Functional Budd-Chiari Syndrome Associated With Severe Polycystic Liver Disease

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ABSTRACT: A 50-year-old woman with end-stage renal disease secondary to autosomal dominant polycystic kidney disease was referred to a quaternary care center due to significantly increased abdominal girth. Her physical examination revealed tense ascites and abdominal collateral veins. A 10-L paracentesis improved abdominal discomfort and disclosed a transudate, suggestive of portal hypertension. A computed tomographic scan revealed massive hepatomegaly caused by multiple cysts of variable sizes, distributed throughout all hepatic segments. Contrast-enhanced imaging uncovered extrinsic compression of hepatic and portal veins, resulting in functional Budd-Chiari syndrome and portal hypertension. Although image-guided drainage followed by sclerosis of dominant cysts could potentially lead to alleviation of the extrinsic compression, the associated significant risk of cyst hemorrhage and infection precluded this procedure. In this scenario, the decision was to submit the patient to a liver-kidney transplantation. After 1 year of this procedure, the patient maintains normal liver and kidney function and refers significant improvement in quality of life.

KEYWORDS: Autosomal dominant polycystic kidney disease, polycystic liver disease, Budd-Chiari syndrome

Introduction

Polycystic liver disease (PLD) is manifested as the most common extrarenal cystic presentation of autosomal dominant polycystic kidney disease (ADPKD) and as the fundamental phenotype of autosomal dominant PLD (ADPLD). Although most cases are asymptomatic, the anatomic changes in liver parenchyma resulting from the progressive nature of cyst growth can occasionally lead to massive hepatomegaly and compressive effects.[1–4]

Obstruction of hepatic venous flow secondary to vascular compression by liver cysts is rare in PLD.[3–6] Given the anatomic relationship among the local structures, however, the compression of the portal vein, inferior vena cava, and hepatic veins may potentially lead to functional Budd-Chiari syndrome (BCS).[3,5,7]

We describe a case of a woman with severe PLD and subsequent development of functional BCS. Kidney-liver transplant resulted in successful treatment of the patient.

Case Report

A 50-year-old woman with the diagnosis of ADPKD was referred to a quaternary care center due to significantly increased abdominal girth and ascites over the past year. This manifestation was handled with repeated relief punctures, as the patient could not tolerate furosemide due to hypotension and spironolactone due to hyperkalemia. The patient denied alcohol use or previous thrombotic episodes. She had positive family history of ADPKD (2 maternal aunts), with 1 of them having started hemodialysis at the age of 45 years. Her physical examination revealed malnutrition and tense ascites with profuse abdominal collateral circulation; however, lower limb edema, jaundice, or flapping was absent. She was submitted to paracentesis for relief at admission, which yielded drainage of 10 L of ascitic fluid. The visual aspect of her abdomen following this procedure is presented in Figure 1A.

