Case Report

Case Report of Transient Abnormal Myelopoiesis in Fetuses with Down Syndrome

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Objective: To report ultrasound findings and the clinical course of transient abnormal myelopoiesis [TAM] in fetuses with Down syndrome.

Case Report: Medical records of two cases of confirmed TAM in Down syndrome were retrospectively reviewed. The authors reviewed prenatal ultrasonographic findings, fetal blood analysis, flow cytometry, and the postnatal clinical course.

Results: Between May 2010 and September 2013, two cases of TAM associated with Down syndrome were confirmed. Sonographic presentations of non-immune hydrops fetalis initially manifested late in the second trimester to the early third trimester, including fetal ascites, hepatomegaly, and cardiomegaly. Congenital infection was precluded. A complete blood count from cord blood in both cases showed abnormal leukocytosis with blast cells and fetal anemia. The platelet count showed thrombocytosis in one patient and thrombocytopenia in the other patient. Preterm birth was the only adverse obstetric outcome found in both cases. TAM spontaneously resolved after birth.

Conclusion: Fetal TAM is a hematological condition causing non-immune hydrops fetalis in fetuses with Down syndrome. Liver failure and anemia-induced high-output heart failure could be the pathogenesis of hydrops.

Keywords: Transient abnormal myelopoiesis, Down syndrome, Hydrops fetalis, Prenatal ultrasonography, Fetal anemia

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Down syndrome is the most common chromosomal abnormality in live birth, with an incidence of 1:800[(1)]. Among many organs involved, hematological disorder is one of the most common diseases found in Down syndrome[(2)]. The incidence of acute myeloid leukemia in Down syndrome is higher than in the normal population[(3)]. A unique white cell abnormality called transient abnormal myelopoiesis [TAM] is found only in fetuses with Down syndrome[(4)]. Most of these fetuses have spontaneous resolution with good neonatal outcomes. Besides white blood cell abnormalities, neonates with Down syndrome also have abnormalities of red blood cells and platelets.

Case Report

Case 1

A 20-year-old pregnant woman, gravida 2, para 1, at 29 weeks of gestation was referred from a private hospital because of the ultrasound finding of hydrops fetalis. Prenatal laboratory results showed a normal complete blood count profile. Hemoglobin typing was A2A without the alpha thalassemia trait. The blood group was B, Rh-positive with normal serology. She did not have any underlying disease. When the patient was gravida one, 2 years ago, she delivered a healthy male neonate. Ultrasound findings were a hydropic fetus with bilateral pleural effusion and ascites (Figure 1). Fetal cardiomegaly (Figure 2) was found without structural heart disease. Hepatomegaly and placentomegaly (Figure 3) were also observed. Middle cerebral artery peak systolic velocity [MCA-PSV] was 60.7 cm/second (Figure 4), which was more than 1.5 multiple of the median value at 29 weeks of gestation. A maternal serum acid elution test was negative. She was admitted for percutaneous cord blood sampling after a full course of dexamethasone. A fetal blood count showed marked leukocytosis with predominantly blast and immature cells, mild anemia, and thrombocytopenia. The result of a complete blood count is shown in Table 1. The immunophenotypes of blast cells in TAM in this case (Figure 5) were CD34+ and dimly CD33+, which are markers for

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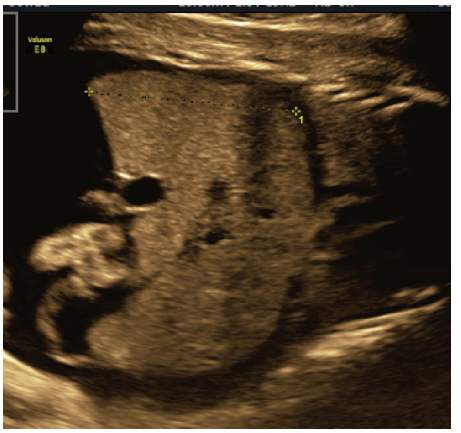

Figure 1. Coronal view showing hepatomegaly (liver length 4.91 cm).

