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PEDIATRICS

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CONGENITAL ACUTE MEGAKARYOCYTIC LEUKEMIA IN NEWBORNS (case report)

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Abstract: Acute megakaryocytic leukemia (AMKL) or acute myeloid leukemia (AML-M7) is a type of pediatric AML accounting for 3-10% of primary childhood AML and 50% of the AML in children with Down's syndrome. Median age of presentation is 6 years (ranging from neonatal period to 16 years). The onset of the disease can be similar to septicemia and congenital infections. Predominantly AMKL has a rapid deterioration that leads to death caused by hemorrhage and infections despite of intensive therapeutic measures. A case of congenital AMKL with manifestation in the neonatal period and without any features of Down's syndrome is presented.

KeyWords: Congenital megakaryocytic leukemia, newborn

A male infant was born from the 5th pregnancy, second premature delivery at gestational age of 32 weeks. This pregnancy was preceded by 3 spontaneous abortions at gestational age less than 12 weeks. Pregnancy proceeded against the background of threatened miscarriage at 28 weeks of gestation, premature rupture of membranes and chronic pyelonephritis in the mother at the stage of remission. X-ray examination of the mother's chest was performed at gestational age of 8-10 weeks. The child's father works at a car service station. Fetal respiratory distress syndrome was prevented by 24 mg of dexamethasone. The infant had a low birth weight of 2240 g, body length of 44 cm, chest circumference of 28 cm and head circumference of 30 cm. These parameters exceeded standard ones for this gestational age. Apgar score was 3-4 points.

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At birth the newborn had a severe condition due to respiratory disorders and neurological deficits on the background of the immaturity of organs and systems as a result of prematurity. Therefore, he was administered resuscitation measures which included sanation of upper airways, prolonged mask lung ventilation twice for 40 seconds, further non-invasive lung ventilation for 30 minutes, gastric probe administration, correction of hypovolemia, water and electrolyte balance and blood gases.

Since the first hours of life the child had severe pathological neurological symptoms (the child was lethargic, did not cry, his reflexes were depressed, with signs of hypersensitivity and muscle dystonia). On the 2nd day of life he developed signs of hemorrhagic syndrome, namely flow of blood from the gastric tube and ecchymosis on the limbs, with manifestations of hepatolienal syndrome. In spite of the therapy, the respiratory disorders grew acute. Blood tests showed anemia, leukopenia, thrombocytosis, distinct myeloid irritation due to promyelocytosis and basophilia. With dynamic management of the infant thrombocytosis increased from 600×109 to 1300×109 and reticulocytes decreased to 1%; leukopenia persisted to 2.5×109.

Differential diagnosis with congenital sepsis, hepatitis, the presence of TORCH-infections was conducted.

However, taking into account the follow-up findings, persisting respiratory disorders, intensification of neurological symptoms, hemorrhagic and hepatolienal syndromes and paraclinical data (thrombocytosis, hyporegeneratoric normochromic anemia, leukopenia, distinct myeloid irritation) suggested hemoblastosis, namely congenital myeloid leukemia (M7 type). Nevertheless, the severity of the condition did not allow to render total oncohematological examination, including myelogram.

The treatment included respiratory support, antibiotic therapy, detoxification, hemostatic therapy and resuscitation. However, with time the infant's condition progressively worsened. The infant died at the age of 9 days due to progressive multiple organ failure.

Postmortem examination showed leukemic infiltrates in the internal organs. The liver and spleen were found to have diffuse proliferation of leukemic cells and hyperthrombocytosis. Besides, examination revealed large venous thrombosis of the hepatic vessels and the spleen with infarction-like haemorrhages in these organs. In addition a large amount of similar cellular infiltrates was found in the lungs, brain and meninges. Microscopic study detected abnormal platelets and large cells (25-40 microns), with a large nuclear-cytoplasmic ratio (i.e., large nucleus) and a relatively poor, variably basophilic cytoplasm. The nuclear chromatin of the large cells was dense and homogeneous. Immunohistochemical studies confirmed that these cells belonged to megakaryoblasts.

The cause of death was determined as multiple organ dysfunction syndrome. The diagnosis of congenital megakaryocytic leukemia was confirmed.

DISCUSSION

This case was characterized by the development of hemoblastosis (myeloid leukemia M7) in a newborn with adverse premorbid background, presenting since the first days of life as severe respiratory and neurologic disorders, hemorrhagic and hepatolienal syndromes, changes in clinical blood tests, such as thrombocytosis, anemia and leukopenia. Diagnosis was extremely difficult due to the low incidence of the disease, especially in infants, and also difficulties in providing the diagnosis by oncohematological approach.

