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Unexpected Intravascular Hemolysis and Methemoglobinemia during Treatment for Lymphoma

James O. Ballard*, Edward J. Wyluda, Hong Zheng, Michael H. Creer

Penn State Hershey Medical Center, Hershey, PA, U.S.A.
*Corresponding author: jballard@hmc.psu.edu

Abstract A patient undergoing chemotherapy for relapsed non Hodgkin lymphoma developed tumor lysis syndrome, hypoxia and the abrupt onset of intravascular hemolysis. A past history of unexplained anemia and the finding of blister cells on peripheral smear led to the suspicion of congenital glucose phosphate dehydrogenase (G6PD) deficiency with intravascular hemolysis induced by the drug rasburicase. G6PD deficiency was confirmed by quantitative G6PD assay one month after the episode. Retrospective review of arterial blood gas data confirmed the transient presence of methemoglobinemia accompanying the hemolytic event. Health care providers should be aware of the potential for patients with previously undiagnosed G6PD deficiency to develop hemolysis and methemoglobinemia when oxidant drugs such as rasburicase are administered.

Keywords: *hemolytic anemia, non-Hodgkin lymphoma, rasburicase, methemoglobinemia*

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1. Introduction

Glucose-6-hosphate dehydrogenase (G6PD) deficiency is a relatively common enzymopathy, especially among African, Mediterranean and Asian populations. When affected patients have not been previously diagnosed with this inherited disorder, they are at risk for hemolytic anemia when inadvertently exposed to oxidant agents.

2. Case Report

A 50-year-old Greek man with a five-year history of stage IIIB follicular non Hodgkin lymphoma (NHL) was admitted for treatment of disease recurrence involving multiple nodal regions. In 2008 follicular lymphoma stage IIIB (grade 1-2), complicated by ureteral obstruction, was detected by needle biopsy of an enlarged para-aortic lymph node. Ureteral stenting and treatment with cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (R-CHOP) was given for eight monthly cycles. Maintenance therapy with rituximab every 2 months was given until recurrent lymphoma was detected in 2011. A second clinical remission was achieved with a combination of bendamustine and rituximab. During the latter therapy he developed pulmonary embolism, treated with unfractionated heparin and extended warfarin therapy. In 2013, biopsy of an enlarging right inguinal lymph node revealed follicular non Hodgkin lymphoma with progression to histologic grade 3. A positron emission tomography scan detected FDG-avid lymphadenopathy in the neck, mediastinum, axillary, retroperitoneal and inguinal areas. He was admitted for salvage chemotherapy.

His past history included type 2 diabetes, hypertension, and chronic kidney disease. He reported that at times in the past, he had been anemic. He denied obvious associated bleeding, but had received red blood cell transfusions without reaction in 2004 and 2008. Medications on admission were glyburide, metoprolol, Lisinopril, warfarin, acetaminophen/oxycodone and multiple vitamins. On admission, subcutaneous enoxaparin was substituted for warfarin, and intravenous hydration and allopurinol were begun. There was no known family history of anemia or hematological malignancy.

Physical examination showed an alert, obese man in no distress. BP, 102/76 mm Hg; pulse, 115; temperature, 36.8°C; and oxygen saturation, 96% on room air. Positive examination findings were limited to two enlarged lymph nodes in the right inguinal area and bilateral lower extremity edema. Laboratory test results on admission are shown in Table 1.

Three days after initiating chemotherapy with rituximab, cytarabine, cisplatin, etoposide and methylprednisolone, he developed non-oliguric renal failure, hyperkalemia, hyperphosphatemia, and hypoxia with arterial oxygen saturations as low as 86%. Rasburicase was given for hyperuricemia, unresponsive to allopurinol. Ventilation/perfusion lung scan, chest x-ray, pulmonary function testing, EKG and echocardiogram were unremarkable. Oxygen saturation normalized with nasal oxygen. Thereafter, his mild anemia acutely worsened and he passed cranberry-colored urine, not accompanied by flank or suprapubic pain.

