CYTOGENOMIC STUDIES IN AN INFANT WITH *BCR-ABL1*(+) NON-DOWN ACUTE MEGAKARYOBLASTIC LEUKEMIA: DE NOVO OR BLAST CRISIS, DOES IT MATTER?

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Objectives

Acute megakaryoblastic leukemia (AMKL) accounts for < 5% of acute myeloid leukemia (AML). This disease is divided into 2 types: AMKL patients with Down syndrome (DS-AMKL) and AMKL patients without DS (non-DS-AMKL). Pediatric non-DS-AMKL represents a heterogeneous group of patients, generally with a poor outcome, and with lower event-free survival than DS-AMKL and pediatric AML.

Childhood Chronic myeloid leukemia (CML) represents 3% of pediatric leukemias, it is a clonal disorder of pluripotent hematopoietic stem cells characterized by the balanced, reciprocal translocation t(9;22)(q34;q11), and it is molecularly characterized by the rearrangement between the ABL1 and BCR genes. In rare occasions, patients with CML can present directly in a blast crisis (BC), and even rarer, BC with features reminiscent of AMKL is observed. In this context, some reports in the literature observe that Ph+ AL and BP-CML are two distinct entities.

Clinically, in AMKL, the median age at diagnosis is reported to be usually younger. Also, splenomegaly, peripheral blood basophilia, and bone marrow basophilia were less commonly observed in AMKL than in CML-MBC (Myeloid Blast Crisis). The literature reports that despite cases of Ph+ AML have lower marrow cellularity and lower bone marrow myeloid/erythroid ratio than CML-MBC cases, there were important morphologic characteristics present in the 2 groups. There are, also, different types and frequencies of additional abnormalities in citogenomic (80% of BP-CML and 68% of Ph+ AML). These observations may suggest that the genetic mechanisms for leukemogenesis in Ph+ AML may differ from those in CML-MBC, which reinforces the importance of detailed cytogenomic and molecular analysis to better define the genomic differences between the patient's karyotypes.

Case Report

An 1-year-old female presented with fever, developmental delay for 4 months and bipalpebral ecchymosis and swelling (Figure 1). She had a splenomegaly reaching the iliac crest and a palpable liver (4 cm from the costal border), without lymphonode enlargement.

Her initial complete blood count showed a leukocyte count (26.5 × 10^3 /µL) with 60% of blasts, hemoglobin (7,6g/dL) and platelet count (25 × 10^3 /µL), and LDH 2.887. Her Bone morrow hadn´t basophilia. Flow cytometry analysis revealed a population of 83% leukemic blast cells that expressed MPO-, CD13+, CD33+, CD117 +, CD42a / CD61+, CD56+, CD42b+, CD71+ and CD123+ characterizing megakaryoblastic leukemia. Being a patient classified as high-risk AML, according to the AML-BFM-2004 protocol. The molecular biology analysis was positive for BCR-ABL1 fusion and Imatinib was immediately initiated.

The first evaluation after induction showed morphologic remission and MDR was 0.12%. Patient experienced partial remission at the end of treatment (MDR 0,32%), but she relapsed after one week, and the bone marrow transplant couldn´t be done.

After relapse, she was treated with FLAG-IDA twice and changed the tyrosine kinase inhibitor to Desatinib but being refractory to therapy. At this moment she remained hospitalized but with active disease.

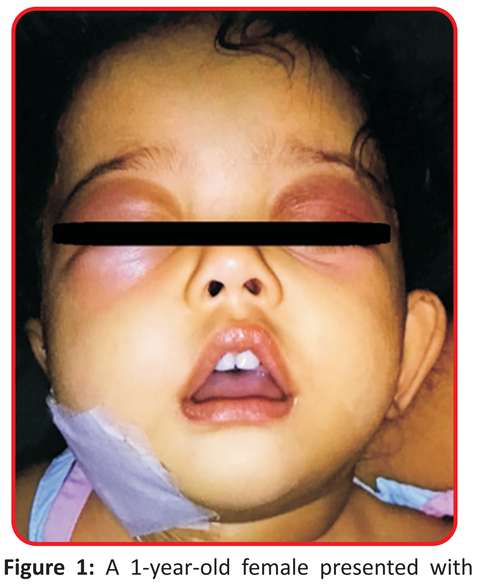

Figure 1: A 1-year-old female presented with bipalpebral ecchymosis and swelling.

