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CASE REPORT
Other

Hemopericardium with subsequent cardiac tamponade secondary to rivaroxaban treatment: a case report

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Background The use and utility of novel oral anticoagulants has been increasing in clinical practice due to their relatively lower incidence of side effects such as intracranial haemorrhage, particularly in the elderly, when compared with vitamin K antagonists. Rivaroxaban is a factor Xa and prothrombinase inhibitor indicated for stroke and venous thromboembolism prophylaxis in non-valvular atrial fibrillation as well as treatment of venous thromboembolism.

Case summary A patient with history of paroxysmal atrial fibrillation on Rivaroxaban presented with generalized malaise, lightheadedness, and dizziness. The patient was found to be in profound cardiogenic shock despite unremarkable cardiac enzymes. Electrocardiogram revealed rate controlled atrial fibrillation and T-wave inversions in the inferolateral leads without associated electrical alternans. Bedside echocardiogram revealed a large pericardial effusion consistent with cardiac tamponade physiology. Following anticoagulation reversal, the patient underwent urgent pericardiocentesis yielding haemorrhagic fluid, with subsequent improvement in haemodynamic status. Despite the presence of retroperitoneal lymphadenopathy on previous computed tomography of the abdomen and concern for underlying malignant effusion secondary to lymphoma, cytology of the fluid revealed no evidence of malignant cells and follow-up flow cytometry and bone marrow biopsy were unremarkable.

Discussion While hemopericardium is not listed as a known side effect of Rivaroxaban, previous cases of hemopericardium secondary to Rivaroxaban have been described in the literature secondary to pre-disposing risk factors including CYP450 drug interactions or cardiac device implantations. In this case, the patient experienced a spontaneous hemopericardium on Rivaroxaban without any previously elucidated risk factors or evidence of malignancy.

Keywords Rivaroxaban • Hemopericardium • Cardiac tamponade • Case report • NOAC • DOAC

Learning points

- Consider Rivaroxaban as the potential offending agent for patients presenting with hemopericardium and subsequent cardiac tamponade secondary to an unclear aetiology.
- Previous cases of hemopericardium due to Rivaroxaban have been attributed to drug interactions from CYP3A4 inhibition or recent elective cardiac device implantations.
- Concurrent medications known to interact with cytochrome P450 should considered and stratified appropriately, particularly in patients with known underlying renal or hepatic dysfunction, and on azole antifungals or protease inhibitors.

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Introduction

The use and utility of novel oral anticoagulants (NOACs) has been increasing in clinical practice due to their relatively lower incidence of side effects such as intracranial haemorrhage, particularly in the elderly, when compared with vitamin K antagonists.[1] NOACs are associated with an overall lower risk of major bleeding and lower incidence of thromboembolic events as compared to warfarin. In addition, a predictable clinical profile along with a lack of need for periodic monitoring makes them a convenient option for patients with baseline debility or dementia. Rivaroxaban is a factor Xa and prothrombinase inhibitor indicated for stroke and venous thromboembolism prophylaxis in non-valvular atrial fibrillation as well as treatment of venous thromboembolism based on the ROCKET AF, EINSTEIN DVT, and EINSTEIN PE studies.[2–4] While hemopericardium is not listed as a known side effect of Rivaroxaban, previous cases of hemopericardium secondary to Rivaroxaban have been described in the literature secondary to pre-disposing risk factors including CYP450 drug interactions or cardiac device implantations.[5–9]

