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The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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CASE REPORT

Successful treatment of severe hepatic impairment in erythropoietic protoporphyria: A case report and review of literature

Tao Zeng, Shu-Ru Chen, Hao-Qiang Liu, Yu-Tian Chong, Xin-Hua Li

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Abstract

BACKGROUND

Erythropoietic protoporphyria (EPP) is a rare genetic disorder stemming from ferrochelatase gene mutations, which leads to abnormal accumulation of protoporphyrin IX primarily in erythrocytes, skin, bone marrow and liver. Although porphyria-related severe liver damage is rare, its consequences can be severe with limited treatment options.

CASE SUMMARY

This case study highlights a successful intervention for a 35-year-old male with EPP-related liver impairment, employing a combination of red blood cell (RBC) exchange and therapeutic plasma exchange (TPE). The patient experienced significant symptom relief and a decrease in bilirubin levels following multiple PE sessions and an RBC exchange.

CONCLUSION

The findings suggest that this combined approach holds promise for managing severe hepatic impairment in EPP.

Key Words: Erythropoietic protoporphyria; Red blood cell exchange; Plasma exchange; Delta-aminolevulinic acid; Ferrochelatase; Case report

Core Tip: Erythropoietic protoporphyria (EPP) is a rare autosomal recessive disorder, with few reported cases of associated hepatic injury, posing significant diagnostic challenges. Conventional therapies frequently fall short in severe cases, leading to the necessity for liver transplantation. Here, we report the case of a 35-year-old patient with EPP experiencing progressive liver dysfunction, unresponsive to standard medical care. A novel intervention comprising combined red blood cell exchange and plasma exchange therapies was administered. This approach resulted in a marked improvement in the patient's liver function, highlighting a potentially effective alternative treatment for serious hepatic manifestations in EPP.

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INTRODUCTION

Porphyria comprises a cluster of metabolic disorders arising from deficiencies in specific enzymes within the heme biosynthesis pathway[1]. This deficiency leads to elevated concentrations of porphyrins or their precursors, such as delta-aminolevulinic acid (δ-ALA) and porphobilinogen, culminating in their abnormal accumulation within tissues and subsequent cellular damage[2]. Porphyria is a relatively rare genetic disorder, with prevalence ranging from 0.5 to 10 per 100000 in different populations[3,4]. High levels of porphyrins can cause significant problems, primarily affecting the nervous system and skin[5].

Based on the main site of porphyrin intermediate metabolite accumulation, porphyria can be divided into erythropoietic protoporphyria (EPP, OMIM 177000) and hepatic porphyria. EPP is a rare autosomal recessive genetic disorder caused by mutations in the ferrochelatase (*FECH*) gene[6]. FECH catalyzes the final step in the heme biosynthetic pathway by chelating ferrous iron with protoporphyrin IX (PPIX). *FECH* deficiency leads to the abnormal accumulation of PPIX, predominantly in erythrocytes, skin, bone marrow, and the liver[7]. EPP is the most common form of porphyria in pediatric patients, and has a prevalence ranging from 1:200000 to 1:75000[8]. The symptoms of EPP include the formation of non-blistering skin lesions within minutes of exposure to sunlight, which begins in early childhood and persists throughout the individual's lifetime, significantly reducing their quality of life[9].

Approximately 10% of EPP patients experience liver damage. Although severe liver damage in EPP is rare, the implications for patient health are, nevertheless, significant[10]. The clinical manifestations of liver damage in porphyrias are varied and can range from mild liver enzyme disturbances to severe acute cholestatic hepatitis with hepatic failure. Furthermore, owing to the rarity of this condition, it can easily be overlooked by clinicians. Currently, the treatment options for severe liver damage in porphyria are extremely limited, and patients often ultimately require liver transplantation. Here, we present a successful case of treatment of severe hepatic injury in EPP through a combination of red blood cell (RBC) exchange and therapeutic plasma exchange (TPE). The results suggest that the combined intervention involving RBC and plasma exchange is a promising strategy for treating severe hepatic complications in EPP.

