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Case Report

Familial Acute Myelogenous Leukemia: Report of Three Cases

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Abstract

Acute myelogenous leukemia (AML) is a hematological malignancy, which accounts for about 15-25% of childhood's leukemia. Genetic factor is one of the most important predisposing elements in childhood acute leukemia, especially AML. In this case report, a rare presentation of familial AML is presented in three monozygotic triplets. Two were 10 months old, and the other one was 16 months old at presentation. Chemotherapeutic regimen was administered for all three sisters with good response and success in maintaining remission.

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Keywords ● Familial AML ● monozygotic triplets ● chemotherapy ● remission

Introduction

Acute myelogenous leukemia (AML) is characterized by a heterogonous group of hematological malignancies, which can originate from myeloid, monocytic, erythroid, and megakaryocytic precursor cells in the bone marrow.[1] Although AML represents about 15-25% of all childhood leukemias, it is responsible for more than 30% of childhood leukemia resulting in death.[1] There are many predisposing elements for a child to develop AML. Some of the most important predisposing factors are environmental and genetic factors.[1-7,11-13]

Few cases of familial leukemia have been reported previously, that were caused by transplacental passage of leukemic cells, pre or postpartum exposure to the leukemogenic elements, and genetic factors.[6,12,13,15-17] In spite of good response of patients with AML reported during the last three decades, in most reports the event free survival (EFS) is less than 50%.[1] The most important causes of poor treatment response and death are drug resistance and treatment complications.[1] It is known that the best treatment regime for most of the patients with AML is allogenic stem cell transplantation (SCT), but if impossible a strong chemotherapeutic regimen would be the treatment of choice.[1]

In this study, three monozygotic triplet patients with AML whose parents are first cousins are presented. They were delivered via cesarean section in a preterm event-free pregnancy with gestational age of about 34 weeks.

Case Report

Patient 1

was the third born child of these triplets, who was delivered with birth weight of 1700 gr. Her HLA typing was A2-B5-CW2-CW4-DRW11-DRW52-DQ1-DQ2, similar to her two other sisters. She was healthy until eight months, the time she admitted to

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Mofid Children's Hospital of Shaheed Beheshti University of Medical Sciences, Tehran, Iran, due to an episode of gastroenteritis. In laboratory work up, thrombocytopenia was reported as shown in Table 1.

Bone marrow aspiration was done which revealed normal cellularity but decreased in megakaryocytes, dyserythropoiesis and megaloblastic change in erythroid series. In this time the patient consumed ferrous sulfate and folic acid (Ferrous sulfate 3 mg/kg/day and folic acid 1 mg/day) and was under close follow-up. Two months later, she was readmitted because of fever, irritability and cough. Her second laboratory findings are shown in Table 1.

In her second bone marrow aspiration, more than 10% premature cells were seen. Due to her clinical findings (e.g. petechia and purpura), bone marrow aspiration and flow cytometry were performed again 2 weeks later that the bone marrow aspiration was in favor of AML M1 and hypercellular, with more than 70% myeloblasts (Table 2).

Chest X Ray was normal and abdominal sonography revealed splenomegaly. Brain CT scan was also done because of vomiting and lethargy, which showed hemorrhage in anterior and posterior saggital sinuses. Analysis of cerebrospinal fluid showed normal results. Based on the above findings the diagnosis of AML was made and the appropriate chemotherapeutic protocol was started for the patient that was as follow: induction chemotherapy with intravenous Cytarabine 200 mg/m^2/day ×7 days, intravenous daunomycin 45 mg/m^2/day ×3 days, 6–Thioguanine (6-TG) 100 mg/m^2 /day peroral ×7 days, for 3 courses. Then consolidation regimen from BFM (Berlin-Frankfurt-Munster) protocol,[1] started for 3 courses which included prednisolone 2 mg/kg/day peroral ×28 days, subcutaneous cytarabine 75 mg/m^2/day, 4 days/week ×8 weeks, intravenous vincristine 1.5mg/m^2/week ×4 weeks, intravenous doxorubicin 20 mg/m^2/week ×4 weeks, 6-Thioguanine (6-TG) 60 mg/m^2/day peroral × 56 days, intravenous cyclophosphamide 600 mg/m^2/day in days 28 and 56. Triple intrathecal prophylaxis: with methotrexate, cytarabine and hydrocortisone were also done in weeks; 5, 6, and 7. Finally maintenance therapy started and continued for 2 years that consisted subcutaneous cytarabine 75 mg/m^2/dose 4 days a week /monthly, intravenous doxorubicin 20 mg/m^2 every other months and 6-TG 40 mg/m^2/day

