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Neonatal " Transient Myeloproliferative Disorder Vsaml" In Down's Syndrome – A Diagnostic Dilemma.

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Summary:

Transient myeloproliferativedisorder (TMPD)is a self resolvingcondition usually indistinguishable from megakaryocytic leukemia which usually occurs in 10% of newborns with Down's syndrome (trisomy21). A 2 day old was boy was admitted for poor feeding &hyperleucocytosis. It was a case of Down's syndrome with a karyotype of 47, XY, +21 presenting with VSD & hepatomegaly. A diagnosis of AML-M7 with erythroid differentiation was made on flow cytometry.TMPD & AML-M7 cannot be differentiated clinically & even by PBS & flow cytometry& the only way to differentiate these conditions is molecular genetics for GATA1. It is very important to differentiate TMPD & AML-M7 because the former undergoes spontaneous regression within 3 months & patient is recovered without any treatment. Approximately 20-30 % of TMPD progress to AML-M7 usually within 1year.Take home message:It is very important to differentiate TMPD from AML as the former resolves spontaneously without any treatment

Keywords : Transient myeloproliferative disorder, Down's syndrome, AML, hyperleucocytosis, flow cytometry,

Introduction

Down's syndrome (DS) is the most common trisomy in humans, occurring in 1/600- 1/800 live births. Transient myeloproliferative disorder (TMPD) (also called as transient abnormal myelopoiesis, transient leukemia) is a self resolvingcondition usually indistinguishable from megakaryocytic leukemia & usually occurs in newborns with Down's syndrome(trisomy21). Children with Down syndrome are 10- to 100-fold increased risk for developing acute leukemia (approximately 1-2% of children with Down syndrome develop AML, the great majority < 5 years).[1]

Peculiarities of TMPD

- Affects 10% of newborns with Down's syndrome
- Resembles congenital acute leukemia; occurs within first days of life with numerous blasts in peripheral blood, more than those in marrow
- High rate of spontaneous resolution; usually resolves in 2-14 weeks in neonates, but 20-30% progress to AML-M7 [FAB] (acute megakaryoblastic leukemia) within 3 years

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● Early death in 17% cases is due to high WBC at diagnosis, increased bilirubin and liver enzymes.**2**

It is very important to differentiate TMPD from AML as the former resolves spontaneously without any treatment.

Case report

A 2 days old full term boy was admitted in NICU with poor feeding &hyper-leukocytosis. The baby was born by vaginal delivery at 39 weeks of gestation with birth weight and body length were 2820 g and 49 cm, respectively.

The neonate was a case of Down's syndrome with a karyotype of 47, XY, +21.The Peripheral blood smear(PBS) results revealed a white blood cell (WBC) count of 139× 10^9 cells/mm^3 with 61% of blasts. Thepatient had hepatosplenomegaly, abdominal distension, hypotonia and dyspnea, probably due to hyperviscosity. Echocardiography revealed a ventricular septal defect (VSD) measuring 15.4mm,pericardial effusion. An ultrasound scan of the abdomen confirmed hepatosplenomegaly with an increased echo signaling of the liver. Biochemical data revealed increasing levels of lactate dehydrogenase (LDH) (3056IU/L) and uric acid (UA) (3.9mg/dL). Results of blood gas analysis were in the normal ranges.

The PBS shows Blasts 61% and many NRBCs (55/100 wbcs). Blasts are large heterogenous cells with mild to moderate cytoplasm, hyperchromatic nuclei (nuclear convolutions in few cells), 1-3 prominent nucleoli. Erythroid differentiation was noted with few erythroblasts & NRBC.

Bone marrow aspiration was not done.

Immunophenotyping of the peripheral blood by flow cytometry shows Blast +vefor CD33, CD34, CD36, CD38, CD45, and the megakaryocytic antigens, CD41 and CD61. Terminal deoxynucleotidyltransferase (TdT) activity is absent and CD7 ,CD56 showed mild expression,20% of cells are +ve forglycophorine&CD 11 . A diagnosis of AML-M7 with erythroid differentiation was made.

Table1 – Laboratory findings on admission & after 1 month

Laboratory findings	**On admission**	**After 1 month**
White blood cell count (×10^9 cells/mm^3)	139.12	14.35(no BLAST)
Hemoglobin (g/dL)	17	15.5
	51	47

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Hematocrit (%)		
Platelets (x 103/ microL)	72	110
Serum biochemistry		
Total protein (g/dL)	3.90	05
Albumin (g/dL)	2.9	3.9
Lactate dehydrogenase (IU/L)	3056	360
Urea (mg/dL)	30	18
Creatinine (mg/dL)	1.8	0.6
Uric acid (mg/dL)	4.6	4.2
Alanine aminotransferase (IU/L)	1025	215
Aspartate aminotransferase (IU/L)	756	125

Discussion

Neonates with DS also may develop a transient myeloproliferativedisorder (TMD), an abnormal proliferation of myeloid blasts in the blood that resolves without therapeutic intervention.

