Allogeneic hematopoietic cell transplantation rescues congenital red cell aplasia in H syndrome due to *SLC29A3* mutations

Diamond-Blackfan anemia (DBA) is the most recognized and understood cause of congenital pure red cell aplasia (PRCA).[1] While most cases of DBA are caused by mutations in ribosomal protein genes, mutations in non-ribosomal protein genes (*GATA1, EPO, ADA2*) have been reported and associated with congenital PRCA.[1] Aside from DBA, genetic diagnoses of congenital PRCA are rare and likely under-reported.

SLC29A3 encodes the human equilibrative nucleoside transporter 3 (ENT3) which functions as an intracellular nucleoside transporter.[2] Mutations in *SLC29A3* were identified as the basis of the autosomal recessive genodermatosis, H syndrome. Clinical manifestations of H syndrome are variable and include hyperpigmentation, hepatosplenomegaly, heart anomalies, low height, hyperglycemia, hematologic abnormalities, immunodeficiency, among other reported features.[2] While hematologic features are not uniformly present, 10% of patients in one series exhibited hematologic disease ranging from PRCA to myelofibrosis, autoimmune hemolytic anemia, pancytopenia, and myeloproliferative disease with increased monocytes and histiocytes in the bone marrow.[2] Mutations in *SLC29A3* have also been identified in patients with familial histiocytosis syndromes.[3]

Slc29a3$^{-/-}$ mice have normal red blood cell counts, hemoglobin, and hematocrit until 8 weeks of age, but then develop progressive anemia that becomes severe at 16 weeks of age.[4] In *Slc29a3*$^{-/-}$ mice, loss of ENT3 results in decreased lysosomal adenosine transport and, in turn, altered adenosine monophosphate kinase (AMPK) signaling, leading to decreased bone marrow cellularity and hematopoietic stem cell renewal capacity.[4,5] Subsequent work demonstrated that ENT3 acts as a facilitative transporter of taurine-conjugated bile acids, shown to prevent endoplasmic reticulum stress and erythroid apoptosis in mice.[5] ENT3 facilitates accumulation of taurine-conjugated bile acids in mouse hematopoietic stem cells and supports erythropoiesis. Importantly, hematopoietic cell transplantation (HCT) was shown to improve survival and resolve anemia in *Slc29a3*$^{-/-}$ mice.

Here we describe a case of H syndrome-related PRCA. Based on correction of anemia by HCT in *Slc29a3*$^{-/-}$ mice, we share the clinical course and successful allogeneic HCT outcome in our patient with *SLC29A3*-related PRCA. This case report was reviewed by the Corewell Health Institutional Review Board (IRB): it was deemed that it did not meet the definition of research on human subjects and did not, therefore, require IRB review and approval. The patient's information has been de-identified and handled in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations.

A Chinese female was adopted at 7 years of age. She had transfusion-dependent anemia since infancy. Initial evaluation at our center showed a normocytic normochromic anemia with a hemoglobin of 4.7 g/dL and reticulocytopenia (3,000/μL). Her ferritin level was 7,134 μg/L and she had no prior history of iron chelation treatment. Baseline liver magnetic resonance imaging (MRI) revealed a liver iron content >43 mg iron/gram dry liver tissue weight and hepatomegaly. Liver biopsy showed patchy pericellular/perisinusoidal fibrosis with mild fibrous portal expansion. No myocardial iron overload was present on MRI (T2* relaxation time 27.8 ms). Echocardiogram revealed a bicuspid aortic valve and a coronary artery aneurysm. She had a prior diagnosis of IgA deficiency, confirmed by IgA <5 mg/dL. Her stature was below the 3rd percentile for age, but there were no records to determine biological mid-parental height. A bone marrow examination confirmed the absence of erythroid cells (Figure 1). A presumptive diagnosis of DBA was made.

