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CASE REPORT

A case of a maintenance hemodialysis patient with autosomal dominant polycystic kidney disease who underwent living donor liver transplantation alone due to refractory liver cyst infection

Taro Akihisa[1] · Ayami Ino[1] · Hiroto Egawa[2] · Yoshihito Kotera[2] · Shunichi Ariizumi[2] · Akiko Oomori[2] · Shingo Yamashita[2] · Yusuke Yamamoto[3] · Ken Tsuchiya[4] · Masakazu Yamamoto[2] · Kosaku Nitta[1] · Toshio Mochizuki[1,5]

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Abstract

Liver cysts are observed in 83% of cases of autosomal dominant polycystic kidney disease (ADPKD). Although not as prevalent as renal cyst infection, liver cyst infection is a serious complication that is sometimes difficult to treat. We report the case of a maintenance hemodialysis patient with ADPKD who received a living donor liver transplantation alone (LDLTA) due to refractory liver cyst infection. The patient was a 67-year-old Japanese man who developed fever and right-side abdominal pain, and liver cyst infection was suspected. Treatment with multiple antibiotics was ineffective. Many liver cysts were observed on magnetic resonance imaging scans and a cyst in liver segment S6, which produced the strongest signal variation, was drained. The fever subsided temporarily, but multiple infected liver cysts were observed on follow-up imaging examination; 4 months later, hepatectomy and LDLTA were performed. Although LDLTA due to refractory liver cyst infection in maintenance hemodialysis patients with ADPKD is risky and should be carefully considered, it may be the only effective treatment.

Keywords Liver transplantation · Hemodialysis · ADPKD · Polycystic kidney disease · Polycystic liver disease · Liver cyst infection

Introduction

Polycystic liver disease (PLD) is a hereditary disease in which cysts arise from biliary epithelial cells in the liver. There are two types of PLD: autosomal dominant polycystic liver disease (ADPLD), in which cysts occur in the liver only, and autosomal dominant polycystic kidney disease (ADPKD), in which cysts occur in both the liver and the kidneys. Liver cysts are observed in 83% of all ADPKD cases, and their frequency increases with age [1]. The gene responsible for ADPKD are *PKD1* [2] and *PKD2* [3], and the genes responsible for ADPLD are *PRKCSH* [4] and *SEC63* [5]. ADPKD and ADPLD give rise to different extra-hepatic symptoms, but the natural history of PLD in both is similar [6]. As the multiple liver cysts enlarge, they compress the adjacent intraperitoneal and intrathoracic organs, causing abdominal discomfort, flatulence, gastroesophageal reflux, shortness of breath, dyspnea, back pain, dorsal pain, and severe nutritional deficiency [6]. Complications of liver cysts include cyst infection, cyst torsion, cyst rupture, and intracystic hemorrhage. Treating cyst infections is difficult,

✉ Toshio Mochizuki
mtoshi@twmu.ac.jp

1 Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

2 Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

3 Department of Plastic and Reconstructive Surgery, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

4 Department of Blood Purification, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

5 Clinical Research Division for Polycystic Kidney Disease, Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

because cysts are closed cavities; consequently cyst infections may lead to complications that lower patient quality of life and are life threatening. Here, we report the case of a maintenance hemodialysis patient with ADPKD who underwent living donor liver transplantation alone (LDLTA) due to refractory liver cyst infection.

Case report

A 67-year-old Japanese man was diagnosed with ADPKD when he first visited our hospital at 52 years of age. His mother, older sister, older brother, and younger brother had been diagnosed with ADPKD. When he developed end-stage renal disease at 65 years of age and was started on hemodialysis, he complained of a severely distended abdomen, which was subsequently found to be due to an enlarged liver and kidneys. A month after starting hemodialysis, he developed back pain on the right side and a fever. He was admitted to our hospital (the first admission). His clinical course is shown in Fig. 1. Although a diagnosis of S8 liver cyst infection was made from magnetic resonance imaging (MRI) scans, no causative bacteria were detected for blood culture. When treatment with ciprofloxacin, ceftriaxone and cefepime proved ineffective, the treatment was switched to meropenem and then changed to faropenem. The symptoms finally abated 2 months after the first admission.

