Case Report

Successful Allogeneic Hematopoietic Stem Cell Transplantation of a Patient Suffering from Type II Congenital Dyserythropoietic Anemia: A Rare Case Report from Western India

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1. Introduction

Congenital dyserythropoietic anemia (CDA) is a rare blood disorder, similar to the thalassemias. CDA is one of many types of anemia, characterized by ineffective erythropoiesis, resulting in a decrease in the number of red blood cells (RBCs) in the body and a less than normal quantity of hemoglobin in the blood. Traditionally, CDA have been classified into 3 major types (CDA I, CDA II, and CDA III); recently, additional variants have been described. CDA type II (CDA II) is the most frequent type of congenital dyserythropoietic anemia.

Congenital dyserythropoietic anemia type II is a genetic hyporegenerative anemia characterized by ineffective erythropoiesis and distinct morphological abnormalities of the erythroblasts in the bone marrow (BM). Type II congenital dyserythropoietic anemia (CDA II) is an autosomal recessive disorder characterized by hemolytic jaundice, mild to moderate hepatosplenomegaly, and normocytic anemia [1, 2]. Most of the patients are transfusion-independent except for 10 to 20% of the cases, who are transfusion-dependent; this could account for the severity of the clinical outcome [3, 4]. Management usually includes blood transfusion, iron chelating therapy, and splenectomy. Transfusion-dependent patients usually require allogeneic HSCT (hematopoietic stem cell transplantation) from HLA identical donor. Only few published case reports of allogeneic HSCT in CDA patients are available.

2. Case Report

Child was apparently asymptomatic till the age of 3 years. He complained of lethargy and weakness for one to two months prior to presentation. His routine investigations
showed hemoglobin (Hb) of 5 gm/dL, indirect hyperbiliru-
binemia, and mild-moderate hepatosplenomegaly. He had
unremarkable birth and family history. His peripheral smear
was showing severe microcytic hypochromic anemia with
anisocytosis, poikilocytosis, and low MCV. After ruling out
hemolytic causes of anemia including thalassemia, sickling
disease, and G6PD deficiency, patient underwent marrow
aspiration and biopsy. It showed erythroid hyperplasia and
feature of dyserythropoiesis such as binucleation (20%),
multinucleation, and karyorrhexis. The other cell lines were
normal. The genetic analysis of the patient’s peripheral blood
revealed SEC23 B gene mutation by real-time polymerase
chain reaction (RT-PCR). In view of marrow picture and
genetic mutational analysis, final diagnosis of CDA II was
made. At the age of 5 years, he was referred to our hematol-
ogy unit for further management. Patient has had up until now
more than 14 mL/kg/month of packed cell volume (PCV).

On examination, he had marked pallor, with stable vitals.
Abdominal examination revealed palpable splenomegaly of
4 cm below the left costal margin and hepatomegaly of 5 cm
below the right costal margin. His pre-HSCT serum ferritin
was 1500 ng/mL; he was on regular iron chelating therapy
throughoutlife,withkineticsimilartuntreatedhereditary
hemochromatosis [14], and at present management of iron
accumulates steadily

HSCT, and rarely splenectomy. Iron accumulates steadily
with dose of CD34+ cells of 7 × 10^6 per kg weight. IV
methotrexate was given on +Day 1, +Day 3, +Day 6, and +Day
11 as graft versus host disease (GVHD) prophylaxis. Initially
supportive measures were taken to correct low hemoglobin
and platelet count. Engraftment for neutrophils was achieved
on +Day 14 with 3 consecutive absolute neutrophils counts
of more than 500 cumm/dL. Engraftment for platelets was
achieved on +Day 19 with 3 consecutive platelet counts of
more than 50000 cumm/dL without any component support.
100% donor chimerism for both myeloid and lymphoid cells
was achieved by +Day 45.

Patient was given prophylactic antibacterial, antifungal,
and anti-P. jirovecii treatment during HSCT procedure.
Engraftment of donor cells was prompt and the post-HSCT
duration was uneventful. No acute or chronic graft versus
host disease (GVHD) was noted. Cyclosporine and acyclovir
were continued for 6 and 12 months, respectively. Post-HSCT
serial complete blood counts and hemoglobin of patient were
normalized on +Day 40 and he was never given PCV (packed
cell volume) or platelets since then. Thirty-three months after
HSCT, the patient is alive with normal hemoglobin level and
is not receiving any immune suppressive therapy at present.
Iron chelating therapy was stopped 3 months after transplant,
when the serum ferritin level was noted to be less than
1000 ng/mL. Now, he is almost 8 years old, under regular
surveillance at our transplant centre without any symptoms.