She received packed red blood cell transfusions every 3 weeks to maintain her hemoglobin >9 g/dL (she was symptomatic at lower hemoglobin concentrations) and was started on iron chelation with deferasirox. She experienced painful mouth sores with increased doses of deferasirox. With presumed DBA, a trial of oral prednisone (2 mg/kg/day) was attempted but there was no improvement of her reticulocyte count. Given her persistent severe iron overload, desferoxamine was added for additional chelation with a subsequent decrease of liver iron content to 7.1 mg iron/gram dry liver tissue weight. She showed no appreciable improvement in erythropoiesis after 6 months of L-leucine supplementation (800 mg twice daily) which has been reported as a successful treatment for DBA.[6]

No significant variants were detected on a 13-gene DBA panel. Subsequent whole-exome sequencing performed as proband only (GeneDx, Gaithersburg, MD, USA) revealed two pathogenic variants in *SLC29A3* (c.1279 G>A p.G427S and c.1087 C>T p.R363W) as per American College of Medical Genetics and Genomics (ACMG) criteria. With the underlying *SLC29A3* mutation, PRCA, heart anomalies, hepatomegaly, IgA deficiency, and low height, the diagnosis of H syndrome was made (Table 1). Intravenous immune globulin was administered for 6 months based on a prior report of PRCA in H syndrome,[7] but our patient showed no response.

While there are no reports of allogeneic HCT in *SLC29A3*-re-

lated disorders or H syndrome, correction of PRCA has been documented in mouse models.[4,5] After weighing risks associated with allogeneic HCT and the patient's present and future quality of life, her adoptive parents decided to proceed with allogeneic HCT when the child was 10 years of age. She underwent laparoscopic oophorectomy for ovarian tissue cryopreservation. Reduced toxicity conditioning was based on published experience in other non-malignant disorders.[8-11] Hydroxyurea (30 mg/kg/day by mouth) was given on days -50 to -23, alemtuzumab (3 mg test dose and then 10, 15, and 20 mg daily subcutaneously) on days -22 to -19, fludarabine (30 mg/m^2/day intravenously [IV]) on days -8 to -4, thiotepa (4 mg/kg × 2 IV) on day -4, and melphalan (140 mg/ m^2 IV) on day -3. She received a 10/10 human leukocyte antigen (HLA)-matched unrelated donor, ABO-compatible, bone marrow graft (5.09x10^8 total nucleated cells/kg with 5.04x10^6 CD34$^+$ cells/kg). Graft-*versus*-host disease prophylaxis was based on prior reports and included tacrolimus starting on day -3 and methotrexate (7.5 mg/m^2/dose IV on days +1, +3, and +6), and augmented with extended abatacept dosing (10 mg/kg IV on days -1, +5, +14, +28, +100, +180, and +278).[7-12]

The course of the HCT was complicated by severe chemotherapy-induced mucositis and prolonged non-infectious diarrhea. The girl required frequent HLA-matched platelet transfusions due to high-titer class I HLA antibodies identified prior to the HCT. Neutrophil engraftment occurred on day +15. She developed headache, hypertension, and

