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Letter to the Editor

Successful hematopoietic stem cell transplantation in a child with congenital erythropoietic porphyria due to a mutation in GATA-1

To the editor,

Congenital erythropoietic porphyria (CEP) is a rare genetic disease that is characterized by a severe cutaneous photosensitivity causing unrecoverable deformities, chronic hemolytic anemia requiring blood transfusion program, and fatal systemic complications (1). Most cases are autosomal recessive and caused by mutations in UROS gene (2). GATA-1, which is well known for its role in transient myeloproliferative disease and acute megakaryoblastic leukemia associated with Down syndrome, is also a regulator of UROS gene (3). CEP caused by mutation in *GATA-1* gene is inherited in an X-linked manner (3). Pierro et al. have described two patients suffering from CEP due to a mutation in GATA-1 gene (4). Here, we describe the hematopoietic stem cell transplantation (HSCT) course in the five-yr-old Turkish boy mentioned in that manuscript who was transplanted from his HLA identical healthy brother. Informed consent was taken from the family before HSCT.

Pretransplant physical examination revealed multiple scars on his face and hands, mild hypertrichosis, brown discoloration of the teeth, and splenomegaly (Fig. 1a,b). His hemoglobin was 8.5 g/dL, leukocyte count 6100/mm^3, platelet count 61 000/mm^3, and ferritin 101 ng/dL. Conditioning regimen consisted of iv busulphan (Bu) 3.2 mg/kg/day for four days and cyclophosphamide (Cy) 50 mg/kg/day for four days. Cyclosporin A (CsA) and short-term methotrexate were administered for graft-versus-host disease (GvHD) prophylaxis. Low molecular weight heparin and ursodeoxycholic acid were administered for the prophylaxis of veno-occlusive disease. He received 5.6×10^8/kg nucleated bone marrow cells and 7.0×10^6/kg CD34 (+) stem cells. On day 0, he developed febrile neutropenia and was treated with empirical antibiotics of piperacillin/tazobactam and amikacin. On day +3, he developed watery diarrhea of 500 cc/day with occult blood positivity on stool. On day +6, the diarrhea persisted and methylprednisolone treatment at a dosage of 2 mg/kg/day was started for possible hyperacute gastrointestinal GvHD. Later on, the analysis of stool showed positivity for rotavirus antigen and he was also treated with oral immunoglobulin. On day +17, the diarrhea resolved and methylprednisolone was slowly tapered. Neutrophil engraftment was achieved on day +21. On day +31, watery and bloody diarrhea started again. Colonoscopic examination was compatible with pancolitis and histopathology revealed acute GvHD. The serology and PCR of Epstein–Barr virus (EBV) and cytomegalovirus (CMV) were all negative in blood and biopsy samples. He was treated with methylprednisolone, octreotide, and budesonide. On day +37, mesenchymal stem cells (1×10^6/kg) were administered intravenously. Platelet engraftment was achieved on day +38 and diarrhea resolved on day +42. He had a generalized tonic clonic seizure and hallucinations on day +58. Cranial MRI was compatible with posterior reversible encephalopathy syndrome (PRES). Plasma level of CsA at onset of PRES was in therapeutical range. His blood pressure was mildly elevated. He had neither metabolic disturbances nor electrolyte imbalance at onset of PRES. He did not show any sign of infections or autoimmune diseases. After ruling out other causes, PRES was attributed to CsA toxicity. Seizures were treated with phenytoin and levetiracetam, and blood pressure was also regulated. CsA was discontinued and replaced with tacrolimus and mycophenolate mofetil (MMF) after PRES. Hallucinations and seizures resolved within one wk. He was discharged from hospital on day +79. Methylprednisolone was discontinued

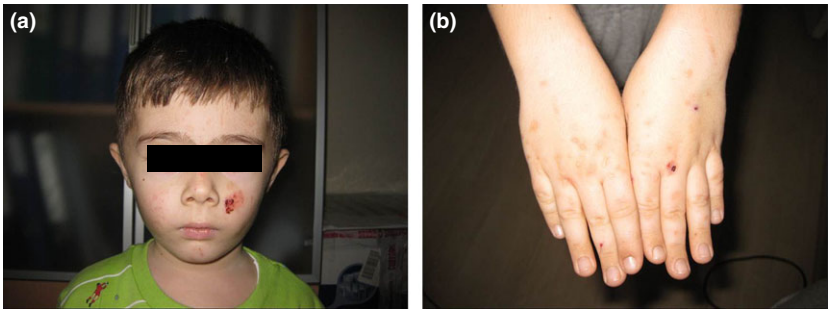


Fig. 1. (a) The scars on patient's face before hematopoietic stem cell transplantation (HSCT). (b) The scars on patient's hands before HSCT.

