The Additive Effects of Hepatitis C Infection and End-Stage Renal Disease in Porphyria Cutanea Tarda

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Various factors contribute to the development of porphyria cutanea tarda (PCT). In this case report, we describe a patient with hepatitis C infection and chronic renal failure. The individual mechanisms, which promote cutaneous disease, are discussed. Finally, we propose that each factor may have an additive effect in prolonging the skin lesions of PCT.

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Porphyria cutanea tarda (PCT) is a photosensitive dermatosis associated with skin fragility, subepidermal bullae formation, erosions, and scarring.[1-3] The prevalence of this disease ranges from 1 in 5000 to 25,000 individuals.[3] PCT is characterized by an acquired or inherited defect of the enzyme uroporphyrinogen decarboxylase from the heme biosynthetic pathway and results in an accumulation of uroporphyrin.[1,4] This buildup of porphyrins then mediates the photosensitivity of PCT.[5]

A number of associated factors precipitate or exacerbate PCT, such as alcohols, estrogens, and chlorinated hydrocarbons.[6] Hepatitis C infection and chronic renal disease are other associated conditions.[7,8]

We describe a patient with hepatitis C infection and chronic renal failure in the setting of PCT and discuss how these medical conditions contributed to his cutaneous disease.

Case Report

A 48-year-old Hawaiian-Chinese fisherman developed blistering eruptions on his arms, knees, and face for a week with a vague history of prior episodes. He initially presented to his primary care physician who prescribed famciclovir for a presumed varicella infection. The lesions persisted and the patient was referred to the dermatology department. His past medical history was significant for hepatitis C infection diagnosed 3 years prior, end-stage renal disease (ESRD) treated with hemodialysis for 3 years, and hypertension. His routine medications included multivitamins with iron, sodium bicarbonate, calcium acetate, aspirin, nifedipine, irbesartan, quinapril, and labetalol. During dialysis, he was treated with erythropoietin (10,000 U subcutaneously every week) and paricalcitol. He denied any recent alcohol consumption, having quit 5 years prior, at which time he had consumed a 6-pack of beer every 3 days for more than 10 years. He had a smoking history of 10 packs per year.

Results of a physical examination revealed an alert thin man who was in no acute distress. The patient had extensive vesicles and bullous eruptions on the dorsal hands, with some extension to the sun-exposed regions of his face, neck, forearms, and knees. The lesions on his hands were warm, swollen, and tender, with skin atrophy and scarring. There was no jaundice or pallor. He had spider nevi on his chest but no gynecomastia. His abdomen was soft and distended, with ascites. Additionally, the patient had a caput medusae, an umbilical hernia, and an enlarged spleen and liver; he had lower leg edema in addition to skin eruptions on his extremities. There was no flapping tremor. Results of the rest of the physical examination were unremarkable.

Laboratory studies disclosed the following abnormal values: serum urea nitrogen, 38 mg/dL (reference range, 7–18 mg/dL); serum creatinine, 7.8 mg/dL (reference range, 0.6–1.2 mg/dL); total calcium, 10.6 mg/dL (reference range, 8.4–10.2 mg/dL); serum phosphorus, 5.4 mg/dL (reference range, 2.7–4.5 mg/dL); hemoglobin, 12.0 g/dL (reference range, 13.5–17.5 g/dL); and hematocrit, 35.9%

