

Case Report Section

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Insertion as an alternative mechanism of CFBF-MYH11 gene fusion in a new case of acute myeloid leukemia with an abnormal chromosome 16

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Clinics

Age and sex

17 years old female patient.

Previous history

No preleukemia, no previous malignancy, inborn condition of note. Thalassemia trait carrier.

Organomegaly

Hepatomegaly, splenomegaly, enlarged lymph nodes, no central nervous system involvement.

Blood

WBC : 138.7 X 10⁹/l

HB : 6.9g/dl

Platelets : 51 X 10⁹/l

Blasts : 76%

Bone marrow : 100 Bone marrow biopsy was hypercellular (100%) and replaced by myeloblasts and monoblasts. Normal hematopoiesis was greatly decreased and there was prominent hemophagocytosis. The majority of the blasts were myeloperoxidase positive however another smaller component of blasts was nonspecific esterase positive.

Cyto-Pathology Classification

Cytology: Acute myeloid leukemia with abnormal eosinophils (AML-M4eos).

Immunophenotype

Flow cytometry of bone marrow aspirate identified a significant population of myeloblasts (49%) expressing

CD34, HLA-DR, CD9, CD13, CD33, CD117 and partially expressing CD15, CD11b, and CD64. A second population of monocytes is also identified (37%) expressing CD4, CD14, CD15, CD36 and CD64.

Rearranged Ig Tcr: Not performed.

Pathology

Bone marrow aspirate revealed myeloblasts, monoblasts, monocytes, and increased eosinophils many of which had abnormal granules (FAB AML-M4eos).

Electron microscopy: Not performed.

Diagnosis

Acute myelomonocytic leukemia with abnormal eosinophils (AML-M4eos) and CFBF/16q22 rearrangement.

Survival

Date of diagnosis: 03-2011

Treatment: Intrathecal methotrexate, hydrocortisone, and cytarabine.

Treatment related death : no

Relapse : no

Status: Alive. Last follow up: 09-2011

Survival: 6 months

Karyotype

Sample: Bone marrow

Culture time: 24 hrs without stimulating agents and 48 hrs with 10% conditioned medium.

Banding: GTG

Results

At time of diagnosis abnormal metaphase cells with the following karyotype was found; 46,XX,ins(16)(q22p13p13)[20] (see Figure 1). Remission bone marrow on 4/20/2011 and 9/13/2011 revealed a normal female karyotype; 46,XX[20].

Other Molecular Studies

Technics:

Fluorescence in situ hybridization (FISH) using LSI CBFβ dual color break-apart rearrangement DNA probes (Abbott Molecular IL, USA), and CBFβ/MYH11 dual fusion translocation DNA probe (Cytocell Inc. Cambridge, UK) were performed.

Results:

The hybridization with the CBFβ break-apart probe produced a split pattern in 62% of interphase cells. On metaphase cells, the 5'CBFβ (SepctrumRed) and 3'CBFβ (SepctrumGreen) signals stayed on the 16q, instead of 5'CBFβ being relocated to 16p as seen in the standard inv(16). The CBFβ signals were separated but maintained the orientation pattern of the 5' and 3' probe, suggesting they were split by an insertion (Figure 2A). Subsequently, using the CBFβ-MYH11 probe on metaphases showed that MYH11 signal on 16p moved and juxtaposed to CBFβ on 16q, confirming the insertion of MYH11 into CBFβ (Figure 2B).

