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CASE REPORT

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Atraumatic splenic rupture in a patient treated with rivaroxaban: A case report and a narrative review

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Abstract

Atraumatic splenic rupture (ASR) is a rare condition mostly associated with neoplastic, infectious, and inflammatory diseases. ASR associated with drug treatment is even rarer. In this case report, we highlight an unusual complication of the direct oral anticoagulant rivaroxaban. A 64-year-old male patient was admitted to the emergency department with complaints of faintness and diffuse abdominal cramps. The patient had no history of recent trauma. Clinical examination revealed hemodynamic instability with a moderate response to filling and mild abdominal discomfort on palpation. His medical history included chronic hypertension, constipation, and recent atrial flutter ablation. The patient was taking amiodarone, bisoprolol, atorvastatin, and rivaroxaban. Splenic rupture was diagnosed several hours later on contrast-enhanced abdominal computed tomography scan. Massive blood transfusions and emergency laparotomy for splenectomy were performed. Anatomopathological analysis did not reveal any neoplastic, inflammatory, or infectious causes. The patient was successfully discharged from the intensive care unit 3 days later. Clinicians must consider the possibility of ASR as a complication of rivaroxaban in patients with abdominal tenderness and hemodynamic instability. Unfortunately, clinical presentation is not always typical of a ruptured spleen. Delayed diagnosis can be life threatening or fatal. Splenectomy via laparotomy remains the best therapeutic option in cases of splenic rupture in unstable patients on direct oral anticoagulants.

KEYWORDS

apixaban, atraumatic splenic rupture, betrixaban, dabigatran, direct oral anticoagulant, edoxaban, rivaroxaban, spontaneous splenic rupture

1 | INTRODUCTION

Abdominal trauma is a well-known cause of splenic rupture.[1] The major problem in atraumatic splenic rupture (ASR) is missed or delayed diagnosis and, consequently, delayed management leading to fatal outcomes. The mortality rate of ASR is approximately 12.2%.[2] Systematic reviews by Aubrey-Bassler et al., and Renzulli et al., have reported that the main etiologies of ASR are infection, neoplasm, and inflammation. Drug-related causes are even

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rarer.[3,4] Since the emergence of direct oral anticoagulants (DOAC) at the beginning of the 21st century, physicians have been increasingly confronted with their adverse effects and complications. In this report, we describe a case of ASR in a patient treated with rivaroxaban. This case report adhered to the CARE guidelines.[5] We also present a literature review of similar cases identified in *PubMed* and *Google Scholar* through a search on June 2022 using relevant keywords. Only cases written in French or English were included. The cases were compared, and the factors promoting splenic rupture and bleeding in patients taking rivaroxaban and other DOAC were investigated.

2 | CASE PRESENTATION

A 64-year-old male patient was admitted to the emergency department with complaints of faintness and diffuse abdominal cramps. His medical history included chronic hypertension, chronic constipation, and atrial flutter ablation 6 days prior. The patient was taking amiodarone, bisoprolol, atorvastatin, and rivaroxaban. There was no history of trauma or infection in the previous months. Moreover, the patient had limited contact with the outside world due to the coronavirus disease (COVID)-19 pandemic. His vital signs on admission were as follows: blood pressure, 85/55 mmHg; sinus rhythm, 76 beats per minute; oxygen saturation level, 99% on room air; and afebrile. Physical examination revealed normal cardiopulmonary auscultation and mild diffuse abdominal tenderness on palpation, without guarding or radiating pain. The patient then underwent several complementary tests. His blood test results (hemoglobin, white blood cells, coagulation, ionogram, liver, and kidney function) were within normal (Table 1). There was no increase in lactate levels in the arterial blood gases. Urinalysis results were unremarkable. The polymerase chain test results for COVID-19 were negative. Electrocardiography showed a sinus rhythm of 70 beats per minute without repolarization abnormalities.

Given his recent flutter ablation, a transthoracic cardiac ultrasound was performed by the cardiologist on call. Normal cardiac function, no valvular disease, no ventricular overload, and no pericardial effusion were observed. Treatment was initiated, and the patient received analgesia with ibuprofen and 1 L of intravenous crystalloid. Subsequently, his blood pressure responded to fluid resuscitation, but the patient still experienced orthostatic discomfort. The cardiologist admitted him to his cardiac service under telemetry for orthostatism on medications and vagal illness on abdominal pain due to chronic constipation. By nighttime, the patient developed agitation, dyspnea, and cutaneous pallor. His blood pressure was low (75/55 mmHg), with a cardiac rate of 80 beats/min. His blood oxygen saturation level was unmeasurable. A clinical examination revealed signs of low capillary perfusion. Considering the rivaroxaban intake and recent atrial flutter ablation, a contrast-enhanced abdominal computed tomography scan was performed and showed a splenic rupture with a subcapsular hematoma (10 × 15 × 13 cm) and diffuse hemoperitoneum (Figure 1).

