Chronic myelomonocytic leukemia with t(12;15) involving dup(1) identified by cytogenetic and molecular cytogenetic approach: A novel favorable-risk translocation

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CASE REPORT


ABSTRACT: According to guideline of WHO classification system of Myeloid malignancies, Chronic Myelomonocytic Leukemia (CMML) is observed as the most frequent entity among myeloproliferative/myelodysplastic syndromes. The blast cells observed in the peripheral and marrow was considered as the major prognostic factor identified at that time. Cytogenetic prognostications are not much clear. We studied a patient with CMML with a successful conventional cytogenetic analysis at diagnosis. Combined results of Fluorescence In Situ Hybridization and Multi Color banding technique revealed a new variant and novel t(12;15) along with duplication of chromosome 1 in CMML. The patient showed BCR-ABL negative in FISH assay result and positive for JAK2 mutation study. Patient achieved remission without any treatment. This is potentially suggestive of a novel favorable-risk translocation in CMML.

Key Words: Chronic Myelomonocytic Leukemia, chromosome, Karyotype, FISH, Multicolor Banding.

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MMML (CMML) is a clonal stem cell disorder and shows overlapping features of Myelodysplastic Syndromes (MDS) and MyeloProliferative Neoplasm (MPN). There is an inherent tendency to transform to Acute Myeloid Leukemia (AML 30%) and CMML-1 often results in peripheral blood mononucleosis. Molecular and epigenetic abnormalities are seen in 49%. Cytogenetic changes with clonal abnormalities are observed in 30% of cases. There are two subtypes of CMML-1 (15% circulating blasts and 10% bone marrow blasts) and CMML-2 (5-19% circulating blasts, 10–19%). About 30% of patients showed clonal cytogenetic changes, whereas 90% of cases showed molecular and epigenetic abnormalities. Mutations observed in CMML involve epigenetic regulators (TET2 60%), chromatin/histone modulators (ASXL1 40%), spliceosome components (SRSF2 50%), transcription factors (RUNX1 15%) and cell signaling (RAS 30%, CBL 15%). Among these, thus far, on multivariable analyses that have included additional CMMML relevant factors, only ASXL1 mutations (frame shift and nonsense) and have been shown to be prognostically disadvantageous (1). According to the World Health Organization (WHO) criteria (2008), CMML is a disorder characterized by: (a) persistent peripheral blood monocytosis $41 \times 10^3 / \text{L}$; (b) absence of the Philadelphia chromosome and the BCR-ABL1 fusion oncogene; (c) absence of the PDGFRα or PDGFRβ gene rearrangements; (d) $<20\%$ blasts and promonocytes in the peripheral blood and BM, and (e) dysplasia involving one or more myeloid lineages. If myelodysplasia is absent or limited to erythroid series of patients with CMML are varied because of different factors like frequency of abnormal karyotype and specific chromosomal abnormalities. The potential impact of Cytogenetics in CMML was unable to find an independent relationship between cytogenetic results and disease outcomes (3). The frequency of abnormal karyotype and specific chromosomal abnormalities in series of patients with CMML are varied because of different factors like small numbers of patients, strict inclusion criteria (WHO or FAB criteria), and referral patterns. Frequency of chromosomal abnormalities in CMML is close to 25% (range 11-42%) 27% in the current study) and the karyotypic aberrations observed are not specific for CMML but also commonly found in other MDS subtypes and AML. There was no deletion of 7 q/monosomy 7, trisomy 8 (4,5). Life expectancy of patients with CMML is variable from several months to years in natural course of treatment. Numerous studies have been conducted to identify factors associated with these different prognoses. Study of prognostic factors may help to know the biology of the disease, develop risk-tailored treatment course, and evaluate new treatments for defined groups (6). In the current research paper, we focus and summarize phenotypic and prognostic cytogenetic and molecular abnormalities in CMML. To the best of our knowledge, this is the first report characterizing a ETV6-RUNL-19P partner gene in a case of CMML with t(12;15), and the first to suggest an unusually favorable outcome.

CASE DETAILS

A 46 years old male with complaints of low grade fever and abdominal pain underwent a bone marrow aspiration and biopsy. Hemoglobin-12 gm/dL, Hematocrit-39%, RBC-3.04x10^12/cm, WBC- 24.5x10^9/cm, Platelets 189x10^9/cm, Blast Cells-3%, Myelocyte-10%, MetaMyelocyte-12%, Polymorpho-9%, Basophils-4%, Lymphocytes-18%, Monocytes-20%, Eosinophils-4%. Bone marrow examinations showed M:E Ratio absent. Megakaryocytes occasionally seen, no Blast cells-2%, Metamyelocytes-22%, Myelocytes-5%, Polymorphs-42%, Eosinophils-3%, Lymphocytes-15%, Monocytes-4%, Early Normoblasts-2%, Inter Normoblasts-3%, Late Normoblasts-2%. Granulocytic precursors and polymorphs were seen. Very few erythroid precursors were seen and showed normoblastic maturation. Megakaryocytes were occasionally seen. Peripheral smear showed RBC normocytic normochromic, with few microcytic hypochromic RBCs. WBC elevated LDH (712.8 U/L), Uric Acid (7.64 mg/dL), Alkaline Phosphatase (ALP) (146 IU/L).

