

Acute kidney injury caused by intravascular hemolysis after mechanical thrombectomy

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SUMMARY

Background A 43-year-old African-American female (*gravid*_{5 para}₀) with an 8-week intrauterine pregnancy presented to the emergency room with crampy abdominal pain, shortness of breath, and shoulder pain. She had normal renal function on admission. CT angiography of the chest revealed bilateral pulmonary emboli; therefore, the AngioJet® (Possis Medical, Inc., Minneapolis, MN) device was used to perform mechanical thrombolysis. The patient subsequently developed hyperkalemia, red urine and anuria.

Investigations Physical examination, measurement of serum creatinine level and electrolytes, dipstick urinalysis and centrifugation of urine and blood.

Diagnosis Acute kidney injury due to hemoglobinuria as a result of non-immune-mediated intravascular hemolysis following the use of a percutaneous mechanical thrombectomy device (AngioJet®).

Management Hydration, alkalization of urine and initiation of hemodialysis (temporarily switched to continuous venovenous hemodiafiltration). Urine output improved after the 20th day of hospitalization, at which point dialysis was discontinued. The patient's renal function completely recovered by day 25.

KEYWORDS acute kidney injury, AngioJet®, hemoglobinuria, intravascular hemolysis, thrombectomy

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the clinical features of pulmonary embolism in a pregnant woman.
- 2 Describe the clinical features of intravascular hemolysis.
- 3 Describe the mechanism of action of the AngioJet®.
- 4 Review the management of acute kidney injury associated with hemolysis.

Competing interests

The authors, the Journal Editor C Harman and the CME questions author D Lie declared no competing interests.

THE CASE

A 43-year-old African-American female (*gravid*_{5 para}₀), with an intrauterine pregnancy of 8 weeks' gestation, presented to the emergency room with crampy abdominal pain, shortness of breath, and shoulder pain. The patient's medical history was notable for hypertension, uterine fibroids, one spontaneous abortion in the first trimester, and three elective therapeutic abortions. She was not taking any prescription medications and had no known drug allergies. The patient's history also indicated that she had smoked one pack of cigarettes per week for 25 years, but she denied alcohol or illicit drug use.

On physical examination, the patient's temperature was 36.0°C, and she had a pulse rate of 118 beats per minute and a blood pressure of 142/87 mmHg. Oxygen saturation was 100% on a nonrebreather mask. The patient was alert

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and oriented to name, place and time but was in visible distress. She was unable to form full sentences and was diaphoretic, with cool extremities. Her jugular venous pressure was elevated to the jaw line. Cardiac examination revealed no murmurs, rubs or gallops. The lungs were clear upon auscultation, and examinations of the abdomen and extremities were unremarkable.

Results from a blood chemistry panel on admission were unremarkable except for a low serum bicarbonate level of 18 mmol/l (Table 1). White blood cell count, hemoglobin and hematocrit were within normal range. A coagulation profile showed a normal prothrombin time, a normal partial thromboplastin time and a normal international normalized ratio. Results from liver function tests were also unremarkable; serum aspartate aminotransferase, serum alanine aminotransferase, serum alkaline phosphatase and total bilirubin levels were all within normal range. A urine toxicology screen was negative and dipstick urinalysis showed +1 protein, +1 ketones, a specific gravity greater than 1.050 and 3 red blood cells per high-power field. Given that the patient had no history of diabetes, the mild elevation of glucose and ketones in the urine could reflect an early gestation-induced diabetic ketoacidosis.

A CT scan of the chest was performed after intravenous administration of contrast agent to reveal any pulmonary embolisms. Large, acute pulmonary emboli were seen in the bilateral main-stem arteries, extending to the subsegmental level (Figure 1), with evidence of right heart strain. A transthoracic echocardiogram showed an ejection fraction of 65–70%, a severely dilated right ventricle, moderately to severely reduced systolic function, and severe hypokinesis. The septum was flattened, consistent with excessive right ventricular pressure and volume overload, and the patient had mild pulmonary hypertension, with a systolic pressure of 42 mmHg.

The patient was admitted to the medicine service and started on an unfractionated heparin drip. During the first day of hospitalization, the patient's blood pressure started to decrease, causing concern about the possibility of hemodynamic instability. The cardiothoracic surgery service was consulted about the use of thrombolytics or surgical intervention to dissolve the emboli. Given the presence of vaginal bleeding and the threat of abortion, the patient was deemed not to be a surgical candidate and thrombolytics were considered to be contraindicated. Accordingly,

Table 1 Results of the patient's blood analysis on admission to the emergency room.