CASE PRESENTATION

Chief complaints

A 35-year-old Chinese male patient with a 32-year history of photosensitivity dermatitis presented with severe abdominal pain, jaundice, and gastrointestinal symptoms, including nausea, vomiting, cessation of bowel movements, and cessation of flatus, at the Department of Infectious Diseases of our hospital on March 10, 2023.

History of present illness

The patient had been experiencing recurrent skin erythema, swelling, pain, and itching within minutes of sunlight exposure since childhood, that typically resolved spontaneously after 2 to 3 d. This had been ongoing for the last 32 years. Eight years prior to this admission, the patient had experienced recurrent symptoms including right upper abdominal pain, poor appetite, aversion to fatty foods, and fatigue. Seeking medical attention at local hospitals, the patient underwent routine gastrointestinal decompression, treatment with ursodeoxycholic acid (UDCA) and glycyrrhizin to promote bile excretion and protect hepatocytes, and high glucose-load therapy to inhibit δ-ALA synthase. Although these treatments resulted in the alleviation of the mentioned symptoms, the condition recurred. One month before this admission, the patient's aforementioned digestive symptoms gradually worsened, leading to the decision to seek inpatient treatment at our hospital.

History of past illness

The patient's medical history showed no significant past illnesses such as viral hepatitis or drug allergies.

Personal and family history

The patient denied any history of tobacco smoking, alcohol consumption, or illicit drug use, reported no remarkable family history of similar illnesses nor three-generation inheritance of genetic disorders or psychiatric illnesses. Genetic screening of the patient's siblings did not reveal any significant abnormalities.

Physical examination

The patient presented with conjunctival icterus and generalized jaundice. Mild tenderness was observed on palpation in the left subxiphoid region.

Laboratory examinations

Following admission, the patient's auxiliary examinations revealed elevated liver enzymes (aspartate aminotransferase: 91 U/L, alanine aminotransferase: 149 U/L) and increased bilirubin levels (total bilirubin: 141.8 mmol/L, direct bilirubin: 104.3 mmol/L). Additionally, vitamin D deficiency was identified (25-hydroxyvitamin D total: 2.47 ng/mL, 25-hydroxyvitamin D2: 1.22 ng/mL, 25-hydroxyvitamin D3: 1.25 ng/mL), although serum ferritin concentrations were found to be unremarkable (139.08 ng/mL).

Imaging examinations

Abdominal X-ray revealed multiple air-filled intestine loops and fecal material accumulation. Further examination through abdominal magnetic resonance imaging demonstrated liver inflammation, hepatic iron deposition, chronic cholecystitis, and splenomegaly. Liver cirrhosis was detected through abdominal ultrasonography.

Histopathological examination and genetic screening

Liver biopsy confirmed chronic inflammatory liver injury (G3S3) with brownish pigment deposition and birefringent particles, suggestive of porphyria (Figure 1A and B). Genetic testing identified mutations in the *FECH* gene (heterozygous p.C202Y and homozygous c.315-48T>C intronic mutations) (Figure 1C and D).

FINAL DIAGNOSIS

The final diagnosis for the presented case is erythropoietic porphyria with severe hepatic involvement and paralytic ileus.

TREATMENT

Upon admission, the patient received high-glucose-load therapy, cimetidine, and arginine heme to inhibit ALA synthase [2]. Simultaneously, cholestyramine and UDCA were administered to enhance bile excretion. However, following initial treatment, the patient's symptoms worsened, with an increase in bilirubin levels and deterioration of liver function. When conventional treatments prove ineffective, the challenge of exploring the next steps in treatment arises. After extensive literature review and considering the pathogenesis of EPP[11-13], our attention shifted towards RBC exchange and TPE. TPE was subsequently performed on multiple occasions (March 20, 22, 24, and 28, 2023), involving the replacement of 1800–2000 mL of fresh frozen plasma during each session. During the red cell exchange (RCE) procedure, where erythrocytes were subjected to ABO-RhD matching, approximately 6 units of RBCs were transfused on March 21, 2023. The detailed procedures for TPE and RCE are presented in Table 1.

OUTCOME AND FOLLOW-UP

The interventions led to a gradual decrease in bilirubin levels (from 273.8 μmol/L to 68.6 μmol/L) (Figure 2), accompanied by the return of anal exhaust, defecation, and relief from abdominal pain. With continued improvement, the patient was discharged from the hospital.

