Prenatal manifestation of Transient Abnormal Myelopoiesis in a genotypically normal fetus: case report and review of the literature

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Case Report

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Abstract

Background: Congenital malignancies are unusual fetal conditions and therefore the data on their prenatal manifestation is limited. Transient abnormal myelopoiesis (TAM) is a hematologic disorder characteristic for babies with trisomy 21 and base on transient appearance of the blast cells in peripheral blood. This paper presents prenatal manifestation of congenital TAM in a genotypically normal newborn and reviews the literature on prenatal manifestation of this disorder.

Case presentation: A pregnant woman in her third pregnancy referred herself to the hospital for reduced fetal movements at 30 weeks of gestation. Admission's ultrasound scan showed an increased middle cerebral artery peak systolic velocity (MCA PSV) together with hepatomegaly. The patient was admitted to the labor ward for cardiotocography monitoring which showed an acute fetal distress with repeated unprovoked decelerations. An emergency cesarean section was conducted and a phenotypically normal female newborn with low Apgar score was delivered. Further examination of peripheral blood revealed anemia and leukocytosis with high blast proportion. A bone marrow aspirate revealed 70.2% of blasts in a sample with an abnormal karyotype of 47,XX+21. Cytogenetic analysis of blasts with later microarray comparative genomic hybridization confirmed the presence of GATA1 mutation. However, the buccal smear showed a normal karyotype in the infant. The disease was classified as TAM. The literature review together with the case presentation showed that increased MCA PSV and hepatosplenomegaly are important risk factors of death in fetuses with TAM.

Conclusions: Our study demonstrates a rare case of prenatal manifestation of TAM in genotypically normal neonate. Obstetricians should pay attention to symptoms like high MCA PSV and hepatosplenomegaly as possible causes of fetal hematological disorders and differentiate it with infection or isoimmunization.

1 Background

Congenital malignancies are unusual fetal conditions. Considering their rarity, data on prenatal symptoms and prognosis are limited to case reports or small case series. The most common congenital malignancies are neuroblastoma, leukemia and retinoblastoma [1].

Transient abnormal myelopoiesis (TAM) is a hematologic disorder that occurs in the perinatal period in up to 10% of infants with down syndrome (DS) or mosaic trisomy 21. TAM is characterized by the transient appearance of the blast cells with megakaryoblastic and/or erythroblastic characteristics in the peripheral blood and it is related to GATA1 pathogenic variants [2–5]. In most cases, TAM resolves spontaneously within the first months of life. However, one in five children who survive the disease will develop another myelodysplastic disease in future [6].

Prenatal manifestation of hematologic disorders varies from asymptomatic to life-threatening which includes hepatosplenomegaly, hydrops fetalis as well as intrauterine death [7–10].

It can be also reflected in easily accessible and routinely assessed fetal dopplers.

Middle cerebral artery (MCA) is an important vessel which is commonly used in the assessment of fetal condition. The fetal MCA peak systolic velocity (PSV) is crucial in diagnosing fetal anemia [11]. The common causes of fetal anemia are isoimmunization, infection, fetomaternal hemorrhage as well as fetal hematological diseases [12].

This paper presents prenatal manifestation of congenital transient myeloproliferative disorder (TMD) in a genotypically normal newborn and reviews the literature on prenatal manifestation of this disorder.

2 Methods

Searches of PubMed, Scopus, Embase and Web of Science (year 1988) were performed to identify all English language studies that reported prenatal presentation of TAM. Studies were identified using the key words “transient abnormal myelopoiesis”, “transient myeloproliferative disorder” and “prenatal manifestation”. We collected only cases with symptoms of TAM described prenatally. The reference lists of retrieved articles were reviewed to locate additional studies. Reviews and articles written in language other than English were excluded from further analysis.

After the initial literature search, publications were analyzed by title and abstract to exclude studies that did not meet the inclusion criteria. Following abstract selection, the remaining full-text articles were screened for eligibility.

