JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.47966
J Inonu Liver Transpl Inst 2023;1(1):18–22

Case Report

Living Donor Liver Transplantation for Erytropoietic Protoporphyria Liver Disease

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Abstract

Porphyrias are an inherited group of diseases caused by the deficiency of enzymes in the heme synthesis pathway. Erytropoietic protoporphyria is associated with a deficiency of ferrochelatase activity.

Liver transplantation is the most effective treatment in cases of liver failure due to EPP. In this study, a case who underwent LDLT goes liver failure due to EPP is presented.

A 15-year-old boy who had had recurrent photosensitive skin reactions due to erythropoietic protoporphyria since the age of 1 year. The patient had elevated liver enzymes, coagulopathy, advanced jaundice, low ferrochelatase activity, and high erythrocyte protoporphyrin activity. Liver biopsy confirmed extensive protoporphyrin deposition with cirrhosis, and so living donor liver transplantation was performed. The clinical and laboratory course of the patient in the early post-transplant period was quite normal. But, on the 12th posttransplant day, there was duodenal perforation, possibly due to burns caused by reduced headlights or surgeons' headlights during the operation. The patient, who had a very complicated course, died on the 43rd day after LT.

LT is lifesaving if acute or chronic liver disease has developed in EPP. Special precautions are required to protect these patients from porphyric crises and phototoxic reaction. Bone marrow transplantation can be performed after LT to eliminate the cause.

Keywords: Liver, protoporphyria, transplant

Please cite this article as "Usta S, Kaplan K, Akatli AN, Ince V, Koc C, Aydin C, Yilmaz S. Living Donor Liver Transplantation for Erytropoietic Protoporphyria Liver Disease. J Inonu Liver Transpl Inst 2023;1(1):18–22".

Porphyria is a term that represents a metabolic disease consisting eight sub-groups.Each one is characterized with an enzyme deficiency determined by a gene mutation in the heme synthesis pathway (Fig. 1). Two of these deficiencies may result in an associated liver disease. Porphyria cutanea tarda, associated liver disease, consisting haemochromatosis with alcoholic liver disease, results in porphyria, presenting with blistering, hirsutes and photosensitivity of the skin. However, liver disease of erythropoietic protoporphyria (EPP) is a result of progressive deposition and accumulation of insoluble protoporphyrin IX in hepatocytes and bile ducts. Ferrochelatase, which is an enzyme of mitochondria, catalyses the insertion of ferrous iron into protoporphyrin (PP) to form heme, and when defective or deficient, accumulation of PP ensues (Fig. 1). This enzyme is abundant in cells that produce heme including erythroid precursors in the bone marrow and hepatocytes.[1,2]

Patients with progressive EPP liver disease may present with attacks of clinical exacerbations, that acutely worsen liver function, increase erythrocyte PP levels and frequently manifested by severe abdominal and back pain. Patients

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Submitted Date: 24.03.2023 **Revised Date:** 31.03.2023 **Accepted Date:** 02.04.2023 **Available Online Date:** 27.04.2023

