



Cryptic e1a2 *BCR-ABL1* Fusion With Complex Chromosomal Abnormality in *de novo* Myelodysplastic Syndrome

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Dear Editor

MDS is a clonal disorder marked by ineffective hematopoiesis, cytopenias, clonal chromosomal abnormalities, and a variable predilection to undergo clonal evolution to AML. Multiple genetic aberrations occur during the clonal evolution of MDS, and in the majority of cases, somatic mutations result from the deletion of all or part of a chromosome [1].

BCR-ABL1 is a hybrid from the *ABL1* gene on chromosome 9 and the *BCR* gene on chromosome 22. The fusion protein encoded from this gene has strong tyrosine kinase activity and is involved in the pathogenesis of several hematologic disorders. *BCR-ABL1* genes are categorized into three types, based on differences in the *BCR* gene's breakpoint, which appear to be related to the disease phenotype. The *BCR-ABL1* fusion gene is found in CML and in some cases of acute lymphoblastic leukemia [2]. However, reports on *BCR-ABL1*-positive MDS cases are extremely rare [3-6]. Here, we report an unusual case of MDS progressing to AML with an e1a2 *BCR-ABL1* fusion transcript and a complex karyotype, including monosomy 7.

A 65-yr-old man was admitted for evaluation of persistent pancytopenia with 9% blasts in the peripheral blood. He pre-

sented with general weakness and breathlessness. Evaluation of the bone marrow (BM) disclosed hypercellularity with mild erythroid hyperplasia, blasts count of 18%, and remarkable dysmatopoiesis (Fig. 1). Immunophenotype analysis of BM cells using flow cytometry showed that the blasts were positive (>20% of cells) for CD13 (45%), CD33 (97%), CD117 (68%), CD34 (97%), and HLA-DR (43%), and negative for other megakaryocytic and lymphoid markers. Multiplex reverse transcriptase polymerase chain reaction (RT-PCR) evaluation of total RNA isolated from BM cells (HemaVision kit; DNA-Diagnostic, Risskov, Denmark) indicated an e1a2 (p190 *BCR-ABL1*) rearrangement, confirmed on two independent cDNAs and via direct sequencing (Fig. 2). Quantitative RT-PCR analysis (Real-Q *BCR-ABL1* quantification kit; BioSewoom, Seoul, Korea) revealed the *BCR-ABL1* to *ABL1* transcript ratio to be 0.001339977. The fluorescence *in situ* hybridization signal for *BCR-ABL1* rearrangement was found in one interphase cell out of 296 analyzed cells (Fig. 1D). There was no evidence of other molecular abnormalities such as mutations in *JAK2* or calreticulin. Conventional cytogenetic analysis revealed a complex abnormality without the Philadelphia (Ph) chromosome: 44,XY,del(5)(q31),-7,del(12)(p12),-

