

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

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July 4, 2022

Abstract

A narrative review based on the case of a patient presenting an atypical symptomatology of an atraumatic splenic rupture induced by rivaroxaban. An emergency splenectomy had to be performed. This complication is rare but increasing since the popularity of direct oral anticoagulants and the diagnosis is often delayed.

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

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Abstract:

Introduction : Atraumatic splenic rupture (ASR) is rare, mostly associated with neoplastic, infectious and inflammatory diseases. ASR related to drug treatment is infrequent. In this case report we highlight an unusual complication of the direct oral anticoagulant rivaroxaban.

Case presentation : A 64-year-old male patient was admitted in the emergency department for lipothymic illness on diffuse abdominal cramps. There is no history of recent trauma. The clinical examination showed hemodynamic instability with moderate response to filling and a mild abdominal discomfort on palpation. His medical history included chronic hypertension, chronic constipation and a recent atrial flutter ablation. He was taking amiodarone, bisoprolol, atorvastatin, and rivaroxaban 20 mg. The diagnosis of splenic rupture was made several hours later with an abdominal CT scan with contrast injection. A massive blood transfusion and an emergency laparotomy for splenectomy were performed. The anatomopathological analysis did not reveal any cause of neoplastic, inflammatory or infectious cause. The patient was successfully discharged from intensive care unit 3 days later.

Conclusion : Clinicians must remember the potential ASR as complication due to direct oral anticoagulants when they are confronted to a patient with abdominal tenderness and hemodynamical instability. Unfortunately, the clinical presentation is not always typical of a ruptured spleen. Delayed diagnosis can be life-threatening and fatal. Splenectomy by laparotomy remain the best therapeutic option in case of splenic rupture in unstable patients on direct oral anticoagulants.

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

Introduction:

The abdominal trauma is a well-known cause of splenic rupture [1]. The major problem in atraumatic splenic rupture (ASR) is the missed or delayed diagnosis and consequently, delayed management leading to fatal outcome. In case of ASR, the mortality rate is around 12,2%. [2] Several systematic reviews of the literature reported that the main etiologies are infectious, neoplastic and inflammatory. The drug-related cause is even more rare [3][4]. Since the emergence of direct oral anticoagulants (DOAC) at the beginning of the 21st century, physicians are increasingly confronted with their adverse effects and complications. In this article we describe a case of ASR in a patient treated with rivaroxaban according to CARE guidelines [5]. Then, we made a narrative review of the literature by searching until June 2022 other similar cases in the *Pubmed* and *Google scholar* databases with relevant keywords. Only cases written in French and English were retained. We compared them and looked for factors promoting splenic rupture and bleeding in patients taking rivaroxaban and other DOAC.

Case presentation:

A 64-years-old male patient was admitted in the emergency department for lipothymic illness on diffuse abdominal cramps. His medical history included chronic hypertension, chronic constipation and an atrial flutter ablation 6 days before. He was taking amiodarone, bisoprolol, atorvastatin, and rivaroxaban 20 mg. There is no history of trauma or infections in the previous months. Moreover, the patient has limited contact with the outside world because of the covid-19 pandemic. His parameters were a blood pressure at 85/55 mmHg, a sinusual cardiac rate at 76 beats per minute, an oxygen saturation level of 99% on room air and a normal body temperature. The physical examination highlighted a normal cardiopulmonary auscultation, a mild diffuse abdominal tenderness at the palpation without guarding or irradiation.

He underwent several complementary tests. His blood tests (hemoglobin, white blood cells, coagulation, ionogram, liver and kidney functions) came back normal (Table 1). There was no increase in lactate on the arterial blood gases. The urine spot is without particularity. The PCR test for covid 19 is negative. The electrocardiogram shows a sinusual rythm with a frequence around 70 beats per minute and no repolarisation troubles.