Usually, transient leukocytosis associated with DS is generally diagnosed in the first few weeks of life. TMD, also known as transient leukemia, occurs in about 10% of neonates with DS. It is often accompanied by hepatosplenomegaly, pericardial and pleural effusions, hepatic disease, as in our patient. Although TMD resolves in the majority of DS babies, 20% to 30% subsequently go on to develop AML-M7, usually within in the first 4 years of life. AML develops either by overt progression or after an apparent remission of TMD with AML arising many months later, presumably from a subcolony of persisting TMD cells that acquire a selective advantage.[3]

Most neonates with TMD do not need chemotherapy as the clinical and laboratory abnormalities spontaneously resolve within three to six months after birth.

TMD and acute myeloid leukemia (AML) in DS show strikingly similar morphologic features.It is often difficult to differentiate TMPD with AML-M7.

The main difference in the clinical presentation of these disorders is the

- Age of onset, with TMD occurring during the first few days of life and AML usually

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manifesting after 1 year.However, there may be diagnostic difficulty in some cases as there have been reports of TMD at later ages (second or third month of life) as well as cases of "congenital leukemia.

- Hematologic and cytogenetic differences between these disorders also have been described. TMD tends to manifest with normal hematocrit and platelet counts, whereas AML generally exhibits cytopenias. Blasts in TMD usually have only the constitutional trisomy 21, whereas blasts in AML may show additional complex cytogenetic abnormalities

Table 2- Clinico-pathological differences between TMD, AML-M7 & CAL

Characteristic	Type of Hematologic Disorder		
	TMD	AML-M7	CAL
Age of onset	Newborn	6 months to 1 year	Newborn
Bone marrow infiltration with blasts	Low	Extensive	Extensive
Cytogenetic features	Isolated trisomy 21	Trisomy 21 with other clonal	11q23/ t(1;22)(p13;q13)
molecular mechanism of disease	GATA-1 mutation	GATA-1 mutation and increased telomerase	MLL gene Rearrangement Or fusion of RBM15 and MKL1 genes

TMPD – transient myeloproliferative disorder CAL- congenital acute leukemia

The morphology and immunephenotypic profile of TMD blasts are essentially indistinguishable from that of AML-M7. It is also important to differentiate TMD from CAL. Congenital acute

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leukemia is defined as a leukemic process presenting between birth and 1 month of age. The incidence of CAL is estimated at 1 in 5 million births.[4]

In this case the PBS shows 61 % BLASTs (probably myeloblasts) and erythroid progenitors. Flowcytometry reported it as AML-M7 with myeloid differentiation. However it was not possible on PBS,flow cytometry& clinical grounds to differentiate TMPD from AML-M7

Molecular genetics in TMPD – the only way to distinguish it from AML –M7,[5,6]

- Mutations in GATA1 gene in almost all cases (compared to 4% of all Down's syndrome infants)
- JAK3 mutations found in 50% cases

After adopting a wait & watch policy of 1 month the CBC and other biochemical & coagulation parameters were almost normal & there was no circulating blasts in the PBS.

Conclusion

Down's syndrome (DS) is the most common trisomy in humans, occurring in 1/600- 1/800 live births .TMPD is encountered in 10% cases of Downs syndrome & it is great mimicker of AML-M7 & is often indistinguishable from the later.

TMPD & AML-M7 cannot be differentiated clinically & even by PBS & flow cytometry.

Molecular genetics for GATA1 is the only which can differentiate these conditions.

