Dig Dis Sci (2009) 54:411–415
DOI 10.1007/s10620-008-0610-6

CASE REPORT

Paralytic Ileus and Liver Failure—An Unusual Presentation of Advanced Erythropoietic Protoporphyria

Simone Negrini · Gabriele Zoppoli · Maurizio Setti · Maria Domenica Cappellini · Francesco Indiveri

Received: 31 August 2006 / Accepted: 4 June 2007 / Published online: 14 November 2008

Introduction

Erythropoietic protoporphyria (EPP) is an uncommon genetic disorder of heme metabolism caused by the deficiency of mitochondrial ferrochelatase, an enzyme that catalyzes the chelation of iron to protoporphyrin (PP) [1–3]. Skin involvement is the most typical feature of this disease. It is characterized by light-sensitive dermatitis (usually developing during childhood). Erosions on the face, healing with scars, or waxy thickening of the skin of the nose and knuckles may ensue [4–6].

Hepatic dysfunction is the most serious and potentially life-threatening complication of EPP, but only a small fraction of EPP patients develop liver abnormalities that seldom can lead to cirrhosis or liver failure [7–9]. Paralytic ileus, typical of other forms of porphyria, has rarely been reported in EPP patients, and is probably caused by protoporphyrin accumulation in autonomic nerves [4, 10–12].

Here we describe a patient with EPP associated with severe liver disease and paralytic ileus, in whom erithroplasma exchanges, hematin infusion, as well as administration of cholestyramine, charcoal, and ursodesoxicholic acid improved abdominal symptoms and liver function. We discuss the clinical course and outcome in the context of the literature.

S. Negrini (✉) · G. Zoppoli · M. Setti · F. Indiveri
Department of Internal Medicine, University of Genoa, V.le Benedetto XV, 6, 16132 Genoa, Italy
e-mail: negrini@unige.it

M. D. Cappellini
Department of Internal Medicine, Centro Anemie Congenite, Maggiore Policlinico Hospital IRCCS , University of Milan, Milan, Italy

Case Report

A 60-year-old man was admitted to our hospital on January 18, 2005, complaining of upper abdominal pain and jaundice of some days' duration.

On questioning him, the patient reported mild photosensitivity since he was 3 years old, characterized by skin swelling and erithema associated with itching and pruritus after sun exposure. These lesions used to remit spontaneously with no medications and without leaving any permanent modification of the skin. Although these episodes were sometimes accompanied by brown-red colored urine emission, they were interpreted as solar urticaria, so they were not further investigated. No other member of his family suffered from these symptoms. The patient reported that, in concomitance with routine examinations, a mild cholestathic parameters elevation (GGT, ALP, bilirubin) was observed; however it was not associated with any clinical manifestation and so additional studies were never performed. Apart from the above-mentioned information, his clinical history was unremarkable until December 2001, when he suddenly complained of upper abdominal colicky pain, nausea, and vomiting; on this occasion, ultrasonography showed small gallstones. These symptoms quickly disappeared spontaneously.

In the following 2 years, the patient referred three other abdominal pain episodes like the previous one. In March 2004, he experienced a more severe abdominal pain attack; for this reason, hospitalization was required and laparoscopic cholecistectomy was planned. During laparoscopic exploration the surgeon noticed an abnormal liver appearance (see Fig. 1), therefore an intraoperatory liver biopsy was performed. The histological section showed micro- and macrovescicular steatosis with no other pathologic

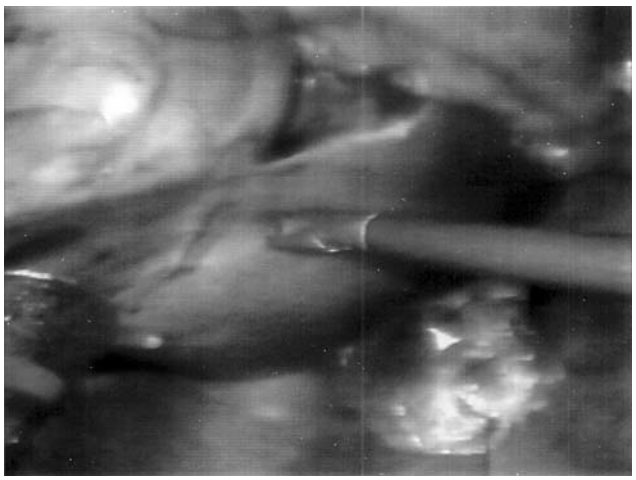

Fig. 1 Macroscopic findings of the liver with laparoscopy. The liver can be seen as enlarged and dark in color with an irregular surface