3 Case presentation

A 29-year-old woman in her third pregnancy, with two previous early miscarriages, referred herself for reduced fetal movements at 30 weeks of gestation. She had gestational diabetes, treated with diet, otherwise the pregnancy was uneventful. Her routine first trimester scan together with the combined test for aneuploidies showed a low-risk result and the second trimester ultrasound examination showed no fetal abnormalities. Routine third trimester growth scan was scheduled in two weeks. Her blood group was A thesus positive and no antibodies were detected. At admission's ultrasound, doppler studies showed an increased middle cerebral artery peak systolic velocity (MCA PSV) with the 2.2 multiple of median (MoM). Also, the liver and spleen appeared enlarged. No fetal movements were visualized on the scan. The patient was admitted to labor ward for cardiotocography monitoring (CTG). CTG showed an acute fetal distress with repeated unprovoked decelerations and STV 2.2-3.4ms. An emergency cesarean section was offered and a female newborn weighting 1600g with low Apgar score (2/6/6/6 at 1 and 5 minutes) was delivered. The infant was admitted to the neonatal intensive care unit (NICU) showing difficulties in breathing and incorrect umbilical artery gas analysis (pH 7.12). First physical examination showed no dysmorphic features. Abdominal palpation revealed enlargement of the liver and spleen.
After admission, blood and urine cultures were taken. A peripheral blood sample revealed a hemoglobin level of 5.4 g/dL, hematocrit 15.5%, elevated white blood cells 124–128 x 10^3 /dL and normal platelets level. Blood smear analysis showed 44% of blasts. Based on these results, acute leukemia was suspected. The baby received urgently a red cells transfusion. Because of suspected oncological disease, patient was transferred to a reference neonatal unit. Subsequent blood analysis showed increased white cells level 161x10^3/uL and biochemical markers of tumor lysis syndrome. Blood smear analysis showed 80% of blasts. Abdominal ultrasound confirmed hepatosplenomegaly. Antimetabolic agents were administered in order to treat tumor lysis syndrome. A bone marrow aspirate revealed 70.2% of blasts in a sample with an abnormal karyotype of 47 XX+21 in a phenotypically normal female neonate. The cytogenetic analysis classified blasts as FAB M7- megakaryoblastic leukemia (AMKL) or TMD/TAM. Taking into account the karyotype of the blast cells and possible diagnosis of Down syndrome (DS), the first line diagnosis was TMD/TAM. Knowing that TMD/TAM resolves spontaneously in most cases, antimetabolic therapy was discontinued. In order to verify the DS diagnosis, the buccal smear was taken for microarray comparative genomic hybridization (aCGH) and GATA1 genetic test which revealed a normal karyotype of the infant.

On the 60th day of life, female infant was discharged home in a good general condition, hemodynamically stable, feeding with breast milk. Blast cells were no longer detectable.

The child has normal mental and physical development.

Literature review

The literature review identified 23 articles that included a total of 43 cases presenting prenatal manifestation of TAM (Table 1). Genetic abnormality that was present in the vast majority of cases was trisomy 21 (42/43 cases).
Table 1
Data of 43 fetuses diagnosed with TAM with prenatal symptoms of the disease.

<table>
<thead>
<tr>
<th>Author</th>
<th>GA (w)</th>
<th>Hydrops</th>
<th>Hepatosplenomegaly</th>
<th>Dopplers</th>
<th>Intrauterine intervention</th>
<th>Birth (w)</th>
<th>Outcome</th>
<th>Fetal karyotype</th>
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<td>Trisomy 21</td>
<td>Anemia, Leukocytos</td>
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<tr>
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GA: gestational age; C: cordocentesis; FBS: fetal blood sampling; NND: neonatal death; TOP: termination of pregnancy; IUD: intrauterine death; PI: pulsatility index; OA: umbilical artery; MCA: middle cerebral artery; PSV: peak systolic velocity; AEDV: absent end diastolic flow.
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GA: gestational age; C: cordocentesis; FBS: fetal blood sampling; NND: neonatal death; TOP: termination of pregnancy; IUD: intrauterine death; PI: pulsatility index; UA: umbilical artery; MCA: middle cerebral artery; PSV: peak systolic velocity; AEDV: absent end diastolic flow.
The diagnosis of TAM was established at a mean gestation age of 31 weeks (23-37 weeks) placing the onset of prenatal manifestation of the disease in the third trimester. A variety of symptoms were identified in the literature. The most common prenatal manifestation of TAM was hepatosplenomegaly (31/43; 72%). Hydrops fetalis was described in 49% of cases (21/43).

