80-Year-Old Man With Anemia and Blistering Skin Lesions

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An 80-year-old man presented to our institution with a 2-month history of pruritic rash, which developed shortly after a fishing trip. This was the first such outbreak, although 3 years previously, 2 nonhealing sores on the back of his neck were found to be seborrheic dermatitis. On further questioning, the patient admitted to dyspnea on exertion, progressively worsening during the past few years, but denied having any chest pain, palpitations, weight loss, fever, night sweats, or orthopnea.

The patient's medical history included paroxysmal atrial fibrillation, aortic stenosis, hypertension, hypothyroidism, and mild anemia. He had smoked 1 pack of cigarettes per day for many years but had quit 20 years previously, and he denied any alcohol or recreational drug use. His father and mother died of liver carcinoma and pancreatic carcinoma, respectively, and his daughter had a "skin disease." Medications and supplements that the patient was taking included atenolol, amlodipine, levothyroxine, aspirin, and folic acid, and he applied Vanicream and Neosporin ointment as needed; none of these were new to his medication regimen.

On physical examination, the patient was alert and oriented. His blood pressure was 176/78 mm Hg, his pulse rate was 66/min, and he was afebrile. Examination of his skin revealed blistering, crusting lesions on the back of his neck and small papules on his face. He also had shallow excoriated, ulcerated lesions on the dorsal aspects of his hands and forearms, as well as diffuse erythematous scaly patches on his right leg. The lesions were strictly in a photodistributive pattern. No areas of hypopigmentation or hypertrichosis were appreciated. His conjunctivae were pale but not icteric, and his neck was supple without thyromegaly. No oral lesions were seen. Carotid bruits were auscultated bilaterally, with intensity greater on the left than on the right. No lymphadenopathy was noted, and findings on lung, cardiac, abdominal, and rectal examinations were unremarkable. Initial laboratory results (reference ranges shown parenthetically) were as follows: hemoglobin, 9.6 g/dL (13.5-17.5 g/dL); platelets, 199 $\times$ 10^9/L (150-450 $\times$ 10^9/L); leukocytes, 3.6 $\times$ 10^9/L (3.5-10.5 $\times$ 10^9/L); mean corpuscular volume, 93.7 fL (81.2-95.1 fL); reticulocytes, 1.92% (0.60%-1.83%); sodium, 140 mEq/L (135-145 mEq/L); potassium, 4.2 mEq/L (3.6-4.8 mEq/L); calcium, 9.2 mg/dL (8.9-10.1 mg/dL); creatinine, 1.3 mg/dL (0.9-1.4 mg/dL); and albumin, 4.1 g/dL (3.5-5.0 g/dL). Skin biopsy revealed subepidermal bullae and mixed dermal inflammation.

1. Which <u>one</u> of the following is the <u>most likely</u> diagnosis in this patient?

a. *Pemphigus vulgaris*
b. *Dermatitis herpetiformis*
c. *Systemic lupus erythematosus (SLE)*
d. *Porphyria cutanea tarda (PCT)*
e. *Toxic epidermal necrolysis (TEN)*

Pemphigus vulgaris is a possibility because of the blistering lesions. However, flaccid bullae typically occur in the oropharynx and may then spread to the skin, with a predilection for the scalp, face, chest, axillae, and groin. Also, affected skin is often painful but rarely pruritic. Our patient had no mucosal lesions, and his rash was pruritic; thus, pemphigus vulgaris is unlikely.

Dermatitis herpetiformis, another condition characterized by pruritic blistering lesions, usually involves papulovesicles in a herpetiform pattern, distributed symmetrically over the extensor surfaces. Histologically, the demonstration of granular IgA deposits along the subepidermal basement membrane confirms the diagnosis. Although our patient had pruritic blisters, mainly on his forearms and hands, the biopsy specimen showed no IgA deposits; thus, dermatitis herpetiformis is unlikely.