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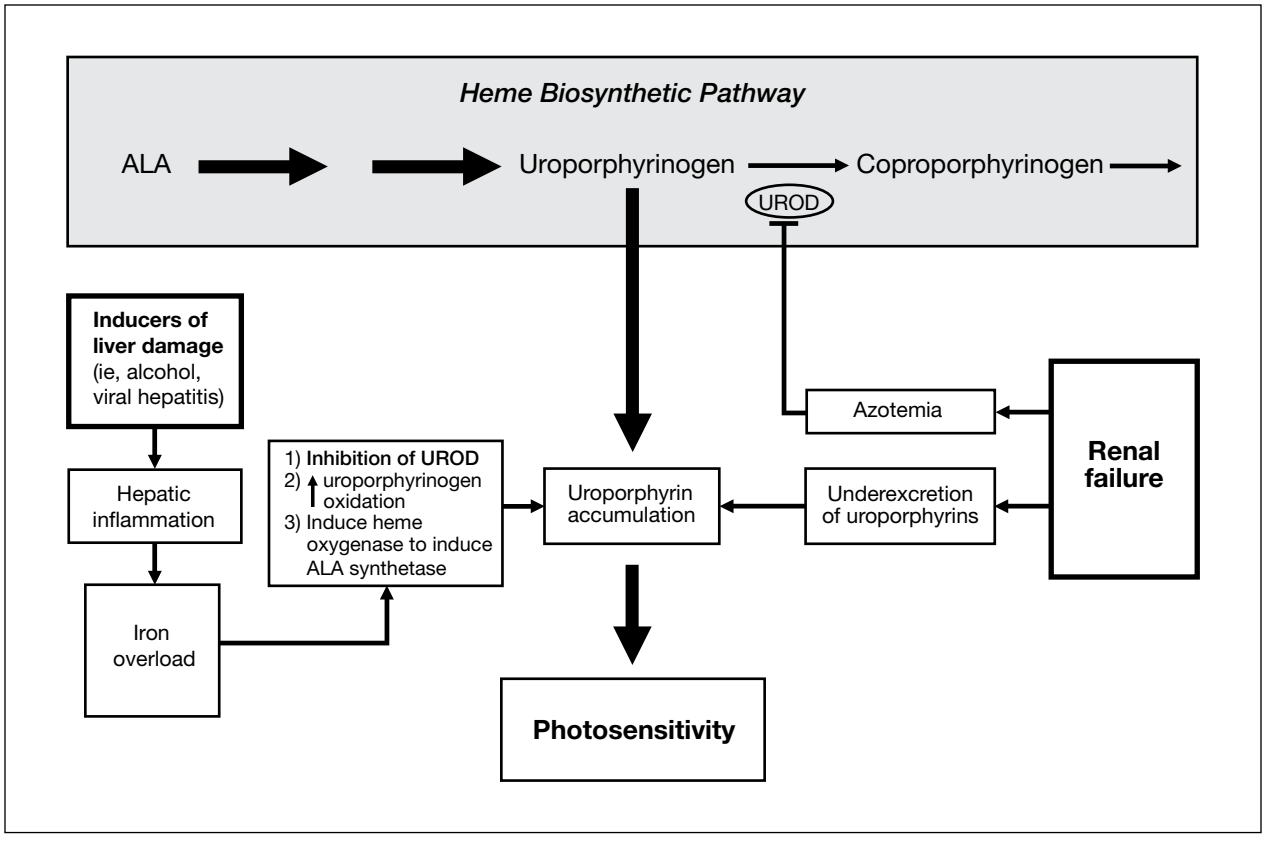

Liver damage and renal failure contribute to the overproduction of uroporphyrin in patients with porphyria cutanea tarda (PCT). Inducers of liver damage and renal failure are key factors promoting PCT. These inducers would shunt the heme biosynthetic pathway to promote uroporphyrin accumulation. ALA indicates aminolevulinic acid; UROD, uroporphyrinogen decarboxylase.

(reference range, 39%–49%). White blood cell and platelet counts were within reference range. The patient's serum porphyrins level was 28.7 μg/dL (reference range, 1.0–5.6 μg/dL) and serum uroporphyrins level was 14.9 μg/dL (reference range, <0.2 μg/dL). Erythrocytic uroporphyrin decarboxylase activity was within reference range. Hemochromatosis DNA testing of the *HFE* gene revealed no C282Y mutation. His γ-glutamyl transpeptidase level was elevated at 100 U/L (reference range, 11–51 U/L). An abdominal ultrasound conducted 5 months prior revealed hepatosplenomegaly with a slightly coarsened liver echotexture and small to moderate ascites.