It is very important to differentiate TMPD & AML-M7 because

- TMPD undergoes spontaneous regression within 3 months & patient is recovered without any treatment.
- Approximately 20-30 % of TMPD progress to AML-M7 usually within 1 year

The very rare nature of the disease and its grave prognosis merits its reporting

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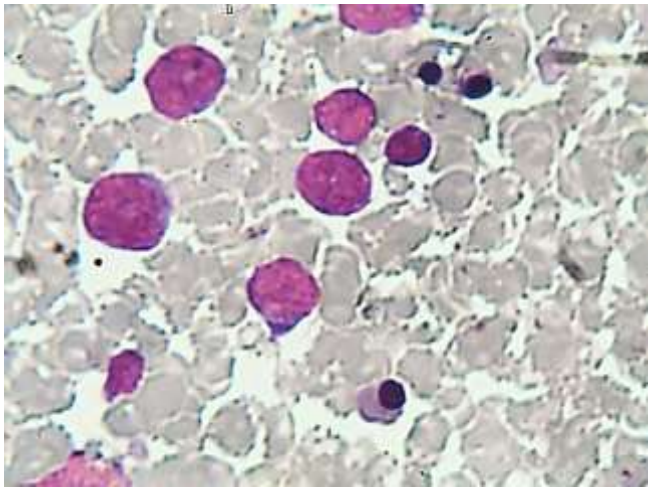
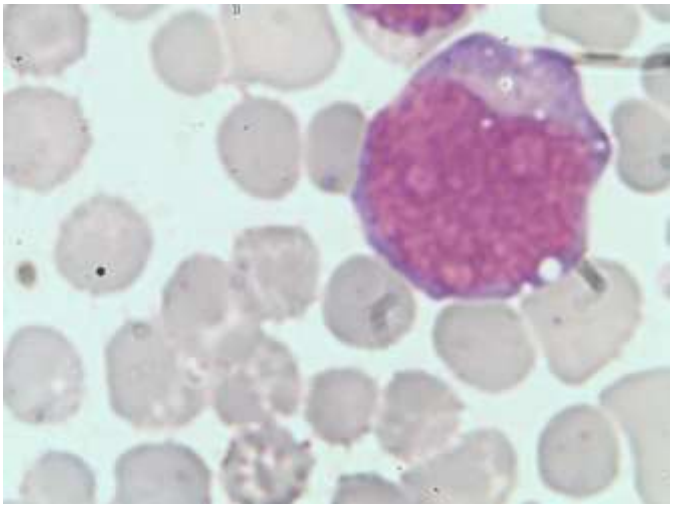


(Giemsa stain: Blast's with multiple nucleoli & NRBC)



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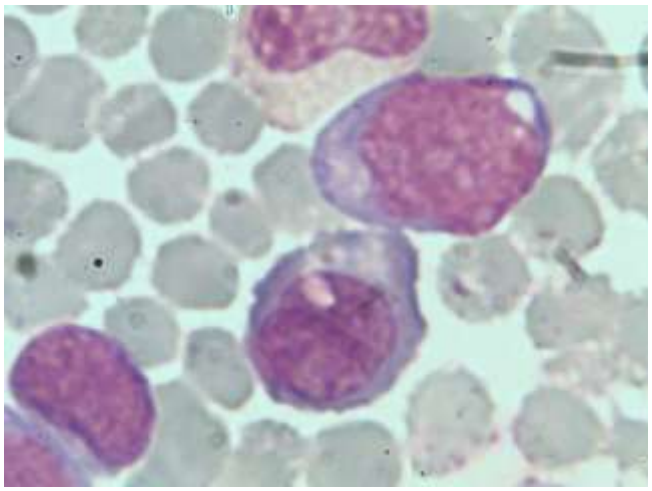
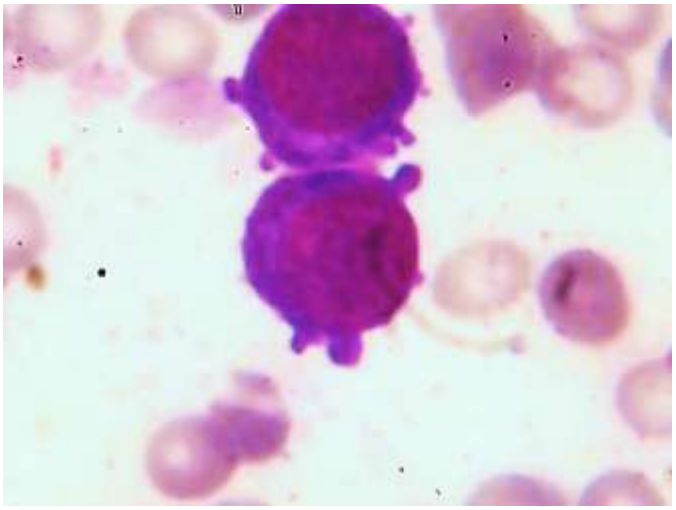
(Giemsa stain: Blast with multiple prominent nucleoli)



(Giemsa stain: Blast's with cytoplasmic vacuolation)



(Giemsa stain: Megakaryoblasts with cytoplasmic projections)

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