

BRIEF REPORT

Clonal Trisomy 11 in a Child With Acute Leukemia: G Banding vs. FISH

Madhavi Jadhav, MD,¹ Barbara Cushing, MD,¹ Öner Özdemir, MD,¹ Anwar Mohamed, MD,²
Y. Ravindranath, MD,¹ and Süreyya Savaşan, MD^{1*}

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Translocations involving the *MLL* gene located at 11q23 have been reported in acute lymphoblastic leukemia (ALL), in 5–10% of cases with acute myeloid leukemia (AML), frequently of the monocytic type, and in biphenotypic leukemias expressing early stem cell as well as both myeloid and lymphoid markers. *MLL* gene rearrangement is the most common cytogenetic abnormality in infant leukemias and it can occur in therapy-related leukemias as well.

Trisomy 11 is the fourth most common acquired trisomy, occurring in 1% of AML/MDS cases [1]. Leukemias with trisomy 11 tend to express CD34, HLA-DR, myeloid antigens CD15, CD13 or CD33, and occasionally CD19. These leukemias are associated with a poor prognosis similar to cases with *MLL* gene rearrangements [1]. Recently, Schnittger et al. [2], in their study of 387 patients, reported the partial tandem duplication of the *MLL* gene, leading to the fusion of the proto-oncogene with itself, in 5.7% of AML patients with normal karyotypes, in 37.5% of cases with trisomy 11 with other cytogenetic abnormalities, and in 79% of cases with trisomy 11 as the sole karyotypic abnormality. Patients with this duplication had varying FAB morphologies and a poor outcome. In addition to their possible contribution to malignant transformation individually, the high incidence of partial tandem duplication of the *MLL* gene in cases with trisomy 11 suggests a link between these two cytogenetic events. Our experience with a 13-year-old south Asian girl is relevant. She had biphenotypic leukemia and at relapse, was found to have trisomy 11 detected by FISH, but not by conventional G banding.

She presented with pancytopenia in December 1998. Family history was significant for several cancers (liver, lung, colon, and brain) among close family members. A maternal aunt with Fanconi anemia developed AML at 5 years of age. Physical examination of the patient was not suggestive of Fanconi anemia and her diepoxybutane (DEB)-induced chromosomal breakage studies performed at the time of relapse were negative. At diagnosis, the

patient's bone marrow aspirate revealed blasts of predominant L1 morphology; other blasts were large with prominent nuclei. The blasts were strongly positive for CD10, HLA-DR, CD19, CD22, CD34 and showed milder expression of myeloid markers CD15 and CD13. Cytochemical staining revealed the blasts to be positive with Sudan black and 3–5% also were positive with peroxidase. Conventional G banding revealed a small number of metaphase cells that were 46 XX. A FISH study for the *MLL* gene revealed two probe signals in both metaphase and interphase. The patient had a good response to a high risk ALL protocol that included high-dose methotrexate, cytarabine, anthracyclines, and teniposide. After 17 months of treatment, while on maintenance therapy, the leukemia relapsed in the bone marrow. Analysis of relapse blasts had similar surface markers but had lost CD34 and Sudan black positivity. The blasts showed no clonal Ig-H variable region rearrangements at that time. Again, conventional cytogenetic analysis showed a normal karyotype; however, FISH study using LSI *MLL* (11q23) dual color DNA probe (5' *MLL* spectrumgreen 3' *MLL* spectrumorange) (Vysis Inc., Downers Grove, IL) revealed three sets of separate fused signals in 89 of 200 interphase cells (44%), but not in any metaphase cells. The results suggested that the non-dividing cells were most likely trisomic for chromosome 11.

¹Department of Pediatric Hematology/Oncology, Children's Hospital of Michigan, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, Michigan

²Department of Molecular Biology, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, Michigan

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*Correspondence to: Süreyya Savaşan, MD, Department of Hematology/Oncology, Children's Hospital of Michigan, 3901 Beaubien, Detroit, MI, 48201. E-mail: ssavasan@med.wayne.edu

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DISCUSSION

There are several interesting points. Most of the reported AML patients with trisomy 11 have been adults. One child was included among the patients reported by Schnittger et al. That child with secondary AML had partial tandem duplication of the *MLL* gene without trisomy 11 [2]. Trisomy 11 appears to be a rare abnormality in pediatric cases. In a recently reported series of 478 children with AML, one had trisomy 11 as the sole cytogenetic abnormality and four others had it as part of an abnormal cytogenetic complex [3]. Our case represents a biphenotypic leukemia with Sudan black positivity and strong expression of B-lineage surface markers at diagnosis. At relapse, the leukemic clone revealed neither Sudan black positivity nor any clonal Ig-H variable region rearrangements.

The detection of trisomy 11 by FISH at relapse, but not at diagnosis, can be explained by either dilution of the trisomy 11 clone by karyotypically normal leukemic clonal cells, or by the emergence of a new clone with trisomy 11 at relapse as suggested by Slovak et al. [1]. Since our patient had received topoisomerase II inhibitors as a part of initial therapy, there is also the possibility of a secondary leukemia in her case. However, similarity between morphologic and immunophenotypic characteristics of the blasts at diagnosis and relapse are against this possibility. If topoisomerase II inhibitors played a role, detection of trisomy 11 could be explained by the induction of secondary cytogenetic changes in the initial leukemic clone. On the other hand, presence of the same type of duplication fusion transcript of the *MLL* gene, at both diagnosis and relapse reported in two cases of AML, with additional karyotypic changes but without trisomy 11 during relapse, suggests that partial tandem duplication of *MLL* gene may be a primary event in leukemogenesis [2]. We did not test our patient for this mutation; it thus could be the case with her.

The detection of trisomy 11 in leukemic cells by FISH, but not by conventional cytogenetics, is another fascinating aspect of this report. This is similar to detection of t(15;17) by FISH but not by G banding in some patients with acute promyelocytic leukemia [4]. In addition to the possibility of the presence of two clones of leukemic cells, three other mechanistic explanations for the detec-

tion of trisomy 11 by FISH (especially in interphase and not in metaphase), but not by G banding are: (1) leukemic cells with trisomy 11 giving rise to poor morphology metaphases resulting in their eventual exclusion from the analysis, as occurs in monosomy 7; (2) decreased proliferation of trisomy cells in the culture, with or without dilution by non-malignant cells; and (3) slow growth rate of trisomy 11 cells in vivo due to unknown intrinsic cell cycle characteristics and/or the effect of recent maintenance chemotherapy [5,6].

The occurrence of trisomy 11 cases without *MLL* gene partial duplication, and the demonstration of duplication in cases with normal karyotypes, hinders the determination of which abnormality precedes the other. FISH analysis of the cases with partial tandem *MLL* gene duplication without trisomy 11 by G banding may be of interest and may contribute toward an understanding of the temporal relationship between the *MLL* duplication and trisomy 11. Finally, as suggested by Tanaka et al. [6], the application of FISH in the search for specific genetic abnormalities in selected cases may provide additional useful information.

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