to SIADH
Methotrexate	AKI	Intratubular crystal formation	Volume expansion, urine pH > 7.0, stop PPI, NSAIDs
Pemetrexed	AKI	Acute tubular necrosis, progressive interstitial fibrosis, nephrogenic diabetes insipidus, and distal renal tubular acidosis	Folic acid and vitamin B_{12}, adequate hydration
Gemcitabine	AKI, hypertension, proteinuria	TMA	Drug withdrawal, complement inhibitors may be considered
Nitrosoureas	CCNU, Me-CCNU, BCNU: chronic interstitial nephritis, Streptozocin-Fanconi syndrome, AKI	Chronic interstitial nephritis: ? tubular cell protein alkylation; AKI: tubular injury	
Trabectedin	AKI	? secondary to rhabdomyolysis	
Doxorubicin	AKI, hypertension, proteinuria	TMA	TMA: drug withdrawal
Mitomycin C	AKI, hypertension, proteinuria	TMA	TMA: drug withdrawal, ? eculizumab
Vinca alkaloids	AKI, hypertension, proteinuria, hyponatremia	TMA, SIADH	TMA: drug withdrawal; SIADH: drug withdrawal

Abbreviations: ADH, antidiuretic hormone; AE, adverse event; AKI, acute kidney injury; ATN, acute tubular necrosis; BCNU, carmustine; Carbo, carboplatin; CCNU, lomustine; Cis, cisplatin; Me-CCNU, methyl-CCNU, semustine; NDI, nephrogenic diabetes insipidus; NSAID, nonsteroidal anti-inflammatory drug; Oxali, oxaliplatin; PPI, proton pump inhibitor; SIADH, syndrome of inappropriate diuresis; TMA, thrombotic microangiopathy.

reveals ATN, with electron microscopy revealing dysmorphic mitochondria. Volume expansion is the only prophylaxis. Childhood survivors of cancer requiring ifosfamide treatment may develop subsequent CKD, particularly if their cumulative ifosfamide exposure was >84 g/m^2. CKD is also reported in adult patients, but the cumulative dose thresholds are undefined. Ifosfamide may also cause hemorrhagic cystitis, for which sodium 2-mercaptoethane sulphonate (mesna) provides prophylaxis.

Cyclophosphamide

Structurally similar to ifosfamide, cyclophosphamide is used as immunosuppression in autoimmune diseases and as chemotherapy for several cancers. The metabolites are different than ifosfamide, explaining why ATN is rare with cyclophosphamide. Hemorrhagic cystitis does occur, and intravenous dosing requires mesna prophylaxis. Cyclophosphamide is also associated with hyponatremia. The mechanism is not fully elucidated, but increased antidiuretic hormone secretion, up-regulation of the V2 receptor, and increased aquaporin permeability have been proposed.

Methotrexate

Used against osteosarcomas, leukemias, and lymphomas, methotrexate inhibits dihydrofolate reductase and thymidine synthase, reducing the availability of nucleotides necessary for cell division.

High-dose intravenous methotrexate (HDMTX: >0.5 g/m^2) vasoconstricts afferent arterioles and forms intratubular crystals when urine is acidic and urine flow is low. Both mechanisms lead to nonoliguric and reversible AKI. Methotrexate is predominantly kidney cleared and accumulates with AKI, increasing the risk of extrakidney toxicities including mucositis, hepatitis, and encephalopathy. NSAIDs, penicillins, and proton pump inhibitors (PPIs) interfere with drug transporter elimination of methotrexate and should be avoided with HDMTX.

Alkali-containing crystalloids to generate urine pH > 7.0 and urine output > 2.5 L/day are essential. High-dose leucovorin within 18-42 hours of HDMTX provides

Table 2. Targeted Therapies, Types of Kidney Disease, and Management of Kidney-related Effects

Drug Type and Name	Type of Kidney AEs	Mechanism of Kidney AEs	Prevention/Treatment
VEGF-inhibitors (bevacizumab, aflibercept, ramucirumab)	HTN, proteinuria, AKI	HTN, proteinuria, AKI from TMA, podocyte and endothelial dysfunction via disrupted VEGF signaling	Serial blood pressure and UPCR.
Multitarget TKIs (sunitinib, sorafenib, axitinib, cabozantinib, vandetanib)	HTN, proteinuria, AKI; electrolyte disorders such as low calcium, phosphorus, magnesium	HTN, proteinuria, AKI: podocyte and endothelial dysfunction and TMA via disrupted VEGF signaling	Monitor blood pressure, urine protein. Antihypertensives including RAAS inhibitors. Drug withdrawal with TMA.
BRAF inhibitors (vemurafenib, dabrafenib)	AKI (ATN/AIN), proteinuria	Proteinuria from podocytopathy	Monitor UPCR
EGFR inhibitors (mAbs: cetuximab, panitumumab; TKIs: erlotinib, afatinib, etc)	Hypomagnesemia, rare glomerular disease from EGFR-TKIs	Hypomagnesemia from inhibition of EGFR-mediated magnesium transport in distal nephron	Magnesium supplements. Potential use of amiloride or SGLT2 inhibitors.
ALK inhibitors (crizotinib, ceritinib, etc)	Pseudo-AKI vs AKI, kidney cyst formation	AKI from ATN, drug may impede tubular secretion of Scr	Check simultaneous cystatin C
BCR-ABL TKIs (imatinib, dasatinib)	AKI	AKI: ATN with Fanconi, TLS	Monitoring for TLS labs
BCL-2 inhibitors (venetoclax)	AKI	TLS- independent of malignancy	Allopurinol regardless of tumor type. Monitoring for TLS labs
CDK 4/6 inhibitors (palbociclib, ribociclib)	Pseudo-AKI; AKI	May affect tubular secretion of Scr; ATN	Check simultaneous cystatin C
PARP inhibitors	Pseudo-AKI	May affect tubular secretion of Scr	Check simultaneous cystatin C

Based in part on data in Sy-Go JPT, Yarandi N, Schwartz GL, Herrmann SM. Ribociclib-induced pseudo-acute kidney injury. *J Onco-Nephrol.* 2022;6(1-2):64-69. https://doi.org/10.1177/23993693221085285. Abbreviations: AE, adverse event; AIN, acute tubulointerstitial nephritis; AKI, acute kidney injury; ATN, acute tubular necrosis; BCL-2, B-cell lymphoma 2; BCR-ABL, breakpoint cluster region-Ableson leukemia virus; BRAF, serine-threonine kinase B-rapidly activated fibrosarcoma; CDK, cyclin-dependent kinases; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; EGFR, epidermal growth factor receptor; HTN, hypertension; mAbs: monoclonal antibodies; PARP, polyADP ribose polymerase; RAAS, renin-angiotensin-aldosterone system; Scr, serum creatinine; SGLT2, sodium-glucose cotransporter-2 TKI, tyrosine kinase inhibitor; TLS, tumor lysis syndrome; TMA, thrombotic microangiopathy; UPCR, urine protein-creatinine ratio; VEGF, vascular endothelial growth factor.

folate rescue when dosed according to serum methotrexate levels. This is critical to prevent and treat renal and extrarenal methotrexate toxicity, but efficacy wanes at methotrexate levels of >10 μM. After HDMTX infusion, the drug levels should be monitored until levels decrease < 0.1 μM.

Hemodialysis may be necessary for prevention of extrarenal toxicities from high methotrexate levels in patients with AKI. Methotrexate is partly protein bound, which is not ideal for extracorporeal removal, and post-dialysis drug levels also commonly rebound.

The recombinant enzyme glucarpidase reduces plasma methotrexate concentrations by up to 99% within 15 minutes of administration without plasma rebound. Glucarpidase is approved by the US Food and Drug Administration for delayed methotrexate clearance with HDMTX-associated kidney impairment. The former is defined by expert guidelines as plasma methotrexate levels of >50 μM, >30 μM, >10 μM, and >5 μM at 24, 36, 42, and 48 hours after HDMTX dosing, respectively. Clinical outcomes with glucarpidase or dialysis versus standard leucovorin rescue have not been systematically studied.

Pemetrexed

Pemetrexed is a methotrexate analog that is approved for non–small cell lung cancer (NSCLC) and mesothelioma, often concurrently with cisplatin. Direct tubular toxicity of pemetrexed causes ATN, nephrogenic diabetes insipidus, and distal renal tubular acidosis (RTA). Dosing in patients with $CL_{cr} < 45$ mL/min is contraindicated. Volume expansion as well as vitamin B_{12} and folate supplementation are preventive measures. Drug cessation usually stabilizes or reverses AKI. Some patients with higher cumulative dosing and exposure will develop CKD from progressive interstitial fibrosis.

