Bullous Skin Lesions in a Patient with End-Stage Renal Disease and Hepatitis C

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Bullous lesions in patients with end-stage renal disease are uncommon and can pose diagnostic and therapeutic challenges. We present a female patient with end-stage renal disease, bullous skin lesions affecting mainly sun-exposed areas, and high ferritin levels. She also had hepatitis C. Her serum porphyrin panel was suggestive of porphyria cutanea tarda. Skin biopsy excluded inflammatory pathologies. Phlebotomy during each hemodialysis, continuation of darbepoetin, and avoidance of any further doses of intravenous iron, with close monitoring of hemoglobin, resulted in a gradual drop in ferritin level and improvement of the skin lesions.

Key words
Porphyria cutanea tarda, bullous lesions, end-stage renal disease, iron overload, hepatitis C

Case description

A 58-year-old African American woman with a past medical history of type 2 diabetes mellitus, arterial hypertension, and hepatitis C (HCV), on hemodialysis (HD) because of end-stage renal disease (ESRD), presented with new blisters over both forearms and the upper anterior chest (Figure 1). The lesions were associated with pruritus, darkening of the skin, and increased hair growth.

No pain, erythema, or systemic complaints such as fever, nausea, vomiting, or diarrhea were present. The patient denied any chest pain or dyspnea. She also denied recent travel, sick contacts, and laundry detergent or body soap changes. There was no exposure to chemicals or history of occupational exposure, and no new medications were being used at the time. The patient had history of allergic reaction to ciprofloxacin and minoxidil. There was a family history of pre-eclampsia and ESRD in her daughter. The patient denied alcohol, tobacco, or illicit drug use. Review of systems was otherwise negative. Medications included nebivolol, irbesartan, insulin glargine, sevelamer, cinacalcet, ergocalciferol, vitamin B complex with vitamin C, folic acid, hydrocodone–acetaminophen, and darbepoetin alfa. She had received 1800 mg of intravenous iron sucrose over 12 months between July 1, 2014, and July 1, 2015, before developing the blisters.

Salient features on physical examination were hypertension, a functioning left upper arm arteriovenous fistula, multiple blisters, bullae over both upper extremities, healed crusted lesions on the upper chest and arms, increased skin fragility, pruritus, hyperpigmentation of the skin without any noticeable erythema, and hypertrichosis of both arms and the face.

Blood tests did not reveal any eosinophilia. The patient was being dialyzed with a polysulfone membrane, which was changed to a cellulose-based membrane. The patient showed no improvement and was referred to a dermatologist for evaluation.

At approximately the same time, the patient began treatment for HCV with a regimen of oral sofosbuvir 400 mg daily and oral simeprevir 150 mg daily. Notably, the patient had previously undergone liver biopsy, which showed very mild histologic changes, with grade 1 – 2 inflammation, 0 – 1 fibrosis, and no indications of hemochromatosis. Early in the diagnosis of her HCV, because of her increased risk for adverse reactions, lower probability for cure, and mild liver abnormalities, the patient was not treated with either interferon or ribavirin. With the success of the newer available therapies and an increased viral load, her condition was revisited, and the decision was made to treat her.

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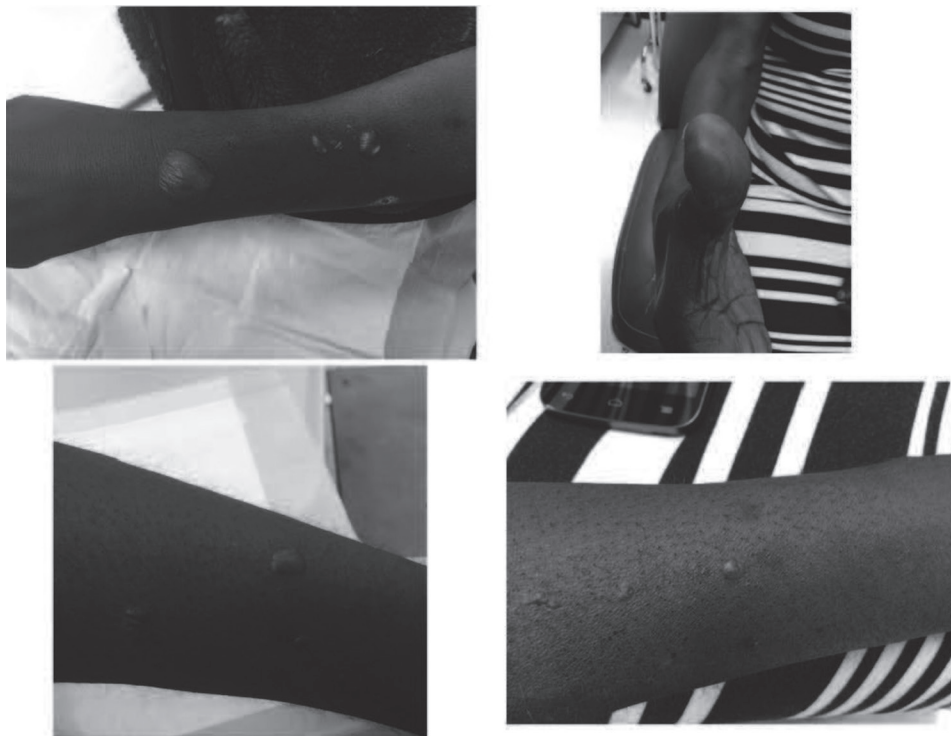

FIGURE 1 The bullae, hyperpigmentation, and hypertrichosis at presentation.

