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Porphyria Cutanea Tarda Masquerading as Epidermolysis Bullosa Acquisita: A Report of Two Cases

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Key Words
Porphyria cutanea tarda · Epidermolysis bullosa acquisita · Histopathology

Abstract
Porphyria cutanea tarda (PCT) is the most common type of porphyria worldwide and is often initially diagnosed when cutaneous manifestations arise. We present two patients where misdiagnosis of PCT occurred due to the condition masquerading as epidermolysis bullosa acquisita histologically. In patients with undifferentiated bullous/erosive skin conditions occurring in photo-distributed regions, PCT should be considered in the differential diagnosis irrespective of histopathological findings on biopsies and further investigated and treated appropriately.

Introduction

Porphyria cutanea tarda (PCT) is the most common type of porphyria worldwide, affecting sun-exposed areas of the skin, manifested by cutaneous fragility, vesicobullae, atrophic scarring and formation of milia [1]. This condition is a disorder of heme biosynthesis caused by a catalytic deficiency in uroporphyrinogen decarboxylase [2]. There are inherited, acquired and toxic forms of the condition and diagnosis is confirmed based on skin symptoms and porphyrin analysis of urine, blood and stool [3]. Without clinical suspicion for this important diagnosis the necessary investigations may not be performed, resulting in a delay of diagnosis and treatment. We present the cases of two patients who were initially misdiag-

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nosed with epidermolysis bullosa acquisita (EBA) predominantly based on histopathology but were subsequently diagnosed with PCT on porphyrin studies due to clinical suspicion.

Case Reports

Case 1

A 36-year-old female presented with a 6-month history of blisters on the dorsal aspects of her hands bilaterally with associated fragility and photosensitivity. This was also associated with a 2-year history of increased hair growth on her cheeks. She had been previously treated with oral antibiotics and topical steroid with no obvious improvement.

The patient had a medical background of asthma for which she was using twice daily fluticasone/salmeterol inhalations and salbutamol inhalations as required. Her only other medication was the oral contraceptive pill, which she had been taking long-term. She had no family history of PCT or haemochromatosis. The patient consumed approximately 15 alcoholic standard drinks per week.

On examination, the patient had multiple blisters and erosions distributed over the dorsa of her hands with a number of milia (fig. 1). A punch biopsy of the right hand index finger and a perilesional biopsy of the left hand were performed. Histopathology showed a partly regenerated subepidermal blister with a heavy inflammatory cell infiltrate between the old roof and the regenerating base (fig. 2a). A small amount of festooning was evident. Immunofluorescence was strongly positive for IgG present along the basement membrane. The pattern was recognized as the 'U-serrated pattern', typical of antibodies to type VII collagen. Based on these findings, EBA was diagnosed and salt split skin preparation was not performed.

Although the initial attending doctor was dissuaded from a diagnosis of PCT on the basis of histology findings, subsequent review favoured PCT clinically and porphyrin studies later confirmed this (table 1). Further blood results demonstrated normal full blood count, renal function and electrolytes. The patient had deranged liver function tests, but her liver screen did not demonstrate any abnormalities, including negative hepatitis B/C and HIV serologies and normal iron studies and alpha fetoprotein levels. A liver ultrasound demonstrated findings of fatty liver. Desmoglein 1 and 3 reactivity and subsequent collagen VII reactivity testing were all negative, excluding a concomitant diagnosis of pemphigus or EBA.

The patient was commenced on hydroxychloroquine 200 mg twice weekly and was given advice on mechanical and photoprotection. She was also commenced on regular venesections, aiming for a ferritin level of 50 μg/l to improve PCT symptoms.

Case 2

A 50-year-old female presented for a second opinion after a 3-year history of spontaneous blistering affecting the extensor surfaces of her hands and forearms with associated scarring. She had been diagnosed with EBA by a previous clinician based on biopsy histopathology findings 3 months earlier. There was a cell-poor subepidermal vesicle containing only a few lymphocytes and with festooning of the dermal papillae and very little dermal inflammatory infiltrate seen (fig. 2b). Direct immunofluorescence studies revealed positive staining for IgG in a linear pattern along the dermoepidermal junction. All other markers were negative and salt split skin studies could not be performed due to technical difficulties.

