CLINICAL VIGNETTE

Tumor Lysis Syndrome in Solid Organ Malignancies

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Introduction

Acute kidney injury (AKI) is a common complication of malignancy, with an up to 17% of patients developing AKI within the first year of diagnosis.[1] Tumor lysis syndrome (TLS) is an uncommon, but clinically significant cause of AKI in patients with cancer. Traditionally, TLS has been associated with the administration of chemotherapy in patients with hematopoietic malignancies, i.e. lymphoma and leukemia. However, recent advances in chemotherapeutic regimens have resulted in an increased recognition of TLS in solid organ malignancies, especially with highly cytotoxic therapies and bulky tumors.[2]

Case Presentation

A 63-year-old female with a recent diagnosis of poorly differentiated endometrial cancer (FIGO stage 3A), diabetes, and hypertension was found to have an elevated creatinine of 2.8 mg/dL on routine laboratory studies performed by her oncologist.

Three months prior the patient presented with post-menopausal vaginal bleeding. She underwent a transvaginal ultrasound demonstrating a heterogeneously thickened endometrium. Endometrial biopsy revealed poorly differentiated endometrial adenocarcinoma. She underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy and retroperitoneal dissection two weeks prior. Operative findings noted extensive omental caking, peritoneal carcinomatosis, and bloody ascites. Gross examination of the uterus revealed extensive myometrial invasion. Following surgery, she reported poor appetite and increased abdominal girth.

On physical examination, the patient had a temperature of 37.1°C, a pulse of 113 beats per minute, blood pressure of 95/63 mmHg, a respiratory rate of 10 breaths per minute, and oxygen saturation of 96% on room air. Her examination was notable for a distended abdomen with positive fluid wave. Her head was normocephalic and atraumatic. Ear, nose and throat exam was unremarkable. Heart was regular rhythm but tachycardic with no murmurs. Her extremities were warm and dry to touch with no edema. Examination of the skin showed no rashes, bruises, or jaundice.

Laboratory data showed a white blood cell count of 11.3 $x10^3$/uL, hemoglobin of 10.1 g/dL, hematocrit of 33.5 %, and platelet count of 743 $x10^3$/uL. Her serum chemistries were notable for a serum sodium of 137 mEq/L, potassium of 4.8 mEq/L, chloride of 102 mEq/L, bicarbonate of 20 mEq/L, BUN 47 mg/dL, creatinine of 2.8 mg/dL, calcium of 7.4 mg/dL, phosphorous of 3.9 mg/dL and uric acid of 14.0 mg/dl (see **Table 1**).

The patient was initially treated with intravenous saline with improvement in her creatinine to 1.2 mg/dL. She underwent a 2.5 L paracentesis for her ascites, which rapidly reaccumulated over the course of 48 hours. Given her extensive disease, carboplatin and paclitaxel were started. One day following the administration of chemotherapy, she became oliguric with 200 ml of urine output over 12 hours. Her creatinine was measured at 2.3 mg/dL (**Table 1**).

Discussion

TLS is a group of metabolic derangements caused by the release of intracellular chemicals. This process may occur spontaneously, but more commonly occurs after administration of cytotoxic chemotherapy. The metabolic complications of TLS are the result of the release of potassium, phosphate and nucleic acids by dying cells, which result in hyperkalemia, hyperphosphatemia, secondary hypocalcemia, and hyperuricemia. Notably, spontaneous tumor lysis syndrome is not associated with hyperphosphatemia and secondary hypocalcemia. This is thought to result from increased phosphorous utilization by growing malignant cells.[3]

Acute kidney injury is a common occurrence in patients with TLS. Historically, this has been mediated by uric acid nephropathy. The excess release of uric acid results in an increased glomerular filtered load, resulting in an abnormally high concentration of uric acid within the tubules. Under these conditions uric acid can precipitate out of the liquid phase and crystalize. In acute uric acid nephropathy, crystalline deposits are diffuse and result in obstruction and acute kidney injury.[4] Patients often present with acute oligoanuria, as in the case described. Recent trends in medical therapy aimed at avoiding uric acid nephropathy, specifically pre-administration of rasburicase and/or allopurinol, has made acute urate nephropathy less common.

