Porphyria cutanea tarda and bullous dermatoses associated with chronic renal failure: a review[1]

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In porphyria cutanea tarda, clinical expression may require the concordance of an inherited deficiency of the hepatic or erythrocyte enzyme uroporphyrinogen decarboxylase and an environmental precipitant, usually alcohol, iron, or estrogens. Recently, PCT and similar vesiculobullous disorders have been reported with increasing frequency in patients with impaired renal function. Many were on hemodialysis and others had ingested the photosensitizing drugs nalidixic acid and furosemide. Aluminum hydroxide and plasticizers from the dialysis tubing have also been implicated. Since abnormalities of porphyrin biochemistry were not found in all cases, more detailed porphyrin studies will be required. Plasma exchange was successful in treating one recent case of PCT in a patient on hemodialysis.

Index terms: Bullous dermatoses • Kidneys, failure • Porphyria cutanea tarda
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Porphyria cutanea tarda (PCT), the most common disorder of porphyrin metabolism in man, is characterized clinically by a photoenhanced dermatosis with vesiculobullous, excoriated or ulcerative skin lesions exposed to sunlight and increased skin fragility on mechanical trauma.[1–3] Hyperpigmentation, hirsutism, milia, and scarring alopecia may also be present. The age of onset is usually in the third or fourth decade. Rare before puberty, the disorder is typically precipitated by ingestion of alcohol, estrogen, or iron, or exposure to toxic chemicals; the condition may be idiopathic. PCT is associated with hepatic siderosis, increased serum iron, and, rarely, hepatic tumors. Biochemical defects include excretion of increased urinary

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uroporphyrins (I > III) and 7-carboxyl porphyrins (III > I), and increased isocoproporphyrins in urine and feces. The inherited nature of a specific enzyme defect has been established in all forms of porphyria with the exception of PCT. However, there is increasing evidence of an enzyme deficiency of uroporphyrinogen decarboxylase in the hepatocytes and/or red blood cells of some patients and their families with PCT. In a previous report from the Cleveland Clinic, we proposed the use of this enzymatic defect to classify patients as having overt, subclinical, or latent PCT.[4]

Several cases of PCT associated with chronic renal disease and hemodialysis have been reported.[5–14] In addition, bullous dermatoses clinically and histologically resembling PCT but with normal porphyrin studies have been observed in uremic patients on hemodialysis. PCT-like eruptions in patients with chronic renal failure receiving nalidixic acid and furosemide have also been described. The purpose of this paper is to review the PCT cases reported to date and the bullous dermatoses associated with chronic renal failure.

Review of the literature

Porphyria cutanea tarda in chronic renal failure treated with hemodialysis: In a report by Poh-Fitzpatrick et al,[5] there were 2 cases of PCT in chronic renal failure occurring after the onset of hemodialysis. The first patient, with subepidermal bullae six months after institution of hemodialysis, had elevated porphyrins in urine, plasma, feces, and blister fluid. Although without vesicles, the second patient had other PCT cutaneous lesions including increased skin fragility on the dorsum of the hands with erosions, scarring, and milia 11 months after hemodialysis had been initiated. Elevated plasma and stool porphyrins were demonstrated. The dialysate from the plasma in both patients contained only minute quantities of uroporphyrin. Plasma porphyrins remained elevated in both patients after completion of hemodialysis.

Fisher[6] described a uremic patient on hemodialysis with erosions and atrophic scars on the scalp, forehead, and dorsa of the hands. Facial hyperpigmentation and malar hypertrichosis were observed. A single tense bulla was apparent on the dorsum of the left hand, which on microscopic examination revealed a subepidermal bulla. Heavy IgG deposition in the vessel walls and floor of the bulla was demonstrated by direct immunofluorescence. Test results for complement, fibrinogen, and IgM deposition were negative. Urine and plasma porphyrin levels were elevated.

Poh-Fitzpatrick et al[7] reported multiple bullae and hypopigmented scars on the dorsa of the hands, fingers, and forearms of a woman with chronic renal failure after four months of hemodialysis. She had mottled hyperpigmentation of the cheeks and forehead along with facial hypertrichosis. Urine and stool uroporphyrin levels were elevated, as were determinations of plasma and blister fluid porphyrins. Her plasma porphyrin levels eventually stabilized in follow-up studies, unlike the previous cases reported by this group. Also, small quantities of porphyrins were measured in the dialysate. The three hemodialyzed patients with PCT seen by this group are black.