The patient was initially treated with potent topical corticosteroids as well as low-dose oral corticosteroids and was still experiencing flares. She was then tried on 100 mg of oral doxycycline, which resulted in some improvement. Her past medical history included mono-

clonal gammopathy of uncertain significance which was managed conservatively. She also reported a positive family history for blistering of the hands affecting her maternal grandmother but no known family history of liver disease. She was a non-smoker and consumed 10–15 alcoholic standard drinks per week. She had been taking the oral contraceptive pill for many years but had recently ceased taking this.

On examination, the dorsal aspects of both hands were erythematous, with evidence of milia and post-inflammatory hyperpigmentation (fig. 3). There was also associated hyperkeratotic scaling and lichenification of the skin. Based on this clinical appearance, further testing was performed, including full blood count, renal function, electrolytes and liver function, which were all normal. In addition no HFE mutations were detected and hepatitis B/C and HIV serologies were negative. Further urine and stool porphyrin studies showed elevated urine porphyrin, faecal porphyrin and porphyria/creatinine ratio, which confirmed the diagnosis of PCT (table 1). Desmoglein 1 and 3 reactivity and collagen VII reactivity testing were negative, excluding a concomitant diagnosis of pemphigus or EBA. The patient was then commenced on hydroxychloroquine and doxycycline was ceased. She was given advice regarding photoprotection and decrease of her alcohol consumption. She was also advised to use gloves and zinc oxide sunscreen to provide physical protection.

Discussion

PCT is a metabolic disorder which can result in the development of hepatocellular carcinoma, advanced liver fibrosis and also liver cirrhosis if cutaneous manifestations are not recognized and properly investigated [3]. There are multiple genetic and environmental triggers of PCT, most commonly including alcohol abuse, oestrogens and liver disease. Other triggering factors include polychlorinated hydrocarbons, iron, viral infections (such as hepatitis C and HIV), dialysis in patients with renal failure and the inheritance of specific mutations in the HFE gene which underlies classic haemochromatosis [1]. Treatment of PCT includes withdrawal of precipitating triggers, phlebotomy and oral anti-malarial agents [4].

The most common symptomatic complaints of patients with PCT are due to cutaneous manifestations which can occur after sun exposure or minor trauma [5]. These include increased photosensitivity and skin fragility with vesicles/bullae and erosions/crusts on sun-exposed sites such as the dorsa of the hands. Crusting of lesions can then take weeks to heal, resulting in atrophic scarring with milia formation. Post-inflammatory hyperpigmentation, scarring alopecia, hypertrichosis and morpheaform/sclerodermoid changes can be also seen [5].

Histological examination of involved skin is not required to confirm the diagnosis of any cutaneous porphyria, rather skin biopsies are obtained to exclude other entities in the differential diagnosis, including EBA, drug-induced pseudoporphyria and phototoxic/bullous drug eruptions. As demonstrated by our cases, this can lead to potential misdiagnosis due to histological similarities between the vesiculobullous differentials. In PCT, characteristic histopathological findings include subepidermal blisters, which lack inflammatory infiltrate, with preservation of dermal papillae in the lesion's floor ('festooning') [1]. Under direct immunofluorescence microscopy, fibrinogen, complement and immunoglobulins, particularly IgG, are often present surrounding blood vessels of the papillary dermis and at the dermal-epidermal junction [1].

As shown in our cases, these findings can be easily confused with EBA in particular, which typically shows similar cell-poor subepidermal blisters and direct immunofluores-

cence microscopy showing IgG deposits at the basement membrane zone, however usually targeting type VII collagen.

Thus, whilst histological examination is important in excluding other differential diagnoses, it is important for clinicians to recognize the potential for misdiagnosis of PCT as a result of findings on histology. In our cases, both patients had skin biopsies reported as EBA, and this could lead to inexperienced clinicians accepting this diagnosis and treating accordingly and inappropriately. Whilst case 1 was managed correctly with porphyrin studies performed despite EBA histopathological findings, in case 2 the histopathological findings were initially accepted and led to misdiagnosis and delay in appropriate PCT treatment. Compounding this diagnostic dilemma is the similar clinical appearances of bullae/milia in both EBA and PCT, which can falsely reassure the clinician not to perform the necessary porphyrin investigations. These typically include porphyrin analysis of urine, blood and stool which reveal increased urinary elimination of uroporphyrin, hepta-carboxylated porphyrins and coproporphyrin, and increased faecal excretion of isocoproporphyrin [5].

