CASE REPORT

Myocardial infarction complicated by left ventricular thrombus and fatal thromboembolism following abrupt cessation of dabigatran

Bethany Weiler, Ellen T Marciniak, Robert M Reed, Michael T McCurdy

Department of Pulmonary and Critical Care Medicine, University of Maryland, Baltimore, Maryland, USA

Correspondence to

Dr Robert Michael Reed, rreed@medicine.umaryland.edu

Accepted 6 June 2014

SUMMARY

Novel anticoagulants are increasingly utilised in lieu of warfarin to treat non-valvular atrial fibrillation. Their clinical use in other non-FDA approved settings is also increasing. We present a case in which a patient abruptly stopped taking dabigatran due to a small bowel obstruction and shortly thereafter suffered a myocardial infarction complicated by left ventricular thrombosis with fatal embolisation to the superior mesenteric artery. In this context, we discuss the possibility of a rebound phenomenon of hypercoagulability with abrupt cessation of novel anticoagulants.

BACKGROUND

Novel anticoagulants such as dabigatran (Pradaxa) and rivaroxaban (Xarelto) are being prescribed with increased frequency for treatment of non-valvular atrial fibrillation as well as for prevention and treatment of venous thromboembolism. A recently published study in the *Canadian Medical Association Journal* demonstrated a rise of prescriptions of dabigatran from 3 to 274 prescriptions/100 000 population over a 24-month period in Ontario.¹ These agents remain unproven for conditions other than non-valvular atrial fibrillation and have been associated with a hypercoagulable state after discontinuation.^{2–3} Additionally, dabigatran has been associated with an increased risk of myocardial infarction (MI) in some studies.^{4–5} We present a case in which the abrupt cessation of dabigatran was associated with MI complicated by left ventricular (LV) thrombus with fatal embolisation to the superior mesenteric artery (SMA).

CASE PRESENTATION

An 84-year-old man with a history of prior abdominal surgery presented to an emergency department after experiencing 2 days of abdominal pain, nausea and vomiting. He carried a diagnosis of non-valvular atrial fibrillation for which he had been treated for 3 months with dabigatran. He had been unable to keep his medications down due to vomiting, and his partial thromboplastin time at presentation was 26 s (normal range 25–36 s), confirming a subtherapeutic level of dabigatran.

The patient's abdomen was distended, diffusely tender and firm, with scars from a prior abdominal surgery. He appeared dehydrated by examination as well as by laboratory assessments of renal function, and he was tachycardic with a normal blood pressure. His mildly elevated troponin-I level of

2.32 ng/mL (normal <0.07 ng/mL) was attributed at the time to demand ischaemia (type 2 MI) with impaired renal function rather than to an atherothrombotic non-ST elevation MI. An ECG remained unchanged from an ECG obtained 3 weeks earlier, although interpretation was limited by the presence of a left bundle branch block.

CT of the abdomen with oral contrast demonstrated a dilated small bowel with a transition point. With his prior abdominal surgery, he was thought to have an adhesion-related small bowel obstruction. A decompressive nasogastric (NG) tube yielded 1.5 L of dark brown fluid. He was transferred to a medical intensive care unit (MICU) at a tertiary care centre for further management.

TREATMENT

On arrival in the MICU, the patient was alert and answering questions appropriately. He was tachycardic but haemodynamically stable. Bright red blood was being suctioned continuously through his NG tube. His distended abdomen was exquisitely and diffusely tender to palpation. Repeated evaluation demonstrated a troponin concentration that had increased to 20 ng/mL, and his ECG remained unchanged with a left bundle branch block.

During subsequent evaluation, a CT angiogram (figure 1) demonstrated a thrombus (red arrow) just beyond the origin of the SMA. Other findings included a non-enhancing jejunum and ileum with pneumatosis and mesenteric gas. Based on these findings consistent with mesenteric ischaemia, the patient was taken emergently for exploratory laparotomy.

Laparotomy revealed extensive adhesions and murky fluid throughout the abdomen. This supported the diagnosis of adhesion-related small bowel obstruction with abdominal catastrophe. Further examination revealed apparent transmural necrosis throughout the vast majority of the small bowel distal to the ligament of Treitz, consistent with the distribution of the SMA. Intraoperative transoesophageal echocardiogram showed a depressed ejection fraction (EF), segmental wall motion abnormalities with dyskinesis of the septal wall and hypokinesis of the inferior and lateral walls. There was also a large density adherent to the lateral wall of the LV apex, consistent with a large thrombus. Findings supported a diagnosis of LV thrombus complicating MI.