Timeline

10 days prior	Patient presents with atypical chest pain. Diagnostic workup including troponins, electrocardiogram, and echocardiogram was unremarkable. Computed tomography (CT) angiogram of chest, abdomen, and pelvis was obtained to assess the aorta, which revealed no acute pathology but did note the presence of retroperitoneal lymphadenopathy. The patient was discharged with outpatient follow-up.
3 days prior	Patient holds Rivaroxaban in anticipation of gastrointestinal endoscopy for evaluation of chronic anaemia.
1 day prior	Patient undergoes upper and lower gastrointestinal endoscopy which reveals no overt bleeding or evidence of malignancy.
Hour 1	Patient presents with generalized malaise, lightheadedness, and dizziness. Found to be hypotensive with a narrow pulse pressure and blood pressure of 80/60 mmHg and tachycardic with a heart rate over 110 b.p.m. On exam, patient is intermittently somnolent with evidence of jugular venous distension, distant heart sounds, prolonged capillary refill, and cool extremities.
Hour 3	Intravenous crystalloids administered and right internal jugular central venous catheter placed for profound hypotension.
Hour 4	Vasopressors initiated with norepinephrine and vasopressin. Admitted to cardiac critical care unit.
Hour 6	Bedside echocardiogram reveals a large global pericardial effusion with concern for cardiac tamponade physiology.
Hour 9	Urgent prothrombin complex concentrate administered to reverse elevated international normalized ratio.
Hour 10	Urgent pericardial drain placed with 1.5 L of haemorrhagic fluid output.
Day 2	Improvement in tamponade physiology on transthoracic echocardiogram.
Day 3	Vasopressors discontinued and pericardial drain removed.
Day 7	Bone marrow biopsy performed. CT-guided biopsy of retroperitoneal lymph node biopsy not performed as the lymph nodes are too small to be biopsied per interventional radiology.
Day 11	Discharged successfully without further complications.
Month 1	Follow-up with haematology outpatient noted unremarkable malignancy workup including pericardial fluid cytology, bone marrow biopsy, flow cytometry of marrow, and chromosome studies of marrow.
Month 3	Evaluated by haematology at another quaternary centre, further testing and bone marrow biopsy were reviewed with no new conclusions.
Month 4	Follow-up CT with contrast of chest, abdomen and pelvis demonstrated no progression of lymphadenopathy or ascending aorta dilation.
Month 5	Follow-up with haematology outpatient with no new developments. Plan for observation and active surveillance.

Case presentation

An 84-year-old man with a past medical history of paroxysmal atrial fibrillation on Rivaroxaban, chronic pancytopenia, coronary artery disease status post remote percutaneous coronary intervention, asymptomatic dilated ascending aorta (5.0 cm in diameter, followed serially, stable for 8 years), essential hypertension and hypothyroidism was admitted for general malaise, lightheadedness, and dizziness. The last dose of Rivaroxaban was 72 h prior to presentation as the patient underwent upper and lower gastrointestinal endoscopy 24 h prior to presentation, for evaluation of chronic anaemia, which revealed non-obstructive schatzki's ring, mild diverticulosis, three small polyps in ascending colon which were resected with follow-up pathology showing tubular adenoma, and non-bleeding internal haemorrhoids. The patient was not taking any medications known to interact with Rivaroxaban. Upon presentation to the emergency department, the patient was noted to be hypotensive with a narrow pulse pressure and blood pressure of 80/60 mmHg and tachycardic with a heart rate over 110 b.p.m. On exam, patient was intermittently somnolent with evidence of jugular venous distension, distant heart sounds, prolonged capillary refill, and cool extremities. The platelet