Gemcitabine

Gemcitabine is an antimetabolite used in ovarian cancer, pancreatic cancer, and other solid tumors. It is associated with TMA, with incidences estimated at 0.31%-1.4%. Patients may develop systemic TMA characterized by microangiopathic hemolytic anemia, thrombocytopenia, proteinuria, and AKI or kidney-limited TMA with AKI/proteinuria. New onset or worsening of hypertension may herald TMA. Stopping gemcitabine stabilizes or improves kidney disease in most patients. Plasma exchange does not have a role unless there is another consideration, such as autoantibodies to complement factor H that predisposed the patient to TMA. Complement inhibition with eculizumab has been successful with good kidney and hematological outcomes in small case series and isolated case reports, and this warrants consideration in refractory cases of gemcitabine-TMA.

Targeted Agents

Vascular Endothelial Growth Factor Inhibitors

Vascular endothelial growth factor (VEGF) inhibitors target VEGF pathways to inhibit tumor angiogenesis in a variety of cancers. They include antibodies (bevacizumab) or soluble receptors (aflibercept) against circulating VEGF as well as antibodies (ramucirumab) against VEGF receptors (VEGF-R). VEGF tyrosine kinase receptor inhibitors (TKIs) are discussed later.

Podocyte-specific VEGF expression is integral to the function of the glomerular basement membrane and glomerular endothelium. Additionally, circulating VEGF promotes pressure natriuresis, lymphangiogenesis, and nitric oxide signaling. Collectively, VEGF inhibition is associated with dose-dependent hypertension, proteinuria, and systemic or kidney-limited TMA. Kidney biopsy may reveal TMA, but minimal change disease (MCD) and focal and segmental glomerulosclerosis (FSGS) have also been described.

Hypertension rates for VEGF inhibitors range from 19% to 30% in large meta-analyses of clinical trials to 45% to 80% in off-trial clinical use. Dihydropyridine calcium channel blockers or renin-angiotensin-aldosterone system (RAAS) inhibitors are the first line of treatment for hypertension due to VEGF inhibitors. Treatment can continue with controlled hypertension and subnephrotic proteinuria. For drug-attributed TMA or nephrotic proteinuria, discontinuation is necessary and usually reverses kidney toxicity.

Tyrosine Kinase Inhibitors

Small-molecule TKIs prevent activation of receptor, cytoplasmic, or dual-specificity tyrosine kinases (TK), inhibiting signaling pathways for cell growth, migration, and apoptosis. These pathways are rendered constitutively active by mutations, leading to unchecked tumor growth. Depending on the specific TK targets (VEGF, epidermal growth factor receptors, anaplastic lymphocyte kinase, etc), there are variable side effects of TKIs. For example, sunitinib, sorafenib, axitinib, cabozantinib, and others downstream of VEGF are associated with hypertension and proteinuria, either isolated or with TMA. Other kidney lesions include MCD, FSGS from healed TMA, acute tubulointerstitial nephritis (AIN), and chronic interstitial nephritis. Electrolyte disorders, including hypocalcemia, hypophosphatemia, and hypomagnesemia, are seen in varying degrees with many multitarget TKIs. Vandetanib has been associated with all 3 of these electrolyte derangements. Thus, it is critical to know the target(s) for a particular TKI in order to evaluate potential TKI-related nephrotoxicity.

BRAF Inhibitors

Serine-threonine kinase B-rapidly activated fibrosarcoma (BRAF) inhibitors, including dabrafenib and vemurafenib, target the BRAF protein, which activates the mitogen-activated protein kinase (MAPK) pathway. Melanoma and other tumors with specific BRAF mutations have pro-oncogenic signaling, and inhibition of the BRAF and MAPK pathways is a potent antitumor treatment. These drugs have been associated with AIN, ATN with Fanconi syndrome, and proteinuric podocytopathy when used in combination with MEK inhibitors.

EGFR Inhibitors

Epidermal growth factor receptor (EGFR) inhibitors are used against a variety of cancers. These include small-molecule TKIs such as gefitinib, erlotinib, and afatinib and monoclonal antibodies (mAbs) such as cetuximab and panitumumab.

Anti-EGFR mAbs have a high incidence of hypomagnesemia via inhibition of transient receptor potential channel M6 (TRPM6)–mediated absorption of magnesium in the distal nephron. Hypokalemia and hypophosphatemia have also been less described. Rare reports of glomerular lesions include crescentic IgA nephropathy, immune-complex glomerulonephritis, and pauci-immune crescentic glomerulonephritis.

Proteasome Inhibitors

Primarily used as treatment for multiple myeloma, proteasome inhibitors (PIs) oppose the clearance of abnormal intracellular proteins, allowing accumulation to toxic levels particularly in tumor cells. PIs are associated with dose-dependent hypertension from increased vascular tone, reactivity, and dysfunction via endothelial injury from proteosome inhibition. PI dosing should be modified in uncontrolled hypertension and discontinued in hypertensive crises. TMA has also been reported as definitively associated with PIs in multiple myeloma patients, more often with carfilzomib compared with bortezomib or ixazomib. Treatment data are limited, but drug discontinuation has been necessary, and use of plasma exchange has been ineffective for PI-associated TMA.

Immunotherapies

Immune Checkpoint Inhibitors

ICIs are mAbs directed against negative regulatory receptor checkpoints of T-cell immunity, including cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) such as ipilimumab, programmed death-1 (PD-1) and PD-1 ligand (PD-L1) pathway (PD-1/PD-ligand-1 [PD-L1]) receptors) such as cemiplimab, nivolumab, pembrolizumab (PD-1), and atezolizumab, avelumab, and durvalumab (PD-L1), which prevent T-cell activation (Fig 2A). ICIs activate dormant antitumor immunity, allowing improved survival in previously difficult-to-treat malignancies such as lung cancer, RCC, and melanoma. They are now increasingly used as the first-line treatment for several early-stage and advanced cancers.

ICIs are associated with off-target immune-related adverse events (IRAEs), commonly involving the skin,