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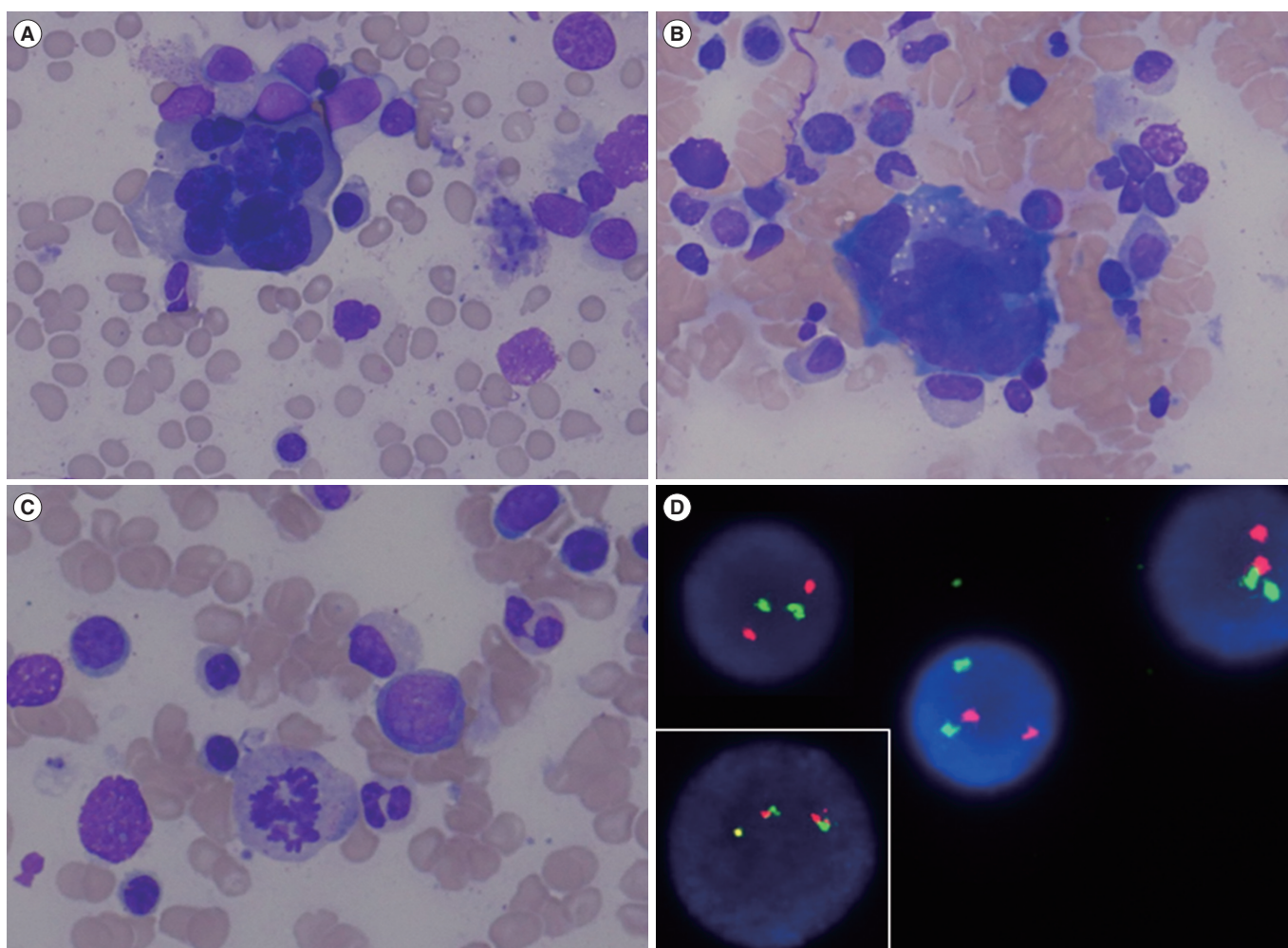


Fig. 1. Morphological and molecular cytogenetic analyses of bone marrow cells. A bone-marrow aspirate from the patient showed dyserythropoiesis (A), dysmegakaryopoiesis (B), and dysgranulopoiesis (C). Fluorescence *in situ* hybridization with a *BCR-ABL1* dual-color dual-fusion probe demonstrated that most cells showed no genomic rearrangement. However, one interphase cell out of 296 analyzed cells harbored a *BCR-ABL1* fusion signal (inner box). The *ABL1* gene on chromosome 9 is labeled in red, and the *BCR* gene on chromosome 22 is labeled in green (D).

14,-16,+mar [cp20]. The final diagnosis was MDS subtype refractory anemia with excess blasts-2 (RAEB-2). The patient died before undergoing a follow-up BM examination owing to lung cancer, which was found shortly after the MDS diagnosis.

BCR-ABL1-positive de novo MDS is a very rare disease, and when it manifests with excess blasts, as in this case, it may be confused with the accelerated phase of CML. However, several features of this case differentiate it from CML. First, our patient did not have organomegalies, such as splenomegaly, or any related symptoms, which are common in CML. Second, our patient did not display basophilia in the peripheral blood or BM, which is common in CML. Third, BM examination showed severe dyshematopoietic features without findings of myeloproliferative neoplasms. Fourth, monosomy 7 and del(5)(q31) identi-

fied using chromosomal analysis are typical aberrations of MDS.

It is common that *BCR-ABL1*-negative MDS changes to *BCR-ABL1*-positive MDS after disease progression [3-6]. In the case of *BCR-ABL1*-positive MDS, most patients show excess blasts on the verge of transformation to AML [6-8], which implies that the appearance of *BCR-ABL1*-positive clones is likely to be closely associated with leukemogenesis and triggers MDS to transform into AML.

Jacobsen *et al.* [9] proposed three possible explanations for the acquisition of the late-appearing Ph chromosome: 1) it may have been present on initial presentation; however, the techniques used were inadequate to detect the *BCR* rearrangement; 2) it may represent further evidence of multistep pathogenesis; and 3) the presence of the Ph chromosome in some cells may

