

CASE REPORT

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Acute myeloid leukemia with *inv(16)(p13.1q22)* and deletion of the 5'*MYH11*/3'*CBFβ* gene fusion: a report of two cases and literature review

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Abstract

Background: Abnormalities of chromosome 16 are found in about 5–8% of acute myeloid leukemia (AML). The AML with *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22)* is associated with a high rate of complete remission (CR) and favorable overall survival (OS) when treated with high-dose Cytarabine. At the inversion breakpoints, deletion of 3'*CBFβ* has been reported, but most of them were studied by chromosome and fluorescence in situ hybridization (FISH) analyses. The genomic characteristics of such deletions remain largely undefined, hindering further understanding of the clinical significance of the deletions.

Case presentation: We report here two AML cases with *inv(16)* and deletion of the 5'*MYH11*/3'*CBFβ* gene fusion, which were characterized by chromosome, FISH, and single nucleotide polymorphism (SNP) microarray analyses. Both cases have achieved CR for more than three years.

Conclusions: Deletion of 3'*CBFβ* in AML with *inv(16)* is also accompanied with deletion of 5'*MYH11* in all the cases studied by SNP microarray, suggesting that 3'*CBFβ* and 5'*MYH11* were most likely deleted together as a fusion product of *inv(16)* instead of occurring separately. In concert with the findings of other published studies of similar patients, our study suggests that deletion of 5'*MYH11*/3'*CBFβ* in AML with *inv(16)* may not have negative impact on the prognosis of the disease.

Keywords: AML with *inv(16)*, Deletion of 5'*MYH11*/3'*CBFβ*, SNP microarray

Background

Abnormalities of chromosome 16 are found in about 5–8% of acute myeloid leukemia (AML) and are one of the three AML defining chromosomal aberrations regardless of blast percentage under the World Health Organization (WHO) classification [1]. The AML with *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22)* is associated with a high rate of complete remission (CR) and favorable overall survival (OS) when treated with high-dose Cytarabine [2, 3]. The *inv(16)* results in a leukemogenic *CBFβ/MYH11* gene fusion [4, 5]. However, additional chromosome changes and/or gene mutations, such as +22, +8, deletion of 7q, and the *CBL*, *FLT3*,

KIT gene mutations, are frequently found in AML with *inv(16)*. These additional changes/mutations may influence the OS positively or negatively [6, 7]. For example, gain of an additional chromosome 22 in AML with *inv(16)* may predict an improved outcome [6, 8], whereas *KIT* mutations appear to have an increased risk of relapse and shorter survival in adult patients [6, 9]. Less commonly, deletions, especially deletion of 3'*CBFβ*, may occur at the inversion breakpoints. Fourteen cases with *inv(16)* and deletion of 3'*CBFβ* have been reported in literature [10–19]. However, only three of them were studied by microarray analysis, and only one was reported with unambiguous breakpoint coordinates [10]. The genomic characteristics of the vast majority of the reported 3'*CBFβ* deletions were undefined.

Here we reported two AML with *inv(16)* cases, both carried an additional deletion at one inversion breakpoint

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involving the fusion between 5'*MYH11* at 16p13.1 and 3'*CBFB* at 16q22. The genomic characteristics of both cases were characterized by chromosome, FISH and SNP microarray analyses. We also reviewed similar cases reported in literature to investigate possible clinical significance of the deletions at the inv(16) breakpoints.

Case presentation

Case 1

A 24-year-old male presented with intermittent fever and sore throat. A complete blood examination demonstrated a hemoglobin (Hb) count of 70 g/L, a white blood cell (WBC) count of $170 \times 10^9/L$ with 80% blasts and a platelet count of $25 \times 10^9/L$. He had no hepatosplenomegaly. His bone marrow (BM) aspirate exhibited greater than 90% myelomonoblastic cells, with increased maturing eosinophils. Cytochemical staining was positive for peroxidase and esterase. Flow cytometry showed 76% positive CD34 and 5% positive CD64, but negative CD14, consistent with a diagnosis of AML. The patient started induction chemotherapy and achieved a complete hematological recovery on day 21. He then received autologous stem cell transplant (ASCT) after two cycles of consolidation chemotherapy and has remained in CR for three years.