Her laboratory tests disclosed the following results: serum urea nitrogen: 48 mg/dL, serum creatinine: 3.77 mg/dL, glomerular filtration rate (measured using the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation): 13 mL/min/1.73 m^2, urinalysis with no hematuria or leukocyturia, 24-hour proteinuria: 120 mg, aspartate aminotransferase: 42 U/L, alanine aminotransferase: 41 U/L, alkaline phosphatase (AP): 186 U/L, gamma-glutamyl transferase (GGT): 73 U/L, normal coagulogram, serum total protein: 7.7 g/L, serum albumin: 3.6 g/L, and negative serologies for hepatitis B, C, and human immunodeficiency virus. The serum-ascites albumin gradient was above 1.1, revealing a transudative pattern for the ascitic fluid, which was also negative for neoplastic cells and microbiological evaluation. The comprehensive clinical picture, therefore, suggested the broad diagnosis of portal hypertension.
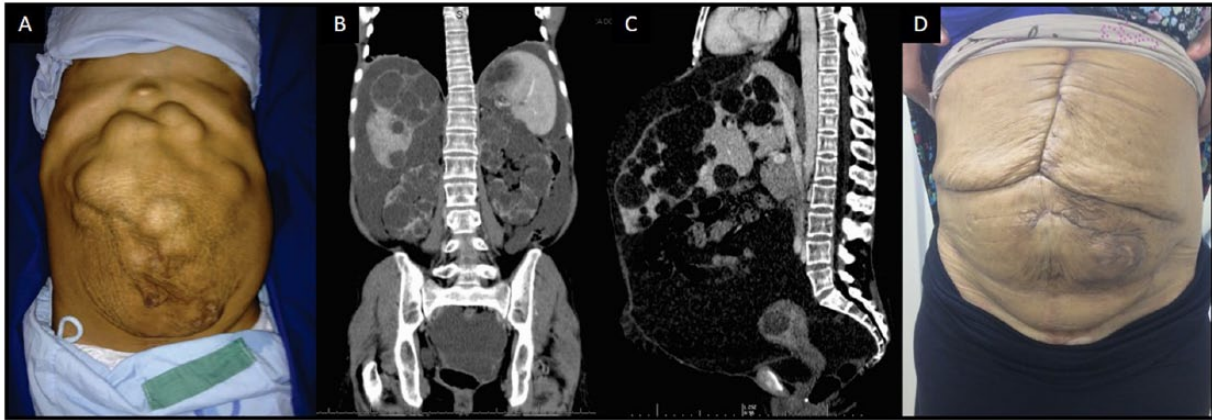
Figure 1. (A) Visual aspect of the patient's abdomen after a 10-L paracentesis; (B) computed tomographic (CT) scan of the abdomen evidencing kidneys of increased size with numerous bilateral cysts and enlarged liver also with multiple cysts; (C) CT scan showing significantly distended abdomen due to large-volume ascites, hepatomegaly, and nephromegaly; and (D) visual aspect of the abdomen after liver-kidney transplantation.
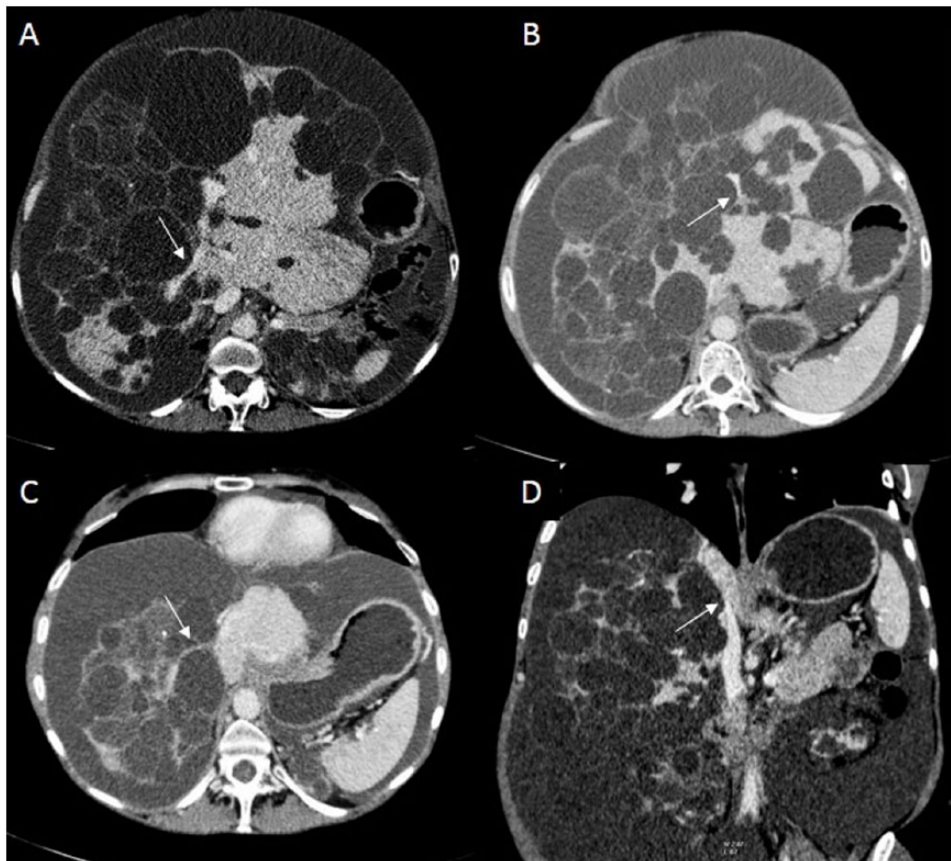

