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Congenital Acute Myeloid Leukemia with t(8;16) and t(17;19) Double Translocation: Case Presentation and Literature Review

Congenital leukemia is uncommon and excluding transient myeloproliferation associated with Down syndrome, makes up approximately 1% of childhood leukemias. A newborn boy was born with multiple subcutaneous nodules and large purpuric papules. Skin biopsy revealed proliferation of atypical hematologic cells in the dermis. Bone marrow morphology was consistent with acute myeloid leukemia (M5) and cytogenetic studies revealed t(8;16) and t(17;19) double translocation. Although prognosis of congenital leukemia is known to be dismal, recent reports showed spontaneous remissions. With the fear of chemotherapy-related toxicity, to treat or not to treat may be a dilemma both to parents and pediatricians. We report our experience and review the literature.

Key Words : *Leukemia; Translocation, Genetic; Leukemic Infiltration; Drug Therapy*

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INTRODUCTION

Congenital leukemia, defined as a leukemia that occurs within 4 to 6 weeks of birth, is rare. Excluding Down syndrome-related transient neonatal myeloproliferation, its incidence is less than 1% of all childhood leukemia (1, 2). The diagnostic criteria include the presence of immature leukemic blasts in the blood and in extrahematopoietic tissues and the absence of congenital infections (syphilis, toxoplasmosis, herpes simplex, cytomegalovirus, rubella, and bacterial infections), hypoxia, and hemolytic disease, which may produce a similar clinical and hematological picture. In addition, there may be absence of chromosomal disorders that may be associated with unstable hematopoiesis, such as trisomy 21 (3).

Although its biology and natural history are still under investigation, it is clear that the leukemic process originated in utero even in infants diagnosed within the first few months of life (2). In infants with congenital leukemia under the age of 1 month, the 6-month survival rate is only one third despite aggressive chemotherapy (4). It has a higher mortality rate than any other congenital cancer, but recently some reports showed spontaneous remissions (3, 5). These findings implicate therapeutic dilemmas on deciding which patients to treat or to wait.

Here we present a case of congenital myeloid leukemia (M5) initially characterized by the presence of leukemia cutis and hyperleukocytosis with chromosomal abnormality (double translocation of t[8;16][p11;p13.2] and t[17;19][?;q13.3]). With the fear of toxic effect of chemotherapeutic agents, parents did not agree to chemotherapy at first. Three weeks later we started chemotherapy but the prognosis was poor. We report our experience and review previous cases in view of treatment dilemmas.

CASE REPORT

A term male infant weighing 3,360 gram was born to a 32-yr-old woman after uncomplicated pregnancy. There was no history of exposure to radiation, any known teratogens, smoking, drinking, or drug use from his mother. A cesarean section was done for previous section. Gross examination of the infant noted at birth to have an unusual purpuric rash on his whole body looking like "blueberry-muffin" rash (Fig. 1). Physical examination showed no hepatosplenomegaly and there were no dysmorphic features. Skin examination revealed widespread, scattered, yellowish-colored firm nodules with multiple purpuric macules and papules predominantly on the face and proximal extremities with a few present on the trunk. A punch-biopsy of a nodule showed proliferation of atypical hematologic cells in the dermis. Blood count at birth revealed white blood cell count of 173×10^9/L with 58.8% neutrophils, 5.3% lymphocytes, 26.1% monocytes, and 0.5% eosinophils; hemoglobin of 13.9 g/dL; platelets of 133×10^9/L.

