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CASE REPORT

Congenital erythropoietic porphyria associated with myelodysplasia presenting in a 72-year-old man: report of a case and review of the literature

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Summary Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disease owing to the deficient activity of uroporphyrinogen III synthase, the fourth enzyme in the porphyrin–haem synthetic pathway. Of the porphyrias, it is the most mutilating type, usually presenting early in life. To date, 12 documented cases of adult onset CEP have been reported. We report the second oldest documented patient with late onset CEP with incidental findings of thrombocytopenia and myelodysplasia with bone-marrow sideroblasts. We further discuss several current and future treatment options for this therapeutically challenging disease.

Key words: congenital erythropoietic porphyria, Günther's disease, myelodysplasia, photosensitivity, uroporphyrinogen III synthase

Congenital erythropoietic porphyria (CEP), or Günther's disease, is an autosomal recessively inherited disorder resulting from a variably deficient, but not absent, activity of uroporphyrinogen III synthase, the fourth enzyme in the porphyrin–haem synthetic pathway. It is a rare disease with approximately 130 cases reported to date.[1] The disease usually manifests in the first decade of life, with only 12 reported cases beginning in adulthood.[2–11] We report the second oldest documented patient of late onset CEP.

Case report

A 72-year-old caucasian male was referred to the Department of Dermatology at Henry Ford Hospital in June 2001 for severe blistering and skin fragility. His skin had been completely normal until September 2000 when he developed two vesicles that later crusted on the left index finger after playing golf. These lesions resolved during the winter months, only to recur when he travelled to Florida in February 2001. His cutaneous manifestations progressively worsened with the development of erythema, oedema, skin fragility, vesicles, crusted erosions and scarring on the sun-exposed areas of his hands, forearms, neck, face and scalp (Fig. 1). This was associated with pruritus, paraesthesia and pain. The colour of both the vesicular fluid and urine were a distinctive rusty-red. Hypertrichosis and erythrodontia were not present. He consumed an average of one alcoholic beverage per week.

Prior to our consultation, the patient underwent two phlebotomies for treatment of suspected porphyria cutanea tarda. Subsequently, full blood count revealed thrombocytopenia and normochromic macrocytic anaemia [haemoglobin: 10·4 g dL^{-1} (13·5–17·0); MCV: 111·2 fl (80–100); MCHC: 33·5 g dL^{-1} (31–37); platelet count: 74×10^9 L^{-1} (150–450)]. Iron studies were within normal limits [iron: 125 μg dL^{-1} (60–140); total iron binding: 317 μg dL^{-1} (250–425); iron saturation: 39% (15–50)]. A bone marrow aspirate analysis revealed erythroid hyperplasia and severe dyserythropoiesis suggestive of myelodysplastic syndrome; in addition, ringed sideroblasts were observed. A shave biopsy of a vesicle performed by the

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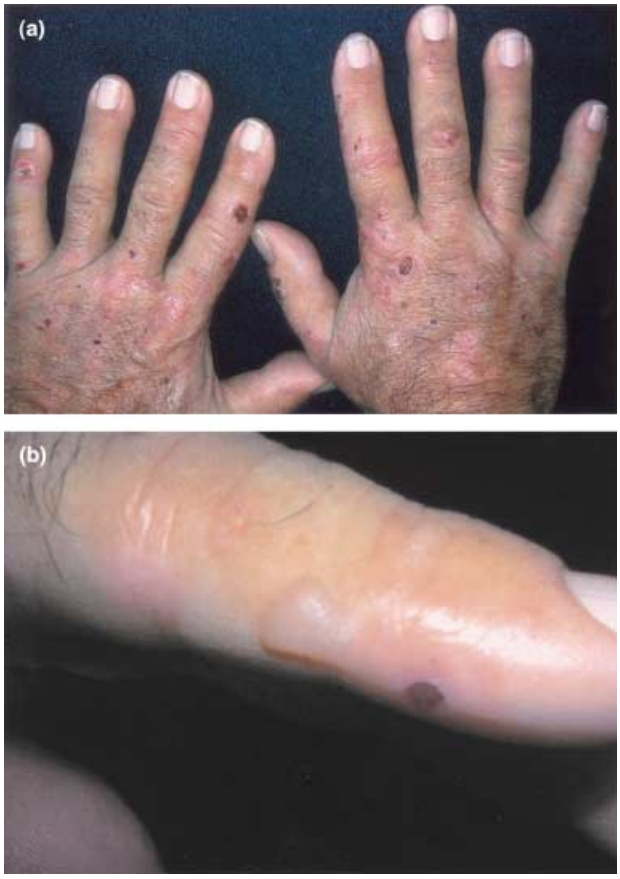

