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Diamond Blackfan Anemia - A Case Report

Lillian Percy Kujur[1], Amalorpavamari Lucas[2], Jayakumari J.[3]

[1]Associate Professor, College of Nursing, CMC Vellore, India

[2] Professor, College of Nursing, CMC Vellore, India

[3] Charge Nurse, BMTU, CMC, Vellore, India

Abstract: ***DiamondBlackfan Anemia (DBA) is a rare bone marrow failure disorder that is associated with mutations in components of the ribosome. DBA is a sporadic inherited anemia with broad spectrum of anomalies that are presented soon after delivery. It is characterized by anemia due to defect in the formation of the red blood cells. A plethora of clinical manifestations are observed. A set of complex diagnostic investigations are required to confirm the diagnosis. Hematopoietic stem cell transplant from a matched sibling donor is currently the only curative treatment. Emerging therapeutic approaches with gene therapy are showing promising outcomes. This article describes a case report with medical and nursing management carried out in a tertiary care hospital in Southern India which is eminent in Hematopoietic stem cell transplantation in India.***

Keywords: Anemia, Diamond Blackfan anemia, genetic disorder

1. Introduction

Diamond-Blackfan Anemia (DBA) is a rare congenital red blood cell aplasia characterized by failed erythropoiesis, congenital abnormalities, and a predisposition to malignancy(Noel, 2019). DBA has also been referred to as congenital pure red cell aplasia, chronic aregenerative anemia, erythrogenesis imperfect and congenital hypoplastic anemia. This paper describes a case report of Master M with DBA who underwent successful Hematopoietic stem cell transplantation.

2. Background

Diamond Blackfan anemia was first reported by Josephs in 1936 and further completely described by Diamond and Blackfan in 1938.(Narla et al., 2011)

3. Incidence

Diamond Blackfan anemia affects approximately 5 to 7 people per million live births per year. In the United States, there are approximately 25-35 new patients born per year. There are approximately 5000 cases world-wide. There are an equal number of males and females with the disease.(*National Organization for Rare Disorders*).

There are limited publications regarding presentation and response to treatment in DBA patients from India.(Singh et al., 2013)

4. Etiology

In about half of the patients with DBA the etiology of DBA is attributed to mutations at the genetic level. All the DBA mutations identified thus far, both in sporadic and familial cases, have been found in genes coding for ribosomal proteins. These genes provide instructions for making several of the approximately 80 different ribosomal proteins, which are components of cellular structures called ribosomes. Ribosomes process the cell's genetic instructions to create proteins. The first DBA gene to be identified in DBA is Ribosomal Protein S19 (RPS19), located on chromosome 19q13.2 and mutated in 25% of DBA patients. Recently, mutations in several other ribosomal proteins, RPS24, RPS17, RPL11, RPL5, RPS7, and RPL35a, have been identified in approximately 20% of DBA patients. In the remaining 55% of DBA patients, no mutations have been reported suggesting the existence of other genes involved in the pathogenesis of DBA.

5. Erythropoiesis in Diamond BlackfanAnemia

Erythropoiesis is a process by which hematopoietic stem cell in the bone marrow differentiate and proliferate into billions of red blood cells. Depending on demand, red cell production can be adjusted and upregulated substantially. A complex network of oxygen sensors, cytokines, such as erythropoietin, and other factors, including regulators of iron metabolism, are involved in the control of steady-state and stress-induced erythropoiesis, thereby ensuring appropriate oxygen supply to the peripheral tissues.

In healthy adults, about 200×10^9 red cells are produced per day in the bone marrow and are released into the peripheral blood. Because hematopoietic progenitor cells are not morphologically distinguishable, they are best characterized by cell-surface marker expression. A common cell-surface marker used to enrich for human progenitor cells is CD34, whereas enrichment of erythroid-cell populations is based on CD71 and glycophorinA expression (Figure 1A). Transcriptional regulation of erythroid differentiation involves intrinsic spatiotemporal expression of transcription factors such as GATA-1, GATA-2, and SCL (Figure1C).
(A) The figure shows a simplified scheme of the series of differentiation processes that takes place during red cell development. The main regulator of terminal erythropoiesis is erythropoietin. Commonly used cell-surface markers that are used to enrich for the different progenitor populations are shown below the cells.

