Case report

Anticoagulant-induced hemorrhagic cholecystitis with hemobilia after deceased donor kidney transplant and literature review

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ABSTRACT

Introduction and importance: Hemobilia and hemorrhagic cholecystitis are uncommon causes of right upper quadrant abdominal pain. The development of intra-gallbladder and biliary bleeding has been primarily associated with abdominal trauma, malignancy, liver transplant, and iatrogenic injury to the biliary tree and vasculature. Spontaneous anticoagulant induced hemorrhagic cholecystitis and hemobilia are incredibly rare events and have only been documented by a handful of case reports.

Case presentation: A 55-year-old male who had recently undergone a deceased-donor kidney transplant was transferred to our academic institution for evaluation of subjective fever, right upper quadrant abdominal and back pain. The patient demonstrated localized tenderness in the right abdomen and was found to have hemorrhagic cholecystitis on imaging. He subsequently underwent urgent cholecystectomy and recovered without any subsequent complications.

Clinical discussion: Hemorrhagic cholecystitis and hemobilia are a rare cause of right-sided or generalized abdominal pain. Diagnosis is made primarily by pathognomonic findings on CT and US imaging. Prompt diagnosis is essential in preventing mortality and/or significant morbidity. The standard treatment consists of urgent/emergent cholecystectomy.

Conclusion: A rare sequelae of anticoagulant use, intra-biliary bleeding must be considered as a differential diagnosis in anticoagulated patients presenting with right upper quadrant abdominal pain.

1. Introduction

Hemobilia and hemorrhagic cholecystitis are uncommon causes of right upper quadrant abdominal pain. The development of intra-gallbladder and biliary bleeding has been primarily associated with abdominal trauma, malignancy, liver transplant, and iatrogenic injury to the biliary tree and vasculature [1,2]. Spontaneous anticoagulant induced hemorrhagic cholecystitis and hemobilia are rare events that have only been described by a handful of case reports. The etiology of spontaneous intra-gallbladder hemorrhage is thought to involve chronic transmural inflammation of the gallbladder wall, leading to ischemia and erosion of the gallbladder mucosa, resulting in an intraluminal bleed [3]. Though a rare, hemorrhagic cholecystitis needs to be considered in the differential as a cause of abdominal pain as delayed diagnosis can lead to morbidity and death.

This case report has been written in line with the 2020 SCARE Criteria [4].

2. Case description

A 55-year-old male with a past medical history of end stage renal disease (ESRD), diabetes mellitus type II, and deceased donor kidney transplant (DDKT) was transferred to our hospital for evaluation of subjective fevers, right quadrant abdominal pain, and back pain. He was hemodynamically stable upon arrival and did not appear to be in distress. He reported that his symptoms had begun approximately three days ago, almost 24 hr after starting apixaban for a left upper extremity deep vein thrombus (DVT). His symptoms had grown progressively...
worse, prompting him to present to his local emergency department. The patient had no known family history of bleeding disorders and denied any recent abdominal trauma. He had no history of tobacco, alcohol, or illicit substance use. No significant psychosocial history.

Laboratory work-up and imaging were obtained prior to transfer and were significant for elevated transaminases, with an aspartate aminotransferase (AST) of 1300 U/L and an alanine aminotransferase (ALT) of 800 U/L. Ultrasound of the right upper quadrant revealed gallbladder distension with evidence of sludge and possible hemobilia. Computer tomographic (CT) imaging of the patient’s abdomen and pelvis was done upon transfer and revealed a distended gallbladder, with heterogeneous, hyperdense material in the lumen suggestive of hemorrhagic contents and biliary sludge in the setting of systemic anticoagulation. A nuclear medicine scan was subsequently obtained with Technetium-99m and was unable to visualize the gallbladder, a finding consistent with acute cholecystitis, most likely hemorrhagic in nature (Fig. 1).

One-month prior to presentation, the patient underwent DDKT with no intraoperative complications. During his outpatient post-operative follow-up with transplant nephrology clinic, he was noted to have right upper extremity pain and edema. Ultrasound imaging was obtained and showed evidence of a DVT and the patient was started on oral anticoagulation (apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily).

Upon transfer to our institution, the patient’s hemoglobin/hematocrit were 7.1 g/dL and 21.3 g/dL respectively. He was found to have a white blood cell count of 9.0 × 10^9/μL. The results of chemistry studies showed a creatinine of 4.07 mg/dL, a creatinine clearance of 23 mL/min, a total bilirubin of 0.8 mg/dL, an alkaline phosphatase of 295 U/L, and an AST/ALT of 322/644 U/L respectively. Prothrombin time (PT) and INR were found to be elevated at 27.2 sec and 2.4 respectively. On physical exam the patient demonstrated localized tenderness in the right upper and lower abdominal quadrants.

The decision was made to take the patient to the operating room for cholecystectomy. His apixaban was held, and a low dose, flat-rate heparin infusion (300–500 units/hr) started. The procedure was performed by a transplant surgeon and was converted from laparoscopic to open due to poor visibility and the inability to safely identify the cystic and common bile ducts. There were no intra-operative complications.

