Diamond-Blackfan like anemia and idiopathic very early onset severe colitis cured by allogeneic hematopoetic stem cell transplantation.

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Abstract

Diamond-Blackfan anemia (DBA) is a rare congenital erythroid hypoplasia. An association with very early onset inflammatory bowel disease (VEO-IBD) has only been reported a few times. We report a Caucasian boy with a transfusion-dependent DBA phenotype from birth and severe ulcerative pancolitis from 10 months of age. He underwent successful allogeneic hematopoietic stem cell transplantation (HSCT) at 2 years of age. On follow-up 8 years old, he had normal bone marrow function and no bowel symptoms. HSCT was curative for both DBA and VEO-IBD. The underlying course of DBA and pancolitis remains elusive.

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Abbreviations:

DBA	Diamond-Blackfan Anemia
e-ADA	erythrocyte Adenosine Deaminase
GVHD	Graft-versus-Host-Disease
Hb	Hemoglobin
Hct	Hematocrit
HSCT	Hematopoietic Stem Cell Transplantation
IBD	Inflammatory Bowel Disease
MCV	Mean Corpuscular Volume
TNF	Tumor Necrosis Factor
VEO	Very Early Onset

Abstract

Diamond-Blackfan anemia (DBA) is a rare congenital erythroid hypoplasia. An association with very early onset inflammatory bowel disease (VEO-IBD) has only been reported a few times.

We report a Caucasian boy with a transfusion-dependent DBA phenotype from birth and severe ulcerative pancolitis from 10 months of age. He underwent successful allogeneic hematopoietic stem cell transplantation (HSCT) at 2 years of age. On follow-up 8 years old, he had normal bone marrow function and no bowel symptoms.

HSCT was curative for both DBA and VEO-IBD. The underlying course of DBA and pancolitis remains elusive.

Introduction

Diamond Blackfan anemia (DBA) is a rare inherited bone marrow disorder with defects in ribosomal proteins leading to severe macrocytic anemia in infancy, paucity of erythroid precursors in an otherwise normocellular bone marrow and often congenital anomalies. To date 20 ribosomal protein (RP) genes have been identified in association with DBA, but also non-RP genes (such as *GATA1, TSR2, ADA2* and*EPO*) have been found to cause a DBA-like phenotype. As gene variations in DBA are increasingly discovered, nonclassical cases with less distinct phenotypes are still described.[1,2,3]

Inflammatory bowel disease (IBD) presenting before the age of 6 is termed VEO-IBD and infant IBD if presenting before the age of 2. VEO-IBD and infant IBD are characterized by high familial aggregation, severe disease course and poor response to most conventional therapy.[4] IBD in general is regarded as a polygenic disease with >230 known disease-associated genes.[5,6] In early presentations of IBD, i.e. in VEO-IBD and infant IBD, the likelihood of finding a monogenic cause is higher compared to later presentations.[6,7]

Most children with VEO-IBD are treated as ulcerative colitis or Crohn disease. With reports of HSCT as a potential cure for both intestinal and extra-intestinal manifestations in some cases of monogenic VEO-IBD,

it has become increasingly important to identify the patients who could benefit from this extensive procedure [8]

We describe a boy with DBA-phenotype without malformations and with severe VEO-IBD.

Case report

The boy was born to healthy non-consanguineous Caucasian parents at 37 weeks of gestation. His birth weight was 2960g. Polyhydramnios was noted (4L), but apart from this the delivery was uneventful.

Two days old he presented with severe anemia (Hb 7.2 g/dL, Hct 19%, MCV 96 fl, reticulocyte count of 11 x 10^9/L). The bone marrow was without dysplasia, normal granulopoiesis and megakaryopoiesis but absent erythropoiesis. Apart from an asymptomatic atrial septal defect which closed spontaneously before 6 months of age he had no congenital anomalies. From birth, he needed erythrocyte transfusion every 3-4 weeks.

From a hematological point of view, he presented as a classical DBA phenotype, but MCV and e-ADA was normal. Comparative genomic hybridization and karyotype 46,XY was unremarkable. Testing for Fanconi anemia with mitomycin C was normal.

