Transient abnormal myelopoiesis at birth in an infant with Down syndrome: A unique entity

Bindhu Vechangi1, Gaurav Gupta2, Swati Umasanker1, Priyanka Gupta3, Kriti Mohan4, Neha Singh5, Nowneet Kumar Bhat6, Swathi Chacham7

From 1Junior Resident, Department of Pediatrics, All India Institute of Medical Science Rishikesh, Uttarakhand, India, 2Senior Resident, Department of Pediatrics, All India Institute of Medical Science Rishikesh, Uttarakhand, India, 3Associate Professor, Department of Anesthesiology, All India Institute of Medical Science Rishikesh, Uttarakhand, India, 4Associate Professor, Department of Pediatrics, All India Institute of Medical Science Gorakhpur, Uttar Pradesh, India, 5Additional Professor, Department of Pathology, All India Institute of Medical Science Rishikesh, Uttarakhand, India, 6Professor and Head, Department of Pediatrics, All India Institute of Medical Science Rishikesh, Uttarakhand, India, 7Additional Professor, Department of Pediatrics, All India Institute of Medical Science Gorakhpur, Uttar Pradesh, India

Correspondence to: Dr. Swathi Chacham, DM Neonatology, Additional Professor, Department of Pediatrics, 6th level (Floor), A block, Medical College Building, All India Institute of Medical Sciences, Rishikesh, Virbhadramarg, Uttarakhand, India. E-mail: swathi.m.lahiri@gmail.com

Received - 24 January 2020 Initial Review - 15 February 2020 Accepted - 18 March 2020

ABSTRACT

Transient abnormal myelopoiesis (TAM) is a hematological disorder, which is rare but unique for children with Down syndrome. It is important to diagnose this entity, as these children are at 500 times higher risk for the development of acute myeloid leukemia (AML) later in life. We report a late-preterm, low birth weight, female baby born to a 35-year-old G4P2L2A1 mother. The baby was diagnosed to have down’s phenotype at birth. On the day one of life, the baby had leukocytosis with increased peripheral blast cells. On 23rd day of life, there was a resolution of leukocytosis and the disappearance of blast cells. The child has been under regular follow-up since then. As these children are at a high risk for the development of AML in later life, a hemogram with total leukocyte counts and differential count should be a part of neonatal follow-up.

Key words: Down syndrome, Neonate, Transient abnormal myelopoiesis

D own syndrome (DS) is the most common congenital disorder (~1/1000 live births) in humans [1]. Transient abnormal myelopoiesis (TAM), in DS (DS-TAM), is a unique and rare megakaryocytic myeloproliferative disorder that typically resolves spontaneously within a few months. It is reported to occur in 10–15% of neonates with DS [1]. The World Health Organization (2016) has defined DS-TAM as a megakaryoblastic proliferation, occurring at birth or within days of birth, and resolving spontaneously 1–2 months later [2]. However, 20–30% of children with a history of DS-TAM may subsequently develop DS-related acute megakaryoblastic leukemia (DS-AMKL) within the first 5 years of life [3-4]. Thus, DS-TAM is considered a preleukemic stage. We report a newborn with DS, who developed DS-TAM at birth, which resolved rapidly and spontaneously within the neonatal period.

CASE REPORT

A female newborn was born at 35 weeks of gestational age to a non-consanguineous couple. The mother was 35-year-old G4P2L2A1. There was no family history of sibling deaths and other siblings were phenotypically normal. Her antenatal period was uneventful. Her intrapartum course was also uneventful, and the baby was born by normal vaginal delivery. The newborn cried immediately and her Apgar scores were 8 and 9 at 0 and 5 min. However, there was mild respiratory distress with mild intercostal retractions. The neonate was shifted to the neonatal intensive care unit (NICU) and oxygen was supplemented. The SpO2 of all the four limbs was 94–96% on minimal oxygen. On examination, there was a systolic murmur present in parasternal areas. There was no hepatosplenomegaly. The chest X-ray was done in view of mild respiratory distress, which showed mild cardiomegaly; however, all lung fields were clear. Umbilical cord samples were sent for baseline investigations, according to hospital policy. C-reactive protein was positive; however, blood culture was sterile. Thyroid-stimulating hormone levels were normal (2.57 µIU/ml).

An urgent call was received from the pathology department of the institute regarding gross abnormality in the hematology picture
of this newborn. The hematology report (day 0) showed packed cell volume: 63%, white blood cell: 60,600/mm\(^3\), neutrophil (N): 39%, lymphocytes (L): 30%, blast cells: 30%, and platelets: 215,000/mm\(^3\). The peripheral smear showed leukocytosis with 30% atypical blast cells showing high nucleo-cytoplasmic ratio (N/C ratio), fine chromatin, 2–3 prominent nucleoli, and pale cytoplasm with granules (Fig. 2a). As the baby was asymptomatic, a probable diagnosis of DS-TAM was made.

