Hepatosplenomegaly Associated with Transient Abnormal Myelopoiesis in Down Syndrome: An Autopsy Case of a Stillborn Fetus

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Key Words

CD61 · Down syndrome · Hepatosplenomegaly · Placenta · Stillbirth · Transient abnormal myelopoiesis · Umbilical cord

Abstract

A 38-year-old primiparous mother (gravida 1, para 0) at 27 weeks and 6 days' gestation reported that fetal movements had been absent for 6 days. All serological markers for infection were negative. Chorionic villus sampling at stillbirth delivery revealed trisomy 21 (47, XX, +21), indicative of Down syndrome. The macerated baby was female and weighed 1,290 g. There was no evidence of hydrops fetalis. Proliferating blast cells expressing megakaryoblastic/megakaryocytic antigen CD61 were mainly seen within the vessels, and some cells infiltrated outside of the vessels in almost all organs. Vessels of the umbilical cord and chorionic villi were filled with proliferating blast cells, but the blast cells were not apparent in the bone marrow. The diagnosis of transient abnormal myelopoiesis in Down syndrome was made. Hepatomegaly (64.5 g) was due to congestion and infiltration of CD61-positive blast cells within the vascular lumina and expanding outside the lumina accompanied by fibrotic change. The cause of death was attributed to liver insufficiency caused by liver fibrosis. An umbilical cord and chorionic villi examination may be helpful in the diagnosis of transient abnormal myelopoiesis when post-mortem examination is not permitted.

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Introduction

Down syndrome is the most common viable human chromosomal disorder with an estimated incidence of 1 in 700 live births [1]. Transient abnormal myelopoiesis (TAM), also referred to as transient myeloproliferative disorder or transient leukemia, a clonal proliferation of predominantly megakaryocytic precursor cells in the peripheral blood, affects 4–10% of individuals with Down syndrome [2]. TAM resembles acute megakaryoblastic leukemia (AMKL) but may originate during intrauterine life and often disappears spontaneously in the absence of chemotherapeutic strategies within the first few months of life. However, still-born cases of TAM in Down syndrome are sporadically reported [3–9]. Here, we report an autopsy case of a female macerated stillborn fetus weighing 1,290 g at 27 weeks' gestation with TAM associated to trisomy 21.

Case Report

A 38-year-old primiparous mother (gravida 1, para 0) presented to Kansai Medical University Hospital. She was at 27 weeks and 6 days' gestation by menstrual history, but fetal movements had been absent for 6 days. All serological markers for infection were negative. Although ultrasound indicated no particular change, chorionic villus sampling at delivery revealed trisomy 21 (47, XX, +21), indicative of Down syndrome.

The post-mortem examination was performed 19.5 h after the delivery. The fetus was at 27 weeks and 6 days' gestational age with death in utero occurring approximately 6 days before delivery. The female fetus weighed 1,290 g, and there was no evidence of hydrops fetalis. As maceration had occurred, characteristic external features of Down syndrome were hard to determine, but no apparent external anomalies were seen; pericardial effusion, pleural effusion, and ascites suggestive of hydrops fetalis were absent. In the abdominal cavity, according to organ weight in relation to total body weight [10], hepatomegaly (64.5 g; normal, 59.8 g) and splenomegaly (5.6 g; normal, 3.4 g) were evident; other visceral organ weights were lighter than the average. No other congenital malformations were detected.

Microscopically, blood vessels in almost all organs contained proliferating blast cells of various sizes (fig. 1a). Immunohistochemically, proliferating cells within the vascular lumina and proliferating outside the lumina expressed megakaryoblastic/megakaryocytic antigen CD61 (fig. 1b). In addition to proliferating CD61-positive cells within the vessels and infiltrating along the sinusoids, the liver showed fibrotic changes (fig. 2a). Fibrous components were seen in the perisinusoidal regions, resembling pericellular fibrosis (fig. 2b). However, bile stasis was not detected by Hall stain (data not shown).

