Acute B Lymphoblastic Leukemia Developing in Patients with Multiple Myeloma: Presentation of Two Cases

Multipl Myelom Hastalarında Akut B Lenfoblastik Lösemi Gelişimi: İki Olgu Sunumu

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To the Editor,

Therapy-related acute myeloid leukemias (t-AMLs) following therapy are well described in the literature, but only rare cases of therapy-related acute lymphoblastic leukemia (t-ALL) have been reported previously. Cases of multiple myeloma (MM) terminating in ALL are even rarer. Herein, we report the clinicopathological, immunological, cytogenetic, and molecular features of two patients diagnosed with B-cell acute lymphoblastic leukemia (B-ALL) and MM who presented with MM at the initial diagnosis.

Patient 1, a 68-year-old male, was diagnosed with MM in 2015. He received 2 cycles of PD (bortezomib and dexamethasone) with a good response, and then maintenance with thalidomide.

Patient 2, a 65-year-old female, was diagnosed with MM in 2012. She received 4 cycles of VAD (vincristine, epirubicin, and dexamethasone) with a partial response. She then relapsed and received treatment with one cycle of TAD (thalidomide, epirubicin, and dexamethasone). After that, she achieved complete remission. In 2016, the patient relapsed again. She continued treatment with BTD (bortezomib, dexamethasone, and thalidomide) and achieved partial response.

In 2017, the two patients both presented with leukopenia. Immunofixation electrophoresis showed monoclonal IgG and K light chain. The bone marrow was heavily infiltrated by lymphoblasts and a few malignant plasma cells. Flow cytometry analysis demonstrated that malignant plasma cells with CD38, CD138, and monoclonal K chain and B-cell lymphoblasts expressed CD10, CD19, CD34, HLA-DR, cCD79a, and CD33. No other aberrant expression of myeloid or T lymphocyte-associated antigens was identified (Figures 1A-1C). The female patient's G-banding cytogenetic results revealed a hypodiploid

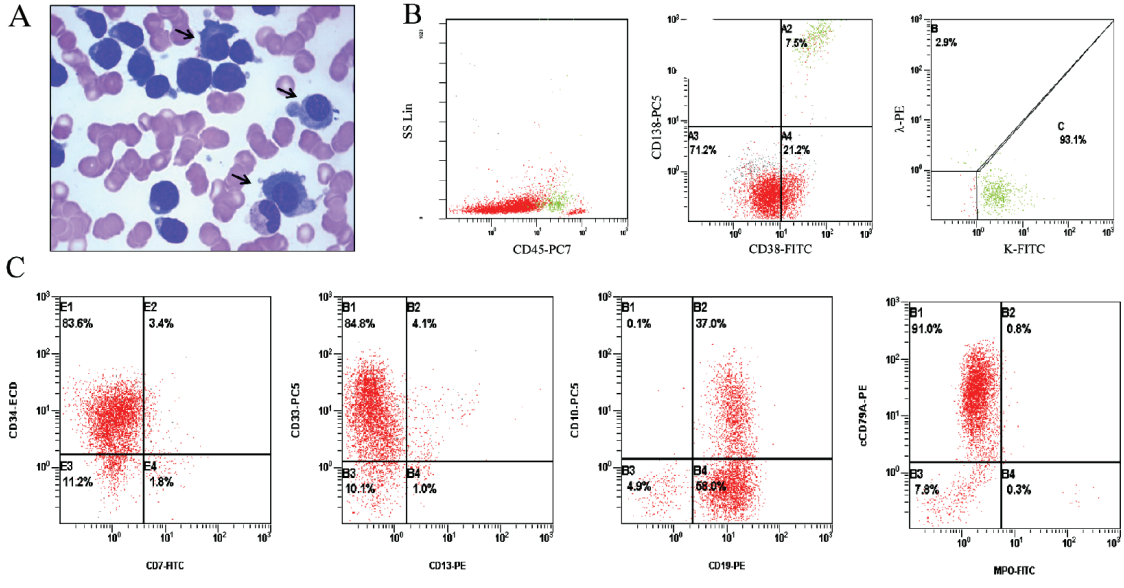

Figure 1. Patient 1: A) Black arrows point at malignant plasma cells, which are very different from other lymphoblasts (Wright-Giemsa staining, 100x). B) Malignant plasma cells were positive for CD38, CD138, and monoclonal kappa (green region of the scatter plot). C) The lymphoblasts were immunophenotyped as B-cell and expressed CD10, CD19, CD34, and cCD79a with aberrant coexpression of CD33. The morphologic and immunological characteristics of Patient 2 were similar.

Table 1. Clinical features of acute lymphoblastic leukemia in patients with previously treated multiple myeloma (MM) from our institution.

