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Transient Abnormal Myelopoiesis in Down Syndrome Patients

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ABSTRACT

Neonates with Down Syndrome (DS) have a propensity to develop the unique myeloproliferative disorder,Transient Abnormal Myelopoiesis (TAM). Transient abnormal myelopoiesis usually resolves spontaneously in ≤ 3 months, but approximately 10% of patients with TAM die from hepatic or multi-organ failure. After remission, 20% of patients with TAM progress into acute myeloid leukemia associated with down syndrome (ML-DS). The patient was a full-term 2-day-old baby girl with a birth weight of 3300 gr. Physical examination revealed dysmorphic facial features, hypertelorism, macroglossia, and low set ears, which is a characteristic sign of DS face, skin rash, and there was no anus. On examination of peripheral blood smears and bone marrow aspiration, hematological abnormalities, and circulating blast cells were found. Early diagnosis of low-lying anorectal malformation (MAR) without fistula and down syndrome. In treating patients with TAM, it is first necessary to know whether they have trisomy 21 syndrome, then trace the existing hematological disorders to find the GATA 1 genetic mutation. The most crucial hematological problem in patients with DS is leukemia. Mutations in the GATA 1 gene and the presence of DS can result in abnormal proliferation of megakaryocytes and erythroid progenitors in the fetus and hematological abnormalities in TAM. Transient abnormal myelopoiesis can be fatal in up to 10% of patients and resolves spontaneously. Therefore, laboratory examinations are very significant, including blood tests, peripheral blood smears, supporting examinations such as bone marrow aspiration, monitoring of clinical symptoms, and close monitoring of comorbidities. Examination repeat or follow-up bone marrow aspiration is required within six months of patient follow-up to reduce the risk of further complications. In this case, a follow-up examination is highly recommended because if there are no changes, the further examination must be carried out.

Keywords: Transient abnormal myelopoiesis, down syndrome, GATA 1

INTRODUCTION

Transient Abnormal Myelopoiesis (TAM) or transient myeloproliferative disorder, also known as transient leukemia, is a disease that occurs in 4-10% of children with Down Syndrome (DS) or trisomy mosaicism.[1]

Transient abnormal myelopoiesis occurs in about 10% of newborns with DS. Over 18 years, between 1980 and 1997, the overall prevalence of DS in Japan was approximately 5.82 per 10,000 live births.[2] Transient abnormal myelopoiesis resolves spontaneously within 3-6 months, but 10% of patients with TAM die of liver or multi-organ failure.[1] After remission, 20% of patients with TAM develop Acute Myeloid Leukemia (AML) associated with DS (Myeloid Leukemia with Down Syndrome: ML-DS).[1,3]

The GATA 1 gene is located on the x chromosome and encodes the "zinc finger" transcription factor, essential for normal erythropoiesis and megakaryopoiesis. Transient abnormal myelopoiesis increases circulating blast cells and harbors a necessary N-terminal truncation mutation in the genetic hematopoietic transcription factor GATA 1. Approximately 10-15% of neonates with DS have a TAM diagnosis with >10% blast and characteristic clinical symptoms.[4,5]

The clinical presentation of TAM can vary from asymptomatic to very severe disease. Clinical and hematological features of TAM such as hepatosplenomegaly, skin rash, pericardial/pleural effusion, ascites, hydrops fetalis, jaundice coagulopathy liver failure, thrombocytopenia, leukocytosis, anemia early death and progressing to MLDS (20%) male in about 20%-30% of cases), thrombocytopenia (40% of cases) and large numbers of circulating blast cells.[6] Ten percent to 25% of patients are asymptomatic.[6,7] The diagnosis is sometimes established as a finding during laboratory evaluation for other causes. Occasionally, the finding of the myeloproliferative syndrome can be the first indication a patient has trisomy 21. The immunophenotype of TAM blasts is the same as acute megakaryoblastic leukemia (AMKL) with

positive blast cells for stem cell markers (CD34, CD117), myeloid markers (CD13, CD33), platelet glycoproteins (CD36, CD42, CD61), CD56 and CD7 with variations between cases.[8,9]

