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Acute on chronic liver failure in erythropoietic protoporphyria: A case report and review of literature

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Abstract

Erythropoietic protoporphyria (EPP) is a disease caused by an inborn error of heme biosynthesis. It manifests as painful photosensitivity in childhood. Liver disease occurs due to the deposition of protoporphyrin. Cholestasis due to protoporphyrin leads to a vicious cycle of worsening, which can lead to liver failure. A 29-year-old woman presented with a three-month history of intermittent low-grade fever and a one-month history of jaundice. She had a history of painful blisters over the skin in childhood that started at two years of age and progressed to multiple contractures from healed ulcers by five years of age. She also had splenomegaly on examination. Her blood tests showed pancytopenia, hyperbilirubinemia, and elevated liver enzymes. Tropical fever workup was negative. Autoimmune hepatitis was considered, as antinuclear antibodies (ANA) were positive with elevated immunoglobulin G (IgG). Skin biopsy showed features suggestive of lipoid proteinosis. However, on review with Periodic Acid-Schiff-diastase (PAS-D) staining, a close mimic, EPP was considered a possibility. Liver biopsy showed features of EPP with infiltration with refractile brown pigment showing bright-red birefringence on polarizing microscopy. Next-generation sequencing (NGS) confirmed EPP with a ferrochelatase enzyme coding gene mutation. The patient developed pneumonia during hospitalization and developed acute on chronic liver failure (ACLF) grade 3a, as defined by the European Association for the Study of the Liver (EASL), with ascites and encephalopathy. She was treated with photoprotective measures, ursodeoxycholic acid, antibiotics, and supportive care. The family was counseled regarding options for sequential hepatic and bone marrow transplants. She was managed with the best supportive care.

Keywords: Acute-on-chronic liver failure; erythropoietic; protoporphyria.

Introduction

Erythropoietic protoporphyria (EPP) (Online Mendelian Inheritance in Man [OMIM], 177000) is a disorder recognized first in 1961, caused by an inborn error of heme biosynthesis due to mutations in the gene encoding the mitochondrial enzyme ferrochelatase (FECH). The clinical presentation of EPP is variable, with a common manifestation of early childhood painful photosensitivity.[1] Liver disease develops in EPP in 1–4% of cases. The clinical spectrum of liver involvement includes mild elevations in liver enzymes, progressive fibrosis, cirrhosis, and, rarely, acute liver failure. Portal hypertension is a common feature of advanced disease. Early recognition of liver involvement is critical, as progression can be rapid and potentially fatal without timely intervention.[2]

Case Report

A 29-year-old lady from India, born to a non-consanguineous marriage, presented with a history of fever for three months and jaundice for one month. There was a history of developing vesicles on the body in childhood, predominantly on sun exposure. Lesions began at two years, initially on the face and scalp, and gradually progressed to involve all the photo-exposed areas. They ruptured spontaneously to form erosions and ulcers. They were associated with pain and a burning sensation and later healed with scarring. By five years of age, she also developed multiple contractures from the healed ulcers but did not develop any new lesions after that. Despite these photosensitivity symptoms since childhood, she had never received a diagnosis for her condition prior to the current admission. She was married with two children, and there was no similar illness in her family. On general examination, there was pallor and icterus. Cutaneous examination revealed generalized atrophic vermicular scarring on the face. Perioral furrowing, a restricted mouth opening, and tongue protrusion were present. Atrophic scars were noted on the dorsa of the hands and legs. There was fibrotic scarring with contractures of the left ring and little fingers, while linear contracted scars were seen on the legs, extending from the right great toe to the knee with areas of depigmentation and crusting (Fig. 1). Hyperkeratotic papules coalescing to form plaques were also noted on the dorsa of the fingers. She had moderate splenomegaly on palpation. The differentials considered were tropical diseases (malaria, Brucella, Leishmaniasis), infective endocarditis, tuberculosis, and lymphoma. Causes of portal hypertension were considered, including pre-hepatic (vascular thrombosis), hepatic (advanced liver disease of various etiologies), and post-hepatic (Budd-Chiari disease) mechanisms. The possibility of lipoid proteinosis, erythropoietic protoporphyria, dystrophic epidermolysis bullosa, and Kindler's syndrome were considered for skin disease.

