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Transient abnormal myelopoiesis at birth with Down syndrome: A rare case report

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Abstract
Down syndrome is associated with rare hematological disorder like Transient abnormal myelopoiesis in infants. We report a case of preterm female baby with low birth weight born to 33 year old mother who is G2A1 at 34 weeks of gestation. Antenatal checkup revealed intermediate risk for Down syndrome. On the first day of birth CBC showed high WBC count of127000/ mm^3 and peripheral smear showed 13% of blast and the total count gradually decreased to normal of 20000/ mm^3 over a period of one month. The baby succumbed to death due to Congestive cardiac failure and late onset sepsis.

Keywords: Transient abnormal myelopoiesis, down syndrome, acute mega karyoblastic leukemia

Introduction
Down syndrome is the most common congenital disorder (~1/1000 live births) in humans. Transient abnormal myelopoiesis is reported to occur in 10-15 % of neonates with Down syndrome [1]. TAM babies have spontaneous resolvation without any treatment within 3-6 months. Respiratory and cardiovascular co-morbidities are mostly reported in these patients and require hospitalization [2]. There are two components of megakaryoblastic leukemia; TAM and acute megakaryocytic leukemia, both are not uncommon manifestation of Down syndrome [3].

In DS there is excessive accumulation of abnormal myeloblats. TAM is a condition which develops before the age of 5 years in 10% of patients. TAM and acute megakaryoblastic leukemia (AMKL) occurs as one or more somatic mutations of transcription factor gene GATA1 [4]. Besides its remission in some cases TAM can affect several organs due to infiltration of blast cells and can be fatal [5].

Case report: A new born was born at 34 weeks of gestation to a non-consanguineous couple. Antenatal scan revealed intermediate risk for Down syndrome with multiple dysmorphic features (figure 1). Emergency LSCS done, APGAR at one minute was 7/10 and at 5 minutes was 8/10. In view of prematurity and respiratory distress baby was shifted to NICU. The following investigations were done. CBC showed Hb of 8 gms, WBC revealed marked leukocyte count of 127000/ mm^3 and platelets were 50,000/ mm^3. The peripheral smear showed large cells resembling myeloid blasts of 13% (figure 2). These cells showed high N: C ratio with open chromatin, 1-3 prominent nucleoli and moderate cytoplasm. LFT was deranged. Ultrasound abdomen showed hepatosplenomegaly. Karyotyping analysis showed trisomy 21 in all metaphases suggestive of Down syndrome (figure 3). Flow Cytometry done from peripheral blood showed positivity for CD34, CD117, CD13, CD33, CD123 and were negative for lymphoid markers indicating the myeloid origin of blasts (figure4).

Course in the hospital: Baby was started on IV fluids and later Ryle's tube feeds after 40hrs of life. On day 36 of life baby was shifted to mother side. However baby developed respiratory distress and was shifted back to NICU. Baby was started on oxygen of 5 L/min, kept NPO and started on IV fluids, antibiotics, diuretics and nebulization. Sepsis screening showed elevated Total count, CRP and Procalcitonin. In view of poor perfusion started on ionotropic dopamine. Despite extensive counseling patient attender was not willing for further active intervention and wanted non exalation in the management to revive the baby. The baby continued to have low saturation and bradycardia and succumbed to illness and expired. CBC at birth showed high TC of 127000/ $mm^{3.}$ After 10 days the total count started to decrease gradually from 83,000 to 42,000 to 20,000 which is indicative of TAM associated with DS.

PREGNANCY MARKER SCREENING PROGRAM (Combined Risk)

Patient: **MRS VRANDA N 33/F** . **REF NO 01129234** .
ID. No.: 10982 -
DOB: **25-Jun-88** ; maternal age at EDD: **33** years. EDD:06-May-22.
Gestational age based on ultrasound scan. Ultrasonographic gestational age 12 weeks, 1 days on date 23-Oct-21 .Real gestational age at screening date: **12 weeks and 1 days.** Screening date: **23-Oct-21.**
Single-fetus pregnancy.

Screening profile: First trimester screening test. Software used: ROCHE SsdwLab 5.

Gaussian markers
Level of **Free beta hCG** 116 IU/l at 23-Oct-21 : **3.29** MoM.
Level of **PAPP-A** 2051 mIU/l at 23-Oct-21 : **0.68** MoM.
Level of **NT** 1.6 mm (CRL of 56.4 mm) : **1.08** MoM.
Marker values have been corrected by, weight (62.6 Kg).