Less common prenatal manifestations of TAM included abnormal dopplers indicative of fetal anemia (4/43), polyhydramnios (4/43), oligohydramnios (1/43) and pathologic cardiotocograph (4/43). TAM diagnosed postnatally is defined as a disease that usually resolves spontaneously. However, the presence of prenatal symptoms seems to worsen the prognosis. Among the 43 cases of TAM presenting prenatally, 24 fetuses had fatal outcomes (12 IUD, 12 NND). In three cases, parents opted for a termination of pregnancy. Only 16 fetuses had a normal follow-up. Among the 12 fetuses who died prenatally, the most common symptoms, present in 10 cases were hepatomegaly and hydrops fetalis. The most common manifestation of TAM among fetuses who died postnatally was hepatomegaly (11/12, 92%). Also, all fetuses with high MCA PSV died before or after birth (4 cases). Three of them had fetal blood sampling which showed anemia, leukocytosis and provided material for karyotyping. In two cases, intrauterine blood transfusion was performed. In the other two cases, procedure was abandoned due to acute deterioration of fetal condition and immediate delivery.

Above mentioned data proves that TAM is characteristic for DS fetuses and can manifest with a variety of symptoms. The diagnosis of TAM in a neonate with normal karyotype is rare. Genotypically normal child born with TAM and trisomy 21 in blast cells was described by Dosedla et al. The fetus presented symptoms of mild hepatosplenomegaly, polyhydramnios and hydrops at 36 weeks of gestation. Fetal dopplers were normal and there was no anemia after birth. Cytogenetic examination with further molecular confirmation of GATA1 gene mutation established the final diagnosis of TAM [13].

### 4 Discussion

This study demonstrates prenatal manifestation of fetal hematopoietic disorder. This is a unique case of TAM in a genotypically normal child with trisomy 21 present in the blast cells only. The study demonstrates prenatal manifestation of TAM with reduced fetal movements, abnormal doppler studies with high MCA PSV as well as hepatosplenomegaly.

In the presented case, the patient was admitted to the hospital because of reduced fetal movements. Counting fetal movement during pregnancy is a simple method to assess fetal well-being [14]. Periods of decreased fetal activity can be physiological, especially with fetal sleep and usually last up to 90 min in a full-term fetus [15]. On the other hand, reduced fetal activity is associated with adverse pregnancy outcomes like fetal growth restriction, anemia, infection or even intrauterine fetal death [16–19]. In the presented case, both admission’s ultrasound and CTG showed abnormal results. It is therefore advisable to perform both CTG and ultrasound whenever pregnant women report reduced fetal activity [20].

In the presented case, high middle cerebral artery peak systolic velocity (MCA PSV) was the main prenatal manifestation of TAM. Middle cerebral artery (MCA) is a vessel commonly used to diagnose fetal anemia [11]. The background of fetal anemia includes isoimmunization, infection, fetomaternal hemorrhage and less frequently fetal hematological diseases [12].

Peripheral blood leukocytosis is a common abnormality described in TAM cases, however impossible to diagnose on ultrasound. While analyzing hemoglobin level in TAM cases, patients are mostly normocytic but they can be polycythemic [21] or anemic [7, 22]. In the presented case, red blood cells count after birth was low, which was reflected in high MCA PSV (Hb 5.4 g/dL, hematocrit 15.5%). Fetal anemia led to pathological CTG and prompted immediate delivery.

Literature review (Table 1) on prenatal manifestation of TAM found only four articles describing fetuses with high MCA PSV suggestive of fetal anemia [39, 41, 44, 45]. However, the majority of newborns included in the literature review were found to be anemic after birth without prenatal suspicion of anemia (12/43). Among the fetuses with incorrect MCA blood flow that had fetal blood sampling, hemoglobin level varied from 2.8 to 9.7 g/dL. All fetuses with high MCA PSV reported in the literature died in utero or immediately after birth. In the presented case, the newborn was born in a severe overall condition receiving 2 points in the Apgar score. It can be therefore assumed that the presence of fetal anemia reflected in high MCA PSV is a significant factor that worsens the
prognosis. Tamblyn et al. in a systematic review of cases with TAM suggested that hepatosplenomegaly is a fatal factor for fetuses with TAM reporting an associated mortality rate of 87.5% (21/24) [23]. Based on our review, together with the case presentation, fetal anemia should be considered as another important risk factor in fetuses with TAM.

