CASE REPORT

Warfarin-induced Acute Kidney Injury with Gross Hematuria following Complex Cardiac Surgical Case

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ABSTRACT

This case report describes persistent gross hematuria following complex cardiac surgery presumed to be a form of warfarin-induced acute kidney injury. In the setting of mechanical prosthetic valve replacement, the diagnosis and treatment of this entity presented a clinical challenge.

Key words: Warfarin, nephropathy, hematuria

INTRODUCTION

Hematuria following open-heart surgery is not an uncommon occurrence with a definable list of probable etiologies. The differential diagnosis includes hemolysis, particularly if the procedure includes aspects that may contribute to red blood cell (RBC) destruction. Acute kidney injury (AKI) may accompany hematuria or hemolysis leading to an increase in morbidity and/or mortality.

CASE REPORT

A 50-year-old woman was admitted through the emergency department with heart failure. Her past medical history was significant for hypertension, diabetes mellitus, and hyperlipidemia. She had a 27-year smoking history with no associated alcohol or drug abuse. Her medications included baby aspirin, enalapril, glipizide, and metformin. She had no known drug allergies. The review of systems was negative for hematuria or bleeding diathesis. Admission laboratory values were within normal limits except for markedly elevated B-type natriuretic peptide (BNP) and glucose; liver enzyme levels were mildly elevated with normal bilirubin. The complete blood counts and coagulation profile were within normal limits. The urinalysis (UA) was clear, yellow, and negative for RBCs, white blood cells, protein, nitrites, and leukocyte esterase. On physical examination, she was found to be mildly tachypneic with hypertension. Her lung sounds were diminished with crackles, and there was significant lower extremity edema.

Cardiovascular investigation with echocardiography and cardiac catheterization demonstrated significant multivessel coronary artery disease and severe mitral and tricuspid valve regurgitationsw. She was medically optimized and taken to the operating room where she underwent mitral valve replacement with a 25-mm St. Jude mechanical prosthesis (St. Jude Medical, St. Paul, MN), and tricuspid valve repairs with a 24-mm Edwards annuloplasty ring (Edwards Lifesciences, Irvine, CA) and coronary artery bypass grafting to the left anterior descending, left circumflex, and right coronary arteries. She was anticoagulated with Coumadin and discharged on the 9th post-operative day. Pre-discharge echocardiography demonstrated proper prosthetic valve and annuloplasty ring function. Her medications included Coumadin, aspirin, atorvastatin, carvedilol, digoxin, furosemide, insulin, hydralazine, isosorbide mononitrate, and lisinopril. The international normalized ratio (INR) at discharge was 2.5.

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A week after discharge, she presented to the emergency room with increasing shortness of breath and lower extremity edema. The BNP level was markedly elevated, the INR was subtherapeutic (1.9), the chest radiograph demonstrated a moderate right pleural effusion, and the UA was clear and yellow. Echocardiography demonstrated no significant changes from the post-surgical echocardiogram. A heparin infusion was instituted while the Coumadin was held in preparation for thoracentesis - this was completed without incident and 500 ml of serosanguinous fluid was removed. Coumadin was resumed while aggressive diuresis was undertaken. Several days later, painless gross hematuria was observed. No evidence of hemolysis was demonstrated on laboratory or urine analyses. An extensive evaluation of the kidneys and urinary tract system showed the following:

- Computerized tomography urogram: Mild bladder wall thickening, left renal cyst, normal ureters, no nephrolithiasis, and no hydroureteronephrosis.
- Ultrasound kidneys and bladder: Diffuse bladder wall thickening without masses; no hydronephrosis and no nephrolithiasis.
- Cystoscopy, bilateral retrograde pyelograms, and bilateral ureteroscopy: Small amount of clot evacuated from bladder, no bladder pathology, blood efflux from bilateral ureteral orifices, no filling defects within ureter, no hydronephrosis on pyelography, and no active bleeding but the presence of organized clot in both renal pelvises.
- Sickle cell screen: Positive.
- Ultrasound kidneys and bladder: Hemorrhagic filling and distension of both renal collecting systems including ureters; collapsed bladder.
- Cystoscopy, bilateral retrograde pyelograms, and bilateral ureteral stent placement: Gross hematuria without clot seen in the bladder. Erythematous ureteral orifices with some clots. Mildly dilated collecting system with no filling defects.
- Bilateral renal angiography: No evidence of renal artery aneurysm, arteriovenous malformation, or any other abnormality.
- Renal ultrasound: Left ureteral stent in place; no hydronephrosis and no nephrolithiasis.
- Renal ultrasound: No hydronephrosis and no nephrolithiasis; ureteral stent no longer present.

Over the course of the next several weeks, the gross hematuria resolved while on the heparin infusion; Coumadin was reinstituted with no recurrence of hematuria [Figure 1]. She was discharged with no further readmissions and normalization of her creatinine [Figure 2].