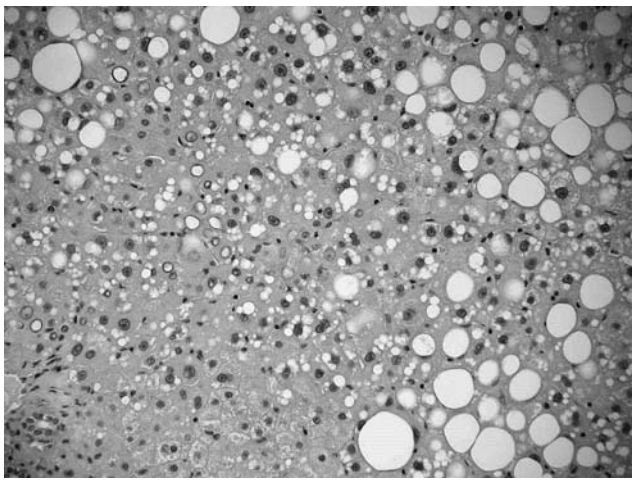

Fig. 2 Non-diagnostic liver histology with micro- and macrovescicular steathosis (Hematoxylin and Eosin staining)

features (see Fig. 2). The formulated diagnosis was NASH (non alcoholic steato-hepatitis) so the patient was dismissed with medical therapy (low-fat diet and statins) and not further investigated. One month before consulting our unit he was admitted to a local hospital for weakness, malaise, and jaundice. Cholangio-MR was performed and did not show any anomaly. Nevertheless, jaundice did not improve and an ERCP was planned. During the ERCP procedure cholangiography, biliary brushing, and papillectomy were done, but no abnormalities resulted from these tests. His hospital course was complicated by iatrogenic pancreatitis secondary to the ERCP. However, clinical and biochemical parameters rapidly normalized with no additional procedures; a residual pancreatic pseudocystis was documented with CT. No other symptoms disturbed the patient until some days before the admission to our unit.

Upon admission, physical examination revealed marked jaundice and a distended abdomen with moderate tenderness and no bowel sounds. The liver edge was palpable 4 cm below the right costal margin at the midclavicular line, with an indistinct margin and firm consistency, whereas the spleen was palpable only during deep inspiration. Mild ascites and lower extremities edema were present. Heart and lung examinations were inapparent; pulse rate was regular and elevated, up to 120 bpm. Body temperature was normal with no difference between rectal and axillary values. No other pathologic signs were observed.

The patient's laboratory test results are shown in Table 1. ANA, AMA, ASMA, and hepatitis B and C serology were all negative, and his serum amylase level was within normal limits.

Findings on abdominal X-ray were consistent with paralytic ileus. Ultrasonography (US) revealed hepatosplenomegaly, a pseudocystis in the pancreas tail, a small amount of free fluid in the Morrison pouch and around the liver, but biliary stones or bile duct dilatation were absent. An abdominal computed tomography (CT) scan and cholangio-MR confirmed the US findings. Color Doppler US showed moderate portal hypertension and portal vein dilatation.

Upper gastroduodenal endoscopy detected esophageal veins dilatation and gastric congestion.

On this occasion, hepatic biopsy was avoided because of the initial clinical suspect of cholangitis.

The clinical picture and the patient's history raised the possibility that he could be affected by a heme synthesis disorder. Therefore we analyzed urine and blood porphyrins pattern, we looked for the presence of autofluorescent erythrocytes (fluorocytes), and a fluorimetric plasma assay was performed. Wood's light examinations of the skin, serum and urine did not demonstrate any fluorescence. The obtained data (as summarized in Table 1) were compatible with EPP, and the diagnosis was finally confirmed by molecular studies with ferrochelatase (FECH) gene analysis.

Clinical, laboratory, and imaging findings suggested primitive paralytic ileus and liver failure in a patient affected by EPP.

The patient was kept at rest and treated with intravenous hyperalimentation without allowing oral food intake.

Antibiotic therapy (ciprofloxacin 500 mg/bid) was administered for the initial suspect of acute cholangitis.

Loop diuretics (furosemide 20 mg ev), aldosterone antagonists (canrenoate 100 mg bid) and albumin i.v. (50 ml 20% bid) were given for liver dysfunction, along with cholestyramine (4 gr tid), activated charcoal (400 mg tid) and ursodesoxicholic acid (300 mg qid).

