Porphyria cutanea tarda associated with \textit{HFE} C282Y homozygosity, iron overload, and use of a contraceptive vaginal ring

James C. Barton, MD\textsuperscript{1,2}\textsuperscript{*} and Corwin Q. Edwards, MD\textsuperscript{3}

\textsuperscript{1}Southern Iron Disorders Center, Birmingham, AL, USA; \textsuperscript{2}Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; \textsuperscript{3}Department of Medicine, Intermountain Medical Center, University of Utah, Salt Lake City, UT, USA

Porphyria cutanea tarda (PCT) is characterized by decreased uroporphyrinogen decarboxylase activity in hepatocytes, uroporphyrin I and heptacarboxyl porphyrin III accumulation, photosensitivity dermatitis, and increased storage iron. In women, estrogen therapy, including oral contraceptives, postmenopausal hormone replacement, and tamoxifen for breast cancer treatment, is a risk factor for PCT. We report the case of a woman who presented with PCT, \textit{HFE} C282Y homozygosity, and hepatic iron overload and was using a contraceptive vaginal ring containing ethinyl estradiol, an estrogen. We discuss this case in the context of characteristics of other persons with PCT, including common \textit{HFE} mutations, iron overload, and estrogen exposure.

Keywords: contraceptives; estrogen; ethinyl estradiol; hemochromatosis; iron overload

*Correspondence to: James C. Barton, Southern Iron Disorders Center, Suite 626, 2022 Brookwood Medical Center Drive, Birmingham, AL 35209, USA, Email: ironmd@isp.com

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Porphyria cutanea tarda (PCT), the most common of the porphyrias, is characterized by decreased activity of uroporphyrinogen decarboxylase (UROD) in hepatocytes, accumulation of uroporphyrin I and heptacarboxyl porphyrin III, photosensitivity dermatitis, and increased storage iron (1). \textit{HFE} p.C282Y and p.H63D alleles are more prevalent in whites of European descent with PCT than in control subjects (2, 3). Other risk factors for PCT include excess iron accumulation from any cause, excessive alcohol consumption, estrogen use, hepatitis C, human immunodeficiency virus (HIV) infection, smoking, and hepatotoxins (1).

We report the case of a woman who presented with PCT, \textit{HFE} C282Y homozygosity, and hepatic iron overload and who was using a contraceptive vaginal ring that contained etonogestrel and ethinyl estradiol. We discuss this case in the context of characteristics of other persons with PCT, including common \textit{HFE} mutations, iron overload, and exposure to estrogens.

Case

In August, 4 months before presentation, a 35-year-old white woman of Scots and English descent developed reddish urine for several days followed by eruption of vesicles and blisters on the dorsal surfaces of her hands and fingers, the sides of her nose, and her upper anterior chest, knees, and legs. She worked as a landscaping contractor and noticed that lesions occurred on areas exposed to sunlight, but application of sunscreen neither diminished the rate at which new lesions appeared, nor promoted healing of older lesions. Her skin was fragile in areas of the lesions and the lesions healed slowly, often with scarring. She also developed dark brown pigmentation and the growth of fine black hair over her cheeks. She had no history of liver disease, iron abnormalities, or related problems. She consumed three glasses of wine each week and had smoked electronic cigarettes for approximately 6 months, having changed from tobacco cigarettes. She took duloxetine 60 mg daily. She had donated three units of blood for transfusion, but none in several years. She had never taken supplemental iron or received erythrocyte transfusion. There was no family history of abnormalities similar to hers. She had no menses in the 12 months before presentation due to the effects of a contraceptive vaginal ring (NuvaRing\textsuperscript{®}; etonogestrel/ethinyl estradiol). A dermatologist performed a punch biopsy of two skin lesions on her left forefinger and referred her for hematology evaluation and treatment.

Physical examination confirmed the presence of new vesicles and bullae with erythematous bases, some as large as 1 cm in diameter, and older lesions in various stages of erosion, resolution, and scarring in the anatomical
distribution described above. Lesions were most prominent on the dorsal surfaces of the hands and fingers (Fig. 1a). Milia were scattered over areas affected with bullous lesions and were especially prominent on skin overlying finger joints. There was moderate hyperpigmentation over her zygomatic arches and upper anterior chest. Hypertrichosis with lanugo appeared only over her zygomatic arches. Examination of typically unexposed skin, the liver, and joints was normal.

