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Case Report

Variegate porphyria: an unusual cause of skin blistering

混合性卟啉病：皮膚水泡的一種不尋常原因

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Variegate porphyria (VP) is an autosomal dominant disorder caused by a partial deficiency of the haem synthesis enzyme protoporphyrinogen oxidase. The gene sequence has been cloned and mapped to chromosome 1q22-23. VP is highly prevalent in South Africa but uncommon among Chinese. VP can present with skin manifestations, acute neurovisceral attack or both. This report documented a young Chinese lady with VP presenting with skin manifestations only.

混合性卟啉病是由於部份缺乏血紅素生成酶原卟啉原氧化酶引致的一種常染色體顯性疾病。引致此病的基因位於1號染色體長臂22-23位。混合性卟啉病於南非很多見，但很少見於華人。此病可以有急性神經內臟症狀、皮膚症狀及兩者併發。本文收錄一例年輕華人女性患有混合性卟啉病而只以皮膚症狀爲首發表現。

Keywords: Chinese, variegate porphyria

關鍵詞：華人，混合性卟啉病

Introduction

Porphyrias are metabolic diseases due to enzyme defects in the haem synthesis leading to accumulation of excess porphyrins. These porphyrins may give rise to neurovisceral attacks, cutaneous manifestations or both. Blistering over sun exposed areas, scarring, milia formation, hyperpigmentation, hypertrichosis and sclerodermoid changes are well known cutaneous findings. Variegate porphyria (VP) is an uncommon porphyria due to the defect of the enzyme protoporphyrinogen oxidase. The following is a case report of a young woman suffering from VP with only cutaneous manifestations.

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Case report

A 23-year-old lady presented with recurrent attacks of itchy blisters over her face and upper limbs for more than one

year which were unrelated to sun exposure. These blisters healed spontaneously with scarring. She had no history of abdominal pain, convulsion or paralysis. Her past health was unremarkable. There was no drug history before the onset of her skin lesions. Family history was unremarkable.

On examination, multiple erythematous maculopapular lesions were noted to distribute symmetrically over her face and upper limbs. Some of them were topped with excoriation or crust, and some had healed with circular atrophic scars (Figures 1 & 2). There was no intact blister, hyperpigmentation or hypertrichosis.

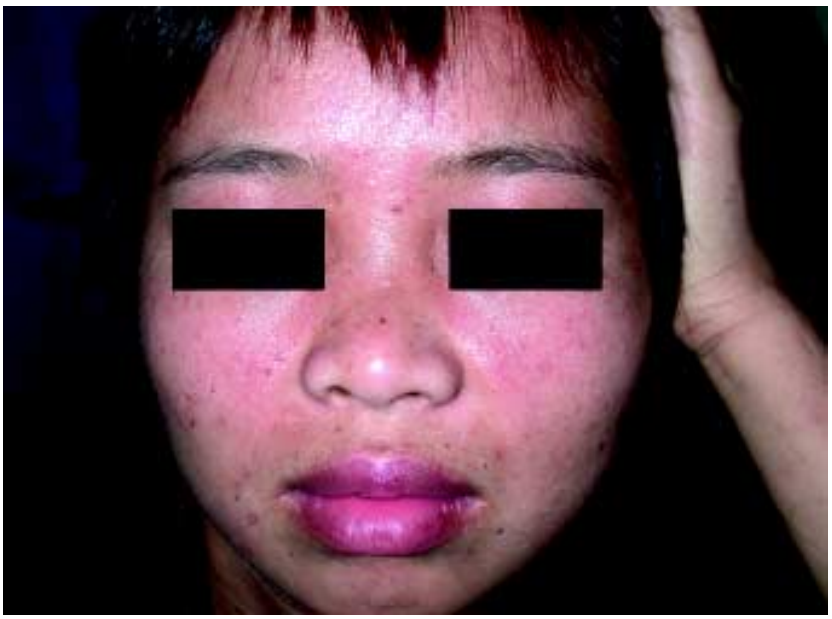

Figure 1. Erythematous maculopapular lesions were noted over her face; some healed with circular atrophic scar.

