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Case Report

Transient leukaemia of down syndrome in a neonate: case report

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ABSTRACT

Transient leukemia of Down syndrome(TL-DS) or transient myeloproliferative disorder (TMD) or transient abnormal myelopoiesis (TAM) is a hematologic abnormality characterized by an uncontrolled proliferation of myeloblasts in peripheral blood and bone marrow which characteristically affects newborns and babies with Down syndrome. Children with Down syndrome (Trisomy 21) have a unique predisposition to develop myeloid leukemia of Down syndrome(ML-DS). In majority of cases of TL-DS, the GATA1 mutant clone goes into spontaneous remission without the need for chemotherapy. However, 10-20 % of neonates with TL-DS and silent TL-DS subsequently develop ML-DS in the first 5 years of life due to additional oncogenic mutations acquired by the persistent GATA1 mutant cells. We present here, one such case of Down syndrome with TL-DS in a neonate.

Keywords: Down syndrome, neonate, Transient abnormal myelopoiesis, Transient leukaemia of Down syndrome, Transient myeloproliferative disorder, Tumor lysis syndrome

INTRODUCTION

Down syndrome (DS) is one of the most frequent chromosomal abnormalities among neonates. Globally, the incidence of DS, approximately is 1:1000 births and is influenced by an increase in maternal age.[1] DS babies are at an increased risk of mortality and morbidity including intellectual and physical disability as well as various medical issues. Hematological disorders, such as transient leukemia of Down syndrome(TL-DS), myelodysplastic syndrome (MDS) and acute leukemia (AL) are one of these multiple medical issues.[2] TL-DS is also known as transient myeloproliferative disorder (TMD) or transient abnormal myelopoiesis (TAM). TL-DS develops in 10%-15% of newborns with DS in the initial days after birth. TL-DS usually resolves spontaneously, except in some cases where myeloid leukemia (ML) can manifest later in life requiring specific treatment.

In this report, we present a case of DS neonate with TL-DS who was successfully treated to prevent tumor lysis syndrome (TLS).

CASE REPORT

A 30 year old elderly primigravida, married since 13 years with no history of abortions and consanguinity, delivered vaginally a 1.6 kg, 32 week preterm female baby. Baby had normal APGAR score at birth and was admitted in NICU for prematurity and low birth weight. Our patient had characteristic DS facies with bilateral pre-auricular tags without organomegaly (Figure 1). Investigations done on the 3rd day of life revealed a total

leukocyte count (TLC) of 49,300/cu.mm, platelet count 40,000/cu.mm, haemoglobin (Hb) 14.3gm% with 85%blasts, 12% neutrophils, 01% lymphocytes, 01%monocytes and 01% basophils on peripheral blood smear (Figure 2 and Table 1). Morphologic and immunophenotypic analysis done on day of life 7 was suggestive of TL-DS showing 82%blasts, 10%neutrophils and 08% lymphocytes on flow cytometry which reconfirmed the initial findings of peripheral blood smear. Antigenically, the blasts were negative for myeloperoxidase (MPO) and neuron specific enolase (NSE). Electrophoretogram (QF PCR) analysis for chromosome specific markers indicated trisomy 21(47, XX,+21) consistent with Down syndrome. A presumptive diagnosis of TL-DS was made in our baby based on the characteristic investigations and clinical features. On serial monitoring, TLC reached a peak of 1.2 lakhs/cu.mm with Hb 9.8gm% and platelet count 45,000/cu.mm on day 17 of life (Table 1).

Table 1: Laboratory hematological, biochemistry values from our patient on day three onwards till follow up at age 13th month of age.