Massive blood transfusions and emergency laparotomy for splenectomy were performed. The patient received seven units packed red blood cells, six units of fresh frozen plasma samples, and one unit of platelets. The intraoperative blood loss was 2 L. Hemostasis was rapidly achieved by ligation of the splenic vessels and

TABLE 1 Patient's blood results on admission

Variables	Value	Unit	Normal values
Hemoglobin Hematocrit	13.6	g/dl	13.1–17.2
Platelets	302	10^3/µl	168–411
White blood cell count	10.15	10^3/µl	3.7–9.5
Neutrophils	6.12	10^3/µl	1.5–6.5
Lymphocytes	3.025	10^3/µl	1.2–3.9
Monocytes	0.548	10^3/µl	0.2–0.8
Eosinophils	0.061	10^3/µl	<0.500
Basophils	0.071	10^3/µl	<0.190
APTT	26.0	Sec	20–30
PTT	>100	%	75–100
INR	1.00		<1.2
Fibrinogen	382	mg/dl	200–400
CRP	8.7	mg/dl	<5
Urea	37	mg/dl	16.6–48.5
Creatinine	0.98	mg/dl	0.70–1.20
Sodium	139	mmol/L	135–145
Potassium	3.8	mmol/L	3.5–5.1
Chloride	104	mmol/L	97–110
Total bilirubin	0.49	mg/dl	≤1.2
Direct bilirubin	0.17	mg/dl	<0.3
Gamma glutamyl transferase	37	U/L	15–85
Alkaline phosphatase	56	U/L	40–129
Alanine aminotransferase	33	U/L	15–37
Aspartate aminotransferase	36	U/L	16–61
Lactate dehydrogenase	143	U/L	87–241
HS Troponin	19.8	pg/ml	<78.5

Abbreviations: APTT: activated partial thromboplastin time; CRP: C-reactive protein; HS Troponin: high-sensitivity troponin; INR: international normalized ratio; PTT: partial thromboplastin time.

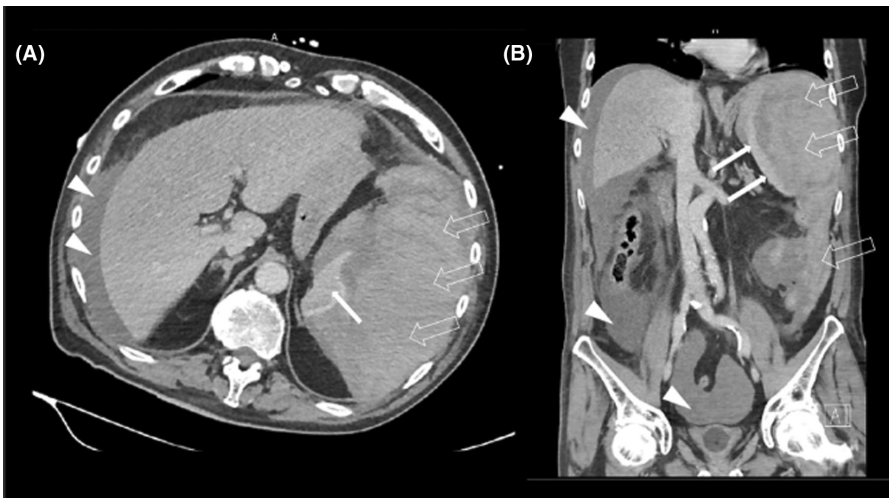

FIGURE 1 CT images showing subcapsular hematoma (empty arrows), diffuse hemoperitoneum (arrow heads) and residue or the ruptured spleen (full arrows). Axial (A). Coronal (B).

total removal of the spleen with a large parenchymal laceration. Anatomopathological analysis did not reveal any neoplastic, inflammatory, or infectious causes. The patient was successfully discharged from the intensive care unit 3 days later. The patient remained in the surgical ward for another week before returning home. Rivaroxaban was permanently discontinued. Vaccines were administered against the encapsulated organisms. A Holter monitor performed by the cardiologist 1 and 4 months postoperatively showed no recurrence of rhythm disorders. Ten months later, the patient was physically well and had completely resumed daily activities.

