

Rivaroxaban Related Bilateral Adrenal Hemorrhage: A Rare Complications of Direct Oral Anticoagulants – A Case Reports

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Patient: Female, 68
Final Diagnosis: Adrenal hemorrhage
Symptoms: Abdominal and/or epigastric pain
Medication: Rivaroxavan
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Rare disease

Background: Adrenal hemorrhage is an uncommon and under-recognized disorder with a wide array of etiologies ranging from pregnancy to septic shock. It is one of the complications of anticoagulation therapy, including direct anticoagulant medications.

Case Report: Here, we present a case of a 68-year-old female with recent right knee arthroplasty who was on rivaroxaban for deep vein thrombosis (DVT) prophylaxis presented to the emergency department (ED) for severe acute onset abdominal pain, computed tomography (CT) of abdomen and pelvis revealed possible left adrenal hemorrhage that was confirmed with magnetic resonance imaging (MRI). On repeat CT, her unilateral adrenal hemorrhage converted to a bilateral adrenal hemorrhage (BAH) and, as a result, the patient developed adrenal insufficiency.

Conclusions: An undiagnosed and untreated adrenal hemorrhage can have catastrophic consequences, leading to adrenal insufficiency with potential shock and death. Therefore, it is important for clinicians to have an increased awareness and knowledge about adrenal hemorrhage.

MeSH Keywords: Adrenal Insufficiency • Anticoagulants • Arthroplasty, Replacement, Knee

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Background

Adrenal hemorrhage is a rare disorder with an estimated 15% of mortality rate [1]. Adrenal hemorrhage has ambiguous symptoms and can develop in many clinical scenarios, its diagnosis so challenging that it is often diagnosed during post-mortem [2]. Symptoms of adrenal hemorrhage include abdominal pain, back pain, flank pain, fever, and hypotension. Predisposing factors for adrenal hemorrhage include the post-operative period, sepsis, stress, physical trauma, coagulopathies, and anticoagulant medications. A useful way to classify adrenal hemorrhage is unilateral versus bilateral, the former of which is usually biochemically silent, and the latter has a worse prognosis [3]. Here, we report a case of adrenal hemorrhage in a patient who recently started on direct oral anticoagulant (DOAC) – rivaroxaban – and presented with abdominal pain, who initially had a unilateral adrenal hemorrhage which later converted to bilateral with ensuing adrenal insufficiency.

Case Report

A 68-year-old female with a medical history of peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), hypertension (HTN), and recent right knee arthroplasty presented to the emergency department (ED) with severe sudden left upper quadrant (LUQ) abdominal pain of one-hour duration. The pain radiated to the left lower quadrant (LLQ) and the epigastric region. The pain was dull in quality, 10 out of 10 in severity

and unlike any pain patient had experienced before and was associated with nausea and one episode of vomiting. The patient could not identify any alleviating or aggravating factors for her pain. Her pain was not worsened by movement and upon interview the patient was rolling around the bed, unable to find a comfortable position. The patient denied fever, chills, recent exposure to sick contacts, constipation, urinary changes, blood in stools and recent trauma.

The vitals on admission were blood pressure 178/78 mmHg, pulse 86/minute, temperature 36.72°C (98.1°F), respiratory rate 18 breaths/minute, and pulse oximetry 97% on room air. Physical examination was significant for LUQ and epigastric tenderness on deep palpation without rebound or guarding.

The patient was started on a 2-week course of rivaroxaban 10 mg for deep vein thrombosis (DVT) prophylaxis after uncomplicated right knee arthroplasty 8 days prior to presentation. Upon arrival in the ED, patient's rivaroxaban was discontinued due to concern for aortic dissection (AD) or a ruptured abdominal aortic aneurysm (AAA) and was kept on sequential compression device (SCD).

Initial laboratory investigation (Table 1, Column 2) was notable only for mild leukocytosis WBC 12.6 cells/L (normal 4.5–11 cells/L), comprehensive metabolic panel, amylase and lipase were within normal limits. Computed tomography angiography (CTA) was negative for AAA and AD but revealed non-specific nodular thickening and surrounding fatty infiltration

Table 1. Summary of laboratory investigations at baseline and follow-up.

