Effectiveness of Open Fenestration for Autosomal Dominant Polycystic Liver Disease

Luiz Fernando Norcia\textsuperscript{a} Erika Mayumi Watanabe\textsuperscript{b} Claudia Nishida Hasimoto\textsuperscript{c} Leonardo Pelafsky\textsuperscript{c} Walmar Kerche de Oliveira\textsuperscript{c} Ligia Yukie Sassaki\textsuperscript{a}

\textsuperscript{a}Department of Internal Medicine, São Paulo State University (Unesp), Medical School, Botucatu, Brazil; \textsuperscript{b}Department of Radiology, São Paulo State University (Unesp), Medical School, Botucatu, Brazil; \textsuperscript{c}Department of Surgery, São Paulo State University (Unesp), Medical School, Botucatu, Brazil

Keywords
Polycystic liver disease · Hepatomegaly · Laparotomy fenestration · Hepatic cysts · Case report

Abstract
Autosomal dominant polycystic liver disease (ADPLD) is a rare disease with variable clinical presentations, characterized by cystic enlargement of the liver. The diagnosis is made based on family history, patient’s age, and liver phenotype and is confirmed by imaging tests. The treatment aims to reduce symptoms caused by the increased liver volume and can be performed by aspiration with sclerotherapy, fenestration, and liver resection. Although ADPLD is a rare disease, it is an important differential diagnosis of cystic diseases such as polycystic kidney disease; therefore, the aim of this article was to present the diagnostic and therapeutic approach of a case of ADPLD and conducting a literature review. This is the case of a 32-year-old male patient, who was hospitalized due to abdominal pain, hepatomegaly, lack of appetite, and weight loss. Imaging propaedeutics showed a significant increase in the liver volume due to hepatic cysts. After a multidisciplinary evaluation, given the clinical changes and the location of the hepatic cysts, fenestration was performed by laparotomy. The postoperative period was uneventful. The treatment was efficient in promoting symptomatic relief and improving the quality of life in this patient. Case reports on this disease are quite limited in the currently available literature, and there are gaps in knowledge with regard to the diagnosis and management of ADPLD. The importance of this article is that it will highlight the limitations in treatment options and allow physicians to make a more informed decision when diagnosing and treating a patient with ADPLD in the future.

© 2022 The Author(s).
Published by S. Karger AG, Basel

Correspondence to:
Luiz Fernando Norcia, lf.norcia@unesp.br
Introduction

Autosomal dominant polycystic liver disease (ADPLD) is a rare genetic disorder characterized by progressive dilation of the bile ducts. The clinical presentation, treatment, and prognosis of ADPLD are directly related to the extent of hepatic involvement. Although most patients are asymptomatic and do not require treatment, a minority of them exhibit symptoms with a wide spectrum of severity, ranging from abdominal pain in the right upper quadrant, early satiety, postprandial fullness, and symptoms of gastroesophageal reflux to malnutrition caused by reduced food intake associated with the symptoms described above. Some patients may have dyspnea due to the presence of cysts in the region of the diaphragmatic dome and rarely portal hypertension due to compression of vascular structures in the region of the hepatic hilum.

The diagnosis of ADPLD is made based on the patient’s age, family history of ADPLD, and liver phenotype and is confirmed by imaging tests such as ultrasonography (US) and computed tomography (CT). The treatment aims to reduce symptoms caused by the increased liver volume and is indicated in symptomatic patients. Aspiration with sclerotherapy, fenestration, and liver resection are some of the available treatments; however, liver transplantation is the only curative treatment indicated for ADPLDs [1].

Although ADPLD is a rare disease, it is an important differential diagnosis of cystic diseases such as polycystic kidney disease. To the best of our knowledge, case reports on ADPLD are quite limited in the currently available literature, and there are gaps in knowledge with regard to the diagnosis and management of the disease. For this reason, we have chosen the presented case to show the diagnostic and therapeutic approach of a case of ADPLD and discuss the most important aspects of treatment of the disease by conducting a literature review.

Case Presentation

A 32-year-old male patient, complaining of abdominal pain in the right upper quadrant, of moderate intensity, of insidious onset, with no aggravating or relieving factors, amass in the right upper quadrant, accompanied by loss of appetite, and loss of weight (3 kg/5% of body weight) for 20 days, was admitted to the emergency department. He denied nausea, vomiting, fever, smoking, or alcohol consumption. He had an excision of a mesenteric cyst 5 years prior to the presentation. His family history was unremarkable. On physical examination, he was in good general condition, well-hydrated, anicteric, and afebrile. The liver was palpable 10 cm below the right costal margin with an elastic consistency, blunt edge, and irregular surface, with pain on palpation. The patient’s liver biochemical test results were normal, and tumor markers were negative (Table 1).