3 | REVIEW OF THE LITERATURE ON ATRAUMATIC SPLENIC RUPTURE

3.1 | General information on ASR

Abdominal trauma is the first and most well-known cause of splenic rupture.[1] Given that ASR is rare, its diagnosis is often delayed, and approximately 12.2% of patients die.[2] Mortality is increased in cases of delayed diagnosis, splenomegaly, underlying neoplastic disease, and age > 40 years.[2,4]

3.2 | Classification and criteria of ASR

ASR can be classified into two categories: pathological rupture (ASR occurring in a diseased spleen) and idiopathic rupture (ASR occurring in a healthy spleen), also called "spontaneous rupture."[6] According to Orloff and Peskin, an idiopathic rupture must meet four criteria: no trauma history, no other diseased organs that can cause splenic rupture, no peri-splenic adhesions or pre-existing scars, and a macroscopically and histologically normal spleen.[7] Crate and Payne later proposed a fifth criterion: no increase in serological antibody titer in the acute and convalescent phases, suggesting a recent viral infection known to be involved in splenic rupture.[8] A systematic review by Aubrey-Bassler et al. showed that splenic rupture was the first symptom of an unknown underlying disease. Indeed, due to its important vascularization, if the spleen is afflicted by the disease, the risk of rupture after trivial stress is increased.[9] In the literature, many authors misuse the word "spontaneous" instead of the term "pathological" or "atraumatic."[3] True spontaneous splenic rupture is very rare.

3.3 | Etiologies, sex ratio, and surgical management percentage

In a systematic review by Kris Aubrey-Bassler and Nicholas Sowers, 47 of 613 (7.6%) cases were associated with drugs, 21 of which were associated with anticoagulants.[3] In another review, Renzulli et al.[4] identified 845 patients with ASR and divided them into six etiological groups (Table 2). The male-to-female ratio was 2:1, and the mean patient age was 45 years. Of the 845 cases, 67 cases were associated with drugs, 22 of which were anticoagulants. Only 59 patients (7%) had a normal spleen, and no causal factor was found. In total, 465 patients (55%) had splenomegaly, and 84% underwent total splenectomy as a first-line treatment. Among the patients who received conservative treatment, 14.9% underwent splenectomy for rebleeding. The percentage of surgical management was much higher than in cases of traumatic rupture. This is explained by the higher rate of conservative treatment failure associated with an abnormal spleen and older age.[4]

TABLE 2 Summary of ASR etiologies

Atraumatic rupture spleen etiologies
1. Neoplastic disorders, 30.3%
2. Infectious disorders, 27.3%
3. Inflammatory non-infectious disorders, 19.9%
4. Drug and treatment related, 9.1%
5. Mechanical disorders, 6.8%
6. Normal spleen, no etiological factors, 6.3%

Spontaneous rupture of a macroscopically and microscopically normal spleen is a controversial entity with an unclear mechanism. In fact, it could be a delayed break on trauma that may have been forgotten by the patient or even not noticed.[6]

3.4 | Pathophysiological mechanisms of ASR

Several hypotheses concerning the pathophysiology of spontaneous rupture have been proposed: the spleen presents a disease focus that disappears during the rupture and is no longer found during the anatomopathological analysis. Anatomical variations make the spleen more mobile, and thus, undergo repeated twisting that leads to congestion and eventually rupture. The congestion can also come from a reflex spasm of the splenic vein, and the splenic artery may rupture on localized vascular anomaly.[6] Physiological activities that increase intra-abdominal pressure may result in repeated injury to the capsule.[10] Indeed, the trauma may be minor such as lifting a heavy weight, coughing, vomiting, or defecating.[10,11]

3.5 | Symptomatology and clinical features

The classic symptomatology is pain in the left hypochondrium that can radiate to the ipsilateral shoulder.[12] Clinical features such as tenderness, muscle guarding on palpation, and signs of hemodynamic shock are often present.[6] However, pain can be described as crampy or sharp.[13] Sometimes, the symptomatology may be more confusing and may mimic myocardial infarction or pulmonary embolism in the setting of chest pain with hemodynamic instability.[14] It can also be confused with gastric ulcers, acute appendicitis, ectopic pregnancy, or diverticulitis.[6] In cases of abdominal pain and hypotension, ASR remains a diagnosis of exclusion.[11]

