

**[ CASE REPORT ]**

# Massive Polycystic Liver with a Poor Performance Status Successfully Treated by ABO-incompatible Adult Living-donor Liver Transplantation While Overcoming Complications

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## Abstract:

We encountered a 47-year-old woman with polycystic liver disease (PLD) and severe malnutrition successfully treated by living-donor liver transplantation (LDLT). Her PLD became symptomatic with abdominal distension and appetite loss. Transcatheter arterial embolization and percutaneous cyst drainage failed to improve her symptoms. ABO-incompatible LDLT from her husband was performed after rituximab administration and mycophenolate mofetil introduction. Although she showed severe postoperative complications, she ultimately regained the ability to walk and was discharged. Because advanced PLD cases are difficult to treat conservatively or with surgery, like fenestration and hepatectomy, liver transplantation should be considered before it becomes too late.

**Key words:** polycystic liver disease, liver transplantation, living-donor liver transplantation, ABO-incompatible, hepatomegaly, malnutrition

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## Introduction

Adult polycystic liver disease (PLD) was first described in 1856 by Bristowe in association with autosomal dominant polycystic kidney disease (PKD) (1). PKD is now one of the most common genetic diseases, affecting nearly 12 million people worldwide (2), and more than three-quarters of patient with PKD also have liver cysts (3). Although most PLD cases are asymptomatic, 10-20% reportedly develop symptomatic hepatomegaly (3). Some genetic factors were investigated as targets for treatment, but the efficacy of such therapy has not been sufficient to improve symptoms (4).

As hepatocellular insufficiency is rarely a feature of PLD, unlike renal involvement (5), treatments for PLD are generally indicated when patients become symptomatic. Some interventional approaches, such as transcatheter arterial embolization (TAE) (6, 7) and needle aspiration with scler-

otherapy (8), have been attempted, but outcomes were insufficient. Treatment for symptoms of PLD, such as pain and digestive and/or respiratory discomfort due to hepatomegaly, thus remains largely surgical, ranging from fenestration with or without partial hepatic resection to liver transplantation (LT) (9). In general, the performance status (PS) is often considered as an adaptation criterion for surgical operations. However, in cases where PLD itself is the cause of deterioration of PS or malnutrition, surgical approaches can lead to radical improvement. However, it may be difficult to determine whether or not surgery should be actively recommended for patients who have been bedridden for a long time due to PLD.

We herein report a severe PLD patient who was successfully treated by ABO-incompatible adult living-donor LT (LDLT) despite having been bedridden for more than a year due to considerable hepatomegaly, malnutrition, and refractory ascites.

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**Table 1. Laboratory Data at Admission.**

Peripheral blood		Virus markers	
WBC	6,870 / $\mu$ L	HBsAg	(-)
RBC	412 $\times 10^4$ / $\mu$ L	HCVAb	(-)
Hemoglobin	10.5 g/dL		
Platelet count	254 $\times 10^9$ /L	Liver fibrosis markers	
		FIB-4	0.77
Coagulation		Tumor markers	
PT activity	68.2 %	CEA	<0.5 ng/mL
PT-INR	1.24	AFP	<2.0 ng/mL
Blood chemistry		Blood type	
Total protein	5.8 g/dL	ABO	O
Alb	2.1 g/dL	Rh	(+)
T-Bil	0.3 mg/dL		
AST	11 IU/L	Urinalysis	
ALT	7 IU/L	Color tone	Yellow
LDH	81 IU/L	Gravity	1.014
ALP	230 IU/L	Protein	(-)
$\gamma$ -GTP	68 IU/L	Occult blood	(-)
Cholinesterase	122 IU/L	RBC	<1 HPF
BUN	15.3 mg/dL	WBC	30-49 HPF
Cr	0.77 mg/dL	Ketone	(-)
eGFR	63.2 mL/min/1.73 m <sup>2</sup>	Glucose	(-)
Na	138 mEq/L		
K	3.7 mEq/L		
Cl	98 mEq/L		
Total cholesterol	142 mg/dL		
LDL cholesterol	89 mg/dL		
HDL cholesterol	34 mg/dL		
Triglyceride	120 mg/dL		
CRP	5.59 mg/dL		
MELD score	2		

