

Successful bone marrow transplantation in an 8-month-old patient with chronic granulomatous disease

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SUMMARY: Kansoy S, Kütükçüler N, Aksoylar S, Aksu G, Kantar M, Çetingül N. Successful bone marrow transplantation in an 8-month-old patient with chronic granulomatous disease. Turk J Pediatr 2006; 48: 253-255.

An eight-month-old boy with chronic granulomatous disease (CGD) received HLA identical sibling bone marrow transplantation (BMT) following busulphan and cyclophosphamide conditioning. No graft-versus-host disease was demonstrated. Five years after transplantation, mixed chimerism was 60% in peripheral blood, and 85% of his neutrophils had normal oxidative burst activity. He is now six years old, in very good health and growing well. In this period, he experienced no severe infectious diseases. To our knowledge, this is the first case of CGD who had BMT in Turkey. His successful outcome illustrates that BMT in a patient with CGD in the first years of life should be considered early if an HLA-matched donor is already available, before development of any recurrent life-threatening infections or irreversible organ damage.

Key words: chronic granulomatous disease, bone marrow transplantation, treatment.

Chronic granulomatous disease (CGD) is an inherited disorder characterized by defective intracellular killing of ingested micro-organisms by polymorphonuclear cells (PMN) and monocytes. Recurrent bacterial and fungal infections causing diarrhea, growth failure and inflammatory lung damage have been frequently observed¹. The other most frequent abnormalities consist of marked lymphadenopathy, chronic infected ulcerations, hepatosplenomegaly, osteomyelitis, pneumonia, and liver and perianal abscess¹. One of the four NADPH oxidase subunits is mutated in the disease and the cells are unable to form superoxide ions. The most widely available tests for diagnosis are the quantitative nitroblue tetrazolium (NBT) test, chemiluminescence assays and the evaluation of oxidase activity of PMN by dihydrorhodamine-123 (DHR-123) flow cytometric burst analysis¹.

The prognosis of CGD patients has improved substantially in the last few decades due to lifelong antibiotic prophylaxis, prompt and aggressive treatment of established infections, interferon- γ treatment and increasing numbers

of experienced immunology centers²⁻⁶. Bone marrow transplantation (BMT) using a genoidentical donor is a safe procedure for CGD, if performed early in the first year of life, before chronic infections and irreversible organ damage have occurred⁷⁻¹¹. If no HLA-genoidentical donor is available, conventional treatment should be preferred while awaiting improvements in transplantation techniques or somatic gene therapy⁷⁻¹⁴.

To our knowledge, among at least 25 CGD patients who underwent BMT, only two of them have been younger than 12 months of age¹⁰. Here we present an eight-month-old male child with a severe form of CGD who received BMT from his HLA-matched sister. He was the first transplanted case with CGD in Turkey and his follow-up has been excellent.

Case Report

An eight-month-old boy of unrelated parents was admitted to hospital with recurrent severe pulmonary infections (3 times) since two months of age. He had a four-year-old healthy

sister and no history of infant death in the family. On physical examination, malnutrition (body weight under 3rd percentile, height 50th percentile) was observed. He had respiratory distress accompanied by suppurative otitis and cervical lymphadenitis. Complete blood count revealed leukocytosis (WBC 147,00/mm³ with 64% band forms) with moderate anemia (9.5 g/dl). Abdominal ultrasonography, and liver and renal biochemical tests were normal. X-ray films of the chest showed bilateral interstitial infiltrates of bronchopneumonia. *Candida albicans* was isolated from his tracheal aspirate and urine cultures. Total neutrophil and lymphocyte counts, peripheral blood lymphocyte phenotyping by flow cytometer and serum immunoglobulin levels were normal. However, only 6% of neutrophil leukocytes showed normal oxidative burst activity by DHR-123 flow cytometric burst analysis (Bursttest, Orpegen Pharma, Germany) (more than 80% of neutrophils show phagoburst activity in healthy children). Thus, he was diagnosed as having CGD.