Down's syndrome Risk; 1 : 274 calculated as Risk at delivery date. **Low Risk.** The maternal age related risk for Down's syndrome is 1: 537 .

Fig 1: Shows pregnancy marker screening program (Combined Risk)

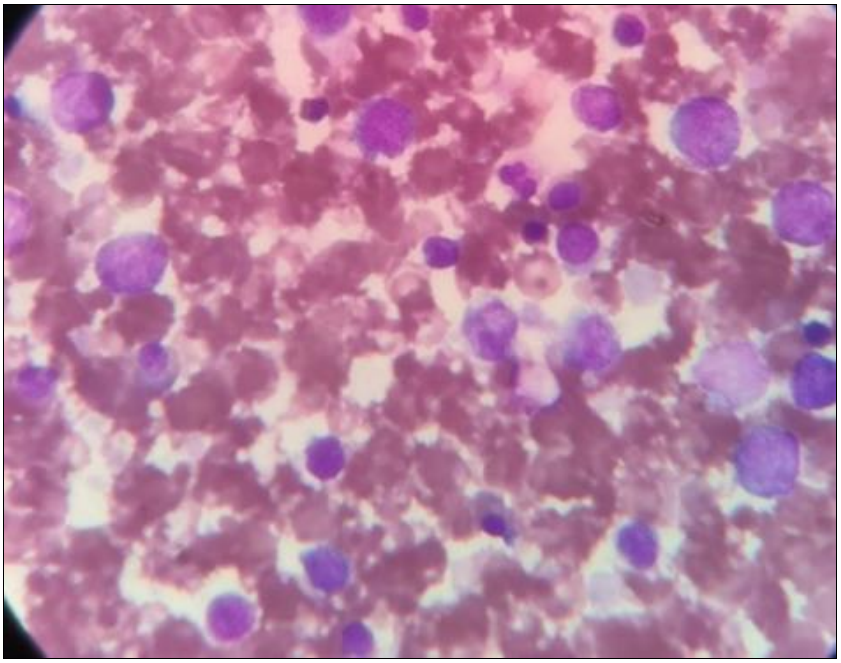

Fig 2: Peripheral smear showing increased WBC counts with blasts

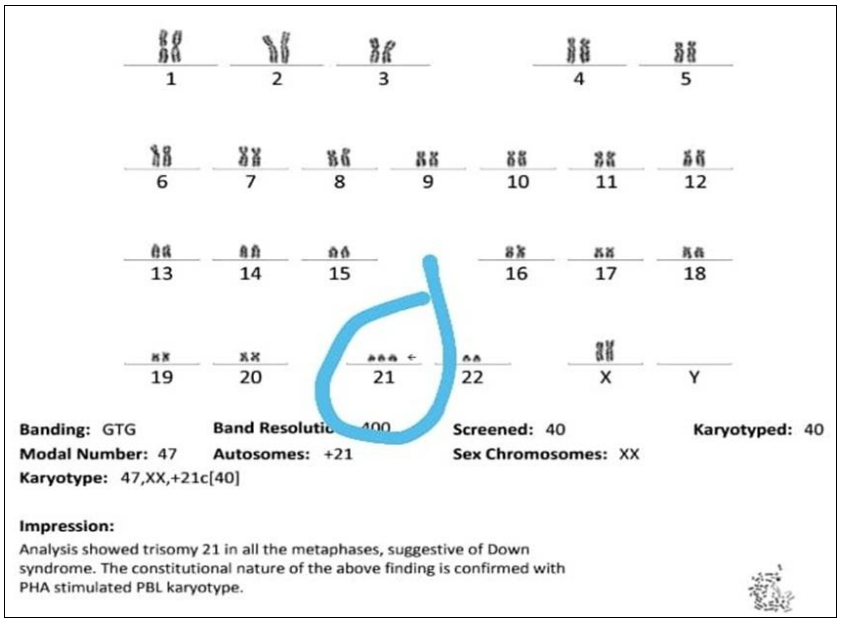

Fig 3: Shows banding band resolution screened karyotyped modal number autosomes sex chromosomes and karyotype

