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Lab Med Online
Vol. 11, No. 3: 211-213, July 2021
https://doi.org/10.47429/lmo.2021.11.3.211

진단혈액학 LMO

핵형분석에서 t(15;17) 결여된 치료관련 급성전골수구성백혈병 1예 보고

A Case of Therapy-related Acute Promyelocytic Leukemia Lacking t(15;17) on Karyotype

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Dear Editor,

Acute promyelocytic leukemia (APL) comprises 5–8% of acute myeloid leukemia (AML) [1]. The t(15;17)(q22;q12) with PML-RARA fusion transcript is reported in 90–95% of APL cases, while other structural rearrangements, including submicroscopic translocation, have been noted in the remaining cases [2]. Therapy-related myeloid neoplasms (t-MNs) comprising therapy-related AML, myelodysplastic syndrome (MDS), and myelodysplastic/myeloproliferative neoplasms (MDS/MPNs) account for 10–20% of all cases of AML, MDS, and MDS/MPNs. Approximately 8–21% APL cases are therapy-related APL (t-APL), and cryptic PML-RARA rearrangement in t-APL has been rarely reported [3, 4]. Here, we report a case of cryptic t-APL patient.

A 66-year-old female patient was admitted to hospital for oral bleeding. In 2016, she was diagnosed with triple-negative breast cancer, left (stage 3, pT2N3M0, P53: 90%, Ki-67: 60%, estrogen receptor: negative, progesterone receptor: negative, human epidermal growth factor receptor 2: negative) and underwent breast conserving surgery with axillary lymph node dissection. After surgery, the patient was treated with six cycles of adjuvant chemotherapy (docetaxel, doxorubicin, and cyclophosphamide) for 3 months with radiation therapy.

The result of initial complete blood count revealed a hemoglobin level of 9.7 g/dL, white blood cell (WBC) count of 48.2×10^9/L (segmented neutrophils, 5%; band form neutrophils, 0%; lymphocytes, 3%; monocytes, 2%; eosinophils, 1%; and blast, 86%), and platelet count of 48×10^9/L. The bone marrow aspirate was filled with morphologically abnormal myeloblasts/promyelocytes, which accounted for 93% of all nucleated cells. These cells had azurophilic granulation and ovoid nuclei; a few of them had Auer rods (Fig. 1A). Bone marrow biopsy demonstrated a hypercellular marrow approaching 95% cellularity. Flow cytometry analysis showed that the blasts were positive for CD13 (bright); CD33, CD117, CD2, CD56 (intermediate); CD54, CD41, and CD7 (dim); and negative for CD34, TdT, HLA-DR, CD15, CD14, CD19, CD19, cCD22, CD3, cCD3, and myeloperoxidase (MPO). The karyotype of this patient was 46,XX in all 20 metaphase cells analyzed (Fig. 1B). Fluorescence in situ hybridization (FISH) analysis using a dual-color dual-fusion PML/RARA probe revealed two fusion signals in 496 out of 500 interphase cells; nuc ish (PML,RARA)×3 (RARA con PML×2)[496/500] (Fig. 1C). Next-generation-sequencing screening for 49 genes related to AML identified internal tandem repeats of the *FLT3* gene (FLT3-ITD); the variant allele frequency (VAF) was 39% at diagnosis, as confirmed by fragment analysis. Reverse-transcriptase polymerase chain reaction (RT-PCR) for PML-RARA rearrangement showed positive result for a fusion transcript (short

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Received: August 20, 2020
Revision received: October 6, 2020
Accepted: October 15, 2020