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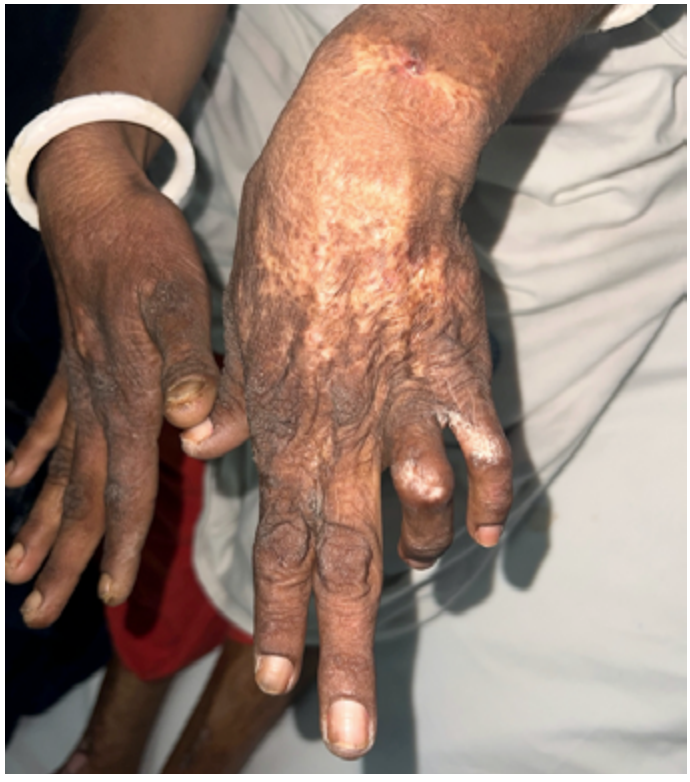

Figure 1. Atrophic scars over dorsum of left hand, hyperkeratotic papules and plaques on the dorsal aspect of fingers with fibrotic scarring and contractures of left ring & little fingers.

On investigation, she had pancytopenia (hemoglobin: 8.8 grams per deciliter (g/dL) [normal range: 11–15 g/dL for women]; leucocyte counts of 2.1×10^9/L [normal range: $4.0–12.0\times10^9$/L]; and platelet counts of 119×10^9/L [normal range: $150–450\times10^9$/L]). Peripheral smear showed a normocytic normochromic picture. She was evaluated with a rapid diagnostic test for visceral leishmaniasis rK39 (antibody detection against recombinant K39), immunoglobulin M (IgM) for Brucella, enzyme-linked immunosorbent assay (ELISA) for IgM Leptospirosis, and TPHA (Treponema pallidum hemagglutination assay) for syphilis, which were negative. Echocardiogram ruled out infective endocarditis. She had hyperbilirubinemia (total bilirubin: 3.28 milligrams per deciliter (mg/dL) [normal range: <1.2 mg/dL]; direct bilirubin: 2.49 mg/dL) with elevated liver enzymes (aspartate aminotransferase: 202 international units per liter (IU/L) [normal range: <40 IU/L]; alanine aminotransferase: 61 IU/L [normal range: <41 IU/L]; alkaline phosphatase: 151 IU/L [normal range: 40–125 IU/L]) and prolonged prothrombin time with an international normalized ratio (INR) of 1.4 (normal range: <1.2). Antinuclear antibodies (ANA) were positive, 1+ at 1:80 dilution, and immunoglobulin G was 3724 mg/dL (normal range: 700–1600 mg/dL). Viral markers (hepatitis B surface antigen and anti-hepatitis C) and autoimmune markers (anti-smooth muscle antibody, anti-liver kidney microsome type 1, antimitochondrial antibody, and anti-soluble liver antigen antibody) were negative. Serum ceruloplasmin was 574 U/L (normal range: 200–1100 U/L). Ultrasound of the liver showed mild coarse echotexture with normal size; the portal vein was normal, and the spleen was enlarged and measured 17.5 cm in the largest dimension. Noninvasive liver stiffness measurement with Acoustic Radiation Force Impulse (ARFI) was in the cirrhotic range (4.6 meters/second (m/s)).

