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Letter to the Editor
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Spontaneous Hemopericardium Complicated with Hemothorax in a Patient Receiving Edoxaban Therapy: A Case Report

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Key Words: Case report • Complication • Edoxaban • Hemopericardium

INTRODUCTION

The introduction of non-vitamin K antagonists oral anticoagulants (NOACs) has been a major stride in stroke prevention for atrial fibrillation (AF). Edoxaban, a factor Xa inhibitor, has a remarkable safety profile and efficacy.[1] Spontaneous hemopericardium is a rare complication of oral anticoagulant and had been reported in patients taking warfarin,[2,3] dabigatran,[4] rivaroxaban,[5] and apixaban.[6] To our knowledge, our case is the first to report a spontaneous hemopericardium in a patient taking edoxaban.

CASE REPORT

A 77-year-old man with type 2 diabetes mellitus, hypertension and resected stage I hepatocellular carcinoma without cirrhosis presented with a day of chest pain and vomiting. He had been diagnosed as paroxysmal AF 2 months earlier. He had no previous renal (creatinine 0.86 mg/dL) or liver dysfunction (bilirubin 0.91 mg/dL, ALT 36 U/L AST 33 U/L) and weigh 58.2 kg when AF was diagnosed. He received amiodarone, bisoprolol and low dose edoxaban 30 mg daily due to P-glycoprotein interaction with amiodarone. The echocardiogram one-week prior showed preserved ejection fraction with a minimal amount pericardial effusion. On examination, he was diaphoretic, hypotensive (71/37 mmHg), tachycardic (128/min) and in respiratory distress (22/min). The jugular veins were engorged. The heart sound was distant but no murmur, S3, or S4 was detected. Electrocardiogram showed AF with rapid ventricular response and low voltage (Figure 1). Initial work up revealed increased international normalized ratio, anemia, acute hepatitis (bilirubin 1.62 mg/dL, AST 1997 U/L, ALT 2108 U/L) and acute kidney injury (creatinine 2.48 mg/ dL). Computed tomography scan revealed massive hyperdense pericardial effusion (48HU) (Figure 2A, B). Bedside echocardiography showed pericardial effusion with diastolic collapse of the right atrium and ventricle. A 16Fr pigtail drain was inserted for tamponade, with an initial output of 590 ml bloody fluid which was followed by dramatic symptomatic and hemodynamic improvement. He then received fluid resuscitation, intravenous tranexamic acid (250 mg q8h for a total of 5 days) and fresh frozen plasma transfusion and chest tube insertion for massive spontaneous left side hemothorax developed on the next day (Figure 2C, D). Because of the unavailability of antidote for edoxaban, he received 2 units of fresh frozen plasma transfusion. The fluid samples were negative for gram stain, acid-fast stain, culture and cytology. The drains were removed successfully, and the patient was discharged to home. After carefully discussed about the risk of bleeding and thrombosis, the patient decided to minimize the risk of bleeding to a minimum. Thus, we did not to restart oral anticoagulatant therapy, he is now currently under regular follow up with no more bleeding or embolic event.

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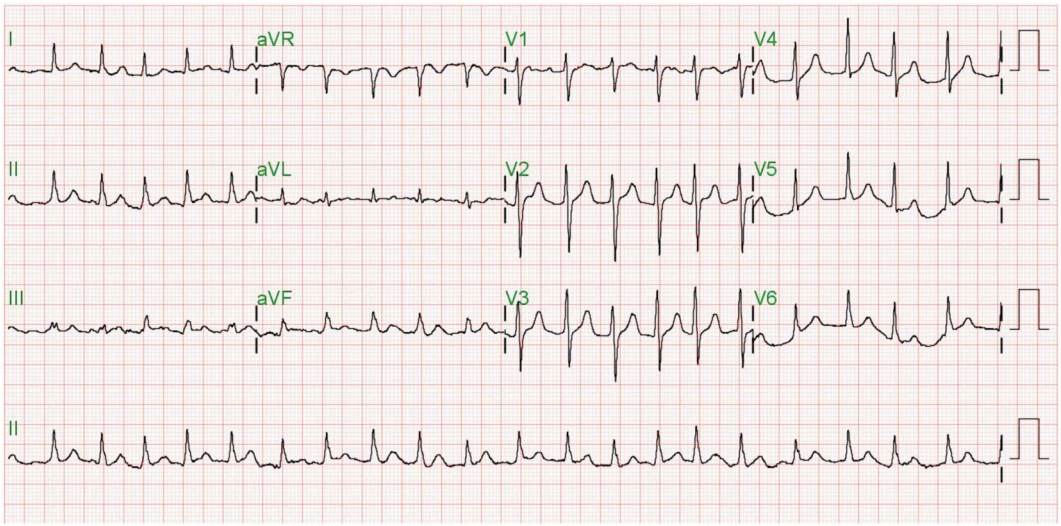

