Renal Complications in Sarcoma

an emerging role for "Pediatric Onco-Nephrology"

Seyed Amirhossein Fazeli, MD

Taleghani General Hospital, SBMU,
Tehran, Iran

Washington University School of Medicine,
St. Louis, MO, USA

CASE

A 10-year-old girl diagnosed with Ewing sarcoma of the right femur has been undergoing multi-agent chemotherapy, including cisplatin, vincristine, doxorubicin, and ifosfamide, now on her 4th cycle. She initially presented with localized bone pain and swelling; a biopsy confirmed Ewing sarcoma. The patient has tolerated treatment relatively well but has recently developed increasing fatigue, muscle cramps, and mild nausea.

She has no history of recent infections or other comorbidities. Her physical exam is notable for mild pallor and mild tenderness at the tumor site. Limb function is preserved with no neurological deficits. Volume status appears normal.

Laboratory data:

Scr: 1.2 mg/dL (baseline 0.5)

Bun: 35 mg/dL

Na^{+}: 140 mEq/L

K^{+}: 3.1 mEq/L

Mg^{2+}: 1.2 mg/dL

PO_4^{3-}: 2.0 mg/dL

Cl^{-}: 112 mEq/L

Uric acid: 4.5 mg/dL

pH: 7.31

$PaCO_2$: 30 mmHg

HCO_3^{-}: 18 mEq/L

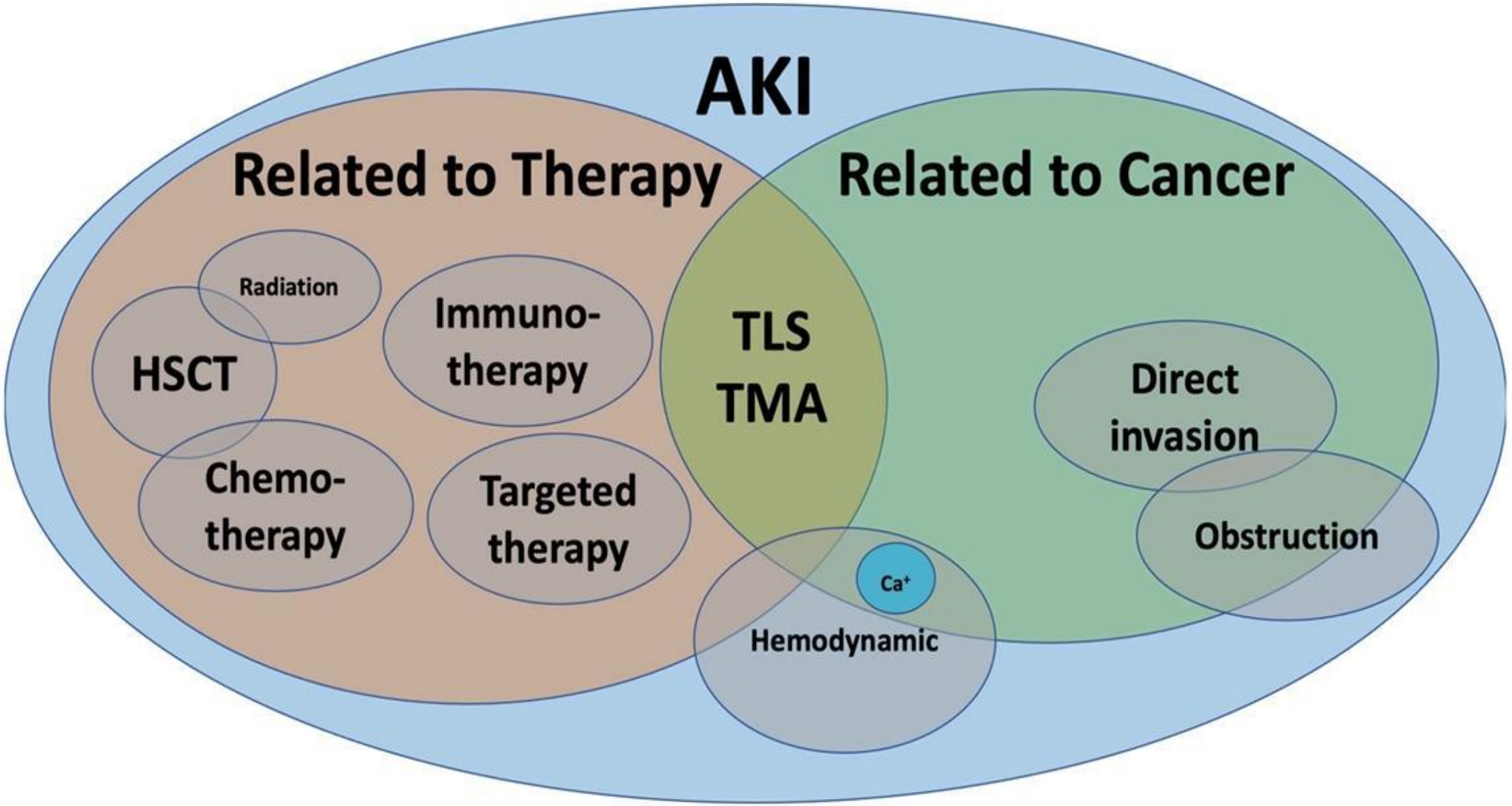
Urine sediment: no dysmorphic RBC or casts