Variables	Value	Unit	Normal values
Hemoglobin Hematocrit	13.6	g/dL	13.1-17.2
Platelets	302	10e3/ μ L	168-411
White blood cells	10.15 6.12 3.025 0.548	10e3/ μ L 10e3/ μ L	3.7-9.5 1.5-6.5 1.2-3.9
count Neutrophils	0.061 0.071	10e3/ μ L 10e3/ μ L	0.2-0.8 < 0.500 < 0.190
Lymphocytes		10e3/ μ L 10e3/ μ L	
Monocytes Eosinophils			
Basophils			
A.P.T.T. P.T.T. I.N.R.	26.0 >100 1.00 382	Sec % mg/dL	20-30 75-100 < 1.2
Fibrinogen			200-400
CRP	8.7	mg/dL	< 5
Urea Creatinine	37 0.98 139 3.8 104	mg/dL mg/dL mmol/L	16.6-48.5 0.70-1.20
Sodium Potassium		mmol/L mmol/L	135-145 3.5-5.1 97-110
Chloride			

Variables	Value	Unit	Normal values
Total bilirubin Direct	0.49 0.17 37 56 33 36	mg/dL mg/dL U/L	[?] 1.2 < 0.3 15-85
bilirubin Gamma	143	U/L U/L U/L U/L	40-129 15-37 16-61
glutamyl transferase			87-241
Alkaline phosphatase			
Alanine			
aminotransferase			
Asparate			
aminotransferase			
Lactate dehydrogenase			
HS Troponin	19.8	pg/mL	< 78.5

Table 1: shows normal blood tests

Abbreviations: *A.P.T.T.* : *activated partial thromboplastin time*; *P.T.T.*: *Partial thromboplastin time* ; *I.N.R.*: *international normalized ratio*; *CRP*: *C-reactive protein*; *HS Troponin*: *high-sensitivity troponin*

Because of his recent flutter removal, a transthoracic cardiac ultrasound is performed by the cardiologist on call and showed: a normal cardiac function, no valvular disease, no ventricular overload and no pericardial effusion.

He received as a treatment a painkiller and a filling of one litter of crystalloid. After that, his blood pressure goes up slightly, but the patient still has orthostatic discomfort. The cardiologist admitted him in his cardiac service under telemetry for orthostatism on medications and vagal illness on abdominal pain due to his chronic constipation.

During the night, the patient presented agitation, dyspnea and cutaneous pallor. His blood pressure was low at 75/55 mmHg with a cardiac rate at 80 beats/minute. His pulsated blood oxygen saturation was unmeasurable. Clinical examination showed signs of low capillary perfusion. Considering the rivaroxaban intake and the recent atrial flutter ablation, an intravenous contrast computed tomography scan of the abdomen was performed and showed a splenic rupture with a subcapsular hematoma (10 cm x 15 cm x 13 cm) and diffuse hemoperitoneum (Figure 1.).

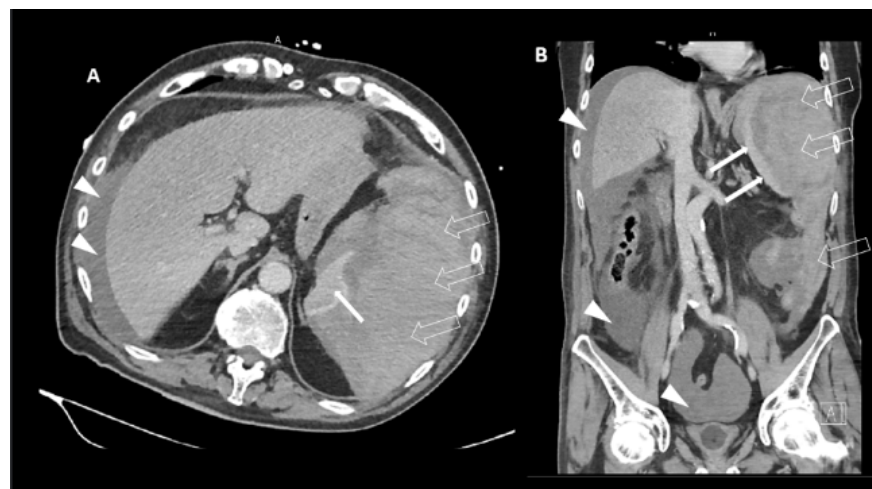


Figure 1: Axial (A) and coronal (B) CT-scan showing subcapsular hematoma (empty arrows), diffuse hemoperitoneum (arrow heads) and residue or the ruptured spleen (full arrows).