US of the right hypochondrium revealed an enlarged liver, with the presence of multiple simple cysts (>20) distributed diffusely throughout the parenchyma. The largest of these cysts occupied a significant portion of the right hepatic lobe, measuring 19.1 cm × 15.2 cm × 15.7 cm with an estimated volume of 2,400 cm³. There was no dilatation of the intra- and extrahepatic bile ducts.

Abdominal CT revealed an enlarged liver with lobulated contours and multiple cystic images (>20) with thin and regular walls and liquid density content, without intravenous contrast enhancement. The largest cystic image was located in the right hepatic lobe, in segments V, VI, and VII, measuring approximately 25.3 cm × 13.2 cm × 16.0 cm with a volume of 2,794 cm³. Other smaller cystic images were present in segments I, II, and IV.
There was no intrahepatic biliary tract dilatation. The spleen had normal topography, dimensions, and densities, presenting two cystic images with thin and regular walls, the largest one measuring 1.9 cm × 1.6 cm in diameter (Fig. 1, 2). The pancreas had normal dimensions and densities. The kidneys had preserved dimensions and contours, and the renal parenchyma had normal thickness, contrast uptake, and elimination with good density, and there was an absence of dilatation of the collecting pathways. There were no enlarged retroperitoneal lymph nodes. Based on the radiological exams performed, the patient received the diagnosis of ADPLD.

After 6 months of outpatient follow-up, the patient developed persistent abdominal pain that was refractory to conventional analgesia. The pain was persistent and daily, located in the right upper quadrant, of moderate intensity, without irradiation, without triggering factors or relieving factors, associated with reduced food intake, and consequent weight loss (3 kg/5% of body weight). The patient also reported dyspnea, distension in the right hypochondrium, and episodes of fever (38°C–39.5°C).

After a multidisciplinary discussion, due to the worsening of the clinical symptoms described above and location of the liver cysts, we decided to perform fenestration of the liver cysts by laparotomy. The procedure revealed a small amount of ascitic fluid and an enlarged liver with multiple cysts, the largest being located in segment VI (Fig. 3). Puncture was performed for emptying and fenestration of the larger cysts.

After the procedure, the patient’s symptoms progressively improved, and he was discharged on the fourth postoperative day. Anatomopathological examination of the surgical specimen revealed the presence of a simple liver cyst. The patient was under outpatient follow-up and did not present with further symptoms.
Fig. 1. CT image. Axial section, with contrast in the portal phase, showing a sequence of multiple cystic liver images, with fluid density and thin and regular walls, without enhancement after contrast injection and splenic cysts (arrow) with similar characteristics.

Fig. 2. CT image. a Coronal section showing right kidney pushed back medially and inferiorly due to the increased dimensions of the right hepatic lobe. b Sagittal section, showing the largest cysts located in the right hepatic lobe, located in segments V, VI, VII, measuring as a whole 25.3 × 16 cm.
Discussion and Conclusions

ADPLD is a rare disease with a prevalence of 1:100,000 [2]. Patients with ADPLD carry mutations involving two main genes; PRKCSH, which encodes the hepatocystin protein, and SEC63, which encodes the SEC63 protein. Hepatocystin and SEC63 are proteins expressed in the endoplasmic reticulum of cholangiocytes that play a role in glycoprotein processing and protein translocation, respectively [2, 3]. Recently, new genes such as PKHD1, SEC61B, GANAB, ALG8, ALG9, and LRP5 have been implicated in the development of ADPLDs [3, 4].

The pathophysiology of ADPLD is complex. The main factors for the development of liver cysts are ductal plaque malformation, ciliary dysfunction, abnormalities in the concentration of intracellular mediators such as adenosine 3′,5′-cyclic monophosphate and calcium, aberrant signaling pathways such as the mitogen-activated protein kinase pathway and the mammalian target protein-mediated signaling pathway of rapamycin, changes in cholangiocyte autophagy, increased fluid secretion, local action of hormones and growth factors, extracellular matrix remodeling, and epigenetic alterations [2].

Most patients with ADPLD are asymptomatic. The disease affects both genders, but it has a more severe clinical course in women [1, 5–7]. Women with ADPLD have cysts greater in number and size [6, 7]. A possible explanation for this is the effect of estrogen on the proliferation and secretion of the cyst lining epithelium [8]. Liver cysts usually start developing during puberty, progressively increasing in number and size with advancing age [1]. The clinical presentation of ADPLD is related to the mass and/or compression effect caused by an increase in liver volume. The main symptoms are abdominal pain and distension, early satiety, dyspepsia, and dyspnea [1, 6, 7]. Hemorrhage, rupture, and infection of liver cysts and portal hypertension are the most frequent complications [1, 6, 7]. The risk factors for disease progression are advanced age, female gender, and exposure to estrogen such as during multiple pregnancies, use of oral contraceptives, and hormone replacement therapy [1, 5–7], none of which were relevant in the case of this study.