Table 1: The results of paraclinical tests in triplets patients with acute myelogenous leukemia

Patient	WBC/ mm3	PMN %	L %	MO %	Band %	Myb %	MetM %	Mye %	Hb (gr/dl)	Pt/ mm^3	ESR	LDH u/l
P1(NE) FIRST CBC (8MO)	13800	42	52	5	__	__	__	__	10	34000	30	__
P1(NE) SECOND CBC (10MO)	10100	30	52	6	1	__	4	7	9/8	47000	45	12000
P2(ND) FIRST CBC (8 MO)	10700	42	57	1	__	__	__	__	11/3	97000	30	__
P2(ND) SECOND CBC (10 MO)	12700	67	16	__	__	12	3	2	10	16000	35	3340
P3(H) (18 MO)	10100	2	73	__	__	3	7	9	9/7	12000	25	3000

WBC=white blood cell, PMN=poly morpho nuclear; L=lymphocyte; MO=monocyte; Myb=Myeloblast; MetM=Meta myelocyte; Mye=Myelocyte, Hb=hemoglobin; Pt=platelet; ESR=estimated sedimentation rate; LDH=lactate dehydrogenase; Bio=Biochemistry

Table 2: The results of bone marrow aspiration (BMA), flow cytometry, cytogenetic study of triplets patients with acute myelogenous leukemia

Patient	BMA Myb %	CD 13%	CD 14%	CD 15%	CD 33%	CD 34%	CD 38%	HLADR %	Staining	Cytogenetic Study
1	70	34	__	__	45	30/3	__	37/2	MPO:+	Hyperdiploidy & no structural abnormality
2	50	56	16/3	11/4	47	__	__	31/2	MPO:+	Hyperdiploidy & no structural abnormality
3	70	36/7	12	__	38/2	30/6	48	29/9	MPO:+	Hyperdiploidy & no structural abnormality

CD=cluster determinants; MPO=myeloperoxidase

peroral every night and triplets intrathecal prophylaxis every two months. At the end of the protocol, the patient's bone marrow aspiration and CD flow cytometry demonstrated normal results. The chemotherapeutic drugs were discontinued. Now she is a 7-year-old nearly normal- appearing girl. Her weight is 18 kg and height 108 cm, on 10th and 5th percentile respectively.

Patient 2

was the second born child of these triplets pregnancy with birth weight of 1850 g. She was also admitted to the same hospital for gastroenteritis at eight months of age when the repeated CBC confirmed thrombocytopenia (Table 1). Bone marrow aspiration indicated normal cellularity with about 10-15% myeloblasts. After two months follow-up, as an out patient, she developed 12% blasts in her CBC (Table 1). At this time her bone marrow aspiration revealed normal cellularity with 50% myeloblasts, in favor of AML M1 (Table 2).

The results of her CSF analysis, chest X-ray, and abdominal sonography were all normal. The chemotherapy protocol started similar to her sister and completed. Three years later, at the age of seven year old, her height was 109 cm and weight 18 kg, on 10th and 5th percentile respectively.