3. Discussion

The congenital dyserythropoietic anemia (CDA) comprises a
group of rare hereditary disorders, characterized by ineffec-
tive erythropoiesis as the predominant mechanism of anemia
and by distinct morphological abnormalities of the majority
of erythroblasts in the bone marrow. The term was first used
by Crookston et al. [11]. The diagnosis should be suspected
in any case of congenital anemia with features of hemolytic
anemia. Various types of CDA are noted of which the most
frequent form is type II. Approximately 370 cases of CDAII
are reported till date. Although this disorder is considered
to be congenital, it is interesting that this type of anemia can
be diagnosed in all age groups. The molecular defects in the
gene SEC23B (Ioci is 20p11.23) are the confirmatory criteria
for the diagnosis of the CDA II [12]. Erythrocytes of CDA II
patients lyse in acidified serum (Ham test) because of an IgM
class antibody that recognizes an antigen present on CDA II
cells but absent on normal cells. So the acronym HEMPAS
(hemolytic anemia with a positive acidified serum test) was
commonly used as a synonym for CDA II [13].

Only 10–20% of the patients have severe anemia; in that
case, management focuses mainly on supportive care with
the use of transfusions, iron chelating therapy, allogeneic
HSCT, and rarely splenectomy. Iron accumulates steadily
throughout life, with kinetics similar to untreated hereditary
hemochromatosis [14], and at present management of iron
overload should follow guidelines for thalassemia. Parents of
our patient did not want lifelong blood transfusion, regular
iron chelating agents, or risk of infection susceptibility after
splenectomy. HSCT was the only curative option to avoid the
above complications.

Curative therapy for CDA focuses on the use of HSCT
using fully matched sibling donors [8]. Some of the CDA II
cases which have been managed successfully with HSCT with
Table 1: HSCT done in various types of CDA.

| Year | Author | Type of CDA |
|------|--------|-------------|
| 1996 | Ariffin et al. [5] | Type not documented |
| 2012 | Iolascon et al. [3] | CDA II with thalassemia trait |
| 2002 | Ayas et al. [6] | CDA I |
| 2002 | Remacha et al. [7] | CDA II with a negative Ham test |
| 2012 | Buchbinder et al. [8] | Unrelated hematopoietic stem cell transplantation in a patient with congenital dyserythropoietic anemia (CDA) and iron overload |
| 2014 | Russo et al. [9] | Successful hematopoietic stem cell transplantation in a patient with CDA II |
| 2014 | Braun et al. [10] | Successful treatment of an infant with CDA II by intrauterine transfusions and postnatal stem cell transplantation |

Excellent results were mentioned in the literature. It has been reported to be curative in a few severe cases of CDA including transfusion-dependent CDA type I, CDA type II, Ham test-negative CDA type II, and an unclassified CDA (Table 1). HSCT was successful in some children with exceptionally severe anemia [15]. So there is a paucity of literature available to guide us through the application of HSCT in this case. In many instances, a matched sibling donor is not available and conventional conditioning may be poorly tolerated in many patients. Lucarelli et al. described risk stratification of thalassemia patients which is defined by the following risk factors: (1) hepatomegaly >2 cm, (2) portal fibrosis of any degree, and (3) inadequate compliance with the chelating agents. Class 1 means no risk factors, Class 2 had one or two risk factors, and Class 3 included all 3 risk factors. We had assigned our patient to Class 2 status (in view of presence of hepatomegaly) in which HSCT has also been reported as the only viable curative option [16].

In developing countries like SEAR regions with financial constraints and limited resources, CDA II patients can be benefited best with the use of myeloablative conditioning regimen, infusion of high stem cell dose, and all the measures which would lead to reduced infection rate and duration of hospital stay. We have demonstrated a successful and safe application of aggressive iron chelating agents before HSCT followed by successful HSCT.

4. Conclusion

Due to rarity of disease, no definitive treatment guidelines are available but allogeneic HSCT should be considered in severe cases. As in thalassemia early and regular iron chelating agents in CDA before HSCT give better results. In the developing world with limited resources and financial constraint, severe case of CDA can be managed successfully with allogeneic HSCT by using myeloablative conditioning regimen, infusing high CD34+ stem cell dose, to ensure early engraftment; appropriate and adequate GVHD measure would contribute to reducing infection rate and duration of hospital stay.

Highlights: Learning Points

(i) The congenital dyserythropoietic anemia (CDA) is a group of rare hereditary disorders, characterized by ineffective erythropoiesis and specific morphologic abnormalities of erythroblasts in the bone marrow.

(ii) Traditionally, CDA have been classified into 3 major types (CDA I, CDA II, and CDA III); recently, additional variants have been described.

(iii) The diagnosis of CDA should be suspected in any case of congenital anemia with features of hemolytic anemia.

