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REFERENCES

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-405.
2. Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood 2017;129:572-81.
3. Totadri S, Singh M, Trehan A, Varma N, Bhatia P. Keeping PACE with Ph positive to Ph-like detection in B-lineage acute lymphoblastic leukemia: a practical and cost effective (PACE) approach in a resource constrained setting. Indian J Hematol Blood Transfus 2018;34:595-601.
4. Thiele J, Laubert A, Vykoupil KF, Georgii A. Autopsy and clinical findings in acute leukemia and chronic myeloproliferative diseases--an evaluation of 104 patients. Pathol Res Pract 1985; 79:328-36.
5. Van de Louw A, Lewis AM, Yang Z. Autopsy findings in patients with acute myeloid leukemia and non-Hodgkin lymphoma in the modern era: a focus on lung pathology and acute respiratory failure. Ann Hematol 2019;98:119-29.
6. Vadillo E, Dorantes-Acosta E, Pelayo R, Schnoor M. T cell acute lymphoblastic leukemia (T-ALL): new insights into the cellular origins and infiltration mechanisms common and unique among hematologic malignancies. Blood Rev 2018;32:36-51.
7. Tasian SK, Loh ML. Understanding the biology of *CRLF2*-overexpressing acute lymphoblastic leukemia. Crit Rev Oncog 2011;16:13-24.
8. Bhatt VR, Viola GM, Ferrajoli A. Invasive fungal infections in acute leukemia. Ther Adv Hematol 2011;2:231-47.
9. Shi D, He J, Lv M, Liu R, Zhao T, Jiang Q. Phlegmonous gastritis in a patient with mixed-phenotype acute leukemia in the neutropenia phase during chemotherapy: a case report. Medicine (Baltimore) 2019;98:e17777.
10. Chiaretti S, Messina M, Foà R. BCR/ABL1-like acute lymphoblastic leukemia: how to diagnose and treat? Cancer 2019;125: 94-204.

Therapy-related acute myeloid leukemia in a patient with B-cell acute lymphoblastic leukemia

TO THE EDITOR: Secondary/therapy-related neoplasms, such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), occur infrequently in adult patients with acute lymphoblastic leukemia (ALL) [1]. Most frequently, therapy-related/secondary myeloid neoplasms are associated with breast cancer and lymphoproliferative diseases [2]. These patients frequently have complex karyotype including many structural abnormalities indicating a poor prognosis [3]. Here, we report a case of secondary AML in an adult patient with B-ALL on maintenance chemotherapy with an unusual complex karyotype.

A 60-year-old female presented in December 2015 with fever, generalized weakness, and dizziness in the last 2 months. On ultrasonography, she had mild splenomegaly. Complete blood count showed hemoglobin of 77 g/L, total leukocyte counts of 2.84×10^9/L and platelets of 70×10^9/L with 2% blasts in peripheral blood smear. Bone marrow aspirate smears were hemodiluted, showing fairly cellular imprint smears with 80% blasts (Fig. 1A). Bone marrow biopsy (Fig. 1B) showed sheets of blasts which are positive for CD10 (Dako, 56C6), PAX5 (Biogenix, ZP007) and negative for MPO and CD33 (Bio SB, RBT-CD33). On flow cytometric immunophenotyping (Fig. 1C), these blasts were positive for CD19, CD10, CD34, HLA-DR, CD22, CD71 (dim), and CD20 (partial), while they were negative for cCD3, cMPO, CD7, CD13, CD33, CD14, CD56, CD4, CD8, CD5, and CD3; these results were consistent with the diagnosis of precursor B-cell acute lymphoblastic leukemia (ALL). Karyotype at this time showed 46,XX. Real-time polymerase chain reaction for t(1;19)(q23 ;p13.3) or TCF-3-PBX1(E2A-PBX1), t(11;19)(q23;p13.3) or MLL-ENL, t(12;21)(p13;q22) or ETV6-RUNX1(TEL-AML1), t(4;11)(q21;q23) or MLL-AF4, t(9;11)(p21-22;q23) or (MLL-AF9), and BCR-ABL1 were negative. She was started on chemotherapy according to the UK ALL protocol. The chemotherapeutic drugs included in the UK ALL treatment regimen were vincristine, daunorubicin, L-asparaginase, prednisolone, and intrathecal methotrexate. Bone marrow after induction therapy was in morphological remission and minimal residual disease by flow cytometry was negative (<0.01%). In February 2017, bone marrow after consolidation therapy was also in morphological remission and minimal residual disease by flow cytometry was negative, and she was started on maintenance chemotherapy. However, in February 2019, she presented with persistent cough. Complete blood count showed hemoglobin of 85 g/L, total leukocyte count of

