

Spontaneous tumor lysis syndrome in breast cancer: a case report and discussion

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Abstract

Tumor lysis syndrome (TLS) refers to the constellation of metabolic disturbances manifested by acute renal failure associated with marked hyperuricemia. TLS may be seen after initiation of cancer treatment. It usually occurs in patients with bulky, rapidly proliferating, treatment-responsive tumors. Spontaneous TLS, occurring prior to the initiation of cancer therapy, has been reported in hematologic malignancies like high grade non Hodgkin's Lymphoma (NHL) and acute leukemia, and in at least one patient with inflammatory breast cancer. The actual incidence of this occurrence is difficult to ascertain. We present, in this report, the case of a woman with a stage IV adenocarcinoma of the breast diagnosed with spontaneous TLS, and we review the current literature on this rare but interesting disease manifestation.

Key words: Tumor, breast, adenocarcinoma, tumor lysis, syndrome, spontaneous

Case presentation

The patient is a 46 year old woman with a history of stage IV breast cancer diagnosed one year prior to her presentation to our hospital. The metastatic cancer was manifested by metastatic pulmonary nodules, hepatic metastasis, and extensive bony metastasis. A biopsy of the liver in another facility revealed adenocarcinoma positive for estrogen and progesterone receptors, AE1/AE3, CK7, CEA, CA 19.9, P53, and GCDPF-15. She was prescribed tamoxifen, but she has not taken the medicine. The patient has not received any other treatment for her cancer and was lost to follow up.

During this hospitalization, she presented with fatigue, tiredness, nausea, multiple episodes of vomiting, abdominal pain, and diarrhea of one week duration. She was treated empirically with antibiotics, as outpatient, with no relief. Her symptoms increased 3 days prior to the hospitalization and progressively worsened over time. She described the diarrhea as yellow watery stool associated with blood and the vomiting as yellow colored fluids. She denied tenesmus. She denied intake of herbal supplements or other medications.

Review of her medical history was significant for hospitalization for hypercalcemia and acute kidney injury, 2 months prior to this current hospitalization, which resolved with intravenous hydration. Her previous surgical history includes a Cesarean section; and her family history was significant for coronary artery disease. Her physical exam was only significant for pale skin and tachycardia with pulse of 102 beats/minute and diffuses abdominal tenderness. Her laboratory results were significant for: Normocytic anemia with hemoglobin (HGB) 11.1 g/dl [normal 12-15], hematocrit (HCT) 32.1% [normal 36-47],

elevated liver enzymes: Aspartate Aminotransferase (AST) 316 Intern Unit/L [normal 12-45], Alkaline phosphatase 863 Intern Unit/L [normal 37-107], low Sodium 123 mmol/L [normal 135-145], calcium 7.9 MG/DL [normal 8.4-10.2], elevated potassium 5.6 mmol/L [normal 3.9-5.3], elevated phosphorus 5.5 MG/DL [normal 2.4-4.7], elevated BUN 182 MG/DL [normal 7-22], and creatinine 13.34 MG/DL [normal 0.5-1.2], elevated serum uric acid 27.9 MG/DL [normal 1.9-8.2, morning CORTISOL was 34.1 mcg/dl [normal AM Level 6.7-22.6]. Her fecal occult blood test was positive, and C-difficile toxin was negative. Her urine analysis showed trace proteinuria, blood, 10-15 RBCs, but was negative for casts or crystals. The urine PH was 6.

Computer tomography scan (CT) of abdomen

Showed multiple hypodense lesions in the liver which represent her metastatic disease; innumerable lytic lesions involving the spine, ribs, sacrum, pelvis and femurs; and multi level vertebral compression fracture deformity in the lower thoracic and in L2 and L3 vertebral bodies (Figure 1A,1B).

Hospitalization course

The patient was admitted to the hospital with a clinical diagnosis of: 1) stage IV Breast Cancer, 2) dehydration due to vomiting and diarrhea, 3) normocytic anemia due to acute blood loss versus anemia of chronic disease, 4) acute kidney injury possibly due to tumor lysis syndrome, 5) hyponatraemia, 6) bloody diarrhea due to infectious causes like *Clostridium difficile* (C Dif) colitis versus tumor. The patient was diagnosed with tumor lysis syndrome, in view of hyperkalemia (despite diarrhea), hyperphosphatemia,