Figure 1. (a) Erosions and crusting on dorsum of hands secondary to skin fragility. (b) Blister at the lateral aspect of a finger.

referring dermatologist showed bullous changes within the corneal layer consistent with spongiotic dermatitis.

The patient's past medical history was significant for a splenectomy performed in the mid-1970s for a lacerated spleen secondary to trauma. Perioperatively, he required multiple transfusions. Hepatitis C antibodies were incidentally detected with a normal liver profile during a sepsis work-up after a coronary artery bypass graft procedure in 1993. He also had a history of prostate carcinoma, for which the patient underwent total prostatectomy.

Following the consultation, analysis of the patient's porphyrin profile at the University of Texas Medical Branch (Galveston, TX, U.S.A.) revealed elevated total plasma, urine, erythrocyte and fecal porphyrins (Table 1). Maximum plasma fluorescence at neutral pH was 617 nm, which could be observed in CEP. In plasma, urine and erythrocytes, the predominant porphyrins were uroporphyrin and coproporphyrin. In all specimens, isomer I predominated. Urine δ-aminolevulinic acid and porphobilinogen, and erythrocyte uroporphyrinogen decarboxylase levels were within normal limits. Altogether, these findings were consistent with CEP. With this diagnosis, cytogenetic analysis was pursued. As our institution does not perform fluorescent *in situ* hybridization (FISH) for CEP, standard chromosomal analysis was done revealing a normal male karyotype (46, XY) without evidence of chromosomal breakage or deletion.

Preventative and symptomatic measures constitute the patient's current treatment. Maximal avoidance of sun-exposure is performed daily by the patient, with the use of photoprotective clothing (Solumbra®), broad-brimmed hat, gloves and a sunscreen of SPF 35 containing zinc oxide and cinnamate. An oral beta carotene (Lumitene® 180 mg day^{-1}) and an oral antipruritic agent have also been administered. These resulted in a moderate decrease in cutaneous symptoms.

Discussion

The first case of CEP was described by Schultz in 1874,[1] and later described in detail by Günther in 1911.[1] It is the most mutilating type of the porphyrias presenting with moderate to severe cutaneous photosensitivity. CEP is due to deficient activity of uroporphyrinogen III synthase. Patients have normal levels of immunoreactive enzyme protein and markedly reduced enzyme activity ($\leq$ 15% normal).[12] This results in the predominant accumulation of uroporphyrin I and coporphyrin I in all cells and tissues. The presence of these porphyrin isomers allows for the absorption of photons in the Soret band spectrum (400–410 nm) with minor absorption between 500 and 700 nm. Photosensitivity develops as a result of generation of reactive oxygen species and inflammatory mediators, leading to tissue damage.[13]

Following sun exposure, infants with CEP typically cry because of a burning and stinging sensation with pruritus of the exposed skin. Cutaneous findings include marked fragility, eroded or intact vesicles and bullae that may contain pink fluorescent fluid, hypertrichosis of lanugo-type hair in sun-exposed areas, dyspigmentation, diffuse scarring and atrophy, which may result in deformity of the ears, nose, fingers and face, scarring alopecia and sclerodermoid changes. Patients also have pink-red urine that fluoresces under Wood's light. Associated complications include keratoconjunctivitis, corneal scarring, scleral ulceration, cataracts, hepatosplenomegaly, and osteolysis.[13–15] Erythrodontia, owing to deposition of porphyrins, is a common finding

