CLINICAL PRACTICE

Clinical Vignettes

Intravascular Hemolysis Secondary to Aorto-atrial Fistula Presenting as Red Urine

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Intravascular hemolysis is a rare but potentially life threatening cause of red urine characterized by brisk hemolysis and release of large amounts of hemoglobin into the urine. We present an unusual case of red urine in a 20-year-old male who was subsequently diagnosed with intravascular hemolysis due to an aorto-atrial fistula. Fistula formation was likely secondary to a recently implanted atrial septal occluder, which is a reported but exceedingly rare complication of the device. We discuss the diagnostic approach to hemolytic anemia and conclude with a literature review of other cases of device associated fistula formation and hemolysis.

KEY WORDS: Amplatzer septal occluder; fistula; hemolysis; complication.

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INTRODUCTION

Red urine is a common presenting complaint and is typically a result of hematuria. The differential diagnosis is vast and includes infections, stones, benign and malignant neoplasm, glomerular disease, trauma, and transient idiopathic hematuria. Red urine in the absence of urinary erythrocytes is an important clinical entity possibly due to medications, foods, porphyria, myoglobinuria, and hemoglobinuria. Hemoglobinuria secondary to intravascular hemolysis is a rare but potentially life threatening cause of red urine that necessitates urgent investigation to determine its etiology.

We present an unusual case of intravascular hemolysis due to a cardiac device related aorto-atrial fistula presenting as red urine. We present a diagnostic approach to hemolytic anemia and a literature review of other cases of device associated fistula formation and hemolysis.

CASE REPORT

A 20-year-old university student presented to the hospital with a five-day history of reddish brown urine. He was otherwise asymptomatic. His past medical history included a congenital

atrial septal defect (ASD) for which he underwent an uncomplicated percutaneous closure with an Amplatzer Septal Occluder 3 weeks prior to presentation. Post-procedure echocardiogram confirmed normal placement of the device. Two weeks after the procedure, he required cardioversion for new onset symptomatic atrial fibrillation, which was felt to be on the basis of post-procedural myocardial irritability. His only medication was aspirin 325 mg daily, which was started after ASD closure.

On examination, he was not in distress and vital signs were stable. Cardiac examination revealed a S1, S2 with fixed splitting, no S3 or S4, and a new systolic ejection murmur 2/6 loudest over the pulmonic area. Jugular venous pressure (JVP) was not elevated and the remainder of the examination was normal.

Initial laboratory investigations revealed an acute rise in creatinine to 1.57 mg/dL from 1.30 mg/dL one week prior (Normal 0.70-1.36 mg/dL), blood urea nitrogen 22.12 mg/dL (Normal 7-19.6 mg/dL), an acute hemoglobin drop to 12.4 g/dL from 15.6 g/dL one week ago (Normal 13.5-17 g/dL), and a borderline thrombocyte count of 149,000/uL (Normal 150,000-400,000/uL). A urine dipstick performed in the emergency department showed hemoglobin 3+, protein 3+, nitrite +, and leukocyte 3+. Urine microscopy was negative for red blood cells, casts, or bacteria and urine culture failed to grow an organism.

Further investigations revealed evidence of hemolysis, with an increased reticulocyte count of 108,000/uL (Normal 10,000-100,000/uL), lactate dehydrogenase (LDH) of 1780 U/L (Normal 91-180 U/L), total bilirubin 1.87 mg/dL (Normal 0.20-1.0 mg/dL), haptoglobin <7 mg/dL (Normal 26-226 mg/dL), and negative urine hemosiderin and direct antiglobulin test. Blood smear was ordered twice but unfortunately not performed. Creatine kinase (CK) was normal. CXR revealed an occluder device in place with no other acute abnormalities (Fig. 1) and the electrocardiogram was unremarkable.

Given the results of the investigations, the patient was diagnosed with hemoglobinuria secondary to intravascular hemolysis complicated by heme pigment nephropathy. Given his cardiac history and new murmur, an urgent trans-esophageal echocardiogram (TEE) was arranged which revealed an ASD (8 mm) at the inferior aspect of the atrial occluder device with left to right shunt. An aorto-atrial fistula connecting the non-coronary sinus of Valsalva to the right atrium with high velocity turbulent flow (4.0 m/s) was also identified (Fig. 2).

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Figure 1. Chest x-ray at presentation to the emergency department. Arrow denotes position of ASD occluder device.