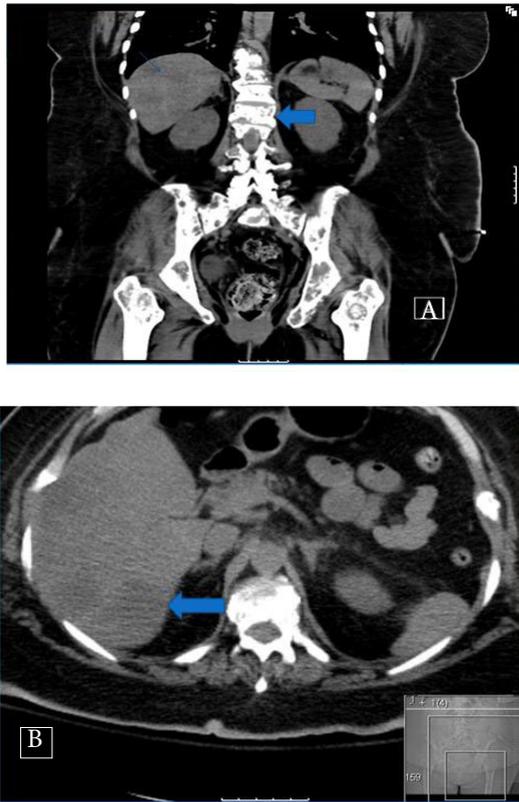


Figure 1. (A) Lytic lesions in lumbar spines see arrow. (B) Multiple hypo dense lesions in the liver, consistent with metastasis.

and severe hyperuricemia associated with acute renal failure.

Treatment

She was started on normal saline intravenously at a rate of 125 ml/hour, which was increased to 200cc/hour, metronidazole 500 mg po TID for presumable *C. Dif.* infection. Nephrology and oncology services were consulted. The patient received allopurinol 100 mg orally daily for 5 days, and one dose of rasburicase 4 mg IV. The patient gradually felt better. Her symptoms improved, both diarrhea and vomiting resolved, and her kidney function improved markedly, creatinine dropped to 9.9 (from 13), BUN became 154, and uric acid dropped to 13.1 (from 27.9). We stopped the metronidazole when the results of stool *C. Dif.* toxins were negative. We discussed with the patient and family the advanced stage of the disease, and the need for compliance with cancer care and follow up. The patient declined chemotherapy. She was discharged to have a return follow up as an outpatient, and was given a prescription of allopurinol 100 mg daily.

Discussion

Tumor lysis syndrome (TLS) is a medical emergency that occurs in patients with certain cancers and is caused by

the rapid and massive breakdown of tumor cells, either spontaneously, or after the initiation of cytoreductive therapy. The rapid release of intracellular contents causes hyperuricemia, hyperkalemia, hyperphosphatemia, and secondary hypocalcemia. These metabolic abnormalities can lead to significant morbidity, putting patients at risk of severe clinical consequences that include acute kidney injury (AKI), cardiac arrhythmias, pulmonary edema, fluid overload, seizures, and even death [1].

Pathophysiology

Although it can occur spontaneously, TLS is associated most commonly with rapid cell breakdown after initiation of chemotherapy and the consequent massive release of intracellular contents that overwhelms the body's homeostatic and excretory mechanisms. Potassium is stored primarily in the intracellular compartment, and its rapid and excessive release into the extracellular compartment can lead to hyperkalemia, cardiac arrhythmia, and possibly sudden death. Similarly, hyperphosphatemia results from massive release of intracellularly stored phosphate. It can lead to secondary hypocalcaemia and deposition of calcium phosphate crystals in the kidney [1].

Tumors most frequently associated with TLS are clinically aggressive non-Hodgkin lymphomas (NHLs) and acute lymphoblastic leukemia (ALL), particularly Burkitt lymphoma/leukemia [2,3,4-8]. Other hematologic malignancies that are commonly associated with TLS include anaplastic large cell lymphoma, T-cell or B-cell precursor ALL, acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and plasma cell disorders, including multiple myeloma and isolated plasmacytomas [2,9,10-14]. TLS has been rarely described after treatment of some nonhematologic solid tumors [15,16]. These include breast cancer [17-19], small cell carcinoma (mostly involving the lung) [15,17], neuroblastoma [17], germ cell tumors [15,20], medulloblastoma [15], sarcoma [15,21], ovarian cancer [22,23], squamous cell carcinoma of the vulva [24], metastatic colorectal cancer [25], urothelial cancer [26], gastrointestinal stromal tumors [27], melanoma [15], and hepatocellular carcinoma [15].

