CLINICAL VIGNETTE

Porphyria Cutanea Tarda

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Introduction

Hereditary porphyrias comprise a group of eight disorders involving the heme biosynthetic pathway, with each individual porphyria representing an abnormality in a specific enzymatic step of the pathway.[1] The major porphyrias can generally be categorized as acute or cutaneous. Acute porphyrias manifest as life threatening crises while cutaneous porphyrias cause chronic cutaneous photosensitivity.[1] Of the cutaneous porphyrias, porphyria cutanea tarda (PCT) is the most common. PCT is caused by a deficiency of uroporphyrinogen decarboxylase (UROD).[2] This enzymatic deficiency causes uroporphyrins to accumulate in the skin and liver, causing skin photosensitivity as well as hepatopathy due to hepatic siderosis.[3] Skin lesions consist of tense blisters that heal, leaving behind scarring and milia.[3] Patients may also experience hypertrichosis and hyperpigmentation, and thickening of sun-exposed skin that can resemble systemic sclerosis.[4] However, some patients present without the characteristic blistering lesions, which can delay diagnosis, and potentially lead to irreversible liver damage from porphyrin build-up and subsequent iron overload.[3]

Two forms of PCT have been identified; sporadic PCT makes up approximately 80% of cases while familial PCT makes up the remaining 20%.[3] Clinically, the cutaneous manifestations are indistinguishable.[2] Patients with sporadic PCT have no UROD mutation and normal liver UROD enzymatic activity between flares.[4] In contrast, patients with familial PCT have heterozygous UROD mutations, with half normal enzymatic activity when asymptomatic.[4] UROD activity must be less than approximately 20 to 30% of normal for a patient to be symptomatic.[3,4]

Many risk factors for and triggers of PCT have been identified. Alcohol use and cigarette smoking are commonly associated with PCT, potentially contributing to the production of UROD inhibitors through induction of cytochrome P450 pathways.[3,5] Alcohol induces the heme biosyntehtic pathway, exacerbating the build-up of porphyrins, and also increases iron absorption, which stimulates free radical production causing hepatotoxity.[2,6] Infection with the Hepatitis C virus (HCV) is also a risk factor, as it causes oxidative stress in the liver, inducing the heme biosynthesis pathway and subsequently causing accumulation of porphyrins; elevated ferritin is also commonly observed in patients with HCV.[5,7] Hemochromatosis gene mutations, particularly C282Y mutations, are also widely accepted triggers as they exacerbate the hepatic siderosis caused by the build-up of porphyrins.[7] Estrogen use has also been linked with the development of PCT.[5] The pathogenesis of estrogen in PCT is unknown; estrogen use is not associated with hepatic siderosis, but its use may place additional oxidative stress on the liver.[5,7] Diabetes mellitus (DM) has traditionally been connected with PCT, although recent studies have shown that alterations in glucose metabolism often occur many years after diagnosis of PCT, with elevated ferritin being an independent risk factor for developing DM.[8]

Of note, studies have shown that most patients with PCT have multiple underlying risk factors, suggesting additive effects of each individual factor. [3,5,7] The common theme in pathogenesis of PCT is iron overload; removal of iron from the body causes UROD levels to return to normal while administering iron causes disease exacerbation.[7] The exact pathogenesis of iron overload in causing PCT is unknown, but it may be due to oxidative damage to intermediates in the heme biosynthetic pathway.[7]

