



Case report

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

Ilya Sakharuk^a, Patricia Martinez^a, Melissa Laub^c, Imran Gani^b, Muhammad Saeed^{a,*}

^a Augusta University, Department of Surgery, United States of America

^b Augusta University, Department of Medicine, United States of America

^c Augusta University, Department of Pharmacy, United States of America

ARTICLE INFO

Keywords:

Hemobilia

Hemorrhagic cholecystitis

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

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computer tomographic; DDKT, deceased donor kidney transplant; ESRD, end stage renal disease; US, ultrasound.

* Corresponding author at: 1120 15th Street, AD-3401, Augusta, GA 30912, United States of America.

E-mail address: msaeed@augusta.edu (M. Saeed).

<https://doi.org/10.1016/j.ijscr.2021.106027>

Received 23 April 2021; Received in revised form 18 May 2021; Accepted 21 May 2021

Available online 26 May 2021

2210-2612/© 2021 Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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 heterogenous, 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-99 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 $9.0 \times 10^3/\mu\text{L}$. 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.



Fig. 1. CT abdomen pelvis without contrast (coronal section), distended gallbladder and incisional hematoma.

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 hepato-pancreatobiliary 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 esophagoduodenoscopy (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,

Table 1
Literature search hemorrhagic cholecystitis case reports with anticoagulation.

Author	Publication year	Journal	Patient age	Patient gender	Indication	Anticoagulation	Management
Hasegawa et al. [6]	2021	American Journal of Case Reports	70	M	Left ventricle thrombus	Warfarin, aspirin and clopidogrel	ERCP + laparoscopic cholecystectomy
Itagaki et al. [7]	2019	Journal of Medical Case Reports	86	F	Atrial fibrillation	Edoxaban	Laparoscopic cholecystectomy
Ma et al. [8]	2019	BMC Surgery	51	F	Cerebral aneurysm	Aspirin	Laparoscopic cholecystectomy
Sweeny et al. [9]	2019	Journal of Surgical Case Reports	78	M	Atrial fibrillation	Warfarin + aspirin	Laparoscopic cholecystectomy
Donn et al. [10]	2018	The Surgery Journal	63	M	DVT	Enoxaparin → warfarin	Laparoscopic cholecystectomy
Kwok et al. [11]	2018	BMJ Case Reports	80	M	Atrial fibrillation	Rivaroxaban	Laparotomy + open cholecystectomy
Kinnear et al. [12]	2017	BMJ Case Reports	74	M	Atrial fibrillation	Apixaban	Laparotomy + open cholecystectomy
Oshiro et al. [13]	2017	International Surgery	61	F	SLE, antiphospholipid antibody syndrome (APS)	Warfarin	Conservative w/IV antibiotics + elective lap cholecystectomy
Shishida et al. [14]	2017	Case Reports in Gastroenterology	79	M	S/p spinal canal stenosis surgery	Cilostazol	ERCP + ENBD
Cho et al. [15]	2015	Korean Journal of Thoracic and Cardiovascular Surgery	61	M	S/p mitral valve replacement	Warfarin	Cholecystectomy drainage
Hicks et al. [16]	2014	BMJ Case Reports	79	F	S/p right hemiarthroplasty	LMWH	Laparoscopy, laparotomy + open cholecystectomy
Matsukiyo et al. [17]	2014	J-Stage	68	F	Cerebral infarction	Thrombolysis	Laparotomy + open cholecystectomy
Kwon et al. [18]	2012	Korean Journal of Hepatobiliary Pancreatic Surgery	75	M	Atrial fibrillation	Warfarin	Laparoscopic cholecystectomy
Vijendren et al. [19]	2012	BMJ Case Reports	74	F	s/p CABG	Aspirin	Open cholecystectomy
Chen et al. [20]	2010	The American Journal of Medical Sciences	N/A - Elderly	M	Unstable angina	Heparin	Laparoscopic cholecystectomy
Lin et al. [21]	2010	Journal of Internal Medicine Taiwan	80	M	Cerebral infarction	Warfarin	Laparoscopic cholecystectomy
Morris et al. [22]	2008	Case Reports in Gastroenterology	91	F	Claudication	Aspirin + clopidogrel	Open cholecystectomy
Pandya et al. [23]	2008	Abdominal Imaging	85	F	DVT	Aspirin + warfarin	Conservative w/IV antibiotics + cholecystectomy
Stempel et al. [24]	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 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.

