A Case of Dabigatran-associated Acute Renal Failure

Salman T. Shafi, MD; Hilmer Negrete, MD; Prakash Roy, MD; Carmen J. Julius, MD; Erdal Sarac, MD

ABSTRACT

Dabigatran is a direct thrombin inhibitor that reduces the risk of systemic embolism in patients with nonvalvular atrial fibrillation. We report a case of an elderly man who developed unexplained rapid decline in renal function 6 weeks after starting dabigatran. A renal biopsy was planned to find out the etiology of acute renal failure, but the patient has significantly prolonged coagulation parameters despite holding medication for 5 days per manufacturer's recommendation. He was started on hemodialysis due to worsening renal function and to ensure dabigatran clearance before renal biopsy. Renal biopsy showed renal atheroembolic disease, which was possibly induced by dabigatran. Although renal atheroembolic disease is a known rare complication following treatment with warfarin, heparin, and thrombolytic agents, this is the first reported case of renal atheroembolic disease potentially caused by dabigatran. This case also highlights the extended duration of prolonged coagulation parameters after holding dabigatran and its implication for timing of nonemergent invasive procedures.

INTRODUCTION

Dabigatran, a direct thrombin inhibitor, is the first available oral anticoagulant alternative to warfarin for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[1] We report a case of an elderly patient who developed unexplained acute renal failure 6 weeks after he started dabigatran. A renal biopsy was planned to determine the cause of renal failure. However, the patient had significantly abnormal coagulation parameters, and we were faced with the clinical dilemma of the need for an urgent renal biopsy vs uncertainty regarding how much time should be allowed to pass before performing a renal biopsy after stopping the medication. Eventually, renal biopsy showed renal atheroembolic disease, which was possibly precipitated by dabigatran. Though rare, renal atheroembolic disease has been described following treatment with warfarin, heparin and thrombolytic agents.[2-5] To our knowledge, this is the first reported case of renal atheroembolic disease possibly induced by dabigatran.

CASE

A 79-year-old African American man was referred to an outpatient nephrology clinic for evaluation of renal dysfunction discovered incidentally during a routine follow-up the week before. His blood urea nitrogen (BUN) was 52 mg/dL (Ref: 9-23 mg/dL), serum creatinine (Cr) was 2.9 mg/dL (Ref: 0.7-1.3 mg/dL), and estimated glomerular filtration rate (eGFR) was 27.2 ml/min/1.73 (Ref: > 60 ml/min/1.73). He had fatigue but no other symptoms. Three months previously, his Cr was 1.3 mg/dL, eGFR was 69 ml/min/1.73 and hemoglobin was 11.0 g/dL (Ref: 12.5-16.5 g/dL) with normal white blood cell differential. His past medical history included hypertension, hyperlipidemia, and a recent diagnosis of atrial fibrillation. His medications included amlodipine 5 mg daily, valsartan 320 mg daily, rosuvastatin 10 mg daily, vitamin D 2000 units daily, and dabigatran 150 mg twice a day, started 6 weeks earlier for atrial fibrillation by his cardiologist. He had undergone no interventional procedures. On physical examination, his blood pressure was elevated at 179/79 mm Hg. Laboratory tests revealed normal white blood cell count and differential, as well as normal platelet count and electrolytes. Hemoglobin was low at 10.0 g/dL. Urinalysis showed 1+ protein and > 20 red blood cells/high power field (hpf) (Ref: < 2/hpf). Urine protein to creatinine ratio was 0.5 (Ref: 0.0-0.2). Repeat BUN was 50 mg/dL, Cr was 3.3 mg/dL, and eGFR was 22 ml/min/1.73.

Urgent renal ultrasound with Doppler was ordered. However, on the day of the renal ultrasound, the patient's blood pressure was severely elevated at 243/109 mm Hg, prompting hospital admission. His hospitalization occurred 5 days after he was first

• • •

Author Affiliations: Department of Internal Medicine, Northeastern Ohio Medical University, Rootstown, Ohio (Shafi, Sarac); Department of Internal Medicine, St Elizabeth Health Center, Youngstown, Ohio (Shafi, Negrete, Roy, Julius, Sarac); Department of Pathology, Northeastern Ohio Medical University, Rootstown, Ohio (Julius).