Table 1 lists serial laboratory values. Urinalysis was negative for red cells but strongly positive for hemoglobin. Stool hemoccult, prothrombin time, partial thromboplastin time and myoglobin assay were all normal. The absolute

reticulocyte count was not elevated. An increase in total and indirect bilirubin, elevated LDH and low haptoglobin level (<10%) were temporally related to the fall in hemoglobin and hematocrit. The polyspecific direct antiglobulin tests and red cell alloantibody screen were negative. Typical blister cells were noted on the peripheral blood smear (Figure 1). G6PD assay was normal.

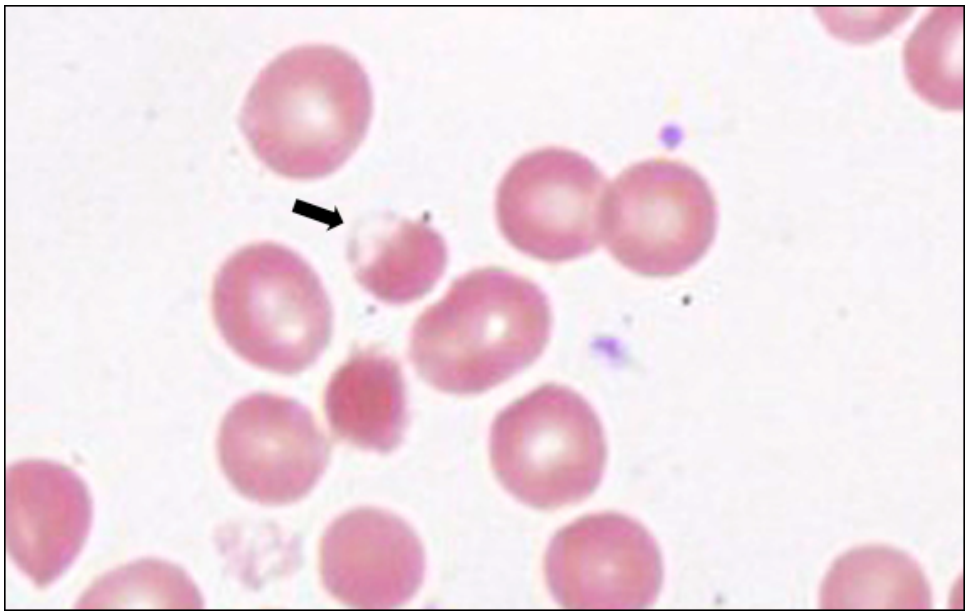

Figure 1. Peripheral blood smear, Wright stain, x1000. (The arrow indicates a blister cell,)

He was weaned from nasal oxygen without difficulty, and hypoxia did not recur during the remainder of the hospitalization. Transfusion of three units of crossmatch-compatible packed RBCs was uneventful. Urine color returned to normal within 3 days, and hemoglobin and hematocrit stabilized at pre-admission levels. Serum creatinine improved, but did not return to pre-admission levels. He was discharged following a period of chemotherapy-associated febrile neutropenia and thrombocytopenia.

As an outpatient one month later, his hemoglobin was 8.9 g/dL, hematocrit 28%, and reticulocyte count, 126.8 K/µL. Repeat quantitative G-6PD level was decreased at 3.8 U per gram hemoglobin (normal range, 4.6-13.5 U per gram of hemoglobin) confirming G6PD deficiency. A review of his hospital medication schedule confirmed that rasburicase had been administered on hospital day 3, two days prior to the fall in hemoglobin (Figure 2).

