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Double Lineage Switch from Acute Megakaryoblastic Leukemia (AML-M7) to Acute Lymphoblastic Leukemia (ALL) and Back Again: A Case Report

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Abstract

A 39-year-old female patient was diagnosed with immune thrombocytopenia in 1981 and treated with prednisolone. In 1997, she was diagnosed with acute megakaryoblastic leukemia (AML-M7), for which she received chemotherapy and achieved partial remission. She received supportive therapy, including blood transfusion. One year later, she was diagnosed with acute lymphoblastic leukemia (ALL-L2). She achieved complete remission (CR) with chemotherapy, but during consolidation therapy, L3 type ALL relapsed. She was given ALL-L3 targeting chemotherapy and achieved CR. However, several months later, AML-M7 relapsed. This is a very rare case of leukemia lineage switch that has not been reported previously.

Keywords: Acute lymphoblastic leukemia; Acute megakaryoblastic leukemia immune thrombocytopenia; Lineage switch

Introduction

Lineage switch from acute myeloid leukemia (AML) to acute lymphoid leukemia (ALL) and vice versa is rare [1-13]. We present herein a case of lineage switch from AML (M7) to ALL and then back again in an adult patient. To the best of our knowledge, this is the first such case report.

Case Presentation

A 39-year-old woman was diagnosed as having immune thrombocytopenia (ITP) in 1981 in another hospital, and she was well controlled with prednisolone. No other immunosuppressive drugs, such as cyclosporine or azathioprine, were used. In 1997, she was diagnosed as having acute megakaryoblastic leukemia (AML-M7) in another hospital. Blasts showed the absence of peroxidase (POX) and positive platelet peroxidase (PPO). She received two cycles of remission induction chemotherapy (cytarabine+idarubicin), but failed to achieve remission. She received supportive therapy, including blood transfusion. In January 1998, cervical lymph node swellings appeared. Bone marrow aspiration showed a dry tap, and peripheral blasts were CD10+, CD19+, and HLA-DR+. Acute lymphoblastic leukemia (ALL) of FAB type L2 was diagnosed in another hospital. She was treated with vincristine and prednisolone and achieved remission.

In April 1998, she was referred to our hospital (Table 1). Bone marrow aspiration revealed no evidence of a blast excess, but a chromosomal abnormality of del (20)(q12) was present (Table 2). She received ALL consolidation therapy (L-17 protocol) and was discharged. In October 1998, ALL relapsed (Figure 1, Tables 1 and 2). Relapsed ALL blasts showed surface markers of CD10+, CD19+, CD20+, and HLA-DR+ (Table 3) and had complex chromosomal abnormalities (Table 2). She received the B-NHL86 protocol and achieved morphological complete remission in January 1999. Chromosome abnormalities of add (17) (p11) and del (8) (q21q24) were present in her bone marrow.

In March 1999, her anemia worsened without any chemotherapy (Table 2). Bone marrow aspiration showed a lack of blasts and predominance of erythroid lineage, suggesting the presence of hemolysis. Undetectable haptoglobin, a negative Coombs test, and positive RBC binding IgG (63, normal range 20-46/RBC) led to the diagnosis of Coombs-negative autoimmune hemolytic anemia. Chromosomal abnormalities of add (17)(p11) and del(8) (q21q24) were still present in her bone marrow. She was treated with high-dose prednisolone (1 mg/kg) and high-dose gamma globulin, but treatment was ineffective.

In April 1999, ALL relapsed (Tables 2 and 3). Chromosomal analysis showed different chromosomal abnormalities from the first ALL onset, with only the del (8) (q21q24) abnormality (Table 2). She received the B-NHL86 protocol and achieved a second morphological complete remission. During preparation for peripheral blood stem cell transplantation (PBSCT), megakaryoblasts appeared in her peripheral blood (Figure 2). The blast phenotype was CD13+, CD33+, and CD41+, and a diagnosis of acute megakaryoblastic leukemia was made. Chromosomal abnormalities showed hyperploidy of 54-57, XX. The patient died in November 1999.