Lab value	Baseline	1 st admission	2 nd admission	After heparin drip	Reference value
BUN	15	15	9	16	5–25 mg/dL
Creatinine	0.85	0.96	0.94	0.98	0.44–1.0 mg/dL
GFR	60	58	54	56	>60
AST	20	27	17	22	10–42 iU/L
ALT	14	24	13	16	10–60 iU/L
Alkaline phosphatase	44	78	73	77	38–126 iU/L
Total bilirubin	Not collected	0.9	0.7	0.4	0.1–1.3 mg/dL
Direct bilirubin	Not collected	<0.1	Not collected	Not collected	
INR	Not collected	1.22	1.35	1.89	0.88–1.55
Leukocytes	9.1	12.6	10.1	10.4	4.5–11 K/uL
Hemoglobin	10.8	10.7	8.2	7.5	12–16 gm/dL
Hematocrit	33.1	33	35.5	23.4	35–48%
Platelets	205	374	90	35	140–450 K/uL

BUN – blood urea nitrogen; GFR – glomerular filtration rate; AST – aspartate aminotransferase; ALT – alanine aminotransferase; INR – international normalized ratio.

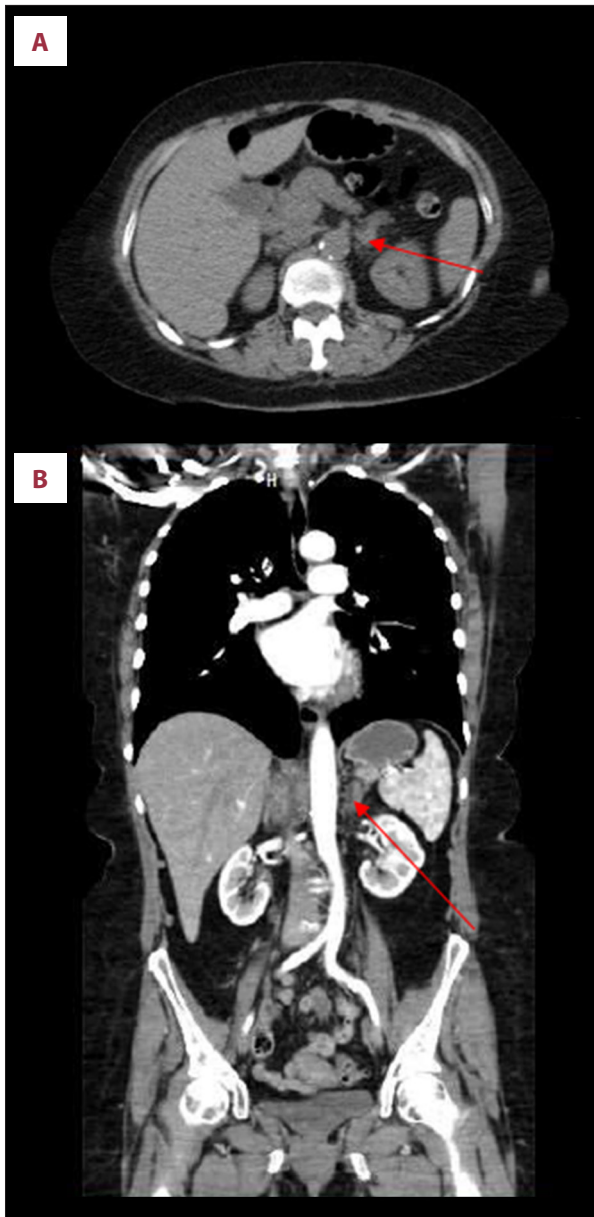


Figure 1. Computed tomography angiography on admission showing fat stranding of the left adrenal suspicious for adrenal hemorrhage. (A) The transverse view; (B) the coronal view. The red arrows indicate the areas of fat stranding.

of the left adrenal gland, possibly indicating an adrenal hemorrhage, less likely pancreatitis and it was difficult to exclude malignancy. For further evaluation, CT abdomen and pelvis was done, which confirmed findings of adrenal hemorrhage and was not suggestive of neoplasm (Figure 1).

As per radiologist's suggestion magnetic resonance imaging (MRI) was performed which revealed a left 2x4x2.6 cm focal area of signal intensity in the left adrenal gland and

