Iron, Genes, and Viruses: The Porphyria Cutanea Tarda Triple Threat

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Porphyria cutanea tarda (PCT) is a vesiculobullous disorder often associated with estrogens, hepatitis C virus (HCV), alcoholism, hereditary hemochromatosis (HH), and human immunodeficiency virus. Hepcidin, a peptide hormone produced by the liver, has been associated with iron metabolism in 3 common precipitating factors for PCT: HCV, HH, and alcohol consumption. We present the case of a patient with erosions and noninflammatory bullae on his hands and forearms who received a diagnosis of PCT. On further examination, the patient was found to be positive for 3 precipitating factors: HCV, an HH gene mutation, and alcohol use. For patients with PCT, it is important to perform phenotypic screening for HCV and HH. Targeting hepcidin with replacement therapy to decrease iron may be a treatment of not only HCV, HH, and alcoholic cirrhosis, but also PCT.

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Porphyria cutanea tarda (PCT) is a vesiculobullous disorder often associated with skin fragility, blistering, erosions, postinflammatory hyperpigmentation, and hypertrichosis on sun-exposed skin. Hepatitis C virus (HCV) infection, hereditary hemochromatosis (HH), and alcohol use are precipitating factors for PCT. Dependence on iron is a central feature of PCT, with phlebotomy being the first-line treatment.[1-3] Studies have highlighted the importance of hepcidin, a peptide hormone produced by the liver, for iron homeostasis and the possibility of treating iron-overload diseases by targeting hepcidin.[4,5] We present the case of a patient with PCT who was found to be positive for HCV, was heterozygous for an HH gene mutation, and used alcohol regularly.

Case Report

A 56-year-old white man with a history of hypertension treated with hydrochlorothiazide sought medical care at our dermatology department for blisters on the dorsal surfaces of his hands and forearms of 2 weeks' duration. He had been taking hydrochlorothiazide for 4 months before the blisters appeared. He reported exacerbation of the blisters with exposure to sunlight. He had no history of asthma or allergies, and he reported no family history of blistering disorders, porphyria, or hemochromatosis. His social history included prior intravenous drug use, and at the time of our initial evaluation, he drank a 12-pack of beer weekly.

Physical examination noted several erosions and intact, tense, noninflammatory bullae on the dorsal aspect of his hands, digits, and forearms bilaterally (Figure 1). Results of a punch biopsy showed subepidermal bullae with a noninflamed base (Figure 2). Direct immunofluorescence studies revealed positive staining for IgG, IgA, and fibrinogen within thick-walled superficial vessels. Staining for IgM was negative, whereas C3 showed granular deposition in the vessel walls.

Levels of porphyrins in the blood were elevated at 120 μg/L (reference range, 0–10 μg/L). Fractionated uroporphyrin, heptacarboxyporphyrin, and hexacarboxyporphyrin levels were increased, whereas levels of pentacarboxyporphyrin, coproporphyrin, and protoporphyrin were within reference range. Results of a 24-hour urine test showed all porphyrins to have elevated levels. All fecal porphyrins measured also were elevated. On the basis of these results, PCT was diagnosed.

Because of the diagnosis, additional testing was done to search for precipitating factors. The

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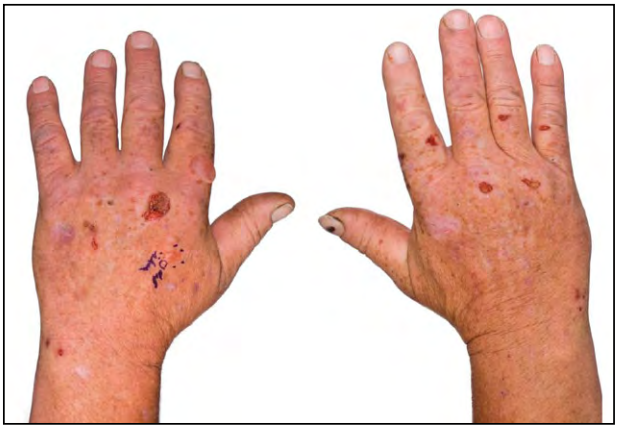

Figure 1. Erosions and bullae on sun-exposed areas.

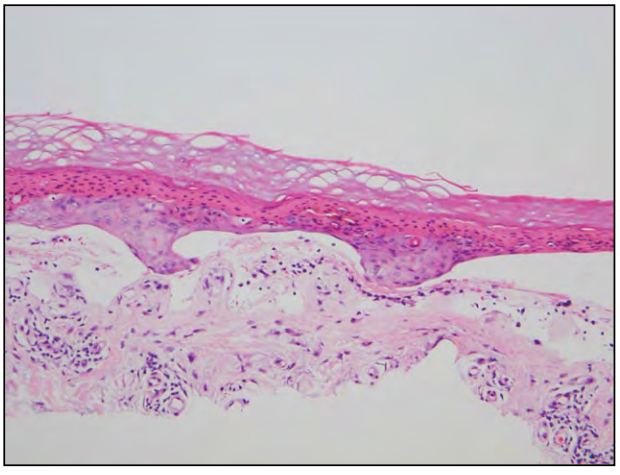

Figure 2. Results of a biopsy specimen showed subepidermal bullae with a noninflamed base (H&E, original magnification ×20).

hemoglobin concentration was 15.3 g/dL (reference range, 13.5–17.5 g/dL) and the alkaline phosphatase level was 87 U/L (reference range, 45–115 U/L). The aspartate aminotransferase and alanine aminotransferase levels were elevated at 70 U/L (reference range, 8–48 U/L) and 99 U/L (reference range, 7–55 U/L), respectively.

