CASE REPORT

Rare CBFB-MYH11 cryptic rearrangement in acute myeloid leukemia with ins(16)(p13.1q22q22)

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Abstract: Acute myeloid leukemia (AML) with CBFB-MYH11 fusion gene is almost always associated with either inv(16) (p13.1q22) or t(16;16)(p13.1;q22). Only a few variants leading to formation of this chimeric gene have been reported. In this report, we describe a novel type of CBFB-MYH11 fusion variant generated by an insertion of CBFB into the MYH11 gene, which is identifiable by fluorescence in situ hybridization (FISH).

Keywords: AML; ins(16); CBFB-MYH11; FISH


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Introduction

Acute myeloid leukemia (AML) with inv(16)(p13.1q22) or t(16;16)(p13.1;q22) is defined by the World Health Organization (WHO) classification as one of the acute myeloid leukemias with recurrent genetic abnormalities[1]. AML with inv(16)/t(16;16) are associated with the French-American-British (FAB) AML subtype M4eo, which characteristically has myelomonocytic differentiation and atypical eosinophils in the marrow. However, occasional cases with this genetic change lack eosinophilia, or show only monocytic differentiation or only myeloid maturation without a monocytic component[2].

Inv(16)(p13.1q22) or the related t(16;16)(p13.1;q22) results in a fusion gene between the core-binding factor beta gene (CBFB) and MYH11 gene, which encodes smooth muscle myosin heavy chain (SMMHC)[3]. This chimeric transcript consists of upstream CBFB fused to downstream MYH11 coding sequence[4]. It has been proposed that CBFB-SMMHC, the protein product of the CBFB-MYH11 fusion gene, acts by binding and dominantly inhibiting the activity of RUNXI. This leads to changes in gene expression that contribute to leukemogenesis[5].

Until now, only three cases with rearrangements in chromosome 16 other than inv(16)/t(16;16) have been reported to generate fusion of CBFB-MYH11[6-8]. In all the three cases reported, CBFB-MYH11 fusion was formed by the insertion of MYH11 into the CBFB gene. Here, we report an AML case with a novel type of variant formation of CBFB-MYH11 fusion through the insertion of CBFB into the MYH11 gene as identified by fluorescence in situ hybridization (FISH). To the best of our knowledge, no case with this cryptic structural change of chromosome 16 has been previously reported.

Case report

A 72-year-old man was admitted with appendicitis and leukocytosis. Lab study revealed prominent leukocytosis (59 × 10^9/L) with approximately 80% circulating promonocytes and few monoblasts. Flow cytometry performed on the peripheral blood identified 81% immature cells with monocytic differentiation. The immature cells were positive for CD4, CD11b, CD11c, CD13, CD14 (subset), CD33, CD45 (dim), HLA-DR, and MPO (subset), while negative for CD3, CD7, CD10, CD19, CD34, CD117, cCD3, cCD22, cCD79a, and TdT. Bone marrow biopsy showed a hypercellular marrow (95%) with markedly increased blasts with monocytic features (60%), consistent with acute myeloid leukemia. Next-generation sequencing study detected FLT3-TKD and TET2 mutations. Cytogenetic studies were performed on the bone marrow specimen. The initial karyotype of this patient was reported as 46.XY[20] (Figure 1). FISH signals from PML/RARA, AML1/ETO, EVI1, BCR/ABL, and MDS panel probes were within reference range. The FISH test with

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**Discussion**

Around 7%–10% of patients with *de novo* AML have recurrent chromosome changes of inv(16)(p13q22) or t(16;16)(p13;q22)\[9\]. The majority of these AML cases show a typical morphology of the FAB subtype AML M4eo, which is characterized by abnormal bone marrow eosinophils and relatively favorable clinical course. Only rare cases of inv(16) lack the typical features of AML M4eo and may be diagnosed as other subtypes\[9,10\]. On the molecular level, inv(16) and t(16;16) are characterized by a reciprocal rearrangement of the CBFB gene on chromosome 16q22 and MYH11 on 16p13, leading to the formation of a novel CBFB-MYH11 fusion gene, which has been considered a major factor of leukemogenesis\[5\].

Three AML cases were previously reported without visible chromosomal abnormality in chromosome 16, but the rearrangements involving both CBFB and MYH11 genes were identified by FISH test\[6–8\]. Two of these cases were confirmed with molecular test for CBFB-MYH11 fusion\[6,8\]. Two of the cases had features of a typical AML-M4eo\[6,7\].
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Based on signal patterns in the interphase and metaphase FISH studies, cryptic chromosomal rearrangements in all three cases were considered as an insertion of parts of MYH11 into the CBFB gene. In this report, we report the fourth case: a normal karyotype but with a cryptic chromosome change identified by FISH with CBFB-MYH11 dual color translocation probes. However, differing from the other cases reported, the cryptic change in our case was caused by a partial insertion of CBFB into the MYH11 gene. The morphology was consistent with acute myeloid leukemia with monocyctic features, but lacking the eosinophilia typically associated with AML-M4eo.

Although it has been recognized that breakpoints at both 16p13 and 16q22 chromosomes are required for the manifestations of complete M4eo syndrome, on the molecular level however, actual type of the CBFB-MYH11 fusion transcripts is strongly correlated with cytology of tumor cells. Since breakpoints at both CBFB and MYH11 gene are variable, the CBFB-MYH11 fusion transcripts are heterogeneous. To date, at least 14 fusions with different lengths have been reported. The majority of AML with inv(16) or t(16;16) show transcript fusions with different lengths have been reported. To date, at least 14 fusion types have been identified in acute myeloid leukemia. A unique cytogenetic-clinico-pathological association. N Engl J Med 1983; 309(11): 630–636. doi: 10.1056/NEJM198309153091103.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Reference


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