Systemic lupus erythematosus can manifest with bullous skin lesions, which result from toxic necrolysis of the skin. However, the skin manifestations of SLE are not limited to sun-exposed surfaces, and thus SLE would be an unlikely cause in our patient. Porphyria cutanea tarda is usually characterized by the appearance of a blistering, pruritic rash on sun-exposed areas, the differentiating feature from other blistering skin diseases. Hyperpigmented macules, atrophic scarring from previous bullae, and milia

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See end of article for correct answers to questions.

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can also be seen. In our patient, it was clear that the blistering rash appeared after intense sun exposure and was present only on sun-exposed areas. Thus, we believed a diagnosis of PCT was most likely.

TEN is a possible diagnosis because it usually manifests with dissemination of purpuric macules and blisters on the face and trunk. It is usually drug induced and typically begins 1 to 3 weeks after the initiation of the causative drug or drug metabolite. Our patient did not start any new therapy before the onset of his rash, and thus TEN is unlikely. Because porphyria was suspected based on the history and physical examination findings, further studies were required to confirm the diagnosis.

2. Which <u>one</u> of the following is the best <u>initial</u> test to help establish a diagnosis in this patient?

a. *Measurement of urinary porphobilinogen (PBG) and porphyrins*
b. *Measurement of fecal porphyrins*
c. *Determination of uroporphyrinogen decarboxylase (UROD) activity*
d. *Measurement of plasma porphyrins*
e. *Skin biopsy*

The initial test for a suspected diagnosis of porphyria, in both the acute (ie, acute intermittent porphyria, hereditary coproporphyria, variegate porphyria) and the cutaneous-only (ie, PCT, congenital erythropoietic porphyria, erythropoietic protoporphyria) variants, is a 24-hour urine collection to measure both PBG and porphyrins. In acute porphyria, urinary PBG excretion (>3 times the reference range of 0-0.5 mg/24 h) must be increased substantially before the diagnosis can be considered seriously. In cutaneous-only porphyrias, urinary PBG excretion is normal, whereas uroporphyrin values are increased markedly in both PCT and congenital erythropoietic porphyria.

Measurement of 24-hour fecal porphyrin values is more useful in determining the subtype of porphyria and thus would not be the initial test for diagnostic purposes; however, it would be helpful after porphyria has been diagnosed.

UROD is the enzyme that converts uroporphyrinogen III into coproporphyrinogen III, an important step in the proper formation of heme. This enzyme is defective in PCT, and thus its measurement in erythrocytes is useful in diagnosing PCT; however, it would be inappropriate for the initial diagnosis of porphyria. Furthermore, UROD levels can be normal in certain cases of acquired PCT.

Plasma porphyrins are found in trace amounts in the serum of healthy patients but are increased in patients with cutaneous porphyrias. Although not necessary for diagnosis, measurement of plasma porphyrins is a useful test when porphyria is suspected as a cause of photosensitivity, and it should be used in conjunction with urinalysis because it is both sensitive and specific.[1] In addition, measuring plasma porphyrin levels is a simple strategy for monitoring treatment response. Because skin histopathologic findings in PCT are similar to those in other cutaneous porphyrias and in pseudoporphyria, skin biopsy provides no specific diagnostic confirmation and thus would not be an appropriate initial test.

Therefore, when porphyria is suspected, the initial test is a 24-hour urine collection; however, if the main complaint is related to skin lesions (as in our patient), measurement of plasma porphyrin levels in conjunction with urinary porphyrin levels would be helpful. In our patient, all urinary and plasma porphyrin levels were high; the most notable elevated levels were urinary uroporphyrin at 4168 μg/24 h (3-25 μg/24 h) and total plasma porphyrin at 16 μg/dL (≤1 μg/dL). Even though PCT was diagnosed, we were concerned that another process might be involved because not all of the patient's clinical signs fit the diagnosis of PCT.

3. Which <u>one</u> of the following clinical signs in our patient is <u>not</u> consistent with his condition?

a. *Erythematous scaly lesions*
b. *Pruritic rash*
c. *Abnormal results on liver function tests*
d. *Hemorrhagic skin vesicles*
e. *Anemia*

Although not a frequent cutaneous manifestation of PCT, diffuse erythema in a photodistributive pattern can be present along with blistering lesions. Minor trauma may cause formation of bullae or denudation of the skin, and previous areas of blisters may appear atrophic, brownish, violaceous, erythematous, and scaly.

A pruritic rash is one of the most common presenting features of PCT, along with blistering lesions. Often, PCT is associated with abnormal results on liver function tests, especially elevated transaminase and γ-glutamyl transpeptidase levels, even in cases not associated with other hepatotoxic conditions. In our patient, aspartate aminotransferase, total bilirubin, and direct bilirubin levels were all mildly elevated at 34 U/L, 1.1 mg/dL, and 0.4 mg/dL, respectively. The skin vesicles and bullae generally found on patients with PCT bleed occasionally because the skin is friable and fragile; thus, hemorrhagic skin vesicles can be present.

Anemia is not part of the clinical picture of patients with PCT and thus was inconsistent with our patient's presentation. This prompted further investigation.

After confirming that the patient's hemoglobin concentration had decreased from 13.1 to 9.6 g/dL over 2 years, iron studies were performed, which revealed that the anemia, surprisingly, was associated with iron overload; the plasma ferritin level was 390 μg/L (20-300 μg/L), PCT saturation was greater than 80% (4%-50%), and the plasma iron level was 208 μg/dL (50-150 μg/dL). This prompted a bone marrow biopsy, which revealed a myelodysplastic syndrome (MDS), subclassified as refractory anemia and ringed sideroblast. Thus, his underlying MDS was likely contributing to the clinical manifestation of PCT.

4. Which one of the following would not likely be associated with the clinical development of this patient's blistering skin disorder?

a. *Hepatitis C virus (HCV) infection*
b. *Eczema*
c. *Mutation of the* HFE *gene*
d. *Exposure to hexachlorobenzene*
e. *Alcohol abuse*

There is a strong association between PCT and HCV infection.[2] The mechanism by which HCV infection might trigger PCT is unclear, but studies have suggested that the virus may have the ability to release free iron. This iron could then uncouple the cytochrome P-450 system, which would further decrease UROD activity and provoke an attack.

Eczema has not been associated with PCT, although some skin manifestations of PCT could resemble those of eczema.

Another factor that might be associated with the manifestation of PCT is mutation of the *HFE* (C282Y) gene, known to be responsible for hereditary hemochromatosis.[3] Indeed, our patient was found to be heterozygous for this mutation. Exposure to hexachlorobenzene has also been associated with development of PCT. It has been suggested that this chemical induces a deficiency of hepatic UROD, leading to patterns of excess porphyrin accumulation,[4] similar to the proposed HCV mechanism. Alcohol abuse could cause the phenotypic manifestation of PCT by promoting cirrhosis and iron overload, thus decreasing UROD activity and provoking an attack.

Although the patient was heterozygous for the *HFE* gene, we suspected that his underlying MDS and associated anemia were playing a larger role in the manifestation of PCT. Because the ineffective hematopoiesis seen with MDS is a stimulus for increased intestinal absorption of iron, which in turn could decrease UROD activity and thus increase porphyrin accumulation and provoke an attack,[5] treatment of this patient's PCT would also need to address MDS.

5. Which one of the following is the most appropriate therapy given this patient's diagnosis and concurrent MDS with anemia?

a. *Phlebotomy and low-dose hydroxychloroquine*
b. *Low-dose hydroxychloroquine alone*
c. *Exogenous erythropoietin followed by phlebotomy*
d. *Deferoxamine*
e. *Thalidomide*

Phlebotomy and hydroxychloroquine are both effective in the treatment of PCT.[6,7] Phlebotomy reduces body iron stores and liver iron content and thus interrupts iron-mediated oxidative inhibition of hepatic UROD. Although the mechanism of hydroxychloroquine activity in PCT has not been established, hydroxychloroquine has been shown to be effective therapy.[7] In this patient, neither treatment is appropriate because of his anemia. Phlebotomy would obviously worsen the anemia, and hydroxychloroquine can interfere with erythropoiesis.

Exogenous administration of erythropoietin would be the best option because it increases the hemoglobin concentration and thus would treat this patient's anemia. Once the anemia is treated, phlebotomy could be performed, resulting in reduction of iron stores and the subsequent stimulus for PCT caused by UROD deficiency. Deferoxamine, an iron chelator, is an alternative treatment when phlebotomy is contraindicated in a patient with iron overload; however, it is considerably less effective[8] and thus would not be the choice in this patient. Thalidomide is a promising treatment, and preliminary studies have shown substantial improvement in clinical and biochemical features of PCT.[9] However, further corroboration would be needed for it to be first-line treatment of PCT.

Our patient responded to 40,000 U of epoetin alfa given weekly, and his hemoglobin concentration increased from 9.1 g/dL to 10.2 g/dL in 3 weeks. At that time, his skin manifestations due to PCT had resolved with strict photoprotection, as well as with topical therapy with Vanicream and triamcinolone. Phlebotomy will be considered in the future when the anemia improves.

DISCUSSION

Porphyria cutanea tarda is one of the porphyrias, a hereditary enzyme disorder that affects heme biosynthesis and results in excess accumulation and excretion of porphyrin or porphyrin precursors. The clinical manifestations of porphyrias depend on the type of precursors that accumulate. If the excess is of the early precursor molecules δ-aminolevulinic acid or PBG, the manifestations are neuropsychiatric. If the excess is of the distal intermediates (uroporphyrins, coproporphyrins, and protoporphyrins),

the manifestations are cutaneous. Porphyria cutanea tarda is the most common of the porphyrias and is characterized by chronic blistering lesions that develop on sun-exposed areas of the skin, most commonly the dorsal aspects of the hands, forearms, and legs and the face. The fluid-filled vesicles rupture easily, and the denuded areas become crusted and heal slowly. Small white plaques, termed *milia*, are also common and may precede or follow vesicle formation. Cutaneous thickening, scarring, and calcification, termed *pseudoscleroderma*, can sometimes be striking and accompanied by hypertrichosis, hyperpigmentation, and photodamage of the conjunctival sclerae.

The 3 types of PCT that have been defined are types I, II, and III. Type I is the most common, and patients have a "sporadic" form of the disease. Levels of UROD in erythrocytes are normal, whereas those in the liver are decreased during active disease. Type II is the familial type and results from an inherited (autosomal dominant) partial deficiency of UROD. The levels of UROD are decreased in all tissues. Type III is similar to type II except that it occurs in more than 1 family member, and onset of the disease is usually at a younger age. Our patient likely had type III PCT because PCT was later diagnosed in his daughter and one of his uncles. The healthy liver has the ability to promote heme synthesis, even with decreased enzyme activity, and patients can remain asymptomatic until UROD activity diminishes to more than 50% or the liver is injured.[10]

Various cofactors have been associated with the phenotypic expression of PCT, through either hepatocyte injury or hepatic iron overload. Excess ethanol consumption, HCV infection, human immunodeficiency virus infection, estrogen use, pregnancy, smoking, low vitamin C and E status, chlorinated polycyclic aromatic hydrocarbons, hemodialysis, inherited partial deficiency of UROD, and mutations of the *HFE* gene have all been shown to cause expression of PCT. As would be expected, patients with PCT may have multiple risk factors. In our patient, 3 factors could have contributed to unmasking PCT. First, he was found to be heterozygous for the *HFE* gene. Second, his lengthy history of smoking could have contributed to a lesser extent to the manifestation of his disease because chemicals in cigarette smoke may contribute to oxidative damage in the liver via induction of cytochrome P-450 enzymes and thus precipitate PCT. Third, our hypothesis is that the underlying MDS could have been the main culprit in the expression of PCT. Ineffective erythropoiesis increases intestinal absorption of iron to the point that patients can have clinical signs of iron overload. For unclear reasons, the degree of iron absorption is much more pronounced with ineffective erythropoiesis than with increased effective erythropoiesis.[5] Because the relationship between iron overload and PCT has long been recognized,[11] it is reasonable to conclude that MDS in our patient contributed to the manifestation of PCT.

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Correct answers: 1. *d*, 2. *a*, 3. *e*, 4. *b*, 5. *c*