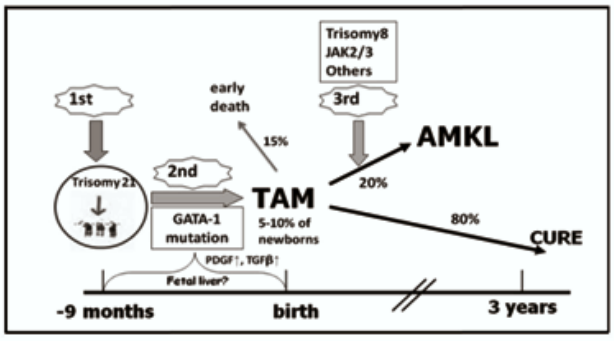

Figure 1. A multi-step model of myeloid leukemogenesis in DS. Trisomy 21 increases the proliferation of fetal liver megakaryoerythroid progenitors via PDGF and/or TGF beta. GATA 1 mutations increase the clonal proliferation of immature megakaryoblasts diagnosed at birth as TAM. Mutation GATA 1 is required, but more is needed to develop into AMKL. Additional genetic events such as trisomy 8 or JAK2/3 mutations have been proposed in the progression from TAM to AMKL[10]

CASE

A 2-day-old a-term baby girl delivered through c-section at Thalia Irham Hospital was referred to Dr. Wahidin Sudirohusodo Hospital, Makassar. The baby was born immediately with crying, no bluish, and a birth weight of 3300 gr. Babies don't have an anus since birth.

The mother was 42 years old, pregnant with her 11th child, and had given birth 8 times and miscarried 3 times. She had routine antenatal care during pregnancy and consumed vitamins from the hospital. Mother had no history of taking drugs, no history of vaginal discharge or fever.

The baby was born by c-section, cried immediately, had an APGAR Score of 8/10, birth weight of 3300 grams, body length of 47 cm, and the mother's gestational age was adequate. The patient was born drinking their mother's milk and had basic immunizations at birth.

Physical examination: Weight: 3300 gr, body length: 47 cm, weight/height: in accordance with gestational age (between 50-75 percentile), height/age: in accordance with gestational age (between 25-50 percentile), weight/age: in accordance with gestational age (between the 50-75 percentile). Result: Good nutrition with general condition, moderately ill/passive/GCS 12/good nutritional status. Vital signs: BP 90/60 mmHg, pulse: 142 x/minute, breathing: 42 x/minute, temperature: 36.5°C, oxygen saturation: 94%, head: head circumference: 33 cm (normal: 44.2-47 cm), impression: microcephaly, neck: no enlarged lymph nodes, thorax: no vesicular breath sounds, no rhonchi and wheezing. The first and second heart sounds were single and regular. Heart murmur not found, abdomen: normal peristalsis, liver and spleen not palpable, extremities: warm acral, no edema, CRT < 2

Table 1. Routine blood test results

Parameter	28/02/2021	15/03/2021	Units	Reference
WBC	70.99	12.25	10^3/µL	5.0-37.00
%Neu	19.7	7.51	%	20-67
%Lym	11.2	3.67	%	16-54
%Mono	73.8	0.62	%	1.0-17.0
%Eos	0.4	0.34	%	1.0-6.0
%Baso	1.50	0.11	%	0.0-2.0
RBC	3.85	2.62	10^6/µL	3.20-6.10
HGB	14.8	9.4	g/dL	12.2-21.5
HCT	41.8	27.2	%	30.0-68.0
MCV	108.6	103.8	fL	93.0-123.0
MCH	38.4	35.9	pg	28.0-42.0
MCHC	35.4	34.6	g/dL	30.0-34.0
RDW-CV	24.2	23.9	%	11.5-14.5
PLT	249	90	10^3/µL	150-400
MPV	----	----	fL	6.50-11.0
PCT	----	----	%	0.15-0.50
PDW	----	----	%	10.0-18.0

seconds, genitalia: vagina (+), vulva (+), there is a vaginal opening and urinary tract, anus: no anal canal was found, degree of dehydration (WHO): general condition is weak, dry lips, sunken crown (-), sunken eyes (+), thirsty child, slightly slowed turgor.

On February 28, 2021, an increase in white blood cells was found where lymphocytes and eosinophils were lower than they should be, while there was an increase in monocytes. MCHC experienced a slight increase, while RDW-CV increased very high. Three weeks later (15/03/2021), a routine blood test was carried out, and white blood cells were found, according to the referral, where monocytes had decreased drastically from the initial examination, and eosinophils had slightly increased. At the same time, lymphocytes were normal, but RBC and HGB had decreased. MCHC was almost normal, and RDW-CV decreased while PLT also reduced.

Hemostasis examinations showed (28/02/2021) a prolonged hemostatic period, which exceeded the reference values (22.0-30.0/sec) up to 36.7/sec.

Blood test results (28/03/2021) showed slightly increased SGOT and SGPT, which were still within normal limits, while the electrolyte examination results were all normal.