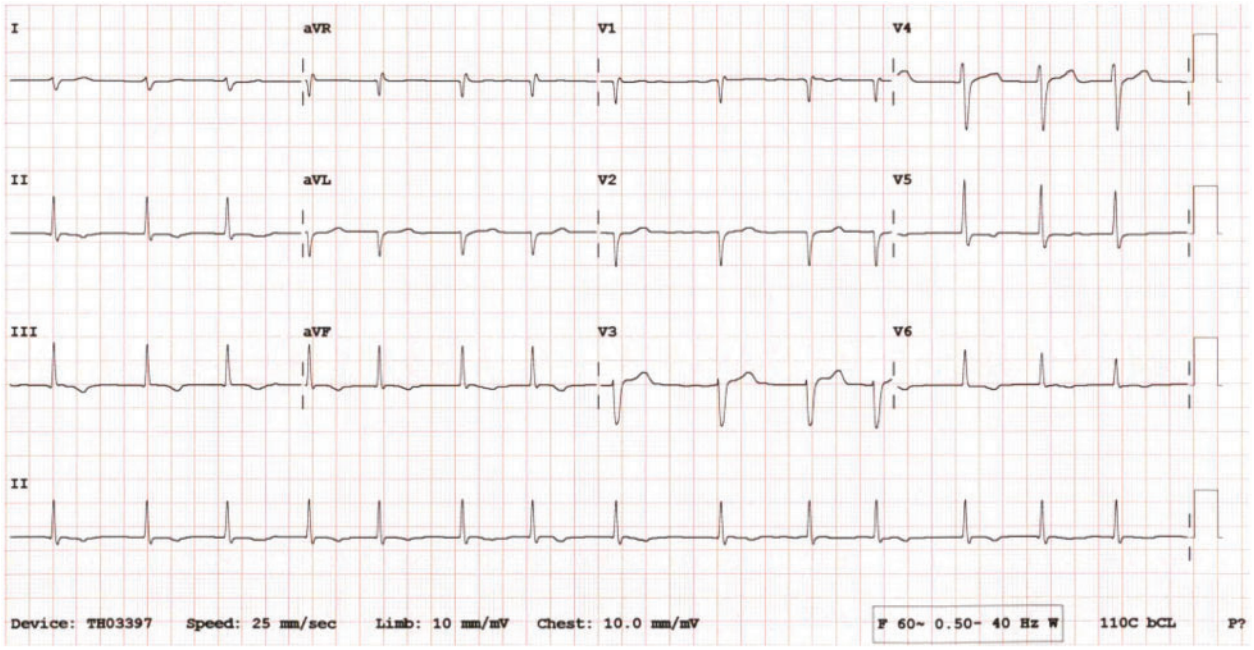


Figure 1 Initial electrocardiogram demonstrating atrial fibrillation and T-wave inversions in inferolateral leads.

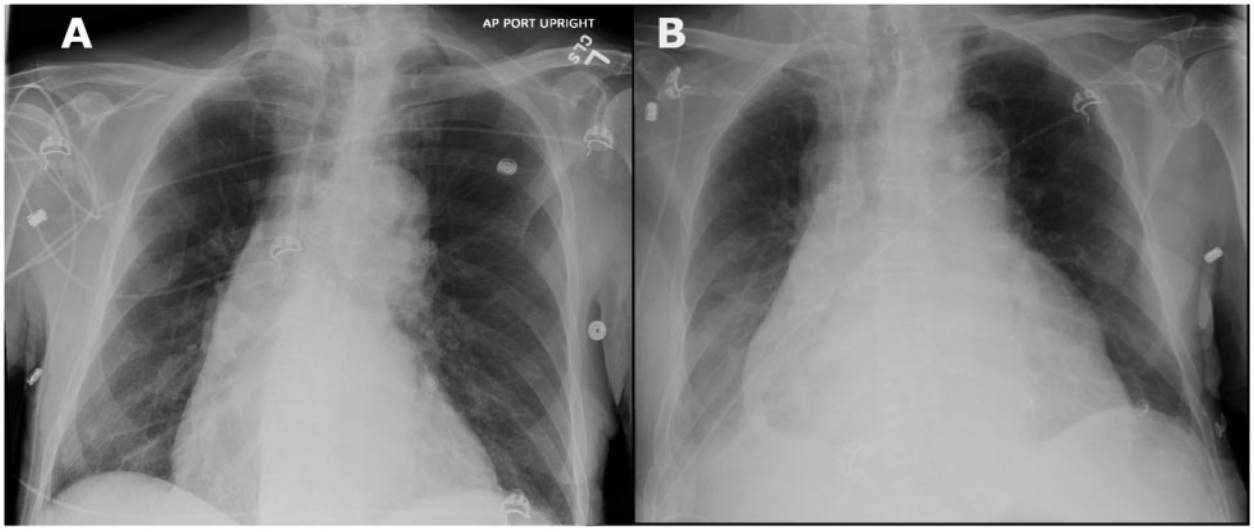
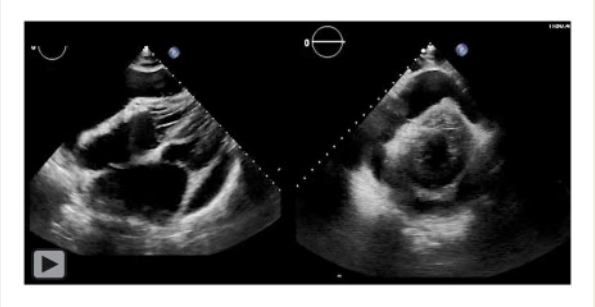