Figure 1. *ECG at admission showed atrial fibrillation with rapid ventricular response rate, low voltage at frontal leads.*

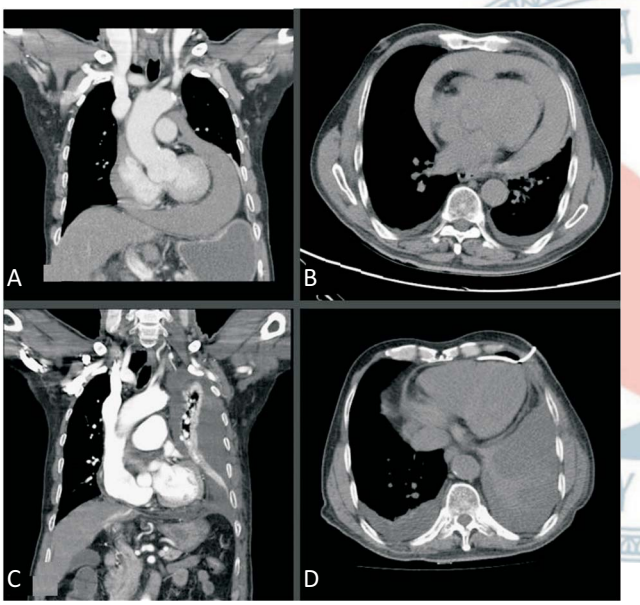

Figure 2. *Panel A and B show the chest computed tomography (CT) at admission with a massive high density (48HU) pericardial effusion implying hemopericadium. Panel C and D show the chest CT 2 days after admission showed only minimal pericardial effusion after pigtail catheter drainage, unfortunately, newly developed massive left side pleural effusion was noted with passive atelectasis.*

DISCUSSION

To the best of our knowledge, this is the first report of spontaneous hemopericardium after a use of edoxaban for AF stroke prevention. Although NOAC offers better safety profile than warfarin, spontaneous hemopericardium related to rivaroxaban,[5] apixaban[6] and dabigatran[4] have been reported. Our report on edoxaban have completed the puzzle showing that spontaneous hemopericardium is universal to all oral anticoagulants. Spontaneous hemopericardium is a rare adverse event of NOAC which has not been reported in all major trials for AF prevention. Previously reported cases were either idiopathic or related to kidney dysfunction[4] and/or drug interaction.[5,6] The reported events were usually not fatal but urgent pericardiocentesis and anticoagulant reversal were essential for clinical stabilization. For our patient, the acute kidney injury and acute liver dysfunction may be a result of shock, as evident by rapid recovery after pericardiocentesis. Interaction between amiodarone and edoxaban through inhibition of P-glycoprotein/ABCB1 metabolism may increase the level of edoxaban in our case. However, in a subgroup analysis of the ENGAGE AF-TIMI 48 trial, concomitant use of amiodarone and low dose edoxaban was not associated with increased risk of major bleeding while the risk of stroke or systemic embolism was lower when compared with those randomized to warfarin or those without concomitant amiodarone use.[7] Hemopericardium with cardiac tamponade require early recognition and immediate pericardiocentesis. Urgent correction of anticoagulation with four-factor prothrombin complex concentrates or fresh frozen plasma is recommended to control bleeding while Andexanet, the first antidote for factor Xa inhibitor has just been approved by the FDA, albeit the reversal of

edoxaban was not covered in the indication.[8] Cautious prescription with correct dosing for patients at high risk of bleeding and potential drug-drug interaction and careful monitoring of renal and liver function may be the necessary to provide protection and safety for patient taking NOACs.

LEARNING POINTS

1. Spontaneous hemopericardium is a rare but critical adverse event of NOACs.
2. Drug overdose, kidney dysfunction, liver dysfunction, and drug interaction were associated with hemopericardium.
3. Immediate pericardiocentesis, urgent correction of anticoagulation with four-factor PCCs or fresh frozen plasma is recommended for the management of spontaneous hemopericardium.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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