(B) In patients with DBA the erythroid development is severely compromised.

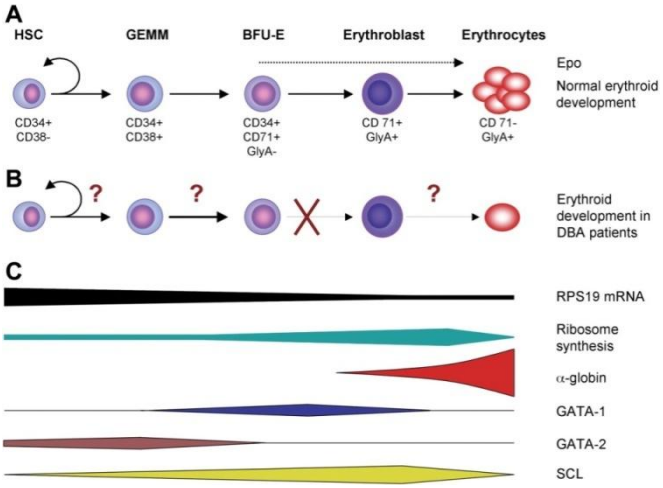

Figure 1: Normal and DBA erythropoiesis. Flygare & Karlsson (2007)

*Epo:erythropoietin; HSC: hematopoietic stem cell; GEMM: granulocyte/erythrocyte/macrophage/megakaryocyte colony-forming unit; BFU-E: erythrocyte burst-forming unit; CD34: positive cell-surface marker for hematopoietic progenitor cells; CD38: negative cell-surface marker for primitive hematopoietic progenitor cells; CD71: transferrin receptor; GlyA: glycophorin A; GATA 1 & GATA 2: erythroid transcription factor; RPS 19mRNA: ribosomal protein.

(C) The expression of RPS19 is high in primitive progenitor cells and decrease in more mature erythroid cells. In contrast ribosome synthesis is low in primitive progenitors, whereas mature erythroid precursors have a very high rate of ribosome synthesis to meet the demand for globin synthesis. The illustration shows the timing of expression of erythroid transcription factor.

Despite significant progress made in identifying mutations in various ribosomal genes in DBA, mechanistic understanding of how these mutations account for DBA pathophysiology including erythroblastopenia remains to be unresolved. An important unanswered question is why in DBA is there a tropism for an erythroid specific defect in the face of defective ribosomal assembly, which should affect the protein synthesis process in all cells and tissues? While it is generally accepted that DBA is an intrinsic defect of erythroid progenitors that are unable to complete normal differentiation process, this intrinsic defect is incompletely elucidated. A shortage of functioning ribosomal proteins may increase the self-destruction of blood-forming cells in the bone marrow, resulting in anemia.(Engidaye et al., 2019).

6. Inheritance

Diamond-Blackfan anemia is most commonly inherited in an autosomal dominant manner. A person with DBA has a 50% chance with each pregnancy of passing along the mutated gene to his or her child. Around 45% of affected people have inherited the mutation from a parent and about 55% have a new (*de novo*) mutation, where the anemia appears for the first time in the family and there are no other cases in the family. People with Diamond-Blackfan anemia may not appear to have a family history of the condition if relatives have very mild signs and symptoms. In rare cases, when caused by mutations in the GATA1 and in the TRS2 gene, Diamond-Blackfan anemia can be inherited in an X-linked manner. (*Diamond-Blackfan Anemia | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program*, n.d.)