Figure 2 Chest X-ray from 8 days prior (*A*) compared to chest X-ray on admission (*B*) demonstrating enlarged cardiac silhouette.

count on arrival was 219 × 10^9/L (150–450 × 10^9/L). There was no significant troponin elevation. Electrocardiogram revealed atrial fibrillation with a rate of 87 and T-wave inversions in the inferolateral leads without associated electrical alternans (*Figure 1*). Chest radiograph showed a right pleural effusion with an enlarged cardiac silhouette increased in size from a previous radiograph (*Figure 2*). Following inadequate response to 2.5 L of isotonic crystalloid, the patient was transferred to the intensive care unit and started on high doses of multiple vasopressors. He was noted to have an elevated lactate of 4.3 mmol/L (0.4–2.0 mmol/L), creatinine of 0.225 mmol/L (0.0530–0.1149 mmol/L), aspartate transaminase (AST) of 1499 U/L (0–41 U/L), alanine transaminase (ALT) of 1813 U/L (0–40 U/L), and international normalized ratio (INR) of 3.7 (0.9–1.2) concerning for renal and hepatic hypoperfusion. Bedside echocardiogram was performed which revealed a large global pericardial effusion with a maximal depth of 30 mm with respiratory collapse of the right ventricle



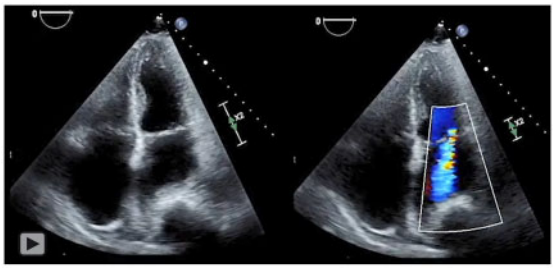
Video 1 Initial echocardiogram demonstrating a large pericardial effusion with right sided tamponade physiology.

consistent with cardiac tamponade physiology (*Video 1*). Due to worsening hypoxia and haemodynamic instability, the patient underwent immediate INR reversal with prothrombin complex concentrate and then urgent pericardiocentesis via subxiphoid approach, while on non-invasive positive pressure ventilation, which yielded 1.5 L of grossly bloody fluid (*Table 1*). A pericardial drain was inserted to prevent further fluid accumulation. Repeat INR was 2.2 (0.9–1.2). Post-procedure echocardiogram revealed resolution of tamponade physiology with newly reduced ejection fraction of 35% and severe mitral regurgitation (*Video 2*). The patient's oxygenation and haemodynamic parameters improved following the procedure and he was successfully discharged without further complications. The patient was discharged without anticoagulation due to concern for significant bleeding risk and potential for recurrent haemorrhagic pericardial effusion.