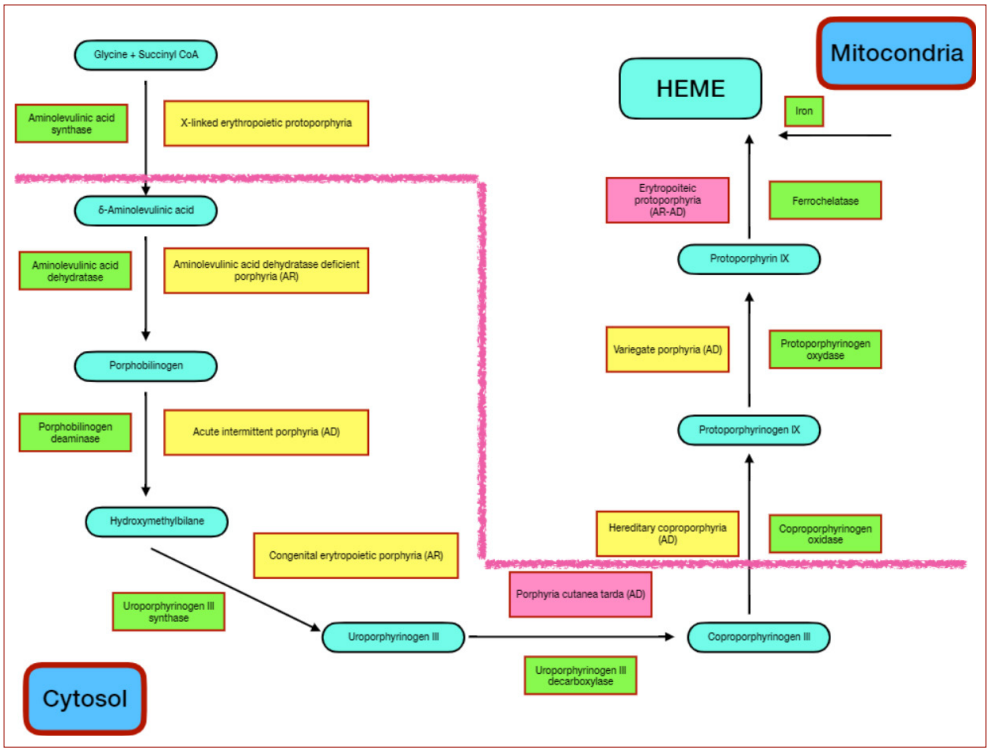

Figure 1. The heme biosynthetic pathway showing the enzyme deficiency and associated porphyria metabolism disorders.

with poor prognosis due to cirrhosis and liver failure significantly benefit from liver transplantation (LT). Unfortunately, LT does not have an impact on the overbundant production of PP by the bone marrow. In this study, a case with liver failure due to EPP in whom we had a living donor liver transplant (LDLT) was presented.

Case Report

A 15-year-old boy patient, who was followed up in another center with the diagnosis of EPP, has hypersensitivity to light since the age of 1 year. Painful rashes appeared on the light-exposed areas, especially on the face and arms. In laboratory tests of the patient, ferrochelatase activity was low and erythrocyte protoporphyrin activity was high. The patient had elevated liver enzymes and jaundice for seven years. He had coagulopathy and advanced jaundice for the last 2 months. When his family history was questioned, it was learned that his brothers aged 19 and 21 died due to the same disease and liver failure. On physical examination, skin and sclera icteric and hepatosplenomegaly were found. There was palpable swelling on the right side of the neck. Doppler sonography revealed a thrombus in the right jugular vein, which was thought to be due to hemin infusion. Liver biopsy performed at the referring center revealed protoporphyrin accumulation and cirrhosis findings. Total bilirubin was 16 mg/dl, INR was 2.3, creatinine was 0.38 mg/dL, and the MELD-Na+ score was 21. Intermittently, hemin infusion and plasmapheresis treatment were started. A living donor liver transplantation was performed for the patient after plasmapheresis. As an operative finding, the black color of the liver due to protoporphyrin accumulation was remarkable (Fig. 2). Headlights and ceilinglights lamps were turned off or dimished to keep the patient from dinjury due to severe light (Fig. 3). Four hundred-forty ml of left lobe (segment 2, 3, 4) from a living donor was transplanted to the patient (Fig. 4). Graft to recipient weight ratio was 1%. There were no complications in the intraoperative period. In the posttransplant period, he was kept from medicines and light exposure that could exacerbate porphyria disease. The macroscopic examination of the explant revealed an enlarged, cirrhotic, and typical black-colored liver with dimensions of 25x16x9 cm (Fig. 5a). The cut surface of the specimen was also black and nodular. Histopathological examination showed a micronodular cirrhotic liver with extensive deposites of dark red-brown porphyrin pigment (Fig. 5b). The porphyrin pigment was present in hepatocytes, Kupffer cells, portal macrophages, bile canaliculi and ductules (Fig. 5c). The deposites were finely granular or lamellar in appearence. These pigment depositions were not positive for iron or copper on special stains. Birefringent pigment crystals were visualized under polarized light. The sections from the lymph nodes