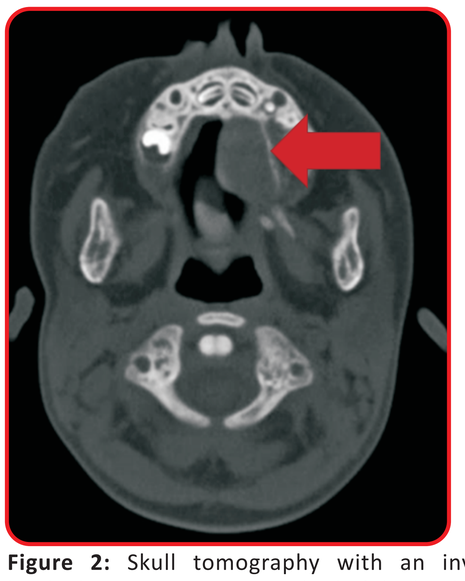

Figure 2: Skull tomography with an invasive biorhythmia mass up to one-third of the hard palate with erosion of the sphenoid cortex compatible with sarcoma.

Material and Methods

In this work, we present cytogenomic data (using G-banding, FISH, a-CGH and NGS), of an infant with BCR-ABL1(+) and WT1, C-KIT, and SETBP1 mutations associated with a very poor prognosis.

Results

Cytogenetic and FISH analysis of the bone marrow cells showed the translocation t(9;22)(q34;q22), and the presence of the fusion BCR-ABL1, in both diploid and polyploid cell populations. Array-CGH showed no deletions in IKZF1 and CDKN2A genes. NGS studies revealed mutations in WT1, C-KIT, and SETBP1 genes.

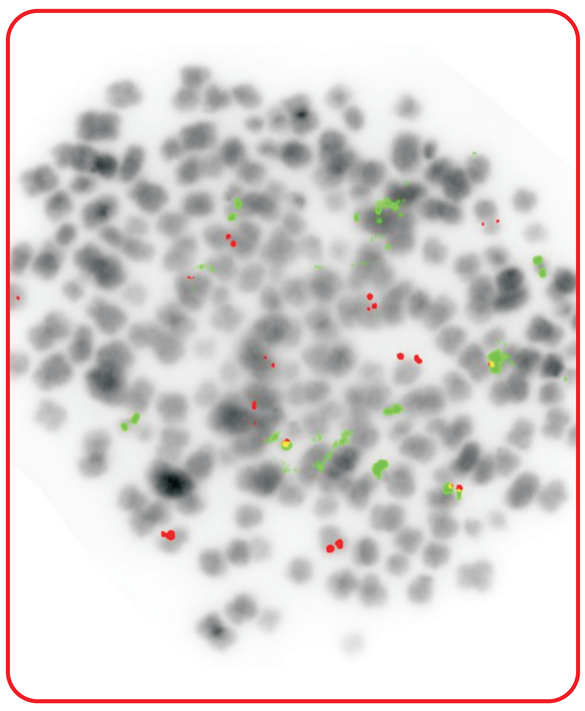

Figure 3: FISH analysis was positive for the BCR-ABL1 gene fusion, both in the cells with 47 chromosomes and in the high-hyperdiploidy cells.

Dicussion and Conclusion

We are presenting for the first time in the literature the case of an 1-year-old child with a philadelphia chromosome-associated an acute megakaryoblastic leukemia. Although, if the clinical and laboratory differenciation between blast crisis or de novo leukemia is fundamental for treatment, similar cases are still needed to complete this question.

However, genomic studies are moving in this direction, as treatment based on molecular target. Studies in the literature showed that T cell receptor gene therapy targeting WT1 can preventing AML recurrence in individuals at increased risk of post-HCT relapse.

So, the importance of unravel the karyotype and molecular profile of each disease will increasingly help in understanding their pathogenesis.

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