However, because right abdominal pain and fever recurred, he was again admitted to our hospital for treatment of suspected liver cyst infection (the second admission). In the laboratory findings on admission, white blood cell count was 7480/μL, but neutrophils were 90.7% with a slight left shift. Serum levels of alkaline phosphatase, γ-glutamyl transpeptidase, and C-reactive protein were increased at 842, 222 U/L and 18.08 mg/dL, respectively. Blood cultures were negative. Multiple liver cysts were observed on computer tomography (CT) and MRI (Fig. 2), including a complicated cyst in the right lobe of the liver. Meropenem therapy was started and γ-globulin was administered. However, since the patient's fever and abdominal pain persisted, and on the 6th day of illness, the S6 liver cyst, which produced the strongest signal variation on the MRI, was drained under ultrasound guidance. 350 mL of a viscous, brownish-red fluid was drained from the indwelling drainage tube, but fluid cultures were negative. Subsequently, 150–200 mL of fluid per day drained from the tube, the patient's body temperature

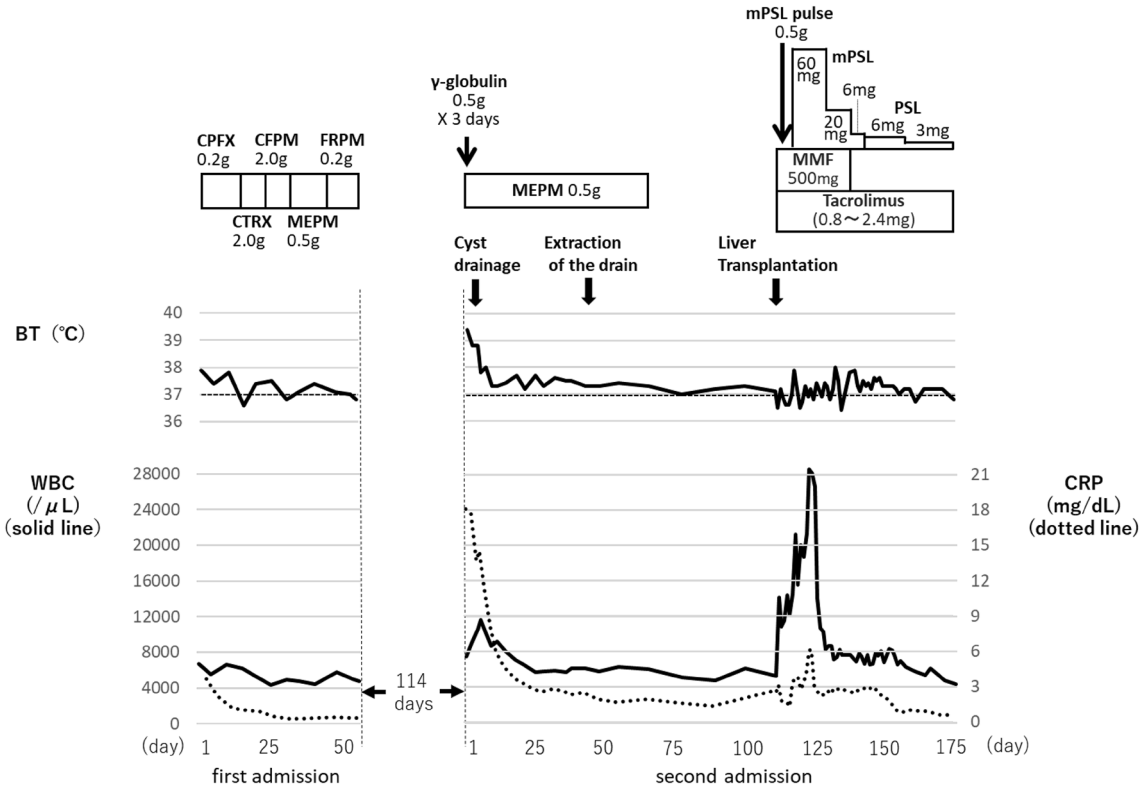

Fig. 1 Clinical course during admission: clinical courses during the first and the second admission are shown on the left and on the right, respectively. The solid line indicates WBC and the dotted line indicates CRP. *CPFX* ciprofloxacin, *CTRX* ceftriaxone, *CFPM* cefepime, *MEPM* meropenem, *mPSL* methyl prednisolone, *PSL* predonisolone, *MMF* mycophenolate mofetil, *BT* body temperature, *WBC* white blood cells, *CRP* C-reactive protein