During this period, four erithroplasma exchanges were performed. For this procedure 2,500 ml of plasma were

Table 1 Initial laboratory investigation and porphyrin study

Peripheral blood	
WBC	8990/μl
RBC	4.4×10^6/μl
Ht	39.3%
Hb	12.1 g/dl
Plt	197×10^3/μl
Coagulation test	
INR	1.20
APTT	43 s
Fibrinogen	585 mg/dl
XDP	391 ng/ml
Chemistry	
TP	5.3 g/dl
ALB	3.1 g/dl
T-Bil	24 mg/dl
D-Bil	19 mg/dl
GOT	387 IU/l
GPT	346 IU/l
LDH	210 IU/l
Ch-E	1,799 IU/l
ALP	419 IU/l
γ-GTP	985 IU/l
NH_3	52 μg/dl
BUN	20 mg/dl
Cre	0.9 mg/dl
T-Chol	379 mg/dl
AMY	121 mg/dl
Na	135 mEq/l
K	6.2 mEq/l
Cl	105 mEq/l
Urinary porphyrins	
Uroporphyrins	116 μg/24 h
Heptaporphyrins	68 μg/24 h
Hexaporphyrins	6 μg/24 h
Pentaporphyrins	8 μg/24 h
Coproporphyrins I	82 μg/24 h
Coproporphyrins III	47 μg/24 h
Plasma fluorymetric essay (635 nm): positive	
Erythrocytic fluorymetric essay (625 nm): positive	
Fluorescent erythrocyte percentage: 99.68%	

exchanged with 2,500 ml 6% albumin solution together with the exchange of three units of RBC. In addition, to maintain an Hct level greater than 35%, two RBCs units were transfused two different times (see Fig. 3).

After 10 days, abdominal pain subsided and bowel sounds were audible.

The patient's liver function tests (see Fig. 3) markedly improved as well as his clinical condition, so he was discharged from the hospital on day 42. He was then referred for OLT evaluation. He was doing well 5 weeks later when we saw him at our day hospital for the last time.

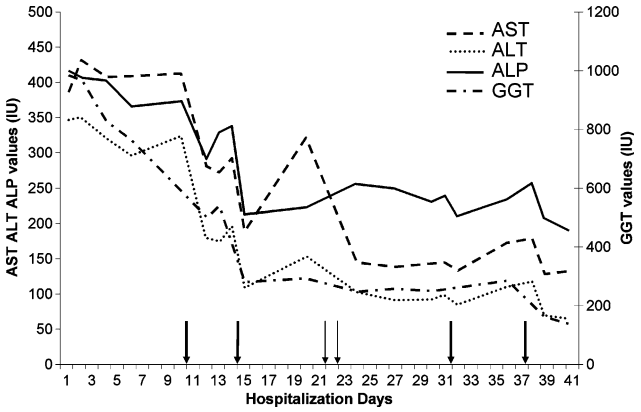

Fig. 3 Clinical course of the patient, laboratory data, and therapy (*thick arrows* represent erithroplasma exchange, *thin arrows* stand for RBC transfusions)

Discussion

We had a patient whose clinical history, evaluation of urinary porphyrin levels, and fluorimetric assay on plasma and erythrocytes led to a diagnosis of erythropoietic protoporphyria (EPP) [1, 13–15]. EPP is a rare genetic disorder of heme metabolism caused by a deficiency of FECH, which catalyzes the last step of heme synthesis [16–19]. This defect leads to accumulation of protoporphyrin IX in erythrocytes, plasma, skin, and liver [3, 5].

In this disease, hepatic dysfunction is a critical outcome determinant [7, 9, 20, 21]. Although hepatic dysfunction is detectable early in the course of EPP, these abnormalities seldom progress, and development of clinically evident liver dysfunction is rare. Up to 35% of patients with EPP have mildly abnormal biochemical tests of liver function, with approximately 15% developing cirrhosis and about 3% dying of hepatic insufficiency [7, 9].

In our patient. FECH gene molecular analysis was performed [13]. A base-pair insertion (ins T^{213}) in the exon 3 of FECH gene and co-inheritance of a low-expression allele were observed [18, 22]. The low-expression allele is the C variant of a single nucleotide polymorphism (SNP; IVS3–48 C/T) in intron 3 of the FECH gene, quite common in general population. Over 70 mutations in the FECH gene have been identified in EPP families (Human Gene Mutation Database: http://www.hgmd.org/). Many individuals who are heterozygous for these mutations are asymptomatic, despite having halfnormal FECH activities [2, 18, 22–24]. For protoporphyrin to accumulate sufficiently to cause photosensitivity, reduction of FECH activity below a critical threshold of about 35% of normal is required [22, 25].