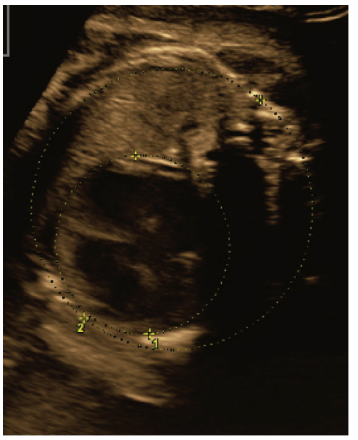

Figure 2. Four-chamber view showing cardiomegaly (cardiothoracic area 0.39).

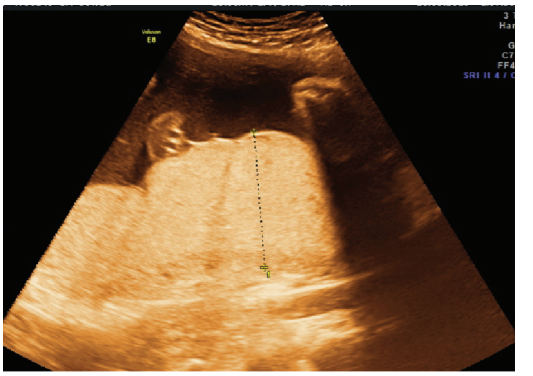

Figure 3. Placentomegaly (maximal thickness 6.34 cm).

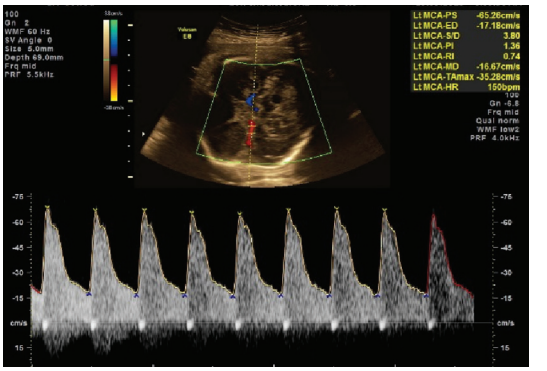

Figure 4. Flow velocity waveform in the middle cerebral artery shows a high peak systolic velocity (>1.5 multiple of the median of his gestational age).

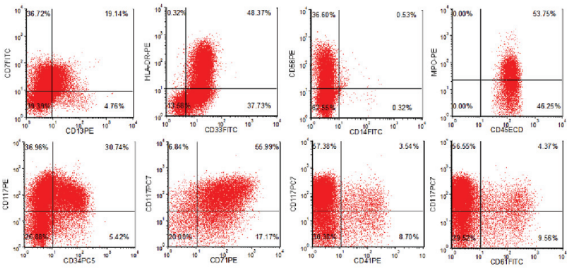

Figure 5. Immunophenotypic characteristics of blast cells.

early myeloid cells[5]. The CD7, which is expressed by T-cell antigens, was also found. However, CD41 and CD61, which are markers for megakaryocytes, were negative. Serology for TORCH and parvovirus B19 were negative. The authors performed intrauterine blood transfusion by 40 ml of Group O, Rh-positive, infiltrated, radiated, leukodepletion packed red cell. The fetal karyotype was 47, XY+21. The fetus was delivered by cesarean section because of fetal distress at 30 weeks of gestation. A male newborn with Down syndrome weighed 2,100 g, with Apgar scores of 5 and 7 at 1 minute and 5 minutes, respectively. He was admitted to the neonatal intensive care unit. TAM

Table 1. Hematological findings of fetal blood

Case	GA at diagnosis of fetal TAM (weeks)	WBC (cell/µl)	Blast cells (%)	Neutrophils (%)	Lymphocytes (%)	Hb (g/L)	Hct (%)	Plt ($x10^3/mm^3$)
1	29	19,970	77	12	10	85	24.0	30
2	33	33,300	64	6	17	105	32.9	1,026

GA = gestational age; TAM = transient abnormal myelopoiesis; WBC = white blood cells; Hb = hemoglobin; Hct = hematocrit; Plt = platelets

was diagnosed and treated by supportive care. The condition spontaneously resolved at 11 weeks after birth. During admission, he developed jaundice with elevated liver function test results. Ultrasonography of the upper abdomen showed hepatomegaly without major obstruction. He died from pneumonia with sepsis at the age of 20 weeks.

