CME

Managing tumor lysis syndrome

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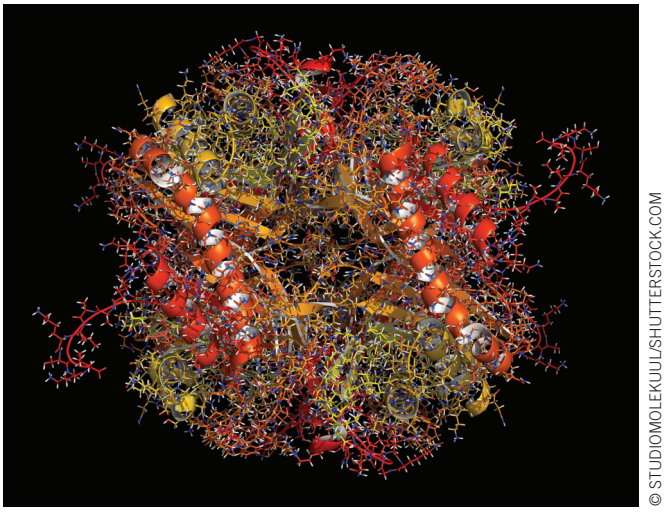
ABSTRACT

Tumor lysis syndrome (TLS) is one of the most common oncologic emergencies, occurring when tumor cell contents are rapidly released into the bloodstream. This release of cellular contents, including uric acid, phosphate, and potassium, can rapidly overwhelm the body's homeostasis mechanisms, leading to renal failure, seizures, cardiac dysrhythmias, or death. With an estimated 1.8 million new diagnoses of cancer projected in 2020 and an increase in the use of targeted agents for treatment, healthcare providers must be able to recognize, diagnose, and manage patients presenting with TLS.

Keywords: tumor lysis syndrome, oncologic emergency, hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia

Learning objectives

- Identify the risk factors for TLS.
- Understand the pathophysiology and clinical manifestations of TLS.
- Understand the appropriate management of TLS, including timing of hematology consult.



Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency that results from the rapid cytolysis of tumor cells.[1] Although TLS most commonly occurs after initiation of cytotoxic chemotherapy, it also can occur spontaneously in patients with high-risk malignancies such as acute leukemia and high-grade lymphoma.[2] Historically, patients with solid tumors rarely developed TLS. However, recent advances in targeted, molecular, and biologic agents have not only enhanced antitumor efficacy, but have increased the risk of developing TLS in patients with malignancies that were formerly considered low-risk, such as breast cancer and multiple myeloma.[1,3] Additionally, although rare, TLS may occur following radiation, surgery, hormone therapy, corticosteroid use, or immunotherapy.[1]

TLS is a set of metabolic complications that can arise as a result of tumor cell death. Few researchers have made attempts to define the syndrome with specific objective criteria. The Cairo and Bishop classification system, created in 2004, is the most widely used and accepted system in oncology.[1,4] The system defines *laboratory TLS* as two or more metabolic abnormalities that occur within 3 days before or up to 7 days after initiation of treatment:

- hyperkalemia, defined as serum potassium of 6 mEq/L or greater, or a 25% increase from the patient's baseline
- hyperphosphatemia, defined as a serum phosphorus of 4.5 mg/dL or greater, or a 25% increase from the patient's baseline
- hyperuricemia, defined as uric acid level of 8 mg/dL or greater, or a 25% increase from the patient's baseline
- hypocalcemia, defined as a serum calcium level of 7 mg/dL or less, or a 25% decrease from the patient's baseline.[4]

Clinical TLS is the presence of laboratory TLS plus at least one of the following: renal insufficiency (serum creatinine of 1.5 or more times the upper limit of normal), cardiac dysrhythmia or sudden death, or seizures.[4]

The Howard criteria, developed in 2011, attempted to improve the Cairo and Bishop classification, and recommended:

- two or more metabolic abnormalities be present simultaneously to qualify for TLS, to limit abnormalities that develop later from other causes.
- a 25% change from baseline laboratory values should not be considered a criterion because these changes may

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Key points

- TLS is an oncologic emergency that most commonly occurs following chemotherapy.
- The electrolyte abnormalities seen in patients with TLS are hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.
- Early consultation of oncology, nephology, and critical care teams often is warranted for optimal management of patients with severe TLS.

not be clinically significant unless they are outside the normal range.