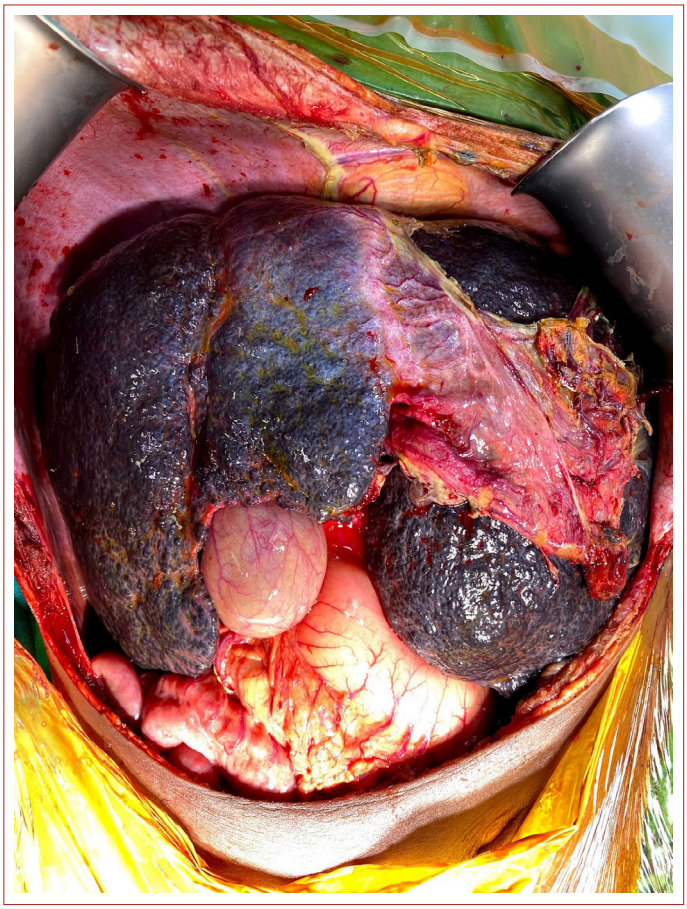

Figure 2. Intraoperative view of the cirrhotic liver with Erytropoietic protoporfiria.

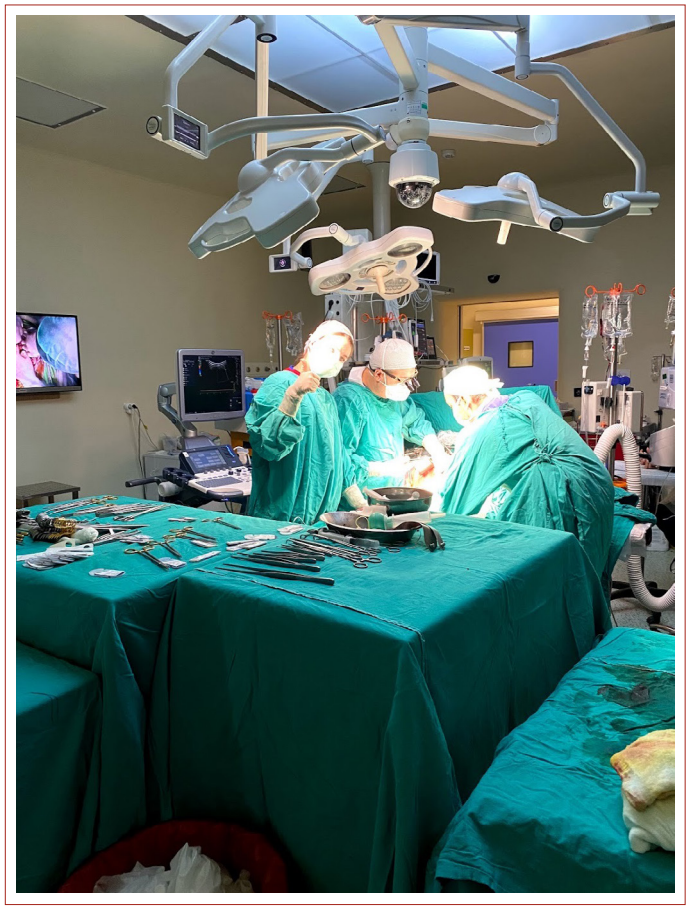

Figure 3. Headlights and ceilinglights lamps were turned off or reduced to protect the patient from damage due to intense light in OR.

both around the liver hilum and the gallbladder neck showed clusters of histiocytes containing cytoplasmic red-brown granular pigment depositions, consistent with sinus histiocytosis with pigmentation (Fig. 5d).

The clinical and laboratory course of the patient in the early post-transplant period was quite normal. On the 12th post-transplant day, there was duodenal perforation, possibly due to burns caused by reduced headlights or surgeons' headlights during the operation, subtotal gastrectomy, duodenal stump was closed to resect the perforated duodenum, and gastrojejunostomy was performed. Percutaneous tracheostomy due to prolonged intubation was performed on posttransplant day 16, hepaticojejunostomy was performed on day 21 due to biliary leak and local peritonitis, and tube duodenostomy was performed on day 33 due to duodenal stump leakage. During this period, the patient had occasional burns on the skin of the anterior abdominal wall. ECMO was performed with pulmonary failure on the 41st posttransplant day and unfortunately the patient died on the 43rd day. The patient required a total of 26 U erythrocyte suspension in the post-transplant period.