Surgical pathology showed a denuded gallbladder with chronic cholecystitis, intraluminal hemorrhage, and hematoma formation. There was no evidence of malignancy. The patient’s post-operative course was uncomplicated, apixaban was restarted without re-bleeding, and he was discharged home. Labs obtained two weeks post-procedure were remarkable only for an elevated creatinine (2.78 mg/dL). He has continued to follow-up regularly in transplant nephrology clinic per protocol.

3. Discussion

Hemorrhagic cholecystitis and hemobilia are a rare cause of right-sided or generalized abdominal pain that present very similarly to other more commonly seen pathologies of the biliary tract. Etiologies of hemobilia are divided into iatrogenic and non-iatrogenic causes. Iatrogenic causes included percutaneous or endoscopic hepatopancreatobiliary interventions and surgery [1,2]. Non-iatrogenic causes included primary or metastatic hepatobiliary malignancy, portal biliopathy, chronic obstruction of the pancreato-biliary tract and intra-ductal infection (Ascaris lumbricoides, Clonorchis sinensis [Chinese liver fluke], and Fasciola hepatica [sheep liver fluke]) [1,2].

Patients experiencing intra-gallbladder bleeding often present with symptoms similar to those seen in acute cholecystitis due to the resulting gallbladder distension and inflammation. Common symptoms include right upper quadrant abdominal pain, biliary colic, radiating back pain, fevers, and jaundice. Quincke’s triad of right upper quadrant abdominal pain, jaundice, and upper gastrointestinal bleeding, first mentioned in 1877, describes the classic symptomatology of hemobilia, but is however only present in 25–30% of patients [1,2]. If bleeding into the biliary tract is rapid, blood passes into the duodenum and manifest as melena or hematemesis. If the bleeding is slow, it may form an intra-biliary clot [2] and overt bleeding may not be present. Tarazi et al. published a literature review and a summary of case reports on hemorrhagic cholecystitis in 2019 [5]. We have updated the list and focused only on cases involving anticoagulation (Table 1).

Laboratory findings are non-specific, with patients experiencing leukocytosis, elevations in liver enzymes, and both alkaline phosphatase and total bilirubin. Imaging is often diagnostic, with right upper quadrant abdominal US showing evidence of acute cholecystitis and blood products in gallbladder lumen. Pseudoaneurysms and aneurysms of hepatic artery may also be found [2,6]. Computed tomography angiogram (CTA) of the abdomen may offer more evidence, showing presence of blood within the gallbladder and biliary tract. Other more invasive diagnostic modalities such as esophagogastroduodenoscopy (EGD), endoscopic retrograde cholangiopancreatography (ERCP), and angiography also play an essential role in the diagnosis and treatment of hemobilia. The choice and order of test may vary based on clinical suspicion and etiology.

Patients may initially be managed non-operatively with intravenous fluid resuscitation, cessation of all anticoagulant medications, and bowel rest. More commonly, patients are managed with cholecystectomy. Hemodynamic stability of patient plays a significant role in decision regarding diagnostic choice and treatment options [1,2]. The placement of cholecystostomy tube can be a viable option, but may not be successful if clot is present within the gallbladder lumen. As hemorrhagic cholecystitis is associated with trauma and bleeding diathesis, patients must undergo complete evaluation to exclude concurrent injuries or other bleeding sites. Mortality and morbidity are known to be high if patients present with intra-abdominal bleeding secondary to gallbladder perforation [1,2,5,12].

The true incidence of spontaneous hemorrhagic cholecystitis and hemobilia are unknown. A comprehensive review of existing literature produced only a handful of case reports. No large-scale studies or meta-analysis have been published, likely due to the rarity of the condition. The etiology of spontaneous intra-gallbladder hemorrhage is thought to involve chronic transmural inflammation of the gallbladder wall,

Fig. 1. CT abdomen pelvis without contrast (coronal section), distended gallbladder and incisional hematoma.
erosion of the gallbladder mucosa, possibly secondary to the presence of cystitis and no evidence of malignancy. Therefore, we postulate that our case, however, was significant only for the findings of chronic chole... hemorrhagic cholecystitis three days after being started on the anticoagulant and the majority of cases were published in the last decade. As the incidence of hemobilia and hemorrhagic cholecystitis will likely rise. The patient described in our case developed symptoms of hemor... hemobilia is an incredibly rare event, we also explored the possibility of a biliary polyp or hemorrhagic cholecystitis. Our literature search revealed 19 case reports describing anticoagulation related hemobilia and hemorrhagic cholecystitis. Patients were more likely to be greater than 60 years of age and the majority of cases were published in the last decade. As the prevalence of anticoagulation increase due to an aging population, the incidence of hemobilia and hemorrhagic cholecystitis will likely rise.

The patient described in our case developed symptoms of hemorrhagic cholecystitis three days after being started on the anticoagulant apixaban. To our knowledge this is the first case report of anticoagulant induced spontaneous hemobilia in a recent deceased donor kidney transplant recipient. As spontaneous isolated hemobilia is an incredibly rare event, we also explored the possibility of a biliary polyp or neoplasm as the source of intraluminal bleeding. Pathology from the case, however, was significant only for the findings of chronic cholecystitis and no evidence of malignancy. Therefore, we postulate that our patient likely developed a spontaneous intraluminal bleed due to erosion of the gallbladder mucosa, possibly secondary to the presence of biliary sludge after anticoagulation initiation.