**Laboratory methods**

Punch biopsy specimens of skin were deposited in immunofluorescence transport medium, flash frozen, and cut for manual immunofluorescence staining. The sections were probed with fluorescein-labeled anti-human antibodies specific for IgG, IgA, IgM, C3, C5b-9, and fibrinogen.

**Results**

Direct immunofluorescence of skin biopsy specimens revealed linear glassy IgA and IgG deposition along the epidermal basement membrane zone and superficial dermal blood vessels, forming a characteristic ‘doughnut’ pattern. There was no positivity for IgM, C3, C5b-9, or fibrinogen.

At diagnosis, hemoglobin and MCV were within respective reference limits (Table 1), as were other complete blood count values (not shown). Serum iron was 54 μmol/L (303 μg/dL), transferrin saturation was > 96%, and serum ferritin was 2,800 pmol/L (1,246 μg/dL) (Table 1). AST and ALT activities were 1.10 μkat/L (66 IU/L) and 2.05 μkat/L (123 IU/L), respectively (reference 0.67 μkat/L (0–40 IU/L)). C-reactive protein was 221 nmol/L (23.2 mg/L) (reference 0.0–46.7 nmol/L (0.0–4.9 mg/L)). Hepatitis B surface antigen and core antibody, HCV antibody, and HIV antibody were not detected. Whole-blood UROD activity was 1.02 relative units (normal reference 1.00–3.00 relative units). Urine porphyrins revealed markedly elevated concentrations of uroporphyrin and heptacarboxyl porphyrin (Table 1). Concentrations of pentacarboxyl porphyrins and coproporphyrins were increased to a lesser extent (Table 1). *HFE* mutation analysis revealed C282Y homozygosity. HLA-A and HLA-B typing detected A*01, A*29; and B*08, B*44, respectively.

The liver specimen was interpreted as mild fatty metamorphosis, moderate chronic triaditis with mild interface hepatitis, 3–4+ diffuse hepatocellular iron deposition, and prominent Kupffer cell iron (Fig. 2). Sections prepared with Mallory’s trichrome and reticulin techniques revealed moderate portal fibrosis with lattice-like...
pericellular fibrosis and early bridging without definite cirrhosis (Fig. 2). Needle-like inclusions in hepatocytes were not observed. There was insufficient tissue for quantitative iron measurement.

Management consisted of therapeutic phlebotomy every 10–14 days, clothing to minimize sun exposure, twice-daily application of high-value ultraviolet-A and ultraviolet-B sunscreen to exposed areas of skin, cessation of alcohol and electronic cigarette use, and removal of the contraceptive vaginal ring. The present patient complied with recommendations except those regarding alcohol consumption and electronic cigarette use. The rate of appearance of new vesicles and bullae decreased soon after treatment commenced. Menses resumed soon after she removed the contraceptive vaginal ring. There was slow resolution of active skin lesions, hyperpigmentation, and hypertrichosis. By the end of phlebotomy therapy, she had no active skin manifestations (Fig. 1b) and developed pagophagia, a moderate decrease in hemoglobin and MCV in comparison with pretreatment values and near-normal urine porphyrin concentrations (Table 1). Ig levels were not measured after iron depletion was achieved. Eight months after presentation, she underwent implantation of a levonorgestrel-releasing intrauterine contraceptive system (Skyla®). Five months after implantation of the contraceptive device, she had not experienced recurrence of photosensitive dermatosis.

Discussion
The present patient had clinical, biochemical, and pathologic abnormalities typical of PCT (1). Affected areas other than the hands and face and facial hypertrichosis like that observed in the present patient were significantly more common in women than men among 152 consecutive patients with PCT in Spain (4). The present patient did not have a family history of PCT, although some carriers of deleterious UROD mutations do not develop PCT (1). Typical of patients with sporadic PCT, her whole-blood UROD relative activity was not decreased. We did not measure her hepatic UROD activity, which is typically decreased in sporadic PCT. In a study of 108 consecutive patients with PCT, 19% were HFE C282Y homozygotes, all had increased iron burdens, and 63% of women used estrogens (2). Most patients with PCT have at least three risk factors (1). Thus, the present patient had three common risk factors for PCT in white women of European descent: HFE C282Y homozygosity, hepatic iron overload, and use of an exogenous estrogen.