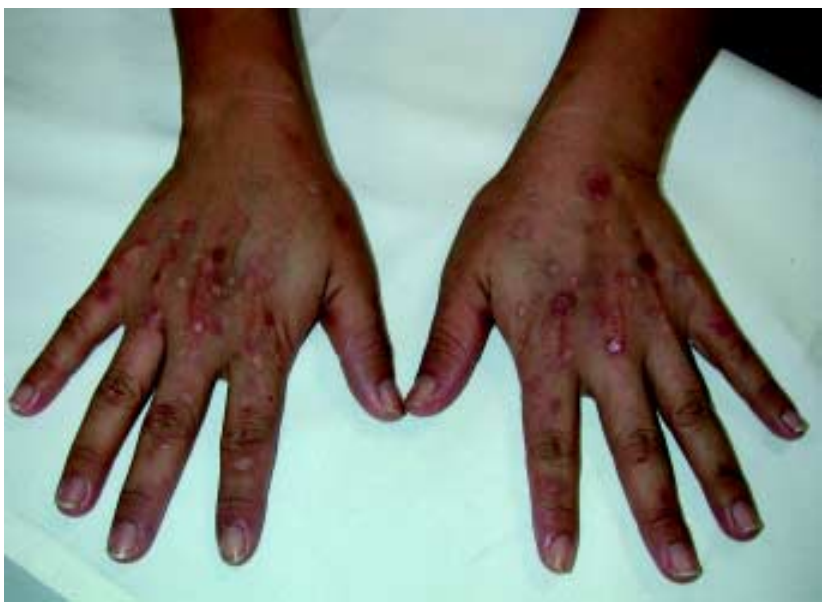

Figure 2. Erythematous maculopapular lesions were found over dorsa of both hands. Some of them were topped with excoriation or crust.

The differential diagnoses included cutaneous porphyria, cutaneous lupus, drug-induced photosensitivity, epidermolysis bullosa acquisita and actinic prurigo.

Investigations including complete blood picture, liver and renal function tests, and ferritin level were normal. Anti-nuclear antibody, anti-extractable nuclear antibody, anti-skin antibody and anti-hepatitis C virus antibody were negative. Anti-hepatitis B antibody was positive. Skin biopsy showed a small subepidermal bulla containing a few mixed inflammatory cells. There was also sparse superficial perivascular lymphocytic infiltrate around thickened capillaries which contained Periodic Acid Schiff Diastase (PASD) positive substances. Immunofluorescence study showed trace superficial vascular staining of IgM and C3. This was consistent with porphyria. Urine examination showed excess porphyrins. Fractionation of porphyrins by reverse-phase high performance liquid chromatography (HPLC) detected isolated elevation of coproporphyrin in the paired urine samples. In the stool sample, excess protoporphyrin and coproporphyrin were detected. Another remarkable band tentatively identified as tricarboxylic porphyrin was also present. Similar pattern was detected in repeated paired urine and stool samples. This consistent, abnormal pattern was almost diagnostic of variegate porphyria although cellular enzymology was necessary to confirm the diagnosis. Porphyrin study of the index patient's mother was normal. Regarding our patient's father, urine examination did not show excess porphyrins. Reverse-phase HPLC of his stool detected abnormally high proportion of coproporphyrin isomer III with a marginally elevated total coproporphyrin excretion. This suggested that her father might also be affected.

As cellular enzymology was not available in Hong Kong, the whole family (the index patient, together with her parents and two younger siblings) underwent DNA mutation analysis. A novel splicing mutation of the protoporphyrinogen oxidase (PPOX) gene (IVS10+1G→A) was detected by denaturing high performance liquid chromatography (DHPLC) in the index patient and her father. Other family members were not affected.[1] The mutation affected the invariant donor splice site of intron 10 (substitution from guanine to adenine) with resultant intron 10 retention and premature termination of protein translation.

Based on mutational analysis, VP was diagnosed in the index patient and her father. Clinically, the index patient suffered from quiescent VP while her father suffered from silent VP. The index patient was advised to avoid sun exposure and use sunscreen containing titanium dioxide. Both of them were advised to avoid the list of drugs that may precipitate acute neurovisceral attack.