Iron studies were normal and revealed the following values: iron, 110 µg/dL (reference range, 50–150 µg/dL); total iron-binding capacity, 277 µg/dL (reference range, 250–400 µg/dL); and transferrin-iron percentage saturation, 40% (reference range, 14%–50%). Genetic studies showed the patient to be heterozygous for a mutation of the hemochromatosis gene, *HFE*, with the amino acid change Cys282Tyr (cysteine at residue 282 replaced by tyrosine), which suggests that, at a minimum, he is a carrier for HH.

Human immunodeficiency virus test results were nonreactive, but the patient was positive for anti-HCV antibody, with HCV RNA detected at 6,870,000 IU/mL. Prothrombin time (9.7 s; reference range, 8.3–10.8 s), albumin level (4 g/dL; reference range, 3.5–5.0 g/dL), and α_1-fetoprotein concentration (1.5 ng/mL; reference range, <6.0 ng/mL) were within reference range. Ultrasonography-guided liver biopsy indicated diffuse hepatic parenchymal heterogeneity involving the entire liver with no obvious hepatic masses noted with mild to moderate iron staining. The patient was diagnosed with HCV grade 2 with mildly active stage 1 to 2 disease.

He was instructed to abstain from alcohol. Phlebotomy was started with a treatment every 2 weeks (500 mL per session); the goal was to keep his hemoglobin level below 13 g/dL and ferritin level below 50 µg/L (reference range, 24–336 µg/L). Urinary porphyrin excretion also was monitored for progress. After 3 months of having phlebotomy every 2 weeks, the patient's bullae improved and the urine porphyrin levels decreased. The patient continues to do well on intermittent phlebotomy.

Comment

Porphyria cutanea tarda is a subepidermal vesiculobullous disorder seen most commonly on sun-exposed skin. Hypertrichosis, postinflammatory hyperpigmentation, scarring alopecia, milia, and erosions also are frequently observed. The sporadic (acquired) variant is more common than the familial (hereditary) variant at a ratio of 3:1 to 4:1. Both forms result from decreased function of the fifth enzyme in heme biosynthesis, uroporphyrinogen decarboxylase (UROD). In the sporadic form of PCT, function of UROD is decreased within hepatocytes only, whereas in the familial form, function of UROD is decreased within all tissues. The decreased function of UROD leads to the accumulation of porphyrins, which are found in serum, urine, and feces, as well as in the skin. When combined with UV light, porphyrins in the skin become cytotoxic and produce blistering. Lançoni et al[6] studied the mechanism of this blistering and reported that the interaction between UV light and porphyrins causes mast cell degranulation, which releases tryptases that damage the basement membrane, similar to the mast cell blistering of bullous pemphigoid.[6]

An important feature of PCT is its iron dependence. Alcohol, estrogens, HH, human immunodeficiency virus, and HCV also have been implicated as possible precipitating factors for PCT.[1] Furthermore, HCV, HH, and alcohol also are known to

