Drug induced pseudoporphyria in CKD: A case report

S. Quaiser, R. Khan, A. S. Khan

Department of Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

ABSTRACT

Pseudoporphyria (PP) is used to describe a photodistributed bullous disorder with clinical and histologic features of porphyria cutanea tarda (PCT) but without accompanying biochemical porphyrin abnormalities. Medications, excessive sun and ultraviolet radiation exposure, have all been reported to develop PP. We report a case of PP in a 49-year-old man with CKD stage 3a, caused due to torsemide intake. This is probably the first reported case of PP developing in a dialysis naive patient CKD due to torsemide intake from India.

Key words: Chronic kidney disease, pseudoporphyria, torsemide

Introduction

Pseudoporphyria (PP) is a rare, photodistributed bullous dermatosis that clinically, histopathologically, and immunologically resembles porphyria cutanea tarda (PCT)[1,2] but is not accompanied by porphyrin abnormalities in the serum, urine, or stool. It was initially described in patients with renal failure on dialysis as "bullous dermatosis of hemodialysis."[3] Subsequently, PP has been associated with numerous photosensitizing medications, hormone replacement, and ultraviolet A (UVA) radiation in tanning beds, hepatitis C, sarcoidosis, Sjogren syndrome, hepatoma, HIV infection and lupus erythematosus. Drugs commonly associated with pseudoporphyria are naproxen, tetracycline, fluoroquinolones, voriconazole, furosemide, chlorthalidone, butamide, hydrochlorothiazide/triamterene, amiodarone, cyclosporine.[4]

Case Report

A 49-year-old hypertensive male presented with swelling over the body for the last 1-month. On detailed clinical and diagnostic workup, he was diagnosed as a case of chronic kidney disease (CKD) stage 3 (estimated glomerular filtration rate 51.6 ml/min/1.73 m^2) of unknown etiology. He was prescribed torsemide, cilnidipine, calcium acetate, ferrous ascorbate, paricalcitol along with low salt and protein restricted diet. Three weeks later he came with complains of several erythematous lesions of the forearm and around the wrist. On clinical examination, several slightly pruritic, round, sharply demarcated, erythematous vesicular plaques were observed, symmetrically distributed over the anterior aspect of the forearm. No evidence of hypertrichosis, hyperpigmentation or sclerodermoid changes was seen [Figure 1].

Dermatological opinion was suggestive of a blistering disorder either porphyria cutaneous tarda or PP. Histological examination undertaken of skin lesion showed hyperkeratosis and acanthosis of the epidermis. In the papillary dermis, we noted subepidermal cleft with preservation of papillae and no inflammatory infiltrate along with periodic acid stain positive, diastase negative, eosinophilic, donut-like rings around the capillaries as shown in Figures 2 and 3. Direct immunofluorescence showed microgranular deposition of the C3 around the papillary dermal vessels as shown in Figure 4. Levels of plasma porphyrins were normal (protoporphyrin <0.5 μg/L (normal <0.75 μg/L), coproporphyrin <0.01 μg/L (normal <0.01 μg/L); urinary levels were normal: Porphobilinogen 6 μmol/dl (normal <8 μmol/dl), uroporphyrin 21 nmol/dl (normal <28 nmol/dl); coproporphyrin I was normal at 12 nmol/dl (normal <35 nmol/dl); and coproporphyrin III was normal at 11 nmol/dl (normal <110 nmol/dl). Fecal total coproporphyrin was also normal at 25 nmol/g (normal

Address for correspondence:
Dr. R. Khan,
Department of Medicine, JNMC, AMU, Aligarh - 202 002,
Uttar Pradesh, India.
E-mail: drruhi5@gmail.com

Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.160335

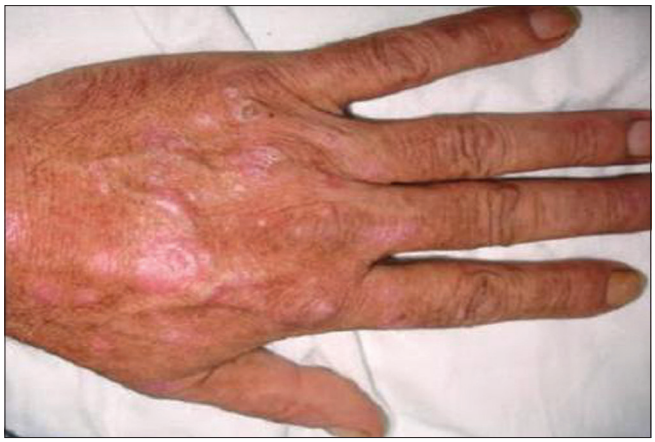

Figure 1: Erythematous vesicular plaques on anterior aspect of the forearm and palm

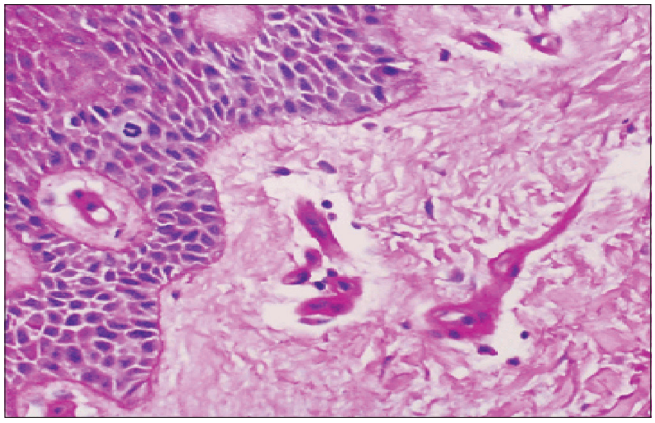

Figure 3: Skin biopsy with Periodic acid Schiff (PAS) stain showing PAS-positive diastase negative hyaline material thickening the wall of dermal vessel and dermo-epidermal junction (×40)

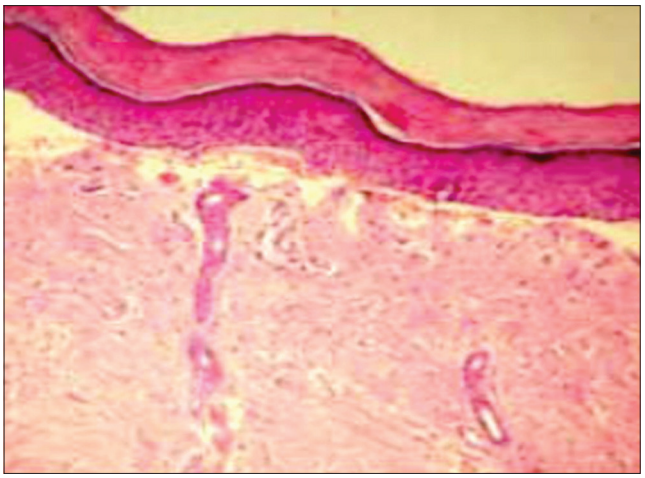

Figure 2: Skin biopsy with hematoxylin and eosin stain showing subepidermal cleft with preservation of papillae with no inflammatory infiltrate (×40)

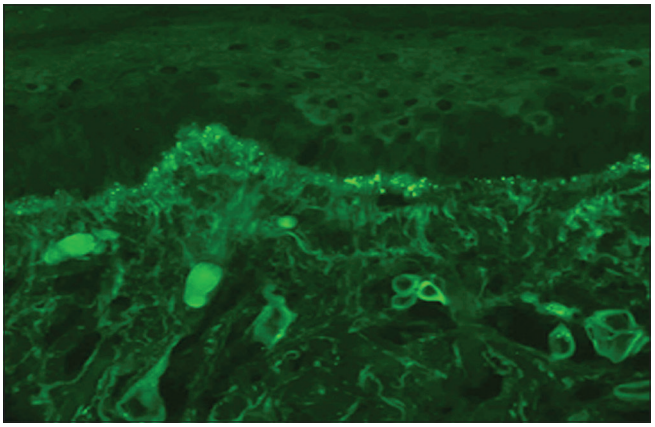

Figure 4: Direct Immunofluorescence - C3 deposits around dermal vessels and dermo-epidermal junction

