

Successful umbilical cord blood stem cell transplantation in a child with WHIM syndrome

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To the Editor:

WHIM (*warts-hypogammaglobulinemia-infections-myelokathexis*) syndrome is an autosomal dominant primary immunodeficiency disorder caused by mutation of the CXC chemokine receptor 4 (CXCR4) gene (1, 2). Affected patients suffer from recurrent infections of the respiratory tract and soft tissues, and marked susceptibility to warts caused by human papilloma viruses from the second decade of life (3, 4). Granulocyte-macrophage colony stimulating factor (G-CSF) has been used to increase and maintain an adequate number of circulating neutrophils, and administration of intravenous immunoglobulin (IVIG) concentrates may help to decrease the number of infectious episodes caused by extracellular pathogens (5, 6). Nevertheless, the optimal therapy of patients with WHIM has not been clearly defined and patients continue to develop infections despite combination therapy with G-CSF and IVIG. None of the patients reported before has received hematopoietic stem cell transplantation (HSCT). We describe here a successful allogeneic HSCT in a girl with WHIM syndrome caused by c.1013G>C sequence variant in the CXCR4 gene.

Clinical and genetic details of this girl were described in the Journal before (2). IVIG infusions and varying doses of G-CSF were started at 6 and half years of age (2). She showed clinical improvement in the beginning but continued to develop respiratory infections leading to chronic obstructive pulmonary disease afterwards. At age 8 she was treated for a prolonged episode of dental periostitis complicated with purulent lymphadenitis. We counseled the family on the possibility of HSCT and umbilical cord blood (UCB) transplantation and the mother decided to become pregnant. She presented with a new pregnancy and at 11 weeks of gestation prenatal genetic testing revealed wild type CXCR4 sequences and HLA genotyping showed matching between the patient and the fetus (Fig. 1). Informed consent was obtained from the parents and the UCB transplantation was approved by the Hungarian National Transplant Committee. Umbilical cord blood stem cells were collected by standard methods

(7). Pretransplant conditioning regimen consisted of intravenous busulphan and cyclophosphamide, followed by a course of rabbit anti-thymocyte globulin. An UCB graft containing 1.2×10^5 CD34⁺ cells/kg and 3.8×10^7 nucleated cells/kg was infused without any adverse effects. Graft versus host disease (GvHD) prophylaxis consisted of methyl-prednisolone and cyclosporin A. A flare up of chronic obstructive bronchitis was observed, and on day +49 she developed pneumonia caused by *Str. pneumoniae*. Meropenem therapy and bronchodilator drugs resolved this lung infection. No signs or symptoms of acute or chronic GvHD were observed. An absolute neutrophil count of $>500/\text{mm}^3$ was achieved on post-transplant day 32, and platelet transfusion independence was achieved on day 48. Reconstitution of the humoral immune system was also robust with normal-for-age serum IgG, IgM, and IgA levels by 100 days after HSCT.

Interphase chromosome analysis and serial variable number of tetra- and pentanucleotide repeats examinations were used to confirm donor cell engraftment. The first chimerism studies at day +55 post-transplant revealed 12% persisting recipient cells, but subsequent serial chimeric analyses demonstrated almost full donor chimerism with less than 5% recipient cells. During follow-up the patient's peripheral blood counts and serum immunoglobulin concentrations have normalized without any cytokine or IVIG support. One year after transplant the patient has near normal hematologic and immunologic parameters. She attends school and takes no medication, and is free of infections or post-transplant complications. Importantly, chronic lung disease was resolved and she is not taking bronchodilator agents.

In children with WHIM syndrome the diagnosis and supportive treatment with IVIG and/or G-CSF may be delayed and severe morbidity or premature death among young individuals have been reported. Fatal outcomes due to septicemia and fulminant Epstein-Barr virus positive intestinal B cell lymphoma have been described (8). Furthermore warts are

generally therapy-resistant requiring repeated laser ablation for management. In addition, the long-term use of supportive therapy can cause significant lifestyle restrictions and poor quality of life and entails significant costs for health care budget as well. Thus, there is a rationale for allogeneic hematopoietic stem cell transplantation as a curative treatment option in patients with WHIM syndrome.

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Figure 1. (A) Clinical phenotype of the patient with WHIM syndrome and her relatives. Half-filled circle, the female patient with WHIM; interrupted square, male fetus. (B) Automated sequencing profile of genomic DNA showing heterozygous c.1013C>G mutation in exon 2 of the *CXCR4* gene in the patient and wild type sequences in her parents and the male fetus. Mutation position is encircled. In hemizygous patients the c.1013C>G sequence variant is predicted to result in p.S338X truncation mutation of the chemokine receptor CXCR4. m, mutant; wt. wild type.

Figure 1

