

Case Report

A man with porphyria cutanea tarda presenting with recurrent blistering over hands and forearms

男性患者遲發性皮膚卟啉症呈手部及前臂反覆水泡發作

SY Wong 黃曉毅

Porphyria cutanea tarda (PCT) is a rare metabolic disorder due to an inherited or acquired deficiency in uroporphyrinogen decarboxylase, the fifth enzyme in the haem synthesis pathway. We report a 57-year-old gentleman who presented with three months history of recurrent blister formation over the sun-exposed areas of his arms and forearms. Elevated porphyrins were detected in his urine and skin biopsy showed characteristic features of PCT.

遲發性皮膚卟啉症為一罕有代謝病，由先天性或後天性尿卟啉原脫羧酶缺乏引起。尿卟啉原脫羧酶為血紅素合成過程中的第五步酶。本例報告一名 57 歲男性患者三個月來於手及前臂的光照部位呈反覆水泡疹發作。患者尿液中卟啉類化合物含量增高，皮膚活檢呈典型的遲發性皮膚卟啉症特徵。

Keywords: Photosensitivity, Porphyria cutanea tarda

關鍵詞：光敏感，遲發性皮膚卟啉症

Case report

A 57-year-old construction site worker presented with on and off itchy rashes with multiple recurrent blister formation over his hands for 3 months. There was no history of trauma or insect bite, and

he was not on any medications. He was a chronic smoker and a heavy drinker. Except for a past history of intravenous drug abuse, he enjoyed good past health and there was no family history of skin disease. Physical examination showed multiple excoriated erosions, milia and atrophic scarring over the dorsa of his hands and forearms i.e. over the sun-exposed areas (Figure 1). One fresh blister was found over his right wrist (Figure 2). The rest of the body was relatively spared with no hypertrichosis, pigmentary changes or sclerodermoid features. The differential diagnoses included bullous pemphigoid, bullous drug eruption, bullous lupus erythematosus, dermatitis herpetiformis, linear IgA disease, porphyria cutanea tarda, pseudoporphyria and epidermolysis bullosa acquista.

Social Hygiene Service, Department of Health, Hong Kong

SY Wong, MBBS (HK), MRCP (UK)

Correspondence to: Dr. SY Wong

Cheung Sha Wan Dermatological Clinic, 3/F, West Kowloon Health Centre, Cheung Sha Wan Government Offices, 303 Cheung Sha Wan Road, Kowloon, Hong Kong



Figure 1. Multiple excoriated erosions, milia, atrophic scarring over dorsa of the hands and forearms.



Figure 2. A tense clear fluid-filled blister over the right wrist.

The blister over the right wrist was removed by excisional skin biopsy. Histology showed a subepidermal blister with very mild perivascular lymphocytic and rare eosinophilic infiltrate (Figure 3). The dermal capillaries possessed thickened basement membrane that was PAS positive. Direct immunofluorescence study showed linear IgG (2+) staining along the capillary wall and basement membrane of the epidermis and skin appendages. Linear C3 (2+) staining was also noted focally in the basement membrane of the skin appendages. Staining for IgA, IgM and fibrin were negative. The findings were compatible with porphyria cutanea tarda with a differential diagnosis of epidermolysis bullosa acquisita. Although the presence of IgG staining was unusual for porphyria cutanea tarda, the overall clinical picture was supportive of the diagnosis.

Elevated porphyrins were detected in the patient's urine though Wood's lamp illumination of the urine failed to show the typical pink-red

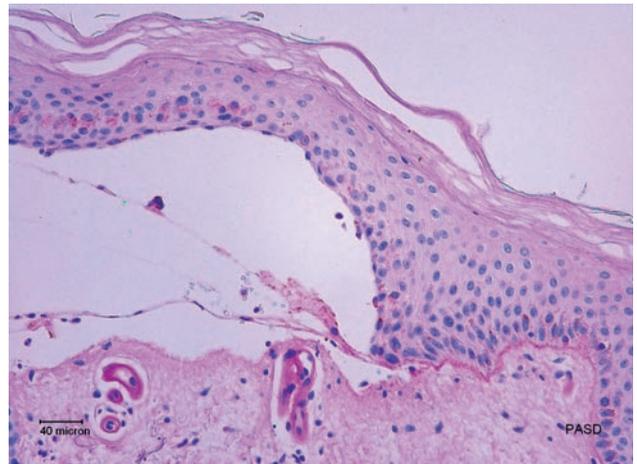


Figure 3. A pauci-inflammatory subepidermal blister with PAS positive, diastase resistant hyaline material around dermal capillaries. Note the row of basement membrane like material incorporated into the epidermis in the roof of the blister, the so-called "caterpillar bodies" (PASD stain).

fluorescence. Blood tests revealed polycythaemia with haemoglobin level of 18.2 g/dL, haematocrit of 0.539 L/L. The liver function tests were also deranged with elevated ALT 128 U/L, and positive anti-HCV antibody was found. HBsAg, HIV antibody and anti-nuclear antibodies were negative, while iron status and fasting glucose were normal.

