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Clinical Review

THE ACUTE HEMOLYTIC ANEMIAS: THE IMPORTANCE OF EMERGENCY DIAGNOSIS AND MANAGEMENT

Jennifer J. Robertson, MD, MSED,* Elizabeth Brem, MD,† and Alex Koyfman, MD‡

*Emory University School of Medicine, Atlanta, Georgia, †UC Irvine Health Chao Family Comprehensive Cancer Center, Orange, California, and ‡University of Texas-Southwestern, Parkland Hospital, Dallas, Texas

Reprint Address: Jennifer J. Robertson, MD, MSED, Emory University School of Medicine, 3645 Habersham Road NE, #T19, Atlanta, GA 30305

□ **Abstract—Background: Hemolytic anemias are defined by the premature destruction of red blood cells. These anemias have many causes that are mostly due to chronic diseases, but, occasionally, cases of acute life-threatening hemolysis can occur. Objective: The objectives of this article were to review the pathophysiology of hemolytic anemias, to discuss the general emergency department (ED) evaluation, and to discuss the assessment and treatment of important and "cannot miss" hemolytic diseases. Discussion: Because hemolytic anemias are rarely seen, the emergency physician may consider a patient's anemia as due to blood loss rather than hemolysis, and the workup and treatment may not be appropriate. The primary goal for the emergency provider is to resuscitate, but he or she also must recognize that a hemolytic process is present. Appropriate laboratory work and specialist consultation should be obtained. While focused treatment is rarely necessary in the ED, the avoidance of certain treatments, such as early platelet transfusion in thrombotic thrombocytopenic purpura, may be necessary. Conclusions: Hemolytic anemias are rare, but should still be considered in the ED differential diagnosis of low hemoglobin. Emergency physicians should first resuscitate, but should also be able to identify the presence of hemolysis and obtain the appropriate laboratory tests. Occasionally, specific treatments are needed but should be discussed in conjunction with a specialist.**

□ **Keywords—hemolysis; anemias**

INTRODUCTION

A 35-year-old female presents to the emergency department (ED) with a 2-day history of fatigue, generalized weakness, dark urine, and mild jaundice. She denies chest pain, difficulty breathing, vaginal bleeding, or any recent illnesses. She denies taking any new medications. The patient states that these symptoms have not occurred before, although there is a family history of systemic lupus erythematous and rheumatoid arthritis. Her vital signs demonstrate a heart rate of 120 beats/min, blood pressure of 90/60 mm Hg, and temperature of 100.4°F. Laboratory testing shows a hemoglobin of 6.5 g/dL and elevated indirect bilirubin. What is the differential diagnosis? What other tests should be ordered and what initial treatments are recommended?

Anemia, defined as a decreased red blood cell (RBC) mass, is a common disease that affects nearly one-quarter of the population worldwide (1,2). Overall, anemia can be categorized as acute or chronic (3,4). Many patients with chronically low hemoglobin values are hemodynamically stable, asymptomatic, and frequently are seen in the ED for unrelated issues. Not every patient with anemia will require evaluation or intervention. The most pressing concerns for the emergency physician are the acute anemias due to blood loss or hemolysis that can cause immediate, life-

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threatening complications (4). A primary goal in the ED is resuscitation, but recognizing the acute anemia and whether it is due to blood loss or hemolysis is imperative because evaluation and treatment differ.

Hemolytic anemia is caused by the premature destruction of RBCs (5). Under normal conditions, the RBCs are in circulation approximately 120 days and then are destroyed via the mononuclear phagocyte system (3,6). However, when a patient has a hemolytic anemia, RBCs are prematurely destroyed via either extravascular or intravascular hemolysis (3,4,6).

DISCUSSION

Extravascular Hemolysis

Pathologic extravascular hemolysis occurs when RBCs are prematurely removed by macrophages in the liver, spleen, or bone marrow due to abnormal shape or binding of an antibody (3,7). The presence of spherocytes on a blood smear denotes extravascular hemolysis (4,5). Extravascular hemolysis is usually better tolerated by patients and tends to demonstrate mild to moderate anemia and mild enlargement of the spleen (7). Examples of conditions that cause extravascular hemolysis include RBC membrane abnormalities such as hereditary spherocytosis, RBC enzyme abnormalities such as glucose-6-phosphate dehydrogenase deficiency (see Table 1), hemoglobinopathies such as sickle cell disease, some autoimmune hemolytic anemias, and hypersplenism (6,8). This is not an exclusive list and, of note, some of these disorders can also undergo intravascular hemolysis (4).

Intravascular Hemolysis

Intravascular hemolysis can present more acutely and severely than extravascular hemolysis and can be more devastating to the patient (4,9). When intravascular hemolysis occurs, hemoglobin is released into the circulation. Free hemoglobin initially binds to haptoglobin and hemopexin, forming a complex that is then transported to the liver. Here, the complex is conjugated to bilirubin and excreted. With large amounts of intravascular hemolysis, the binding system can become saturated and free hemoglobin can appear in the bloodstream and urine, leading to hemoglobinemia and hemoglobinuria (4,10). A marker of intravascular hemolysis on a peripheral blood smear is the schistocyte (5). In addition, one should only see hemoglobinuria with intravascular hemolysis (11).

Examples of causes of rapid intravascular hemolysis include mechanical trauma from prosthetic heart valves, disseminated intravascular coagulation (DIC), toxins such as the brown recluse spider venom, infections such as malaria, ABO incompatibility reactions, paroxysmal nocturnal hemoglobinuria, and autoimmune hemolytic anemias (3,4). Similar to extravascular hemolysis, chronic disorders such as chronic renal failure can present as an acute hemolytic anemia if the balance between RBC production and destruction is acutely upset (4).

Table 1. Medications/Exposures That Cause Hemolysis in Glucose-6-Phosphate Dehydrogenase Deficiency

Trimethoprim/ Sulfa (Bactrim)	Aniline Dyes
Nitrofurantoin	Naphthalene (mothballs, deodorizers)
Phenazopyridine	Henna
Dapsone	Fava beans
Primaquine	
Rasburicase	

Presentation, History, and Physical Examination

It may be difficult to determine whether a patient is presenting with intravascular or extravascular hemolysis by clinical presentation alone (6). Both intravascular and extravascular hemolytic anemias can present with similar symptoms. Emergency physicians should consider hemolysis in the differential when a patient presents with signs or symptoms of anemia such as fatigue, tachycardia, pallor, shortness of breath, or chest pain (1,3,5). More specific symptoms concerning for an acute hemolytic process can include new-onset jaundice, dark-colored urine, fever, abdominal pain, back pain, and altered mental status (3–5,9).

If hemolysis is a concern, the review of systems should include questions about changes in the color of their urine or feces, recent bleeding or trauma, fever, malaise, night sweats, or other systemic symptoms. Medical history is important and should specifically address whether there is a history of connective tissue disease, renal failure, malignancy, or prosthetic heart valve placement. Patients should be asked about a family history of anemia or jaundice. Physicians should inquire whether these symptoms have ever happened before and whether patients have recently started a new medication (1,4).

The physical examination should initially be focused on vital signs (4). After initial stabilization of any hemodynamic instability, the rest of the examination should include evaluating for heart murmurs consistent with prosthetic heart valves, hepato- or splenomegaly, signs of liver disease such as ascites, lymphadenopathy, and skin changes such as purpura or petechiae (1,4). Lymphadenopathy may suggest a lymphoproliferative disease, while petechiae or bruising may suggest concomitant thrombocytopenia, which can help narrow