The patient was urgently transferred to cardiac surgery for surgical explanation of his ASD occluder device, patch closure of his ASD, and fistula repair. He had an uncomplicated operative course and achieved full recovery.

DISCUSSION

Red urine is a common presenting complaint and the work up for it must differentiate true hematuria from other causes. The traditional initial work up of red urine involves centrifugation of a urine specimen. Presence of red sediment confirms true hematuria whereas red supernatant suggests hemoglobinuria, myoglobinuria, or other causes. However, since many laboratories do not report on the color of the

supernatant or sediment when performing centrifugation prior to urine microscopy, this approach requires the clinician to personally spin down the urine. This is a time consuming process and requires the clinician to have access to a centrifuge.

Instead, we propose an alternate diagnostic approach that does not require personal access to a centrifuge (Fig. 3). The initial evaluation should involve urine dipstick for hemoglobin and urine microscopy for red blood cells. Dipstick negative red urine yields a limited differential diagnosis consisting of foods, medications, and porphyria. Among dipstick positive red urine, routine urine microscopy available at most labs allow for the differentiation between true hematuria and hemoglobinuria or myoglobinuria. In our case, urine dipstick for blood was positive, urine microscopy was negative for red blood cells, and hemolysis work up was positive resulting in a diagnosis of hemoglobinuria.

Figure 2. Trans-esophageal ECHO demonstrating ASD and aorto-atrial fistula (RA right atrium, LA left atrium, ASD atrial septal defect).

Figure 3. An approach to red urine.

Hemolytic anemia can be classified based on etiology (Table 1). Intrinsic causes, which are usually hereditary in nature, include cell membrane defects, enzyme deficiencies, and hemoglobinopathies. Extrinsic causes, which represent extracorporeal pathologies, are numerous and are generally acquired. Hemolytic anemia can also be differentiated into intravascular and extravascular causes. In reality, a relative degree of intravascular and extravascular hemolysis may coexist within a single patient. Thus, the dichotomous distinction between intravascular and extravascular hemolysis is artificial and hemolysis should instead be viewed as a spectrum with intravascular and extravascular hemolysis at opposing ends. However, the importance of recognizing significant intravascular hemolysis is in its limited differential diagnosis, which includes microangiopathic hemolytic anemia, valvular and other intracardiac devices, acute transfusion

reactions, severe burns, and paroxysmal nocturnal hemoglobinuria.

The laboratory evaluation of hemolysis should include reticulocyte count and smear as a first step. The smear may be helpful in distinguishing intravascular hemolysis from extravascular hemolysis, since intravascular hemolysis is associated with schistocytes, while spherocytes are characteristic of extravascular hemolysis. Other laboratory investigations, including bilirubin, LDH, haptoglobin, plasma free hemoglobin, urine hemosiderin and hemoglobin confirm the presence of hemolysis and help differentiate between intravascular and extravascular hemolysis (Table 2). Further testing such as direct antiglobulin test, cold agglutinin, hemoglobin electrophoresis, platelet count, INR/PTT, fibrinogen and d-dimer are guided by the clinical picture and help to determine the cause of hemolysis.

Table 1. Etiology of Hemolytic Anemia ¹

Mechanism		Examples
Intrinsic	Enzyme deficiency	Pyruvate kinase deficiency, G6PD
	Hemoglobinopathy	Sickle cell, thalassemia
	Membrane defect	Hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria
Extrinsic	Immune	Autoimmune, transfusion reaction, drugs (eg, dapsone)
	Traumatic	Microangiopathic hemolytic anemia, cardiac devices/valves, burns
	Toxin/Infection	Malaria, clostridial sepsis, snake and spider bites, hypotonic solutions
	Sequestration	Hypersplenism

Table 2. General Laboratory Findings in Hemolytic Anemia

	Intravascular	Extravascular
Reticulocyte	↑	↑
Bilirubin (unconjugated)	↑	↑
LDH	↑↑	↑
Haptoglobin	↓↓	↔/↓
Plasma free hemoglobin	↑↑	↔/↑
Urine hemosiderin	+	–
Urine hemoglobin	+	–
Fibrinogen	↔/↓ ^a	↔
d-Dimer	↔/↑ ^a	↔
INR	↔/↑ ^a	↔