Day and Eales[8] described two cases of a cutaneous blistering eruption after the onset of maintenance hemodialysis. Patient 1 had porphyria-like skin changes on the exposed areas of the hands, face, and feet. He had been on dialysis for seven years prior to the development of cutaneous lesions. An elevated plasma uroporphyrin level and an increased isocoproporphyrin fraction in the stool were found. Patient 2 had been on dialysis for 20 months prior to the appearance of skin lesions on the dorsa of the hands and face associated with increased fragility. Urinary and plasma uroporphyrins as well as stool isocoproporphyrins were elevated. Six hours of hemodialysis did not reduce elevated plasma porphyrin levels. Examination of his dialysate extract failed to demonstrate any significant porphyrin levels.

García-Parrilla et al[9] described a 16-year-old boy with chronic glomerulonephritis who developed skin fragility, hyperpigmentation, and multiple bullae on his face and the dorsa of his hands one year after institution of hemodialysis. The diagnosis of PCT in this severely oliguric patient was made by measuring elevated plasma porphyrin levels and decreased erythrocyte (RBC) uroporphyrinogen decarboxylase activity. The fecal isocoproporphyrin:coproporphyrin ratio was also elevated. Treatment with 75 mg chloroquine weekly for two months and cholestyramine was unsuccessful. However, the plasma porphyrin level was reduced by almost 50% after hemodialysis, which may have been due to the employment of a high-permeability membrane. Decreased RBC uroporphyrinogen decarboxylase activity and increased urinary excretion of heptacarboxylic porphyrins were documented in

the patient's sister and mother, indicating subclinical PCT.

Wilkin et al[10] reported bullae on the forehead and dorsa of both hands along with milia in a uremic patient after one year of hemodialysis. Microscopic examination revealed a subepidermal bulla. IgG was demonstrated along the basement membrane by direct immunofluorescence. Urine uroporphyrin and coproporphyrin levels were elevated.

Lichtenstein et al[11] described blisters, hyperpigmentation, and hypertrichosis of the face accompanied by depigmented scars on the dorsa of both hands in a woman two years after commencement of hemodialysis. Subepidermal bullae with festooning of the dermis were demonstrated on biopsy specimens. No IgM, IgG, or C3 deposition along the dermo-epidermal junction was evident by indirect immunofluorescence. The diagnosis of PCT was established by elevated plasma porphyrins and decreased RBC uroporphyrinogen decarboxylase. Total urinary and fecal porphyrin levels were normal. Hemodialysis with membranes with molecular filtration limits of 5000 and 20,000 had no effect upon plasma porphyrin levels. The dialysate did not contain any detectable porphyrins. However, three 500-ml phlebotomies resulted in a significant decrease in plasma porphyrin concentrations with concomitant clinical improvement.

Topi et al[12,13] reported porphyria-like skin changes in a woman two years after institution of hemodialysis. Sclerodermiform patches were observed a few months later and were distributed along the dorsa of the hands and on the scalp and face. Increased urinary and markedly elevated plasma porphyrins were demonstrated. Erythrocyte and stool porphyrins were at normal levels. Biochemical evidence of PCT was also documented in a son, a niece, and a sister. The sclerodermiform lesions usually develop over a period of several years, not a few months as in this patient. It was speculated that the rapid evolution of these lesions may be due to the extraordinarily elevated plasma porphyrin levels with a subsequent increase in transport into the tissues along with a corresponding increase in photocutaneous activity. Hemodialysis with the use of different filtration membranes was unsuccessful in reducing plasma porphyrin levels to those usually associated with PCT.

Hanno and Callen[14] reported the development of facial hyperpigmentation and hypertrichosis along with milia, bullae, and crusts on the dorsa of both hands in a woman after six years of hemodialysis. Plasma porphyrins were increased in a manner consistent with PCT. She responded partially to a regimen of topical sunscreens, a topical antibiotic-steroid preparation, and saline soaks.

The cases discussed above are summarized in *Table I.*

Bullous dermatosis of hemodialysis: Several patients on chronic hemodialysis have presented with clinical and histologic features indistinguishable from PCT but with negative laboratory findings. This bullous eruption occurred in 1.2% to 18% of hemodialyzed patients studied.[7] This syndrome is most commonly referred to as pseudoporphyria or bullous dermatosis of hemodialysis (BDH).