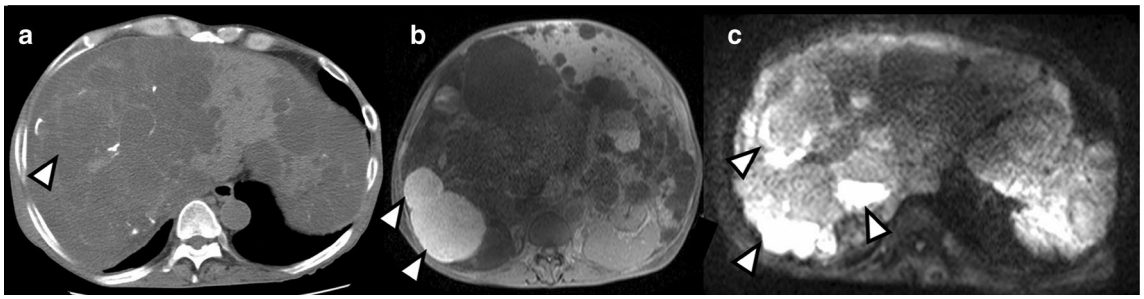

Fig. 2 Abdominal contrast-enhanced CT and MRI (on the second admission): multiple cysts of various sizes were observed in the enlargements of the liver and both kidneys. Almost the entire liver was converted into cysts, although the parenchyma remained in some areas (Gigot Classification Type III). Multiple complicated and non-complicated cysts including the cyst represented by red arrow were observed in the right lobe of the liver, but no clear evidence of active inflammation was observed (**a**). High signal intensity was observed in the T1-weighted images (**b**) and diffusion-weighted images (**c**), and multiple-liver-cyst infection was suspected. A cyst in liver segment S6 cyst measured 79.7 mm × 75.8 mm, and had high signal intensity. White triangles show infected cysts

decreased to approximately 37 °C, and his C-reactive protein levels decreased. The drain was removed on the 23rd day. However, the patient's body temperature rose to 38 °C again, and his C-reactive protein levels dropped to 2–3 mg/dL. MRI on the 32nd day revealed that the signal of the S6 liver cyst had decreased (Fig. 3), although another region with multiple high signal intensities was observed in the liver, indicating multiple-liver-cyst infection.