In most patients, this additional reduction results from inheritance of a low-expression FECH allele trans to a severe mutation [9, 16, 26]. It's worth noting that no other member of our patient's family suffered from photosensitivity, but genetic analysis performed on his two brothers revealed the presence of the low-expression allele (SNP; IVS3–48 C/T) with no other mutation.

On the contrary, the causes of liver disease in people affected by EPP are still incompletely explained. Liver dysfunction seems to be associated with very low levels of FECH activity but not with specific FECH gene mutation [9, 16, 26]. However, a significant genotype-phenotype correlation between "null allele" mutations and protoporphyrin related liver disease has been found [22, 24]. Also recessive inheritance seems to carry a higher risk of liver disease [26] as well as other genetic and acquired factors, such as alcohol abuse or chronic HCV infection [9, 16, 20, 21]. In a recent report, male gender, anemia, total erythrocyte protoporphyrin, and low serum ferritin are all independently significantly associated with abnormal liver function [27]. The first three factors were all present in our patient's case.

Noticeably the skin symptoms he referred had always been mild and moreover chronic changes, like scarring, anomalous pigmentation, or thickening of the skin, commonly described in EPP, had never developed; this could explain why diagnosis was delayed for so many years. As liver function markedly declined, photosensitivity became invalidating due to protoporphyrin accumulation, to the point that before admission the patient reported a severe sunburn even after a mild sun exposure, previously tolerated with no particular consequences [12, 28–30].

Various mechanisms were considered in the differential diagnosis of abdominal pain and paralytic ileus.

The first was choledocholithiasis, which is a well-known complication of EPP [7, 25, 31, 32]. However, in our patient, the gallbladder had been previously removed. In addition, extrahepatic bile duct appeared normal on various imaging modalities, further negating the causal role of biliary stones for the episode.

Another cause of abdominal pain could have been acute pancreatitis, which has been advocated in at least one case report as cause of abdominal pain and ileus in end stage EPP and in other forms of porphyria [6, 21]. We excluded the diagnosis of pancreatitis, because no well-known risk factors such as the presence of bile duct gallstones, alcohol, or drug abuse were present. Moreover in our patient, the serum amylase and lipase were not increased, whereas AST, ALT, ALP, GGT, and bilirubin were dramatically elevated.

Also acute cholangitis could have explained the clinical situation we observed, but once again it was ruled out for the absence of fever, the lack of benefit of antibiotic therapy and the normal bile duct appearance on different imaging techniques.

A more likely possibility that could have justified the acute abdomen and the pain symptoms is an autonomic neurological syndrome, that closely resembles the one seen in acute porphyria. This condition has been observed by various authors in EPP patients with advanced liver failure [4, 9–12, 29, 33].

When hepatocellular damage progresses to a critical stage, PP accumulation is markedly accelerated, since biliary excretion is impaired. Under these conditions, plasma PP itself may act as a neurotoxin, because of its lipophilic nature [9, 25, 31, 33].

The absence of any other evident cause of paralytic ileus and the gradual improvement from the patient's acute symptoms was concomitant with the EPP therapy, strongly suggesting that porphyric neurotoxicity was the main cause of the acute abdomen observed in this patient.

Unfortunately, we did not perform tests to clarify the role of autonomic neuropathy (such as histological examination of peripheral nerves or electrophysiologic studies) because of the initially severe conditions of the patient and the fast symptomatic answer to the therapeutic strategies we applied.

Cholestyramine and activated charcoal were administered as biliary adsorbents in order to interrupt the enterohepatic circulation of protoporphyrin. Ursodesoxicholic acid was given to promote biliary fluid excretion [1, 4–6, 30].

Erithroplasma exchange was performed to suppress erythropoiesis and to facilitate the elimination of toxic protoporphyrins. This procedure has recently been reported to be more effective than plasmapheresis plus i.v. hematin or plasmapheresis alone for the treatment of EPP [34–36].

RBC transfusions were adopted to avoid severe anemia, which can increase heme synthesis by a positive feedback mechanism and thereby enhance the production of harmful protoporphyrins [25, 36–38]. Intravenous hematin therapy, usually used for acute porphyria attacks, was administered to suppress protoporphyrin production [34–36, 38].