DISCUSSION

EPP is a rare genetic disorder and liver damage associated with porphyria is even more rare, often leading to clinical misdiagnosis and oversight. Currently, treatment options for EPP are limited and primarily encompass the following approaches: First, there is an emphasis on promoting bile secretion, wherein UDCA is administered to enhance the excretion of protoporphyrin in bile[14,15]. However, its efficacy in EPP remains controversial. Second, efforts are directed towards reducing the synthesis of protoporphyrin precursors. Hemoglobin, through feedback inhibition, can suppress the activity of ALA synthase, consequently decreasing the production of protoporphyrin[1,16]. Cimetidine has also been shown to inhibit ALA synthase, thus reducing the protoporphyrin load in patients with EPP, and may also possess antihistamine effects that ameliorate pruritus associated with the condition[17,18]. Disruption of the enterohepatic

Table 1 Procedure details of therapeutic plasma exchange and red cell exchange

Parameter	RCE	TPE
Blood type	A+, RhD+	A +, RhD+
Th name of the apheresis machine or blood cell separator	COM.TEC	JAFRON
Total blood volume measured by the equipment	4.1 L	NA
Blood volume processed	2270 mL	NA
Calcium dose	12 mL (10% Calcium Gluconate)	10 mL (10% Calcium Gluconate)
Red cell replacement	6 units (approx. 750 mL)	NA
Plasma volume targeted	NA	1800-2000 mL
Replacement fluid volume	NA	1800-2000 mL
Blood flow rate	30 mL/min	80-120 mL/min
Adverse reactions	None reported	None reported

NA: Not available (indicating missing or not applicable values); TPE: Therapeutic plasma exchange; RCE: Red cell exchange.

