Sequential Liver-Kidney Transplantation for Recurrent Liver Cysts Infection in a Patient With Autosomal Dominant Polycystic Kidney Disease: A Case Report

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent hereditary kidney disorder. Liver cysts are the most common extrarenal manifestation of the disease and usually remain asymptomatic. Liver cyst infection is rare, and its treatment is challenging. Liver transplantation (LT) is the only curative therapeutic option in symptomatic polycystic liver disease associated with ADPKD. Only a few cases of LT for recurrent liver cyst infection have been published. To our knowledge, we report the first case of sequential liver-kidney transplantation for recurrent liver cysts infection in a patient with ADPKD. A 55-year-old woman with ADPKD who had a kidney transplantation (KT) presented with multiple liver cysts infection 9 months after her KT. These episodes started after biliary tract complications due to an ampullary adenoma necessitating multiple endoscopic interventions. Her general status gradually degraded because antibiotic treatment was not effective, and she underwent LT for recurrent liver cysts infection 1 year and 9 months after her KT. LT in this setting turned out to be challenging but was possible. We think that better biliary tract workup before KT may prompt better care in these patients.

AUTOSOMAL dominant polycystic kidney disease (ADPKD) has an estimated prevalence between 1 in 1000 and 1 in 2500 individuals, making it the most common hereditary kidney disorder. It is mostly caused by mutations in the genes *PKD1* and *PKD2,* with more than 1500 different mutations described so far. It leads to the development and expansion of multiple cysts in the kidney parenchyma, which leads to progressive loss of kidney function and end-stage kidney disease (ESKD) [1].

Liver cysts are the most common extrarenal manifestation of the disease and usually remain asymptomatic [2]. Liver cyst infection is a rare but potentially severe complication that can lead to death, and its treatment is challenging [3]. Liver transplantation (LT) is the only curative therapeutic option in symptomatic polycystic liver disease (PLD) associated with ADPKD. Altered quality of life and malnutrition are its main indications in patients with a large polycystic liver [4,5].

Only a few cases of LT for recurrent liver cyst infection have been reported in the literature [4]. To the best of our knowledge, we present the first case of sequential liver-kidney transplantation for recurrent liver cysts infection in a patient with ADPKD.

CASE PRESENTATION

A 55-year-old woman had a deceased-donor kidney transplantation (KT) in January 2018 for ESKD secondary to ADPKD. Liver workup before KT included an upper ultrasound (US) examination that showed multiple bilateral liver cysts with no biliary abnormalities. She had a history of multiple kidney cyst infections before KT but no history of hepatic cyst infection. Immunosuppressive treatment after KT included tacrolimus, mycophenolate mofetil, and corticosteroids. The immediate

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post-KT course was uncomplicated, and plasma creatinine rapidly stabilized around 1.0 mg/dL.

Two months after KT, the patient was admitted to the hospital with fever and jaundice. Magnetic resonance cholangiopancreatography showed bilateral intrahepatic biliary dilation together with dilation of both the main bile duct (MBD) and the main pancreatic duct (MPD) with a suspected obstacle at the ampulla. Endoscopic retrograde cholangiopancreatography (ERCP) showed regular narrowing of the distal MBD and no dilation of the MPD. The duodenal papilla appeared to be normal. The patient was treated with intravenous antibiotics only because endoscopic treatment was technically difficult.

Two months later, the patient presented with a new episode of cholangitis. A new ERCP was performed with pre-cut papillotomy and a balloon sweep of the MBD, but no bile stones were visible. A biliary stent was placed for drainage. The patient was treated with a new course of intravenous antibiotics with good clinical outcome.

In August 2018, 7 months after KT, the patient was referred to our transplantation center for a new episode of cholangitis with multiple-cause bacteremia (*Enterococcus faecium, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*). Upper endoscopic ultrasound (EUS) and ERCP were performed, and a small ampullary adenoma was suspected with retrodilation of both the MBD and the MPD. Endoscopic ampullectomy was performed, with placement of a metallic biliary stent and a prophylactic plastic pancreatic stent. Histologic analysis confirmed the diagnosis of ampulloma with high-grade dysplasia. The stents were removed 3 months later. Evolution was then marked by recurrent episodes of bacteremia. In this context, mycophenolate mofetil was withdrawn and tacrolimus trough levels were decreased, at 4 to 5 ng/mL. The patient had fever, liver tenderness, and an elevated C-reactive protein level. Her carbohydrate antigen 19-9 (CA19-9) level was elevated, at 191.1 kU/L. Computed tomography (CT) excluded hepatic cyst hemorrhage. Positron emission tomography (PET) was performed and showed multiple hepatic cysts infections in segments VI, II, and VII (Fig. 1). PET/CT did not show any predominant infected liver cyst that would have been accessible for percutaneous drainage, and the patient was treated with intravenous antibiotics alone.