Urine output: 1.2 mL/kg/hr

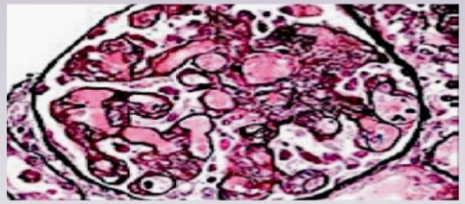
Question:

Which diagnosis best explains this patient's acute kidney injury and biochemical abnormalities?

A) Cisplatin-induced nephrotoxicity
B) Tumor lysis syndrome (TLS)
C) Thrombotic microangiopathy (TMA)
D) Ifosfamide-induced nephrotoxicity

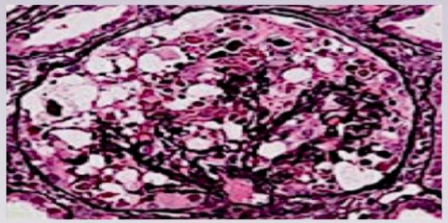

AKI
Related to Therapy
Related to Cancer
Radiation
HSCT
Immuno-therapy
Chemo-therapy
Targeted therapy
TLS
TMA
Direct invasion
Obstruction
Ca+
Hemodynamic

Thrombotic microangiopathy



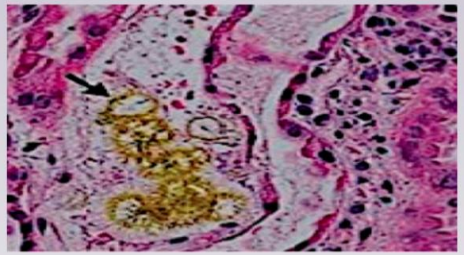
- Mitomycin C
- Gemcitabine
- Antiangiogenesis drugs

Focal segmental glomerulosclerosis



- Pamidronate
- Interferon
- Antiangiogenesis drugs

Crystalline nephropathy



- Dysproteinemia-related
- Drug-induced
- Metabolic

Afferent arteriole

Efferent arteriole

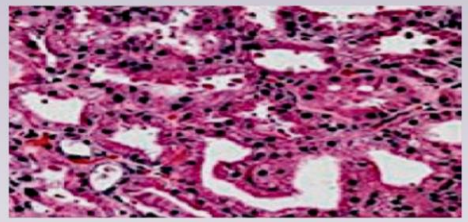
Glomerulus

Proximal convoluted tubule

Collecting tubule

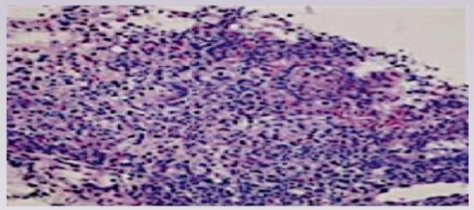
Distal convoluted tubule

Acute tubular injury



- Platinums
- Ifosfamide
- Pemetrexed
- Crizotinib
- Zoledronic acid

Tubulointerstitial injury



- Tyrosine kinase inhibitors
- BRAF inhibitors

Loop of Henle

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

Hyponatremia

Reduced GFR from any cause
SIAD (Small cell lung cancer, head & neck cancer)
Volume depletion from paracentesis/thoracentesis
Cancer-associated nausea, pain
Cancer-associated vomiting, diarrhea
Chemotherapy (cisplatin, cyclophosphamide, vinca alkaloids)
Immunotherapy-induced thyroiditis/adrenalitis/hypophysitis
CAR-T-associated CRS& volume depletion

