



A Case of Pentasomy 21 With Two Isochromosome 21s in Acute Megakaryoblastic Leukemia Associated With Down Syndrome

Yeongchun Park, M.D., Jinsook Lim, M.D., Yong Hyun Ko, M.D., Jimyung Kim, M.D., Gye Cheol Kwon, M.D., and Sun Hoe Koo, M.D.

Department of Laboratory Medicine, Chungnam National University Hospital, Daejeon, Korea

Dear Editor

Down syndrome (DS) patients exhibit a 50-fold increase in acute leukemia incidence during the first five years of life, compared with those without DS. Trisomy 21, with or without other cytogenetic abnormalities, is reported in ~3% of AML and MDS cases; however, tetrasomy 21 and pentasomy 21 are unusual [1, 2]. Isodicentric chromosome 21 is a rare but recurrent cytogenetic abnormality in acute leukemia patients [3]; however, pentasomy 21q with two isochromosome 21s is very rare and has not yet been reported in pediatric DS patients with acute megakaryoblastic leukemia (AMKL).

Here, we report a first case of 19-month-old girl diagnosed as having DS, who was later diagnosed as having AMKL with pentasomy 21. The patient was admitted at 14 months of age, because bicytopenia was detected during a routine visit. Complete blood count (CBC) revealed the followings: Hb 8.6 g/dL; white blood cell (WBC) count, $4.6 \times 10^9/L$; and platelet count, $27 \times 10^9/L$. Peripheral blood smear showed anisopoikilocytosis with some elliptocytes and dacrocytes. DS was diagnosed at birth, and the patient's karyotype was 46,XX,+21c,der(21;21)(q10;q10)c. Although an attempted bone marrow aspiration resulted in a "dry tap," a needle biopsy specimen showed moderate fibrosis and mega-

karyocytic hyperplasia (4.9/high power field) with dysmegakaryocytic features. She was diagnosed as having transient myeloproliferative disorder, received one unit of packed red blood cells, and was subsequently discharged.

Five months later, a follow-up CBC revealed leukoerythroblastic reaction, and a physical examination revealed hepatosplenomegaly. Bone marrow study revealed persistent megakaryocytic hyperplasia and grade 3 fibrosis (Fig. 1). Cytogenetic analysis revealed a 49,XX,+11,+19,+21c,der(21;21)(q10;q10)c,+der(21;21)[19]/46,XX,+21c,der(21;21)c[9] karyotype, per the International System for Human Cytogenetic Nomenclature (ISCN) 2013. FISH confirmed pentasomy 21 (Fig. 2). *JAK2* mutation and *BCR/ABL* fusion were not detected. She received conservative therapy, and one month later, the disease progressed such that the peripheral blood presented 15% blasts. The patient was transferred to another hospital where she was diagnosed as having DS-associated AML. The blast count was 30% on the bone marrow aspirate, and the immunophenotype of the neoplastic cells was characteristic of megakaryoblasts: CD13+, CD33+, CD34+, CD64w+, CD117+, CD41w+, CD7+, HLA-DR+, MPO-, and nTdT-. *GATA1* mutation was not detected; however, an additional trisomy 11-associated *MLL* gain was detected by FISH.

Received: October 1, 2014

Revision received: November 7, 2014

Accepted: February 7, 2015

Corresponding author: Sun Hoe Koo

Department of Laboratory Medicine, Chungnam National University Hospital, 33 Munhwa-ro, Jung-gu, Daejeon 301-721, Korea
Tel: +82-42-280-7798, Fax: +82-42-257-5365
E-mail: shkoo@cnu.ac.kr

© The Korean Society for Laboratory Medicine.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