We advised the patient to abstain from alcohol intake and avoid sun exposure and referred him to the regional hospital for investigations of his deranged liver function, hepatitis C infection and consideration of venesection.

Discussion

The porphyrias are a group of clinically and genetically heterogeneous metabolic disorders. They result from either an inherited or an acquired dysfunction of enzymes crucial for haem biosynthesis. The different porphyrias are characterised by particular patterns of accumulation and excretion of porphyrins and their precursors in the plasma, urine and stool.

The porphyrias can be classified clinically into acute and non-acute types (Table 1). The former is susceptible to acute neurovisceral attacks, and the latter to photosensitive cutaneous manifestations. The exceptions are variegate porphyria (VP) and hereditary coproporphyria, which are referred to as neurocutaneous porphyrias, as they demonstrate both neurovisceral and cutaneous manifestations.

Porphyria cutanea tarda (PCT) is the most common type of porphyria worldwide. The prevalence is estimated at about 1 in 70000.¹ It usually develops in middle age and the name "tarda" means late. The incidence is similar in males and females. Fung reviewed 10 cases in a period of 15 years from 1982 to 1997 in three local dermatological clinics and found a low incidence of the condition locally.²

PCT is due to an inherited or acquired deficiency in uroporphyrinogen decarboxylase, the fifth enzyme in the haem synthesis pathway. It is encoded by a single gene on the short arm of chromosome 1. PCT is classified into two broad categories, namely the acquired/sporadic type (Type I) and the hereditary type (Type II). The target enzyme is deficient only in the liver in the sporadic type of PCT, while it is decreased by approximately 50% in all tissues in the hereditary type. About 20% of PCT patients have the hereditary type of PCT, which is inherited in an autosomal dominant fashion with relatively low penetrance, thus the majority of these individuals do not manifest the disease.³

Deficiency in uroporphyrinogen decarboxylase leads to accumulation of porphyrins in the circulation and excess deposition in the skin. Porphyrin molecules are ring structures that are easily transformed to excited states after absorbing visible light. Excessive concentrations of porphyrins exposed to daylight generate free radicals with consequent lipid peroxidation, protein cross-linking and eventually leading to cell membrane damage and death.¹

Table 1. Classification of porphyrias

Acute porphyria	Non-acute porphyria
<i>ALA-D deficient porphyria</i>	<i>Porphyria cutanea tarda</i>
<i>Acute intermittent porphyria</i>	<i>Erythropoietic protoporphyria</i>
<i>Variegate porphyria</i>	<i>Congenital erythropoietic porphyria</i>
<i>Hereditary coproporphyria</i>	

Many chemicals and conditions are known to contribute to the development of PCT such as alcohol, oestrogens, iron overload, viral infections (e.g. hepatitis C, HIV), polychlorinated hydrocarbons and haemodialysis in renal failure patients.

Furthermore, PCT has been reported to be associated with various other systemic diseases such as systemic lupus erythematosus, discoid lupus erythematosus, subacute lupus erythematosus, haematological malignancies and hepatocellular carcinomas. Local data from Fung suggested an association between PCT with hepatitis B infection as well.²

Cutaneous manifestations of PCT include skin fragility and blistering over sun-exposed areas, especially those subjected to trauma such as the dorsa of the hands and feet, forearms and the face. The blisters are fluid-filled which rupture easily and heal with crusting, scarring and milia formation. Mottled areas of hyperpigmentation and hypopigmentation may also occur. Non-virilizing hypertrichosis is a diagnostic sign, more evident in females and more severe in children, with increase in hair growth mainly along the temples, forehead, cheeks and between the eyebrows. Lastly, sclerodermoid plaques may develop on both sun-exposed and sun-protected skin. These are usually scattered, waxy yellow to white indurated plaques that resemble morphea and scleroderma. Neurological symptoms that are common in acute porphyrias are not features of PCT.