Notably, 10 days prior, patient had presented to the hospital with atypical chest pain. Diagnostic workup including troponins, electrocardiogram, and echocardiogram was unremarkable. Computed tomography (CT) angiogram of chest, abdomen, and pelvis was obtained to assess the aorta, which revealed no acute pathology but did note the presence of retroperitoneal lymphadenopathy (*Figure 3*). The patient was discharged as the chest pain was deemed to be pleuritic in nature, of non-cardiac aetiology and resolved spontaneously. Given subsequent presentation for hemopericardium, there was concern for underlying malignant effusion, but cytology of the pericardial fluid revealed no evidence of malignant cells. Bone marrow biopsy revealed no overt dysplasia, only normal cellularity with trilineage haematopoiesis. Flow cytometry and chromosome studies of marrow were also unremarkable. A retroperitoneal lymph node biopsy was not performed as the lymph nodes were not deemed pathological by size criteria and were too small to be biopsied per interventional radiology. Haematology recommended long-term follow-up with repeat imaging. Follow-up CT with contrast of chest, abdomen and pelvis 4 months later demonstrated no progression of lymphadenopathy or ascending aorta dilation. Evaluation by two independent haematologists at major quaternary centres including a repeat reading of the bone marrow biopsy, found no evidence of malignancy, recommending observation and active surveillance.

Table 1 Biochemical and histological examination of the pericardial fluid

Specimen type	Pericardial fluid
Colour	Red
Clarity	Grossly bloody
Red blood cell count	2 617 534/μL
Nucleated cell count	1553/μL
Neutrophils	92%
Lymphocyte	4%
Macrophages	4%
Amylase	47 U/L
Glucose	10 mg/dL
LDH	779 U/L
Total protein	6 g/dL
Culture	No growth after 5 days
Gram stain	WBC present on direct smear, no organisms seen
Anaerobic culture	No growth after 5 days
Fungal smear	No fungal elements seen on concentrated smear
Fungal culture	No fungus isolated after 4 weeks
AFB smear	No acid fast bacilli (concentrated smear)
AFB culture	No acid fast bacilli isolated in 8 weeks
Cytology	No malignant cells identified



Video 2 Post-procedure echocardiogram demonstrating trivial pericardial fluid with resolution of tamponade physiology, also a reduced ejection fraction of 35% with severe mitral regurgitation.

Discussion

Previous cases of hemopericardium due to Rivaroxaban have been attributed to interactions with CYP3A4 via inhibitors such as saw palmetto or amiodarone leading to increased haemorrhagic risk.[7,10] In addition, two reported cases detail patients who underwent elective pacemaker or cardiac device implantation 3–6 months prior.[8,9] Typically, grossly haemorrhagic pericardial fluid raises suspicion for underlying malignancy, and given our patient's history of chronic pancytopenia, a thorough workup was conducted which ruled out this