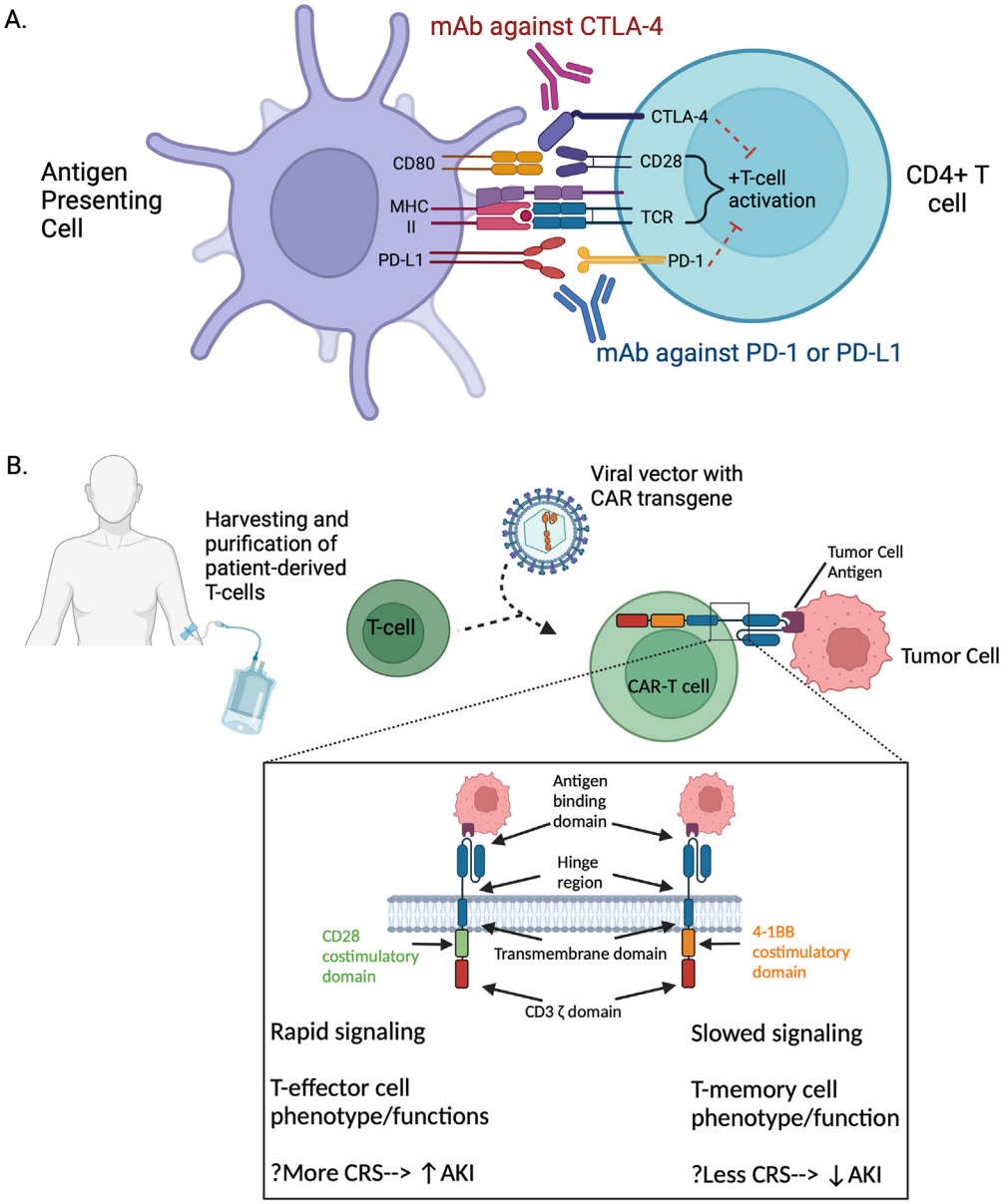

Figure 2. The design and rationale of immunotherapy. (A) T cells are normally activated by 2 signals. (1) Antigen presenting cell displaying an antigen in the context of a self-MHC molecule to a T cell with receptor specificity for that antigen. (2) Binding of a costimulatory molecule (eg, CD28) on the T cell to its cognate ligand on the antigen presenting cell (eg, CD80/CD86). Negative regulatory checkpoints such as CTLA-4 or PD-1 on the T cell interfere with costimulation or bind to PD-L1, respectively, to inactivate T cells. Monoclonal antibodies against PD-1 and CTLA-4 prevent T-cell anergy against tumor cell antigen by preventing the inactivation of T cells. (B) CAR-T production begins with harvesting of T cells from the patient who is a candidate for CAR-T therapy. These T cells are transfected with vectors (generally viral) that genetically engineer the T cell to express a chimeric antigen receptor consisting of (1) an antigen binding domain with a flexible hinge region to facilitate recognition of a tumor cell surface protein independent of MHC; (2) a transmembrane domain; (3) a costimulatory domain; and (4) a CD3 ζ chain domain. Thus, critical steps of T-cell activation are combined into 1 signal receptor that activates the CAR-T for effector mechanisms that are outlined in Figure 3. All commercially available CAR constructs contain the same regions but may differ in their antigen-binding domain (unique to the cancer type) and costimulatory domain (either CD28, as seen in axicabtagene ciloleucel and brexucabtagene autoleucel or 4-1BB, as seen in tisagenlecleucel, ciltacabtagene autoleucel, lisocabtagene maraleucel, and idecabtagene vicleucel). These differences in costimulatory domain impact on CAR-T signaling, putatively impacting on severity of cytokine release syndrome and resulting AKI. Created with Biorender.com. Based on information in Sury K, Perazella MA, Shirali AC, Cardiorenal complications of immune checkpoint inhibitors. *Nat Rev Nephrol*. 2018;14:571-588. https://doi.org/10.1038/s41581-018-0035-1; and Tian Y, Li Y, Shao Y, Zhang Y, Gene modification strategies for next-generation CAR T cells against solid cancers. *J Hematol Oncol*. 2020;13:54. https://doi.org/10.1186/s13045-020-00890-6). Abbreviations: AKI, acute kidney injury; CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine release syndrome; CTLA-4, cytotoxic T-lymphocyte antigen-4; mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell death protein; PD-L1, programmed cell death protein ligand 1; TCR, T-cell receptor.

endocrine system, and gastrointestinal tract. Although the kidney is less involved, nephrotoxicity occurs in up to 2% to 5%, with a higher risk with combination ICIs. Risk factors for ICI-AKI include use of PPIs and NSAIDs.

AKI is the most common kidney IRAE from ICIs, and AIN is the most reported histopathologic finding. Glomerular diseases such as MCD, FSGS, MN, lupus nephritis have also been described, as have electrolyte derangements including distal renal tubular acidosis. Although all these kidney syndromes are likely manifestations of kidney autoimmunity, the increased risk of AIN-ICI with concomitant PPIs and NSAIDs raises the question of whether ICIs remove the immune brake over non-ICI drug-induced AIN.

ICI-AKI warrants drug suspension pending workup of AKI. Unless contraindicated, kidney biopsy should be offered. Urinary and serum biomarkers are under study to distinguish ICI-AIN from other etiologies of ICI-AKI and may one day allow for noninvasive diagnosis. In either suspected or confirmed AIN, corticosteroid dosing at 1-2 mg/kg allows recovery from ICI-AIN. Biopsy should be considered for patients whose AKI does not respond to such dosing. The optimal dose and duration of corticosteroids for ICI-AIN is unclear though observational data have suggested that shorter-term (~1 month), tapered dosing may be reasonable if AKI recovery is sustained after taper. Rechallenge after ICI-AKI may be offered for patients who have had clinical benefit from ICIs and no life-threatening IRAEs. Recent retrospective data from >400 patients have shown a recurrent ICI-AIN rate of 16.5%.

Chimeric Antigen Receptor T Cells

Chimeric antigen receptor T-cells (CAR-T) are patient-derived T cells modified ex vivo to express a chimeric receptor with an external tumor antigen domain allowing direct CAR-T activation via linked costimulation and CD3 ζ chain domains. Current commercial CAR-T share all domains but differ in their antigen binding and/or costimulatory domains (Fig 2B). Upon infusion, CAR-T recognize tumor antigens and become activated to release of proinflammatory cytokines, particularly interleukin 6 (IL-6) (Fig 3).

Cytokine-release syndrome (CRS) is clinically characterized by fever, hypotension, diarrhea, and potential for IL-6-driven severe neurotoxicity. Hemodynamic shifts may result in AKI on the prerenal to ATN spectrum, though tumor lysis and macrophage activation syndromes have also been described (Fig 3). Retrospective data report AKI rates of 5% to 30% with CAR-T, which correlates with the incidence of CRS. This wide range of AKI is likely related to the type of costimulatory domain, as CD28 is thought to have more potent CAR-T activation and CRS (Fig 2B).

CRS management, which often includes intensive care monitoring, includes corticosteroids and IL-6 receptor blockade (tocilizumab), especially for patients with CRS-related neurotoxicity.

Nephrotoxicity of Other Therapies Used in Anticancer Management

Bisphosphonates

Used to counteract up-regulated osteoclasts, high-dose intravenous bisphosphonates have been associated with cumulative, dose-dependent FSGS (pamidronate) and ATN (zoledronate). CKD patients need dose adjustments and frequent monitoring of serum creatinine before redosing is necessary. Dosing is not recommended for most of these agents for $CL_{cr} < 30$ mL/min, though the benefits may outweigh the risks with short-term pamidronate use. Reducing cumulative doses and increasing dose intervals may prevent bisphosphonate nephrotoxicity.

Mammalian Target of Rapamycin Inhibitors

Everolimus and sirolimus are used in various malignancies, including RCC, breast neuroendocrine tumors, and angiomyolipomas. Proteinuria has been reported in 3% to 36% of patients on everolimus and sirolimus. Although mechanistically unclear, kidney biopsies of patients with mammalian target of rapamycin (mTOR) inhibitor-induced proteinuria have displayed FSGS. Proteinuria induced by an mTOR inhibitor is treated with RAAS inhibitors, but nephrotic range proteinuria requires drug discontinuation.

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) are used as immunosuppressants with certain glomerular diseases, with solid organ transplantation, and as prophylaxis against graft-versus-host disease (GVHD) for allogeneic hematopoietic stem cell transplantation (SCT). CNIs cause afferent arteriolar vasoconstriction, which if prolonged can cause ischemic ATN. Toxic ATN also has been described, resulting in characteristic vacuolization of tubular cell cytoplasm. CNIs are infrequently associated with systemic or kidney-limited TMA. Additionally, CNIs may cause magnesium wasting in the kidney, which mechanistically occurs via TRPM6 down-regulation.