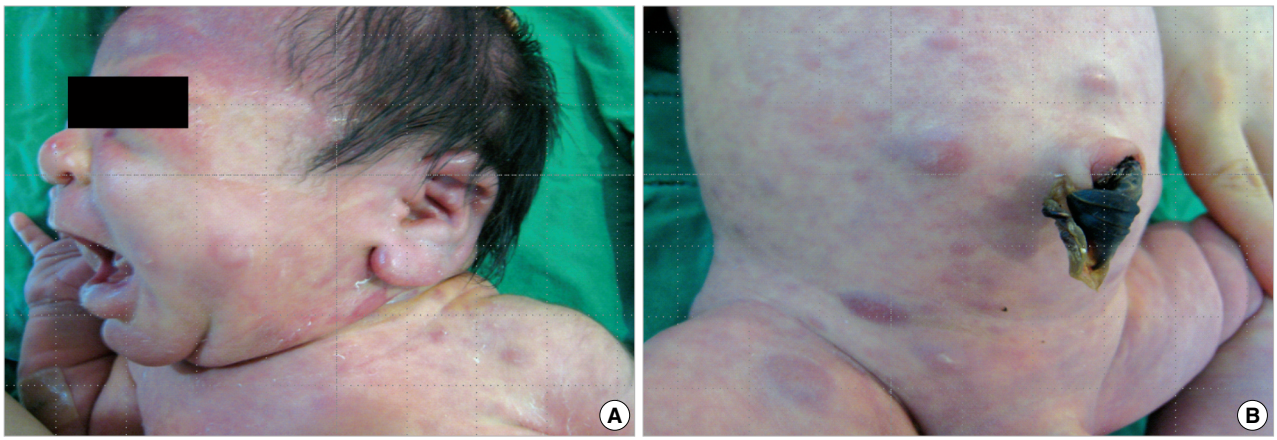

Fig. 1. Gross view of the skin. (A, B) There are widespread, scattered, yellowish-colored firm nodules with multiple purpuric macules and papules predominantly on the face and the trunk.

TORCH titers (against toxoplasmosis, cytomegalovirus, herpes simplex virus, rubella, and syphilis) were all negative and blood cultures were also negative. Peripheral blood morphology showed marked leukocytosis with 32% of immature cells and monocytosis. Immunophenotyping showed that blasts were positive for CD14, CD33 and HLA-DR(+). Flow cytometry on the bone marrow showed the blasts to be acute myeloid leukemia (M5) in the French-American-British classification based on the morphologic features and special stains. Bone marrow aspiration and biopsy also showed 90% of leukemic blasts. The results of special stain were peroxidase (+), PAS (-), ANAE with NaF inhibition (+). Cytogenetic analysis revealed 46, XY karyotype with multiple chromosomal defect, t(8;16)(p11;p13.2), t(17;19)(?;q13.3). Serial white blood cell count showed a progressive rise up to 256×10^9/L with thrombocytopenia of 88×10^9/L. Leukemia cutis also progressed and it became more pronounced on the face and somewhat hardened. Parents only wanted conservative treatment at first. Three weeks after birth, parents agreed to chemotherapy. Initial chemotherapy was started with daunorubicin, etoposide, and cytarabine, but, he died at 27 days of age.

DISCUSSION

Leukemia is the most common malignancy presented during the childhood, however, congenital leukemia is a very rare disease, representing less than 1% of all childhood leukemia. It should be differentiated from transient leukemoid reaction and other small round cell tumors (3).

Several risk factors are known to be associated with the development of congenital leukemia. Maternal alcohol consumption, tobacco smoking, maternal exposures to radiation, high birth weight, high levels of insulin-like growth factors, maternal consumption of topoisomerase II inhibitors, such as fruits and vegetables, coffee, tea, cocoa, wine, and soybeans are those factors (2, 6). However, as in our case, some had been reported to have no known risk factors. Frequently, reported cases of congenital leukemia with constitutional chromosomal abnormalities have led to suspicion whether congenital leukemia is a result of chromosomal fragility (2).

Congenital leukemia may reflect the early onset of intrauterine leukemia, that is, leukemic process originated in utero even in infants diagnosed within the first few months of life. Since embryonic hematopoiesis begins in undifferentiated mesenchyme starting the third week after fertilization, leukemia cutis may be a primary event and the first manifestation of congenital leukemia (6).