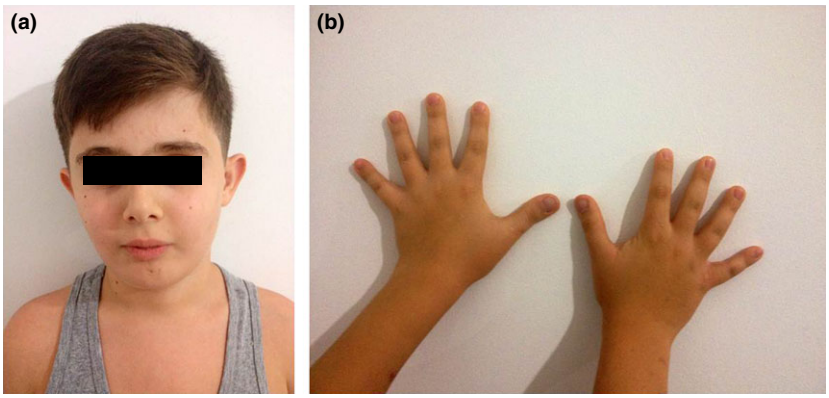


Fig. 2. (a) The disappearance of scars on patient's face after hematopoietic stem cell transplantation (HSCT). (b) The disappearance of scars on patient's hands after HSCT.

Table 1. The patient's hemoglobin, platelet values, porphyria analysis, and chimerism results before and after hematopoietic stem cell transplantation (HSCT)

	Before HSCT	+1st month	+3rd month	+6th month	+9th month	+12th month	+2nd	+3rd
Hb (g/dL)	8.5	11.3	13.1	10.4	12.5	12.8	12.3	12.6
Plt (/mm^3)	61.000	27.000	50.000	166.000	135.000	140.000	145.000	150.000
Chimerism (% donor)	–	85	85	75	68	62	58	–
Total urinary porphyrin* (nmol/mmol of creatinine)	5414	20	171	–	–	–	19	–
Uroporhyrin I, %	52	25	91	–	–	–	63	–
Plasma total porhyrin** (nmol/L)	312	–	29	–	–	–	9.7	–

*normal: <35; **normal: <10.

on day +150, and MMF, on day +180. Currently, the patient is at post-HSCT +43 month with good clinical condition and no sign of the primary disease or any complication of HSCT. His scars resolved and uroporphyrin levels have been maintained within normal limits (Fig. 2a,b). Lansky performance score was 80% before HSCT and it was 100% after HSCT. He had relatively stable mixed chimerism for more than three yr and did not need any transfusions (Table 1).

Up to date only one patient was reported to be CEP with GATA-1 mutation and treated with HSCT (5). This report documents the clinical and biochemical effectiveness of HSCT in a five-yr-old child with a severe clinical picture of CEP due to GATA-1 mutation. GATA-1-related CEP seems to be a tranplantable disease, even in more advanced cases. The frequently used conditioning regimen of Bu/Cy and GvHD prophylaxis of CsA/Mtx seems to be effective. The phenotype of the patient did not just arrested but also reversed after HSCT. In spite of the slowly decreasing donor chimerism, the patient's clinical condition has remained well for more than three yr, indicating that mixed chimerism is sufficient for transfusion independency in CEP. Due to the favorable clinical response and improvement of

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the laboratory results, donor lymphocyte infusion was not considered for mixed chimerism.

Authors' contributions

Neslihan Karakurt: Participated in the study conception and design, and analyzed and interpreted the data; Betul Tavil, Fatih Azik, Zeynep Karakas, and Bahattin Tunc: Participated in data collection; Betul Tavil and Duygu Uckan-Cetinkaya: Participated in the critical revision of the data.

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