According to the literature review (Table 1), hepatosplenomegaly is a common symptom of TAM (31/43 cases). Differential diagnosis of enlarged fetal liver or spleen includes isoimmunization disorders, fetal anemia, cytomegalovirus or parvovirus B19 infection, congestive heart failure and hepatic tumors [24]. In the presented case, hepatosplenomegaly was a manifestation of TAM. Hepatomegaly in fetuses with TAM results from liver fibrosis, infiltration of blast cells to the liver as well as extramedullary hematopoiesis [22, 25].

In the presented case, the decision to deliver the baby was made based on the pathological indices of CTG which was nonreactive with repeated unprovoked late decelerations and short-term variability of 2.2-3.4ms. Hartung et al. presented a similar case of a patient at 31 weeks of gestation admitted to the hospital because of reduced fetal movements, reversed end-diastolic flow in the umbilical fetal arteries, decreased indices in the middle cerebral artery suggestive of the brain-sparing effect. Two days later, urgent cesarean section was performed due to late decelerations in CTG. The neonate had genotype of DS with incorrect peripheral blood examination that was later classified as TAM [26]. Presented cases highlight the need for considering fetal hematological disorders when reduced fetal movements are accompanied by hepatosplenomegaly on ultrasound and incorrect CTG.

The postnatal diagnosis of TAM in neonate with normal karyotype is extremely rare. In order to diagnose this condition, assessment of the total blood count and blast proportion has to be performed. The final diagnosis of TAM is established after cytogenetic analysis and classification of the blast cells with further test for GATA1 mutation [27–28].

The strength of the study is sharing of data on symptoms of TAM in a fetus with normal karyotype. Presented case emphasize the need to put a special attention to fetal symptoms mentioned above, even if karyotype is normal and not to reject TAM diagnosis in genotypically normal neonates.

The limitations of the study are related to its nature of case report and the rarity of the condition. Also, fetal blood sampling was not performed since the condition of the fetus prompted urgent delivery. However, the case highlights the importance of performing an ultrasound evaluation upon admission of a patient referred for reduced fetal movements. The examination should include doppler examination also in normally grown fetuses.

5 Conclusion

Even though literature reports good prognosis and self-limiting nature of TAM, fetuses presenting high MCA PSV or hepatosplenomegaly seem to have a fatal outcome. Our study demonstrates rare manifestation of TAM in genotypically normal neonate with prenatal presentation of hepatosplenomegaly and anemia.

Literature reports leukocytosis as typical disorder in TAM cases, but this cannot be detected prenatally with non-invasive tolls. Anemia often coexists in TAM cases and is easy detectable by noninvasive MCA doppler examination. This can be an accessory marker to suspect hematological disorders especially in fetuses presenting hepatosplenomegaly.

Obstetricians should pay attention to symptoms like high MCA PSV and hepatosplenomegaly as possible causes of fetal hematological disorders and differentiate it with infection or isoimmunization. The CTG together with ultrasound examination should be routinely offered

if a pregnant women reports decreased fetal movements. To confirm the TAM diagnosis, it is recommended to perform fetal blood sampling with analysis of the blast karyotype.

Implication for clinical practice:

1. High MCA PSV without infection or immunization can be a symptom of TAM in fetuses presenting hepatosplenomegaly.
2. TAM is a possible cause of non-immune hydrops fetalis, fetal anemia and hepatosplenomegaly.
3. This case illustrates the importance of performing an ultrasound examination that includes doppler studies even if the fetus is normally grown in patients presenting with reduced fetal movements.
4. Do not assume that TAM occurs only in DS neonates.

Abbreviations

GA
gestational age
C
cordocentesis
FBS
fetal blood sampling
NND
neonatal death
TOP
termination of pregnancy
IUD
intrauterine death
PI  
pulsatility index

UA  
umbilical artery

MCA  
middle cerebral artery

PSV  
peak systolic velocity

AEDV  
absent end diastolic flow

TAM  
Transient abnormal myelopoiesis

DS  
down syndrome

CTG  
cardiotocography

AMKL  
megakaryoblastic leukemia

aCGH  
comparative genomic hybridization

NICU  
neonatal intensive care unit

Declarations

Consent to participate: The patient’s informed consent to the study unit was obtained. All data related to the patient has been anonymized and does not allow identification of the patient.

Consent for publication: The patient gave informed and full consent to participate in the study and for publication.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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