Despite antibiotic treatment, the patient continued to present with multiple episodes of bacteremia with increasingly resistant pathogens (extended-spectrum beta-lactamase−producing *K pneumoniae, Pseudomonas citronellolis, Stenotrophomonas maltophilia,* extended-spectrum beta-lactamase−producing *Citrobacter amalonaticus,* etc.), which resulted in prolonged hospital stay, weight loss, malnutrition, and considerable deterioration of her general status. A gastrostomy tube was placed for enteral feeding. Surprisingly, kidney function remained stable.

In this context of recurrent multiple liver cysts infection, the patient was eligible for LT. She was placed on the eligibility list in January 2019—that is, 1 year after KT. She received a right split-liver transplant from a deceased donor in October 2019. The weight of the explanted liver was 3900 g (patient's weight was 49 kg), and many infected liquid-filled cysts were observed (Fig 2). Pathologic findings confirmed the presence of multiple liver cysts with important signs of infection. Perioperative cultures of intracystic liquid were negative. Immunosuppressive treatment at that time included tacrolimus, corticosteroids, and mycophenolate mofetil that was restarted.

In the postoperative period, the patient developed a liver abscess (*E faecium*) that was successfully treated by intravenous

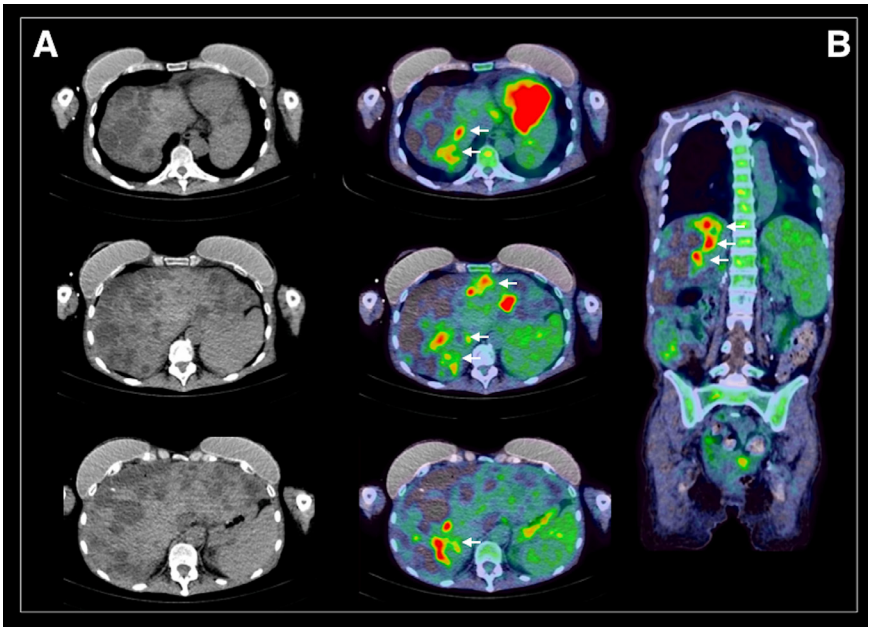

Fig 1. 18F-FDG positron emission tomography/computed tomography in **(A)** transverse and **(B)** coronal planes demonstrated multiple pathological foci (white arrows) in both liver lobes, surrounding diffusely spread intraparenchymal liver cysts.

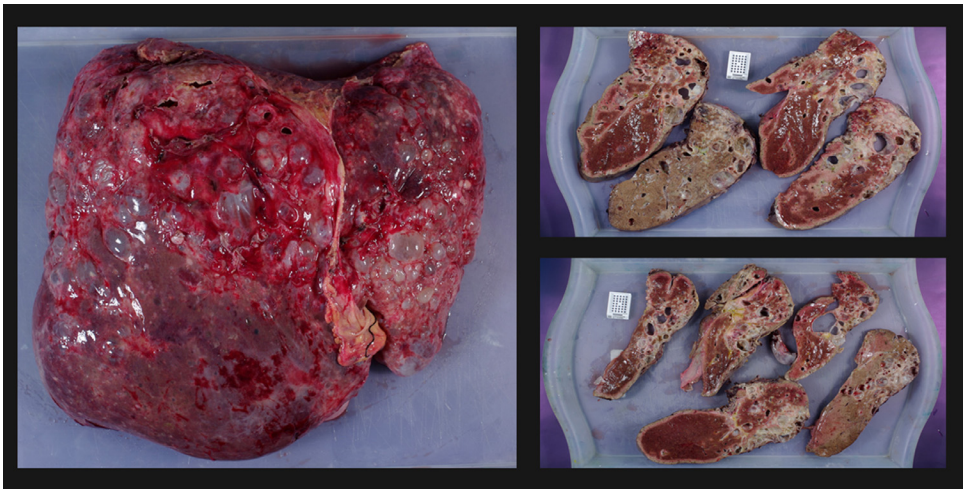

Fig 2. Macroscopic images of the explanted polycystic liver with infected cysts.

antibiotics and percutaneous drainage. Immunosuppressive treatment was adapted by lowering tacrolimus trough levels during the sepsis. In this context, her renal function worsened but then completely recovered after treatment. The patient's clinical course then gradually improved, and she was discharged 2 months later. At 18 months of follow-up, she is doing well.