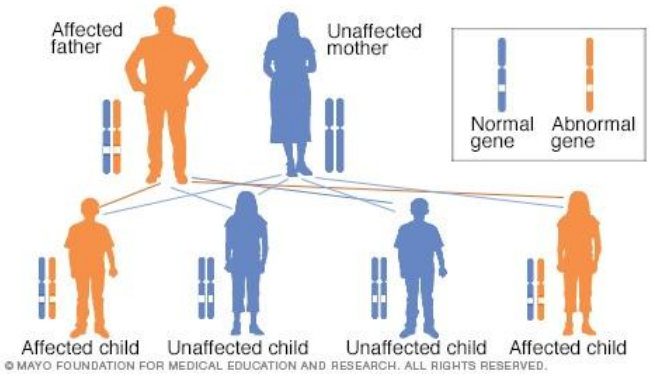

Figure 2: Autosomal dominant disorder

7. Clinical manifestations

DBA is characterized by a wide range of clinical features.
Anemia: It is the most prominent feature of DBA. It often manifests within the first few months after birth. Anemia is revealed by pallor, failure to thrive and sucking difficulty during feeding.Premature birth occurs in 20% of cases, and hypotrophy at birth and growth retardation have also been documented. Blood investigation reveals normochromic and macrocytic anemia with normal leukocytes and platelets.

A plethora of anomalies are reported in 50% of DBA-affected patients.

a) **Head and face:** Microcephaly; hypertelorism, epicanthus, ptosis; microtia, low-set ears; broad, depressed nasal bridge (Figure 3) cleft lip/palate, high arched palate; micrognathia; low anterior hairline (Figure 4).
b) **Eye:** Congenital glaucoma, congenital cataract, strabismus

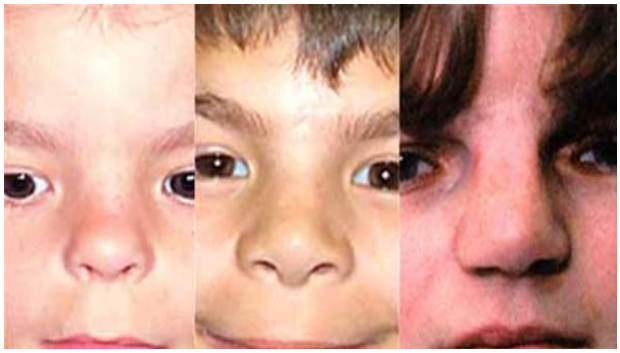

Figure 3: Low set eyes, flat nasal bridge

c) **Neck:** Webbing, short neck, Klippel-Feil anomaly, Sprengel deformity (Figure 4).

Figure 4: Microcephaly, low set ears, webbed neck, cleft palate

d) Upper limb and hand including thumb: Absent radial artery; flat thenar eminence; triphalangeal, duplex, bifid, hypoplastic, or absent thumb (Figure 5)

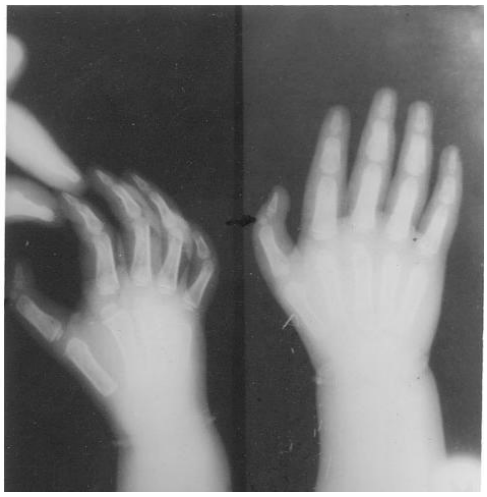

Figure 5: Triphalangeal thumb

e) **Genitourinary:** Absent kidney, horseshoe kidney; hypospadias.
f) **Heart:** Ventricular septal defect, atrial septal defect, coarctation of the aorta, other cardiac anomalies
g) **Growth:** Low birth weight and growth retardation.
h) **Malignancy:** DBA is associated with an increased risk for acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), and solid tumors including osteogenic sarcoma. (Da Costa, 2020)

8. Diagnosis

Diagnosing DBA is usually tough due to its partial phenotypes and the wide inconsistency of clinical expressions.