• any symptomatic hypocalcemia should be considered a criterion for clinical TLS.[5]

RISK FACTORS

The incidence of TLS greatly depends on the underlying malignancy and baseline patient characteristics. The current schema for identifying those at risk of TLS recommends stratifying patients into low-, intermediate-, or high-risk categories.[3,4]

Low-risk patients are those with solid-tumor malignancies, except for bulky chemosensitive diseases such as neuroblastoma, germ cell tumors, and small-cell lung cancer, which are considered intermediate-risk.[3] Hematologic malignancies, especially acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and Burkitt leukemia/lymphoma, are all considered high-risk for TLS.[3,6] Some studies have shown the risk of TLS with AML and ALL increases with a white blood cell (WBC) count greater than 100,000 cells/mm^3 and lactate dehydrogenase greater than twice the upper limit of normal.[3] Other studies report a WBC greater than 25,000 cells/mm^3 alone as a risk factor.[1] Hematologic malignancies such as multiple myeloma and the chronic leukemias are generally considered low-risk, except for CLL treated with certain targeted agents or with high presenting WBC level.[1,3]

Experts have researched other malignancy-related factors that increase patients' risk of TLS. Patients with bulky disease (greater than 10 cm in diameter), bone marrow involvement, palpable splenomegaly and/or hepatomegaly, or tumor involvement of the kidney are all considered to be at risk for TLS.[3]

Other researchers work to determine risk factors unrelated to the underlying malignancy. Patients with preexisting renal disease are at high risk for TLS.[2,5,6] A study of almost 1,200 patients with non-Hodgkin lymphoma revealed that in the 63 patients who went on to develop TLS, 68% had evidence of kidney dysfunction on admission.[6] This finding relates to the underlying pathophysiology that will be discussed in more detail later. Additionally, men, older adults with comorbidities, and patients taking multiple medications are at increased risk for TLS.[2,6]

PATHOPHYSIOLOGY

In TLS, massive tumor cell death leads to the release of intracellular components into the bloodstream. These components include cytosol, which is broken down into potassium; proteins that are broken down into phosphates; and nucleic acids that are broken down into uric acid.[1] In a patient with a small amount of lysis and normally functioning kidneys, the body's homeostasis mechanism can compensate for this change in extracellular electrolyte levels. However, if large amounts of lysis product flood the kidneys and/or the patient has baseline renal dysfunction, the kidneys can be quickly overwhelmed.[1,5] These lysis products can cause acute kidney injury (AKI) intrinsically, worsening clearance of these toxic metabolites and compounding AKI and TLS.[1,6] Pathophysiology of TLS is discussed in detail below.

• *Hyperuricemia.* In patients with TLS, hyperuricemia is the result of the catabolism of purine nucleic acids to hypoxanthine. Next, the enzyme xanthine oxidase catabolizes hypoxanthine to xanthine and then to uric acid (**Figure 1**).[1,3,6] The proximal renal tubules normally are responsible for clearing uric acid. However, humans lack the enzyme to break down uric acid into the much more soluble compound allantoin.[7] Therefore, the kidneys can quickly become saturated with high levels of uric acid, leading to precipitation of uric acid crystals, micro-obstruction, and reduced glomerular filtration rate (GFR).[1,6] Hyperuricemia also has been shown to cause higher vascular resistance in peritubular capillaries, increase the release of proinflammatory cytokines, and increase use of nitric oxide, leading to more direct kidney injury.[6]

• *Hyperphosphatemia and hypocalcemia.* Cancer cells may contain up to four times the phosphorus concentration found in normal cells.[1] When high levels of phosphorus are present in the bloodstream, the body attempts to compensate with renal elimination. However, phosphorus binds extracellular calcium that can lead to the precipitation of calcium phosphate crystals in the renal tubules, as well as in other soft tissues. This can worsen kidney injury already present due to hyperuricemia.[1]

• *Hyperkalemia.* Intracellular potassium concentrations that can be as high as 120 mEq/L are released from a lysing tumor cell.[6] Under normal conditions, the liver, muscles, gastrointestinal tract, and kidneys work together to remove excess potassium from the body.[6] However, the acute efflux of potassium in patients with TLS may overwhelm normal mechanisms, leading to systemic end-organ effects.[7]

