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Living-Donor Liver Transplantation for Erythropoietic Protoporphyria: A Case Report and Literature Review

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Erythropoietic protoporphyria (EPP) is a very rare disease with an estimated prevalence of 1 in 200,000 individuals. Decreased ferrochelatase activity causes the accumulation of protoporphyrin in the body, and light exposure results in the generation of active oxygen, causing photosensitivity. Liver damage has the greatest influence on the prognosis, and liver transplantation is the only treatment option for patients with decompensated liver cirrhosis. We report a case of living-donor liver transplantation for decompensated liver cirrhosis associated with EPP. The patient was a 52-year-old male who led a normal life except for mild photosensitivity. When the patient was 37-year-old, hepatic dysfunction was noticed. At 48-year-old, high erythrocyte protoporphyrin levels, skin biopsy, and genetic tests resulted in a diagnosis of EPP. The patient underwent living- donor liver transplantation because of decompensated liver cirrhosis. In the operating room and intensive care unit, a special light-shielding film was applied to all light sources to block light with harmful wavelengths during treatment. Due to the need for special measures, a lecture on patients with EPP was given before surgery to deepen understanding among all medical professionals involved in the treatment. As a result, no adverse events occurred during the perioperative period, and the patient was discharged on the 46th post-operative day. Currently, the transplanted liver is functioning extremely well, and the patient is alive 3 years post-transplant. Herein, we describe a case of living donor liver transplantation for EPP with a brief literature review.

Key words: erythropoietic protoporphyria; lecture on erythropoietic protoporphyria; light shielding film; living-donor liver transplantation; perioperative management
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Introduction

Erythropoietic protoporphyria (EPP) is a very rare genetic disease with an estimated prevalence of 1 in 200,000 individuals (Magnus et al. 1961; Elder et al. 1990). EPP is caused by a mutation in the ferrochelatase (FECH) gene. Protoporphyrin accumulates in the bone marrow, red blood cells, skin, and liver because of FECH deficiency (Whitcombe et al. 1991; Bloomer et al. 2005). Protoporphyrin absorbs light at a wavelength of approximately 400-470 nm and release active oxygen, which causes tissue damage (Bloomer et al. 1989; Wahlin et al. 2008). EPP often develops due to photosensitivity in childhood, resulting in edematous erythema and blisters with itching and pain after sun exposure (Magnus et al. 1961; Schneider-Yin et al. 2000). Protoporphyrin also accumulates in hepatocytes and causes liver injury, leading to decompensated liver cirrhosis in some cases (Bloomer et al. 2005). Liver transplantation is the only treatment available for patients who have reached the stage of decompensated liver cirrhosis (Anstey and Hift 2007). Approximately 60 cases of liver transplantation for EPP have been reported worldwide (McGuire et al. 2005; Wahlin et al. 2011), but most of these are deceased-donor liver transplantation cases, and only four cases of living-donor liver transplantation have been reported (Tanaka et al. 1994; Wahlin et al. 2011; Yamashita et al. 2020). Herein, we report a case in which living-donor liver transplantation was safely performed through sufficient simula-

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tion, preparation, and information sharing prior to surgery.

Case Presentation

The patient was a 52-year-old male who had led a normal life except for mild photosensitivity. From 37 years of age, the patient was diagnosed with hepatic dysfunction and follow-up observations were conducted. At 48-year-old, detailed examinations were conducted, and high erythrocyte protoporphyrin levels, skin biopsy, and genetic tests resulted in the diagnosis of EPP. Skin biopsy revealed Alcian-blue- positive mucus and genetic testing revealed a mutation in exon 8 of the FECH gene. The exon 8 mutation was c.892C>T (p.R298∗) / wild type and IVS3-48 was T/C. Both mutations have been reported to cause EPP. Light-shielding treatment was subsequently administered, however, his liver dysfunction rapidly worsened, and the patient developed decompensated liver cirrhosis. Table 1 shows the preoperative laboratory data. The Child-Pugh score was 10 (Grade C), and the Model for End-stage Liver Disease score was 14. The erythrocyte protoporphyrin levels were high. Computed tomography revealed liver cirrhosis, splenomegaly, ascites, and a prominent collateral circulation (Fig. 1).

Table 1. Preoperative laboratory data.

