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Outcome of hematopoietic stem cell transplantation in hyper-IgM syndrome caused by CD40 deficiency

To the Editor:

We reported in *The Journal of Pediatrics* the case of an infant with severe respiratory infections, chronic diarrhea, failure to thrive, and disseminated *Cryptosporidium parvum* infection. Laboratory investigations had disclosed the diagnosis of hyper-IgM syndrome caused by CD40 deficiency (hyper-IgM syndrome type 3 [HIGM3]). She was the fourth case reported in literature.

In this letter, we report her outcome, because she was the first case with HIGM3 who received a hematopoietic stem cell transplantation (HSCT). The first three cases of HIGM3 had lower respiratory tract infections, but regular administration of intravenous immunoglobulins, and prophylactic administration of trimethoprim-sulfamethoxazole prevented them from severe infections and they did not need HSCT.[1]

Before receiving matched-sibling stem cell transplantation, our patient showed growth failure, chronic lung disease with bronchiectasis, and respiratory distress (that required tracheostomy), tracheal colonization by *Pseudomonas aeruginosa*, hepatomegaly, and sclerosing cholangitis associated with *Cryptosporidium parvum* infection.

The patient's 11-year-old human leukocyte antigen-matched brother served as the donor for HSCT. Peripheral blood stem cells (PBSC) were mobilized with granulocyte colony-stimulating factor (G-CSF), that was administered subcutaneously to the donor at the dosage of 5 μg/kg for 5 consecutive days. PBSC were then collected by leukopheresis on the fifth day of G-CSF administration. The patient received a nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m^2×5 (days −7 to −3), melphelan 100 mg/m^2 (day −2) and antithymocyte globulin 2.5 mg/kg×5 (day −6 to 2), followed by the infusion of PBSC, containing 14.6×10^8/kg mononuclear cells and 17.5×10^6/kg CD34 (+) cells. Standard-dose cyclosporin A was used for prophylaxis of graft-versus-host disease. Subcutaneous low-molecular-weight heparin (100 U/kg/day) was used for prophylaxis of veno-occlusive disease (day −6 to +12). G-CSF (10 μg/kg/day) was started on day +7 until engraftment.

Intravenous immunoglobulin 0.5 g/kg per week, and prophylactic co-trimoxazole, ceftazidime, acyclovir, and fluconazole were used to prevent infections. In addition, the patient received paromomycin (30 mg/kg/day orally), azithromycin (10 mg/kg/day orally), and nitozoxamide (200 mg/day orally) with the aim of preventing disseminated *Cryptosporidium parvum* infection. Inhaled tobramycin (3 mg/kg/day) was also used because of intratracheal *Pseudomonas* colonization.

The posttransplant course was complicated by high fever of undefined origin on day +5, which responded to broad-spectrum antibiotics and amphotericin B. Neutrophil engraftment (>1×10^9/L) was achieved on day +10. However, at day +15, the patient developed severe pulmonary infection and respiratory distress, leading to hypoxia and generalized seizures. She died at day +16, after cardiorespiratory arrest. Molecular investigations with highly polymorphic DNA markers failed to reveal engraftment of donor-derived lymphocytes.

Bone marrow transplantation has been proposed and successfully used in HIGM1 (CD40 ligand deficiency), because of the severity of long-term outcome.[2] However, optimal treatment of HIGM3 is debated, because the potential benefit of such approach in HIGM3 is less obvious, because it would not correct lack of CD40 expression by endothelial and epithelial cells, which may play a role in the decreased resistance to opportunistic intracellular pathogens in HIGM3.[3,4] Although assessment of the efficacy of HSCT in HIGM3 will require broader experience, our case supports the observation in HIGM1 that the presence of *Cryptosporidium* infection and chronic lung disease represent high-risk factors.

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