Family history of ADPLD, age, and liver phenotype of the patient are used in making a diagnosis of ADPLD [9] (Table 2). US and CT are the imaging tests of choice used in clinical practice. The reported patient had an insignificant family history, and his age was <40 years. Imaging revealed >20 liver cysts and no kidney cysts. There is no indication for radiological

Fig. 3. Images of the laparotomy surgery for resection of liver cysts. a Aspect of the liver. Visualization of liver cysts. b Aspect of the liver after resection of liver cysts.
monitoring of asymptomatic patients [1, 5–7]. Elevated serum levels of gamma-glutamyl transferase and alkaline phosphatase were observed. The values of aspartate aminotransferase, alanine aminotransferase, and total bilirubin were within the normal limits as is expected in ADPLD patients [6, 7].

A study carried out by Waanders et al. [10] involving patients with polycystic liver disease observed a direct correlation between liver volume and serum levels of carbohydrate antigen 19-9 (CA 19-9). However, this was not observed in our case, which suggests that despite the previously mentioned correlation, further studies are needed to establish CA 19-9 as a useful biomarker in clinical practice. Molecular biological tests can help in the diagnosis of ADPLD, but they have limited usefulness as a large number of mutations involved in the development of ADPLD have not yet been identified [1].

Autosomal dominant polycystic kidney disease (ADPKD) is a differential diagnosis of ADPLD. Polycystic liver disease is a common extrarenal manifestation of ADPKD [11]. Differentiating between these two entities can be difficult because patients with ADPKD can present with associated renal cysts [1, 4, 5]. Patients with ADPLD usually have liver cysts of a greater number and size with a more benign clinical course, fewer symptoms and comorbidities, and no associated renal dysfunction [1, 7]. There are reports of extrahepatic manifestations of ADPLD, such as valvular dysfunction and intracranial aneurysms [5]. However, the clinical significance of these reports is limited, and further studies are needed to confirm this association. The presence of cysts in the spleen and ovaries has also been described in patients with ADPLD [7]; however, in most cases, liver involvement is the only manifestation of ADPLD [1, 5, 7]. On the other hand, patients with polycystic liver disease secondary to ADPKD have cysts of smaller numbers and sizes. They are more symptomatic and have a greater number of comorbidities that are mainly associated with renal impairment. Intracranial aneurysms and valve dysfunction are also common in these patients, and they may also present with cysts in the pancreas, ovaries, spleen, and testicles [7, 11].

The treatment of ADPLD aims to reduce symptoms caused by increased liver volume and is indicated in symptomatic patients. The treatment of choice is based on the patient’s characteristics (age, surgical history, and presenting symptoms) and liver phenotype (degree of hepatomegaly, number, size, and location of the cysts). The known treatment modalities are aspiration with sclerotherapy, fenestration, liver resection, and liver transplantation [12, 13].

Aspiration with sclerotherapy is performed under radiological guidance. The procedure consists of the aspiration of a large cyst (diameter >5 cm), followed by the administration of a sclerosing agent that promotes the destruction of the epithelial lining of the cyst [12, 13]. Fenestration is a procedure that combines aspiration and disarrangement of the cystic wall. It can be performed by laparotomy or laparoscopy and is indicated for patients with multiple large, superficial cysts. Laparoscopic fenestration requires a shorter hospital stay and leads to fewer complications and is currently the procedure of choice. However, in situations when it is difficult to access liver cysts, such as when the cysts are located in the right posterior segments (VI and VII) or in the liver dome (segment VIII), open fenestration becomes the best
option [12, 14]. A study by Drenth et al. [12] observed immediate relief of symptoms in 92% of patients undergoing fenestration (laparoscopic or open). However, during the follow-up period, recurrence of cysts and symptoms was observed in 24% and 22% of the patients, respectively. Ascites, pleural effusion, hemorrhage, and bile leakage were the chief complications observed postoperatively [12]. Segmental liver resection is another intervention for patients with diffuse involvement of the liver parenchyma by multiple cysts of varying sizes, but this is only performed with at least one preserved liver segment [14]. A disadvantage of surgical procedures is that they can potentially cause distortion of the intrahepatic vasculature and the biliary system, which may lead to complications. Furthermore, the risk of subsequent adhesions may compromise a possible liver transplant in the future [12, 13].

Liver transplantation is the only curative treatment for ADPLD. It is indicated for patients who present with disabling symptoms, recurrent or intractable complications, significant impairment of the quality of life, or failure of conventional therapy [12, 13]. The Model for End-stage Liver Disease (MELD), a score used to indicate liver transplantation for a patient, does not adequately represent advanced-stage ADPLD as most of the patients for whom the MELD is used have normal liver function. Therefore, careful clinical evaluation and the adoption of exception criteria are essential for the indication of liver transplantation in patients with ADPLD [15].