	Measured value	Reference value
White blood cell count, /μL	6,300	4,000-9,000
Hemoglobin, g/dL	7.3	12.0-16.0
Platelet count, $\times 10^4/\mu$L	3.8	15.0-35.0
Prothrombin time, %	34.4	> 70.1
Active partial thromboplastin time, sec	47.3	29.6-40.8
International normalized ratio	1.67	< 1.15
Total protein, g/dL	5.2	6.7-8.1
Albumin, g/dL	2.4	3.8-5.3
Total bilirubin, mg/dL	16.3	0.2-1.0
Aspartate aminotransferase, IU/L	52	8-38
Alanine transaminase, IU/L	39	4-43
Alkaline phosphatase, IU/L	241	115-359
γ-Glutamyl transpeptidase, IU/L	81	< 50
Blood urea nitrogen, mg/dL	7	8.0-20.0
Creatinine, mg/dL	0.42	0.32-0.84
Protoporphyrin, μg/dL RBC	4,693	30-86

To prepare for living-donor liver transplantation, the light sources in the operating room and intensive care unit were covered with a polyimide film (Kapton 200H, Du Pont-Toray Co., Ltd., Tokyo, Japan) to block the wavelength of 400-470 nm, which is harmful in EPP (Fig. 2). Additionally, EPP has restrictions regarding the drugs that can be used, and therefore, we collaborated with a pharmacist and confirmed the availability of frequently used drugs prior to surgery. Before surgery, we gave lectures on EPP treatment to the healthcare professionals in charge of the patient's treatment, and information was shared. Additionally, a traffic line simulation for patient transport, a manual for patient handling during the perioperative period, and outpatient consultation were formulated in advance to prevent phototoxicity to the greatest extent possible. The donor was his wife, a 48-year-old female with an ABO match. The graft was her right lobe which weighted 672 g, and the graft-to-recipient weight ratio was 0.98%. The recipient's superficial femoral vein was used to reconstruct a branch of the middle hepatic vein and prevent congestion of the transplanted liver. The operating time was 784 min, warm ischemia time was 48 min, cold ischemia time was 202 min, and blood loss was 5,513 mL. Although the operating time was long, there were no burns in the abdominal cavity or skin because of the effective light shielding. The explanted liver was dark brown and demonstrated cirrhosis (Fig. 3A). Light microscopy showed Kupffer cells with phagocytosed brownish deposits in the sinusoids (Fig. 3B) and fibrotic progression (Fig. 3C). Polarizing microscopy showed birefringent pigments that were protoporphyrin crystals (Fig. 3D). The immunosuppressants used included basiliximab, glucocorticoids, tacrolimus, and mycophenolate mofetil. The patient developed phrenic nerve palsy

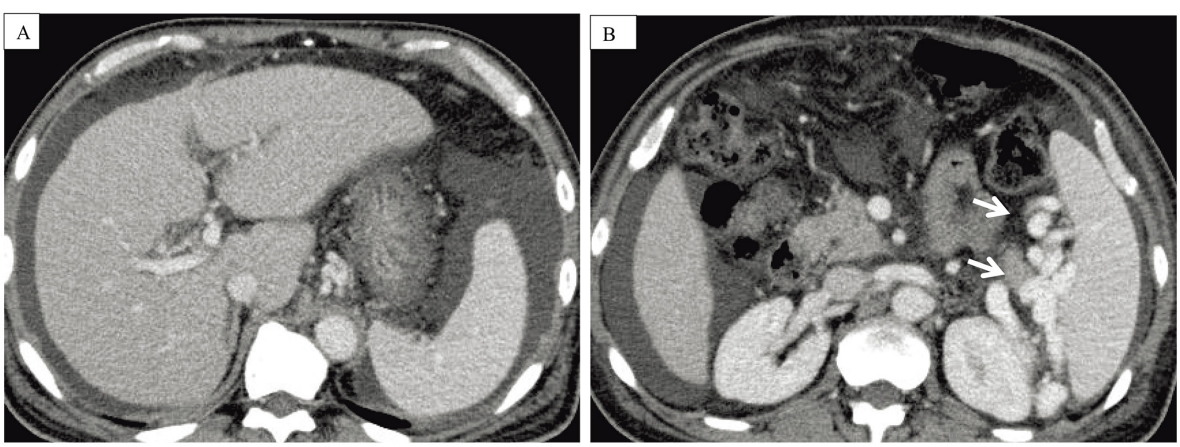

Fig. 1. Pre-transplant computed tomography images.
A. Image shows liver cirrhosis and ascites. B. Image shows splenomegaly and prominent collateral circulation (arrow).