The prevalence of HFE C282Y homozygosity is ~60-fold higher in persons with PCT than in control subjects (2). C282Y homozygosity was associated with an earlier onset of skin lesions in both familial and sporadic PCT (5), consistent with features of the present patient. Regardless, many C282Y homozygotes do not develop iron overload (3) and most C282Y homozygotes do not develop PCT (3). In Basques with PCT, the prevalence of C282Y was not increased (3). In 190 German patients with sporadic PCT, serum and hepatic iron, serum ferritin, transferrin saturation, and liver enzyme measures did not differ significantly between patients with or without HFE mutations (3). These observations emphasize that non-iron heritable, hemorrhage-related factors also influence the development of PCT.

Table 1. Laboratory measures in woman with PCT and HFE C282Y/C282Y

| Characteristics                  | Reference limita | Day 0   | Day 133  | Day 254  |
|----------------------------------|------------------|---------|----------|----------|
| Uroporphyrins, µg/L              |                  | 4,892   | 457      | 49       |
| Uroporphyrins, µg/24 h           | 0–24             | 6,849   | 548      | 88       |
| 7-CP, µg/L                       |                  | 2,193   | 144      | 11       |
| 7-CP, µg/24 h                    | 0–4              | 3,070   | 173      | 20       |
| 6-CP, µg/L                       | <1               | <1      | <1       | 15       |
| 6-CP, µg/24 h                    | 0–1              | <1      | <1       | 27       |
| 5-CP, µg/L                       |                  | 12      | 17       | 1        |
| 5-CP, µg/24 h                    | 0–4              | 255     | 20       | 2        |
| Coproporphyrin I, µg/L           |                  | 81      | 34       | 8        |
| Coproporphyrin I, µg/24 h        | 0–24             | 113     | 41       | 14       |
| Coproporphyrin III, µg/L         |                  | 214     | 59       | 4        |
| Coproporphyrin III, µg/24 h      | 0–74             | 300     | 71       | 22       |
| Hemoglobin, g/L (g/dL)           | 120–180 (12.0–18.0) | 143 (14.3) | 115 (11.5) | 116 (11.6) |
| MCV, fL                          | 80.0–97.0        | 96.4    | 90.0     | 83.1     |
| Serum ferritin, pmol/L (µg/L)    | 45–450 (20–200)  | 2,800 (1,246) | 85 (38) | 97 (43) |
| Cumulative QFe, g                |                  | 0       | 2.0      | 2.4      |

PCT, porphyria cutanea tarda; 7-CP, heptacarboxyl porphyrin; 6-CP, hexacarboxyl porphyrin; 5-CP, pentacarboxyl porphyrin; MCV, mean corpuscular volume; QFe, iron removed by phlebotomy.

aBlank spaces represent items for which reference limits are undefined.

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acquired, or environmental characteristics trigger or contribute to the pathogenesis of PCT in some C282Y homozygotes and other persons with common \textit{HFE} mutations.

Excessive iron in hepatocytes, an almost universal finding in patients with PCT, is also important in PCT pathogenesis. Iron excess causes production of reactive oxygen species that increase the rate at which the UROD substrate uroporphyrinogen is oxidized (6). The consequent production of uroporphomethene (7) or another UROD inhibitor decreases UROD activity further. We attributed iron overload in the present patient predominantly to \textit{HFE} C282Y homozygosity. Her lack of menses in the year before presentation with PCT may have worsened iron overload. PCT has also occurred in patients with iron overload associated with beta-thalassemia minor, beta-thalassemia major, and refractory anemia with chronic erythrocyte transfusion.

Ajioka et al. compared hepatic \textit{HAMP} expression in 96 patients with PCT with that in 88 \textit{HFE} C282Y homozygotes who had marked hepatic iron overload (8). In patients with PCT, \textit{HAMP} expression was significantly lower, regardless of \textit{HFE} genotype, than that of C282Y.
homozgyotes with iron overload of similar severity but without PCT, suggesting that hepatic siderosis associated with PCT is caused by dysregulated hepcidin (8). In contrast, Darwich et al. observed that mean serum hepcidin levels were significantly higher in patients with PCT than in patients with chronic hepatitis C without PCT or in control subjects, suggesting that mechanisms regulating iron homeostasis in PCT differ from those involved in other related disorders, such as hemochromatosis, HCV infection, or excessive alcohol consumption (9).

