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Rasburicase-Induced Methemoglobinemia in a Patient with Aggressive Non-Hodgkin's Lymphoma

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 74
Final Diagnosis: Rasburicase-induced methemoglobinemia
Symptoms: Acute shortness of breath
Medication: Rasburicase
Clinical Procedure: Attempted percutaneous coronary intervention (PCI)
Specialty: Oncology

Objective: Unusual or unexpected effect of treatment

Background: Rasburicase is a recombinant urate oxidase enzyme that converts uric acid to allantoin (an inactive and soluble metabolite that is readily excreted in urine). It is used for the management of tumor lysis syndrome (TLS) in cancer patients receiving chemotherapy. Although rasburicase is a generally safe and effective treatment, it can be associated with the rare and potentially severe complication of methemoglobinemia. Here, we report a case of rasburicase-induced methemoglobinemia in a patient who was diagnosed with aggressive non-Hodgkin's lymphoma.

Case Report: A 74-year-old man with aggressive non-Hodgkin's lymphoma was admitted for initiation of chemotherapy. Upon admission, the patient was found to have hyperkalemia, hyperuricemia, hyperphosphatemia, elevated LDH levels, and acute renal failure. As a result, he was diagnosed with TLS. Rasburicase 6 mg was administered intravenously over a period of 30 min to treat TLS. Later, methemoglobinemia developed, with requirements for oxygen supplementation. Multiple units of packed red blood cells were transfused for recurrent significant anemia secondary to his cancer co-morbidity. The patient was tested for glucose-6 phosphate dehydrogenase (G6PD) deficiency, which returned negative; therefore, methylene blue was considered. After transfusion, the methemoglobin level normalized over the course of a few days, and the oxygen saturation improved without the use of methylene blue. However, during his hospitalization, the patient also developed a pulmonary embolism and had evidence of acute coronary syndrome. Later, the patient died of multiple complications related to his cancer co-morbidity on day 12 of admission.

Conclusions: Blood transfusion and supplemental oxygen, without the use of methylene blue, may be an appropriate therapeutic alternative in rasburicase-induced methemoglobinemia treatment.

MeSH Keywords: Drug-Related Side Effects and Adverse Reactions • Lymphoma, Non-Hodgkin • Methemoglobinemia • Methylene Blue

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Background

Rasburicase is a recombinant urate oxidase enzyme that converts uric acid to allantoin (an inactive and soluble metabolite that is readily excreted in urine) [1]. It is used for the management of TLS in cancer patients receiving chemotherapy [1]. TLS is a fatal condition that occurs more frequently in patients with hematologic malignancies compared to those with solid tumors [2].

According to the Guideline for the Management of Pediatric and Adult Tumor Lysis Syndrome, TLS should be treated by aggressive hydration and allopurinol or recombinant urate oxidase (rasburicase) [2]. Although rasburicase is a generally safe and effective treatment, it can be associated with the rare and potentially severe complication of methemoglobinemia [3]. Methemoglobinemia develops when the iron moiety in hemoglobin is oxidized from the ferrous form (Fe^{2+}) to the ferric form (Fe^{3+}) [4,5]. The ferric form of the iron in the hemoglobin is unable to bind to the oxygen, leading to hypoxia [4,5]. Depending on the methemoglobin levels, the patient may develop cyanosis, hemolysis, altered mental status, tachycardia, acidosis, seizure, coma, or even death (Table 1) [5,6]. Rasburicase-induced methemoglobinemia has been reported in several cases, often with concurrent glucose-6-phosphate dehydrogenase deficiency [7–13]. Glucose-6-phosphate dehydrogenase deficiency is considered a risk factor for developing rasburicase-induced methemoglobinemia [3]. Unfortunately, no standard treatment is available for rasburicase-induced methemoglobinemia. Methylene blue (if G6PD deficiency is ruled out) or blood transfusion, in addition to oxygen, has been used for treatment.

Case Report

A 74-year-old African-American male with a height of 175 cm and a weight of 119 kg presented to the oncology outpatient clinic with a rapidly swelling mass in his right jaw and supraclavicular region. A core needle biopsy was performed, which demonstrated an aggressive non-Hodgkin's lymphoma with suspicion for a large B-cell, Burkitt's, or double-hit lymphoma. The patient was admitted to the hospital for initiation of

1 cycle of dose-adjusted EPOCH-R chemotherapy regimen and 1 cycle of intrathecal prophylaxis with methotrexate, cytarabine, and methylprednisolone.

However, prior to initiation of the chemotherapy, the patient was found to have hyperkalemia, hyperuricemia, hyperphosphatemia, elevated LDH levels, and acute renal failure, for which he was diagnosed with TLS. A single dose of rasburicase 6 mg intravenously over a period of 30 min was administered to treat TLS.