Table 2. Hemostasis test results

Parameter	28/02/2021	Units	Reference
Hemostasis			
PT	13.9	seconds	10-14
INR	1.38		---
APTT	36.7	seconds	22.0-30.0

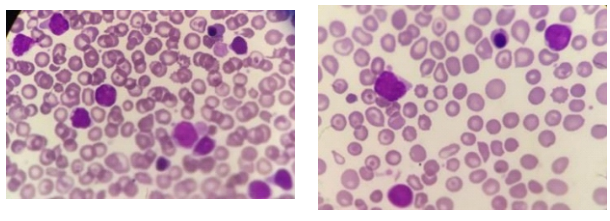

Figure 2. Examination of peripheral blood smear on March 1, 2021 (with 100x magnification) (source: personal documentation)

Immuno-serological examination of thyroid function resulted in subclinical hypothyroidism in the patient. Supporting investigations included an echocardiography examination (03/03/2021), impression: patent foramen ovale left to right shunt, and bone marrow aspiration examination (12/03/2021).

Table 3. Results of peripheral blood smear

Parameter	1/03/2021	9/03/2021
Erythrocyte hematology	Normocytic normochrom ic, anisocytosis, ovalocyte (+), inclusion body (-), normoblast (+)	Normocytic normochrom ic, anisocytosis, ovalocyte s (+), inclusion body (_), normoblast (+)
Leukocytes	Increased number, polymorphonuclear (PMN)> lymphocytes, toxic granules (+), vacuolization (+), predominance of pleomorphic cells, suspicious of myeloblasts	Increased number, PMN > Lymphocytes, toxic granules (+), vacuolization (+), predominance of pleomorphic cells suspici ous of myeloblasts
Platelets	Sufficient quantity, normal morphology Suspected Acute Non-Lymphoblastic	Sufficient quantity, normal morphology Suspected Acute Non-Lymphoblastic
Impressions /suggestions	Leukemia (ANLL) DD Transient Abnormal Myelopoiesis (TAM)	Leukemia (ANLL) DD Transient Myelopoiesis Abnormal

Table 4. Results of blood chemistry and electrolyte examination

Parameter	28/02/2021	Units	Reference
Blood Chemistry			
Glucose	84	mg/dL	140
Urea	37	mg/dL	10-50
AST/SGOT	64	U/L	<38
ALT/SGPT	56	U/L	<41
Creatinine	0.96	mg/dL	M(<1.3);F(<1.1)
Electrolyte			
Sodium	137	mmol/L	136-145
Potassium	5.6	mmol/L	3.5-5.1
Chloride	107	mmol/L	97-111

Table 6. Results of immune-serological examination of thyroid function

Parameter	3/03/2021	6/04/2021	Units	Reference
Thyroid function				
Ft4	1.27	1.20	ng/dL	0.93-1.71
TSHs	12.29	8.2	mlU/mL	0.27-4.20

Definitive diagnosis: down syndrome, low-lying anorectal malformations, transient abnormal myelopoiesis, and cyanotic congenital heart disease.

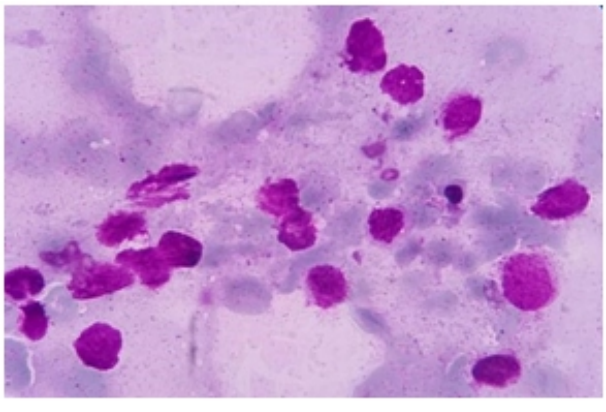

Figure 3. Examination of bone marrow aspiration (12/03/2021)

Impression: normocellular cellularity; Adequate erythropoietic activity and erythroid precursors were found; Leukopoietic features were dominated by myeloid series cells; Myeloblasts <10%;Thrombopoietic activity was found in megakaryocytes, no plasma cells were found; Mitosis was found; ME ratio 3:1, with the impression of TAM

DISCUSSION

The patient came with complaints of flatulence, unable to defecate for two days, and no anal canal. On the patient's face, the typical features of DS were found (dysmorphic face, hypertelorism, and low-set ears).

On March 1, 2021, the patient underwent an anoplasty operation with indications of functional saving or action to create an anal canal. During the operation, no transfusion was performed. Post-operative therapy injection: Ampicillin 165 mg/hour, inj. Amikacin was 50 mg/24 hours, and Paracetamol was 40 mg/8 hours. The patient was in an incubator.