The therapies applied in this patient rapidly ameliorated his abdominal symptoms and markedly improved his liver function with different mechanisms. The dramatic response observed is probably due to the simultaneous effect of the drugs both on porphyrins elimination and porphyrins synthesis inhibition. Obviously, along with the specific therapy aimed to lower the porphyrins levels also support therapy was administered in order to manage the complications of the severe liver failure. Nevertheless, in EPP patients with hepatic complications, once jaundice develops, there is nearly always a rapid decline in liver function [7, 9, 20, 21] and truly effective agents for the treatment of EPP are unavailable at present. Therefore OLT should be considered the only life-saving treatment, although even this approach is not curative and disease may recur in the graft [9, 20, 39, 40].

References

1. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med*. 2005;142:439–450.
2. Gouya L, Puy H, Robreau AM, et al. The penetrance of dominant erythropoietic protoporphyria is modulated by expression of wildtype FECH. *Nat Genet*. 2002;30:27–28.
3. Peters TJ, Sarkany R. Porphyria for the general physician. *Clin Med*. 2005;5:275–281.
4. Murphy GM. Diagnosis and management of the erythropoietic porphyrias. *Dermatol Ther*. 2003;16:57–64.
5. Sarkany RP. Erythropoietic protoporphyria (EPP) at 40. Where are we now? *Photodermatol Photoimmunol Photomed*. 2002; 18:147–152.
6. Thunell S, Harper P, Brun A. Porphyrins, porphyrin metabolism and porphyrias. IV. Pathophysiology of erythyropoietic protoporphyria–diagnosis, care and monitoring of the patient. *Scand J Clin Lab Invest*. 2000;60:581–604.
7. Doss MO, Frank M. Hepatobiliary implications and complications in protoporphyria, a 20-year study. *Clin Biochem*. 1989; 22:223–229.
8. Gross U, Frank M, Doss MO. Hepatic complications of erythropoietic protoporphyria. *Photodermatol Photoimmunol Photomed*. 1998;14:52–57.
9. Meerman L. Erythropoietic protoporphyria. An overview with emphasis on the liver. *Scand J Gastroenterol Suppl*. 2000; 232:79–85.
10. Herbert A, Corbin D, Williams A, Thompson D, Buckels J, Elias E. Erythropoietic protoporphyria: unusual skin and neurological problems after liver transplantation. *Gastroenterology*. 1991; 100:1753–1757.
11. Lock G, Holstege A, Mueller AR, et al. Liver failure in erythropoietic protoporphyria associated with choledocholithiasis and severe post-transplantation polyneuropathy. *Liver*. 1996;16:211–217.
12. Rank JM, Carithers R, Bloomer J. Evidence for neurological dysfunction in end-stage protoporphyric liver disease. *Hepatology*. 1993;18:1404–1409.
13. Martinez di Montemuros F, Di Pierro E, Patti E, et al. Molecular characterization of porphyrias in Italy: a diagnostic flow-chart. *Cell Mol Biol (Noisy-le-grand)*. 2002;48:867–876.
14. Mathews-Roth MM, Wise RJ, Miller BA. Burst-forming units-erythroid from erythropoietic protoporphyria patients fluoresce under 405 nm light. *Blood*. 1996;87:4480–4481.
15. Todd DJ, Nesbitt GS, Lavery TD, Trimble ER, Burrows D. Erythropoietic protoporphyria. The problem of a suitable screening test. *Acta Derm Venereol*. 1990;70:347–350.
16. Chen FP, Risheg H, Liu Y, Bloomer J. Ferrochelatase gene mutations in erythropoietic protoporphyria: focus on liver disease. *Cell Mol Biol (Noisy-le-grand)*. 2002;48:83–89.
17. Dailey HA, Sellers VM, Dailey TA. Mammalian ferrochelatase. Expression and characterization of normal and two human protoporphyric ferrochelatases. *J Biol Chem*. 1994;269:390–395.
18. Rufenacht UB, Gouya L, Schneider-Yin X, et al. Systematic analysis of molecular defects in the ferrochelatase gene from patients with erythropoietic protoporphyria. *Am J Hum Genet*. 1998;62:1341–1352.