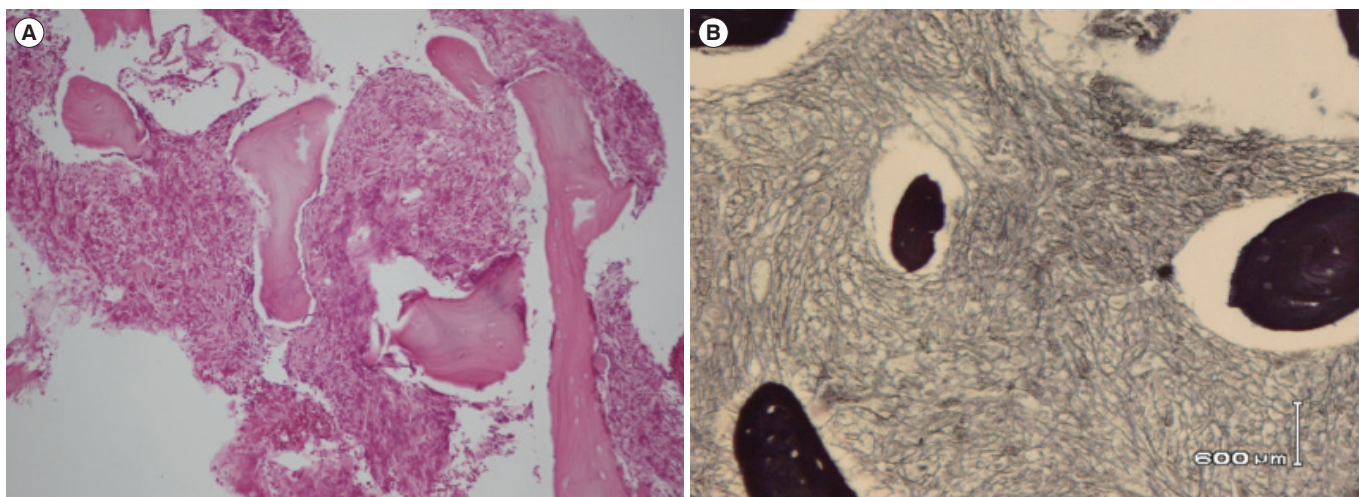


Fig. 1. (A) Bone marrow needle biopsy specimen, showing grade 3 fibrosis (H&E stain, $\times 100$). (B) Reticulin staining showing grade 3 fibrosis (Reticulin stain, $\times 200$).

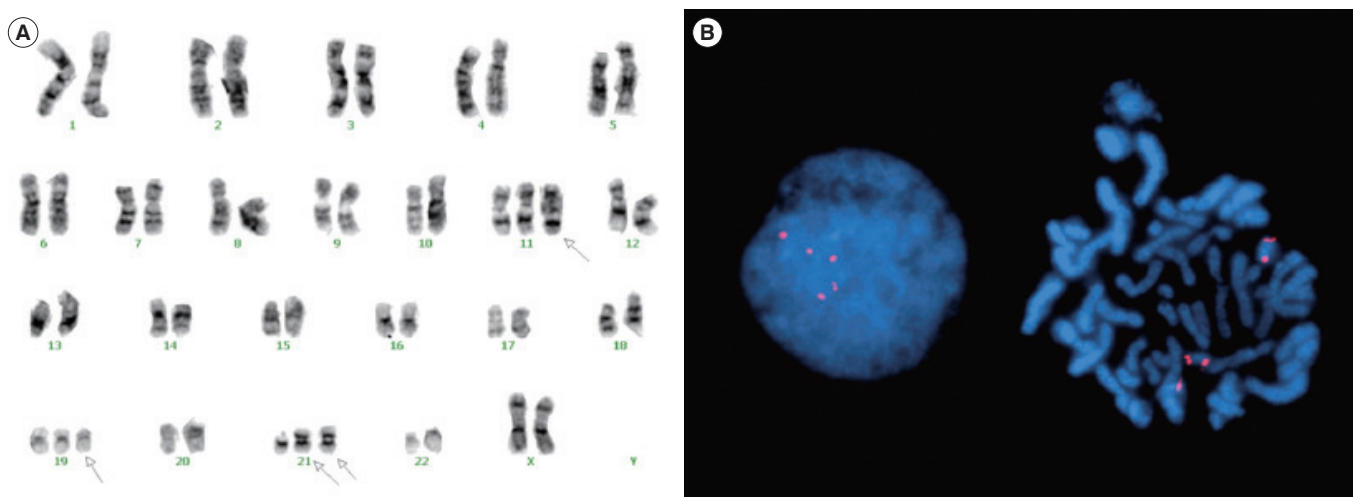


Fig. 2. Patient with Down syndrome exhibiting primary myelofibrosis with pentasomy 21. (A) Karyogram (Karyotype: 49,XX,+11,+19,+21c,der(21;21)(q10;q10)c, +der(21;21)[19]/46,XX,+21c,der(21;21)(q10;q10)c[9]. Arrows indicate abnormal chromosomes of 11, 19, and 21. (B) FISH analysis with a locus-specific probe for 21q22.13-q22.2, revealing pentasomy 21.

Calreticulin gene mutation test was not performed. The patient underwent cytarabine plus daunorubicin induction chemotherapy but failed to respond to the treatment and expired six months later.