Case 2

A 31-year year-old pregnant woman, gravida 2, para 1, at 33 weeks of gestation was referred from a primary hospital because of the ultrasound finding of hydrops fetalis. Prenatal laboratory results showed normal hemoglobin and hematocrit levels with a low mean corpuscular volume. Hemoglobin typing was A2A without the alpha thalassemia trait. The blood group was AB, Rh-positive with normal serology. She did not have any underlying disease. Her first child, eight years ago, was delivered by vaginal delivery. Ultrasound findings showed hydrops fetus including pericardial effusion, pleural effusion, and ascites (Figure 6). Fetal cardiomegaly was found without structural heart disease (Figure 7). Other findings included a short femur and right renal pyelectasis (Figure 8). Doppler of MCA-PSV was unremarkable (42.7 cm/second) (Figure 9). PUBS showed marked leukocytosis with blast cells predominantly, mild anemia, and thrombocytosis (Table 1). A peripheral fetal blood smear showed abnormal giant platelets, megakaryoblasts, and promegakaryoblasts. The fetal karyotype was 47, XY+21. A male neonate was vaginally delivered at the primary hospital at the gestational age of 35 weeks with birth weight of 3,450 g. He was then referred to Ramathibodi Hospital. Bone marrow aspiration was performed and showed acute myeloid leukemia (M7 pattern). Diagnosis of TAM was made with spontaneous resolution six weeks after birth. He developed jaundice with elevated liver function test

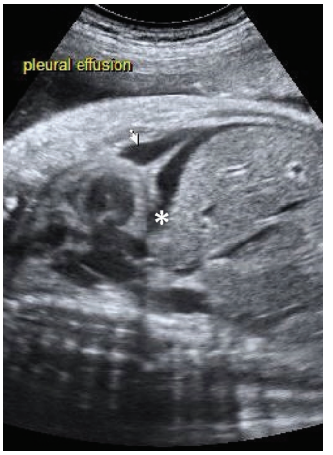

Figure 6. Sagittal view showing pleural effusion (arrow).

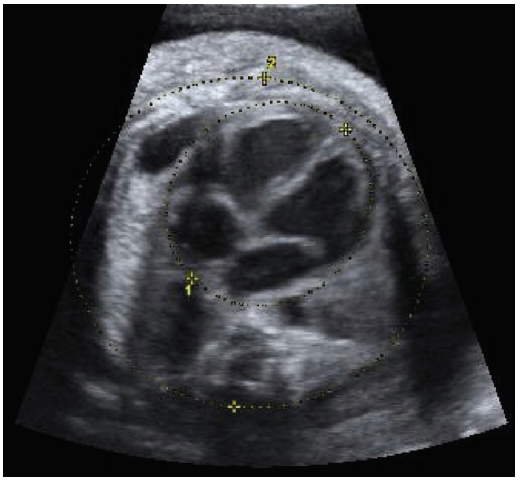

Figure 7. Four-chamber view showing borderline cardiomegaly (cardiothoracic area 0.35) and ascites (asterisk).

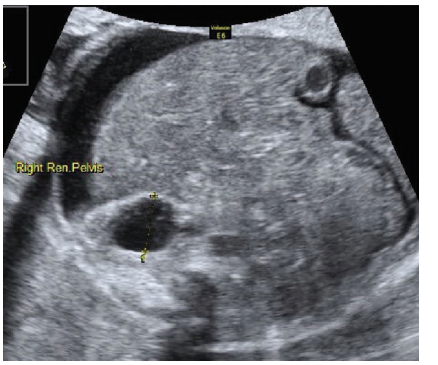

Figure 8. Axial view showing right renal pelvic dilatation of 1.6 cm.

