Tumor Lysis Syndrome

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KEYWORDS

• Tumor lysis syndrome • Oncologic emergencies • Rasburicase • Acute kidney injury

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Tumor lysis syndrome (TLS) can occur as a consequence of tumor-targeted therapy (chemotherapy/another pharmacologic antitumor treatment, embolization therapy, and radiation therapy) or spontaneously. Hematologic cancers constitute many TLS cases because of their rapid division rate and sensitivity to chemotherapy.
2. Central to pathogenesis is the rapid release of intracellular potassium, phosphorus, and uric acid from dying cancer cells into the extracellular space overwhelms existing homeostatic mechanisms, potentially leading to acute kidney injury (AKI), arrhythmia, neurologic deficits, and death.
3. Spontaneous TLS is in the differential diagnosis of any patient with AKI of unknown cause. It requires a high index of suspicion because it can be the initial presentation leading to the diagnosis of cancer.
4. Every hospitalized patient with cancer, especially if receiving chemotherapy, needs to be stratified for the risk of TLS.
5. Patients at highest risk for developing TLS can have hematologic malignancies, advanced or metastatic disease, bulky tumor, and/or tumors with a high Ki-67 (a marker of cell proliferation). These patients may already be in spontaneous tumor lysis.
6. Patients with compromised renal function or with risk factors for renal dysfunction are at increased risk for TLS.
7. The ideal management of TLS is prevention. Prevention strategies include hydration and prophylactic rasburicase in high-risk patients, hydration plus allopurinol or rasburicase for intermediate-risk patients, and hydration and optional allopurinol and close monitoring for low-risk patients.

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8. Potential complications of rasburicase include anaphylaxis, hemolytic anemia, methemoglobinemia. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.
9. If hyperkalemia is asymptomatic, treatment with Kayexalate or furosemide (as long as the patient's renal function is normal) should be prioritized.
10. Hypocalcemia should not be treated unless the patient is symptomatic.
11. In hyperphosphatemia, use sevelamer, and not calcium acetate, to bind phosphate, because the latter can increase serum calcium levels and cause calciphylaxis.
12. Patients with established TLS or at high risk, especially in the context of renal insufficiency or with renal involvement by their malignancy, should be monitored in the intensive care unit.
13. Indications for renal replacement therapy are urate nephropathy, metabolic acidosis, severe electrolyte abnormalities, calcium-phosphorus product of 70 mg^2/dL^2 or more, oliguria, volume-overloaded state preventing effective diuresis without cardiopulmonary compromise, symptomatic uremia with encephalopathy, or pericarditis.

DEFINITIONS

What is tumor lysis syndrome (TLS)?

TLS is a potentially preventable oncologic emergency triggered by the rapid release of intracellular contents from lysing malignant cells. The rapid shift of potassium, phosphorus, and nucleic acids from cancer cells into the extracellular space can overwhelm existing homeostatic mechanisms, leading to acute kidney failure, arrhythmia, neurologic deficits, and potentially death.

What is the pathophysiology of TLS?

In malignancies with a large tumor burden, high proliferative rate, and high sensitivity to treatment, the initiation of tumor-targeted therapy can cause rapid lysis of tumor cells, leading to hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia.

Hyperuricemia is the result of nucleic acid catabolism. Purine nucleic acids are catabolized to hypoxanthine, then xanthine. Xanthine oxidase then metabolizes xanthine to uric acid (**Fig. 1**). A high burden of uric acid both supersaturates and directly obstructs renal tubules; uric acid crystallization injures tubules and microvasculature.[1–4] Renal vasoconstriction ensues via decreased release of nitric oxide (NO) and local granulomatous inflammation. This process may explain the paradoxic lack of benefit of diuretics in the management of acute kidney injury (AKI) associated with TLS. In a retrospective review of 83 patients with non-Hodgkin lymphoma, the relative risk of developing TLS or renal events correlated with uric acid level.[5]

Phosphorus levels in malignant cells can be up to four times higher than those found in normal cells.[3,6,7] Release of phosphorous from lysing cells overwhelms tubular transport mechanisms, leading to increased serum phosphorus levels. AKI caused by uric acid may further exacerbate hyperphosphatemia. When the calcium-phosphorus multiple exceeds 70 mg^2/dL^2, calcium phosphate precipitation risk in renal tubules increases, potentially exacerbating renal failure.[1,8–10] Calcium