Apixaban Causing Hepatic Cystic Bleeding: A Rare but a Life-Threatening Complication

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Abstract
Cystic lesions of the liver are a heterogeneous group of disorders with varied etiology, prevalence, and clinical manifestations. Fibropolycystic liver disease encompasses a spectrum of related liver and biliary tract lesions caused by abnormal embryologic development of the ductal plates. These disorders include congenital hepatic fibrosis, biliary hamartomas, polycystic liver disease (PCLD), choledochal cysts, and Carolis disease. PCLD is arbitrarily defined as a liver that contains >20 cysts. Most liver cysts are incidentally found on imaging studies, and the majority of the patients with liver cysts are asymptomatic. Rarely, complications such as compression, infection, and bleeding within the cyst can occur. Under the effect of the increased pressure, the epithelial lining of the cyst undergoes necrosis and sloughing, causing injury of the fragile blood vessels, leading to intracystic bleeding. The bleeding within or from the cyst can be precipitated by anticoagulation. We present a patient with PCLD who developed intracystic bleeding after he was started on apixaban for the prevention of thromboembolism.
Introduction

Fibropolycystic liver disease encompasses a spectrum of liver and biliary tract lesions that are caused by abnormal embryologic development of the ductal plates [1]. These disorders include congenital hepatic fibrosis, biliary hamartomas, choledochal cysts, Carolis disease, and polycystic liver disease (PCLD) [2]. PCLD is arbitrarily defined as a liver that contains >20 cysts. The condition is associated with 2 genetically distinct diseases: a primary phenotype is isolated PCLD and an extrarenal manifestation in autosomal dominant polycystic kidney disease [3].

Liver cysts are believed to originate from malformation of the ductal plate during embryonic development of the liver, leading to discrete intralobular bile ductules called von Meyenburg complexes that progressively dilate and lose connection with the biliary tree [4, 5]. Other processes involved in hepatic cystogenesis include concomitant abnormal fluid secretion, altered cell-matrix interaction, and cholangiocyte hyperproliferation [3]. Cysts are histologically delineated by an inner layer of cuboidal, flattened epithelial cells, a middle layer of compact connective tissue containing blood vessels, and an outer layer of loose connective tissue with large blood vessels, bile ducts, and occasional von Meyenburg complexes [4]. The cysts can be confined in 1 segment or involve the entire liver, and they grow slowly over time. The growth rate is associated with several risk factors such as advanced age, female gender, exogenous estrogen use, multiple pregnancies, and the volume of the renal cysts itself [3, 5]. We present a patient with PCLD who developed intracystic bleeding after he was started on apixaban for the prevention of thromboembolism.

Case Report

Our patient is a 69-year-old Hispanic man who presented to our hospital with the complaints of right upper quadrant pain for the past 3 days. His pain was sudden in onset, sharp in character, and had progressively increased with time. He denied any history trauma to the abdomen. The patient’s medical history was significant for hypertension, hypothyroidism, chronic obstructive pulmonary disease, and multiple renal and liver cysts which were incidentally diagnosed 2 years ago during a routine ultrasound. One month before the presentation, he was admitted for COVID-19 pneumonia. Due to elevated d-dimer levels and high risk for thromboembolic events, he was started on oral apixaban 5 mg twice daily which he was currently taking.

In the emergency room, his physical examination was significant for a heart rate of 113 beats per minute, blood pressure of 156/94 mm Hg, respiratory rate of 28, and saturation of 98% on room air. The abdomen was nondistended and tender to palpation in the right upper quadrant without any rigidity or guarding. Murphy’s sign was negative. The rest of the physical examination was unremarkable. The initial laboratory tests showed a hemoglobin level of 6.6 g/dL (baseline 9.3 g/dL), hematocrit 20.2%, white blood cell count 11.2 k/μL, and platelets 204 k/μL. The rest of his laboratory tests are shown in Table 1.

A limited abdominal ultrasound showed an enlarged liver measuring 22.1 cm with multiple anechoic and hypoechoic cystic lesions. There was a dominant cystic lesion in the right lobe, 16 cm in its largest diameter, with mixed internal echogenicity, and with areas of heterogeneously hyperechoic internal densities, which could represent hemorrhage. This has been presented in Figure 1. There were no intra or extra-biliary dilatation, and the gallbladder was normal in appearance. Color-flow imaging of the portal vein demonstrated proper flow to the liver without thrombosis. An abdominal magnetic resonance 6 months prior to presentation had showed multiple liver cysts, with the largest one being 9.7 cm in the right hepatic lobe. This has been presented in Figure 2.
The patient received intravenous fluids and blood transfusion. Apixaban was stopped, and after the initial resuscitation, he was transferred to a specialized center for liver surgery. The patient underwent laparoscopic deroofing and partial resection of the right hepatic lobe. Intraoperatively, a large cyst with dense adhesions to the abdominal wall was identified. Careful blunt dissection was performed to release the cyst from the

