Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Case Report

Congenital Erythropoietic Porphyria: Complete Resolution of Symptoms Following Allogeneic Stem Cell Transplant

Iftikhar R[1]*, Shamshad UG[1], Akram Z[1], Ghafoor T[2], Satti MT[1], Chaudhry QN[1] and Mahmood KS[1]

[1]Department of Clinical Hematology, Armed forces Bone Marrow Transplant Centre, Rawalpindi Pakistan

[2]Department of Pediatrics, Armed forces Bone Marrow Transplant Centre, Rawalpindi Pakistan

***Corresponding author:** Raheel Iftikhar, Armed forces Bone Marrow Transplant Centre, Rawalpindi Pakistan

Received: February 11, 2019; **Accepted:** March 14, 2019; **Published:** March 21, 2019

Abstract

Congenital Erythropoietic Porphyria (CEP) is a rare inherited disorder mainly due to a defect in Uroporphyrinogen III Synthase (UROS), an enzyme that is involved in heme synthesis [1-3]. As a result elevated levels of uroporphyrin I and coproporphyrin I accumulate in red cells, plasma, feces, urine, teeth and bones leading to oxidative damage on exposure to sunlight [4]. The affected patients develop hemolytic anemia, severe cutaneous photosensitivity, reddish discoloration of urine and brownish discoloration of teeth [5]. In mild cases the treatment is generally supportive like avoidance of sun-exposure to eyes and skin. Red cell transfusions may be needed for correction of anemia. In severe cases, allogeneic stem cell transplant remains the only curative option4 however; significant mortality and morbidity are important concerns. We describe the case of a 4-year-old girl presenting with severely symptomatic CEP, who underwent an allogeneic stem cell transplant from a matched sibling donor that resulted in complete resolution of her symptoms.

Keywords: Congenital erythropoietic porphyria; Photosensitivity; Allogeneic stem cell transplant

Case Presentation

A 4 year old girl belonging to Himalayan region of Pakistan presented to our institute in August 2017 with history of passing reddish urine soon after birth. She had been reviewed by a general practitioner initially and was diagnosed to have hematuria. She had also been reviewed by different paediatricians but no diagnosis could be established. Later her parents noticed brownish discoloration of erupted teeth, skin blistering and scarring on exposure to sunlight. She gradually developed progressive lethargy, pallor and yellowish discoloration of sclera.

She was than referred to Armed Forces Bone Marrow Transplant Centre (AFBMTC) with suspicion of haemolytic anemia. On examination she was pale with generalized hypertrichosis, erythrodontia, blistering and scarring of skin on sun exposed areas (Figure 1) and mild splenomegaly. Her urine had a reddish appearance but was negative for RBCs on microscopy. She had haemoglobin of 90 g/L alongwith reticulocytosis (6%), indirect hyperbilirubinemia and elevated serum lactate dehydrogenase level. Her Coombs antiglobulin test was negative.

On strong clinical suspicion of congenital erythropoietic porphyria her porphyrin levels were requested which were diagnostic of CEP (Table 1). Her DNA sample was sent abroad for detection of mutations associated with porphyria by Next Generation Sequencing (NGS). The NGS panel included screening for mutations in ALAD, ALAS2, CPOX, FECH, GATA1, HMBS, PPOX, UROD and UROS genes. However, no mutation could be identified. The proband had no family history of similar disorder.

Considering the ongoing hemolysis and marked photosensitivity, she was planned for allogeneic Hematopoietic Stem Cell Transplant (HSCT). She had a 6 year old HLA matched brother who was normal on physical examination and did not have elevated porphyrin levels on biochemical profile. She was given myeloablative conditioning for HSCT using busulphan (IV 12.8 mg/kg), cyclophosphamide (200 mg/kg). Graft *Versus* Host Disease (GVHD) prophylaxis was done using methotrexate on day +1, day +3 and day +6 and cyclosporine with target trough levels between 200-250 ng/ml. She achieved neutrophil engraftment on day +14 and on day +19 her urine colour started to normalize. Her post-transplant course was uneventful. Cyclosporine tapering was started at 6 month and ultimately stopped at 9 months post-transplant. Currently she is more than 1-year post transplant; her total plasma porphyrins were repeated and they were 1.0 µg/dL (reference 0.1-1.0 µg/dL). Her symptoms including photosensitivity, reddish discolouration of urine and haemolytic anemia have all settled.

Discussion

Porphyrias are a group of inherited disorders involving enzymes implicated in heme synthesis pathway. The defective or absent activity of these enzymes results in accumulation of pathogenic intermediary compounds in different body tissues which are also excreted in urine and feces. This results in a variety of signs and symptoms like hemolysis, photosensitivity, scarring of skin and neurological manifestations. Porphyrias can be broadly divided into two subgroups; Hepatic Porphyrias and Erythropoietic Porphyrias [6,7]. Congenital Erythropoietic Porphyria (Günthers disease) is a type of Erythropoietic Porphyria resulting from either biallelic UROS pathogenic variants inherited in an autosomal recessive manner (~98%) or by a GATA1 pathogenic variant inherited in

Citation: Iftikhar R, Shamshad UG, Akram Z, Ghafoor T, Satti MT, Chaudhry QN, et al. Congenital Erythropoietic Porphyria: Complete Resolution of Symptoms Following Allogeneic Stem Cell Transplant. Ann Hematol Oncol. 2019; 6(5): 1246.

