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A NOVEL VARIANT OF T(17;17)(Q12;Q21) IN CHILD WITH ACUTE PROMYELOCYTIC LEUKEMIA.

Genetics

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ABSTRACT

Variant translocations are rare in acute promyelocytic leukemia (APML) and are seen only in about 1-2% of cases .Here we describe a novel variant translocation (17;17)(q12;q21) in an 18 month old child with APML and its implications in planning his course of therapy. This variant translocation case report highlights the importance of Karyotyping for both diagnosis and prognosis in APML.

KEYWORDS

APML, Variant t(17;17),Karyotyping

INTRODUCTION

The characteristic chromosomal aberration in acute promyelocytic leukemia (APML) is reciprocal translocation (15;17) (q24.1;q21.2) which results in the expression of the promyelocytic leukemia (PML) - Retinoic acid receptor-α (RARA) fusion protein seen in 98% of cases . However, 1-2% of APML cases are due to rare variant translocations, which typically involve RARA gene with other partner chromosomes (1,2). The identification of specific chromosomal abnormality plays an important role to determine therapy and prognosis in subtypes of acute myeloid leukemia (AML). APML is very rare in children below 10 years of age (3). In pediatric AML inv(16),t(16;16), t(8;21),t(15;17) and normal karyotypes are associated with favorable prognosis. However, poorer outcome is observed in t(1;22),inv(3),t(3;3),-5,-7,t(7;12), t(11q23) and other complex abnormalities. Translocation (11)(q23) involving with other partner chromosomes is most common among infants, whereas t(8;21) and t(15;17) are more common in older children with AML (4). Till date seven different variant translocation partners 11q23,11q13,5q35,17q21.1-21.2,17q24, Xp11 and 4q12 of RARA gene have been reported (5). In this article, we discuss about a case of APML with variant translocation involving both the chromosomes 17 in a 18 month old male child and his treatment outcomes.

CASE REPORT

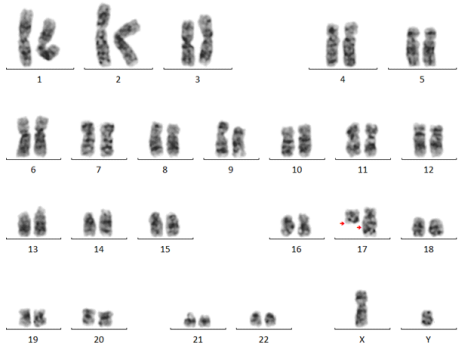
In March 2017, an eighteen month old male child had presented to our hospital with a painless swelling over the left preauricular region for 4 months duration. Clinical examination revealed diffuse boggy soft tissue swelling over the temporal regions, bilateral proptosis and gum hypertrophy causing angulation of the teeth. The child had respiratory distress due to stridor from upper airway obstruction. His past history was unremarkable and he was born to non consanguineous parents, full term by Caesarean section with a birth weight of 2.9 kg, with no perinatal issues and normal development.

Investigations revealed a Hb of 11.1gm%, white blood cell count of $25x10^3/mm^3$ and a platelet count of $48x10^3/mm^3$ with leucocytosis. The child was coagulopathic with prolonged PT and APTT and low fibrinogen. A bone marrow aspiration showed hypercellular particles with myelomonocytic preponderance and a flow cytometry could not be performed. The clinical picture did not correlate with a diagnosis of Juvenile Myelomonocytic Leukemia. The results of Karyotyping with t (17;17)(q12;q21) clinched the diagnosis of APML variant translocation .

Cytogenetic Studies

Chromosomal analysis was done as per standard cytogenetic protocol. Unstimulated cultures of bone marrow aspirate were set up in RPMI-1640 medium supplemented with 20% fetal bovine serum. The cultures were incubated for 48 hours in 5% CO2 incubator. After incubation the culture were terminated by 50µl Colcemid for 1hour followed by hypotonic treatment (0.075M KCL) and fixed with methanol & acetic acid in a ratio of 3:1. The slides were prepared by air-dry method and stained using GTG Banding. Twenty metaphases were analyzed and the karyotype showed 46, XY, der(17), t(17;17)(q12;q21) (Figure No:1) described as per the international system for Human Cytogenomic Nomenclature 2016 (6).

Fig: 1 Karyotype showing 46, XY, t(17;17)(q12;q21)



DISCUSSION

APML is commonly associated with t(15;17) (q22;q21) reciprocal translocation. Usually, APML diagnosis is done by Real Time Polymerase chain reaction (RT-PCR), however the novel variant translocations and other secondary chromosomal abnormalities would be missed by this technique .This highlights the importance and necessity of conventional Karyotyping in the diagnosis, prognosis and follow-up of variants.

Variant chromosomal translocations fuse RARA with one of the partner genes other than PML (1). The variants include t(11:17)(q23;q21) that express a PLZF-RARA fusion; t(5;17)(q35;q21) encodes NPM-RARA; t(11;17) (q13;q21) encodes NUMA- RARA;t (11;17) (p11;q21) encodes BCOR/RARA; t(4;17)(q12;q21) encodes FIPILI/RARA;t (X;17)(p11;q21) encodes BCOR/RARA and der(17)that fuses STAT 5B/RARA (5) .

