A case report and literature review of congenital leukemia

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Abstract

BACKGROUND

Acute leukemia in newborns is also known as neonatal or congenital leukemia (CL) and is a rare disease with an incidence rate of 1-5 per 1,000,000 Live births. After birth, infants with CL exhibit infiltrative cutaneous nodules, hepatosplenomegaly, thrombocytopenia, and immature leukocytes in the peripheral blood. These symptoms are frequently accompanied by congenital abnormalities including trisomy 21, trisomy 9, trisomy 13, and/or Turner syndrome. Despite significant advances in disease management, the survival rate is approximately 25% at 2 years.

CASE SUMMARY

Here, we document a case of trisomy 21-related acute myeloid leukemia (AML) in a female neonate. The baby was sent to the neonatal intensive care unit because of anorexia, poor responsiveness, and respiratory distress. She was diagnosed with AML based on bone marrow aspiration and immunophenotyping. Genetic sequencing identified a mutation in the GATA1 gene. After receiving the diagnosis, the parents decided against medical care for their child, and the baby died at home on day 9 after birth.
CONCLUSION
The newborn infant was diagnosed with trisomy 21-related AML. Genetic sequencing identified a mutation in the GATA1 gene. The parents abandoned medical treatment for their infant after receiving the diagnosis, and the infant died at home on the 9th day after birth.

Key Words: Case report; literature review; congenital leukemia; Trisomy 21; GATA1; AML.


Core Tip: We documented a case of trisomy 21 acute myeloid leukemia (AML) in a baby. Due to her anorexia, poor responsiveness, and respiratory distress, she was sent to the newborn critical care unit. A diagnosis of AML was made by bone marrow aspiration and immunophenotyping. Using genetic sequencing, a mutation in GATA1 was found. Parents abandoned medical care for their 9-day-old after receiving the diagnosis, and the baby died at home.

INTRODUCTION
Congenital leukemia (CL) accounts for <1% of all the reported cases of pediatric leukemia and is often manifested during the first 28 days of life[1]. CL is the third-most prevalent malignancy in infants after teratoma and neuroblastoma[2]. The estimated frequency of newborn leukemia in the UK is 3 cases per million newborns with about 2 cases of newborn leukemia reported every year[3]. A retrospective investigation in Brazil confirmed 77 cases of newborn leukemia during a 25-year period between 1990 and 2013[4]. In 2002, Bresters et al reported that 15 cases of congenital leukemia were diagnosed over 25 years in the Netherlands[5]. In China, the accurate incidence rates of
CL are not available because of unreliable case recording and a lack of comprehensive investigations of leukemia. The spectrum of CL includes Down syndrome (DS)-related newborn leukemia, which often manifests as transitory abnormal myelodysplasia (TAM), and non-DS-related neonatal leukemia[6]. Non-DS-related neonatal leukemia is rarer than DS-related newborn leukemia.

Fetal exposure to a cancer-causing mutation is considered the starting point for childhood leukemia. However, for a newborn infant with the first mutation, a "second hit" must occur sometime after delivery to develop leukemia. The hematological and clinical hallmarks of neonatal leukemia are present in the newborn, as all the pathogenic cancer mutations already develop during pregnancy. Neonatal leukemia often presents as acute myeloid leukemia (AML) in 56–64% of cases, but other patients may show one of many immunophenotypes, including blastic plasmacytoid dendritic cell neoplasm, mixed phenotype acute leukemia (MPAL), or acute lymphoblastic leukemia (ALL)[1,3]. Infants with CL often exhibit aggressive characteristics including high white blood cell (WBC) counts, reduced platelet counts, hepatosplenomegaly, central nervous system (CNS) involvement, and skin-infiltrative cutaneous leukemia[7,8]. In extreme circumstances, multiple organs are affected. In contrast with childhood leukemia, lymphadenopathy is rare in newborn leukemia. The prognosis for CL is typically poor, with death rates of 68–74% within 2 years of diagnosis in the neonates because of higher resistance to chemotherapy and increased toxicity from treatment[5,9]. However, spontaneous remission (SR) has been documented in at least 20 cases[10]. The following criteria are used to diagnose CL[11]: (1) Diagnosis within 28 days of birth; (2) specific number or proportion of primitive or immature cells in the bone marrow aspirate, and significantly high peripheral blood leukocyte counts (>25×10⁹/L); (3) spread of primitive cells to areas beyond the blood and bone marrow; and (4) no evidence of other disorders (e.g., newborn sepsis or neonatal hemolysis) that might cause infiltration of non-hematopoietic tissues.
Here, we describe a case of DS-related newborn leukemia caused by a GATA1 mutation. We also review the clinical, cytogenetic, and molecular characteristics of CL.

