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Case Report

Tumor lysis syndrome and acute anemia in an African-American man with chronic lymphocytic leukemia

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Tumor lysis syndrome (TLS) is a life-threating hematologic emergency caused by massive lysis of tumor cells into the blood stream. TLS can be prevented and treated with rasburicase. Rasburicase-induced hemolysis and methemoglobinemia is a rare but serious complication. Screening for G6PD should be considered for patients at higher risk for G6PD deficiency who may be also at high risk for TLS on the basis of clinical parameters. G6PD level in G6PD-deficient patients may be normal during an acute hemolytic episode and may not help to clarify the diagnosis at the time of presentation. The characteristic peripheral blood smear findings of 'bite' and 'blister' cells representing oxidative damage to red blood cells can help to quickly establish the diagnosis of G6PD deficiency-related hemolysis. The treatment of an acute hemolytic episode in a patient with G6PD deficiency requires avoiding the source of oxidative stress and using transfusion support as needed.

INTRODUCTION

Tumor lysis syndrome (TLS) is a hematologic emergency caused by massive lysis of tumor cells into the blood stream. It is characterized by hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia and development of uric acid nephropathy, oliguria, acute kidney injury (AKI) and, in severe cases, seizures, cardiac arrhythmias and death. TLS is typically associated with rapidly proliferating lymphoid neoplasms such as high-grade non-Hodgkin lymphomas (particularly Burkitt lymphoma) and acute leukemias with white blood cell (WBC) counts of over 100 000/μl, although uncommon it may also be seen in chronic lymphocytic leukemia (CLL) treated with chemoimmunotherapy and occasionally in solid tumors, such as small cell lung cancer or testicular cancer [1].

The diagnosis of TLS is based on consensus recommendations put forth by Cairo and Bishop [2]. Laboratory TLS (LTLS) is defined as two or more of the above-mentioned metabolic abnormalities occurring within 3 days before or up to 7 days after the initiation of therapy, whereas clinical TLS is defined as LTLS plus AKI, seizures, cardiac arrhythmias or death. Patients are classified as low, intermediate or high risk for TLS based on tumor characteristics (e.g. tumor aggressiveness and stage) and patient characteristics including renal impairment at the time of TLS diagnosis [3].

Here, we report a case of severe TLS, complicated by the development of hemolytic anemia.

CASE REPORT

A 72-year-old African-American man with CLL and chronic kidney disease presented to the hematology clinic with AKI and hyperuricemia 4 days after initiation of chemotherapy with bendamustine and rituximab (BR). He had been diagnosed with Rai Stage 1 CLL 5 years earlier and was successfully treated with BR. He was followed expectantly for the next few years, then 1 month prior to the current presentation he developed drenching night sweats, progressive lymphadenopathy and a surge in lymphocyte count, with a WBC count that increased from a baseline of 10 700/μl to 31 200/μl (normal 4000−10 000/μl), and a hemoglobin that remained at his baseline value of 10 g/dl. He was retreated with BR, then 4

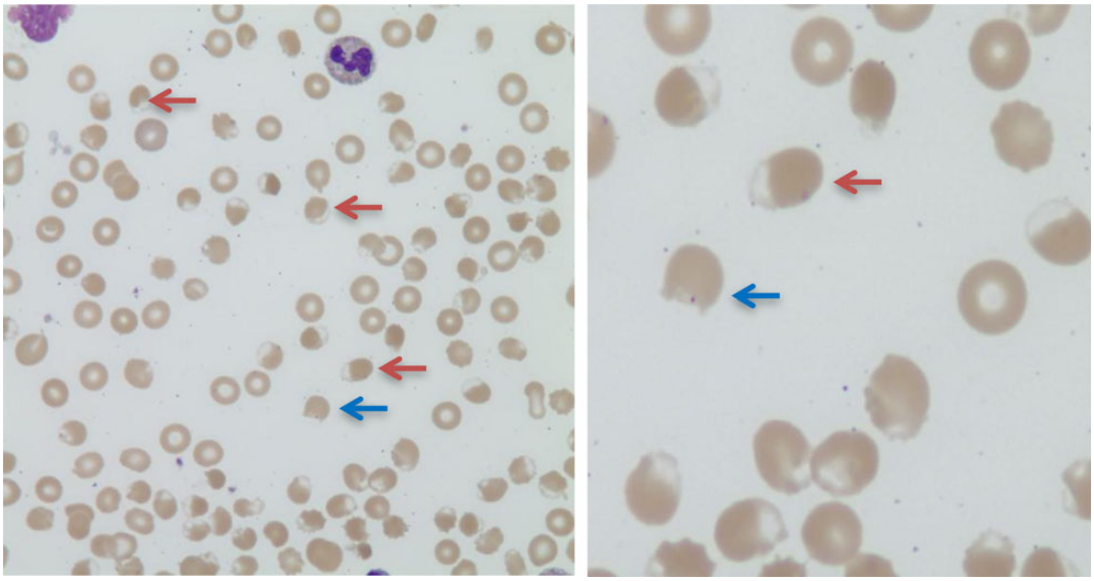

Figure 1: Peripheral blood smear (Wright–Giemsa stain); red and blue arrows point to representative 'blister' and 'bite' cells, respectively.

days later had laboratory studies that showed a creatinine of 2.3 mg/dl (baseline, 1.7 mg/dl), uric acid of 13 mg/dl (normal, 3.5–7 mg/dl), potassium of 5.8 mmol/l (normal, 3.5–5 mmol/l), phosphorus of 8.5 mg/dl (normal, 2.5–4.5 mg/dl), calcium of 7.2 mg/dl (normal, 7.8–10.2 mg/dl) and lactate dehydrogenase (LDH) of 702 U/l (normal, 118–242 U/l). He was diagnosed with clinical TLS and was hospitalized for further treatment.