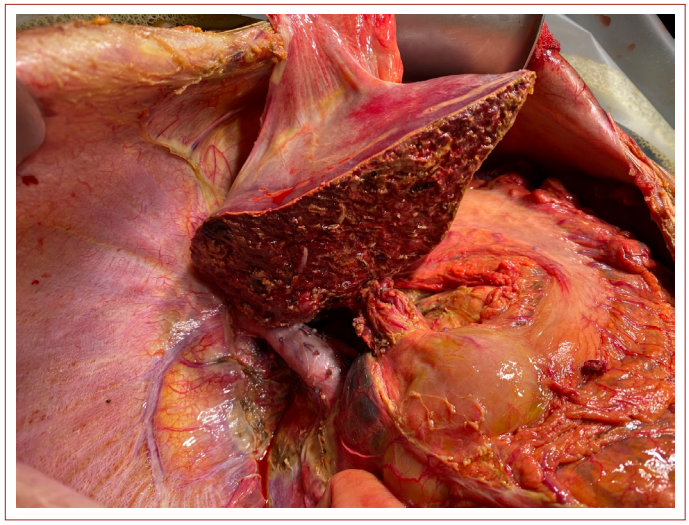

Figure 4. The view of transplanted left lobe liver graft.

Discussion

Heme synthesis is mostly present in liver and bone marrow tissues. EPP is originated from ferrochelatase deficiency, which is the last enzyme of this synthesis pathwa. Some of the EPP patients progress into liver cirrhosis, indicating