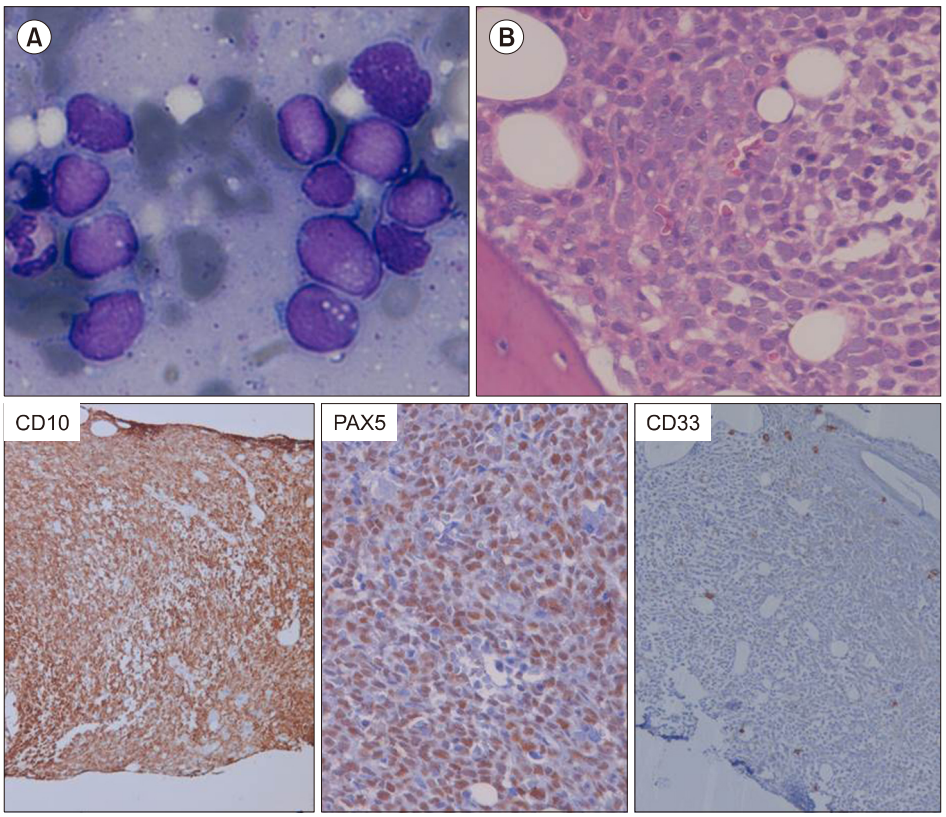

Fig. 1. Bone marrow aspirate showed lymphoblasts with scanty agranular cytoplasm **(A)**. Bone marrow biopsy (Haematoxylin and Eosin stain, ×400) with IHC showed positivity for CD10 and PAX5 and negativity for CD33 **(B)**.