The preliminary laboratory investigations for the diagnosis of DBA include:

Laboratory tests: total "blood count, reticulocyte count, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration fetal hemoglobin level and an erythrocyte adenosine deaminase(eADA)activity,(elevated eADA levels are present in approximately 80-85% of patients with DBA).

Bone marrow aspirate and biopsy: reveals a normo-cellular marrow with normal myeloid maturation, adequate megakaryocytes, and a deficiency of red cell precursors.

Karyotyping: to identify any significant chromosomal abnormalities. Translocation involving the gene encoding *RPS19* and a large deletion on chromosome 3q involving the coding region for *RPL35a*, is often observed
Next Generation Sequencing (NSG) test: examines the sequencing of DNA fragments(Jahan et al., 2020)

Diagnostic criteria for Diamond Blackfan Anemia (2008).

Diagnostic criteria	*Supporting criteria*	
	Major criteria	*Minor criteria*
• Age less than 1 year • Macrocytic anemia with no other significant cytopenias • Reticulocytopenia • Normal marrow cellularity with a paucity of red cell precursors • Near normal, but variable, neutrophil and/or platelet counts	• Gene mutation described in "classical" DBA • Positive family history	• Elevated erythrocyte adenosine deaminase activity • Congenital anomalies described in "classical" DBA (Congenital anomalies mainly involve the head, upper limbs, heart, and genitourinary system.) • Elevated HbF (fetal hemoglobin) • No evidence of another inherited bone marrow failure syndrome.

9. Management

Some persons with DBA have mild signs and symptoms and do not require treatment. In people who require treatment it may include:

Corticosteroids: Corticosteroid treatment is recommended in children over 1 year of age; this treatment can initially improve the red blood count in approximately 80% of persons with DBA. Prednisone initial dose is 2 mg / kg / day given orally once a day.

Blood transfusions to keep the hemoglobin levels above 8 g/dL.

Bone marrow/stem cell transplantation: It is the only curative treatment for the anemia. Results are better for children younger than ten years of age if transplanted using a Human Leukocyte Antigen (HLA) matched sibling.(*Diamond-Blackfan Anemia | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program*, n.d.)

Gene therapy: Decades of research in this field have shown promising results. However, they are in the trial phase. (Aspesi et al., 2018)

10. Prognosis

The prognosis is generally good. However, complications of treatment and a higher incidence of cancer may reduce life expectancy. Disease severity depends on the quality and response to treatment. For patients undergoing regular transfusions, quality of life is altered as they can develop transfusion related infections and iron overload.(Engidaye et al., 2019)

11. Case Report

Master M a 4 month old child presented to our hospital in August 2012 with history of being born at term to consanguineous married parents in Southern India. There was no family history of malignancy. At Day 27, the child was evaluated at local hospital for poor feeding and not gaining weight. He was found to have hemoglobin of 3gm/dL. and was supported with packed cell transfusion and was cared for in the ICU. After 2 weeks the Hb increased to 8gm/dL and he continued to require multiple transfusions and hospitalization. Bone marrow aspiration revealed cellular marrow with marked erythroid hypoplasia and myeloid maturation arrest. He was diagnosed to have probable PaediatricMyelodysplastic Syndrome. He was started on Tab. Prednisolone 5mg BD from August 2012 to December 2012, however, there was no response to steroid therefore the therapy was gradually tapered and discontinued. Master M was started on Syr. Cyclosporine17.5mg BD as it has been reported to improve the treatment response.

In 2013, Master M was brought for reassessment as he did not have satisfactory response with steroid therapy. The parents were counseled for Hematopoietic Stem Cell transplantation, however, they declined due to financial constraints despite Master M's older sister having 8/8 HLA match.

