



CASE STUDY

Spontaneous cardiac tamponade associated with dabigatran use in an elderly woman

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Case Presentation: We report here a rare case of dabigatran-related spontaneous cardiac tamponade, which appeared in absence of the known risk factors that predispose the patient to bleed related to anticoagulant drugs. A 65-year-old lady presented to the emergency room with sudden onset dyspnea which woke her up in the early morning hours. Four days earlier, she had been started on dabigatran therapy for DVT. On examination, she was in shock. Transthoracic echocardiography confirmed cardiac tamponade. Emergent pericardiocentesis was done, draining 480 ml of haemorrhagic fluid, which tested negative for microbes and malignant cells. The patient recovered rapidly and fluid did not re-accumulate after withdrawal of dabigatran therapy. Spontaneous cardiac tamponade is rare with the use of direct anticoagulants, especially dabigatran, in the absence of predisposing risk factors.

Conclusions: This case study highlights the need for clinicians to be cognizant of this potentially life-threatening adverse drug reaction of dabigatran so that appropriate timely action can be taken toward diagnosis and management of this complication.

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Introduction

Dabigatran etexilate is a direct oral anticoagulant (DOAC), used in the prevention and treatment of thromboembolism in patients with deep vein thrombosis (DVT) and non-valvular atrial fibrillation (NVAF).

We are reporting here a rare case of Dabigatran-related spontaneous cardiac tamponade which appeared in absence of the known risk factors that predispose to DOAC related bleeding. This case is unique due to many reasons: (a) Although cardiac tamponade has been reported several times in patients on DOACs, undergoing surgical or

electrophysiological interventions (Yui *et al.*, 2018), the spontaneous tamponade occurring with this class of drugs is rare (Asad *et al.*, 2019; Sablani *et al.*, 2017; Sigawy *et al.*, 2015); (b) in the previously reported instances of cardiac tamponade with DOACs, almost all cases were found to be having at least one of the factors known to predispose to spontaneous bleeding in anticoagulated patients. Such factors include renal dysfunction, deranged coagulation parameters, or concomitant administration of drugs, that either increase the serum levels of the DOAC, or produce a synergistic effect on their anticoagulation properties. However, the patient described here, did not



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have any of these factors; (c) among all the cases of DOAC related spontaneous tamponade reported in the past, the majority occurred in patients taking direct factor Xa inhibitors apixaban or rivaroxaban (Oladiran *et al.*, 2018) rather than dabigatran. It is speculated that Dabigatran may be less likely to cause bleeding complications because, unlike other DOACs, its metabolism is not dependent upon the cytochrome P450 3A4 enzyme in the liver. Therefore, patients on co-prescription of cytochrome P450 3A4 enzyme inhibitors and DOACs other than dabigatran may acquire higher levels of anticoagulant effect. However, in the currently described case, the patient was on dabigatran, which does not undergo metabolism through this particular cytochrome enzyme.

Case presentation

A 65-year-old lady presented to the Emergency Room (ER) of our tertiary care center with sudden onset severe dyspnea and uneasiness, which woke her up in the early morning hours. She did not report chest pain, palpitation, syncope, cough, or fever. There was a history of recent hospitalization for DVT, for which she was started on dabigatran 150 mg twice daily, four days before the current episode. The dose used was appropriate for her age, weight,

and renal function. The patient was discharged from the hospital two days earlier, when her trans-thoracic echocardiography (TTE) and routine blood investigations, including total and differential leukocyte counts, coagulation profile, renal and liver parameters, were normal. She has also been prescribed Pantoprazole for epigastric discomfort.

On examination, she was in shock and had a barely palpable pulse. Her lungs were clear with bilateral normal air entry and vesicular breath sounds. The electrocardiogram revealed sinus bradycardia and no ischemic changes. An urgently done trans-thoracic echocardiogram (TTE) confirmed large pericardial effusion causing the near-total phasic collapse of the right ventricle in early diastole.

An emergent pericardiocentesis was performed, which yielded 480 mL of hemorrhagic fluid. The patient immediately became comfortable and alert, with normalization of the blood pressure and pulse. The laboratory parameters obtained on pericardial fluid analysis were, as mentioned in **Table 1**. Cultures for anaerobic or aerobic micro-organisms were negative, and malignant cells were not seen.

Table 1: Pericardial fluid analysis

Parameter	Result	Parameter	Result
Appearance	sanguineous	Specific gravity	1.019
RBC	present	Total protein	3.14 g/dL
WBC	200 cells/ μ L	LDH	189 IU
Cell type	neutrophils (70 %)	Gram staining	negative
Malignant cells	absent	Culture	no growth

Dabigatran was discontinued and substituted with Unfractionated Heparin, adjusting the dose under frequent monitoring of activated partial thromboplastin time. TTE, done the following day, ruled out any re-accumulation of fluid in pericardial space.