3.6 | Diagnosis and management

The diagnostic procedure is based on the hemodynamic status. Thus, Extended Focused Assessment Sonography for Trauma (E-FAST) is the technique of choice for rapid demonstration of free fluid in unstable patients. Intravenous contrast computed tomography of the abdomen remains the gold standard for stable or well-stabilized patients.[15] Hemodynamically unstable patients (transfusion- or vasopressor-dependent) should undergo emergency laparotomy for splenectomy.[15]

3.7 | General information about DOACs

At the end of the first decade of the 21st century, DOACs have been introduced for the prevention of stroke and systemic thrombus in non-valvular atrial fibrillation and for the treatment of deep vein thrombosis and pulmonary embolism. They are increasingly prescribed because unlike vitamin K antagonists, they do not require close monitoring and are safer with respect to the risk of major bleeding, with less intracranial bleeding.[16] However, physicians are also increasingly confronted with complications. Although DOACs have fewer drug interactions than vitamin K antagonists, some molecules have an impact on their metabolism and increase the risk of bleeding. These molecules are permeability glycoprotein inhibitors and enzyme 3A4 of cytochrome P450 (CYP3A4) inhibitors. Co-medication with antiplatelet therapy also increases the risk of bleeding.[17,18] DOAC should also be adjusted or avoided in cases of renal or hepatic impairment.[17] Wheelock et al.[19] showed that the prescription of DOACs increased annually in the United States between 2013 and 2018. The prescription of apixaban increased from 75,948 to 7,741,247, and the prescription of rivaroxaban increased from 1,271,758 to 4,835,049. Rivaroxaban and apixaban are the two most commonly prescribed DOACs worldwide.[20] Dabigatran is losing popularity, and its prescription rate is decreasing. Its renal elimination rate is 80%, while that of other DOACs is lower.[21]

3.8 | General information about rivaroxaban

Rivaroxaban was the second DOAC approved by the FDA after dabigatran. It is a direct non-prodrug inhibitor of factor Xa. Its bioavailability is increased by food intake, and the maximum plasma concentration is reached between 2 and 4 h. Rivaroxaban has a volume distribution of 50 liters and is 90% bound to plasma

proteins. Its half-life varies from 5 to 9 h in young adults and from 9 to 11 h in older adults. It is 67% metabolized by the liver via cytochrome P450 (mainly CYP3A4), and 33% is eliminated by the kidneys. The drug dose should be adjusted for creatinine clearance <50 ml/min and avoided in cases of creatinine clearance <30 ml/min. Owing to its extensive hepatic metabolism, rivaroxaban is contraindicated in patients with moderate to severe liver dysfunction.[21]

3.9 | Cases of ASR related to DOACs found in the literature

The two systematic reviews mentioned above were conducted in 2008[4] and in 2011[3] and did not mention the type of anticoagulant used. Therefore, we searched the literature for cases of ASR associated with DOACs. *PubMed* and *Google scholar* were searched for cases of ASR related to DOACs with the keywords "rivaroxaban," "apixaban," "dabigatran," "betrixaban," "edoxaban," and "splenic rupture." Abstracts and full text written in French and English until June 2022 were included in our research. We found 13 cases in addition to ours.[22–34] The results are summarized in Table 3.

4 | DISCUSSION

In our patient, the symptomatology was unclear because the pain was cramped and diffuse. The pain was not localized to the left hypochondrium and did not radiate into the homolateral shoulder. Its intensity was milder than expected and there was no muscle guarding on palpation. Given his recent history of atrial fibrillation ablation, we wanted to exclude tamponade or other cardiac problems. Moreover, biology and arterial blood gases were reassuring upon admission. Finally, although the patient was on bisoprolol and amiodarone, he did not present with tachycardia. The diagnosis was initially missed, and management was delayed because the patient had no history of trauma, ASR is rare, and his symptomatology was nontypical, putting the patient's life at risk. We hypothesized that the patient first injured his spleen consecutive to multiple efforts of defecation. This physiological activity increases intra-abdominal pressure and may cause multiple repeated injuries to the renal capsule. Rivaroxaban intake led to a painful subcapsular hematoma that eventually tore the capsule and parenchyma. Therefore, the spleen rupture can be called atraumatic because there was no history of real trauma, but it cannot be defined as spontaneous with certainty because of potential injuries. Despite a healthy parenchyma, splenic rupture probably occurred considering the lack of evidence for neoplastic, inflammatory, or infectious etiologies. Moreover, anatomopathological examination of the spleen was macroscopically and microscopically normal.