Corresponding Author: Salman Tahir Shafi, MD; 807 Southwestern Run, Boardman, OH 44514; phone 330.729.0059; fax 330.729.9297; email salmanshafi@email.com.

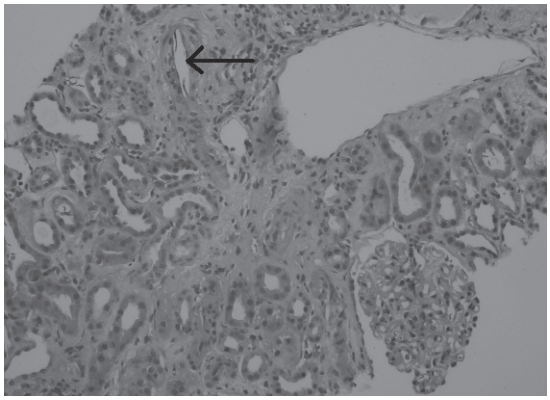
CME available. See page 176 for more information.

Table 1. Coagulation Parameters, Serum Creatinine, and Timing of Hemodialysis and Renal Biopsy in Patient after Hospitalization

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
PT/INR (0.8-1.2)	2.9		3.7	3.2	2.5	2.1	1.8	1.7	1.5	1.4	1.4	
aPTT (23-32s)	66.1		71.2	65.7	55.2	47.7	43.5	40.6	33.7	28.7	26.8	25.7
TT (11.8-17.6s)							>120	>120	>120			89
SCr (mg/dL)	3.2	3.1	3.2	3.4	3.7	4.1	4.3	4.8	4.2	4.3	5.1	4.1
Procedure								HD	HD		HD	Biopsy

Abbreviations = PT/INR, prothrombin time/international normalized ratio; aPTT, activated partial thromboplastin time; TT, thrombin time; SCr, serum creatinine; HD, hemodialysis.

Figure 1. Renal Biopsy (200 X)



Irregular outline of occlusive atheroembolus within artery/arteriole (arrow). Formalin fixation removes the lipid but the jagged outline remains.

seen in the renal clinic and nearly 7 weeks after he was first started on dabigatran. Renal ultrasound with Doppler was suspicious for left renal artery stenosis. Repeat blood work showed hemoglobin at 10.8 g/dL and peripheral eosinophil% at 10 (Ref: 0-6%); erythrocyte sedimentation rate was 39 mm/hr (Ref: 0-15 mm/hr), BUN was 47 mg/dL, creatinine was 3.2 mg/dL, and eGFR was 22 ml/min/1.73. He had no eosinophiluria. Complete serological workup, including antinuclear antibody, antineutrophilic cytoplasmic antibody, complement 3 and 4, hepatitis B surface antigen, hepatitis C antibody, antiglomerular basement membrane antibody, cryoglobulins, serum, and urine protein electrophoresis were found to be normal over subsequent days. Due to unexplained renal failure, we opted for renal biopsy. The patient was empirically started on intravenous (IV) methylprednisolone to cover for possible acute interstitial nephritis or rapidly progressive glomerulonephritis. Dabigatran was stopped on the day of admission. All coagulation parameters, including prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), and thrombin time (TT) were significantly abnormal. These results are shown in Table 1. Fibrinogen was normal. Mixing studies suggested the presence of inhibitor or anticoagulation effect. The patient was started on hemodialysis on day 8 of hospitalization due to worsening renal function and abnormal coagulation parameters. Placement of a temporary femoral hemodialysis catheter was uneventful despite prolonged aPTT, PT/INR and TT. A renal biopsy was performed on day 12 of hospital admission. There was no major post-procedure bleeding. Renal biopsy showed cholesterol emboli, ischemic glomerular changes, and hypertensive glomerulosclerosis (Figure 1). Dabigatran was permanently discontinued. The patient continued on hemodialysis, but renal function did not recover.

