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Porphyria Cutanea Tarda and Systemic Diseases – a Report of 10 Cases and Review

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ABSTRACT

Porphyria cutanea tarda (PCT) is a metabolic photodermatosis and has been reported in association with a variety of systemic disorders in the West. The clinical characteristics of 10 patients diagnosed to have PCT seen during a 15-year period in four major Dermatology Clinics in Hong Kong were reviewed retrospectively. All 10 patients were type I (sporadic) PCT. Nine patients (90%) were associated with medical diseases. There were five patients with liver-related diseases including hepatitis B, hepatitis C infection and alcoholic cirrhosis; two patients with haematological malignancies including histiocytic lymphoma and myelofibrosis; one patient with systemic lupus erythematosus and one with pulmonary melioidosis. Despite its primarily cutaneous presentation, PCT is often associated with different potentially life-threatening systemic diseases. A review of the literature and evidence supporting a causal association were presented.

Keywords: Porphyria cutanea tarda, review, systemic diseases

INTRODUCTION

Porphyria cutanea tarda (PCT) is a metabolic disorder in the heme biosynthetic pathway and includes a heterogenous group of conditions which may be inherited, or more commonly, acquired. Affected patients have reduced hepatic uroporphyrinogen decarboxylase activity.

Uroporphyrinogen decarboxylase (URO-D) is present in liver and red cells. There are three types of PCT. The two commonest types are the type I and type II PCT. In type I acquired (sporadic) PCT, the enzyme is deficient in liver only and there is no family history of overt PCT. This sporadic type may be triggered by a variety of hepatotoxic chemicals, such as ethanol, estrogens, iron and the toxin hexachlorobenzene. Type I PCT accounts for up to 80% of patients. Next common is the type II inherited PCT and the enzyme is partially deficient (approximately 50%) in a number of tissues and cells including hepatocytes and erythrocytes. It is inherited in an autosomal dominant pattern. In other families with PCT, affected individuals have defective hepatic but normal erythrocyte enzyme activity (type III PCT). Regardless of the type of PCT, the clinical features are similar.

Porphyria cutanea tarda usually presents in the third and fourth decade and rarely occurs before puberty. Cutaneous lesions include vesicles, bullae and increased skin fragility at light exposed areas especially those subjected to trauma, such as dorsa of hands and forearms. The vesicles often heal with linear scarring and milia. Clinically mottled chloasma-like pigmentation and sometimes hypopigmentation appear on the face. Non-virilizing hypertrichosis occurs along temples, forehead, between eyebrows and cheeks. Sclerodermatous feature, which is more common in females, is found on both light exposed and unexposed skin.

Porphyria cutanea tarda may be associated with many potentially life threatening systemic diseases such as hepatitis C virus (HCV) infection,[1-3] hepatitis B virus (HBV)[4] and even Human Immunodeficiency Virus

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(HIV) infection.[5] Connective tissue disorders including systemic lupus erythematosus (SLE),[6] discoid lupus erythematosus (DLE)[7] and subacute lupus erythematosus (SCLE)[8] have been reported in patients with PCT. PCT has also been associated with a variety of neoplastic disorders such as lymphoma,[9,10] hairy cell leukaemia[11] and hepatocellular carcinoma.[12] The demographic data, clinical presentations, laboratory results and the associations with other systemic diseases of 10 patients suffering from PCT were presented. A review and comparison with previously reported series of patients with PCT were made.

PATIENTS AND METHODS

Patients diagnosed with porphyria cutanea tarda in four major Dermatology Clinics during a 15-year period, from 1982 to 1997, were reviewed retrospectively. The involved clinics included Sai Ying Pun Dermatological Clinic, Yaumatei Dermatological Clinic, Tuen Mun Dermatological Clinic and Li Ka Shing Dermatological Clinic. A total of 10 Chinese adult patients were diagnosed.

The diagnosis of PCT was suggested by the clinical history and confirmed biochemically by the abnormal porphyrin profile. Relevant history such as social history of alcohol drinking, past medical health and previous medications were included as to identify any possible precipitating causes. The clinical features included the appearance of vesicles, blisters, atrophic scars and milia on sun-exposed areas, the presence of pigmentary changes, non-virilizing hypertrichosis or sclerodermoid plaques. Skin biopsy on the vesicles was performed in each patient. The characteristic features were cell-poor subepidermal blisters with festooning of the dermal papilla, and a periodic acid-schiff positive, diastase-resistant, hyaline material around the thickened papillary vessels of the affected skin. Solar elastosis was a common but non-specific feature.

Further tests for porphyria included spot urine for porphyrin and ratio of spot urine porphyrin/spot urine creatinine. The diagnosis of PCT in each patient was then confirmed by identifying the characteristic pattern of increased uroporphyrin and 7-carboxylporphyrin in urine and increased isocoproporphyrin and 7-carboxylporphyrin in stool.