BDH was initially reported in 1975 by Gilchrest et al.[15] She described five uremic patients with bullae on the dorsa of the hands and hyperpigmentation of sun-exposed skin 2–24 months after the institution of hemodialysis. Hypertrichosis was noted in one patient. No milia were observed. Biopsy specimens revealed subepidermal bullae with minimal perivascular lymphocytic infiltration and edema of the dermal papillae. Electron microscopy demonstrated hypogranulated mast cells in the superficial dermis and homogeneous thickening of venule walls in the upper papillary dermis. Biopsy specimens processed for direct immunofluorescence showed small perivenular deposits of IgA in 2 patients; IgG was deposited focally along the floor of the bulla in one patient and deposited in broad rings around superficial vessels of the dermis in 3 patients. Urine, stool, and predialysis and postdialysis uroporphyrins and coproporphyrins were at normal levels. Light testing in the Soret band (400–410 nm) failed to produce lesions. Three patients showed no clinical improvement after a one- to three week- trial of topical sunscreens.

Korting[16] described blisters, erosions, cutaneous fragility, and pruritus of the dorsa of the hands and fingers in 2 hemodialysis patients. An increase in the levels of urinary uroporphyrin type I and uroporphyrin type III was observed in one patient (*Table I*).

Griffon-Euvrard et al[17] studied the dermatological manifestations of 50 patients undergoing chronic hemodialysis. Two had skin fragility, ulcerations, and atrophic scars on the dorsa of the hands. One patient also had bullae and milia in these areas. Immunofluorescence revealed deposits of IgG, complement, and fibrinogen

Table 1. PCT in chronic renal failure patients

Author	Cases	Age/Sex	Possible precipitating factors	Porphyrin analysis: Dialysate	Urine	Plasma	Total erythrocyte	Feces	RBC-U/D
Poh-Fitzpatrick et al[5] (1978)	2	a) 30/M	Ethanol Prior viral hepatitis Ferrous gluconate	0.02 μg/L	T = 154.8–240.0 μg/24 hr (N = <100)	a) T = 152.3–373.8 μg/dl (N = <1)	59–65 μg/dl (N = <90)	Iso (I @ 189), C (N @ 1076), P (N @ 392), μg/24 hr	ND
		b) 55/F	Unknown	ND	ND (patient essentially anuric)	b) 30.8–32.2 μg/dl	33 μg/dl	U (I @ 301), C (I @ 1592), P (N @ 488) μg/24 hr	ND
Fisher[6] (1979)	1	63/M	Ethanol Cirrhosis	ND	U = 521 μg/24 hr (N = <100) C = 52 μg/24 hr (N = ND)	U = 249 μg/dl serum (N = <1)	ND	ND	ND
Poh-Fitzpatrick et al[7] (1980)	1	43/F	Ferrous sulfate Ethanol	0.09–0.484 μg/dl	U = 1365 μg/24 hr (N = <40) C = 66.2 μg/24 hr (N = <160)	T = 123 μg/dl (N = <1)	32 μg/dl (N = <90)	U (I @ 27.2), C (N @ 18.8), P (N @ 2.2), μg/g of dry weight	ND
Day and Eales[8] (1980)	2	a) NA/M	Ethanol Iron overload	ND	ND	a) U = 60.4 μg/100 ml (N = <0.19)	ND	U (I @ 23.9), C (I @ 39.5), P (N @ 18.5), Iso (I @ 82.5) μg/g of dry weight	ND
		b) NA/M	Unknown	ND	U = 217.1 μg/day (N = 0–12.2)	b) U = 10.6 μg/dl Pre d U = 11.1 μg/dl Post d	76.2 μg/dl	U (I @ 0.8), C (N @ 16.4), P (N @ 18.2), Iso (I @ 11.3) μg/g dry weight	ND
García-Parrilla et al[9] (1980)	1	16/M	Iron-dextran Familial	T = 25 nmol/L (79 L total volume)	ND	T = 1630 nmol/l Pre d (N < 5) T = 990 nmol/l Post d	ND	$\frac{\text{Iso}}{\text{C}}$ ratio = 1.2 (N = ND)	D
Wilkin et al[10] (1980)	1	55/M	Unknown	ND	U = 114 μg/24 hr (N = <30) C = 419 μg/24 hr (N = <100)	ND	ND	ND	ND
Lichtenstein et al[11] (1981)	1	51/F	Iron-dextran	None detected	T = 3.2 μg/24 hr (N = 50–290)	T = 14.9–66.3 μg/dl (N = 0–6)	49 μg/dl (N = 2.2–92)	U (I @ 182), C (N @ 1025), P (N @ 642), ISO (ND)* μg/24 hr (* Patient in remission)	D
Topi et al[12,13] (1980/81)	1	63/F	Familial	1–3 mg	T = 0.0508 μg/24 hr (N = ND)	Extraordinarily high (T = 1.51 mg/L)	Normal (Copro = 35.33 μg/ml PRC) (Proto = 21.09 μg/ml PRC)	C (N @ 9.16), P (N @ 35) μg/g	ND
Hanno and Callen[14] (1981)	1	41/F	Unknown	ND	ND	Elevated	ND	ND	ND