After antibiotic and anti-fungal therapy and disappearance of pulmonary symptoms, the patient received a BMT from his healthy four-year-old HLA-compatible sister. At the time of BMT, he was free of infection. No granulomatous lesion was detected with computerized abdominal and chest tomography. Cardiac evaluation using ECG and echocardiography was normal.

Preconditioning therapy consisted of busulphan (12 mg/kg) and cyclophosphamide (120 mg/kg). A total of 3.9×10^8 cells were infused on day 0. Standard-dose cyclosporin A was used for prophylaxis of graft-versus-host disease (GVHD). Granulocyte-macrophage colony-stimulating factor (GM-CSF) (10 µg/kg/day) was commenced on day +7 until engraftment. He was also given acyclovir, fluconazole, cotrimoxazole and intravenous immunoglobulin for infection prophylaxis. His post-transplant course was complicated by a high fever on day +8 and *Klebsiella pneumoniae* and coagulase negative *Staphylococcus* were demonstrated in his urine and blood cultures, respectively. The patient responded to broad-spectrum antibiotics. Neutrophil engraftment ($>1 \times 10^9/L$) occurred on day +18 and the platelet count increased to $50 \times 10^9/L$ on day +20. No GVHD was observed throughout the post-BMT period. Oxidative burst activities

by flow cytometry were 61%, 71% and 85% at 2, 5 and 24 months of the post-transplant period, respectively. Mixed chimerism in peripheral blood was 50% after five years of transplantation. During the 60 months of follow-up, the patient has had no severe infectious diseases. In addition, normal growth parameters were attained at four years of age.

Discussion

Clinical signs and symptoms of CGD may occur from early infancy to young adulthood. The disease transmission is X-linked in 60 to 70% of patients and autosomal recessive in the other cases. Patients with X-linked CGD have an earlier disease onset and poorer prognosis. The long-term survival of patients developing symptoms in the first year of life is significantly worse than that of patients whose illness started after infancy⁵. Our patient belonged to the high-risk group as he presented early with serious pulmonary infections. His age at diagnosis was eight months and the onset of symptoms was two months. The infections reported prior to the diagnosis are bronchopneumonia and lymphadenitis, as often seen in CGD. Although genetic analysis could not be performed, he was diagnosed as X-linked CGD because of his history and clinical findings.

In CGD, patients' leukocytes have absent oxidative burst activity, whereas carriers may have normal or reduced values^{1,2}. Donor's neutrophil leukocytes showed 94% normal oxidative burst activity by flow cytometric burst analysis and there was no need to perform a molecular analysis for the donor examination before BMT. In previous studies, it has been reported that flow cytometric neutrophil oxidative burst analysis is an appropriate diagnostic tool for the examination of the donors of CGD patients before BMT¹⁵.

Slatter et al.¹⁴ performed BMT for 10 CGD patients. The youngest was three years old. Eight patients survived after a median follow-up of 12.5 months. To date, at least 25 CGD patients have undergone BMT, with varying results⁷⁻¹⁴. In these cases, complications occurring after BMT generally correlated with the severity of the basic disease. The patients with recurrent bacterial and fungal infections gradually leading to organ disability had a

worse outcome than patients transplanted early without these complications¹⁰⁻¹³. Among the 13 patients who underwent BMT for CGD between 1973-1998, three patients who were younger than 18 months did not suffer from BMT-related complications such as GVHD¹⁰. Therefore, authors concluded that patients with CGD should preferably be transplanted early, before they develop an irreversible organ damage¹⁰.

In most of the reported patients, the pre-BMT conditioning consisted of myeloablative busulphan and cyclophosphamide, like in our patient^{10,12}. In recent years, non-myeloablative conditioning has been shown to ensure engraftment with reduced conditioning-related morbidity and mortality in patients with CGD^{11,13}.

In conclusion, we believe that BMT should be considered for X-linked CGD treatment when an HLA-compatible sibling is available and when recurrent life-threatening infections are observed. In addition, BMT should be performed in the first years of life before development of an irreversible organ damage.

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