4. Conclusion

Hemorrhagic cholecystitis and hemobilia are a rare cause of right upper quadrant pain and must be worked up as part of the differential diagnosis in the right clinical setting. High index of suspicion should be maintained in patients on systemic anticoagulants. The importance of timely diagnosis and treatment is essential as the condition may be fatal if not appropriately managed. There is also a need for prospective randomized trials to assess the safety and efficacy of apixaban in patients with impaired renal function.

Table 1

| Author              | Publication year | Journal                                      | Patient age | Patient gender | Indication                           | Anticoagulation | Management                      |
|---------------------|------------------|----------------------------------------------|-------------|----------------|--------------------------------------|-----------------|----------------------------------|
| Hasegawa et al.     | 2021             | American Journal of Case Reports             | 70          | M              | Left ventricle thrombus              | Warfarin, aspirin and clopidogrel | ERCP + laparoscopic cholecystectomy |
| Itagaki et al.      | 2019             | Journal of Medical Case Reports              | 86          | F              | Atrial fibrillation                  | Edoxaban        | Laparoscopic cholecystectomy     |
| Ma et al.           | 2019             | BMC Surgery                                  | 51          | F              | Cerebral aneurysm                    | Aspirin         | Laparoscopic cholecystectomy     |
| Sweeney et al.      | 2019             | Journal of Surgical Case Reports             | 78          | M              | Atrial fibrillation                  | Warfarin + aspirin | Laparoscopic cholecystectomy     |
| Donn et al.         | 2018             | The Surgery Journal                          | 63          | M              | DVT                                  | Enoxaparin → warfarin | Laparoscopic cholecystectomy     |
| Kwok et al.         | 2018             | BMJ Case Reports                             | 80          | M              | Atrial fibrillation                  | Rivaroxaban      | Laparotomy + open cholecystectomy |
| Kinnear et al.      | 2017             | BMJ Case Reports                             | 74          | M              | Atrial fibrillation                  | Apixaban         | Laparotomy + open cholecystectomy |
| Oshiro et al.       | 2017             | International Surgery                       | 61          | F              | SLE, antiphospholipid antibody syndrome (APS) | Warfarin Conservative w/IV antibiotics + elective lap cholecystectomy |
| Shishida et al.     | 2017             | Case Reports in Gastroenterology             | 79          | M              | S/p spinal canal stenosis surgery    | Gliostazol      | ERCP + ENBD                       |
| Cho et al.          | 2015             | Korean Journal of Thoracic and Cardiovascular Surgery | 61          | M              | S/p mitral valve replacement        | Warfarin         | Cholecystectomy drainage         |
| Hicks et al.        | 2014             | BMJ Case Reports                             | 79          | F              | S/p right hemiarioplasty             | LMWH            | Laparoscopy, laparotomy + open cholecystectomy |
| Matsukiyo et al.    | 2014             | J-Stage                                      | 68          | F              | Cerebral infarction                 | Thrombolysis     | Laparotomy + open cholecystectomy |
| Kwon et al.         | 2012             | Korean Journal of Hepatobiliary Pancreatic Surgery | 75          | M              | Atrial fibrillation                  | Warfarin         | Laparoscopic cholecystectomy     |
| Vijendren et al.    | 2012             | BMJ Case Reports                             | 74          | F              | s/p CABG                            | Aspirin          | Open cholecystectomy             |
| Chen et al.         | 2010             | The American Journal of Medical Sciences     | N/A - Elderly | M            | Unstable angina                     | Heparin          | Laparoscopic cholecystectomy     |
| Lin et al.          | 2010             | Journal of Internal Medicine Taiwan          | 80          | M              | Cerebral infarction                 | Warfarin         | Laparoscopic cholecystectomy     |
| Morris et al.       | 2008             | Case Reports in Gastroenterology             | 91          | F              | Claudication                        | Aspirin + clopidogrel | Open cholecystectomy            |
| Pandya et al.       | 2008             | Abdominal Imaging                            | 85          | F              | DVT                                  | Aspirin + warfarin | Conservative w/IV antibiotics + cholecystectomy |
| Stempel et al.      | 1993             | Journal of Vascular and Interventional Radiology | 78          | M              | s/p AAA repair                      | Heparin during AAA repair | Cholecystectomy drainage        |

leading to ischemia and erosion of the gallbladder mucosa, resulting in an intraluminal bleed [3]. Bleeding is thought to be more pronounced in patients taking anticoagulant medications and can progress to hemobilia or hemorrhagic cholecystitis. Our literature search revealed 19 case reports describing anticoagulation related hemobilia and hemorrhagic cholecysitis. Patients were more likely to be greater than 60 years of age and the majority of cases were published in the last decade. As the prevalence of anticoagulation increase due to an aging population, the incidence of hemobilia and hemorrhagic cholecystitis will likely rise.
the data, and controlled the decision to publish.

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