A massive blood transfusion and an emergency laparotomy for splenectomy were performed. In total, the patient received seven packed red blood cells, six fresh frozen plasma and one pool of platelets. During the laparotomy, the surgeon sucked out more than two liters of fresh blood and clots. Hemostasis was rapidly obtained by ligation of the splenic vessels and total removal of the spleen that had a large parenchymal laceration. The anatomopathological analysis did not reveal any cause of neoplastic, inflammatory or infectious cause. The patient was successfully discharged from intensive care unit 3 days later. He remained in the surgical ward for another week before going home. Rivaroxaban has been permanently discontinued. The vaccines against encapsulated organisms have been administered. A holter monitor was performed by the cardiologist at 1 and 4 months after surgery and showed no recurrence of rhythm disorders. 10 months later, the patient is morally and physically well and has completely resumed his daily activities.

Discussion:

The abdominal trauma is the first and well-known cause of splenic rupture [1]. Because ASR is rare, its diagnosis is often delayed, and mortality is estimated at 12,2% [2]. Mortality is increased in cases of delayed diagnosis, splenomegaly, underlying neoplastic disease and an age above 40 years [2] [4].

The ASR can be classified into 2 categories: a pathological rupture (ASR occurred on a diseased spleen) and idiopathic rupture (ASR occurred on a healthy spleen), also called “spontaneous rupture” [6]. According to Orloff and Peskin, an idiopathic rupture must meet 4 criteria: no trauma history; no other diseased organs that can cause the splenic rupture; no peri-splenic adhesions or pre-existing scars; a macroscopically and histologically normal spleen [7]. Later, Crate and Payne proposed a 5th criterion: no increase in serological antibody titer in the acute and convalescent phase suggesting a recent viral infection known to be involved in splenic rupture [8].

In a systematic review, F Kris Aubrey-Bassler and Nicholas Sowers showed that most of the time spleen rupture was the first symptom of an unknown underlying disease. Indeed, due to its important vascularization, if the spleen is afflicted by disease, the risk of rupture after a 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. In this same review, 47 cases out of 613 (7,6%) were associated with drugs, 21 of which were associated with anticoagulants [3]. In another review, P. Renzulli et al. identified 845 patients with ASR and divided them into 6 etiological groups (Table 2). They showed a ratio male : female of 2 : 1 and a mean age of 45. Of the 845 cases, 67 were associated with drugs, 22 of which were anticoagulants. Only 59 patients (7%) had a spleen described as normal and no causal factor was found. 465 patients (55%) had splenomegaly. 84% underwent total splenectomy as first-line treatment. 14.9% of the patients with a conservative treatment had splenectomy for rebleeding. The percentage of surgical management is much higher than in the case of traumatic rupture. This is explained by a higher rate of conservative treatment failure associated with an abnormal spleen and by an older population [4].

Atraumatic rupture spleen etiologies
Neoplastic disorders 30.3%
Infectious disorders 27.3%
Inflammatory non infectious disorders 19.9%
Drug and treatment related 9.1%
Mechanical disorder 6.8%
Normal spleen, no etiological factors 6.3%

(Table 2)

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

Several hypotheses concerning the pathophysiology of spontaneous rupture have been put forward: the spleen presents a diseased focus which disappears during the rupture and is no longer found during the anatomopathological analysis; anatomical variations make the spleen more mobile, which undergoes repeated twisting that leads to congestion and eventually rupture; the congestion can also come from a reflex spasm of the splenic vein; 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].

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

The diagnostic procedure is based on the hemodynamic status of the patient. Thus, in the unstable patient, the extended focused assessment sonography for trauma (E-FAST) is the technique of choice for rapid demonstration of free fluid. While the intravenous contrast computed tomography scan of the abdomen remains the gold standard for the stable or well stabilized patient [15].

Hemodynamically unstable patients (transfusion dependent or on vasopressors) should have an emergency laparotomy for splenectomy [15].