Table 1. Porphyrin profile of the patient

Specimen	Test	Value (normal range)*
Plasma	Total porphyrins	42·9 μg dL^{-1}L (0–0·9)
	Uroporphyrin	9·9 μg dL^{-1}
	Heptacarboxyl porphyrin	10·7 μg dL^{-1}
	Hexacarboxyl porphyrin	0·9 μg dL^{-1}L
	Pentacarboxyl porphyrin	6·4 μg dL^{-1}
	Coproporphyrin	14·6 μg dL^{-1}
	Maximum fluorescence at neutral pH	617 nm
Urine (3500 mL 24 h^{-1})	Total porphyrins	24 160 nmol 24 h^{-1} (0–300)
	Uroporphyrin	59% (0–30% of total)
	Heptacarboxyl porphyrin	1% (0–5% of total)
	Hexacarboxyl porphyrin	1% (0–5% of total)
	Pentacarboxyl porphyrin	5% (0–5% of total)
	Coproporphyrin	34% (50–100% of total)
	δ-Aminolevulinic acid	2·8 mg 24 h^{-1} (0–7)
	Porphobilinogen	1·3 mg 24 h^{-1} (0–4)
Erythrocytes	Total porphyrins	695 μg dL^{-1} (20–80)
	Uroporphyrin	327 μg dL^{-1}
	Heptacarboxyl porphyrin	21 μg dL^{-1}
	Hexacarboxyl porphyrin	7 μg dL^{-1}
	Pentacarboxyl porphyrin	28 μg dL^{-1}
	Coproporphyrin	306 μg dL^{-1}
	Uroporphyrinogen decarboxylase	59·3 nmol mL RBC^{-1} h^{-1} (35–60)
Faeces	Total porphyrins	3050 nmol g^{-1} dry weight (0–200)
	Pentacarboxyl porphyrin	1% (0–10% of total)
	Coproporphyrin	98% (30–100% of total)

*All porphyrins are predominantly isomer I by high performance liquid chromatography.

Table 2. Patients with late onset congenital erythropoietic porphyria*

Case	Authors and ref. (year)	Sex	Ethnicity	Age at onset (years)	Thrombocytopenia	Myelodysplasia
1	Kramer *et al.*[2] (1965)	M	Bantu	54	+	
2	Pain *et al.*[3] (1975)	M	Australian	58	+	+
3	MacDonald *et al.*[4] (1978)	M	Greek	51	+	+
4	Deybach *et al.*[5] (1981)	M	French	36		
5	Deybach *et al.*[5] (1981)	M	Algerian	23		
6	Mukerji *et al.*[6] (1985)	M	White	53		
7	Horiguchi *et al.*[7] (1989)	M	Japanese	26		
8	Horiguchi *et al.*[7] (1989)	F	Japanese	36		
9	Rank *et al.*[8] (1990)	M	E. European	51	+	+
10	Yamauchi and Kushibiki[9] (1992)	M	Japanese	63	+	+
11	Murphy *et al.*[10] (1995)	M	Caucasian	65	+	+
12	Ibbotson *et al.*[11] (1998)	M	NR	74	+	+
13	Kontos *et al.* (this paper)	M	German/French	72	+	+

*Modified from Fritsch *et al.*[1] NR, not reported.

of CEP. Predominant elevation of uroporphyrin I and coproporphyrin I in urine, and coproporphyrin I in faeces, with normal urinary δ-aminolevulinic acid and porphobilinogen levels are found.

