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CASE REPORT

Rasburicase-induced methemoglobinemia: case report, literature review, and proposed treatment algorithm

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Key Clinical Message

Rasburicase for the treatment of tumor lysis syndrome has been associated with hemolytic anemia and methemoglobinemia, usually in patients with G6PD deficiency. Risks and benefits should be considered prior to use of rasburicase in at-risk patients. Methylene blue will worsen the hemolytic anemia in G6PD deficiency and should be avoided.

Keywords

Hemolytic anemia, methemoglobinemia, rasburicase, tumor lysis syndrome.

A 56-year-old African American male with a history of systolic congestive heart failure (CHF), pulmonary thromboembolism (PTE) and gout presented to the emergency department with shortness of breath. He had been seen in a walk-in clinic the previous week with similar symptoms and was told his white blood cell (WBC) count was very elevated. On examination, he was in no acute distress. He weighed 194 kg (BMI 63). Temperature was 37.1°C, pulse 113, respiratory rate 22, blood pressure 127/81 mm Hg, and oxygen saturation 100% on ambient air. His cardiac examination revealed tachycardia without murmurs. His lungs were clear. He had 3+ edema in the right lower extremity and 2+ edema in the left lower extremity with weeping of clear fluid.

The patient's WBC count was 62.4 × 10^9/L, with 62% neutrophils, 5% bands, 10% lymphocytes, 13% monocytes, and 5% metamyelocytes. The hemoglobin level was 13.3 g/dL [133 g/L] with a mean corpuscular volume of 95 μm^3. Platelet count was 267.0 × 10^9/L. The serum sodium was 131 mmol/L, potassium 3.7 mmol/L, blood urea nitrogen (BUN) 20 mg/dL (7.14 mmol/L), and creatinine (Cr) 1.6 mg/dL [141.4 μmol/L], an increase from 1.1 mg/dL [97.2 μmol/L] 18 months earlier. Liver function tests and cardiac enzymes were normal. The prothrombin time was normal. A computed tomographic angiogram (CTA) of the chest was negative for PTE and showed no obvious pulmonary infiltrate.

The cause of a leukocytosis can either be a primary bone marrow problem, such as a myeloproliferative disorder, or secondary to another systemic problem, such as infection, inflammation, physiologic stress, etc. The cell differential can be helpful in making this distinction. This patient exhibited a left shift with a significant amount of metamyelocytes, which can be seen in both infectious and

inflammatory processes. However, more premature WBC forms such as myelocytes, promyelocytes and blasts were not reported in the automated differential, though a review of the peripheral smear would be prudent in a patient with this degree of leukocytosis. Additionally, further testing with flow cytometry can detect a clonal expansion of a single cell line indicative of malignancy. The normal hemoglobin levels and platelet count indicate preservation of adequate trilineage hematopoiesis in the bone marrow. The elevated creatinine may be related to hypovolemia from increased diuretics. The CTA of the chest essentially rules out a PTE.

The patient was admitted for further monitoring and he was started on vancomycin for possible cellulitis. His WBC count continued to hover around 60.0×10^9/L. Neutrophil alkaline phosphatase (NAP) score was 45 (20–150). Peripheral smear confirmed marked leukocytosis with predominately mature elements. Flow cytometry showed a small subset of immature myeloid cells (0.27% of all cells, CD34+).

The NAP score is a marker of neutrophil maturity and is sometimes used to help differentiate between a leukemoid reaction and chronic myeloid leukemia (CML). CML typically presents in the sixth to seventh decade and often times in a relatively asymptomatic patient with an elevated WBC count as the presenting finding. In the vast majority of patients, it is caused by a translocation between chromosomes 9 and 22, creating a *BCR-ABL1* fusion product that allows myeloid cells to proliferate uncontrollably. Neutrophil alkaline phosphatase is an enzyme that is present in the cytoplasm of mature neutrophils. A lower score is suggestive of immature neutrophils and thus more consistent with CML, however, bone marrow biopsy and testing for the Philadelphia chromosome is required to make a diagnosis of CML. The peripheral smear analysis and flow cytometry are not suggestive of acute leukemia or lymphoma, but could be consistent with CML.