RBC-U/D = red blood cell uroporphyrinogen decarboxylase, T = total porphyrins, Iso = isocoproporphyrins, I = increased, C = coproporphyrins, N = normal, P = protoporphyrins, ND = not determined or given, U = uroporphyrins, NA = not available, Pre d = predialysis, D = decreased, Post d = postdialysis, PRC = packed red cells.

around the vessels of the dermis and along the basement membrane. Urinary and stool porphyrin levels were normal.

Thivolet et al[18] found nine of 100 patients undergoing hemodialysis who had bullous eruptions similar to those of PCT. The bullae were transient, giving rise to erosions, scars, and milia. Histologic studies revealed subepidermal bullae; fecal and urine porphyrin determinations were negative. Minute quantities of coproporphyrins were detected in the dialysate of one patient.

Griffon-Euvrard et al[19] described bullae, atrophic scars, and erosions of the hands in 16 of 100 hemodialysis patients studied. Porphyrin levels were not measured.

Perrot et al[20] studied by electron microscopy the sun-exposed skin from the dorsum of the hand of three heavily hemodialyzed patients with a PCT-like bullous skin eruption. Ultrastructural vascular changes were similar to PCT except for greater thickness of the basement membrane and presence of granular material in the perivascular ring. Endothelial cell changes are much more prominent in these specimens than in PCT, where they are absent or slight. The large quantity of granular material in the dermis appears unique to this process and is similar to the hyalin seen in lipoid proteinosis. No mention is made of porphyrin analyses in these patients.

Rufli and Brunner[21] reviewed the literature on patients with bullous eruptions resembling PCT and described another patient with normal urinary porphyrin levels.

Brivet et al[22] examined 500 patients on maintenance hemodialysis and discovered 6 who had developed a bullous eruption 2–54 months after the onset of dialysis. Four patients demonstrated increased skin fragility secondary to trauma. Sclerodermatous changes were apparent on the hands of one patient. No milia were seen. Biopsy specimens revealed subepidermal bullae. Immunofluorescence studies were negative for IgG, IgM, IgA, C3, and fibrin in biopsy specimens of 2 patients. Protoporphyrin and coproporphyrin levels in the stool specimens of 6 patients and in the erythrocytes of 4 patients were normal. The dialysis fluid of one patient did not contain any detectable uroporphyrin, coproporphyrin, or porphobilinogen. All 6 patients had been taking aluminum hydroxide gel. It was speculated that aluminum hydroxide may be a precipitating factor in porphyria, since abnormal aluminum accumulation has been documented in the liver of some dialysis patients, and chronic aluminum hydroxide administration has been demonstrated to cause porphyria in rats. However, 4 patients with BDH had normal plasma aluminum levels. The authors commented on the heterogeneity of normal plasma aluminum levels, thus allowing them to refrain from any conclusions regarding possible aluminum intoxication. They suggested that skin or liver aluminum levels might be more helpful in determining an aberration in aluminum metabolism in these patients. It is important to note that the blistering eruption occurred in 3 patients who were receiving estrogen therapy, a frequently associated etiologic factor in PCT induction.

In their 1978 report, Poh-Fitzpatrick et al[5] mentioned 2 hemodialyzed patients with bullous dermatoses in whom plasma porphyrin levels were normal.

Webster and Dahlberg[23] reported bullous dermatosis on the dorsa of the hands in a uremic patient who had been on dialysis for at least six years. He was noted to have increased skin fragility and several denuded areas near the original bullous lesions. Porphyrin assays were not performed. Some improvement was initially observed with the use of 0.5% triaminolone acetonide cream and 1% hydrocortisone acetate in Eucerin®. The bullous eruption cleared after three to four weeks.