Case 2

A 47-year-old male presented with intermittent low-grade fever and progressive fatigue. A complete blood examination demonstrated a Hb count of 92 g/L, a WBC count of $3.5 \times 10^9/L$ and a platelet count of $43 \times 10^9/L$. This patient had splenomegaly. His BM aspirate showed 50% myeloid blasts. Flow cytometry showed 50% blasts expressed CD34, CD117, CD13, CD33, HLA-DR, and myeloperoxidase (MPO), consistent with a diagnosis of AML. The patient started induction chemotherapy and achieved a complete hematological recovery. He then received two cycles of consolidation chemotherapy. The patient has been in CR for four years.

Methods

Chromosome and FISH analyses

Chromosome G-banding was performed following standard techniques on BM aspirate. FISH was carried out with the commercial *CBFB* dual-color break-apart probe kit (Abbott Laboratories, Lake Bluff, IL) following the manufacturer's protocol. The results were analyzed using the Leica CytoVision system (Leica Biosystems, San Jose, CA).

SNP microarray analysis

Genomic DNA was extracted from BM using QIAGEN EZ1 kit (Qiagen, Hilden, Germany). SNP microarray was set up using Illumina CytoSNP-850 K v1.1 BeadChip (Illumina, San Diego, CA) and analyzed using BlueFuse

Multi (Illumina), based on human genome build GRCh37/hg19.

The nomenclature for the chromosome, FISH and array findings is based on the International System for Human Cytogenomic Nomenclature (ISCN) 2016 [20].

