Trisomy 19 in Acute Megakaryocytic Leukemia

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A 13-month-old boy was referred to the hospital due to recurrent fever for 1 month. The abnormal findings in his physical examination were petechiae on the left and right foots and pallor. Paraclinical evaluation revealed leukocytosis, anemia, and thrombocytopenia (White blood cell = $22.64 \times 10^9/L$, Hemoglobin = 65 g/L, Platelet = $110 \times 10^9/L$). Peripheral blood smear showed 16% variably sized blasts with cytoplasmic blebs (Fig. 1) which were positive for CD117, CD41, CD61, CD33 and negative for CD34, MPO, CD13, CD14, CD64, CD2, CD3, CD19, CD10, CD20 and CD79 in flowcytometry, confirming the diagnosis of acute megakaryocytic leukemia, AML-M7 (Fig. 2). Transient abnormal myelopoiesis (TAM) was a differential diagnosis which was excluded due to high age

of the patient and lack of Down syndrome features (TAM usually happens exclusively in the background of Down syndrome during the first month of life and usually resolves in several weeks). Molecular study for t(8:21)/RUNX1-RUNX1T1, t(15;17)/PML-RARA, inv(16)/CBFB-MYH11 and FLT3 ITD and D835 mutations was negative. Bone marrow culture and its cytogenetic study by Giemsa Trypsin G-banding (GTG) method and a resolution of 350 bands per haploid set revealed trisomy 19 in all 30 analyzed metaphases (Fig. 3). He underwent induction chemotherapy with ADE (Cytarabine, Danurobicin, and Etoposide) regimen and achieved a complete remission. Five months later, the leukemia relapsed with 40% blasts in peripheral smear showing the previous morphologic and immunophenotypic features.

Cytogenetic abnormalities of AML-M7 are age-dependent. Most common cytogenetic aberrations in children with AML-M7 include t(1; 22) (p13; q13) (approximately in half of the cases), + 21, + 19, + 8 (approximately in 40% of the cases) [1, 2]. The remaining 10% have normal karyotype [1]. Trisomy 19 has been detected in 20–30% of cases by comparative genomic hybridizations in some studies [3]. Adults with AML-M7 have complex karyotype in 60–70% of cases (especially 5-/7-). The remaining 20–30% show 3q21–3q26 aberrations. Trisomy 19 and 21 are the most common chromosome gains. Therefore, trisomy 19 can be observed in both age groups and is relatively more common in children.

There are eight genes on chromosome 19 which have been determined as candidate genes in pathogenesis of acute megakaryocytic leukemia with gain of chromosome 19. These genes include KCNK6, APOC1, CD33, CEA-CAM5, CCNE1, PPF1A3 (all located on long arm), NR2F6 and ASF1B (both located on short arm).

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Fig. 1 Peripheral blood smear shows variable sized blasts with cytoplasmic blebs (Giemsa stain $\times$ 1000)

Fig. 2 Flowcytometry on peripheral blood showed 16% blast population (A) with positive reaction for CD117 (B), CD33 (C), CD41 and CD61 (D)

Interestingly 80% of these genes have a relationship with cell growth and/or maintenance [4].

Trisomy 19 can be observed in other myeloid neoplasms like acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and chronic myeloid leukemia (CML). Isolated trisomy 19 is usually associated with a de novo AML and its pathogenic and prognostic effects remains to be more elucidated in the future. In CML, trisomy 19 is one of additional major cytogenetic aberrations which is usually associated with acceleration of disease and poor prognosis [5].

Finally, it's noteworthy that constitutional trisomy 19 is not compatible with life and there are few reports of stillbirths with mosaic trisomy 19 in literature which is characterized by hydrops and dysmorphic features like hypertelorism, epicanthal folds, low set ears, flat nasal bridge, and small mouth [6].

Fig. 3 Chromosome analysis showed an abnormal male chromosome complement with an extra chromosome 19

Compliance with Ethical Standards

Conflict of interest Authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from individual participant included in the study.

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