The umbilical cord was normal, and the placental maturation was appropriate for the gestational age with no inflammatory cell infiltration. Characteristically, vessels of the umbilical cord and chorionic villi contained proliferating blast cells of various sizes (fig. 3). However, the bone marrow lacked these proliferating cells. Based on these data, liver fibrosis associated with TAM in Down syndrome was diagnosed.

Discussion

A GATA1 mutation leading to the production of N-terminally truncated GATA1 (GATA1s) in the early megakaryocyte/erythroid progenitor stage is linked to the onset of TAM [9, 11]. However, cytogenetic analysis of GATA1 mutation was not performed in the

present case. While the majority of TAM patients undergo spontaneous regression within 3–6 months of age, 20–30% of patients develop AMKL (FAB; M7) [2]. Apart from this outcome, stillborn cases of TAM associated with Down syndrome occur in less than 10% of TAM patients [3–9]. Hydrops fetalis and/or hepatosplenomegaly may be a sign of TAM in fetuses with Down syndrome [6], but the cause of fetal death remains uncertain.

Hepatosplenomegaly in TAM is caused by the hepatic invasion of blast cells and/or secondary hepatic fibrosis [12]. Cytokines from megakaryocytes, especially transforming growth factor (TGF)- β , may promote liver fibrogenesis [13, 14]. Hepatic stellate cells play an important role in the development and progression of hepatic fibrosis [14, 15]. Megakaryocytes of the liver are often associated with fibrosis [16] by stimulating stellate cells. The main cause of death in fetuses with TAM is hepatic infiltration by blast cells and the ensuing hepatic fibrosis leading to hepatic insufficiency [12, 17]. In agreement with previous reports, the development of hepatic fibrosis seems to be the primary pathogenic abnormality in early death [18, 19]. Also, blast cell proliferation, hepatic infiltration, and hepatic fibrosis causing hepatomegaly in fetuses and newborns are included in the diagnostic criteria of TAM. The pathologic distinction between TAM and AMKL is problematic, since the proliferating cells of TAM and AMKL are indistinguishable [7]. However, in agreement with the present case, although intralobular diffuse liver fibrosis was present, myelofibrosis, a well-known complication of AMKL, is not detected in TAM [13]. TAM is distinct from AMKL in that TAM originates from the fetal liver while AMKL originates from the bone marrow several years after birth [8].

Hydrops fetalis may also cause fetal death. Non-immune hydrops fetalis occurs in TAM associated with Down syndrome [4], probably by extensive tissue infiltration of proliferating blast cells leading to very high mortality rates [20]. Heart failure (pericardial effusion) followed by generalized hydrops is also fatal [17]. However, hydrops fetalis was not seen in the present case. Moreover, brain atrophy with periventricular leukomalacia has also been described in fatal cases of fetal TAM [6]. In the present case, brain autolysis prevented the histological examination of the brain.

Post-mortem examinations of stillborn infants are not always permitted by the parents. Although permission to perform a fetal autopsy may not be granted, TAM can be diagnosed by the presence of abnormal cells within umbilical and chorionic vessels [2, 21, 22]. In some cases, proliferating blast cells of fetal origin invade the vascular wall of the placenta and exist in the maternal space [2, 21, 23]. The presence of fetal blast cells in the maternal space is associated with a 90% rate of stillbirth or death in early life [21]. In stillborn cases of TAM in Down syndrome, hydrops fetalis, periventricular leukomalacia, or maternal involvement of fetal blast cells, as well as liver fibrosis, as seen in the present case, may be the cause of intrauterine fetal death.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no potential conflicts of interests with respect to the authorship and/or publication of this article.

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Fig. 1. Lung of stillborn infant with Down syndrome and TAM. Proliferating blast cells with CD61 positivity are seen within the vessels and infiltrating outside the lumina. **a** HE. $\times 200$. **b** CD61. $\times 200$.

Fig. 2. Liver of stillborn infant with Down syndrome and TAM. Proliferating blast cells are seen within the vessels and along the sinusoids accompanied by pericellular fibrosis. **a** HE. $\times 200$. **b** Masson-Trichrome. $\times 200$.

Fig. 3. Chorionic villi of stillborn infant with Down syndrome and TAM. Proliferating blast cells are seen within the vessels. HE. $\times 200$.