CASE PRESENTATION

Chief complaints
A 3-day-old female neonate was referred to our hospital with anorexia, poor reactivity for 2 days, and shortness of breath for 1 day.

History of present illness
The 3-day-old female infant was born at 38 wk and 3 days of gestation. At birth, she weighed 3300 g, with a normal amniotic fluid, umbilical cord, and placenta, and achieved a perfect score of 10 on the Apgar scale. One day after birth, she was sent to the neonatal intensive care unit (NICU) because of anorexia and poor reaction. At first, she was suspected to have "neonatal pneumonia" and was provided with non-invasive ventilator support. She was also treated with an antibiotic combination of ceftazidime and penicillin. The patient was then sent to our facility because her symptoms did not improve and she continued to experience breathing difficulty.

History of past illness
No specific past medical history.

Personal and family history
The patient was the family's third child. The first child had died because of an illness, within a month of delivery. Both parents and her elder sister (the family's second child) did not show any disease symptoms. The family did not have any significant medical history of a similar disease. The maternal age at delivery was 24 years. There was no history of the mother being exposed to quinolone antibiotics, pesticides, hormone medicines, or radiation, and she was a non-smoker and non-drinker. However, the
mother had been exposed to mosquito repellents during pregnancy. A week before delivery, the mother suffered a respiratory illness and was treated with cefazolin.

**Physical examination**

The patient’s vitals at admission were as follows: axillary temperature, 36.8°C; respiratory rate, 58 beats/min; pulse rate, 150 times/min; BP, 64/32 mmHg; and transcutaneous oxygen saturation, 90%.

Physical examination showed evidence of DS phenotype, namely simian crease, hypertelorism, and hypotonia. The trunk skin had developed red maculopapular rashes. Heart and lung auscultation did not reveal any murmurs or rales. Both the liver and spleen could be easily palpated at 3 and 5 cm below the costal border, respectively.

**Laboratory examinations**

The results of complete blood analysis were as follows: total leukocyte count, 79.37×10⁹/L; neutrophils, 17.40%; lymphocytes, 8.40%; monocytes, 71.10%; hemoglobin, 16.2 g/dL; and platelet count, 514×10⁹/L. Fifty-eight percent of the total cells in the peripheral blood smear were primitive and naive cells. The reticulocyte counts were 126.80×10⁹/L (2.99%).

After testing the blood solution, the concentration of potassium ions was 7.44 mmol/L.

All the body fluids of the patient, including the cerebrospinal fluid (CSF), blood culture, and urine, were within the normal range.

Details of the bone marrow smear are shown in Figure 1. Hyperplasia of the bone marrow was clearly observed in the bone marrow smear, and approximately 35% of the bone marrow cells were classified as primitive. These cells showed the following morphological characteristics: (1) rounded nuclei, fine and loose nuclear chromatin, and the presence of 1–3 nucleoli; (2) dynamic proliferation of myeloid cells; (3) suppressed growth of new erythroblasts; (4) 8% of the total bone marrow cells were lymphocytes; and (5) megakaryocytes were rare and primordial cells.
The results of chromosome analysis showed DS. The karyotype was 47, xx, +21. GATA1 mutation was identified based on gene sequencing analysis. The variation information was NM_002049:exon2:c.1A>G:p.M1. The chromosome position was chrX:48649517A >G with a mutation frequency of 99.4%.

**Imaging examinations**
None

**FINAL DIAGNOSIS**
Acute myeloid leukemia with trisomy 21

**TREATMENT**
The NICU staff of our hospital administered oxygen therapy; penicillin with cefoperazone sulbactam sodium to prevent infections; and hydration, alkalinization, allopurinol, and hydroxyurea to aid in the decrease of white blood cells after the baby was admitted. The whole treatment lasted for 3 days.

**OUTCOME AND FOLLOW-UP**
The parents abandoned medical care for the patient after the diagnosis. The baby passed away at home on day 9 day after birth.