	Patient 1	Patient 2
Sex/age (years) at the time of MM diagnosis	Male/68	Female/65
Time interval between last therapy for MM and the ALL diagnosis	26 months	3 months
Laboratory findings		
WBC, $x10^9$/L	0.87	0.8
% Blasts, peripheral blood	0	0
Hb, g/L	79	99
Platelets, $x10^9$/L	56	105
Immunofixation electrophoresis	IgG/kappa	IgG/kappa
Serum free κ light chain (mg/L)	25.4	>163
Serum free λ light chain (mg/L)	17.1	5.76
Bone marrow findings		
BM cellularity	Hypercellular	Hypercellular
Immunophenotype	95% blasts (CD10, CD19, CD33, CD34, HLA-DR, cCD79a), 0.3% plasma cells (CD38, 138, monoclonal kappa)	86.3% blasts (CD10, CD19, CD33, CD34, HLA-DR, cCD79a), 7.5% plasma cells (CD38, 138, monoclonal kappa)
Cytogenetics	Not detected	MLL rearrangement (-), bcr-abl (-)
PCR detection	(-)*	(-)*
Clinical diagnosis	MM with B-ALL	MM with B-ALL
Therapy for original disease (MM)	Bortezomib, dexamethasone	Vincristine, epirubicin, dexamethasone, thalidomide, epirubicin, dexamethasone, bortezomib-dexamethasone, thalidomide
Therapy for MM with B-ALL	Declined any treatment due to poor performance status and died four months later	Treated with low-dose chemotherapy (vincristine, epirubicin, dexamethasone, bortezomib); did not respond well and died one month later

(-)*: RT-PCR for detection of 30 fusion genes was negative (including *MLL-AF9, MLL-AF4, MLL-ENL, MLL-AF10, MLL-SEPT6, MLL-ELL, MLL-AF17, MLL-AF1q, MLL-AF1p, MLL-AF6, PML-RARA, NPM-RARA, PLZF-RARA, AML1-ETO, AML1-MDS1/EVI1, AML1-MTG16, AML1-EAP, TEL-AML1, TEL-PDGFRB, TEL-ABL, E2A-PBX1, E2A-HLF, BCR-ABL, CBFβ-MYH11, SIL-TAL1, FIP1L1-PDGFRA, DEK-CAN, SET-CAN, TLS-ERG*, and *NPM-MLF*).

RT-PCR: Reverse transcription polymerase chain reaction, MM: multiple myeloma, ALL: acute lymphoblastic leukemia.

and complex karyotype. Reverse transcription-polymerase chain reaction for detection of fusion genes in the two patients was negative. Both patients were diagnosed with B-ALL with MM. The male patient declined any treatment due to poor performance status and died four months later. The female patient was treated with low-dose chemotherapy (vincristine, epirubicin, dexamethasone, and bortezomib) and did not respond well; she died one month later. The clinical features of the two patients are summarized in Table 1.

It has been reported in the literature that therapy-related acute leukemia comprises 2 major types: alkylating agent/radiotherapy-related and topoisomerase II inhibitor-related [1]. Alkylating agent-related acute leukemia is associated with abnormalities of chromosomes 5 and/or 7, while topoisomerase II inhibitor-related acute leukemia has been linked to 11q23 [2,3]. The female patient received a topoisomerase II inhibitor while the male did not, and neither of them showed specific genetic abnormalities. Intriguingly, the clinical, morphologic, and immunological characteristics of the two patients were similar. MM is a plasma cell neoplasm derived from mature B-lymphocytes, whereas B-ALL is a B-cell neoplasm derived from early B-precursors. It is possible that MM and B-ALL may derive from the same stem cell clones, or MM cells dedifferentiate into immature B cells that develop B-ALL [4]. They may have identical karyotypes and immunophenotyping, and they may share some cytogenetic abnormalities [5,6]. The possibility of MM and B-ALL deriving from two independent clones cannot be excluded, either. Future studies such as molecular and cytogenetic studies to explore their relationship would be intriguing.

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Keywords: Acute lymphoblastic leukemia, Multiple myeloma, Therapy-related, Genetics, Immunophenotyping

Anahtar Sözcükler: Akut lenfoblastik lösemi, Multipl myelom, Terapi ilişkili, Genetik, İmmünfenotipleme

Conflict of Interest: The authors of this paper have no conflicts of interest including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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ALK+ Anaplastic Large Cell Lymphoma of Null Cell Phenotype with Leukemic Transformation and Leukemoid Reaction

Lösemi Transformasyonu ve Lökomoid Reaksiyon ile Giden "Null" Hücre Fenotipli ALK+ Anaplastik Büyük Hücreli Lenfoma

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To the Editor,

Anaplastic large cell lymphoma (ALCL) frequently involves both nodal and extranodal sites and is rarely leukemic. A 21-year-old male presented with abdominal pain. His complete blood count, which had been normal four months ago, showed increasing white cell counts from $14.9x10^9$/L to $95.5x10^9$/L in a month, with neutrophils ranging from 81.6% to 89.6%. Blood cultures were negative. Laparoscopic nodal biopsy showed sheets of medium-sized lymphocytes diffusely expressing CD30, TIA-1, granzyme B, and ALK, but not T-cell markers including CD2, CD3, CD4, CD5, CD7, CD8, and βF1, indicating ALK+ ALCL of null cell phenotype. Bone marrow biopsy showed two small aggregates of tumor cells in a background of normal tri-lineage hematopoiesis. ALK immunostaining revealed singly scattered positive cells (Figure 1A) in addition to those in small aggregates. The staining pattern was both nuclear and cytoplasmic, indicating translocation t(2;5)(p23;q35). We retrospectively reviewed the blood smear and found that 4.5% of the last peripheral smear were tumor cells, which were overlooked by the clinical laboratory. The leukemic cells were large with vesicular nuclei, irregular nuclear contours, and