The diagnosis of PCT depends on a compatible history, characteristic clinical signs and biochemical profile. The examination of urine with a Wood's lamp will rarely exhibit the pink-red fluorescence. While measurement of total urinary porphyrins is a useful and sensitive screening test, some laboratories use total plasma porphyrin levels as the screening test, which is relatively more specific. Determining the patterns of individual

porphyrins by HPLC (high performance liquid chromatography) separation will provide more specific information but is much more costly.

There are three main features of porphyrins excretion in PCT: (1) increased urinary excretion of uroporphyrin and other acetate substituted porphyrins; (2) a distinctive pattern of urinary excretion of isomer series I and III porphyrins with a particular ratio of uroporphyrin to coproporphyrin which differentiates between PCT and VP; and (3) increased excretion of faecal isocoproporphyrin.^{3,4}

It should be noted that porphyrin abnormalities can occur in cases of lead poisoning, haemolytic and iron deficiency anaemia, renal failure, cholestasis and liver diseases, but photosensitivity has only rarely been documented in these cases.

Characteristic histopathological features of PCT are cell-poor subepidermal blisters with festooning of the dermal papillae. Direct immunofluorescence studies reveal deposition of C3 and IgG in a granular pattern at the dermal-epidermal junction and around vessel walls.⁵

Investigations for associated systemic diseases should also be done, these include complete blood picture, liver and renal function tests, iron/ferritin level, alpha-fetoprotein, fasting glucose, serum ANA, hepatitis B, hepatitis C serology and HIV serology.

Identification and elimination of precipitating factors alone will lead to gradual improvement of symptoms. Repeated phlebotomies and low-dose oral antimalarials remain the first-line treatment for faster symptomatic control in PCT. Phlebotomy depletes the excessive iron stores characteristic of PCT and is effective in both iron overload and non-iron overload patients, resulting in clinical and biochemical remission.

Oral antimalarial drugs are an alternative in patients for whom phlebotomy is not recommended or contraindicated, e.g. anaemia or cardiopulmonary disorders. Low dose chloroquine 125 mg twice weekly has been shown to be effective in PCT and six to twelve months of treatment is usually required.⁶ Pre-treatment and subsequent regular eye assessments are needed to monitor for retinopathy. Glucose-6-phosphate-dehydrogenase (G6PD) status should also be checked before starting antimalarials in our local population. Other treatment strategies include combination therapy with phlebotomy and antimalarials, the use of iron-chelating agents such as desferrioxamine, and interferon-alpha in hepatitis C related cases of PCT.

Recent research on PCT demonstrated a significantly higher frequency of the C282Y mutation in the haemochromatosis gene in PCT patients from United Kingdom, Netherlands, Southern Italy, Spain, Australia and United States when compared with controls.⁷ PCT may thus be an invaluable cutaneous marker for patients with subclinical haemochromatosis, the most common single-gene inherited disorder in Caucasians.

Although PCT is a rare cause of photosensitive blistering conditions, dermatologists should be vigilant as it is often associated with underlying systemic diseases that require further investigations and treatment.

References

1. Murphy GM. The cutaneous porphyrias: a review. The British Photodermatology Group. *Br J Dermatol* 1999; 140:573-81.
2. Fung WK. Porphyria cutanea tarda and systemic diseases- a report of 10 cases and review. *HK Dermatol Venereol Bull* 2001;9:152-7.
3. Elder GH, Lee GB, Tovey JA. Decreased activity of hepatic urogenecarboxylase in sporadic porphyria cutanea tarda. *N Eng J Med* 1978;299:274-8.
4. Elder GH, Smith SG, Smyth SJ. Laboratory investigation of the porphyrias. *Ann Clin Biochem* 1990;27:395-412.
5. Wolff K, Hönigsmann H, Rauschmeier W, Schuler G, Pechlaner R. Microscopic and fine structural aspects of porphyrias. *Acta Derm Venereol Suppl (Stockh)* 1982; 100:17-28.
6. Adjarov D, Naydenova E, Ivanov E, Ivanova A. Choice of therapy in porphyria cutanea tarda. *Clin Exp Dermatol* 1996;21:461-2.
7. Mehrany K, Drage LA, Brandhagen DJ, Pittelkow MR. Association of porphyria cutanea tarda with hereditary hemochromatosis. *J Am Acad Dermatol* 2004;51:205-11.