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

Sufana Shikdar *, Yuan Ying, Mohamad Khawandanah

Department of Hematology/Oncology, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, United States

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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 Flowcytometry, 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.

* Corresponding author at: Hematology/Oncology fellow, Department of Medicine, Division of Hematology-Oncology, Stephenson Cancer Center // University of Oklahoma Health Sciences Center, 800 NE 10th St., 6th Floor, Oklahoma City, OK 73104.
E-mail address: Sufana.shikdar@gmail.com (S. Shikdar).

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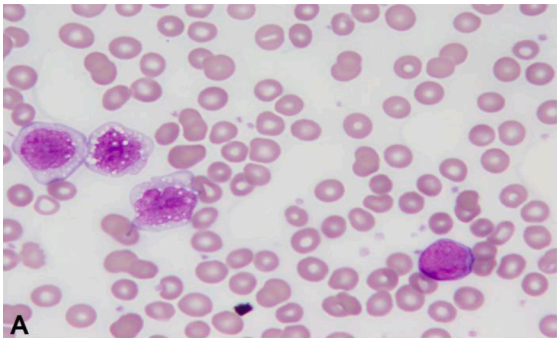

Fig. A. Peripheral blood smear showing a blast (far right), a promonocyte (far left), and two more mature monocytes (Wright stain, 100X in oil immersion).

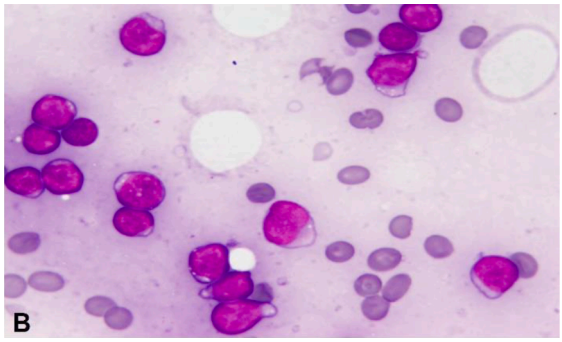

Fig. B. Touch imprint showing variably sized blasts with relatively little cytoplasm (Wright stain, 100X in oil immersion).

Table 1
HemaVision panel that detects the following recurrent chromosomal rearrangements associated with leukemia.

Translocations	Genes involved
t(5;17) (q35;q21)	NPM1-RARA
t(12;22) (p13;q11)	ETV6-MN1
t(6;9) (p23;q34)	DEK-NUP214
t(15;17) (q24;q21)	PML-RARA
t(6;11) (q27;q23)	MLL-MLLT4
inv(16) (p13;q22)	CBFB-MYH11
t(8;21) (q22;q22)	RUNX1-RUNX1T1
t(16;21) (p11;q22)	FUS-ERG
t(9;9) (q34;q34)	SET-NUP214
t(17;19) (q22;p13)	TCF3-HLF
t(9;11) (p22;q23)	MLL-MLLT3
t(X;11) (q13;q23)	MLL-FOXO4
Translocations	Genes involved
del1(p32)	STIL-TAL1
t(9;12) (q34;p13)	ETV6-ABL1
t(1;11) (p32;q23)	MLL-EPS15
t(9,22) (q34;q11)	BCR-ABL1
t(1;11) (q21;q23)	MLL-MLLT11
t(10;11) (p12;q23)	MLL-MLLT10
t(1;19) (q23;p13)	TCF3-PBX1
t(11;17) (q23;q21)	MLL-MLLT6
t(3;5) (q25;q34)	NPM1-MLF1
t(11;17) (q23;q21)	ZBTB16-RARA
t(3;21) (q26;q22)	RUNX1-MECOM
t(11;19) (q23;p13.1)	MLL-ELL
t(4;11) (q21;q23)	MLL-AFF1
t(11;19) (q23;p13.3)	MLL-MLLT1
t(5;12) (q33;p13)	ETV6-PDGFRB
t(12;21) (p13;q22)	ETV6-RUNX1

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 + 3+cladribine (daunorubicin 60 mg/m^2+ cytarabine 200 mg/m^2/d + cladribine 5 mg /m^2) was initiated. A complete response (CR) was achieved after one cycle of induction. Then she received 4 cycles of high dose cytarabine (HiDAC) consolidation. NPM1 was not detected after induction or completion of therapy for AML and her CR persisted for 5 years.

In 2020, she presented with pancytopenia with a white blood cell count of 2.6 × 10^9/ L (2% blasts), hemoglobin 8.9 g/dL, and platelets 7 × 10^9/L. Flow cytometry was not performed due to limited marrow aspirate but the cytogenetics, and FISH for t(9;22) were performed from the biopsy touch imprint. The biopsy touch imprint from 2020 showed a relatively monotonous population of variably sized lymphoid cells with immature nuclear chromatin, one or more nucleoli, and scant cytoplasm (Fig. B). Immunohistochemical staining of the bone marrow biopsy showed that these lymphoid cells were positive for CD34, TdT, CD20, pax-5, CD79a, and CD10 and negative for myeloperoxidase and CD163. These findings were consistent with B lymphoblastic leukemia. FISH was negative for 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, Oncovrin, methotrexate and 6-mercaptopurine).