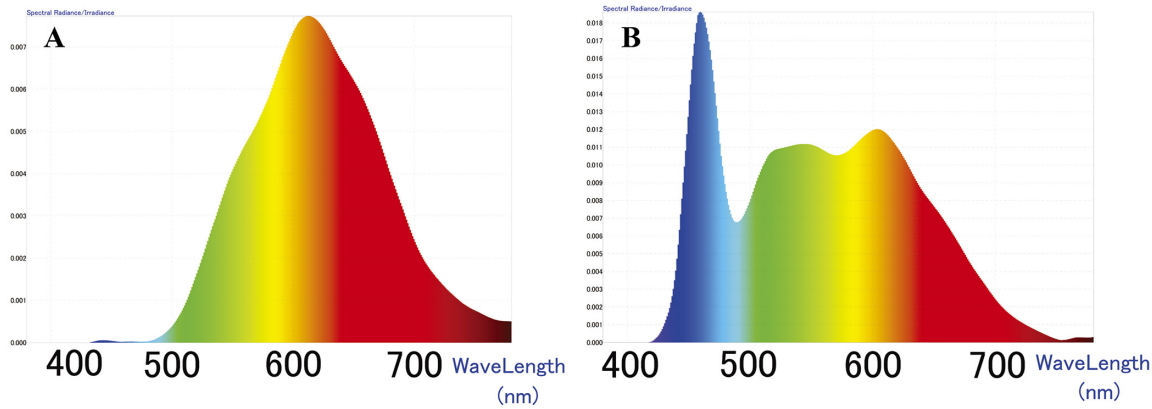

Fig. 2. Measurement of filter transmittance of the light in the operating room.
A. The light sources were covered with a polyimide film. B. The light sources were not covered with a polyimide film. The polyimide film blocked the light at a wavelength of 400-470 nm, which is harmful for erythropoietic protoporphyria (EPP).

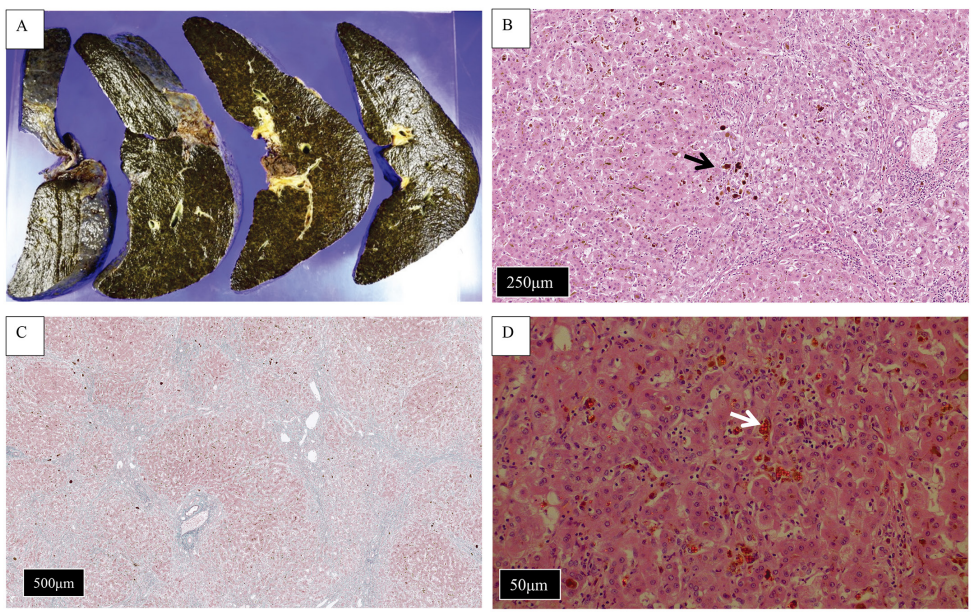

Fig. 3. Histopathological findings of the explanted liver.
A. Macroscopic findings of the explanted liver. The explanted liver was dark brown and demonstrated cirrhosis. B. Light microscopy showed Kupffer cells with phagocytosed brownish deposits in the sinusoids (black arrow). C. Light microscopy showed fibrotic progression. D. Polarizing microscopy showed birefringent pigments that were protoporphyrin crystals (white arrow).

postoperatively and required long-term mechanical ventilation, however, this condition improved spontaneously. The transplanted liver function remained favorable, and the patient was discharged from the hospital on the 46th postoperative day. No skin disorders or liver dysfunction caused by EPP were observed. The patient was alive 3 years after surgery with good liver function.