DISCUSSION

Renal atheroembolic disease, also known as cholesterol embolization, causes a decline in renal function due to occlusion of renal arteries, arterioles, and glomerular capillaries by cholesterol crystals, which dislodge from atherosclerotic plaques.[2] In clinical practice, 3% to 10% of all cases of acute renal failure may be attributed to renal atheroembolic disease.[2] Renal atheroembolic disease is usually found in adults older than 60 years with diffuse atherosclerosis.[2] The most common etiology is an interventional or surgical procedure involving manipulation of the aorta or other major blood vessels.[2] Renal atheroembolism is also a rare complication in patients on anticoagulants (including warfarin, heparin, low molecular weight heparin) and thrombolytic agents.[2-5] In studies of biopsy-proven renal atheroembolic diseases, anticoagulation could be implicated in only 7% of cases without preceding vascular interventional procedures.[2] Among patients taking warfarin, the incidence of systemic cholesterol embolism is low (0.7% to 1.0%).[6,7] The exact mechanism underlying anticoagulant- or thrombolytic-induced atheroembolic renal disease is not clear. One proposed explanation is that anticoagulants and thrombolytics may disrupt or dissolve protective thrombi that cover ulcerated atherosclerotic plaques, exposing the lipid core to the systemic circulation.[2] Spontaneous atheroembolic disease is rare with reported incidence of 1.9% to 13%.[2]

The patient in this case report has risk factors for atherosclerosis including advanced age, history of hypertension, and hyperlipidemia. Though spontaneous atherombolic disease is a possibility in our patient, the temporal relationship between starting dabigatran and onset of renal failure in the absence of any vascular interventional procedure makes it likely that dabigatran was the predisposing factor in this patient. To our knowledge, this is the first reported case of renal atheroembolic disease potentially induced by dabigatran.

The most common extra-renal manifestation of atheroembolic renal disease is skin involvement in the form of livedo reticularis, blue toe syndrome, ulceration, gangrene, and purpura, with recent studies reporting a frequency of 75% to 96%.[2] Other organs, including the retina, gastrointestinal tract, central nervous system, and heart also may be affected.[2] Our patient exhibited no extra-renal manifestations but had eosinophilia, which was suggestive but not specific for renal atheroembolic disease. Overall, the patient's clinical presentation was not suggestive of renal atheroembolic disease. But comprehensive evaluation for other causes of renal failure was unremarkable and renal biopsy was conclusive, which is the definite test to diagnose atheroembolic disease.[2]

An additional highlight of our case is the patient's abnormal coagulation profile and its impact on our decision to delay renal biopsy and initiate dialysis prior to renal biopsy. Dabigatran is primarily cleared by the kidneys (85%).[1] The manufacturer recommends holding dabigatran for 1 to 2 days (if creatinine clearance > 50 ml/min) and 3 to 5 days (if creatinine clearance < 50 ml/min) before any interventional or surgical procedure.[8] However, in our patient, coagulation parameters, including PT/INR, PTT, and TT were prolonged well beyond 5 days, which made us hesitant to perform renal biopsy on day 5.

Routine monitoring of the coagulation profile in patients taking dabigatran is not indicated,[1] but it may be essential in special circumstances like this case. The effect of dabigatran on coagulation parameters has been the subject of several recent studies and reviews.[9-12] In the latest study,[12] aPTT and hemoclot thrombin inhibitor assay were found to be the most useful monitoring tests, with the latter regarded as the gold standard. Ecarin clotting time was found to be reliable, while TT was considered too sensitive and was not recommended. However, a normal TT rules out any dabigatran effect.[9] Of all these tests, only aPTT and TT are readily available in most institutions. The correlation between aPTT, TT, and clinical bleeding has not been determined in patients on dabigatran, which limits interpretation of these coagulation tests in assessing clinical safety.[10] In addition, PT/INR is not considered a sensitive indicator of dabigatran activity, except perhaps at supratherapeutic concentrations.[10-12] But patient had significantly prolonged PT/INR, and this has been found in other case reports of elderly patients who developed gastrointestinal hemorrhage in the context of renal failure while on dabigatran.[13,14]

Since there is no effective antidote for dabigatran[1] and hemodialysis is effective in removing 62% to 68% of the drug,[15] we performed 3 hemodialysis sessions before proceeding with renal biopsy. It was only after holding dabigatran for 10 days and after 2 hemodialysis sessions that PT/INR and aPTT returned to normal. TT was improved but still prolonged on day 12, perhaps due to residual dabigatran activity although, as mentioned above, the test has been found to be too sensitive. In addition, the patient did not exhibit significant bleeding on placement of the dialysis catheter on day 8. We felt it was probably safe to perform renal biopsy after holding dabigatran for 12 days and after 3 hemodialysis sessions. There were no post-procedure complications.