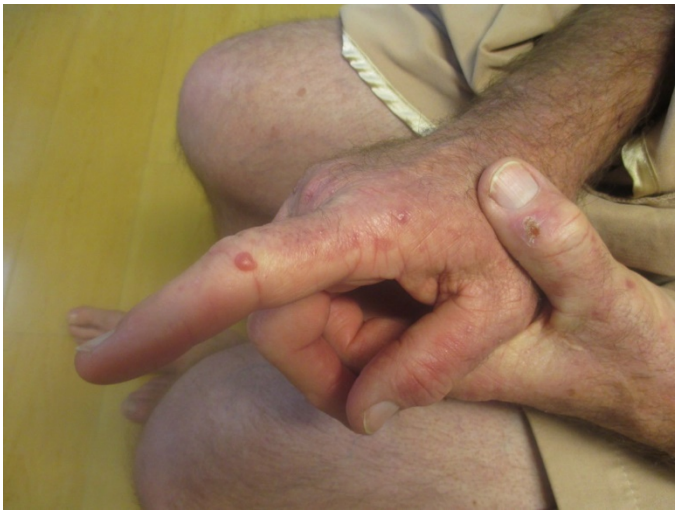
PCT is diagnosed through observation of clinical cutaneous manifestations and via laboratory studies. Laboratory work-up can include measurement of urine, fecal, and plasma porphyrin levels; twenty-four hour urine collection may provide a more accurate indication of plasma levels than a random urine sample.[6] A fluorescent spectrum of plasma porphyrins is thought to be the best diagnostic test for cutaneous porphyrias.[9] Histopathologic examination often shows cell-poor blistering beneath the epidermis as well as hyaline material deposition in the dermal vessels, which stains positive with periodic acid Schiff reagent.[2] Although histologic examination is not needed for diagnosis when laboratory work and clinical exam suggest PCT, it is helpful to rule out other diseases since the differential diagnosis includes cutaneous porphyrias, bullous drug eruptions, and autoimmune bullous diseases.[2]

