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Severe Combined Immunodeficiency (SCID) Presenting with Neonatal Aplastic Anemia

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Abstract

Aplastic anemia in the neonate is rare. We report a case of severe combined immunodeficiency (SCID) presenting with neonatal aplastic anemia. This report highlights the importance of considering SCID early in the evaluation of neonatal aplastic anemia prior to the development of infectious complications.

Keywords

Aplastic anemia; Severe Combined Immunodeficiency (SCID); neonatal

INTRODUCTION

We report the case of an infant presenting with neonatal aplastic anemia. The baby presented at birth with bruising and was noted to have anemia, thrombocytopenia, and intermittent lymphopenia. The patient's cytopenias progressed and a bone marrow evaluation confirmed

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severe aplastic anemia. A comprehensive evaluation was diagnostic for SCID. The patient underwent definitive treatment with hematopoietic cell transplantation (HCT).

RESULTS

The patient was born at 39–6/7 weeks gestation after an uncomplicated pregnancy to a 31 year old gravida 3, para 1 mother. Maternal serologies were negative for HIV and hepatitis B surface antigen, rubella-immune and RPR non-reactive. Testing was negative for maternal group B strep. Mother was blood type O positive and the infant was blood type A, Rh positive, antibody screen negative. There was no history of maternal medications, infections, or hypertension.

Physical exam at birth revealed weight 2,650 gm (5th percentile), length 48 cm (15th percentile) and head circumference 32 cm (5th percentile). There was extensive bruising on the scalp, trunk and extremities. No dysmorphologies were noted. The platelet count was 9,000/mm³, hematocrit was 34%, red cell mean corpuscular volume was 132 fL, and absolute lymphocyte count was 1,800/mm³. The initial absolute neutrophil count was 3,712/mm³. A comprehensive infectious evaluation was negative including blood cultures, testing for CMV and EBV, and virology testing on CSF, nasal and rectal samples. She was treated empirically with broad spectrum antibiotics.

She developed progressive anemia and persistent thrombocytopenia requiring regular transfusions (Figure 1A). Neutropenia with an ANC of 320/mm³ developed by day of life 13. The absolute lymphocyte count (ALC) fluctuated between 1,200/mm³ and 2,400/mm³ (Figure 1B). A bone marrow aspirate and biopsy on day of life 13 revealed 10% cellularity with decreased trilineage hematopoiesis without dysplasia or ring sideroblasts (Figures 1C and 1D). CD3 and CD79 stains showed numerous scattered T lymphocytes but fewer number of B lymphocytes. Cytogenetic evaluation and FISH studies for MLL, p53/CEP17 and chromosomes 5q, 7q, 8, 20q were normal.

An evaluation for inherited marrow failure included chromosomal breakage analysis for Fanconi anemia, telomere length assessment for dyskeratosis congenita and mitochondrial DNA deletion and duplication studies for Pearson syndrome, all of which were negative. Genetic testing was negative for dyskeratosis congenita, Shwachman-Diamond Syndrome and Diamond-Blackfan Anemia. After informed consent was obtained on an institutional IRB-approved protocol, the patient's DNA was analyzed on a targeted gene capture panel followed by next generation sequencing for over 90 genes associated with bone marrow failure, acute myelogenous leukemia and myelodysplastic syndrome but no causative mutations were identified. [1] Genetic evaluation is summarized in Table I.

At three months of age she was admitted for fever with neutropenia and was empirically started on cefepime. A comprehensive immunologic evaluation was sent. She developed respiratory distress prompting bronchoscopy with bronchoalveolar lavage (BAL) that demonstrated *Pneumocystis jiroveci* (PJP). She was treated with trimethoprim/sulfamethoxazole and filgrastim with poor neutrophil response. Her course was further

complicated by pulmonary aspergillosis requiring antifungal agents and granulocyte transfusions.

