Extreme photosensitivity in a patient with erythropoietic protoporphyria

Introduction

The porphyrias represent a collection of conditions caused by errors in heme biosynthesis. Eight distinct types are recognized, which can be broadly divided into acute hepatic, hepatic cutaneous and erythropoietic cutaneous. Each type results from a deficiency of a specific enzyme in heme biosynthesis. Erythropoietic protoporphyria results from decreased activity of ferrochetalase, the last enzyme in the heme cascade, which is responsible for the introduction of iron into protoporphyrin (Balwani and Desnick, 2012).

Discussion

This patient suffers from erythropoietic protoporphyria, one of eight genetically distinct haemoglobin synthesis disorders (Puy et al, 2010). The predominant clinical feature of erythropoietic protoporphyria is photosensitivity (DeLeo et al, 1976). Around 5% of cases patients may also develop anaemia and severe liver dysfunction as a result of hepatic protoporphyrin accumulation. This patient can sustain exposure to sunlight without pain in the winter months for a few hours, reducing to 15–20 minutes in the spring and to less than a minute in full summer sun. Pain of a burning nature can be excruciating and is frequently not relieved by narcotic analgesics (Balwani and Desnick, 2012). It may be accompanied by skin blistering and potential chronic scarring in sun-exposed areas. The wavelengths of light that induce symptoms (around 400 nm wavelength) are not excluded by domestic or vehicle window glass and may be precipitated by exposure to several artificial light sources, including within an operating theatre.

The differential diagnoses include a rarer form of erythropoietic porphyria, termed congenital erythropoietic porphyria, which results in severe mutilating photosensitivity, haemolytic anaemia, splenomegaly, urine that develops a red hue on standing (as a result of uroporphyrin) and red-brown discolouration of the teeth. A clinically indistinguishable form of erythropoietic protoporphyria, related to an X-linked mutation, has also been reported (Whatley et al, 2008).

However, penetrance and clinical features may vary within these forms and the acute hepatic and hepatic cutaneous forms of porphyria, making accurate blood, urine and faecal 'porphyrin' measurements essential (Deleo et al, 1976). More recently, genetic analysis allows confirmation of the type of erythropoietic porphyria by demonstrating mutations among the specific genes (*FECH* gene in erythroprotoporphyria, *ALAS2* gene in X-linked erythroprotoporphyria and *UROS* gene mutations in congenital erythropoietic porphyria). More than 135 *FECH* gene loss-of-function mutations have been described (Gouya et al, 2006). Gall-stones and splenomegaly may occur in erythropoietic protoporphyria, the latter usually composed of protoporphyrin, and were seen in this patient.

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Case Report

A 51-year-old man gave a lifetime history of extreme photosensitivity. At the age of 18 months and with exposure to mid-summer sun he was noted to be uncomfortable and crying. Referred to a paediatric dermatologist he was provisionally given a diagnosis of either congenital erythropoietic porphyria or erythropoietic protoporphyria, dependent on further testing. At the age of 7 years he had positive red blood cell fluorescence, a feature considered specific for a diagnosis of erythropoietic protoporphyria. Later fluorescence spectroscopy showed the porphyrin was more than 90% free protoporphyrin. Urinary total porphyrin level was normal at <5 nmol/mmol (normal range 0–34 nmol/mmol) with urine porphobilinogen and 5-aminolaevulinic acid at normal levels of 0.9 umol/mmol and <0.5 umol/mmol respectively. Subsequent annual blood tests have demonstrated levels of reticulocyte free-protoporphyrin in excess of 52 000 nmol/cell (normal range <200 nmol/cell). Full blood count and liver function tests are consistently entirely normal. Recent abdominal ultrasound examination demonstrated a normal-sized spleen, increased echogenicity of the liver consistent with diffuse fatty infiltration, and several gall-stones. These results are all compatible with a diagnosis of erythropoietic protoporphyria.

As a child he experienced blistering and scabbing in sun-exposed areas of the hands, nose, neck and ears. Currently, the patient remains extremely sensitive to sunlight and requires the curtains to be drawn at home in summer months. The patient's occupation involves him largely working within buildings, reducing the risk of ultraviolet light exposure. Journeys are planned to coincide with the greatest shade or after sundown. This can include sheltering in motorway service stations when the sun is not directly over the car to offer shade. The patient drives a car with tinted windows and on occasions wears gloves and a motorcycle-style balaclava to cover his neck and face.

Treatment over the years has included protective clothing, topical sun blocks, beta-carotene and omega-3 fish oil supplements, cholestyramine (to absorb protoporphyrin and block enterohepatic circulation) in addition to phototoxicity 'hardening' through the prescription of both narrow- and broad-band ultraviolet radiation therapy. Despite extreme lifestyle modifications and medical supplements he has sustained blistering and scarring of his face and hands (*Figures 1* and *2*).

