Acute kidney injury and undiagnosed immunoglobulin A nephropathy after dabigatran therapy

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ABSTRACT

Dabigatran, a new oral anticoagulant, is a direct thrombin inhibitor used as an alternative to warfarin to reduce the risk of stroke and systemic embolism with nonvalvular atrial fibrillation. We report a case of a man who resumed dabigatran after 6 weeks of prior therapy and began experiencing hematuria with worsening kidney function. Renal biopsy with immunofluorescence and electron microscopy showed mesangial deposits consistent with immunoglobulin A nephropathy. With discontinuation of dabigatran and addition of methylprednisolone, the gross hematuria cleared and urine output improved.

KEYWORDS Acute kidney injury; dabigatran; hematuria; immunoglobulin A nephropathy

Dabigatran is a new oral anticoagulant that works as a direct thrombin inhibitor.¹ Approved by the Food and Drug Administration in October 2010 as the first available oral anticoagulant alternative to warfarin in the United States for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation,^{1,2} it has a rapid onset of action with predictable pharmacokinetics that does not require routine blood monitoring. We report a case of a man who developed gross hematuria and unexplained acute kidney injury following the resumption of dabigatran after 6 weeks of prior therapy.

CASE DESCRIPTION

An 81-year-old white man with prior chronic kidney disease stage 3b and no prior home nephrotoxic medications presented with gross hematuria and elevated serum creatinine. The patient had undergone successful bilateral laminectomies at multiple lumbar levels for spinal stenosis 10 weeks prior to admission. His serum creatinine was 1.35 mg/dL preoperatively, with a baseline of approximately 1.40 mg/dL over the previous 2 years. Two weeks after his surgery (6 weeks prior to admission), he was restarted on dabigatran 150 mg twice daily, along with aspirin 81 mg daily for paroxysmal atrial fibrillation. The patient noted daily hematuria approximately 2 weeks after restarting the dabigatran and aspirin. He associated the hematuria with the dabigatran and self-managed by taking the

dabigatran 150 mg once instead of twice daily, with a resultant decrease in hematuria. He was seen by his primary care physician shortly after the onset of the hematuria with a serum creatinine of 2.26 mg/dL, corresponding to an estimated glomerular filtration rate (eGFR) of 28 mL/min/1.73 m². Urinalysis showed slightly cloudy yellow urine with hematuria and proteinuria (*Table 1*, day –24). He was referred to the urology clinic. Urinalysis 10 days later showed gross hematuria and proteinuria (*Table 1*, day –15). Serum creatinine increased to 3.44 mg/dL (*Figure 1*) with an eGFR of 17 mL/min/1.73 m². Urine cytology was negative for cancerous cells. Computed tomography of the abdomen and pelvis without contrast was remarkable for left renal hypodensity, consistent with a cyst, and findings of prior gunshot wound with metallic pellets in soft tissue. He underwent bladder cystoscopy and was instructed by his physician to go to the hospital due to his increasing serum creatinine and acute kidney injury.

On admission for acute kidney injury, initial pertinent laboratory results were remarkable for anemia (hemoglobin of 8.8 g/dL), acute kidney injury (creatinine of 5.35 mg/dL and eGFR of 10 mL/min/1.73 m²), and elevated coagulation markers (international normalized ratio [INR] of 2.1, prothrombin time of 23.7 seconds, and activated partial thromboplastin time of 87.5 seconds). A urinalysis (*Table 1*, day 1) revealed proteinuria, hematuria, and few leukocytes with occasional bacteria. From this urine specimen and initial serum

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Table 1. Urinalyses prior to and during hospitalization

Variable	Day					
	–24	–15	1 ^a	3	4	17
Color	Yellow	Red	Yellow	Red	Red	Yellow
Appearance	Clear	Cloudy	Cloudy	Clear	Cloudy	Clear
pH	5.0	6.0	5.0	6.0	6.0	5.0
Specific gravity	1.030	1.012	1.011	1.010	1.011	1.014
Protein (mg/dL)	300	≥500	30	100	100	30
Glucose (mg/dL)	Neg	Neg	Neg	Neg	Neg	1+
Ketones (mg/dL)	Trace	Neg	Neg	Neg	Neg	Neg
Blood	3+	3+	3+	3+	3+	3+
Bilirubin (mg/dL)	1+	Neg	Neg	Neg	Neg	Neg
Leukocyte esterase	Neg	Neg	Neg	Neg	Neg	Neg
Nitrite	Neg	Neg	Neg	Neg	Neg	Neg
Urobilinogen (IU/dL)	1	<2	<2	<2	<2	<2
RBC (per HPF)	—	>50	>50	>50	>50	20–50
WBC (per HPF)	—	20–50	10–19	1–2	10–19	1–2
Bacteria		Moderate	Occ	Rare	Occ	Rare
Osmolality (mosm/kg)			358			
Random creatinine (mg/dL)			86.8			
Random Na ⁺ (mEq/L)			60			

Neg indicates negative; RBC, red blood cell; HPF, high-power field; WBC, white blood cell; Occ, occasional; Na⁺, sodium.