In July 2020, Master M was brought to our hospital for Hematopoietic Stem Cell transplant. A repeat bone marrow aspiration and biopsy was done which revealed hypocellular marrow with marked erythroid hypoplasia and decreased megakaryocytes, reduced erythroids. The Cytogenetics and Karyotyping test was normal. The Next Generation Sequencing (NSG) test however, revealed RPS 19 mutation. The child was diagnosed to have Diamond Blackfan Anemia. Master M however did not manifest any morphological anomalies. He had received 80 units of red cell transfusion since birth.

Master M was admitted for HSCT on 10thAugust 2020, his older sister (8/8 HLA match) was the donor. He was admitted in the Bone Marrow Transplant Unit on Day -9. His conditioning regimen consisted of Inj. ATGAM 750mg, Inj. Thiotepa 180mg,InjTreosulphan 15mg, Inj. Fludarabine50mg. On Day '0'(21.09.2020) Master Mreceived 217 ml of peripheral blood stem cell infusion, which had a cell dose of CD34= 9.3 x10^{6}cells/kg. He was given aGVHD prophylaxis with Inj. Cyclosporine 75 mg Q12H IV and Inj. Methotrexate 5.8 mg IV stat as per the protocol and was closely monitored for acute post transplant complications. Master M had an uneventful peri-transplant period and he was discharged on Post transplant Day +18, (08.09.2020). During discharge, Master M was afebrile, his blood tests were as follows: WBC=5500/cumm, Platelets:48,000/cumm,Hb= 9.5gm/dL. He was on immunosuppression therapy with

Syr.Cyclosporine100mg BD. He visited the Post transplant clinic on 19.09.2020. He did not have any sign of aGVHD, his chimerism test revealed total donor cell chimerism. He was advised to continue to attend the post follow up clinic.

Nursing Care

Pre-transplant period

1. ***Nursing diagnosis***: Risk for ineffective tissue perfusion related to decreased Oxygen carrying capacity of the blood.

Expected outcome: Optimal tissue perfusion will be achieved and maintained.

Nursing interventions

- Assessed the vital signs including the Oxygen saturation two hourly.
- Monitored the Hb levels daily, it ranged between 7.2gm/dL.-10.7 gm/dL.
- Administered blood transfusion to maintain Hb above 8 gm/dL.
- Encouraged the child to take adequate rest, to minimize the oxygen demand of the body.

Evaluation: Adequate tissue perfusion was maintained, Master M did not have any dyspnea SaO2=100% on room air.

2. Nursing diagnosis: Parental fear and anxiety related to the disease condition, HSCT and outcome of the disease.

Expected outcome: Parental fear and anxiety will be minimized.

Nursing interventions:

- Established a good rapport with the child and parents.
- Encouraged them to verbalize their fears and doubts.
- Clear information was given about the disease condition and the transplant procedure.
- Psychological and spiritual support was given
- Explained about the availability of the Chaplain.
- Explained that Master M's mother was permitted to accompany him in the BMTU.

Evaluation: Anxiety was minimized as evidenced by relaxed facial expression.

Post Stem Cell Transplant

3. Nursing diagnosis: Risk for infection related to immune-compromised state.

Expected outcome: Infection is prevented as evidenced by normothermia and absence of bacterial growth in blood culture.

Nursing interventions:

- Monitored vital signs. Tem: 98.4 ^{0}F – 103^{0}F, HR: 86-158/min
- Followed meticulous hand hygiene.
- Maintained strict aseptic technique for all invasive procedures.
- Performed central line dressing regularly.
- Hydrated him adequately with intravenous fluids and oral fluids.
- Monitored total blood counts, blood culture, and serum Procalcitonin levels. Blood culture did not have any growth of microorganisms, Procalcitonin levels ranged between 0.46-0.60ng/ml)
- Administered antimicrobials as prescribed: Inj. Meropenem 900mg IV Q8H, Inj. Amikacin 300mg IVOD, Inj. Fluconazole 70mg IVOD, Inj. Acyclovir 110mgIV Q8H.
- Administered Inj. GrafeelS/C OD.
- Reverse barrier nursing was followed.
- Provided low microbial diet.
- Ensured adequate personal hygiene: Chlorhexidine 0.2% mouth washes, daily bath, hand washing before meals, and before and after using toilet.
- Educated his parents on prevention of infection.