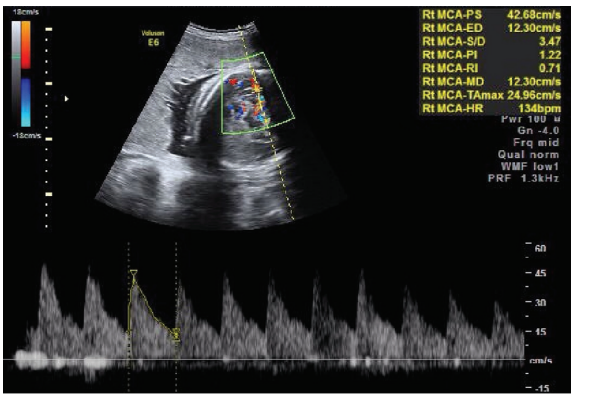

Figure 9. Flow velocity waveform in the middle cerebral artery shows normal peak systolic velocity.

results. Ultrasonography and a DISIDA scan showed hepatomegaly without biliary tract obstruction and a prominent right renal pelvis. He was lost to follow-up after discharge from the hospital.

Discussion

Generally, children with Down syndrome have a 10-fold higher risk of developing acute leukemia compared with normal children[3]. The most common type of leukemia in patients with Down syndrome is acute megakaryoblastic leukemia, which is a rare type of pediatric leukemia. TAM is a unique hematological abnormality that is found in fetuses with Down syndrome or Down syndrome mosaicism[4,6]. One of the characteristics of this condition is the presence of abnormal blast cells in the lineage of white cells, red cells, and platelets. Some cases develop hydrops fetalis, which is detected in utero. This condition has different prognosis from acute leukemia by TAM is self-limiting disease.

A peripheral blood smear of TAM is characterized by numerous blast cells, whereas the numbers of neutrophils and lymphocyte are usually normal or subtly decreased. Hemoglobin concentrations in fetuses with TAM are typically in the normal range. Anemia is not common in TAM[7]. Both fetuses of our patients developed mild anemia in utero as confirmed by hemoglobin levels from PUBS. One case showed an increase in MCA-PSV of more than 1.5 multiple of median of gestational age[8], but the other case did not. The platelet count in TAM may be normal, decreased or significantly increased. In our cases, one had severe thrombocytopenia and the other had thrombocytosis. In the case of thrombocytosis, MCA-PSV did not increase, even though the fetus had anemia. This finding might be explained by high blood viscosity induced by thrombocytosis, resulting in MCA-PSV in the normal range.

From immunophenotypic and cytological aspects, TAM has similar features to the most common type of acute myeloid leukemia in children with Down syndrome, acute megakaryoblastic leukemia[9]. Peripheral blood smears in TAM often show cells resembling megakaryoblasts, which have a basophilic cytoplasm occupied by coarse basophilic granules and cytoplasmic blebs. Dysplastic megakaryocytes and platelets have also been found in blood smears[10].

The molecular pathogenesis of TAM has been previously reported. Mutation of the *GATA1* gene, which is located on the X chromosome, is pathognomonic of TAM[12]. The consequence of a *GATA1* mutation is production of N-terminal truncated GATA1 protein. This mutated protein has loss of function for controlling differentiation of megakaryocytes[11].

Non-immune hydrops fetalis is the leading prenatal ultrasonographic finding of TAM in fetuses with Down syndrome. Other abnormalities are cardiomegaly, hepatosplenomegaly, and abnormalities of peripheral blood smears[13]. The pathogenesis of hydrops results from anemia-induced hypoxia, which may affect vascular epithelial integrity. High-output heart failure from anemia is another factor involved in hydrops fetalis. Hepatosplenomegaly is secondary to extramedullary hematopoiesis. Then resulted in liver fibrosis and hypoalbuminemia. Our patients developed neonatal jaundice. Liver function tests showed elevated AST, ALT, and total bilirubin levels without biliary tract obstruction. Reflecting an intrauterine hypoxic status, arterial Doppler flow velocity in case 1 showed a brain sparing effect, which resulted from an increase in placental vascular resistance. Case 2 had normal arterial Doppler flow velocity. Venous Doppler of both fetuses was normal. The situation of fetuses with TAM can result in stillbirth.

The prognosis of TAM is good. In most children, TAM spontaneously resolves within three months[11]. Treatment in these cases is hydration to prevent tumor lysis syndrome, which may develop because of spontaneous cytolysis of lymphoproliferative malignancy[13]. A previous study showed some benefits of treatment of TAM by chemotherapy, using low-dose cytosine arabinoside, in symptomatic neonates with a high blast cell count or liver dysfunction[11]. The mortality rate of TAM is 20%. Another important aspect of TAM is that approximately 20% of patients show progression into acute myeloid leukemia, which requires chemotherapy.