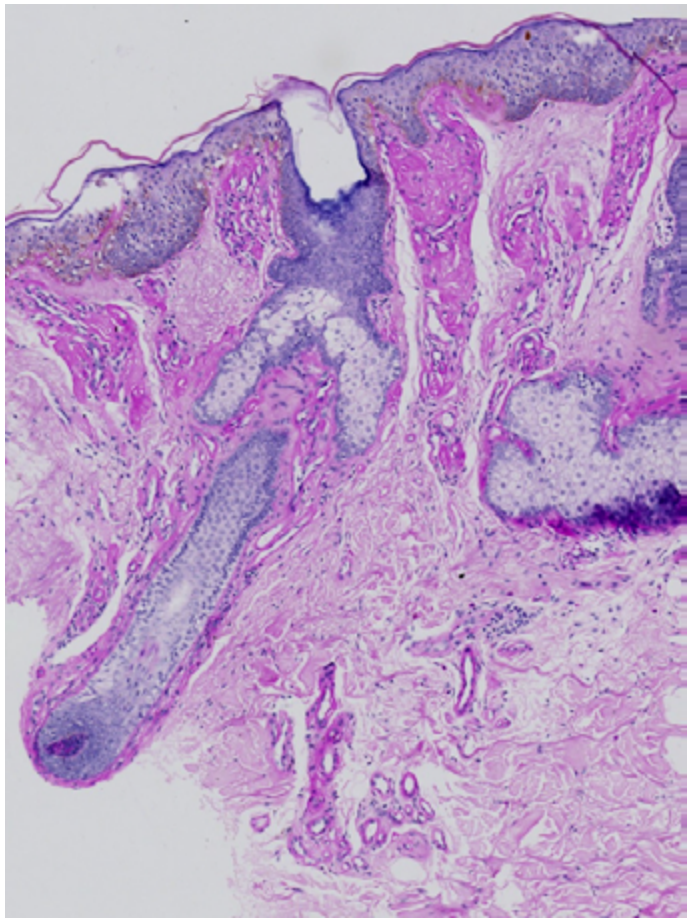

Figure 2. Skin biopsy with abundant eosinophilic material around superficial dermal vessels which is PAS positive and PASD resistant, H & E, 100x.

The skin lesions were biopsied and showed benign papillomatous lesions with eosinophilic material around superficial dermal blood vessels and sweat gland complexes. The initial interpretation was lipoid proteinosis. A literature review found a case report of lipoid proteinosis mimicking erythropoietic protoporphyria.[3] The skin biopsy was then reviewed with special Periodic Acid-Schiff (PAS) and Periodic Acid-Schiff-diastase (PAS-D) stains. The eosinophilic material around the blood vessels was found to be PAS-positive and diastase-resistant, but it was not seen around the sweat gland complexes. The diagnosis of EPP was considered (Fig. 2).

A transjugular liver biopsy was done, and lobular parenchyma showed diffuse ballooning of hepatocytes, some containing a coarse brown granular pigment. Some of the Kupffer cells and canaliculi also contained coarse brown refractile pigment. The refractile brown pigment showed bright-red birefringence with a centrally located, dark Maltese cross on polarizing microscopy (Fig. 3). The features were suggestive of porphyria, particularly erythropoietic protoporphyria. Next-generation sequencing (NGS) for porphyria and related disorders showed a homozygous mutation in the ferrochelatase enzyme coding gene (FECH:c.1153G>A), confirming the diagnosis of EPP.

She developed pneumonia during the hospital stay. Within a week, she developed acute-on-chronic liver failure (ACLF) as defined by the European Association for the Study of the Liver - Chronic Liver Failure-Sequential Organ Failure Assessment (EASL-CLIF), with ascites

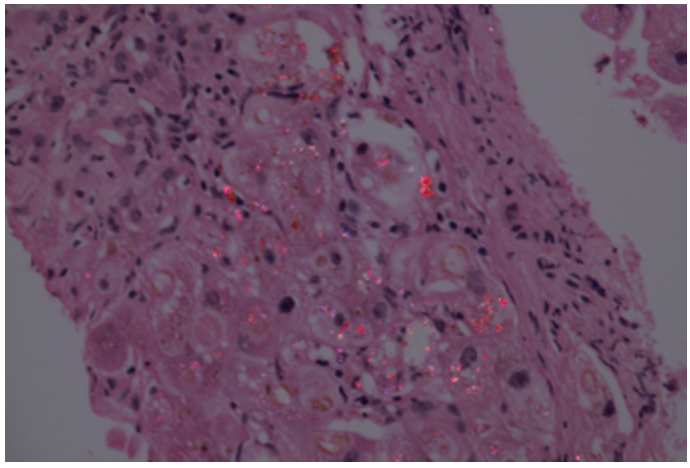

Figure 3. Photomicrograph displaying red birefringence and clusters of brilliantly illuminated granules seen in the deposits within the hepatocytes, bile ducts and canaliculi, in a Maltese cross appearance, H&E, 20x.

and encephalopathy. Her jaundice worsened, with a total bilirubin of 16.1 mg/dL, direct bilirubin of 13.8 mg/dL, and elevated liver enzymes (aspartate aminotransferase: 266 IU/L; alanine aminotransferase: 76 IU/L; alkaline phosphatase: 127 IU/L). Her EASL-CLIF grade was 3a with three organ failures (liver, cerebral, and respiratory). She was managed with photoprotective measures, ursodeoxycholic acid, intravenous antibiotics, and standard treatment for hepatic encephalopathy. The family was counseled regarding treatment options, including transplants. She was managed with the best supportive care and succumbed to her illness after discharge from the hospital.