	Day 3	Day 17	Day 22	Day 32	F/U 13th month of age
WBC count (cells/µL)	49,300	1,20,000	45,700	10,800	9,400
Blast Count % (peripheral smear)	85%	68%	60%	10%	No blast
Hemoglobin (gm%)	14.3	9.8	12.5	11.8	11.0
Haematocrit (%)	56.5	40.7	30.4	31.2	32.7
Platelets (cells/µL)	40,000	45,000	79,000	1,60,000	2,13,000
Total protein (g/dL)	4.4	4.6	4.2	4.0	4.6
Albumin (g/dL)	2.1	2.5	2.8	2.6	2.8
Urea (mg/dL)	16.9	16.5	16.3	16.4	14.2
Creatinine (mg/dL)	0.6	0.7	0.6	0.5	0.6
Sodium (mEq/L)	139	141	138	136	140
Potassium (meq/L)	4.4	4.3	4.0	3.8	4.0
Phosphorus (mg/dL)	4.0	4.3	4.2	4.5	4.3
Calcium (mg/dL)	6.5	7.5	9.0	9.2	9.6
Uric acid (mg/dL)	3.1	3.4	4.0	3.2	3.5
Alanine aminotransferase (IU/L)	26	36	28	20	22
Aspartate aminotransferase (IU/L)	16	20	18	14	16
Serum TSH (micro IU/ml)	2.32 Reference range (0.72-11)				
Serum Free T3 (pmol/L)	4.67 Reference range (3-9.28)				
Serum Free T4 (pmol/L)	34.6 Reference range (11.5-28.3)				

Baby was started on oral allopurinol and intravenous fluid hydration for 10 days to prevent complications of tumour lysis syndrome (TLS). Metabolic parameters including uric acid were normal throughout the entire hospital stay of the baby. Chemotherapy was not started for our baby in view of absence of clinical signs of life-threatening symptoms (LTS) of TL-DS such as hyper viscosity, blast count >100,000/ml, hepato-splenomegaly, coagulopathy, effusions or multiorgan failure.[3-5] Liver function tests(LFT), renal function tests (RFT), serum electrolytes, serum calcium, serum phosphorus and blood gas analysis were normal. 2D-ECHO, abdominal ultrasonography including kidney, ureter and bladder (KUB) was also normal. The baby was started on oral levothyroxine (15ug/kg/day) for hypothyroidism detected during the hospital stay. Subsequently, a gradual reduction in peripheral blood blast cells was observed which finally reduced to 10% with TLC 10,800/cu.mm and platelet count 1.6 lakh/cu.mm on day 32 of life (Table 1). Baby was exclusively breastfed, asymptomatic and was discharged at the age of 1month 10 days. On follow up after 15 days of discharge, CBC was normal with no blasts. Subsequently clinical as well as laboratory monitoring every 3 months was normal. Currently, she is 13 months old growing normally without organomegaly or any other complications (Figure 3).

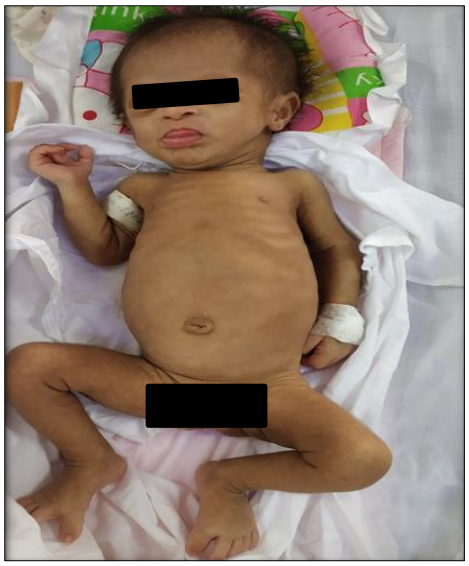

Figure 1: Clinical features of down syndrome with pre-auricular tag.

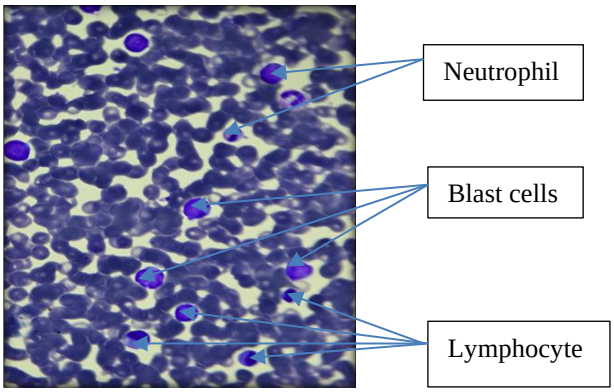

Figure 2: Peripheral blood smear slide.