He received intravenous fluids, allopurinol and a single dose of 6 mg of intravenous rasburicase, with normalization of his uric acid level by the next day, and return of his electrolytes and creatinine to baseline levels. However, 2 days after admission, his hemoglobin dropped from 10 to 5.8 g/dl and he developed dark brown urine. Fecal occult blood testing was negative. His LDH rose to 1290 U/l (normal, 118–242 U/l); haptoglobin level was undetectable, reticulocyte count 1.9%, total bilirubin 6.29 mg/dl (normal, <1.2 mg/dl) and direct bilirubin 0.28 mg/dl (normal, <0.20 mg/dl). Direct antiglobulin test was negative. His peripheral blood smear revealed numerous 'blister' cells (Fig. 1, red arrow) and a few 'bite' cells (Fig. 1, blue arrow). G6PD deficiency was immediately suspected based on the blood smear morphology.

He received 11 units of packed red blood cell (RBC) transfusion over a 1-week period, with eventual resolution of hemolysis. His G6PD level measured during that time was 10 IU/g Hb (normal, 6–11 U/g Hb), whereas his methemoglobin level was 5.6% (normal, <2%). Four months later, a repeat G6PD level was low at 2 IU/g Hb, confirming the diagnosis of G6PD deficiency.

DISCUSSION

G6PD deficiency is the most common enzymatic deficiency of RBCs. It is an X-linked disorder with more than 300 variants identified. G6PD deficiency is largely seen in patients of African, Mediterranean or Southeast Asian descent, with ~10% of African-American males in the USA affected [4]. Most patients with G6PD deficiency have only moderate enzyme deficiencies and are asymptomatic; however, under oxidative stress induced by illness, medications or ingestion of fava beans, massive hemolysis can occur. G6PD levels in G6PD-deficient patients are often normal during an acute hemolytic episode, as most RBCs with low G6PD levels are hemolyzed while reticulocytes or transfused RBCs will have normal G6PD levels. Methemoglobin, a byproduct of oxidant damage to hemoglobin, may be a more useful laboratory marker of oxidant injury in the acute setting. The treatment of an acute hemolytic episode of G6PD deficiency includes transfusion support and withdrawal of the offending medication. Methemoglobinemia can result in cyanosis when methemoglobin level rise to the range of 8–12%, causing an oxygen saturation gap, with preserved saturation as gauged by pulse oximetry, but decreased saturation by arterial blood gas measurement [5]. While methylene blue may be effective in treating methemoglobinemia from a variety of causes, patients with G6PD deficiency lack nicotinamide adenine dinucleotide phosphate to reduce methylene blue, therefore using it may worsen hemolysis. Ascorbic acid has been used in a few cases to treat methemoglobinemia in G6PD-deficient patients [6]. Outpatient had mild methemoglobinemia and treatment was not warranted.

The approach to hemolytic anemia in general relies on a number of clinical and laboratory findings, including the presence or absence of jaundice or urinary discoloration, measurements of bilirubin and haptoglobin levels, and direct Coombs test, all of which allow for categorization of a hemolytic crisis as intravascular or extravascular and as immune- or non-immune-mediated (Table 1). A central aspect of this evaluation is the peripheral blood smear, as specific RBC

Table 1: Classification of hemolytic anemia

Immune-mediated hemolytic anemia
Transfusion reactions
Idiopathic autoantibodies
Drug-induced: e.g. methyldopa, penicillin G, sulfonamides, 6-mecaptopurine, rifampin
Connective tissue disease: e.g. systemic lupus erythematosus
Non-immune-mediated hemolytic anemia
Hereditary RBC membrane defects: spherocytosis, elliptocytosis
Paroxysmal nocturnal hemoglobinuria
RBC enzyme deficiencies: e.g. glucose-6-phosphate dehydrogenase deficiency; pyruvate kinase, hexokinase, glutathione synthetase deficiency
Sickle cell anemia
Thalassemia
Microangiopathic hemolytic anemia
Malaria, babesiosis

morphologies will be seen with different types of hemolysis. The finding of 'blister' and 'bite' cells on peripheral blood smear is the key to diagnosis of G6PD deficiency during an acute hemolytic episode. These represent oxidatively damaged RBCs that, during the process of migrating from splenic cords to sinusoids, are too rigid to traverse interendothelial pores one-fifth the size of the RBC diameter and therefore lose portions of their cell membrane, leading to formation of a bite defect or a surface vesicle [7].

Rasburicase, a recombinant urate oxidase, is a rare but well-reported cause of hemolysis and methemoglobinemia, occurring in $<1\%$ of all patients who receive the drug [8, 9]. The incidence of these complications is higher in patients with G6PD deficiency than in normal patients due to decreased tolerance to oxidative stress [10]. Screening for G6PD should be considered for patients at higher risk for G6PD deficiency (e.g. African-Americans) who may be also at high risk for TLS and thus may require rasburicase treatment.

Conflict of interest statement

Dr Alfred Ian Lee is a consultant for Pfizer.

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