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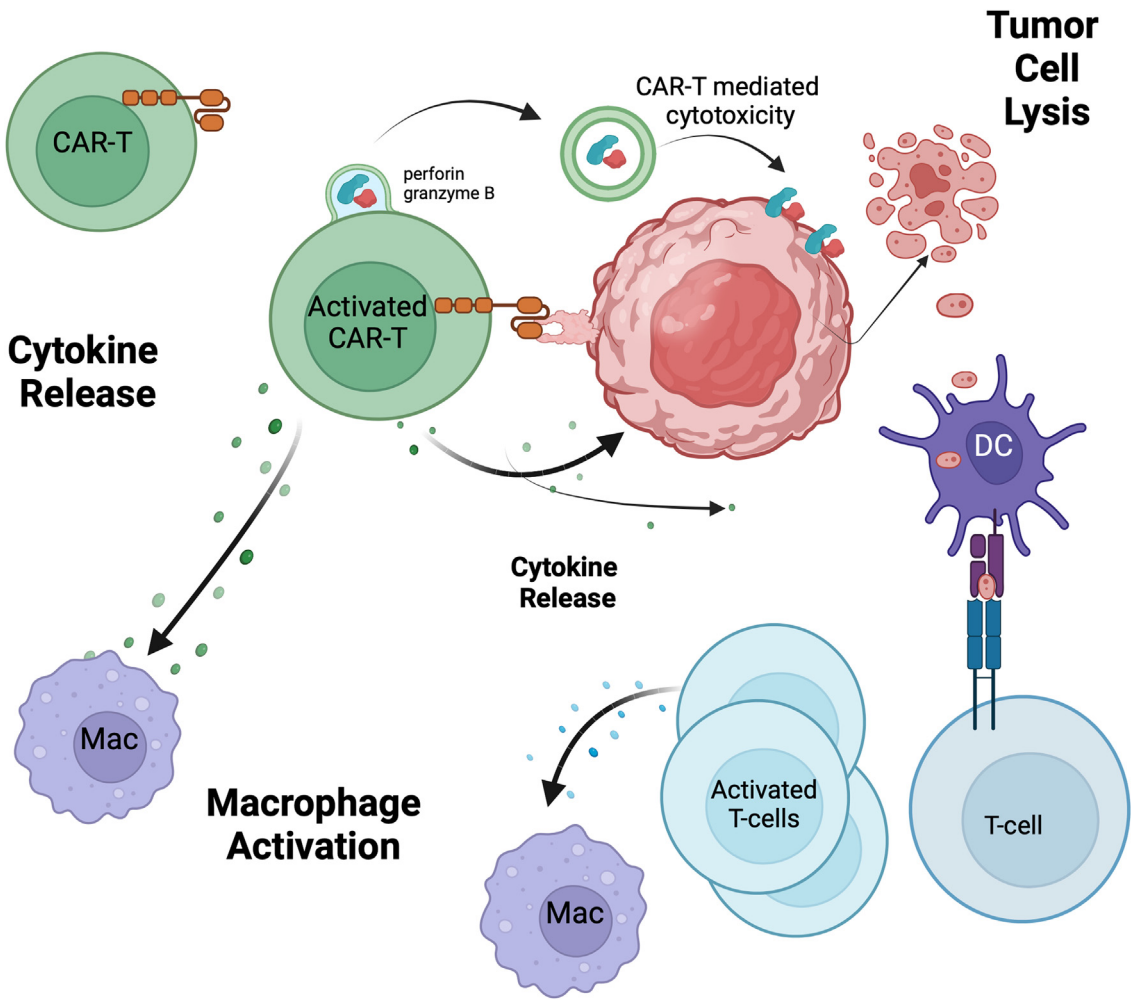

Figure 3. A schema of the various inflammatory responses with CAR-T. Recognition of tumor specific antigen activates CAR-T effector mechanisms aimed at tumor control including cytokine release, tumor lysis, and macrophage activation. These mechanisms may occur simultaneously or independently of each other. Cytokines released by CAR-T include IL-2, which allows expansion of CAR-T cells in vivo, while IL-6 and IFN-γ have tumoricidal properties. Additional cytotoxicity of CAR-T is mediated by perforin/granzyme B. Depending on the scale of tumor cell death, tumor lysis syndrome may result. Tumor cell death also releases novel antigen that if processed by antigen-presenting cells such as DCs and macrophages can activate native T cells. Activated T cells have their own effector mechanism of cytokine release. Thus, multiple pathways can converge to result in cytokine release syndrome, a large, systemic inflammatory cascade that is characterized by fever, hypotension, and other manifestations of severe inflammation. Created with Biorender.com. Abbreviations: CAR-T, chimeric antigen receptor T-cells; DC, dendritic cells; IFN-γ, interferon γ; IL, interleukin; MAC, macrophages; and TLS, tumor lysis syndrome.

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Electrolyte and Acid-Base Disorders in Cancer

Electrolyte and acid-base disturbances in cancer patients result from malignancy or its treatment and are evaluated and managed same as in patients without cancer (Fig 4). The reader is referred also to notable reviews and previous *AJKD* Core Curriculum installments on electrolyte and acid-base disturbances. Here, we focus on hypercalcemia.

Case 3: *A 55-year-old woman with CKD stage 2, hypertension, and breast cancer with skeletal metastases, who was receiving palbociclib therapy, is referred to nephrology for hypercalcemia. She also reports constipation. Her medications include hydrochlorothiazide, vitamin D at 1,000 IU, amlodipine. She is not taking calcium supplements. Her physical examination is normal. The laboratory results reveal creatinine, 1.0 mg/dL; calcium, 13.0 mg/dL; and albumin, 4 g/dL. Her parathyroid hormone (PTH)-related peptide (PTHrP) is 1 pmole/L (reference: <2 pmole/L) and intact PTH is 10 pg/mL (reference: 15-65 pg/mL).*

Question 3: Which of the following best mechanistically explains her hypercalcemia?

(a) Increased renal tubular reabsorption of calcium
(b) Calcium-alkali syndrome
(c) Receptor activator of nuclear factor-kB (RANK) and RANK-ligand (RANKL) interaction
(d) Increased 1,25-dihydroxyvitamin D [1,25$(OH)_2$ D_3] production

For the answer to this question, see the following text.

Hypercalcemia in malignancy is promoted by tumor-derived factors (including PTHrP in humoral hypercalcemia of malignancy, HHM) that stimulate osteoclasts or by lytic release of calcium from bone cancer (primary or metastatic). Both pathways involve binding between RANK on osteoclast precursors and osteoclasts and RANKL on osteoblasts and bone marrow stromal cells. In the non-cancer steady state, RANK–RANKL interactions maintain bone stability, but malignancy shifts the equilibrium in favor of osteolysis to release calcium. In HHM, tumor-secreted PTHrP or rarely ectopic PTH directly up-regulates RANKL. Lymphomas or tumor-associated macrophages may overexpress 1-α-hydroxylase, converting 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which increases gastrointestinal calcium absorption. Lytic release of calcium from bone is stimulated by tumor deposits that release cytokines and other inflammatory mediators to increase osteoclast activity.

Saline diuresis and calcitonin to increase urinary calcium excretion is first-line therapy for malignancy-associated hypercalcemia. Loop diuresis should be provided for hypercalcemia only if volume overload is present. Inhibition of osteoclasts with bisphosphonates suppresses hypercalcemia but, as noted previously, is linked to kidney injury. RANKL inhibitors such as denosumab directly target downstream pathways of HHM and are preferable for use in patients with AKI/CKD.

All the answers for question 3 are potential explanations for hypercalcemia, but this particular patient likely has HHM, which is mediated by RANK–RANKL interactions, so the answer is (c). Although thiazide diuretics decrease urinary calcium excretion, calcium elevation in patients taking thiazide diuretics is generally milder unless advanced CKD is present. The same is true with calcium-alkali syndrome, which would require excessive exogenous calcium and vitamin D intake to manifest hypercalcemia of this degree in patient with relatively preserved GFR. 1,25-dihyrdroxyvitamin D production is more likely with lymphomas than breast carcinomas.

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Kidney Injury in Hematologic Malignancies

The kidney is a target for end-organ injury in patients with hematological cancers, either directly due to the malignancy or indirectly via its treatment. We will review herein kidney injury associated with tumor lysis syndrome,