CrossMark

To cite: Weiler B, Marciniak ET, Reed RM, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-203910

Figure 1 CT angiogram of the abdomen illustrating embolus in the superior mesenteric artery (red arrow).

OUTCOME AND FOLLOW-UP

Because of the dramatic extent of necrosis in the bowel and the patient's very poor prognosis, the surgeons closed his abdomen and returned him to the MICU for comfort care. A fentanyl drip was administered, and the patient expired shortly thereafter. The family declined autopsy.

DISCUSSION

This patient most likely initially experienced a small bowel obstruction attributable to adhesions from a prior surgery. As a result, he was unable to continue taking dabigatran and subsequently experienced an acute MI complicated by an LV thrombus with embolisation to the SMA. This case highlights previously raised concerns over the possibility of rebound hypercoagulability following cessation of dabigatran.

The safety of novel anticoagulants outside of approved indications is not yet well established. In the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Erexilate in Patients after Heart Valve Replacement (RE-ALIGN), investigators attempted to validate a new dosing regimen for dabigatran, as compared with warfarin, for the prevention of thromboembolism in patients with mechanical heart valves.⁶ The study was terminated early because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. The results of RE-ALIGN suggest that dabigatran is inferior to warfarin for mechanical heart valves, and they call into question whether the novel anticoagulants, when compared with warfarin, provide comparable protection against embolism in high-risk conditions. Even after the cessation of newer anticoagulants, a rebound hypercoagulability manifesting as a delayed increase in thromboembolic events has been noted.³ A recently published study in the *Journal of Thrombosis and Haemostasis* demonstrated in vitro and in vivo evidence that low levels of direct thrombin inhibitors enhance thrombin generation.⁷

The apparent rapid development and embolisation of the LV thrombus in this case warrants discussion. A ventricular thrombus can complicate a wide variety of cardiac pathologies, including coronary vasospasm, myocarditis, LV aneurysm and MI. Other predisposing, albeit rare, conditions are blunt cardiac

trauma,⁸ protein C deficiency,⁹ systemic lupus erythematosus and antiphospholipid syndrome.¹⁰ Like any thrombus, LV thrombus formation requires the presence of Virchow's triad. Peri-infarction risk factors include: (1) haemostasis resulting from LV dyskinesia or akinesis; (2) endothelial injury (especially following a transmural infarct); and (3) hypercoagulability due to increased concentrations of prothrombin, Von Willebrand factor and platelet activation.¹¹ The aetiology of this patient's LV thrombus was likely an acute MI in the setting of a hypercoagulable state related to the discontinuation of his dabigatran.

The likelihood of developing an LV thrombus after an acute MI varies with infarct location and size, but conditions such as anterior wall akinesis, an EF <35% and apical dyskinesia or aneurysm also increase the risk of thrombus formation.¹² LV thrombi can occur within 24 h of the event, and approximately 90% form within 2 weeks.¹¹ In the case we present, we lack imaging to precisely define the timing of LV thrombus formation but suspect it occurred acutely shortly after presentation. While the initial mild elevation of troponin noted at presentation was reasonably attributed to demand ischaemia (type 2 MI) and dehydration, it is alternatively conceivable that a myocardial event had occurred in the days prior to presentation and had resulted in gastrointestinal symptoms that mimicked a small bowel obstruction. If that were the case, an MI would have occurred while the patient was receiving full treatment with dabigatran. Notably, peri-infarction anticoagulation fails to decrease the likelihood of thrombus development,¹³ but the abrupt cessation of dabigatran may have contributed to the fulminant course at presentation.

