MAYO CLINIC

50-Year-Old Man With New-Onset Acute Kidney Injury

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See end of article for correct answers to questions.

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A 50-year-old man with a history of angioimmunoblastic T-cell lymphoma presented to the emergency department with malaise and low back pain and was hospitalized with the diagnosis of new-onset acute kidney injury (AKI). The patient had a history of autologous stem cell transplant and disease recurrence, for which he underwent salvage chemotherapy with dexamethasone, 2 doses of cytarabine, and 1 dose of cisplatin 4 days before the current presentation. He also had hyperlipidemia but did not take medication. The patient reported no fever, chills, chest pain, dyspnea, nausea, vomiting, abdominal pain, diarrhea, dysuria, hematuria, or change in urinary output. He did not take nonsteroidal anti-inflammatory drugs (NSAIDs). On physical examination, the patient was not in acute distress and had a normal heart rate, regular rhythm, and no extra heart sounds. Faint rales were heard at the lung bases bilaterally; he had mild abdominal distention and no lower extremity edema.

The patient's creatinine level was increased to 3.7 mg/dL from a baseline of 0.8 mg/dL measured 2 days earlier. Additional laboratory investigations revealed the following (reference ranges provided parenthetically): sodium, 125 mmol/L (135-145 mmol/L); potassium, 4.0 mmol/L (3.6-5.2 mmol/L); phosphorus, 7.2 mg/dL (2.5-4.5 mg/dL); calcium, 6.5 mg/dL with a corrected value for albumin of 7.6 mg/dL (8.9-10.1 mg/dL); and lactate dehydrogenase, 1028 U/L (122-222 U/L). Urinalysis identified no casts, red blood cells, proteins, or crystals. The patient's urinary output was 2050 mL in the first 24 hours.

1. **Which *one* of the following additional tests should be performed *next* to obtain information about the etiology of this patient AKI?**
   a. Renal ultrasonography
   b. Measurement of urinary eosinophil level
   c. Bladder scan
   d. Measurement of urinary protein and creatinine levels
   e. Measurement of serum uric acid level

Renal ultrasonography outlines the anatomy of the kidneys and ureters and therefore could detect the presence of hydronephrosis, which would point to an obstructive etiology such as prostate enlargement, nephrolithiasis, or neurogenic bladder. Our patient's preserved urinary output makes obstruction unlikely. Detection of urinary eosinophils would support the diagnosis of acute interstitial nephritis (AIN), which is usually caused by penicillins or NSAIDs. However, our patient had not taken these medications in the weeks leading to the diagnosis of AKI. In addition, the presence of urinary eosinophils is neither sensitive nor specific for AIN.[1] A bladder scan provides information on the amount of residual urine after voiding, which is often seen in prostate disorders. However, our patient had no changes in urinary output or difficulty urinating that would be consistent with prostatism. Measurement of urinary protein and creatinine levels would be useful in patients in whom nephrotic or nephritic syndrome is suspected; however, our patient had only trace protein on urinalysis and had no symptoms of extensive proteinuria such as edema or frothy urine. Serum uric acid measurement would provide additional information on the most likely cause of this patient's AKI because he had recently received chemotherapy.

Further work-up revealed no hydronephrosis or shadowing calculus on renal ultrasonography. The patient's serum uric acid level was 18.0 mg/dL (3.7-8.0 mg/dL), the urinary sodium level was 83 mmol/L, and the urinary creatinine concentration was 26 mg/dL. The calculated fractional excretion of sodium (FeNa) was 9.4%.

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2. Which *one* of the following is the *most likely* etiology of this patient's AKI?

a. Hypovolemia
b. Benign prostatic hyperplasia
c. Tumor lysis syndrome (TLS)
d. AIN
e. Acute tubular necrosis (ATN)

Hypovolemia can cause prerenal azotemia by decreasing perfusion to the kidneys. Common causes including volume loss such as vomiting, diarrhea, bleeding, or excess insensitive losses yield a low FeNa, possibly below 1%, as the kidneys attempt to retain sodium. Obstructive uropathy secondary to benign prostatic hyperplasia is part of the differential diagnosis for a patient with a FeNa of less than 1%; however, the absence of hydronephrosis or decreased urinary output makes it unlikely in our patient. In the context of recent chemotherapy for lymphoma, AKI, electrolyte abnormalities, and increased uric acid level, AKI secondary to TLS is the most likely diagnosis. The mechanism of kidney injury in TLS is multifactorial and involves increased crystallization of uric acid in renal tubules, tubular obstruction from cell sloughing, crystal-independent mechanisms such as uric acid–induced renal vasoconstriction, and calcium-phosphate complex precipitation.[2,3]