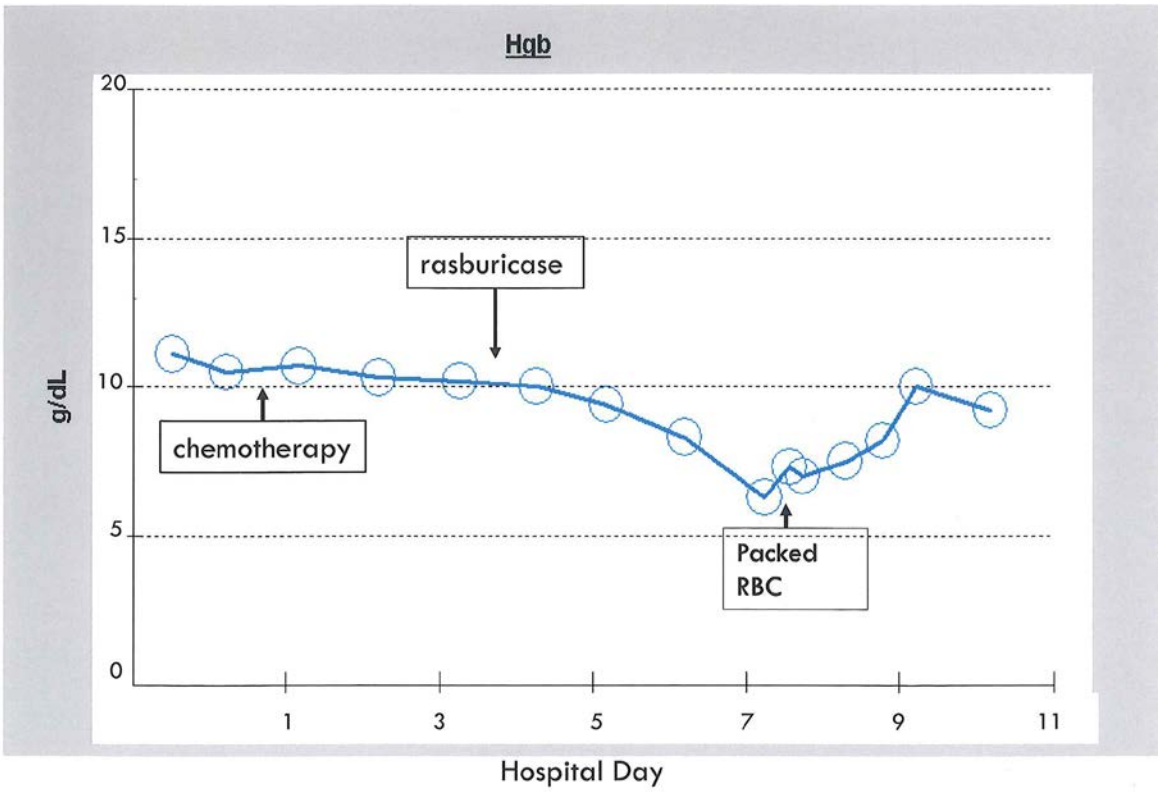

Figure 2. Serial hemoglobin values and relationship to rasburicase administration

Retrospective analysis of archived arterial blood gas data (Table 1) collected during the patient's episode of hypoxia showed a transient elevation of methemoglobin to 5.6% of total hemoglobin (normal range, 0-3%) on day 7, which temporally correlated with the occurrence of hemoglobinuria and arterial hypoxia. By day 9, methemoglobin level had decreased to 3.8%.

Table 1. Serial laboratory values on admission (Adm) and on days following initiating treatment for recurrent lymphoma