Discussion

Liver transplantation for EPP requires several important countermeasures. Firstly, measurements of the light source are required. Third-degree skin burns and intestinal perforations have been reported to occur during liver transplantations performed under normal lights (McGuire et al. 2005). Actually, the patient underwent laparoscopic cholecystectomy under normal lights before he was diagnosed EPP and that may have been one of the causes of worsening liver function. In the present surgery, all light sources were covered with a polyimide film to block light at a wavelength of < 470 nm. We applied the film to all light sources that emit light, such as operating lights, ceiling lights, monitor screens, headlights, and microsurgery lights used for arterial anastomoses. We confirmed in advance that the film effectively blocked the light. Similar measures were taken in the intensive care unit and general hospital ward, and no skin damage or liver dysfunction due to phototoxic-

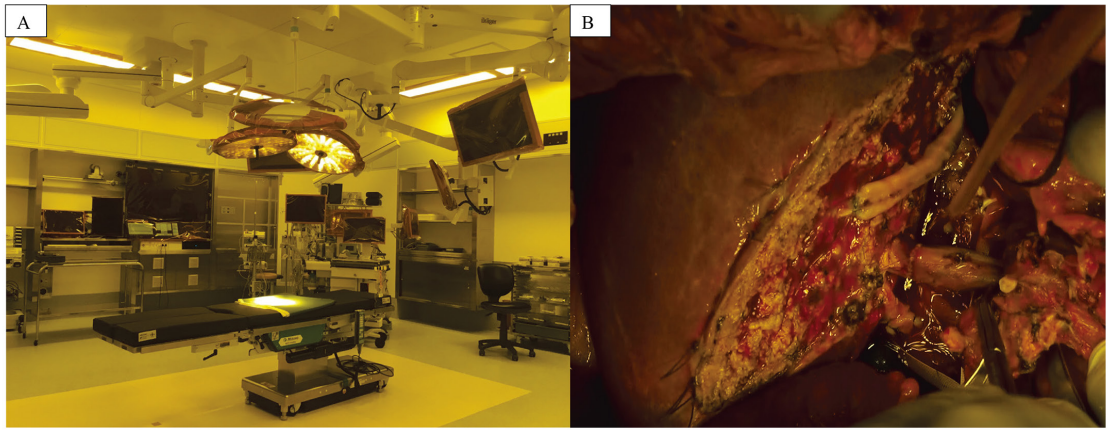

Fig. 4. Views during the surgery.
A. Panoramic view of the operating room. B. View of the surgical field. It was possible to identify tissues including blood vessels and bile ducts, and there was no significant adverse effect on the surgical technique.

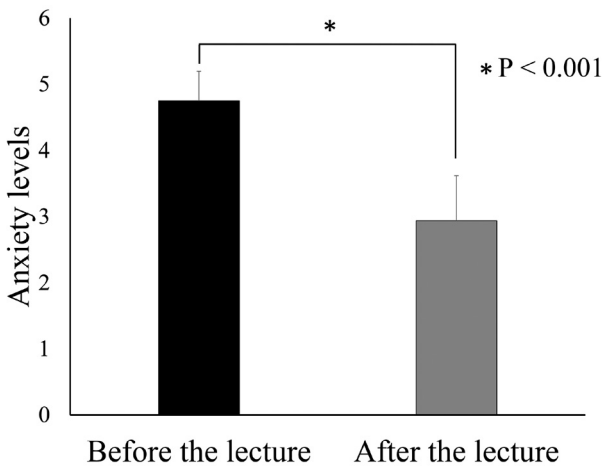

Fig. 5. The results of evaluating the anxiety levels before and after the lecture.
The anxiety level was significantly lower after the lecture on liver transplantation for erythropoietic protoporphyria (EPP). Data are shown as mean ± standard deviation (n = 16).