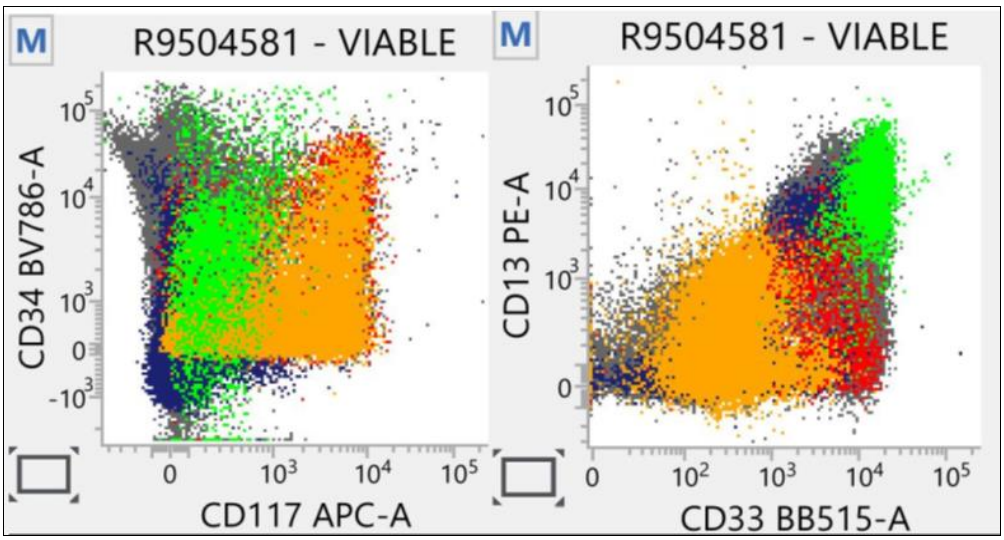

Fig 4: Flow Cytometry with blasts showing positivity for CD 34, CD117, CD13, CD33

Discussion

DS is associated with stunted physical growth and mental retardation but may also be associated with congenital heart disease, renal defect, GI malformation and hematological disorder [6]. Full trisomy 21(non-disjunction) account for 3.3%, and mosaicism accounts for the remaining 2.4% cases of Down syndrome [7]. The effect of trisomy 21 on liver hemopoiesis with megakaryocyte progenitor and common myeloid progenitor in DS maybe the cause for TAM [8].

The GATA1 gene are present on the X-chromosome encodes a hemopoietic transcription factor that is essential for normal megakaryopoiesis. Most of the babies with TAM have acquired mutations at the N-terminal of the GATA1 [9]. The GATA1 gene mutation occurs as the somatic mutation at exon 2 which blocks differentiation of megakaryocytic lineage beyond megakaryoblast stage. These mutations may be present at birth and disappear when TAM enters into remission [9].

Around 20-30% of DS children who develop TAM may develop acute megakaryocytic leukemia later within 5 years of life [10]. Immuno phenotyping and karyotyping has similar features to most common type of AML in children with DS, acute megakaryocytic leukemia [11]. Peripheral blood In TAM shows cells resembling megakaryoblasts with basophilic cytoplasm and granules. Also these blasts show cytoplasmic blebs [12]. Non-immune hydrop's fetalis is the leading prenatal ultra sonographic finding of TAM in fetuses with Down syndrome. Other abnormalities are cardiomegaly, hepatomegaly splenomegaly and abnormal blood smear [13]. The pathogenesis of hydrop's results from anemia-induced hypoxia, and high output heart failure from anemia. Hepato spleenomegaly results in hypoalbuminemia and fibrosis. LFT shows elevated AST, ALT and total bilirubin levels.

The prognosis of TAM is good. Treatment in these cases is hydration to prevent lysis syndrome, which may develop because of spontaneous cytolysis of lymphoproliferative malignancy [13]. Some studies showed treatment of TAM by chemotherapy using low dose cytosine, arabinoside in a symptomatic patient with high blast count [14]. The mortality rate of TAM is 20%. Approximately 20 % of patients show progression to acute myeloid leukemia which requires chemotherapy.

Conclusion: TAM is uncommon, unique hematological disorder in Down syndrome children. TAM presented from day one in our case karyotyping is the most important investigation in diagnosing Down syndrome. Also the flow cytometry with positivity for these markers CD34, CD117, CD13, CD33 and CD123 are useful for typing TAM blasts. Rarely TAM can progress to acute leukemia and regular monitoring is required.

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