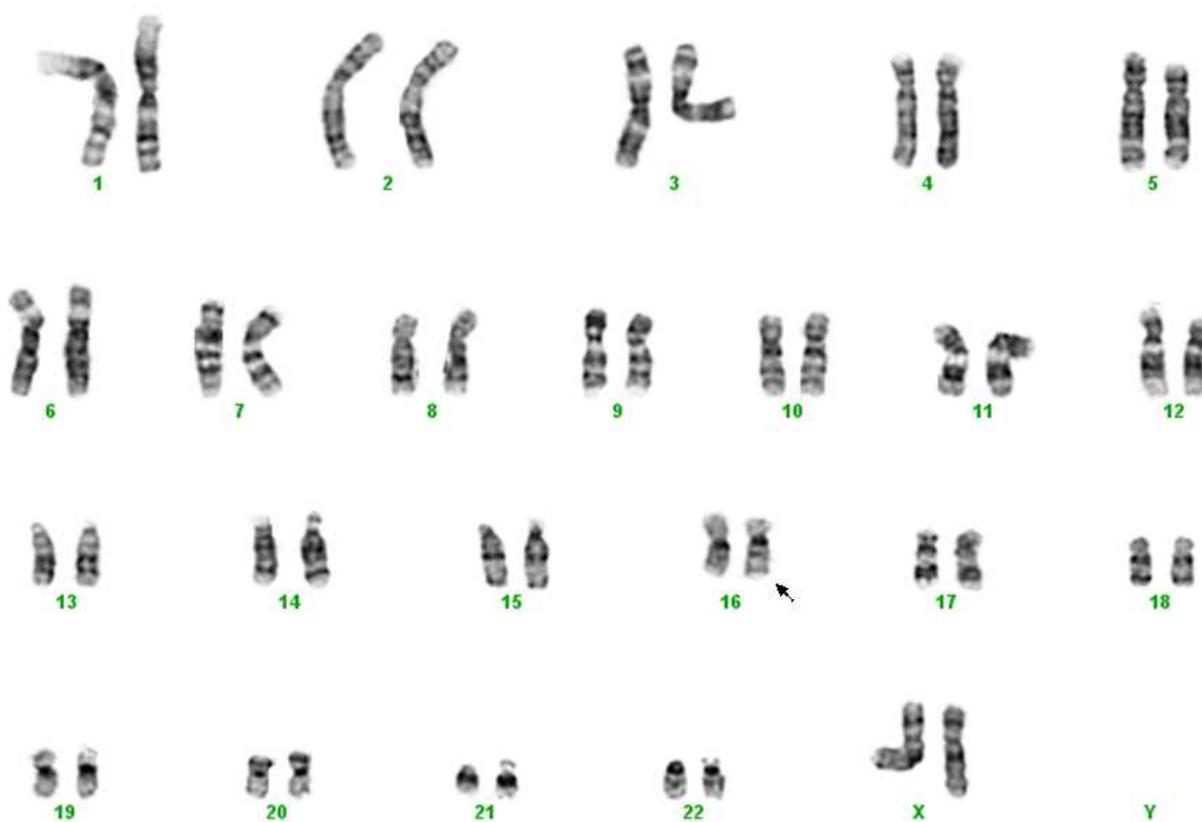


Figure 1. G-Banded karyotype from the diagnostic bone marrow sample demonstrating the ins(16)(q22p13p13) (arrowed).

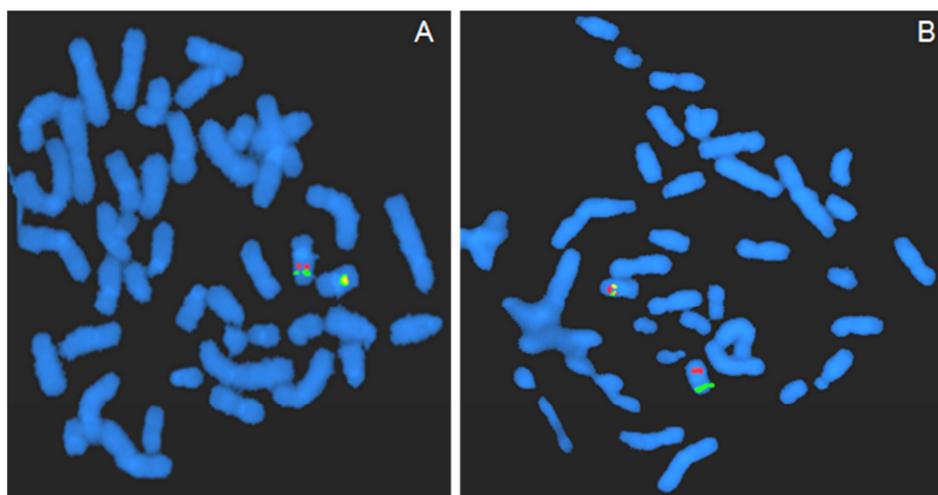


Figure 2. **A.** Metaphase FISH using LSI CBFB/q22 breakapart rearrangement probe showing one normal fusion signal and split signals (red and green) on 16q (arrow). **B.** Metaphase hybridized with CBFB/MYH11 probe showing insertion of MYH11 green signal (appearing yellow) within CBFB/16q22 red signal (arrow).

Comments

The patient described here is a 17 year old female presented with upper respiratory tract infection and bruises for 2 weeks. Subsequently she was diagnosed with AML (FAB M4 eos). Cytogenetics, performed on bone marrow aspirate revealed a unique structural abnormality of chromosome 16 which was interpreted as insertion; 46, XX, ins(16)(q22p13p13). FISH confirmed that the MYH11/p13 gene was inserted into the CBFB/16q22 gene region (Figure 2B). The result of this unusual structural rearrangement was the fusion of CBFB /MYH11 genes commonly seen in inv(16)(p13q22) bearing leukemia.

The CBFB/MYH11 gene fusion is strongly associated with AML-M4 with abnormal eosinophils. Generally, the fusion is generated from inv(16)(p13q22) or t(16;16) with the inversion being much more common than translocation (Le Beau et al., 1983; Tobal et al., 1995). The case presented here demonstrates that insertion is another mechanism in producing CBFB/MYH11 gene fusion in AML-M4eos. To our best knowledge, there is only one reported case of AML-M4 having similar structural abnormality of chromosome 16 and CBFB/MYH11 fusion (O'Reilly et al., 2000). These two cases suggest that insertion

represents a variant rare rearrangement for the formation of this fusion. FISH is highly recommended to characterize unusual abnormalities of chromosome 16 and to confirm the CBFB-MYH11 fusion.

References

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