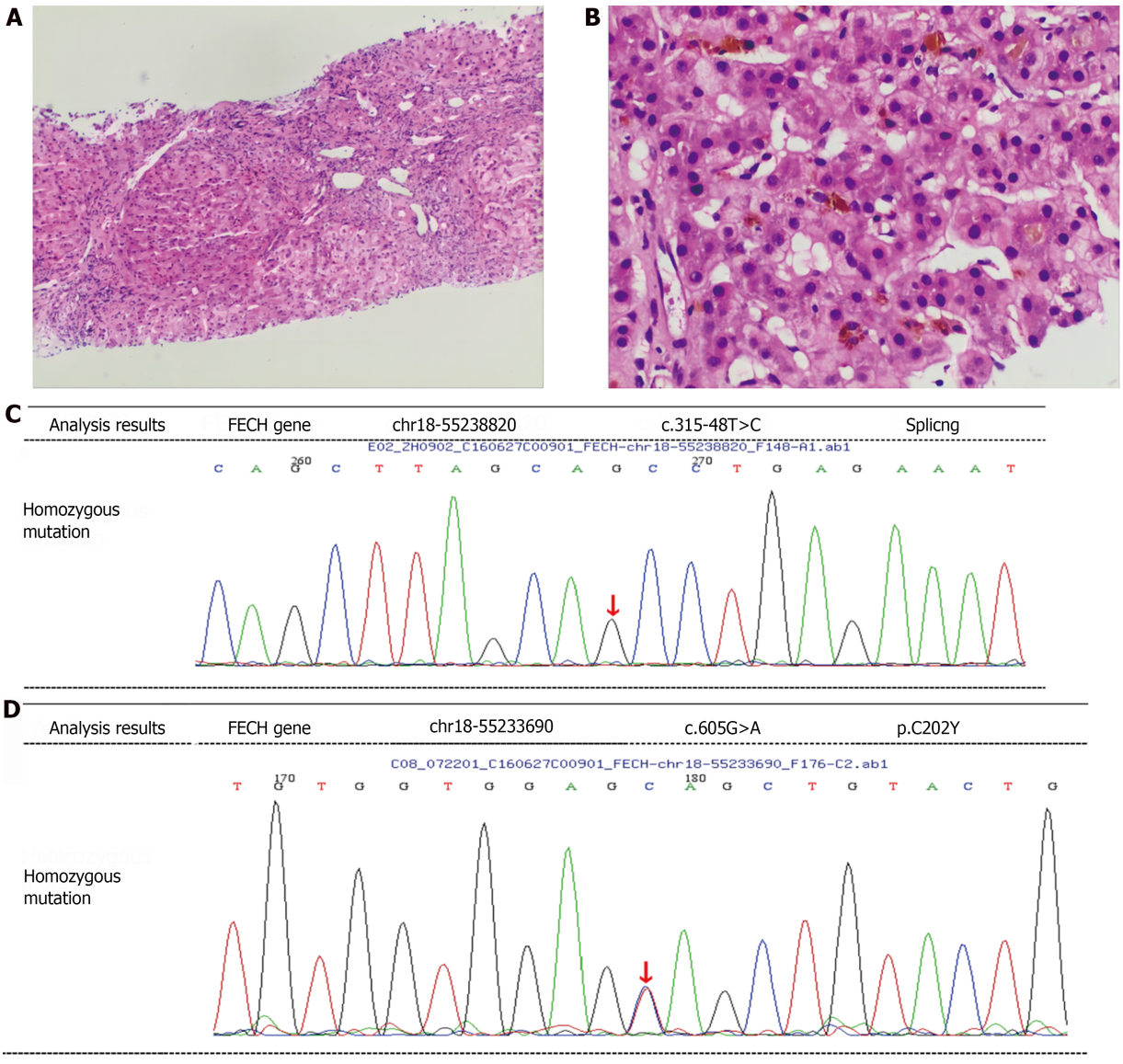

Figure 1 Hepatic pathology and genetic screening. A and B: Liver histopathology demonstrates brown-yellow granule deposits in hepatocytes, capillary

ducts, and Kupffer cells within the hepatic sinusoids. Enlarged portal area with increased lymphocyte and neutrophil infiltration, fibrous tissue hyperplasia, and hyperplasia of small bile ducts consistent with G3S3 chronic inflammatory liver injury; C and D: Genetic analysis reveals *ferrochelatase* gene mutations: homozygous intron c.315-48T>C mutation and heterozygous p.C202Y mutation. FECH: *Ferrochelatase*.