In conclusion, ADPLD has a clinically heterogeneous hepatic phenotype. Most patients with ADPLD do not require treatment, but a minority suffer from significant morbidities due to extensive hepatomegaly. The diagnostic criteria for ADPLD include the patient’s family history of ADPLD, age, and liver phenotype observed on imaging tests, especially on US and CT. Despite advances in understanding the mechanisms of hepatic cystogenesis and the discovery of possible therapeutic targets, the treatment options currently available are limited. Continuous monitoring and individualized assessment are fundamental factors that can reduce the impact of the disease and improve the quality of life of these patients.

Statement of Ethics

The study was approved by the Ethics Committee of Botucatu Medical School/São Paulo State University, approval number 3.556.857. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare regarding the present work.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

All the authors contributed to the manuscript. Luiz Fernando Norcia, Erika Mayumi Watanabe, Claudia Nishida Hasimoto, Leonardo Pelafsky, Walmar Kerche de Oliveira, and Ligia Yukie Sassaki contributed to the conception and design of the study; the acquisition,
analysis, and interpretation of data; drafting the article, revising it critically for important intellectual content, and approving the final version to be submitted.

**Data Availability Statement**

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

**References**

1. Qian Q. Isolated polycystic liver disease. *Adv Chronic Kidney Dis*. 2010;17(2):181–9.
2. Perugorria MJ, Masyuk TV, Marin JJ, Marzioni M, Bujanda L, La Russo NF, et al. Polycystic liver diseases: advanced insights into the molecular mechanisms. *Nat Rev Gastroenterol Hepatol*. 2014;11(12):750–61.
3. Lee-Law PY, Van de Laarschot LFM, Banales JM, Drenth JPH. Genetics of polycystic liver diseases. *Curr Opin Gastroenterol*. 2019;35(2):65–72.
4. Besse W, Chang AR, Luo JZ, Triffo WJ, Moore BS, Gulati A, et al. ALG9 mutation carriers develop kidney and liver cysts. *J Am Soc Nephrol*. 2019;30(11):2091–102.
5. Qian Q, Li A, King BF, Kamath PS, Lager DJ, Huston J 3rd, et al. Clinical profile of autosomal dominant polycystic liver disease. *Hepatology*. 2003;37(1):164–71.
6. Van Keimpema L, De Koning DB, Van Hoek B, Van Den Berg AP, Van Oijen MG, De Man RA, et al. Patients with isolated polycystic liver disease referred to liver centres: clinical characterization of 137 cases. *Liver Int*. 2011;31(1):92–8.
7. Hoevenaren IA, Wester R, Schrier RW, McFann K, Doctor RB, Drenth JP, et al. Polycystic liver: clinical characteristics of patients with isolated polycystic liver disease compared with patients with polycystic liver and autosomal dominant polycystic kidney disease. *Liver Int*. 2008;28(2):264–70.
8. Alvaro D, Mancino MG, Omori P, Franchitto A, Alpini G, Francis H, et al. Estrogens and the pathophysiology of the biliary tree. *World J Gastroenterol*. 2006;12(22):3537–45.
9. Patel A, Chapman AB, Mikolajczyk AE. A practical approach to polycystic liver disease. *Clin Liver Dis*. 2019;14(5):176–9.
10. Waanders E, van Keimpema L, Brouwer JT, Van Oijen MGH, Aerts R, Sweep FCGJ, et al. Carbohydrate antigen 19–9 is extremely elevated in polycystic liver disease. *Liver Int*. 2009;29(9):1389–95.
11. Ghata J, Cowley BD Jr. Polycystic kidney disease. *Compr Physiol*. 2017;7(3):945–75.
12. Drenth JP, Chrispijn M, Nagorney DM, Kamath PS, Torres VE. Medical and surgical treatment options for polycystic liver disease. *Hepatology*. 2010;52(6):2223–30.
13. Zhang ZY, Wang ZM, Huang Y. Polycystic liver disease: classification, diagnosis, treatment process, and clinical management. *World J Hepatol*. 2020;12(3):72–83.
14. Schnelldorfer T, Torres VE, Zakaria S, Rosen CB, Nagorney DM. Polycystic liver disease: a critical appraisal of hepatic resection, cyst fenestration and liver transplantation. *Ann Surg*. 2009;250(1):112–8.
15. Arrazola L, Moonka D, Gish RG, Everson GT. Model for end-stage liver disease (MELD) exception for polycystic liver disease. *Liver Transpl*. 2006;12(Suppl 3):S110–1.