

Porphyria Cutanea Tarda, Hepatitis C, Alcoholism, and Hemochromatosis: A Case Report and Review of the Literature

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Porphyria cutanea tarda (PCT) is associated with estrogen, certain medications, alcohol abuse, hepatitis viruses, and iron overload. Numerous studies have demonstrated an increased incidence of hepatitis C in patients with PCT; therefore, hepatitis screening should be routinely performed on these patients. On the other hand, although studies have long suspected hereditary hemochromatosis (HH) to be an underlying condition of PCT, many physicians have a low index of suspicion. Also, diagnosis of HH has been difficult until recently, when the gene mutation was identified. We present a case of a patient with PCT, hepatitis C, and alcoholism who was homozygous for the HH gene mutation.

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Case Report

A 51-year-old white man presented to the dermatology clinic with a 5-year history of periodic blistering on his dorsal hands that worsened in the summer. He had no known drug allergies and was not taking any medications. His primary care physician had previously prescribed oral antibiotics for presumed staphylococcal infection. The patient's history was significant for a partial small bowel resection after an abdominal gunshot wound in 1970, which required a blood transfusion. He also had a history of significant alcohol abuse but denied any intravenous drug use. Physical examination revealed pronounced

hypertrichosis of the forehead, temples, and cheeks (Figure). Additionally, there were several crusted erosions and scarring on the bilateral dorsal hands with an occasional intact vesicle and milia.

Laboratory examination results revealed a differential white blood cell count of $9.29 \times 10^3/\mu\text{L}$ (reference range, $4.8 \times 10^3/\mu\text{L}$ – $10.8 \times 10^3/\mu\text{L}$), hemoglobin level of 16.0 g/dL (reference range, 14–18 g/dL), hematocrit level of 49.4% (reference range, 42%–52%), platelet count of $124 \times 10^3/\mu\text{L}$ (reference range, $150 \times 10^3/\mu\text{L}$ – $500 \times 10^3/\mu\text{L}$), mean corpuscle volume level of 102.4 fL (reference range, 80–94 fL), iron count of 220 $\mu\text{g}/\text{dL}$ (reference range, 50–160 $\mu\text{g}/\text{dL}$), total iron binding capacity level of 238 $\mu\text{g}/\text{dL}$ (reference range, 261–478 $\mu\text{g}/\text{dL}$), total protein level of 7.7 g/dL (reference range, 6–8 g/dL), albumin level of 3.9 g/dL (reference range, 3.2–5.5 g/dL), total bilirubin level of 1.3 mg/dL (reference range, 0.2–1 mg/dL), alkaline phosphatase level of 69 U/L (reference range, 42–121 U/L), and alanine aminotransferase level of 96 U/L (reference range, 10–60 U/L). Hepatitis C antibody enzyme-linked immunosorbent assay II test results were positive. Hepatitis B surface antigen, hepatitis B surface antibody, and human immunodeficiency virus test results were nonreactive. Results of 24-hour urinary porphyrin profile studies included: octacarboxylporphyrin 3500 $\mu\text{g}/24 \text{ h}$ (reference range, 0–27 $\mu\text{g}/24 \text{ h}$), heptacarboxylporphyrin 1800 $\mu\text{g}/24 \text{ h}$ (reference range, 0–6 $\mu\text{g}/24 \text{ h}$), hexacarboxylporphyrin 260 $\mu\text{g}/24 \text{ h}$ (reference range, 0–3 $\mu\text{g}/24 \text{ h}$), pentacarboxylporphyrin 160 $\mu\text{g}/24 \text{ h}$ (reference range, 0–5 $\mu\text{g}/24 \text{ h}$), and tetracarboxylporphyrin 140 $\mu\text{g}/24 \text{ h}$ (reference range, 0–72 $\mu\text{g}/24 \text{ h}$).

The patient was diagnosed with PCT. Phlebotomy was performed on the patient every 2 to 4 weeks; however, his condition deteriorated with the continued development of new vesicles. Hydroxychloroquine 200 mg twice a week was initiated. However, the patient's liver function values

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increased to greater than 2 times the upper limit of normal, and the hydroxychloroquine was discontinued. The frequency of phlebotomy was increased to every 1 to 2 weeks, and the patient minimized his alcohol intake. He subsequently had a significant decrease in skin lesions. The patient was lost to follow up from September 1996 to December 1998, when he began to develop more vesicles and returned to the clinic to restart periodic phlebotomy. The patient's serum ferritin level was elevated at 780.8 ng/dL (reference range, 32–284 ng/dL), and he was evaluated by the hepatology service for hemochromatosis. He was found to be homozygous for the HFE gene mutation C282Y on chromosome 6 for hemochromatosis.

