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Lineage Switch at Relapse of Childhood Acute Leukemia: A Report of Four Cases

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Lineage switch in acute leukemia is an uncommon event at relapse, and therefore rarely reported in the literature. Here, we have described the clinical laboratory features of four cases in which the cell lineage switched from acute lymphoblastic leukemia (ALL) to acute myeloid leukemia (AML). One patient was initially diagnosed with B-ALL, switched to T-ALL at the first relapse, and eventually, AML at the second relapse. A lineage switch represented either relapse of the original clone with heterogeneity at the morphologic level or emergence of a new leukemic clone. Further sequential phenotypic and cytogenetic studies may yield valuable insights into the mechanisms of leukemic recurrence, with possible implications for treatment selection.

Key Words: Lineage Switch; Acute Leukemia

INTRODUCTION

"Lineage switch" is the term used to describe the phenomenon of acute leukemia that meets standard French-American-British (FAB) criteria for a specific lineage (lymphoid or myeloid) at initial diagnosis, but converts to the opposite lineage upon relapse (1). This situation rarely occurs, and prognosis is variable. Although different hypotheses have been proposed to explain the occurrence of lineage switch, the specific causative factors have not yet to be identified. Here, we present the clinical and laboratory features of four cases in which the cell lineage switched from acute lymphoblastic leukemia (ALL) to acute myeloid leukemia (AML).

CASE DESCRIPTIONS

Case 1

A 15-month-old boy was diagnosed with pro-B cell ALL L1 in June 2001. Immunophenotypic analysis revealed CD19+ and HLA-DR+. Cytogenetic analysis showed 46, XY. The patient achieved complete remission (CR) after induction chemotherapy, and completed chemotherapy in January 2005. Thirty-three months after completion of therapy, the patient presented with fever and cervical lymph node enlargement. Bone marrow (BM) analysis revealed 87.0% small-to-medium-sized leukemic blasts with a moderate amount of cytoplasm. Cytochemical and immunocytochemical staining revealed a negative reaction for myeloperoxidase (MPO) and anti-MPO. Flow cytometric analysis showed positivity for CD33, cyCD13, cyCD33, and CD117. Data supported the diagnosis of AML M0. Cytogenetic analysis showed 46, XY, t(9;11)(p22;q23). Fluorescence in situ hybridization (FISH) analysis with a MLL-probe showed a signal in 97.5% of blasts. AML-directed reinduction therapy was initiated and the patient achieved a second CR at the end of this period with no evidence of MLL gene arrangement. The patient subsequently underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT), and remained in CR for 36 months.

Case 2

A 6-yr-old boy was diagnosed with B-lineage common cell ALL L1 in March 2003. Immunophenotypic analysis revealed HLA-DR, TdT, CD10, CD19 and CD22 positivity. Cytogenetic analysis showed 56, XY, +X, +Y, +Y, +4, +8, +10, +14, +17, -20, +21, +21, +21[6]/57, idem, +Y[19]. After induction chemotherapy, the patient achieved CR. During chemotherapy, at 9 months after the initial diagnosis, the patient presented fever with pancytopenia. BM revealed a homogeneous population of large blasts with abundant basophilic cytoplasm. Cytochemical staining revealed positivity for MPO and α-naphthyl-butyrate esterase (ANBE). Blasts were positive for HLA-DR, CD13, CD14, and CD33. Cytogenetic analysis showed 46, XY, t(8;16)(p11.2;p13.1). The patient was re-diagnosed with AML M4, and achieved a second remis-

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sion after salvage therapy. Due to lack of available donors for HSCT, chemotherapy was continued for 2 yr. The patient has remained in CR for 79 months since the second remission.

Case 3

A 7-yr-old girl was diagnosed with B lineage ALL L2 in May 1999. A BM study revealed 89% of blasts showing medium-sized nuclei with some nuclear indentation or cleavage. Immunophenotypic analysis revealed positivity for HLA-DR, cytoplasmic IgM with aberrant CD33. Cytochemical staining showed a block-dot positive reaction for Periodic Acid Schiff (PAS) and a negative for MPO and nonspecific esterase (NSE). Immunocytochemistry was negative for anti-MPO. The 46, XX karyotype was identified. After induction chemotherapy, the patient achieved CR. During chemotherapy, at 14 months after diagnosis, the patient presented with prolonged fever. BM study revealed 68.2% leukemic lymphoblasts. Cytochemical staining data were similar to those at initial diagnosis. However, immunophenotypic analysis showed positivity for CD2, CD5, CD7, CD34, and HLA-DR with aberrant CD33, indicating that the relapse was T cell ALL. Cytogenetic analysis showed trisomy 13. At 45 days after the initiation of ALL reinduction therapy, the patient showed relapse, that was identified AML M1. Cytochemical staining revealed a coarse granular pattern for PAS, and negativity for MPO and ANBE. Immunocytochemistry revealed positivity for anti-MPO. Immunophenotypic staining showed positiivity for CD13, CD33, CD34 and HLA-DR with aberrant CD7. The patient received AML-directed chemotherapy, but did not achieve CR, and died of disease progression 9 months after AML relapse.