Blood tests for screening of associated systemic diseases included complete blood picture (CBP), liver/renal function tests (L/RFT) and iron/ferritin for serum iron status. Viral screening included serum HBV, HCV and antibody to HIV 1 and 2. Routine chest X-ray was taken. Further tests were only offered if they were clinically indicated, such as pseudomonas pseudomallei antibody in a case with melioidosis (patient 2). Liver biopsies were performed in patient 3 and 6. Lymph node and bone marrow biopsies were performed in patient 6. Finally, ultrasonography of liver was performed if there was biochemical evidence suggestive of space-occupying lesions or cirrhosis.

RESULTS

All 10 patients were adult Hong Kong Chinese, and there were six men and four women. The mean age at diagnosis was 47.9 years (range: 24-66 years). All of them were of type I sporadic (acquired) PCT. Concerning the initial presentation, vesicular formation on sun-exposed areas was the commonest feature (6/10), hyperpigmentation was the second commonest (4/10), followed by hypertrichosis (3/10) and skin fragility (3/10). The initial cutaneous manifestations, the clinical course and the relevant social history were shown in Table 1. Six patients had abnormal liver function tests with an increase in parenchymal enzymes. Iron was an important precipitating factor and seven patients had evidence of iron overload. Viral screening and other relevant results were listed in Table 2.

Nine out of 10 patients had other underlying medical diseases (Table 3). Five of them had liver-related diseases: two had HCV (patient 1 and 4), two had HBV infections (patient 3 and 10) and one had alcoholic liver cirrhosis (patient 5). Two other patients were diagnosed to have haematological malignancies: histiocytic lymphoma (patient 6) and myelofibrosis (patient 7). Patient 2 had melioidosis of the lung and patient 9 had SLE. Only one out of 10 patients (patient 8) had no associated systemic medical disease. Six patients were diagnosed to have PCT and other medical diseases simultaneously. Three patients developed PCT years after the diagnosis of associated conditions. A summary of systemic associations with PCT and the time interval between diagnoses were shown in Table 3.

Table 1. An overview of demographic data, clinical details and social history

Patient	Initial presenting features	Other features	Possible precipitating factors
Patient 1 M/49	• Photosensitive vesicles on sun-exposed area of forearms, hands, face and upper chest	• Hypertrichosis • Generalized hyperpigmentation (no skin fragility)	• Ex-intravenous drug addict • Chronic alcoholic
Patient 2 F/66	• Photosensitive vesicles on extensor aspect of both forearms and hands • Skin fragility		• Antibiotics-related
Patient 3 M/41	• Recurrent episodes of blisters on sun-exposed areas of both forearms and hands	• Hypertrichosis • Skin fragility • (No hyperpigmentation)	• Chronic alcoholic
Patient 4 M/46	• Diffuse hyperpigmentation on face, trunk and limbs	• Hypertrichosis • (No vesicles) • (No skin fragility)	• Chronic alcoholic
Patient 5 M/64	• Hyperpigmentation over the body • Hypertrichosis on the face	• (No vesicles) • (No skin fragility)	• Chronic alcoholic • Intravenous drug abuser
Patient 6 F/45	• Hyperpigmentation on face & upper limbs and hypertrichosis around eyebrows • Anorexia, subjective weight loss, ascites and bilateral ankle oedema	• Peripheral neuropathy of both lower limbs • Peritonitis • (No vesicles)	
Patient 7 F/66	• Hypertrichosis • Hyperpigmentation	• (No vesicles)	
Patient 8 M/24	• Photosensitive vesicles on upper limbs • Skin fragility		• Chronic alcoholic
Patient 9 F/40	• Photosensitive vesicles on sun-exposed area of upper limbs, face and neck • Arthralgia of small joints of hands		
Patient 10 M/38	• Photosensitive vesicles on forearms, hands • Skin fragility		• Chronic alcoholic

DISCUSSION

The mean age of our patients was 47.9 years, which conformed to global findings with the highest incidence in the middle-age group. The male to female ratio was 6:4. In all 10 patients, there were no family history of porphyria and all belonged to the type I sporadic (acquired) PCT. Sporadic PCT usually presents late in life, but age of onset has been shown to be significantly lower in people who developed the metabolic abnormality in association with HCV and/or HIV infection.[1,5] In this study the onset of PCT in the two HCV-positive patients (patient 1 and 4) were at 49 and 46 years respectively, while the mean age of onset for the eight HCV-negative patients was 48 years.

