"A case with a cytogenetically cryptic variant of the inv(16)(p13q22)/t(16;16)(p13;q22)"

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CORRESPONDENCE

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Acute myeloid leukemia (AML) with the inv(16)(p13q22) or t(16;16)(p13;q22) is a specific clinico-biological entity with predominant abnormal monocytic and eosinophil differentiation; however, occasional cases have been described without the characteristic bone marrow eosinophilia (1).

The inv(16)/t(16;16) is found in 4% of cytogenetically abnormal AML and is associated with a better prognosis (2,3). The inv(16)(p13q22)/t(16;16)(p13;q22) leads to a fusion between the core binding factor B gene (*CBFB*) on 16q22 and the smooth muscle myosin heavy chain gene (*MYH11*) on 16p13. The inv(16)/t(16;16) can be routinely detected by cytogenetic examination, fluorescence in situ hybridization (FISH), or reverse transcriptase PCR. Here, we describe a case with a cytogenetically cryptic variant of the inv(16), due to an insertion of 16p13 into 16q22.

A 57-year-old female patient was admitted with chest pain, mild fever, and a leg wound that was not responding to antibiotics. Lab examination revealed anemia (hemoglobin 7.2 g/dL), an elevated leukocyte count (34.5 $\times$ 10^9/L, with 0.6 $\times$ 10^9/L neutrophils), and thrombocytopenia (43 $\times$ 10^6/L). Coagulation results were normal.

A peripheral blood smear showed an excess of myeloblasts. Bone marrow examination revealed the presence of a population of blast cells (37%), an increased percentage of (pro) monocytes, and suppression of erythroid and megakaryocytic proliferation. A diagnosis of AML-M4 was confirmed according to the French-American-British (FAB) classification.

Cytogenetic analysis showed a normal karyotype (46,XX [20/20]); however, unexpectedly, PCR was positive for a type A *CBFB/MYH11* fusion transcript.

The patient was treated according to the "Hovon 102" AML protocol, consisting of remission induction with idarubicin and cytarabine, followed by two consolidation courses: daunorubicin and cytarabine, and etoposide and mitoxantrone. After the first cycle, a complete morphological remission was obtained, persisting for 6 and 9 months after diagnosis. A 1–3 log reduction of the *CBFB/MYH11* transcript occurred 6 months after diagnosis. At 8 months, the fusion transcript remained stable. The patient relapsed 10 months after diagnosis at morphological (60% blasts in bone marrow) and molecular levels.

Cytogenetic analyses at diagnosis showed R-banded metaphases that were of good quality without evidence of an inv(16) (Figure S1).

The LSI CBFB/16q22 Break Apart Rearrangement Probe (Abbott Molecular, Des Plaines, IL) showed a normal hybridization pattern in 10 of 10 metaphases and in 198 of 200 interphase nuclei; however, an XL CBFB/MYH11 translocation-dual fusion probe (Metasystems) revealed an abnormal hybridization pattern in 70 of 100 interphase cells and in 8 of 10 metaphase cells. In metaphases, a pattern was observed, in which part of the MYH11 probe was inserted into 16q22, without reciprocal translocation of *CBFB* to 16p, whereas the expected pattern in an inv(16) is one fusion signal on 16p13 and one fusion signal on 16q22 (Figures S2 and S3). FISH analysis with the dual color/dual fusion probe revealed an insertion of 16p13 into 16q22, as a cytogenetically cryptic variant of the inv(16)(p13q22)/t(16;16)(p13;q22). An experiment with three probes (XL CBFB/MYH11 translocation-dual fusion probe, and in-house designed subtelomere probes (16p and 16q)) confirmed that the subtelomere of 16q was on the same arm as 16q22, proving the insertion of 16p13 into 16q22 and ruling out a variant. This resolves the discrepancy between the normal cytogenetic result and the positive *CBFB-MYH11* fusion transcript.

To our knowledge, this is only the second reported case of AML with a *CBFB/MYH11* transcript resulting from a cytogenetically cryptic insertion of 16p13 into 16q22 (3). One other case of AML with a *CBFB* fusion transcript, a normal karyotype, and a normal FISH result with break-apart CBFB probes was also described (4).

According to present European Leukemia Net (ELN) recommendation, the molecular detection of an inv(16) is optional in AML with a normal karyotype, and is mandatory only in the case of mitotic failure, poor banding, or cytological features suggestive of AML with inv(16). This observation illustrates that, in rare cases, this may lead to a failure to correctly diagnose AML with inv(16): indeed, there was no cytological indication of AML with inv(16), despite metaphases of good quality. In addition, the widely used LSI CBFB break-apart rearrangement probe also yielded a normal result because no separation of the centromeric and telomeric *CBFB* (16q22) flanking regions occurred in this case. This case suggests that it might be prudent to always perform cytogenetic analysis in combination with molecular detection of the *CBFB-MYH11* transcript. If, alternatively, molecular detection of the fusion is done by FISH, dual color/dual fusion probe sets are recommended, because the cryptic insertion will escape detection by the widely used LSI CBFB/16q22 Break Apart Rearrangement Probe.

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Supplementary data

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References

1. Arber DA, Brunning RD, Le Beau MM, et al. Acute myeloid leukaemia with recurrent genetic abnormalities. In: Swerdlow SH, Campo E, Lee Harris N, et al., editors. WHO Classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC; 2008. pp. 110–123.
2. Johansson B, Harrison J. Acute myeloid leukemia. In: Heim S, Mitelman F, editors. Cancer cytogenetics. New York: Wiley-Blackwell; 2009. pp. 45–139.
3. Le Beau MM, Larson RA, Bitter MA, et al. Association of an inversion of chromosome 16 with abnormal marrow eosinophils in acute myelomonocytic leukemia. A unique cytogenetic-clinicopathological association. N Engl J Med 1983;15(309): 630–636.
4. Pirc-Danoewinata H, Dauwerse HG, König M, et al. CBFB/MYH11 fusion in a patient with AML-M4Eo and cytogenetically normal chromosomes 16. Genes Chromosomes Cancer 2000;29: 186–191.

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