Parameter	Value	Reference range
Serum bicarbonate	18 mmol/l	22–24 mmol/l
Serum sodium	137 mmol/l	135–145 mmol/l
Serum potassium	3.6 mmol/l	3.5–5.0 mmol/l
Serum chloride	106 mmol/l	98–106 mmol/l
Blood urea nitrogen	2.856 mmol/l	7–18 mmol/l
Serum creatinine	97.24 μ mol/l	31–106 μ mol/l
Blood glucose	7.77 mmol/l	3.88–6.10 mmol/l
Total protein	69 g/l	60–84 g/l
Serum albumin	34 g/l	35–50 g/l
Partial thromboplastin time	26.9 s	25–35 s
Prothrombin time	12.5 s	12–15 s
International normalized ratio	0.9	0.8–1.2
White blood cell count	$9.7 \times 10^9/l$	$4.3\text{--}10.8 \times 10^9/l$
Hemoglobin	129 g/l	120–160 g/l
Hematocrit	0.387	0.377–0.487
Platelet count	$221 \times 10^9/l$	$150\text{--}400 \times 10^9/l$

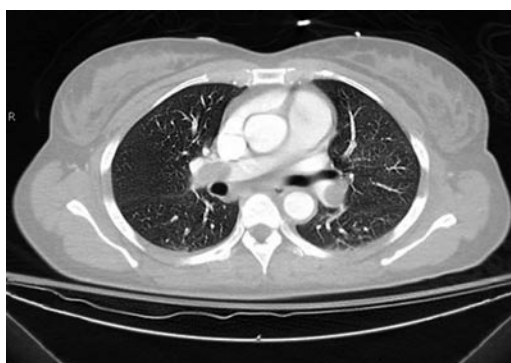


Figure 1 Contrast-enhanced CT of the chest showing pulmonary emboli at the subsegmental level of the right and left pulmonary arteries.

the patient underwent thrombectomy of the right pulmonary artery by use of the AngioJet® (Possis Medical, Inc., Minneapolis, MN) device, as well as inferior vena cava filter placement, on the second hospital day. The thrombectomy procedure was terminated early because of sustained bradycardia, with a lowest recorded heart rate of 42 beats per minute. The thrombectomy procedure was successful as symptoms of shortness of breath resolved. The patient was then transferred to the intensive care unit.

Immediately following thrombectomy, a repeat serum analysis showed a grossly elevated potassium level of 7.8 mmol/l, indicating hemolysis, along with a bicarbonate level of 10 mmol/l, a blood urea nitrogen level of 5.0 mmol/l and a serum creatinine level of 185.6 μ mol/l. The serum potassium value of 7.8 mmol/l was confirmed by repeat measurement, indicating that hyperkalemia was not an artifact caused by hemolysis during blood collection. The patient's serum lactate dehydrogenase level was elevated at 2,094 U/l (reference range 105–333 U/l) and her haptoglobin level was less than 0.5 μ mol/l (reference range 2.7–13.9 μ mol/l). The patient began to exhibit red urine and decreased urine output immediately following thrombectomy. Urinalysis was positive for nitrites, showed a urobilinogen level of 4.0 Ehrlich units, trace levels of protein, a pH of 6.0, +2 blood, +1 ketones, +1 bilirubin, +1 glucose, 17 white blood cells per high-power field and 64 red blood cells per high-power field.

A nephrology consultation was requested for the evaluation and treatment of acute kidney injury (AKI) and hyperkalemia. Centrifugation of a urine sample produced a red supernatant. Dipstick testing indicated that the supernatant was positive for heme, which is consistent with a diagnosis of hemoglobinuria or myoglobinuria. Centrifugation of a blood sample yielded red plasma, consistent with a diagnosis of hemoglobinuria. Alkalinization of the patient's urine was undertaken with intravenous administration of sodium bicarbonate every 6 h along with hydration. The sodium bicarbonate concentration was obtained by dissolving two ampules of sodium bicarbonate (50 mEq each) in 1 l of normal saline, and the resulting solution was administered at a rate of 125 ml per hour. In total, 1 l of the sodium bicarbonate solution was administered. Hemodialysis was initiated to manage the hyperkalemia, and once hyperkalemia had resolved after 3 h, the patient was switched to continuous venovenous hemodiafiltration at a dose of 30 ml/kg per hour. After 48 h of admission, the patient left the intensive care unit, and she returned to hemodialysis (on alternate days), but remained oliguric for the following 20 days. Gradually, however, her urine output improved and hemodialysis was discontinued on day 21, when she exhibited signs of renal recovery. Her serum creatinine level finally returned to normal (1.4 mg/dl) on the 25th day of hospitalization after AngioJet®-mediated thrombectomy.