1.19×10^9/L, and platelet count of 68×10^9/L with peripheral blood smear showing 15% blasts. Bone marrow aspirate showed 50% blasts (Fig. 2A) which are larger in size and have abundant granular cytoplasm. On bone marrow biopsy (Fig. 2B), these blasts were positive for CD34 (Dako, QBEnd10), CD33 (Bio SB, RBT-CD33), and CD117 (Biogenix, YR145), and negative for CD10 (Dako, 56C6), CD79a (Dako, JCB117), and PAX5 (Biogenix, ZP007). On flow cytometry (Fig. 1D), these blasts were positive for CD45, CD34, CD13, CD33, CD117 (partial), HLA-DR, CD38, and CD19 and negative for cCD3, cCD79a, CD7, CD22, CD10, CD14, CD64, CD123, CD11b, CD56, and CD58, consistent with the diagnosis of AML. Karyotype, which in December 2015 showed 46,XX, now showed a highly complex karyotype (Fig. 3A). Real-time quantitative PCR for *PML- RARA, AML1-ETO, CBFB - MYH11, BCR-ABL, FLT3* [*ITD & TKD* (*D835*)], *NPM1,* and *KIT* gene mutations were negative. She was started on the 7+3 regimen of AML induction chemotherapy. During the stay, she was supported with multiple pRBC and platelet transfusions. She was shifted to the intensive care unit (ICU) on Day 12 due to repeated hypoglycemia and respiratory distress. She had multiple organ failure and succumbed on Day 16 of induction chemotherapy. This is a case of a patient diagnosed with B-ALL on multiparametric analysis in December 2015, which responded to therapy and was on maintenance therapy, but 4 years later developed secondary AML showing all features consistent with the diagnosis of AML. However, at this time, she showed a complex karyotype with many structural abnormalities.

Secondary leukemia with morphologic and immunophenotypic features distinct from the primary leukemia following chemotherapy may be secondary to chemotherapy (therapy-related), which is clonally unrelated to the primary neoplasm or a lineage switch which represent clonal evolution of the primary neoplasm. Genetic analysis in the secondary leukemia is required to diagnose whether the second neoplasm is related to the primary neoplasm or not by comparing cytogenetic and/or molecular abnormalities between the primary and secondary leukemia. Diagnosis of lineage switch requires retention of a genetic signature in the secondary leukemia with the switched phenotype [4]. In our cases, cytogenetic analysis demonstrated a change in cytogenetics between the initial B-ALL and relapsed AML. Therapy-related AML is caused by an acquired somatic mutation in hematopoietic stem cells and progenitor cells induced by cytotoxic chemoradiotherapy. Majority of therapy-related leukemia result from the use of alkylating agents, topoisomerase-II inhibitors, and rarely antimetabolites. Daunorubicin, a topoisomerase-II inhibitor, was used in our patient, which may have induced development of secondary AML. The risk of a secondary neoplasm from ALL in adults is lower than that in children; the majority of cases are AML and MDS, non-Hodgkin's lymphoma (NHL),

