Rasburicase-induced Hemolytic Anemia in an Adolescent With Unknown Glucose-6-Phosphate Dehydrogenase Deficiency

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Rasburicase, used in the prevention and treatment of tumor lysis syndrome (TLS), may cause hemolytic anemia and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Although routine screening for G6PD deficiency has been recommended, given the turnaround time for test results and the urgency to treat TLS, such screening may not be feasible. We report a case of rasburicase-induced hemolytic anemia without methemoglobinemia in an adolescent with T-cell lymphoblastic lymphoma, TLS, and previously unrecognized G6PD deficiency. Previous reports of hemolytic anemia with rasburicase are reviewed, mechanisms discussed, and preventative strategies presented.

ABBREVIATIONS ASCO, American Society of Clinical Oncology; FDA, food and drug administration; G6PD, glucose-6-phosphate dehydrogenase deficiency; ICU, intensive care unit; LDH, lactate dehydrogenase; NADPH, nicotinamide adenine dinucleotide phosphate; TLS, tumor lysis syndrome; WBC, white blood cell

KEYWORDS case report; glucose-6-phosphate dehydrogenase deficiency; hemolytic anemia; pediatric intensive care; rasburicase

J Pediatr Pharmacol Ther 2017;22(6):471–475

DOI: 10.5863/1551-6776-22.6.471

Introduction

Tumor lysis syndrome (TLS) is a potentially life-threatening oncologic emergency, which can result in end-organ damage, such as renal failure, brain injury resulting in seizures and cardiac arrhythmias. Severe TLS can even lead to death in 20% to 40% of cases.¹ This metabolic complication of rapid cellular turnover and destruction in highly proliferative tumors, such as high-grade lymphomas and acute leukemias, can occur prior to or during the administration of chemotherapy.² The classic metabolic derangements of TLS include hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. Hyperuricemia plays a central role in the development of acute kidney injury, one of the complications of TLS that predicts mortality.³ Vigorous hydration and drug therapy (allopurinol or rasburicase) to treat or prevent high uric acid levels are the cornerstone principles for TLS management. Given its mechanism of action, rasburicase, a recombinant urate oxidase, approved by the US Food and Drug Administration (FDA) for children in 2002, has been shown to rapidly lower uric acid levels than allopurinol, by converting pre-existing uric acid to allantoin compared to allopurinol, which inhibits the production of uric acid.^{4,5} Despite its proven safety and effectiveness, rasburicase is contraindicated in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency as it may provoke hemolysis and methemoglobin formation.⁶

G6PD deficiency is the most common red cell enzyme deficiency, affecting approximately 400 million people worldwide. It is an X-linked inherited disorder, most commonly affecting persons of African, Southeast Asian, and Mediterranean ethnicity with a gene frequency of 5% to 25%.^{7,8} In the United States, African American males are most commonly affected, with a prevalence of approximately 10%.⁹ Females are also affected by G6PD especially in populations where the homozygosity rate is high and “skewed X-inactivation” has been noted.¹⁰ Given the risks of hemolysis, screening of patients at high risk of G6PD deficiency has been recommended prior to the administration rasburicase. We report a case of rasburicase-induced hemolytic anemia in a patient with previously unrecognized G6PD deficiency.

Case Report

Institutional Review Board approval is not required at Nationwide Children’s Hospital (Columbus, Ohio) for the presentation of single case reports. A 14-year-old, 90 kg, African American male with a history of asthma was transferred to our facility with a 6-day history of progressive shortness of breath and cough. Chest radiograph revealed cardiomegaly and bilateral pleural effusions. Further imaging demonstrated a pericardial effusion and a large anterior mediastinal mass impinging on the mediastinum, heart, airway, and great vessels. Given the patient’s presentation and risk of acute airway compromise, he was transferred to the pediatric intensive care