Hypertrichosis was noted in 6 out of 10 patients which was the commonest clinical feature in this series, paralleled by vesicles or bullae (6/10), and followed by hyperpigmentation (4/10). The incidence of hypertrichosis was unexpectedly high as vesicles and blisters had been more frequently reported. Vesicles or blisters never appeared in four patients in our series. Hyper-pigmentation was not an uncommon clinical feature. It was the initial presenting complaint in three patients. This illustrated that PCT could present in many different ways.

Table 2. Summary of biochemical profiles

Patient	LFT	Serum ferritin	Virology HBV HCV HIV	Miscellaneous
Patient 1	Abnormal	Increased	- / + / -	
Patient 2	Normal	Increased	- / - / -	• Pseudomallei antibody: 1/160
Patient 3	Normal	Increased	+ / - / -	• USG: normal • Liver biopsy: increased iron deposit, grade 3/4
Patient 4	Abnormal	Normal	- / + / -	
Patient 5	Normal	Normal	- / - / -	
Patient 6	Abnormal	Increased	- / - / -	• Liver biopsy: increased iron deposit • Bone marrow biopsy: mild erythroid hyperplasia • Impaired xylose absorption test
Patient 7	Abnormal	Increased	- / - / -	• Liver biopsy: increased iron deposit, 3/4 in grade
Patient 8	Abnormal	Increased	- / - / -	
Patient 9	Normal	Normal	- / - / -	• ANA: homogenous, >1/320 • AntidNA: -ve • AntiENA: Anti-Ro+ve
Patient 10	Abnormal	Increased	+ / - / -	

Table 3. Summary of systemic associations with PCT

Patient	Age at PCT diagnosis (year)	Age at diagnosis of associated disease (year)	Interval between diagnosis of PCT and associated disease (year)
Patient 1	49	DM: 45 HCV: 49	DM: -4 HCV: 0
Patient 2	66	DM: 59 Thyrotoxicosis: 62 Melioidosis: 64	DM: -7 Thyrotoxicosis: -4 Melioidosis: -2
Patient 3	41	HBV: 41	HBV: 0
Patient 4	46	HCV: 46	HCV: 0
Patient 5	64	Alcoholic cirrhosis: 59	Alcoholic cirrhosis: -5
Patient 6	45	Histiocytic lymphoma: 45	Histiocytic lymphoma: 0
Patient 7	66	Myelofibrosis: 53	Myelofibrosis: -13
Patient 8	24	Nil	-
Patient 9	40	SLE: 40	SLE: 0
Patient 10	38	HBV: 38	HBV: 0

Although the main clinical symptoms of PCT are cutaneous, it is in the liver where the metabolic abnormality lies. The increased amount of uroporphyrin, which is characteristic of the condition, originates in the liver. An iron-dependent hepatic abnormality involving the oxidative stress is fundamental in the development of disease.[11] Therefore sporadic PCT should be regarded as a hepato-cutaneous syndrome in which two different oxidative tissue-damaging reactions operate. In this series, there were five PCT patients associated with liver disease: two had HCV infection, two had HBV infection and one had alcoholic cirrhosis. The incidence of HCV infection associated with PCT varied from 18% to 91% in Western studies.[1,4,11] In general, many studies quoted the figure of more than 50%.[15] The incidence of HBV infection was much lower, usually reported from 29% to 41%.[1,4,11] Navas et al. reported that the frequency of past HBV infection (41%) in PCT patients is approximately half than that of past HCV infection (91%).[4] Our study showed an equal incidence of these two viruses infections. This finding is striking because HBV is a more infectious agent than HCV. Secondly, the prevalence of HBV (9.6%)[12] in the general population is much higher than that of HCV (0.5%)[13] in Chinese. Because HCV and HBV infections are common in patients with PCT and these patients may be asymptomatic for liver disease and only 50% have abnormal liver function tests, it is strongly recommended that screening for HCV and HBV infections should be done in all patients with PCT.[14]

The two HCV positive patients (patient 1 and 4) both had very high levels of γGT of at least ten times normal and a moderate increase in liver parenchymal enzymes (Table 2). All the other HCV negative patients did not have such a significant degree of biochemical liver derangement even though some of them were chronic alcoholic. This phenomenon has also been reported in other studies.[1,2] De Castro et al. showed that liver enzymes levels including γGT, ALT and AST, in patients with PCT associated with HCV antibodies were higher than in patients with PCT who had no HCV antibodies.[2] Cribier et al. reported the same finding and detected HCV RNA in all their HCV-positive patients.[1] The presence of HCV RNA in the serum reflects active replication of the virus, accounting for the abnormal liver biochemistry. Although HCV RNA were not checked in the two HCV positive patients, they were likely to be positive as suggested by the grossly abnormal liver function tests. However, there was no correlation between the severity of the viral disease and the manifestations of PCT. Most observations argued against HCV being a direct and sufficient causative factor in PCT and were in favour of the predisposition of some individuals to develop PCT, once infected. The mechanism of action of HCV on PCT is unknown. Various hypothesis have been proposed: (1) HCV could decrease the activity of URO-D in the liver,[2] (2) a URO-D inhibitor could be produced by the damaged liver cells[15] or by the excess of hepatocellular iron,[16] and (3) immunologic mechanisms could be implicated,[16] but autoimmunity is not frequent in a large series of patients with HCV infection.[17]

