Case Reports

Acute Myeloid Leukemia Presenting Simultaneously in Two Siblings

Vandana Jain
Sameer Bakhshi
Mei-Yoke Chan*
L.S. Arya

The rare occurrence of acute myeloid leukemia simultaneously in two siblings, 3-year male and 1-year female, in the absence of any known predisposing condition is reported. We speculate that an initial in-utero genetic alteration followed by subsequent environmental exposure to some unknown toxin may have resulted in leukemogenesis.

Key words: *Acute Myeloid Leukemia, Cytogenetics, Siblings*.

Acute myeloid leukemia (AML) accounts for 15-20% of childhood leukemias. Certain genetic conditions like Down syndrome, Bloom syndrome, Fanconi anemia, Diamond-Blackfan anemia and Kostmann syndrome; exposure to drugs like alkylating agents, topoisomerase inhibitors and ionizing radiation, are associated with greater risk of developing AML. However, majority of children have no known predisposing conditions. Familial predisposition to AML has not been proved although there are reports of two or more members of a family developing AML. Here we report an uncommon occurrence of AML simultaneously in two siblings, a three-year-old boy and his one-year-old sister.

*From the Department of Pediatrics, Division of Pediatric Oncology, All India Institute of Medical Sciences, New Delhi 110 029, India and *Department of Pediatrics, K.K. Women's and Children's Hospital, Singapore 229 899.*

Correspondence to: Prof. L.S. Arya, Department of Pediatrics, Division of Pediatric Oncology, All India Institute of Medical Sciences, New Delhi 110 029. E-mail: lsarya@rediffmail.com

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Case Report

Sibling 1: A 3-year-old developmentally normal male child, product of nonconsanguineous marriage between parents of North Indian origin, residing in Singapore for last 9 months had complaints of high grade fever associated with cough for 10 days and generalized rash for 2 days. There was no past history of recurrent infections, anemia or blood transfusions, exposure to ionizing radiations or chemotherapeutic agents. Child's father had expired 10 months back following a brief illness comprising of fever, malaise and scattered petechial rash for one week followed by sudden onset of massive hematemesis, coma and death. He had no prior history of hypertension, hematemesis or any other major systemic illness. He was not investigated and the cause of death could not be established. There was no history of abortions or sibling deaths and no history of malignancies in the family. Both parents were computer professionals. On examination, child was febrile, pale with presence of scattered petechiae and no significant lymphadenopathy. There were no dysmorphic features or abnormal skin pigmentation. Hepatomegaly of 3 cm and splenomegaly of 2 cm below the costal margin were present.

Investigations revealed hemoglobin of 11.4 g/dL; white blood cell (WBC) count 2700 cell/mm^3 with peripheral smear showing 60% lymphocytes, 2% neutrophils, 38% atypical cells; and platelet count of 1,27,000/mm3. A diagnosis of AML-MI subtype was made on bone marrow aspiration based on morphology and cytochemistry (positive for Sudan black and myeloperoxidase). Bone marrow cytogenetic studies showed two abnormal clones one with an interstitial deletion of short arm of chromosome 7 and another with an interstitial deletion of long arm of chromosome 9. Cerebrospinal fluid (CSF) cytology was negative for blasts. The parents decided against the use of chemotherapy. The patient was thus managed symptomatically with antibiotics and transfusion support. Two and a half months later he was brought in with fever and altered sensorium. He was critically sick and was diagnosed to have septicemia with pyogenic meningitis. He expired after 5 days inspite of aggressive antibiotic therapy and supportive care.

Sibling 2: The younger sibling of the same family, one-year old developmentally normal female child born at term by cesarean section also had complaints of intermittent low-grade fever of 15 days duration without any localizing symptoms. While the older child was being investigated, she developed two episodes of epistaxis. Physical examination revealed pallor, hepatomegaly of 3 cm and splenomegaly of 1 cm with no evidence of dysmorphism or abnormal skin pigmentation. Investigations showed a WBC count of 11,000/mm^3 with 63% blasts on peripheral smear. A diagnosis of AML-M2 subtype based on morphology and cytochemistry was established on bone marrow biopsy. CSF was negative for blasts.

This child was started on chemotherapy consisting of triple intrathecal therapy (methotrexate, hydrocortisone and cytosine arabinoside), intravenous daunorubicin, etoposide and cytosine arabinoside. However, four days later she developed fever and bilateral chest crackles; chest radiograph showed bilateral pneumonitis associated with an absolute neutrophil count of zero. She progressively worsened despite broad-spectrum antibacterial and antifungal agents. She expired after 15 days due to septic shock complicated by pulmonary hemorrhage.

