Tumor Lysis Syndrome: Oncologic Supernova **Twitter/Instagram: @emboardbombs**

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Introduction

Tumor lysis syndrome (TLS) is a common oncologic emergency, and due to its high mortality rate must be quickly recognized and treated. It is typically seen in hematologic malignancies such as high-grade lymphomas (e.g. Burkitt's lymphoma, acute lymphoblastic leukemia), BUT it can occur in any solid tumor that is highly responsive to therapy (e.g. small-cell lung cancer, testicular cancer). Let's review the pathophysiology, diagnosis, and management of this classic oncologic emergency.

Pathogenesis

TLS usually occurs during or shortly after cytotoxic therapy (chemotherapy or radiation), which leads to tumor cell lysis and the subsequent release of large amounts of intracellular potassium, phosphate, and nucleic acids. You MUST know these three classic metabolic abnormalities.

Hyperkalemia: The Na/K ATPase maintains a gradient of high intracellular potassium. Cytotoxic therapy leads to an increase in cellular metabolism which depletes ATP, making it difficult to maintain this gradient (6). This, along with the lysis of cells, releases intracellular potassium, and leads to hyperkalemia.

Hyperphosphatemia: Phosphate is found in the lipid bilayer of all cell membranes, and is a vital component of intracellular DNA, RNA, and proteins. Phosphate is released into the extracellular environment during cell lysis, at which point it also binds with calcium, leading to a *secondary hypocalcemia*.

Hyperuricemia: Enormous amounts of intracellular DNA are released during cell lysis, which is then catabolized to uric acid by xanthine oxidase. Usually, the buildup of uric acid is recycled via the purine salvage pathway, but the massive amounts released in TLS overwhelm this pathway, leading to hyperuricemia (9). Of note, don't expect to see hyperuricemia as much as the other abnormalities. While the use of allopurinol and rasburicase has drastically reduced this complication, TLS still occurs in around 3-5% of patients receiving chemotherapy (7).

Presentation

Patients with TLC may present with nonspecific symptoms of nausea, vomiting, diarrhea, fatigue, and decreased appetite (4).

The most immediately life-threatening complication to catch is a c*ardiac arrhythmia* from hyperkalemia (4).
Additionally, hyperphosphatemia and hypocalcemia can cause tetany, seizures, and acute kidney injury (AKI) (1, 2, 6).
Hyperphosphatemia and hypocalcemia can both also cause cardiac arrhythmias (6).

Why AKI? Calcium phosphate crystals and/or uric acid crystals precipitate in renal tubules, which can form renal stones or directly damage renal tubules (6). Some patients may present with volume overload, secondary hypertension, and/or pulmonary edema (6)
Additionally, adenosine is released during cell lysis which causes renal vasoconstriction, further worsening an AKI (6).

Diagnosis

The Cairo Bishop Definition was created in 2004 to provide diagnostic criteria for TLS as well as a severity grading scale. You do not need to memorize this scoring system; we discuss it here simply to help you better diagnose patients who are "on the border." .

- Laboratory TLS = ≥ 2 abnormal serum values (defined as abnormal or a 25% change from baseline) within 3 days before or 7 days after cytotoxic therapy. This must be in the setting of euvolemia/hypervolemia and a hypouricemic agent (5).
- Clinical TLS = lab TLS + ≥1 or more of the following: cardiac arrhythmia, Cr ≥1.5x the upper limit of normal, sudden death, and/or seizure (5).

Treatment

1. FLUID RESUSCITATION
   2-3 L/m2/day to maintain diuresis 100-200 mL/hr. Increasing intravascular volume and urinary output leads to increased excretion of electrolytes and decreases precipitation of renal stones (6). The only contraindication is inability to tolerate hypervolemia, as in CHF (6). Still, judicious fluid administration should be attempted in these patients.

2. CORRECT ELECTROLYTES
   Hyperkalemia: May be elevated within 12-24 hours and is life threatening! Immediately administer IV 50mL of 50% dextrose with 10 units of insulin (5 if ESRD) (6). Only give calcium gluconate 1g if there are EKG changes. Loop diuretics may be used to assist with potassium excretion but you must carefully monitor the patient's volume status (6)
   Hyperphosphatemia: May be elevated within 24-48 hours once the kidneys have reached their excretion capacity. It may resolve with IV fluids alone if kidney function is intact (6). Give isotonic crystalloid to maintain kidney function and phosphorus excretion (6).

Hypocalcemia: If phosphorus levels are well controlled, normalization of calcium levels will follow. However, if ECG changes or tetany occur, administer the lowest dose possible of IV calcium gluconate in order to avoid calcium-phosphate precipitation (6). In short, do not administer Ca-gluconate empirically to every patient, unless there are EKG changes.

3. RASBURICASE
   0.15-0.2 mg/kg/day in 50mL of sodium chloride 0.9% infusion for 30 minutes 1x/day for 2 days (6). Rasburicase leads to catabolism of uric acid to allantoin, which is more soluble and easily excreted. The only contraindication is G6PD deficiency because of hemolysis risk (8).
   Additionally, while you can give allopurinol (100mg/m2 every 8 hours with max 800 mg/day), it can cause renal stone formation and is associated with hypersensitivity syndromes (3, 6).

4. RENAL REPLACEMENT THERAPY
   Discuss this with your friendly nephrologist if your patient is not responding to the above medical treatment or if there are contraindications to fluid resuscitation.

Disposition:
Admission is generally to the ICU to monitor electrolytes and uric acid every 4-6 hours and to provide any urgent treatments that may arise.

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