Other Laboratory Investigations

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Mutation Analysis

JAK2 mutation analysis was carried out using Real Time PCR using Exon 14 mutation of V617F and results were positive for mutation.

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Received: June 28, 2018, Accepted: August 06, 2018, Published: August 20, 2018

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J Blood Disord Treat Vol 1 No 2 May 2018
MATERIALS & METHODS

Conventional Cytogenetic

For conventional cytogenetic study standard cytogenetic protocol was followed using Bone marrow sample. Short term culture and GTG banding were carried out for reporting. Metaphases with well spread and good morphology were captured in scanning and capturing system Metafer (Zeiss-Germany) and analysis using IKAROS software and karyotype description was done using ISCN 2016 guidelines.

Fish Study

Fluorescence In Situ Hybridization (FISH) for BCR-ABL Dual Color Dual Fusion (DCDF) probe, del5q, del7q, Whole Chromosome Paint (WCP) FISH probes for chromosome 1 Spectrum Green (SG) and WCP 15 Spectrum Orange (SO) was applied on metaphase cells. Due to scarcity and unavailability of WCP FISH probes, we couldn’t able to apply WCP 12 probe so we used CEP 12 FISH probe and WCP 15 in subsequent studies (Abott Molecular, USA).

Multicolor Banding Technique

Multicolor banding (mBAND) analysis using mBAND probe sets for chromosome 1 (MetaSystems, Altlussheim, Germany). The mBAND results were evaluated using MetaSystems software.

RESULTS

Conventional Cytogenetic Data

GTG banding for Karyotype analysis

In conventional cytogenetic study, G banded karyotype report showed 46 chromosomes. There was additional chromosomal material on q arm of chromosome 1. Also translocation of Chromosome 12 and 15 were observed in conventional cytogenetic study. So Karyotype result was 46,XY,dup(1)(q),t(12;15)(p12;q22) [20] (Figure 1).

Fish

FISH with BCR-ABL DCDF Probe

FISH was carried out using LSI DCDF FISH BCR-ABL probe. Results showed 2O2G signals indicating negative for BCR-ABL fusion (Figure 2).

FISH with WCP 1 (SG) and WCP 15 (SO) Probe

FISH was carried out using WCP1 and WCP 15 and result showed there was a duplication of chromosome 1 in all metaphases and deletion of chromosome 15 and part of orange signal was observed on p arm of C group chromosome. The results revealed that there was no translocation between chromosome 1 and 15. So further FISH was carried out using WCP15 and CEP 12 (Figures 3a & b).

FISH with WCP15 (SO) and CEP 12(SG)

FISH results with WCP 15 and CEP 12 revealed orange signals of chromosome 15 present on p arm of chromosome 12(SO). So final karyotype with combined result of conventional cytogenetic and FISH was 46,XY,dup(1)(q),t(12;15) (Figures 4a & b).

FISH with deletion 5q Probe

FISH was also carried out using Deletion 5q probe. Results showed that 2O2G signals indicating that there was no deletion of 5q (Figure 5).

FISH with deletion 7q Probe

FISH was carried out using Deletion 7q probe. Results showed 2O2G signals indicating that there was no deletion of 7q (Figure 6).

![Figure 1](https://example.com/image1.png) Conventional cytogenetic results with G banded karyotype showed 46,XY,dup(1)(q34),t(12;15)(p12;q22)

![Figure 2](https://example.com/image2.png) FISH with BCR-ABL dual color Dual fusion probe showed 2O2G signals indicating negative for BCR-ABL fusion
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M-Band Analysis

Multicolor Banding analysis revealed that, there was a duplication of q arm of chromosome 1 (Figure 7).

DISCUSSION

Peripheral Monocytosis with clonal stem cell disorder is the indication of myeloproliferative and myelodysplastic characteristics are the main hallmark.
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In summary, here, we report a case of CMML with novel t(12;15) showed monocytosis with favorable prognosis. Characterizations by cytogenetic and molecular cytogenetic methods are necessary for prognostication and understanding the disease. This report may be helpful for clinician to have a similar case treated. However, more cases are still to be required to study to identify the involved genes and the frequency of this translocation and to assess its potential prognostic value.

CONCLUSION

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