Transient Leukemia in Down Syndrome: Report of Two Cases with Review of Literature

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Abstract Transient leukemia (TL) also referred to as transient abnormal myelopoiesis (TAM) or transient myeloproliferative disorder (TMD) is a unique syndrome that frequently occurs in newborns with Down syndrome (DS). It manifests in the first few days of life and shows leukocytosis with blast cells in the blood and bone marrow. This leukemia resolves spontaneously within first few months of life in the majority of cases. In this report we describe two newborns with a karyotype of 47,XY,+21, presented with marked leukocytosis and many blast cells in the peripheral blood. In both the cases, the blasts disappeared and the total leukocyte count reverted to normal without any specific treatment.

Keywords Transient leukemia · Down syndrome · Transient abnormal myelopoiesis · Transient myeloproliferative disorder

Introduction:

Down syndrome (DS) is the most common chromosomal disorder with an incidence of 1 in 700 live births. Children with DS show a spectrum of hematologic abnormalities such as neutrophilia, thrombocytopenia, polycythemia, anaemia, thrombocytosis and macrocytosis. They have an increased predisposition to acute leukemia, predominantly myeloid type. The major morphological subtype is acute megakaryoblastic leukemia (AMKL) [1]. Approximately

10% of the neonates with DS exhibit a unique disorder known as transient leukemia (TL) or transient myeloproliferative disorder (TMD) or transient abnormal myelopoiesis (TAM) that presents with clinical and morphologic findings indistinguishable from AML and shows a high rate of spontaneous remission. The majority of affected patients are clinically asymptomatic at presentation and are detected incidentally by finding of abnormal blood counts and circulating blasts in the peripheral blood and bone marrow. They may show peripheral blood basophilia and erythroid and megakaryocytic dysplasia in bone marrow. Less commonly they display hepatosplenomegaly, jaundice and rarely effusions with hydrops fetalis. In most patients TL is self limiting and remission occurs during first 3 months of life without any therapy [2]. We present two cases of TL with DS and discuss their clinicohematological profile.

Case Report

Case 1

A 3 day old male baby was admitted with history of mild fever and not accepting the feeds. The mother was a 25 years old, third gravida, delivered normally after 34 weeks of gestation. The baby weighed 1,900 g and was noticed to have mongoloid slant, low set ears, epicanthic folds, high arched palate, short neck and hypotonic posture; the features suggestive of DS which was confirmed by karyotypic analysis. The liver and spleen were palpable 1 and 3 cm below costal margins, respectively.

A routine hemogram showed that the total leukocyte count (TLC) was $140 \times 10^9/l$, platelet count was $50 \times 10^9/l$ and hemoglobin (Hb) was 14 g/dl. The peripheral blood smear showed 74% blast cells, 5%

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Fig. 1 Peripheral blood smear showing blasts, the blast in the center shows dense blue cytoplasm and blebs (megakaryoblast) [Leishman stain, $\times 1000$]

promyelocytes, 5% myelocytes, 10% polymorphs, 1% eosinophils, 5% basophils and 40 nRBCs/100 WBCs. The blasts were medium to large sized with round nuclei having fine reticular chromatin, 1–4 nucleoli and basophilic cytoplasm. Some of the blasts showed cytoplasmic granules, blebs or projections; morphologically consistent with megakaryoblasts (Fig. 1). Cytochemical staining with MPO, SBB, PAS and NSE was negative. Total bilirubin was 9.5 mg% and indirect bilirubin was 8.5 mg%. Ultrasonography revealed mild pleural effusion on right side. Karyotyping showed 47,XY,+21. With these clinical and hematological findings along with cytogenetic study, a presumptive diagnosis of transient leukemia with DS was considered. The parents were counseled and close hematological follow up was advised. The baby was given only supportive care and chemotherapy was not given. Follow up smears after 1 week showed similar blood picture. Baby gradually improved clinically and was discharged on 20th day. Peripheral smear at the time of discharge showed 30% blasts. After 8 weeks of follow up, the hematologic profile returned to normal (TLC $8.8 \times 10^9/l$, platelet count $150 \times 10^9/l$ and Hb 11 g/dl). The peripheral smear did not show blast cells and differential count was within normal limits. The baby was lost for follow up and on enquiring the parents informed that the baby died in sleep at the age of 4½ months.

Case 2

A 21 year old lady with history of III⁰ consanguineous marriage delivered a male baby by caesarian section at 34 weeks of gestation. The indication for LSCS was severe pregnancy induced hypertension with failure of induction.

The baby weighed 2,100 g and showed phenotypic features of DS.