Estrogen therapy in women, including oral contraceptives (1), postmenopausal hormone replacement (1), and tamoxifen for breast cancer (3), is a risk factor for PCT. In men with prostate cancer, PCT has been associated with diethylstilbestrol or fosfestrol treatment (1). There were no significant differences in serum iron and ferritin measures, liver iron grade, and HCV status in women with PCT who were taking estrogens and those who were not (2). A plausible mechanism by which estrogens may act to increase PCT risk is increased estrogen quinone formation and consequent enhanced generation of free radicals.

The present patient used a contraceptive vaginal polymeric ring for 1 year before presentation with PCT. This product is estimated to deliver 120 µg of etonogestrel (a progestin) and 15 µg of ethinyl estradiol (an estrogen) each day of use, on average (10). We were unable to identify reports of PCT in large series of women who used this vaginal contraceptive ring or reports of PCT associated with etonogestrel. On the other hand, ethinyl estradiol, a component of several oral contraceptive preparations, has been explicitly associated with PCT (1). Like the use of oral contraceptives, use of contraceptive vaginal rings has been associated with increased risk of deep venous thrombosis/pulmonary thromboembolism (11). This indicates that significant amounts of active estrogen are transferred from the vaginal rings to the blood. Based on these observations, we infer that ethinyl estradiol contributed to the development of PCT in the present patient. We cannot exclude the possibility that other reports of PCT in women who used Nuvaring® have been submitted to the US Food and Drug Administration or corresponding regulatory agencies in other countries. In contrast, transdermal estrogens were safe and effective for postmenopausal hormone replacement in four women previously treated for PCT (12). The intrauterine contraceptive device selected by the patient and her gynecologist after removal of the contraceptive vaginal ring is based on levonorgestrel (a progestin). Taken by mouth as an emergency contraceptive, levonorgestrel was associated with acute porphyria but not PCT (13).

Cigarette smoking is common in persons with PCT (1, 2) and is often associated with alcohol consumption. Smokers developed cutaneous manifestations of sporadic PCT at younger ages than non-smokers, on average. Cytochrome P450 CYP1A2 is important for the metabolism of estrogens and exogenous compounds. Although smoking increases CYP1A2 activity, Bulaj et al. observed no correlation of histochemical evidence of CYP1A2 activity in hepatocytes of patients with expression of familial or sporadic PCT (2). We were unable to identify reports of PCT in persons who smoked electronic cigarettes, like the present patient.

Excessive alcohol consumption was more common in men than women with PCT (2) and in persons with PCT who also had infections with HCV (2) or HIV (14). There was a significant positive association of alcohol intake and porphyrinuria in 1,613 non-porphyric adults in Madrid after correcting for gender, age, and body mass index (15). In rats treated with hexachlorobenzene, decreased UROD activity induced by ethanol predisposes to the development and progression of porphyria. Although the present patient reported that she consumed alcohol in moderation, a role of alcohol in the causation of her PCT cannot be excluded.

The present patient had mild fatty liver not attributed to excessive alcohol consumption. Fatty liver is relatively common in persons with PCT (6), and it has been suggested that non-alcoholic fatty liver disease (NAFLD) predisposes to the development of PCT (16). Hepatic iron levels are increased in persons with NAFLD (17).

Therapeutic phlebotomy is the predominant treatment for most patients with PCT because phlebotomy removes excess iron from hepatocytes (1). The present patient had HFE hemochromatosis with iron overload, for which phlebotomy is also the preferred management (3). Chelation therapy with intravenous deferoxamine, subcutaneous deferoxamine, and oral deferasirox has also been used to remove excessive iron in patients with PCT and should be considered in patients with PCT who are intolerant of phlebotomy (18). The rate of clinical and biochemical remission in the present patient was representative of that in other PCT cases (1).

Conclusions

PCT in the present patient was associated with three predominant risk factors: HFE C282Y homozygosity, hepatic iron overload, and exposure to an exogenous estrogen via a contraceptive vaginal ring. Smoking, alcohol consumption, and NAFLD may have contributed to PCT pathogenesis.

Authors’ statement

The authors have no conflicts of interest to report. JCB evaluated and treated the patient. CQE consulted on this case. Both authors conceived and contributed to the manuscript, performed photography, and approved the final manuscript.
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