The most common APML variant is t(11; 17) (q23;q21) observed in 0.8% of APML Patients which fuses ZBTB16 (formerly PLZF [promyelocytic leukemia zinc finger]) with RARA and results in the production of the ZBTB16-RARA fusion protein and the RARA-ZBTB16 reciprocal fusion protein (2). This variant was first described

by Chen et al in 1994(7). The second most common variant is t(5;17)(q35;q21), results in the fusion of NPM (Nucleophosmin Gene) to RARA fusion protein. This variant translocation has been reported in pediatric patients with unfavorable prognosis and poor response to Receptor for all- trans -retinoic acid (ATRA) (8).

The therapy for APML is entirely different to other types of acute myeloid leukemia. The disease is not sensitive to cytarabine which forms the backbone of AML therapy. Differentiating agents such as ATRA and Arsenic trioxide have helped improve cure rates to over 90% in this unique type of AML. Anthracyclines and differentiating agents such as ATRA or Arsenic Trioxide and ATRA combinations form the basis of therapy for APML. However, some variants are not responsive to this therapy and these children need to be treated with AML chemotherapy that includes anthracyclines and cytarabine (9).

Identification of novel variant translocation (17;17) (q12;q21) by Karyotyping in this APML case has helped to plan an appropriate therapy .

The child completed induction as per the UKMRC AML17 protocol with two cycles of cytarabine, daunomycin and etoposide - ADE chemotherapy. A PET CT scan at the end of induction revealed complete resolution of all bone lesions and the bone marrow was in remission with no minimal residual disease as per flow cytometry. The child has completed two further cycles of high dose cytarabine and is currently on follow ups.

CONCLUSION

This case report highlights the importance of chromosomal analysis in planning therapy for patients with variant translocation APML. Novel variants may not respond to conventional treatment and require individualized therapy to optimize better outcomes.

REFERENCES

1. Grimwade D, Howe K, Langabeer S, Davies L, Oliver F, Walker H, Swirsky D, Wheatley K, Goldstone A, Burnett A, Solomon E. Establishing the presence of the t(15;17) in suspected acute promyelocytic leukaemia: cytogenetic, molecular and PML immunofluorescence assessment of patients entered into the M.R.C. ATRA trial. M.R.C. Adult Leukaemia Working Party.Br J Haematol. 1996 Sep;94(3):557-7
2. Grimwade D1, Biondi A, Mozziconacci MJ, Hagemeijer A, Berger R, Neat M, Howe K, Dastugue N, Jansen J, Radford-Weiss I, Lo Coco F, Lessard M, Hernandez JM, Delabesse E, Head D, Liso V, Sainty D, Flandrin G, Solomon E, Birg F, Lafage-Pochitaloff M Characterization of acute promyelocytic leukemia cases lacking the classic t(15;17): results of the European Working Party. Groupe Français de Cytogénétique Hématologique, Groupe de Français d'Hematologie Cellulaire, UK Cancer Cytogenetics Group and BIOMED 1 European Community-Concerted Action "Molecular Cytogenetic Diagnosis in Haematological Malignancies". Blood, 2000 Aug 15;96(4):1297-308.
3. Ribeiro RC, Rego E. Management of APL in developing countries: epidemiology, challenges and opportunities for international collaboration. Hematology Am Soc Hematol Educ Program. 2006:162-8.
4. Manola KN Cytogenetics of pediatric acute myeloid leukemia. Eur J Haematol. 2009 Nov; 83(5):391-405. Epub 2009 Jun 25
5. Adams J, Nassiri M Acute Promyelocytic Leukemia: A Review and Discussion of Variant Translocations. Arch Pathol Lab Med. 2015 Oct; 139(10):1308-13
6. McGowan-Jordan, Jean; Simons, Annet; Schmid, M (Michael); International Standing Committee on Human Cytogenomic Nomenclature.ISCN : an international system for human cytogenomic nomenclature (2016) Basel ; New York : Karger, [2016]
7. Chen Z1, Guidez F, Rousselot P, Agadir A, Chen SJ, Wang ZY, Degos L, Zelent A, Waxman S, Chomienne C. PLZF-RAR alpha fusion proteins generated from the variant t(11;17)(q23;q21) translocation in acute promyelocytic leukemia inhibit ligand-dependent transactivation of wild-type retinoic acid receptors. Proc Natl Acad Sci U S A. 1994 Feb 1;91(3):1178-82
8. Zamecnikova A, al Bahar S. t(5;17)(q35;q21) NPM1/RARA. Atlas Genet Cytogenet Oncol Haematol. in press.2017
9. Li EQ1, Xu L, Zhang ZQ, Xiao Y, Guo HX, Luo XQ, Hu Q, Lai DB, Tu LM, Jin RM. Retrospective analysis of 119 cases of pediatric acute promyelocytic leukemia: Comparisons of our treatment regimes. Exp Ther Med. 2012 Jul;4(1):93-98. Epub 2012 Apr 17.