Day and Eales[8] described a patient with elevated plasma porphyrins and bullous lesions. In contrast to 2 of their other patients (*Table 1*) they felt that this patient did not have overt PCT; her porphyrin status was similar to that of unaffected dialysis patients in their series.

Olmstead and Clack[24] described 4 patients with BDH. Patient 1, on long-term replacement iron therapy, had bullae on the dorsa of the hands and forearms, along with atrophic scars. Stool and urine porphyrin levels were normal. Patient 2 presented with pruritus, and excoriations and bullae of the bald scalp. Microscopic examination demonstrated subepidermal bullae. Urinary uroporphyrins were negative, but stool and blood porphyrin levels were not determined. The third patient was described as having a single tense blister on the right fifth finger along with hemorrhagic crusted lesions of the hands, forearms, and bald scalp. Biopsy specimens revealed a subepidermal bulla. Urine porphyrin studies were not obtainable. No mention was made of porphyrin analyses of plasma, erythrocytes, or stool. Patient 4, although lacking bullae, had several hemorrhagic crusted lesions on the sun-exposed

areas of the arms and hands. An actual diagnosis of BDH was never documented because the patient refused the appropriate tests. A significant decrease in symptoms and clearing of lesions were observed in the first 2 patients after deliberate reduction of serum iron levels by holding back a small quantity of blood (less than 100 ml) after several dialysis treatments.

Lichtenstein et al[11] mentioned 6 control patients for their overt PCT. These patients had chronic renal failure and were on hemodialysis; one had a blistering disease resembling PCT (*Table 1*). Porphyin studies were apparently normal.

Thivolet and Euvrard[25] mentioned 8 similar patients with PCT-like eruptions and normal plasma uroporphyrin levels. They were included in a group of 11 hemodialyzed patients with PCT-like eruptions, the remaining 3 of whom had elevated plasma uroporphyrin levels.

Antonello et al[26] described pseudo-PCT in 3 patients with functioning transplanted kidneys. All 3 had undergone dialysis prior to transplantation; however, whether the skin eruption occurred during dialysis is not clear from reviewing the article. Porphyrin studies are not specifically mentioned. In 2 of the patients who had also been taking aluminum hydroxide gel, the rash resolved when proglumide was substituted for the gel.

The cases discussed above are summarized in *Table 2.*

Bullous dermatoses due to nalidixic acid and furosemide in chronic renal failure: Nalidixic acid (Negram), an antibiotic used in the treatment of urinary tract infections, has been implicated as a cause of phototoxic bullous eruptions resembling PCT, and some of the patients have had impaired renal function.[27–29] PCT-like blistering of sun-exposed areas from furosemide (Lasix) has been reported, occasionally in uremic patients treated with high doses of the drug.[30–34] No abnormalities of porphyrin metabolism were documented in these patients.

Susskind and Lyell[27] described 2 patients with suspected reactions to nalidixic acid. In one patient, in chronic renal failure, blistering developed on the dorsa of the hands and feet, tip of the nose, lower lip, and forearms two days after the start of a course of Negram. Urine porphyrin levels were normal and no mention was made of other porphyrin analyses. The eruption subsided in both patients with "routine treatment."

Mathew[28] reported bullous eruptions in 5 patients who had been receiving 4000 mg of nalidixic acid per day for two to six weeks. The drug was given for a documented gram-negative urinary tract infection in each patient. Three of the 5 patients had impaired renal function. The lesions, all on exposed areas, were initially erythematous but then progressed to frank bullous eruptions. In all cases, the bullae resolved without scarring within two to eight weeks. No mention was made of porphyrin determinations.

Birkett et al[29] described the development of blisters after sun exposure on the hands and feet of 5 patients who were receiving daily doses of 750–3000 mg of nalidixic acid. Porphyrin investigations were not performed in the 2 patients with renal failure. Urinary porphyrin levels were normal in the other 3 patients. Stool and blood porphyrin levels were normal in 2 of these patients and were not evaluated in the third. Microscopic examination demonstrated subepidermal bullae without accumulation of PAS-positive material around the small vessels in these 3 patients.

