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Case Report

Pediatric acute myeloid leukemia with t(8;21) variant: what is the value on clinical outcome?

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ABSTRACT

Acute myeloid leukemia (AML) is characterized by clonal expansion of undifferentiated myeloid precursors that results in the bone marrow (BM) failure. Some cytogenetic alterations can be used to predict the prognosis of the disease. AML with t(8;21), presenting *RUNX1/RUNX1T1* gene fusion, is associated to favorable prognosis and it is one of most prevalent structural abnormalities in pediatric AML. Variants of t(8;21) has been described, though the prognostic value of these changes remains controversial, especially in pediatric patients. Thereby, we report a pediatric patient with AML with *RUNX1/RUNX1T1* fusion presenting the variant t(1;21;8). The diagnosis was confirmed by myelogram, immunophenotyping, cytogenetics and molecular biology. After the diagnosis, the patient was subjected to chemotherapy and submitted to related allogeneic BM transplant. Until this date, the patient has no clinical complaints, predicting a favorable outcome. The register of variants and its proper follow up contributes to a better understanding of the mechanisms involved in these rearrangements and provides information that may be relevant for an appropriate classification and risk stratification of these patients.

Keywords: Acute myeloid leukemia, *RUNX1/RUNX1T1*, t(8;21) variant

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal disease that affects bone marrow (BM) and it is characterized by the uncontrolled proliferation of progenitor cells of myeloid lineage.[1] This phenomenon is the result of a series of cumulative genetic changes that lead to maturation block and acquisition of proliferative advantage.[2] Despite the growing knowledge about the pathophysiology of the disease and the emergence of new therapeutic targets, genetics and molecular heterogeneity characteristic of clonal expansion still accounts for the possible relapse and subsequent death of most patients.[3] Specific cytogenetic alterations are currently used to stratify patients and establish the treatment protocol. According to World Health Organization (WHO), t(8;21) with *RUNX1/RUNX1T1* gene fusion refers to a distinct type of AML that is associated with a favorable prognosis. This abnormality is found in approximately 10% of cases AML-M2 (French-American-British classification) and it is one of most prevalent structural abnormalities in pediatric AML, representing 7% to 30% of all cases.[1,4-6]

The *RUNX1* gene, located on chromosome 21, encodes the transcription factor CBF (Core Binding Factor) which regulates the expression of several genes related to myeloid differentiation. The *RUNX1/RUNX1T1* gene fusion results in coding of a transcriptional repressor protein that blocks the normal differentiation process. It is believed that this protein has a fundamental role in the onset of leukemogenesis.[7] However, despite the *RUNX1/RUNX1T1* fusion being regarded as

pathognomonic for AML, secondary events, such as mutations of the *c-KIT*, *RAS*, *FTL3*, among others, are required for the onset of the disease and its clinical implications.[8]

Variants of t(8;21), involving 3 or 4 chromosomes, has been described and account for 3-4% of AML patients with *RUNX1/RUNX1T1* fusion.[9] Due to the rarity and diversity of the chromosomes and genes involved, the prognostic value of these changes remains controversial, especially in pediatric patients, which are a singular population study.[10-13] Addressing this issue, we report in this paper a pediatric patient with AML with *RUNX1/RUNX1T1* fusion presenting the variant t(1;21;8).

CASE REPORT

In March 2010, a 6-year-old boy, characterized by its initials DCS, was admitted to the emergency of Albert Sabin Children Hospital (Fortaleza, Brazil). The clinical signs and symptoms at diagnosis were progressive pallor, abdominal pain, intermittent fever and vomiting. The initial clinical suspicion was bilateral pneumonia or autoimmune hemolytic anemia. The CBC showed 6.07g/dl of hemoglobin, $7.75x10^9$/l of leukocytes, $3.06x10^9$/l of platelets and 59% of cells with blast characteristics. The patient was sent to the hematology service where he was subjected to aspiration of BM for myelogram, immunophenotyping, cytogenetics and molecular biology. Biopsy of the BM was not performed.

The myelogram showed normocellular content presenting heterogeneous population of 76% of medium-sized blasts, low ratio nucleus-cytoplasm, irregular nucleus with delicate chromatin, weak basophilia, few cytoplasmic granulations, absence of vacuoles and nucleoli present. Auer rods were not visualized. Blasts were positive for Sudam Black B.

The immuno-phenotypic research by flow cytometry was positive for CD45, HLA-DR, CD13, CD33, CD64, CD117, CD34, MPO, TdT, and reveal aberrant expression of CD19. Immunophenotyping, together with the morphological description of myelogram, was compatible with the M2 subtype, by FAB classification.[4]

Cytogenetic evaluation, by G-banding technique, showed karyotype with presence of translocation involving chromosomes 1 and 8, and the loss of chromosome 19 (Figure 1A). Since it is an AML-M2, as immuno-morphological analysis, the transcript of gene fusion *RUNX1/RUNX1T1* was screened by molecular assay by RT-PCR that showed a positive result, with an amplicon of 395bp (Figure1B).[14] Karyotype was described as 45, XY, t(1;21;8) (p36;q22;q22),-19, according to the criteria of ISCN 2013.[15]

After the diagnosis, the patient was subjected to chemotherapy, complying with the Berlin-Frankfurt-Münster Protocol (BFM-2004).[16] In accordance with this protocol, being an AML-M2 with absence of Auer rods, DCS patient was stratified as high risk with indication for transplantation. After complete remission, the patient continued on maintenance therapy until submitted to related allogeneic BM transplant, in December 2011.