Prognosis of congenital leukemia is dismal and has a progressive downhill course, even with chemotherapy. However, there are some reported cases of spontaneous remission (Table 1) (3, 7-19). The reason that spontaneous remissions may occur in newborn infants is unclear (1). The period of spontaneous remission varied widely from months to years, and several of the children with relapses remained in prolonged remission after chemotherapy (3, 15). There appear to be no common clinical features between those who progressed and those that had spontaneous remissions. Neither bone marrow involvement at diagnosis nor hyperleukocytosis appears to increase the risk of relapse (3, 4, 15-17, 19). Chromosome abnormalities affecting chromosome 11 band q23 are involved in the majority of infant leukemia cases. The major translocations involving the 11q23 locus are t(4;11) and t(11;19) (13, 16). Translocation involving 11q23 band or reciprocal translocations involving chromosomes 8 and 16 are known to be mapped with oncogene(s) and are known to be associated with a poor prognosis (6, 10, 30). Hence, even cytogenetic abnormality of 11q23 rearrangement of skin without involvement of bone morrow was also treated aggressively (6). Moreover, AML with the t(8;16) is associated with a young age at diagnosis, myelomonocytic (FAB M4) or monocytic (FAB M5) morphology, erythrophagocytosis, disseminated intravascular coagulation and a poor outcome (9).

The gene at 11q23, known as MLL (ALL-1, HRX, HTRX,

Table 1. Reported cases of congenital nonlymphocytic leukemia from 1980 to 2007

Case	Reference	Sex	Age at diagnosis	Leukemia cutis	Leukocytosis (100 >10^9/L)	Bone marrow infiltration	FAB	Karyotype	Chemotherapy given	Age at relapse	Outcome
With spontaneous remission											
1	Landers (7)	Male	Birth	Yes	No	23% blasts	M4	46,XY, t(5;9)	No	No	Alive at 8 months
2	Van Den Berg (8)	Female	Birth	Yes	No	Normal	M2	46,XX	No	No	Alive at 41 months
3	Weintraub (9)	Male	1 week	Yes	No	70-80% blasts	M4	46, XX, t(8;16) (q11;p13)	No	No	Alive at 15 months
4	Grundy (5)	Male	Birth	Yes	No	Normal	M4/M5	46,XX	No	No	Alive at 26 months
5	Dinulos(3)	Male	Birth	Yes	No	Normal	M5	46,XY, inv(9)	No	No	Alive at 4 yr
6		Female	1 week	Yes	No	30% blasts	M4	46,XX, t(8;16) (p11;p13) del(9) (q12;q32) at relapse	Yes at relapse	24 months	Alive at 44 months
7		Male	Birth	Yes	No	ND	M5	46,XY	Yes at relapse	16 months	Alive at 6 yr
8	Sainati (10)	Male	Birth	Yes	No	62% blasts	M5	46,XY, t(8;6) (p11;p13)	No	No	Alive at 18 months
9	Mayer (11)	Female	Birth	Yes	No	90% monoblasts	M5	46,XX, t(5;6) (q31;q21)	No	No	Alive at 10 months
10	Gottesfeld (12)	Male	Birth	Yes	No	25% blasts	M5	ND	No	No	Alive at 24 months
11	Issacs (13)	Male	Birth	Yes	Yes	Involved	AML	46,XY	No	No	Alive at 6 yr
12	Lampkin (14)	Female	Birth	Yes	Yes	52% blasts	M5	46,XX	No	No	Alive at 16 yr
13	Chu (15)	Female	Birth	No	Yes	Involved	AML	46,XX	Yes at relapse	3 weeks	Alive at 16 yr
14	Lilleyman (16)	Male	Birth	Yes	No	Involved	M5	46,XY	Yes at relapse	3 months	Dead
15	Penchansky (17)	Male	6 weeks	No	No	20% blasts	M1	46,XY	Yes at relapse	12 yr	Dead
16	Monpoux (18)	Male	Birth	Yes	No	Dry tap	M5	46,XY, t(9;11) (p21-22;q23) at relapse	Yes at relapse	3 months	Dead
17	Francis (19)	Male	Birth	Yes	No	Involved	M5	46,XY	Yes at relapse	12 months	Alive at 10 yr
Without spontaneous remission											
18	Zhang (6)	Female	Birth	Yes	No	11% blasts	AML	11q23 rearrangement	Yes		Dead at 3 days
19	Ferguson (4)	Male	Birth	No	Yes	ND	M1	46,XY, t(6;17) (q23;q11.2)	Yes		Dead at 2 days
20	Morerio (20)	Female	Birth	No	No	ND	M5b	46,XX, t(10;11) (p11.2;q23)	Yes		Dead at 45 days
21	Fernandez (21)	Male	Birth	Yes	Yes	30% blasts	M5b	46,XY, t(5;11) (q31;q23)	Yes	No	Alive at 17 months
22	Mori (22)	Male	Birth	Yes	No	Involved	M6/M7	46,XY	Yes	No	Alive at 14 months
23	Carroll (23)	Female	4 weeks	ND	No	30% blasts	M7	46,XX, t(1;22) (p13;q13)	Yes		Dead
24		Female	4 weeks	ND	No	7% blasts	M7	46,XX, t(1;22) (p13;q13)	No		Dead before chemotheray
25	Hanada (24)	Male	2 weeks	Yes	No	57% blasts	M5b	46,XY, t(8;16) (p11;p13)	Yes		ND
26	Ohyashiki (25)	Male	Birth	Yes	Yes	90% blasts	M5b	46, XY, t(11;19) (q23;p13)	No		Dead before chemotherapy
27	Sait (26)	Male	Birth	Yes	No	30% blasts	M7	46,XY, t(1;22) (p13;q13.3)(p21;p23)	Yes		Dead
28	Resnik (27)	Male	Birth	Yes	Yes	68% blasts	M5	46,XY, t(6;17), t(13;11)	Yes		Dead
29	McCoy (28)	Female	Birth	Yes	Yes	ND	M4	46,XX, t(8;22) (p11;q13)	No		Dead before chemotherapy
30	Warrier* (29)	Female	Birth	No	Yes	ND	AML	46,XX, 18p	Yes		Dead
31	Pui (30)	Male	Birth	No	Yes	25% blasts	M4	46,XY, t(10;11) (p11;q23)	Yes		ND
32	this case	Male	Birth	Yes	Yes	90% blasts	M5	t(8;16)(p11;p13.2), t(17;19)(?;q13.3)	Refuse/Yes		Dead at 3 days