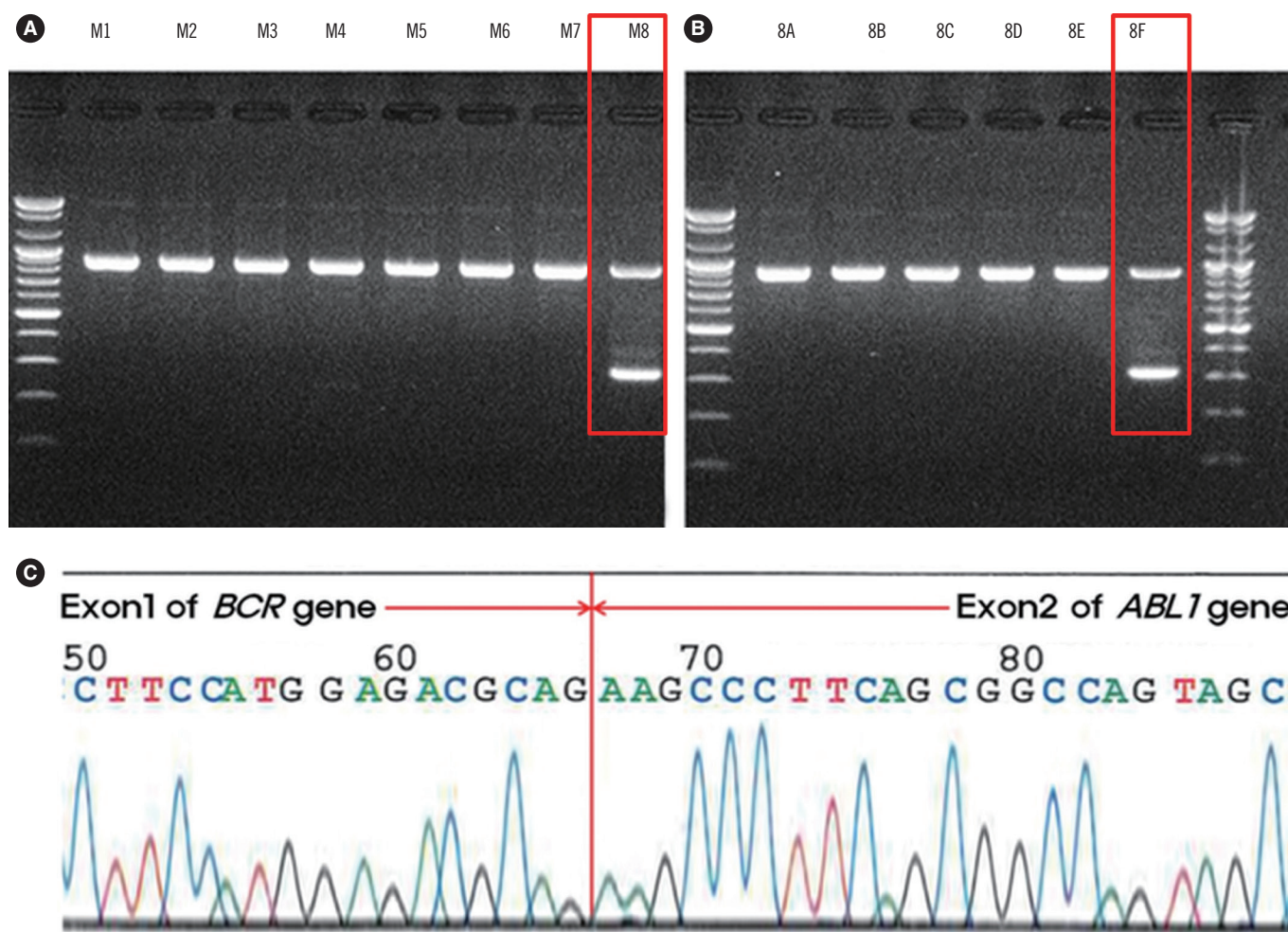


Fig. 2. Detection of p190 *BCR-ABL1* fusion transcript by multiplex reverse transcriptase -PCR and direct sequencing. Analysis of RNA samples collected from the patient's bone marrow (A, B). The screening kit produced a single band in the M8 lane (A), and the split-out kit produced a single 320-base-pair band in the 8F lane (B), indicating the minor presence of the *BCR-ABL1* fusion transcript (e1a2 type). Direct sequencing for the confirmation of a *BCR-ABL1* gene rearrangement showed the fusion between exon 1 of the *BCR* gene and exon 2 of the *ABL1* gene (C).

represent the development of a new clone of cells in leukemic relapse. In this case, we presume that the third explanation may be fitting. The *BCR-ABL1*-positive clone was most likely detected on emergence because the *BCR-ABL1* copy number and *BCR-ABL1* to *ABL1* transcript ratio during quantitative RT-PCR analysis were found to be very low. Moreover, a typical Ph chromosome was not found in 20 metaphase cells by conventional cytogenetic analysis. To the best of our knowledge, this is the first report of de novo MDS RAEB-2 with the cryptic e1a2 subtype of *BCR-ABL1* rearrangement and complex chromosomal abnormality in Korea. Currently, there is no established treatment method that is distinguished from the usual MDS treatment. In the future, a more systematic study of this disease is needed with respect to serial biologic monitoring, therapy, and outcome.

Authors' Disclosures of Potential Conflicts of Interest

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

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