A case of therapy-related acute lymphoblastic leukemia following the treatment of acute myeloid leukemia

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ABSTRACT

Therapy-related acute lymphoblastic leukemia represents a distinct entity associated with inferior survival compared with de novo acute lymphoblastic leukemia. It consists of a subset of patients who have had exposure to chemotherapy or radiation for a previous malignancy. Here, we describe a case of acute myeloid leukemia who later developed precursor B cell acute lymphoblastic leukemia and discuss the current relevant literature. Our case highlights the importance of classifying therapy-related acute lymphoblastic leukemia as a separate as entity based on its biologic and clinical features.

1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of hematological malignancies characterized by abnormal clonal proliferation of myeloid blast cell in the bone marrow, peripheral blood and/or other tissues affecting one or more cell lines. Induction chemotherapy with antimetabolites and anthracyclines followed by consolidation therapy with chemotherapy, or hematopoietic stem cell transplantation are highly effective treatment for AML. As survival of AML patients continues to increase, second primary malignancies (SPM) are becoming a concern for these patients. The 5-year incidence of SPM in AML is 10% [1]. Analysis of Surveillance, Epidemiology and End Results (SEER) cancer registry data showed a threefold higher rate of SPM patients with AML younger than 60 years of age; the majority of them developed lung or breast cancer [2].

Second primary malignancy of acute lymphoblastic leukemia (ALL) following AML is very rare and only a few cases have been reported [3–5]. The use of cytotoxic chemotherapies for treatment of AML is related to the development of ALL and these cases have been recognized as therapy-related ALL [1,6,7,8]. The most common cytogenetic abnormalities have been reported so far were a MLL rearrangement at the 11q23 gene locus in children, and a Philadelphia chromosome with t (9;22) translocation in adults [9]. Therapy-related ALL is associated with poor survival, with overall survival of 2.5 months [1].

To our knowledge, very few cases of therapy-related ALL following AML have been reported. Herein, we present a patient diagnosed with ALL five years after induction and consolidation chemotherapy for AML.

2. Case report

A 36-year-old female was admitted to the hospital for hemoptysis, dyspnea and weight loss in 2014. She was found to have a white blood cell count of 24.54 × 10^9/L with 22% blasts, hemoglobin 8.2 g/dL, and platelet 398 × 10^9/L. The peripheral blood smear from 2014 showed scattered circulating blasts with fine chromatin, nucleoli, and a variable amount of cytoplasm; no Auer rod was noted. There were promonocytes with convoluted or folded nuclei, fine chromatin and more abundant cytoplasm with no more than sparse granularity as well as abnormal/immature monocytes with more elongated nuclei and clumped chromatin (Fig. A). She underwent Flow cytometry, cytogenetics, FLT3, NPM1, C KIT, CEBPA, DNTM3A, and FISH panels for Chromosomes 5 & 7 in addition to a HemaVision panel at the time of diagnosis. The HemaVision panel is a leukemia screening test for 28 chromosome translocations and more than 145 breakpoints associated with leukemia (Table 1) [10]. The morphologic differential showed 22% blasts/blast equivalents (promonocytes), while flow cytometry revealed 8% blasts and 51% monocytic cells. The blasts expressed CD45 (dim), CD13 and CD33 with partial expression of HLA-DR, CD15 and CD4 and minimal expression of CD34, CD14 and CD64, and the monocytic cells expressed CD45 (bright), CD33, HLA-DR, CD4, CD14, CD64 and CD15 with partial expression of CD13 and no expression of CD34. These features were consistent with a diagnosis of AML with monocytic differentiation.

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A spinal fluid evaluation was unremarkable. Therapy with 7 molecular studies including C-Kit, CEBPA, and DNMT3A were negative. A MLL mutation was not detected after t(9;22). She received 4 cycles of HyperCVAD (cycle A: cyclophosphamide 300 mg/m$^2$ + vincristine 2 mg + doxorubicin 50 mg/m$^2$ + dexamethasone 40 mg, and cycle B: methotrexate 1000 mg/m$^2$ + cytarabine 3000 mg/m$^2$) for Philadelphia negative B-ALL. She achieved CR with positive minimal residual disease (MRD). She then achieved MRD negativity after blinatumomab. Currently she is receiving treatment with POMP (Prednisone, Oncovin, methotrexate and 6-mercaptopturine).

### Table 1

| Translocations | Genes involved |
|----------------|----------------|
| t(5;17) (q35;q21) | NPM1-RARA |
| t(12;22) (p13;q11) | ETV6-MN1 |
| t(6;9) (p22;q34) | DEK-NUP214 |
| t(15;17) (q24;q21) | PAL-RARA |
| t(6;11) (q27;p23) | MLL-MLT74 |
| inv(16) (p13q22) | CBFB-MYH11 |
| t(8;21) (q22p22) | RUNX1-RUNX1T1 |
| t(16;21) (p11q22) | FUS-E8 |
| t(9;9) (q34q34) | SET-NUP214 |
| t(17;19) (q22p13) | TCF3-ILF |
| t(9;11) (p22q23) | MLL-MLT3 |
| t(X;11) (q13p23) | MLL-FOXO4 |

### 3. Discussion

Therapy-related ALL accounts for less than 10% of all ALL cases [6]. The use of topoisomerase II inhibitors is well recognized to be associated with therapy-related AML as a late complication and is established under a distinct classification by the World Health Organization (WHO). By contrast, topoisomerase II inhibitor associated therapy-related ALL is uncommon. Our patient had a long latency period following AML with normal cytogenetics. The patient’s bone marrow biopsy pathology slides from 2014 to 2020 were compared and they were totally different in terms of morphology under the microscope and immunophenotype based on flowcytometry hence the diagnosis in our case of therapy-related ALL.