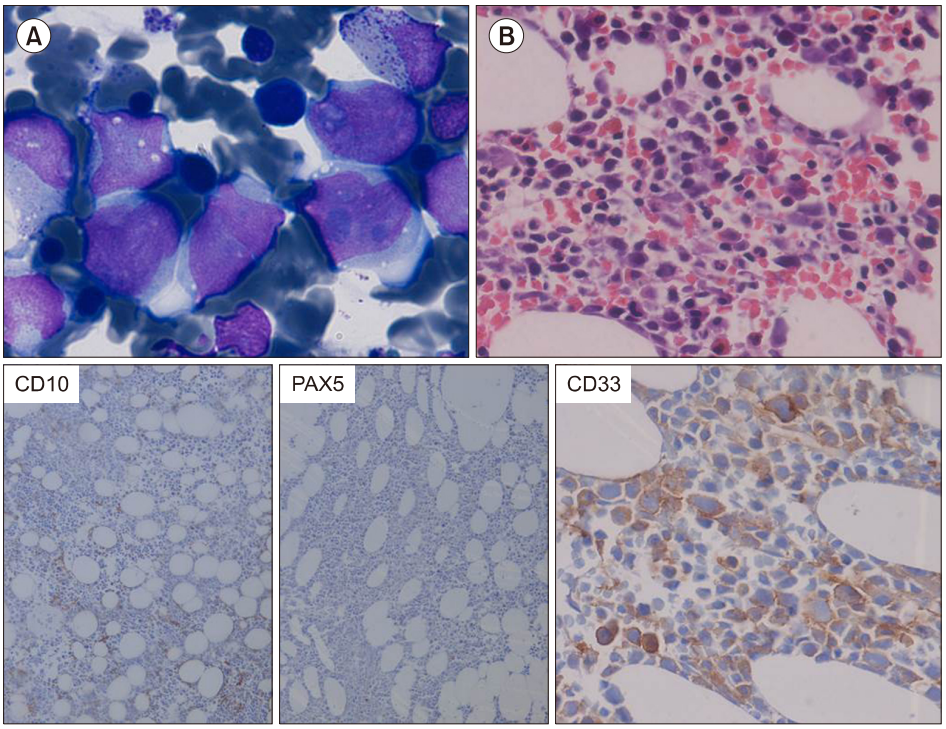

Fig. 2. Bone marrow aspirate showed myeloblasts that were larger in size and had moderate granular cytoplasm **(A)**. Bone marrow biopsy (Haematoxylin and Eosin stain, ×400) with IHC showed positivity for CD33 and negativity for CD10 and PAX5 **(B)**.

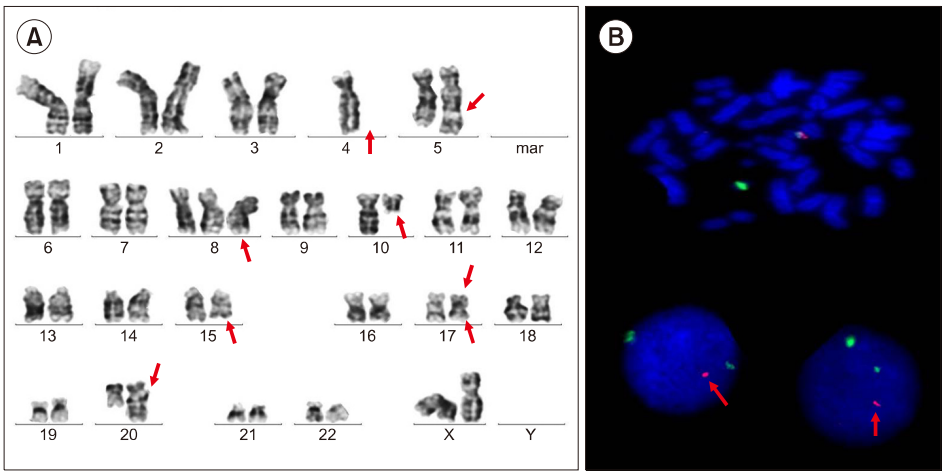

Fig. 3. Karyogram showed 46,XX, -4, +8, der(17) t(15;17)(q24;q23), del(17)(p13), der(20) t(10;20) (q11.2; q13.3), +der(11)t(5;11)(q31;q13), using GTG staining and banding method, ×100 oil immersion, and Carl Zeiss Axioscope Z2, and was processed using IKAROS software **(A)**. Interphase nuclei and metaphase showed monoallelic deletion of TP53 gene localized on 17p13.1 by FISH using LSI 17p13.1(TP53/ CEN17) deletion probe [TP53-red, CEN17-green], Zytovysion, Germany **(B)**.

or rarely solid malignancies. Pagano *et al* [5]. reported a median latency of 74 months for the diagnosis of ALL to a secondary hematological neoplasm in adult patients. Tavernier *et al.* [6] reported that the development of all secondary neoplasms was within 0.5 to 13.8 years (median, 4.5 yr) after the diagnosis of ALL, with an overall cumulative risk of secondary neoplasms being 2.1% at 5 years, 4.9% at 10 years, and 9.4% at 15 years. For hematological neoplasms, they reported that the cumulative risk of a second malignancy was 1.8% at 5 years, 2.2% at 10 years, and 3.3% at 18 years [7]. In our case secondary AML developed after 38 months of ALL diagnosis. Complex karyotype is more common in secondary or therapy-related AML rather than in de novo AML. Monosomy 5, del(5q), and monosomy 7 are are also more common in these patients than de novo AML. In our case, the karyotype showed a highly complex karyotype with monosomy 4 and trisomy 8 and 11. An unbalanced translocation between chromosomes 5q and 11q was seen. There was a deletion in the short arm of chromosome 17 at breakpoint p13, which was confirmed on fluorescence in situ hybridization (FISH) using the TP53 deletion probe. A balanced translocation between long arm of chromosome 15q24 and long arm of chromosome 17q23 was also noted. This translocation is different from t(15;17)

of acute promyelocytic leukemia, which was seen at breakpoint 15q24 and 17q21. Another balanced translocation between long arm of chromosome 10 and long arm of chromosome 20 was also identified.

