Porphyria Cutanea Tarda: A Case Presentation and Discussion

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Abstract
The porphyrias are metabolic disorders caused by altered activity of enzymes in the heme biosynthetic pathway. Porphyria cutanea tarda (PCT) is the most common subtype, with a prevalence of about 1 in 10,000 people, and is due to deficient activity of uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the heme biosynthetic pathway. Cutaneous findings are common and include photosensitivity, bullae, skin fragility, erosions, scarring, and milia in sun-exposed areas. The cause of PCT may be multifactorial, related to genetic and environmental factors. Generally, there is a strong association with liver disease, and one should consider possible triggers including but not limited to alcohol abuse, iron overload including possible hereditary hemochromatosis, hepatitis C virus infection, and estrogen use. The diagnosis can be made through screening of serum, urine, and fecal porphyrin levels. We present a case of a 57-year-old female with PCT and secondary hemochromatosis.

Case Report
A 57-year-old white female presented to our outpatient dermatology clinic with complaints of blisters and bumps on her hands for three months’ duration. She stated the lesions would start out as little blisters that would easily break open, leave her with painful sores, and heal with “little white, pimple-like” bumps. The patient reported she had not developed any new blisters for a few weeks. She didn’t recall any inciting triggers and denied any other affected areas. She reported starting nabumetone a few months earlier for arthritis but admitted taking it only as needed. She denied any other medications. Past medical and family histories were unremarkable. She reported a long history of alcohol consumption, consuming five to six “shots” of whisky a night for 15 years.

Two weeks prior to our visit, she had previously been seen by a nurse practitioner who diagnosed her with dyshidrotic eczema. She was given an intramuscular corticosteroid injection, which she reported did not help.

On physical exam, there were multiple hyperpigmented macules, with areas of shallow scarring and multiple milia on her bilateral dorsal hands (Figures 2, 3). Her skin appeared bronze in nature, but she denied using tanning beds, and she reported having the darkest skin in her family. Examination of her face revealed noticeable hypertrichosis (Figure 4). The rest of her physical exam was unremarkable.

Given the lack of new bullae, no biopsy was performed, and she agreed to return for a biopsy if a new one arose. Based on history and clinical presentation, her case seemed most consistent with pseudoporphyria or porphyria cutanea tarda (PCT). She was instructed to hold her nabumetone, avoid other NSAIDS, and start decreasing her alcohol intake and sun exposure.

Laboratory workup, including a CBC, complete metabolic profile, iron studies, hepatitis B/C, HIV screen, HbA1C, CRP, and ANA, was unremarkable except for mildly elevated AST/ALT in a 2:1 ratio and a significantly elevated ferritin at 637 ng/ml (reference interval 15 ng/ml to 115 ng/ml). A urinary porphyrin screen was performed, which showed considerably elevated uroporphyrins (uroporphyrin I – 794.0 mcg [normal 4.1 mcg].
Porphryia cutanea tarda is a form of porphyria worldwide. Like all forms of porphyria, PCT is caused by abnormalities in the heme biosynthetic pathway, specifically in the enzyme uroporphyrinogen decarboxylase (UROD). Type 1, the most common, is sporadic and non-familial. The sporadic form accounts for 75% to 80% of PCT cases. UROD levels are normal, but enzymatic activity in the liver, exclusively, is reduced by at least 50%. Many factors can lead to the enzymatic deficiency, including smoking cigarettes, alcohol or estrogen use, iron overload, hemochromatosis, and viral infections.

Many genetic and acquired susceptibility factors have been identified and studied in PCT patients. Most PCT patients have three or more precipitating factors. The most common are cigarette smoking, alcohol or estrogen use, iron overload, hemochromatosis, and viral infections.

Cigarette smoking has been found in 81% of patients with PCT. PCT patients who smoke tend to develop cutaneous symptoms at a younger age than non-smoking PCT patients. Smoking induces CYPIA2 synthesis that may in turn lead to increased production of UROD inhibitor.

Alcohol use has been reported in up to 80% of PCT patients. Although alcohol consumption is a common factor among PCT patients, it is uncommon for users of alcohol to develop PCT. There are several possible mechanisms by which alcohol consumption could cause PCT. Alcohol increases iron absorption, dissociates iron from its binding proteins, simulates ALA synthase, and inhibits UROD. Alcohol can also stimulate production of free radicals and reactive oxygen species, leading to oxidative changes that inhibit UROD.

Elevated estrogen levels have been found in many PCT patients, with one study finding up to 66% of female PCT patients using exogenous estrogen. Oral contraceptives, postmenopausal hormone replacement, and tamoxifen are common precipitating factors for PCT in women. Infrequently, PCT has also been stimulated by pregnancy and childbirth. A possible mechanism by which estrogen might cause PCT is via increased estrogen quinone formation leading to increased free-radical production.

Hepatic iron overload is found in nearly all patients with PCT, but the mechanism is somewhat unclear. Iron may increase production of peroxides and free radicals, leading to oxidation of uroporphyrinogen in the cell, liver damage, inhibition of UROD or enzyme modification. Most patients with iron overload have HFE gene mutations, and HFE mutations are found more commonly in PCT patients than in the general population, so gene testing should be considered if clinical suspicion is high. The two most common types of mutations are C282Y and H63D. Heterozygous C282Y mutation causes iron overload in an estimated 50% of patients. H63D mutation is a very common mutation in the Caucasian population, but it rarely develops into hemochromatosis. Even though hemochromatosis is a common precipitating factor for PCT, most patients with hemochromatosis never develop the disease.

