Letter to the Editor

ADPKD, COVID-19, and Apixaban: The Treacherous Intracystic Bleeding – A Letter on Apixaban Causing Hepatic Cystic Bleeding by Shehi et al.

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Dear Editor,

Shehi et al. [1] report on a 69-year-old Hispanic man who presented to the hospital with complaints of right upper quadrant pain for the past 3 days without any history of trauma to the abdomen. Multiple renal and liver cysts were incidentally diagnosed 2 years previously during a routine ultrasound in the patient's medical history. The patient was on oral apixaban because of COVID-19 pneumonia, elevated D-dimer levels, and a high risk of thromboembolic events. The patient received intravenous fluids, and blood transfusion and apixaban were stopped. Then, the patient underwent laparoscopic deroofing and partial resection of the liver, including a large cyst with adhesions to the abdominal wall. Histopathology discovered a fibrotic cyst wall with hemosiderin deposition and features of fibro-polycystic liver disease. After surgery, he recovered and was successfully discharged home [1].

Apixaban is an anticoagulant medication used to prevent thromboembolic events, directly inhibiting factor Xa of the coagulation cascade [2, 3]. This drug was approved for medical use in the European Union in May 2011 and in the USA 18 months later. In late 2019, generic versions of the drug were approved in the USA and Canada [4]. COVID-19 pneumonia and Vaccine-induced Immune Thrombotic Thrombocytopenia are severe conditions and rare adverse events following SARS-CoV-2 infection or adenovirus vector COVID-19 vaccines, respectively. In both situations, there may be a treacherous inflammasome activation [5, 6]. In addition, there is recent evidence that the use of apixaban should be cautiously balanced between pros and cons in patients with end-stage renal disease or multiple hepatic and renal cysts, as seen in Shehi et al.'s [1] patient [7–10].

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Hepatorenal fibrocystic syndromes are a heterogeneous group of monogenic conditions with constant developmental abnormalities [11–13]. They are characterized by multiple cysts of the liver and kidney and histological changes in the parenchyma and stromal connective tissue of these two organs as well as other organs [11, 14]. These changes include the proliferation and dilation of epithelial ducts in these tissues and defects in the deposition and buildup of the extracellular matrix. The intimate connection of the vascular system with the extracellular matrix where the cysts are embedded is a predisposing condition to bleeding and thromboembolic events. The ductular proliferation probably arises from an imbalance between proliferation and apoptosis [15]. The excessive growth of the biliary epithelium may be associated with a defect in complex epithelial-mesenchymal interactions, increasing the frailty of the pericystic connective tissue. The earliest form of the intrahepatic bile ducts takes the shape of a cylinder called the “ductal plate,” from which ductular structures subsequently differentiate. Some congenital conditions are characterized by an insufficient breakdown of the primitive embryonic ductal plate, which leads to ductular proliferation. Ductal plate malformation (DPM) is a histopathological characteristic of many autosomal recessive conditions such as Meckel-Gruber syndrome (MGS), hepatic-pancreato-renal syndrome (HPRS), and Jeune asphyxiating thoracic dystrophy (JATD) [13]. Hepatorenal fibrocystic diseases may harbor defects, including central nervous system and skeletal abnormalities, dysmorphic features, and developmental delay, other than a fibrocystic change of liver and kidney. Deficiencies in several metabolic pathways may also cause some developmental defects. There is substantiated evidence that the association of hepatic and renal malformations in these syndromes is not random and that concomitant defects are due to their standard developmental and genetic features. We should distinguish several congenital conditions of abnormality of the biliary system because they have different outcomes. Hepatic fibrocystic diseases harboring a DPM are a group of congenital disorders exhibiting an abnormal embryogenesis of the biliary ductal system invariably. These abnormalities include syndromic DPM, congenital hepatic fibrosis, choledochal cyst, Caroli disease and Caroli syndrome, cysts-associated with the autosomal dominant polycystic liver disease (ADPKD), and biliary hamartoma or von Meyenburg complex. The hepatic lesions can also be associated with renal anomalies such as autosomal recessive polycystic kidney disease (ARPKD), medullary sponge kidney, and nephronophthisis. Understanding the ductal plate’s embryology and pathogenesis is central to accurately diagnosing DPM, which in turn is relevant for both clinical management and genetic counseling.

Three underlying mechanisms may be behind the DPM. They include (1) abnormal differentiation of hepatoblasts to ductal plate cells with perturbation of cell polarization and abnormal lumen formation; (2) abnormal duct expansion after a correct ductal plate cells differentiation and maturation of primitive ductal structures; and (3) failure of maturation of the nearly remodeled interlobular bile ducts. Substantially, the diameter of malformed ducts determines the type of DPM. The consequence of it is, thus, that von Meyenburg complexes or congenital hepatic fibrosis/ARPKD occur if small primitive biliary structures are involved. Conversely, liver cysts of the ADPKD occur if medium-sized biliary structures are affected, while Caroli disease takes place when the dilatation involves large intrahepatic bile ductular segments. Both ADPKD and Caroli are usually present in adulthood, while ARPKD mainly occurs in infancy and childhood. Von Meyenburg complex is an isolated phenomenon and may be encountered at different ages of life.