CLINICAL MANIFESTATIONS

Hyperkalemia in a patient with TLS is defined as potassium level of 6 mEq/L or greater.[4] Hyperkalemia poses the most immediate concern in a patient with TLS because it can cause life-threatening dysrhythmias and death.[3,7] On ECG, the most common changes are peaked T waves, increased PR interval, decreased QT interval, QRS widen-

ing, P-wave flattening, sine wave formation, complete heart block, ventricular tachycardia, ventricular fibrillation, and asystole.[1] Hyperkalemia also may present as muscle cramps, anorexia, fatigue, and paresthesias.[4]

Hyperuricemia in a patient with TLS is defined as uric acid of 8 mg/dL or greater.[4] If the amount of circulating uric acid overwhelms the kidneys, a patient may develop acute renal obstructive uropathy and renal dysfunction.[1] Clinical manifestations can include hematuria, hypertension, azotemia acidosis, edema, oliguria, anuria, lethargy, and somnolence.[4,8] Flank pain may occur in patients with renal pelvic or ureteral stone formation. Urinalysis classically shows uric acid crystals or amorphous urates with high urine pH, but may be normal if output is diminished.[7] If renal injury persists, the patient may develop acute renal failure.[1]

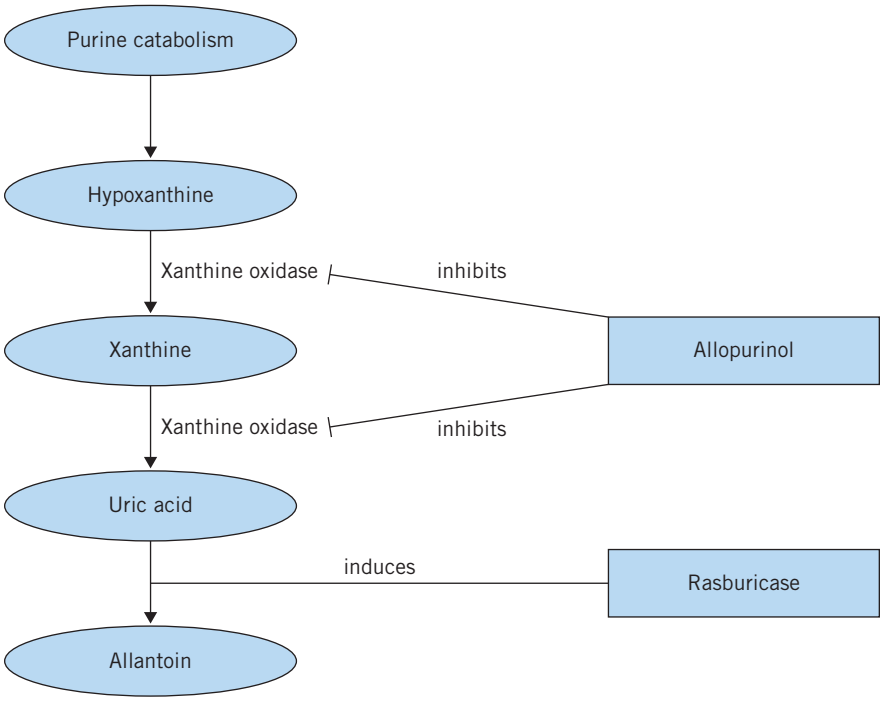

FIGURE 1. Purine catabolism pathway

Hyperphosphatemia in patients with TLS is defined as phosphorus of 4.5 mg/dL or greater.[4] Excess levels may lead to AKI and reduced calcium levels. A patient with hyperphosphatemia may present with nausea, vomiting, diarrhea, lethargy, and seizures.[1] Often, the more emergency manifestations of hyperphosphatemia result from the hypocalcemia that occurs through the chelation of excess phosphorus.[7]

Hypocalcemia in a patient with TLS is defined as calcium level of 7 mg/dL or less.[4] Patients may present with muscular, cardiovascular, and/or neurologic complications as seen in hypocalcemia from other causes.[6] Muscular manifestations include muscle cramps and spasms, paresthesias, and tetany. Cardiac complications include dysrhythmias, heart block, and hypotension. Neurologic abnormalities include hallucinations, seizures, and altered mental status.[4]

See **Table 1** for a summary of clinical manifestations in patients with TLS.