**DISCUSSION**
Genetic factors play a significant role in the pathogenesis of CL. A high proportion of infant leukemias are cytogenetically characterized by balanced chromosomal translocations. The most frequent cytogenic abnormality in CL is t (4;11) (q21.3;q23.3)/KMT2A-AFF1, followed by t(1;22)(p13.3;q13.1)/RBM15-MKL1 and t(8;16)(p11.2;p13.3)/KAT6A-CREBBP[3, 12-14]. Among them, rearrangements in the histone lysine methyltransferase 2A gene (KMT2A, formerly known as the mixed lineage leukemia [MLL] gene) occur in 75% of ALL and 50% of AML in
CL. KMT2A rearrangements results in the fusion of the N-terminus of the KMT2A gene with the C-terminus of a partner gene. In infant ALL, the most common KMT2A partner gene is AFF1, and in infant AML, the most common KMT2A partner gene is MLLT3[15]. Trisomy 21 is the most frequent chromosomal anomaly in the human genome. Leukemia or lymphoma was the cause of death in one-fifth of DS patients in the ≤1-year-old group group in Japan[16]. Children with DS are associated with a 150-fold higher risk of AML and a 20-fold higher risk of ALL than children without DS[17]. CRLF2 gene rearrangement (either inter- or intra-chromosomal) is the most prevalent genetic abnormality that causes DS-ALL followed by ETV6::RUNX1 and C/EBP-altered[18]. Moreover, GATA1 mutations are reported in 30% of children with DS. GATA1s mutations induce uncontrolled proliferation of the fetal megakaryocytic cells and aberrant terminal erythroid differentiation[19]. GATA1 mutations cause transient abnormal myelopoiesis (TAM) in 50% infants diagnosed with DS[20]. According to the literatures, we summarized the clinical features, laboratory tests, treatment and prognosis of TAM and AMKL associated with mutations in the GATA1 gene in children with DS, as shown in Table 1. Transient aplasia of the megakaryoblast and erythroblast (TAM) cells in the fetal liver, peripheral blood, and bone marrow is a characteristic feature of DS and has not been reported for any other disorder[26, 27]. About 5 and 10% patients with TAM develop AML within 4 years because of the accumulation of additional oncogenic mutations[28]. Our patient was diagnosed with DS-related AML accompanied by a GATA1 mutation. She had signs of organ invasion soon after delivery. Her parents decided to stop treatment after diagnosis. Additional risk factors for CL include prenatal exposure to adrenocortical hormones, antihistamines, psychiatric therapeutics, and exposure to radiation and magnetic fields[29]. Viral infections have also been linked with CL[30, 31]. The patient’s mother was exposed to chemicals during pregnancy.

The most prevalent clinical manifestations of non-DS newborn leukemia include pleural effusions, ascites, jaundice, skin lesions, splenomegaly, hepatomegaly, renal and hepatic failure, acidosis, hypoxia, and respiratory distress[32]. Central nervous system
infiltration has been reported in newborn leukemia[8]. Nodules of varying firmness and color (blue, red, brown, or purple) are a common symptom of cutaneous infiltrates and are referred to as "blueberry muffin" rash. Newborns with AML are more likely to exhibit cutaneous infiltrates than those with ALL[5, 33]. Cutaneous infiltrates are also observed in patients with blast plasmacytoid dendritic cell neoplasms (BPDCN)[34]. Symptoms of DS-related newborn leukemia range from the absence of any symptoms to those caused by multiple organ failure [35]. Peripheral blood smear is recommended for all the infants with DS because abnormal blood counts and circulating megakaryoblasts are highly prevalent in hematologic malignancies[36]. The first symptom reported in this case was dyspnea. Peripheral blood tests indicated significantly high white blood cell counts. In our patient, dyspnea was the most prominent symptom. Hepatosplenomegaly was also detected, but skin infiltration was not observed.

Leukocytosis, anemia, thrombocytopenia, and coagulation disorders are the most common hematological manifestations of newborn leukemia. The counts of white blood cells and blast cells were higher than 50×10⁹/L in newborn leukemias, in contrast to other infections that may cause neonatal leukocytosis. Neonatal leukemia must be differentiated from congenital infections, hemolytic illnesses, and leukemoid responses. Clinically, newborns with severe infections show high counts of myelocytes, metamyelocytes, and neutrophils; whereas, circulating blast cells seldom surpass 8% of the total peripheral blood cells. Moreover, these variations disappear within the third or fourth day after delivery.

A “watch and wait” approach with careful monitoring (including frequent physical examinations and blood counts) is necessary for CL with stable illness, because there is a possibility of spontaneous remission without the use of chemotherapeutic medications that are associated with adverse effects[10, 37]. According to the newly released guidelines, a low-dose cytarabine therapy is recommended for cases with multiorgan failure, high white blood cell counts (>100 x 10⁹/L), hepatopathy, and other life-threatening diseases. Besides, hematopoietic stem cell transplantation is recommended for patients with juvenile myelomonocytic leukemia (JMML) [38].
CL is associated with poor survival outcomes. The main factors for poor prognosis are as follows: (1) presence of leukemia detected in the central nervous system at the time of diagnosis; (2) the initial white blood cell counts are $>50 \times 10^9/L$; (3) leukocyte differentiation antigen CD10 is negative in the bone marrow; (4) myeloid leukemia cell surface antigens are present on the leukemic cells; and (5) AML genes have been rearranged at the 11q23 Locus [39].

CONCLUSION
Our patient was a female neonate diagnosed with DS-related AML. Gene sequencing identified a mutation in the GATA1 gene. Because the prognosis was poor, the parents decided to abandon therapy and rejected further investigation. The child died at home on day 9 after birth.

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