Hepatitis C- and HIV-induced porphyria cutanea tarda

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Patient: Male, 47
Final Diagnosis: Porphyria cutanea tarda
Symptoms: Chills • cough dry • thumb swelling
Medication: —
Clinical Procedure: —
Specialty: Metabolic Disorders and Diabetics

Objective: Challenging differential diagnosis
Background: Porphyria cutanea tarda (PCT) is the most common type of the porphyria. It occurs due to the deficiency of enzyme uroporphyrinogen decarboxylase (UROD), which is the fifth enzyme in the biosynthesis of heme and catalyzes the conversion of uroporphyrinogen to coproporphyrinogen. The risk factors for PCT include hereditary hemochromatosis, hepatitis C infection, ethanol abuse, estrogen use, HIV, smoking, chlorinated polycyclic aromatic hydrocarbons, and hemodialysis.

Case Report: A 47-year-old Hispanic man presented with right thumb swelling, redness, and pain for approximately 1 week. Past medical history included HIV/AIDS, hepatitis C infection, alcohol abuse, heroin abuse, and CMV retinitis. Skin examination revealed blistering and hypo/hyper pigmented lesions over the dorsal aspects of the hands and other sun-exposed areas. Serum porphyrins were discovered to be elevated. The quantitative urine porphyrins revealed elevation of uroporphyrins, heptacarboxyl-porphyrins, hexacarboxy-porphyrins, pentacarboxyl-porphyrins and coproporphyrin. Genetic mutation of UROD was not detected. Due to the classic cutaneous lesions, laboratory findings, and associated risk factors, we were able to confirm our suspicion of the sporadic (type 1) form of PCT.

Conclusions: A strong correlation has been demonstrated between the sporadic (type 1) form of PCT and hepatitis C virus (HCV) infection in multiple studies. The mechanism through which HCV infection may cause or trigger PCT is unknown. PCT has been described for many years, but still eludes the differential diagnosis in a patient with cutaneous findings. The uniqueness of our case is the possibility that combined risk factors have an effect on PCT.

MeSH Keywords: HIV • Phlebotomy • Chloroquine • Hepatitis C – complications • Porphyria Cutanea Tarda

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Porphyria cutanea tarda (PCT) is the most common type of porphyria worldwide. It has an estimated prevalence of 1:10 000 to 1:70 000 and the sex ratio is approximately equal [1]. The wide range in prevalence is due to its geographical variation. It usually becomes apparent during the fourth or fifth decade of life but can also present earlier. It occurs due to the deficiency of enzyme uroporphyrinogen decarboxylase (UROD). UROD is the fifth enzyme in the biosynthesis of heme and catalyzes the conversion of uroporphyrinogen to coproporphyrinogen [2]. The 2 main sites of heme synthesis are erythrocytes and the liver. A decrease in the activity of UROD therefore leads to accumulation of uroporphyrin and other highly carboxylated porphyrins in various organs, most commonly the liver and skin. PCT usually manifests with dermatological signs caused by deposits of uroporphyrin and partially decarboxylated porphyrins in the skin [2]. The cutaneous findings include photosensitivity, blisters, erosions, and milia on the sun-exposed areas of the body. In addition, hypertrichosis, hyper- or hypo-pigmentation, sclerodermoid plaques, and scarring alopecia may also be observed [3]. There is also a risk of secondary skin infections. These types of skin damage are subsequent to the photoactivation of porphyrins by long-wave ultraviolet light [3]. Skin lesions are the main reason these patients first seek medical attention. Several studies have analyzed the coexistence of factors considered to contribute to development of porphyria cutanea tarda. The risk factors for PCT include normal or increased amounts of hepatic iron (e.g. in hereditary hemochromatosis), hepatitis C infection, alcohol abuse, estrogen use, HIV, smoking, chlorinated polycyclic aromatic hydrocarbons, and hemodialysis [4]. PCT can be divided into 2 types: type 1 PCT (sporadic; no UROD mutation) and type 2 PCT (familial PCT, caused by heterozygosity for a UROD mutation), which are clinical indistinguishable from each other. Type 1 accounts for approximately 75–80% of patients with PCT in which the deficiency of UROD is limited to the hepatocytes [5]. The level of UROD in the erythrocytes is normal, but those in the liver are low. In patients with type I PCT, there is a significant association with liver disease triggered by genetic and environmental factors such as alcohol abuse, estrogen use, hepatitis C virus infection, hemochromatosis, and polychlorinated hydrocarbons [6]. Type 2 accounts for approximately 20–25% of cases in which there is partial deficiency of UROD in all tissues such as both erythrocytes and hepatocytes [6]. Type 3 (familial; without UROD mutation) is a very rare form in which there exists an apparently genetic predisposition that leads to decreased UROD activity limited to hepatocytes. Chronic liver disease is common in sporadic PCT but it is infrequent in inherited PCT [7].