Hypernatremia

Cancer or therapy-associated vomiting, diarrhea
Decreased fluid intake (lack of thirst, dysgeusia)
Diabetes insipidus (Central- CNS tumors; Nephrogenic-ifosfamide)

Hypomagnesemia

Cancer-associated vomiting, diarrhea
Decreased dietary intake with cancer-associated anorexia
Decreased absorption (PPI)
Chemotherapy (cisplatin, EGFR inhibitors)

Hypokalemia

Cancer-associated, poor intake
Diarrhea/vomiting from chemotherapy or cancer Ileal conduit
Leukemia/lymphoma blast crisis
Lysozymuria with certain leukemias
Cisplatin, ifosfamide-induced tubulopathy
ACTH/renin/aldosterone-secreting tumors
GM-CSF, Vitamin B-12 therapy
Post-AKI diuresis (ATN, obstruction, etc.)

Hyperkalemia

AKI/CKD from any cause in a cancer patient
Tumor lysis syndrome

Hypophosphatemia

Decreased dietary intake with cancer-associated anorexia
Tumor osteomalacia (FGF-23 secretion from hemangiopericytomas, giant cell tumors)

Hyperphosphatemia

AKI/CKD from any cause in a cancer patient
Tumor lysis syndrome

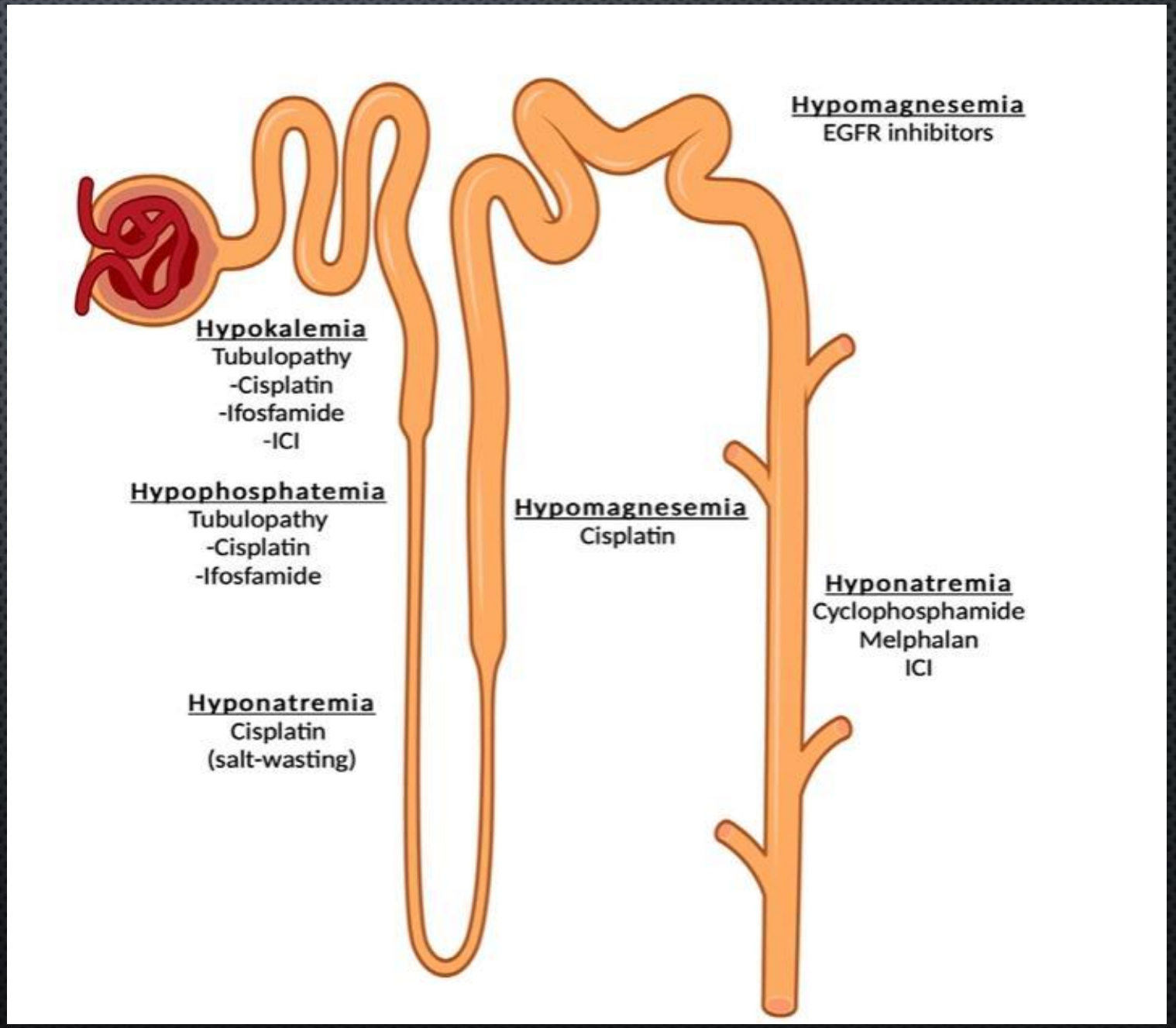
Acid-Base Disorders

Metabolic acidosis
Type A LA (infection, etc.)
Type B LA (lymphoma, leukemia, other tumors)
Fanconi syndrome (chemotherapy, MM)

Metabolic alkalosis