^aDay 1 corresponds with the day of hospital admission.

studies, fractional excretion of urine was calculated to be 2.6%, suggestive of intrinsic kidney injury. Dabigatran, aspirin, and nephrotoxic home medications were withheld. The patient's serum creatinine level continued to increase (*Figure 1*), despite withholding dabigatran and aspirin. Prothrombin time and INR remained elevated above 1.4 and 16.7 seconds, respectively, throughout his hospitalization. Four days after admission, INR decreased to 1.5 after two units of fresh frozen

Figure 1. Serum creatinine prior to and during the patient's hospitalization with a steady upward trend peaking on hospital day 11. (Day 1 corresponds to the day of hospital admission.)

plasma, the threshold at which renal biopsy could be performed. The renal biopsy revealed tubular damage and atrophy with moderate to severe interstitial fibrosis and mild interstitial inflammation including eosinophils (5–20 per high-power field). Glomerular sclerosis was noted in two of 10 glomeruli. Granular mesangial deposits of immunoglobulin (Ig)A (2+) and C3 (2+) were noted on immunofluorescence, along with rare mesangial deposits with paramesangial extension on electron microscopy, suggestive of IgA nephropathy. IgG, IgM, fibrinogen, albumin, C3, C1q, C4, and kappa and lambda immunofluorescence stains were negative, but the average membrane thickness was 238.36 nm, which is consistent with a diagnosis of thin basement membrane nephropathy.

He received methylprednisolone 500 mg intravenously for 3 days, followed by oral prednisone 40 mg daily. Days later, the patient's urine cleared of gross hematuria and urine output improved. On hospital day 11, serum creatinine peaked at 7.17 mg/dL with an eGFR of 7 mL/min/1.73 m² (*Figure 1*). He was discharged on hospital day 13 and continued to have an elevated serum creatinine, with a creatinine of 5.62 mg/dL approximately 3 months after hospital admission.

DISCUSSION

Anticoagulant-related nephropathy is a form of acute kidney injury caused by excessive anticoagulation. First described with warfarin and previously known as warfarin-related nephropathy,^{3,4} anticoagulant-related nephropathy should be considered in patients with unexplained acute kidney injury, defined as a serum creatinine increase >0.3 mg/dL within 1 week of INR measurement >3 in patients taking warfarin, not attributed to other etiology of acute kidney injury.^{3,4} Similarly, multiple studies suggest warfarin-related nephropathy-like syndromes occurring with other anticoagulants, such as acenocoumarol^{5,6} and dabigatran.^{3,4,7–10}

Our patient presented on admission with acute kidney injury. However, he did not have moderate or severe coagulopathy based on his presenting INR of <3. He was self-regulating the dosage of dabigatran for nearly 1 month prior, basing his dosage on the amount of gross hematuria. Therefore, his INR could have been >3 within the prior month when he was taking his full dosage of dabigatran. Detecting excessive anticoagulation with dabigatran use is difficult due to the lack of routine monitoring and poor availability of the tests that reflect anticoagulation with dabigatran.⁸

Dabigatran is excreted primarily (approximately 85%) by the kidneys.¹¹ Subsequently, it is renally dosed with recommendations of 150 mg twice daily in patients with creatinine clearance >30 mL/min and 75 mg twice daily for patients with creatinine clearance of 15 to 30 mL/min.¹² Ryan et al⁴ published one of the first studies that investigated kidney injury associated with dabigatran. Chan et al¹⁰ also performed a large-scale study with an Asian cohort with the presence of kidney disease and absence of it. They concluded that dabigatran was associated with a reduced risk of acute kidney injury (increase in serum creatinine >0.3 mg/dL) in comparison to warfarin. In an editorial comment, Asinger and Shroff¹³

examined a study by Böhm et al¹⁴ in which they noted that long-term administration of warfarin and new oral anticoagulants such as dabigatran caused a decline in eGFR.