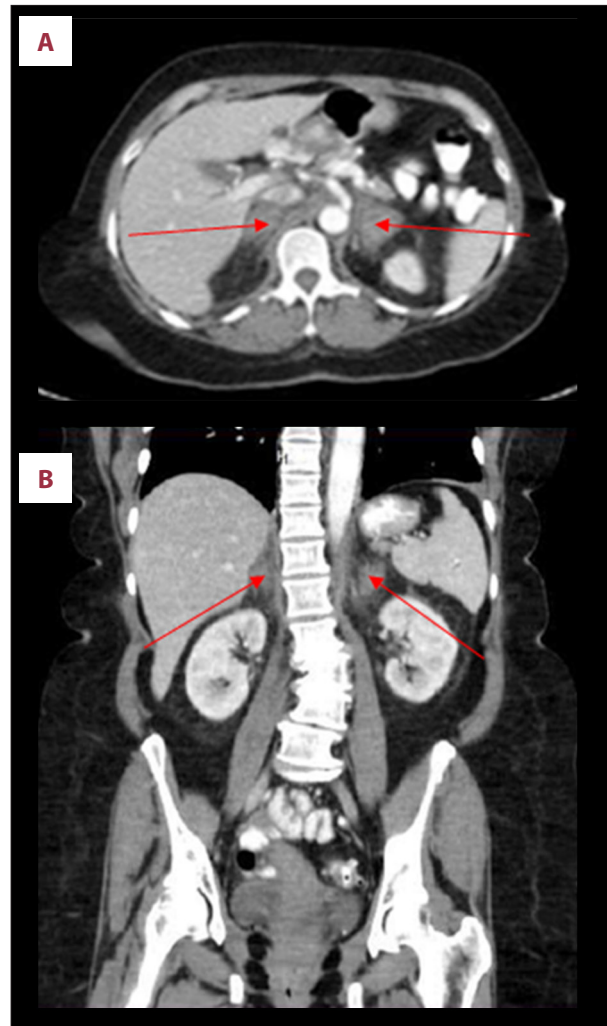


Figure 2. Repeat computed tomography showing interval increase in the left adrenal hemorrhage with development of a new right adrenal hemorrhage. (A) The transverse view; (B) the coronal view. The red arrows indicate the areas of fat stranding.

inflammatory changes in adjacent fat consistent with an adrenal hemorrhage, negative for any lymphadenopathy, organomegaly or findings suggestive of malignancy. The endocrine surgical team was consulted and recommended for conservative management and close monitoring for adrenal insufficiency. After 2 days, the pain intensity decreased but the patient became hypotensive and hypoglycemic. Stress dose of intravenous steroids along with intravenous fluids and glucose supplementation were started. On day 4 of hospitalization, repeat CT abdomen/pelvis was performed to evaluate adrenal hemorrhage which showed interval increase in the left adrenal hemorrhage as well as development of a right adrenal hemorrhage (Figure 2) and a probable small pulmonary embolism in the left lower lobe. After that, CTA of the chest/abdomen/pelvis was done which confirmed the interval development of small

thrombotic pulmonary emboli within branches of the left lower lobe pulmonary arterial tree. Doppler ultrasounds of the lower extremities were negative for DVT and the patient was kept on sequential compression devices (SCDs). No anticoagulation was given due to development of bilateral adrenal hemorrhage (BAH). Inferior vena cava (IVC) filter was placed by interventional radiology.

As per endocrinology, the patient was weaned down to oral steroids. Patient was discharged home after consultation with hematologist without any oral anticoagulation and with a scheduled repeat CT in 1 week to evaluate her BAH. Unfortunately, 4 days after discharge she came back to the ED with complaints of mild right lower quadrant (RLQ) abdominal pain and was found to have a complete DVT extending inferiorly from the IVC filter to the right femoral, right popliteal, right posterior tibial, right peroneal, and right anterior veins along with a partial DVT of the right common femoral vein. She was started on a heparin drip after discussion with hematologist. The next day, she developed thrombocytopenia. Heparin induced thrombocytopenia (HIT) was considered after excluding other potential causes of thrombocytopenia including reviewing of the medication lists, heparin drip was stopped and switched to argatroban. Later, serotonin release assay (SRA-HDA) heparin dependent platelet antibody came back positive of 2.430 optical units (reference range under 0.399 optical units) confirming HIT. Later the argatroban was switched to warfarin and was discharged home with close follow-up with her hematologist, oncologist, and endocrinologist. On follow-up, the patient was continued on oral steroids and regularly follow-up in endocrine clinic.

Discussion

Adrenal hemorrhage is an uncommon cause of abdominal pain which is often missed by clinicians. The exact pathologic process of spontaneous non-traumatic adrenal hemorrhage is unknown, but it is hypothesized to be related to the adrenal gland's vascular structure possibly triggered by adrenal congestion [1]. Patients with this condition can decompensate quickly and needs careful monitoring.