Figure 2. Angio-computed tomography of the patient's abdomen showing multiple liver cysts and, as a result, severe compression of the (A) right hepatic vein (arrow), (B) left hepatic vein (arrow), (C) portal vein (arrow), and (D) inferior vena cava (arrow).

As part of her extended assessment, echocardiographic analysis revealed mild diastolic dysfunction with preserved left ventricular ejection fraction and no evidence of right-sided heart failure or pulmonary hypertension. A computed tomography (CT) angiography scan of her abdomen showed kidneys of increased size and massive hepatomegaly, translated into an estimated liver volume of 8 L (Figure 1B and C). Numerous cysts of variable sizes were distributed throughout all hepatic segments, with no evidence of splenomegaly (Figure 1B and C). Contrast enhancement disclosed a compressive effect of such cysts on hepatic veins, leading to the more defined diagnosis of functional BCS associated with portal hypertension caused by extrinsic portal compression (Figure 2). Ultrasound Doppler of upper abdomen showed patent arteries and veins, with narrowed hepatic veins due to cyst-mediated compression, with no signs of thrombosis. Upper digestive endoscopy, in turn, revealed severely congestive gastropathy but no esophageal varices.
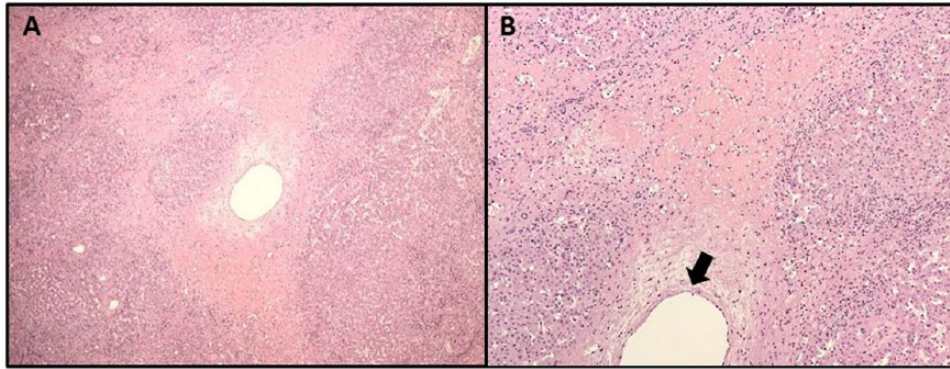
Figure 3. Liver explant histopathology. (A) Evidence of chronic venous flow obstruction, with signs of recent hemorrhage in the centrilobular area (hematoxylin-eosin, 50x) and (B) reduction in centrilobular vein lumen (black arrow) (hematoxylin-eosin, 100x).