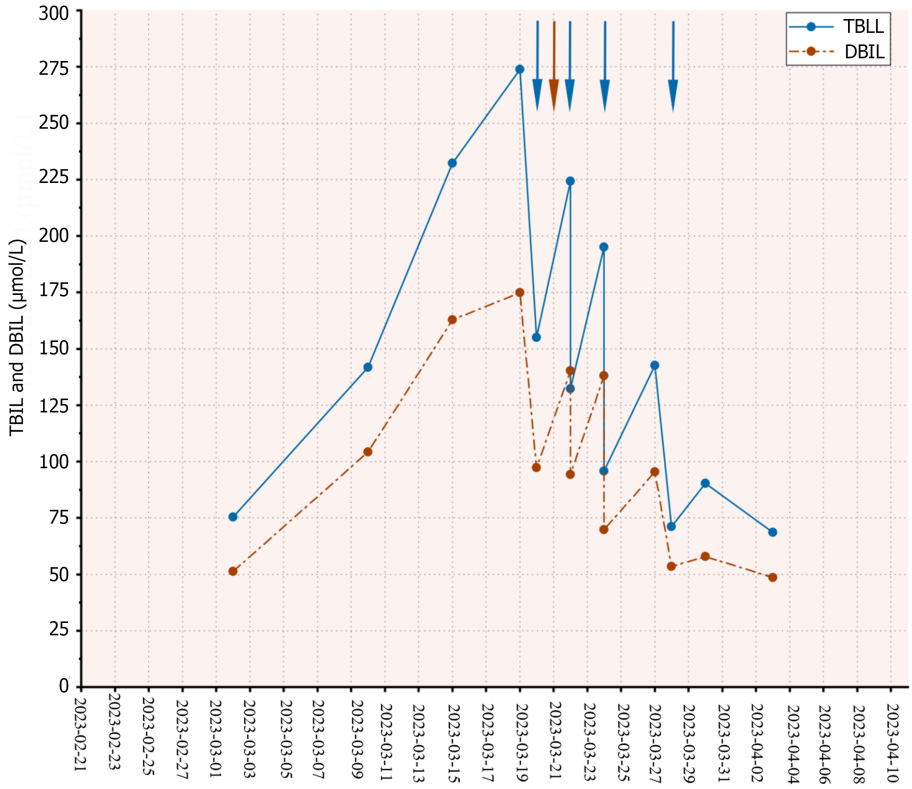

Figure 2 Dynamic changes in total bilirubin and direct bilirubin levels in the patient. Plasma exchange treatments were conducted on March 20, 22, 24, and 28, 2023 (involving the replacement of 1800-2000 mL of fresh frozen plasma during each session), and a red blood cell exchange treatment was performed on March 21, 2023 (approximately 6 units of red blood cells were transfused). Blue arrows represent plasma exchange procedures while brown arrow denotes red blood cell exchange treatments. TBIL: Total bilirubin; DBIL: Direct bilirubin.

circulation of protoporphyrin is achieved using agents such as cholestyramine and activated charcoal, which can bind to protoporphyrin, facilitating its elimination through feces[19-21]. Additionally, measures are taken to protect hepatocytes from toxic damage, using reducing agents such as β-carotene, cysteine, and vitamin C to clear reactive oxygen species[9,22,23]. Circulating protoporphyrin levels are lowered through techniques such as plasma exchange[24]. Nevertheless, it is crucial to note that the effectiveness of these measures in EPP has not been conclusively confirmed. Similarly, in this case, despite adequate conventional treatment, the patient's bilirubin levels continued to progressively rise and his liver function deteriorated.

Severe EPP-related liver damage can have significant consequences, often necessitating liver transplantation. However, post-transplantation relapse is possible because of the continuous release of the erythrocyte precursor protoporphyrin from the bone marrow[25]. Currently, on the options for effectively managing EPP-related liver damage are limited, posing a challenging clinical problem in the field of porphyria-associated liver diseases.

The exact cause of liver damage in EPP is not fully understood. It is believed that the deposition of protoporphyrin in the bile canaliculi and subsequent oxidative stress play a role[26]. Impaired bile excretion leads to further protoporphyrin accumulation, causing cholestatic liver disease, inflammation, fibrosis, and end-stage liver disease[27]. Cholestatic liver failure is a critical complication of EPP that can rapidly progress to a fatal condition called EPP hepatic crisis[28]. Intensive treatment, including TPE and RBC exchange, is necessary to rapidly reduce protoporphyrin levels and promote liver recovery. Given the concentration of free protoporphyrin in RBCs is approximately 10 times higher than in plasma [29], TPE alone may not be adequate. However, RBC exchange can increase circulating hemoglobin levels, triggering negative feedback inhibition of ALA synthase and avoiding iron overload. Therefore, the inclusion of RBC exchange becomes necessary.

However, the therapeutic efficacy of RBC in combination with TPE for conditions such as EPP-related liver disease is currently a subject of debate, primarily because of the paucity of robust clinical evidence. According to the American Society for Apheresis guidelines for TPE[30], the recommendation for employing TPE/RBC exchange in these conditions is modest (Category II, Grade 2C), reflecting reliance on lower-quality evidence or the presence of divergent opinions among experts. This cautious stance is further underscored by the existence of contradictory case reports—some suggest that this treatment modality may improve liver function, while others have not demonstrated a significant reduction in

protoporphyrin levels, thus casting doubt on its clinical benefit[11]. Notably, in this case, a regimen of four TPE sessions and one RBC exchange session was associated with a marked decrease in bilirubin levels and alleviation of clinical symptoms, without a significant rebound upon follow-up. These findings suggest that TPE/RBC exchange may hold therapeutic promise in the management of EPP.

CONCLUSION

In summary, treatment options and evidence-based medicine for EPP-related liver disease are currently very limited. RBC exchange combined with TPE holds potential for managing EPP-related liver damage. However, owing to the rarity of the disease, there is a continued need to gather clinical evidence in order to further validate its effectiveness.

FOOTNOTES

Author contributions: Zeng T contributed to writing the original draft, methodology, software development, and data curation; Chen SR was involved in methodology, data curation, and visualization; Liu HQ contributed to investigation and software development; Chong YT provided supervision and methodology; Li XH was responsible for conceptualization and supervision. All authors have read and approved the final manuscript.

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