

Correspondence

A new case of IPEX receiving bone marrow transplantation

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At 4 months old, a male infant was admitted to hospital because of intractable secretory diarrhea and repeated episodes of sepsis. At admission, the child appeared malnourished (body weight 4180 g, <3rd percentile) and with a widespread exfoliative ichthyosiform dermatitis. Duodenal biopsy showed villous atrophy and flattened mucosa. Serum IgG, IgA, IgM were normal, but IgE were elevated (763 kU/ml). A high titer (1:320) of anti-nuclear antibodies, and antibodies against insulin, glutamic acid decarboxylase (GAD-65) and enterocytes were found, leading to the hypothesis of immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome.¹ Genetic analysis of *Foxp3*, the causative gene of IPEX,^{2,3} did not show any mutation in the coding region of the gene, but markedly reduced levels of *Foxp3* mRNA (as low as 32% of control subjects) were demonstrated by real-time PCR. A mutation (deletion) in the promoter region, as shown by PCR amplification, was identified about 6600 bp upstream from the start codon, suggesting that this mutation might account for the defective *Foxp3* mRNA expression. IPEX is an X-linked disorder characterized by multiple autoimmune manifestations, including various combinations of severe enteropathy, type I diabetes mellitus, hypothyroidism, eczema and development of autoantibodies with onset in early infancy.³ Immunosuppressive treatment may attenuate or delay the clinical course, but continuous administration of corticosteroids and/or cyclosporine often leads to drug toxicities.³ Although partial engraftment after bone marrow transplantation (BMT) in the *scurfy* mouse, that is the equivalent of human IPEX, is sufficient to rescue the animals and to prevent fatal outcome,⁴ prior attempts at BMT in three children affected by IPEX were ultimately not successful.^{2,5}

In our patient, clinical remission and disappearance of autoantibodies were obtained by immunosuppressive treatment with high doses of corticosteroids (10 mg/kg of methylprednisolone per day for 2 days followed by 2 mg/kg of methylprednisolone per day and oral cyclosporine A at 5 mg/kg per day). At 2 months after discharge, upon reduction of corticosteroids dosage, the patient presented again with growth failure, eczema and diarrhea. Therefore, at 1 year of age, he was considered for BMT from his healthy, 4 years old, HLA-identical sister. The conditioning regimen consisted of intravenous fludarabine (30 mg/m²/day), from day -13 to day -10, oral busulphan (5 mg/kg/day from day -9 to day -6), intravenous cyclophosphamide (50 mg/kg/day from day -5 to day -2) and anti-T-lymphocyte globulin (2.5 mg/kg/day from day -5 to day

-4). A total of 7.85×10^6 CD34+ cells/kg, including 50×10^6 CD3+ cells/kg were infused.

Complete engraftment of both mononuclear and polymorphonuclear cells was demonstrated at day +18. Cutaneous and gastrointestinal GVHD (II grade) was successfully treated with corticosteroids. At 1 month after BMT the child was discharged, and after three additional months immunosuppressive therapy was suspended. At 16 months after BMT he resumed normal feeding without cow's milk proteins and eggs, displayed optimal weight and length with normal hematological function. Stable donor mixed chimerism was found at 3, 5 and 12 months after transplantation in T-lymphocytes, B-lymphocytes and polymorphonuclear cells. Quantization of relative proportion between donor and autologous cells in the various cell lineages has shown that T, B and PMN cells were respectively 70, 30 and 50% of donor origin. *Foxp3* mRNA expression, as assessed by real-time PCR, was above levels detected in normal subjects, the *in vitro* T-lymphocyte stimulation was within normal range at 4 months after transplantation and the serum IgG, IgA and IgM concentrations were within normal range at 6 months after transplantation. Serum IgE level has decreased although they are still elevated (242 kU/l) and skin testing with allergen extracts is positive for cow's milk proteins and eggs, whereas autoantibodies are undetectable.

Our study suggests that partial chimerism is sufficient to obtain a complete rescue of IPEX, as hypothesized on the basis of the observations made in *scurfy* mice,⁴ thus confirming that *Foxp3* expressing cells have a dominant regulatory activity on effector cells.^{2,3} Moreover, complete clinical and immunological remission at 16 months after BMT in a IPEX child indicates that this is indeed an effective form of treatment for this otherwise fatal disease, drawing attention to the use of BMT as novel treatment of immune-mediated disorders associated to secretory diarrhea.

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