



ORIGINAL ARTICLE

## Haploidentical stem cell transplantation in a boy with chronic granulomatous disease

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### KEYWORDS

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**Abstract** Chronic granulomatous disease is a primary immunodeficiency caused by mutations in any one of the five components of the NADPH oxidase in phagocytic leucocytes. This causes impaired microbial killing, which leads to severe life-threatening bacterial and fungal infections. Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for chronic granulomatous disease, although gene therapy may provide a new therapeutic option for the treatment of patients with CGD. Haploidentical HSCT provides a potentially curative treatment option for patients who lack a suitably HLA-matched donor, but only a few cases have been reported in the literature. Herein, we report a boy with X-linked chronic granulomatous disease treated successfully by haploidentical HSCT with post-transplant cyclophosphamide using a treosulfan-based conditioning regimen.

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### Introduction

Chronic granulomatous disease (CGD) is an uncommon inherited immunodeficiency, occurring in about one in 250,000 individuals. It is a genetically heterogeneous condition characterized by recurrent, life-threatening bacterial and fungal infections and granuloma formation. CGD is caused by defects in the phagocyte nicotinamide adenine

dinucleotide phosphate (NADPH) oxidase, which constitutes the phagocyte oxidase (phox). CGD results from constitutional inactivating mutations in the *CYBB*, *CYBA*, *NCF1*, *NCF2* or *NCF4* genes that encode subunits of phagocytic NADPH oxidase. X-linked CGD (with mutation of *CYBB* gene encoding the gp91<sup>phox</sup> subunit) is the most frequent form of the disease accounting for 65% of cases. These genetic defects result in the inability of phagocytes (neutrophils, monocytes and macrophages) to destroy certain microbes.

The cornerstones of CGD management are antimicrobial and immunomodulatory prophylaxis, early diagnosis of infections, and aggressive management of infectious complications. Currently, allogeneic hematopoietic stem cell

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transplantation (HSCT) is the only established curative therapy for CGD, although gene therapy may provide a new therapeutic option for the treatment of patients with CGD.

Reports on haploidentical HSCT for CGD are scarce, however, haploidentical HSCT could be an option in some CGD patients for whom HLA-matched related or unrelated donors are not available. We report the case of a pediatric patient who had CGD complicated by severe pulmonary disease and chronic inflammatory bowel disease and was successfully treated by haploidentical HSCT with high-dose post-transplant cyclophosphamide.

## Case report

We report an 11-year-old boy with X-linked CGD who underwent haploidentical HSCT with high-dose post-transplant cyclophosphamide.

He was the younger of two children of non-consanguineous parents. He lived with his uncle and aunt on his father's side who had the legal custody of the patient. There was no family history of immunodeficiency. He was vaccinated with Bacillus Calmette-Guérin (BCG) in infancy, which was complicated by a BCGitis at the injection site on his arm. At 12 months of life, he was admitted with a bronchopneumonia that responded well to antibiotic treatment. At three years old he was diagnosed of pulmonary tuberculosis and he was on anti-tuberculosis treatment.

At seven years old he was admitted to our hospital because of a two-month history of asthenia, failure to thrive, loss of weight and respiratory symptoms, with the initial suspicion of disseminated tuberculosis, which was ruled out after relevant studies, including a lung biopsy that showed necrotizing granulomatous inflammation. The patient had no detectable NADPH-oxidase activity in the dihydrorhodamine (DHR) and the nitroblue tetrazolium (NBT) test. Subsequently, mutation analysis detected a mutation in exon 2 of the *CYBB* gene encoding the gp91<sup>phox</sup> protein in the boy (X-linked disease).

In spite of continued antimicrobial prophylaxis (cotrimoxazole, itraconazole) and immunomodulatory treatment (interferon- $\gamma$ ), the patient developed severe complications including restrictive lung disease, consisting of dyspnea and hypoxemia, diffuse interstitial infiltrates in chest radiographs and a restrictive pattern in pulmonary function tests.

He progressively developed chronic inflammatory bowel disease with intermittent abdominal pain, diarrheic stools, decrease appetite and moderate malnutrition. At nine years old he underwent an esophagogastroduodenoscopy and colonoscopy, which showed pancolitis with gross pathologic features, resembling Crohn's disease. Colonic biopsies showed extensive granulomatous inflammation. Laboratory tests were significant for anemia, hypoalbuminemia, iron deficiency, elevated inflammatory markers and markedly elevated stool calprotectin. Treatment was initiated with prednisone and mesalazine, and a few months later, also with azathioprine as maintenance therapy because he had symptomatic relapse when tapered to low-dose prednisone.

Throughout the following months, he presented a torpid evolution of chronic inflammatory bowel disease and no improvement of pulmonary disease.

At diagnosis, human leukocyte antigen (HLA) typing of the patient, his biological parents, and his sister was performed, and a rare HLA-haplotype was detected in the patient. He did not have a matched sibling donor and a search for an unrelated donor was initiated, although no unrelated matched donor was found either within an appropriate time frame since the diagnosis. Thus, given the torpid clinical evolution, we proposed to perform a haploidentical HSCT. The father was preferred as the haploidentical donor because his biological mother had hepatitis C viral infection.

The patient underwent HSCT with peripheral blood stem cells (PBSC). The conditioning regimen consisted of treosulfan (14 g/m<sup>2</sup> on day -7, -6 and -5) and fludarabine (30 mg/m<sup>2</sup> over five days). In addition, rabbit anti-thymocyte globulin was given at a total dose of 7 mg/kg. He received high doses of cyclophosphamide post-HSCT (50 mg/kg days 3 and 4). Graft versus host disease (GvHD) prophylaxis consisted of tacrolimus and mycophenolate mofetil. Supportive care was given according to the protocol of our center.

The patient received  $10.018 \times 10^8$  kg<sup>-1</sup> of total nucleated cells (CD34+ cells,  $4.007 \times 10^6$  kg<sup>-1</sup>; CD3+ cells,  $2.053 \times 10^8$  kg<sup>-1</sup>). Neutrophil and platelet engraftments were achieved at 17 and 14 days after HSCT, respectively. Febrile neutropenia developed seven days after HSCT and no cytomegalovirus or Epstein-Barr virus infections have been detected at routine check-ups. No granulocyte infusions were performed. His superoxide production normalized two months after transplantation. Chimerism analysis revealed that 0.06% of myeloid cells were recipient cells at 30 days, and chimerism status has been sustained without important fluctuation. The most recent chimerism test was performed nine months after HSCT.

Inflammatory bowel disease was resolved completely after transplantation, although the patient has not yet crossed the percentiles for height and weight. Otherwise, improvement of respiratory symptoms was observed throughout the follow-up period after transplantation. It was possible to discontinue antibiotic and antifungal prophylaxis, as well as all medication for inflammatory bowel disease.

This case has been followed for 15 months. The patient does not have clinical manifestations of chronic GvHD.

## Discussion

CGD is a rare, primary immunodeficiency disorder of phagocytes. It is characterized by repeated bacterial and fungal infections with excessive inflammation and granuloma formation.<sup>1</sup> HSCT is a potentially curative therapy for CGD leading resolution of infections and inflammatory complications.<sup>2</sup> Moreover, published data demonstrate that children with CGD who had undergone HSCT have better quality of life compared with those managed conservatively.<sup>3</sup> It has been demonstrated that there are fewer infections and admissions to the hospital and improved growth in patients after transplantation compared with those who had not undergone transplantation.<sup>4</sup> Acceptable rates of engraftment without transplant related mortality or GvHD are the goals of transplantation. Good results achieved with matched related donors have justified the extension to alternative donors, especially matched

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