unit (ICU). A diagnosis of T-cell lymphoblastic lymphoma was made following histological examination of the pleural fluid. His initial white blood cell (WBC) count and chemistry profile were within normal limits except for an elevated uric acid level of 8.6 mg/dL (normal range: 4–8 mg/dL) and a lactate dehydrogenase (LDH) of 1073 U/L (normal range: 350–850 U/L). With the diagnosis of T-cell lymphoma and large tumor burden, our patient was considered as high risk for developing TLS and was consequently given a single dose of rasburicase (6 mg) intravenously, started on daily course of allopurinol in addition of vigorous hydration and corticosteroids (hospital day 1). On hospital day 2, induction chemotherapy with vincristine and daunorubicin was started per protocol. Over the following 12 to 24 hours, his WBC count increased from 10 to $22 \times 10^3/\text{cu.mm}$ (normal range: $4.5\text{--}13.5 \times 10^3/\text{cu.mm}$) and the total bilirubin increased from 10.9 to 18.8 mg/dL (normal range: 0.1–1.0 mg/dL) with an associated indirect hyperbilirubinemia of 9.2 mg/dL (normal range: 0.1–1.0 mg/dL). Transaminases and other liver function tests were normal. An abdominal ultrasound revealed mild hepatosplenomegaly without evidence of gall stones. Allopurinol was discontinued because of its known association with liver injury. However, because of our patient's large tumor burden at presentation, the perceived continued risk for TLS and contraindication for allopurinol, a second dose of rasburicase (6 mg) was administered intravenously. On hospital day 3, scleral icterus was noted on physical examination. His urine was also observed to be red in color. As the urinalysis did not reveal significant red blood cells, the red color was attributed to hemoglobinuria. During this time, the hemoglobin precipitously dropped from 16.3 to 5.9 g/dL (normal range: 13.5–17.5 g/dL). The total bilirubin increased further to 22.3 mg/dL, and the LDH increased from 931 to 4523 U/L. The haptoglobin level was low (<30 mg/dL). He received supportive care, which included serial monitoring of complete blood count and chemistry profile, supplemental oxygen therapy, transfusion of packed red blood cells, and vigorous hydration. Given his ethnic background, G6PD deficiency was suspected; however, the methemoglobin level was low and the initial G6PD level was normal. No additional doses of rasburicase were administered. There was rapid resolution of the hyperbilirubinemia without further hemolysis. The LDH slowly returned to normal after several weeks. One year after his initial presentation, qualitative screening revealed a decreased G6PD level, thus confirming our initial suspicion of undiagnosed G6PD deficiency.

Discussion

Rasburicase, a recombinant urate oxidase, approved by the FDA for the management of TLS in children, can cause significant hemolysis and methemoglobinemia in patients with G6PD deficiency. These potentially severe side effects of rasburicase therapy require prompt

recognition and management. Although rasburicase-induced hemolytic anemia and methemoglobinemia is more common in G6PD deficient patients, hemolysis has also been reported in patients with normal G6PD enzyme levels.¹¹ As noted in our patient, in the setting of G6PD deficiency, the onset of hemolysis may be rapid, occurring after a single dose of rasburicase. Although screening for G6PD deficiency has been suggested prior to initiating therapy with rasburicase, the time to obtain results from such tests may preclude routine screening as emergent therapy may be needed to prevent end-organ damage from hyperuricemia related to TLS. In such settings, the risk-benefit ratio of initiating therapy with rasburicase must be considered.

Drug therapy to prevent hyperuricemia during TLS may include allopurinol and/or rasburicase. Both are generally included in the management of TLS management. Uric acid, a byproduct of purine catabolism, is a major cause of acute renal failure through formation of uric crystal formation in the renal tubules.¹² The presence of renal failure with TLS or in the ICU setting significantly increases the risk of mortality thereby mandating early and aggressive therapy to prevent the end-organ effects of hyperuricemia. Allopurinol, a competitive inhibitor of xanthine oxidase, inhibits the synthesis of uric acid.¹³ However, it is not the ideal treatment for TLS because of its slow onset of action and its inability to inactivate circulating uric acid.¹⁴ On the other hand, rasburicase converts hydrophobic uric acid to the highly hydrophilic allantoin, which is readily excreted by the kidneys. It is superior to allopurinol in rapidly lower serum uric acid levels and is associated with less risk of acute kidney injury.^{5,15,16} Rasburicase is recommended by the 2008 American Society of Clinical Oncology (ASCO) Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome as the initial management of patients with high risk of developing TLS and in patients with intermediate risk if hyperuricemia occurs despite allopurinol prophylaxis.¹⁷ Although cost-effectiveness and outcomes related to its use are yet to be conclusively proven, rasburicase is considered to be a standard of care for patients at high risk of TLS. The recommended dose of rasburicase is 0.15 to 0.2 mg/kg daily (maximum dose of 6 mg per our institutional guidelines) with a duration of therapy from 1 to 7 days.^{17,18} Our patient's initial clinical presentation with a large tumor burden, diagnosis of T cell lymphoma, and significant risk of continued rise in uric acid with initiation of chemotherapy, placed him at a high risk for complications related to TLS. Given these concerns, therapy with rasburicase was administered.

G6PD is critical for the production of nicotinamide adenine dinucleotide phosphate (NADPH) by erythrocytes, which maintains normal levels of reduced glutathione. The latter protects the erythrocytes from oxidative damage from endogenous and exogenous substances. In the presence of oxidizing agents, eryth-

rocytes in patients with G6PD deficiency are rapidly depleted of glutathione. As a result, the sulfhydryl groups on hemoglobin are oxidized leading to methemoglobin formation, Heinz body formation, red cell rigidity, and subsequent destruction by macrophages in the reticulo-endothelial system leading to the hemolytic process.^{19,20} As an inherited disorder, G6PD deficiency should be considered in children with a family history of jaundice, anemia, splenomegaly, or cholelithiasis, especially in those of Mediterranean or African descent.²¹ Although quantitative enzyme assays are the mainstay of detecting G6PD deficiency, the ultraviolet fluorescence spot test, which detects the generation of NADPH, is more commonly used as a qualitative screening test. The latter is interpreted only as adequate or low without an exact measurement of the enzyme level. Our patient had an initial qualitative G6PD screen, which was interpreted as adequate. Results such as this are not uncommon during an episode of acute hemolysis because older erythrocytes with a lower enzyme level are destroyed, leaving young erythrocytes and reticulocytes with normal or near-normal enzyme activity to be tested, thus leading to false-negative results.