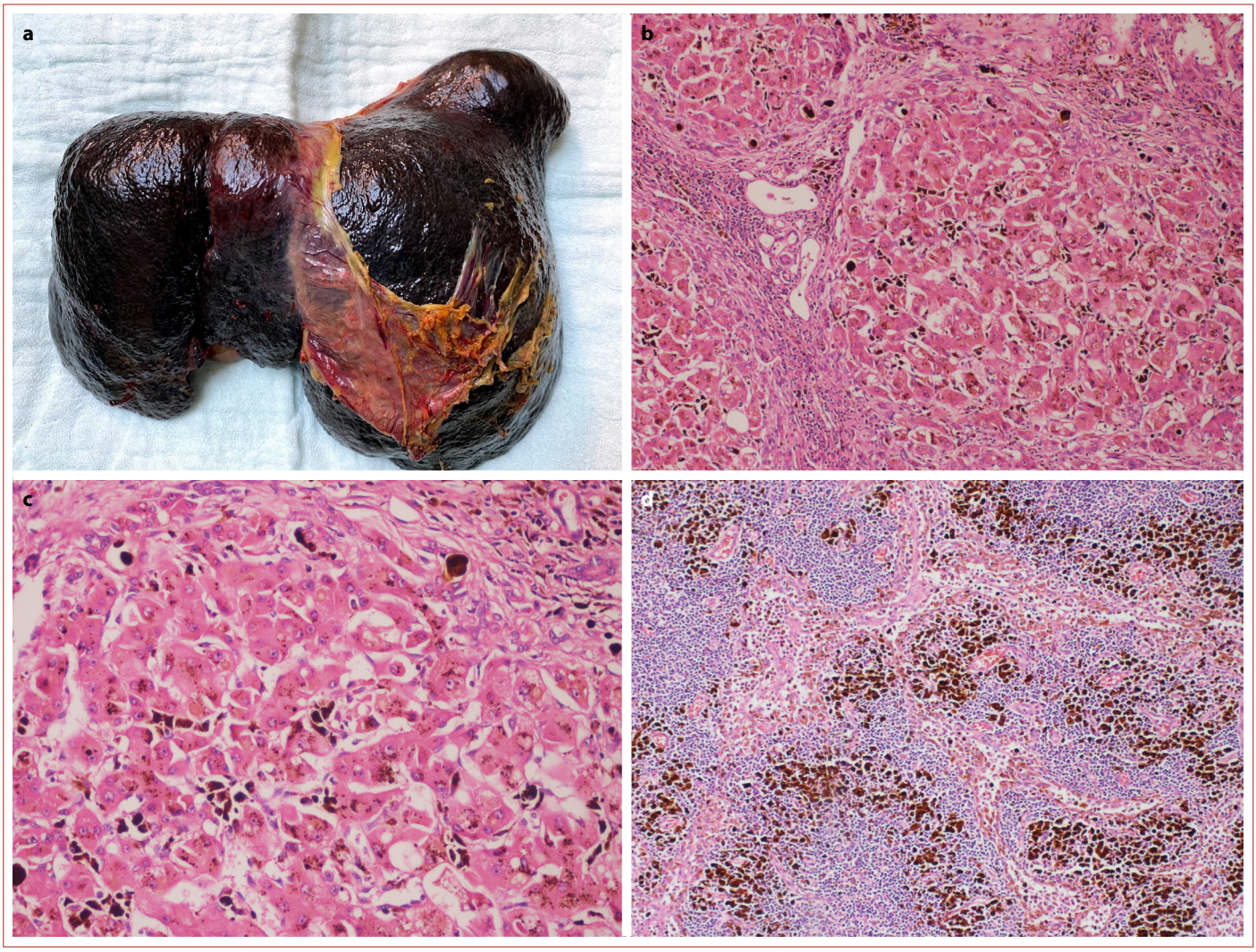

Figure 5. (a) The macroscopic examination of the explant revealed an enlarged, cirrhotic, and typical black-colored liver. **(b)** Micronodular cirrhosis pattern with brown pigmentation in liver paranchyme (H&E,100x). **(c)** Pigmentation in hepatocytes, macrophages and bile canaliculi with associated degenerative changes in hepatocytes (H&E,200x). **(d)** A large number of sinus histiocytes with porphirin deposits (H&E,100x).

LT.[3,4] However, liver transplantation can not be a definitive solutionwhen gene problems in EPP orginate from erythroid cells. The main production site of PP in EPP is erythroid cells. The plasma concentritation of PP will increase as the PP in the red spheres protrude out of cells. PP in plasma is pick up hepatocytes and secrated to the bile ducts. PP in the bile ducts have a cytotoxic effect. This will eventually cause a liver failure.[1,5,6]

EPP attacks are manifested by intolerable abdominal pain, acute liver failure, and increased serum PP levels. The spleen becomes enlarged and hemolysis may ensue. Progressive photosensitivity due to a further reduction in biliary free-PP excretion warns for the upcoming fulminant disease which is rarely reversible and, usually mortal in cases which LT is not offered as a treatment option. EPP may rarely manifest with acute liver failure.[7-9] The presented patient had a more chronic course and had a high MELD-Na score.

If PP crisis is suspected in a patient, it will be necessary to initially look for urinary porphobilinogen. Then, enzyme levels in the HEME synthesis pathway are examined in both urine and plasma. Genetic examination and liver biopsy are the most important diagnostic tools. In our patient, ferrochelatase activity was low and erythrocyte protoporphyrin activity was high. Liver biopsy performed at the referring center revealed PP accumulation and cirrhosis findings.

EPP patients are prone to intra-abdominal organ burns caused by both ceiling and headlight in LT. Specific anti-light filters have been developed to avoid this problem. Damage to the skin and abdominal organs by phototoxic reaction may occur with operating room light. Third-degree skin burns and intraabdominal organ injuries have been published.[10] In the presented case, the ceiling lights were turned off and the head-lights were reduced during LT. Despite this, duodenal perforation was observed in the

patient after LT, and this complication played a leading role in the patient's mortality. Regarding this complication, we can conclude how important the use of a special filter is on PP-induced tissue injuries. Perhaps our attempt to reduce the ceiling and OR head-lights has not been successful. For surgeries of prolonged duration, light filters that limit transmission of wavelengths 340-470 nm.[11] But there have not any special light filter in Turkey for these type of patients.

Respiratory muscle paralysis may occur due to neurological dysfunction after LT. As a matter of fact, ECMO was applied in our patient due to prolonged intubation, loss of proximal motor muscle strength and eventually lung parenchymal failure.

The different forms of treatment for EPP both before and after LT have been directed at specific pathogenetic mechanisms as follows:[1,12] To increase the excretion of PP into bile by the oral administration of the bile salts chenodeoxycholic acid or ursodeoxycholic acid, to reduce PP production by suppressing erythropoiesis using iron, red cell transfusions or infusion of hemin, all of which are intended to reduce the drive for heme synthesis, to reduce the pool of circulating plasma PP by plasmapheresis and haemodialysis, to reduce PP levels by interrupting the enterohepatic circulation with administration of cholestyramine, to reverse oxidative stress in EPP by vitamin E therapy.

In conclusion, LT is lifesaving if acute or chronic liver disease has developed in EPP. Special precautions are required to protect these patients from porphyric crises and phototoxic reaction. Bone marrow transplantation can be confirmed after LT to eliminate the cause.

Disclosures

Informed consent: Written, informed consent was obtained from the patient's family for the publication of thís case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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