WBC: white blood cell count, RBC: red blood cell count, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase,  $\gamma$ -GTP:  $\gamma$ -glutamyltransferase, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein, CRP: C-reactive protein, MELD: model for end-stage liver disease, HBsAg: hepatitis B surface antigen, HCVAb: antibody to hepatitis C virus, FIB-4: fibrosis-4, CEA: carcinoembryonic antigen, AFP: alpha-fetoprotein

## Case Report

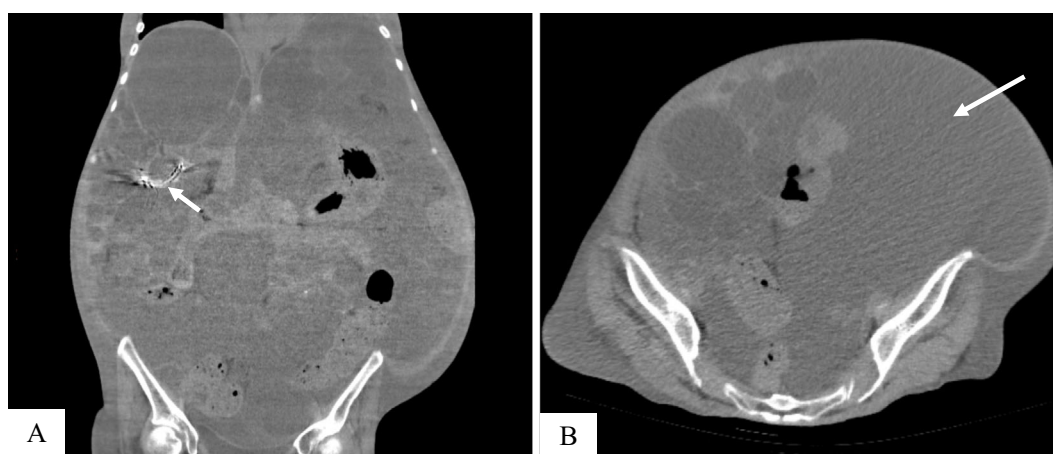
A 47-year-old woman was transferred from another medical institution to our hospital because of severe malnutrition and a decreased physical activity due to PLD. She had been first diagnosed with PLD and PKD at 20 years old. Her PLD gradually progressed and became symptomatic, so she was treated with TAE two years ago. She was also treated with diuretics, including tolvaptan, but none of these approaches proved effective. Thus, she had been subsequently treated by percutaneous drainage many times. Eight months ago, she had developed biliary peritonitis after the drainage tube was removed. She had been treated by endoscopic nasobiliary drainage at another hospital, and her peritonitis improved. However, her physical activity was markedly deteriorated due to the long-term hospitalization and the re-

progression of her PLD. Her poor condition proved intractable despite rehabilitation, so she consulted our hospital and was transferred.

Although she had no medical history other than PLD, her father had been treated by hemodialysis for chronic renal failure due to PKD and was also complicated with asymptomatic PLD. She had no habits of alcohol intake or smoking.

Physical examinations at admission revealed marked abdominal distension and edema in both lower limbs. Although no objective abnormalities were observed in her consciousness and chest, she was no longer able to turn over in bed on her own due to her muscle atrophy and abdominal weight. Furthermore, she had a decubitus in her sacral region.

Laboratory examinations at admission to our hospital (Table 1) showed a decrease in levels of total protein, albumin (Alb), aspartate aminotransferase, lactate dehydrogenase,



**Figure 1.** The findings of computed tomography at admission. The abdominal cavity was occupied by a huge cystic liver (A) and ascites (B, arrow). A platinum coil (A, arrow) placed in the branch of the hepatic artery by transcatheter arterial embolization was ineffective for reducing the cyst.

cholinesterase, high-density lipoprotein, and hemoglobin levels and the increase in  $\gamma$ -glutamyltransferase, creatinine (Cr), and C-reactive protein. In addition, urinary leukocyte was positive. Her ABO-blood type was O-type, and her Rh-blood type was Rh (+). Both hepatitis B virus surface antigen and anti-hepatitis C virus antibody were negative. Regarding tumor markers and liver fibrosis markers, carcinoembryonic antigen (CEA), alfa-fetoprotein (AFP), fibrosis-4 (FIB-4) index, and the platelet count were within normal ranges. The Model for End-Stage Liver Disease (MELD) score was 2. On computed tomography (CT), the abdominal cavity was occupied by a huge cystic liver (Fig. 1A), with a steel coil (Fig. 1A, arrow) placed in the branch of the hepatic artery by transcatheter embolization, and massive ascites (Fig. 1B, arrow). No solid components suggesting cystadenocarcinoma were detected in those cysts. Furthermore, no emphysema was found in either of her lungs. On brain magnetic resonance angiography, no cerebral aneurysms, a well-known complication of PLD, were observed (10).