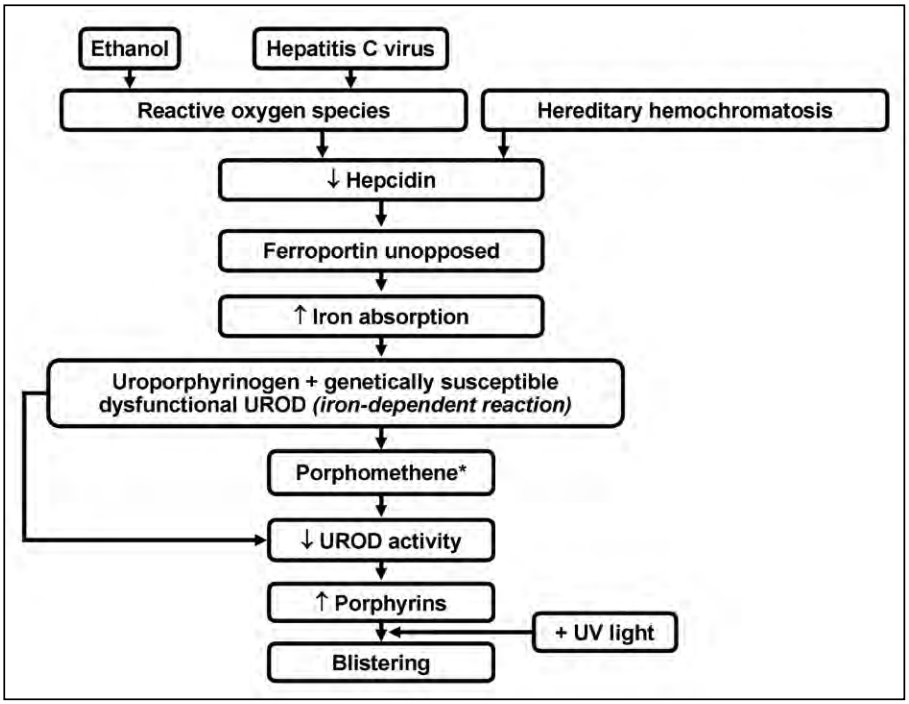

Figure 3. The proposed mechanism for hepcidin's role in porphyria cutanea tarda. Decreased hepcidin results in increased iron through unopposed ferroportin. The interaction between uroporphyrinogen and dysfunctional uroporphyrinogen decarboxylase (UROD) produces porphomethene, which further inhibits dysfunctional UROD. Increased porphyrins combined with UV light produces blistering. Asterisk indicates disputed role in pathogenesis.

increase iron stores within the body through their negative effects on hepcidin, a hormonal peptide that decreases iron absorption in the intestine.[2,5,7,8]

New discoveries have been made regarding HCV's role in iron-overload conditions and PCT. Through the production of reactive oxygen species, HCV evokes histone deacetylase activity, which in turn inhibits the expression of hepcidin.[5] Under normal circumstances, when iron is in excess, hepcidin binds to ferroportin on the plasma membrane of intestinal epithelium to prevent the absorption of redundant iron. However, if hepcidin is not expressed, ferroportin remains active and absorbs excess iron.[4,7] Excess iron absorption then leads to further organ damage and, on occasion, PCT (Figure 3).[1,2]

Hereditary hemochromatosis is the most common disease caused by a recessive genetic mutation in white individuals; it involves hepcidin dysfunction. However, with HH, the dysfunction involves genetic mutations that lead to a disrupted hepcidin/ferroportin interaction. Five genetic mutations associated with HH have been identified to date: mutations in 3 genes (*HFE*; transferrin receptor 2 gene, *TFR2*; and *HFE2*) inactivate the signaling pathway that normally upregulates hepcidin expression; mutation of 1 gene (solute carrier family 40 [iron-regulated transporter], member 1 gene, *SLC40A1*) prevents the ferroportin transporter from being recognized by hepcidin; and mutation of 1 gene (hepcidin antimicrobial peptide gene, *HAMP*) causes a dysfunctional hepcidin protein.[4] All defects lead to iron excess, which is responsible for the hyperpigmentation of the skin and damage to the liver, spleen, and pancreas that often leads to premature death.

Since the 1950s, alcohol has been considered an important risk factor for PCT.[3] It also has been known for decades that alcohol appears to increase iron absorption, sometimes to the point of iron overload.[8] Even low doses of alcohol on a regular basis seem to increase the risk for PCT, which suggests that the consistent use of alcohol affects PCT more than the quantity of alcohol ingested.[3] As in HCV infection and iron overload, alcohol increases oxidative stress. However, until recently, the connection between oxidative stress and iron overload was not clear. The increase in oxidative stress due to alcohol appears to decrease the function of hepcidin in its inhibitory actions on iron absorption, leaving iron absorption in the intestine unopposed.[2,5,7,8]

One study has suggested a mechanism for the iron dependence of PCT. For unknown reasons, an iron-dependent reaction occurs in susceptible individuals in which a substrate for UROD (uroporphyrinogen) is oxidized to porphomethene (an inhibitor of UROD). With the inhibition of UROD, porphyrins build up in the skin and become phototoxic upon exposure to UV light.[9] However, this theory is not supported by all authors.[10] It remains unclear how and why a dysfunctional iron-dependent UROD arises in some patients and leads to PCT.

Nonetheless, phlebotomy improves the symptoms of PCT, whereas iron overload exacerbates them.[3]

With recent advances suggesting that hepcidin has a prominent role in the iron overload associated with common precipitating factors for PCT, curiosity about hepcidin's role in the development and maintenance of PCT naturally follows. In one study, hepcidin levels were found to be lower in patients with PCT. Unfortunately, the study did not control for other possible causes of low hepcidin in the study group, such as estrogen, HCV, and alcohol use.[2] Furthermore, new research proposes targeting hepcidin for the treatment of iron-overload diseases such as HCV, HH, and alcoholic cirrhosis.[4,5] Because many iron-overload diseases also are precipitating factors for PCT, therapies directed toward hepcidin also may prove beneficial in the treatment of PCT.

Our case is an interesting example of the role of iron, along with genetic susceptibility and infectious disease, in the development of PCT. It is rare for one patient to have 3 precipitating factors. This case further highlights the importance of screening for both HCV and HH in patients with PCT.

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