Here we present the case of a patient diagnosed with type 1 porphyria cutanea tarda (PCT) that presented with classical cutaneous findings and multiple risk factors, including alcohol abuse, HIV/AIDS, and hepatitis C infection that have been strongly associated with the sporadic form of PCT.

Case Report

A 47-year-old Hispanic man presented with right thumb swelling, redness, and pain for approximately 1 week. He denied any recent trauma or insect bite to the affected area. Other complaints included feeling febrile, chills, and a non-productive cough. He denied any headache, chest pain, palpitations, short of breath, nausea, vomiting, abdominal pain, diarrhea, or dysuria. Further review of his medical records revealed multiple previous hospitalizations within the past 10 years for similar presentations as on this admission except the swelling would occur at a different location such as his neck, face, or arm. On these admissions he was diagnosed and subsequently treated for cellulitis and abscesses of that particular area. His past medical history included being diagnosed with HIV and hepatitis C (HCV) 10 years ago, alcohol abuse, intravenous drug abuse with heroin, and CMV retinitis. Medications taken at home included lopinavir/ritonavir 800 mg/200 mg PO every day and trimethoprim/sulfamethoxazole 80/400 at 160 mg PO every day for PCP prophylaxis. All vital signs were stable on admission and within normal range except a fever of 39.0°C. Physical examination demonstrated a swollen, erythematous right distal phalanx of the thumb that was exquisitely tender to palpation. Skin examination (Figure 1A–C) revealed blistering, hypo- and hyper-pigmented lesions over the dorsal aspects of the hands and other sun-exposed areas. The patient reported that these lesions started to occur in his early 40’s. The rest of his body, and non-sun exposed areas lacked any similar lesions (Figure 1D). His pupils were 3 mm bilaterally, equally round, and reactive to light. No peripheral lymphadenopathy was palpated. Heart and lung examination revealed a regular rate and rhythm, no murmurs noted, and breath sounds were clear bilaterally. Abdominal examination showed a soft abdomen that was not distended or tender to palpation. No hepatosplenomegaly was present. Physical examination found other body systems were unremarkable.

Initial laboratory workup (Table 1) was remarkable for mild hyponatremia, minimal elevations in liver transaminases, ESR, and CRP. Iron panel revealed a low serum iron of 43 mcg/dL, low transferrin of 123 mg/dL, low TIBC of 151 mcg/dL, transferrin saturation of 28%, and elevated ferritin of 989.2 ng/mL. Several labs were ordered to assess the status of his HIV/AIDS and hepatitis C. The HIV Western blot test result was positive, HIV PCR 141 000 copies/ml, absolute CD3 count of 179 cells/mcL, absolute CD4 count of 21 cells/mcL, absolute CD8
count of 158 cells/mcL, HCV reactive, HCV genotype 1a, and HCV PCR 1800,000.00 iu/L. Our differentials were plentiful but porphyria cutanea tarda (PCT) was high on the list due to the characteristic skin lesions. Serum porphyrins were discovered to be elevated at 42.0 mcg/L. Due to our suspicion, we opted to evaluate the urine for the presence of porphyrins. The results from the quantitative urine porphyrins are shown in Table 2. The quantitative urine porphyrins revealed elevation of uroporphyrins, heptacarboxyl-porphyrins, hexacarboxy-porphyrins, pentacarboxyl-porphyrins, and coproporphyrin. A genetic mutation of UROD was not detected. Due to the classic cutaneous lesions, laboratory findings, and associated risk factors, we were able to confirm our suspicion of PCT, and, more specifically, allowed us to classify it as the sporadic form of PCT (type 1). Other labs tests, which included an ANA, anti-centromere, cryoglobulin, Scl-70 antibody, beta-2 glycoprotein-1 antibody, and RNA polymerase 3 antibody IgG were all negative, erythropoietin was 30.1 (high), and reticulocyte count was 5.4% (low).