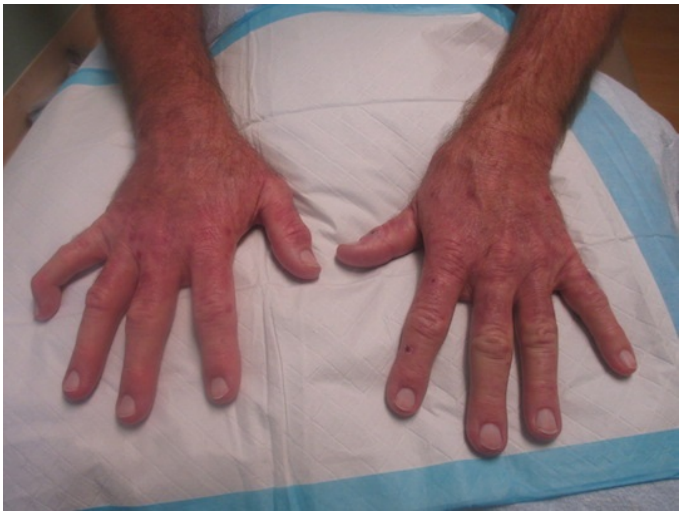
Case Report

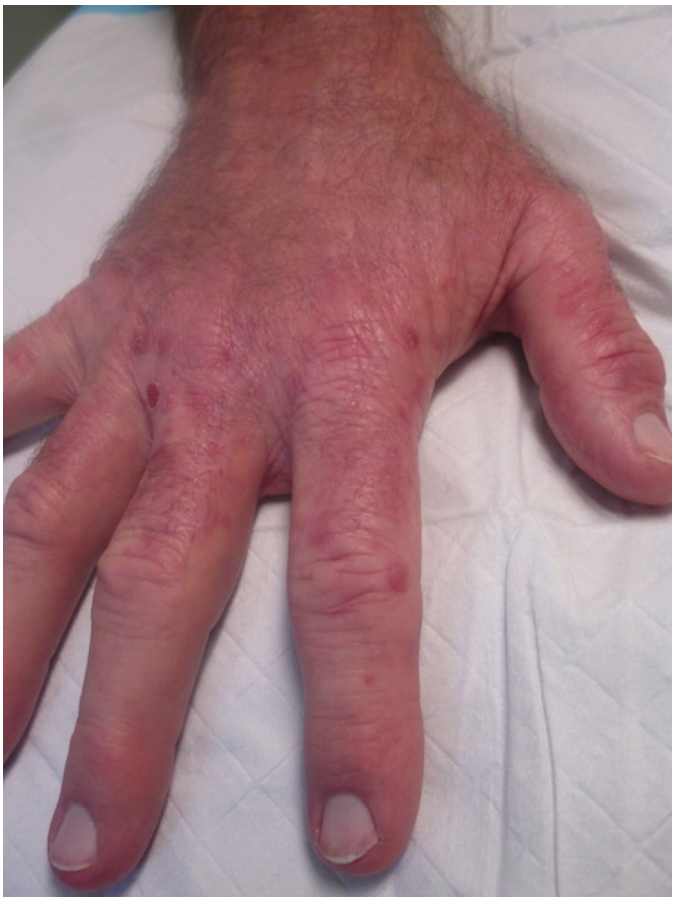
Our patient is a 59-year-old male, who was referred to UCLA Dermatology from his primary physician for a ten-year history of blistering on his hands that worsened with sun exposure. According to the patient, the blistering would heal without intervention within approximately one week, and was associated with white bumps. A prior physician suggested that his symptoms could be caused by a reaction to non-steroidal anti-inflammatory drugs (NSAIDs), although the patient discontinued NSAIDs without relief. Before his presentation to

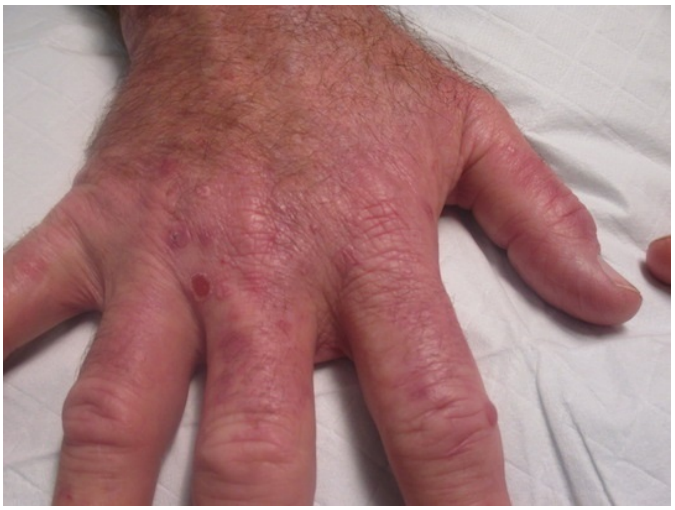
dermatology, he had not undergone any treatment for these blisters. His social history was significant for daily alcohol use, totaling approximately 15 drinks per week, as well a ten pack year history of smoking.

On exam, the patient was noted to have a tense one centimeter bulla on the right index finger. There were milia, scarring, and multiple crusted papules on the bilateral dorsal hands. His skin was diffusely dry, rough, cracked, and scaly (see images). The patient underwent a punch biopsy of the right index finger, which revealed a pauci-inflammatory sub-epidermal blister with underlying sclerosis. The papillary dermis contained thickened hyalinized blood vessels, consistent with a clinical impression of PCT. A direct immunofluorescence was also performed and was negative, which ruled out autoimmune bullous disease.









After his biopsy results, the patient was referred to hematology for further work-up and treatment. Hematology started the patient on a bi-monthly therapeutic phlebotomy regimen. Quantitative and qualitative urine porphobilinogen and whole blood porphyrin studies were sent, and were unremarkable, potentially due to low disease activity at the time. Bloodwork did reveal the patient to be a heterozygote for the C282Y hemochromatosis mutation. Hepatitis C screening was negative. Liver function testing and ferritin were within normal limits. Upon initiating treatment with phlebotomy, the patient experienced resolution of his blisters.