Iron is also often considered as a precipitating factor for PCT. In most cases of either familial or sporadic PCT, abnormally high tissue iron stores can be demonstrated, particularly in liver cells. Seven patients developed markedly elevated serum ferritin and three of them also had increased iron deposit in liver tissue (Table 2). Similar results have been found in 30/38 (79%) PCT patients by Siersema et al.[18] The incidence of siderosis varied between 72% and 91% in patients with PCT.[18] Iron had been shown to mediate the generation of active oxygen species for the oxidation of porphyrinogens to porphyrins.[19] Increased concentration of iron are metabolized from ferritin in a pro-oxidant form and are capable of interacting with cellular free radical reactions. The precipitating agents could trigger off oxidative stress reactions in which iron may then participate as a catalyst. Iron plays a central role in the mechanism of PCT by (1) interacting with the environmental precipitating factors that have been discussed above, (2) potentiating synergistically their porphyria-inducing effect, (3) mediating the oxidative stress process for the formation of uroporphyrin, and (4) producing the long-lived inhibitor of the decarboxylase.

Porphyria cutanea tarda has been reported in association with a variety of myeloproliferative and lymphoproliferative disorders, suggesting a possible association between these conditions. Two patients (patient 6 and 7) in our series were diagnosed with histiocytic lymphoma and myelofibrosis respectively. The former patient (patient 6) developed PCT simultaneously and died soon after porphyria and peripheral neuropathy became clinically evident. The lymphoma of this patient was complicated by syndrome of inappropriate anti-diuretic hormone (SIADH) and peripheral neuropathy, both of these are well known paraneoplastic phenomena of lymphoma. The symptoms of PCT developed when her lymphoma was at an advanced stage suggesting that PCT might be a third paraneoplastic manifestation. PCT developing in the latter stages of haematologic malignancy had been described in previous reports, suggesting that PCT might be a poor prognostic indicator in this group of patients.[20] The possible explanations as to why PCT could have been precipitated include the malignancy itself, its treatment or alternatively factors that were independent of the hematological disturbance, such as susceptibility to iron overload, viral infection or alcohol excess.[20]

Melioidosis varies from subclinical infection to fulminating disease with multiple organ involvement. Although endemic in South-East Asia and northern Australia, it is rare in our locality. The linkage may be purely incidental but it may not be the case regarding the rarity of both melioidosis and PCT in the territory. The possible association between melioidosis and PCT in this patient may be related to iron overload. Iron is often considered as a precipitating factor that occupies a central and strategic role in the pathogenesis of PCT. As mentioned previously, viral infection may sensitize the liver to the toxic effects of iron. Bacterial infection like melioidosis in this patient may also have a sensitizing effect as seen in viral infection, although the cause of iron overload is unknown.

The association of SLE with PCT had been reported in many studies. Gibson reported that 15 out

of 676 patients with porphyria (all types) had coexistent SLE, suggesting that this combination may be more common than previously recognized.[6] PCT occurred either before or simultaneous with SLE in almost 50% of patients.[6] The possible explanations for the coexistence of SLE and porphyria included:[21] (1) a common genetic abnormality, (2) porphyria triggering an autoimmune response such as SLE, (3) pre-existing SLE resulting in an acquired metabolic defect leading to porphyria, and (4) SLE precipitating a genetically determined metabolic defect resulting in porphyria. Excessive porphyrins and their precursors can induce cell damage, resulting in the formation of autoantibodies and possibly connective tissue disease in those who are genetically predisposed.[22] The gene for URO-D has been mapped to chromosome 1;[23] a candidate chromosome 1 region, 1q41-q42, has also been linked to SLE.[24]

CONCLUSION

Although PCT is mainly characterized by cutaneous symptoms of photosensitivity, it is often associated with many different systemic diseases that require thorough investigations. As HCV and HBV infections are commonly seen in patients with PCT, their presence may not be noticed by patients and only 50% of them have abnormal liver function tests. It is strongly recommended that screening for HCV and HBV infections should be done in every patient with PCT.

Learning points:

Despite its primarily cutaneous presentation, porphyria cutanea tarda is often associated with different potentially life-threatening systemic diseases, which should be ruled out upon diagnosis.

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