DISCUSSION

To the best of our knowledge, we report the first case of sequential liver-kidney transplantation for recurrent liver cysts infection in an ADPKD patient. Our patient received an KT 1 year after KT for multiple liver cyst infections that did not respond to treatment and led to the deterioration of her general status with anorexia and malnutrition. LT in this setting tuned out to be challenging but was possible.

ADPKD is often associated with PLD, which is present in about 90% of patients after the age of 35 [1,2]. Risk factors for liver cyst enlargement are female sex, previous pregnancy, history of female hormone administration, older age, severity of renal disorder, and larger renal cyst size [4]. Liver cysts remain generally asymptomatic with preserved liver function; however, in 20% of cases, patients experience symptoms mainly as a result of liver cyst burden, including pain, early satiety, gastroesophageal reflux, and nutritional deficiencies [1,4].

Complications of liver cysts include cyst rupture, intracystic hemorrhage, and cyst infection [4]. Liver cyst infection is a rare (5%) [2] but severe complication of PLD that can potentially lead to sepsis and death [3]. It is now well established that PET/CT is the best imaging technique in diagnosing liver cysts infection compared with US, CT, or magnetic resonance imaging (MRI) [3,6]. Another diagnostic marker has been suggested by Kanaan et al [7], who showed that CA 19-9 levels are markedly higher in ADPKD patients with liver cysts infection compared to those in asymptomatic ADKPD patients. They suggested a cutoff value of 106 kU/L in ADPKD patients because CA 19-9 levels may be increased in these patients at baseline.

Liver cysts infections are considered to be of hematogenous origin by the portal vein [4]. In our patient, we think that it was secondary to recurrent cholangitis in the setting of biliary obstruction by the ampullary adenoma leading to multiple endoscopic interventions. Although a possible association between ADPKD and ampullary adenomas has been suggested in 2 case reports [8,9], it is more likely a rare finding superimposed on a common genetic disorder rather than a potential association between the 2 diseases [10].

In their systematic review of 41 case series and reports, Lantinga et al [3] highlighted that liver cyst infection treatment has a high rate of failure with antimicrobials alone (70%) and requires cyst drainage or surgery in 64% of the cases. Recurrence rate of liver cyst infection was high (20%), and 9% of patients died as a result of complications of cyst infection.

Our patient had recurrent liver cysts infection with increasingly resistant bacteria that started 9 months after her KT for ADPKD. In the previously mentioned review, 46% of patients who developed liver cysts infection recurrence had a documented history of renal transplantation. It can be speculated that infection recurrence was promoted by the immunosuppressive regimen in the setting of endoscopic sphincterotomy, which increases the risk for retrograde infection.

Percutaneous drainage of the infected cysts was not possible because of the simultaneous infection of multiples cysts in different liver segments making them inaccessible to drainage. In this setting, LT was the only option for a cure in our patient. LT in PLD associated with ADPKD is the only curative therapeutic option. The main indications are Gigot Classification type III cases (multiple bilateral cysts) complicated by malnutrition and ascites, with altered quality of life [4].

In ADPKD, LT is often performed simultaneously with KT because of usually concomitant advanced renal insufficiency (ie, glomerular filtration rate <30 mL/min/1.73 m^2) [4,11]. In a series of 36 ADPKD patients who underwent LT or combined liver-kidney transplantation from April 1990 to March 2003, the 1- and 5-year patient survival rates were high (86%) [5].

Table 1. Summary of Published Cases of Liver Transplantation for Liver Cyst Infection in ADPKD

