Acquired erythropoietic uroporphyria associated with clonal cytopenia of undetermined significance

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INTRODUCTION

Congenital erythropoietic porphyria (CEP) or Günther's disease is a rare disorder of heme biosynthesis resulting from decreased uroporphyrinogen III synthase (UROS) activity.[1,2] In most cases, CEP is a genetic disorder caused by pathogenic germline variants in either UROS or GATA1.[3] A small number of late-onset patients with underlying myeloid malignancy, termed acquired erythropoietic uroporphyria (AEU) have been reported with clinical and biochemical features of CEP without detectable pathogenic gene variants.[4-7] We report a woman with AEU in association with clonal cytopenia of undetermined significance (CCUS).

Abbreviations used:

AEU:	acquired erythropoietic uroporphyria
CCUS:	clonal cytopenia of undetermined significance
CEP:	congenital erythropoietic porphyria
MDS:	myelodysplastic syndrome
UROS:	uroporphyrinogen III synthase

CASE REPORT

A 52-year-old woman with a history of type 2 diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, and peripheral vascular disease presented with painful blistering skin of 3 years duration. She was initially diagnosed with porphyria cutanea tarda at her local clinic without investigations, and had no history of hepatitis C, HIV, alcoholism, or estrogen use. Her clinical condition deteriorated to more extensive blistering with subsequent ulceration and scarring involving sun-exposed areas, particularly the face, scalp, dorsal hands, and arms. She noted red urine and developed pancytopenia requiring blood transfusion.

On examination, she had thick, waxy, scar-like changes and dyspigmentation surrounding erosions and ulcerations on sun-exposed skin. Sclerodermoid changes were prominent on the distal aspects of the upper extremities. An intact hemorrhagic bulla was located on the digit (Fig 1, *A-C*). Biopsy of the bulla revealed a subepidermal blister with pink hyalinized globular deposits arranged in a linear fashion in the epidermis. Biopsy of sclerotic intact skin revealed mild deposition of periodic acid Schiff plus diastase stain-positive hyalinized, lamellated material surrounding superficial blood vessels (Fig 1, *D* and *E*). Direct immunofluorescence from bulla and intact

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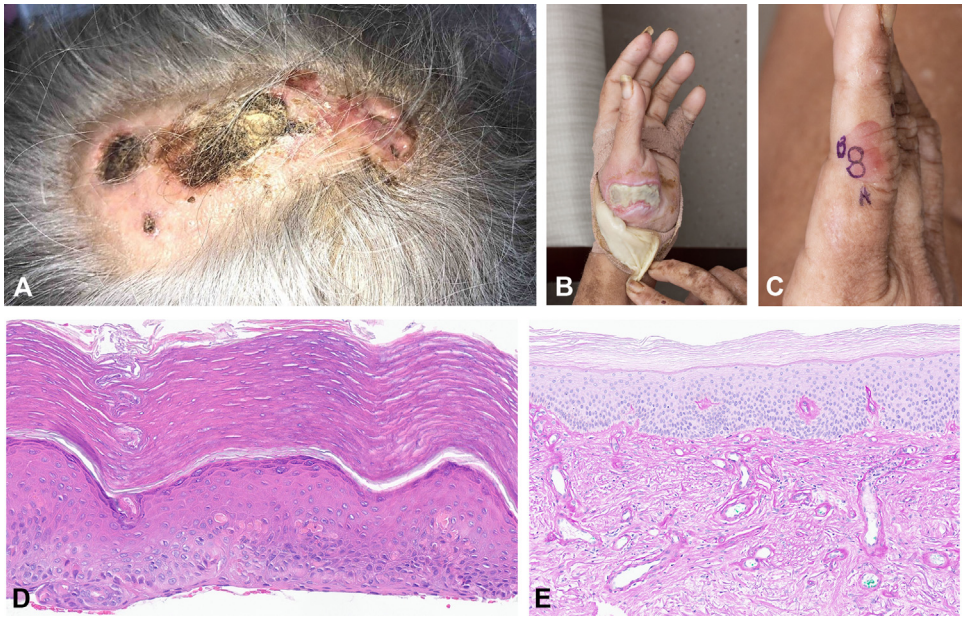