Lymphocyte subset analysis revealed an absence of B and NK cells with an absolute CD3 count of 1,366 and a CD4/CD8 ratio of 1.4. Naïve T cells (CD4 CD45 RA+) accounted for 80% of CD4 positive cells. T cell proliferation to phytohemagglutinin (PHA) was profoundly decreased measuring 2% of control. Quantitative immunoglobulins, including IgM, were normal for age. Vaccine response was not assessed. She received replacement immunoglobulin therapy. Adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) activity in lymphocytes was normal. A genetic evaluation for immunodeficiencies was negative for pathogenic mutations (Table I). T-cell receptor excision circles were assayed from her saved newborn screen blood spot and were normal. She was diagnosed with a genetically undefined T positive, B negative, NK negative SCID with accompanying severe aplastic anemia. Maternal engraftment was negative as assessed by PCR-amplified fragment length polymorphism analysis of short tandem repeat microsatellite loci (Promega PowerPlex 16, chimerism detection sensitivity 1–5%).

A follow-up bone marrow aspirate demonstrated hypocellular marrow particles. MDS FISH panel was negative for monosomy 5, deletion 5q, monosomy 7, deletion 7q, trisomy 8 and deletion 20q. Due to limited sample, karyotype and flow cytometry could not be performed.

A T-cell replete 10/10 HLA-matched unrelated donor was identified with the goal of achieving rapid immune reconstitution of neutrophils and T-cells given her disseminated aspergillosis infection. She underwent nonmyeloablative conditioning with fludarabine (total dose 90 mg/m²) and 2 Gy TBI at 5 months of age. [2] She rejected the bone marrow graft and underwent a second 10/10 HLA matched unrelated donor peripheral blood stem cell (PBSC) HCT at 7 months of age with reduced-intensity conditioning consisting of fludarabine (total dose 120 mg/m²), cyclophosphamide (total dose 1200 mg/m²) and alemtuzumab (total dose 0.8 mg/kg). [3] She is currently alive and well with full donor engraftment one year following HCT.

DISCUSSION

Aplastic anemia is characterized by multilineage cytopenias resulting from reduced or absent production of blood cells in the bone marrow. [4] Neonatal aplastic anemia is uncommon and necessitates evaluation of acquired and inherited etiologies.

Causes of aplastic anemia include infections, drugs/toxins, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria (PNH), inherited marrow failure syndromes and immune disorders. [4–8] Our patient underwent a comprehensive infectious workup which was negative for both vertically and horizontally transmitted diseases in addition to a thorough maternal medication history which ruled out perinatal toxin exposure. Myelodysplastic syndrome (MDS) in children often presents with hypocellular marrows. [6,7] Our patient's bone marrow, cytogenetic and genetic evaluations were negative for MDS.

Aplastic anemia can develop in patients with inherited bone marrow failure syndromes including Fanconi Anemia, Dyskeratosis congenita, Shwachman-Diamond Syndrome, and Congenital Amegakaryocytic Thrombocytopenia. [8] Although typically associated with red cell aplasia, Diamond-Blackfan Anemia and Pearson syndrome may present with multi-lineage cytopenias. [9,10] These syndromes are variable in presentation from mild cytopenias to severe pancytopenias, and physical anomalies may be lacking. [8] Our patient had a genetic evaluation which did not identify pathogenic mutations in previously identified genes implicated in bone marrow failure or immunodeficiency.

Immune dysregulation and immunodeficiencies have also been associated with aplastic anemia. [5] Although autoimmune disorders are uncommon in neonates, aplastic anemia in a neonate with lupus erythematosus has been reported. [11] Immunodeficiency has been associated with aplastic anemia in patients with several inherited marrow failure syndromes, including Shwachman-Diamond Syndrome, Dyskeratosis congenita and *GATA2* mutations. [12–14] Mutations in *IKZF1* have also been reported to affect both hematopoiesis and immune development. [15] No mutations in known genes causing marrow failure or immunodeficiency were identified so further genetic studies are underway.

Our patient met criteria for a genetically undefined leaky SCID in accordance with recently proposed diagnostic criteria for typical and leaky SCID. [16] Alloreactivity from maternal engraftment has also been implicated in bone marrow aplasia in patients with SCID. [17] Our patient's peripheral blood chimerism analysis was negative for maternal engraftment. It is possible that our patient harbors a novel genetic mutation associated with both hematopoiesis and immune regulation.

