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Porphyria cutanea tarda and melioidosis

遲發性皮膚卟啉症和類鼻疽

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 Porphyria cutanea tarda is a metabolic disorder in the haem biosynthetic pathway. It includes a heterogeneous group of conditions, which may be inherited or, more commonly, acquired. Although porphyria cutanea tarda presents with cutaneous lesions only, it is often associated with systemic disease. A 64-year-old Chinese patient, who developed sporadic porphyria cutanea tarda 1 year after the diagnosis of pulmonary melioidosis, is discussed. The patient presented with a history of recurrent photosensitive vesicles, blisters, and skin fragility on the sun-exposed areas of both forearms and hands, 6 months after commencing doxycycline and amoxicillin. Both the histological and biochemical findings were characteristic of porphyria cutanea tarda. All the lesions subsided after cessation of these antibiotics. The patient was free of further lesions at follow-up 6 months later. The association seen in this case between porphyria cutanea tarda and melioidosis is unlikely to be coincidental, because these two diseases are both very rare in Hong Kong. In addition, the temporal relationship between the antibiotic therapy and the clinical course of skin lesions in this patient suggests that the drugs were a trigger factor, precipitating their appearance.

Key words:

Adult;
 Antibiotic;
 Melioidosis;
 Porphyria cutanea tarda/diagnosis

關鍵詞：

成人；
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遲發性皮膚卟啉症是血紅素生物合成過程中的一種新陳代謝紊亂。它包括可能是遺傳或更常見的後天的不同組條件。儘管遲發性皮膚卟啉症僅呈現皮膚性損傷，它卻常與全身性疾病有關。本文討論了一位64歲的華人患者，他於一年前被診斷為患有肺部類鼻疽，現在患有間歇性的遲發性皮膚卟啉症。在服用多西環素和阿莫西林後6個月，患者的兩前臂和手部皮膚被日光照射的部位產生水疱，並出現周期性發作對光敏感的小泡，皮膚並且變得脆弱。組織學和生物化學診斷均為遲發性皮膚卟啉症。患者在停用這些抗生素後，所有這些損傷都減退了，並且在隨後的6個月沒有進一步的損傷。在這病例中所見的遲發性皮膚卟啉症和類鼻疽之間的關聯不可能是巧合的，因為這兩種病在香港都非常罕見。此外，在這患者中抗生素治療和皮膚受損的臨床過程之間的時間性，說明這些藥物是促成所見病徵的引發因素。

Introduction

Porphyria cutanea tarda (PCT) is a heterogeneous group of diseases. It is characterised biochemically by inhibition of liver uroporphyrinogen decarboxylase, with consequent accumulation of uroporphyrin and other highly carboxylated porphyrins, and clinically, by cutaneous features of photosensitivity, often associated with evidence of liver damage.¹ Porphyria cutanea tarda has been reported in association with many systemic diseases, including viral infection, haematological malignancy,

renal failure, and autoimmune connective tissue disorders.¹

We report the case of a patient who developed PCT during maintenance treatment with antibiotics (doxycycline and amoxicillin) for melioidosis, and achieved remission after cessation of these drugs. This patient is the first reported case of PCT associated with melioidosis, and it is postulated that the antibiotics, either individually or in combination, gave rise to the porphyria-inducing effect seen.

Case report

A 64-year-old Chinese woman presented to the Queen Mary Hospital in April 1995 with a low-grade fever, decreased appetite, lethargy, and cavitating lung lesions in both lung fields. There was no history of cough, shortness of breath, or haemoptysis. The patient had had thyrotoxicosis in 1993, which was treated by thyroidectomy, and diabetes mellitus since 1990. Apart from a sulphonylurea, she was taking no other medication. The patient did not smoke or drink, she had not travelled recently, and her family history was insignificant. Findings on physical examination were normal, with the exception of a low-grade fever. Biochemical tests, including a complete blood count, liver and renal function tests, and immune markers were normal. Repeated sepsis diagnostic tests on sputum, blood, and urine were negative. Sputum acid-fast bacillus smears and cultures were also negative. Radiologically, multiple cavitating lesions were found in the right middle and left upper lobes of the lungs. Computed tomography of the thorax, with contrast enhancement, confirmed the presence of abscesses, although there was no mediastinal or paratracheal lymph node enlargement. The patient was treated empirically with intravenous (IV) cefaclor and clindamycin for 3 weeks with little improvement.