Keczkes and Farr[30] reported the development of bullous eruptions on the dorsa of the fingers and hands in 5 uremic patients receiving doses of furosemide ranging from 40 to 2000 mg daily. Four of these patients were also taking aluminum hydroxide in unknown dosages. One patient had been undergoing peritoneal dialysis, 2 were on maintenance hemodialysis, and one patient had never received hemodialysis. In a fifth patient, bullae developed prior to institution of hemodialysis. Histologic studies revealed subepidermal bullae in each patient. Urine and erythrocyte porphyrin levels were normal in all 5. Fecal porphyrin levels were measured in 4 patients and also found to be normal. Topical corticosteroids and oral chlorpheniramine maleate appeared to aid in the resolution of lesions in one of 2 patients.

Burry and Lawrence[31] implicated furosemide as the cause of phototoxic blisters on the dorsa of the hands and feet in 4 patients with chronic renal failure; daily dosage ranged from 80 to 2000 mg. The biopsy specimen of one patient demonstrated a subepidermal bulla. Porphyrin studies in 2 patients were stated as being "negative."

Kennedy and Lyell[32] described 7 uremic patients who developed what they termed "acquired epidermolysis bullosa" while on high-dose furosemide. The daily dose varied from 500 to 2000 mg. Most patients had undergone high-dose furosemide therapy for several months before the development of cutaneous lesions. Superficial

Table 2. Bullous dermatosis of hemodialysis

Author	Cases	Age	Sex	Possible precipitating factors	Porphyrin Analyses				
					Urine	Plasma	Erythrocytes	Feces	Dialysate
Gilchrest et al[15] (1975)	5	36–67	1F, 4M	Chlorothiazide in 1 case	N	N	N	N	ND
Korting[16] (1975)	2	47, 49	2F	ND	I in 1‡ of 2 cases	ND	ND	ND	ND
Griffon-Euvrard et al†[17] (1976)	2	30, 44	2M	ND	N	ND	N	ND	ND
Thivolet et al†[18] (1977)	9	30–61	9M	Hepatitis in 3 cases	N	ND	ND	N	C in 1 case
Griffon-Euvrard et al†[19] (1977)	16	33–62	1F, 15M	Medication and/or Australia antigen in several cases	ND	ND	ND	ND	ND
Perrot et al†[20] (1977)	3	42–62	3M	Medication, $AlOH_3$	No mention made of porphyrin determinations				
Rufli and Brunner[21] (1977)	1	52	M	ND	N	ND	ND	ND	ND
Brivet et al†[22] (1978)	6	23–49	5F, 1M	$AlOH_3$, hepatitis and/or medication	ND	ND	N in 4 cases studied	N	N in 1 case studied
Poh-Fitzpatrick et al[5] (1978)	2	ND	ND	ND	ND	N	ND	ND	ND
Webster and Dahlberg[23] (1980)	1	54	M	$AlOH_3$	ND	ND	ND	ND	ND
Day and Eales[8] (1980)	1	ND	F	Hepatitis	ND	U = 1.72‡ μg/dl (N = <0.19)	P = 1.72‡ μg/dl (N = 5–45)	N	ND
Olmstead and Clack[24] (1981)	4	37–63	4M	Iron in 1 case	N in 2 cases studied	ND	ND	N in 1 case studied	ND
Lichtenstein et al[11] (1981)	1	ND	ND	ND	Porphyrin studies apparently normal in this renal failure control patient				
Thivolet and Euvrard†[25] (1982)	8	ND	ND	ND	ND	N	ND	ND	ND
Antonello et al*[26] (1980)	3	29–38	3M	$AlOH_3$	No alteration in porphyrin metabolism				

* = Renal transplant patients.
† = Some patients may have been included in more than one report.
‡ = Not considered by author(s) to be overt PCT (See Table 1 in Day and Eales report).
$AlOH_3$ = aluminum hydroxide gel.
See Table 1 for abbreviations.

bullae were present on the dorsa of the hands or fingers and, in 2 patients, also on the dorsa of the feet. Biopsy specimens revealed a subepidermal bulla with minimal inflammatory infiltrate in the dermis and very few inflammatory cells in the blister fluid. Urine, blood, and stool specimens for porphyrin were negative in the 3 patients studied. The lesions resolved over three to nine weeks even if furosemide was continued.