His parents and all five of his children appear unaffected, although his sister has been informed that she may be a carrier. The patient has been advised to have an annual review to check blood porphyrin levels, full blood count and liver function tests.

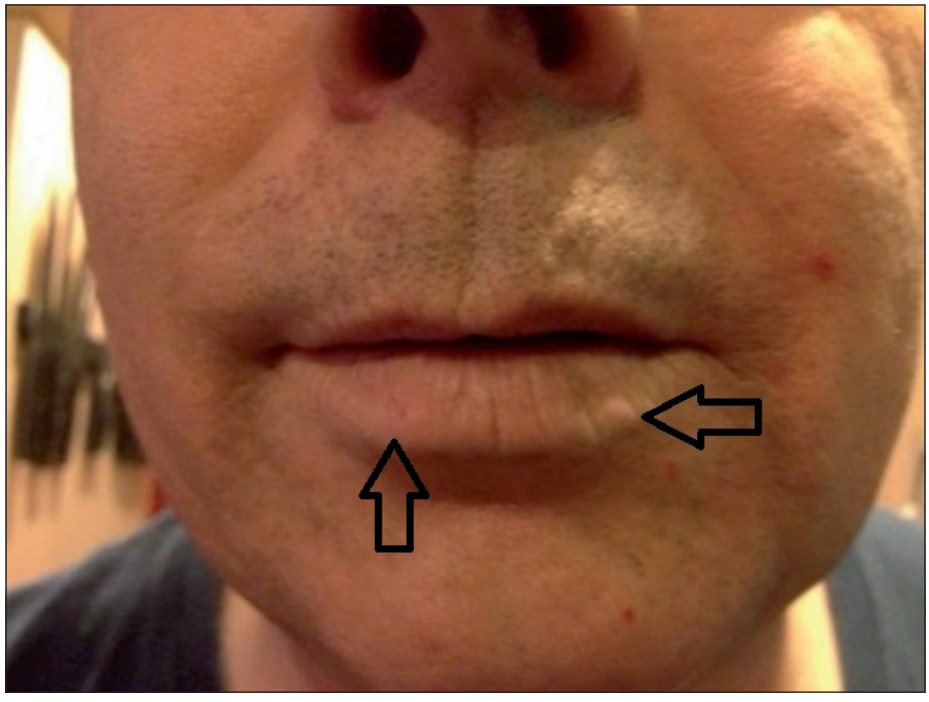

Figure 1. Phototoxicity scarring on the lower lip (arrows) following sunlight exposure. Note the pale complexion.

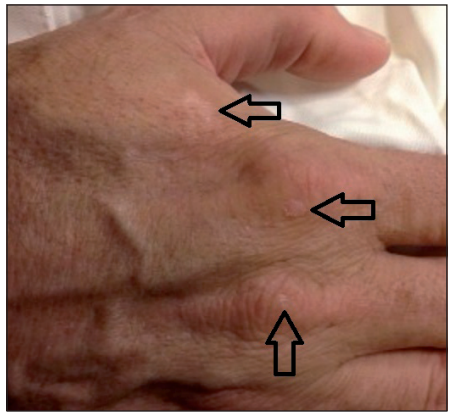

Figure 2. Localized waxy thickening of the skin over the metacarpophalangeal joints (arrows), a cutaneous feature of erythropoietic protoporphyria.

Treatments include an α-melanocyte-stimulating hormone analogue which, through increasing skin pigmentation, can improve tolerance to sunlight exposure (Harms et al, 2009). Because of the possibility of liver compromise, patients are advised to avoid any medications that might cause metabolic or obstructive cholestasis and to have regular assessment of hepatic function. In the event of severe liver involvement, liver transplantation has been successfully performed (McGuire et al, 2005; Dowman et al, 2011). Although rarely performed, recurrence of disease in the transplanted liver can theoretically be managed by bone marrow transplantation, to remove the ongoing bone marrow production of protoporphyria (Dowman et al, 2011). BJHM

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LEARNING POINTS

- The clinical phenotype of erythropoietic protoporphyria is variable and can vary from 'unrecognized' in non-sunny climates to severe blistering and scarring in some individuals in sun-exposed regions.
- Therapy predominantly involves sun-blocking pharmacological agents and skin photosensitivity hardening with ultraviolet light therapy.
- Severe dermatological complications and liver failure are rare in erythropoietic protoporphyria.
- The diagnosis of erythropoietic protoporphyria is highly probable in the presence of erythrocyte free-protoporphyrin with normal urine levels.
- A biochemical diagnosis, if available, is frequently confirmed by mutation analysis of the *FECH* gene.