Evaluation: Infection was prevented, Master M was afebrile during discharge.

4. Nursing diagnosis: Imbalanced nutrition related to decreased dietary intake.

Expected outcome Optimal nutritional status will be maintained.

Nursing interventions:

- Assessed the nutritional status daily.
- Provided low microbial diet.
- Encouraged to take high protein and high calorie diet.
- Monitored daily weight, (pre-transplant=21kg, at discharge=21.8 kg)
- Encouraged to take small frequent foods.
- Encouraged parents to prepare food according the child's likes and dislikes within the dietary restrictions)
- Avoided any painful procedure during meal times.

Evaluation: Optimal nutritional status was maintained, Master M did not have significant weight loss.

5. Nursing diagnosis: Risk for aGVHD related to HSCT.

Expected outcome: Master M will not develop GVHD.

Nursing interventions:

- Administered GVHD prophylaxis: Inj. Methotrexate 5.8mg IVStat, Inj Cyclosporine 75 mg IV Q12H as per the protocol.
- Monitored for signs of GVHD: assessed the skin, monitored for loose stools, palpation of liver enlargement. Liver function tests were performed.
- Strict intake and output chart was monitored.

Evaluation: Master M did not develop any sign of GVHD, he had normal bowel pattern, no evidence of skin rashes and liver functions were within acceptable range.

6. ***Nursing diagnosis*** :Diversional activity deficit related to therapeutic restrictions, protective isolation secondary to hempatopoietic stem cell transplantation.
Expected outcome: Play needs will be met.
Nursing interventions:

- Established a good rapport with the child and parents.
- Assessed the play needs of the child.
- Scheduled care and treatment to allow for paly activities.
- Encouraged parents to bring age appropriate toys.
- Provided age appropriate toys.
- Ensured that toys are autoclaved/ disinfected to prevent infection.
- Provide play activities that include educational needs for a school-age child.

Evaluation:Master M's play needs were met. Age appropriate toys were provided.

7. ***Nursing diagnosis***: Readiness for enhanced knowledge regarding home care as evidenced by verbalizing interest to know the information to be followed at home.

Expected outcome: Parents will be able to verbalize about the home care instructions.

Nursing interventions:

- Assessed his parents' understanding about home care, identifying complication & follow-up.
- Explained about the importance of follow up check-up, monitoring blood counts.
- Discussed the need for procedure such as regular central venous catheter care and blood sampling during follow up.
- Instructed about the importance of prevention of infection; personal hygiene, perineal hygiene, oral hygiene and protective environment.
- Educated the parents about food hygiene.
- Facilitated discussion about prophylactic anti-infective therapy and immune suppressive therapy: Tab Acyclovir 200mg TID, Tab Pantocid 20mg OD, Syr. Cyclosporine100mg BD, Tab Pentid 2LU BD, Tab. Fluconazole100mg OD
- Explained about resuming activities of daily living gradually.
- Encouraged to report warning signs such as fever, breathlessness, large episodes of loose stools, severe head ache, abdominal pain, immediately.

Evaluation: Parents were able to verbalize the instructions for home care.

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Author Profile

Mrs. Lillian Percy Kujur, Associate Professor, College of Nursing, CMC, Vellore.

Mrs. Amalorpavamari Lucas, Professor, College of Nursing, CMC, Vellore.

Mrs. Jayakumari J., Charge Nurse, BMTU, CMC, Vellore.