In summary, our cases demonstrate the possible difficulty in differentiating PCT from EBA and the potentially significant consequences of this misdiagnosis. In patients with undifferentiated bullous/erosive skin conditions occurring in photo-distributed regions, PCT should be considered in the differential diagnosis irrespective of histopathological findings on biopsies and further investigated appropriately. Without a healthy clinical suspicion for PCT, which is generally more common than EBA, diagnostic porphyrin screening of urine, blood and stool may not be performed, thus leaving the patient untreated and ultimately at increased risk of developing chronic liver disease and possible hepatocellular carcinoma.

Statement of Ethics

The authors state that the patients gave their informed consent. The research complies with all ethical guidelines for human studies.

Disclosure Statement

The authors have no conflicts of interest and no funding sources to disclose.

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Table 1. Blood testing and porphyrin studies

Investigations	Case 1	Case 2
Blood testing		
Full blood count	normal	normal
Electrolytes	normal	normal
Renal function	normal	normal
Liver function		
Bilirubin (3–35 µmol/l)	8 µmol/l	12 µmol/l
ALP (20–105 U/l)	102 U/l	45 U/l
GGT (5–35 U/l)	50 U/l	21 U/l
ALT (5–30 U/l)	108 U/l	44 U/l
AST (10–35 U/l)	60 U/l	23 U/l
HFE test	not performed	no mutation
Ferritin	normal	254 µg/l
Hepatitis B/C and HIV serology	negative	negative
Intercellular substance (pemphigus) Abs (<10)	40	640
Basement membrane (pemphigoid) Abs (<10)	<10	<10
Porphyrin studies		
Urine porphyrin (<250 nmol/l)	3,700 nmol/l	3,200 nmol/l
Faecal porphyrin (<35 nmol/l)	330 nmol/l	320 nmol/l
Isocoproporphyrin (<200 nmol/g)	not performed	38 nmol/l

Figures in parentheses are normal ranges.

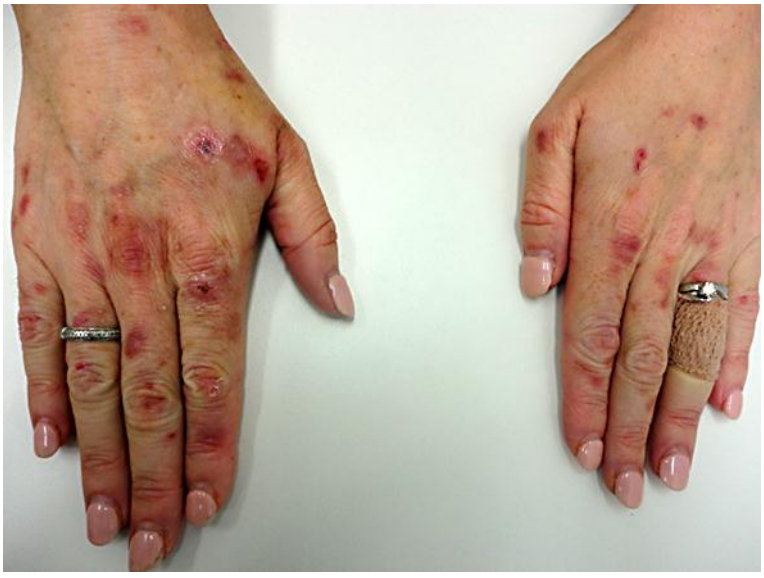

Fig. 1. Clinical photograph of lesions in case 1.