Discussion

VP is an autosomal dominant disorder caused by a partial deficiency of the haem synthesis enzyme PPOX. The gene sequence has been cloned and mapped to chromosome 1q22-23.[2,3] The disease is highly prevalent in South Africa and a number of different mutations including missense, frameshift, splice site and nonsense have been identified.[4,5]

Clinically, porphyrias can be divided into acute or non-acute depending on whether or not there is any acute neurovisceral attack (Table 1). The precipitation of an acute attack, in turn, depends on the accumulation of early haem precursors, that is, aminolaevulinic acid (ALA) and porphobilinogen (PBG). The accumulation of porphyrins in skin results in skin manifestations.[6] In VP, the skin manifestations can be explained by the accumulation of the oxidized products of protoporphyrinogen (PP) and coproporphyrinogen (CP). It is postulated that the accumulation of PP causes the inhibition of PBG deaminase, with resultant ALA and PBG elevation and subsequent acute attack.

The diagnosis of VP depends on the demonstration of abnormal porphyrin excretion in urine and stool, and the differentiation of the abnormal profile from other porphyrias. In stool, protoporphyrin and coproporphyrin are classically elevated; in urine, coproporphyrin is more elevated than uroporphyrin (the reverse situation in PCT). In acute attack, ALA and PBG are also elevated in urine. However, this sort of biochemical analysis has imperfect sensitivity and specificity.[6] Asymptomatic patient may not have detectable porphyrin excretion abnormality. Fluorescence emission spectroscopy of plasma using light at 405 nm has been reported to have 100% specificity and 86% sensitivity for the detection of asymptomatic VP.[7] PPOX is not present in erythrocytes. Its activity level in lymphocytes is also low. Enzyme assay is also difficult to perform. All these factors make enzyme assay not suitable for routine laboratory diagnosis of VP.[6] As the whole PPOX gene has been characterized, DNA-based diagnosis, with the help of DHPLC, is possible, as illustrated in the present family.

VP presents with skin manifestations and acute neurovisceral attack. The skin manifestations are similar to those of PCT while acute neurovisceral attack is similar to that of AIP (Table 2). These have been summarized elsewhere.[8] Clinically, VP

Table 1. Classification of porphyria.

Acute porphyria	**Enzyme defect**
ALA dehyratase deficient porphyria	Aminolaevulinic acid dehydratase
Acute intermittent porphyria (AIP)	Porphobilinogen deaminase
Hereditary coproporphyria (HC)	Coproporphyrinogen oxidase
Variegate porphyria (VP)	Protoporphyrinogen oxidase (PPOX)
Non-acute porphyria	
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase
Porphyria cutanea tarda (PCT)	Uroporphyrinogen decarboxylase
Erythropoietic protoporphyria (EPP)	Ferrochelatase

Table 2. Clinical manifestations of variegate porphyria.

Cutaneous	**Neurological**
Skin fragility	Neuropathy
Blistering	Paralysis
Ulcer	Convulsion
Scarring / scarring alopecia	Psychosis
Milia	Coma
Hypertriochosis	
Hyper / hypo-pigmentation	
Scleroderma	
Cardiovascular	**Gastrointestinal**
Tachycardia	Vomiting
Hypertension	Abdominal pain
	Constipation
	Diarrhoea

can be classified into silent, acute and quiescent depending on the presence or absence of biochemical abnormality and skin signs. Namely, acute VP refers to cases with a current acute presentation and elevated urine porphobilinogen. Quiescent VP are biochemically expressing but are currently either asymptomatic or have skin disease only. Silent VP are cases where a genetic mutation is identified, but the patient remains clinically and biochemically normal.

As gene therapy is still not possible, treatment of VP aims at prevention of skin manifestations and acute attacks. Concerning skin manifestations, chloroquine, venesection, beta-carotene and activated charcoal are ineffective. The only treatment that is effective is sun avoidance and sunscreens containing zinc oxide or titanium dioxide which can filter out the activating spectrum of light.[6] Concerning acute attacks, patient is advised to avoid drugs that can precipitate them. These include anti-depressants, barbiturates, enzyme-inducing anti-convulsants, sulphonamides and oral contraceptives. Alcohol and smoking should be avoided. Woman should be warned that pregnancy may precipitate acute attacks.[9] Treatment of acute attack has been summarized elsewhere.[9]

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