CLINICAL VIGNETTE

Tumor Lysis Syndrome and Possible G6PD Deficiency

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Tumor lysis syndrome (TLS) is a potentially serious complication of aggressive hematologic malignancies.[1] Management of tumor lysis, particularly in the setting of hyperuricemia and acute kidney injury (AKI), can be challenging. We describe the case of an HIV positive man with a high-grade lymphoma, in whom hyperuricemia and AKI was present prior to the initiation of cancer chemotherapy. Consideration was given to administering a urate oxidase medication (rasburicase), however his serum G6PD activity level was found to be low.

Case Presentation

A 33-year-old man presented to clinical attention with new onset bilateral leg edema, dyspnea on exertion, and anorexia with weight loss >30 lbs. He had been diagnosed with HIV 6 months prior, and started combination antiretroviral therapy. Baseline CD4 was 113/mcl and viral load >70,000 copies/ml. He was diagnosed with neurosyphilis about one month later, when he presented with subacute vision loss, and was successfully treated with 2 weeks of IV penicillin. Most recent CD4 was 170 with viral load 169 copies/ml, just prior to presentation. In the emergency department, his D-dimer was very elevated at >10,000 ng/ml (nl <500). Doppler ultrasound of the legs revealed extensive occlusive deep venous thrombosis bilaterally, extending proximally to the iliac veins and IVC. PE protocol CT revealed a left sided pulmonary embolus, with an area of peripheral lung infarction. Intravenous heparin infusion was started, and he soon proceeded to catheter directed thrombolysis with tPA. This successfully reduced the clot burden in his legs, and he eventually had angioplasty and stenting of the IVC and bilateral iliac veins.

With absence of any obvious provoking factors for venous thromboembolism (immobilization, recent surgery, family history), and given significant weight loss, CT imaging of the abdomen and pelvis was performed looking for occult malignancy. Focal bowel wall thickening of the cecum, prominence of the gastric fundus and body, and a 17-mm left para-aortic lymph node were seen. GI was consulted, and endoscopy revealed thickening and nodularity of the gastric folds. Biopsies revealed a high-grade B cell lymphoma, EBV+, with proliferative index >95%.

On admission, his blood urea nitrogen (BUN) and serum creatinine (sCr) were normal at 15 mg/dL and 0.6 mg/dL. Uric acid was 6.5 mg/dL (nl <8.8), although LDH was very high at 1594 U/L (nl <256). The lymphoma diagnosis was obtained 2 weeks into his hospital stay, at which time BUN was 23, sCr 1.14, uric acid 12.4, and lactate dehydrogenase (LDH) 1934. Serum potassium was 5.1 mmol/L (nl <5.3), phosphorus 4.7 mg/dL (nl <4.4), both increased from the time of admission. This raised concern for spontaneous tumor lysis in the setting of a high-grade lymphoma. Allopurinol 300 mg BID was started, in addition to copious IV fluids. An oral phosphate binder (sevelamer) was also given. G6PD testing was performed, per local protocol, prior to administration of a urate oxidase (rasburicase). The result came back abnormally low the following day at 9.6 U/gm hemoglobin (nl 9.9-16.6). Rasburicase was therefore not given.

Over the next 48 hours, however, he became oliguric with progressive volume overload. Serum creatinine climbed to 3.08, potassium peaked at 5.6 and phosphorus 5.5. Uric acid remained elevated at 11-12, with LDH now >2000. Lumbar puncture revealed lymphoma cells in the CSF. Hemodialysis was initiated, however, he developed clinical worsening, with hypotension and altered mental status. He was transferred to the ICU, intubated, and vasopressors were started. Systemic chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) was given. In addition, intrathecal chemotherapy twice weekly (cytarabine alternating with methotrexate) was administered. His ICU course was protracted over several weeks, but he improved. The LDH, uric acid, and sCr declined, and oliguria resolved. Pressor support was weaned, and he was extubated with intact mental status. His CSF was eventually cleared of lymphoma, at which time the frequency of intrathecal treatments was decreased. He received the second cycle of systemic chemotherapy prior to hospital discharge.

Discussion

Tumor lysis syndrome (TLS) is a set of metabolic abnormalities that occur subsequent to the lysis of malignant cells and release of their intracellular contents.[1] It is most common in lymphoid hematologic malignancies, including acute lymphoblastic leukemia/lymphoma (ALL) and high grade B-cell non-Hodgkin lymphomas. It is typically observed after the administration of cytotoxic therapy (chemotherapy or immunotherapy), but may also occur spontaneously. Upon cell lysis, proteins, nucleic acid, potassium and phosphorus are released into circulation, and may lead to life threatening hyperkalemia, hypocalcemia, hyperphosphatemia and hyperuricemia. The latter two can cause acute kidney injury, through the crystallization of calcium phosphate and uric acid, in the renal tubules. Uric acid can also cause kidney injury via renal vasoconstriction, decreased blood

flow, and inflammation.[1] TLS is also associated with cytokine release, which may cause a systemic inflammatory response syndrome and organ dysfunction/failure.[2]