Skin biopsy showed cell-poor subepidermal blisters, sparse superficial dermal lymphohistiocytic inflammation, and rare eosinophils, again possibly important in differentiating an allergic reaction. Pathology also described weak perivascular deposition of immunoglobulin G and immunoglobulin A, and focal strong perivascular deposition of C3, with no signs of vasculitis. Differential diagnoses by biopsy included porphyria cutanea tarda (PCT), pseudoporphyria, and porphyria variegata. As Table I shows, marked elevation in the porphyrin fractions uroporphyrin, heptacarboxyporphyrin, hexacarboxyporphyrin, and pentacarboxyporphyrin, with normal levels of coproporphyrin and protoporphyrin indicated deficient activity of uroporphyrinogen decarboxylase (UROD), suggestive of PCT.

Even though porphyrins can be elevated in individuals with ESRD (Table I), the much higher elevations in our patient, together with the clinical presentation and skin biopsy findings, clinched the diagnosis. A phlebotomy regimen tailored to the patient—50 mL 3 times weekly before each HD session—was initiated in the dialysis unit. The patient continued to receive darbepoetin alfa to treat anemia of chronic kidney disease, which likely assisted in mobilizing her iron stores.

Serum ferritin before initiation of phlebotomy was 1328 ng/dL. During the course of her treatment, the patient was referred for a hematology evaluation for possible iron chelation therapy, but it was decided to continue with phlebotomy therapy and to monitor for improvement. As demonstrated in Figure 2, the patient eventually responded to phlebotomy. With concomitant use of darbepoetin, hemoglobin was maintained in the target range. The phlebotomy volume was reduced to 25 mL 3 times weekly before it was stopped altogether when serum ferritin declined below 100 ng/dL. Transferrin saturation and ferritin levels trended down in response to treatment, and the patient's skin lesions ultimately resolved. Table II shows serial hemoglobin, transferrin saturation, and ferritin measurements in relation to initiation of phlebotomy.

Discussion

Porphyria cutanea tarda is the most common of the porphyrias. It results from deficient activity of the

TABLE 1 Sample reference porphyrin levels alongside levels for the patient in the present case (converted to nanomoles per liter)

Porphyrin variable	*Value (nmol/L)*			
	Healthy subjects[a]	*Patients with renal failure*[a]	*Patients with pseudoporphyria*[a]	*Patient in the present case*
Uroporphyrin	0–11	4–50	4–37	63.4
Heptacarboxyporphyrin	0–5	1–8.2	0–4.4	46.5
Hexacarboxyporphyrin	0–2	0–1.6	0–1	29.4
Pentacarboxyporphyrin	0–2	0–1.6	0–0.5	13.4
Coproporphyrin	0–10	0–5.1	0–7.7	1.1
Protoporphyrin	—	—	—	0.1
Total porphyrin	—	—	—	153.9

[a] Hindmarsh *et al.,* 1999 (1).

FIGURE 2 Resolution of hyperpigmentation and bullae after 4 and 5 months of phlebotomy.

heme biosynthetic enzyme UROD in the liver. Its common precipitating factors are iron overload, alcohol, smoking, HCV, estrogen use, and HIV infection. Our patient presented at least 2 of those factors in the presence of ESRD as an additional factor.

In patients with chronic kidney disease, PCT commonly presents as bullae on the dorsal surfaces of the hands, feet, and face. Facial hyperpigmentation and hypertrichosis might also be seen. Secondary infection of the bullous lesions often occurs, and healing can be

TABLE II Trend of hemoglobin, transferrin saturation, and ferritin in relation to initiation of phlebotomy

Date	*Hemoglobin*	*Transferrin saturation*	*Ferritin*
Apr 9, 2015	10.8	45	801
May 14, 2015	11.6	49	
Jun 11, 2015	11.6	60	
Jul 9, 2015	12	65	1328
Aug 13, 2015	12.8	41	
Sep 1, 2015	Phlebotomy initiated; 50 mL per hemodialysis session, 3 days weekly		
Sep 10, 2015	10.9	45	
Oct 15, 2015	9.5	40	588
Nov 12, 2015	9.6	36	459
Dec 10, 2015	10.2	17	239
Jan 14, 2016	11.2	19	97
Jan 28, 2016	Phlebotomy reduced to 25 mL, 3 days weekly		
Feb 11, 2016	10	18	63
Feb 23, 2016	Phlebotomy discontinued		

associated with scarring. The sporadic form of PCT occurs in approximately 5% of patients on dialysis (2).