CONCLUSION

Dabigatran may induce renal atheroembolic disease in elderly patients with appropriate risk factors for atherosclerosis. This diagnosis should be considered in patients who develop unexplained renal failure while taking dabigatran. Additional case reports of renal atheroembolic disease in setting of dabigatran may confirm that this disease can be induced by dabigatran like other anticoagulants and thrombolytics.

Funding/Support: None declared.

Financial Disclosures: None declared.

Planners/Reviewers: The planners and reviewers for this journal CME activity have no relevant financial relationships to disclose.

REFERENCES

1. Spinler S. The Pharmacology and Therapeutic Use of Dabigatran Etexilate [Epub ahead of print January 31, 2012]. *J Clin Pharmacol.* doi:10.1177/0091270011432169.

2. Scolari F, Ravani P. Atheroembolic renal disease. *Lancet.* 2010;375(9726):1650-1660.

3. Scolari F, Ravani P, Gaggi R, et al. The challenge of diagnosing atheroembolic renal disease: clinical features and prognostic factors. *Circulation.* 2007;116(3):298-304.

4. Feder W, Auerbach R. "Purple toes": an uncommon sequela of oral coumarin drug therapy. *Ann Intern Med.* 1961;55:911–917.

5. Schwarz MW, McDonald GB. Cholesterol embolization syndrome. Occurrence after intravenous streptokinase therapy for myocardial infarction. *JAMA.* 1987;258(14):1934–1935.

6. Blackshear JL, Zabalgoitia M, Pennock G, et al. Warfarin safety and efficacy in patients with thoracic aortic plaque and atrial fibrillation. SPAF TEE Investigators. Stroke Prevention and Atrial Fibrillation. Transesophageal echocardiography. *Am J Cardiol.* 1991;83(3):453-455.

7. Tunick PA, Nayar AC, Goodkin GM, et al. Effect of treatment on the incidence of stroke and other emboli in 519 patients with severe thoracic aortic plaque. *Am J Cardiol.* 2002;90(12):1320-1325.

8. Pradaxa [prescribing information]. Ingelheim, Germany: Boehringer Ingelheim; 2012. http://www.pradaxa.com. Accessed July 8, 2013.

9. Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;103(6):1116-1127.

10. Iyer V, Singh HS, Rieffel JA. Dabigatran: comparison to warfarin, pathway to approval, and practical guidelines for use. *J Cardiovasc Pharmacol Ther.* 2012;17(3):237-247. doi:10.1177/1074248412436608.

11. Lindahl TL, Baghaei F, Blixter IF, et al. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. *Thromb Haemost.* 2011;105(2):371-378.

12. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogné. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. *Thromb Haemost.* 2012;107(5):985-997.

13. Wychowski MK, Kouides PA. Dabigatran-induced gastrointestinal Bleeding in an elderly patient with moderate renal impairment. *Ann Pharmacother.* 2012;46(4):e10. doi: 10.1345/aph.1Q747.

14. Béné J, Saïd W, Rannou M, Deheul S, Coupe P, Gautier S. Rectal bleeding and hemostatic disorders induced by dabigatran etexilate in 2 elderly patients. A*nn Pharmacother.* 2012;46(6):e14. doi:10.1345/aph.1Q705.

15. Stangier J, Rathgen K, Stähle H, Masur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet.* 2010;49(4):259-268.

CME

To receive CME credit, complete this quiz and return it to the address listed below. See CME-designated article on pages 173-175.