Spontaneous abortion had occurred on the seventh day of hospitalization and intrauterine evacuation was performed 2 days later to remove any retained products of conception.

DISCUSSION OF DIAGNOSIS

Hemoglobinuria

Intravascular hemolysis of various causes can result in acute tubular necrosis due to hemoglobinuria. Multiple case reports have been published of patients with AKI due to paroxysmal nocturnal hemoglobinuria.^{1,2} To our knowledge, this is the first reported case of AKI that required dialysis as a result of massive intravascular hemolysis following use of AngioJet®. Intravascular hemolysis was indicated by the presence of red urine, a low haptoglobin level, an elevated serum lactate dehydrogenase level, and an elevated urine bilirubin concentration. Bilirubinuria arises in fact when the capacity of the liver to conjugate bilirubin, a product of the physiological degradation of hemoglobin, is overwhelmed and lactate dehydrogenase is released from hemolyzed red blood cells.

Intravascular hemolysis seems to occur in this case via a non-immune-mediated mechanical mechanism. The resulting hemoglobinuria can present as red urine. Centrifugation of urine aids in the differential diagnosis of hemoglobinuria. In cases of hematuria, red cells remain in the sediment and the supernatant appears straw-colored. If the supernatant appears red but is negative for heme upon dipstick testing, the possibility of porphyria or ingestion of beets, food dyes, the bladder analgesic phenazopyridine, or other medications should be explored.^{3,4} If the urine supernatant appears red and is positive for heme on a dipstick test, hemoglobinuria or myoglobinuria are the probable diagnoses.⁵

Centrifugation of blood helps to differentiate hemoglobinuria from myoglobinuria. In patients with hemoglobinuria, the resulting plasma is red or pink, whereas in the case of myoglobinuria, the plasma retains its normal straw-yellow color. The results of centrifugation of urine and blood in combination with low haptoglobin levels (see below) and markedly elevated levels of lactate dehydrogenase confirm the diagnosis of intravascular hemolysis.⁵ Myoglobin is a small monomer (~17,000 kDa) that tends not to bind other proteins and is, therefore, filtered from the blood and excreted rapidly in the presence of normal renal function, so it does not affect the color of plasma. Hemoglobin, on the other

hand, is a larger molecule (~69,000 kDa in its tetrameric form) that binds haptoglobin, and the resulting complex restricts the filtration and excretion of hemoglobin tetramers. Once the plasma concentration of dimeric hemoglobin overwhelms the reabsorptive capacity of the proximal tubule, however—for example, when total serum free hemoglobin concentration exceeds 1.0–1.5 g/l⁶—the dimers are instead filtered and excreted, causing urine to assume a red color. Enzyme-linked immunosorbent assay of serum free hemoglobin can confirm the diagnosis of hemoglobinuria, but it was not absolutely necessary to conduct this assay in the case described here. This highly sensitive assay can be used, however, if subclinical hemoglobinuria is suspected and the centrifuged urine supernatant is only weakly positive or negative for heme.

Hemolysis caused by thrombectomy

Percutaneous mechanical thrombectomy involves the use of specifically designed devices and techniques to clear intravascular thrombi. The rheolytic thrombectomy device AngioJet® is one of the most efficacious techniques available for removing the clots responsible for peripheral arterial thrombosis and occlusions of multiple graft types (i.e. arteriovenous or aortic bypass) through mechanical dissolution, fragmentation and aspiration. Although not FDA-approved for pulmonary embolism, a handful of case reports have shown the effectiveness of AngioJet® in this setting.^{7,8}

AngioJet® works by selectively trapping and destroying thrombi via hydraulic recirculation, whereby a hydrodynamic vortex is created by retrogradely oriented high-speed fluid jets from the tip of the AngioJet® catheter. This vortex results in a stagnant pressure gradient, which traps, solubilizes, and passively evacuates the thrombus.⁹ This process also results in the mechanical lysis of red blood cells.^{7,10,11} Hemolysis following use of AngioJet® has been reported, which in one case (where the device was used to treat portal vein thrombosis) caused transient elevation of the serum creatinine level.¹¹ The Amplatz thrombectomy device uses a similar mechanical approach to that of AngioJet®, by creating a hydrodynamic vortex to dissolve the clot. Nazarian *et al.* have demonstrated the hemolytic effect of Amplatz thrombectomy in dogs and humans.¹⁰ Use of AngioJet® in the setting of pulmonary embolism seems indicated when there is hemodynamic

instability or contraindications to anti-coagulation, both of which applied to the patient under discussion.^{8,9,12,13} AngioJet® has also been used when there is a massive clot burden, in the absence of hemodynamic instability or contraindications to anticoagulation.⁸

