Overexpression of the MLL Gene Combined With 11q Trisomy in a Child With Acute Lymphoblastic Leukemia

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Introduction

Leukemias bearing translocations involving chromosome region 11q23 are of particular interest because of their unique clinical and biological characteristics.1 This recurrent chromosomal translocation group is found in childhood acute myeloid (18%) and lymphoid (8%) leukemias.2,3 The translocation has been implicated in approximately 1% of adult cases of acute myeloid leukemia/myelodysplastic syndrome and is associated with poor prognosis.4-7

Chromosomal translocations, however, are not the only mechanisms by which MLL participates in leukemogenesis. MLL overexpression has been implicated in approximately 1% of adult cases of acute myeloid leukemia/myelodysplastic syndrome and is associated with poor prognosis.5-7

Here, we present a case of de novo B-cell progenitor (BCP) childhood acute lymphoblastic leukemia (ALL) with an 11q extra copy that originated from an unbalanced translocation resulting in an overexpression of the MLL gene.

MLL, which encodes a large multidomain protein ubiquitously expressed in hematopoietic cells including stem cell and progenitor populations5 with several genes resulting in overexpression of MLL.

Chromosomal translocations, however, are not the only mechanisms by which MLL induces leukemic transformation. Other chromosomal changes could result in MLL overexpression, such as amplification and extra copies of MLL. Although MLL-associated translocations have been extensively characterized, little is known about the implication of MLL extra copies (11q trisomy) in childhood leukemias.1-4 This abnormality has been described in approximately 1% of adult cases of acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), but is rarely observed in pediatric AML. It is associated with an internal tandem duplication of the MLL gene (or amplification of the genomic region encompassing MLL), and it is also highly associated with a poor prognosis, similar to cases with MLL rearrangement.5-7

Here, we present a case of de novo B-cell progenitor (BCP) childhood acute lymphoblastic leukemia (ALL) with an 11q extra copy that originated from an unbalanced translocation resulting in an overexpression of the MLL gene.
Case Report

A 13-year-old girl presented to the local hospital with a week-long history of generalized pain, fever, ecchymosis, and difficulty breathing. Physical examination revealed hepatosplenomegaly (liver was palpable 8 cm from the right costal margin and spleen at 12 cm from the left costal margin). The complete blood count showed a hemoglobin level of 6 g/dL and a white blood cell count of 43 × 10^9/L with 85% abnormal lymphoid cells. The platelet count was 9 × 10^9/L, and lactate dehydrogenate was 3269 U/L. Flow cytometry analysis of the peripheral blood revealed lymphoblasts that expressed CD19, CD10, CD20, CD22, CD34, CD38, CD79a, cIgM (cytoplasmic immunoglobulin heavy chain M), TdT (terminal deoxynucleotidyl transferase), and HLA-DR (human leukocyte antigen class II), findings compatible with pre-BCP e ALL. The patient was treated according to the high-risk arm of the Brazilian ALL 99 protocol. She achieved complete remission on day 28 of treatment and has been in continuous complete remission for 10 months.

G-banding studies revealed the karyotype 46,XX, der(9;11)(p11;q11) in 10 of 20 metaphases analyzed (Fig. 1A). Further, fluorescence in situ hybridization (FISH) analyses using the MLL break-apart probe did not find a split signal pattern for MLL, but the analyses revealed 3 signals of the MLL gene, at the 2 normal 11 chromosomes and 1 signal at the der(9;11) in 60% of 210 analyzed cells (Fig. 1B), a finding compatible with a trisomy of the MLL. To confirm the presence of der(9;11)(p11;q11) we performed FISH analyses using cyclin dependent kinase 2a gene (CDKN2A)/ chromosome 9 centromeric region (CEP9). These analyses revealed that 60% of cells had a homozygous deletion of the CDKN2A gene; also, the presence of 2 CEP9 signals showed that the centromeric region was not involved (Fig. 1C). The FISH analyses for breakpoint cluster region (BCR)/v-abl Abelson murine leukemia viral oncogene homolog 1 (ABL1) and ETS variant gene 6 (ETV6)/runt-related transcription factor 1 (RUNX1) fusions and E2A (immunoglobulin enhancer binding factors E12/E47) rearrangement were negative. The MLL gene transcript was expressed 45-fold in the MLL-r+ control (a patient known to have the MLL gene translocation) compared with the tested patient, and was not detected in a healthy donor (Fig. 1D).

Discussion

Although 11q23-related rearrangements have been extensively studied, the prognostic implication of MLL extra copies and trisomy 11 in pediatric leukemia is less understood, because of its rarity. Overexpression of MLL in both of these cytogenetic abnormalities seems to play an important role in the development of
hematological malignancies as a gain-of-function mutation. Moreover, this overexpression seems to have a bad prognostic meaning in AML and MDS. In addition to the MLL trisomy, our patient showed a homozygous deletion of the CDKN2A gene. This very common abnormality is found in more than 60% of pediatric T-cell lineage ALL cases and 20% to 30% of pediatric BCP-ALL cases, but its prognostic significance remains unclear.

**Conclusion**

To our knowledge, this is the first pediatric BCP-ALL case with MLL overexpression caused by 11q trisomy to be described. Additional cases with this molecular and cytogenetic profile are required to determine the prognostic implication of this gain-of-function mutation in pediatric ALL.

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**Disclosure**

The authors have stated that they have no conflicts of interest.

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