Discussion

Porphyria cutanea tarda (PCT) and erythropoietic protoporphyria (EPP) are the two forms of porphyria known to cause liver disease. The liver disease precedes the onset of skin disease in PCT and vice versa in EPP.[4] It has been recently discovered that EPP is usually inherited in an autosomal recessive manner.[5] EPP is typically characterized by painful photosensitivity in childhood. The estimated prevalence of the disease in Europe was previously determined to be 1 in 109,000. However, recent data from exome databases suggest a prevalence of approximately 1 in 17,000 among Caucasians.[6]

The FECH gene, located on chromosome 18, encodes the FECH enzyme. FECH is responsible for catalyzing the insertion of iron into a protoporphyrin ring to produce heme, the end product. A partial decrease in FECH activity results in the accumulation of protoporphyrin. Protoporphyrin builds up in the development of red blood cells during hematopoiesis. Upon entering circulation, free protoporphyrin diffuses across the red blood cell membrane and binds to plasma proteins. Cutaneous lesions occur due to the presence of protoporphyrin in erythrocytes and plasma in skin vasculature. Hyaline PAS-positive perivascular material deposits can be found, with extensive fine fibrillar material and reduplication of blood vessel walls and epidermal basal lamina upon histological examination.[1]

The liver retrieves protoporphyrin from the plasma, where most of it is excreted in its original form via bile. At the same time, the remaining amount is converted to heme through liver ferrochelatase metabolism. Protoporphyrin deposition in the liver presents as dark brown deposits exhibiting a Maltese-cross appearance upon polarizing microscopy.[4] The hepatobiliary system clears protoporphyrin, which has a concentration-dependent hepatotoxic effect. Cholestasis caused by protoporphyrin results in additional protoporphyrin accumulation, initiating a vicious cycle of escalating cholestasis and decreased protoporphyrin excretion. Severe liver disease is fatal in the absence of liver transplantation.[4] Biochemical screening for EPP involves testing for total erythrocyte protoporphyrin levels, followed by fractionation into metal-free and zinc protoporphyrin. The diagnosis of EPP is confirmed by demonstrating an increase in total erythrocyte protoporphyrin levels (>3–4 times the upper limit of normal), with predominantly (>85%) metal-free protoporphyrin.[6]

Various treatment options for erythropoietic protoporphyria (EPP) have been reported, including ursodeoxycholic acid (UDCA), haematin infusion, plasmapheresis, hemodialysis, exchange transfusions, and intravenous vitamin E therapy.[4] Liver transplantation is an option for restoring normal liver function, with nearly 100 cases of liver transplantation for EPP documented.[5] It does not address the underlying deficiency of the FECH enzyme, leading to a high rate of recurrent EPP. A study found that 11 out of 17 patients (65%) who survived for more than two months after liver transplantation experienced a recurrence.[7] Sequential liver transplantation followed by bone marrow transplantation has also been reported as a success.[8] Givosiran, a small interfering ribonucleic acid (RNA) that prevents the accumulation of delta-aminolevulinic acid and porphobilinogen, has been recently approved for acute hepatic porphyrias. However, its role in EPP is not yet defined.[9] Another drug, afamelanotide, an α-melanocyte-stimulating hormone analog, is approved for photoprotection in EPP.[10]

The significance of this case lies in its demonstration of the rare but devastating progression to ACLF in a patient with long-undiagnosed EPP. Despite classic photosensitivity symptoms since childhood, the diagnosis remained elusive until advanced liver disease developed, highlighting the importance of early recognition. The diagnostic challenges in EPP, particularly when mimicking other conditions like lipoid proteinosis, emphasize the utility of specialized staining techniques and genetic testing for confirmation. The rapid deterioration following infection and the potentially fatal outcome also reinforce the need for research into novel therapeutic approaches, as current interventions remain largely supportive.

Conclusion

EPP is a rare disease characterized by photosensitivity, skin lesions, and liver disease. ACLF due to EPP is a rare entity with high mortality. Sequential hepatic and bone marrow transplantation is considered for severe cases of EPP with hepatic involvement.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: The patient provided written informed consent for the publication of this case report, including the use of medical images, and their personal details were anonymized in accordance with privacy guidelines.

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