Congenital leukemia is a term including the cases presenting with clinical and hematologic syndromes in the first days of life. Leukemia in children of the first months of life is a very rare disease. According to Bajwa RP, Skinner R, Windebank KP, Reid MM. (2004), the incidence of congenital leukemia is 4.3 - 8.6 per million livebirths [2]. AML-M7 or AMKL is a very rare type of AML, which is about 1% of all cases of leukemia in children, with the incidence rate of 0.5 cases per million per year [1].

Primary thrombocytosis is a clonal myeloproliferative disorder with an estimated annual incidence of about 2 cases per million of adult population [3] and 0.09 cases per million of children [4, 5].

Literature review revealed a few descriptions of manifestation of congenital leukemia in the neonatal period. The youngest case of congenital myeloid leukemia not associated with Down’s syndrome has been described at the age of 1 day [6], and congenital megakaryocytic leukemia without Down’s syndrome has been described at the age of 17 days [1]. Another case of AMKL has been reported in a newborn at the age of 4 weeks and the infant was found to have only infiltration in the liver [7].

An increase in the incidence of congenital leukemia in infants was shown to be 2 times higher in mothers exposed to X-rays for diagnostic purposes [8].

At the same time healthy children are born from mothers who have leukemia. This fact excludes transplacental transmission of leukemia. Studies showed that maternal part of the placenta contained leukemic cells with their absence in the fetal part [9].

Risk factors for congenital leukemia are mother's age exceeding 35 years, fetal death in past history, macrosomia, cancer in family history and immunodeficiency states [10, 11].

Clinical criteria of congenital leukemia include anemic syndrome, haemorrhagic syndrome, intoxication syndrome, proliferative syndrome, neuroleukemia [12].

Such clinical signs as toxicity, bacterial, fungal or protozoal infection, fever, hemorrhagic syndrome (associated with both thrombocytopenia and intravascular thrombosis due to thrombocytosis), jaundice, leukemic infiltration, hepatosplenomegaly, neurological symptoms, testicular enlargement in boys should be considered as clinical manifestations of leukemia in neonates.

Clinical "masks" of acute leukemia include patients with sepsis, pneumonia, purulent skin lesions, congenital hepatitis, patients with hepatolienal syndrome of unknown origin, congenital syphilis, children with low birth weight. The greatest challenge is to make the differential diagnosis between leukemia and sepsis.

Main laboratory criteria of congenital leukemia are myeloid line (promyelocytes, myelocytes), anemia, thrombocytopenia or thrombocytosis, increased ESR.

Bone marrow aspiration and biopsy with the detection of blast cells in myelogram (more than 25%) are known to be the diagnostic gold standard.

Megakaryocytic leukemia is characterized by the following:

- Hyperthrombocytosis in blood, varying from 700×109/L to 1000×109/L and higher (sometimes up to 2000-4000×109/L)
- Abnormal forms of platelets in peripheral blood
- Occasional slight polycythemia, leukocytosis with a shift of leukocyte formula to the left
- Histological specimens are suggestive of bone marrow hyperplasia of megakaryocytic lineage (more than 5-7 megakaryocytes in the field of view)
- In the majority of cases the spleen is not or slightly enlarged and is palpable at the costal margin. The tendency to thrombosis is triggered by hyperthrombocytosis.
- Bleeding results from impaired platelet aggregation, disseminated intravascular coagulation.

By hematological signs congenital leukemia is similar to chronic myeloid leukemia, which allowed several authors [17] to suggest that congenital leukemia is a chronic myeloid leukemia, but with a rapidly progressive course.

However, the majority of experts regard congenital leukemia as acute myeloid leukemia.

When considering the development of thrombocythemia, some authors [18] suggest the following mechanism: in megakaryocytic leukemia myelopoiesis of all lineages is clonal. The descendants of the mutated cell have an ability to proliferate uncontrollably, retaining the ability to differentiate into mature forms, which can explain the histologic similarity of acute myeloid and chronic megakaryocyte leukemia.

CONCLUSIONS

1. Congenital leukemia is a rare abnormality that is not yet well understood.
2. Groups of patients requiring further follow-up with a heamatologist with oncohemological approach include patients with sepsis, pneumonia, congenital syphilis, congenital hepatitis, hepatolienal syndrome of unknown origin and other, which implies that the non-responsive diseases require early intervention.
3. Patients with sepsis due to polyorganic clinical manifestations present the greatest challenge when providing diagnosis of congenital leukemia.
4. In case of doubt, urgent bone marrow examination is mandatory.

CONFLICT OF INTERESTS

There is no conflict of interests.

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