Provenance and peer review

Not commissioned, externally peer reviewed.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

This is a case report paper.

Funding

None.

Guarantor

Corresponding author, Dr. Muhammad Saeed accepts full responsibility for the work and/or the conduct of the study, has access to

the data, and controlled the decision to publish.

Research registration number

Not applicable.

CRediT authorship contribution statement

IS – participated in writing manuscript, literature search, case report editing and patient care

ML – participated in case report editing and patient care

IG – participated in case report editing and patient care

MIS – participated in writing manuscript, literature search, case report editing and patient care.

Declaration of competing interest

There are no conflicts of interest.

Acknowledgements

Rachel Stephens Pharm D for reviewing the document.

References

- [1] R. Berry, J. Han, A. Kardashian, N.F. LaRusso, J.H. Tabibian. Hemobilia: etiology, diagnosis, and treatment, *Liver Res.*, Volume 2, Issue 4, 2018, Pages 200–208, ISSN 2542-5684.
- [2] M.H. Green, R.M. Duell, C.D. Johnson, N.V. Jamieson, Haemobilia, *Br. J. Surg.* 88 (6) (2001) 773–786, <https://doi.org/10.1046/j.1365-2168.2001.01756.x>.
- [3] M. Shishida, M. Ikeda, N. Karakuchi, K. Ono, N. Tsukiyama, M. Shinomura, et al., Hemorrhagic cholecystitis in a patient on maintenance dialysis, *Case Rep. Gastroenterol.* 11 (2) (2017) 488–493, <https://doi.org/10.1159/000479497>.
- [4] Agha RA, Franchi T, Sohrabi C, Mathew G, for the SCARE Group. The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines, *Int. J. Surg.* 2020;84:226–230.
- [5] M. Tarazi, F.T. Tomalieh, A. Sweeney, D. Sumner, Y. Abdulaal, Literature review and case series of haemorrhagic cholecystitis, *J. Surg. Case Rep.* 1 (2019) (2019), rjy360.
- [6] D.H. Chinn, E.L. Miller, N. Piper, Hemorrhagic cholecystitis. Sonographic appearance and clinical presentation, *J. Ultrasound Med.* 6 (6) (1987) 313–317, <https://doi.org/10.7863/jum.1987.6.6.313>.
- [7] H. Itagaki, S. Katuhiko. "Gallbladder hemorrhage during orally administered edoxaban therapy: a case report." *J. Med. Case Rep.*, vol. 13, no. 1, 26 Dec. 2019, doi:<https://doi.org/10.1186/s13256-019-2328-9>.
- [8] Z. Ma, B. Xu, L. Wang, Y. Mao, B. Zhou, Z. Song, Anticoagulants is a risk factor for spontaneous rupture and hemorrhage of gallbladder: a case report and literature review, *BMC Surg.* 19 (1) (2019), <https://doi.org/10.1186/s12893-018-0464-6>.
- [9] A. Sweeny, N.A. Smith, J.A. Serfin. "Hemorrhagic cholecystitis causing hemobilia and common bile duct obstruction." *J. Surg. Case Rep.* 2019.3 (2019): rjz081.
- [10] E. Donn, I. Atkinson, A. McCague. "Hemorrhagic cholecystitis after warfarin use for deep vein thrombosis." *Surg. J.*, vol. 04, no. 02, 18 June 2018, doi:<https://doi.org/10.1055/s-0038-1660450>.
- [11] A. Kwok, T.Y. Chern, R. Winn, Acute cholecystitis and gallbladder perforation leading to massive haemoperitoneum in a patient taking rivaroxaban, *BMJ Case Rep.* (2018), <https://doi.org/10.1136/bcr-2018-226870>.