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]. The pathogenesis of therapy-related ALL is associated with DNA damage and cytogenetic abnormalities in the form of chromosomal aberration, gene rearrangement and chromosomal instability [9,11]. 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

inhibitors. In addition, myeloid mutation pattern (ie. DNMT3A, RUNX1), lymphoid mutation (ie. ASXL1, CDKN2A) and germline mutation (BRCA1, 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 gene 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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References

[1] B. Bouchacourt, C. Zemmour, J. Rey, E. d'Incan, A. Charbonnier, B. Mohty, et al., Post-remission therapy of adults aged 60 and older with acute myeloid leukemia in first complete remission: role of treatment intensity on the outcome, Ann. Hematol 99 (4) (2020) 773–780.
[2] K.B. Ghimire, B.K. Shah, Second primary malignancies in adult acute myeloid leukemia-A US population-based study, Anticancer Res. 34 (7) (2014) 3855–3859.
[3] P. Chevallier, C. Al Nawakil, S. Vigouroux, P. Talmant, J.L. Harousseau, R Garand, Two cases of acute lymphoblastic leukaemia following acute myeloid leukaemia, Leuk. Res. 32 (6) (2008) 1001–1003.
[4] A. Lounici, P. Cony-Makhoul, P. Dubus, F. Lacombe, J.P. Merlio, J. Reiffers, Lineage switch from acute myeloid leukemia to acute lymphoblastic leukemia: report of an adult case and review of the literature, Am. J. Hematol. 65 (4) (2000) 319–321.
[5] B.G. Park, C.J. Park, S. Jang, E.J. Seo, H.S. Chi, J.H. Lee, Erythroleukemia relapsing as precursor B-cell lymphoblastic leukemia, Korean J. Clin. Lab. Sci. 31 (2) (2011) 81–85.
[6] C. Saygin, A. Kishtagari, R.D. Cassaday, N. Reizine, I. Yurkiewicz, M. Liedtke, et al., Therapy-related acute lymphoblastic leukemia is a distinct entity with adverse genetic features and clinical outcomes, Blood Adv. 3 (24) (2019) 4228–4237.
[7] A.S. Rosenberg, A. Brunson, J.K. Paulus, J. Tuscano, T. Wun, T.H. Keegan, et al., Secondary acute lymphoblastic leukemia is a distinct clinical entity with prognostic significance, Blood Cancer 7 (9) (2017) e605.
[8] I. Aldoss, T. Stiller, N.C. Tsai, J.Y. Song, T. Cao, N.A. Bandara, et al., Therapy-related acute lymphoblastic leukemia has distinct clinical and cytogenetic features compared to de novo acute lymphoblastic leukemia, but outcomes are comparable in transplanted patients, Haematologica 103 (10) (2018) 1662.
[9] R. Matnani, V. Parekh, U. Borate, J. Brazelton, V. Reddy, D. Peker, Therapy-related B-lymphoblastic leukemia associated with P hiladelphia chromosome and MLL rearrangement: single institution experience and the review of the literature, Pathol. Int. 65 (10) (2015) 536–540.
[10] Berglund L. HV01-Screen CN, HemaVision screen. 2019. Accessed from https://dna-diagnostic.com/products/human/rt-qpcr/on February 12, 2022.
[11] I. Aldoss, D. Douer, V. Pullarkat, Therapy-related acute lymphoblastic leukemia: where do we stand with regards to its definition and characterization? Blood Rev. 37 (2019), 100584.
[12] S. Ishizawa, M.L. Slovak, L. Popplewell, V. Bedell, J.E. Wrede, N.H. Carter, et al., High frequency of pro-B acute lymphoblastic leukemia in adults with secondary leukemia with 11q23 abnormalities, Leukemia 17 (6) (2003) 1091–1095.
[13] J.M. Ribera, Therapy-related acute lymphoblastic leukemia, Haematologica 103 (10) (2018) 1581.
[14] E. Dorantes-Acosta, F. Arreguin-Gonzalez, C.A. Rodriguez-Osorio, S. Sadowinski, R. Pelayo, A. Medina-Sanson, Acute myelogenous leukemia switch lineage upon relapse to acute lymphoblastic leukemia: a case report, Cases J. 2 (1) (2009) 1–5.
[15] B.P. Hanley, E. Yebra-Fernandez, R. Palanicawandar, E. Olavarria, K.N. Naresh, Lineage switch from acute myeloid leukemia to T cell/myeloid mixed phenotype acute leukemia: first report of an adult case, Am. J. Hematol. 93 (12) (2018) E395–E397.