Quiz: A Case of Dabigatran-associated Acute Renal Failure

EDUCATIONAL OBJECTIVES

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

1. Understand some of the pharmacology of dabigatran and how its activity can be monitored.
2. Understand the etiology and pathophysiology of renal atheroembolic disease.

PUBLICATION DATE: August 15, 2013

EXPIRATION DATE: August 15, 2014

QUESTIONS

1. Dabigatran is a direct thrombin inhibitor.
   ❑ True ❑ False
2. Dabigatran is indicated to reduce the risk of systemic embolism in patients with atrial fibrillation due to valvular heart disease.
   ❑ True ❑ False
3. Renal atheroembolic disease, also known as cholesterol embolization, causes a decline in renal function due to occlusion of renal arteries, arterioles, and glomerular capillaries by cholesterol crystals, which dislodge from atherosclerotic plaques.
   ❑ True ❑ False
4. In clinical practice, almost half of all cases of acute renal failure may be attributed to renal atheroembolic disease.
   ❑ True ❑ False
5. The most common extra-renal manifestation of atheroembolic renal disease is skin involvement in the form of livedo reticularis, blue toe syndrome, ulceration, gangrene, and purpura.
   ❑ True ❑ False

• • •

You may earn CME credit by reading the designated article in this issue and successfully completing the quiz (75% correct). Return completed quiz to *WMJ* CME, 330 E Lakeside St, Madison, WI 53715 or fax to 608.442.3802. You must include your name, address, telephone number, and e-mail address.

The Wisconsin Medical Society (Society) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The Wisconsin Medical Society designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

6. The most common cause of renal atheroembolic disease is a result of an interventional or surgical procedure involving manipulation of the aorta or other major blood vessels.
   ❑ True ❑ False
7. Renal atheroembolic disease is a not uncommon complication following treatment with warfarin, heparin and thrombolytic agents and can be implicated in more than 20% of cases without preceding vascular interventional procedures.
   ❑ True ❑ False
8. Spontaneous atheroembolic disease is rare with reported incidence of 1.9% to 13%.
   ❑ True ❑ False
9. The exact mechanism underlying anticoagulant- or thrombolytic-induced atheroembolic renal disease is not clear; however, one proposed explanation is that anticoagulants and thrombolytics may disrupt or dissolve protective thrombi that cover ulcerated atherosclerotic plaques, exposing the lipid core to the systemic circulation.
   ❑ True ❑ False
10. Renal atheroembolic disease is usually found in adults older than 60 years with diffuse atherosclerosis.
    ❑ True ❑ False
11. Dabigatran is primarily cleared by the liver.
    ❑ True ❑ False
12. The prothrombin time/international normalised ratio (PT/INR) is recommended for use in monitoring dabigatran activity in clinical practice.
    ❑ True ❑ False
13. The thrombin time (TT) is considered too sensitive to monitor dabigatran activity; however, a normal TT rules out any dabigatran effect.
    ❑ True ❑ False
14. Hemodialysis is not effective in removing dabigatran.
    ❑ True ❑ False
15. The authors of this case report suggest that dabigatran may induce renal atheroembolic disease in elderly patients with appropriate risk factors for atherosclerosis.
    ❑ True ❑ False

advancing the art & science of medicine in the midwest

WMJ

The mission of *WMJ* is to provide a vehicle for professional communication and continuing education for Midwest physicians and other health professionals.

WMJ (ISSN 1098-1861) is published by the Wisconsin Medical Society and is devoted to the interests of the medical profession and health care in the Midwest. The managing editor is responsible for overseeing the production, business operation and contents of the *WMJ.* The editorial board, chaired by the medical editor, solicits and peer reviews all scientific articles; it does not screen public health, socioeconomic, or organizational articles. Although letters to the editor are reviewed by the medical editor, all signed expressions of opinion belong to the author(s) for which neither *WMJ* nor the Wisconsin Medical Society take responsibility. *WMJ* is indexed in Index Medicus, Hospital Literature Index, and Cambridge Scientific Abstracts.

For reprints of this article, contact the *WMJ* at 866.442.3800 or e-mail wmj@wismed.org.

© 2013 Wisconsin Medical Society