The diagnosis of melioidosis was made by serology as the *Burkholderia pseudomallei* antibody was high, with a titre of 1:640. Clindamycin was replaced by oral co-trimoxazole 960 mg three times daily. The fever subsided and the antibody titres gradually decreased to 1:80. Serial chest X-rays showed gradual resolution of lung shadows—the lesions in the right lung subsided completely, whereas the lesions in the left lung decreased by 80%. The patient was discharged and instructed to take ciprofloxacin 500 mg twice daily and doxycycline 100 mg four times daily for 6 months.

At follow-up in October 1995, new lesions had developed in both lung fields, although the patient was

clinically asymptomatic. The relapse of melioidosis was confirmed by a rise of antibody titres to 1:320. The patient was readmitted and treated with IV cefaclor. Her condition improved and she was discharged on drug therapy of co-amoxiclav 375 mg three times daily, and doxycycline 100 mg four times daily. The patient was monitored in the outpatient clinic and improved radiologically with good drug therapy compliance, although antibody titres remained high at 1:160.

In April 1996, the patient presented with a history of recurrent, itchy blistering, and skin fragility on the extensor aspect of both forearms and hands. The rashes were mild and subsided slowly after treatment with potent topical steroids. There was no family history of any vesico-bullous diseases. Examination showed multiple small blisters and milia on the sun-exposed areas of both forearms and the dorsum of both hands. Some lesions had already crusted and healed with scarring. There was no hypertrichosis or pigmentary change.

Skin biopsy showed a subepidermal bulla containing scanty fibrin, with a small number of chronic inflammatory mononuclear cells. Festooning was seen at the dermal papillae, at the floor of the bulla. The dermal vessels were thickened and lined with homogeneous, eosinophilic and pulmonary artery stenosis-positive deposits. Direct immunofluorescence staining demonstrated deposits of immunoglobulin G (IgG) and complement 3 (C3) in the vessel walls, especially in the superficial vessels. Weaker granular discontinuous deposits of IgG and C3 were also noted at the dermal-epidermal junction. This information was consistent with porphyria. Urine showed pink-red fluorescence under Wood's lamp examination. The 24-hour urine coproporphyrin levels were 800, 815, and 600 nmol/d (normal range, 68-276 nmol/d) over 3 consecutive days. The corresponding 24-hour urine uroporphyrin levels were 6850, 7400, and 7150 nmol/d (normal range, 6-24 nmol/d), at least 280-fold higher than normal. The ratio of urine uroporphyrin to coproporphyrin was more than three, which is the upper limit of normal. Serum δ -aminolevulinic acid and red cell uroporphyrinogen decarboxylase were normal. Chromatography of stool and urine showed an increase in isocoproporphyrin and 7-carboxylporphyrin, and the diagnosis of sporadic PCT was made. The serum lead level was normal. The serum iron level was on the high normal range. The serum ferritin was increased to 1680 pmol/L (normal range, 15-331 pmol/L), and the transferrin saturation was 58% (normal range, 15%-45%). Virology screening, including hepatitis B virus (HBV), hepatitis C virus (HCV), and human

immunodeficiency virus (HIV) types 1 and 2, was negative. Anti-nuclear factor, double-strand DNA, and anti-skin antibody testing were all negative. The patient's melioidosis was not in complete remission at this point, as reflected by the persistent serological titres of 1:160. The patient continued to receive maintenance therapy with co-amoxiclav and doxycycline. Skin lesions recurred, despite using sunblock, and monthly venesection for 3 months. In March 1998, the *B pseudomallei* antibody remained at a level of 1:80 after a follow-up period of 6 months. All antibiotics were then discontinued. Blisters and vesicles did not recur after the cessation of antibiotic therapy.