Although several hypotheses discussed in the literature can be involved in the development of therapy-related ALL, the mechanisms of therapy-related ALL are yet to be elucidated. Therapy-related ALL primarily presents as a late complication following cytotoxic therapy with an alkylating agent, topoisomerase II inhibitor and/or radiotherapy for prior malignancy [9]. Ishizawa et al. analyzed the cytogenetic and immunophenotypic features of 152 adults with therapy-related ALL, and found a higher frequency of MLL gene rearrangements especially t(4;11) with therapy-related ALL than with therapy-related AML [12]. This genetic aberration was commonly observed among pediatric patients and topoisomerase II inhibitor exposure was also frequently found to be associated with MLL gene rearrangement [8,9,11]. According to prior studies, adult patients most commonly presented a Philadelphia (pH) chromosome (BCR-ABL rearrangement) in therapy-related ALL but no difference was observed between therapy-related AML and de novo ALL [9,11]. Patients with a MLL gene rearrangement were characterized by a shorter latency period and those with a pH-positive chromosome showed a longer latency [13].

Matnani et al. and Aldoss et al [9,11], reported that the monosomy karyotype, hypodiploidy with deletion of chromosomes 5, and 7, were the most common cytogenetic abnormalities observed in patients with prior exposure to cytotoxic chemotherapy including topoisomerase II

**Bone marrow biopsy showed AML with monocytic differentiation. Cytogenetic analysis showed no abnormality. An AML FISH panel was negative for chromosome 5 and 7 deletions. A MLL mutation was not detected. FLT3-TKD and NPM1 mutations were detected. The rest of the molecular studies including C-Kit, CEBPA, and DNMT3A were negative. A spinal fluid evaluation was unremarkable. Therapy with 7 molecular studies including C-Kit, CEBPA, and DNMT3A were negative. A MLL mutation was not detected after t(9;22). She received 4 cycles of HyperCVAD (cycle A: cyclophosphamide 300 mg/m$^2$ + vincristine 2 mg + doxorubicin 50 mg/m$^2$ + dexamethasone 40 mg, and cycle B: methotrexate 1000 mg/m$^2$ + cytarabine 3000 mg/m$^2$) for Philadelphia negative B-ALL. She achieved CR with positive minimal residual disease (MRD). She then achieved MRD negativity after blinatumomab. Currently she is receiving treatment with POMP (Prednisone, Oncovin, methotrexate and 6-mercaptopturine).**

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| t(9;11) (p22q23) | MLL-MLT3 |
| t(X;11) (q13p23) | MLL-FOXO4 |

**Fig. A.** Peripheral blood smear showing a blast (far right), a promonocyte (far left), and two more mature monocytes (Wright stain, 100X in oil immersion).

**Fig. B.** Touch imprint showing variably sized blasts with relatively little cytoplasm (Wright stain, 100X in oil immersion).
inhibitors. In addition, myeloid mutation pattern (ie. DNMT3A, RUNX1), lymphoid mutation (ie. ASXL1, CDKN2A) and germline mutation (BRCAl, BRCA2, TP53, CHEK2) genes were also reported but were less frequent [6,9,11]. Although abnormal cytogenetics is associated with an unfavorable prognosis, the overall prognosis of the patients with therapy-related ALL is generally considered poor with a median survival rate of 3-14 months [9,11].

Lineage switching from a myeloid to a lymphoid phenotype is another possibility that has been discussed in the literature [11,14,15]. Approximately 6%–9% of patients exhibit lineage switching with acute leukemia; this usually presents within 4 years after initial diagnosis [11,15]. The precise mechanism is still unclear, but previous studies have identified several mechanisms that potentially can cause lineage switch. Exposure to chemotherapy can alter the original leukemic clone and subsequently amplify the neoplastic subclone of a different phenotype as clonal selection process [4]. In addition, stem cell plasticity can play a role in the lineage switch. Also, the initial neoplastic clones can convert to a new phenotype without altering the cell genotype [15]. However, an acute lineage switch is very rare and both IgH and TCRg rearrangements have been found to be associated with this phenomenon [4].

In the present case, the AML diagnosis was in 2014, and myeloid next generation sequencing was not available at our institution that time; nevertheless, it is now standard on all cases. Our patient received a topoisomerase II inhibitor (daunorubicin) for induction chemotherapy, and an antimetabolite agent for conditioning therapy. In our case, the patient did not carry the BCR-ABL translocation (she was Philadelphia chromosome negative) and had a normal chromosomal study. While 8% of the therapy-related ALL can also exhibit a normal karyotype, topoisomerase II inhibitor related ALL is possibly support our diagnosis of therapy-related ALL in our patient. Moreover, the patient’s diagnosis of ALL more than 5 years after the initial diagnosis, with different leukemic clones suggest that lineage switch is unlikely.

Therapy related leukemia is associated with poor prognosis and allogeneic bone marrow transplant is suggested. With the advancement of targeted treatment, an increase in survival of AML patients has been observed in the last few years. It is important keep in mind the risk of treatment-related cancer development among the cancer survivors. We recommend classifying the therapy-related ALL as a distinct category which will guide us to streamline the treatment strategies and establish a clinical guideline specific for this condition. Furthermore, it is also necessary to obtain comprehensive molecular profiling to explore a targeted treatment option for therapy-related ALL.

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5. Informed consent

The patient provided informed consent for the inclusion of her data in this report. The patient understood that the results will be fully anonymized, and she cannot be identified via this report.

Declaration of Competing Interest

The authors confirm that there are no known conflicts of interest associated with this publication.

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