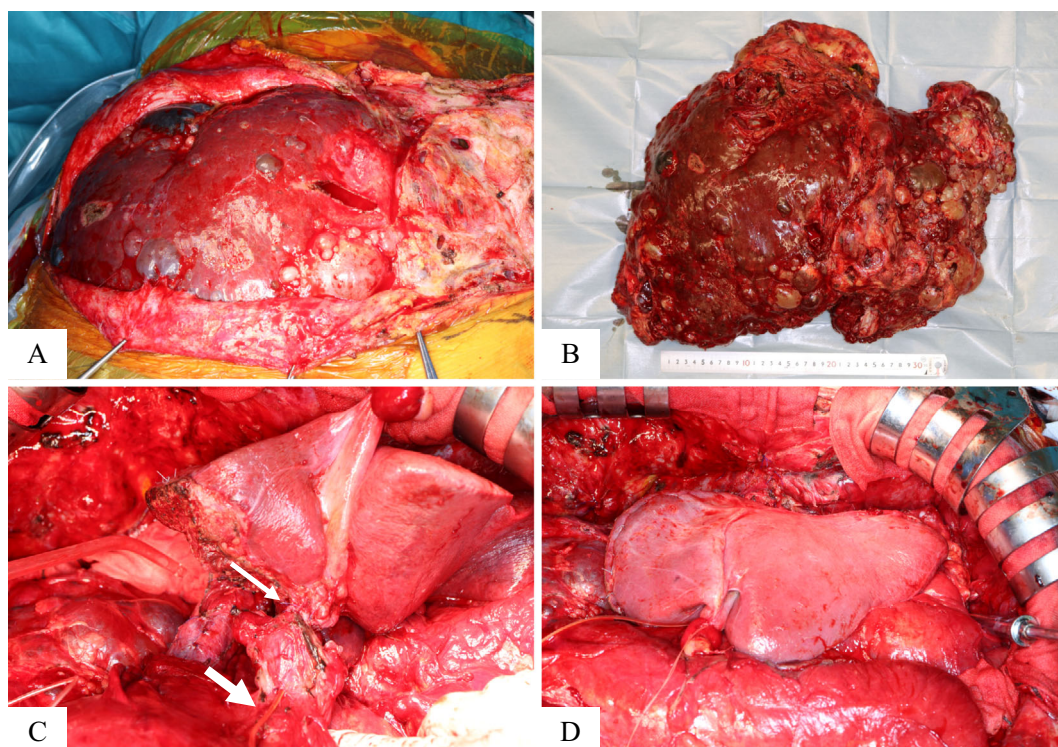
After her transfer to our hospital, we increased the diuretics administration, but this was not effective. Due to her history of peritonitis, we deemed drainage of the cysts inappropriate. Percutaneous ascites drainage was often needed to reduce her abdominal distension. Although lymphocytes accounted for 90% of the cells contained in the exudative ascites, bacterial culture of ascites was negative, including no findings for tuberculosis. No malignant cells were detected by cytology, nor were any elevations of tumor markers, such as CEA and AFP, observed in her ascites. In addition to the treatments with diuretics and ascites drainage, intervention by a dietitian and continued rehabilitation were performed. However, her oral intake could not be improved, and the malnutrition and decreased physical activity became exacerbated. Tube feeding was not employed because the patient was alert and was motivated to improve her poor condition through usual oral intake. Furthermore, because she had to excrete into a diaper, she often suffered from urinary tract infections due to the unsanitary condition and was treated

with antibiotics. We believed it would be difficult to improve the prognosis of the patient even with continuing the current treatments, so we considered LT.

After consulting with the patient's family, her husband expressed his clear intention to donate his liver. We therefore considered him to be a donor candidate and consulted with the department of transplant surgery at another institution, even though his ABO-blood group was B, which was incompatible with the recipient. At that point, the donor candidate was advised to improve his obesity and fatty liver to ensure safe and effective LDLT. The donor consequently began strict dietary and exercise therapy, eventually reducing his body weight by 13 kg and improving his fatty liver, as confirmed by ultrasonography. He was officially approved as a donor for LDLT by the indication committee of the medical institution.

