CLINICAL VIGNETTE

Emergent Considerations for Tumor Lysis Syndrome

Joah Lee and Thomas E. Blair, MD

Case Presentation

An 83-year-old male with a past medical history of paroxysmal atrial fibrillation on apixaban, non-obstructive coronary artery disease, non-ischemic cardiomyopathy, chronic kidney disease, hypertension, and hyperlipidemia was referred to emergency department (ED) by his primary care physician for abnormal labs. Routine outpatient labs, found new onset leukocytosis, anemia, thrombocytopenia, and elevated creatinine.

On ED presentation the patient complained of mild fatigue for three weeks that limited his ability to take long walks and work in his garden. He denied chest pain, shortness of breath, cough, fever, chills, night sweats, abdominal pain, or headaches. Initial vital signs were temperature 36.4° C, pulse 64 bpm, respirations 16/min, blood pressure 95/40 mmHg, and 0_2 saturation 100% on room air.

A thorough physical exam was unremarkable except for trace edema in bilateral lower extremities. Repeat labs revealed white blood cells of 40 k/uL, hemoglobin 8.7 g/dL, and platelets 105 k/uL. The differential blood count showed lymphocytosis and no peripheral blasts. Chemistries showed elevated potassium at 5.9 mmol/L and creatinine 4.02 mg/dL (baseline 1.43 mg/dL). Phosphate was normal at 4.4 mg/dL. There was elevation of uric acid 15.4 mg/dL, and LDH 380 U/L. Ionized calcium was decreased at 1.1 mmol/L.

A portable chest radiograph was unremarkable and electrocardiogram demonstrated first degree heart block, without peaked T waves or QRS widening. Patient was initially given 1 liter of normal saline as well as intravenous furosemide 20mg for hyperkalemia. In consultation with Hematology & Oncology (HemOnc), the patient was started on rasburicase and allopurinol. CT chest/abdomen/pelvis revealed mediastinal and intra-abdominal adenopathy and he was admitted to the intensive care unit for further management. During the hospitalization, he had significant laboratory and clinical improvement. Peripheral blood smear showed "morphologic findings compatible with lymphoproliferative disorder." Bone marrow biopsy results showed findings consistent with mantle cell lymphoma. The patient's final diagnosis was spontaneous tumor lysis syndrome secondary to mantle cell lymphoma. He was discharged home with plans to initiate chemotherapy.

Discussion

Tumor lysis syndrome (TLS) is an oncologic emergency in which a large number of malignant cells abruptly break down, and release their cell contents including DNA, phosphate, potassium, and cytokines.[1] The sudden release of intracellular contents may cause hyperkalemia, hyperphosphatemia, and hyperuricemia as uric acid is a metabolic product of nucleic acids. Uric acid may precipitate into the renal tubules leading to acute kidney injury. Elevated phosphorus may also precipitate as calcium phosphate in the renal tubules causing further renal injury and secondary hypocalcemia.

Clinical manifestations are direct results of these metabolic changes such as renal failure, dysrhythmias (due to hyperkalemia), and seizures/tetany (due to hypocalcemia).[2]

TLS has most often been associated high grade lymphoma or acute leukemia, but it can occur with all tumor types that have large tumor burden or sensitivity to cytotoxic therapy.[3] It is most commonly precipitated by the initiation of chemotherapy, however, it may present spontaneously. Interestingly, as illustrated in this case, spontaneous TLS is less associated with hyperphosphatemia than chemotherapy induced TLS. This distinction is because living tumor cells are able to utilize the additional phosphorous to increase cell growth.[4]

The Cairo-Bishop (Table 1)[4] definition was created to provide laboratory criteria for the diagnosis of TLS within 3 days before or 7 days after the start of the chemotherapy. Laboratory TLS is defined as either any two or more abnormal serum values or 25 percent increase in serum value over baseline. Cairo-Bishop definition of clinical tumor lysis syndrome[5] includes increases in creatinine, seizure, cardiac arrhythmia, or sudden death.

Early recognition and treatment of patients at risk for TLS is essential in preventing mortality. Patients undergoing cancer treatment should be closely monitored with laboratory tests. Prevention is the best management of TLS patients. High-risk patients should be treated with preventive measures such as intravenous hydration, allopurinol, or rasburicase prior to initiation of chemotherapy. Patients presenting with TLS should receive supportive care, cardiac monitoring, serial measurements of electrolytes, creatinine, and uric acid.[3] Coordination of care with oncology, nephrology, and critical care is often required for appropriate management of TLS.

Emergent treatment begins with aggressive hydration.[6] Intravenous fluids improve renal perfusion and decrease uric acid and calcium phosphorous deposition in renal tubules. Caution is required in patients with significant renal failure, oliguria, or congestive heart failure. Loop diuretics may be required to maintain adequate urine output, and for their hypokalemic effect.

The second step in treatment focuses on lowering uric acid levels with allopurinol and rasburicase. Allopurinol is a purine analog. It acts as a xanthine oxidase inhibitor, preventing the conversion of hypoxanthine to xanthine and uric acid. This leads to decreased risk of uric acid precipitation in the renal tubules and decreased renal injury.[7] Rasburicase is a recombinant urate oxidase. Urate oxidase is the enzyme that converts uric acid into allantoin, which is 5-10 times more soluble in urine than uric acid.[1]

Hyperkalemia is the most immediate life-threatening component of TLS due the cardiac dysrhythmias and sudden death. It initially occurs from cell lysis, but may be exacerbated by renal dysfunction. EKG signs of severe hyperkalemia should prompt empirical treatment with calcium to reduce the risk of dysrhythmia. Glucose, insulin, albuterol, loops diuretics, sodium bicarbonate, potassium binders, and hemodialysis should also be considered to shift or remove excess potassium.

Asymptomatic hypocalcemia generally should not be repleted until hyperphosphatemia is corrected due to risk of calcium phosphate precipitation.[2] Intravenous calcium is generally reserved for symptomatic hypocalcemia or hyperkalemia with EKG changes.

Initial treatment of moderate hyperphosphatemia is intravenous hydration. Severe hyperphosphatemia will require hemodialysis. As noted, patients may develop symptomatic hypocalcemia due to hyperphosphatemia-induced hypocalcemia.

This case highlights the importance of recognizing the metabolic pattern of tumor lysis syndrome and underlying risk factors. Spontaneous cases may occur in patients without a prior diagnosis of malignancy. Early recognition and early initiation of allopurinol and rasburicase can lead to dramatically improved outcomes.

Uric acid	Uric acid >8.0 mg/dl (475.8 µmol/liter)
Potassium	Potassium >6.0 mmol/liter
Phosphorous	Phosphorus >4.5 mg/dl (1.5 mmol/liter)
Calcium	Corrected calcium <7.0 mg/dl (1.75 mmol/liter) or ionized calcium <4.5 mg/dl (1.12 mmol/liter)

Table 1: Cairo-Bishop definition of laboratory tumor lysis syndrome

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