Although image-guided percutaneous drainage or cyst fenestration could potentially lead to alleviation of extrinsic compression, the diffuse cystic involvement of the liver and the risk of hemorrhage and/or infection associated with this procedure led us to avoid its performance. In this scenario, and based on the progressive nature of her clinical presentation and stage 5 of chronic kidney disease (CKD), the decision was to submit the patient to liver-kidney transplantation from cadaveric donor. Total hepatectomy, performed for liver graft implantation, was uneventful. Histopathologic analysis of the liver explant showed blocking alterations of venous flow secondary to perisinusoidal fibrosis, congestion, with no evidence of thrombosis, consistent with the diagnosis of BCS (Figure 3). After 1 year of this procedure, the patient is on mycophenolate sodium 360 mg twice daily, prednisone 5 mg daily, and tacrolimus 3 mg twice daily, with normal liver function and serum creatinine of 0.8 mg/dL. She shows significant improvement in quality of life following the reduction in abdominal volume (Figure 1D).

Discussion

Autosomal dominant polycystic kidney disease is among the most common inherited human diseases, with a prevalence of 1:500-1000 in general population,[1] although a recent study estimates it as approximately 1:2500 individuals.[8] Polycystic liver disease is the most frequent extrarenal manifestation in this disorder, affecting up to 94% of the patients.[1–4]

Patients with PLD are most often asymptomatic, usually not requiring treatment directed to the liver phenotype. In some cases, however, cyst expansion may lead to compression of neighboring structures, giving rise to clinical manifestations.[2,4,6,9] Most of the cases associated with intrahepatic compression comprise women at the fourth or fifth decades of life. In addition to age, exposure to increased levels of estrogen during the reproductive period confers women a trend of higher growth rates of liver cysts and, as a consequence, increased incidence of compressive complications.[1,2] In such situations, the most common clinical presentation includes ascites, abdominal pain, hepatomegaly, and abdominal collateral circulation.[9] Liver function tests are classically normal in asymptomatic patients, whereas elevated levels of AP and GGT constitute the most common finding in symptomatic individuals. Alterations in transaminases are not common.[1,3]

Ascites is an uncommon finding in patients with ADPKD and ADPLD with significant cystic liver involvement.[4] When displaying ascites, these patients must be investigated for cardiogenic, renal, and infectious causes, as well as for concomitant parenchymal hepatic diseases progressing to cirrhosis, congenital hepatic fibrosis, and conditions associated with obstruction of hepatic venous flow. In such cases, extrinsic compression by cysts, intrahepatic thrombotic phenomena, or association between both of these processes should be considered.[3,5]

Obstruction of hepatic venous flow in PLD, secondary to vascular compression by liver cysts, is relatively rare but has been previously reported.[3–7,9,10] In addition to cyst-mediated extrinsic compression, concomitant venous thrombosis may also occur due to associated thrombophilia[4] or following nephrectomy of a native polycystic kidney when hypotension is frequent and may cause low blood flow and thrombotic events.[6,9] In this second situation, the slowing of intrahepatic blood flow associated with compressive cysts, and the decrease in hepatic blood flow determined by nephrectomy may lead to thrombotic events.[6,9] Interestingly, given the anatomic relationship among the considered structures, there might occur compression of the portal vein, inferior vena cava, and hepatic veins, leading to a functional BCS, ascites, and lower limb edema.[3] In cases with associated portal hypertension, clinical manifestations such as splenomegaly and esophageal or gastric varices can lead to upper gastrointestinal bleeding or other related complications.[7,10]

The diagnosis of vascular compression can be established using noninvasive methods, such as Doppler ultrasound, CT angiography, and magnetic resonance imaging (MRI) angiography, or by invasive techniques, such as venography.[9]

Different strategies can be applied to resolve intrahepatic venous compression caused by cyst enlargement. According to the features of each case, the possibilities include percutaneous puncture with cyst drainage, to be considered for dominant, large cysts, associated or not with sclerotherapy according to the anatomic relationship among structures; cyst fenestration, to be considered when they are superficial; and

resection of a liver segment, in severe cases with preserved areas of liver parenchyma. Although portosystemic shunt may be an option for functional BCS, this procedure is not recommended in patients with CKD,[3,5] such as our present case.