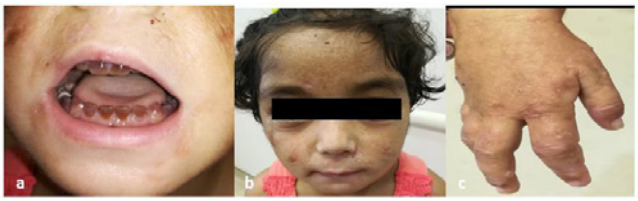

Figure 1: (a): Erythrodontia. (b,c): Hypertrichosis and scarring.

Table 1: Biochemical testing for porphyria.

Ser No	Test	Result (µg/dL)	Reference (µg/dL)
1	Total plasma porphyrins	46.2	0-1
2	Urinary porphyrins		
	Coproporphyrin (CP I) levels	>1472	0-15
	Coproporphyrin (CP III) levels	55	0-49
	Hepatocarboxyl (7-CP)	17	0-2
	Hexacarboxyl (6-CP)	29	0-1
	Uroporphyrins (UP)	1060	0-20
	24 hour Urinary PBG	4	<11

X-linked manner (~1%) [8]. Both of these lead to markedly reduced activity of uroporphyrinogen III synthase [9]. It was first described in 1874 by Shultz in a 33 year old male presenting with cutaneous photosensitivity, hemolytic anemia, splenomegaly and reddish urine [10]. In 1911, Günther first recognized it as inborn error of metabolism and named it "hematoporphyria congenital" [7].

CEP is an extremely rare disorder with only 200 cases reported so far [11]. It occurs with equal frequency in males and females. The age of onset is from birth to 5th or 6th decade. Clinical manifestations occur as a result of deposition of lipid soluble uroporphyrin I, a photosensitizing compound. In skin this leads to phototoxic reactions and increased collagenase production resulting in second- or third-degree burns that ultimately form vesicles and bullae [12]. Yet, the severity of symptoms is highly variable in patients ranging from mild photosensitivity to severe hemolytic anemia, photomutilation of nose, ears and eyelids and non-immune hydrops fetalis [11]. Conventionally, the treatment of CEP has been nonspecific; involving avoidance of sunlight to prevent the skin lesions and splenectomy or regular transfusions for the hemolytic anemia. However, the only curative treatment option for CEP is HSCT [13,14]. As the manifestations of CEP are highly variable, only severely affected patients should be considered for transplantation due to the morbidity and mortality associated with BMT.

Our search of English literature revealed approximately 10 patients who have been transplanted for CEP until now. The first documented use of SCT for CEP was published by Kauffman et al in 1991 [15]. Their patient, a 10-year-old girl fully engrafted, but later on died of CMV pneumonitis 11 months post BMT. Even if the donor is a heterozygote, it leads to complete resolution of symptoms. One such case was reported by Thomas et al in a 22-month-old girl with CEP who became completely asymptomatic 1 year after her HSCT [16]. Her donor was a heterozygote with 50% enzyme activity, a level she attained after transplant. This patient however required a second bone marrow infusion from the same donor at 8 months post-transplant when she started to develop graft failure.

The longest follow up of a CEP patient post-transplant was reported by Faraci et al in a 12-year-old adolescent who underwent HSCT from an unrelated donor. He was followed up for 84 months and his cutaneous lesions had improved significantly [17]. Similarly Tezcan et al describe a follow up of 3 years in their patient [18]. In a case reported by Singh et al, a 14-year post pubertal boy with CEP underwent allogeneic HSCT from a sibling donor that resulted in marked reduction in photosensitivity, absence of blistering and decreased redness of urine [19]. It has been 12 months post HSCT in our patient with complete resolution of her symptoms and she is now able to play with her siblings outside in the sun. This patient had negative result of NGS for the main porphyria genes despite clear clinical signs and elevated urophorphrin I and corproporphyrin I levels indicating CEP. One of the possible explanations could be that sequence analysis methods can only detect 90% of the variants in UROS gene [7]. In patients were diagnosis is in doubt and cannot be established by customized molecular gene panels, analysis of URO-synthase activity in erythrocytes or more comprehensive genomic testing like exome sequencing can be done. However, due to limited funds available and clear clinical and biochemical profile these were not requested.

The long-term effectiveness of HSCT in CEP needs to be followed along with the results of matched unrelated donor HSCT and stored cord blood in CEP [20]. Till such time gene therapy is developed HSCT remains the only curative option for CEP patients with severe disease.