The patient was transferred from our hospital to the institution with a department of transplant surgery 140 days after the first admission to our hospital (day 140). The next day, 500 mg of rituximab was administered to the recipient to prevent graft rejection due to ABO-blood type incompatibility. In addition, 2,000 mg/day of mycophenolate mofetil was started from day 152. ABO-incompatible LDLT was then performed on day 159. At the time of LDLT, her MELD score had deteriorated to 11. The patient's laparotomy was performed by a Mercedes-Benz incision. Due to the effects of polycystic liver and the previous treatments, adhesion was noted between the liver and peritoneum. After detaching the adhesions, 10,027 g of polycystic liver was removed (Fig. 2A, B). The donor provided a 456-g graft of the left and caudate lobe, which constituted 37.8% of the recipient's standard liver volume. The hepatic veins and portal vein were reconstructed first, and after reperfusion of the liver graft, the hepatic arteries and bile ducts were reconstructed. Finally, hemostasis was performed, and LDLT was completed (Fig. 2C, D). The operation took 17 hours and 53 minutes, and the bleeding volume was 81,600 mL. A total of 244 units of red blood cell concentrate, 274 units of





**Figure 2.** The laparotomy findings during living-donor liver transplantation. Polycystic liver before (A) and after (B) removal. The transplanted liver from donor (C, D): 1.7 mm of the pancreatic duct tube (C, thick arrow), reconstructed bile duct (C, thin arrow).

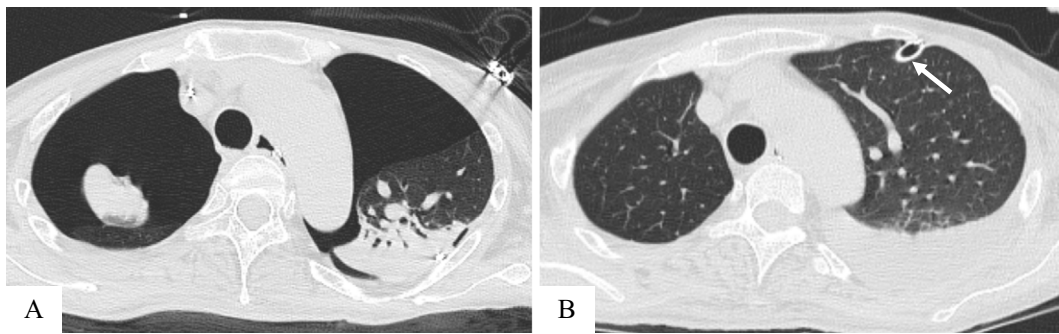
fresh-frozen plasma, and 120 units of platelet concentrate were needed during the operation.

After LDLT, tacrolimus was initiated, and the dose was adjusted based on the blood trough levels. On day 163, the recipient was withdrawn from the ventilator, but her respiratory condition deteriorated after a few hours, and she was diagnosed with bilateral pneumothorax on CT (Fig. 3A). Chest tubes were thus inserted to drain the air in each side of the pleural cavity (Fig. 3B). On day 166, her transaminase levels were markedly elevated. Acute cellular rejection (ACR) to the graft was pathologically confirmed by a liver biopsy, and steroid pulse therapy was performed. The next day, she showed dyspnea associated with weakened respiratory muscles. A tracheotomy was thus performed for continuous management with a ventilator. On day 170, the recipient showed septic shock and was treated with antibiotics and noradrenaline. Mycophenolate mofetil was temporarily suspended. With these treatments, her circulatory state, respiratory state, and liver function gradually improved. She became able to undergo rehabilitation, and the dose of steroid was able to be decreased. Although the recipient developed adhesive small bowel obstruction on day 213 (Fig. 4A), it was cured via adhesion release with re-laparotomy. She was withdrawn from the ventilator on day 208, and the chest drainage tube was removed on day 279. Her Alb level gradually increased as her physical activity and oral intake improved. She regained her ability to walk, achieving a distance of 70 meters on her own, and was transferred to our hospital again on day 316. She continued