The patient was prescribed cephalexin 500 mg twice daily for 7 days. Additional treatment consisted of a 120-cc phlebotomy 3 times a week with hemodialysis. Three months after the initiation of the phlebotomies, the patient's hemoglobin level decreased from 12.0 g/dL to 10.4 g/dL, his plasma ferritin level decreased from 211 ng/mL to 53 ng/mL (reference range, 15–200 ng/mL), and his serum uroporphyrins level decreased from 14.9 μg/dL to 2.5 μg/dL. Eight to 9 months after the start of the phlebotomies, the bullous lesions gradually resolved and healed with focal residual scarring.

Comment

PCT results from inhibited uroporphyrin decarboxylase in the heme biosynthetic pathway, which leads to an accumulation of uroporphyrin I and III.[4] The porphyrins absorb light in the 400- to 405-nm range; the absorbed energy then is transferred to cellular structures or molecular oxygen, imparting subsequent tissue damage.[5] As a result, individuals with PCT have a unique predisposition to photosensitivity.

Iron overload, hepatitis C infection, and chronic renal disease are conditions associated with PCT. Most patients with PCT have some evidence of abnormal iron metabolism, often with elevated plasma ferritin or transferrin saturation levels.[9,10] Lambrecht and Bonkovsky[10] reported that iron has the potential to enhance uroporphyrin overproduction via multiple mechanisms. First, iron increases the rate at which uroporphyrinogen is oxidized to uroporphyrin.[11] Next, iron decreases the enzymatic activity of uroporphyrinogen decarboxylase, resulting in uroporphyrin overproduction. Finally, iron

induces heme oxygenase, which then increases the activity of δ-aminolevulinic acid synthetase.[12,13] This activity promotes the heme biosynthetic pathway and the production of the pathway's porphyrin metabolites.

Chronic hepatitis C infection is associated with PCT.[8,14-16] Bonkovsky and Lambrecht[4] reported that the prevalence of hepatitis C infection in patients with PCT is 56% in the United States. Di Bisceglie et al[17] postulated that chronic hepatitis C infection promotes cutaneous lesions of PCT by inducing iron overload through hepatic necroinflammation. This inflammation causes the release of cellular iron and/or ferritin into the circulation, which induces the cutaneous lesions of PCT. The literature documents elevated iron stores in individuals infected with hepatitis C virus.[17-19] Treatment of hepatitis C infection with interferon ameliorates the skin lesions of PCT, lending support for the connection between hepatitis C infection and PCT.[20-22]

An association between PCT and renal disease is recognized; however, fewer case reports exist.[7,23-25] The plasma porphyrin levels in patients with renal failure often are elevated because excess porphyrins are not excreted in the urine or effectively removed by hemodialysis.[26] These accumulated porphyrins exacerbate the cutaneous photosensitivity of PCT. In addition, elevated blood urea levels observed in patients with chronic renal failure may contribute to porphyrin buildup. Day and Eales[27] reported that azotemia decreases the activity of uroporphyrinogen decarboxylase and thus promotes uroporphyrin production.

Our patient had nonfamilial PCT with associated hepatitis C infection and ESRD. His liver disease, as evidenced by his elevated γ-glutamyl transpeptidase level, ascites, and hepatomegaly, presumably was secondary to hepatitis C infection and an extensive alcohol consumption history. He also had ESRD with chronic azotemia, which necessitates hemodialysis. His liver and renal diseases both likely contributed to uroporphyrin accumulation and subsequent photosensitivity (Figure). Porphyrins collect in the liver, circulate in plasma, and are excreted in urine.[28] Damage to the hepatic or renal systems presumably would impair porphyrin metabolism.

Hepatitis C infection and ESRD are 2 factors that mediate the photosensitivity of PCT. We propose that each factor has an additive effect in contributing to the severity and duration of the cutaneous lesions of PCT. Although the literature is limited to a few case reports comparing the severity and course of patients with PCT and ESRD versus patients with PCT, hepatitis C infection, and ESRD, the literature does support an additive effect.[23-25,29-32]

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