TLS should be suspected in any patient who develops acute kidney injury with hyperuricemia and hyperphosphatemia,

especially following chemotherapy for high grade and/or bulky malignancies. In 2004 the Cairo-Bishop classification system was developed for tumor lysis syndrome (**Table 2**).[5] TLS is defined by laboratory data and clinical presentation. In the case described above, the patient experienced a > 25% increase in serum potassium, phosphorous and uric acid in conjunction with acute oligoanuric renal failure, consisting clinical tumor lysis syndrome.

The treatment of TLS is focused on avoiding the syndrome altogether. Pretreatment with allopurinol and intravenous hydration to maintain a urine output > 2.5 L/day are the mainstay of therapy. Urinary alkalinization to avoid uric acid precipitation is no longer recommended, as an alkaline pH increases the risk of calcium phosphate crystallization. An alternative to allopurinol is rasburicase, a synthetic urate oxidase enzyme that degrades uric acid.[6] Rasburicase can be given at a dose of 0.2 mg/kg daily for up to 5-7 days. Its major side effects include: hemolysis (in patients with G6PD deficiency), methemoglobinemia, spuriously low uric acid measurements ex vivo, and anaphylaxis.

Once laboratory TLS develops, management is directed at controlling the metabolic abnormalities and reducing uric acid deposition within the kidney. Renal replacement therapy may be needed in cases of severe electrolyte abnormalities and acute kidney injury with reduced urine output **(Table 3)**. Uric acid, potassium, and phosphorous are small compounds which are readily removed with dialysis. However, continued cell death results in a rapid accumulation of metabolites following dialysis, necessitating repeated sessions until the effects of chemotherapy have waned.

Conclusion

This patient was given rasburicase and started on hemodialysis for acute kidney injury secondary to tumor lysis syndrome. Her uric acid rapidly decreased and she was maintained on dialysis for 3 weeks before regaining renal function. Six months following her initial admission, she completed her 6th cycle of carboplatin, paclitaxel and bevacizumab. She remained off hemodialysis with a serum creatinine of 0.6 mg/dL. Repeat PET-CT scan demonstrated continued diffuse abdominal and pelvic carcinomatosis.

Table 1: Patient Laboratory Results

	Baseline (3 mos prior to admission)	Admis-sion (Day 2)	Day 0	Day 2 post chemo-therapy	6 months post initial consulta-tions
Sodium (mEq/L)	140	137	133	132	140
Potassium (mEq/L)	3.8	4.8	4.6	6.0	3.6
Chloride (mEq/L)	101	102	101	99	102
Bicarbonate (mEq/L)	30	20	20	16	27
BUN (mg/dL)	6	47	30	47	13
Creatinine (mg/dL)	0.6	4.4	1.2	2.3	0.6
Uric Acid (mg/dL)	6.4	14	n/a	17.1	5.4
Calcium (mg/dL)	7.9	7.4	8.1	7.6	9.5
Phosphorous (mg/dL)	1.9	3.9	n/a	5.1	3.1

Table 2: Cairo-Bishop Tumor Lysis Classification in Adults

Laboratory Tumor Lysis Syndrome
Uric Acid > 8 mg/dL Potassium > 6 mEq/L Phosphorus > 4.5 mg/dL Calcium < 7 mg/dL
Clinical Tumor Lysis Syndrome
Evidence of laboratory tumor lysis syndrome + Acute kidney injury (AKI) or Cardiac arrhythmias or Seizure

*Laboratory tumor lysis syndrome requires that two or more of the following metabolic abnormalities occur within 3 days before or up to 7 days after the initiation of therapy. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

**A few refinements could improve this classification. First, it should be stipulated that two or more metabolic abnormalities be present simultaneously, because some patients may present with one abnormality, but later another one may develop that is unrelated to the tumor lysis syndrome (e.g., hypocalcemia associated with sepsis). Second, in contrast to Cairo and Bishop's definition, a 25% change from baseline should not be considered a criterion, since such increases are rarely clinically important unless the value is already outside the normal range. Third, any symptomatic hypocalcemia should constitute clinical tumor lysis syndrome.[4]

Table 3: Indications for Hemodialysis in Tumor Lysis Syndrome

Severe oliguria or anuria
Persistent hyperkalemia
Hyperphosphatemia induced symptomatic hypocalcemia
Calcium-Phosphate product $\geq$70 mg^2/dL^2

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