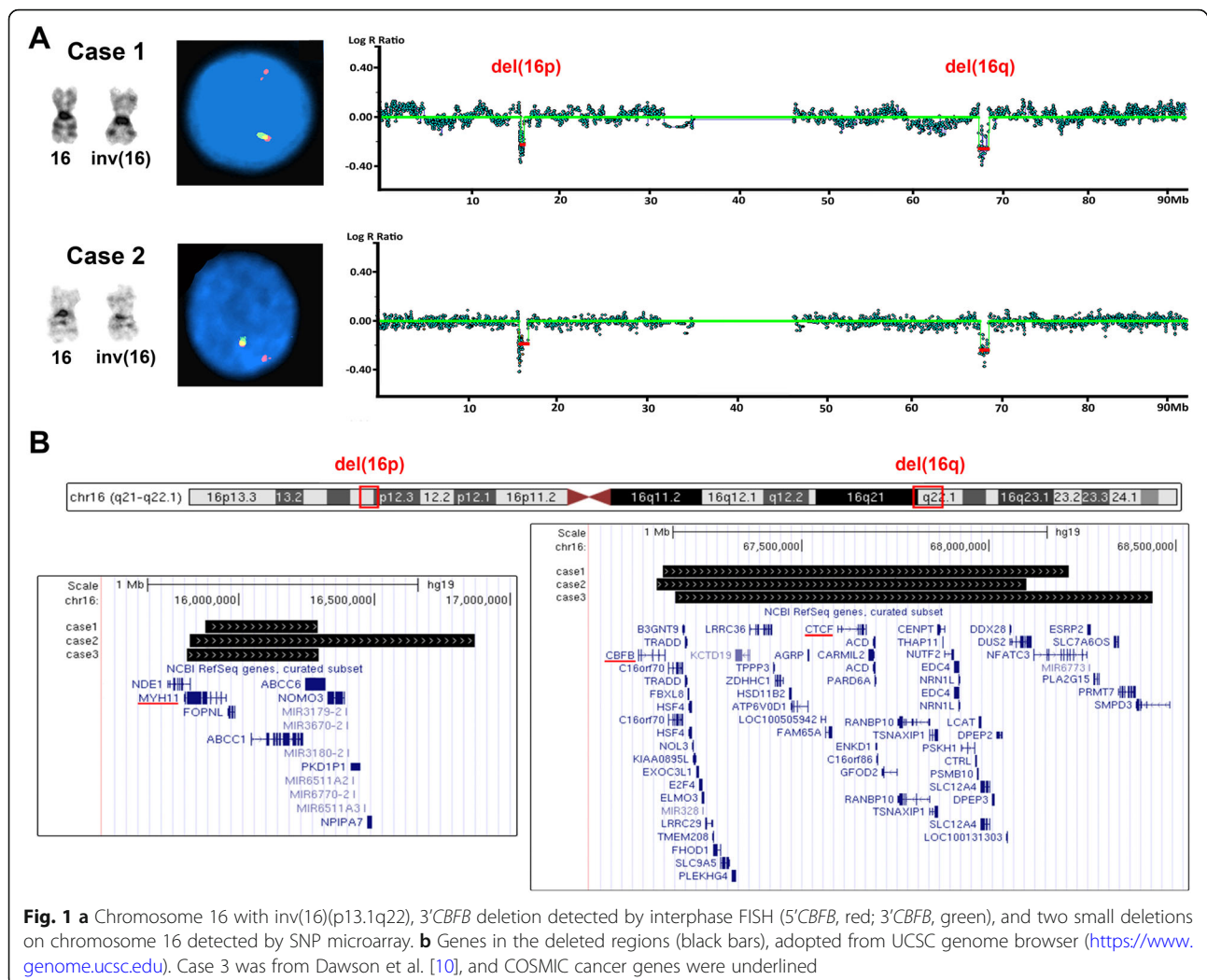
Results

In case 1, chromosome analysis detected an abnormal karyotype with a pericentric inversion of chromosome 16 in all 20 cells analyzed (Fig. 1a), consistent with the diagnosis of AML with inv(16)(p13.1q22); *CBFB-MYH11*. In addition, 4 of these cells showed an extra copy of chromosome 22, which is a common secondary change in this disease. FISH analysis confirmed the inversion but also detected a deletion of 3'*CBFB* in approximately 95.5% of the interphase cells examined (Fig. 1a). SNP microarray confirmed the gain of chromosome 22 and a 1.1 Mb deletion involving 3'*CBFB* on the long arm of chromosome 16 within 16q22.1, and further detected a 416 Kb deletion involving the 5'*MYH11* gene on the short arm of chromosome 16 within 16p13.11. The 16q22.1 deletion involved 53 known genes including 3'*CBFB*, and the 16p13.11 deletion involved 7 known genes including 5'*MYH11* (Fig. 1b). The nomenclature of the cytogenomic findings in case 1 can be described as: 46,XY,inv(16)(p13.1q22)[16]/47,idem,+22[4].nuc ish(5'*CBFB*x2,3'*CBFB*x1)(5'*CBFB* con 3'*CBFB*x1)[191/200].arr[GRCh37] 16p13.11(15875744_16291983)x1[0.9], 16q22.1(67128019_68214140)x1[0.9],(22) x3[0.8].

In case 2, a similar inversion of 16 with gain of additional chromosomes 9 and 22 was detected in all 20 metaphases analyzed by chromosome analysis (Fig. 1a). FISH revealed a similar abnormal signal pattern with a deletion of 3'*CBFB* in approximately 83.5% of the interphase cells examined (Fig. 1a). Similar to case 1, SNP microarray confirmed the chromosome and FISH findings and detected an additional deletion on the short arm of chromosome 16 (Fig. 1a). The 16p13.11p12.3 deletion is 1.1 Mb in size involving 14 known genes including 5'*MYH11*, and the 16q22.1 deletion is 986 kb in size involving 52 genes including 3'*CBFB* (Fig. 1b). The cytogenomic findings of case 2 can be described as: 48,XY,+9,inv(16)(p13.1q22),+22[20].nuc ish(5'*CBFB*x2, 3'*CBFB*x1)(5'*CBFB* con 3'*CBFB*x1) [167/200].arr[GRCh37] (9)x3[0.7],16p13.11p12.3(15817490_16869754)x1[0.7], 16q22.1(67113418_68099821)x1[0.7],(22)x3[0.7].