On the 112th day, living donor liver transplantation using the right lobe obtained from the patient's wife (graft weight: 620 g) was performed. A solid adhesion between the liver and the right diaphragm, which had developed as a result of repeated cyst infections was observed intraoperatively and was carefully peeled away. The weight of the explanted liver was 6400 g and many abscessed or infected fluid-filled cysts were observed. After the native liver was removed, a right hemo-pneumothorax was noticed. Because insertion of a thoracic drain was ineffective, emergency thoracoscopic pleurodesis was performed, and a thoracostomy tube was inserted. Pneumothorax improved and the right thoracostomy tube was removed on postoperative-day 27. He had bile leakage requiring revision of the biliary anastomosis thereafter. Immunosuppression was induced with steroids, tacrolimus and mycophenolate mofetil. Methyl predonisolone 0.5 g was administered just after reperfusion of the liver graft. Thereafter, steroids were gradually tapered. Mycophenolate mofetil was administered at a dose of 500 mg and was discontinued on postoperative-day 16. The dose of tacrolimus was adjusted according to each trough level of 10 to 12 ng/mL (Fig. 1). In the pathological findings, there were macroscopically innumerable cysts in various sizes on surgical specimen (Fig. 4). Microscopically, hepatic cells were excluded by multiple cysts and revealed atrophy and falling degeneration leading to pericellular fibrosis. However, no detail of infected cyst was detected. The patient was discharged on postoperative-day 67. Liver and biliary enzymes were elevated twice due to acute rejection reaction 2 months after discharge and acute cholangitis complicated with bile duct stenosis 4 months after discharge. However, acute rejection reaction was treated with steroid pulse therapy and resumption of mycophenolate mofetil, and acute cholangitis was treated by insertion of bile duct stent with administration of antibiotics. Thereafter, the levels of C-reactive protein and liver and biliary enzymes have been continued within normal limit. After

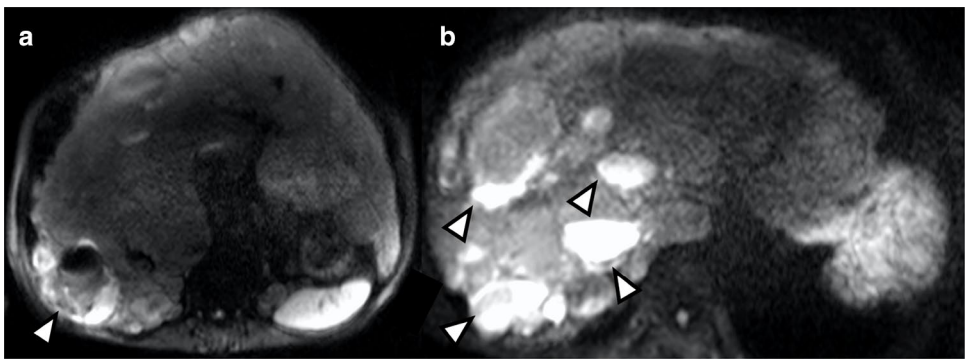

Fig. 3 Abdominal MRI (day 32 in the second admission): the high signal intensity in the diffusion-weighted image of the cyst in liver segment S6 represented by red arrow decreased after drainage (**a**). Another region with multiple high signal intensities was observed in the liver, indicating multiple-liver-cyst infection (**b**). White triangles show infected cysts