In the meantime, the patient complained of recurrent abdominal discomfort, for which a Gastroenterology opinion was sought. A detailed evaluation, including computerized tomography (CT) scan of the abdomen,

revealed carcinoma of the colon. A plain and contrast-enhanced computerized tomography (CECT) scan of the chest was done to rule out metastatic involvement of thoracic structures. It revealed enlarged mediastinal lymph nodes. The pericardium thickness and appearance were normal, there was no pericardial invasion by malignant tissues, and there was no re-accumulation of fluid (**Figure 1**). This scan was done thirteen days after pericardiocentesis.

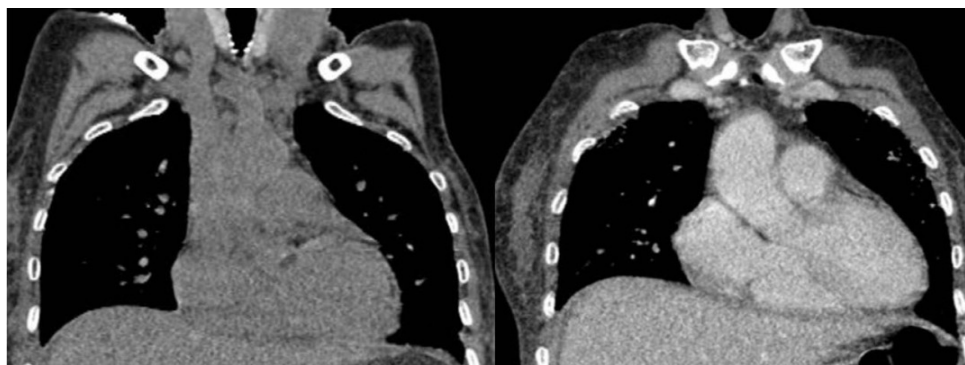


Figure 1: Plain (left) and contrast-enhanced (right) computerized tomography scans of the chest showing normal pericardium.

The patient was started on enoxaparin for long-term management of DVT and was transferred to the oncology unit for further management.

The estimation of the probability that a drug caused a particular adverse event is usually based on clinical judgment. Several observations are suggesting that the cardiac tamponade, in this case, was not related to the abdominal malignancy. These include the absence of malignant cells in the pericardial fluid, no evidence of pericardial invasion in the CECT chest (Fig 1), and no recurrence of pericardial fluid accumulation after dabigatran was discontinued. Hence, the clinical and temporal courses were strongly in favor of the fact that dabigatran was the cause for cardiac tamponade in this case.

An assessment using the adverse drug reaction (ADR) scale, the Naranjo causality scale (Naranjo *et al.*, 2018) revealed a score of 8, suggesting the probability of a strong causal association. The ADR was classified as type A (augmented) according to the classification suggested by Edwards and Aronson (Edwards *et al.*, 2000). Since the cardiac tamponade necessitated the patient to receive intensive medical care, the reaction was classified as level 5 (severe) by Modified Hartwig and Siegel criteria (Hartwig *et al.*, 1992). The modified Schumock and Thornton's criteria of preventability (Schumock *et al.*, 1992) indicated that the reaction was probably preventable.

Conclusions

Dabigatran is considered a relatively safe choice for long-term DVT prophylaxis; however, spontaneous hemopericardium can occur with its use, even with doses appropriated for age, weight, and renal function.

This report has important clinical implications. First, although, the current evidence supports the use of DOACs in DVT associated with malignancy (Rojas-Hernandez *et al.*, 2019), there is a possibility that these agents cause disproportionately more severe bleeding in cancer patients; therefore, more studies are required for the assessment of their safety in this scenario. This risk has been indicated in a recent meta-analysis also (Papanastasiou *et al.*, 2020), albeit more with VKA than with DOACs. Second, as

spontaneous cardiac tamponade has been observed with DOACs often, there should be a high index of suspicion for this diagnosis while treating patients taking DOAC, when they present with shock or unexplained dyspnea. Third, there is a possibility of some unknown mechanism by which DOACs cause spontaneous cardiac tamponade, which needs to be investigated, probably using immuno-histochemistry studies of the pericardial biopsy tissue from such patients.

This case study highlights the need for clinicians to be cognizant of this potentially life-threatening adverse drug reaction so that appropriate timely action can be taken. Further research is essential to identify the mechanisms behind spontaneous hemopericardium associated with DOACs and to review the safety of their use in patients with malignancy.

Conflict of interests

The authors declare that there is no conflict of interests

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