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Rasburicase-induced Reds and Blues

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Introduction

G6PD deficiency (G6PDD) is a genetic disorder resulting in low levels of the G6PD enzyme, which plays a key role in preventing cellular damage from oxidative stress. We report a case of newly diagnosed G6PDD manifesting as methemoglobinemia (MetHb) and non-autoimmune hemolytic anemia (NIHA) following rasburicase administration in an elderly gentleman. This case is uncommon given that this phenomenon occurred in a patient with no prior history of G6PDD and presented later in life. This case is also unique, given that the reason for administering rasburicase was secondary to tumor lysis syndrome (TLS) in a patient with chronic lymphocytic leukemia (CLL). This type of cancer rarely causes TLS and when it does, it typically follows administration of chemotherapy, which was not the case in our patient. We also review the treatment of rasburicase-induced methemoglobinemia, including treatment limitations in patients with G6PDD.

Case Report

A 78-year-old male with a past medical history of untreated CLL, congestive heart failure and hypertension presented with altered mental status and acute kidney injury.

Physical Exam

- Vitals: B/P:169/80 HR:103 T:37C Sat: 96% on room air
- General: Well developed, Well nourished 78 y.o. male in no acute distress. Lethargic.
- Cardiovascular: Regular rate and rhythm. +S1/S2, Equal Pulses . No Lower Extremity Edema
- Pulmonary: Clear to auscultation bilaterally. No Wheezes or Rhonchi. No Accessory Muscle Usage
- Neurological: A&O x1. No focal neurological deficits.

Laboratory findings

Initial labs revealed a creatinine of 6.89 mg/dL, potassium of 5.2 mEq/L, phosphate of 6.1mg/dL, calcium of 9.0mg/dL, uric acid of 13.9mg/dL, leukocytosis of $68 \times 10^9/L$, and hemoglobin of 8.5 g/dL.

Case Report

Imaging findings

CT scan of his head was negative for any acute abnormalities. Renal ultrasound (figure 1) exhibited enlarged kidneys without hydronephrosis.

Treatment plan

Due to concern for infiltrative CLL and spontaneous tumor lysis syndrome (TLS), he was treated with 6mg of rasburicase.

Follow up

The next day, the patient was noted to be hypoxic with an oxygen saturation of 87% while on non-rebreather. Imaging found no evidence of pulmonary embolism, pneumonia or pulmonary edema. ABG displayed a PaO₂ of 280 mmHg. Given the discrepancy between pulse oximetry and ABG, there was concern for MetHb secondary to G6PDD. Subsequent testing revealed elevated methemoglobin levels and low G6PD levels. Given his G6PDD, methylene blue was contraindicated. He required high flow nasal cannula at 85% FiO₂ and 45L. One day following rasburicase administration, it was noted that the patient's hemoglobin was decreasing and he required red blood cell transfusion. Peripheral smear and serum labs were consistent with NIHA. Dialysis was initiated for his AKI and he eventually weaned down to room air. He ultimately was discharged home.



Figure 1: Enlarged right kidney measuring 13.1 cm in length

Discussion

G6PDD is an enzymatic deficiency affecting less than one-half percent of the population worldwide. Identification of this enzyme deficiency is often related to the magnitude of hemolysis. This case is unique given the older age of onset of the patient coupled with the rare instance of spontaneous TLS in a patient with CLL. It also illustrates the challenges with typical management strategies of TLS. Administering rasburicase along with aggressive hydration and electrolyte repletion is the usual care for patients with TLS.

However, rasburicase administration is contraindicated in people with G6PDD due to its potential to cause MethHb and NIHA. The main role of rasburicase is to convert uric acid to allantoin, a product that is more soluble than uric acid and excreted renally. A byproduct of this reaction is hydrogen peroxide, a potent oxidizing agent. When present in abundance, it results in the conversion of ferrous acid to ferric acid which does not bind oxygen molecules. The remainder of the ferrous atoms bind oxygen more tightly and are less likely to release oxygen, leading to functional anemia. In addition, the increased oxidative stress leads to Heinz body formation and red blood cell destruction via the reticuloendothelial system, resulting in hemolytic anemia. Dialysis is considered a reasonable alternative to clear the elevated uric acid levels when TLS is suspected in a patient with G6PDD.

Conventional treatment for MethHb includes the administration of methylene blue, which works to convert ferric iron back into ferrous iron. However, this is contraindicated in patients with G6PDD because of its oxidant properties, resulting in further hemolysis. High doses of IV vitamin C have been considered as an alternative in treating MethHb in patients where methylene blue is contraindicated.

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