

## CLINICAL VIGNETTE

# Erythropoietic Protoporphyrinuria

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### Case Report

A 73-year-old male presented with new onset jaundice for the past 1-2 weeks. He denied abdominal pain, fevers, chills, nausea, or vomiting, as well as any similar episodes in the past. There is no history of gallstones, pancreatic disease, or hepatitis. He denies any change in his diet, recent sick contacts, or recent travel. His past medical history includes coronary artery disease, hypertension, hyperlipidemia, and diabetes. He has no significant family history and denies the use of tobacco, alcohol, or illicit drugs. His medications include metoprolol, insulin, furosemide, and darbepoetin. On physical exam, he had a temperature of 99.1, heart rate of 88, and blood pressure of 110/50. His exam revealed scleral icterus and mild bilateral lower extremity edema. The remainder of his exam was unremarkable, including abdominal exam.

Laboratory evaluation revealed a hemoglobin of 11.6, platelet count of 278, total bilirubin of 9.9, direct bilirubin of 6.5, AST of 336, ALT of 283, alkaline phosphatase of 245, albumin of 3.9, creatinine of 1.2, and INR of 1.0. A right upper quadrant ultrasound showed cholelithiasis and was otherwise normal. Laboratory studies were negative for viral hepatitis, CMV, EBV, autoimmune hepatitis, Wilson's disease, and hemochromatosis. MRCP was unremarkable, other than cholelithiasis. His total bilirubin continued to rise and was 13.4 on the fifth day of his hospitalization. At that point, a liver biopsy was performed.

While awaiting the results of his liver biopsy, patient was noted to have a well-demarcated erythematous rash on his lower extremities. He was wearing hospital socks and had been lying by the window. The rash was only seen on the sun exposed areas of his legs. Further laboratory evaluation revealed the following:

	24 Hour Urine	Fractionated Plasma
<b>Porphobilinogen</b>	2.0 (<3.0 mg/24hr)	
<b>5-ALA</b>	4.8 (1.5-7.5 mg/24hr)	
<b>Uroporphyrin</b>		0.5 (<1.1 ug/dL)
<b>Heptacarboxyporphyrin</b>		0.2 (<1.1 ug/dL)
<b>Hexacarboxyporphyrin</b>		<0.1 (<1.1 ug/dL)
<b>Pentacarboxyporphyrin</b>		0.5 (<1.1 ug/dL)
<b>Coproporphyrins</b>		0.9 (<1.1 ug/dL)
<b>Protoporphyrins</b>		164.7 (<1.1 ug/dL)
<b>Total Porphyrins</b>	98.4 (10-150 ug/24hr)	167.2 (<1.0 ug/dL)
<b>Erythrocyte Protoporphyrin</b>		1048 (<36 ug/dL)

Based on these findings, he was diagnosed with erythropoietic protoporphyria.

### Discussion

Porphyrias are a group of metabolic disorders of heme biosynthesis in which there are defects in the normal pathway. The biochemical hallmark of the porphyrias is overproduction and overexcretion of compounds called porphyrins, which have a dark red or purple color. The clinical manifestations can be highly variable. There are two major clinical forms: acute and cutaneous. Acute porphyrias usually are manifested by recurrent bouts of pain, especially abdominal pain. The typical presentation of cutaneous porphyrias usually includes painful skin lesions. The porphyrias are classified based on the principal site of expression of the enzymatic defect. The rate limiting step in heme synthesis begins with the conversion of glycine and succinyl-CoA to 5-Aminolevulinic acid (ALA) by the action of ALA synthase. ALA synthase activity is decreased by the end-product of the pathway, heme. The enzyme activity is increased by substances that induce the hepatic cytochrome P450 pathway. A series of several additional steps converts ALA to protoporphyrin IX. In the final step of the pathway, this is coupled to ferrochelatase to create heme.

Erythropoietic protoporphyria (EPP) is usually inherited with incomplete penetrance. It is primarily classified as a cutaneous porphyria with urticaria and erythema. Hepatic manifestations can occur in 10% of patients. EPP results from a deficiency of ferrochelatase in all heme-forming tissues.<sup>1,2</sup> The activity of ferrochelatase in clinically affected people is only 15-25% of normal, and parents of many patients are phenotypically normal and asymptomatic (although they may have decreased ferrochelatase activity). The clinical expression is highly variable and may consist of burning, edema, itching, erythema, and anemia. Less common manifestations include scarring, vesicles, and gallstones.<sup>3</sup>

In EPP, excess protoporphyrin accumulation causes effects on the liver.<sup>3,4</sup> Regardless of its origin, excess protoporphyrin is excreted by the liver into bile and enters the enterohepatic circulation. Protoporphyrin is hydrophobic and is not filtered by the kidneys. This becomes insoluble in bile and exerts cholestatic effects leading to architectural changes, from mild inflammation to fibrosis to cirrhosis. Liver biopsy with fluorescent birefringence will usually demonstrate intracellular precipitates of protoporphyrin.<sup>5-7</sup>

The diagnosis of EPP is made by demonstrating increased concentrations of total and free erythrocyte protoporphyrin in the bone marrow, circulating erythrocytes, plasma, bile, and feces. This is the only heme pathway intermediate that accumulates significantly in EPP. Porphyrin and its precursor concentrations in the urine are normal in EPP.

There is no effective way of lowering porphyrin levels. Therefore, patients should be instructed to avoid sunlight or fluorescent light. Some studies have suggested that beta carotene use may increase tolerance to sunlight, but this has not been validated by all studies.<sup>8</sup> There have been numerous proposed medical treatments to address the hepatopathy associated with EPP, including cholestyramine, intravenous hemin, plasmapheresis, and vitamin E.<sup>9-11</sup> However, these are not reliably effective and are generally considered a bridge to liver transplant. Liver transplantation in patients with EPP related hepatopathy has similar overall survival compared to liver transplants done for other indications.<sup>12</sup> However, the transplantation does nothing to correct the underlying metabolic abnormality, so there may be a risk of recurrent liver disease.

### **Clinical Case Follow-up**

It is very unusual for a patient to be newly diagnosed with erythropoietic protoporphyria at the age of 73. On further review of his case, it was discovered that the patient had been diagnosed with anemia in the recent past. The etiology of his anemia was not defined. However, he was started on darbepoetin by his outside physician. This, in turn, stimulated the heme synthesis pathway enough to overwhelm the previously unknown and undiagnosed deficiency of ferrochelatase.

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