Discussion

Cases of conversions from AML to ALL and vice versa are extremely rare [1-13]. Several hypotheses have been suggested to explain lineage conversion in leukemias, but the precise mechanism remains unclear. One possibility is that a particular chemotherapy regimen might successfully suppress or eradicate the dominant leukemic clone at diagnosis, but it might permit the expansion of a chemoresistant subclone that has a phenotype of a different lineage. Alternatively,

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CBC Analysis		1998.10.12	1999.3.1	1999.5.1	1999.8.18
WBC	/ul	4524	4170	11100	6090
RBC		229	227	292	263
Hb		7.6	7.5	9.8	8
Ht		23.3	23	34.2	24.8
Plt		1.1	5.6	6.9	1.4
Neut	%	57.1	64.5	53.5	67.5
Lymph	%	41.5	28.0	6.5	24.0
Mono	%	0.3	4.0	4.0	3.0
Eos	%	1.1	0.5	1.0	1.0
Baso	%	0.0	0.0	1.0	0.0
Blast	%	47.0	0.0	23.0	0.0
Myelo	%	4.0	1.0	5.5	+
Met	%	2.0	0.0	0.5	1.0

Biochem	1998.10.12
TP	5.7
Alb	3.5
T.Bil	0.7
AST	57
ALT	96
LDH	1543
BUN	5.8
Cr	0.8
UA	8.4
Na	145
K	2.9
Cl	102
CRP	4.5

Table 1: Hematological data.

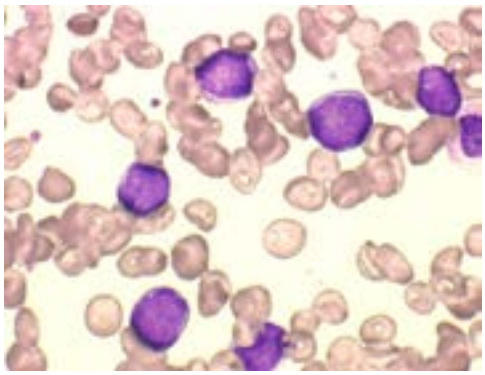

Figure 1: Acute lymphoblastic leukemia cells(x400).

chemotherapy could modify the original leukemic clone by amplifying or suppressing the differentiation programs, resulting in a lineage switch. Chronic myeloid leukemia at blast transformation provides a model of pluripotent stem cell malignancy capable of an acute transformation into either myeloid or lymphoid cell lines. Complete phenotypic and genotypic lineage switch from the same clone that carried a hybrid bcr/abl gene has been reported [6]. However, in this case, no Philadelphia chromosome abnormality was observed on repeated analysis.

Molecular profile tracking is important for analyzing the pathogenesis of lineage switch leukemia. Activating NOTCH1 mutation in a patient with lineage conversion from AML to T-ALL was reported [7]. Activating NOTCH1 mutations are present in over 50% of human T-ALL cases, but very few are present in AML. Its presence in AML and T-ALL cells suggests that these mutations may occur in a leukemic stem cell that precedes both myeloid and T-lineage commitment. Clonality analysis of a 22-year-old patient with precursor B-cell ALL and relapsing AML showed rearrangement of the Ig heavy chain gene locus of the cells of both lineages; the origin of the ALL and AML cells was the same leukemic clone [8]. Similar case was reported as clonal rearrangements of the Ig heavy chain gene locus both in B cell ALL and subsequent AML cells [12]. The case of conversion from B cell lymphoblastic leukemia to erythroleukemia has complex karyotypic abnormalities in addition of original monosomy 5 and monosomy 7 [13].

