Lineage Switch from Acute Lymphoid Leukemia to Acute Myeloid Leukemia

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Abstract

Lineage switch acute leukemia is a rare condition mostly reported in pediatrics. Despite new advances in the treatment of acute leukemia, switching between lymphoid and myeloid lineages at relapse could worsen outcome of the disease. Awareness of this phenomenon might be beneficial in terms of early detection and applying more aggressive or more specific therapy specially in the context of some genetic alterations.

Keywords: Acute lymphoblastic leukemia; Acute myeloid leukemia; Lineage switch; Flow cytometry; Cytogenetics

Introduction

Lineage switch defines as an acute leukemia that initially presents with either lymphoid or myeloid phenotype, and then converts to the other one when relapses, while keeping the same genotype. Lineage switch (conversion) is a rare entity that is mostly reported in childhood (0.6% of pediatric acute leukemia) and shown to be associated with poor prognosis [1-3]. There are different hypotheses to explain this phenomenon including selection of a resistant subclone or reprogramming of a malignant pluripotent stem cell. Lineage conversion is associated with some gene alterations including Lysine [K]-specific methyl transferase 2A (KMT2A) located on 11q23 region. KMT2A rearrangement, previously called as mixed-lineage leukemia 1 (MLL1), has been reported in about 10% of all acute leukemia [4]; this genetic abnormality is usually being detected in acute lymphoblastic leukemia (ALL) of infancy or in acute myeloid leukemia (AML) in young adults. KMT2A is involved in epigenetic regulation of certain developmental genes like Homeobox (HOX) which is involved in hematopoietic cell differentiation; rearranged KMT2A could result in HOX overexpression which blocks maturation process and cause leukemia in precursor cells [4,5].

Case Presentation

A 65-year-old previously healthy woman presented with 7 months history of progressive constitutional symptoms; weight loss, lack of appetite, and night sweats. Blood work showed marked leukocytosis (WBC: 129.7 x 10⁹/L), anemia (hemoglobin: 66g/L), and thrombocytopenia (PLT: 29 x 10⁹/L). The bone marrow examination demonstrated 95% blasts; small to medium size, high N/C ratio and no granules (Figure 1A). By flow cytometry (Figure 1D), blasts show CD7+, (dim/heterogeneous), CD19+ and cCD79a+ expression along with lack of expression of TDT, MPO, CD15, CD33, CD34, CD65 and CD117. PCR was negative for BCR-ABL fusion. Cerebrospinal fluid cytology was negative for leukemia. Karyotype analysis showed t(11;19) (q23;p13.3) as the sole abnormality, and fluorescence in situ hybridization (FISH) study confirmed KMT2A rearrangement (Table1); thus, the diagnosis of B-lymphoblastic leukemia with t;v(11q23.3); KMT2A-rearranged was rendered. The patient received induction chemotherapy with modified Dana-Farber protocol followed by complete remission; There was neither a delay nor interruption in the chemotherapy regimen, however, twenty-one months after achieving complete remission, while the patient was on maintenance therapy, she developed pancytopenia; the peripheral blood film showed circulating blasts with variable size and moderate to high N/C ratio, lightly basophilic cytoplasm and a few granules (Figure 1B). A bone marrow aspiration was hemodiluted with scattered blasts; however, the bone marrow biopsy revealed a hypercellular marrow with grade 2 fibrosis and 40% blasts (Figure 1C).

Flow cytometry of bone marrow aspirate showed: the blasts were positive for MPO, CD15, CD33 (weak), CD34 (partial), CD65, CD79a (weak), but negative for cCD3, CD7, CD19 and cCD22 expression (Figure 1E). Cytogenetics was inconclusive, however, FISH study detected KMT2A-rearrangement (Figure 2). Immunohistochemical (IHC) staining showed MPO positive (Figure 3) but weak CD79a expression on blasts; the diagnosis of AML with some aberrant expression of B-lymphoid markers at relapse consistent with lineage switch from B-ALL to AML was made. The patient underwent complete remission after re-induction chemotherapy with FLAG-IDARUBICIN but relapsed again five months after second remission. The second

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<tr>
<td>Bone marrow blast count</td>
<td>95% lymphoblasts</td>
<td>Less than 2% blasts</td>
<td>40% Myeloblasts</td>
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<td>Flow cytometry</td>
<td>HLA-DR+, CD7+ (dim), CD19+, cCD22+ (dim), CD38+, cCD79a+</td>
<td>MRD undetectable</td>
<td>MPO+, HLA-DR+, CD13+ (dim), CD15+, CD33+, CD34+ (partial), CD38+, CD65+ (partial), CD79a+ (dim)</td>
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<tr>
<td>Cytogenetics</td>
<td>46,XX,t(11;19) (q23;q13.3)</td>
<td>Not tested</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Negative</td>
<td>Not tested</td>
<td>Negative</td>
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Table 1: Clinical and laboratory features.

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Discussion

In case of developing a new myeloid leukemia after chemotherapy, relapse showed similar phenotype. We do not have her follow-up after that because the patient willing to continue her treatment outside the country.

Figure 1: (A) Bone marrow aspiration at diagnosis; B-lymphoblastic leukemia (B) Peripheral blood at first relapse: AML (C) Bone marrow biopsy at first relapse: AML (D and E) BM aspirate flow cytometry at diagnosis and first relapse, respectively: red dots shows blasts; blue and green dots show normal T-cells and mature granulocytes, respectively.

Figure 2: FISH study showed KMT2A (MLL) break apart rearrangement in 11q23 region at first relapse. ISCN: Nucish(MLL×2)/(5’MLL sep 3’MLL×1) [20/200]. The signal pattern observed by interphase FISH was consistent with presence of MLL rearrangement in 10.0% of nuclei, with a straight-forward break-apart pattern, with no additional or missing signal. Given the history of t(11;19) by karyotyping, this result is most in keeping with recurrence of the previous leukemia clone.

Figure 3: MPO expression on bone marrow biopsy at first relapse.
of adult lineage switch from B-ALL, KMT2A-r to AML; although some of them could classify either as t-AML or biphenotypic MPAL [2,9]. Recently, there are some case reports of lineage switch from B-ALL to AML followed by CD19 chimeric antigen receptor (CAR) T-cell therapy; the phenotypic conversion from CD19+ lymphoblasts to CD19- blasts with myelomonocytic markers could reveal possible mechanisms of immune escape from targeted therapy [10,11].

Conclusion

In this paper, we reported an adult patient with a rare condition of switching from lymphoid to myeloid acute leukemia at the time of relapse in the context of genetic rearrangement of KMT2A. Considering the risk of lineage conversion in this particular genetic defect, it may necessitate more specific therapy for KMT2A-r acute leukemia.

References