(iv) The molecular defects in the gene SEC23B (loci is 20p11.23) are the cause of CDAII.

(v) There is a paucity of literature available to guide the management of CDA.

(vi) Allogeneic HSCT is the only curative strategy available in severe transfusion-dependent CDA patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] K. Y. Wong, G. Hug, and B. C. Lampkin, "Congenital dyserythropoietic anemia type II: ultrastructural and radioautographic studies of blood and bone marrow," Blood, vol. 39, no. 1, pp. 23–30, 1972.

[2] N. Alloisoio, P. Texier, L. Denoroy et al., “The cisternae decorating the red blood cell membrane in congenital dyserythropoietic anemia (type II) originate from the endoplasmic reticulum,” Blood, vol. 87, no. 10, pp. 4433–4439, 1996.

[3] A. Iolascon, M. R. Esposito, and R. Russo, "Clinical aspects and pathogenesis of congenital dyserythropoietic anemias: from morphology to molecular approach," Haematologica, vol. 97, no. 12, pp. 1786–1794, 2012.

[4] R. Russo, A. Gambale, C. Langella, I. Andolfo, S. Unal, and A. Iolascon, “Retrospective cohort study of 205 cases with congenital dyserythropoietic anemia type II: definition of clinical and molecular spectrum and identification of new diagnostic scores,” The American Journal of Hematology, vol. 89, no. 10, pp. E169–E175, 2014.

[5] W. A. Ariffin, S. Karnaneedi, K. E. Choo, and J. Normah, “Congenital dyserythropoietic anemia: report of three cases,” Journal of Paediatrics and Child Health, vol. 32, no. 2, pp. 191–193, 1996.

[6] M. Ayas, A. Al-Jefri, A. Baothman et al., “Transfusion-dependent congenital dyserythropoietic anemia type I successfully treated with allogeneic stem cell transplantation,” Bone Marrow Transplantation, vol. 29, no. 8, pp. 681–682, 2002.

[7] A. F. Remacha, I. Badell, N. Pujol-Moix et al., “Hydrops fetalis-associated congenital dyserythropoietic anemia treated with
intrauterine transfusions and bone marrow transplantation,” *Blood*, vol. 100, no. 1, pp. 356–358, 2002.

[8] D. Buchbinder, D. Nugent, D. Vu et al., “Unrelated hematopoietic stem cell transplantation in a patient with congenital dyserythropoietic anemia and iron overload,” *Pediatric Transplantation*, vol. 16, no. 3, pp. E69–E73, 2012.

[9] R. Russo, A. Gambale, C. Langella, I. Andolfó, S. Unal, and A. Iolascon, “Retrospective cohort study of 205 cases with congenital dyserythropoietic anemia type II: definition of clinical and molecular spectrum and identification of new diagnostic scores,” *American Journal of Hematology*, vol. 89, no. 10, pp. E169–E175, 2014.

[10] M. Braun, M. Wölfl, V. Wiegering et al., “Successful treatment of an infant with CDA type II by intrauterine transfusions and postnatal stem cell transplantation,” *Pediatric Blood & Cancer*, vol. 61, no. 4, pp. 743–745, 2014.

[11] J. H. Crookston, T. F. Godwin, K. J. R. Wightmann, J. V. Dacie, S. M. Lewis, and M. Patterson, “Congenital dyserythropoietic anaemia (abstract),” in *Proceedings of the 11th Congress of the International Society of Haematology*, Sydney, Australia, August 1966.

[12] E. Fermo, P. Bianchi, L. D. Notarangelo et al., “CDAII presenting as hydrops foetalis: molecular characterization of two cases,” *Blood Cells, Molecules, and Diseases*, vol. 45, no. 1, pp. 20–22, 2010.

[13] A. Tomita and C. J. Parker, "Aberrant regulation of complement by the erythrocytes of hereditary erythroblastic multinuclearity with a positive acidified serum lysis test (HEMPAS)," *Blood*, vol. 83, no. 1, pp. 250–259, 1994.

[14] H. Heimpel, V. Anselstetter, L. Chrobak et al., “Congenital dyserythropoietic anemia type II: epidemiology, clinical appearance, and prognosis based on long-term observation,” *Blood*, vol. 102, no. 13, pp. 4576–4581, 2003.

[15] S. N. Wickramasinghe and W. G. Wood, "Advances in the understanding of the congenital dyserythropoietic anaemias," *British Journal of Haematology*, vol. 131, no. 4, pp. 431–446, 2005.

[16] G. Lucarelli, M. Galimberti, P. Polchi et al., "Marrow transplantation in patients with thalassemia responsive to iron chelation therapy," *The New England Journal of Medicine*, vol. 329, no. 12, pp. 840–844, 1993.