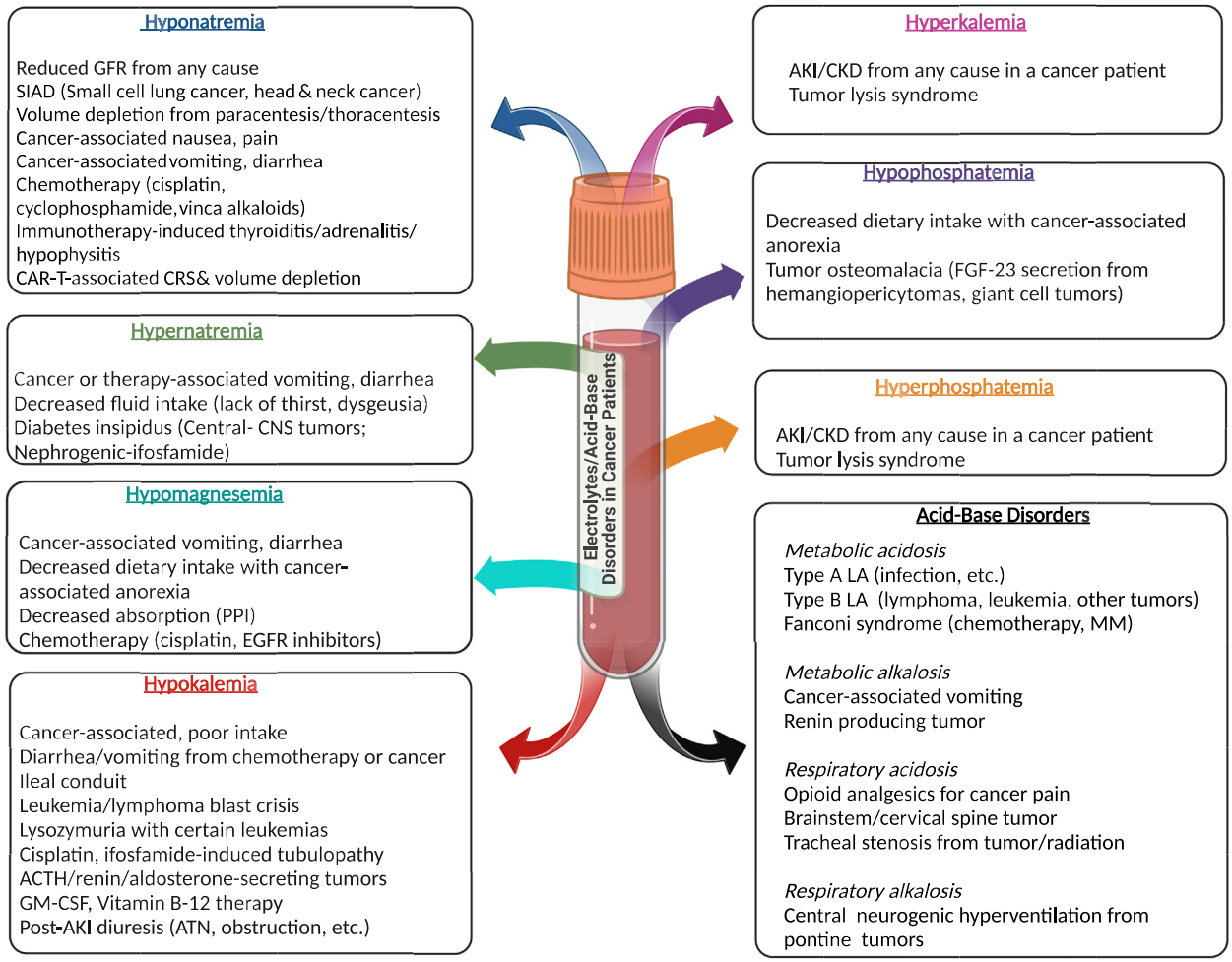

Figure 4. Electrolyte and acid-base disorders in patients with cancer, including hyponatremia, hypernatremia, hyperkalemia, hypokalemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, metabolic acidosis/alkalosis, and respiratory acidosis/alkalosis. Hypercalcemia is separately discussed within the text. Created with Biorender.com. Abbreviations: ACTH, adrenocorticotropin releasing hormone; AKI, acute kidney injury; ATN, acute tubular necrosis; CAR-T, chimeric antigen receptor T cell; CKD, chronic kidney disease; CNS, central nervous syndrome; CRS, cytokine release syndrome; EGFR, epidermal growth factor receptor; FGF-23, fibroblast growth factor 23; GFR, glomerular filtration rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; LA, lactic acidosis; MM, multiple myeloma; PPI, proton pump inhibitors; SIAD, syndrome of inappropriate antidiuresis.

monoclonal gammopathy-related kidney disease, and leukemia/lymphoma.

Tumor Lysis Syndrome

Case 4: *A 68-year-old man with diffuse large B-cell lymphoma (DLBCL) and chronic prostatitis with a recent urinary tract infection that was treated with trimethoprim/sulfamethoxazole is admitted for induction chemotherapy with Rituxan, cyclophosphamide, doxorubicin, vincristine, and prednisone. He is on allopurinol prophylaxis. Four days later he reports tremors and weakness. His laboratory results reveal potassium, 6.9; calium, 7.0; phosphorus, 7.2; uric acid, 12 (baseline: 4); and Scr, 2.5 mg/dL (baseline: 0.98 mg/dL). His electrocardiogram (ECG) reveals a heart rate of 40 bpm and QRS of 130 ms.*

Question 4: In addition to administering insulin and glucose, which of the following is the most appropriate treatment?

(a) Refer for an implanted pacemaker insertion by cardiology
(b) Start hemodialysis with low potassium dialysate
(c) Initiate aggressive intravenous fluid administration
(d) Administer rasburicase
(e) Replace allopurinol with febuxostat

For the answer to this question, see the following text.

Tumor lysis syndrome (TLS) describes biochemical and clinical abnormalities from spontaneous or therapy-induced tumor cell death that releases nucleic acids, proteins, and electrolytes. The Cairo-Bishop classification is

commonly used to define laboratory and clinical TLS (Table 3) but uses nonstandard AKI definitions and does not include spontaneous TLS. TLS risk is highest with bulky, high-turnover malignancies like Burkitt-type lymphoma, less common with chronic leukemias and multiple myeloma, and uncommon in solid malignancies. Treatment with venetoclax carries an independent risk for TLS regardless of tumor type. Increased age, pre-existing CKD, and baseline hyperuricemia add to the risk of TLS.

TLS results when purine nucleotides released from dying tumor cells are converted to xanthine and uric acid by xanthine oxidase. Acidic conditions favor uric acid precipitation in the PTEC lumen, causing ATN from direct injury and inflammatory pathways. Cell death also releases electrolytes, leading to hyperkalemia and hyperphosphatemia. Phosphorus complexes with calcium, causing hypocalcemia and calcium-phosphorus nephrocalcinosis, the latter also contributing to AKI.

Prophylactic allopurinol and febuxostat prevent further rises in baseline uric acid levels. This does not treat existing hyperuricemia, and high-level xanthine accumulation may result, which is also potentially nephrotoxic. Allopurinol requires GFR dose adjustment, and hypersensitivity has been noted. Febuxostat's cost and availability have limited its use. Recombinant rasburicase cleaves uric acid to the soluble allantoin and is used prophylactically in high-risk TLS patients. It effectively lowers pre-existing high uric acid levels but is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. Finally, uric acid excretion with saline diuresis to target urine output ≥ 2 mL/kg/h is standard practice. Urine alkalinization should be avoided because it worsens calcium-phosphate precipitation. Prompt lowering of uric acid levels reduces the risk of AKI, though some patients will nonetheless develop AKI requiring renal replacement therapy. Continuous dialysis modalities may be required if rebound hyperkalemia follows intermittent hemodialysis.

The patient in case 4 meets the Cairo-Bishop criteria for laboratory and clinical TLS and has critical hyperkalemia with an ECG displaying conduction defects. This requires immediate treatment of hyperkalemia, which is being provided by temporizing measures of insulin and glucose administration. A pacemaker should not be inserted for a reversible cause of bradycardia such as hyperkalemia. He should receive volume expansion, but this alone may not significantly reduce his serum uric acid levels because urinary excretion of uric acid will be diminished with AKI. Dialysis may eventually be required for refractory hyperkalemia, but the next treatment step should focus on lowering his uric acid levels to prevent worsening crystal nephropathy. Febuxostat will not reduce pre-existing hyperuricemia. Although rasburicase should never be given to patients with known or suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency, withholding the drug while waiting for enzyme testing in all patients is not advised, given the emergent nature of TLS requiring quick lowering of uric acid levels. This patient was dosed with sulfamethoxazole without incident, so it is unlikely that he has G6PD deficiency. Thus, question 4, the answer is (d), rasburicase dosing as the most appropriate treatment.

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Monoclonal-Gammopathy-Related Kidney Disease

Proliferating plasma cells produce monoclonal immunoglobulins that may be pathologic to different kidney compartments. This is well-recognized in the context of multiple myeloma, but B-lymphocytes also produce these immunoglobulins in lymphoplasmacytic lymphoma (Waldenström Macroglobulinemia) and chronic lymphocytic lymphoma.

Case 5: *A 64-year-old man with a past medical history of osteoarthritis presents to the emergency department with cough, fatigue, and low back pain for 3 weeks, which has been refractory to daily ibuprofen used once a week. His physical examination is remarkable for blood pressure of 160/84, heart rate of 115, coarse breath sounds at the bases, and pallor. The laboratory results reveal Scr, 4.2 mg/dL (1 month prior: 0.8 mg/dL); white blood cell count, 25; hemoglobin, 6.6 g/dL; calcium, 12.5 mg/dL; total protein, 9 mg/dL; and albumin, 2.5 mg/dL. The urinalysis reveals +1 protein with no blood or glucose.*

Question 5: What is the most likely diagnosis for this patient's kidney dysfunction?

(a) ATN secondary to NSAID use
(b) Multiple myeloma cast nephropathy
(c) Hypercalcemia-associated AKI
(d) Light chain proximal tubulopathy

For the answer to this question, see the following text.