Acute interstitial nephritis is classically associated with β-lactam antibiotics and NSAIDs; however, other less recognized medications such as proton pump inhibitors are a leading cause of AIN in the current era.[4] Although present in only 5% of cases, its classic triad consists of rash, fever, and arthralgia. Our patient did not have exposure to medications implicated in AIN or classic findings of AIN. Acute tubular necrosis is caused by nephrotoxins or ischemia. Cisplatin is a potent nephrotoxic agent, but ATN related to its administration is usually seen approximately 10 days after chemotherapy and is associated with low magnesium and potassium levels.[5] Another feature of ATN is the presence of muddy brown casts in the urinary sediment. The time course of our patient's clinical presentation and the increased uric acid levels, low calcium values, high phosphate concentrations, and normal potassium levels make cisplatin-induced nephrotoxicity unlikely.

With the diagnosis of AKI secondary to TLS, the patient was transferred to a cardiac telemetry unit to monitor for potential arrhythmias.

3. Which *one* of the following is the *most likely* cause of hypocalcemia in this patient?

a. Hypoalbuminemia
b. Acute pancreatitis
c. Vitamin D deficiency
d. Hyperphosphatemia
e. Celiac disease

Calcium is an electrolyte bound to albumin in the serum. In low-albumin states such as nephrotic syndrome and malnutrition, total calcium levels decrease; however, there was no evidence of protein loss or hypoalbuminemia in our patient. Acute pancreatitis can induce hypocalcemia by saponification of fatty acids, but the patient's lack of acute abdominal pain would make this diagnosis unlikely. Our patient had not undergone dietary restrictions or sunlight deprivation that could increase the risk of vitamin D deficiency. Hyperphosphatemia induced by the breakdown of cancer cells precipitates calcium, leading to the formation of calcium-phosphate complexes and subsequent hypocalcemia. The calcium-phosphate deposits may cause tubular obstruction and AKI, as seen in our patient. Celiac disease can induce hypocalcemia by impairing the absorption of vitamin D in the brush border of the duodenum, but in the absence of diarrhea, iron deficiency, or malabsorption, this diagnosis could not be substantiated.

The patient calcium levels remained stable and no neurologic symptoms developed.

4. Which *one* of the following intravenous fluid preparations should be administered *first* for the treatment of AKI secondary to TLS?

a. Normal saline
b. Lactated Ringer solution
c. Bicarbonate-based fluids
d. Albumin
e. Half-normal saline

Isotonic normal saline should be used first in the treatment of AKI due to TLS. The administration of fluids and subsequent diuresis decrease the concentration of electrolytes that are abnormally elevated in the serum and prevent the

deposition of crystals in renal tubules. Fluids rich in potassium or phosphate should be avoided.[6] Lactated Ringer solution contains 4 meq/L of potassium, which could worsen hyperkalemia and lead to the development of lethal cardiac arrhythmias. Alkalinization of the urine with bicarbonate-based fluids is no longer advocated because it can result in increased calcium phosphate deposition in the kidney and other organs in the setting of hyperphosphatemia.[6] There is no current data on the use of albumin or half-normal saline for fluid resuscitation in the setting of TLS.

The patient received aggressive intravenous fluid resuscitation with 0.9% normal saline at a rate of 250 mL/h, with a goal urinary output of 80 to 100 mL/m^2.

5. Which *one* of the following should be initiated along with intravenous fluids?

a. Allopurinol
b. Rasburicase
c. Sevelamer
d. Acetazolamide
e. Sodium bicarbonate

Aggressive intravenous hydration is an important component of TLS treatment, but it is ineffective in controlling serum acid levels. Nucleic acids from dead cancer cells are released into the circulation and converted to uric acid, which in turn crystallizes and causes AKI. Allopurinol decreases uric acid production by inhibiting xanthine oxidase but does not affect already existing uric acid. Rasburicase is a urate oxidase enzyme that converts existing uric acid into allantoin, which is 5 to 10 times more soluble in urine than uric acid.[7] It is the preferred agent in patients with serum uric acid levels greater than 7.5 mg/dL, such as our patient whose levels reached 18.0 mg/dL. Sevelamer is a phosphate binder that can be used for hyperphosphatemia in end-stage renal disease; however, insufficient evidence exists on its effectiveness in TLS. Although diuretics may be necessary to promote diuresis after aggressive volume expansion, acetazolamide would promote urine alkalinization by inhibiting carbonic anhydrase, which can exacerbate crystal precipitation of calcium phosphate. Sodium bicarbonate is not recommended for the treatment of TLS because alkalinization of the urine can induce the formation of calcium phosphate stones and worsen the kidney injury.