Discussion

Although PCT is the most common porphyria in some Caucasian populations, it is not common among Chinese people.² As in this patient, the diagnosis of PCT is suggested by the clinical history, and confirmed biochemically by the characteristic porphyrin profile. The main differential diagnoses are pseudoporphyria and other photodermatoses, such as polymorphic light eruption. Porphyria cutanea tarda has been reported in association with infections such as HCV,^{3,4} HBV,⁵ HIV,⁶ a variety of myeloproliferative/lymphoproliferative disorders,⁷ and autoimmune connective tissue diseases.⁸ To our knowledge, this is the first report of PCT associated with melioidosis.

Burkholderia pseudomallei, the causative agent of melioidosis, is widely distributed in water and soil in the tropics. The disease prevails in parts of South-east Asia, northern Australia, and Central and South America. In Singapore and Hong Kong, serology surveys suggest a significant proportion of the population have been exposed to this infective agent.^{9,10} Although an epidemiological study of melioidosis in Hong Kong has not been conducted, it is generally believed to be a rare disease. In humans, infection is usually acquired by direct contact with contaminated soil or water, or by cutaneous inoculation. Less commonly, the infection may be spread by inhalation or ingestion of contaminated soil or water. The organism can infect any organ system, but the lung is the most common organ affected. This patient had no recent travel history, no history of residence in an endemic area, and no occupational history of close contact with rice paddies. Thus, the source of infection could not be ascertained in this case.

There are two interesting findings concerning the association between PCT and melioidosis seen in this patient, the first relating to the antibiotic treatment

given. The onset of skin lesions 6 months after the prescription of doxycycline and amoxicillin for pulmonary melioidosis, and the remission of all vesicles after ceasing these drugs, suggests that doxycycline, amoxicillin, or both, are a trigger factor for the condition. Neither doxycycline nor amoxicillin have previously been reported to be associated with porphyria, and consequently, this case represents the first report of a patient in whom PCT may have been induced by use of these drugs. It is well known that drugs such as frusemide and amiodarone can induce pseudoporphyria—a condition clinically and histologically identical to PCT but in which there is no demonstrable abnormality of porphyrin metabolism. Though tetracycline has also been reported to be associated with pseudoporphyria,¹¹ other later generation tetracyclines, such as doxycycline, have not. The precise mechanism underlying the induction of porphyria by drugs is unknown. It has been postulated that PCT-inducing drugs are converted by the drug-metabolising (cytochrome P450-dependent) system into derivatives capable of inhibiting uro-decarboxylase-D (URO-D).¹²

The second possible association between the development of melioidosis and PCT in this patient may relate to iron overload. Although the cause of iron overload in PCT is unknown, iron is often considered a precipitating factor, occupying a central and strategic role in the pathogenesis of PCT.¹³ It has been postulated that the primary effect of excess iron is porphyrinogen oxidation, leading secondarily to decreased activity of URO-D, which impedes the haem biosynthetic pathway.¹⁴ In PCT, liver damage and hepatitis (secondary to a hepatotropic virus, or alcohol-induced), and possibly also genetic factors, may contribute to the development of porphyria by sensitising the liver to the toxic effects of iron.

Iron has been shown to mediate the generation of active oxygen species for the oxidation of porphyrinogens to porphyrins.¹³ Increased concentrations of iron are metabolised from ferritin in a pro-oxidant form, and are capable of interacting with cellular-free radical reactions. Precipitating agents could trigger oxidative stress reactions in which iron may then participate as a catalyst. Thus, iron may play a central role in the mechanism of PCT by interacting with other precipitating factors. Iron could synergistically potentiate their porphyria-inducing effect, mediating the oxidative stress process leading to the formation of uroporphyrin, and producing the long-lived inhibitor of decarboxylase.¹³ It is hypothesised, therefore, that phenotypic expression of PCT would depend on

inheritance of more than one of an array of genes, including a mutation for URO-D and genes conferring enhanced susceptibility to iron-mediated oxidative processes, or to environmental hepatotoxins. As seen in this patient, bacterial infections such as melioidosis, may have a similar effect to that of viral infections, although the cause of iron overload in this case remains unclear.