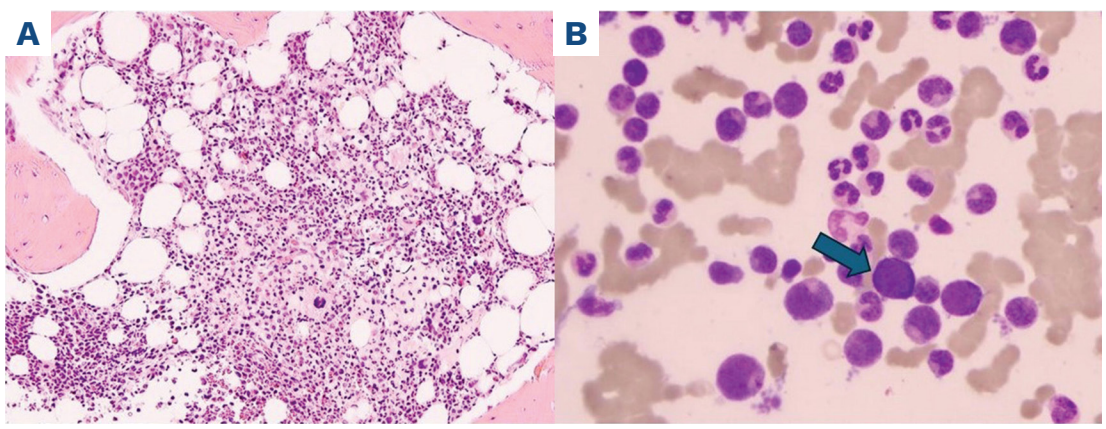

Figure 1. Diagnostic bone marrow examination showing the absence of erythroid cells. (A) Hematoxylin & eosin-stained section of bone marrow core biopsy demonstrating normocellular bone marrow, estimated 80-90% cellularity. Megakaryocytes are present in normal numbers and show normal morphological features. Erythroids not identified. Granulocytes mature to full neutrophil stage. There is no increase in lymphocytes, blasts, or plasma cells (10x magnification). (B) Wright-stained bone marrow aspirate smears with cellular spicules with well-preserved cells for morphological evaluation. Erythroids are essentially absent with only one erythroid form seen (arrow) (40x magnification).

Table 1. Features of H syndrome.

Literature reported findings	Our case prior to HCT	Our case 2.5 years after HCT
Hyperpigmentation	None	None
Hearing loss	None	None
Hypertrichosis	None	None
Lymphadenopathy	None	None
Diabetes (hyperglycemia)	None	None (required insulin with corticosteroid exposure during HCT)
Hepatomegaly	Increased liver size	Normal liver size
Splenomegaly	None	None
Heart anomalies	Bicuspid aortic valve, coronary artery aneurysm	Persistent
Short stature	<3rd percentile for age	<3rd percentile for age
Hematologic abnormalities	Pure red cell aplasia (transfusion-dependent)	Hb 12.7 g/dL (12-15 g/dL) (transfusion-independent)
Immune deficiency	IgA <5 mg/dL	IgA 61 mg/dL (53-204 mg/dL)
Mucositis (not reported)	Yes (with deferasirox)	None after HCT recovery (severe during HCT course)

HCT: hematopoietic cell transplantation; Hb: hemoglobin; IgA: immunoglobulin A.

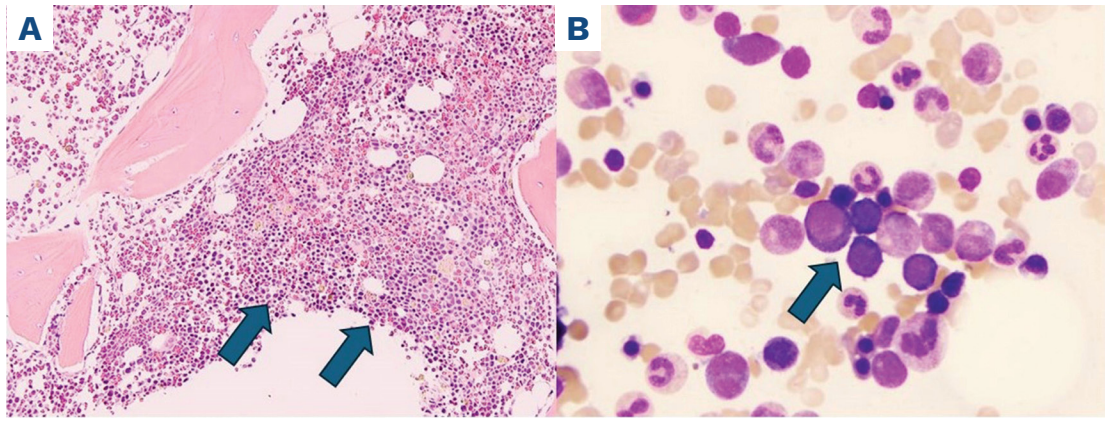

Figure 2. Bone marrow exam demonstrating erythroid cells following allogeneic hematopoietic cell transplantation. (A) Hematoxylin eosin-stained section of bone marrow core biopsy demonstrating normocellular bone marrow, estimated at 90% cellularity, with trilineage hematopoiesis and full maturation of all cell lines. Erythroids show full maturation and are present in erythroid islands (arrows) (10x magnification). (B) Wright-stained bone marrow aspirate smears with cellular spicules with well-preserved cells for morphological evaluation. Erythroids are present in adequate numbers with full maturation and no evidence of dysplasia. Arrows point to erythroid cells (40x magnification).