Fig 1. Eroded and ulcerated skin with overlying crust and surrounding dyspigmentation involving sun exposed sites (**A, B**). Intact hemorrhagic bulla of the finger (**C**). Histopathology of bulla showing pink hyalinized globular deposits (caterpillar bodies) in the epidermal lining of subepidermal blister (**D**). Histopathology of intact, sclerotic skin showing periodic acid Schiff plus diastase stain positive hyalinized material surrounding vessels in lamellated pattern (**E**). (Hematoxylin and eosin stain, 400× original magnification [**D**]; periodic acid Schiff plus diastase special stain, 200× original magnification [**E**].)

skin showed homogenous deposition of IgG, IgA, and fibrinogen along the basement membrane zone and within walls of dermal vessels.

Porphyrin analyses in urine, stool, and erythrocytes revealed a biochemical profile typical of CEP: increased excretions of uroporphyrin and coproporphyrin in urine, markedly elevated levels of coproporphyrin I in feces with elevated isomer I to III ratio, and mildly elevated total porphyrins in erythrocytes (Table I). In contrast to classic CEP, the enzymatic activity of UROS in erythrocytes was normal. Enzymatic activity of uroporphyrinogen decarboxylase in whole blood was within the normal range.

DNA extracted from whole blood was analyzed using a next-generation sequencing panel of 11 genes associated with porphyria. No pathogenic variants were detected, including in *UROS* and *GATA1*.

Laboratory tests revealed pancytopenia and hemolysis [hemoglobin: 7.9 g/dL (11.6-15); leukocyte counts: 2.1 × 10^9/L (3.4-9.6); platelet count 51 × 10^9/L (157-371); absolute reticulocyte count: 200.6 × 10^9/L (30.4-110.9); lactate dehydrogenase: 757 U/L (122-222); bilirubin: 1.3 mg/dL (<1.2); haptoglobin: <14 mg/dL (30-200); antibody screen: negative]. Splenomegaly was observed on abdominal imaging. A bone marrow biopsy showed erythroid hyperplasia with dyspoiesis limited to the erythroid lineage and hypercellularity of 95%. Molecular DNA analysis of the bone marrow using a next-generation sequencing panel targeting 42 genes associated with hematologic neoplasm demonstrated a frameshift mutation in BCL-6 interacting corepressor (c.2382del; p.Lys795Argfs*12) and a frameshift mutation in Tet methylcytosine dioxygenase 2 (c.3893del; p.Cys1298Leufs*65). In addition, a variant of unknown significance was detected in *GATA2* (c.1402G>A; p.Gly468Ser). Based on the persistent cytopenia, the presence of somatic mutations, and not meeting the morphological criteria for myeloid neoplasm, the patient was diagnosed with CCUS.

The patient received supportive care with packed red blood cell transfusions. Timolol solution and mupirocin ointment were prescribed to facilitate wound healing. There was a consideration for initiation of systemic treatment with azacitidine. Unfortunately, systemic infectious complications delayed initiation of therapy, and she passed away due to infection.

DISCUSSION

CEP, Günther's disease, is a rare cutaneous porphyria caused by deficient activity of UROS, the enzyme that catalyzes the fourth step of heme biosynthesis.[1] Deficient UROS activity leads to the overproduction of uroporphyrinogen I and