Case 4

A 3-month-old girl was diagnosed with pre-B cell ALL L1 in December 2008. BM revealed small-to-medium sized lymphoblasts comprising 92.4% of all nucleated cells. Immunochemical staining showed PAS+, MPO-, and ANBE-. Flow cytometric analysis revealed positivity for CD19, CD34, and TdT with aberrant CD33. Cytogenetic studies showed t(4;11)(q21;q23), which was further confirmed by FISH analysis. After induction chemotherapy, BM analysis revealed morphologic CR, however, FISH with the MLL-probe showed a signal in 5.5%. During chemotherapy, 2 months after initial diagnosis, the patient relapsed as AML M4. Blasts were positive for CD2, CD13, CD14, CD33, CD41, and CD65. FISH with the MLL probe showed a signal in 2%. Cytochemical staining showed positivity for MPO and ANBE. The patient underwent allo-HSCT four months after AML-directed chemotherapy. She remained in remission for 17 months following the second CR.

DISCUSSION

All the cases reported here were initially diagnosed as ALL, but relapsed as AML. In the first three cases, the original karyotype had been replaced by an entirely different abnormal karyotype, while in case 4, lineage switch represented a relapse of the same leukemic clone.

In case 1, the patient was initially diagnosed as ALL L1 with normal karyotype, which switched to AML M0 with t(9;11) at relapse with complete immunophenotypic changes. In chemotherapy-associated secondary AML, which has a mean latency period of 2 yr, monocytic subtypes are more common and associated with translocations involving the MLL gene on 11q23 (2). Considering the long duration between diagnosis and relapse and the multiple antineoplastic drugs administered to the patient before relapse, we cannot conclude the effect of that chemotherapy for the relapse with clonal change.

In case 2, ALL L1 switched to AML M4, with loss of CD10 and TdT. In terms of gain or loss of phenotypic markers at relapse of acute leukemia, one of the most common changes is loss of CD10 and/or TdT activity (3-5). Pui et al. (3) previously suggested that loss of CD10 might be related to malignant transformation of pluripotent stem cells after eradication of the original stem cell line with chemotherapy, but the precise significance of this finding remains unknown. AML-t(8;16), diagnosed at relapse, is characterized by monocytic differentiation of AML M4/M5 and poor prognosis. The t(8;16) gene fuses the MOZ gene encoding histone acetytransferase located on 8p11 with the CBP gene, which also encodes histone acetyltransferase located on 16p13. Recent reports have indicated that the chimeric transcription of MOZ-CBP is essential for leukemogenesis (5). The majority of the documented AML-t(8;16) cases are de novo, and, to the best of our knowledge, 12 cases of secondary t(8;16) leukemia (including our case 2) have been reported to date (6-8). However, the relationship between histone acetylase and secondary leukemia is yet to be determined.

In case 3, the original diagnosis was B-ALL with aberrant expression of the myeloid marker, CD33. At first relapse, the patient showed immature T-lymphoid phenotype of CD7+, CD4-, CD8-, CD1-, retaining CD 33 expression, in addition to the emergence of a new clone, trisomy 13. Finally, the patient switched to AML retaining aberrant T-lymphoid cell marker CD7. Trisomy 13, observed in our patient at relapse, is associated with undifferentiated or biphenotypic acute leukemia, and is rarely described in lymphocytic disorders (9). The first transformation of B-ALL was T-lineage ALL coexpressing myelocytic and undifferentiated markers, such as CD33 and CD34. A subset of hematopoietic precursors that lack mature T-cell and myeloid antigens retains the potential to differentiate into T-lymphoid and myeloid cells. Hurshfield and co-workers (10) described the in vivo conversion of CD7+, CD4-, CD8- lymphoid cells to the myeloid lineage, while Kurtzberg et al. (11) suggested that CD7+, CD4-, CD8- leukemias arise from immature hematopoietic stem cells with lineage infidelity. Moreover, several authors have proposed that

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NOTCH1 mutations occur in leukemic stem cells that precede both myeloid and T-lineage commitment (12). Considering the rapid lineage switch between the first and second relapse and early immature T-lymphoid phenotype in case 3, we suggest that lineage switch may arise from very immature cells belonging to a common T-cell/myeloid progenitor.

Lineage switch in infant leukemia has been previously described in the literatures (13, 14). The most common chromosomal abnormality reported in infant leukemia is t(4;11) (15). Rearrangement of the MLL gene is known to play an important role in leukemogenesis (16). Some authors have suggested that the MLL gene rearrangement occurs in B lymphocyte-monocyte bipotential stem cells (13). Although the prognosis of MLL-infant leukemia is poor (15), our patient 4 remained in CR after allo-HSCT.

Lineage switch may be regarded as a variation of mixed-lineage leukemia in which the lineage at onset is converted to another at a later time (17). However, the relationship between lineage switch and mixed-lineage leukemia is yet to be determined. In some cases, lineage switch may be part of the biologic spectrum of mixed-lineage leukemia. An example of this is the patients 3 and 4, who met the morphologic and cytochemical criteria for diagnosis of ALL, but displayed positivity for CD33 with the expanded immunophenotype panel.

In conclusion, although our current findings are insufficient to confirm the mechanism of lineage switch, each case indicates different possibilities. Sequential phenotypic and cytogenetic studies may yield valuable insights into the mechanisms of leukemic recurrence, with possible implications for individualized treatment selection.

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