Cancer-associated vomiting
Renin producing tumor

Respiratory acidosis
Opioid analgesics for cancer pain
Brainstem/cervical spine tumor
Tracheal stenosis from tumor/radiation

Respiratory alkalosis
Central neurogenic hyperventilation from pontine tumors


Hypomagnesemia
EGFR inhibitors
Hypokalemia
Tubulopathy
-Cisplatin
-Ifosfamide
-ICI
Hypophosphatemia
Tubulopathy
-Cisplatin
-Ifosfamide
Hypomagnesemia
Cisplatin
Hyponatremia
Cyclophosphamide
Melphalan
ICI
Hyponatremia
Cisplatin
(salt-wasting)

CASE

A 10-year-old girl diagnosed with Ewing sarcoma of the right femur has been undergoing multi-agent chemotherapy, including cisplatin, vincristine, doxorubicin, and ifosfamide, now on her 4th cycle. She initially presented with localized bone pain and swelling; a biopsy confirmed Ewing sarcoma. The patient has tolerated treatment relatively well but has recently developed increasing fatigue, muscle cramps, and mild nausea.

She has no history of recent infections or other comorbidities. Her physical exam is notable for mild pallor and mild tenderness at the tumor site. Limb function is preserved with no neurological deficits. Volume status appears normal.

Laboratory data:

Scr: 1.2 mg/dL (baseline 0.5)