Kidney-specific injury from multiple myeloma includes AKI and/or proteinuria via different mechanisms that result in diverse clinicopathologic findings We will detail multiple myeloma cast nephropathy (MCN)—the most common multiple myeloma–related kidney disease—with other manifestations of monoclonal-gammopathy-related kidney disease in glomerular and tubular compartments noted in Figure 5. MCN is distinct from light chain cast nephropathy, which may occur in B-lymphocyte clonal disorders. Serum free light chains (SFLCs) that have been filtered undergo endocytosis by PTECs; however, in MCN the SFLCs reabsorbed to excess trigger hydrogen peroxide–induced inflammatory pathways and direct tubular toxicity. Distal tubular injury occurs when SFLCs

Table 3. Cairo-Bishop Definitions for Tumor Lysis Syndrome, Along With Grading by Severity of End-Organ Complications

Laboratory TLS: ≥2 or More Derangements 3 Days Before or 7 Days After Chemotherapy		
Electrolyte/Metabolic-Breakdown Product	**Absolute Value**	**Percent Change From Baseline**
Calcium	<7.0 mg/dL	Decrease of at least 25%
Phosphorus	>4.5 mg/dL (adults), >6.5 mg/dL (children)	Increase of at least 25%
Potassium	>6 mEq/L	Increase of at least 25%
Uric acid	>8.0 mg/dL	Increase of at least 25%

Clinical TLS: Laboratory TLS *and* ≥1 Clinical Complication						
End-Organ Complication	**Grade of Organ Injury**					
	0	**1**	**2**	**3**	**4**	**5**
Cardiac arrhythmia *or* sudden death	None	No indication for intervention	Only nonurgent medical intervention	Incomplete control with medication or use of AICD	Severe life-threatening arrhythmia (syncope, heart failure, etc)	Death
Serum creatinine	<1.5 × ULN	1.5 × ULN	>1.5-3 × ULN	>3-6 × ULN	>6 × ULN	Death
Seizures	None	Not defined	One brief generalized seizure controlled with AEDs or infrequent focal motor seizures	Seizures with altered consciousness, breakthrough generalized seizures	Prolonged, repetitive or difficult to control (status epilepticus, refractory to meds)	Death

Based on information in Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127:3-11. https://doi.org/10.1111/j.1365-2141.2004.05094.x. Abbreviations: AEDs, antiepileptic drugs; AICD, automated implantable defibrillator; TLS, tumor lysis syndrome; ULN, upper limit of normal.

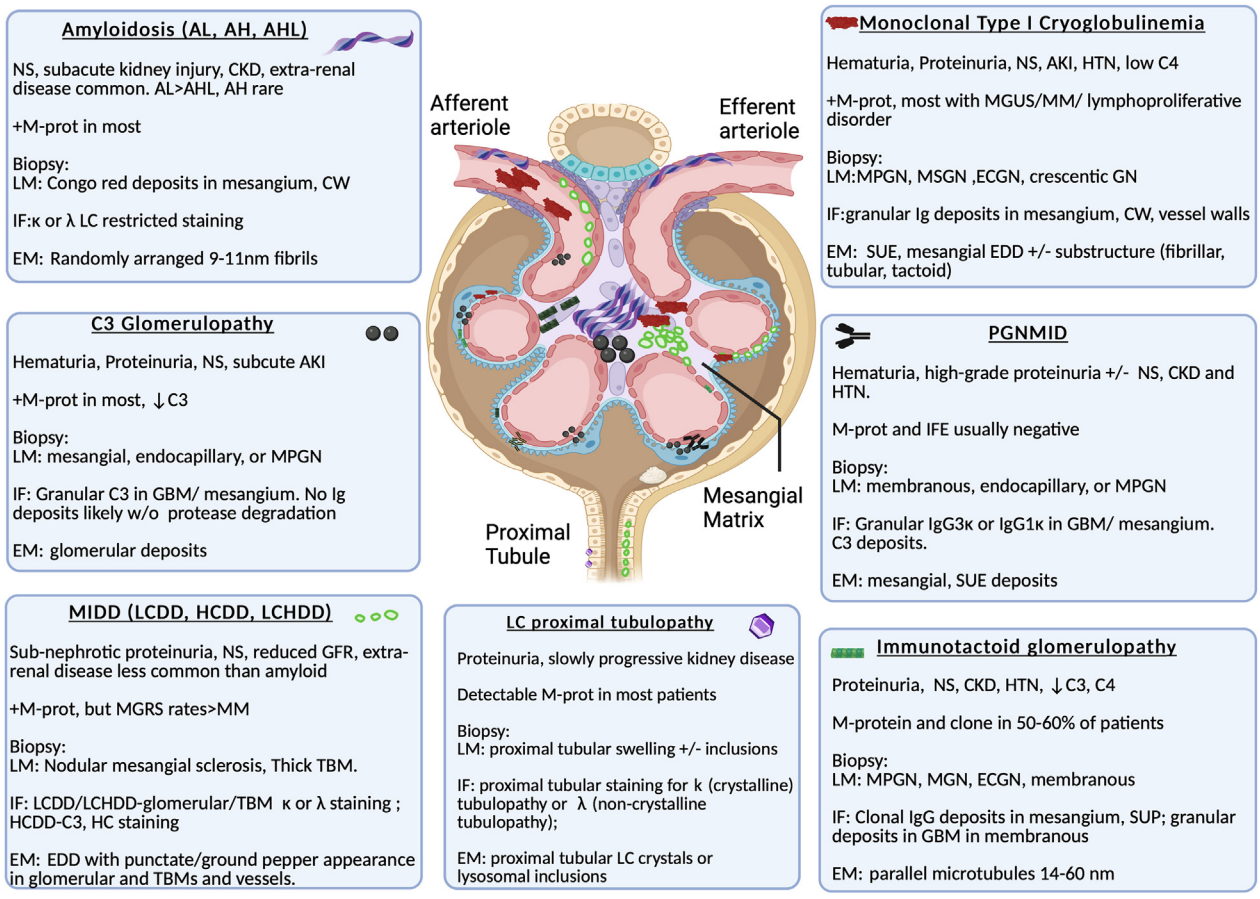

Figure 5. Clinical presentation, laboratory data, and kidney biopsy findings (with figure showing localization to glomeruli, vessels, or tubules) in different monoclonal gammopathy-related kidney diseases. With the exception of C3 glomerulopathy, which involves immunoglobulin-mediated activation of complement, these diseases are associated with monoclonal immunoglobulin deposition by clonal plasma cells or B-lymphocytes in various kidney compartments. All kidney compartments are affected in amyloidosis and MIDD whereas LC proximal tubulopathy only involves the tubules. Immunotactoid glomerulonephritis, C3 glomerulopathy, and PGNMID involvement is restricted to glomeruli. Cryoglobulin deposition is usually seen in glomeruli though intravascular cryoglobulin thrombi may be seen in vessels. Immunotactoid glomerulopathy, type I cryoglobulinemic glomerulonephritis, and PGNMID involve deposition of the entire immunoglobulin, whereas heavy chain restriction is noted for AH amyloidosis and HCDD. Most of these diseases present with variable degrees of proteinuria, including nephrotic syndrome. Created with Biorender.com. Abbreviations: AH, heavy chain amyloidosis; AHL, light and heavy chain amyloidosis; AL, light chain amyloidosis; CKD, chronic kidney disease; CW, capillary wall; ECGN, endocapillary glomerulonephritis; EDD, electron dense deposits; EM, electron microscopy; GBM, glomerular basement membrane; GFR, glomerular filtration rate; HC, heavy chain; HCDD, heavy chain deposition disease; HTN, hypertension; IF, immunofluorescence; IFE, immunofixation by electrophoresis; Ig, immunoglobulin; LC, light chain; LCDD, LC deposition disease; LCHDD, light chain/heavy chain deposition disease; LM, light microscopy; MIDD, monoclonal immunoglobulin deposition disease; MGN, mesangial glomerulonephritis; MGRS, monoclonal gammopathy of renal significance; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; M-prot, M-protein; MPGN, membranoproliferative GN; NS, nephrotic syndrome; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits; SUB, subendothelial deposits; SUE, subendothelial; SUP, subepithelial; TBM, tubular basement membrane; w/o, without.

bind to uromodulin (Tamm-Horsfall) protein via unique complementarity-determining regions to form obstructive casts that incite inflammation. The risk of MCN increases with NSAID use and hypercalcemia.

MCN requires prompt treatment of multiple myeloma to quickly reduce the SFLC levels. The current standard of care for multiple myeloma treatment is the use of PIs as triplet treatment with corticosteroids and cyclophosphamide or thalidomide/thalidomide derivatives or, increasingly, the anti-CD38-mAb daratumumab. Progressive AKI may require hemodialysis for usual clinical indications, but the role of the extracorporeal therapies high-cutoff (HCO) hemodialysis or plasma exchange to remove SFLC is unsettled.

There is increasing consensus that monoclonal immunoglobulins may cause kidney disease without meeting the formal criteria for multiple myeloma or lymphoplasmacytic lymphoma. For example, multiple myeloma diagnosis requires a bone marrow plasma cell

burden > 10% as well as criteria for end-organ damage or 1 of the 3 multiple myeloma–defining events (>60% bone marrow plasma cell burden; serum involved/uninvolved SFLC ratio > 100; or >1 focal magnetic resonance imaging lesion > 5 mm). If the plasma cell burden is < 10% in the absence of kidney disease, patients are considered to have monoclonal gammopathy of undetermined significance. The diagnostic entity known as monoclonal gammopathy of renal significance (MGRS) defines those patients who do not meet the criteria for multiple myeloma but manifest kidney lesions classically associated with multiple myeloma. These kidney lesions may lead to progressive CKD and have high recurrence rates after kidney transplantation, which supports the collaborative treatment for MGRS by hematologists and nephrologists.