Bone marrow biopsy was deferred as the procedure would have been technically difficult given the patient's body habitus. Fluorescence in situ hybridization (FISH) for *BCR-ABL1* was pending. His acute kidney injury abruptly worsened on hospital at day three with an increase in his BUN to 27 mg/dL [9.64 μmol/L] and Cr to 5.1 mg/dL [450.8 μmol/L]. He remained tachycardic and spiked a fever to 38.5°C. Repeat chest X-ray showed increased interstitial markings. Urinalysis was obtained and was notable for 3+ blood, 3+ protein, negative nitrite, 3+ leukocyte esterase with >50 WBC per high-powered field. Piperacillin/tazobactam was added for gram-negative coverage for presumed sepsis from urinary tract infection versus healthcare-associated pneumonia. The following day, his creatinine rose to 6.2 mg/dL [548.1 μmol/L] with an increase in his WBC count to over 70.0×10^9/L. WBC differential was notable for 10% eosinophils and urine eosinophil stain was positive. Uric acid level was elevated at 11.8 mg/dL [701.9 μmol/L]. Potassium was 4.3 mmol per liter, calcium was 8.3 mg/dL [2.08 mmol/L], and phosphorous was 5.5 mg/dL [1.78 mmol/L].

The worsening renal function is likely multifactorial. The patient received intravenous contrast on presentation which is nephrotoxic. The development of eosinophilia and presence of urine eosinophils is consistent with acute interstitial nephritis, which likely resulted from the addition of piperacillin/tazobactam. The elevated uric acid level may be explained by the patient's underlying gout, however, in light of the rising WBC count and concern for malignancy could also be indicative of tumor lysis syndrome (TLS). TLS occurs as a result of the release of massive amounts of intracellular nucleic acids, potassium, and phosphorous during periods of extensive tumor cell necrosis. It is frequently an expected complication from the initiation of cytotoxic chemotherapy in hematologic malignancies, but can also occur spontaneously. The renal damage occurs from the deposition of uric acid or calcium phosphate crystals in the renal tubules. Patients at risk are typically pretreated with intravenous hydration and allopurinol to help lower uric acid levels. Patients who go on to develop TLS typically receive rasburicase, which is recombinant urate oxidase enzyme. Urate oxidase converts uric acid to water-soluble allantoin, which can then be freely excreted in the urine. Although formal diagnostic criteria to make a diagnosis of TLS exist, given the emergent nature of the syndrome and high efficacy and tolerability of rasburicase, it is not uncommon to treat with rasburicase if clinical suspicion exists.

The patient received one dose of rasburicase 6 mg (0.03 mg/kg) on hospital day five and his serum uric acid dropped to 5.2 mg/dL [309.3 μmol] the following day. His renal function also began to improve and his Cr had fallen to 2.2 mg/dL [130.9 μmol/L] by hospital day eight. However, during that time period, the patient was noted to be progressively more encephalopathic. On hospital, at day eight, he became hypoxic with oxygen saturation of 82% on 100% oxygen via non-rebreather. He was intubated and transferred to the medical intensive care unit where labs were notable for WBC 127.4×10^9/L and hemoglobin 8.0 mg/dL, which had been12.4 mg/dL 3 days prior. Other notable labs included total bilirubin 6.4 mg/dL [106.0 μmol/L], indirect bilirubin 4.4 mg/dL [75.3 μmol/L], LDH 1829 U/L [30.5 μkat/L], and haptoglobin 9 mg/dL [90 g]. Arterial blood gas showed methemoglobin level of 9.5%.