Genetic testing was done by Ambry Genetics NGS panel and revealed no mutations in *RPL5* , *RPL11* , *RPL9* , *RPL26* ,*RPL35A* , *RPS7* , *RPS10* , *RPS17* , *RPS19* ,*RPS24* or *RPS26* . A subsequent whole-exome sequencing analysis at a mean target coverage >80x was performed as a trio analysis of the patient and his parents. All genes known to be involved in causing either VEO-IBD or DBA/DBA-like disease were screened for pathogenic or potentially pathogenic variants, but none were identified.

He was within normal range for weight (-1SD) and height (-2SD). There were no signs of increased tendency of infections and immunoglobulin levels (IgA, IgG and IgM) were normal.

He presented with severe hemorrhagic pancolitis 10 months old. Endoscopy showed severe inflammation. Biopsies showed histologically limited inflammation and did not identify any specific cause of colitis. Search for genetic causes of VEO-IBD (including *IL10* , *FOXp3*) were negative. He started on high-dose prednisolone (2.5 mg/kg/day) without any significant effect on neither the colitis nor the bone marrow function with reticulocytes persistently < 5 x 10^9/L despite Hb of 6 g/dL. Two months later azathioprine (3 mg/kg/day) was started with a modest amelioration of the colitis.

TNF inhibitor (infliximab) 5-10mg/kg was added with a short effect on the hemorrhagic colitis. Renewed colonoscopy showed severe pancolitis with fibrosis and cobblestone configuration, but, as earlier, only non-specific histological changes. At 22 months of age, adalimumab 4mg/kg sc. was started with some improvement of the gastrointestinal symptoms but still significant flares with blood and mucus. At this point colectomy was considered.

An unrelated matched donor was identified and at the age of 29 month, he received an HSCT with a 10/10 allele matched unrelated donor after myeloablative conditioning with busulfan and fludarabine. Graft-versus-host diseases (GVHD) prophylaxis was given in the form of antithymocyte globulin, cyclosporine and low dose methotrexate. The transplantation course was uneventful, engraftment occurred on day +14 without signs of GvHD. The colitis regressed during the first month post-transplant. Three months post-transplant the colitis relapsed. Colonoscopy showed no signs of GvHD. Stool culture was positive for Yersinia enterocolitica and Clostridium difficile. After this infection remission was achieved with slow tapering of immunosuppressive treatment until discontinuation 9 months post-HCT. There has been only one short flare of the colitis 12 months after HSCT which was treated with steroids and mesalazine (30mg/kg).

The patient is now more than 8 years from HSCT with full donor chimerism, full hematological recovery, no GVHD, normal stools and off medical treatment.

Discussion

Severe hemorrhagic colitis has only been reported with DBA a few times and hence there is no consensus regarding the indication of HSCT[9,10] A case of *RPL9* DBA, transfusion dependent at 6 months, failure to

thrive, microcephaly, and thumb anomaly was also described to have severe pancolitis, and was, as in our case, treated with steroid and azathioprine.[10]

HSCT is the only curative treatment for DBA and has been used for more than 40 years. There is an excellent survival if patients are transplanted younger than 10 years of age[11] and a consensus guideline has been developed to identify DBA patients for whom HSCT is indicated.[12]

The indication for allogeneic HSCT as a treatment for IBD in general and VEO-IBD is more controversial.[13] Management of infant IBD is challenging, especially in the absence of known monogenic etiology. Standard treatments are sometimes insufficient and there is no clear indication of whether HSCT will be beneficial or not in those cases.

Some monogenic VEO-IBD patients are unlikely to benefit from allogeneic HSCT, e.g. those associated with epithelial barrier dysfunction like TTC7A defects.[14] but in general HSCT may be considered in severe immunodeficiency with associated IBD symptoms.[15,16] In our case the first genetic investigations were repeated adding all new known genetic causes of both DBA and VEO-IBD to the panel, but without pathogenic variants (see Supplementary Material, S1). Thus, although it seems unlikely that two such rare conditions were caused by two independent events, no causative correlation was revealed.

In conclusion the underlying cause of our case of DBA disease combined with severe pancolitis remains unknown. HSCT was feasible and curative using conditioning with busulfan and fludarabine and slow tapering over 9 months of post-transplant immunosuppressive treatment to reduce the risk of relapse of the colitis in this case of DBA with concomitant severe ulcerative colitis.

Conflict of Interest

The authors declare that there is no conflict of interest directly relevant to the content of this article.

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