References

1. Romeo G, Levin E. Uroporphyrinogen III cosynthase in human congenital erythropoietic porphyria. Proc Natl Acad Sci USA. 1969; 63: 856.
2. Rimoin DL, Connor JM, Pyeritz REMc Govern MM, Anderson KE, Astrin KH, Desnick RJ, et al. Inherited porphyrias PERIOD! Emery and Rimoin's Principles and Practice of Medical Genetics, vol. 2. ed 3. Churchill-Livingstone; New York, NY; 1996. 2009.
3. Scriver CS, Beaudet AL, Sly WS, Valle DKappas A, Sassa S, Galbraith RA, et al. The porphyrias PERIOD! The Metabolic and Molecular Bases of Inherited Disease. ed 7. McGraw-Hill; New York, NY; 1995; 2103.
4. Tezcan I, Xu W, Gurgey A, Tuncer M, Cetin M, Öner C, et al. Congenital erythropoietic porphyria successfully treated by allogeneic bone marrow transplantation. Blood. 1998; 92: 4053-4058.
5. Lagarde C, Hamel-Teillac D, De YP, Blanche S, Thomas C, Fischer A, et al. Allogeneic bone marrow transplantation in congenital erythropoietic porphyria. Gunther's disease. In Annales de dermatologie et de venereology. 1998; 125: 114-117.
6. Camaschella C, Hoffbrand AV, Hershko C. Iron metabolism, iron deficiency and disorders of haem synthesis. Postgraduate Haematology. 2015; 14: 21-39.
7. Norman RA. Past and future: porphyria and porphyrins. Skinmed: Dermatology for the Clinician. 2005; 4: 287-292.
8. Erwin A, Balwani M, Desnick RJ. Of the NIH-Sponsored PC, Network RD. Congenital erythropoietic porphyria.
9. Blouin JM, Bernardo-Seisdedos G, Sasso E, Esteve J, Ged C, Lalanne M, et al. Missense UROS mutations causing congenital erythropoietic porphyria reduce UROS homeostasis that can be rescued by proteasome inhibition. Human molecular genetics. 2017; 26: 1565-1576.
10. Deybach JC, Phung N, Nordmann Y, Puissant A, Boffety B. Congenital erythropoietic porphyria (Günther's disease): enzymatic studies on two cases

of late onset. The Journal of laboratory and clinical medicine. 1981; 97: 551-558.

11. Katugampola RP, Badminton MN, Finlay AY, Whatley S, Woolf J, Mason N, et al. Congenital erythropoietic porphyria: a single-observer clinical study of 29 cases. British Journal of Dermatology. 2012; 167: 901-913.

12. Shaw PH, Mancini AJ, McConnell JP, Brown D, Kletzel M. Treatment of congenital erythropoietic porphyria in children by allogeneic stem cell transplantation: a case report and review of the literature. Bone marrow transplantation. 2001; 27: 101.

13. Badminton MN, Elder GH. Management of acute and cutaneous porphyrias. International journal of clinical practice. 2002; 56: 272-278.

14. Taibjee SM, Stevenson OE, Abdullah A, Tan CY, Darbyshire P, Moss C, et al. Allogeneic bone marrow transplantation in a 7-year-old girl with congenital erythropoietic porphyria: a treatment dilemma. British Journal of Dermatology. 2007; 156: 567-571.

15. Kauffman L, Evans DI, Stevens RF, Weinkove C. Bone-marrow transplantation for congenital erythropoietic porphyria. The Lancet. 1991; 337: 1510-1511.

16. Thomas C, Ged C, Nordmann Y, de Verneuil H, Pellier I, Fischer A, et al. Correction of congenital erythropoietic porphyria by bone marrow transplantation. The Journal of pediatrics. 1996; 129: 453-456.

17. Faraci M, Morreale G, Boeri E, Lanino E, Dallorso S, et al. Unrelated HSCT in an adolescent affected by congenital erythropoietic porphyria. Pediatric transplantation. 2008; 12: 117-120.

18. Tezcan I, Xu W, Gurgey A, Tuncer M, Cetin M, Öner C, et al. Congenital erythropoietic porphyria successfully treated by allogeneic bone marrow transplantation. Blood. 1998; 92: 4053-4058.

19. Singh S, Khanna N, Kumar L. Bone marrow transplantation improves symptoms of congenital erythropoietic porphyria even when done post puberty. Indian Journal of Dermatology, Venereology, and Leprology. 2012; 78: 108.

20. Zix-Kieffer I, Langer B, Eyer D, Acar G, Racadot E, Schlaeder G, et al. Successful cord blood stem cell transplantation for congenital erythropoietic porphyria (Gunther's disease). Bone marrow transplantation. 1996; 18: 217-220.

Ann Hematol Oncol - Volume 6 Issue 5 - 2019
ISSN : 2375-7965 | www.austinpublishinggroup.com

Citation: Iftikhar R, Shamshad UG, Akram Z, Ghafoor T, Satti MT, Chaudhry QN, et al. Congenital Erythropoietic Porphyria: Complete Resolution of Symptoms Following Allogeneic Stem Cell Transplant. Ann Hematol Oncol. 2019; 6(5): 1246.