Hydrops fetalis associated congenital dyserythropoietic anemia (CDA) treated with intrauterine transfusions and bone marrow transplantation.


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Hydrops fetalis is rarely caused by congenital dyserythropoietic anemia (CDA). We report a patient with hydrops fetalis due to severe anemia. This patient needed intrauterine transfusions from 21 weeks of gestation until birth. The hematological study showed an atypical CDA (hydrops fetalis associated CDA) characterised by features resembling CDA type II, but negative acidified serum lysis test (HEMPAS negative). The patient was regularly transfused for a year after which an allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling was successfully carried out. His actual Hb is 127 g/l and he has not received transfusions for more than a year. In conclusion, intrauterine transfusions and BMT could cure an otherwise lethal atypical CDA.
Introduction

Congenital dyserythropoietic anemias (CDA) are an uncommon inherited cause of anemia characterized by ineffective erythropoiesis with dysplastic morphological features. The anemia is usually mild to moderate in CDA patients; however, it may be more serious requiring transfusions. Anemia is rarely very severe, resulting in fatal hydrops fetalis.

Apart from the three classic types of CDA (CDA type I, II and III), defined by Heimpel and Wendt (1) a number of CDAs are heterogenous and cannot be included in these types. Recently, at least three or four new categories have been proposed, designated as IV (CDA with non-specific erythroid dysplasia), V (Congenital ineffective erythropoiesis without significant dysplasia), VI (Vitamin B12-and folate-independent megaloblastic and dysplastic erythropoiesis) and CDA with intraerythroblastic precipitation of a non-globin protein, although many cases remain to be classified in a subgroup of CDA (2).

Bone marrow transplantation (BMT) has been used to treat severe congenital erythroid disorders such as major thalassemias or hemoglobinopathies, and BMT is now considered as a potential curative option for many cases with transfusion-dependent disorders.

We report a case with hydrops fetalis due to a severe transfusion-dependent CDA who was successfully treated with a BMT.

Study design

Hematological parameters were determined by standard procedures including blood cell counts, reticulocytes, iron, vitamin B12, folate, haptoglobin, etc. Other causes of dyserythropoiesis were ruled out after studying the propositus and his parents. Accordingly, enzyme, membrane and thalassemia-
hemoglobin disorders and sideroblastic anemia were excluded using conventional methods and genetic molecular studies (α and β thalassemia) in the propositus and his family. Acidified serum lysis test (Ham’s test), sucrose lysis test, CD55 and CD59 glycoprotein analyses and laboratory tests for excluding fetal isoimmunization were performed following routine methods.

For transmission electron microscopy, bone marrow cells were fixed with glutaraldehyde in cacodylate buffer, postfixed with osmium tetroxide, dehydrated in ethanol, and embedded in Epon 812®. The ultrathin sections were stained with uranyl acetate and lead citrate, and were examined at 80 Kv.

Results and discussion

The propositus was a gypsy boy who was diagnosed with hydrops fetalis due to severe anemia in the prenatal diagnosis unit during an echographic control. His parents, who were cousins, showed apparently normal hematological values. He was the fourth pregnancy (two live brothers, one dead hydropic fetus and the patient). During the pregnancy, the patient needed five intrauterine transfusions from diagnosis at 21 weeks of gestation (intrauterine Hb 16 g/l with marked erythroblastosis) until birth at week 34 by cesarean section (Hb 69 g/l). Intrauterine cytogenetic study showed 46 XY chromosomes without abnormalities. Intrauterine infections were also excluded.

At birth his weight was 1,915 g, and he showed pallor, jaundice (maximal total bilirubin: 190 µmol/l at 4 days of life) and generalized edema. The patient required phototherapy, which was initiated at 24 hours (total bilirubin: 120 µmol/l), and mechanical ventilation during the newborn period.

In this period, an extensive study ruled out red cell enzyme, membrane, hemoglobin and thalassemic diseases. Tests for maternofetal isoimmunization
were normal and a bone marrow biopsy showed a normal osteogenesis with erythroid hyperplasia, excluding an aplastic red cell anemia. His red cells showed a normal agglutinability with anti-i antibody and an acidified serum lysis test was negative (HEMPAS negative) in three samples and against twenty-five sera. At three months of life when the immunohematological study was carried out, his Hb was 67 g/l, MCV 80fl, platelets 568 x 10^9 /L, leucocytes 10.2 x 10^9 / including 10% of nucleated red cells and reticulocytes 0.5% (0.013 x 10^{12} /L). Red cell morphology in peripheral blood showed scant binuclear erythroblasts (2%) (Figure 1).

At the age of two months a bone marrow exam showed erythroid hyperplasia and markedly abnormal erythropoiesis (Figure 1), including a substantial proportion of binuclear erythroblasts (20%) and a much smaller proportion of tri, tetra and multinuclear erythroblasts (2%). Sideroblastic or megaloblastic anemias were ruled out. Granulocytopoiesis and megakaryocytopoiesis were normal.