This article is available from https://www.labmedonline.org

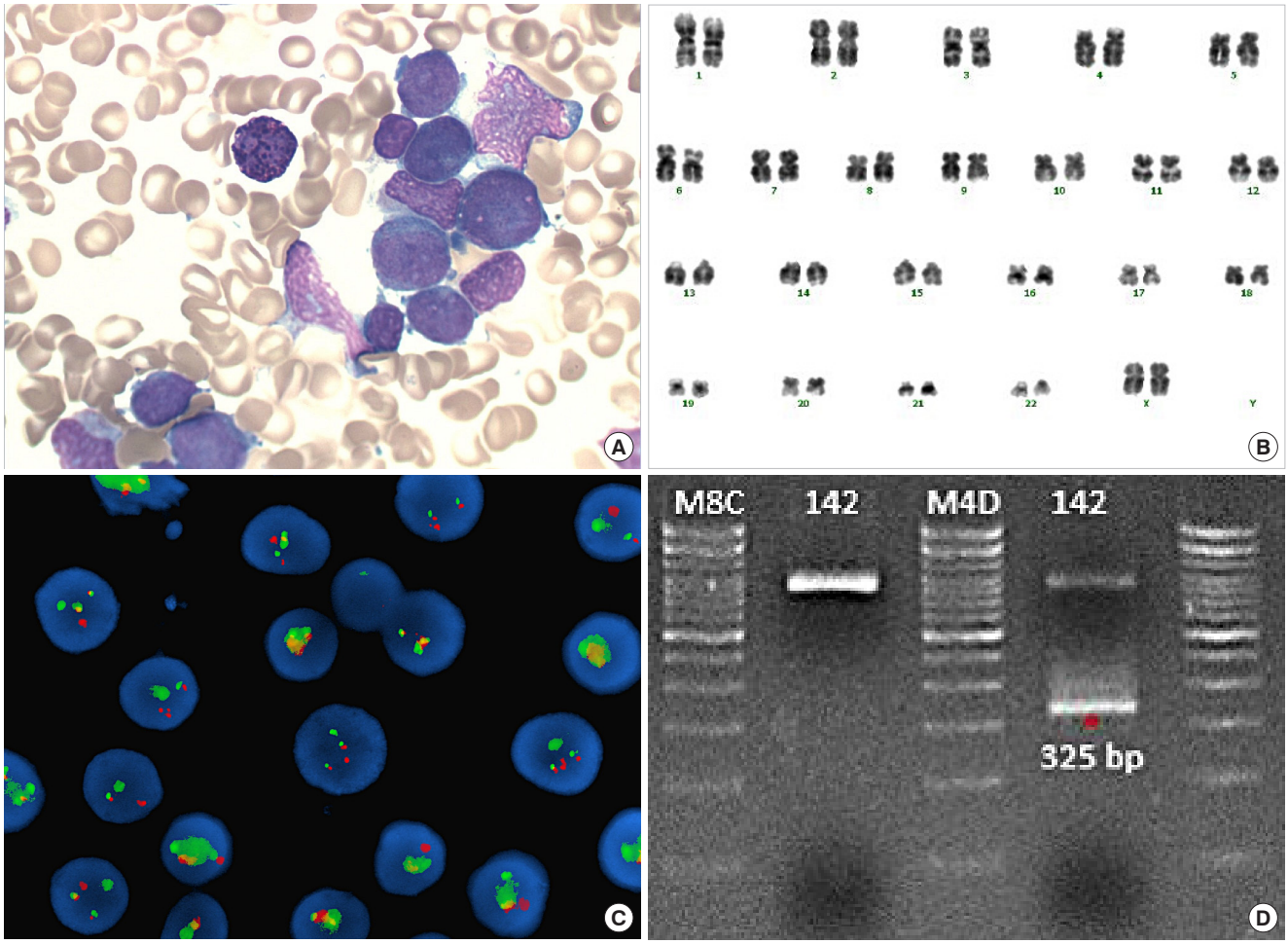

Fig. 1. (A) Granular promyelocytes from bone marrow aspiration smear (Wright-Giemsa stain, ×1,000). (B) Giemsa-banding karyotyping of the bone marrow cells at diagnosis reveals the karyotype 46,XX. (C) Fluorescence in situ hybridization (FISH) study using a *PML/RARA* dual-color, dual-fusion translocation probe at diagnosis. Fusion signals were observed. (D) RT-PCR for *PML/RARA* fusion transcripts. S-form (325 bp) *PML/RARA* chimeric transcripts were amplified.
Abbreviation: RT-PCR, reverse-transcriptase polymerase chain reaction.

form, bcr3) (Fig. 1D). Therefore, the patient was diagnosed with t-APL. Treatment with all-trans-retinoic acid (ATRA) was initiated. On the 6th day of admission, pulmonary hemorrhage and pneumonia worsened, which led to pneumonic septic shock and multi-organ failure. The patient died at day 35 after hospitalization.

To reduce life-threatening complications such as disseminated intravascular coagulation and improve treatment results, accurate and rapid diagnosis of APL is imperative and arsenic trioxide and ATRA and arsenic trioxide (ATO)-based therapies must be initiated. Chromosome analysis can detect PML-RARA fusion in about 90% of APL cases but not in cryptic APL [5], necessitating FISH or PCR to detect the abnormality of the fusion transcript. Further, APL that is PML-RAR negative in FISH is rare but does exist [6]. It seems important to perform RT-PCR test as well as chromosome analysis and FISH for clinical assessment of PML-RARA.

Mutations involving *FLT3*, including internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations, occur in 35–40% of APL. The FLT3-ITD mutation is the most common and associated with higher WBC counts, microgranular granulocytes, and bcr3 breakpoint in PML [7].

The difference in survival outcomes in de novo APL or t-APL patients is controversial. In a previous study, the outcome of t-APL was similar to that of de novo APL [4]. Nevertheless, for all subtypes of AML, clinical outcomes were worse for patients with therapy-related disease [8]. Elevated WBC counts predict worse prognosis, but the FLT3-ITD mutation of APL has no significant effect

https://doi.org/10.47429/lmo.2021.11.3.211

on prognosis. However, a higher FLT3-ITD mutation/wild-type ratio (≥0.5%) indicated adverse prognosis [9].

To our knowledge, this is the first report of cryptic t-APL in Korea. Further study is warranted to estimate the prevalence of cryptic t-APL and to evaluate response to treatment and prognosis in t-APL patients.

Conflicts of Interest

None declared.

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