Rasburicase has been reported to cause both methemoglobinemia and hemolytic anemia as a result of increased oxidative stress inside the erythrocyte, typically

Figure 1. Therapeutic plasma exchange for removal of free plasma hemoglobin. The green fluid in the bags is the patient's plasma, which is discolored due to the presence of byproducts of the breakdown of the free hemoglobin released into the circulation as a result of massive intravascular hemolysis.

Table 1. Cairo-Bishop laboratory criteria for TLS diagnosis.

	Value	Change from baseline
Uric acid	≥476 μmol/L (8 mg/dL)	25% increase
Potassium	≥6.0 mmol/L (or 6 mEq/L)	25% increase
Phosphorous	≥1.45 mmol/L (4.5 mg/dL) for adults	25% increase
Calcium	≤1.75 mmol/L (7 mg/dL)	25% decrease

in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. When rasburicase converts uric acid to allantoin, the byproduct is hydrogen peroxide, an oxidizing agent. Methemoglobin is formed when the iron moiety in the heme molecule is oxidized from the ferrous (Fe^{++}) to the ferric (Fe^{+++}) state which cannot bind oxygen molecules. In addition, the remaining ferrous atoms in the heme tetramer have increased oxygen affinity and thus are less likely to release oxygen molecules in the periphery. This results in a left shift in the oxyhemoglobin dissociation curve and produces a functional anemia. The increased oxidative stress also leads to Heinz body formation, red cell rigidity, and erythrocyte destruction by macrophages in the reticuloendothelial system, producing the hemolytic anemia. The combination of this functional and hemolytic anemia can result in large drops in the serum hemoglobin levels and a significant impairment in oxygen delivery to vital organs. Methemoglobinemia is typically treated with methylene blue, which catalyzes one of the reactions in which methemoglobin is reduced back to hemoglobin. However, in individuals with G6PD deficiency, this pathway is inactive and methylene blue cannot catalyze the reaction but instead becomes oxidized itself, further increasing the oxidative stress on the cell.

Methylene blue was not given due to concern for G6PD deficiency and the patient was started on ascorbic acid 1 g daily. He underwent double volume red cell exchange transfusion on hospital at day eight with 5.1 L of allogeneic packed red blood cells. On hospital, at days nine and 10, he underwent therapeutic plasma exchange for elevated free plasma hemoglobin levels (Fig. 1). On day 12, the FISH for *BCR-ABL1* returned positive, but imatinib therapy was deferred as the patient remained critically ill, intubated and on vasopressors. He slowly improved clinically and was eventually able to be extubated and transferred to the hematology service where he began therapy for his CML with imatinib on hospital day 25.

Commentary

This patient presented with shortness of breath and was found to have a significant leukocytosis. In the course of his work up, he developed acute kidney injury. While the patient had multiple plausible etiologies for his worsening renal function, due to the concern for underlying malignancy, TLS was suspected. In 2004, the Cairo-Bishop [1] laboratory diagnostic criteria (Table 1) and grading system for TLS severity (Table 2) were proposed. Our patient met two of the four criteria, which would be consistent with a diagnosis of TLS, and his rise in creatinine would classify his TLS as grade 3.

Since the use of rasburicase began, we are aware of 15 reported cases of methemoglobinemia with or without associated hemolysis (Table 3) [2–14]. It was first reported in patients with G6PD deficiency [2], but has also been seen in patients without G6PD deficiency [5, 8]. The majority of cases are mild and treatment consists of supportive treatment with oxygen and red blood cell

Table 2. Cairo-Bishop grading scale for severity of TLS.

Complication	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine	<1.5 ULN	1.5 × ULN	>1.5–3.0 × ULN	>3.0–6.0 × ULN	>6.0 × ULN	Death
Cardiac arrhythmia	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and not adequately controlled	Life-threatening	Death
Seizure	None	–	Brief seizure, well controlled	Seizure with LOC or poorly controlled	Prolonged, repeated seizures	Death

ULN, upper limit of normal; LOC, loss of consciousness.

Table 3. Reported cases of rasburicase-induced methemoglobinemia and hemolytic anemia.