Hepatitis C and HIV infection have both been found to precipitate PCT. HCV is a very common precipitating factor. Two possible mechanisms by which HCV causes PCT are its triggering of increases in free hepaticollary iron and free radical oxidative due to increased oxidative stress. HIV can play an independent role in the development of PCT, but it is often found with HCV coinfection. The mechanisms by which HIV produces PCT are altered porphyrins, direct hepatic damage, impaired cytochrome oxidase, and increased estrogen levels. PCT has been associated with many other conditions such as diabetes mellitus, dialysis-dependent chronic renal failure, discoid
lupus erythematosus, myeloproliferative diseases, lymphoproliferative diseases, and hepatic disease.\textsuperscript{6,19}

Clinical presentation usually provides strong evidence to suspect PCT, and a variety of studies help improve diagnostic accuracy. Total plasma or urine porphyrin is the initial exam to confirm porphyria. A 24-hour urine specimen with fractionation reveals elevated uroporphyrins and a uroporphyrin-to-coproporphyrin ratio of 3:1 to 5:1, which distinguishes PCT from other cutaneous porphyrias, including pseudoporphyria, which would have normal urinary porphyrins.\textsuperscript{3,20} Urinary delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels also aid in differentiating between porphyrias.\textsuperscript{21} PCT has normal urinary ALA and PBG levels. In office, the urine sample examined under Wood’s light will fluoresce pink or coral-red.\textsuperscript{4} Normal erythrocyte total porphyrins help distinguish PCT from hepat erythropoietic porphyria (HEP), which has markedly elevated erythrocyte porphyrins.\textsuperscript{20} Decreased measured erythrocyte UROD activity points to familial PCT, as sporadic PCT has normal erythrocyte UROD activity.\textsuperscript{3} A detailed history will help reveal some possible precipitating factors such as alcohol consumption, oral estrogen use, or smoking. Liver studies, including serum bilirubin, prothrombin time, and hepatic enzymes, should be performed. Complete blood count, metabolic panel with creatinine, and iron studies with an emphasis on serum ferritin levels will help in management. HFE genetic testing looking specifically at C282Y and H63D mutations should be used for hemochromatosis diagnosis.\textsuperscript{2,5,12} UROD mutation testing improves diagnostic accuracy for PCT type. Viral serology will help find the possible precipitating presence of HCV or HIV infection.\textsuperscript{2,4,6,16}

Histopathology of PCT reveals a subepidermal bulla with little to no inflammatory infiltrate and an undulating, festooning dermal papilla projecting into the bulla.\textsuperscript{3,4,23} Thickened blood-vessel walls in the dermis occur due to deposition of PAS-positive material.\textsuperscript{4,21} Caterpillar bodies, a common, but not diagnostic, characteristic of PCT consist of PAS-positive cosinophilic, elongated, wavy structures usually found in the epidermis above the bulla.\textsuperscript{4,6,23} Direct immunofluorescence shows IgG, IgM, fibrinogen, and complement (C3) in the basement membrane and around vessels of the upper dermis.\textsuperscript{3,4,6,21}

Management of PCT begins with avoidance of all possible precipitating factors like alcohol and estrogen.\textsuperscript{2,24} Physical barriers and sun protection, such as clothing and sunscreens containing zinc oxide, and avoiding skin trauma protect against worsening skin disease. This initial approach may be sufficient to treat PCT.

Phlebotomy is the preferred treatment for PCT. Phlebotomy of 450 mL (one unit) at two-week intervals is performed until serum ferritin falls below 25 ng/mL, or until hemoglobin falls below a preset point, to prevent anemia.\textsuperscript{2,25} Clinical improvement may take several months. Skin fragility and bullous formation will be the first clinical symptoms to improve. More chronic symptoms such as hypertrichosis and sclerosis will improve at a slower rate.\textsuperscript{26} Antimalarial medications (chloroquine and hydroxychloroquine) can be used as an alternative to phlebotomy. Low-dose treatment with hydroxychloroquine (100 mg) or chloroquine (125 mg) given twice a week has shown similar results as phlebotomy.\textsuperscript{27}

While treating with antimalarials, monitor urine and plasma porphyrin levels.\textsuperscript{2,4,6,16} Therapy is discontinued when porphyrin levels are normal. Treat underlying HCV and/or HIV infection if found to be present.\textsuperscript{18} Iron chelation can be used if other treatments are contraindicated, but is not as effective as phlebotomy or antimalarials.

Conclusion

Porphyria cutanea tarda should be suspected in patients with bullae and increased skin fragility in sun-exposed areas. The diagnosis can be confirmed biochemically by characteristically elevated uroporphyrins and coproporphyrins in the urine. Given the diagnosis of PCT, investigations may include, but are not limited to, liver function tests, iron studies, HCV and HIV serology, alcohol intake, and current medication review. With the possible association of hereditary hemochromatosis, one may consider gene screening if PCT is clinically suspected. The patient should continue to be monitored closely, both clinically and biochemically, to ensure response to treatment and monitor for possible relapse. Of the various treatment options available, the preferred modality is phlebotomy combined with avoidance of sunlight and other precipitating factors.
References