SCID is a life-threatening disease wherein outcomes are improved by early diagnosis and treatment. [18–20] Infections are the major cause of morbidity and mortality so timely initiation of prophylactic antimicrobial agents and curative therapy are critical to medical management. This case emphasizes the importance of early consideration of SCID in the differential diagnosis of neonatal aplastic anemia.

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Figure 1. Platelet, hematocrit, absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) during the first 100 days of life (A and B). Hypocellular bone marrow biopsy in the proband at (C) low (4X) and (D) high (40X) power magnification.

Table 1

Genetic Evaluation

	Dyskeratosis congenita	Diamond-Blackfan anemia	Fanconi anemia	Congenital neutropenia	Other inherited BME/MDS	Familial MDS/Leukemia	AML and MDS	Immunodeficiencies	
	<i>CTC1</i>	<i>GATA1</i>	<i>FANCA</i>	<i>ELANE</i>	<i>ABCB7</i>	<i>CBL</i>	<i>ABL1</i>	<i>NRAS</i>	<i>ADA</i>
	<i>DKC1</i>	<i>RPL11</i>	<i>FANCB</i>	<i>G6PC3</i>	<i>ANKRD26</i>	<i>CEBPA</i>	<i>ASXL1</i>	<i>PML</i>	<i>AK2</i>
	<i>NHP2</i>	<i>RPL35a</i>	<i>FANCC</i>	<i>GFI1</i>	<i>ATM</i>	<i>ETV6</i>	<i>BCL2L11</i>	<i>PRPF40B</i>	<i>DCLRE1C</i>
	<i>NOP10</i>	<i>RPL5</i>	<i>BRCA2 (FANCD1)</i>	<i>HAX1</i>	<i>ATR</i>	<i>GATA2</i>	<i>BCOR</i>	<i>RARA</i>	<i>IKZF1</i>
	<i>RTEL1</i>	<i>RPS10</i>	<i>FANCD2</i>	<i>JAGN1</i>	<i>ATRX</i>	<i>PAX5</i>	<i>BCR</i>	<i>RPS14</i>	<i>LIG4</i>
	<i>TERC</i>	<i>RPS17</i>	<i>FANCE</i>	<i>TCIRG1</i>	<i>C15ORF41</i>	<i>RUNX1</i>	<i>BRAF</i>	<i>SF1</i>	<i>NHEJ1</i>
	<i>TERT</i>	<i>RPS19</i>	<i>FANCF</i>	<i>VPS45</i>	<i>CDAN1</i>		<i>DNMT3A</i>	<i>SF3A1</i>	<i>PGM3</i>
	<i>TINF2</i>	<i>RPS24</i>	<i>FANCG</i>	<i>WAS</i>	<i>MPL</i>		<i>EZH2</i>	<i>SF3B1</i>	<i>RAC2</i>
	<i>WRAP53</i>	<i>RPS26</i>	<i>FANCI</i>		<i>NBN</i>		<i>FLT3</i>	<i>SRSF2</i>	<i>RAG1</i>
		<i>RPS7</i>	<i>BRIP1 (FANCI)</i>		<i>RMRP</i>		<i>IDH1</i>	<i>STAG2</i>	<i>RAG2</i>
			<i>FANCL</i>		<i>SBDS</i>		<i>IDH2</i>	<i>TET2</i>	
			<i>FANCM</i>		<i>SRP72</i>		<i>JAK2</i>	<i>TP53</i>	
			<i>PALB2 (FANCN)</i>				<i>KIT</i>	<i>U2AF1</i>	
			<i>RAD51C (FANCO)</i>				<i>KRAS</i>	<i>U2AF2</i>	
			<i>SLX4 (FANCP)</i>				<i>MET</i>	<i>WT1</i>	
			<i>ERCC4 (FANCO)</i>				<i>MLL</i>	<i>ZRSR2</i>	
							<i>NPM1</i>		