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CASE REPORT

Congenital acute megakaryocytic leukemia

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ABSTRACT

Congenital leukemia (CL) is an extremely rare disorder in the newborn, significant proportion of which is of myeloid origin, primarily of M4 or M5 morphology. As compared to pediatric leukemia, CL is a more aggressive disease. Acute myeloid leukemia (AML-M7) or acute megakaryocytic leukemia is a rare type of AML with an incidence of 0.5 per million per year. Median age of presentation is 6 years, and children may present with a broad variety of symptoms including low-grade fever, diarrhea, easy bruising, failure to gain weight and life-threatening conditions.

Key words: *Congenital megakaryocytic leukemia, neonate, sepsis*

INTRODUCTION

Acute megakaryocytic leukemia (AKML) 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 (DS). Median age of presentation is 6 years (ranging from 3 months to 16 years). We report a rare case of congenital AKML manifesting in the neonatal period with no features of DS. Children may present with conditions simulating septicemia and congenital infections. Course of the illness is one of rapid deterioration and death from hemorrhage and infection in spite of aggressive therapeutic measures.

CASE REPORT

A 17-day-old female born to a 21-year-old primigravidae out of a non-consanguineous marriage, at term gestation, presented with progressively increasing abdominal distension for 4 days and loose stools for 2 days. Pregnancy was unbooked, but antenatal period was uneventful with no complaints of fever, rash, nodular swellings or joint pains. The neonate was predominantly breast fed along with sips of water intermittently. Child remained well till day 13 of life when the mother noticed generalized but progressively increasing abdominal distension, unaccompanied by vomiting, overlying skin changes or swelling over any part of the body. This was followed by the onset of small volume, non–foul-smelling watery stools, up to 10–15 episodes/day. There was no history of fever, altered sensorium, decreased oral acceptance or decline in urine output. At admission, the child was moderately hypothermic and lethargic, while the vitals, hydration, oxygen saturation and blood sugar levels were maintained. Weighing 3 kg, the baby displayed a grossly distended abdomen with an inverted umbilicus and no overlying skin changes. There was no dysmorphism, hypotonia, lymphadenopathy, mucocutaneous bleed or nodular skin changes. Abdominal examination revealed a girth of 39 cm, firm liver with sharp margins reaching 9 cm below costal margin in the midclavicular line (spanning 12 cm) and a firm spleen palpable 9 cm below costal margin in the direction of the umbilicus. There was no free fluid and bowel sounds were normal. Rest of the systemic examination was noncontributory. Laboratory parameters revealed hemoglobin 13.3 g%, total leukocyte count 37,250 cells/mm^3, platelet count 13,000/mm^3, I/T ratio 30%, C-reactive protein (CRP) levels of 65 mg/L and erythrocyte sedimentation rate (ESR) of 10 mm/hr. Peripheral smear reported 20% neutrophils, 10% lymphocytes, 5% eosinophils and 65% blast cells containing high nuclear:chromatin ratio with opened up nuclear chromatin showing one to two prominent nucleoli. Tests to rule out congenital group of infections were negative, and blood groups of both mother and child were B+ve. Bone marrow aspirate displayed infiltration of the marrow with blasts comprising 65% of the marrow nucleated cells. Cytochemistry proved negative for myeloperoxidase (MPO) and Periodic acid Schiff (PAS). Immunophenotyping revealed markers negative for CD10 and positive for CD61 antigen, suggestive of AMKL. Therapy with intravenous fluids and antibiotics was initiated. At 20 hrs of admission, the child had profound pulmonary

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bleed culminating in respiratory failure and circulatory shock. Bleeding profile revealed thrombocytopenia and prolonged prothrombin time, suggestive of disseminated intravascular coagulopathy (DIC). Investigations such as fibrinogen levels, d-dimer assays to support DIC and karyotype analysis were planned; however, parents refused investigations on the child due to financial constraints. Ventilatory support, volume resuscitation, inotropic, vasopressor support and blood products were appropriately administered; however, the neonate succumbed to the illness at 36 hrs of admission. Post-mortem liver biopsy disclosed infiltration of tissue with giant cells containing irregular nuclei with high nuclear:chromatin ratio. On cytochemistry, these blasts were negative for MPO, PAS and Sudan black. Immunophenotyping revealed the cells to be negative for CD10 and positive for CD61.