*One case of Warrier had incomplete data and omitted it.
ND, no data.

or Hu-ets-1), is required for the production of normal numbers of hematopoietic precursors and for their proper differentiation (2, 13). Chromosomal translocations can theoretically occur between any gene loci. 11q23-MLL gene rearrangements after DNA damage occur most frequently with AML. Translocations involving MLL may fuse with other genes and hence MLL usually retains at least two DNA binding domains (2, 13). Since there are a few reports of double translocations as our case, exact meaning of double gene translocation is yet to be discussed.

Because of the rarity of this disease, there is no standard protocol of chemotherapy. Treating congenital leukemia means exposure of the toxic chemotherapeutic agents to the neonate. Although there had been reported cases of prolonged periods of remission, rapidly downhill course were also noted in some cases and some of them died after relapse during the course of chemotherapy (16-18). While some cases with t(8; 16) remitted spontaneously without treatment (3, 9, 10), paradoxically, those who had chromosomal abnormalities died after initiation of chemotherapy as our case (4, 6, 20, 23, 26-29). It seems like that karyotypic findings in blasts in the neonatal period may not be predictive of whether or not a spontaneous remission will occur (2).

For our case, hyperleukocytosis, progressive leukemia cutis, bone marrow involvement, double translocation involving (8;16) made us to decide to treat at first. However, with the fear of unknown toxic effect of chemotherapeutic agents, parents refused to treat. Three weeks later after parents' agreement, we treated with daunorubicin, etoposide, and cytarabine but he died of pulmonary hemorrhage three days after induction chemotherapy. He may died of leukemia itself but, we are not sure whether he died due to chemotherapy or he could have survived with only conservative management as other spontaneous remitted cases. That is because it is the first case of congenital AML with double translocation of (8;16) and (17;19) to be reported in the English literature to the best of our knowledge.

Although congenital leukemia remains a rare disorder, an international collection of data or register system is indispensable for establishing an optimal treatment protocols.

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