The symptoms of adrenal hemorrhage are non-specific such as nausea, vomiting, fever, severe abdominal pain along with symptoms of possible adrenal insufficiency such as lightheadedness, hypoglycemia, hyperkalemia, hyponatremia, and hypotension [4]. Two of the most classic features are fever which occurs in about 70% of cases and abdominal pain, the latter of which was seen in this patient [1]. Given the vague nature of the symptoms of adrenal hemorrhage imaging plays a key diagnostic role. CT imaging is usually sufficient for a diagnosis and reveals oval masses which are in reality adrenal

hematomas along with soft-tissue stranding around the adrenal gland [1–4]. However, in some patients, like our patient, CT is insufficient to diagnose adrenal hemorrhage and an MRI is indicated. Although MRI is more accurate, CT is more practical and time efficient and is recommended as the initial imaging modality [1,4]. In some cases, as with ours, MRI can be used to rule out the presence of an underlying mass [1].

Since the physical examination and presenting symptoms for adrenal hemorrhage are ambiguous, it is important to take a good history and physical to find historical risk factors for adrenal hemorrhage [3]. Risk factors for adrenal hemorrhage include sepsis, anticoagulation medications, coagulopathies (such as HIT and antiphospholipid syndrome), sepsis (leading to Waterhouse-Friderichson syndrome, especially in the setting of meningococcal septicemia), disseminated intravascular coagulation (DIC), severe physiological stress, underlying adrenal tumor (especially pheochromocytomas, myelolipomas, and metastasis), pregnancy [5], and trauma [2]. The clinician should be aware of the various etiologies of adrenal hemorrhage, and if no cause is obvious, should investigate to find and treat the underlying cause. Even in cases with an identified initial trigger for adrenal hemorrhage, there may be another underlying cause – as seen in our patient, who had recently started rivaroxaban but was also found to be HIT positive. There have been case reports of patients who developed bilateral adrenal hemorrhage after starting on DOACs for DVT prophylaxis after knee and hip replacement surgery [6,7]. Although development of BAH is uncommon in these patients, clinicians should be aware that it has been associated with development of BAH especially in patients who are on post-operative days 4 through 10 [7].

It is estimated that 40% to 80% of post joint replacement surgical patients develop DVT without DVT prophylaxis [7]. BAH has been reported in patients who have been placed on DOACs along with patients on subcutaneous heparin and oral warfarin for DVT prophylaxis post joint replacement surgery [6–9]. Upon literature review, only few cases of BAH have been reported with DOACs being used for DVT prophylaxis post joint replacement, three patients on enoxaparin, one patient on dalteparin and one patient on dabigatran [7–9]. There were no cases reported so far highlighting the findings of BAH being on rivaroxaban for DVT prophylaxis post joint replacement, although there was one case reported by Ly et al., who developed unilateral adrenal hemorrhage (UAH) while being on rivaroxaban [6]. The patient in Ly et al. case report was a 61-year-old male who had a bilateral total knee replacement and developed left adrenal hemorrhage on day 14 post procedure. BAH is more common after total knee replacement than after total hip replacement and has usually been described in patients age 61 to 82 years old on days 4 to 10, peaking at days 6 to 7 post-operation [7,8]. Another case of BAH associated with

rivaroxaban has been reported by Comuth et al. [10]. In that case report, a 63-year-old female with history of multiple DVTs who was recently switched from warfarin to rivaroxaban due to ease of compliance presented with abdominal pain radiating to the back. That patient was diagnosed with BAH via a CT scan. Later the patient developed adrenal insufficiency which responded to steroids and fluid resuscitation and was managed non-operatively. The patient in the Comuth et al. case report was found to have antiphospholipid syndrome and was transitioned back to warfarin [10].

Some case reports have been reported showing increased bleeding risk with concurrent use of novel oral anticoagulants (NOACs) with amiodarone, fluconazole, rifampin, and phenytoin. But our patient was not taking any medications which can lead to drug interaction [11–13].

Once the diagnosis of adrenal hemorrhage is made, the clinician should assess for hemodynamic stability and monitor closely for signs of adrenal insufficiency which is more common in patients with BAH as compared to unilateral adrenal hemorrhage [3]. UAH can usually be managed conservatively.

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Conclusions

Diagnosis of adrenal hemorrhage can be overlooked due to its vague and non-specific symptoms which can lead to life-threatening consequences. So, the diagnosis in a timely manner and adequate management is crucial. Use of DOACs are increasing day by day due to their compliance and safety profile. The clinicians should be aware of serious adverse effects of these medications in appropriate clinical context and evaluate the patient accordingly.

Conflict of interests

None.