0–46 nmol/g), and fecal total porphyrin was 10 nmol/g (normal 0–50 nmol/g). Other laboratory investigations were as follows: Hemoglobin 9.6 g/dl (normal range 11.5–14.5 g/dl); serum iron 23 μmol/L (normal range 10–30 μmol/L); ferritin 207 μg/L (normal range 50–250 μg/L); alkaline phosphatase 102 U/L (normal range 40–120 U/L); alanine aminotransferase 15 U/L (normal range 10–55 U/L); and aspartate aminotransferase 19 U/L (normal range 10–40 U/L). Screening for hepatitis viruses and the human immunodeficiency virus were negative. Based on clinical and histological grounds, a diagnosis of PP was made. Torsemide was withdrawn, and the patient was treated for 4 weeks with antihistaminic with an only minimal improvement, which were then withdrawn. On 2 month follow-up, there was a significant improvement while in 4 months the lesions cleared completely with only residual post-inflammatory hyperpigmentation.

Discussion

In 1964, Zelickson was first to describe this type of phototoxic reaction in patients after the use of nalidixic acid.[5] In a retrospective study of 20 cases, the mean age at diagnosis was 50 years.[6] Among patients with the end-stage renal disease, PP has been estimated to occur in 1.2–18% of those on hemodialysis and, less frequently, in those on peritoneal dialysis.[3]

Clinically, PP is characterized by bullae, developing on the photo-exposed skin, most commonly on the dorsum of the hands and feet, forearms, face, and neck. The lesions heal with scaring and milia formation. In contrast to PCT, hypertrichosis, hyperpigmentation, and sclerodermoid plaques only rarely occur.

Of critical importance for the diagnosis of PP is the exclusion of true porphyria, especially PCT. By definition, in PP porphyrin profile is normal or near normal.[6] Individuals with CKD tend to have higher serum porphyrin levels than normal, with some levels determined to be within the lower end of the range commonly found in PCT patients with normal renal function. Furthermore, plasma uroporphyrin levels are generally higher in patients on

hemodialysis compared with those on peritoneal dialysis, which may explain the lower incidence of PP in the latter group.

If the diagnosis of PP is suspected, biopsies for histologic evaluation with hematoxylin and eosin stains and direct immunofluorescence should be performed. Serum samples may also be obtained for indirect immunofluorescence evaluation to aid in the exclusion of bullous pemphigoid. The histologic features of PP are similar to those of PCT with subepidermal bullae and festooning of the dermal papillae and granular deposits of immunoglobulins, mostly IgG, and C3 at the basement membrane zone and in the perivascular region. Although direct immunofluorescence is not a useful tool in distinguishing PP from PCT, it is helpful in the evaluation of other entities in the differential diagnosis of PP, specifically epidermolysis bullosa acquisita. Epidermolysis bullosa acquisita can be ruled out by the lack of intense, linear immunoreactants at the dermal-epidermal junction. Neither PCT nor PP has circulating autoantibodies detected by indirect immunofluorescence study.