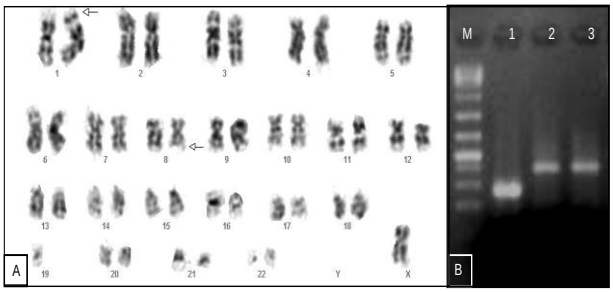

Figure 1A: Karyotype with presence of translocation involving chromosomes 1 and 8. B: RT-PCR showing a positive result, with an amplicon of 395bp. M: 1kb DNA ladder; Line 1: ABL patient control; Line 2: positive control to t(8,21); Line 3: patient.

Currently, the patient is under observation and has no clinical complaints, presenting in his last CBC in May 2016: 12,8g/dl of hemoglobin, 4,295 x 10^9/l of leukocytes, 295 x 10^9/mm3 of platelets and 63% of lymphocytes.

DISCUSSION

Among the variants of t(8;21) reported in the literature, t(8;12;21), t(8;16;21) and t(8;11;21) were associated with favorable prognosis and outcome positive clinical.[9,12,17,18] However, translocations t(4;21;8) and t(X;8;21) had poor prognosis with adverse clinical outcome.[19,20] In addition, reports of variant t(8;13;21) are associated with both favorable and unfavorable prognosis, which settles the uncertainty in the prognostic value of these variations.[13,17]

The variant t(1;21;8), observed in the patient DCS, was reported by other authors in reports related to adult patients.[9,21-23] The only pediatric case reported with this variant and the presence of *RUNX1/RUNX1T1* gene fusion had an unfavorable clinical outcome, with mortality after allogeneic BM transplant.[17] According to Rubnitz *et al*., 2004, half of pediatric patients experience recurrence and eventual death due to the toxicity and side effects related to high doses of the treatment of AML.[24] This data does not corroborate with our results, in which patient DCS was submitted to BM transplantation and, to date, has no clinical complaints, predicting a favorable outcome.

Rearrangements involving genes present in regions of the short arm of chromosome 1p36 have been associated with hematologic malignancies. These include the *MDS2*, associated with Myelodysplastic Syndromes (MDS), the *PIK3CD* and *PRDM2* associated with AML and *PRDM16* involved with MDS and AML.[25-28] Our Study

indicates that the different clinical outcomes observed between variants t(8;21) are directly linked to the involvement of genes located on the third and/or fourth chromosome. However, it was not possible to establish which of these were associated with the variant found in our patient.

CONCLUSION

The register of variants, as well as its proper follow up, contributes to a better understanding of the mechanisms involved in these rearrangements, and provides information that may be relevant for an appropriate classification and risk stratification of these patients. As it is a rare abnormality, information about the prognostic value of these variants are still inconsistent. Our study reinforces the need to explore cases like the one mentioned in this study in greater details to elucidate the clinical significance of these variants.