Spontaneous TLS

Spontaneous acute renal failure associated with marked hyperuricemia prior to the initiation of therapy has been described in lymphomas and acute leukemias [4,10,28,29]. It usually occurs in patients with bulky, rapidly proliferating, treatment-responsive tumors and has been described in inflammatory breast cancer [30]. The actual incidence of this syndrome is difficult to ascertain. Interestingly, spontaneous TLS is associated with hyperuricemia but frequently without hyperphosphatemia [10]. It has been postulated that rapidly growing neoplasms with high cell turnover rates produce high serum uric acid levels through rapid nucleoprotein turnover but that the

tumor is able to reutilize released phosphorus for resynthesis of new tumor cells. In contrast, TLS after chemotherapy is due to cell destruction in the absence of reuptake of phosphorus, and thus, hyperphosphatemia [10].

Clinical manifestations of TLS

The symptoms associated with TLS largely reflect the associated metabolic abnormalities (hyperkalemia, hyperphosphatemia, and hypocalcaemia). These symptoms may include nausea, vomiting, diarrhea, anorexia, lethargy, edema, fluid overload, hematuria, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and possibly sudden death [30]. Although these symptoms are multifactorial and may occur before the start of chemotherapy, they are observed more commonly within 12 to 72 hours after the initiation of cytoreductive therapy. Complications resulting from TLS can compromise the efficacy or further administration of chemotherapy [31]. Urinalysis classically shows many uric acid crystals or amorphous urates in acidic urine, but is occasionally relatively normal due to lack of output from the obstructed nephrons.

Management of TLS

Tumor lysis syndrome management requires the initiation of preventive measures in high-risk patients prior to cancer treatment, as well as the prompt initiation of supportive care for patients who develop acute tumor lysis syndrome during treatment. Patients with evidence of pretreatment acute tumor lysis syndrome should be started immediately on appropriate therapy, with cancer treatment withheld if possible until all parameters are corrected. It would be important to identify high-risk patients before treatment by assessing the extent of tumor burden, histopathologic findings, and renal function. Cancer patients who present with, or develop TLS during therapy should receive intensive nursing care with continuous cardiac monitoring and measurement of electrolytes, creatinine, and uric acid every four to six hours [32]. Effective management involves the combination of treating specific electrolyte abnormalities, and/or acute renal failure, and the use of allopurinol, a xanthine oxidase inhibitor administered to reduce the conversion of nucleic acid byproducts to uric acid in order to prevent urate nephropathy and subsequent oliguric renal failure [33]. It is usually given orally at 600 mg daily for prophylaxis and 600-900 mg daily (up to a maximum of 500 mg/m² daily) for treatment of tumor lysis syndrome. Patients unable to take oral medications can be given intravenous allopurinol.

On October 16, 2009, the Food and Drug Administration (FDA) granted approval for the use of rasburicase (recombinant urate oxidase) for the initial management of plasma uric acid levels in adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis and

subsequent elevation of plasma uric acid. Urate oxidase is an enzyme involved in purine metabolism and is responsible for the oxidation of uric acid to allantoin, which is shown to be 5–10 times more soluble in urine than uric acid [34]. This enzyme is found in most mammals, but not in humans, because of a nonsense mutation in the coding region of the gene during hominoid evolution [35]. Rasburicase is isolated as a cDNA clone from *A. flavus* and is expressed in *Aspergillus flavus* the yeast strain *Saccharomyces cerevisiae* [36]. Rasburicase can be used in cases of TLS when uric acid levels cannot be lowered sufficiently by standard approaches [37]. The advantages of rasburicase are its rapid onset of action and its unique mechanism of action. It lowers preexisting uric acid and prevents the further accumulation of uric acid, therefore, minimizing the risk of tumor lysis syndrome. On the other hand, allopurinol does not have a lowering effect on preexisting uric acid and has a delayed onset of action [37]. Rasburicase is administered at a dose of 0.15 or 0.2 mg/kg per dose for 5 days. Dosing beyond 5 days or administration of more than 1 course is not recommended by the manufacturer [37]. It is contraindicated in glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and pregnancy [37].

In addition to the above measures, attempting to wash out the obstructing uric acid crystals with a loop diuretic and intravenous fluids is frequently needed, and the appropriate use of renal replacement therapy may become necessary [38]. Indications for hemodialysis include: severe oliguria or anuria, persistent hyperkalemia, hyperphosphatemia-induced symptomatic hypocalcaemia [38].

Conclusion

Tumor lysis syndrome (TLS) is an oncologic emergency that is caused by massive tumor cell lysis. It can occur after initiation of cytotoxic therapy, but also can occur spontaneously. TLS should be included in the differential diagnosis of patients with breast cancer who present with acute kidney injury even if they did not receive chemotherapy.

Competing interests

The authors declare that they have no competing interests.

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