The association between melioidosis and PCT seen in this patient is unlikely to be coincidental given that both diseases are rare in Hong Kong. Although melioidosis has been shown to occur most often in people with an underlying disorder such as diabetes mellitus, blood glucose levels in this patient had been well controlled for years with a single oral hypoglycaemic drug, and there was no evidence of diabetes-related complications. Neither had the patient suffered from severe systemic disease such as liver disease, renal failure, or haematological malignancy, or been treated with systemic steroids, any of which may increase the risk of developing melioidosis.

Conclusions

In the patient presented, the initial pulmonary melioidosis along with the subsequent prescription of antibiotics may have acted as precipitating factors, sensitising the liver to the toxic effects of iron overload. Iron overload then may have served as the catalyst for the consequent development of PCT.

References

1. Sweeney GD. Porphyria cutanea tarda, or the uroporphyrinogen decarboxylase deficiency diseases. *Clin Biochem* 1986;19:3-15.
2. Liao KH. Cutaneous porphyrias in China. *J Dermatol* 1991;18:307-10.
3. Cribier B, Petiau P, Keller F, et al. Porphyria cutanea tarda and hepatitis C viral infection. A clinical and virological study. *Arch Dermatol* 1995;131:801-4.
4. DeCastro M, Sanchez J, Herrera JF, et al. Hepatitis C virus antibodies and liver disease in patients with porphyria cutanea tarda. *Hepatology* 1993;17:551-7.
5. Navas S, Bosch O, Castillo I, Marriott E, Carreno V. Porphyria cutanea tarda and hepatitis C and B viruses infection: a retrospective study. *Hepatology* 1995;21:279-84.
6. O'Connor WJ, Murphy GM, Darby C, et al. Porphyrin abnormalities in acquired immunodeficiency syndrome. *Arch Dermatol* 1996;132:1443-7.
7. McKenna DB, Browne M, O'Donnell R, Murphy GM. Porphyria cutanea tarda and hematologic malignancy—a report of 4 cases. *Photodermatol Photoimmunol Photomed* 1997;13:143-6.
8. Gibson GE, McEvoy MT. Coexistence of lupus erythematosus and porphyria cutanea tarda in fifteen patients. *J Am Acad Dermatol* 1998;38:569-73.
9. So SY, Chau PY, Aquinas M, Gabriel M, Lam WK. Melioidosis: a serological survey in a tuberculosis sanatorium in Hong Kong. *Trans R Soc Trop Med Hyg* 1987;81:1017-9.
10. Tan AL, Ang BS, Ong YY. Melioidosis: epidemiology and antibiogram of cases in Singapore. *Singapore Med J* 1990;31:335-7.
11. Epstein JH, Seibert JS. Porphyria-like cutaneous changes induced by tetracycline hydrochloride photosensitization. *Arch Dermatol* 1976;112:661-6.
12. Sinclair PS, Granick S. Uroporphyrin formation induced by chlorinated hydrocarbons (lindane, polychlorinated biphenyls, tetrachlorodibenzo-p-dioxin). Requirements for endogenous iron, protein synthesis and drug-metabolizing activity. *Biochem Biophys Res Commun* 1974;61:124-33.
13. De Matteis F. Porphyria cutanea tarda of the toxic and sporadic varieties. *Clin Dermatol* 1998;16:265-75.
14. O'Reilly FM, Darby C, Fogarty J, et al. Screening of patients with iron overload to identify hemochromatosis and porphyria cutanea tarda. *Arch Dermatol* 1997;133:1098-101.