Conclusion

To the best of our knowledge, karyotype is one of the important investigations in fetus with non-immune hydrops fetalis. Because of chromosome aneuploidy such as trisomy 21 (Down symdrome) or monosomy X (Turner syndrome) are common found. An abnormality of myeloproliferation should be considered when a fetus with trisomy 21 has hydrops fetalis, despite this condition not being as common as a lymphatic disorder. TAM can be diagnosed from a peripheral blood smear or bone marrow smear. Knowledge of the immunophenotype adds little value in the diagnosis of TAM. Stillbirth can be complication in utero. In the neonatal period, most cases of TAM have a favorable

outcome from this preleukemic condition, but some progress to leukemia.

What is already known on this topic?

Some cases of TAM were reported internationally but few cases were reported in Thailand. The pathophysiology and the clinical causes were already reported.

What this study adds?

This is the first few case reports in Thailand that have been diagnosed prenatally. The information includes ultrasonographic finding, complete blood count, and flow cytometry from percutaneous umbilical blood sampling.

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Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Committee on Practice Bulletins--Obstetrics, Committee on Genetics, and the Society for Maternal-Fetal Medicine. Practice Bulletin No. 163: Screening for Fetal Aneuploidy. Obstet Gynecol 2016;127:e123-37.
2. Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, et al. Genetics. In: Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, et al., editors. Williams obstetrics. 24th ed. New York, NY: McGrawHill Education; 2014:538-82.
3. Xavier AC, Taub JW. Acute leukemia in children with Down syndrome. Haematologica 2010;95: 1043-5.
4. Malinge S, Izraeli S, Crispino JD. Insights into the manifestations, outcomes, and mechanisms of leukemogenesis in Down syndrome. Blood 2009; 113:2619-28.
5. Webb D, Roberts I, Vyas P. Haematology of Down syndrome. Arch Dis Child Fetal Neonatal Ed 2007;92:F503-7.
6. Brodeur GM, Dahl GV, Williams DL, Tipton RE, Kalwinsky DK. Transient leukemoid reaction and trisomy 21 mosaicism in a phenotypically normal newborn. Blood 1980;55:691-3.
7. Smrcek JM, Baschat AA, Germer U, Gloeckner-Hofmann K, Gembruch U. Fetal hydrops and hepatosplenomegaly in the second half of pregnancy: a sign of myeloproliferative disorder in fetuses with trisomy 21. Ultrasound Obstet Gynecol 2001;17:403-9.
8. Mari G, Norton ME, Stone J, Berghella V, Sciscione AC, Tate D, et al. Society for Maternal-Fetal Medicine (SMFM) Clinical guideline #8: the fetus at risk for anemia--diagnosis and management. Am J Obstet Gynecol 2015;212:697-710.
9. Massey GV, Zipursky A, Chang MN, Doyle JJ, Nasim S, Taub JW, et al. A prospective study of the natural history of transient leukemia (TL) in neonates with Down syndrome (DS): Children's Oncology Group (COG) study POG-9481. Blood 2006;107:4606-13.
10. Wang SA, Hasserjian RP. Acute Erythroleukemias, Acute megakaryoblastic leukemias, and reactive mimics: A guide to a number of perplexing entities. Am J Clin Pathol 2015;144:44-60.
11. Carpenter E, Valverde-Garduno V, Sternberg A, Mitchell C, Roberts I, Vyas P, et al. GATA1 mutation and trisomy 21 are required only in haematopoietic cells for development of transient myeloproliferative disorder. Br J Haematol 2005; 128:548-51.
12. Hojo S, Tsukimori K, Kitade S, Nakanami N, Hikino S, Hara T, et al. Prenatal sonographic findings and hematological abnormalities in fetuses with transient abnormal myelopoiesis with Down syndrome. Prenat Diagn 2007;27:507-11.
13. Abe Y, Mizuno K, Horie H, Mizutani K, Okimoto Y. Transient abnormal myelopoiesis complicated by tumor lysis syndrome. Pediatr Int 2006;48: 489-92.