Patient 3

was the first born of these triplets. Her birth weight was 1750 g. Because of icter and total bilirubin of 20mg/dl, she was admitted to the hospital for phototherapy and exchange transfusion. During her hospital course she developed seizure and received Phenobarbital (10 mg/kg loading dose and then 5mg/kg/day every 12 hour for maintenance). When she was eight-month-old, she became readmitted in the neurological ward with repeated seizure and visual disturbance, albeit normal laboratory work ups. Ophthalmologic evaluation revealed severe optic nerve atrophy. In MRI, a hypodense lesion was seen in the occipital region and her neurological evaluations showed the possibility of infantile spasm. Appropriate drug therapy was started immediately (Sabril, 50mg/kg/day in divided doses, every 12 hours).

In spite of her normal CBC, she underwent closed observation because of AML detection in her siblings. Finally, when she was 15-month-old, the AML characteristics were presented exactly as of her other two sisters. Her routine CBC examination showed many blasts (Table 1). Bone marrow aspiration was in favor of AML M1 showing normo cellular BM with about 70% myeloblasts (Table 2). Her CSF analysis, CXR and abdominal sonography were normal.

The patient received and tolerated chemotherapy well like her two sisters. Therapy was discontinued after precise evaluation including bone marrow aspiration and flow cytometry .Two years after discontinuation of the treatment, when she was seven year old, her weight was 18 kg and height was 106 cm, both below 5th percentile of her age. Because of developmental delay, intelligence coefficient (IQ) was determined which was around 70.

Discussion

Several risk factors have been identified that predispose children to develop AMl.[1,5-10] Among all predisposing factors, genetic factor is an important and well known predisposing factor in all leukemias including AML.

The first case report of concordant leukemia in twins' children appeared in the Germany literature in 1882.[11] To the best of our knowledge, more than 70 same –sex or known monozygotic twin pairs with concordant disease have been recorded.[11] Concordant leukemia in unlike sex or known dizygotic twin pairs is exceedingly rare. McMahon and Levy's provided the first estimate of concordance rates of childhood leukemia that was between 5-25% for acute leukemia (including acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML).[11]

In Leukemia Research Foundation (Institute of Cancer Research, London, UK) there were 2 sets of triplets with ALL.[11] In first triplets, two monozygotic twins that had shared a single placenta developed ALL. The third co-twins which were dizygotic developed in a separate placenta and remain leukemia free. In second triplets, all three twins were monozygotic and all of them developed ALL. These data suggest that monozygosity, placental status and intrauterine clonal factors may be critical risks for concordant leukemia.[7-11,12-15,17-19] Our triplet patients were monozygotic and diagnosed as having AML too.

The role of French-American-British classification (FAB) and immunophenotyping with outcome measures have been controversial for pediatric patients with AML.[1] Tumor burden, site of involvement, initial WBC count, CNS disease at diagnosis are from the most important factors interfering with prognosis.[1] Chromosomal abnormalities in childhood leukemia are not similar to adult AML. For example, in pediatric age groups, translocations like t (8/21) and t (15/17) can increase remission rate, but not survival.[1] Some other abnormalities like monosomy 7 are strongly related to poor prognosis.[1,10] The type of AML in our patients was AML M1. Their WBC were not high, (Table 1) and

cytogenetic studies in our patients didn't reveal any type of chromosomal abnormality.

Treatment of patients with AML consists of strong chemotherapy with the use of Cytosar, anthracycline, etoposide, and 6-Thioguanine.[1] Further, stem cell transplantation is a good substitute for chemotherapy and can be more effective. Treatment protocol can be chosen based on patient's status and his risk factors.[1]

In our cases, because of the triplet's low age, the absence of stem cell donor, and good response to chemotherapy, we decided to use only chemotherapy. Fortunately the treatment was well tolerated and the patients are still in remission after about three years from discontinuation of treatment.

Conclusion

Although twins may present simultaneously with clinical symptoms of leukemia, this is not always the case. It is infrequent to find one twin of a pair to have leukemia, while the other co-twin healthy. If one twin has malignancy and the other one is healthy, the healthy twin must be investigated and followed up carefully and the parents should be educated about early signs of leukemia.

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