To further evaluate the swelling of the right thumb, a radiograph of the right thumb revealed osteomyelitis of the first distal phalanx. Incision and debridement of the first distal phalanx that was done by the orthopedic service on the

Figure 1. (A–C) Blistering, hypo/hyper pigmented lesions over the dorsal aspects of the hands and other sun-exposed areas. (D) No similar lesions on non-sun exposed areas (back).
second hospital day. Vancomycin 1000 mg IV every 12 hours and piperacillin/tazobactam 3.375g IV every 6 hours were empirically initiated on admission. Blood cultures were negative. By the fourth hospital day, the cultures from the debridement of the first distal phalanx grew methicillin-sensitive Staphylococcus aureus (MSSA) and pan-sensitive Klebsiella pneumonia. The initial antibiotic regime was discontinued and ceftriaxone 2g IV daily was initiated. The infectious disease service was consulted and recommended the placement of a PICC line for 8 weeks duration of ceftriaxone 2 g IV daily. A transthoracic echocardiogram was obtained to rule out endocarditis due to the patient history of intravenous drug use. It revealed a normal left ventricle with an ejection fraction of more than 70%.

Our patient had several risk factors that made him susceptible for PCT. It is very difficult to determine which factors were relevant in this case of PCT, but there is a strong association between HCV and PCT. The patient was treated for osteomyelitis and counseled on cessation of alcohol abuse. He was also advised to take appropriate precautions to protect himself from UV sun exposure. He subsequently followed up with the hematology service in our clinic for scheduled phlebotomy. He was subsequently discharged by the sixth hospital day with discharge medications of ceftriaxone 2g IV daily for 8 weeks, emtricitabine/tenofovir disoproxil 200/300 at 1 tablet PO daily, and lopinavir/ritonavir 400 mg/100 mg PO every 12 hours. Due to his history of CMV retinitis, hydroxychloroquine was not considered as a viable alternative.

### Discussion

PCT is usually suspected on clinical grounds and the diagnosis is confirmed by the characteristic urinary porphyrin excretion profile. The diagnosis of PCT can be confirmed by specific biochemical analyses. The most useful initial test for PCT is a total serum porphyrin. This is sensitive and specific test for the cutaneous porphyrias; further testing should be pursued if porphyrin is discovered in the serum. In the urine an increased excretion of uroporphyrin, hepta-carboxylated porphyrins, and coproporphyrin can be detected [8], and in the feces an increased excretion of coproporphyrin and isocoproprophyrin can be detected [8]. The diagnosis can also be made through measurement of hepatic uroporphyrinogen decarboxylase (UROD) activity [9]. Erythrocyte UROD activity can also be measured to distinguish the sporadic from the inherited form of PCT. It is pertinent to obtain additional diagnostic testing because many factors contribute to PCT. Therefore, patients should be screened for hepatitis C infection, HIV infection, iron panel studies, and genetic testing for HFE mutations.

A strong correlation has been demonstrated between the sporadic (type 1) form of PCT and hepatitis C virus (HCV) infection in multiple studies. Gisbert et al performed a systematic review

### Table 1. Initial laboratory work up.

| Test                      | Result          |
|---------------------------|-----------------|
| White blood cell count    | 8.79×10^3 uL    |
| Hemoglobin                | 10.6 g/dL       |
| Hematocrit                | 33.7%           |
| Platelet count            | 238×10^3 uL     |
| Sodium                    | 133 mmol/L      |
| Potassium                 | 4.1 mmol/L      |
| BUN                       | 16 mg/dL        |
| Creatinine                | 0.95 mg/dL      |
| Serum glucose             | 76 mg/dL        |
| Albumin                   | 3.3 g/dL        |
| Bilirubin                 | 1.0 mg/dL       |
| AST                       | 126 unit/L      |
| ALT                       | 140 unit/L      |
| Alkaline phosphatase      | 273 unit/L      |
| CRP                       | 5.09 mg/dL      |
| ESR                       | 32 mm/hr        |