This case highlights an unusual case of secondary AML in an adult patient with B-ALL during maintenance chemotherapy, which evolved from a normal karyotype during ALL to a highly complex karyotype as AML developed. It also highlights the importance of performing immunophenotyping at the time of relapse in every case of acute leukemia to identify any change in immunophenotyping or any lineage switch to administer the correct therapy and to analyze minimal residual disease on follow-up.

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REFERENCES

1. Verma D, O'Brien S, Thomas D, et al. Therapy-related acute myelogenous leukemia and myelodysplastic syndrome in patients with acute lymphoblastic leukemia treated with the hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimens. Cancer 2009;115:101-6.
2. Morton LM, Dores GM, Tucker MA, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood 2013;121:2996-3004.
3. Kayser S, Döhner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 2011;117:2137-45.
4. Wu B, Jug R, Luedke C, et al. Lineage switch between B-lymphoblastic leukemia and acute myeloid leukemia intermediated by "Occult" myelodysplastic neoplasm: two cases of adult patients with evidence of genomic instability and clonal selection by chemotherapy. Am J Clin Pathol 2017;148:136-47.
5. Pagano L, Annino L, Ferrari A, et al. Secondary haematological neoplasm after treatment of adult acute lymphoblastic leukemia: analysis of 1170 adult ALL patients enrolled in the GIMEMA trials. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. Br J Haematol 1998;100:669-76.
6. Tavernier E, Le QH, de Botton S, et al. Secondary or concomitant neoplasms among adults diagnosed with acute lymphoblastic leukemia and treated according to the LALA-87 and LALA-94 trials. Cancer 2007;110:2747-55.
7. Grosicki S, Barchnicka A, Bodzenta E, Haus O, Jaśkowiec A. Secondary acute myeloid leukemia (sAML) immediately after intensive chemotherapy of acute lymphoblastic leukemia (ALL). J Leuk 2013;1:1000102.

Efficacy of ponatinib prior to and after allogeneic hematopoietic stem cell transplantation in an adolescent with chronic myeloid leukemia in blast phase

TO THE EDITOR: *BCR-ABL1* kinase domain mutations confer resistance to imatinib in chronic myeloid leukemia (CML) patients. Ponatinib is the only tyrosine kinase inhibitor (TKI) able to eradicate leukemic cells harboring the T315I mutation, which replaces a threonine with isoleucine within the ATP binding site of the tyrosine kinase protein [1]. However, the drug is currently only approved for adult CML patients, with limited reports of its use in children and adolescents. Here, we report on the efficacy of ponatinib before and after allogeneic hematopoietic stem cell transplantation (HSCT) in an adolescent patient with blast phase chronic myeloid leukemia (CML) who relapsed with the T315I mutation.

A 16-year-old male patient was diagnosed with B lymphoid blast phase (BP) CML, and received initial treatment with prednisolone combined with imatinib at 600 mg/day for 4 weeks. A follow-up bone marrow (BM) study showed complete hematologic response (CHR) with major cytogenetic response. While maintaining imatinib with the aim of undergoing allogeneic HSCT, the patient relapsed to accelerated phase (AP) 4 months after achieving initial CHR. Complete blood count at the time of AP relapse showed a white blood cell count of 11.77×10^9/L (8% blasts), hemoglobin 8.6 g/dL and platelet count of 82×10^9/L, while the BM showed 18% blasts (Fig. 1). The patient progressed to B lymphoid BP again one month later. Molecular studies for *BCR-ABL1* kinase domain mutations done at the time of AP relapse showed the T315I mutation. As ponatinib, the only TKI with efficacy against CML cells with the T315I mutation, is not approved for children and adolescents, the patient received a 4-drug reinduction regimen consisting of vincristine, daunorubicin, asparaginase and dexamethasone, as well as intrathecal chemotherapy; this resulted in second CHR, although the *BCR-ABL1* transcript value, reported as the ratio of *BCR-ABL1* to *ABL1* measured by real-time quantitative reverse transcription-polymerase