Electron microscopic aberrations were more prominent in late erythroblasts (Figure 2). The nuclear outline was often undulated or lobulated and the nuclear-membrane-associated heterochromatin was frequently absent over large areas of the nuclear membrane. In some cells, the heterochromatin was spongy and showed numerous “punched out” areas. The main cytoplasmic anomaly was the presence of abundant cytoplasmic membranes which are composed of excessive smooth endoplasmic reticulum. These characteristic cisternae usually ran parallel beneath the cell outer membrane producing the so-called “double membrane”. The dilatation of the space between the two
layers of these cytoplasmic membranes was frequently observed, as was the
dilatation of the space of the nuclear membrane.

The patient was regularly transfused to maintain Hb exceeding 80 g/l
every 3-4 weeks for one year. During this year an extensive examination did not
show other dysmorphic features and the development was normal.

The patient had the main features of the atypical CDA causing severe
transfusion-dependent anemia presenting as hydrops fetalis. Cantù-Rajnoldi A
et al. (3) reviewed the characteristics of five cases and suggested the name of
"hydrops fetalis associated congenital dyserythropoietic anaemia". The
hematological findings are very similar in all cases including a CDA II-like
erthroblast morphology with a negative Ham’s test. Typically, the family history
revealed repeated abortions and consanguinity. All patients who have survived
are transfusion dependent (3).

Bone marrow transplantation is a potential curative treatment in patients
with many hematological severe diseases, including erythroid disorders such as
major thalassemia, severe hemoglobinopathies, etc. The results are excellent
when the procedure was carried out as early as possible and from an HLA-
matched sibling. Thus, BMT is an alternative to regular transfusions and
chelation treatment (4). In this regard, a BMT from his HLA-matched 12-year old
brother was carried out, although at that time the literature did not contain
reports of the results of BMT in patients with CDA.

At the age of 13 months the BMT was carried out. The patient was 0, Rh-
(M-) and the serology for cytomegalovirus was positive. His 12-year-old brother
was also 0, Rh- (M+) and also positive for cytomegalovirus. Both were HLA-
identical (A, B and DRB1). Donor blood counts were normal (Hb 140 g/l, MCV
86 fl, platelets 220 x 10^9 /L and leucocytes 5.9 x 10^9 /L), as was his bone marrow including erythroid cells.

The conditioning treatment was oral Busulfan (16 mg/kg over 4 days) and intravenous Cyclophosphamide (200 mg/ kg over 4 days). Cyclosporine A was used for GVHD prophylaxis, until day + 30 in continuous infusion and after this date p.o. until 9 months after BMT. A total number of 7.7 x 10^8/kg mononuclear cells or 16.7 x 10^6/kg CD34+ cells were infused on October 27, 2000. The hemopoietic reconstitution was observed on day +12 for neutrophils and on +29 for platelets.

The patient has not shown acute or chronic GHVD complications. As transplant related complications during the BMT procedure, the propositus only showed transient arterial hypertension related to Cyclosporine and a respiratory tract infection without a known microorganism.

A total chimerism was demonstrated by a DNA study from +11 day to +236 day. Mixed chimerism persists now at +391 day in T lymphocytes (58% donor) and in granulocytes (52% donor). However, red blood cells belong to the donor (M+) and the patient did not require more transfusion since day +30. The patient is now 3-years old and his current Hb is 127 g/l and has not received red cell transfusion for more than a year.

To our knowledge, this case is the first in which a severe transfusion-dependent CDA causing hydrops fetalis has been treated with intrauterine transfusions and BMT. This raises the possibility of a curative treatment for patients with this rare disease. During the follow-up of our patient a case with a classical CDA type II in association with beta-thalassemia trait and severe iron overload was successfully treated with a bone marrow transplantation (5).
References


Figure 1.
Optical microscopy morphology of peripheral and bone marrow hematopoiesis.

Binucleate erythroblast in peripheral blood (A). Erythroid hyperplasia with marked abnormalities (bi, tri and multinucleate late erythroblasts) (B). Abnormal erythroblasts showing anomalous distribution of chromatin (C,D), binucleate erythroblasts and isolated trinuclear, tetranuclear (B) and aberrant multinuclear erythroblasts (B and D).

Figure 2
Electron micrographs of several bone marrow late erythroblasts (original magnification: A, x10.600; B and C, x18.000).

Multinucleate erythroblasts showing striking “double membranes” with partial dilatation of the intramembranous space (A). Erythroblasts revealing non dilated cisternae (B, C). Late erythroblast depicting spongy heterochromatin with numerous “punched out” areas (B). Binucleate erythroblasts showing large areas of nuclear membrane without attached heterochromatin (C).
Figure 1.
Figure 2
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