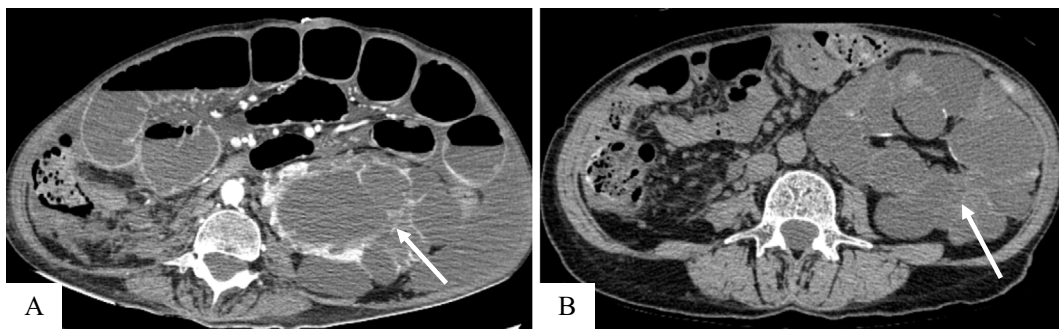
rehabilitation, and the dose of tacrolimus was decreased from 2.4 mg/day to 2.2 mg/day. No findings suggesting ACR to the graft liver, such as elevation of hepatobiliary enzyme levels, were observed, and her nutrition status improved further. Finally, she was discharged from our hospital on day 330, her first time returning home in over 1.5 years. During the course, cytomegalovirus antigenemia was sometimes detected, and valganciclovir was administered to the recipient each time. In addition, sulfamethoxazole/trimethoprim (ST) and itraconazole were also given to prevent pneumocystis infection and mycosis, respectively.

Her renal function subsequently deteriorated gradually, an event that seemed to be due to PKD and drug-induced renal dysfunction attributed to tacrolimus. The patient was therefore admitted again to the same department of transplant surgery, and tacrolimus was switched to 1.0 mg/day of everolimus on day 516. During this hospitalization period, the patient was diagnosed with anastomotic stenosis of the bile duct (Fig. 5A, arrow), and balloon dilation and plastic stent placement (Fig. 5B) were performed under endoscopic retrograde cholangiopancreatography (ERCP). Prednisolone was discontinued 12 months after LDLT, and prophylactic treatment with ST and itraconazole was also finished. Furthermore, although she had taken laxatives since the development of adhesive small bowel obstruction, her bowel movement improved, and no intestinal dilatation was observed on CT (Fig. 4B). Thus, those medicines were also discontinued.

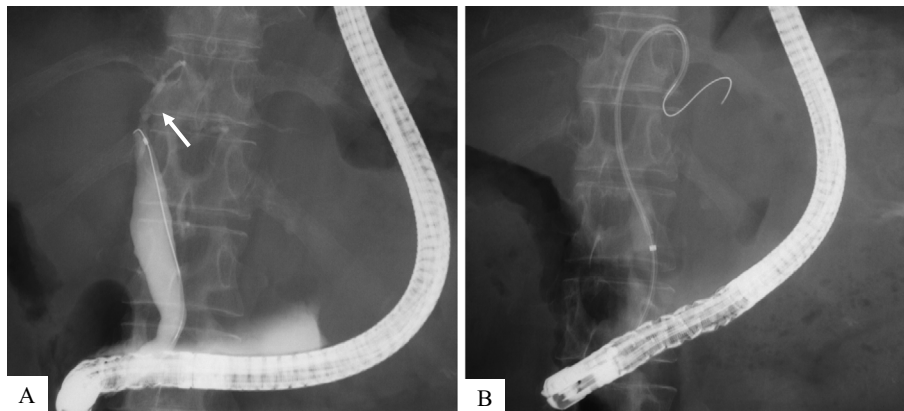
One and half years since the first admission to our hospital and one year since the LDLT have passed. She has regu-



**Figure 3.** The findings of computed tomography at the development of bilateral pneumothorax (A) and after the placement of a chest tube (B, arrow).



**Figure 4.** The findings of computed tomography at the development of adhesive small bowel obstruction (A) and 515 days after the first admission to our hospital (B). Although the contrast effect in the gastrointestinal wall was confirmed, the marked dilation of the small intestine was observed (A). The dilations of the small intestine disappeared (B). On both images, polycystic kidney is indicated with an arrow.