Bun: 35 mg/dL

Na^{+}: 140 mEq/L

K^{+}: 3.1 mEq/L

Mg^{2+}: 1.2 mg/dL

PO_4^{3-}: 2.0 mg/dL

Cl^{-}: 112 mEq/L

Uric acid: 4.5 mg/dL

pH: 7.31

$PaCO_2$: 30 mmHg

HCO_3^{-}: 18 mEq/L

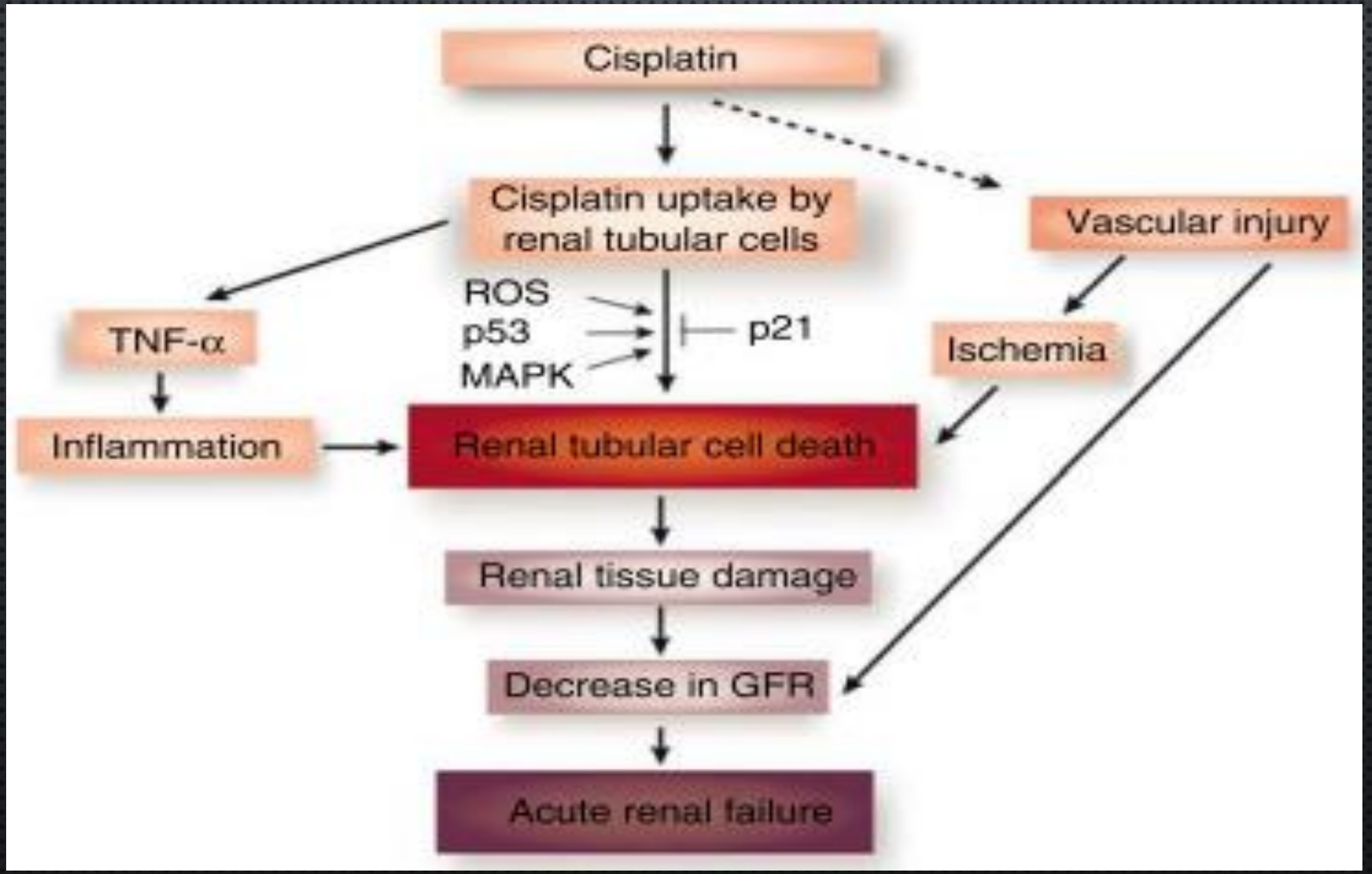
Urine sediment: no dysmorphic RBC or casts

