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Case Report Open Access

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 10^9/L), anemia (hemoglobin: 66g/L), and thrombocytopenia (PLT: 29 x 10^9/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, cCD3, CD13, 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

Clinical and biologic data	At diagnosis	Follow up	At relapse
Bone marrow blast count	95% lymphoblasts	Less than 2% blasts	40% Myeloblasts
Flow cytometry	HLA-DR+, CD7+ (dim), CD19+, cCD22+(dim), CD38+, cCD79a+ TDT-, MPO-, CD13-, CD15-, CD33-, CD34-, CD65-, CD117-	MRD undetectable	MPO+, HLA-DR+, CD13+ (dim), CD15+, CD33+, CD34+ (partial), CD38+, CD65+ (partial), CD79a+ (dim) TDT-, CD7-, CD19-, cCD22-, CD117-
Cytogenetics	46,XX,t(11;19) (q23;p13.3)	Not tested	Inconclusive
FISH	Positive for KMT2A rearrangement	Not tested	Positive for KMT2A rearrangement
Lumbar puncture	Negative	Not tested	Negative

Table 1: Clinical and laboratory features.

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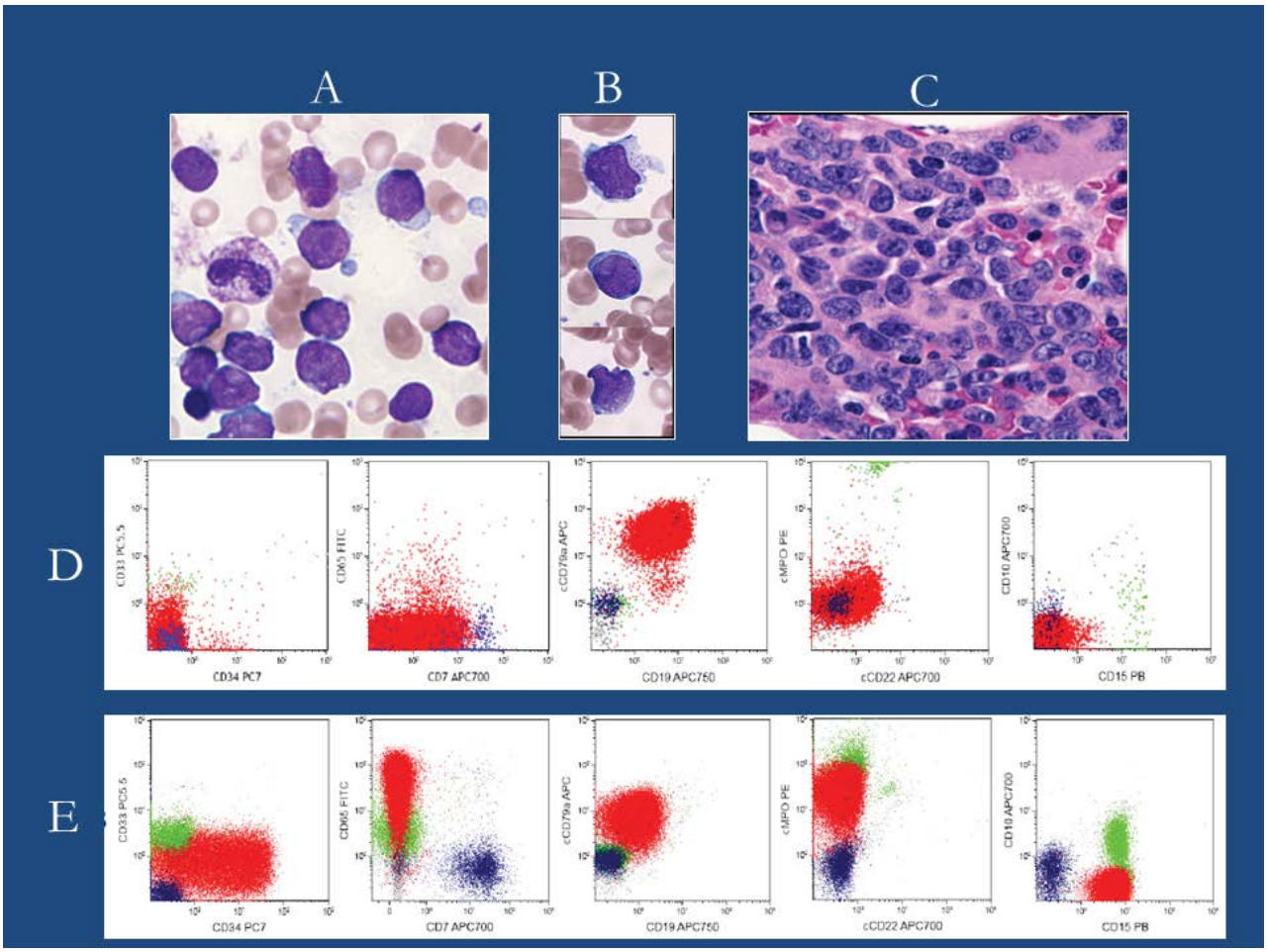