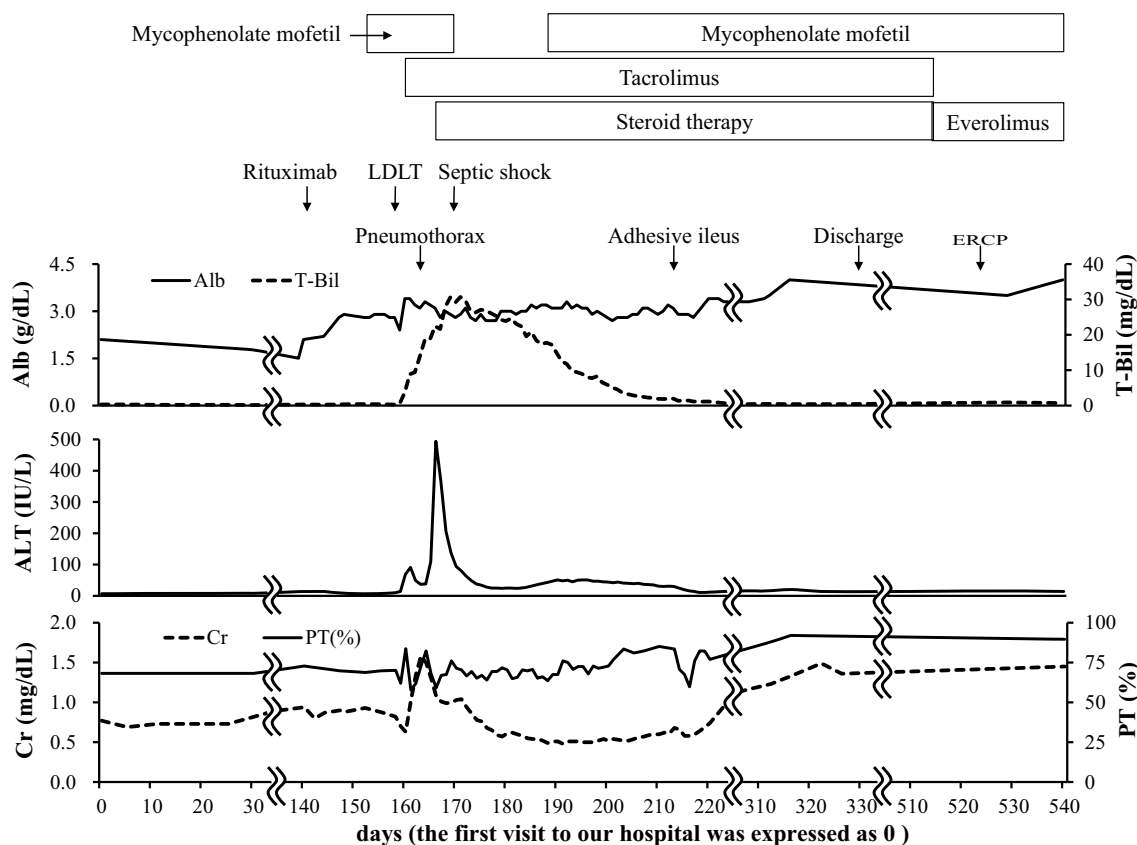


**Figure 5.** The findings of endoscopic retrograde cholangiopancreatography at the time of bile duct stenosis. Stenosis was observed in the bile duct near the hepatic hilum (A, arrow). Balloon dilation followed by plastic stent placement (B) was performed.

larly visited our hospital for follow-up and remains in good health. Neither proteinuria nor deterioration of the renal function have yet been observed. Her nutrition status has also been well maintained, and she can walk without a cane. The clinical course of this case is shown in Fig. 6.

## Discussion

In the present case, the patient showed marked malnutrition and decreased physical activity due to PLD weighing more than 10 kg before LDLT. Furthermore, after ABO-incompatible LDLT, several serious complications developed. However, we eventually achieved an excellent out-



**Figure 6.** The clinical course of the present case. Days indicates the number of days after the first admission to our hospital. Alb: albumin, ALT: alanine aminotransferase, Cr: creatinine, ERCP: endoscopic retrograde cholangiopancreatography, LDLT: living-donor liver transplantation, T-Bil: total bilirubin

come by improving her nutrition status and performing appropriate countermeasures for the complications.