Figure 1: Urine appearance

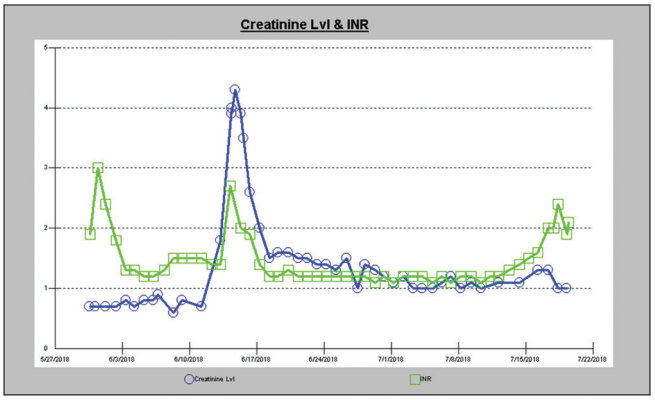

Figure 2: Creatinine and international normalized ratio levels

DISCUSSION

Hematuria versus hemoglobinuria is an important distinction in patients who develop bloody appearing urine following open-heart surgery, particularly in those cases where a mechanical prosthetic heart valve with the need for anticoagulation is necessary. The differential diagnoses, evaluations, and treatments for each entity have been described by previous investigators[1] with the consequence of AKI, resulting in an increased mortality and/or the need for dialysis.[2] While the more common etiologies for grossly hematuric urine include aspects of cardiac surgery with cardiopulmonary bypass, trauma from indwelling urinary catheters, urinary tract tumors and infections, and exposure to large doses of heparin, a less common, but significantly important entity is warfarin-induced AKI.

Anticoagulant-related nephropathy (ARN) is a type of AKI that may result from excessive anticoagulation with warfarin and other anticoagulants - it may or may not manifest with gross hematuria and it may or may not always be associated with a markedly elevated INR. Although the strict definition requires an INR >3, examples of ARN have been seen with lower values. In some studies, the mechanism is believed to be warfarin-induced thrombin depletion; more recent reports suggest disruption in activated protein C and endothelial protein C-receptor signaling pathways.[3,4] The pathogenesis is based on histological analysis of kidney tissue obtained by biopsy and on experiments in animal models which suggests a multifactorial process that includes glomerular hemorrhage, obstruction of renal tubules by RBC casts, and tubular epithelial cell injury.[5,6] Although the exact mechanism is still debated, the prognosis has been associated with an increase in morbidity and mortality for both medical and surgical patients alike.

In this case, alternative opinions for the gross hematuria and the AKI were entertained including the possibility of a sickle

cell-related pathology. The elucidation of sickle cell trait in this patient, for example, was consistent with a papillary necrosis phenomenon. Renal papillary necrosis may occur in up to 50% of patients with sickle cell trait who present with hematuria.[7] Yet, although our patient was positive for sickle cell trait, analysis of the urine as well as imaging studies and procedures of the urinary tracts failed to show sloughed papilla within tubules - features that should have been present if this was a sickle cell-associated pathology. Instead,

this case demonstrated features consistent with a warfarin-related nephropathy (WRN). Although renal biopsy was not performed, the evidence for WRN was convincing. In an editorial comment by Brodsky and Hebert, a presumptive diagnosis can be assigned to ARN in the absence of histologic proof based on non-histologic data.[8] Furthermore, they comment that the incidence of WRN is more prevalent than most clinicians realize - potentially on the order of >500,000 cases/year in the United States alone - and that novel oral anticoagulants may not be exempt from this phenomenon.[8]

In summary, this case represents the diagnostic and therapeutic challenges of ARN manifested by gross hematuria in a cardiac surgical patient dependent on chronic warfarin anticoagulation following mechanical valve replacement. Although the natural history of this disorder is variable, outcomes range from reversible renal function to dialysis-dependent renal failure. A clinical awareness of this entity should be on the differential diagnostic list of post-operative AKI following cardiac surgery in which warfarin therapy is instituted and that gross hematuria may be a presenting sign.

REFERENCES

1. Vercaemst L. Hemolysis in cardiac surgery patients undergoing cardiopulmonary bypass: A review in search of a treatment algorithm. J Extra Corpor Technol 2008;40:257-67.
2. Mariscalco G, Lorusso R, Dominici C, Renzulli A, Sala A. Acute kidney injury: A relevant complication after cardiac surgery. Ann Thorac Surg 2011;92:1539-47.
3. Brodsky SV, Nadasdy T, Rovin BH, Satoskar AA, Nadasdy GM, Wu HM, *et al.* Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int 2011;80:181-9.
4. Wheeler DS, Giugliano RP, Rangaswami J. Anticoagulation-related nephropathy. J Thromb Haemost 2016;14:461-7.
5. Brodsky SV, Satoskar A, Chen J, Nadasdy G, Eagen JW, Hamirani M, *et al.* Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: A report of 9 cases. Am J Kidney Dis 2009;54:1121-6.
6. Ware K, Brodsky P, Satoskar AA, Nadasdy T, Nadasdy G, Wu H, *et al.* Warfarin-related nephropathy modeled by nephron reduction and excessive anticoagulation. J Am Soc Nephrol 2011;22:1856-62.
7. Zadeii G, Lohr JW. Renal papillary necrosis in a patient with sickle cell trait. J Am Soc Nephrol 1997;8:1034-9.
8. Brodsky SV, Hebert LA. Anticoagulant-related nephropathy: Is an AKI elephant hiding in plain view? J Am Coll Cardiol 2016;68:2284-6.

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