Including the patient described herein, there has been a total of only 13 cases of CEP reported worldwide with age of onset older than 18 years, with our patient being the second oldest (Table 2). The age of onset ranged from 23 to 74 years; only one of the 13 patients was female. Compared to early onset CEP, patients with late onset disease tend to have less severe manifestations presumably due to a less severe deficiency of the uroporphyrinogen III synthase activity. Whether the splenectomy performed in our patient 25 years prior to the cutaneous manifestation resulted in the delayed onset of the disease remains purely speculative at this

time. Of interest, eight of the 13 patients with late onset disease had thrombocytopenia, and seven of them had myelodysplasia. All of the patients with myelodysplasia were older than 50 years, while only two of the six without myelodysplasia were older than 50 years. Therefore, it is possible that there may be two types of late onset CEP, one associated with myelodysplasia with acquired mutation of the *UROS* gene, while the other is caused by germ-line *UROS* gene mutations with mild phenotypic expression. Ringed sideroblasts were observed in the bone marrow of our patient. Of interest, deletion of the ferrocheletase gene and the presence of ringed sideroblasts as part of the myelodysplastic process have been recently reported in late onset erythropoietic protoporphyria (EPP).[16] In addition, sideroblastic anaemia, photosensitivity, and abnormal porphyrin profile (elevated erythrocyte, plasma and fecal protoporphyrin, and elevated urinary coporphyrin) have been reported previously in at least six other patients, two of whom are patients with late onset EPP.[17]

At least 22 mutations responsible for CEP have been identified in the uroporphyrinogen III synthase gene located on chromosome 10. These include 18 point, deletion and insertion mutations,[1,12,18] and four promoter mutations.[19] The heterogeneity of these mutations may provide a better understanding of predicting the severity of CEP. Of all the documented mutations, the most severe and common mutation is a single, missense mutation designated C73R.[20–22] It has been suggested that late onset CEP may represent a heterozygous state;[3] however, Deybach *et al.*[5] refute this hypothesis based on their observations of markedly suppressed uroporphyrinogen III synthase activity in two patients with late onset CEP.

Treatment of CEP is very challenging. The use of photoprotective clothing, broad-brimmed hats, and UV-protected sunglasses should be recommended. The only topical agents fully protective at the Soret band range are non-micronized inorganic sunscreen agents such as titanium dioxide and zinc oxide; however, because of the pasty nature of the preparations, they are not practical for daily use. Therefore, while currently available organic and micronized inorganic sunscreen agents do not adequately absorb the Soret band range, they are still recommended to patients as part of the total sun-avoidance package. Recently, newly formulated sunscreens containing pigmentary titanium dioxide with zinc oxide offered protection to the UVB and UVA spectra with extended coverage into the blue light region of the visible spectrum, making this an exciting option for photosensitive patients.[23] Oral beta carotene at doses of 120–180 mg day^{-1} have been reported to improve light tolerance in some.[1,13,24] The use of oral charcoal and cholestyramine to interrupt the enterohepatic circulation of porphyrins has been variably successful.[1,6,13,15,24,25] Splenectomy transiently improves haemolytic anaemia and increases the lifespan of erythrocytes, leading to a decrease in photosensitivity.[1,13,15,22] The concomitant use of erythrocyte transfusion and hydroxyurea has been shown to decrease porphyrin production and excretion by suppression of erythropoiesis in bone marrow.[15,22] However, the risk of iron overload and/or acquiring an infectious disease must be taken into consideration. Pyridoxal 5-phosphate has been used to treat anaemia in a patient with late onset CEP and myelodysplastic syndrome; urinary porphyrin concentration decreased to normal levels, but the anaemia worsened.[1,9] The use of cyclophosphamide has been implemented in a patient with late onset CEP and nephrotic syndrome. Erythrocyte uroporphyrin and coproporphyrin and urinary coproporphyrin levels were reduced, with little cutaneous photosensitivity seen 7–12 months after cessation of therapy.[26] Allogeneic stem cell transplantation has been shown to be an effective, if not curative, treatment option for severe CEP.[15,27,28] *In vitro* retroviral-mediated transfer of the uroporphyrinogen III synthase gene into cells deficient in uroporphyrinogen III synthase has been shown to completely restore enzymatic activity in cultured stem cells, showing promise for *ex vivo* therapy for severe CEP.[15,22,29]

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