Heydenreich et al[33] reported subepidermal bullae on the dorsa of the hands and fingers in 12 of 56 uremic patients treated with furosemide in daily dosages of 500 to 2000 mg. Duration of treatment prior to eruption varied from one to 16 months. Nine patients had undergone hemodialysis. In all patients, the bullous eruptions had begun during the summer months and disappeared spontaneously after varying periods whether furosemide was continued or not. Urinary porphyrin levels were normal in the 8 patients studied. Erythrocyte and plasma porphyrin determinations in 7 patients with bullae were found to be the same as in 7 hemodialysis patients without bullae. Serum furosemide levels were similar in patients with and without bullae.

Rotstein[34] described 8 patients with chronic renal failure in whom blistering of the sun-exposed areas of the dorsa of the hands and feet appeared to be induced by minor trauma. Three of these patients were undergoing hemodialysis and 7 were receiving furosemide in daily dosages ranging from 80 to 3000 mg when the bullous eruptions occurred. Milia, scarring, malar hypertrichosis, and sclerodermatous changes were not observed. Uroporphyrin, protoporphyrin, and coproporphyrin levels in the urine of 6 patients and in the stool specimens of 7 patients were normal. Blood porphyrin studies were not performed. Histologic studies revealed the following differences from PCT: degranulated mast cells were found in the dermis and, on PAS stain, the basement membrane was found to be intact and on the floor of the blister. In PCT, the basement membrane has been reported to be partially *in* and partially *on* the blister roof as shown by PAS stain. Rotstein postulated that furosemide and hemodialysis are probably not important etiologic factors in blister production, as one patient had not taken furosemide for four months and 5 patients had not been on hemodialysis prior to the eruption. Rather, he suggested that intense sunlight and trauma to exposed skin may be significant factors in these bullous eruptions.

The cases discussed above are summarized in *Table 3.*

Discussion

The division of the overt PCT and PCT-like eruptions into the above three categories is presented as the cases were reported and is somewhat arbitrary. A simpler classification would be to divide patients with vesiculobullous dermatoses of chronic renal failure into those with and without porphyria.

Since elevated urinary uroporphyrins have been pathognomonic of PCT, and since dialysis patients are essentially anuric, the diagnosis of PCT may have been missed in some cases.[35] Additionally, uroporphyrin levels may not be an accurate reflection of body porphyrin content in the uremic patient. Today, more sophisticated methods are in use to diagnose PCT, especially the plasma porphyrin level, and more particularly to determine the relationship between concentration of the porphyrin isomers of uroporphyrin, heptaporphyrin, hexaporphyrin, and pentacarboxylic porphyrin via thin-layer chromatography, the fecal concentration of isocoproporphyrin and ultimately the measurement of uroporphyrinogen decarboxylase activity in hepatocytes or erythrocytes. With these methods, porphyria may indeed be shown to be a more common cause of bullae in patients undergoing hemodialysis,[36,37] or with phototoxic bullae from nalidixic acid or furosemide.[34]

Recently plasma porphyrin levels have been measured in nonporphyric patients on hemodialysis. Topi et al[12] found increased plasma porphyrin levels in 46 of 75 such patients and Poh-Fitzpatrick et al[37] reported increased plasma porphyrin levels in 69% of a series of nonporphyric patients on hemodialysis for renal failure. The latter also found that 10% of those patients had elevated plasma porphyrin levels overlapping the lower levels of the range in the 24 patients with PCT and normal renal function. Since uroporphyrin is normally excreted by the kidneys, elevated plasma levels might be expected in chronic renal failure. Uroporphyrin has a molecular weight of 831 that should allow it to be moderately dialyzable. However, no significant change in plasma uroporphyrin levels was found after hemodialysis in 3 patients of Poh-Fitzpatrick et al,[5,7] which suggests that protein binding may occur. One patient was dialyzed with a more permeable membrane, resulting in a marked de-

Table 3. Phototoxic (PCT-like) drug eruptions associated with chronic renal failure