The patient was also referred to hepatology. Repeat blood and urine evaluation for PCT was un-revealing, although the patient had already been undergoing phlebotomy treatment at that time. Of note, the patient stopped phlebotomy treatment to undergo a twenty-four hour urine collection, which caused a recurrence of his blisters. The patient was tested for lead and arsenic, which may mimic PCT, both of which were negative. An abdominal ultrasound showed the liver to be homogenous, normal in size, and without focal lesions. Alpha fetoprotein testing was normal.

The patient returned for a three-month dermatologic follow-up. At this visit, his blisters showed significant improvement, with mild scarring on the bilateral dorsal hands and some crusted papules that had previously been blisters. The patient had begun to cut back on his alcohol intake, quit smoking, and was advised to continue phlebotomy given good clinical response.

Discussion

This case represents a remarkable interdisciplinary case with coordination of care from dermatology, hematology, and hepatology. Particularly notable was the extended time between symptom onset and diagnosis of PCT. Interestingly, the patient was cautioned about avoidance of NSAID use in the past. Ingestion of NSAIDs, as well as furosemide and tetracycline antibiotics, have a well-established association with pseudoporphyria, which presents clinically similarly to PCT.[2] However, a diagnosis other than pseudoporphyria should have been sought after his symptoms failed to resolve with discontinuation of NSAIDs.

Also notable was the classic combination of risk factors present in this patient; his alcohol use, cigarette smoking, and hemochromatosis gene mutation all likely contributed to the pathogenesis of his PCT. Recent studies have shown that while PCT is rare in patients with underlying hemochromatosis, it may be the presenting sign of the disease, as was for our patient.[10] Retrospective studies of patients with both hemochromatosis and PCT has shown up to 63% of patients had signs and symptoms of PCT that led to the discovery of underlying hemochromatosis.[10] Patients with both PCT and hemochromatosis have an increased risk of developing hepatocellular carcinoma than those with PCT alone, which is why testing for underlying hemochromatosis gene mutations is so crucial.[10]

The cornerstone of treatment for PCT is avoidance of known triggers, including avoiding alcohol use, smoking cessation, discontinuing estrogen, photoprotection, avoiding mechanical trauma and discontinuing iron supplements.[2,4,6] For this patient specifically, it seems that alcohol avoidance and smoking cessation has contributed to improvement of blistering lesions. Phlebotomy is also commonly used to reduce hepatic iron, with most protocols calling for one unit of blood to be removed every two weeks.[4] Phlebotomy is done to reduce ferritin to the lower limits of normal with frequent monitoring of hemoglobin to prevent anemia.[4] Clinical improvement with phlebotomy is generally apparent within 2 to 4 months, and improvement may also be documented by a decrease in plasma porphyrins.[2,4] Studies have shown that low dose chloroquine treatment may be just as effective and less expensive than frequent phlebotomy.[11] Chloroquine is thought to accelerate the secretion of porphyrins and may also inhibit porphyrin synthesis.[2] Remission with chloroquine therapy can take up to 6 to 9 months, although combination of chloroquine and phlebotomy may induce remission faster.[2] Cimetidine has also demonstrated effect in case studies, potentially through modulation of hepatic enzyme activity.[12] Although there have been no large studies on cimetidine use for PCT, it may present a viable alternative to patients with anemia and severe liver dysfunction who are not good candidates for phlebotomy or chloroquine treatment.[12]

This case highlights the importance of a high clinical suspicion for PCT and a low threshold for further investigation in any patient presenting with bullous skin lesions. The blistering lesions of PCT are significant in that they present a unique window to the rest of the body and may reflect underlying liver dysfunction or states of iron overload that necessitate additional study. However, physicians must also be aware that laboratory work up may not always reflect underlying disease, as was the case with our patient. Our patient demonstrated the classic clinical skin manifestations, biopsy results, and improvement with phlebotomy, but never had laboratory work up consistent with PCT, suggesting that for some patients clinical manifesttations may be the only clue to diagnosis.

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