



A RARE JUMPING TRANSLOCATION 46,XY,der(18)t(1;18)(q24;q22)/der(15)t(1;15)(q24;p11.2) DETECTED IN A PATIENT WITH CONCURRENT MORPHOLOGIC, FLOW CYTOMETRIC AND FISH ANALYSIS.

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Abstract

We received a bone marrow sample in our laboratory from an 86 year old male with a 5 year history of myelodysplastic syndrome (MDS) after multiple cycles of chemotherapy. Cytogenetics, FISH, morphology and flow cytometry testing were performed on this sample. The cytogenetics karyotype showed a JT of 46,XY,der(18)t(1;18)(q24;q22)[7]/der(15)t(1;15)(q24;p11.2)[5]/46,XY[8]. In our sample the distal portion of chromosome 1q24 jumped between two different partners including band 15q24 and band 18q22. FISH analysis utilizing the PML/RARA gene fusion showed a normal signal pattern (i.e. no fusion signals present) which confirmed the cytogenetic breakpoint of chromosome 15q24 being distal to the PML gene located at 15q22. The flow cytometry analysis showed a population of abnormal CD117+ blasts (37%). In addition, abnormal myeloid and monocytoid maturation was detected. The flow cytometric findings in this case indicate MDS with increased blasts or AML with myelodysplastic-related changes. The jumping translocation (JT) is a rare chromosomal abnormality in which a specific chromosomal segment translocates onto the ends of various chromosomes (jumps)1. In most cases, the region distal to 1q21 jumps onto numerous (different) telomeres2. Usually jumping translocations are unbalanced rearrangements. In most cancer cases, the donor segments originated from the long arm of chromosome 1. The chromosome segment can be characterized by the relocation of the same part of a donor to several recipient chromosomes. Although JT occasionally are constitutional, most are associated with hematologic malignancies. In such cases, JT usually arise during disease progression and are associated with poor prognosis4. There have been fewer than 70 cases of acquired jumping translocations reported in the literature thus far, and 20 cases have been reported in leukemias3. Reported cases of JT in myeloproliferative disease are rare and require more data to study. Additional molecular studies specific to oncogenes involved and subtelomere FISH for chromosome 1, 18, 15, and 17 may provide additional information on this case.

Materials and Methods

Standard cytogenetics.

BM aspirates were analyzed at the time of diagnosis by standard cytogenetic G-banding methods according to the specifications of the International Standing Committee on Human Cytogenetic Nomenclature (ISCN, 2005).

Interphase-FISH.

Standard cytogenetic preparations were used for FISH. Unstimulated BM cell cultures were prepared as described previously. FISH was performed with various commercially available probes (Vysis, Downers Grove, IL, USA), which hybridize to genes or polymorphic loci specifically involved in MDS and APL. The following probes were used: LSI 5q31 (EGR1), LSI 7q31 (D7S522), LSI CEP 8 (D8Z2), LSI 11q23 (MLL), LSI 16 (CBFB), LSI t(8q22;21q22)(ETO/AML1), LSI t(15;17)(q22;q21)(PML-Red)/(RARA-Green).

Flow Cytometry

A five color panel of monoclonal antibodies were set up using a standard lyse/wash method and acquired on a 2 laser, 5 color Beckman Coulter FC500 benchtop flow cytometer. Specific leukocyte populations were identified using dot plots with forward angle light scattering, right angle light scattering, and fluorescence. These parameters were acquired as pulse height signals for 60,000 events. Subsequent analysis was performed using layouts created in FC Express™ Clinical software. A hematopathologist interpreted the analysis display along with other test results on this case.

Morphologic Analysis

Bone marrow biopsies displaying were evaluated by morphology and immunohistochemistry including CD117 and CD61.