Figure 1: (A) Bone marrow aspiration at diagnosis; B-lymphoblastic leukemia **(B)** Peripheral blood at first relapse: AML **(C)** Bone marrow biopsy at first relapse: AML **(D and E)** BM aspirate flow cytometry at diagnosis and first relapse, respectively: red dots shows blasts: blue and green dots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

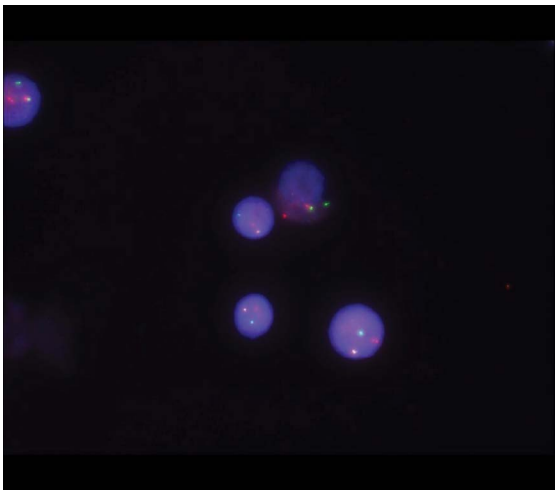

Figure 2: FISH study showed KMT2A (MLL) break apart rearrangement in 11q23 region at first relapse. ISCN: Nucish(MLL×2)(5'MLL sep 3'MLL×1) [20/200]. The signal pattern observed by interphase FISH was consistent with presence of MLL rearrangement in 10.0% of nuclei, with a straight-forward break-apart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

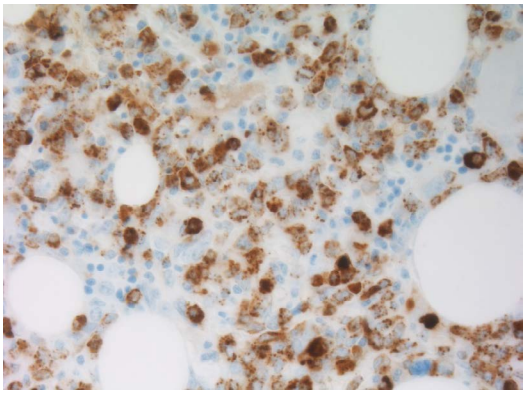

Figure 3: MPO expression on bone marrow biopsy at first relapse.

relapse showed similar phenotype. We do not have her follow-up after that because the patient willing to continue her treatment outside the country.

Discussion

In case of developing a new myeloid leukemia after chemotherapy,

one of the differential diagnosis would be therapy-related AML (t-AML). t-AML usually occurs in an unrelated clone with a different genetic feature. About 30% of therapy-related myeloid neoplasms (t-MNs) were previously treated for a hematological neoplasm; more frequently after non-Hodgkin lymphoma. Therapy-related neoplasms imply on mutation events in hematopoietic stem cells/bone marrow microenvironment, or selection of a myeloid clone that is prone for mutation events as a result of cytotoxic therapy. Two types of t-MNs are generally recognized; the first type usually presents 5-10 years after exposure to alkylating agents and are commonly associated with unbalanced loss of genetic material, often involving chromosomes 5 and/or 7, complex karyotypes or mutations/loss of TP53. The second type usually presents 1-5 years after treatment with topoisomerase II inhibitors. Most cases in this subtype present with overt AML without preceding myelodysplasia, and often associated with a balanced chromosomal translocation which frequently involve 11q23 (*KMT2A*) [6,7]. However, our patient had *KMT2A* rearrangement in the first place, and less than 2 years after complete remission following chemotherapy including doxorubicin which is a topoisomerase inhibitor, again showed the same genetic abnormality, although we do not have the cytogenetic result on the relapsed specimen, however, based on the FISH result, the relapse is most likely due to the recurrence of the same leukemia clone with different phenotype.