MANAGEMENT

Initial patient management should involve a detailed history and physical examination with attention to any symptoms suspicious for an underlying cancer diagnosis (if unknown at presentation), including weight loss, fevers, bruising, bleeding, or lymphadenopathy. Baseline testing should include a basic metabolic panel, calcium, phosphorus, uric acid, lactate, urinalysis, and ECG.[2,7] If laboratory TLS is identified, consult with the oncology and nephrology teams for assistance with management.[3]

Initially, monitor the patient's laboratory values every 4 to 6 hours.[8] Closely monitor urinary output and consider ordering other diagnostic tests pertinent to the patient's presenting symptoms.[7] Given the need for close cardiac and laboratory monitoring, consider admitting the patient to the ICU; this admission is critical in patients symptomatic from electrolyte derangements.[1,2] Specific steps in TLS management are detailed below.

- *Hydration.* In patients who are intermediate- or high-risk for TLS, aggressive fluid hydration with an isotonic fluid is recommended.[1,4,6,7] The goal of resuscitation should be at least 2 to 3 L daily for all patients with a urine output goal of 80 to 100 mL/h.[1,6,9] Consider IV hydration even for patients at low risk for TLS, provided they have no contraindications to volume expansion, such as a history of heart failure.[4-6] Hydration is effective both for prophylaxis and treatment of TLS, because it expands intracellular volume, increases renal blood flow and GFR, and dilutes extracellular electrolyte concentrations.[1] Potassium-lowering loop diuretics also can be used to maintain appropriate urine output and lower extracellular potassium concentrations in patients who are not volume-depleted.[7]
- *Reducing uric acid levels.* Allopurinol, a structural isomer of hypoxanthine, inhibits xanthine oxidase, preventing the conversion of hypoxanthine to uric acid. The drug has no immediate lowering effect on the serum uric acid, making it an effective choice for patients at risk for TLS, but unsuitable as monotherapy in patients who are hyperuricemic or have clinical signs of TLS.[3,6]

TABLE 1. Possible clinical manifestations of TLS[1,3,4,7]

Laboratory finding	Possible clinical manifestations
Hyperkalemia	Cardiac dysrhythmia, muscle cramps, anorexia, fatigue, paresthesias, sudden cardiac death
Hyperuricemia	Hematuria, oliguria, anuria, edema, hypertension, flank pain, lethargy, somnolence, AKI, and renal failure
Hyperphosphatemia	AKI, hypocalcemia, nausea, vomiting, lethargy, seizures
Hypocalcemia	Muscle cramps, paresthesias, tetany, cardiac dysrhythmias, hypotension, hallucinations, altered mental status, seizures

Rasburicase, or recombinant urate oxidase, converts uric acid into allantoin, a metabolite that is 5 to 10 times more soluble in urine than uric acid.[1] Rasburicase reduces serum uric acid levels within hours and generally is well tolerated. However, it is contraindicated in patients with G6PD deficiency and in pregnant or lactating women.[2] Additionally, its high cost often limits its use.[6]

Previously, urine alkalization was recommended to promote uric acid excretion. However, it is no longer recommended as no studies have shown benefit, and alkalization may increase precipitation of calcium phosphate crystals in the kidneys.[1,7]

• *Correcting electrolyte abnormalities.* Hyperkalemia associated with TLS can be approached similarly to hyperkalemia from other causes. Albuterol, insulin with glucose, sodium bicarbonate, and loop diuretics may be used. Calcium may be used to help stabilize the myocardium; however, administer calcium with caution, because excess levels may lead to increased calcium phosphate precipitation in the kidneys and worsening AKI.[7] Hemodialysis is recommended for treatment of life-threatening hyperkalemia, and continuous renal replacement therapy (CRRT) may be required to prevent rebound hyperkalemia.[6]

Initially, manage hyperphosphatemia with hydration and restriction of phosphorus intake. If hyperphosphatemia persists, oral phosphate binders such as sevelamer can be used to reduce intestinal absorption of phosphate. Patients with severe hyperphosphatemia also may require dialysis. Because phosphorus and calcium are linked, correcting phosphorus levels should improve hypocalcemia.[7] Symptomatic hypocalcemia can be treated with calcium gluconate, but clinicians should attempt correction at the lowest possible dose to prevent additional renal calcium phosphate precipitation.[1]

CONCLUSION

With the incidence of cancer continuing to grow and increased use of novel targeted treatments, the incidence of TLS also is likely to increase. Because cancer treatments have become more accessible and tolerated, many patients are treated as outpatients, so clinicians in all settings should know the risk factors, symptoms, diagnosis, and management of TLS. Prompt recognition and treatment can significantly reduce morbidity and mortality associated with TLS.[1,5] **JAAPA**

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