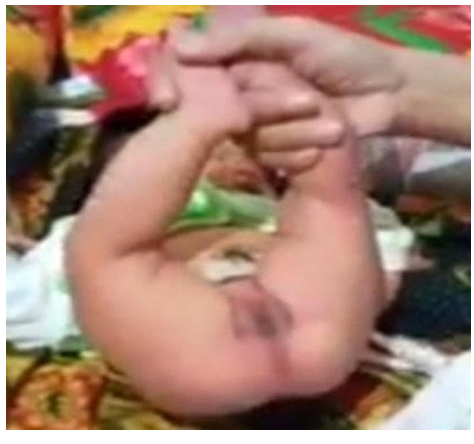

Figure 5. Photo of the absence of anus in the baby (Source: Personal Documentation)

Laboratory examination revealed leukocytosis (70.99x10^3/µL), and pleomorphic cells suspected as myeloblasts were found on Peripheral Blood Smear (PBS) examination. Clinical features due to TAM hematological abnormalities were found in skin rash, leukocytosis, and anemia. Investigations carried out by echocardiography examination showed an impression of congenital heart disease patent foramen ovale. Bone marrow aspiration examination showed TAM. The patient was diagnosed with low-

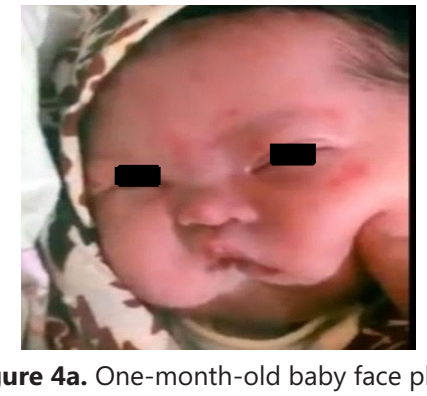

Figure 4a. One-month-old baby face photo Source: Personal Documentation)

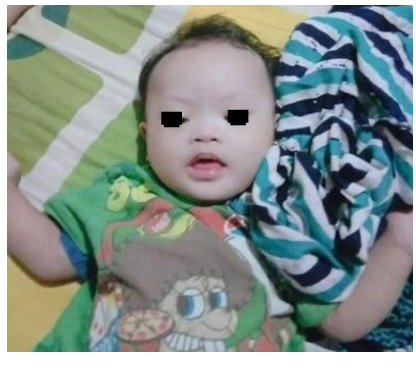

Figure 4b. Photo of a 4-month-old baby, clinical signs of skin rash were not found

lying anorectal malformation, DS, TAM, and A cyanotic congenital heart disease.

Pathophysiology of TAM in this patient occurred due to mutations in the gene, namely the GATA 1 gene located on the X chromosome, which encodes the "zinc finger" transcription factor, which is essential for normal erythropoiesis and megakaryopoiesis. Trisomy 21 or DS is the most common genetic disorder with mental retardation, cardiovascular problems, and hematological and gastrointestinal-related disorders. The most crucial hematological problem in patients with DS is leukemia. Mutations in the GATA 1 gene and the presence of DS can result in abnormal proliferation of megakaryocytes and erythroid progenitors in the fetus and transient abnormal myelopoiesis hematological abnormalities.[4,10]

More than 5% of blast cells were found in the peripheral blood smear at the age of less than six months, and in this case, circulating blast cells were found on the peripheral blood smear on March 1, 2021, and March 9, 2021. The patient underwent a bone marrow aspiration examination for a definitive diagnosis. The existence of TAM (March 12, 2021). Transient Leukemia in Down's syndrome (TL-DS) is temporary and can resolve within 3 to 6 months after birth. This spontaneous recovery is characterized by infiltration of hematopoietic cells back into the bone. In this case, management is only supportive of the treatment of comorbidities, such as antibiotic therapy to control sepsis, fluid therapy, and clinical nutrition of the patient. Initial treatment is supportive therapy. Chemotherapy was not used in this patient. Chemotherapy is used in patients with severe manifestations such as impaired hepatic or cardiorespiratory function and severe leukocytosis. There is no specific therapy for transient leukemia because pathophysiologically, this disorder will heal spontaneously with the increase of the patient's age.

On April 2, 2021, the patient went home and returned to the Outpatient Clinic on May 18, 2021, for control. The patient's general condition was good and showed improvement.

CONCLUSION

Transient abnormal myelopoiesis can be fatal in up to 10% of patients and resolves spontaneously. Therefore, laboratory examinations are very significant, including blood tests, peripheral blood smears, supporting examinations such as bone marrow aspiration, monitoring of clinical symptoms, and close monitoring of comorbidities. Examination repeat or follow-up bone marrow aspiration is required within six months of patient follow-up to reduce the risk of further complications. In this case, a follow-up examination is highly recommended so that further assessment can be carried out if there is a lack of clinical improvement.

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