On the following day, the patient started rituximab but later demonstrated acute shortness of breath and hypoxemia with an oxygen saturation of approximately 70% (Figure 1). In addition, the methemoglobin was elevated (10.9%) (Figure 2). He responded to supplemental oxygen therapy and further evaluation was done by the medical team. Cardiac enzyme studies showed an elevated troponin value. The patient was taken emergently for cardiac catheterization, which later revealed a small distal right coronary artery lesion, but intervention was not indicated. Shortly thereafter, the patient's oxygen saturation again dropped to approximately 80% and a CT scan showed acute pulmonary emboli within the right lower lobe interlobar pulmonary artery, multiple segmental right lower lobe arteries, and distal middle lobe pulmonary embolism. As a result, the patient was transferred to the intensive care unit with a 100% non-breathing mask.

The evaluation in the intensive care unit found that the patient had significant methemoglobinemia, which was most likely induced by rasburicase. The G6PD enzyme level was normal. The patient's oxygen saturation remained in the upper 80s, thus the decision was made to initiate a previously ordered blood transfusion first, then consider methylene blue to treat rasburicase-induced methemoglobinemia if refractory. After the blood transfusion, the methemoglobin level dropped to 7.6% and oxygen saturation improved to the low 90s. The methemoglobin levels reduced further to 4.2%, 2.8%, and then to 0.8%, and the oxygen saturation increased to 95%. The methemoglobinemia resolved with blood transfusion and no methylene blue was necessary.

The patient appeared to be doing relatively well until he developed a suspected aspiration that required full ventilator

Table 1. Signs and symptoms associated with methemoglobin levels [5,6].

Methemoglobin levels (%)	Signs and symptoms
<10%	Cyanosis or asymptomatic
10–20%	Cyanosis and/or hemolysis
20–50%	Mental status changes, headache, fatigue, anxiety, confusion, dizziness, weakness, exercise intolerance, syncope, tachycardia, and/or tachypnea
>50%	Metabolic acidosis, seizures, coma, dysrhythmias, or potential death

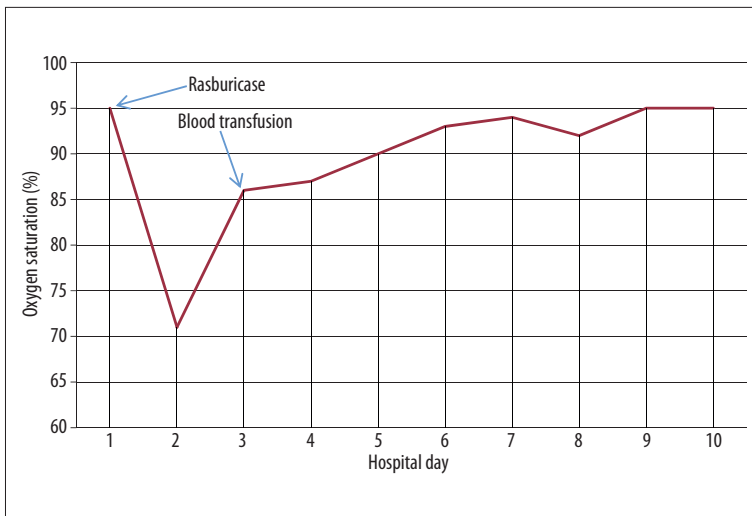


Figure 1. Oxygen saturation trending.

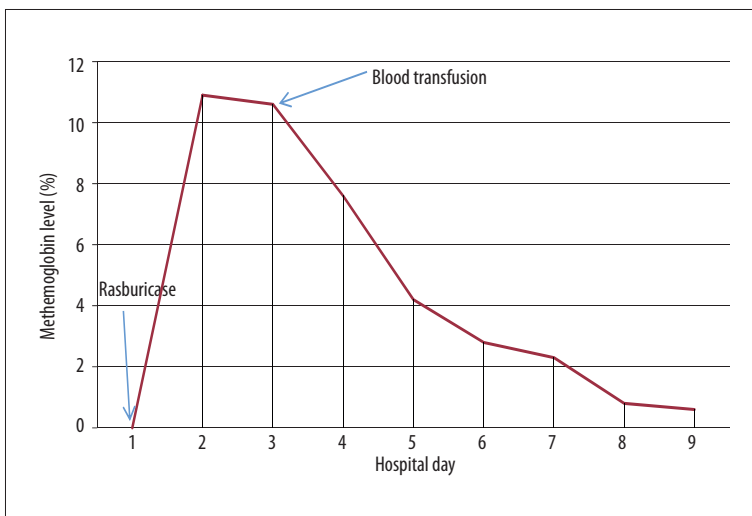


Figure 2. Methemoglobin level trending.

support, along with renal failure. All chemotherapy was discontinued due to his worsening renal function. The serum creatinine level continued to rise to 5.7 mg/dL and BUN to 151. A right femoral dialysis catheter was inserted and dialysis was recommended by nephrology. Subsequently, the patient developed multi-organ system failure syndrome and he became severely septic. A CT scan of the brain was performed due to the lack of responsiveness of the patient after withdrawal of sedation. The CT scan showed a new hypodense lesion in the posterior aspect of the right internal capsule, with right ventricular system effacement from central nervous system involvement of his non-Hodgkin's lymphoma. De-escalation of advanced life support was pursued by family, with subsequent death.