Our patient had acute kidney injury and newly identified, biopsy-proven IgA nephropathy as previously reported in patients with IgA nephropathy who developed acute kidney injury while being treated with dabigatran.^{3,8,9} The focus of studies to date, to our knowledge, has primarily been on overall renal decline and nephropathy caused by anticoagulants or determining which anticoagulants have reduced risk of acute kidney injury. However, the link between thin basement membrane or IgA nephropathy, dabigatran, and acute kidney injury has not been assessed, which was our intent with this case report. Our patient might have experienced a risk of dabigatran therapy that occurs in patients with chronic kidney disease and predisposing factors that can lead to bleeding as reported in a case series.¹⁵ Though several questions related to IgA nephropathy, treatment with dabigatran, and glomerular basement membrane disease remain unanswered, the underlying pathophysiology of dabigatran-related injury will require further investigation to determine the actual cause of dabigatran-related nephropathy.

1. Blommel MM, Blommel AL. Dabigatran etexilate: a novel oral direct thrombin inhibitor. *Am J Health Syst Pharm*. 2011;68:1506–1519. doi:10.2146/ajhp100348.
2. Boehringer Ingelheim. US FDA approves Pradaxa (dabigatran etexilate)—a breakthrough treatment for stroke risk reduction in non-valvular atrial fibrillation [press release]. October 20, 2010. <https://www.businesswire.com/news/home/20101020005862/en/FDA-Approves-Pradaxa%C2%AE-dabigatran-etexilate-%E2%80%93-break-through>. Accessed March 28, 2018.
3. Escoli R, Santos P, Andrade S, Carvalho F. Dabigatran-related nephropathy in a patient with undiagnosed IgA nephropathy. *Case Rep Nephrol*. 2015;2015:298261. doi:10.1155/2015/298261.
4. Ryan M, Ware K, Qamri Z, et al. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. *Nephrol Dial Transplant*. 2014;29:2228–2234. doi:10.1093/ndt/gft380.
5. Martin Cleary C, Moreno JA, Fernandez B, et al. Glomerular haematuria, renal interstitial haemorrhage and acute kidney injury. *Nephrol Dial Transplant*. 2010;25:4103–4106. doi:10.1093/ndt/gfq493.
6. Gois M, Azevedo A, Carvalho F, Nolasco F. Anticoagulant-related nephropathy in a patient with IgA nephropathy. *BMJ Case Rep*. 2017. pii:bcr2016218748. doi:10.1136/bcr-2016-218748.
7. Shafi ST, Negrete H, Roy P, Julius CJ, Sarac E. A case of dabigatran-associated acute renal failure. *WMMJ*. 2013;112(4):173–175.
8. Moeckel GW, Luciano RL, Brewster UC. Warfarin-related nephropathy in a patient with mild IgA nephropathy on dabigatran and aspirin. *Clin Kidney J*. 2013;6:507–509. doi:10.1093/ckj/sft076.
9. Kalaitzidis RG, Duni A, Liapis G, et al. Anticoagulant-related nephropathy: a case report and review of the literature of an increasingly recognized entity. *Int Urol Nephrol*. 2017;49:1401–1407. doi:10.1007/s11255-017-1527-9.
10. Chan YH, Yeh YH, See LC, et al. Acute kidney injury in Asians with atrial fibrillation treated with dabigatran or warfarin. *J Am Coll Cardiol*. 2016;68:2272–2283. doi:10.1016/j.jacc.2016.08.063.
11. Spinler S. The pharmacology and therapeutic use of dabigatran etexilate. *J Clin Pharmacol*. 2013;53:1–13. doi:10.1177/0091270011432169.
12. Lexicomp. *Dabigatran etexilate*. Wolters Kluwer Clinical Drug Information, Inc.; 2017. Accessed April 8, 2017.
13. Asinger RW, Shroff GR. Atrial fibrillation and renal function: how high is the price of anticoagulation? *J Am Coll Cardiol*. 2015;65:2494–2495. doi:10.1016/j.jacc.2015.04.043.
14. Böhm M, Ezekowitz MD, Connolly SJ, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. *J Am Coll Cardiol*. 2015;65:2481–2493. doi:10.1016/j.jacc.2015.03.577.
15. Goriacko P, Yaghdjian V, Koleilat I, Sinnett M, Shukla H. The use of idarucizumab for dabigatran reversal in clinical practice: a case series. *P T*. 2017;42:699–703.