The exact mechanism by which HCV infection increases the risk for PCT is unknown. One theory involves the ability of the virus to release "free" iron from within hepatocytes, which in turn leads to production of a UROD inhibitor by an oxidative process (3). Hepatitis C also increases oxidative stress in hepatocytes and increases iron absorption by dysregulating hepcidin, which increases iron absorption in the gut (4).

Iron overload can result from an extensive history of blood transfusions or intravenous iron therapy. Each unit of packed red blood cells is estimated to contain 200 mg elemental iron. As expected in renal patients, iron is poorly utilized because of ineffective erythropoiesis. In a study of patients with serum ferritin levels exceeding 1000 ng/mL, serum malonyldialdehyde was increased, indicating oxidative stress, likely because of iron toxicity (5). Erythropoiesis-stimulating agents have helped to counteract that stress as they mobilize iron stores, leading to fewer blood transfusions.

In patients on dialysis, UROD inhibition is thought to be attributable to nitrogen retention, to decreased losses through urinary excretion, and to improper clearance by dialysis of porphyrins (6). Hindmarsh *et al.* (1) demonstrated that elevated porphyrin levels can be seen in dialysis patients without PCT lesions. The present study also shows how serum porphyrin assays can be used to distinguish between PCT and the pseudoporphyria of dialysis patients.

Differential diagnosis

The cause of bullous lesions in an ESRD patient could be as simple as an allergic reaction to dialysis membranes or drugs or could indicate a rare condition such as PCT. But the main differential diagnosis when considering PCT should be pseudoporphyria.

Pseudoporphyria occurs in patients with ESRD on chronic HD or PD. Suspected pathophysiology includes the photosensitizing agents, aluminum hydroxide found in dialysis solutions, or chemicals in polyvinyl chloride dialysis tubing (1). Other theories include an inability to handle oxidative stress. Of all dialysis patients, 60% have moderately increased plasma porphyrins without clinical signs indicating PCT (2). The plasma porphyrin assay is used to distinguish between pseudoporphyria and PCT, with plasma porphyrin levels being lower in the former condition. The predominance of the heptacarboxyporphyrin fraction typically seen in PCT is also lacking.

Treatment overview

The goal of PCT treatment is to promote the elimination of accumulated porphyrins and reduce the iron overload observed in most patients. Preventive measures that can be taken include photo-protection, avoidance of alcohol ingestion, and avoidance of other hepatotoxic agents or photo-sensitizers (6). As the present case demonstrates, phlebotomy is an effective treatment, especially when serum iron and ferritin are elevated. The phlebotomy volume should be tailored to the patient so as to prevent worsening of anemia. Small repetitive phlebotomies, with maintenance of a stable hemoglobin of 10 – 11 g/dL until serum ferritin fell below 100 ng/dL, resulted in symptom resolution in our patient. Continued concomitant use of erythropoiesis-stimulating agents further enhanced efficacy through mobilization of iron.

Other therapies such as antimalarial drugs can be dangerous in ESRD patients because they form a hydrosoluble complex with porphyrins, facilitating excretion, but those complexes are not eliminated by dialysis and can lead to hepatotoxicity (6). Iron chelation therapy—for example, deferoxamine—after each

dialysis might be useful. Plasma exchange is possible but expensive, and kidney transplantation would be the ultimate therapy, especially for refractory cases.

Our patient's story is presented for several reasons: It is important to suspect PCT and pseudoporphyria when bullous lesions affect a patient on dialysis. Marked elevation in the uroporphyrin, heptacarboxyporphyrin, hexacarboxyporphyrin, and pentacarboxyporphyrin fractions, with normal levels of coproporphyrin and protoporphyrin, is highly suggestive of PCT. Blisters with normal or slightly elevated levels of porphyrins suggest pseudoporphyria of dialysis. Treatment of PCT with phlebotomy is very easy to handle in patients on HD. Our patient's case also exemplifies how hemoglobin can be maintained in the desirable range without raising serum ferritin higher than normal limits. On a concerning note, Fishbane *et al.* (7) showed that, in the U.S. dialysis population, mean serum ferritin has increased to 799 ng/mL in 2014 from 300 ng/mL in 1993. They also showed that, as serum ferritin doubled during that period, the rate of bacteremia and sepsis increased approximately 40%.

Summary

In patients with bullous lesions, high serum ferritin, and elevated serum porphyrin, PCT should be suspected. Phlebotomy sufficient to lower serum ferritin below 100 ng/mL results in improvement of skin lesions. Anemia should be managed with erythropoiesis-stimulating agents, and iron should be used only minimally or not at all in such patients.

Disclosures

AS has a patent pending for "intradialytic use of sodium thiosulfate." No other author has a conflict of interest to disclose.

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