Tumor Lysis Syndrome
A Unique Solute Disturbance

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KEYWORDS

• Tumor lysis syndrome • Hyperuricemia • Hyperphosphatemia • Hyperkalemia
• Malignant cell metabolism

KEY POINTS

- Any patient with a cancer diagnosis who presents with electrolyte disorders or acute renal insufficiency should be evaluated for tumor lysis syndrome.
- Patients with tumor lysis syndrome may present with hyperuricemia, hyperphosphatemia, hypocalcemia, and/or hyperkalemia.
- Tumor lysis syndrome is highly associated with hematologic or bulky tumors, but may also occur in other types of cancer.
- Rasburicase reduces existing uric acid levels; allopurinol only prevents the formation of uric acid.
- Rasburicase is contraindicated to patients with glucose-6-phosphate dehydrogenase deficiency, therefore patients of African and Mediterranean descent should be screened before treatment.

Tumor lysis syndrome (TLS) is a worst-case scenario of specific electrolyte disturbances in which a sudden destruction of cancer cells releases massive amounts of intracellular solute into the general circulation. The abrupt increases in the levels of extracellular uric acid, phosphate, and potassium threaten cardiac and renal function, along with precipitating significant hypocalcemia that elicits central nervous system symptoms.[1,2] When the mass effects of solute overwhelm the body's ability for excretion, the patient may develop potentially fatal cardiac dysrhythmias or acute renal failure. Although historically associated with the initiation of chemotherapy in hematologic malignancy, TLS is now known to occur in the absence of exposure to

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chemotherapy or radiotherapy (spontaneous TLS), and in a variety of solid tumors if treated with powerful cytotoxic agents.[3] A high index of suspicion has now become warranted in patients with many types of cancer because preventive measures and early recognition increase the opportunity for successful medical treatment of this oncologic emergency. The high acuity of both affected and at-risk patients suggests that the critical care team should not only be well versed in the causes and management of this disorder, but should be involved early in the course of their clinical care.[4]

PATHOPHYSIOLOGY OF TUMOR LYSIS SYNDROME

Cancers cells reproduce quickly and, when combined with a high malignant cell burden or in bulky tumors, these cells are a rich source of intracellular electrolytes and organic substances. Lysis of cancer cells releases typically compartmentalized nucleic acids, intracellular proteins, and electrolytes into the circulation, often overwhelming the compensatory mechanisms of homeostasis.[2] Although slow or subtle increases in uric acid, phosphate, or potassium may be tolerated, rapid and dramatic increases in plasma levels can become life threatening. In the presence of preexisting renal dysfunction or increased baseline levels of these solutes, rapid solute accumulation increases the risk of TLS.

Hyperuricemia and Acute Uric Acid Nephropathy

Unlike hemolysis of anucleated red blood cells, the lysis of tumor cells releases large amounts of nuclear material, including the building blocks deoxyribonucleic and ribonucleic acid (DNA and RNA). This release introduces free purines (adenine and guanosine), pyrimidines (cytosine, thymine, and uracil), and phosphate into the plasma. Although the nitrogen in pyrimidines is excreted in the form of water-soluble urea, purine metabolism leads to the production of uric acid. Functioning kidneys can effectively excrete excess urea, but the excretion of largely insoluble uric acid is transport dependent, and thus more problematic in the context of extremely high tubular loads. Urate is both reabsorbed and secreted in the proximal tubule, and the balance of these processes determines the eventual plasma level.[5,6]

When a high load of urate in acidic tubular fluid arrives in the distal tubule and collecting ducts, the mostly unionized uric acid precipitates. In TLS, monosodium urate crystal formation can obstruct renal tubules and cause renal injury, particularly in the presence of dehydration. Uric acid may also be directly nephrotoxic by several mechanisms.[7] First, uric acid inactivates the endogenous vasodilator nitric oxide, contributing to renal vasoconstriction and ischemia. Second, vascular smooth muscle exposed to uric acid produces proinflammatory mediators that can cause tissue injury. Third, uric acid can inhibit proliferation of cells in the proximal tubule which comprises the primary route of electrolyte handling in the kidney. Thus, an increasing serum uric acid level is associated with a progressively increased risk of TLS and acute kidney injury.[8]

Hyperphosphatemia and Secondary Hypocalcemia

Intracellular fluid has a high concentration of inorganic phosphate and, along with the phosphate backbones of DNA and RNA, spillage of cell contents can cause significant hyperphosphatemia. Rapidly proliferating malignant cells are said to contain higher levels of phosphate than normal cells, which significantly augments the plasma phosphate load after cell lysis.[9,10] These conclusions were inferred from analysis of white cell counts and plasma phosphorous levels before and after initiation of chemotherapy and tumor lysis in patients with lymphoma and leukemia.[10] As leukocyte counts