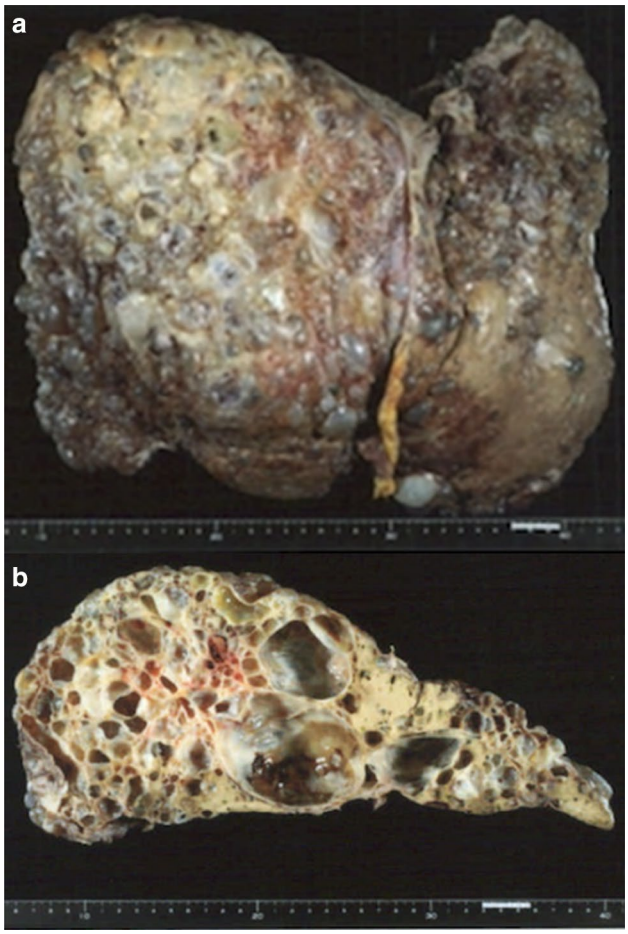

Fig. 4 The explanted liver specimen. Macroscopic findings (**a**) and cross section (**b**) of the explanted liver. Macroscopically innumerable cysts in various sizes both on the surface (**a**) and inside of the liver (**b**)

6 months, immunosuppression has been maintained with tacrolimus and mycophenolate mofetil.

Discussion

Female, history of pregnancy, female hormone administration, older age, severity of renal disorder, and larger renal cyst size are reported to be risk factors for liver cyst enlargement in PLD [7–9]. Approximately 3% of PLD cases are classified as severe [10]. The severity of PLD is evaluated on the basis of the number of cysts, their size, and their distribution on CT. Gigot classification is widely used [11]. In our case, according to the CT, almost the entire liver had been converted into cysts, and only part of the parenchyma remained. The patient's PLD was evaluated as Gigot Classification Type III.

Renal cyst infection is a complication in 30–50% of ADPKD patients [12]. In contrast, liver cyst infection is observed in only 3% of ADPKD patients in end-stage renal disease [12]. Many renal cyst infections develop as retrograde infections from the urinary tract; however, this is not the case for liver cyst infections, which are considered to be of hematogeneous origin via the portal vein [13]. Therefore, liver cyst infections are less common than renal cyst infections. Because liver cyst infection occurs inside the liver cyst, which is a closed cavity, it is a serious complication that can become treatment intractable or repeatedly recur. These features of liver cyst infection make its diagnosis and treatment difficult, and it may lead to severe conditions including sepsis and even death [13, 14]. Antibiotics that are fat soluble and that can be transported into the cyst are the preferred treatment for cyst infections. These antibiotics act on Gram-negative bacilli, which are most frequently detected as microorganism. However, treatment with antibiotics alone is sometimes insufficient. In 14 cases of liver cyst infection, six of seven patients in whom antibiotics and early drainage were performed recovered [13]. However, only one of the other seven patients treated with antibiotics alone recovered. In addition, the recurrence rate in 54 cases of liver cyst infection was 30% in cases of antibiotics alone, 5.8% for percutaneous drainage, and 14.3% for laparoscopic drainage and partial hepatectomy [15]. Therefore, percutaneous drainage and surgery are the preferred treatments for liver cyst infections.

Liver cyst infection recurred in our patient even though percutaneous drainage was concomitantly performed with antibiotics in the early phase. Since multiple cyst infections occurred in the right lobe of the liver, resection of the right liver lobe was considered. However, the left lobe contained almost no liver parenchyma because of the presence of numerous cysts, and postoperative liver failure was a concern. Therefore, total hepatectomy and liver transplantation from a living donor was selected.

Since 1988, there have been many reports of liver transplantation for PLD [16–20]. Favorable cases for liver transplantation in PLD are Gigot Classification Type III cases complicated by nutrition and ascites, the cases in which quality of life is significantly affected, the cases in which hepatectomy would be difficult because of severe intravascular transposition, and the cases in which the remaining liver parenchyma constitutes less than 30% of the liver [21]. In patients with ADPKD, liver transplantation is often performed simultaneously with kidney transplantation because of renal failure [21, 22]. According to the European Liver Transplantation Registry database, 42% of 734 patients who received a liver transplantation for PLD also underwent combined liver–kidney transplantation [23].