The most dreaded complication of LV thrombus formation is embolism, which occurs in 10–15% of patients not treated with anticoagulation. According to a 1993 meta-analysis of 11 studies involving 856 patients with an anterior MI, the OR for an embolic event was 5.5 (95% CI 3.0 to 9.8) for those with an LV mural thrombus documented on echocardiography.¹⁴ Most embolic complications occur within 3 or 4 months after thrombus development. Although most emboli cause central nervous system infarcts, LV thrombi can also embolise to the abdominal vessels to cause mesenteric ischaemia. In a study by Acosta *et al*,¹⁵ 58 of 122 patients with SMA embolism had an intracardiac thrombus implicated as the source. The nature of the thrombus appears to affect its propensity to embolise; approximately half of mobile, protruding thrombi and about 10% of immobile, flat thrombi embolise without anticoagulation.¹⁶

Although no randomised trials exist to guide therapy, observational studies support anticoagulation to reduce the likelihood of embolisation in patients with an LV thrombus following MI. In a meta-analysis of seven observational studies that included

Learning points

- ▶ Abrupt cessation of direct thrombin inhibitors may trigger a hypercoagulable 'rebound phenomenon'.
- ▶ Perimyocardial infarction (MI) anticoagulation fails to decrease left ventricular (LV) thrombus development, but observational studies support anticoagulation to prevent embolisation of a post-MI LV thrombus.
- ▶ The recommended duration of treatment for an LV thrombus varies. The American Heart Association recommends lifelong anticoagulation with warfarin, whereas the European Heart Association recommends treatment for 3–6 months.

270 patients with anterior MI and echocardiographically documented LV thrombi, anticoagulation (compared with no anticoagulation) was associated with an 86% reduction in the rate of embolisation (odds ratio = 0.14; 95% CI 0.04 to 0.52).¹⁵ Currently, the American Heart Association recommends lifelong anticoagulation with warfarin, whereas the European Heart Association recommends treatment for 3–6 months.¹¹ Up to 65% of thrombi will resolve after 1 or 2 years of appropriate anticoagulation.¹⁶

Contributors All authors contributed to the research, drafting and revision involved in writing this manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Xu Y, Holbrook AM, Simpson CS, *et al.* Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. *CMAJ* 2013;1:115–E119.
- Patel MR, Hellkamp AS, Lokhnygina Y, *et al.* Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). *J Am Coll Cardiol* 2013;61:651–8.
- Hermans C, Claeys D. Review of the rebound phenomenon in new anticoagulant treatments. *Curr Med Res Opin* 2006;22:471–81.
- Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012;172:397–402.
- Schulman S, Kearon C, Kakkar AK, *et al.* Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013;368:709–18.
- Van de Werf F, Brueckmann M, Connolly SJ, *et al.* A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: THE Randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). *Am Heart J* 2012;163:931–7.
- Perzborn E, Heitmeier S, Buetehorn U, *et al.* Direct thrombin inhibitors, but not the direct factor Xa inhibitor rivaroxaban, increase tissue factor-induced hypercoagulability in vitro and in vivo. *J Thromb Haemost* 2014 Apr 27. doi:10.1111/jth.12591. [Epub ahead of print].
- Tenzer M. The spectrum of myocardial contusion: a review. *J Trauma Inj Infect Crit Care* 1985;7:620–7.
- Matitiau A, Tabachnik E, Stoecker D, *et al.* Thrombus in the left ventricle of a child with systemic emboli: an unusual presentation of hereditary protein C deficiency. *Pediatrics* 2001;107:421–2.
- Leung WH, Wong KL, Lau CP, *et al.* Association between antiphospholipid antibodies and cardiac abnormalities in patients with systemic lupus erythematosus. *Am J Med* 1990;89:411–19.
- Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction. *Heart* 2012;98:1743–9.
- Keren A, Goldberg S, Gottlieb S, *et al.* Natural history of left ventricular thrombi: their appearance and resolution in the posthospitalization period of acute myocardial infarction. *J Am Coll Cardiol* 1990;15:790–800.
- Stratton JR, Resnick AD. Increased embolic risk in patients with left ventricular thrombi. *Circulation* 1987;75:1004–11.
- Yadava OP, Yadav S, Juneja S, *et al.* Left ventricular thrombus sans overt cardiac pathology. *Ann Thorac Surg* 2003;76:623–5.
- Acosta S, Ogren M, Sternby NH, *et al.* Clinical implications for the management of acute thromboembolic occlusion of the superior mesenteric artery: autopsy findings in 213 patients. *Ann Surg* 2005;241:516–22.
- van Dantzig JM, Delemarre BJ, Bot H, *et al.* Left ventricular thrombus in acute myocardial infarction. *Eur Heart J* 1996;17:1640–5.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow