A 66-year-old woman presented to the internal medicine clinic with a 1-month history of painless vesicular lesions on her hands. A tense blister was first noted on the lateral aspect of her right index finger. This lesion lasted for about 7 days and then spontaneously resolved. Subsequently, 2 similar lesions appeared on her left index finger. She denied lesions elsewhere on her body, including palmar surfaces, soles, and mucosal areas. She denied trauma to the lesions of concern. She denied fevers, chills, night sweats, abdominal pain, arthralgias, joint swelling, rash, pruritus, photosensitivitiy, neurologic symptoms, and constitutional symptoms. On detailed questioning, she acknowledged that her urine appeared red-tinged with her first morning void. Her medical history was notable for depression, impaired fasting glucose, osteopenia, and hypertension. She had no known history of rheumatologic conditions, liver disease, or diabetes. Her medications, all long-term, included metformin, metoprolol, a multivitamin, calcium, and aspirin. She did not smoke or drink alcohol, had no history of intravenous drug use, and was in a monogamous relationship with her husband. Family history was remarkable for similar symptoms in her mother and sister. Her occupation involved office work, and she denied activities involving constant rubbing. Her hobbies included gardening.

Physical examination revealed a 9-mm × 6-mm tense blister on the lateral surface of the left index finger. A 2-cm-wide patch of erythematous hyperpigmentation surrounded this blister and was focused at the site of her previously healed blister (Figure). Excessive fine hair growth was observed on her lateral face. The remainder of her examination was unremarkable.

1. Which one of the following is the most likely diagnosis in this patient?
   a. Dermatitis herpetiformis
   b. Pemphigoid
   c. Pompholyx (dyshidrotic eczema)
   d. Pemphigus
   e. Porphyria cutanea tarda (PCT)

   All of these conditions can present with vesicular lesions; however, their distribution and appearance vary. In contrast to the lesions described in this case, clusters of vesicular or papular lesions characterize dermatitis herpetiformis and are often found on extensor surfaces or points of pressure, particularly the elbows, knees, buttocks, and neck. Unlike the lesions in this case, those associated with dermatitis herpetiformis are often intensely pruritic or associated with burning or stinging discomfort. Pemphigus typically presents with large, tense bullae (>6-mm vesicles) and most commonly affects elderly patients (in particular, those aged 70-89 years). In contrast to this case, pemphigoid has a predilection for the flexural areas of the body. Pompholyx can occur on the lateral or medial aspects of the digits; however, these lesions are typically pruritic, and the vesicles are clear and resemble tapioca, in contrast to the nonpruritic, tense blisters seen in this case. Pemphigus presents with flaccid bullae developing in crops in which the overlying skin can be easily slipped from the dermis on rubbing (Nikolsky sign). These bullae predominantly involve the face and trunk rather than the extremities. Pemphigus, which involves the oral mucous membranes in about two-thirds of patients, was unlikely in our patient who had no oral lesions.

2. Which one of the following investigations would be most useful at this point in the management of the patient?
   a. Urine porphyrin and porphobilinogen (PBG) levels
   b. Fecal porphyrin analysis
   c. Erythrocyte free protoporphyrin level
   d. Urinary aminolevulinic acid level
   e. Serum antitissue transglutaminase level

   When cutaneous porphyria is suspected, the best initial investigation is a 24-hour urine collection for measurement of urinary aminolevulinic acid.
of urine porphyrin levels.\textsuperscript{3,4} Urinary porphyrins, including urinary PBG levels, help to differentiate between acute porphyrias (including acute intermittent porphyria, hereditary coproporphyria, and porphyria variegate), in which urinary PBG levels are normal and uroporphyrin levels are markedly increased.\textsuperscript{4} Fecal porphyrin analysis is most helpful for classifying the porphyria into its subtype after the diagnosis of porphyria has been confirmed. Erythrocyte free protoporphyrin measurement can be useful in the diagnosis of EPP, which typically presents in childhood with acute photosensitivity; it would be of little use in this case. The urinary aminolevulinic acid level, while helpful in identifying acute intermittent porphyria, would be expected to be normal in PCT and would not be a good screening test for initial diagnosis. Serum antitissue transglutaminase levels are useful for the diagnosis of celiac disease (which is associated with dermatitis herpetiformis) but are not helpful in the diagnosis of porphyrias.

This patient’s total urinary porphyrins were markedly elevated (reference ranges provided parenthetically) (3242 μg/24 h [3-25 μg/24 h]), whereas urinary PBG levels were normal (0.3 mg/24 h [<0.5 mg/24 h]). Urinary and fecal stool samples were then checked for porphyrin subanalysis and showed markedly increased porphyrins with a pattern suggestive of PCT (see Discussion).

3. Which one of the following laboratory tests is not indicated for this patient at this time?

a. Serum ferritin test
b. Hepatitis serology
c. Antinuclear antibody test
d. Parathyroid hormone (PTH) test
e. Ultrasonography of the abdomen to evaluate liver

Porphyria cutanea tarda has been associated with multiple medical conditions, including hemochromatosis and hepatitis C. Of 70 patients with PCT in a North American study, 73% had allelic variants in the \textit{HFE} (hemochromatosis) gene and thus should be screened by checking the serum ferritin level. If the serum ferritin level is elevated, \textit{HFE} gene testing should be performed.\textsuperscript{3} The same study found that 56% of patients with PCT had coexistent hepatitis C infection. Thus, hepatitis serology should also be performed in all patients with PCT.

Systemic lupus erythematous (SLE) is also independently associated with PCT, although less frequently so than hemochromatosis or hepatitis C. A Mayo Clinic case series involving 6179 cases of SLE and 676 cases of porphyria (all variants) found 15 patients to have coexistent lupus erythematosus and PCT.\textsuperscript{4} Porphyria cutanea tarda has not been associated with hyperparathyroidism, and testing of parathyroid hormone is unlikely to be beneficial. Ultrasonography of the liver is useful for assessing for associated liver diseases, including hemochromatosis and hepatocellular carcinoma, and for providing a baseline for future evaluation. Additional laboratory testing was notable for elevated levels of iron (215 μg/dL [35-145 μg/dL]), ferritin (330 μg/dL [11-307 μg/dL]), aspartate aminotransferase (93 U/L [8-43 U/L]), and alanine aminotransferase (163 U/L [7-45 U/L]). Serologic results and levels of hemoglobin, serum electrolytes, creatinine, and antinuclear antibodies were within normal limits. Given the elevated ferritin levels and concern for coexisting hemochromatosis, \textit{HFE} gene testing was performed and showed that this patient was homozygous for the C282Y sequence variation, consistent with the presence of hereditary hemochromatosis. Ultrasonography of the abdomen showed diffuse fatty infiltration of the liver. An ultrasonography-guided liver biopsy was performed to assess for the presence of hepatocellular carcinoma and to determine the patient’s prognosis. The liver biopsy showed mildly active steatohepatitis (grade 1/3), with pericellular and portal fibrosis (stage 2/4), as well as moderate patchy hepatocellular iron accumulation (3+) consistent with iron overload as seen in hemochromatosis.

4. Which one of the following therapies would be most helpful in managing this patient’s medical condition?

a. Phlebotomy
b. Iron chelators
c. Chloroquine
d. Prednisone
e. Dapsone

Phlebotomy is the standard therapy for PCT, especially in the presence of hemochromatosis. Phlebotomy reduces the hepatic and body iron stores, thereby inhibiting the oxidation of hepatic porphyrinogens to porphyrins. Iron chelators also reduce iron stores and may be used when phlebotomy is contraindicated. Chloroquine, which can be used when phlebotomy is difficult or contraindicated, is particularly useful when iron stores are nearly normal. Prednisone therapy can be useful if PCT is secondary to a connective tissue disease.
such as SLE but is not otherwise used. Dapsone therapy has not been reported to be helpful in the treatment of PCT.

This patient was initially treated with weekly to bweekly phlebotomies until her target hemoglobin levels (10-11 g/dL) were reached, at which time the interval between therapeutic phlebotomies was reduced to once monthly as determined by pretreatment laboratory values. She responded well to therapy and has noticed marked improvement in her cutaneous lesions, decreased facial hair, and resolution of urine discoloration. Her liver enzymes have also decreased to near-normal levels.

5. Which one of the following is not contraindicated in the long-term management of this patient?
   a. Alcohol
   b. Estrogen
   c. Iron supplementation and vitamin C
   d. Nonsteroidal anti-inflammatory drugs (NSAIDs)
   e. Topical sunscreens

   Alcohol, smoking, and estrogens are known exogenous risk factors for PCT. These agents are thought to lead to induction of cytochrome P450 enzymes and thus could exacerbate porphyria. Intake of supplemental iron or vitamin C is generally contraindicated in patients with hemochromatosis because it can worsen iron stores. Nonsteroidal anti-inflammatory drugs, which can cause cutaneous manifestations similar to PCT (pseudoporphyria) that could be confused with PCT exacerbation, should be avoided. Sun exposure may exacerbate the cutaneous lesions associated with PCT, and topical sunscreens are of benefit in preventing these exacerbations.

**DISCUSSION**

Porphyrias are a group of disorders characterized by deficiency of enzymes in the biosynthetic pathway of heme synthesis, leading to accumulation of intermediate products or porphyrins. These excess products accumulate in the tissues, leading to diverse clinical manifestations ranging from abdominal pain to mental status changes.

The predominant clinical symptoms associated with porphyrias are abdominal (abdominal pain, nausea, vomiting), neurological (numbness, tingling, muscle weakness, mental status fluctuation or personality changes), hematological (particularly hemolytic anemia), and cutaneous (particularly photosensitivity). On the basis of the predominant systems involved, porphyrias can be broadly divided into 3 major groups: neurovisceral, cutaneous, and hematological. Acute intermittent porphyria is characterized by predominantly neurovisceral involvement, whereas porphyria cutanea tarda, the most common porphyria, is characterized by predominantly cutaneous involvement.

When cutaneous porphyria is suspected, a 24-hour urine collection test should be performed for measurement of porphyrins and PBG levels. Although not essential for diagnosis, the sensitivity and specificity of plasma porphyrin measurement make this a helpful test when done in conjunction with urinalysis or as a screening test if the suspicion for porphyria is low. Plasma porphyrin measurement is also useful for monitoring treatment response. Once the diagnosis of porphyria has been confirmed, fecal porphyrin analysis may be helpful for classifying the porphyria into its subtype. On the basis of the levels and types of porphyrins measured, the appropriate diagnosis can be made.

Porphyria cutanea tarda is characterized by elevated levels of porphyrins (porphyria) with hemorrhagic skin blisters on sun-exposed areas (cutanea) in middle-aged adults (tarda). The lesions eventually crust and resolve, leaving atrophic scars, hyperpigmentation, and skin thickening (pseudoscleroderma). The lesions may be preceded by small white plaques called milia. Other associated features include hypertrichosis and pink urine (due to elevated urinary porphyrins).

Deficiency of the uroporphyrinogen decarboxylase (UROD) enzyme, which is involved in heme synthesis, causes PCT. When the level of UROD enzyme falls below 50%, or in the presence of liver dysfunction, the enzyme deficiency results in excess production of 7-C porphyrin and isocoproporphyrin, leading to the development of PCT. The urinary uroporphyrins (reddish pigments) result in the characteristic pink urine and also have a unique fluorescence emission peak at neutral pH near 619 nm. Of PCT cases, 75% result from sporadic enzyme deficiency (type I). Familial cases (such as our index case) are classified into type II and type III on the basis of the number of family members involved and the age at onset. Familial PCT has an autosomal dominant inheritance and occurs as a result of sequence variations in the UROD gene. A genetic test to detect UROD sequence variations is currently being developed and holds promise for identifying asymptomatic family members and for enhancing genetic counseling.

The major risk factors for PCT include alcohol use, estrogen use, hemochromatosis, and hepatitis C. Hepatitis C virus, alcohol, and estrogen are all thought to result in induction of the cytochrome P450 enzyme, which results in decreased UROD enzyme activity, leading to elevated porphyrins and development of PCT in susceptible individuals. Hemochromatosis, and to some extent alcohol and hepatitis C virus, lead to an overload of iron (and heme), which cannot be metabolized because of the relative deficiency of the UROD enzyme, leading to elevated porphyrins and development of PCT.

Other less common risk factors for PCT include human immunodeficiency virus infection, SLE, long-term dialysis,
and diabetes. Patients with PCT should be screened for these disorders, including testing for the \textit{HFE} gene to evaluate for the presence of subclinical hemochromatosis; \textit{HFE} allelic variants can be detected in up to three-fourths of patients with PCT.\(^5\) Multiple toxic agents, including fungicides such as dichlorophenols, trichlorophenols, and \(2,3,7,8\)-tetrachlorodibenzo-p-dioxin, can result in induction of cytochrome P450 enzyme and have also been implicated as etiological agents for PCT.

In addition to skin, the other major organ involved in PCT is the liver. Liver involvement could reflect associated coexisting disease, such as hepatitis C, alcohol abuse, or hemochromatosis, or it could result from isolated PCT. The latter is due to accumulation of excess porphyrins and iron in the liver, leading to hepatic dysfunction.\(^9\) Abnormalities can range from mild elevation in liver enzymes to cirrhosis. Patients with PCT, particularly those with a long-standing history or those with chronic active hepatitis, advanced fibrosis, or cirrhosis, are at increased risk of developing hepatocellular carcinoma and should be screened with serum \(\alpha\)-fetoprotein level and ultrasonography with or without biopsy depending on the clinical scenario.\(^14\)

Phlebotomy (about 450 mL of blood each session) is the standard therapy for PCT; it is used to maintain a hemoglobin level of around 10 g/dL and to deplete excess iron stores.\(^15\) This therapy usually leads to resolution of cutaneous symptoms in 3 to 4 weeks and complete resolution of the disease in 9 to 12 months.\(^16\) When phlebotomy is contraindicated, alternative interventions include iron chelation therapy (such as deferoxamine) or low-dose chloroquine.\(^17\) The latter is particularly useful when the iron stores are close to normal. Although the exact mechanism by which chloroquine acts is unknown, it is thought to bind porphyrins and form complexes that enhance porphyrin excretion. Low-dose chloroquine (125-250 mg by mouth twice weekly) is used for treatment of porphyria because normal dosing (125-250 mg/d) could result in excessive porphyrin release, potentially leading to further liver damage. Treatment of coexisting disorders, such as interferon-alpha for hepatitis C, antiretroviral therapies for infection with human immunodeficiency virus, or erythropoietin for end-stage renal disease, also helps in disease remission.\(^18\)

Agents that can exacerbate PCT should be avoided.\(^19\) Exacerbating agents include alcohol, estrogens (including oral contraceptives and postmenopausal estrogen replacement), and iron supplements. Patients should also protect themselves against excessive sun exposure. Long-term follow-up is essential to monitor for exacerbations and to manage liver disease and other coexisting conditions. Patients’ symptoms and serum ferritin and porphyrin levels should be carefully monitored to assess therapeutic efficacy.\(^20\)

Porphyria cutanea tarda should be considered in any patient with painless, hemorrhagic, vesicular lesions on sun-exposed areas, particularly on the dorsal surface of the hand and fingers. If PCT is suspected, diagnostic testing should be performed with urinary porphyrin evaluation. Patients with newly diagnosed PCT should be screened for associated conditions, particularly hemochromatosis and hepatitis C. Standard therapy for PCT includes phlebotomy to deplete excess iron stores and avoidance of precipitating factors, particularly alcohol, estrogen, and iron supplements.

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\textbf{REFERENCES}


\textbf{Correct answers: 1. e, 2. a, 3. d, 4. a, 5. e}