Discussion and conclusion

AML with inv(16) and deletion of 3'*CBFB* has been reported in at least 14 cases and most of the deletions were detected by FISH using *CBFB* break-apart probes [10–19]. To our knowledge, only three cases were analyzed using microarray, and of these cases, only one reported unambiguous genomic coordinates of the deletion [10, 11]. Noteworthy, all the cases analyzed with microarray,



including the ones in this report, showed an additional deletion of 5'*MYH11*, suggesting that the 3'*CBFB* and 5'*MYH11* were most likely deleted together as a fusion product of inv(16) instead of being deleted separately. More than 10 *CBFB*-*MYH11* fusion transcripts with different sizes due to various genomic breakpoints have been reported [21, 22]. In this study, *CBFB* exons 1–5 fused with *MYH11* exons 8–42 in case 1 and *CBFB* exons 1–4 fused with *MYH11* exons 33–42 in case 2. Both are typical gene fusions in AML-associated inv(16), and the 5'*CBFB*/3'*MYH11* fusion genes are believed to be responsible for the disease of the patients [23]. However, there is no evidence of additional phenotypical effects of deletion of the 5'*MYH11*/3'*CBFB* fusion genes. Both patients in this study responded to chemotherapy well and achieved CR for multiple years. Three cancer-related genes listed in the Cancer Gene Census (CGC) in the Catalogue of Somatic Mutations in Cancer (COSMIC) were involved in the deleted regions, including *MYH11* in 16p, *CBFB* and *CTCF* in 16q (Fig. 1b) [24]. *CBFB*/*MYH11* gene fusion caused by

inv(16) or t(16;16) results in two fusion genes, 5'*CBFB*/3'*MYH11* and 5'*MYH11*/3'*CBFB*. The former is a known pathogenic cause of AML, but the pathogenic effect of the latter is uncertain. We further reviewed reported AML cases with inv(16) and deletion of 3'*CBFB* (Table 1) and did not find significant phenotypical differences caused by the deletion of 3'*CBFB*. Of the 14 cases with clinical data available, 11 (79%) were known to achieve CR with known survival time up to 48 months at the time of report. This small cohort data appears to be in line with the CR rate (86–88%) and the five-year OS rate (50%) in AML with inv(16) [8, 25]. Taken together, the findings suggest that the 5'*MYH11*/3'*CBFB* fusion gene may play minimal roles in AML pathogenesis. *CTCF* is thought to be a tumor suppressor gene [26]. Kemp et al. reported *CTCF* haploinsufficiency destabilized DNA methylation and predisposed mice to cancer [27]. However, deletion of this gene in the current cases apparently did not result in additional phenotypical changes. Such changes, if there are any, may be less significant or overlapped with that of the AML

