A NEW PEDIATRIC ACUTE MYELOID LEUKEMIA CASE INVOLVING *KMT2A-MLLT6* FUSION WITH A HETEROZYGOUS RARA GENE DISPLACEMENT: CYTOGENOMICS AND CLINICAL DATA EVALUATION

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Objectives

In pediatric acute leukemias, chromosomal rearrangements frequently generate gene fusions involving the lysine (K)-specific methyltransferase 2A gene (KMT2A, also known as MLL).

Specific KMT2A fusion partners are associated with the disease phenotype (lymphoblastic vs. myeloid), and different prognosis can be observed depending on the type of KMT2A rearrangement. So far, 80 different direct KMT2A fusion partners and 120 different reciprocal KMT2A fusion variants have been reported in acute leukemia. In this sense, recent studies have reported that the follow-up of patients during treatment and therapy adjustment based on minimal residual disease (MRD) monitoring has a very strong impact on the outcome.

However, the KMT2A partner gene cannot always be identified by banding karyotyping and other conventional approaches. To overcome this matter, different scientific groups have combined efforts to establish a network to study the cytogenomic landscape of the KMT2A breakpoints in patients.

Moreover, verify the KMT2A fusion to precisely confirm the diagnosis, monitoring the MRD, and uncover new partners implicated in childhood leukemogenesis. Here we present rare cytogenomic and clinical data from a pediatric acute myeloid leukemia patient with *KMT2A-MLLT6* fusion and a heterozygous RARA gene displacement.

Material and Methods

Bone marrow sample from a 15-year-old girl was referred to the Laboratory of Cytogenetics, INCA. Immunophenotyping showed 85% of blast cells, and a profile compatible with acute monocytic leukemia, being treated under the AML-BFM-2004 protocol. She evolved with disseminated intravascular coagulation (DIC), pancytopenia, and intense bleeding. The patient presented 21% of blast cells in the first assessment (induction phase, day 21). The girl did not experience remission after the first cycle of chemotherapy, and due to the presence of a rare cytogenetic alteration, she was referred to high-risk protocol, and indicated to allogeneic bone marrow transplantation. Cytogenetic analysis was performed on bone marrow under standard protocols. Long-distance inverse polymerase chain reaction (LDI-PCR) assays were used to identify the KMT2A partner genes and their corresponding breakpoints.

Results

Cytogenetic studies showed the karyotype: 50,XX,+4,+8,t(11;17) (q23;q12-21),+18,+19 (Figure 1). The FISH analysis revealed KMT2A gene rearrangement and a RARA gene displacement (Figure 2). The LDI-PCR sequencing revealed the fusion *KMT2A-MLLT6*.

Discussion

The t(11;17)(q23;q12-21) / *KMT2A-MLLT6* is rare in childhood AML. By G-banding and FISH we observed that the patient presented a t(11;17) involving 11q23 e KMT2A-r. Although, she was tested for PML-RARA because there was a hypothesis of a variant PML-RARA, as suggested by the pediatrician, and due to a severe DIC, but it was negative.

So far, three MLL fusion partners, namely LASP1, ACACA, and MLLT6 have been identified in 17q12-21; MLLT6 (MLLT6, PHD Finger Containing) is a Protein Coding gene.

These translocations cannot be distinguished cytogenetically and the accurate detection of the specific fusion gene requires refined FISH analysis and/or cytogenomic assays.

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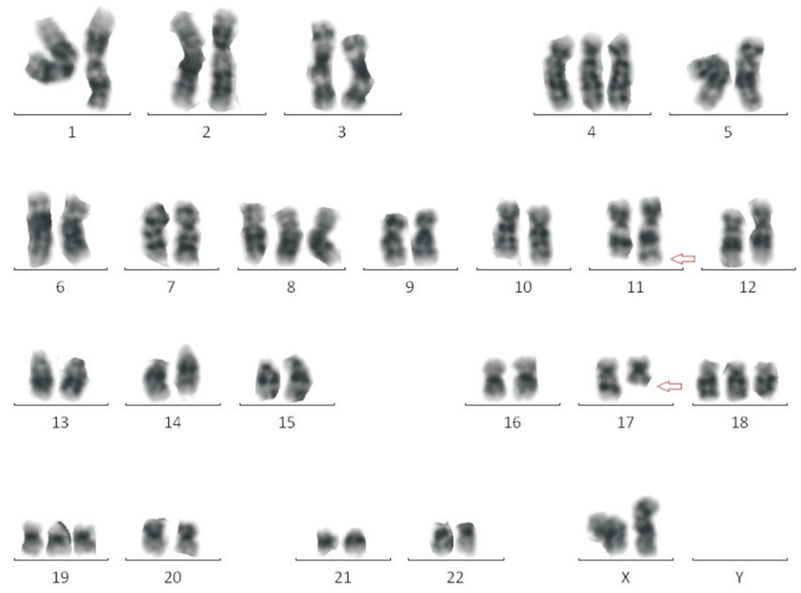

Figure 1: G-banding showed a karyotype 50,XX wih trisomy of chromosomes 4, 8, 18 and 19, besides t(11;17) (q23;q12-21) as the ed arrows

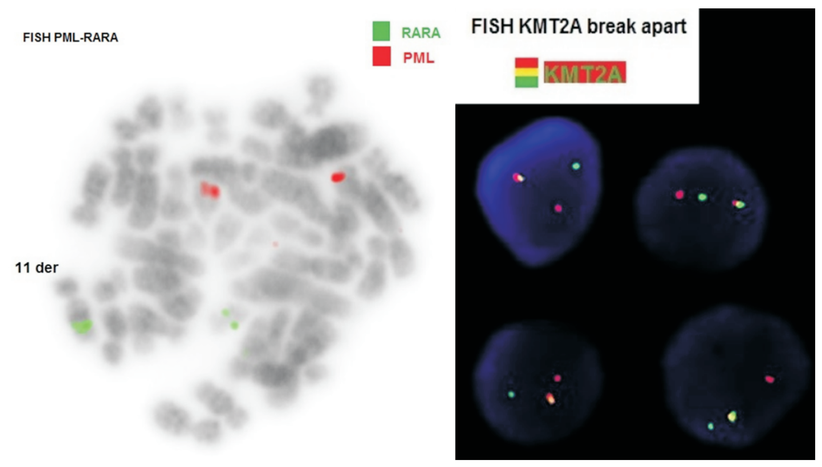

Figure 2: FISH analysis revealed KMT2A gene rearrangement and a RARA gene displacement.

Figure 3: Results of LDI-PCR assay. The LDI-PCR sequencing identified the *KMT2A-MLLT4* fusion gene, and the corresponding breakpoints.

Conclusion

Currently, further genomic analyses are being conducted to elucidate the role of the *KMT2A-MLLT6* fusion in this case and the RARA gene displacement prognostic implication. In our case the patient has been on remission for 4 months. However, it is not enough to conclude the role of this new translocation. Additional cases are needed to delineate the true epidemiology of this rare entity.

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