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Two Successful Bone Marrow Transplantations Improved Lung Functions in Patients with Chronic Granulomatous Disease

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ABSTRACT

Chronic Granulomatous Disease (CGD) is a rare inherited primary immune deficiency disorder with defective respiratory burst activity in phagocytes, resulting in recurrent pyogenic infections. In this study, we described two CGD patients who had done bone marrow transplantation (BMT). As Bone marrow transplantation (BMT) is the definitive treatment of the disease, we evaluated the function of their lungs before and after BMT. In both patients, the BMT was from their siblings. In case 1, the patient's pulmonary function (PFT) before BMT was: FEV1: 34, FVC: 40, FEV1 / FVC: 72%, and after BMT was: FEV1: 66, FVC: 40 by 49, FEV1 / FVC: 64%. In case 2, the patient's PFT before BMT was: FEV1: 22, FVC: 36, FEV1 / FVC: 41%, and after BMT was: FEV1: 47, FVC: 33, FEV1/FVC: 43%. BMT significantly improved their Pulmonary Problems and Preclinical (PFT). In addition, after BMT, both patients' well-tolerated clinical signs and the infection rate, and the number of hospitalizations in both patients decreased.

Introduction

Chronic granuloma disease (CGD) was first described in 1954 as a disorder with recurrent infections and hypergammaglobulinemia [1]. CGD is a defect in killing catalase-positive microorganisms due to several mutations in components of an enzyme complex named Phagocyte Oxidase (Po). It is a rare disease with an incidence of 4-5 per 1 million individuals [2, 3] and is associated with recurrent pneumonia, lymphadenitis, hepatic or subcutaneous or other abscesses, and osteomyelitis at multiple sites. Other clinical features include chronic Colitis or enteritis, gastric outlet, or ureteral obstruction from

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granulomas [4, 5]. The attack's rate and severity of the infection are extensively variable. Approximately three-fourths of the patients with CGD are men who have inherited their disorder due to mutations in CYBB Gene, an X-chromosome gene encoding gp91 Po [6].

The most common pathogen is Staphylococcus aureus (S. aureus), although any other catalase-positive microorganisms may also be involved. Other frequent organisms that cause infections include Serratia marcescens, B. cepacia, Aspergillus, Candida albicans, Nocardia, and Salmonella [5]. Aspergillus fumigatus (A. Fumigates) is the most commonly isolated fungus in these patients. Fungal and bacterial respiratory infections often lead to bronchiectasis and reduced lung function [7, 8]. The patients must have an aggressive treatment with antibiotics, antifungal, IFN-gamma, and supportive treatment. As a therapeutic approach, gene therapy was tested on patients with CGD using retroviral vector-based delivery into autologous stem cells [9-11]. However, the treated patients eventually encountered malignant changes, and this kind of therapy was not continued anymore [12, 13]. Recently, the definitive treatment is bone marrow transplantation (BMT) [14]. However, further investigation is needed to elucidate the outcome of BMT in such patients fully. In this report, two patients with CGD are described who underwent BMT. Both patients were under the direct supervision of the fellowship doctor.

Case 1

The patient was diagnosed with infancy CGD. He was infected with recurrent pneumonia before the age of one. He had an abdominal mass at 18 months of age, and surgery was performed on the patient. Smear and mass culture were performed, drainage of secretions was positive for acid-fast bacilli, and he was treated with anti-TB drugs. He had cervical lymphadenitis and a fistula in the skin. Lung biopsy and pulmonary lesions were carried out for the patient. The biopsy result was the formation of non-caseous granulomas. At the last visit to the center for examination, he had a fever of 38°C, hepatomegaly, and splenomegaly. The patient's pulmonary function (PFT) was FEV1: 34, FVC: 40, FEV1 / FVC: 72%.

Moreover, he had proteinuria. The tests were as follows: urine analysis: 3+ proteinuria and CBC diff: WBC: 4300, Neut: 2279, Lym: 980, Mixed Eos and Bas: 1041. Albumin serum: 2.3 gr/lit. BUN and Cr: normal. LFT: Normal. NBT: 0%. Immunoglobulin and flow cytometry levels were normal. He was hospitalized and treated with vancomycin and meropenem, and we consulted with a nephrologist to work up the proteinuria. His proteinuria range was >3 g of protein in 24 hours. A renal biopsy was performed, and its pathology result was amyloidosis. Renal sonography and Doppler sonography were performed, and the findings were normal. His Lung CT showed a fibrotic band and emphysematous changes. He had no features of autoimmunity. He was treated, and his treatment was followed up. About 18 months after his first visit to Masih Daneshvari hospital, he had done a BMT at this hospital at the age of 23. Due to renal diseases, he was treated with Cyclosporine (Sandimmune), cotrimoxazole, Itraconazole, folic acid, and Valsartan. The total daily dosage of Sandimmune was 25 mg/kg for 1 year.

The patient's donor was his HLA identical brother, who received a transplant from a matched male donor. The patient was good after BMT and his latest laboratory results were as follow: CBC, Diff: WBC: 4400, Neut: 50%, Lym: 44%, Mixed Eos and Bas: 6%, HB: 10, MCV: 66, PLT: 333000, NBT: 99%, Urine Analysis: +3 protein, ESR: 15, BUN: 39, and Cr: 1.5. His last PFT (Pulmonary Function Test) result was: FEV1: 66 by BD (bronchodilator) -79, FVC: 40 by B.D49, FEV1 / FVC: 64%, TLC: 91, and RV: 259. His latest renal sonography indicated an Increase in echogenicity of the renal parenchyma and nephrocalcinosis. Abdominal sonography also showed increased size and echogenicity of liver parenchyma, portal hypertension, and splenomegaly. The latest HRCT indicated bilateral scar and bronchiectasis.