Discussion

Simultaneous development of AML in two siblings is a very rare occurrence. Although there are reports of AML developing in two or more siblings or different generations of the same family in world literature, no case has been reported to the best of our knowledge in which two or more siblings were diagnosed with AML at the same time. Also, this is the first report of familial AML from India.

Snyder, *et al.*(1) had reported six AML cases in a family over three generations including three siblings aged 11, 3 and 6 years who were diagnosed to have AML at intervals of 5 and 9 years between the first-second and second-third case respectively. Increased susceptibility of skin fibroblasts to transformation by SV40 virus was noted in one of the siblings with AML, her unaffected mother and unaffected sibling who later developed AML. Goudsmit, *et al.*(2) reported AML in two siblings, 7 year female and 14 year male diagnosed 11 years apart. Associated finding of high proportion of neutrophils showing Dohle bodies was seen in all siblings.

Kaur, *et al.* reported(3) five siblings; two died of AML diagnosed at an interval of 7 years, one died of myelofibrosis and the two surviving siblings had hematological findings consistent with preleukemia with bone

marrow evidence of an abnormal cytogenetic clone with an extra chromosome in C-group. In addition, neutrophils of all 5 siblings revealed Felger Huet anomaly suggestive of transmission of a specific genetic defect in an autosomal dominant pattern.

Larsen, *et al.*(4) reported a family in which 3 siblings, aged 18, 21 and 14 year were diagnosed to have AML at intervals of 8 months and 13 months from each other. Bone marrow examination in two of these revealed monosomy in C-group chromosomes. In a recent report(5), 4 male members of a family over 3 generations were diagnosed to have AML at intervals of atleast 3 years, showing phenomenon of anticipation, that is, successive generations getting affected at younger ages. Cytogenetic anomaly of 6q deletion was found in a second-generation affected patient. Other reports of AML diagnosed in siblings at intervals of atleast two years from each other are available in which no definite cytogenetic or immunological findings were noted(6,7,8). In one case(6) both sibs developed AML of same subtype (M4), while in the other(8) the two siblings had AML of different subtypes (M1 and M6).

In another report AML of subtype M1 was seen in a 33-year-old male and myelodysplasia progressing to AML in his sister at an interval of 2 years. This family had a familial platelet disorder with predisposition to myeloid malignancies, and three out of 5 siblings in this family were found to have single nucleotide mutation in CBF A2 gene on chromosome 21(9). Some investigators have also found the cytogenetic abnormality of monosomy7(10) or loss of long arm of chromosome 5(11) in cases of familial AML. However, till date the molecular mechanisms for the occurrence of leukemia in multiple members of a family have not been fully elucidated.

In the present cases, AML-MI and AML-M2 occurred simultaneously in the two siblings. The cytogenetic studies in the older sibling showed two abnormal clones, one with an interstitial deletion of 7p and another with an interstitial deletion of 9q. These abnormalities have been reported in cases of AML. However, unfortunately cytogenetic studies could not be obtained on the younger sibling.

Recent reports have established prenatal origins of certain leukemia translocations like t(8:21) AML1-ETO translocation in childhood AML(12) suggesting thereby that an in utero genetic alteration may be an initiating event in childhood AML and a subsequent second event, possibly environmental exposure can lead to development of AML. It may be speculated that a similar mechanism might have been operative in the present case that led to simultaneous occurrence of AML in both siblings.

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Growing Skull Fractures

Shivram Gopal Iyer
Puneet Saxena
Ghanshyam D. Kumhar*

Growing skull fractures or craniocerebral erosions are rare sequel to cranial fractures where progressively growing cranial defects follow lacerations involving the duramater. Their usual site is the parietal region. They present as a cystic, non-tender swelling with an underlying palpable bony defect. One such case is reported.

Keywords: *Craniocerebral erosions, Growing skull fractures, Leptomeningeal cysts.*

Growing skull fracture, recently termed as craniocerebral erosion, is a rare complication of skull fractures seen mainly in infancy and early childhood. It is characterized by progressive diastatic enlargement of the fracture line. This late complication is also known as leptomeningeal cyst because of its frequent association with a cystic mass filled with CSF.

Case Report

A 3-month male infant presented with a history of fall 15 days back. The infant had a gradually increasing swelling over the left parietal region. He was conscious and there was no history of seizures, vomiting or any discharge from the ears or nose. On physical

Departments of Pediatrics and Radiodiagnosis, G.R. Medical College & J.A. Group of Hospitals, Gwalior, Madhya Pradesh, India.*

Correspondence to: Dr. Shivram Gopal Iyer, M-601, Dharma Apartments, Patparganj, I.P. Extension, Delhi-110 092. E-mail: shivram27@msn.com

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