Table 1 The previously reported AML cases with inv(16) and 3'CBFB deletion

Cases	Sex	Age (yrs)	Karyotype	FISH	Microarray	CR	Survival (months)
Case 1	M	24	46,XY,inv(16)(p13.1;q22)[16]/47,idem,+22[4]	nuc ish(5'CBFBx2.3'CBFBx1)(5'CBFB con 3'CBFBx1)[191/200]	arr[GRCh37] 16p13.1(15875744_16291983)x1[0.9], 16q22.1(67128019_68214140)x1[0.9],(22)x3[0.8]	Yes	36+
Case 2	M	47	48,XY,+9,inv(16)(p13.1;q22)+22[20]	nuc ish(5'CBFBx2.3'CBFBx1)(5'CBFB con 3'CBFBx1)[167/200]	arr[GRCh37] (9)x3[0.7],16p13.1(15817490_16869754)x1[0.7],16q22.1(67113418_68099821)x1[0.7], (22)x3[0.7]	Yes	48+
Dawson et al.	M	30	46,XY,del(7)(q32),del(16)(q22)[10]	ish_der(16)inv(16)(p13.1;q22)del(16)(q22q24)(p13.3)(pter+)(p13.1)(5'CBFB+)(q22)(3'CBFB)(q24)(qter+)[20]	arr[GRCh36] 16p13.1(15714571_16201064)x1, 16q22.1(65726391_66930693)x1	Yes	16+
Haferlach et al. case36	M	39	inv(16)(p13q22)	NA	arr16q22.1(65663366_66436096)x1	NA	NA
Haferlach et al. case37	M	70	45,X,-Y,inv(16)(p13q22)[17]/46,XY[3]	NA	arr16p13.1(157354443_16623582)x1,16q22.1(65654291_66288890)x1	NA	NA
Tirado et al.	M	13	46,XY,inv(16)(p13.1;q22)[2]/46,idem, del(7)(q22q32)[16]/46,idem,t(9;22;19)(q34;q11.2;p13.1)[2]	ish_inv(16)(p13.1)(5'CBFB+)(q22) (3'CBFB-[20],nuc ish(5'CBFBx2.3'CBFBx1) (5'CBFB con 3'CBFBx1)[191/200]	ND	Yes	10+
Spencer et al.	M	8	46,XY,inv(16)(p13.1;q22)[6]/46,XY, der(16)inv(16)del(16)(q22)[5]/46,XY[9]	Deletion of 3'CBFB	ND	Yes	2+
Hung et al.	M	32	46,XY,inv(16)(p13.1;q22)[5]/46,idem, del(7)(q32)[9]/47,idem,+22[3]/48,idem, del(7)(q32)+20,+22[3]	Deletion of 3'CBFB	ND	Yes	Died
Kelly et al. case 1	F	76	46,XX,inv(16)(p13q22)[10]	Deletion of 3'CBFB	ND	Yes	4+
Kelly et al. case 2	F	20	46,XX,inv(16)(p13q22)[8]/46,XX[2]	Deletion of 3'CBFB	ND	No	NA
Kelly et al. case 3	M	68	47,XY,+8,inv(16)(p13q22)[12]/46,XY[3]	Deletion of 3'CBFB	ND	No	Died
Egan et al.	M	17	46,XY,inv(16)(p13.1;q22)[17]/47,idem,+22[3]	Deletion of 3'CBFB	ND	Yes	Relapse
Kolomietz et al. case 1	NA	NA	inv(16)(p13q22)	Deletion of 3'CBFB	ND	Yes	Relapse
Kolomietz et al. case 2	NA	NA	inv(16)(p13q22)	Deletion of 3'CBFB	ND	No	Died
Pirc-Danoewinata et al.	F	18	47,XX,+22[20] ^a	Deletion of 3'CBFB	ND	Yes	42+
Batanian et al.	M	2.5	46,XY,der(16)inv(16)(p13q22)del(16)(q22)[17]/45;idem,-Y[3]	Deletion of 3'CBFB	ND	Yes	NA

M male, F female, NA not available, ND not done, CR complete remission

^a5'CBFB/3'MYH11 gene fusion was detected by RT-PCR

with inv(16). Nevertheless, the significance of deletion of *CTCF* in AML with inv(16) needs to be further investigated. There are five cases with inv(16) and deletion of *3'CBFB*, which either did not achieve CR or relapsed (Table 1). Since the deletion sizes and other genomic characteristics of these cases were undefined, it is unclear whether additional genes or other genomic elements were affected. Array analysis of similar cases may provide more insights on genomic changes and corresponding pathogenic effects in these cases.

Deletion of the *3'CBFB* gene is a recurrent finding in AML with inv(16). It most likely represents deletions of the *5'MYH11/3'CBFB* gene fusion from the inv(16) as a secondary change following the inversion. The *5'CBFB/3'MYH11* fusion resulting from the inv(16) is a known pathogenic cause of AML, but the *5'MYH11/3'CBFB* fusion may play a minimal role in AML pathogenesis. The *CTCF* gene adjacent to the *3'CBFB* was deleted in the current cases, suggesting that deletions of *CTCF* in AML with inv(16) may not have prognostic significance either. However, potential pathogenic effects of other genes involved in extended deletion regions may not be excluded.

Abbreviations

AML: Acute myeloid leukemia; ASCT: Autologous stem cell transplant; BM: Bone marrow; CGC: Cancer Gene Census; COSMIC: Catalogue of Somatic Mutations in Cancer; CR: Complete remission; FISH: Fluorescence in situ hybridization; Hb: Hemoglobin; ISCN: International System for Human Cytogenomic Nomenclature; MPO: Myeloperoxidase; OS: Overall survival; SNP: Single nucleotide polymorphism; WBC: White blood cell

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Authors' contributions

LL and ZQ collected the data and wrote the draft of the manuscript. JY reviewed the manuscript and made critical revision of the manuscript before submission. All authors read and approved the final manuscript.

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Availability of data and materials

The data used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All patient-related data were collected retrospectively and anonymously. The study was approved by the Institutional Review Board (IRB) of University of California San Francisco.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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