The patient in case 5 has presented with back pain, AKI, anemia, and hypercalcemia. Although hypercalcemia may be contributing to AKI, it is unlikely to be the lone cause of severe AKI in this case. NSAIDs may cause ATN, but this patient's history suggests he had time-limited use. The low albumin/globulin (total protein) ratio along with AKI, anemia, and hypercalcemia are worrisome for a paraprotein malignancy such as multiple myeloma. This would require confirmation with bone marrow biopsy, serum protein electrophoresis (SPEP) with immunofixation, and measurement of SFLCs. Both MCN and light chain proximal tubulopathy/Fanconi syndrome are seen with multiple myeloma. However, this patient's lack of glucosuria makes answer (b), MCN, the more likely diagnosis and the best response to question 5.

Lymphomatous and Leukemic Kidney Disease

Kidney disease in patients with leukemias and lymphomas may be clinically silent or present with proteinuria and/or AKI. Leukemic or lymphomatous kidney infiltration is usually asymptomatic, but bilateral interstitial involvement that increases interstitial pressure may cause AKI via compressive tubular injury. Flank pain and hematuria are among the signs and symptoms. Glomerular infiltration more commonly results in isolated proteinuria versus AKI. Kidney ultrasound in patients with infiltrating leukemia/lymphomas classically shows symmetric kidney enlargement. Metabolic uptake in the kidney on positron emission tomography-CT scan may be seen. Kidney biopsy provides definitive diagnosis and tumor typing.

Several paraneoplastic glomerular lesions have been noted with different lymphomas/leukemias. Most common among these are MCD and FSGS, which have been described in Hodgkin lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), and acute and chronic myeloid leukemias, among others. CLL also has associations with MCD/FSGS, MN, and membranoproliferative glomerulonephritis. Leukemias with white blood cell counts > 100,000/mm^3 may rarely lead to intravascular leukostasis causing ATN from microvascular ischemia. Management of kidney disease due to hematological malignancies requires treatment of the underlying cancer.

Unique to monocytic leukemias, particularly chronic myelomonocytic leukemia (CMML), lysozyme nephropathy is another type of kidney injury associated with hematological malignancies. Lysozyme undergoes glomerular filtration and reabsorption by the proximal tubule. CMML and other leukemias excessively produce lysozyme which is directly toxic to proximal tubule cells with supraphysiological reabsorption. Serum and urine lysozyme are markedly elevated in lysozyme nephropathy. SPEP may show a gamma-region spike, but immunofixation electrophoresis (IFE) will be negative for a monoclonal component. Clinically, patients experience AKI from ATN as well as nonalbumin proteinuria from lysozyme excretion into urine. Hypokalemia may also be present. Light microscopy typically reveals ATN with hypereosinophilic granules within the PTEC cytoplasm that stain positive for lysozyme on immunohistochemistry. Electron microscopy shows numerous autophagolysosomes.

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Kidney Disease Associated With Hematopoietic Stem Cell Transplantation

Hematopoietic SCT is curative-intent therapy for both malignant and non-malignant hematological and non-hematological diseases. In autologous SCT, the patient self-donates stem cells; in allogeneic SCT, related/unrelated donors provide cells. Allogeneic SCT requires GVHD prophylaxis. Conditioning may be myeloablative for cancer and bone marrow eradication or non-myeloablative with sufficient immunosuppression to allow engraftment. Depending on the type of SCT, patients may experience kidney disease due to bone marrow conditioning treatments in the pretransplant phase, prophylactic drugs after transplant, or direct effects of the transplant itself.

Case 6: *A 38-year-old woman with acute myelocytic leukemia (AML) with unfavorable risk cytogenetics and in remission following 7+3 (cytarabine and daunorubicin) induction treatment undergoes haploidentical allogeneic SCT with myeloablative conditioning with cyclophosphamide and busulfan. Her posttransplant course was complicated by acute skin GVHD, requiring corticosteroids. She is on sirolimus and tacrolimus for GVHD prophylaxis. Her baseline creatinine was 0.9 mg/dL. Four months after SCT, she is urgently referred to nephrology with new-onset hypertension of 180/100 mm Hg from a baseline of 118/72 mm Hg. The examination is notable for +2 edema in the lower extremities. Her skin examination is normal. The data show that her creatinine is at 2.2 mg/dL. The other data show lactate dehydrogenase, 600 U/L; haptoglobin, 10 mg/dL; hemoglobin, 7.6 mg/dL; platelets, 60,000; and UPCR, 1.5. The peripheral smear shows schistocytes.*

Question 6: What is the most likely diagnosis?

(a) Busulfan-associated TMA
(b) Transplant-associated TMA
(c) Chronic GVHD
(d) Postengraftment syndrome

For the answer to this question, see the following text.

The range of multifactorial kidney syndromes including AKI, CKD, and proteinuria that occur relative to the start of bone marrow conditioning, donor infusion, and engraftment, and potential development of acute (aGVHD) or chronic (cGVHD) GVHD are illustrated in Figure 6. These are linked to drug nephrotoxicity, infections, GVHD, transplant-associated TMA (TA-TMA), and hepatic sinusoidal obstruction syndrome (SOS), some of which are reviewed herein.

AKI is common in SCT. A recent meta-analysis revealed a 55.1% AKI incidence rate, of which 8.3% had stage 3 AKI. In another study of 408 patients postallogeneic SCT, the incidence of AKI was 64.2% at 100 days and was associated with increased 2-year mortality.

SCT patients are susceptible to indirect and direct nephrotoxicity of myeloablative conditioning regimens. These treatments are associated with mucositis, vomiting, and diarrhea, all of which may lead to volume depletion and AKI along the prerenal/ATN spectrum. Clofarabine and melphalan used in such regimens have been linked to direct tubular toxicity, though biopsy data are sparse and confounding risk factors for AKI exist in the post-SCT period.

AKI features prominently in engraftment syndrome, a constellation of rash, fever, pulmonary edema, and other symptoms that is typically seen within 7-10 days of SCT. SOS presents with abdominal pain, jaundice, and elevated liver enzymes from hepatic sinusoidal injury, which if prolonged results in portal hypertension. AKI with SOS is similar to hepatorenal syndrome.

GVHD represents immune-mediated organ injury by donor cells. The classic definition of aGVHD/cGVHD is time based; however, updated consensus criteria are both time and symptom based. Kidney biopsies in suspected kidney-GVHD have shown infiltrating tubulointerstitial T cells. Patients with kidney-GVHD may present with AKI with or without proteinuria as well isolated proteinuria. MN in SCT can be a manifestation of chronic GVHD. Reported target antigens include PLA_2R, NELL-1, and FAT1. MCD and FSGS have also been described.

TA-TMA is similar in clinical presentation to TMA in the non-SCT setting, with reported incidence rates of 8.2% to 39.0%. Management of AKI and CKD after SCT is tailored to the etiology of AKI. For example, GVHD requires increased immunosuppression whereas TMA may require holding CNIs out of concern for drug-induced TMA. Defibrotide is approved in the United States for treatment of SOS. The patient in case 6 meets the criteria for TMA with microangiopathic hemolytic anemia, thrombocytopenia, and proteinuric AKI. Busulfan is a risk factor for TA-TMA but is not thought to be the primary driver for TMA after transplant. The patient is not exhibiting skin changes consistent with skin cGVHD. Postengraftment syndrome is an inflammatory reaction that occurs in the immediate posttransplant period as neutrophils recover. He likely has TA-TMA, particularly given the multiple risk factors, including GVHD, CNI use, and myeloablative conditioning, meaning that answer (b) is the best response to question 6.