Author	Cases	Age	Sex	Possible precipitating factors	Porphyrin Analyses				
					Urine	Plasma	Erythrocytes	Feces	Dialysate
Susskind and Lyell[27] (1965)	1	25	F	Nalidixic acid	N	ND	ND	ND	ND
Mathew[28] (1966)	3	ND	ND	Nalidixic acid	No mention made of porphyrin determinations in these patients				
Birkett et al[29] (1969)	2	4 4–5	M M	Nalidixic acid	No mention made of porphyrin determinations in these patients				
Keczkes and Farr[30] (1976)	5*	22–55	3F, 2M	Furosemide $AlOH_3$ and iron	N	ND	N	N in 4 cases studied	ND
Burry and Lawrence[31] (1976)	4	45–53	3F, 1M	Furosemide	"Investigations for porphyria were negative" in 2 cases and were not mentioned in 2 cases.				
Kennedy and Lyell[32] (1976)	7	17–57	2F, 5M	Furosemide	N in 3 cases studied	ND	N	N in 3 cases studied	ND
Heydenreich et al[33] (1977)	12†	25–69	5F, 7M	Furosemide	N in 8 cases	N in 7 cases studied	N in 7 cases studied	ND	ND
Rotstein[34] (1978)	8‡	19–56	3F, 5M	Furosemide $AlOH_3$ and iron	N in 6 cases studied	ND	ND	N in 7 cases studied	ND

* = 2 patients were on peritoneal dialysis.
† = 9 patients were on chronic hemodialysis.
‡ = 3 patients were on chronic hemodialysis.
ND = not mentioned, N = normal.

crease in plasma porphyrin at the completion of a dialysis session. Although average plasma porphyrin levels were only slightly higher in nonporphyric hemodialysis patients than in controls, 5 patients reached porphyrin levels measured in the plasma of patients with PCT and normal renal function. An increased incidence of cutaneous manifestations of PCT might be explained in this patient population as a result of build-up of porphyrin levels due to inadequate excretion. However, none of these patients had or developed any cutaneous lesions similar to PCT.

In the laboratory of Poh-Fitzpatrick[7], plasma porphyrin values of symptomatic patients with PCT without renal disease were generally lower than those of PCT patients on hemodialysis, and rarely exceeded 25 μg/dl. Uroporphyrins appeared to be readily excreted into the urine in those PCT patients without renal disease.

Uroporphyrinogen decarboxylase levels were decreased in 2 patients with PCT on hemodialysis (*Table 1*). This enzymatic defect in PCT may result from an autosomal dominant gene[38] and must have been present before the onset of renal disease. Chronic hemodialysis, like alcoholic liver disease with siderosis, may be associated with PCT because it is able to clinically manifest an otherwise occult enzyme defect. Why hemodialysis should have such an effect is not clear. The iron overload common in patients undergoing hemodialysis may be a triggering factor. These patients may also produce or be exposed to drugs or chemicals that affect hepatic heme synthesis. These include aluminum hydroxide and plasticizers exuded from the tubing or other apparatus to which blood is exposed during dialysis.[25] Ethanol abuse or diabetes mellitus may be other factors.

PCT-like phototoxic eruptions have also been reported from tetracycline hydrochloride and the sulfones. However, impaired renal function was not reported in these patients. Epstein[39] states that although these drugs are weak photosensitizers, prolonged repeated solar irradiation seems to be an essential concomitant. Sun exposure also seems to be the major factor producing the bullous eruptions from nalidixic acid and furosemide.

Treatment of a patient with PCT who is undergoing hemodialysis is difficult. Chloroquine has been demonstrated to be ineffective and the inevitable anemia is generally a contraindication to phlebotomy. The major porphyrin in

the plasma of such patients is uroporphyrin, which circulates bound to albumin and hemopexin and is not effectively cleared through any of the standard dialysis membranes. Thus, it seems likely that more effective removal of the porphyrins from the plasma of PCT patients would be beneficial. Plasma exchange has been recently reported by Disler et al[35] to be successful in treating a hemodialysis-related PCT case (the patient previously reported by Day and Eales[8]). The procedure of plasma separation was performed for one hour on two occasions 48 hours apart. On each occasion, 4.0 liters of plasma were removed from the patient and discarded, and reconstitution of the red cells was achieved with fresh frozen plasma. Rapid clinical response paralleled a significant drop in plasma porphyrin levels. These levels decreased even further over the following few months on additional therapeutic intervention. Shortly thereafter, porphyrin levels rose slowly and the cutaneous manifestations recurred. This rebound effect was not reported in the other 2 patients in the literature with PCT who were treated with plasma exchange.[35] Disler et al[35] proposed exchanging less plasma as a way of avoiding rapid concentration changes and the rebound rise. Plasma exchange appears to offer promise in the treatment of the dialysis-related PCT patient for whom no alternative therapy exists for the cutaneous problems.

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