ADPKD-associated cysts are usually large. The number of liver cysts can go up with the age of the patient. The biliary abnormalities and hepatic fibrosis that are characteristic of ARPKD are virtually absent in most cases of patients with ADPKD. Deficiencies in two genes have been mainly involved in ADPKD. Mutations in *PKD1* restricted at the chromosome 16p13,23 appear to cause a more frequent and severe ADPKD compared with *PKD2* mutations. *PKD2* is located at the chromosome 4 (4q21–q23). Remarkably, *PKD1* encodes an integral

membrane glycoprotein, polycystin-1, that is implicated in cell-cell or cell-matrix interactions. Polycystin-1 comprises multiple transmembrane domains and an N-terminal extracellular region that binds ligands in the extracellular compartment. In the C-terminal cytoplasmic region of polycystin-1, there are phosphorylation sites and consensus sequences for several signaling molecules. This conformation suggests a role in intracellular signal transduction for this protein. The *PKD2* gene product, polycystin-2, shows some remarkable qualities. There is a significant homology to a voltage-activated Ca^{2+} channel in the intracellular C-terminal domain. Both polycystin-1 and polycystin-2 seem to interact to form a heterodimeric ion channel at the plasma membrane to regulate renal tubular morphology and function. Overall, we should emphasize that anticoagulants need to be cautiously administered to patients with multiple cysts in the liver and kidney because of the potential occurrence of a hepatorenal fibrocystic disease.

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Author Contributions

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References

- 1 Shehi E, Fortuzi K, Ghazanfar H, Mehershahi S, Balar B. Apixaban causing hepatic cystic bleeding: a rare but a life-threatening complication. *Case Rep Gastroenterol*. 2021 Sep-Dec;15(3):904–9.
- 2 Wang Z, Xiang Q, Hu K, Zhang X, Xie Q, Liu Z, et al. Comparison of the safety and efficacy of direct oral anticoagulants and warfarin in atrial fibrillation or venous thromboembolism in patients with renal impairment: systematic review, meta-analysis and network meta-analysis. *Am J Cardiovasc Drugs*. 2021; 21(6):643–57.

- 3 Raymond J, Imbert L, Cousin T, Duflot T, Varin R, Wils J, et al. Pharmacogenetics of direct oral anticoagulants: a systematic review. *J Pers Med*. 2021;11(1):37.
- 4 Tichy EM, Hoffman JM, Suda KJ, Rim MH, Tadrous M, Cuellar S, et al. National trends in prescription drug expenditures and projections for 2021. *Am J Health Syst Pharm*. 2021;78(14):1294–308.
- 5 Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. *Lancet Haematol*. 2021;9(1):e73–80.
- 6 Sergi CM, Chiu B. Targeting NLRP3 inflammasome in an animal model for Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). *J Med Virol*. 2021;93(2):669–70.
- 7 Starr JA, Pinner NA, Mannis M, Stuart MK. A review of direct oral anticoagulants in patients with stage 5 or end-stage kidney disease. *Ann Pharmacother*. 2021. Epub ahead of print.
- 8 Cheung CYS, Parikh J, Farrell A, Lefebvre M, Summa-Sorgini C, Battistella M. Direct oral anticoagulant use in chronic kidney disease and dialysis patients with venous thromboembolism: a systematic review of thrombosis and bleeding outcomes. *Ann Pharmacother*. 2021;55(6):711–22.
- 9 Abdullah HM, Ullah W, Jafar MS, van Zyl M, Saeed R, Alam M, et al. Safety and efficacy of apixaban, rivaroxaban, and warfarin in end-stage renal disease with atrial fibrillation: a systematic review and meta-analysis. *Cardiovasc Revasc Med*. 2021;30:26–32.
- 10 Launay M, Demartin AL, Ragey SP, Mismetti P, Botelho-Nevers E, Delavenne X. Severe inflammation, acute kidney injury, and drug-drug interaction: triple penalty for prolonged elimination of apixaban in patients with Coronavirus disease 2019: a grand round. *Ther Drug Monit*. 2021;43(4):455–8.
- 11 Dorn L, Menezes LF, Mikuz G, Otto HF, Onuchic LF, Sergi C. Immunohistochemical detection of polyductin and co-localization with liver progenitor cell markers during normal and abnormal development of the intrahepatic biliary system and in adult hepatobiliary carcinomas. *J Cell Mol Med*. 2009;13(7):1279–90.
- 12 Sergi C, Adam S, Kahl P, Otto HF. Study of the malformation of ductal plate of the liver in Meckel syndrome and review of other syndromes presenting with this anomaly. *Pediatr Dev Pathol*. 2000;3(6):568–83. Available from:
- 13 Johnson CA, Gissen P, Sergi C. Molecular pathology and genetics of congenital hepatorenal fibrocystic syndromes. *J Med Genet*. 2003;40(5):311–9. Available from:
- 14 Sergi CM. *Pathology of childhood and adolescence. An illustrated guide*. 1st edn. Springer; 2020. p. 1617.
- 15 Sergi C, Kahl P, Otto HF. Contribution of apoptosis and apoptosis-related proteins to the malformation of the primitive intrahepatic biliary system in Meckel syndrome. *Am J Pathol*. 2000;156(5):1589–98.