Source	Age/ Gender	Race	Dx	Peak MetHb (%)	Uric acid (mg/dL)	Rasburicase dose	Methylene blue	Ascorbic acid	Transfusions	Outcome	G6PD status
Pui et al. [2]	12 M	AA	ALL	15.6	Unk	100 U/kg	No	No	No	Recovery	Deficient
Bosly et al. [3]	Pediatric	Unk	None	Unk	Unk	0.2 mg/kg	Unk	Unk	Unk	Unk	Deficient
Browning et al. [4]	50 M	AA	None	9.8	14.6	0.21 mg/kg	No	No	8 units pRBCs	Recovery	Deficient
Kizer et al. [5]	Adult	Unk	Mycosis fungoides	14.9	13.6	0.2 mg/kg	No	No	2 units pRBCs	Recovery	Normal
Kizer et al. [5]	Adult	Unk	DLBCL	21.5	14.0	0.2 mg/kg	Yes	No	2 units pRBCs	Recovery	Unk
Bhat et al. [6]	12 M	Laotian	T-ALL	10.1	22.1	0.2 mg/kg	Yes	No	Double volume exchange transfusion	Recovery	Deficient
Borinstein et al. [7]	14 M	Cambodian	Burkitt's lymphoma	12.6	10.8	0.2 mg/kg	No	No	3 units pRBCs	Recovery	Deficient
Bauters et al. [8]	6 M	Caucasian	ALL	17.3	Unk	0.2 mg/kg	No	No	No	Recovery	Normal
Ng et al. [9]	16 M	AA	Burkitt's lymphoma	8.0	11.1	0.2 mg/kg	No	No	4 units pRBCs	Recovery	Clinical diagnosis
Bucklin et al. [10]	62 M	AA	CLL/SLL	19.3	12.5	0.04 mg/kg 2	Yes	No	12 units pRBCs	Death	Suspected
Cheah et al. [11]	46 M	Mauritian-Chinese	CLL	7.2	Unk	0.07 mg/kg	No	Yes	8 units pRBCs	Recovery	Deficient
Sonbol et al. [12]	52 M	AA	Multiple myeloma	12.9	16.1	6 mg	No	Yes	8 units pRBCs	Recovery	Deficient
Roberts et al. [13]	43 F	AA	Metastatic colon cancer	6.3	11.6	6 mg	No	No	None	Death	Deficient
Roberts et al. [13]	70 F	AA	Multiple myeloma	13.0	16.0	6 mg	No	Yes	3 units pRBCs	Recovery	Deficient
Bontant et al. [14]	5 M	Congolese	ALL	20.0	3.6	0.2 mg/kg	No	No	1 unit pRBCs	Recovery	Deficient
Our case	56 M	AA	CML	9.5	11.8	0.03 mg/kg	No	Yes	Double volume exchange transfusion	Recovery	Deficient

AA, African American; ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic leukemia; pRBCs, packed red blood cells.

transfusions. Death has occurred in two cases [10, 13], one of which [10] was notable for the use of methylene blue in a patient whose G6PD status was unknown, but was suspected to be deficient.

We treated our patient with double volume exchange transfusion, which has been employed in one other case with good results [6]. However, double volume exchange transfusion in our patient was logistically difficult given his size (BMI 63), requiring 5.1 L of packed red blood cells. He also required therapeutic plasma exchange for the removal of free plasma hemoglobin as a result of severe hemolytic anemia. Six months following the hospitalization when the transfused red blood cells were no longer circulating, our patient was confirmed to be G6PD deficient. Our case suggests that the severity of hemolysis and methemoglobinemia does not appear to be dose dependent, as our patient received 0.03 mg/kg of rasburicase in a single dose. Similarly, the patient in one of the reported deaths [10] received two doses of 0.04 mg/kg.