Nine cases of liver transplantation due to cyst infection with ADPKD have been reported worldwide (Table 1) [24, 25]. Among them, three of four cases with maintenance hemodialysis underwent combined liver–kidney

Table 1 Summary of previous reports of liver transplantation due to liver cyst infection in ADPKD patients

No.	Age	Sex	HD	Other complication	Self liver weight (kg)	Graft	Kidney transplantation	Perioperative complications	Period of observation (months)	Outcome	References
1	41	F	–	Ascites, cachexia, dyspnea	9.4	Full	–	–	10	Alive	[24]
2	53	F	–	–	2.8	Full	–	–	110	Alive	[24]
3	47	F	–	–	4.0	Full	–	Initial graft nonfunction re-LTX	2	Death (pneumonia, myocardinal infarction)	[24]
4	52	F	+	Cyst bleeding	8.3	Full	+	–	47	Alive	[24]
5	53	F	–	–	5.2	Full	+	Revision of the anastomosis of hepatic artery	66	Alive	[24]
6	60	F	+	Ascites, cachexia, dyspnea	6.7	Full	+	Biliary leakage	23	Alive	[24]
7	56	F	+	Ascites	12	Full	+	–	44	Alive	[24]
8	66	F	+	Cyst rupture		Right lobe	–	Bile fistula, abdominal abscess	147	Alive	[25]
9	63	F	+	IVC compression, malnutrition, dyspnea		Right lobe	–	Renal failure	101	Alive	[25]

HD hemodialysis, *IVC* inferior vena cava, *LTX* liver transplantation

transplantation. Only one case with maintenance hemodialysis underwent LDLTA due to liver cyst infection and liver cyst rupture [25]. The patient was a 66-year-old Japanese woman. In Japan, deceased donors were very rare, so that most of liver transplantation depends on living donor. Furthermore, moderate or severe renal insufficiency at preoperative period was independently a poor prognosis factor in liver transplantation. According to the database of adult liver transplantation recipients ($n = 19{,}261$) from United Network for Organ sharing in 1988–1996, primary graft non-function and 30-day mortality rates were higher and graft and patient survival rates were lower in patients with moderate or severe renal failure [26]. Furthermore, in LDLTA, the survival rates at 1 year and 5 years in the recipients with maintenance renal replacement therapy (MRRT) ($n = 28$) were significantly worse than that in the recipients without MRRT ($n = 237$) (1 year; 66.1 vs 83.8%, 5 years; 57.3 vs 80.0%) [27]. A multivariate analysis on patient survival rates after LDLTA showed that MRRT had the highest hazard ratio [27]. Collectively, LDLTA for the patients with MRRT might be tended to be avoided. However, liver transplantation should be considered in severe cases of PLD like our patient, because liver transplantation is the only curative treatment.

Although LDLTA in our patient was successful, pneumothorax were complicated as reported in several cases after liver transplantation for PLD. Pneumothorax was thought to have been caused by intraoperative damage to the diaphragm when an adhesion was peeled away [28, 29]. In our patient, the visceral pleura was peeled off from a wide area of the pulmonary parenchyma because of rapid expansion of the lung after removing the liver, and thus the cause of pneumothorax was considered to be the expansion of the lung rather than surgical damage. Pneumothorax is a typical complication that needs careful attention to avoid during liver transplantation for PLD.

In conclusion, liver transplantation due to intractable liver cyst infection in maintenance hemodialysis patients with ADPKD entails various risks, and selection of this course of action requires careful consideration. Nonetheless, LDLTA may be the only curative treatment in maintenance hemodialysis patients with ADPKD.

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Compliance with ethical standards

Conflict of interest Toshio Mochizuki and Ken Tsuchiya received travel fees and honoraria for lectures from Otsuka Pharmaceutical Co. Toshio Mochizuki belongs to an endowed university department

sponsored by Otsuka Pharmaceutical Co, Chugai Pharmaceutical Co, Kyowa Hakko Kirin Co, MSD Co, and JMS Co.

Ethical approval All procedures performed in the patient study were in accordance with the 1964 Helsinki Declaration and its later amendments, or with comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

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