Laboratory values (reference range)	*Adm*	*Day 3*	*Day 7*	*Day 9*	*Day 32*
Hemoglobin, g/dL (13-17)	11.1	10	6.3	7.5	8.9
Hematocrit % (39-48)	35.9	30.8	19.8	22	27.5
Reticulocytes, 10^3/μL (16.7-96.7)			17.7		126.8
Total bilirubin, mg/dL (0.2-1.3)	0.4		3.3	3.7	
Direct Bilirubin, mg/dL (0.2-0.9)			0.6	1.0	
Lactic dehydrogenase, U/L (313-618)	470		1761		
Haptoglobin, mg/dL (30-200)			<10		
Direct antiglobulin test (neg.)					
Urinary hemoglobin (neg.)					
Urine microscopic:		neg.	neg.		
RBCs per high power field (0-4)		0-4	large		
WBC per high power field (0-4)		0-4	0-4		
Erythrocyte G6PD, U/G hgb (4.6-13.5)			5-9	5.6	3.8
RBC antibody screen (neg.)			neg.		
Creatinine, mg/dL (0.7-1.3)	1.38	2.31	3.04		2.28
Phosphorus, mg/dL (2.5-4.5)	3.8	6.9	6.2		
Uric acid, mg/dL (3.5-8.5)	9.0	9.3	2.7		
Prothrombin time, secs. (12-14.2)	14			11.8	
Partial thromboplastin time, secs. (23-35)	30				
Fibrinogen, mg/dL (208-435)				634	
Arterial oxygen saturation %			(Room air) 89%	(2L/min) 100%	
Arterial blood gases			(Room air)		
pH unit (7.35-7.45)			7.48		
$p0_2$ mm hg (83-108)			65		
$pC0_2$ mm Hg (35-48)			47		
HCO_3 mmol/L (21-28)			35		
Methemoglobin, % of total hgb (3-6)			6	3.6	

3. Discussion

During the week following the initiation of chemotherapy for recurrent, bulky follicular lymphoma this patient developed tumor lysis syndrome, then intravascular hemolysis and methemoglobinemia. His past history of anemia, ethnic background, acute intravascular hemolysis, and the presence of blister cells on peripheral blood smear led to the suspicion of occult G6PD deficiency. This diagnosis was confirmed one month following the hemolytic event. Rasburicase given 3 days before the onset of intravascular hemolysis appears to have been the oxidant trigger for the hemolysis.

Congenital deficiency of erythrocyte G6PD affects an estimated 400 million individuals worldwide, with a higher prevalence among African, Mediterranean and Asian populations. The disease is inherited as an x-linked disorder with a spectrum of erythrocyte enzyme deficiency from moderate (40-60% of normal) to severe (<10% of normal) [1]. The clinical course of the disorder also varies depending primarily on the degree of enzyme deficiency—asymptomatic state, episodic hemolysis, or chronic hemolytic disease [2]. Normal levels of erythrocyte G6PD are required to ensure an adequate supply of NADPH and reduced glutathione, which are required for the elimination of intracellular oxidation products by the glucose monophosphate shunt. When present in excess amounts oxidants such as hydrogen peroxide denature globin forming Heinz bodies, which attach to the red cell membrane. These erythrocyte inclusions target the defective erythrocytes for removal in the spleen. Increased formation of methemoglobin accompanies the course of drug induced hemolysis of G6PD deficient cells [3].

It is not uncommon for patients with the milder forms of G6PD deficiency such as the African variety (G6PD A^-) to remain asymptomatic until acute hemolysis occurs unexpectedly during bacterial or viral infection, diabetic ketoacidosis or one to two days following exposure to oxidant agents [1]. Drugs known to cause hemolysis in some but not all patients include primaquine, sulfonamides, dapsone, nitrofurantoin, and the fluroquinolones. Treatment of hyperuricemia with rasburicase [4] has more recently been identified as being unsafe for use in patients with known G6PD deficiency [5,6,7]. An extensive list of drugs, chemicals and food substances to be avoided or used with caution in affected individuals is available for physicians and their patients [8].

In the common G6PD A^- deficiency state, older erythrocytes with decreased G6PD content are destroyed while the younger reticulocytes containing normal concentrations of the enzyme are resistant to hemolysis [3]. For this reason, screening tests for G6PD deficiency will frequently be normal during active hemolysis. As in our patient, the deficiency state usually cannot be established until hemolysis has ended and a stable RBC population containing sufficient numbers of both older and younger red cells is restored in the circulating blood.

4. Conclusion

Physicians should be aware of the potential for patients with previously undiagnosed G6PD deficiency to develop acute intravascular hemolysis and methemoglobinemia when oxidant drugs such as rasburicase are administered. In the absence of an assay that can confirm the deficiency state during the acute hemolytic phase, the provisional diagnosis rests on careful review of clinical and demographic data.

Disclosure

All authors certify that they have no competing interests or financial relationships associated with the subject matter or therapies discussed in this report.

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