Comment

PCT is the most common type of porphyria with an estimated prevalence of 1 per 70,000 population. It is caused by reduced activity of uroporphyrinogen decarboxylase in the liver, and the diagnosis can be confirmed by characteristic porphyrin excretion profiles. Clinical manifestations include a vesicular eruption of the hands and face, scarring, photosensitivity, milia formation, skin fragility, and hypertrichosis. Risk factors for PCT include exposure to halogenated hydrocarbons, ingestion of alcohol or exogenous estrogens, and infection with human immunodeficiency virus or hepatitis viruses. Iron overload and hepatic siderosis are common.¹

An association between hereditary hemochromatosis (HH) and PCT previously has been suspected. The term *hemochromatosis* was first coined by von Recklinghausen in 1889, and as late as 1975, Simon et al demonstrated an association with HLA-A3 on chromosome 6.^{2,3} HH is an autosomal-recessive condition whereby excess iron is absorbed by the intestine and deposited into the skin, liver, pancreas, heart, and joints with subsequent organ damage. This can lead to hyperpigmentation, cirrhosis, diabetes mellitus, cardiomyopathy, and arthropathy. Initial symptoms are vague and include fatigue, malaise, and arthralgias.⁴ Its prevalence in white individuals is approximately 3 to 5 per 1000 population, and the carrier rate is 1 in 10 people. It usually is asymptomatic until patients reach between the ages of 50 and 70 years. The perception of HH as an uncommon disease may result from its underdiagnosis. Also, because of incomplete penetrance of the mutation, iron overload does not always develop.⁵ The major histocompatibility complex class I gene mutation for HH, called HFE (previously termed *HLA-H*), located on the short arm of chromosome 6, was described in 1996. Two missense mutations have been identified in this

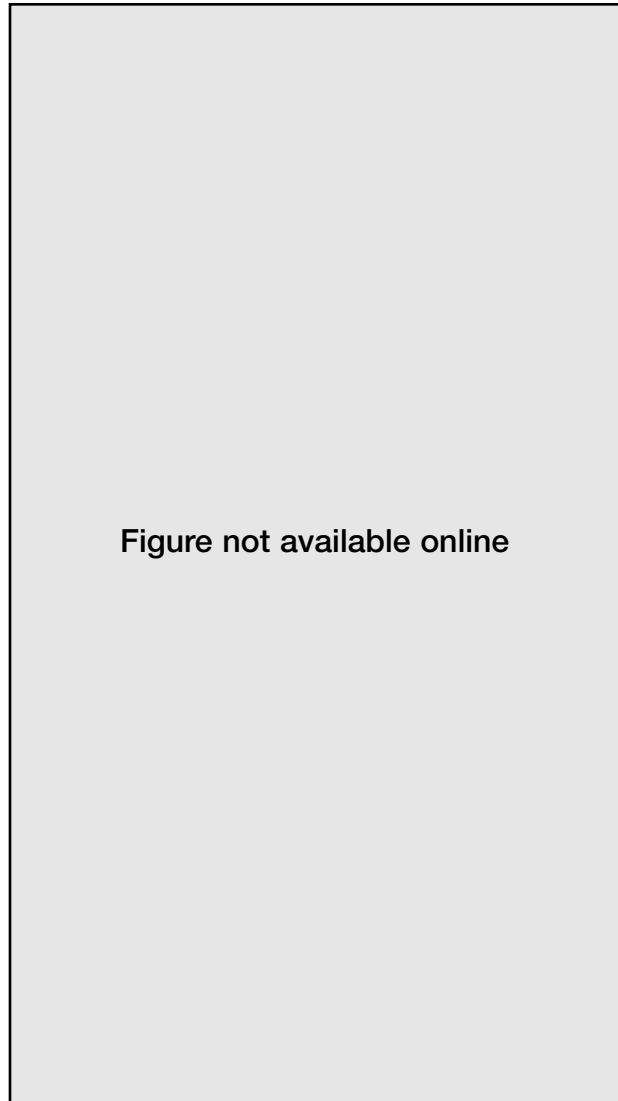


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Hypertrichosis of the forehead, temples, and cheeks.

gene. The major mutation has a tyrosine substitution for cysteine at position 282 (C282Y). Approximately 80% to 90% of patients with HH are homozygous for this mutation. A second mutation has an aspartate substitution for histidine at position 63 (H63D), but its significance is unclear.⁶ The genetic test for HH is a PCR amplification of the HFE gene DNA.⁵ Treatment with phlebotomy prior to the development of cirrhosis can lead to a normal life expectancy, though morbidities such as arthropathy may continue. Unfortunately, without treatment, the disease is often fatal, especially when increased iron stores are present. Hepatocellular carcinoma is the most common cause of death. Additionally, diabetes, cardiomyopathy, and cirrhosis are more frequent causes of death in patients with PTC than in the general population.⁷

Our patient had contributing factors of alcohol abuse and hepatitis C positivity. The prevalence of hepatitis C has been shown to be increased among patients with PCT, particularly in studies from Spain, France, and Italy.⁸⁻¹⁰ Bonkovsky et al⁷ evaluated PCT, hepatitis C, and HFE gene mutations among patients in North America and found that 39 of 70 (56%) patients with PCT were positive for HCV. The authors were able to perform mutational analyses on 26 of the patients with PCT and found that 42% (11/26) carried the C282Y mutation (19% [5/26] homozygous) and another 31% (8/26) carried the H63D mutation (8% [2/26] homozygous). Thus, mutations in the HFE gene were found in 73% (19/26) of the patients with PCT.¹⁰ This finding has been supported by reports from several other countries including the United Kingdom, The Netherlands, and Australia.^{3,12,13} It is therefore recommended that all patients with PCT be tested for both HCV infection and HFE gene mutations, particularly C282Y. This simple test will enable dermatologists to identify entire families that are homozygous or heterozygous for the gene mutations of hemochromatosis and thus facilitate early diagnosis.

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