### Table 2. Quantitative urine porphyrins.

| Type of prophyrin     | Result (mcg/g creatinine) | Normal range (mcg/g creatinine) |
|-----------------------|---------------------------|---------------------------------|
| Uroporphyrins         | 1321.0                    | <22.0                           |
| Heptacarboxy-porphyrins | 1642.0                   | <4.6                            |
| Hexacarboxy-porphyrins | 399.2                     | Not Detected                    |
| Pentacarboxy-porphyrins | 308.7                   | <1.7                            |
| Coproporphyrin        | 365.0                     | 23.0–130.0                      |
| Total Porphyrins      | 4036.0                    | 31.0-139.0                      |
of 50 studies that included a total of 2167 patients with PCT, and found that the overall prevalence of HCV was 50%. The prevalence of PCT among HCV-infected patients has been reported at 1–5% [10]. However, Gisbert et al noted that there is a significant geographic distribution. The lowest prevalences (20–30%) were observed in Australia, the Czech Republic, and France. The highest prevalence rates (71–85%) were observed in Japan, Italy, and Spain. The prevalence in the United States is 66%.

The mechanism through which HCV infection may cause or trigger PCT is unknown. Chronic HCV infection has been thought to impair porphyrin metabolism through a reduction of glutathione in hepatocytes. This lack of glutathione causes a decreased ability to reduce oxidized uroporphyrins, leading to their accumulation, and thus exerting an inhibitory effect on UROD [11]. It has been observed that HCV-infected individuals develop PCT at an earlier age compared to persons without HCV infection. Interferon therapy for chronic viral hepatitis C with has been shown to improve PCT [12]. In a patient with multiple risk factors for PCT, the risks seem to aggravate the clinical course of PCT. HIV has also been strongly implicated in the precipitation of the sporadic (type 1) form of PCT [13]. HIV and HCV co-infection appear to be significantly associated with elevated serum porphyrins [14].

Pegylated interferon in combination with ribavirin is the current standard of care for patients with chronic hepatitis C genotype 2, 3, or 4. Patients with hepatitis C genotype 1 should be treated with peginterferon, ribavirin, and a protease inhibitor. Alpha interferons are type-1 interferons that play a role in the innate and adaptive immune responses. Alpha interferons induce interferon-stimulated genes by binding to cell surface receptors, which in turn activate a cascade that stimulates multiple interferon-stimulated genes that block viral protein synthesis.

Porphyria cutanea tarda has been shown to improve with the treatment of hepatitis C with peginterferon through the suppression of HCV RNA.

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Treatment of PCT consists of the avoidance of trigger factors (alcohol, estrogen use, or sunlight), iron depletion, and the elimination of porphyrins. The avoidance of UV light exposure, wearing sun-protective clothing, and regular use of sunscreen are critical. Besides the avoidance of aggravating factors, the 2 main treatment regimens for PCT are phlebotomy and low-dose chloroquine therapy. Phlebotomy is the only non-pharmacological treatment with proven efficacy. It is recommended that about 450 to 500 mL of blood be removed weekly or every other week until the serum ferritin is less than 25 ng/mL [15]. Chloroquine is thought to work by accelerating the urinary excretion of porphyrins and by inhibition of porphyrin synthesis [15]. The standard dosage of chloroquine is 125 mg twice a week. Complete remission can be expected within 6 to 9 months. Chloroquine and phlebotomy in combination have been shown to induce remission quicker.

Conclusions

The sporadic form (type 1) of PCT is strongly associated with HCV infection; however, our patient presented with several other associated risk factors. This situation makes it very difficult to establish which risk factor is the inciting culprit. Even though PCT has been described for many years, it still eludes the differential diagnosis in a patient with cutaneous findings. This case report aims to provide information to help in prompt recognition of PCT, so that these patients can receive the appropriate therapy. Several studies have established the relationship between HCV and PCT. The uniqueness of our case is the possibility that combined risk factors such as HIV and HCV have on the effect of PCT. We suggest routine screening for HIV and hepatitis C in all patients with PCT, because HIV and HCV infection are major predisposing factor for the disease.

Disclosures

All authors who participated in this study declare no financial, professional, or personal conflicts. No grant support was received for this case report. All authors were involved in manuscript preparation and literature review.
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