The neonate received oxygen for 2 days. On 3\(^{rd}\) day, she was transferred to the postnatal ward from the NICU. Intravenous (IV) antibiotics were administered for 3 days. She was otherwise active and feeding well, voided urine, and passed stool. The parents were counseled about the probability of DS in the neonate and it was confirmed by karyotyping. In view of the presence of a systolic murmur, a 2D transthoracic echo was done, there was a small 2–3 mm atrial septal defect (ASD) with mild pulmonary artery hypertension. There was good ventricular function. The ultrasound abdomen and cranium were within normal limits.

On the 6\(^{th}\) day, the peripheral smear and total leukocyte counts (TLC) were repeated and reported as TLC: 45,400; N:26%, L:38%, and blasts:35%. As the neonate was thriving well and was otherwise asymptomatic, she was discharged from the hospital on the 8\(^{th}\) day and asked to come for follow up after 15 days. On the 23\(^{rd}\) day of life, TLC and peripheral smear were repeated and reported as TLC: 8600, N:16.4%, L:69.9%, no blasts, and normal platelets (Fig. 2b). Thus, the resolution of leukocytosis and disappearance of blast cells confirmed the diagnosis of DS-TAM. The parents were counseled about the possibility of a child developing acute myeloid leukemia (AML) in the future and were advised to be under regular follow-ups.

The child has been followed up to 2.5 years of age and still currently under follow-up. She has developed gross motor and fine motor milestones and social communication skills according to development scale for children with DS. Her height, weight, and head circumference are around the 10\(^{th}\) percentile of the WHO growth chart. 2D-Echo was done at the age of one year, and spontaneous closure of ASD was noted. Till now, there is no clinical/ laboratory evidence of the development of AML.

**DISCUSSION**

DS is not only associated with stunted physical growth and mental retardation but may also be associated with congenital heart disease, renal defect, gastrointestinal malformations, skeletal deformities, and hematological abnormalities [5]. Full trisomy 21 (non-disjunction) accounts for 94% cases of DS, translocations account for 3.3%, and mosaicism accounts for the remaining 2.4% cases of DS [6]. All cytogenetic types of DS are predisposed to develop leukemia. The risk of development of AML increases up to 150 times in children with DS of <5 years of age. The risk of development of acute lymphoblastic leukemia (ALL) increases up to 40 times in the children with DS below 5 years of age and 12 times in the age group between 5 and 30 years [7].

The development of TAM in DS may be due to the effect of trisomy 21 on liver hematopoiesis together with megakaryocyte–erythroid progenitor frequency with common myeloid progenitor. The GATA1 gene is present on the X chromosome and encodes a hematopoietic transcription factor that is essential for normal megakaryocytopoiesis. Almost all the babies with TAM have acquired mutations at the N-terminal of the GATA1 gene [8]. The GATA1 gene mutation (somatic mutation at exon 2) blocks differentiation of the megakaryocytic lineage beyond the megakaryoblast stage. In the absence of trisomy 21, these mutations may cause anemia or neutropenia but are not leukemogenic. These mutations may be present during fetal life or after birth and disappear when TAM enters into remission [8]. TAM affects 4–10% of neonates with DS [9]. However, 20–30% of DS children who develop TAM may develop AMKL later within 5 years of life [4].

There are variable clinical presentations of TAM among children with DS. Most of the children are asymptomatic and diagnosed during routine testing by the presence of circulating blast cells with or without leukocytosis. TAM may also present with hepatomegaly (60%), splenomegaly (35–40%), jaundice (15%), pericardial effusion (15%), pleural effusion (10–15%), ascites (10%), respiratory distress (10%), and bleeding diathesis.
The hematological findings include moderately raised leukocytes counts, an increased number of peripheral blasts with or without thrombocytopenia [11]. A bone marrow examination is usually not done as abnormalities in marrow pictures are less pronounced than those in the peripheral blood [12,13]. Almost all cases of DS-TAM present within 2 months of age, few of them may manifest before or at birth with either intrauterine death or hydrops fetalis [4,11]. The most common age of presentation is between 3 and 7 days of life [11-13]. More than 80% undergo spontaneous remission by the age of 3–6 months [4].

This child was diagnosed to have DS-TAM on the very first day of life which is new and unique to this case. In our hospital, there is a hospital protocol to order baseline investigations of all the sick newborns, which also includes, hemogram comprising TLC and differential leukocyte counts. The presentation of DS-TAM on the 1st day of life supports that it is a fetal hematopoietic disorder. Congenital leukemia could also be a differential diagnosis for this patient. However, this child remained asymptomatic and there was the spontaneous resolution of leukocytosis and disappearance of blast cells at the 23rd day of life, which supports the diagnosis of DS-TAM. We report this case as the earliest diagnosis of DS-TAM (1st day of life), and also earliest spontaneous remission (23rd day of life).

CONCLUSION

TAM is a rare hematological disorder unique to down syndrome, which has a spontaneous resolution. However, it is crucial to diagnose this entity, as these children are at substantial risk to develop AMKL. It is vital to screen all the neonates with down syndrome for this entity.

ETHICAL CLEARANCE

Institute ethical committee NO: AIIMS/IEC/16/148

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Funding: None; Conflicts of Interest: None Stated.


Doi: 10.32677/IJCH.2020.v07.i06.011