ity was observed throughout the perioperative period. Additionally, to block visible blue light, the light source was set to orange, and the appearance of the tissues differed from that of tissues during normal surgery. Although there was some unease due to unfamiliarity, it was possible to identify the individual tissues, including blood vessels and bile ducts, and there was no significant effect on the surgical technique (Fig. 4). We reduced phototoxicity to the greatest extent possible by formulating a traffic line for patient transport and a manual for outpatient visits in advance to ensure a favorable surgical course. Unfortunately, liver transplantation is not a definitive treatment for EPP. The definitive treatment for EPP is bone marrow transplantation. However, it is necessary to consider the indication for bone marrow transplantation carefully since bone marrow transplantation after liver transplantation is extremely invasive. As reported by Rand et al. (2006), bone marrow transplantation should be considered only when EPP-induced phototoxicity is severe, and damage to the transplanted liver is uncontrollable by other alternative therapies. Therefore, it is necessary to continue the light-shielding treatment as much as possible in order to preserve liver function after liver transplantation.

Several drugs exacerbate symptoms of porphyria (Sassa 2006). A list of drugs that could be used during the perioperative period was prepared. The Pharmacy Department determined the availability of drugs with reference to the Drug Database for Acute Porphyria (http://www.drugs-porphyria.org/) and the Drug Database of the American Porphyria Foundation (https://porphyriafoundation.org/drugdatabase/). Two drugs typically used for liver transplantation were determined to be of restricted use: spironolactone and sulfamethoxazole/trimethoprim. Therefore, we replaced these drugs with other diuretic drugs and atovaquone, respectively.

In the present case, a lecture on liver transplantation for EPP and a corresponding manual were prepared for nurses in advance to alleviate their anxiety. Fig. 5 shows the results of evaluating anxiety levels before and after the lecture using a five-point scale. The anxiety level before the lecture was 4.75 ± 0.44 (mean ± standard deviation, n = 16), and the anxiety level after the lecture was 2.94 ± 0.68, with a significant improvement after the lecture ($p < 0.001$). The usefulness of the lectures was rated as 4.56 ± 0.73 on a five-point scale. Nurses spend the longest time caring for patients, and in the case of rare diseases, it is important that information is shared through lectures and manuals, as in the present case.

Sixty-six cases of liver transplantation for EPP have been reported (Tanaka et al. 1994; McGuire et al. 2005; Wahlin et al. 2011; Hanaki et al. 2020; Yamashita et al. 2020; Endo et al. 2022; Shizuku et al. 2022), and almost all of them were reports of decreased-donor liver transplantation. Only four cases of living-donor liver transplantation have been reported (Tanaka et al. 1994; Wahlin et al. 2011;

Yamashita et al. 2020), and our report is the only one that describes the detailed perioperative management and prognosis. It has been reported that administration of hemin (Bloomer and Pierach 1982), plasmapheresis (Reichheld et al. 1999), red blood cell exchange (Reichheld et al. 1999), and ursodeoxycholic acid and cholestyramine (Anstey and Hift 2007) may suppress the effects of accumulated protoporphyrin. In our case, ursodeoxycholic acid was used to suppress the liver damage. Measures for light sources have been reported in many studies (Wahlin et al. 2008; Hanaki et al. 2020; Levoska et al. 2020; Yamashita et al. 2020), and a polyimide film (Kapton 200H, Du Pont-Toray Co., Ltd.) was able to effectively block harmful light sources in our case. EPP leads to respiratory muscle paralysis associated with neuropathy (Rank et al. 1993), and our patient required long-term artificial ventilation after surgery. The patient's condition improved with rehabilitation. When dealing with rare diseases such as EPP, it is important to share information among all staff involved in the treatment. In our case, we demonstrated the usefulness of pre-lectures. Living-donor liver transplantation poses problems not associated with deceased-donor liver transplantation, such as small for size (Ben-Haim et al. 2001; Soejima et al. 2003) and donor safety (Ringe and Strong 2008). In addition, since EPP is a hereditary disease, genetic testing of the donor is necessary when performing living-donor liver transplantation with a blood relative as the donor. However, living-donor liver transplantation can be planned as an elective procedure. In rare diseases such as EPP, which require careful preparations, living-donor liver transplantation could be a useful option because of the above-mentioned advantages.

In conclusion, living-donor liver transplantation for EPP can be safely performed with careful preoperative preparation.

Conflict of Interest

The authors declare no conflict of interest.

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