Case report

Congenital acute myeloid leukemia in Down syndrome

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Abstract

Congenital leukemia is an uncommon myeloproliferative disorder usually diagnosed in the first month of life. Newborns with Down syndrome have an increased susceptibility to acute megakaryoblastic leukemia. We report a case of a newborn with Down syndrome diagnosed with acute myeloid leukemia. The diagnosis was established by clinical and hematological work-up.

Keywords: *congenital leukemia; newborn; Down syndrome*

Introduction

Congenital leukemia (CL) is an uncommon myeloproliferative disorder of the newborn, with an incidence of 4.3 - 8.6 per million live births [1]. Down syndrome (DS) is the most common chromosomal disorder, affecting 1 in every 700 newborns. Hematological abnormalities in a newborn with DS include a variety of benign and malignant disorders. Patients with DS are found to have an increased incidence of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) – most frequent AML-M7 type [2, 3].

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Case report

A term female infant was born by vaginal delivery with normal birth weight, body length and APGAR score, from a 42-year-old mother with 13 previous pregnancies resulting in 3 miscarriages and 10 live births. The mother had no history of antenatal medical illness nor of exposure to smoking, drinking and other drugs. At birth, general and systemic examination revealed a round face, single palmar crease, left precordial systolic murmur. Two hours after birth a deterioration of the general condition occurred, with generalized hypotonia, cyanosis, poor feeding. The blood count revealed white blood cell count of $35.6*10^3$/μL with $20.6*10^3$/μL, 57.9% monocytes, normal neutrophils, lymphocytes and eosinophils count, hemoglobin levels of 19.1 g/dl and $27*10^3$/μL platelets count. The acute phase reactants were negative. Because she maintained the altered general condition and the platelets ranged between 17-18 $*10^3$/μL, on the 8th day after birth she was referred to our unit for proper diagnosis and treatment. Physical examination showed a

phenotype suggestive for Down syndrome, later confirmed by karyotyping (47, XX + 21). She was lethargic, tachypneic and a systolic heart murmur was observed. The liver was 2 cm below the right costal margin, along with a slight enlargement of the spleen. The laboratory tests on the first day of admission in our unit revealed a white blood count of $15.8*10^3$/µL, with an abnormal monocyte count (increased absolute and percentile count: $5.66*10^3$/µL, respectively 35.5%), normal absolute neutrophil count ($5.53*10^3$/µL), a hemoglobin level of 15.9 g/dl and severe thrombocytopenia ($15*10^3$/µL). The biochemical parameters including electrolytes, uric acid, creatinine, bilirubin, liver enzymes were normal. The serum lactate dehydrogenase was raised. The bacterial culture work-up and titers of antibodies against toxoplasmosis, cytomegalovirus, Epstein Barr virus, hepatitis C, HIV were negative. The peripheral blood smear presented atypical cells. The bone marrow aspiration showed hemodiluted aspirate with blast cells. Immunophenotyping revealed 23% blast cells, positive for megakaryocytic markers (CD42b, CD41, CD61), myeloid markers (CD33), progenitor cell markers (CD117, CD34) and T cell marker - CD7 positive. MPO and HLA/DR were negative. The mutational status of *AML-ETO*, *PML-RARα*, *FLT3* and *NPM1* fusion genes came out absent. The positive diagnosis was acute megakaryoblastic leukemia (AMKL).

The echocardiography found a patent foramen ovale. The infant underwent chemotherapy according to the Down syndrome-specific AML chemotherapy protocol, consisting in four cycles of treatment: the first two cycles (induction phase) included combinations of cytarabine and liposomal daunorubicin and the last two cycles (consolidation phase): etoposide, cytarabine and mitoxantrone. Our patient aquired clinical and hematological remission without serious adverse events.

Discussion

Congenital leukemia (CL) is an extremely rare pathology, with a high mortality rate. This rare pathology, with a high mortality rate. This condition applies to children in their first month of life [4]**.** In this age group, acute myeloblastic leukemia is more common than acute lymphoblastic leukemia, and among the subtypes of AML, subtypes M5 and M4 account for approximately 50% of congenital leukemia; the M7 subtype is little involved [3, 5, 6]. Acute megakaryoblastic leukemia (AMKL) is a subtype of acute myeloid leukemia, a rare heterogenous malignancy in adults and more frequent in children, characterized by abnormal megakaryoblasts that are immunophenotypically positive for CD41, CD42b and CD61.

Extensive myelofibrosis in the bone marrow has also been reported [7-9]. Congenital leukemia is associated with certain genetic pathological entities such as Down syndrome, Turner syndrome or Klippel-Feil syndrome [10]. Trisomy 21 was detected in our patient.

Children with DS are at high risk of developing hematological abnormalities such as neutropenia, thrombocytopenia, myelodysplasia, acute myeloid leukemia, acute lymphoid leukemia [11]. In young children with Down syndrome, there is a 46 to 83-fold increased risk of acute myeloblastic leukemia. AMKL is estimated to be 400 times than other children from general population and accounting for 50% of all cases of AML associated with DS. Newborns with DS have a 20-fold increased risk of developing acute leukemia [12-14].

The *GATA-1* gene encodes the essential hematopoietic transcription factor. Acquired mutations in the *GATA-1* gene have been found in blast cells in DS with myeloid leukemia [15]. The *GATA1* mutation could not be performed in our patient. The most common clinical signs encountered immediately postnatal in most newborns are respiratory distress, possibly due to secondary leukemic infiltration, hepato-splenomegaly, petechiae, and in exceptional cases leukemia, cutis [16]. Signs of respiratory distress lethargy, hepatosplenomegaly were noted in our patient immediately after birth, with no skin manifestations. The laboratory workup revealed myeloid blasts on both blood smear and bone marrow, confirmed by flowcytometry.

The diagnosis criteria of CL according to *Bresters et al.* are: presentation in the first month of life, proliferation of immature myeloid, lymphoid or erythroid cells, infiltration of these cells into non-haematopoiectic tissues and absence of other diseases that may explain the proliferation [5]. In 4-10% of cases, Down syndrome associates transient myeloproliferative disease (TMD), this being one of the most important differential diagnoses. TMD may mimic acute leukemia and presents hepatic infiltration, pancytopenia, blast cells in bone marrow and spontaneous remission within three to seven months of onset without any chemotherapic treatment [3, 5, 17]. The differential diagnosis of CL also includes intra-uterine infections and sepsis, which in our patient were excluded by viral serology and negative peripheral cultures [3].

The treatment of congenital leukemia means exposure of the newborn to toxic chemotherapeutic agents. Children with DS have an increased risk of secondary cardiac toxicity to anthracycline due to the existing cardiac malformations in this disease [18]. The ultrasound aiming to reveal patent *foramen ovale* and cardiac follow-up is especially indicated in this population. The prognosis of CL is poor, with a surviving rate of 23% at 2 years [5]. AMKL associated with Down syndrome (DS-AMKL) has a superior outcome compared with the sporadic form, with long-term survival [3, 19]. The follow-up period for our patient was 1 year and 3 months and she is still in complete remission. Our case is similar with the literature data in which children with DS-AMKL present a better treatment response and survival rate compared to children with sporadic AMLK. In order to assess disease evolution, periodical clinical and hematological work-up (CBC and bone marrow aspiration) need to be performed.

Conclusion

The prognosis of congenital leukemia depends on the immunocytological form and the tolerance of the newborn to chemotherapy. Recent studies suggest a superior outcome in children with Down syndrome and AML compared to children with sporadic AMLK. For our patient a prolonged follow-up period is needed.

Conflict of interest

The authors have no conflict of interest to declare.

Patient consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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