The majority of reported cases of rasburicase-induced hemolytic anemia have been in association with methemoglobin formation. Rasburicase itself does not cause hemolysis rather hydrogen peroxide, a byproduct of the enzymatic oxidation of uric acid into water-soluble allantoin by rasburicase, results in an oxidative stress to the erythrocytes and triggers hemolysis and methemoglobinemia in patients with G6PD deficiency. Methemoglobinemia develops when the iron moiety in hemoglobin is oxidized from the ferrous form (Fe^{++}) to the ferric form (Fe^{+++}). The normal methemoglobin level is less than 2%. Elevated levels result in clinical findings of cellular hypoxemia including metabolic acidosis, mental status changes, headache, confusion, and lethargy. Tissue hypoxia generally occurs when the methemoglobin levels exceed 20%.^{22,23} Levels greater than 50% lead to central nervous system changes including seizures, dysrhythmias, and death.^{23,24} Treatment includes methylene blue in symptomatic patients with a methemoglobinemia level greater than 20% to 30%.²³ Methylene blue is a NADPH-dependent reducing agent and the treatment of choice for methemoglobinemia. However, because of the inability to produce NADPH, methylene blue is not recommended for G6PD-deficient patients, as it may behave as an oxidizing agent and cause worsening methemoglobinemia and hemolysis.²⁵ Supportive treatment including supplemental oxygen, allogeneic blood transfusion, and ascorbic acid have been suggested in the management of methemoglobinemia in G6PD-deficient patients.^{19,26–30} Our patient's methemoglobin level was less than 2% thereby being one of the few reported cases of rasburicase-induced hemolysis without methemoglobinemia.

Additional mechanisms have been postulated in

rasburicase-induced hemolytic anemia and methemoglobin formation other than oxidant stress related to hydrogen peroxide formation (see above). Alternatively, as serum uric acid is a potent free-radical scavenger, its rapid reduction following the administration of rasburicase may compromise this anti-oxidant mechanism and thus facilitate acute hemolysis and methemoglobin formation.³¹ As a recombinant form of mammalian urate oxidase, rasburicase can potentially result in a drug-induced, immune-mediated hemolytic anemia.²⁷ The direct Coombs test was negative in our patient during his episode of acute hemolysis hence making an immune-mediated mechanism less likely.

The diagnosis of hemolytic anemia in our patient required a high index of suspicion since he had no prior G6PD screening, a falsely adequate level of G6PD on the qualitative screen during the time of acute hemolysis, and a normal methemoglobin concentration. A rapid decrease in the hemoglobin concentration with the associated classical findings of a low haptoglobin, indirect hyperbilirubinemia, hemoglobinuria, and elevated LDH, should alert the clinician to the possibility of rasburicase-induced hemolytic anemia, even in the absence of methemoglobin and an initial normal G6PD enzyme screen.

The reported prevalence of rasburicase-induced hemolytic anemia and methemoglobin is less than 1%.¹² However, most studies do not include ethnic groups that are at high risk for G6PD deficiency; hence, the true prevalence is unknown. Given the FDA boxed warning and clinical guidelines that recommend the screening of high risk patients for G6PD deficiency prior to rasburicase use, it may be beneficial for ICUs using rasburicase, to develop screening protocols for G6PD deficiency, provided that such assays can be rapidly obtained. Routine screening may be challenging, since the cost-effectiveness of screening might be difficult to determine given the lack of data on true prevalence of rasburicase-induced hemolytic anemia. The challenges of such screening may be magnified by the potential for a false-negative assay, as commonly used test kits for G6PD screening have different sensitivities.³² Additionally, G6PD screens can be falsely negative during acute hemolytic episodes and when the testing is done after blood transfusion, as donor red blood cells can mask G6PD deficiency.³³ Furthermore, it can be logistically difficult to delay rasburicase therapy because of the high morbidity and mortality associated with delayed treatment of TLS and variability in turnaround time of G6PD screening results. Hence it might be practically inevitable to initiate rasburicase therapy without prior screening of patients with high risk of TLS. With no prior screening, a high index of suspicion remains crucial in any patient who develops signs of methemoglobinemia or hemolysis following rasburicase therapy.

In summary, we present an adolescent who developed significant hemolysis following a single dose of

rasburicase to treat hyperuricemia related to TLS. Rasburicase has been reported to cause severe hemolytic anemia with methemoglobinemia in patients with G6PD deficiency. As noted in our patient, such hemolysis may occur even in the absence of methemoglobin formation. In addition to the production of an oxidant stress, other etiologies for rasburicase-induced hemolysis have been reported including an immune-mediated mechanism. As time permits, patients from high prevalence ethnicities should be screened for G6PD deficiency prior to the administration of rasburicase. If prior screening is impractical, close monitoring for the development of adverse effects of rasburicase therapy, such as in our case, is crucial.

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

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