We identified pentasomy 21 with two isochromosome 21s in DS-associated transient abnormal myeloproliferative disorder, which was later transformed into AMKL. Transient myeloproliferative disorder occurs in $\sim 10\%$ of newborns with DS, and non-transient AML develops one to three years later in $\sim 20\text{--}30\%$ of such cases [4]. Fifty percent of cases of DS-associated acute leukemia are usually AMKL. In $\sim 70\%$ of AMKL cases preceded by a pre-leukemic phase, which is characterized by thrombocy-

topenia and dysplastic changes, and often accompanied by marrow fibrosis, the disease may last several months or even years [5]. The present patient showed a similar disease course, transforming eventually into AMKL a few months later. Trisomy 19 that was observed in this patient might be due to some unknown role played by the leukemic transformation, as the most common abnormality in AMKL [6], and in the *AKT2*, cyclin E, and *MLL2* genes in the 19q12 region, which have been implicated in solid tumors and are under investigation in hematologic malignancies [7].

Genes on chromosome 21 play an important role in leukemogenesis [8]. One gene—*RUNX1* (*AML1*) at 21q22— plays a

crucial role in hematopoiesis during embryonic development, and is frequently involved in chromosomal rearrangements observed in various myeloid malignancies [9]. Isochromosome 21q, formed as idic(21)(p10;p10), could result in an increased gene copy number on the entire long arm of chromosome 21 [10]. Furthermore, the duplication of idic(21)(p10;p10) gave rise to pentasomy 21q and to amplification of oncogenes at 21q, such as *RUNX*, *ETS*, and *ERG*, which may be involved in the development of leukemia. Moreover, the *MLL* gene gain due to trisomy 11, might be associated with the poor prognosis in this particular patient. To date, 16 cases of pentasomy 21 with two isochromosomes have been reported in hematologic malignancies, but the clinical features common to these cases are unknown [3].

This case shows us that hematologic surveillance of peripheral blood is needed in DS newborns, and close follow-up as well as optimal molecular and cytogenetic studies should be performed in cases with abnormal peripheral blood findings. Clarification of the mechanism underlying myelofibrosis and leukemogenesis in pentasomy 21q with two isochromosomes, in myeloid leukemia associated with DS, requires further studies.

Authors' Disclosures of Potential Conflicts of Interest

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

REFERENCES

1. Cortes JE, Kantarjian H, O'Brien S, Keating M, Pierce S, Freireich EJ, et al. Clinical and prognostic significance of trisomy 21 in adult patients with acute myelogenous leukemia and myelodysplastic syndromes. *Leukemia* 1995;9:115-7.
2. Ohsaka A, Hisa T, Watanabe N, Kojima H, Nagasawa T. Tetrasomy 21 as a sole chromosome abnormality in acute myeloid leukemia. fluorescence in situ hybridization and spectral karyotyping analyses. *Cancer Genet Cytogenet* 2002;134:60-4.
3. Shimoyama M, Yamamoto K, Nishikawa S, Minagawa K, Katayama Y, Matsui T. Duplication of isodicentric chromosome 21, idic(21)(p11.2), leading to pentasomy 21q in acute myeloid leukemia with multilineage dysplasia. *Cancer Genet Cytogenet* 2009;194:38-43.
4. Baumann I, Niemeyer CM, Brunning RD, Arber DA, Porwit A. Myeloid proliferations related to Down syndrome. In: Swerdlow SH, Campo E, Harris NL, et al. eds. WHO classification of tumours of haematopoietic and lymphoid tissue. 4th ed. Lyon: IARC, 2008:142-4.
5. Roy A, Roberts I, Norton A, Vyas P. Acute megakaryoblastic leukaemia (AMKL) and transient myeloproliferative disorder (TMD) in Down syndrome: a multi-step model of myeloid leukaemogenesis. *Br J Haematol* 2009;147:3-12.
6. Alvarez S, MacGrogan D, Calasanz MJ, Nimer SD, Jhanwar SC. Frequent gain of chromosome 19 in megakaryoblastic leukemias detected by comparative genomic hybridization. *Genes Chromosomes Cancer* 2001;32:285-93.
7. Nimer SD, MacGrogan D, Jhanwar S, Alvarez S. Chromosome 19 abnormalities are commonly seen in AML, M7. *Blood* 2002;100:3838-9.
8. Fonatsch C. The role of chromosome 21 in hematology and oncology. *Genes Chromosomes Cancer* 2010;49:497-508.
9. Hilgenfeld E, Padilla-Nash H, McNeil N, Knutsen T, Montagna C, Tchinda J, et al. Spectral karyotyping and fluorescence in situ hybridization detect novel chromosomal aberrations, a recurring involvement of chromosome 21 and amplification of the MYC oncogene in acute myeloid leukaemia M2. *Br J Haematol* 2001;113:305-17.
10. Robinson HM, Harrison CJ, Moorman AV, Chudoba I, Strefford JC. Intrachromosomal amplification of chromosome 21 (iAMP21) may arise from a breakage-fusion-bridge cycle. *Genes Chromosomes Cancer* 2007;46:318-26.