Cytogenetics results

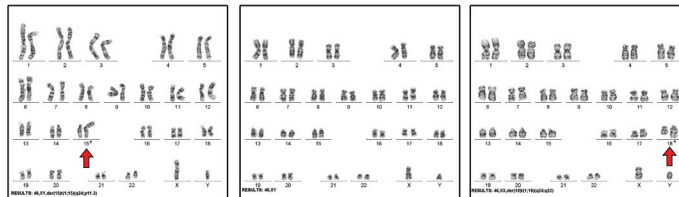


Figure 1-1

Cytogenetic results: Two abnormal cell line clones each sharing a jumping translocation of 46,XY,der(18)t(1;18)(q24;q22)[7] and der(15)t(1;15)(q24;p11.2)[5] and a normal male cell line of 46,XY[8]

FISH Results

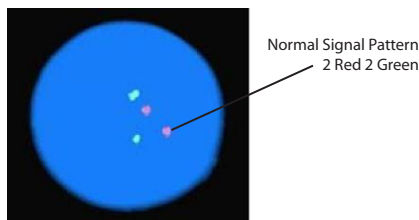


Figure 1-2

FISH results: The Acute promyelocytic leukemia probe for t(15;17) of the PML (located on chromosome 15q22) & RARA (located on chromosome 17q21) genes showed a normal signal pattern (i.e. no fusion signals present) which confirmed the cytogenetic breakpoint of chromosome 15q24 being distal to the PML gene

Flow Cytometry results

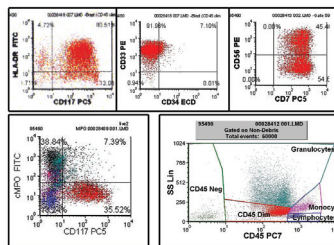


Figure 1-3

Flow Cytometry results: An abnormal population of CD117+, CD45dim+, CD4dim+, CD7mod+, CD13dim+, CD33mod+, CD34-, CD38mod+, CD56bright+, are identified comprising 46% of the cellularity. Abnormal myeloid and monocytoid maturation is identified.

Morphology Results

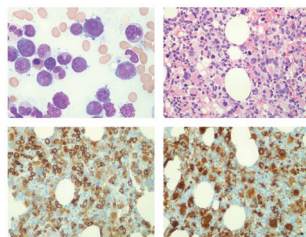


Figure 1-4

Morphology results: Hypercellular marrow (70-80%) with increased blasts consistent with acute myeloblastic leukemia with myelodysplasia related changes.

Conclusion

The patient sample received was studied with several different concurrent oncology assays which included conventional Cytogenetics analysis, Flow Cytometry, interphase FISH analysis, and Morphologic examination. Abnormal findings in Cytogenetics, Flow Cytometry and Morphologic studies were observed. The Cytogenetic findings showed a rare JT of two different clones as 46,XY,der(18)t(1;18)(q24;q22) and der(15)t(1;15)(q24;p11.2) (Figure 1-1). This is an unfavorable complex Cytogenetic result. The FISH analysis utilized a PML/RARA gene fusion probe that showed a signal pattern which is consistent with cytogenetic nomenclature indicating a 15q24 breakpoint distal to the PML gene located at 15q22 (Figure 1-2). Flow cytometry testing demonstrated an abnormal population of CD117+ blasts (37%) with abnormal myeloid and monocytoid maturation (Figure 1-3). Morphologic studies showed a hypercellular marrow (70-80%) with increased blasts (Figure 1-4). These Flow Cytometry and Morphologic results are diagnostic of Acute myeloid leukemia with myelodysplasia-related changes per the WHO Classification. The presence of complex Cytogenetic abnormalities along with abnormal Flow Cytometry and Morphologic results indicate a very poor prognosis. Patients with complex cytogenetic abnormalities will have a 25% survival rate at 1 year and ~5% at 2 years-5-6. Such patients will likely not respond to conventional therapies and may be considered candidates for experimental protocol treatments. Thus Cytogenetic results in this case serve as a very strong adverse prognostic indicator. The patient is known to have a 5 year history of myelodysplastic syndrome and underwent multiple cycles of chemotherapy. We feel the concurrent testing of Cytogenetics, FISH, morphology and flow cytometry aided in elucidating the patient's condition and prognosis for case management. Thus when possible, it is valuable from a clinical stand point to run these tests together.

References

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