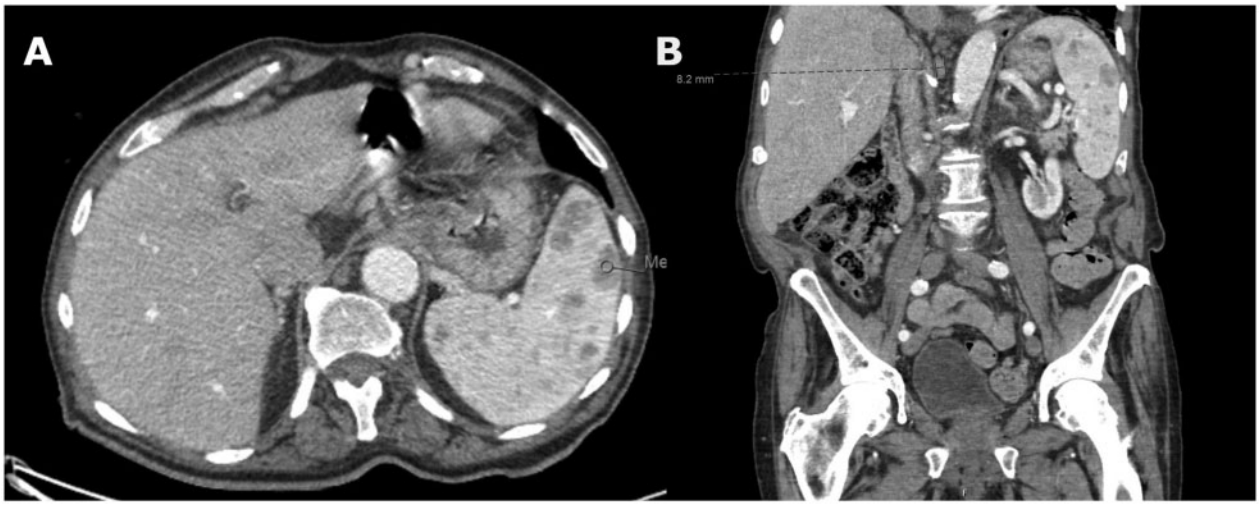


Figure 3 Retroperitoneal lymphadenopathy demonstrated on computed tomography angiogram abdomen with axial view (*A*) and coronal view (*B*).

possibility. Another aetiology includes myocardial infarction, but this was less likely based on electrocardiographic and laboratory evidence. While this appears to be a spontaneous event in the setting of Rivaroxaban use, the patient's underlying pancytopenia may have increased the risk of hemopericardium.

Rivaroxaban is primarily metabolized via hepatic cytochrome P450 enzymes including CYP3A4/5 and CYP2J2 but approximately one-third of the dose is unmetabolized and eliminated via renal excretion via P-glycoprotein transporters.[11] The remainder is via breast cancer resistance proteins and oxidative biotransformation and non-CYP mediated hydrolysis of amide bonds.[12] Cases of hemopericardium are sporadic overall but given the possibility of severe complications, changes to guidelines and protocols for monitoring levels of these NOACs may be indicated. A higher level of clinical suspicion may be appropriate in patients currently taking NOACs who present with non-specific symptoms similar to our gentleman with anaemia of unknown aetiology. While significant renal dysfunction is a contraindication for the administration of Rivaroxaban, reduced doses can be utilized in patients with up to stage 4 chronic kidney disease. Subsequently, concurrent medications known to interact with cytochrome P450 must be considered and stratified appropriately, particularly in patients with known underlying renal or hepatic dysfunction. The significance of the interaction must also be considered as many medications may not produce a clinically relevant effect while strong inhibitors such as azole antifungals and protease inhibitors lead to significantly elevated serum levels of Rivaroxaban.[12]

Typically, anti-Factor Xa chromogenic assays are used to measure the drug concentration of Rivaroxaban but these levels reportedly do not have any direct correlation with anticoagulant activity[13] further emphasizing the need for careful assessment of concurrent medications and supplements for potential interactions. For our patient, urgent reversal with recombinant factor Xa was considered but due to the urgent nature of the situation and concurrent hepatic dysfunction, prothrombin concentrate was utilized instead. A previous randomized, double-blind study demonstrated efficacy in reversing elongated prothrombin time induced by Rivaroxaban with prothrombin complex concentrate albeit with a limited sample size.[14] However, our patient was felt to be outside the window period for recombinant factor Xa administration as he had not taken his dose of Rivaroxaban prior to presentation. Administration of recombinant factor Xa demonstrated significant haemostasis in a majority of patients within 12 h of major bleeding but currently, data for bleeding outside of intracranial and gastrointestinal sources available based on the ANEXXA-4 study is limited.[15] Larger scale trials in the future would be helpful to obtain more information regarding pharmacokinetics and potential reversal agents in order to guide proper clinical use.

Lead author biography

Pinang Shastri, D.O. is a resident physician at the University of Toledo College of Medicine and Life Sciences. His research interests include cardiac imaging, novel anticoagulation therapies, and cardiac critical care.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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