At the end of the first decade of the 21st century, DOACs arrived on the market 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 in terms of major bleeding with less intracranial bleeding [16]. As a result, the physician is increasingly confronted with its complications. Although DOACs have fewer drug interactions than vitamin K antagonists, molecules can interfere with their metabolism and increase the risk of bleeding. Those molecules are the permeability glycoprotein (P-gp) inhibitors and enzyme 3A4 of cytochrome P450 (CYP3A4) inhibitors. Co-medication with antiplatelet therapy also increases de bleeding risk [17][18].

DOAC intake should be adjusted or even avoided in case of renal or hepatic impairment [17].

The two reviews mentioned above were conducted up to 2008 [4] and 2011 [3] and do not mention the type of anticoagulant. We therefore searched the literature for cases of RSA related to DOACs.

We therefore searched *Pubmed* and *Google scholar* for cases of ASR related to DOACs with the keywords "rivaroxaban" "apixaban" "dabigatran" "betrixaban" "edoxaban" and "splenic rupture". Abstracts and full texts written in French and English until June 2022 were included in our research. We found 13 other cases in addition to ours [19][20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30]. We have summarized them in Table 3.

First author	Year/ Country	DOAC	Age / gender (M.: male) (F.: female)	Treatment	Biopsy analysis	Splenomegaly?
Gonzva J. et al.	2014/ USA	Rivaroxaban	67 years / M	splenectomy	Not mentioned	Not mentioned
Hattab Y.A. 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 H. C. et al	2012/ USA	Dabigatran	78 years / M	Embolization	Not applicable	Not mentioned
Lowry A.L. 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 H.C.V. 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

Table 3.: cases of atraumatic splenic rupture in patients treated with DOAC.

Table 3 provides interesting informations:

- Several authors, such as Gonzva, use the term "spontaneous splenic rupture" in the title of their article without mentioning whether they had previously looked for diseases affecting the spleen [19][20][21][22][23][24][25][26][27]. Spontaneous splenic rupture in the literature is more frequent than in real life due to the abuse of language.
- The population with ruptured spleen associated with DOAC is much older than the all-cause population. Their respective mean ages are 72.2 versus 44.
- The ratio male : female is 1,33 : 1 if we include our own case.
- There are many more cases described with rivaroxaban and apixaban. We did not find any cases described in the literature with edoxaban and betrixaban
- The failure rate of non-operative treatment by embolization of the splenic artery is 71%.

In our patient, the symptomatology was unclear, the pain was crampy and diffuse without muscle guarding. Given his recent history of atrial fibrillation ablation, we wanted to exclude a tamponade or another cardiac problem first. Moreover, the biology and arterial blood gases were reassuring on admission. A posteriori we hypothesized that the patient first injured his spleen consecutive to the multiple efforts of defecation. Then rivaroxaban led to a painful subcapsular hematoma that eventually tore the capsule and parenchyma. Our diagnosis was delayed. Moreover, the patient being on bisoprolol and amiodarone never presented with tachycardia. We did not make the diagnosis in the cardiology unit with the E-FAST because the computed tomography scan of the abdomen was directly available at a standard procedure in our institution. Splenic rupture was most likely spontaneous based of the lack of evidence for neoplastic, inflammatory or infectious etiologies. Moreover, the anatomopathological examination of the spleen was macro and microscopically normal.

Conclusion

We will remember that the symptomatology of a ruptured spleen can be very atypical. The diagnosis can be difficult. Facing a patient presenting with unspecific abdominal pain and hypotension, an E-FAST should be performed. Even though ruptured spleen remains a diagnosis of exclusion, it can be favoured using DOAC. Often, splenic rupture is associated with an underlying disease and should be defined as "atraumatic" and not "spontaneous". Splenectomy remains the gold standard for an unstable patient.

Patient perspective

The patient does not remember the hours before the surgery and being taken to the operating room. With his median laparotomy and his constipation problems in spite of an adapted diet and treatment, he is anxious

when he has to go to the stool even 10 months later. For the rest, he is happy to have been able to resume his daily activities as usual.

Consent

The patient has given consent for his medical data and images to be described in this article.

Conflict of interest disclosure

Non declared.

Funding statement

none

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