PLD is generally classified into three types according to the identified genetic abnormality: (i) autosomal dominant PLD, (ii) autosomal recessive PLD, and (iii) isolated sporadic PLD. The most common type is autosomal dominant PLD. In this type, the identified mutations are in the PKD 1 gene (85%) and PKD 2 gene (15%) (5). Determining the genetic diagnosis is indicated in cases without a familial history if the presentation is atypical (discovery before 20 years old) or during an evaluation for intra-familial organ donation. In our present case, the father of the patient had suffered from chronic renal failure due to PKD with asymptomatic PLD. In addition, the patient had first been diagnosed with PLD and PKD at 20 years old. Therefore, despite no genetic diagnosis, we considered her PLD potentially the autosomal dominant type.

Regarding the risk factors for progression of hepatic cysts, Gabow et al. reported that autosomal dominant PKD (ADPKD) cases with PLD were significantly older than ADPKD without PLD ( $p < 0.001$ ), women were more likely to have massive PLD than men ( $p < 0.05$ ), and women with hepatic cysts were likely to have a history of pregnancy ( $p < 0.001$ ) (11). The effect of estrogen (oral contraception or pregnancy) in women has also been reported, as estrogen

may regulate the growth of various liver-derived cells, since estrogen receptors have been identified in human hepatocytes, hepatic adenoma, and focal nodular hyperplasia (12, 13) and were reduced in a hepatic adenoma by treatment with tamoxifen (14). Biliary or cystic epithelium may also be responsive to this hormone (11), which can cause progression of PLD. Thus, although the prevalence of PLD is identical in men and women, 90% of symptomatic PLD patients are women (5). In the present case as well, the effects of estrogen were highly conceivable. We suspect that after the initial diagnosis of PLD and PKD at 20-year-old, PLD gradually progressed with her pregnancy and aging, resulting in a symptomatic manifestation at 45-year-old.

Treatments for hepatomegaly due to PLD include medical treatments, needle aspiration with or without sclerotherapy, interventional radiology, and surgical approaches. The usefulness of somatostatin analogs as medical treatments for PLD has been reported (15). However, that medicine is not yet covered by Japanese insurance. In addition, since the mean decrease in total liver volume was reported to be  $< 10\%$ , it might have been difficult to relieve the symptoms of our patient with a huge cystic liver, even if it had been administered.

The efficacy of TAE has been also reported (6, 7). However, previous studies have included only a small number of



**Table 2. Schnelldorfer Lesional Classification of Polycystic Liver (17).**

	Type A	Type B	Type C	Type D
Symptoms	Absent or moderate	Moderate or severe	Severe	Severe
Size and number of cysts	Few	Few but large in size	Few and small in size	Few to numerous
Number of spared liver segments	>3 segments	≥2 segments	≥1 segment	<1 segment
Presense of collateral venous circulation in the spared segment	Moderate	Absent	Absent	Present
Recommended treatment	Therapeutic abstention or medical treatment	Fenestration	Partial hepatectomy with fenestration of contralateral cysts	Hepatic transplantation

patients, so large-scale studies are needed in order to investigate the efficacy and safety of TAE. Furthermore, needle puncture and an evacuation of the cyst contents followed by injection of a sclerosing agent, such as 95% ethanol or ethanolamine oleate solution, can result in significant clinical improvement in cases with an isolated liver cyst (8, 16). However, it is difficult to improve the symptoms caused by innumerable cysts as present case, and rather, there should be concern about the risk of complications such as leakage of sclerosing agent and/or cyst content, and infections associated with multiple punctures. In fact, although our patient had been treated by TAE and percutaneous drainage at other institution, her liver volume and symptoms had failed to be improved, and biliary peritonitis developed.

Among several PLD classifications used recently, the Schnelldorfer classification is the most complete and useful for clarifying indications for partial hepatectomy versus transplantation because it takes into account venous involvement and the presence or absence of symptoms (17) (Table 2). The present case was classified as type D because of severe abdominal distention, malnutrition, numerous liver cyst, and a lack of spared liver segments. We therefore considered LT the most appropriate treatment. The frequency of LDLT for PLD is 0.4% (32/8,572) (18), and the availability of deceased donors has recently increased the rate of transplantation to 3% in Japan (18). The recent frequency of LT for PLD is thus comparable to the rate of 1.4% in a Canadian study (19), and the survival rate has been acceptable (20). In the present case as well, the recipient achieved a significant improvement in her physical activity after LDLT, evidently due to not only the loss of the weight of PLD and ascites but also the increased muscle strength associated with her cured malnutrition and hypoproteinemia. In general, since hepatocellular insufficiency does not occur in patients with PLD, the pathophysiology of malnutrition and hypoproteinemia in PLD cases differs from that of sarcopenia and hypoproteinemia in liver cirrhosis cases. Patients with major hepatomegaly due to PLD often show gastric and duodenal compression, resulting in post-prandial discomfort, gastroesophageal reflux, and digestive intolerance. Food restriction can lead to severe malnutrition with loss of muscle mass, which is often aggravated by a patient's increasingly sedentary habits with the reduction in their physical activity (21, 22). Furthermore, the height-adjusted total liver volume (htTLV) measured by CT >1,600 mL/m was reportedly