Case 2

The patient's hyperactivity airway disease was treated at the age of 4, and after a year, he suffered from dyspnea, coughing and fever. Our diagnosis was pneumonia, and we were treated with antibiotics. He was good until he was 18 years old. In medical history, his brother had CGD. He was not followed until he was 30 years old, and then he was referred to Masih Daneshvari hospital with shortness of breath and coughing. We observed that the patient's oxygen saturation in the emergency room was 90%. A reduction in bilateral lung auscultation noise was observed. His chest X-ray showed hyperinflation, and the lung CT represented a mosaic pattern and hyperinflation.

CBC Diff was normal (WBC: 9000, Neut: 69%, Lym 25%, Mix: 6%. HB: 15.5. mg /dl and PLT 230000), ESR: 2, BUN and Cr: normal, LFT: normal, Urine Analysis: normal, and NBT: 0%. Immunoglobulin and flow cytometry levels were normal. He was hospitalized and treated with cotrimoxazole, itraconazole, azithromycin, and steroid 250 µg. His PFT test was FEV1: 22, FVC: 36, FEV1 / FVC: 41%,

TLC: 123. The test pattern showed severe obstructive disease. The patient's abdomen and pelvis sonography were normal. Serum galactomannan was negative. A bronchoscopy was performed for this patient. His smear and culture were negative for fungus, bacteria, and viruses. The tuberculosis test was negative (PPD and gastric lavage for tuberculosis) due to respiratory problems under treatment of Ciprofloxacin, Amikacin, Prednisolone, Cotrimoxazole, Voriconazole, and Seroflo. The patient was hospitalized several times in Masih Daneshvari Hospital. Our review of the patients for supportive therapy has always been negative during hospitalization, but oral antibiotics treatment made him feel better. He did not show autoimmune features. After two years after the first visit to this hospital, a BMT was performed in Namazi Hospital at 30.

He was treated with Prednisolone Cyclosporine (Sandimmune), Cotrimoxazole, Itraconazole, folic acid, and Inhalation corticosteroid for 6 months. The total daily dosage of Sandimmune was 25 mg/kg for 6 months. The patient's donor was his HLA identical sister, who had received a transplant from a matched related male donor. The patient remained thrombocytopenic after BMT. There was no evidence of graft versus host disease (GVHD). Fourteen months after BMT, his respiratory symptoms decreased, and his PFT showed significant improvement. His latest PFT were as follows: FEV1: 47 by BD (bronchodilator) -117, FVC: 33 by B.D114, FEV1 / FVC: 43%, FEF25-75: 6 by BD 113.NBT: 99%. THE PATIENT'S vitamin D and calcium levels were tested several times during admission, and the initial investigation to find the cause was negative. The patient was treated with calcium tablets and Levothyroxine for post-transplantation hypothyroidism.

Discussion

The CGD is a rare inherited primary immune deficiency disorder with defective respiratory burst activity in phagocytes, resulting in recurrent pyogenic infections. BMT is the definitive treatment of the disease [7]. Prophylactic antimicrobial agents, including Trimethoprim /sulfamethoxazole (TMP/SMX) and Itraconazole, are the main treatments for CGD patients [2, 11, 14]. IFN-gamma reduces the severe infections and duration of hospitalization in these patients [5]. BMT for patients with CGD has begun since 1973. This treatment improves patients' symptoms, especially when there is a severe infection. This treatment has a prominent effect on neutrophil function. Patients with CGD should be transplanted early before any irreversible organ damage occurs [13, 15].

We introduced two CGD patients who had abnormalities in subunits of NADPH oxidase. CGD is transmitted as an X-linked and autosomal recessive disease [1, 4]. Patients with X-linked CGD have an earlier disease onset and the most severe and poorest prognosis [9, 10]. Hence, these patients have to be under more aggressive treatment. Despite the use of antibiotic prophylaxis, our patients belonged to high-risk groups. Young children rarely suffer from BMT-related complications such as GVHD.

Furthermore, IFN-gamma is less effective in older patients with CGD. In our patients, Immune reconstitution, severe opportunistic infections, neutrophil recovery, Colitis, and chronic lung disease long-term complications improved after BMT. The stem cells were obtained from their siblings, and both patients had well-tolerated clinical signs after BMT in both cases. The infection rate and the number of hospitalizations in both patients were decreased. Their pulmonary problems and preclinical PFT were significantly improved.

A major study recently published in the Lancet Medical Journal revealed a successful reduction as a pre-transplant treatment for people undergoing BMT for CGD. However, this therapy was carried out for the high-risk BMT patients, including adolescents and adults with multiple infections, and was not tested using standardized procedures. The results suggested that BMT should be considered even in patients with high-risk CGD if a matched unrelated donor is identified [16]. Some previous studies also showed improved pulmonary function in patients after BMT [17, 18]. In many patients, CGD results in recurrent pulmonary infections and granuloma in the lungs, leading to reduced lung function [19].

In conclusion, we transplanted two adult patients with high risk and observed that not only did the infection rate and the number of hospitalizations in both patients were decreased, but also their pulmonary functions were significantly improved. However, to achieve more accurate results and information about the patients' improvements, these patients did not refer to the hospital despite our demands for follow-up. Altogether, since the number of patients with CGD who underwent BMT is scarce and our knowledge about BMT in these patients is still very superficial; therefore, more studies are necessary to completely elucidate the status of infections, GVHD, and also lung functions.

Ethical Considerations

Compliance with ethical guidelines

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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Conflict of interest

The authors declared no conflict of interest.

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