19. Sellers VM, Wu CK, Dailey TA, Dailey HA. Human ferrochelatase: characterization of substrate-iron binding and proton-abstracting residues. *Biochemistry*. 2001;40:9821–9827.
20. Ishibashi A, Ogata R, Sakisaka S, et al. Erythropoietic protoporphyria with fatal liver failure. *J Gastroenterol*. 1999;34:405–409.
21. Komatsu K, Shimosegawa T, Uchi M, Maruhama Y, Toyota T. Erythropoietic protoporphyria with severe liver dysfunction and acute pancreatitis. *J Gastroenterol*. 2000;35:391–395.
22. Gouya L, Martin-Schmitt C, Robreau AM, et al. Contribution of a common single-nucleotide polymorphism to the genetic predisposition for erythropoietic protoporphyria. *Am J Hum Genet*. 2006;78:2–14.
23. Gouya L, Puy H, Lamoril J, et al. Inheritance in erythropoietic protoporphyria: a common wild-type ferrochelatase allelic variant with low-expression accounts for clinical manifestation. *Blood*. 1999;93:2105–2110.
24. Gouya L, Puy H, Robreau AM, et al. Modulation of penetrance by the wild-type allele in dominantly inherited erythropoietic protoporphyria and acute hepatic porphyrias. *Hum Genet*. 2004;114:256–262.
25. Bloomer JR. Hepatic protoporphyrin metabolism in patients with advanced protoporphyric liver disease. *Yale J Biol Med*. 1997;70:323–330.
26. Whatley SD, Mason NG, Khan M, et al. Autosomal recessive erythropoietic protoporphyria in the United Kingdom: prevalence and relationship to liver disease. *J Med Genet*. 2004;41:e105.
27. Holme AS, Anstey AV, Badminton MN, Hood K, Elder GH. Risk factors for developing liver disease in EPP. In: *14th Congress of European Academy of Dermatology and Venereology*. London; 2005.
28. Nordmann Y. Erythropoietic protoporphyria and hepatic complications. *J Hepatol*. 1992;16:4–6.
29. Shehade SA, Chalmers RJ, Prescott RJ. Predictable and unpredictable hazards of erythropoietic protoporphyria. *Clin Exp Dermatol*. 1991;16:185–187.
30. Todd DJ. Erythropoietic protoporphyria. *Br J Dermatol*. 1994; 131:751–766.
31. Bloomer JR. The liver in protoporphyria. *Hepatology*. 1988;8:402–407.
32. Rademakers LH, Cleton MI, Kooijman C, Baart de la Faille H, van Hattum J. Early involvement of hepatic parenchymal cells in erythrohepatic protoporphyria? An ultrastructural study of patients with and without overt liver disease and the effect of chenodeoxycholic acid treatment. *Hepatology*. 1990;11:449–457.
33. Muley SA, Midani HA, Rank JM, Carithers R, Parry GJ. Neuropathy in erythropoietic protoporphyrias. *Neurology*. 1998;51:262–265.
34. Dellon ES, Szczepiorkowski ZM, Dzik WH, et al. Treatment of recurrent allograft dysfunction with intravenous hematin after liver transplantation for erythropoietic protoporphyria. *Transplantation*. 2002;73:911–915.
35. Do KD, Banner BF, Katz E, Szymanski IO, Bonkovsky HL. Benefits of chronic plasmapheresis and intravenous heme-albumin in erythropoietic protoporphyria after orthotopic liver transplantation. *Transplantation*. 2002;73:469–472.
36. Eichbaum QG, Dzik WH, Chung RT, Szczepiorkowski ZM. Red blood cell exchange transfusion in two patients with advanced erythropoietic protoporphyria. *Transfusion*. 2005;45:208–213.
37. Todd DJ. Therapeutic options for erythropoietic protoporphyria. *Br J Dermatol*. 2000;142:826–827.
38. Reichheld JH, Katz E, Banner BF, Szymanski IO, Saltzman JR, Bonkovsky HL. The value of intravenous heme-albumin and plasmapheresis in reducing postoperative complications of orthotopic liver transplantation for erythropoietic protoporphyria. *Transplantation*. 1999;67:922–928.
39. Leone N, Marzano A, Cerutti E, et al. Liver transplantation for erythropoietic protoporphyria: report of a case with medium-term follow-up. *Dig Liver Dis*. 2000;32:799–802.
40. McGuire BM, Bonkovsky HL, Carithers RL Jr, et al. Liver transplantation for erythropoietic protoporphyria liver disease. *Liver Transpl*. 2005;11:1590–1596.