Table I. Porphyrin levels in urine, erythrocytes, and feces

Specimen	Analyte	Value	Normal range
Urine, nmol/L			
	Uroporphyrin	**12,529**	≤30
	Heptacarboxylporphyrin	**544**	≤7
	Hexacarboxylporphyrin	**267**	≤2
	Pentacarboxylporphyrin	**854**	≤5
	Coproporphyrin	**5666**	≤110
	Porphobilinogen	400	≤1300
Erythrocytes, mg/dL			
	Total porphyrins	**115**	<80
Feces, μg/24 h			
	Uroporphyrin III	<1	<120
	Heptacarboxylporphyrin I	19	<40
	Heptacarboxylporphyrin III	6	<40
	Isoheptacarboxylporphyrin	9	<30
	Hexacarboxylporphyrin I	**17**	<10
	Hexacarboxylporphyrin III	2	<10
	Isohexacarboxylporphyrin	**43**	<10
	Pentacarboxylporphyrin I	**176**	<20
	Pentacarboxylporphyrin III	7	<20
	Isopentacarboxylporphyrin	45	<80
	Coproporphyrin I	**>10,222**	<500
	Coproporphyrin III	**2875**	<400
	Isocoproporphyrin	**283**	<200
	Protoporphyrin IX	37	<1500

Values in bold are outside the normal range.

coproporphyrinogen I, primarily in erythroid precursors in the bone marrow. Type I porphyrinogens cannot be used for heme synthesis due to the stereospecificity of coproporphyrinogen oxidase, and therefore, accumulate within erythroid cells. Type I porphyrinogens subsequently undergo auto-oxidation to their corresponding porphyrins, are released into plasma by hemolysis or diffusion, and are subsequently deposited in tissues or excreted in urine and feces.[2] Uroporphyrin I and coproporphyrin I are photoreactive compounds that absorb light in the long-wave ultraviolet and visible spectrum. The high concentration of porphyrins deposited in the skin of CEP patients induces phototoxic damage to sunlight-exposed areas.[8-10]

In most cases, CEP is an autosomal recessive disease caused by homozygous or compound heterozygous pathogenic mutations in the gene encoding for UROS.[3] Specific pathogenic variants of the X-linked transcription factor GATA1 have also been reported to cause CEP in a few patients.[11] The age of onset and clinical severity is highly variable ranging from hydrops fetalis in utero to a mild adult-onset form presenting only with cutaneous symptoms. However, most individuals present before 5 years of age with characteristic cutaneous photosensitivity and hematological manifestations. The most common symptoms include skin fragility, blistering, and scarring upon exposure to sunlight (and artificial light in some cases), neonatal jaundice, and hemolytic anemia with or without thrombocytopenia and splenomegaly. Other clinical findings include facial hypertrichosis, erythrodontia, and red urine.[2,3] Up to one third of cases are misdiagnosed as porphyria cutanea tarda.[7]

In rare instances, patients have been reported with clinical and biochemical features of CEP in association with myeloid disorders, termed AEU.[4-7] All cases reported so far have been men who presented with cutaneous symptoms after 50 years of age and were diagnosed with myelodysplastic syndrome (MDS) or myeloproliferative disorder. The underlying cause of the excessive porphyrin production in these patients is unknown. It has been hypothesized that a small subpopulation of myelodysplastic clones with defective UROS activity might be responsible for the biochemical and clinical symptoms.[5] This subpopulation, carrying a pathogenic variant in *UROS* or *GATA1*, would be too small to detected by standard molecular methods but sufficiently large to cause the CEP-like phenotype. However, other potential mechanisms are possible, such as epigenetic alteration influencing UROS activity in a subset of myeloproliferative cells.

CCUS is a premalignant clonal cytopenia associated with a 75% likelihood of evolving to MDS at 5 years.[12] BCL-6 interacting corepressor and Tet methylcytosine dioxygenase 2 regulate hematopoiesis and are mutations contribute to myeloid clones.[13] There is no standard of care for CCUS management.[14] MDS treatment is risk-based, and hypomethylating agents such as azacitidine are considered in low and high-risk cases.[15] Hematopoietic stem cell transplantation is a curative option for both MDS and CEP[10,15]; although just 1 published case of AEU has been treated with hematopoietic stem cell transplantation to date.[6]

The case presented here falls within this group of patients with AEU associated with myeloid neoplasm, bringing the number of reported cases to a total of 15.[5,7] Furthermore, this case is exceptional for presentation in a woman before 50 years of age with a pre-myeloid disorder, CUS, leading to her presentation.

Conflicts of interest

None disclosed.