We did not make the diagnosis in the cardiology unit with E-FAST because the computed tomography scan of the abdomen was directly available as a standard procedure in our institution. Given the hemodynamic instability of our patient, emergency splenectomy by laparotomy was the only acceptable therapeutic solution, as indicated in the guidelines. If we look at the cases of splenic rupture related to DOACs in the literature (summarized in Table 3), we can observe multiple factors. Several authors, such as Gonzva, use the term "spontaneous splenic rupture" in the title of their article

TABLE 3 Cases of atraumatic splenic rupture in patients treated with DOAC

First author	Year/Country	DOAC	Age/sex	Treatment	Biopsy analysis	Splenomegaly
Gonzva J et al.	2014/ USA	Rivaroxaban	67 years/M	Splenectomy	Not mentioned	Not mentioned
Hattab YA et al.	2015/USA	Rivaroxaban	70 years/F	Splenectomy	Not mentioned	Not mentioned
Nassem Z et al.	2016/Australia	Rivaroxaban	68 years/M	Splenectomy	Not mentioned	Not mentioned
Amin A et al.	2016/USA	Rivaroxaban	68 years/F	Embolization + splenectomy	Not mentioned	Not mentioned
Nagaraja V et al.	2018/Australia	Rivaroxaban	77 years/F	Embolization	Not mentioned	No
Pietsch H et al.	2019/Germany	Rivaroxaban	76 years/F	Splenectomy	Normal	Normal
Moore HC et al.	2012/USA	Dabigatran	78 years/M	Embolization	Not applicable	Not mentioned
Lowry AL et al.	2016/USA	Apixaban	83 years/M	Embolization + splenectomy	Not mentioned	Yes
Abdelhady A et al.	2018/Ireland	Apixaban	62 years/F	splenectomy	Not mentioned	Not mentioned
Janke A et al.	2019/USA	Apixaban	57 years/F	Embolization + splenectomy	Not mentioned	Not mentioned
Basnet A et al.	2019/USA	Apixaban	86 years/M	Embolization + splenectomy	normal	Not mentioned
Yau HCV et al.	2020/Australia	Apixaban	66 years/M	Embolization + splenectomy	normal	Not mentioned
Natarajan P et al.	2021/USA	Apixaban	81 years/M	Conservative	Not applicable	Not mentioned

without mentioning whether they had previously looked for diseases affecting the spleen.[22–31] Spontaneous splenic rupture in the literature is more frequent than in real life due to language abuse. The population with a ruptured spleen associated with DOAC was much older than the all-cause population (mean age: 72.2 vs 44 years). The male-to-female ratio is 1.33:1 if the current case is included. Among patients who undergo non-operative treatment by embolization of the splenic artery, the treatment failure rate is 71%.

Finally, many cases of ASR in patients with rivaroxaban and apixaban have been described. We did not find any cases with edoxaban and betrixaban until June 2022. Of the 13 patients described, six patients were taking rivaroxaban, six patients were taking apixaban, and only one patient was taking dabigatran. This could be explained by the fact that rivaroxaban and apixaban are the two most commonly prescribed DOACs. Edoxaban and betrixaban are newer and are thus less commonly prescribed.

5 | CONCLUSION

The symptomatology of a ruptured spleen can be atypical, and the diagnosis is difficult. E-FAST should be performed in patients presenting with non-specific abdominal pain and hypotension. Although a ruptured spleen remains a diagnosis of exclusion, it can be favored in consideration of rivaroxaban treatment. Several cases of ASR with rivaroxaban use have been described in the literature. This may be because it is widely prescribed, and therefore, more reported than other DOACs. Often, splenic rupture is associated with an underlying disease and should be defined as "atraumatic" and not "spontaneous." Splenectomy remains the gold standard of treatment for unstable patients.

AUTHOR CONTRIBUTIONS

MLL involved in main work, data collection, manuscript writing, and final revision. MDK involved in data collection and manuscript revision.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

The patient provided consent for the use of medical data and images described in this article.

PATIENT PERSPECTIVE

The patient did not remember the hours before the surgery and was taken to the operating room. With his median laparotomy and constipation problems despite an adapted diet and treatment, he was anxious when he had to defecate even 10 months later. However, he was happy to have been able to resume his daily activities.

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