Although hemoglobin has a crucial role in the transport of oxygen and removal of carbon dioxide, high amounts of the heme protein can cause oxidative stress, leading to systemic toxicity. The erythrocyte cell membrane acts as a barrier to the proinflammatory effects of hemoglobin's byproducts, such as heme. In addition, several mechanisms to clear the hemoglobin molecule during normal physiological hemolysis have evolved in the human body. For instance, tetrameric hemoglobin released into the vascular compartment as a result of intravascular hemolysis is rapidly bound by haptoglobin to form a complex that is sequestered with high affinity by monocytes and macrophages and subsequently degraded through endocytosis. In addition, ferrous heme released from hemoglobin is oxidized to ferric heme, which is bound with high affinity by the glycoprotein hemopexin and then degraded by liver enzymes. Finally, nitric oxide quickly and irreversibly oxidizes hemoglobin (i.e. oxidation of ferrous heme to ferric heme) to produce nitrate ions and methemoglobin, a form of hemoglobin that cannot bind oxygen and does not, therefore, cause oxidative damage. However, when these protective mechanisms are overwhelmed by massive hemolysis, as in the patient presented here, a number of physiologic and clinical adverse effects can arise, including those resulting from depletion of nitric oxide (i.e. impaired regulation of smooth muscle tone, vascular constriction and intravascular thrombosis).¹⁴

Although the exact mechanism by which hemoglobinuria causes kidney injury is unclear, heme proteins (e.g. hemoglobin and myoglobin) are thought to precipitate cast formation and obstruction of renal tubule, resulting in acute tubular necrosis of the proximal tubule cells. Experimental studies showed that infusion of hemoglobin after a multifactorial insult predisposed rats to kidney injury, including ischemic damage.¹⁵ In addition, the presence of methemoglobin was associated with severe azotemia and tubular necrosis.¹⁴ Infusion of hemoglobin in rats when the blood is acidemic also caused azotemia, but not as severe as that seen with methemoglobin.^{16,17}

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Competing interests

The authors declared no competing interests.

TREATMENT AND MANAGEMENT

Following the diagnosis of AKI, hydration and intravenous administration of sodium bicarbonate were undertaken to alkalinize the patient's urine to raise the urine pH to above 6.5 and diminish the renal tubular toxicity of hemoglobin. Administration of sodium bicarbonate was, however, discontinued after the first liter because of concern about volume overload in the setting of oliguria. Notably, this problem can often be avoided by direct injection of sodium bicarbonate without prior dilution in normal saline. Hemodialysis was then initiated to manage hyperkalemia; removal of free tetrameric hemoglobin during hemodialysis is minimal because of the molecule's large molecular weight, and thus this was not an objective. Hemodialysis was the initially chosen therapy in this case as it is a far more effective modality to manage severe life-threatening hyperkalemia in a rapid fashion compared with continuous venovenous hemodiafiltration. Once acute hyperkalemia resolved, continuous venovenous hemodiafiltration was chosen for overnight renal replacement therapy as rebound hyperkalemia was a concern. Hemodialysis was re-initiated on alternate days once concern for rebound hyperkalemia, volume overload and need for vasopressors abated. Had this patient's renal function not recovered to a satisfactory degree so that long-term hemodialysis would be needed, a tunneled dialysis catheter could have been considered for access. In this case, the patient's predialysis serum creatinine level would have needed to be measured and her urine output monitored to assess the continued need for renal replacement therapy.

CONCLUSIONS

To our knowledge, this is the first reported case of AKI that required renal replacement therapy as a result of the AngioJet® thrombectomy device. This case demonstrates that massive intravascular hemolysis can occur following use of the AngioJet® device and that this large-scale hemolysis can lead to hemoglobinuria. Acute tubular necrosis that is severe enough to require renal replacement therapy can result. Centrifugation of

urine and blood confirms the diagnosis of hemoglobinuria. This case implies that the prognosis of AKI in the setting of thrombectomy-induced intravascular hemolysis is good in the absence of other risk factors; however, few published data are available to confirm this theory. The risk of AKI should be explained to patients before undergoing thrombectomy by use of AngioJet®.

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