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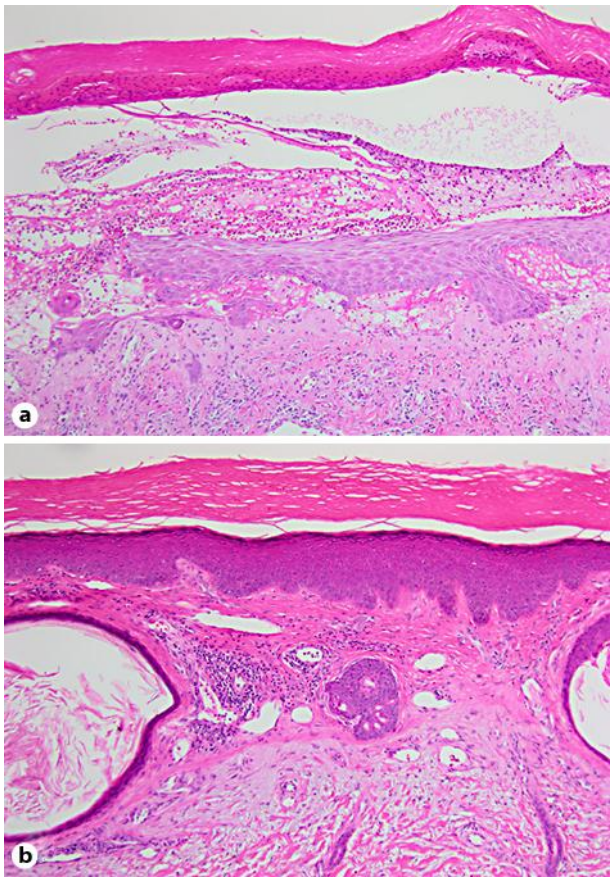

Fig. 2. **a** Histopathology of a left hand lesion in case 1 (H&E, ×10). **b** Histology of a right hand lesion in case 2 (H&E, ×10).

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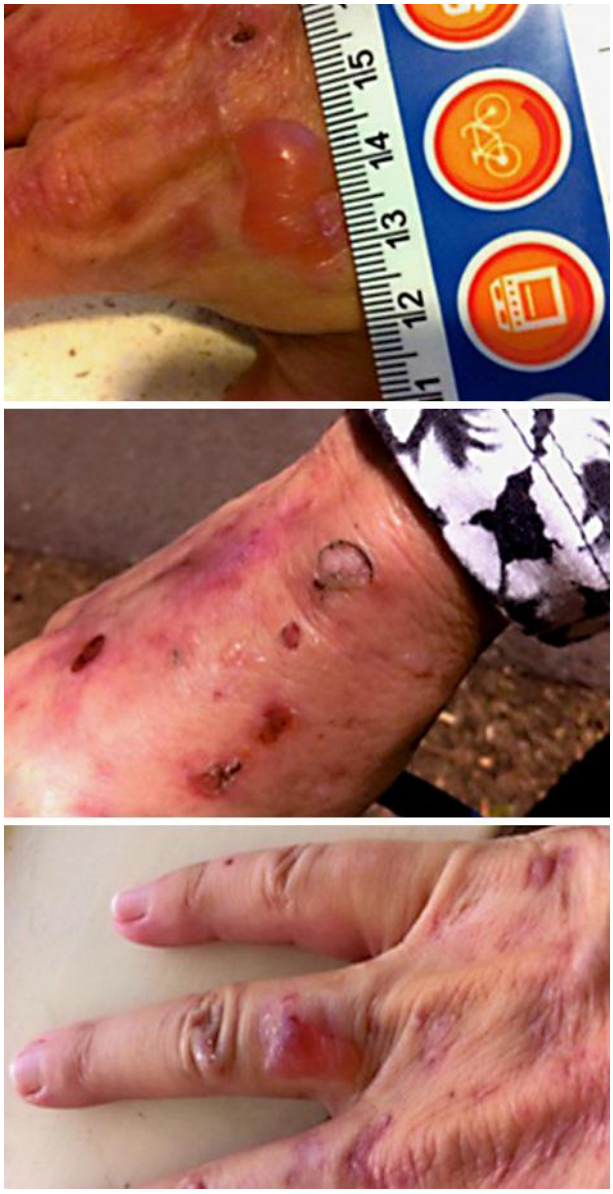

Fig. 3. Clinical photographs of lesions in case 2.