When the cystic involvement of the liver is diffuse and extensive, liver transplantation often becomes the best therapeutic choice.[1,2,4,9] In these cases, when the patient presents advanced CKD, as in the current case, double liver-kidney transplantation should be considered because this alternative has been reported to significantly improve ascites and quality of life.[3]

In conclusion, ascites is an unusual complication in ADPKD. In the setting of a transudate, extrahepatic diseases and renal failure in the setting of nephrotic syndrome must be excluded. The absence of such conditions should be followed by a complete workup focused on liver disease. Computed tomography or MRI with angiography or Doppler ultrasound should carefully assess the possibility of significant extrinsic compression by cysts. More invasive approaches, such as liver biopsy, must be balanced against the risk for bleeding, infection, and biliary fistula. In the current case, the diagnosis was established based on the combination of portal hypertension and extrinsic compression of the hepatic venous outflow. It must be pointed out, however, that the association of portal hypertension with the absence of signs or symptoms of liver failure and peripheral edema is already highly suggestive of the diagnosis of BCS from a clinical standpoint.

Functional BCS, therefore, is a serious potential complication in patients severely affected with PLD and should be considered in those who develop ascites in the absence of other superimposed liver diseases. Although in this particular case, cyst drainage or fenestration would have not changed the medical follow-up, early diagnosis may be helpful in a number of cases, allowing strategic cyst intervention and avoidance of the clinical consequences of portal hypertension and hepatic failure.

Author Contributions

PDMdMN, BEPB, and LFO worked in planning and conducting the study; collecting/interpreting data; drafting the manuscript; and approved the final draft submitted. EHW, VR-S, WA, and LACA worked in planning and conducting the study; drafting the manuscript; and approved the final draft submitted.

REFERENCES

1. Gevers TJG, Drenth JPH. Diagnosis and management of polycystic liver disease. *Nat Rev Gastroenterol Hepatol*. 2013;10:101–108.
2. Abu-Wasel B, Walsh C, Keough V, Molinari M. Pathophysiology, epidemiology, classification and treatment options for polycystic liver diseases. *World J Gastroenterol*. 2013;19:5775–5786.
3. de la Piscina PR, Duca I, Estrada S, et al. Combined liver and kidney transplant in a patient with Budd-Chiari syndrome secondary to autosomal dominant polycystic kidney disease associated with polycystic liver disease: report of a case with a 9-year follow-up. *Case Rep Gastrointest Med*. 2014;2014:585291.
4. Uddin W, Ramage JK, Portmann B, et al. Hepatic venous outflow obstruction in patients with polycystic liver disease: pathogenesis and treatment. *Gut*. 1995;36:142–145.
5. Chauveau D, Grünfeld JP, Durand F, Belghiti J. Ascites in a polycystic patient. *Nephrol Dial Transplant*. 1997;12:228–230.
6. Clive DM, Davidoff A, Schweizer RT. Budd-Chiari syndrome in autosomal dominant polycystic kidney disease: a complication of nephrectomy in patients with liver cysts. *Am J Kidney Dis*. 1993;21:202–205.
7. DelGuercio E, Greco J, Kim KE, Chinitz J, Swartz C. Esophageal varices in adult patients with polycystic kidney and liver disease. *N Engl J Med*. 1973;289:678–679.
8. Willey CJ, Blais JD, Hall AK, Krasa HB, Makin AJ, Czerwiec FS. Prevalence of autosomal dominant polycystic kidney disease in the European Union [published online ahead of print June 19, 2016]. *Nephrol Dial Transplant*. doi:10.1093/ndt/gfw240.
9. Torres VE, Ratogi S, King BF, Stanson AW, Gross JB, Nagorney DM. Hepatic venous outflow obstruction in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1994;5:1186–1192.
10. Campbell GS, Bick HD, Paulsen EP, Lober PH, Watson CJ, Vargo RL. Bleeding esophageal varices with polycystic liver: report of three cases. *N Engl J Med*. 1958;259:904–910.