associated with an increase in pressure symptoms in ADPKD cases with PLD (23). In the present case, the height of the patient was 160 cm, and the weight of the cystic liver was over 10 kg, constituting serious hepatomegaly considering her physique. Based on these findings, the improvement of malnutrition, hypoproteinemia and physical activity in our case may have been mainly induced by the remission of the pressure effect of hepatomegaly (compression of surrounding organs, ascites due to portal hypertension). The urinary protein level was negative or low both before and after LDLT. In addition, the serum Alb level was clearly improved after LDLT. Thus, the effect of urinary protein on the serum protein level seemed small. However, we may have to reconsider this, depending on the progress of PKD in the future.

Wallace et al. reported that an impaired PS was associated with an increased duration of hospitalization in the initial posttransplant period, spending time in the intensive-care unit, and the incidence of renal failure and infection (24). The recipient in the present report had been bedridden for over a year before LDLT due to the weight of her huge polycystic liver and marked ascites as well as muscle atrophy. As a result, she showed various complications after LDLT. In particular, bilateral pneumothorax and respiratory failure due to respiratory muscle weakness were characteristic complications in the present case. Biffl et al. described in their report regarding anorexia nervosa that prolonged starvation led to reductions in the total lung protein content, connective tissue, hydroxyproline, and elastin, and malnutrition was a well-known impediment to normal wound healing (25). Furthermore, ventilators can cause secondary pneumothorax (26). We suspect that her lungs failed to tolerate mechanical ventilation because of the tissue fragility caused by malnutrition.

Common complications, such as ACR to the graft liver, bacterial infection, postoperative adhesive small bowel obstruction, and bile duct stenosis, were also observed in the present patient. To overcome the shortage of donors during efforts to promote organ donation, LDLT has been progressed in Japan (27). Given the shortage of ABO-compatible donors and shallow donor pool, ABO-incompatible liver transplantation remains the only option for many patients with a rapidly worsening liver function or who have been on the waiting list for a long time (28, 29). Rituximab acts on the CD20 antigen present on B cells, thus

reducing the production of B cells, which are mainly responsible for ACR and antibody-mediated rejection (AMR) (30, 31). The introduction of rituximab to the desensitization protocol has brought about a significant reduction in the incidence of AMR and improved the outcome of ABO-incompatible LDLT (32-35). In our case as well, LDLT was performed after the administration of rituximab and the introduction of mycophenolate mofetil. Although the recipient showed ACR to graft liver, she was treated with steroid pulse therapy, and since then, the dose of steroid and immunosuppressive agents has been able to be gradually reduced safely. In addition, both adhesive small bowel obstruction and septic shock were successfully managed by general treatment, namely adhesion release surgery and the administration of antibiotics with pressor agents, respectively. However, the incidence rates of biliary stricture were reported to be significantly higher in ABO-incompatible LDLT cases than in ABO-compatible LDLT cases (36). In our case, stricture developed as a late complication. There was no evidence of intra-hepatic biliary stricture suggestive of biliary complications associated with ABO-incompatible LDLT. Fortunately, at that time, the patient had achieved significant improvement in her nutritional status and general condition, so treatment by ERCP was well tolerated. It is necessary to continue to be alert for plastic stent occlusion and re-stenosis of the bile duct in the future.

In conclusion, we encountered a female PLD patient who suffered from an extremely huge cystic liver and showed severe malnutrition. Although her physical activity was markedly poor and she had been bedridden for over a year, the patient was successfully treated by LDLT while overcoming accompanying complications and was reintegrated into society. In PLD cases classified as Schnelldorfer type D, conservative treatment, such as oral medicine, percutaneous drainage, and TAE, are relatively ineffective and may in fact cause several complications. Therefore, LT, including LDLT, should be considered before it becomes too late in such cases.

Informed consent was obtained from the patient reported in the study.

**The authors state that they have no Conflict of Interest (COI).**

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