Date	Chromosome analysis	Disease status
1998/4/10	46,XX,del(20)(q12) [1-2] 46,XX[27]	morphological CR
1998/9/16	46,XX,del(20)(q12) [1] 46,XX [32]	morphological CR
1998/10/5	45,XX,t(1;12)(q21;q24), t(2;15)(p11;p11), -3, add(6)(p23), -7, del(8)(p22), der(9)t(7;9)(q11;p13), +mar [10] 47, idem, +add(9), +mar [1] 46,XX [9]	ALL(L3)
1999/1/29	46, XX, add(17)(p11) [3] 46, idem, -20 [4] 46, XX, del(8)(q21q24) [1] 46,XX [11]	ALL-morphological CR
1999/3/31	46, XX, add(17)(p11) [5] 46, XX, del(8)(q21q24) [1] 46,XX [6]	Hemolytic anemia
1999/4/30	46, XX,add(8)(q?22) [15] 46, idem, -10, +mar [1] 46,XX [4]	ALL relapse
1999/11/15	54-57,XX,+146,XX [11,+2 [11],+6 [11],+8 [11],-12 [9] +13 [9],+14 [3],+15 [9]+16 [7],add(17)(q22) [9], +19 [10], add(19)(p13.1) [7],add(19)(p13.1) [2] +20 [3],del(20)(q12) [11],+21 [10],-22 [2], +mar [10],+mar2 [10], +mar3 [7],+mar4 [2] <cp11)	AML(M7)

Table 2: Chromosomal analysis.

	1998.10.5	1999.4.30	1999.10.18
Disease Status	ALL(L3)	ALL(L3) relapse	AML-M7
CD1	1.1	ND	1.1
CD2	1.7	0.2	7.9
CD3	0.6	0.4	1.8
CD4	1.3	1.2	27.7
CD5	3.4	1.5	4.4
CD7	0.5	ND	6.1
CD8	0.8	1.1	4.9
CD10	93.7	87.5	9.4
CD19	96.0	87.5	1.4
CD20	72.4	69.2	2.7
CD13	3.7	ND	65.3
CD14	1.1	ND	17.9
CD33	4.2	1.3	86.7
CD41	1.3	ND	85.0
CD34	31.6	6.5	1.8
CD56	1.3	3.6	18.5
HLA-DR	94.5	90.4	3.1
K-chain	ND	1.1	ND
L-chain	ND	1.6	ND

Table 3: Surface marker analysis.

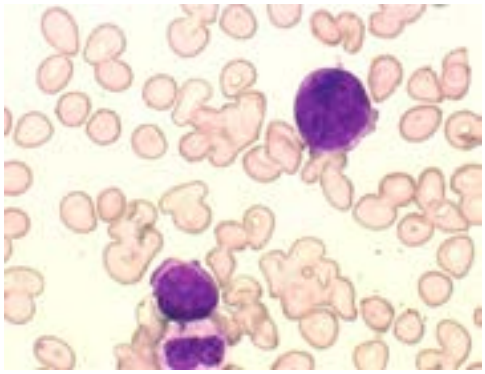

Figure 2: Megakaryoblastic leukemia cells(x400).

Our patient had no common chromosomal abnormalities during the clinical course. The profile of her chromosomal abnormalities was not always linked to disease status. Unfortunately, we did not have any specific molecular marker for determining the clonality of the leukemia clones in this patient. In this patient, FISH analysis such as bcr-abl was negative.

Because her leukemic clone at onset showed normal karyotypes, chromosomal instability and fragility induced by chemotherapy comprise one possible explanation for these inconsistent abnormalities.

In cases of lineage switch leukemia, the possibility of a secondary neoplasm due to treatment should be considered. However, in the present case, the interval between treatment and conversion was relatively short. Secondly, we did not find any chromosomal abnormalities, particularly those involving chromosome 5,7, and especially 11q23, which occur preferentially in the malignant transformation of pluripotent stem cells. In the present patient's history, AML was not preceded by myelodysplastic syndrome. It is unlikely that her leukemia profile was secondary to chemotherapy.

To the best of our knowledge, there are no reports demonstrating a relationship between AML-M7 and ITP or Evans syndrome. Among the various types of lineage switch reported in the literature, AML-M7 is extremely rare. Hatae et al. reported a 20-month-old infant with minimally differentiated acute leukemia (M0) who underwent a lineage switch to AML-M7 on relapse [9]. However, no case of lineage switch from AML-M7 to ALL and vice versa has been reported.

Thus, the present report is the first case of leukemia with repeated lineage switch in association with chemotherapy.

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