The hematological investigations were requested to look for the possibility of TL with DS. The hemogram showed Hb –19 g/dl, TLC— $56 \times 10^9/l$ and platelet count $<20 \times 10^9/l$. The peripheral blood smear showed 44% blast cells, 4% promyelocyte, 8% myelocytes, 6% meta-myelocyte, 30% neutrophils, 7% lymphocytes, 1% eosinophils and 7 nRBCs/100 WBCs. The blast morphology was suggestive of megakaryoblasts and cytochemical staining with MPO, PAS, SBB and NSE was negative. A tentative diagnosis of transient myeloproliferative disorder/transient leukemia with DS was rendered. Bone marrow aspiration yielded dry tap. USG revealed mild hepatosplenomegaly, minimal ascites and moderate pericardial effusion. Total serum bilirubin was 5.6 mg% (Indirect—0.6 and direct—5 mg %). Cytogenetic studies showed a karyotype of 47,XY,+21. The blasts were positive for CD34, HLA-DR, CD117, CD61 and CD41 by flow cytometry, indicating megakaryoblastic lineage. The baby was observed and treated symptomatically. The parents were counseled and close clinical and regular hematologic follow up was advised. Spontaneous remission was observed in 2 months and the hematological findings were within normal limits except for peripheral blood basophilia (7%). The baby is under regular follow up for last 5 months and is healthy.

Discussion

One of the unique hematologic abnormalities seen in neonates with DS is transient leukemia (TL-DS), characterized by transient appearance of blast cells in the peripheral blood which disappear spontaneously. According to some authors the blasts in TMD represent precursor cells with pluripotent potential for megakaryoblastic, erythroid and basophilic differentiation and thus they can resemble myeloblast, lymphoblast, erythroblast and even monoblast rendering correct lineage assignment difficult. The transient nature of this condition can be explained by the great capacity of TMD blasts to proliferate and differentiate into various kinds of cells including basophils, neutrophils, eosinophils monocytes and erythrocytes [3]. Peripheral blood basophilia was noted in both of our cases. Recent studies have shown the blasts of TMD to be clonal in origin and show GATA1 mutation in nearly all patients with TMD [4]. The blasts in TL-DS are almost always megakaryoblasts and are virtually indistinguishable from the blasts of AMKL. These blasts mark as megakaryoblasts by cytochemical stains. They are strongly positive for acid phosphatase, occasionally granular to block positive for PAS and negative for SBB, MPO and chloroacetate esterase. Electron microscopy and flow cytometry also confirms

Table 1 The clinicohematological profile of TMD cases from India

Source	Year	C	PA	S	Clinical features	GA	Hematologic findings				R	Follow up	
							TLC	Blasts	Cyto	IP			BMB
Dhaded et al.	1996	1	Newborn	F	DS, resp. distress, Lo So	37 wk	44000/μl	90%	NM	NM	NM	4 wks	Wt gain
Jindal et al.	2000	1	20 days	F	DS, icterus, L5 cm, S2 cm	NM	NM	38%	MPO–	CD34+	4%	8 wks	Died at 3½ mths
Amar Shah et al.	2003	1	1 mth	M	DS, left renal lump, LoSo, PUJ obstruction	FT	40200/μl	41%	SBB+	NM	43%	6 mth	Well at 9 mths of age
Prabhu et al.	2004	1		F	DS, liver++, spleen+	NM	46923/μl	64%	PAS–	NM	60%	3 wks	Died at 6 mths, by AML
Anshu Awasthi et al.	2005	1	Birth	F	DS, resp.distress, L2 cm, S2 cm	NM	41000/μl	40%	NM	NM	NM	2 mths	NM
	2	Birth	F	NNJ, GI bleeds, LoSo			48000/μl	85%	NM	NM	NM	1 mth	NM
	3	1.5 wk	M	Resp.distress, L5 cm, S1 cm			60000/μl	81%	NM	NM	NM	2 mth	NM
	4	2 wks	M	NNJ, L8 cm, S3 cm			42000/μl	56%	NM	NM	NM	1 mth	NM
Sarda et al.	2007	1	2 days	M	DS, imperforate anus,	FT	65600/μl	74%		NM	NM	3 mth	NM
					Myeloblast								
Shenoy et al.	2008	1	14 days	M	DS, resp. distress, pericardial effusion with eosinophils, L5 cm, S3 cm	FT	150000/μl	46%	NM	CD33+	72%	3 wks	Well at 1 year of age
										CD43+			
										CD10+			
Hema, Anand et al.	2009	1	Newborn	F	DS	NM	57000/μl	70%	Negative	CD34+	NM	8 wks	NM
										CD33+			
Present cases	2009	1	3 days	M	DS, L1 cm, S3 cm, pleural effusion, raised bilirubin.	34 wk	140000/μl	74%	MPO–	NSE–	ND	8 wks	Died at 4 mths
	2	Newborn	M	DS, L1 cm, S1 cm, pericardial effusion, ascites and raised bilirubin	34 wk		56000/μl	44%	SBB–	PAS–		8 wks	Well at 5 mths
									MPO–	NSE–	CD34+		
									SBB–	PAS–	CD41+		
											CD61 +		