Figure 3: Baby at 13 month age, growing well.

DISCUSSION

TL-DS is defined as presence of a GATA1 mutation along with peripheral blood blasts more than 10% and/or clinical features suggestive of TL-DS in a DS or mosaic Trisomy 21 child.[6] Most commonly, TL-DS presents between day 3 and 7 after birth as in our baby but may be delayed till 2 months. TL-DS is a spectrum of clinical features ranging from overt clinical features to serious medical complications. It can also be completely asymptomatic, in which case can only be identified through blood film and/or GATA1 mutation analysis.[6] Commonest clinical manifestations include hepatomegaly (60%), splenomegaly (35-40%), jaundice (15%), pericardial effusion (15%), pleural effusion (10-15%), ascites (10%), respiratory distress (10%), and bleeding diathesis (10%), while hydrops fetalis, liver fibrosis, and renal failure are less common features.[7] Children with trisomy 21 have a high risk of developing myeloid leukemia of Down syndrome(ML-DS) which is preceded either by a asymptomatic phase or by TL-DS. Although TL-DS resolves in the majority of DS babies, 20% to 30% subsequently go on to develop AML, usually in the first 4 years of life.[8,9] Silent TL-DS is characterized by lack of clinical features and peripheral blood blasts 1-10% with 50% of DS having GATA1 mutation positivity.[10]

The pathophysiology of TL-DS involves a number of factors, including the proliferation of abnormal hematopoietic precursors (megakaryocyte-erythroid progenitor cells) in the fetal liver caused by genetic instability in the presence of trisomy 21 along with the acquisition of mutations in the GATA1 gene, located on chromosome X, which is essential for erythroid and megakaryocytic maturation. The impaired differentiation of megakaryocytes (dysmegakaryopoeisis) is responsible for causing thrombocytopenia as seen in our patient.[10] GATA1 mutations occur in all cases of TL-DS and in 25-30% cases of all neonates with DS.[10] GATA1 mutation alone can-not predict which patient with TL-DS later progress to ML-DS. Additional genetic events along with GATA1 mutation and Trisomy 21 further are responsible in transforming haemopoietic cells from a usual TL-DS to ML-DS. Most neonates with TMD do not need chemotherapy treatment as the clinical and laboratory abnormalities spontaneously resolve in 80% of cases within 3 to 6 months after birth. Distinguishing features of TL-DS from ML-DS are: younger age at presentation, higher haemoglobin concentration, higher platelet counts and higher blast cells in peripheral blood smear than in marrow.[11] We considered TL-DS in contrast to ML-DS in our patient due to the distinct cytogenic profile specific to TL-DS and absence of neutropenia which occurs in ML-DS.[10] Only careful monitoring suffices in the milder case; supportive care being the cornerstone in most of the symptomatic patients. But in the presence of one or more LTS, intervention like low-dose cytosine arabinoside is advised.[12] TLS, a metabolic complication occurring in TL-DS should be closely monitored for in all cases of TL-DS with DS. TLS includes hyperkalemia, hyperphosphatemia, hyperuricemia and hyperuricosuria, hypocalcemia, consequent acute uric acid nephropathy and acute renal failure.[13,14] Our patient had none of these metabolic complications. There are few reports of TLS

associated with TL-DS.[15,16] Kato et al, reported a case of a baby with DS who developed TLS as a result of TL-DS and was successfully treated with allopurinol and diuretics.[15] The risk factors for mortality in TL-DS are hyperleukocytosis, hepatic dysfunction, effusions, prematurity, low birth weight and renal failure.[11] Overall mortality is 20-30% out of which 50% of deaths occur due to hepatic fibrosis as a sequelae to blast cell infiltration.[10]

CONCLUSION

All newborns with either known or a high suspicion of DS must be examined in the first 3 days of life for clinical features of TL-DS followed by full blood count with blood film formally assessed by a pediatric haematologist. Management of TL-DS in DS requires a close disciplinary approach between a fetal medicine specialist, neonatologist and a pediatric haematologist along with a regular follow up.

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