Recognition and management of TLS is essential to prevent morbidity. The initial strategy should include aggressive IV fluid administration, to increase urine flow and promote uric acid, potassium, and phosphate excretion by the kidneys. Alkalinization of the urine with sodium bicarbonate is not recommended.[1] Labs (LDH, uric acid, chemistries) should be assessed at regular intervals (q8-12 hours), and electrolyte abnormalities (hyperkalemia, hypocalcemia, and hyperphosphatemia) corrected promptly. Nephrology consultation and initiation of hemodialysis may be necessary in the setting of kidney injury associated with hyperphosphatemia and hyperuricemia.[1] Close monitoring in an ICU setting is recommended in patients deemed to be at high risk for TLS and its complications, including those with CKD or significant baseline elevations in LDH and uric acid.[2]

Drugs to lower serum uric acid levels play an essential role in TLS treatment. Allopurinol is a xanthine analog which acts as a competitive inhibitor of xanthine oxidase, preventing the formation of uric acid during purine nucleotide catabolism. It reliably decreases uric acid levels over days, and lowers the incidence of uric acid nephropathy when used as part of a preemptive strategy in patients at risk for TLS.[1] Rasburicase is a recombinant urate oxidase that metabolizes uric acid to allantoin, which is much more soluble in urine and therefore more easily excreted. It acts rapidly (over hours) to sharply reduce the serum uric acid to very low levels, and a single dose is usually sufficient in the course of treatment, along with other supportive measures (IV fluids, allopurinol administration).[1] Early studies of a non-recombinant urate oxidase (uricozyme, isolated from *Aspergillus spp*) revealed hemolysis or methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[1]

G6PD deficiency is due to quantitative or qualitative abnormalities in the enzyme, associated with several polymorphisms common in certain parts of the world, particularly the Mediterranean, Africa, Middle East, and South and East Asia.[3] The gene is on the X chromosome, and therefore hemizygous males are at particular risk of complications. Nonetheless, there may also be disease expression in heterozygous females due to random X-inactivation.[3] G6PD is an essential enzyme in the pentose phosphate pathway, necessary for the production of NADPH and therefore an adequate supply of glutathione.[4] These are essential components of the cellular response to oxidative stress. In the presence of certain medications (primaquine, dapsone, and rasburicase, among others), brisk red cell hemolysis (both intravascular and extravascular) and methemoglobinemia may develop, and depending on their severity and the clinical setting, can be fatal.[4]

In our patient, it was evident at the time of his lymphoma diagnosis that spontaneous tumor lysis was present, prior to the administration of any chemotherapy, with serum uric acid >12 and LDH ~2000. IV fluids and allopurinol were started. The decision was made to check G6PD enzyme activity in the blood given his ethnic background (African American) and sex, despite no known history of drug-induced hemolysis. The result came back the following day, revealing modestly decreased enzyme activity (9.6 U/gm Hb; nl >9.9). He had been transfused 2 units of *donor* red blood cells in the preceding two weeks, and there was concern that the actual G6PD activity in *his* red cells may be lower. Given his precarious clinical state, rasburicase was not administered. In retrospect, earlier initiation of hemodialysis may have prevented some of the complications of TLS in this case, including kidney failure and a sepsis like syndrome with multi-organ dysfunction.

REFERENCES

1. **Coiffier B, Altman A, Pui CH, Younes A, Cairo MS**. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008 Jun 1;26(16):2767-78. doi: 10.1200/JCO.2007.15.0177. Review. Erratum in: *J Clin Oncol*. 2010 Feb 1;28(4):708. PubMed PMID: 18509186.
2. **Howard SC, Jones DP, Pui CH**. The tumor lysis syndrome. *N Engl J Med*. 2011 May 12;364(19):1844-54. doi: 10.1056/NEJMra0904569. Review. Erratum in: *N Engl J Med*. 2018 Sep 13;379(11):1094. PubMed PMID: 21561350; PubMed Central PMCID:PMC3437249.
3. **Luzzatto L, Seneca E**. G6PD deficiency: a classic example of pharmacogenetics with on-going clinical implications. *Br J Haematol*. 2014 Feb;164(4):469-80. doi: 10.1111/bjh.12665. Epub 2013 Dec 28. Review. PubMed PMID: 24372186; PubMed Central PMCID: PMC4153881.
4. **Relling MV, McDonagh EM, Chang T, Caudle KE, McLeod HL, Haidar CE, Klein T, Luzzatto L; Clinical Pharmacogenetics Implementation Consortium**. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. *Clin Pharmacol Ther*. 2014 Aug;96(2):169-74. doi: 10.1038/clpt.2014.97. Epub 2014 May 2. PubMed PMID: 24787449; PubMed Central PMCID: PMC4111801.

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