Additional Readings

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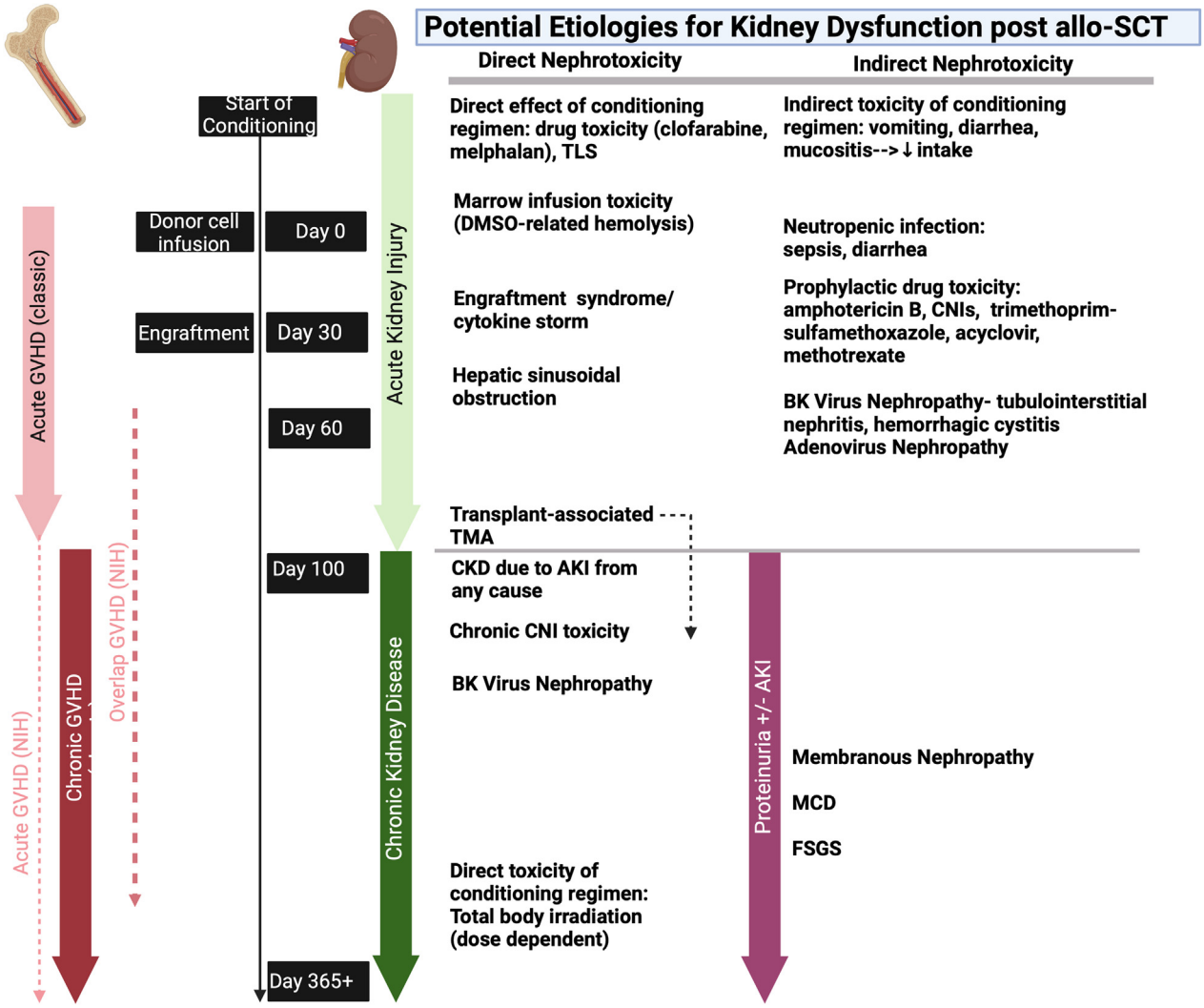

Figure 6. Manifestations of kidney disease post allogeneic-SCT include AKI, CKD, and proteinuria. Many of the etiologies of AKI occur at or around specific time ranges relative to pre-SCT conditioning, donor cell infusion, engraftment as well as relative to GVHD. Both aGVHD and cGVHD have classically had time-based definitions (solid, filled arrows), which have evolved into time- and symptom-based definitions (dotted, colored arrows). Other etiologies of post-SCT AKI may evolve into post-SCT CKD. Proteinuria may be seen as a manifestation of kidney-specific cGVHD, with biopsy revealing inflammatory infiltration and/or MCD, FSGS or MN. Created with Biorender.com. Abbreviations: aGVHD, acute graft-versus-host disease; AKI, acute kidney injury; cGVHD, chronic graft-versus-host disease; CKD, chronic kidney disease; CNI, calcineurin inhibitor; DMSO, dimethyl sulfoxide; FSGS, focal and segmental glomerulosclerosis; MCD, minimal change disease; SCT, stem cell transplant; TLS, tumor lysis syndrome; TMA, thrombotic microangiopathy.

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Cancer in Kidney Transplant Recipients

Patients with CKD and/or end-state renal disease have a heightened cancer risk that is thought to reflect uremic immune dysfunction. In kidney transplant recipients (KTRs), improved GFR may restore that dysfunction, but posttransplant immunosuppressants abrogate that advantage.

Case 7: *A 52-year-old man with kidney failure secondary to MN treated with cyclophosphamide, prednisone, and rituximab undergoes deceased donor kidney transplantation with basiliximab induction. His maintenance immunosuppression includes tacrolimus, mycophenolate mofetil, and prednisone. One year later, he develops a solitary crusted nodule on his back. Biopsy shows squamous cell carcinoma. The most recent Scr is 1.5 mg/dL.*

Question 7: What would be the next best step after excision with clear margins?

(a) Stop tacrolimus and mycophenolate mofetil and increase the prednisone dose.
(b) Reduce tacrolimus and mycophenolate mofetil dose and start sirolimus.
(c) Stop tacrolimus and mycophenolate mofetil and start sirolimus.
(d) Observation with serial dermatology skin checks.

For the answer to this question, see the following text.

Cancer is the second-leading cause of death in KTRs. Compared with the general population, KTRs have a 2- to 3-fold higher cancer risk, underscoring why patients with cancer need cancer-specific and stage-specific time periods of remission before waitlist activation. KTRs may share cancer risk factors with the general population, but transplant immunosuppression provides a unique additional risk (Table 4).

Standardized incidence ratios in KTRs are highest for Kaposi sarcoma, non-melanoma skin cancers, RCC, and posttransplant lymphoproliferative disorder (PTLD); the standardized mortality ratios are highest for PTLD, RCC, and melanoma. Given this, annual dermatological screening is minimal standard for all KTRs. No screening guidelines exist for RCC though some advocate for kidney ultrasound for patients with pretransplant native

Table 4. Induction and Maintenance Agents With Their Risk Associations With Malignancy and Mechanisms for Those Associations

Immunosuppression	Immunosuppressive Agent	Risk of Malignancy	Mechanism
Maintenance	Calcineurin inhibitors (tacrolimus, cyclosporine)	Increased	• Increase protumor cytokines TGF-b, IL-6. • Impair DNA repair pathways (promutagenic).
	Azathioprine	Increased, particularly in non-melanoma skin cancers	• Sensitizes skin to UV radiation. • Impairs repair from UV radiation-induced DNA damage repair. • Increases development of macrosatellite DNA instability.
	Myocophenolate analogs (MMF, MPA)	Not increased/?decreased (overall cancer incidence has decreased since advent of MMF, MPA)	• Decrease in cancer risk after MMF/MPA introduction may be confounded by overall decreased net immunosuppression.
	mTOR inhibitors	Decreased	• Direct antitumor effects of inhibiting mTOR pathways. • Reduce protumor TGF-b, IL-10, direct antitumor effects. • Inhibit tumor angiogenesis by decreased VEGF signaling.
	Belatacept (CTLA fusion Ig)	Increased incidence of PTLD in EBV seronegative patients but not in EBV seropositive patients	• Unknown
Induction	T-cell depleting agents (anti-CD52), antithymocyte globulin, muromonab-CD3)	Increased incidence of PTLD and melanoma	• Putative mechanism is T-cell depletion including antitumor memory T cells that fail to repopulate and provide cancer surveillance.

Abbreviations: CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte associated antigen 4; IL, interleukin; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; PTLD, posttransplant lymphoproliferative disorder; TGF, transforming growth factor; UV, ultraviolet; VEGF, vascular endothelial growth factor.

cystic kidneys because RCCs in KTRs are more common in native kidneys. PTLD in KTRs is rare, but the mortality risk approaches 50%. Most PTLD is associated with Epstein-Barr virus (EBV), and opinion-based recommendations suggest viral load monitoring for EBV higher-risk KTRs (recipient EBV-seronegative, donor EBV-seropositive).

Cancer diagnoses in KTRs require complex decision making because (1) anticancer therapy has the same potential for nephrotoxicity in native versus allograft kidneys and (2) maintenance immunosuppression sustains transplant tolerance but opposes tumor regression. This requires collaboration between oncologists and transplant nephrologists to individualize cancer treatment based on residual kidney allograft function and patient goals. A consideration for KTRs is use of ICIs, which carries acute rejection rates of ~40% in multiple studies. Concurrent use of mTOR inhibitors may reduce this rejection risk while maintaining antitumor efficacy, but studies are pending. Although mTOR inhibitors do have antineoplastic activity and may reduce relapse rates in SCC patients, there is concern that mTOR inhibitors carry a higher mortality risk in KTRs. The decision to use mTOR inhibitors requires careful consideration.

The patient in case 7 had localized one-time SCC that was excised with clean margins. In the absence of other skin findings, frequent dermatologic screenings are a reasonable first step and therefore (d) is the best response to question 7. Recurrent or multiple SCC would warrant consideration of immunosuppressant modification. In that case, transition to sirolimus with planned taper of other agents rather than sudden withdrawal is the best course to avoid acute rejection.

Additional Readings

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