The thickness of the blood vessel wall may prove helpful in differentiating PP from PCT. In a comparative histologic study from biopsy samples of patients with PCT and PP, Maynard and Peters found thickened blood vessel walls in 11 of 13 patients with PCT. In contrast, similar findings in only 1 of 9 patients with PP were present.[7]

The exact pathophysiological mechanism of PP is unknown. Formation of phototoxic metabolites in genetically predisposed individuals may trigger the development of bullous lesions. In general, the action spectrum has been assumed to be in the range of UV radiation or possibly, visible light. There is evidence that some of the causally associated drugs also induce photosensitivity. Reactive oxygen species have been incriminated in the pathogenesis of dialysis-associated PP. These patients are at high-risk of oxidative stress due to deficiency of glutathione in the blood and erythrocytes, which may increase their susceptibility to the effects of UV exposure at even lower porphyrin levels. In addition, clearance of plasma-bound porphyrin precursors may lead to excessive porphyrin deposition in the skin. It could also be related to aluminum hydroxide, which is found in the dialysis solution and has been shown to produce a porphyria-like reaction to rats.

In cases of drug-induced PP, withdrawal of the suspected photosensitizing medication results in improvement usually within weeks to months (average 8 weeks) which were seen in our case. Strict UV rays protection, including a broad spectrum sunscreen, is crucial. In hemodialysis-associated PP, there are reports of complete resolution after treatment with N-acetylcysteine (800–1200 mg p.o. daily for 8 weeks), a glutathione precursor, but some authors noticed recurrence when the drug was discontinued.[8-10] Chloroquine also has been tried with satisfactory results after 1-month.

Our patient is probably the second reported case,[11] of PP developing in dialysis naive CKD patient, first from India. The question whether it is the disease CKD or the management (hemodialysis) which contributes most to the occurrence of PP remains to be answered. Dialysis in genetically predisposed patients may indeed contribute to PP development, either by the resulting in oxidative stress or by reflecting a more advanced stage of renal failure. Finally, but a thorough drug history should be ascertained in such cases, which might minimize the morbidity associated with this disorder.

References

1. Rapini RP, Bolognia JL, Jorizzo JL. Dermatology: 2-Volume Set. St. Louis: Mosby; 2007.
2. James WD, Berger TG, Dirk Elston MD. Andrews' Diseases of the Skin: Clinical Dermatology. United States. Saunders Elsevier; 2006. ISBN: 978-1-4377-0314-6.
3. Green JJ, Manders SM. Pseudoporphyria. J Am Acad Dermatol 2001;44:100-8.
4. Suarez SM, Cohen PR, DeLeo VA. Bullous photosensitivity to naproxen: "Pseudoporphyria". Arthritis Rheum 1990;33:903-8.
5. Zelickson AS. Phototoxic reaction with nalidixic acid. JAMA 1964;190:556-7.
6. Schanbacher CF, Vanness ER, Daoud MS, Tefferi A, Su WP. Pseudoporphyria: A clinical and biochemical study of 20 patients. Mayo Clin Proc 2001;76:488-92.
7. Maynard B, Peters MS. Histologic and immunofluorescence study of cutaneous porphyrias. J Cutan Pathol 1992;19:40-7.
8. Guiotoku MM, Pereira Fde P, Miot HA, Marques ME. Pseudoporphyria induced by dialysis treated with oral N-acetylcysteine. An Bras Dermatol 2011;86:383-5.
9. Vadoud-Seyedi J, De Dobbeleer G, Simonart T. Treatment of haemodialysis-associated pseudoporphyria with N-acetyleysteine: Report of two cases. Br J Dermatol 2000;142:580-1.
10. Tremblay JF, Veilleux B. Pseudoporphyria associated with hemodialysis treated with N-acetylcysteine. J Am Acad Dermatol 2003;49:1189-90.
11. Pérez-Bustillo A, Sánchez-Sambucety P, Suárez-Amor O, Rodríguez-Prieto MA. Torsemide-induced pseudoporphyria. Arch Dermatol 2008;144:812-3.

How to cite this article: Quaiser S, Khan R, Khan AS. Drug induced pseudoporphyria in CKD: A case report. Indian J Nephrol 2015;25:307-9.

Source of Support: Nil, **Conflict of Interest:** None declared.