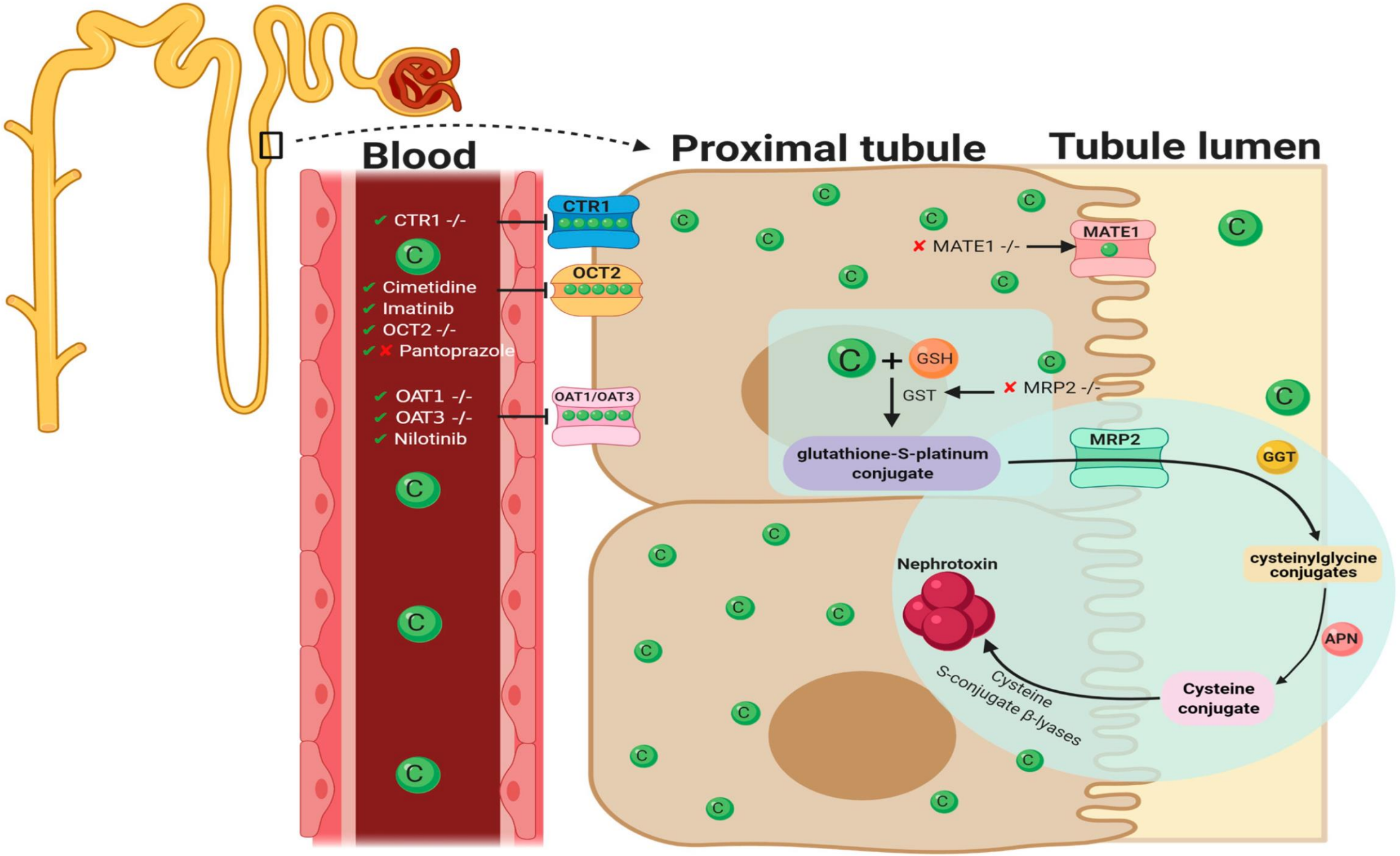
Urine output: 1.2 mL/kg/hr

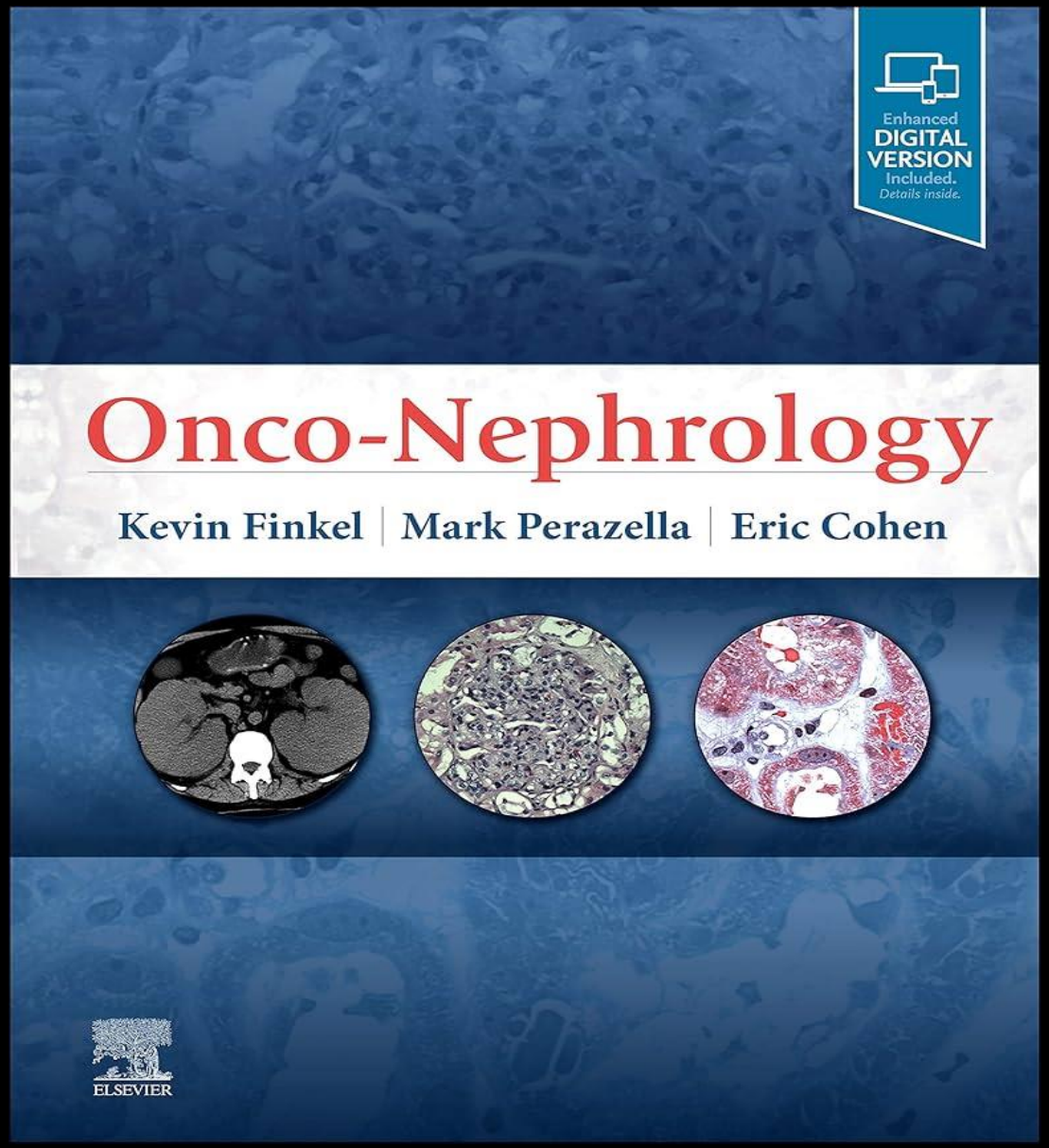
Question:

Which diagnosis best explains this patient's acute kidney injury and biochemical abnormalities?

A) Cisplatin-induced nephrotoxicity
B) Tumor lysis syndrome (TLS)
C) Thrombotic microangiopathy (TMA)
D) Ifosfamide-induced nephrotoxicity


Cisplatin
Cisplatin uptake by renal tubular cells
Vascular injury
ROS
p53
MAPK
p21
TNF-α
Ischemia
Inflammation
Renal tubular cell death
Renal tissue damage
Decrease in GFR
Acute renal failure


Blood
Proximal tubule
Tubule lumen
✔ CTR1 -/-
✔ Cimetidine
✔ Imatinib
✔ OCT2 -/-
✔ ✘ Pantoprazole
✔ OAT1 -/-
✔ OAT3 -/-
✔ Nilotinib
CTR1
OCT2
OAT1/OAT3
✘ MATE1 -/-
MATE1
GSH
GST
✘ MRP2 -/-
glutathione-S-platinum conjugate
MRP2
GGT
cysteinylglycine conjugates
APN
Cysteine conjugate
Cysteine S-conjugate β-lyases
Nephrotoxin



Pediatric Nephrology › Article

Pediatric onco-nephrology: time to spread the word

Part I: early kidney involvement in children with malignancy

Educational Review
Published: 27 November 2020

Volume 36, pages 2227–2255, (2021)
Cite this article