Though typically well tolerated, rasburicase therapy has been associated with adverse reactions with the potential to cause significant morbidity and mortality. To avoid rasburicase-induced hemolytic anemia and methemoglobinemia, we would recommend screening all patients at risk for G6PD deficiency, including African Americans, prior to the initiation of cytotoxic chemotherapy for hematologic malignancies with a high tumor burden. When TLS presents urgently and precludes screening, clinicians should weigh risks and benefits prior to using rasburicase in at risk populations. In patients at risk for G6PD deficiency who cannot be screened, close monitoring of hemoglobin levels and oxygen saturation is warranted following rasburicase administration. If methemoglobinemia and hemolysis are observed, patients should be assumed to be G6PD deficient and should not receive methylene blue. In severe cases, red cell exchange transfusion has been used twice with good results. More recently, ascorbic acid [11–13] has been used as an antioxidant with relatively few side effects and appears to be well tolerated.

Conflict of Interest

None declared.

References

1. Cairo, M. S., and M. Bishop. 2004. Tumour lysis syndrome: new therapeutic strategies and classification. Br. J. Haematol. 127:3–11.
2. Pui, C. H., M. V. Relling, F. Lascombes, P. L. Harrison, A. Struxiano, J. M. Mondesir, et al. 1997. Urate oxidase in prevention and treatment of hyperuricemia associated with lymphoid malignancies. Leukemia 11:1813–1816.
3. Bosly, A., A. Sonet, C. R. Pinkerton, G. McCowage, D. Bron, M. A. Sanz, et al. 2003. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer 98:1048–1054.
4. Browning, L. A., and J. A. Kruse. 2005. Hemolysis and methemoglobinemia secondary to rasburicase administration. Ann. Pharmacother. 39:1932–1935.
5. Kizer, N., E. Martinez, and M. Powell. 2006. Report of two cases of rasburicase-induced methemoglobinemia. Leuk. Lymphoma 47:2648–2650.
6. Bhat, P., I. Sisler, A. B. Collier. 2008. Exchange transfusion as treatment for rasburicase induced methemoglobinemia in a glucose-6-phosphate dehydrogenase deficient patient. Pediatr. Blood Cancer 51:568.
7. Borinstein, S. C., M. Xu, and D. S. Hawkins. 2008. Methemoglobinemia and hemolytic anemia caused by rasburicase administration in a newly diagnosed child with Burkitt lymphoma/leukemia. Pediatr. Blood Cancer 50:198.
8. Bauters, T., V. Mondelaers, H. Robays, H. De Wilde, Y. Benoit, B. De Moerloose. 2011. Methemoglobinemia and hemolytic anemia after rasburicase administration in a child with leukemia. Int. J. Clin. Pharm. 33:58–60.
9. Ng, J. S., E. M. Edwards, and T. A. Egelund. 2012. Methemoglobinemia induced by rasburicase in a pediatric patient: a case report and literature review. J. Oncol. Pharm. Pract. 18:425–431.
10. Bucklin, M. H., and C. M. Groth. 2013. Mortality following rasburicase-induced methemoglobinemia. Ann. Pharmacother. 47:1353–1358.
11. Cheah, C. Y., T. E. Lew, J. F. Seymour, and K. Burbury. 2013. Rasburicase causing severe oxidative hemolysis and methemoglobinemia in a patient with previously unrecognized glucose-6-phosphate dehydrogenase deficiency. Acta Haematol. 130:254–259.
12. Sonbol, M. B., H. Yadav, R. Vaidya, V. Rana, and T. E. Witzig. 2013. Methemoglobinemia and hemolysis in a patient with G6PD deficiency treated with rasburicase. Am. J. Hematol. 88:152–154.
13. Roberts, D. A., and J. A. Freed. 2014. Rasburicase-induced methemoglobinemia in two African-American female patients: an under-recognized and continued problem. Eur. J. Haematol. 94:83–85.
14. Bontat, T., S. Le Garrec, D. Avran, S. Dauger. 2014. Methaemoglobinaemia in a G6PD-deficient child treated with rasburicase. BMJ Case Rep. doi:10.1136/bcr-2014-204706.