Case No.	Age at Tx (years)	Sex	Associated Clinical Symptoms	GFR Before Tx (mL/min)	Combined L-K Tx	Liver Graft	Ex Liver Weight (kg)	Perioperative Complications	IS Regimen	Follow-up Period / Outcome	GFR at End of Follow-up (mL/min)	Published by (year)
1	41	F	Ascites, cachexia, dyspnea	/	No	Full-size	9.4	None	TRL + Pred + MMF	10 months/alive	61	Kirchner et al[5] (2006)
2	53	F	/	/	No	Full-size	2.8	None	CsA + Pred + MMF	5 months/alive	28	Kirchner et al[5] (2006)
3	47	F	/	/	No	Full-size	4.0	Initial graft malfunction, reTx	/	61 days post-reTx/ dead (pneumonia, myocardial infarction)	/	Kirchner et al[5] (2006)
4	52	F	Cyst bleedings	HD	Yes	Full-size	8.3	None	CsA + Pred	47 months/alive	68	Kirchner et al[5] (2006)
5	53	F	Portal hypertension	26	Yes	Full-size	5.2	Revision of the hepatic artery anastomosis	TRL + Pred	66 months/alive	76	Kirchner et al[5] (2006)
6	60	F	Ascites, cachexia, dyspnea	HD	Yes	Full-size	6.7	Biliary leakage	CsA + Pred	23 months/alive	45	Kirchner et al[5] (2006)
7	56	F	Ascites	HD	Yes	Full-size	12.0	None	CsA + Pred	44 months/alive	26	Kirchner et al[5] (2006)
8	66	F	Cyst rupture	HD	No	Right lobe	/	Bile fistula, abdominal abscess	/	147 months/alive	/	Ogawa et al[12] (2014)
9	63	F	IVC compression, malnutrition, dyspnea	HD	No	Right lobe	/	Renal failure	/	101 months/alive	/	Ogawa et al[12] (2014)
10	67	M	/	HD	No	Right lobe	6.4	Right hemo-pneumothorax, bile leakage	TRL + Pred + MMF	6 months/alive	/	Akihisa et al[4] (2018)

Abbreviations: CsA, cyclosporine; Ex liver, explanted liver; F, female; GFR, glomerular filtration rate; HD, hemodialysis; IS, immunosuppressive; IVC, inferior vena cava; L-K Tx, liver-kidney transplantation; M, male; MMF, mycophenolate mofetil; Pred, prednisolone; reTx, re-transplantation; TRL, tacrolimus; Tx, transplantation.

A total of 10 cases of LT because of recurrent hepatic cyst infection with ADPKD were reported in the literature (summary in Table 1). Of them, 7 were reported by Kirchner et al [5], including 4 patients who underwent combined liver-kidney transplantation because of ESKD. They all received a full-size liver from deceased donors. Survival rates were excellent, and quality of life improved dramatically after transplantation. Of the 10 cases, 2 were reported by Ogawa et al [12] regarding two 63- and 66-year-old female patients who received a right hepatic lobe from living donors for cyst infection.

The most recent case was published by Akihisa et al [4] in 2018, who reported the case of a 67-year-old Japanese man who underwent a living-donor LT alone for refractory liver cyst infection. It is to be noted that both this patient and the 66-year-old woman reported by Ogawa et al, were on maintenance hemodialysis at the time of their LT. The authors remind us that despite good outcomes in their patients, LT in maintenance hemodialysis patients with ADPKD is risky, implying careful considerations when selecting patients [4,12].

To our knowledge, there is no report in the literature of sequential liver-kidney transplantation in ADPKD for recurrent liver cysts infection. Becker et al [13] reported the cases of 9 patients who underwent sequential liver-kidney transplantation between 1984 and 2000. Only 1 of those patients had polycystic disease and received an LT 4 years after the KT for cholestatic fibrosis.

In our patient's case, we think the *primum movens* of liver cysts infection was recurrent cholangitis caused by obstruction of the biliary tract by the ampullary adenoma leading to multiple ERCPs performed afterward. This forces us to rethink our pre-KT workup regarding liver and biliary tract complications in ADPKD. The patient had only a US of the liver before KT, which is an acceptable diagnostic tool for liver cysts [10]. However, it is insufficient to detect potential biliary complications that would be easier to detect with MRI.

Biliary tract complications are rare and less well recognized in ADPKD compared to autosomal recessive PKD that is associated with Caroli disease and recurrent cholangitis [14]. Judge et al [14] recently published a case series and large disease association study including more than 23,000 patients with ADPKD. They showed that biliary tract disease is as frequent in people with ADPKD as liver complications and that it has a distinct clinical presentation. These include, apart from infective and compressive complications caused by polycystic livers, biliary tract infections, gallstones, and cholecystitis.

Moreover, Kumar et al [15] recently reported a case of a 70-year-old man known for ADPKD who presented with recurrent cholangitis years after KT and was eventually diagnosed with Caroli disease. Only a few cases of Caroli disease associated with ADPKD have been reported in the literature, and authors insist on the fact that diagnosis before KT is vital.

Our case, together with these recent findings, raises the question of expanding liver and biliary workup before KT in patients with ADPKD. It is essential to remain aware of biliary complications in patients with ADPKD before KT to prompt better care for these patients because treatment may be less challenging with no immunosuppressive treatment. Therefore, we think it should include biliary tract investigation by cross-sectional imaging, preferably MRI.

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