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REFERENCES

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. World Healthy Organization (WHO): classification of tumours of haematopoietic and lymphoid tissues; 2008.
2. Longo DL, Dohner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. N Engl J Med. 2015;373:1136-52.
3. Saultz JN, Garzon R. Acute myeloid leukemia: a concise review. J Clin Med. 2016;5:33-51.
4. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, et al. Proposed revised criteria for the classification of acute myeloid leukemia: A report of the French-American-British Cooperative Group. Ann Intern Med. 1985;103:620-5.
5. Manola KN. Cytogenetics of pediatric acute myeloid leukemia. Eur J Haematol 2009;83:391-405.
6. Müller AMS, Duque J, Shizuru JA, Lübbert M. Complementing mutations in core binding factor leukemias: from mouse models to clinical applications. Oncogene. 2008;27:5759-73.
7. Hatlen MA, Wang L, Nimer SD. ML1-ETO driven acute leukemia: insights into pathogenesis and potential therapeutic approaches. Front Med. 2012;6:248-62.
8. Mosna F, Gottardi M. Stem cell modeling of core binding factor acute myeloid leukemia. Stem Cells International; 2016.
9. Huang L, Abruzzo LV, Valbuena JR, Medeiros LJ, Lin P. Acute myeloid leukemia associated with variant t(8;21) detected by conventional cytogenetic and molecular studies. Am J Clin Pathol. 2006;125:267-72.
10. Ahmad F, Kokate P, Chheda P, Dalvi R, Das BR, Mandava S, Molecular cytogenetic findings in a three-way novel variant of t(1;8 21)(p35;q22;q22): a unique relocation of the AML1/ETO fusion gene 1p35 in AML-M2. Cancer Genet Cytogenet. 2008;180:153-7.
11. Bae SY, Kim JS, Ryeu BJ, Lee KN, Lee CK, Kim YK, et al. Acute myeloid leukemia (AML-M2) associated with variant t(8;21): report of three cases. Cancer Genet Cytogenet. 2010;199:31-7.
12. Yamamoto K, Yakushijin K, Funakoshi Y, Sanada Y, Kawamoto S, Matsuoka H, et al. A new complex translocation t(8;11;21)(q22;q24;q22) in acute myeloid leukemia with RUNX1/RUNX1T1. J Clin Exp Hematop. 2014;167-70.
13. Matos RRC, De Figueiredo AF, Liehr T, Alhourani E, De Souza MT, Binato R, et al. A novel three-way variant t(8;13;21)(q22;q33;q22) in a child with acute myeloid leukemia with RUNX1/RUNX1T1: the contribution of molecular approaches for revealing t(8;21) variants. Acta Haematol 2015;134:243-5.
14. Van Dongen JJM, Macintyre EA, Gabert JA, Delabesse E, Rossi V, Saglio G, et al. Standardized RT-PCR analysis of fusion gene transcripts from chromosome aberrations in acute leukemia for detection of minimal residual disease. Leukemia 1999;13:1901-28.
15. Shaffer LG, McGowan-Jordan J, Schmid M. ISCN 2013: an international system for human cytogenetic nomenclature. Karger Medical and Scientific Publishers; 2013.
16. Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN, Fleischhack G, Graf N, et al. Randomized trial comparing liposomal daunorubicin with idarubicin as induction for pediat-ric acute myeloid leukemia: results from Study AML-BFM 2004. Blood. 2013;122:37-43.
17. Rubnitz JE, Raimondi SC, Halbert AR, Tong X, Srivastava DK, Razzouk BI, et al. Characteristics and outcome of t(8;21)-positive childhood acute myeloid leukemia: a single institution's experience. Leukemia 2002;16:2072-7.
18. Kakosaiou K, Daraki A, Zomas A, Manola KN. A novel variant translocation t(8;16;21) (q22;q24;q22) in acute myeloid leukemia expressing both myeloid and lymphoid markers. Hospital Chronicles. 2015;10:174-6.
19. Kelly MJ, Meloni-Ehrig AM, Manley PE, Altura RA: Poor outcome in a pediatric patient with acute myeloid leukemia associated with a variant t(8;21) and trisomy 6. Cancer Genet Cytogenet 2009;189:48-52.
20. Vunditi BR, Kerketta L, Madkaikar M, Jijina F, Ghosh K. Three way translocation in a new variant of t(8;21) acute myeloid leukemia involving Xp22. Indian J Cancer 2008;45:30-32.
21. Kim H, Moon HW, Hur M, Yun YM, Lee MH. Acute myeloid leukemia with a RUNX1-RUNX1T1

t(1;21;8)(q21;q22;q22) novel variant: a case report and review of the literature. Acta Haematol. 2011;125:237-41.
22. Gmidène A, Frikha R, Sennana H, Elghezal H, Elloumi M, Saad A. T (1; 21; 8)(p34; q22; q22): a novel variant of t (8; 21) in acute myeloblastic leukemia with maturation. Medic Oncol. 2011;28:509-12.
23. Tirado CA, Chen W, Valdez FJ, Henderson S, Doolittle J, Garcia R, et al. Acute myeloid leukemia (M2) with a cryptic RUNX1/RUNX1T1 t (1; 21; 8)(p36; q22; q22) variant. Cancer Genet Cytogenet. 2009;193:67-9.
24. Rubnitz JE, Lensing S, Zhou Y, Sandlund JT, Razzouk BI, Ribeiro RC, et al. Death during induction therapy and first remission of acute leukemia in childhood. Cancer 2004;101:1677-84.
25. Odero MD, Vizmanos JL, Rom´n JP, Lahortiga I, Panizo C, Calasanz MJ, et al. A novel gene, MDS2, is fused to ETV6/TEL in a t(1;12)(p36.1;p13) in a patient with myelodysplastic syndrome. Genes, chromosomes and cancer. 2002;35:11-9.
26. Nishikata I, Sasaki H, Iga M, Tateno Y, Imayoshi S, Asou N, et al. A novel EVI1 gene family, MEL1, lacking a PR domain (MEL1S) is expressed mainly in t(1;3)(p36;q21)-positive AML and blocks G-CSF-induced myeloid differentiation. Blood. 2003;102:3323-32.
27. Min YH, Eom JI, Cheong JW, Maeng HO, Kim JY, Jeung HK, et al. Constitutive phosphorylation of Akt/PKB protein in acute myeloid leukemia: its significance as a prognostic variable. Leukemia 2003;17:995-7.
28. Sasaki O, Meguro K, Tohmiya Y, Funato T, Shibahara S. Sasaki T. Altered expression of retinoblastoma protein-interacting zinc finger gene, RIZ, in human leukaemia. Br J Haematol. 2002;119:940-8.

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