- [12] D. Liefman, M. Wullschlegler, Hemorrhagic cholecystitis: a rare cause of presentation with upper gastrointestinal bleeding, *Int. Ann. Med.* 2 (5) (2018), <https://doi.org/10.24087/iam.2018.2.5.480>.
- [13] N. Kinnear, D.B. Hennessey, R. Thomas. "Haemorrhagic cholecystitis in a newly anticoagulated patient." *BMJ Case Rep.*, 12 Apr. 2017, doi:<https://doi.org/10.1136/bcr-2016-214617>.
- [14] Y. Oshiro, S. Tsukamoto, Y. Owada, K. Takahashi, T. Oda, N. Sakamoto, et al., Hemorrhagic cholecystitis during anticoagulant therapy in a patient with systemic lupus erythematosus and antiphospholipid syndrome undergoing elective laparoscopic cholecystectomy, *Int. Surg.* (2017), <https://doi.org/10.9738/int Surg-d-15-00319.1>.
- [15] S.H. Cho, H.Y. Lee, H.S. Kim, Anticoagulant therapy-induced gallbladder hemorrhage after cardiac valve replacement, *Kor. J. Thorac. Cardiovasc. Surg.* 48 (6) (2015) 432–434, <https://doi.org/10.5090/kjtcs.2015.48.6.432>.
- [16] N. Hicks. "Haemorrhagic Cholecystitis: an unusual cause of upper gastrointestinal bleeding." *Case Rep.*, vol. 2014, no. jan17 1, 2014, doi:<https://doi.org/10.1136/bcr-2013-202437>.
- [17] H. Matsukiyo, M. Wantanabe, K. Asai, T. Saito, H. Kodama, J. Nagao, et al., A case of hemorrhagic cholecystitis during anticoagulant therapy after cerebral infarction, *J-Stage* 28 (5) (2014) 808–814, <https://doi.org/10.11210/tando.28.808> (article in Japanese only).
- [18] J. Kwon. "Hemorrhagic cholecystitis: report of a case." *Kor. J. Hepatobiliary Pancreat. Surg.*, vol. 16, no. 3, 30 Aug. 2012, pp. 120–122., doi:[10.14701/kjhbps.2012.16.3.120](https://doi.org/10.14701/kjhbps.2012.16.3.120).
- [19] A. Vijendren, K. Cattle, M. Obichere, Spontaneous haemorrhagic perforation of gallbladder in acute cholecystitis as a complication of antiplatelet, immunosuppressant and corticosteroid therapy, *BMJ Case Rep.* 2012 (July 2012) (doi: bcr1220115427).
- [20] Y.Y. Chen, C.H. Yi, C.L. Chen, Y.H. Hsu, S.C. Huang, Hemorrhagic cholecystitis after anticoagulation therapy, *Am J Med Sci* 340 (4) (2010) 338–339, <https://doi.org/10.1097/maj.0b013e3181e9563e>.
- [21] H.P. Lin, Y.C. Lin. "Isolated intraluminal gallbladder hemorrhage after anticoagulation therapy: report of a case." *J. Int. Med. Taiwan*, vol. 21, no. 1, Feb. 2010.
- [22] D.S. Morris, J.R. Porterfield, M.D. Sawyer, Hemorrhagic cholecystitis in an elderly patient taking aspirin and cilostazol, *Case Rep. Gastroenterol.* 2 (2) (2008) 203–207, <https://doi.org/10.1159/000135693>.
- [23] R. Pandya, C. O'Malley, Hemorrhagic cholecystitis as a complication of anticoagulant therapy: role of CT in its diagnosis, *Abdom. Imaging* 33 (6) (2008) 652–653, <https://doi.org/10.1007/s00261-007-9358-2>.
- [24] L.R. Stempel, R.L. Vogelzang, *J. Vasc. Interv. Radiol.* 4 (3) (1993) 377–380, [https://doi.org/10.1016/s1051-0443\(93\)71882-5](https://doi.org/10.1016/s1051-0443(93)71882-5).