REFERENCES

1. Günther H. Die Hämatoporphyrie. *Dtsch Arch Klin Med*. 1911;105:89-146.
2. Xu W, Astrin KH, Desnick RJ. Molecular basis of congenital erythropoietic porphyria: mutations in the human uroporphyrinogen III synthase gene. *Hum Mutat*. 1996;7:187-192. https://doi.org/10.1002/(SICI)1098-1004(1996)7:3<187::AID-HUMU1>3.0.CO;2-8
3. Katugampola RP, Badminton MN, Finlay AY, et al. Congenital erythropoietic porphyria: a single-observer clinical study of 29 cases. *Br J Dermatol*. 2012;167:901-913. https://doi.org/10.1111/j.1365-2133.2012.11160.x
4. Kontos AP, Ozog D, Bichakjian C, Lim HW. Congenital erythropoietic porphyria associated with myelodysplasia presenting in a 72-year-old man: report of a case and review of the literature. *Br J Dermatol*. 2003;148:160-164. https://doi.org/10.1046/j.1365-2133.2003.05040.x
5. Sarkany RP, Ibbotson SH, Whatley SD, et al. Erythropoietic protoporphyria associated with myeloid malignancy is likely distinct from autosomal recessive congenital erythropoietic porphyria. *J Invest Dermatol*. 2011;131:1172-1175. https://doi.org/10.1038/jid.2011.5
6. Podlipnik S, Guijarro F, Combalia A, et al. Acquired erythropoietic uroporphyria secondary to myelodysplastic syndrome with chromosome 3 alterations: a case report. *Br J Dermatol*. 2018;179:486-490. https://doi.org/10.1111/bjd.15927
7. Serra-García L, Morgado-Carrasco D, Pérez-Valencia AI, et al. Acquired erythropoietic uroporphyria secondary to myeloid malignancy: a case report and literature review. *Photodermatol Photoimmunol Photomed*. 2022;38:86-91. https://doi.org/10.1111/phpp.12720
8. Afonso SG, Enríquez de Salamanca R, Batlle AM. The photodynamic and non-photodynamic actions of porphyrins. *Braz J Med Biol Res*. 1999;32:255-266. https://doi.org/10.1590/s0100-879x1999000300002
9. Menon IA, Persad SD, Haberman HF. A comparison of the phototoxicity of protoporphyrin, coproporphyrin and uroporphyrin using a cellular system in vitro. *Clin Biochem*. 1989;22:197-200. https://doi.org/10.1016/S0009-9120(89)80077-3
10. Hogeling M, Nakano T, Dvorak CC, Maguiness S, Frieden IJ. Severe neonatal congenital erythropoietic porphyria. *Pediatr Dermatol*. 2011;28:416-420. https://doi.org/10.1111/j.1525-1470.2010.01376.x
11. Solis C, Aizencang GI, Astrin KH, Bishop DF, Desnick RJ. Uroporphyrinogen III synthase erythroid promoter mutations in adjacent GATA1 and CP2 elements cause congenital erythropoietic porphyria. *J Clin Invest*. 2001;107:753-762. https://doi.org/10.1172/jci10642
12. Dana-Farber Cancer Institute. What is clonal cytopenia of undetermined significance (CCUS)? April 30, 2019. Accessed April 4, 2022. https://blog.dana-farber.org/insight/2019/04/what-is-clonal-cytopenia-of-undetermined-significance-ccus/
13. Schaefer EJ, Fares I, Meyer C, et al. Dual effects of BCOR-PRC1.1 dependent gene regulation mediate cooperation of BCOR and TET2 mutations in myeloid transformation. *Blood*. 2018;132:651. https://doi.org/10.1182/blood-2018-99-119519
14. DeZern AE, Malcovati L, Ebert BL. CHIP, CCUS, and other acronyms: definition, implications, and impact on practice. *Am Soc Clin Oncol Educ Book*. 2019;39:400-410. https://doi.org/10.1200/edbk_239083
15. Platzbecker U. Treatment of MDS. *Blood*. 2019;133:1096-1107. https://doi.org/10.1182/blood-2018-10-844696