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A Case of Therapy-Related Acute Myeloid Leukemia With a Normal Karyotype After Sustained Molecular Complete Remission of Acute Promyelocytic Leukemia

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Dear editor,

Given that the current therapeutic regimen for acute promyelocytic leukemia (APL) includes idarubicin (a topoisomerase II inhibitor) and methotrexate (an alkylating agent), therapy-related acute myeloid leukemia (t-AML) can develop after APL treatment, and several cases have been reported to date [1-13]. Most of these cases involved the development of secondary clonal cytogenetic abnormalities following successful treatment of APL, and, to our knowledge, only 2 cases involving a normal karyotype at t-AML diagnosis have been reported [5, 12]. We report a rare case of t-AML with a normal karyotype after sustained molecular complete remission of APL.

A 58-yr-old man was admitted in January 2010 because of gingival bleeding and thrombocytopenia. His hemogram results were as follows: White blood cell (WBC) count, 11.4×10^9/L; Hb, 12.3 g/dL; and platelets, at 51×10^9/L. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were within the reference range (12.5 sec for PT and 25.8 sec for aPTT). The fibrinogen level was decreased (156 mg/dL), and the levels of both D-dimer and fibrinogen degradation product were increased (23.0 μg/mL and 43.9 μg/mL, respectively). A peripheral blood smear showed a large number of blasts (60%) with abundant cytoplasmic granules, and bone marrow (BM) aspiration revealed a scattered distribution of blasts (60%) and abnormal promyelocytes (16%) with occasional Auer rods. The patient's karyotype was 46,XY,t(15;17;19)(q22;q21q13.3)[20], consistent with APL with a t(15;17) variant clone. Reverse transcriptase polymerase chain reaction (RT-PCR) was used to detect a breakpoint cluster region 1 (bcr1) isoform of the *PML-RARα* fusion transcript. The *PML-RARα* fusion transcript was quantified in the BM sample, using the Real-Q *PML-RARα* Quantification kit (BioSewoom, Seoul, Korea), showing a *PML-RARα/ABL* ratio of 0.91. On the basis of these results, the patient was diagnosed as having APL, and induction chemotherapy with idarubicin (10 mg/m^2 for 4 days) and ATRA (200 mg/m^2 for 7 days) was administered. After 4 weeks of treatment, the patient acquired complete remission (CR) and his *PML-RARα/ABL* quantification ratio reduced to 0.006. He was finally assessed as negative in April 2010. Maintenance chemotherapy with methotrexate (15 mg/m^2 per week) and 6-mercaptopurine (90 mg/m^2 per day) was administered for 20 months, and the *PML-RARα* fusion transcript was not detected for 32 months.

In March 2013, the patient was re-admitted because of the presence of blasts in the blood. The morphology of blasts in the peripheral blood (37%) and BM (23.2%) (large amount of cytoplasm without azurophilic granules) was different from that

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Table 1. Comparison of the characteristics of two previously reported t-AML cases with a normal karyotype after sustained molecular complete remission of acute promyelocytic leukemia and the present case

Cases	Sex	Age at APL diagnosis (yr)	Interval from APL diagnosis to development of t-AML	Karyotype at t-AML	Type of t-AML	Outcome
Latagliata et al. [5]	F	31	24 months	46,XX	Not clarified	Alive in CR after allogeneic SCT
Montesinos et al. [12]	F	68	39 months	46,XX	AML M5	Death after 3 months from diagnosisof t-AML
The present case	M	58	38 months (32 months of molecular CR)	46,XY	AML M2	Alive in CR after allogeneic SCT

Abbreviations: APL, acute promyelocytic leukemia; t-AML, therapy-related acute myeloid leukemia; F, female; M, male; CR, complete remission; SCT, stem cell transplantation.

noted at diagnosis of APL. The HemaVision (DNA Technology, Aarhus, Denmark) result was negative for all detectable fusion transcripts. The patient's karyotype had changed to 46,XY[20], indicating a loss of the APL clone, and the assay for *PML-RARα* in both peripheral blood and BM samples was also negative. On the basis of these findings, the patient was diagnosed as having t-AML with a normal karyotype, relapsed as the FAB M2 subtype. Comparison of the characteristics of two previously reported t-AML cases with a normal karyotype after sustained molecular CR of APL and our case is summarized in Table 1.

The median time from molecular CR of APL to the development of t-AML has been reported to be 43 months (range, 17-68 months) [13], and the latency period (32 months) from the achievement of molecular CR to the development of t-AML was similar in the present case. Patients who developed t-AML have been reported to show partial or complete deletion of chromosome 5 or 7, which is associated with prior alkylating agent therapy in most cases [4, 5, 12, 14]. Balanced translocations involving *MLL*/11q23 regions, which are associated with prior topoisomerase II inhibitor therapy, have been observed in some cases [12]. Most cytogenetic abnormalities described in reported cases of t-AML derived after APL treatment are high-risk abnormalities (e.g., monosomy 5, monosomy 7, and complex karyotype) [6-13]. Therefore, cases of t-AML with a normal karyotype after sustained molecular CR of APL are thought to be extremely rare, and only 2 such cases have been reported to date [5, 12]. In conclusion, we report a rare case of t-AML with a normal karyotype after sustained molecular CR of APL.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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