DISCUSSION

Congenital leukemia (CL) is an exceedingly uncommon disease in the newborn. A study in northern region of England reported its incidence to be between 4.3 and 8.6 per million livebirths.[1] AML-M7 or AMKL is a very rare type of AML which represents approximately 1% of all leukemias during childhood, with an incidence of 0.5 per million per year. To the best of our knowledge, such an early presentation of this rare leukemia has not been reported before. Over the last 10 years, its incidence has been estimated to be 4–7% of pediatric AML by large co-operative group studies in developed countries.[2] AKML accounts for 50% of AML in children with DS and there is a 500-fold increased risk of AKML in these patients.[3]

Criteria for diagnosis of CL are as follows: a) disease presentation at or shortly after birth (<30 days), b) proliferation of immature white cells, c) infiltration of the cells into extra hematopoietic tissues, and d) absence of any other condition that mimics CL.[4] A large proportion of CLs are of myeloid lineage, while pediatric leukemias are usually of lymphoid origin.[4] AML-M7 is defined under FAB classification by more than 20% blasts of megakaryocytic lineage in bone marrow aspirate as determined by morphology and immunocytochemistry.[5] The marrow may be difficult to aspirate as more than two thirds have significant fibrosis, the latter as a result of the stimulation of the normal fibroblasts by the local secretion of platelet-derived growth factor by the leukemic cells. Under such circumstances, bone marrow biopsy proves helpful.[6,7]

About half of congenital AML is of M4 or M5 morphology.[8] There is no gender preponderance; however, there is ethnic variation with a higher incidence of pediatric AML in Asians and Hispanics. The median age of presentation is 6 years, ranging from 3 months to 16 years, but cases (40%) have been seen in children of age 41 months or younger.[9] The youngest reported case of AML-M7 reported earlier was a 4-week-old neonate who presented with hepatic infiltration only.[10]

Etiological considerations in CL have included chromosomal defects, intrauterine environmental insults, viral infections and exposure to radiation in pregnancy.[11] Children may present with a broad variety of atypical symptoms including low-grade fever, diarrhea, easy bruising, failure to gain weight and life-threatening conditions.[12] The clinical signs of leukemia may be evident at birth with hepatosplenomegaly, petechiae and ecchymosis.[11] Leukemia cutis is less common. Severe infection may occur due to diminished neutrophil count and function. As compared to pediatric leukemia, CL is a more aggressive disease with increased incidence of leukocytosis, massive hepatosplenomegaly, thrombocytopenia and DIC.[13] As in the present case, complications due to bleeding are known to contribute to 7–10% of the mortality that is observed during the first few days after diagnosis.[14]

The diagnosis of FAB AML-M7 relies on multiple criteria including peripheral blood and bone marrow aspirate smear morphology, routine cytochemistry stains, immunophenotyping and ultrastructural studies. Cytochemically, megakaryoblasts show no reactivity with MPO or Sudan black. The standard for diagnosis of FAB M7- is demonstration of CD41/61 by immunophenotyping. Ultrastructural platelet peroxidase reaction by cytochemistry is also diagnostic; however, as these are difficult to perform, they are largely replaced by immunophenotyping.[6] It is pertinent to mention here that transient myeloproliferative disorder (TMD) and AML in DS show strikingly similar cytomorphological features. TMD usually manifests during the first few days of life, with normal hematocrit and platelet counts. While hematogenic and cytogenic differences have been cited, none of them absolutely differentiate between the two.[15] Reported survival in TMD is good.[16,17]

Myeloablative treatment in the form of intensive multidrug chemotherapy or radiotherapy followed, whenever possible, by allogeneic or autologous bone marrow transplant is the treatment of choice. Patients with AML-M7 have a dismal prognosis. The outcome of children with non-Down's syndrome AMKL is generally poor.

With this report, we would like to create awareness regarding the unusual early presentation and encourage clinicians to keep a high index of suspicion of megakaryocytic leukemia even in the neonatal period.

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