### Table 1. Laboratory test results

| Parameter                          | Day of presentation | One month before | Reference range  |
|-----------------------------------|---------------------|------------------|------------------|
| Hemoglobin, g/dL                  | 6.6                 | 9.3              | 12.0–16.0        |
| Hematocrit, %                     | 20.2                | 29               | 42.0–51.0        |
| Platelet, k/µL                    | 204                 | 300              | 150–400          |
| White blood cell count, k/µL      | 11.2                | 9.1              | 4.8–10.8         |
| Partial thromboplastin time, s    | 37.6                | 25.9             | 27.2–39.6        |
| Prothrombin time, s               | 17.5                | 12               | 9.9–13.3         |
| INR                               | 1.47                | 1.01             | 0.85–1.14        |
| Creatinine, mg/dL                 | 3.1                 | 2.5              | 0.5–1.5          |
| Albumin, g/dL                     | 4                   | 4.1              | 3.2–4.6          |
| Aspartate aminotransferase, unit/L| 45                  | 28               | 9–36             |
| Alanine aminotransferase, unit/L  | 51                  | 47               | 5–40             |
| Alkaline phosphatase, unit/L      | 83                  | 85               | 53–141           |
| Bilirubin total, mg/dL            | 0.5                 | 0.2              | 0.2–1.2          |
| Bilirubin direct, mg/dL           | 0.2                 | 0.1              | 5–40             |

*Fig. 1. Ultrasound showing the liver cyst with intracystic bleeding.*

The patient received intravenous fluids and blood transfusion. Apixaban was stopped, and after the initial resuscitation, he was transferred to a specialized center for liver surgery. The patient underwent laparoscopic deroofing and partial resection of the right hepatic lobe. Intraoperatively, a large cyst with dense adhesions to the abdominal wall was identified. Careful blunt dissection was performed to release the cyst from the
abdominal wall. The cyst was opened, and murky fluid and debris were aspirated. The other part of the cyst wall was attached to the liver parenchyma, and a LigaSure device was used to circumferentially resect the cyst wall along with a portion of the right lobe. Pathology revealed a fibrotic cyst wall with hemosiderin deposition and a predominantly denuded epithelial lining. The adjacent liver parenchyma showed several von Meyenburg complexes. These findings were consistent with benign liver cyst and features of a fibro-polycystic liver disease. The remainder of the hospital course was uncomplicated, and he was discharged home.

**Discussion**

Most of the patients with liver cysts are asymptomatic. One in 5 patients with PCLD will experience symptoms from direct compression of the nearby structures, the most common being abdominal pain or distention, nausea, vomiting, esophageal reflux, early satiety, shortness of breath, and lower back pain [6]. Rarely, cysts can cause compression of the biliary tree or hepatic vasculature, causing obstructive jaundice, portal vein thrombosis, or complications from portal hypertension, respectively [7]. Cyst complications can also occur, with the most common being infection, rupture, and bleeding. The intracystic bleeding is a rare but a life-threatening complication. It can be spontaneous or precipitated by trauma or anticoagulation. Several mechanisms have been proposed to explain spontaneous intracystic bleeding. Gaviser [4] hypothesized that under high intracystic pressure, the cyst’s epithelial lining undergoes necrosis and sloughing, causing injury of the fragile blood vessels in the cyst wall and leading to intracystic bleeding. Other proposed mechanisms are the presence of hemangioma and vascular malformation near or within the cyst wall. Trauma can also precipitate intracystic bleeding [8]. Although it is not widely recognized, the cyst’s size might be an essential factor that predisposes to bleeding [9]. Cases of intracystic bleeding have been reported in patients who are on anticoagulation, especially in the setting of supratherapeutic INR [10, 11]. Cystic rupture has been reported in a patient who was newly started on rivaroxaban for pulmonary embolism [12]. The incidence of cyst rupture has not been reported in the literature, but most cases of ruptures occur when the cyst size is >10 cm [13]. Our patient was incidentally diagnosed with PCLD after a routine ultrasound. He was asymptomatic for years until anticoagulation was started. The patient had a preexisting dominant cystic lesion of 9.7 cm, which almost doubled in size after apixaban was initiated. The intracystic bleeding was precipitated by apixaban. His biopsy
showed a denuded epithelial line, supporting that the increase in the intracystic pressure leads to epithelial necrosis and sloughing, exposing fragile blood vessels. Fortunately, in our case, despite the large cyst size, the intracystic bleeding did not result in the cyst rupture. The patient underwent laparoscopic deroofing and partial right lobe resection and is doing well after discharge.

Conclusions

The American College of Gastroenterology guides the management of simple hepatic cysts, but there are no guidelines about the use of anticoagulation in these patients. Intracystic hemorrhage remains a serious and life-threatening complication that clinicians should be aware. The risks versus benefits of anticoagulation should be carefully evaluated. When possible, anticoagulation should be avoided, especially in patients with large cysts.

Statement of Ethics

The patient has given written informed consent to publish his case including publications of images. Research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This manuscript is a case report, and in presence of the patient’s written consent does not need review from the IRB at the Bronxcare Hospital Center.

Conflict of Interest Statement

The authors have no conflicts of interest.

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Author Contributions

The first author (Elona Shehi) and the coauthors (Ked Fortuzi, MD; Haider Ghazanfar, MD; Shehriyar Mehershahi; and Bhavna Balar, MD) were all involved in summarizing this case report, writing the manuscript, and proofreading the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.
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