Legend: ↑ increased, ↑↑ significantly increased, ↔ normal, ↓ decreased, ↓↓ significantly decreased, + positive, – negative ^aDepending on the cause of hemolysis

Figure 4. Schematic drawing of the base of the heart showing how a rigid atrial septal defect device placed in the superior-anterior atrial septum could impinge on the aortic root resulting in the formation of a fistula. (ANT = anterior; Circ. = circumflex; LA = left atrium; LAD = left anterior descending artery; LV = left ventricle; LCC = left coronary cusp; LMCA = left main coronary artery; MV = mitral valve; NCC = noncoronary cusp; POST = posterior; RA = right atrium; TV = tricuspid valve; RCA = right carotid artery; RCC = right coronary cusp; RV = right ventricle).¹¹

With intravascular hemolysis, free release of hemoglobin into the blood stream occurs, which is readily bound by haptoglobin causing a decrease in this serum protein. As hemolysis continues, the binding capacity of haptoglobin is saturated and free plasma hemoglobin can be detected. Free hemoglobin is then filtered by the kidney and resorbed by the proximal tubule, which catabolizes hemoglobin to hemosiderin. This can be detected in the urine 5–7 days later when renal tubular cells are sloughed off by staining the urine sediment with Prussian blue². In our case, the urine hemosiderin was negative and this was likely a result of the delay phenomenon as our sample was drawn on day 5. With brisk intravascular hemolysis, the resorptive capacity of the kidney is overwhelmed and urine hemoglobinuria is seen. With extravascular hemolysis, the hemolytic process occurs within the reticuloendothelial system, which is able to metabolize the degradation products more efficiently. Since fewer degradation products are released into the circulation in extravascular hemolysis, the laboratory changes are of a lesser magnitude and urine hemosiderin and hemoglobin are negative (Table 2).

In the case of our patient, initial blood work revealed a pattern consistent with brisk intravascular hemolysis. Given his significant cardiac history, a cardiac cause of intravascular hemolysis was suspected. The recurrence of his ASD and the development of an aorto-atrial fistula with turbulent flow seen

on trans-esophageal echocardiography were the likely cause of his hemolysis.

Aorto-atrial fistulas are a rare but reported complication of ASD closure with the Amplatzer septal occluder. Since receiving Food and Drug Administration (FDA) approval in the United States for the closure of ostium secundum ASDs in 2001, over 30,000 devices have been implanted worldwide with only eight case reports of aorto-atrial fistulas^{3–10}. Three patients presented with asymptomatic continuous murmurs^{4,7,8}, three on routine echocardiograms^{3,5,9}, one with hemolytic anemia⁶, and one incidentally while undergoing cardiac surgery for a different reason¹⁰. Six cases required surgical repair, one closed spontaneously, and one was closed percutaneously. Although the precise etiology remains unknown, it has been postulated that fistula formation is secondary to erosion of the right or left atrial rims of the occluding device through the atrial wall into the aorta (Fig. 4). Risk factors for device erosion include overstretching during balloon sizing, oversizing of the occluder device and the presence of a deficient aortic and/or superior rim. All of these factors increase the likelihood of contact between the rims of the occluder and the atrial wall¹². Contact between the occluder rims and the atrial wall promotes erosion through the wall, which can result in a hemopericardium, if the communication is with the pericardial space, or an aorto-atrial fistula, if the communication is with the aorta.

Compared to previous case reports, our case is unique because of the potential role of cardioversion in precipitating fistula formation. In our case, since the occluder was confirmed to be ideally positioned by a post-procedural echocardiogram, we speculate that the cardioversion one week prior to admission likely dislodged the device, resulting in malposition and fistula formation. However, since there have been no prior reports of cardioversion associated dislodgement of occluder devices, its precise role in this case remains uncertain.

The case presented highlights an unusual cause of a common presenting complaint, red urine. Red urine resulting from intravascular hemolysis may be the first sign of a life threatening disease process that requires urgent investigation to determine its etiology. The clinical relevance for readers of this case is recognizing intravascular hemolysis as a rare cause of red urine and to include intracardiac device malfunction in their differential diagnosis (Table 3). Although rare, intracardiac device malfunctions such as this are potentially lethal and therefore important to recognize.

Table 3. Take Home Points

Intravascular hemolysis is a rare cause of red urine that requires urgent investigation to determine its etiology as many causes are life threatening.
Intracardiac device malfunction represents an important etiology of intravascular hemolysis.

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