Discussion

TLS is a serious and life-threatening condition that is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia,

and hypocalcemia due to the abrupt release of cellular components to the bloodstream from rapid cancer cell lysis [2]. This condition is most commonly seen in patients with hematologic malignancies than in those with solid tumors [2]. TLS, if left untreated, may lead to renal failure or even death [2]. The Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome recommend aggressive hydration combined with allopurinol or recombinant urate oxidase (rasburicase) for the treatment of TLS [2]. The recommended rasburicase dose is 0.15–0.2 mg/kg daily infused over a period of 30 min and the duration of therapy ranges from 1 to 7 days [2]. Our patient presented with TLS; aggressive hydration was ordered and rasburicase was administered.

Although rasburicase-induced methemoglobinemia is a rare adverse effect, it could be life-threatening and require immediate management [3]. Methemoglobinemia develops when the iron moiety in hemoglobin is oxidized from the ferrous form (Fe^{2+}) to the ferric form (Fe^{3+}) [4,5]. The transformation in the iron

moiety makes the hemoglobin unable to bind to the oxygen, leading to hypoxia [4,5]. Patients with G6PD deficiency are at higher risk of this rare adverse effect, but it still can occur in patients with normal G6PD enzyme level [3]. In general, it is recommended to use methylene blue in symptomatic patients with a methemoglobin level >20–30% [5]. However, methylene blue is not recommended in patients with G6PD deficiency, since it may worsen methemoglobinemia and hemolysis [14].

In our case, a total of 6 units of packed red blood cells were transfused to correct his pre-existing anemia. His methemoglobin level decreased from 10.6% to 0.8% over 3–4 days. Therefore, the addition of methylene blue was not necessary. Many cases of rasburicase-induced methemoglobinemia have been reported in which oxygen, methylene blue, blood

transfusion, and/or ascorbic acid were used [7–13]. Most of these cases were in patients with G6PD deficiency, but our patient had a normal G6PD enzyme level.

Conclusions

Rasburicase-induced methemoglobinemia is a rare complication that may occur in patients with normal G6PD enzyme activity. Blood transfusion and appropriate levels of supplemental oxygen may provide sufficient treatment for rasburicase-induced methemoglobinemia without the need for methylene blue. Our patient's death following this reaction was most likely due to the myriad of complications that the patient developed during his hospitalization and underlying cancer co-morbidity.

References:

1. Cairo MS, Bishop M: Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*, 2004; 127: 3–11
2. Coiffier B, Altman A, Pui CH et al: Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*, 2008; 26: 2767–78
3. Sanofi-Aventis. Rasburicase: highlights of prescribing information. <http://products.sanofi.us/elitek/elitek.html#section-9>. Accessed December 23, 2014
4. Mansouri A, Lurie AA: Concise review: methemoglobinemia. *Am J Hematol*, 1993; 42: 7–12
5. Umbreit J: Methemoglobin – it's not just blue: a concise review. *Am J Hematol*, 2007; 82: 134–44
6. Wright RO, Lewander WJ, Woolf AD: Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med*, 1999; 35(5): 646–56
7. Browning LA, Kruse JA: Hemolysis and methemoglobinemia secondary to rasburicase administration. *Ann Pharmacother*, 2005; 39: 1932–35
8. Borinstein SC, Xu M, Hawkins DS: Methemoglobinemia and hemolytic anemia caused by rasburicase administration in a newly diagnosed child with Burkitt lymphoma/leukemia. *Pediatr Blood Cancer*, 2008; 50: 189
9. Ng JS, Edwards EM, Egelund TA: Methemoglobinemia induced by rasburicase in a pediatric patient: a case report and literature review. *J Oncol Pharm Pract*, 2012; 18: 425–31
10. Ku F-C, Lin Y-C, Chang C-M et al: Rasburicase-induced methemoglobinemia and hemolysis in a patient with malignant lymphoma. *J Cancer Res Pract*, 2013; 29: 22–27
11. Bucklin MH, Groth CM: Mortality following rasburicase-induced methemoglobinemia. *Ann Pharmacother*, 2013; 47: 1353–58
12. Sonbol MB, Yadav H, Vaidya R et al: Methemoglobinemia and hemolysis in a patient with G6PD deficiency treated with rasburicase. *Am J Hematol*, 2013; 88: 152–54
13. Roberts DA, Freed JA: Rasburicase-induced methemoglobinemia in two African-American female patients: an under-recognized and continued problem. *Eur J Haematol*, 2015; 94(1): 83–85
14. Rosen PJ, Johnson C, McGehee WG, Beutler E: Failure of methylene blue treatment in toxic methemoglobinemia. Association with glucose-6-phosphate dehydrogenase deficiency. *Ann Intern Med*, 1971; 75: 83–86