C Cases, PA age of presentation, mth month, wk week, S sex, F female, M male, DS Down syndrome, L liver, S spleen, PUJ pelviureteric junction, resp respiratory, NNJ neonatal jaundice, GA gestational age, NM not mentioned, FT full term, Cyto cytochemistry, IP immunophenotyping, BMB bone marrow blast, – Negative, + positive, ND not done, DT dry tap, R remission

them as megakaryoblasts. They express CD45, CD34, CD33, CD38, CD36, CD56, HLA-DR, CD7 and at least one of the megakaryocytic markers CD41, CD42a or CD61 [4]. In our cases morphologically blasts were consistent with megakaryoblasts and in the second case megakaryoblastic lineage was confirmed by flow cytometry.

Review of literature reveals enormous information about the natural history, biology and varied clinicohematologic features of TMD. The various prognostic factors and controversies about treatment indications have been extensively studied, however, literature search shows that only 11 cases have been reported from India [5–12]. The first case of TMD from India is reported in 1996 [5]. The clinicohematological profile of these cases are presented in the Table 1. Rare associations of TL-DS with different types of congenital anomalies like imperforate anus or urological anomaly have been reported in Indian literature [7, 10].

Though TL-DS occurs almost exclusively in neonates with DS or trisomy 21 mosaicism, rare cases of TL/TMD without DS have also been described. Studies have shown that the presence of trisomy is essential for the disease. In phenotypically normal infants without constitutional trisomy 21 but with TMD, the TMD clone carries trisomy 21. Cytogenetic and molecular analysis have shown trisomy 21 and GATA 1 mutation restricted to leukemic cells [10].

The differential diagnosis for this condition includes leukemoid or leukoerythroblastic reaction and congenital leukemia. Causes of leukemoid reaction such as intrauterine infections, neonatal sepsis and erythroblastosis fetalis should be ruled out. TL cannot be readily distinguished from congenital leukemia which has an aggressive behavior. TL is usually a benign self limiting process that resolves spontaneously in the first few months of life and the diagnosis is confirmed only on follow up. The blasts are morphologically indistinguishable from the blasts in the cases of persistent leukemia. The magnitude of leukocyte count or the degree of thrombocytopenia are not reliable distinguishing features. However, a clue to the diagnosis of TL is that TL has lower blast percentage in the bone marrow as compared to the peripheral blood [2, 4].

Though TL-DS resolves spontaneously in the majority of cases, early death and development of myeloid leukemia, especially AMKL may occur. The prognostic factors and treatment indications for chemotherapy have not been firmly established. About 22% of TL patients die at an early age (<6 months of age) [13, 14]. The main causes of death were organ failure, particularly hepatic and cardiopulmonary failure [14]. In some of these patients hepatic fibrosis is associated with megakaryoblastic infiltration of the liver [14]. The various risk factors which predict poor outcome are early gestational age (<37 weeks), high TLC ($\geq 100 \times 10^9/l$), high percentage of peripheral blasts,

elevated aspartate transaminase, elevated direct bilirubin and low APGAR scores. In high risk neonates one week course of low dose of cytarabine has been documented to be helpful [13]. In our first case early gestational age (34 weeks), high TLC ($140 \times 10^9/l$) with 74% blasts, raised serum bilirubin and hepatosplenomegaly with pleural effusion were present, which correlates with early death of the baby and supports the studies described by Hideki et al. [13]. About 30% of infants after resolution of TMD eventually develop AML mostly M7 before 4 years of age. AMKL occurs more frequently in TMD that initially had additional cytogenetic abnormality in addition to trisomy 21. Other findings such as complete blood count, percentage of blasts, liver enzyme activities are not predictive of eventual AMKL [14].

In conclusion, neonatal leukemia must be diagnosed with caution, especially in babies with DS, as this can be TL-DS which has a benign course. They usually need only supportive care with clinical and regular hematologic follow up and may not need chemotherapy. However, if they show deterioration and progressive course, chemotherapy should be considered.

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