photophobia on day +16 and was found to have hypertensive hemorrhagic encephalopathy on brain MRI, likely related to transplantation-associated thrombotic microangiopathy, diagnosed by laboratory criteria.[13,14] Symptoms resolved with supportive care and eculizumab complement blockade, and platelet engraftment occurred on day +49. Reticulocytosis was first noted on day +20 (47,000/μL) and she has been transfusion-independent since day +34. A bone marrow examination at that time showed normal cellularity with trilineage hematopoiesis, including normal and full erythroid maturation (Figure 2). She has had sustained donor engraftment (>99% donor by whole blood short tandem repeat chimerism analysis) through 2.5 years since her HCT. Tacrolimus was discontinued at day +156 after tapering. No acute or chronic graft-*versus*-host disease was observed. Table 1 summarizes reported features of H syndrome, some of which were present in our patient, and those that resolved following allogeneic HCT. Therapeutic phlebotomy resolved iron overload after HCT. She now has a normal IgA level (61 mg/dL). While our patient has demonstrated growth over time, her height remains below the 3rd percentile for age throughout.

Genetic diagnoses and understanding of congenital PRCA, aside from DBA, are rare and have potential treatment implications. Our case highlights *SLC29A3* mutation as a rare etiology of congenital PRCA and extends knowledge about the clinical spectrum of H syndrome.

As previously described, there appears to be significant heterogeneity in the number and severity of manifestations in patients with H syndrome.[2] While congenital PRCA was our patient's most severe manifestation, it is likely that her heart abnormalities, hepatomegaly, and short stature are *SLC29A3*-related. Autoinflammation, IgA deficiency, and PRCA have been described with reported resolution of PRCA after intravenous immune globulin and steroids.[7] Our patient showed no response to intravenous immune globulin or steroids as treatment for PRCA. Of note, our patient's IgA deficiency corrected following HCT. This may suggest a potential role for allogeneic HCT to correct immunodeficiency in H syndrome. Our patient does not have diabetes, a disorder common in H syndrome, but she experienced significant hyperglycemia during brief exposure to corticosteroids while managing immune-mediated thrombocytopenia early after the HCT.

Allogeneic HCT was successful in correcting our patient's *SLC29A3*-related PRCA. The optimal approach to conditioning prior to allogeneic HCT for *SLC29A3*-related disorders is unknown. We used reduced toxicity conditioning, which is typically well-tolerated in a wide range of non-malignant disorders. However, our patient experienced severe mucositis uncommon with this regimen. Of note, our patient experienced mouth sores with deferasirox chelation prior to HCT, raising the possibility that mouth sores were related to her underlying H syndrome as this has not been reported with deferasirox. Given that *SLC29A3* is ubiquitously expressed in the body, exemplified by multiorgan involvement in H syndrome, we hypothesize that affected patients may be prone to acute toxicity from chemotherapy or total body irradiation. Further experiments of allogeneic HCT in *Slc29a3*$^{-/-}$ mice should focus on broad-ranging toxic effects of conditioning treatments.

H syndrome is an under-recognized cause of congenital PRCA. Additional genetic testing for *SLC29A3* is warranted in non-DBA congenital anemia and has important therapeutic implications. Allogeneic HCT can successfully correct *SLC29A3*-related PRCA and improve quality of life, but we advise a cautious approach until the toxic effects of conditioning treatments in such patients are better understood.

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TCQ is on a speaker bureau for Jazz Pharmaceuticals and formerly for Alexion AstraZeneca Rare Disease. BAK, LHS, ARH and UAD have no conflicts of interest to disclose.

Contributions

TCQ primarily wrote and revised the manuscript. BAK, LHS, ARH and UAD critically reviewed and revised the manuscript.

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Data-sharing statement

Original data are available upon request to the corresponding author.

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