Another differential diagnosis in the present case is mixed phenotype acute leukemia (MPAL); MPAL could be bilineal or biphenotypic; the former applies to leukemia containing two populations of blasts at the same time and the latter contains a single population of blasts co-expressing antigens of two lineages; our patient did not fulfill the criteria of MPAL because of having a single clone in flow and the lack of simultaneous expression of lymphoid and myeloid markers. Instead, it showed B-cell markers at initial presentation and myeloid markers at relapse; therefore, lineage conversion from B-ALL to AML is the most likely diagnosis.

Lineage switching is an example of the lineage heterogeneity in acute leukemia; one of the possible mechanisms of lineage switch in patients who develop relapse after therapy is clonal selection; Karyotype analyses often show same cytogenetic alterations in the first and the relapsed clones. Chemotherapy might eradicate the initially dominant leukemic clone; allow a different subclone to expand. Another hypothesis is reprogramming of the bipotential B/Myeloid precursor result in developing a new clone with similar genotype but different phenotype [5,8].

Rossi et al. presented 7 pediatric cases of *KMT2A-r* lineage switch from B-ALL to AML at relapse [3]. However, there are very few reports 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

1. Stass S, Mirro J, Melvin S, Pui CH, Murphy SB, et al. (1984) Lineage switch in acute leukemia. Blood 64: 701-706.
2. Gagnon GA, Childs CC, LeMaistre A, Keating M, Cork A, et al. (1989) Molecular heterogeneity in acute leukemia lineage switch. Blood 74: 2088-2095.
3. Rossi JG, Bernasconi AR, Alonso CN, Rubio PL, Gallego MS, et al. (2012) Lineage switch in childhood acute leukemia: An unusual event with poor prognosis. Am J Hematol 87: 890-897.
4. Winters AC, Bernt KM (2017) MLL-rearranged leukemias-an update on science and clinical approaches. Front Pediatr 5: 4.
5. Dorantes-Acosta E, Pelayo R (2012) Lineage switching in acute leukemias: A consequence of stem cell plasticity? Bone Marrow Res 2012: 406796.
6. Sill H, Olipitz W, Zebisch A, Schulz E, Wölfler A (2011) Therapy-related myeloid neoplasms: Pathobiology and clinical characteristics. Br J Pharmacol 162: 792–805.
7. Vardiman JW, Arber DA, Brunning RD, Larson RA, Matutes E, et al. (2017) Therapy-related myeloid neoplasms. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA (Eds), WHO classification of tumours of haematopoietic and lymphoid tissues. IARC, Lyon pp: 153-155.
8. Della Starza I, Ceglie G, Nunes V, Gianfelici V, Marinelli M, et al. (2016) A case of lineage switch from B-cell acute lymphoblastic leukaemia to acute myeloid leukaemia. Role of subclonal/clonal gene mutations. Br J Haematol 174: 648-651.
9. Imataki O, Ohnishi H, Yamaoka G, Arai T, Kitanaka A, et al. (2010) Lineage switch from precursor B cell acute lymphoblastic leukemia to acute monocytic leukemia at relapse. Int J Clin Oncol 15: 112-115.
10. Gardner R, Wu D, Cherian S, Fang M, Hanafi LA, et al. (2016) Acquisition of a CD19-negative myeloid phenotype allows immune escape of MLL-rearranged B-ALL from CD19 CAR-T-cell therapy. Blood 127: 2406-2410.
11. Zoghbi A, Zur Stadt U, Winkler B, Müller I, Escherich G (2017) Lineage switch under blinatumomab treatment of relapsed common acute lymphoblastic leukemia without MLL rearrangement. Pediatr Blood Cancer p. 64.