The patient was treated with a single 6-mg dose of rasburicase, and the uric acid level decreased from 18.0 mg/dL to 3.8 mg/dL over approximately 24 hours. The creatinine level increased to a maximum of 5.9 on hospital day 4 but later returned to baseline. Because the patient's urinary output remained intact and electrolytes stabilized within the normal range, he did not require hemodialysis.

DISCUSSION

Tumor lysis syndrome is an oncological emergency that can be fatal if not treated promptly and effectively. It is caused by the release of intracellular contents such as electrolytes and nucleotides into the circulation after cancer cells die as a consequence of chemotherapy and/or radiation. This syndrome is associated mainly with soft tissue malignancies with a rapid dividing rate, such as leukemias and lymphomas, and may occur spontaneously before anticancer treatment is administered. However, advanced and metastatic solid tumors can cause TLS as well.[8] Cairo and Bishop[9] classified TLS into a laboratory variant and a clinical variant. Laboratory TLS must include 2 or more of the following metabolic abnormalities within 3 days before or 7 days after chemotherapy: hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia. Clinical TLS is present when these laboratory abnormalities are accompanied by increased creatinine levels, seizures, cardiac arrhythmia, or death.

Although our understanding of the pathophysiology, prevention, and treatment of TLS has increased in recent years, the short-term death rate remains high. A recent study of 997 patients hospitalized for TLS revealed a mortality rate of 14.4%.[10] Another group reported that 6 months after intensive care unit admission, mortality was significantly higher in patients presenting with TLS and AKI.[11]

The main strategies in the prevention of TLS are intravenous hydration and the prechemotherapy administration of allopurinol. Fluids should be administered at a rate of 2 to 3 L/m^2 daily to reach a goal urinary output of 80 to 100 mL/m^2 per hour in adults with normal renal and cardiac function. There are no evidence-based guidelines for the optimal duration of intravenous hydration; however, continuing volume resuscitation until the tumor burden is reduced and no laboratory evidence of TLS

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remains is usually recommended.[6] Allopurinol exerts a beneficial effect by reducing uric acid concentrations through its inhibitory activity on xanthine oxidase. However, the clinical benefits of this biochemical process may be limited once large amounts of uric acid have already been released by dying tumor cells. Rasburicase, a recombinant urate oxidase that catalyzes the conversion of uric acid to the more water-soluble molecule allantoin, is the medication of choice for patients with TLS and an established high uric acid load.[7] Special handling of blood samples is necessary because rasburicase degrades uric acid at room temperature and may produce a falsely low value. For that reason, blood samples must be placed on ice immediately after collection.[7] Patients of African or Mediterranean ancestry should be evaluated for glucose-6-phosphate dehydrogenase deficiency before its use because of an increased risk of severe hemolysis.[7] After administration of rasburicase, health care staff should watch for serious adverse effects such as anaphylactic reaction and methemoglobinemia.[7] Its high cost remains a limiting factor, but a meta-analysis found that a single dose of rasburicase as prophylaxis for or treatment of TLS was superior to allopurinol and not inferior to the US Food and Drug Administration–approved 5-day rasburicase course.[12]

Despite optimal care, some patients will require renal replacement therapy for the treatment of TLS. Although the criteria for hemodialysis are the same as those for patients with AKI, including severe acidosis, electrolyte abnormalities, volume overload, and uremia, a low threshold for renal replacement therapy is warranted in this population, especially in oliguric patients, because the continuous release of electrolytes in the circulation may lead to lethal arrhythmias.

Tumor lysis syndrome is a life-threatening condition and should be treated promptly and aggressively. It is extremely important to identify patients at high risk for this syndrome, begin timely prophylaxis and treatment, and monitor patients closely to prevent its potentially catastrophic consequences.

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CORRECT ANSWERS: 1. e. 2. c. 3. d. 4. a. 5. b