

Sporadic Porphyrria Cutanea Tarda as the Initial Manifestation of Hereditary Hemochromatosis

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ABSTRACT

Porphyrria cutanea tarda (PCT) is a skin disorder characterized by abnormal heme synthesis. We present a 45-year-old man with intermittent skin lesions recurring annually for years. Skin biopsy and measurement of serum heme precursors confirmed a diagnosis of PCT. He had persistently elevated alanine and aspartate transferase. He was referred to hematology and had genetic testing with iron studies which also revealed hereditary hemochromatosis (HH). Therapeutic phlebotomy was initiated, which led to resolution of iron overload and skin lesions. We highlight the associated conditions of PCT and HH, their common therapy of phlebotomy, and initial manifestations of HH.

INTRODUCTION

Porphyrria cutanea tarda (PCT) is the most common subtype of the porphyrias.^{1,2} It is characterized by photosensitivity, causing various skin lesions.^{1,2} PCT is associated with hereditary hemochromatosis (HH). HH is the most common genetic disease in the whites of Northern European descent and is characterized by deposition of iron in various organs causing chronic inflammation, most notably in the liver.³ This report seeks to identify the frequency and incidence of PCT as the initial manifestation of HH.

CASE REPORT

The patient is a 45-year-old man who presented to his primary care provider with episodes of pustules on his dorsal hands, occurring intermittently during the summer for many years with associated periumbilical abdominal pain. He has a medical history of gout and osteoarthritis. He is adopted with an unknown family history, drinks heavily, and has no known allergies. Physical examination was notable for obesity, nontender abdomen, and erythematous papulonodular lesions in various stages of healing on the dorsal hands. A complete metabolic panel, complete blood count, urinalysis, and chest x-ray were remarkable for an elevated alanine transaminase (ALT) of 122 U/L and aspartate transaminase (AST) of 169 U/L. The patient was diagnosed with presumed nonalcoholic fatty liver disease, so alcohol cessation and exercise were advised. When ALT and AST remained elevated 4 months later, an abdominal computed tomography was ordered, which showed no hepatic lesions or cirrhosis. Viral hepatitis laboratory results were negative, and iron studies were not ordered at this time.

Two years later, the patient established care with a new primary care provider and presented with worsening chronic joint pain. Laboratory results showed similarly increased ALT and AST. One year later, he developed a recurrence of skin lesions which prompted dermatology referral. A skin biopsy showed “caterpillar bodies,” which are indicative of either PCT or pseudoporphyria, a rare condition histologically identical to PCT in the absence of porphyrin abnormalities.⁴ He was referred to hematology and was found to have high urine heterogeneous carboxylated porphyrins with normal erythrocyte porphyrins, which is diagnostic of sporadic PCT. On further workup, an iron panel illustrated iron overload with high serum ferritin (3,586 ng/mL), high serum iron (266 µg/dL), and low transferrin (206 mg/dL). He had genetic testing which confirmed a diagnosis of HH with homozygosity of the C282Y gene. The patient subsequently began therapeutic phlebotomy. Endocrinology referral evaluated possible involvement of the pancreas, testicles, thyroid, and pituitary gland yielding negative results. At a follow-up appointment 9

months after starting phlebotomy, laboratory results, including AST, ALT, and ferritin, were within normal limits. The patient also denied joint pain and reported no recurrent skin lesions in the last 6 months.

DISCUSSION

PCT is a dermatological disease in the porphyria family, a group of diseases caused by abnormal heme synthesis.¹ It affects 1 in 25,000 Americans and comprises 80%–90% of porphyrias.² In PCT, the deficient activity of uroporphyrinogen decarboxylase inhibits conversion of uroporphyrinogen to coproporphyrinogen.² This causes accumulation of carboxylated porphyrins in the skin which absorb UV-A light and creates peroxides causing oxidative skin damage.² This manifests as skin fragility, ulceration, white papules, vesicles/bullae, hypertrichosis, and hyperpigmentation.¹ Biopsy of bullae reveals eosinophilic periodic acid Schiff-positive globules in the epidermis called “caterpillar bodies”.⁵ Despite this specific pathological finding, presenting signs are often nonspecific, making porphyrias an underdiagnosed entity.¹

HH is the most common genetic disease in the whites of Northern European descent. It is caused by a mutation in iron metabolism proteins, most commonly the hemochromatosis protein, encoded by the HFE gene.³ Around 85%–90% of those affected are homozygous for the HFE C282Y mutation.³ Pathophysiology of HH involves increased intestinal iron absorption, deposition of iron in tissues, and resultant oxidative damage. Iron can accumulate in the liver, spleen, heart, joints, endocrine organs, and skin, causing complications including cirrhosis, hepatocellular carcinoma, heart failure, diabetes, arthritis, hypogonadism, hypothyroidism, and in the subject of this case, PCT.³

HH commonly co-occurs in patients with a diagnosis with PCT, unsurprising given these conditions share a common pathophysiology.⁶ Evidence of iron overload has been demonstrated in most PCT patients, with siderosis found on liver biopsy and evidence of iron overload by labs.⁷ Around 39%–47% of PCT patients from primarily white populations have at least one C282Y HFE mutation vs 3%–12% in controls.^{8–11} Furthermore, a large meta-analysis of patients with genetic susceptibility for HH found that in those homozygous for C282Y, there was a 48-fold increase in the chance of developing PCT.¹² Given these findings, it is likely that patients may present with PCT to their hepatologist.²

When diagnosed with HH, most patients are asymptomatic and are identified after iron studies conducted for other reasons or by family genetic screening.¹³ Early HH symptoms, including fatigue, abdominal pain, arthralgias, and weakness, are vague and nonspecific, lending little information to inform diagnosis.³ Our patient had abdominal pain associated with flares of PCT and arthritic symptoms potentially due to HH. Although these symptoms were present for 5 years before diagnosis of HH, it

was only after diagnosis of PCT that HH was considered, making diagnosis of PCT the most specific indication for exploring the underlying HH. This delay is consistent with a survey of 374 HH patients in which 42% of patients presenting symptomatically were diagnosed months to years after presentation.¹⁴ Although our patient’s HH was diagnosed soon after his PCT diagnosis, one case series of 8 patients with PCT and HH found that median time to diagnosis of HH after diagnosis of PCT was 1.9 years.⁶ During this delay, 25% of patients developed diabetes, likely due to HH.⁶ In 5 of these patients and in 2 other patients, detailed in separate case reports, PCT was the initial manifestation of HH.^{6,15,16}

Many HH patients initially present with irreversible tissue damage causing cirrhosis, heart failure, hepatocellular carcinoma, or diabetes.³ However, PCT diagnosis offers an opportunity for early intervention to prevent these complications. The diagnosis of PCT should prompt iron studies and liver function tests to screen for HH with a low threshold for genetic testing. In conclusion, our case contributes to evidence demonstrating that PCT is a specific and early manifestation of HH that, if promptly diagnosed, can lead to the prevention of advanced sequelae of HH.

DISCLOSURES

Author contributions: MV Edwards and JM Ray collected data, wrote, and edited the manuscript. BR Bacon oversaw writing of the manuscript. JM Ray is the article guarantor.

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