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LETTER TO THE EDITOR

ZMYM2-FGFR1 fusion as secondary change in acute myeloid leukemia

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Gene fusions in hematopoietic malignancies are often primary drivers that define many aspects of these diseases. For example, *BCR-ABL1* fusion is a diagnostic marker that encodes a therapeutic target for CML and subgroups of ALL and AML. Late-appearing secondary *BCR-ABL1* fusion is very rarely reported [1–3]. Chromosome rearrangements involving 8p, which lead to *FGFR1* fusion with various partners, are associated with myeloid/lymphoid neoplasms with eosinophilia. In a recent issue of Leukemia & Lymphoma, Strati et al. described the largest series of patients with *FGFR1*-rearranged hematological neoplasms. Each of the 17 cases had a chromosome 8p aberration, with *FGFR1* rearrangement confirmed by FISH [4]. More than 80 *FGFR1*-rearranged hematological neoplasms have been described in other publications, and *FGFR1* rearrangement was present in the main cytogenetic abnormal clone in all cases. Indeed, *FGFR1* rearrangement was the sole cytogenetically demonstrable aberration in most of these cases [4–5]. This study reports the first case of AML in which t(8;13) *FGFR1* rearrangement occurred as a secondary aberration, as a subclone of the initial *EVI1*-rearranged leukemia.

A 70-year-old female presented with fatigue, weakness, and lightheadedness. Physical examination was negative for adenopathy, bruise/bleed, hepatomegaly or splenomegaly. Complete blood count demonstrated pancytopenia with WBC 3.5, Hg 6.1, HCT 17.6, and Plt 89. Bone marrow biopsy showed that approximately 70% of the bone marrow cellularity was an interstitial infiltrate of intermediate sized blasts with round nuclei, dispersed chromatin, indistinct nucleoli and small amounts of eosinophilic cytoplasm, as confirmed by CD34 and c-Kit immunostains. Erythroid elements were markedly proportionally increased and exhibited maturation. Myeloid elements were markedly proportionally decreased and exhibited maturation. Megakaryocytes were markedly increased and occurred in occasional loose clusters, and included frequent dysplastic small hypolobated forms. Bone marrow cytogenetic analysis showed a translocation between chromosomes 3 and 8 in all 15 metaphases, with 2 of these abnormal cells also showing a translocation between chromosomes X and 2. FISH analysis showed that the t(3;8) led to *MECOM (EVI1)* rearrangement (Figure 1(A,B)). A targeted gene panel assay found mutations in *U2AF1*, *ASXL1,* and *PTPN11*. A diagnosis of AML with myelodysplasia-related changes was made. The patient was treated with standard daunorubicin and cytarabine on a 7 + 3 regimen, HiDAC (1.5 g/m^{2}x8) reinduction and subsequently 3 cycles of decitabine (20 mg/m^2 daily, for 10 days) (Table 1). However, a complete remission was never achieved, and blast cells fluctuated between 10% and 50%. Karyotype analysis from 3 additional biopsies all showed the t(3;8) as the sole cytogenetic aberration. Bone marrow biopsy 12 months after the initial diagnosis demonstrated a jump in blasts to 80–90%. Karyotype analysis demonstrated the t(3;8) in 9 cells, of which 4 cells also contained a newly acquired t(8;13) (Figure 1(C)). FISH assays confirmed *FGFR1* rearrangement (Figure 1(D)). FISH was also performed on 2 previous samples retrospectively, which showed no *FGFR1* rearrangement in 200 interphase nuclei (positive cutoff value >1% in this lab), while *MECOM* rearrangement was detected as expected in both samples; confirming a late-appearing *FGFR1* rearrangement (data not shown). The patient succumbed to the disease one month later.

We describe, here, *FGFR1* rearrangement as a secondary change in AML with *MECOM* rearrangement. The secondary *FGFR1* rearrangement was associated with rapid disease progression. Interestingly, 2 cases of late-appearing t(9;22) have also been reported in leukemias with *MECOM* rearrangement [1–2]. Further, in a series of 42 *MECOM*-rearranged myeloid malignancies, all but one case harbored mutations in the genes activating RAS or receptor tyrosine kinase (RTK) signaling pathways, suggesting synergistic oncogenic relationship between dysregulated *MECOM* expression and RAS/RTK signaling [6]. *ZMYM2* is a zinc finger transcription factor whose fusion with *FGFR1* in the t(8;13) produces a cytoplasmic chimeric protein with ligand-independent dimerization, leading to constitutional activation of FGFR1 kinase signaling [7]. In addition to *ZMYM2*, 13 different *FGFR1* fusion partners have been reported, although *ZMYM2-FGFR1* is the most common fusion, accounting for ~40%

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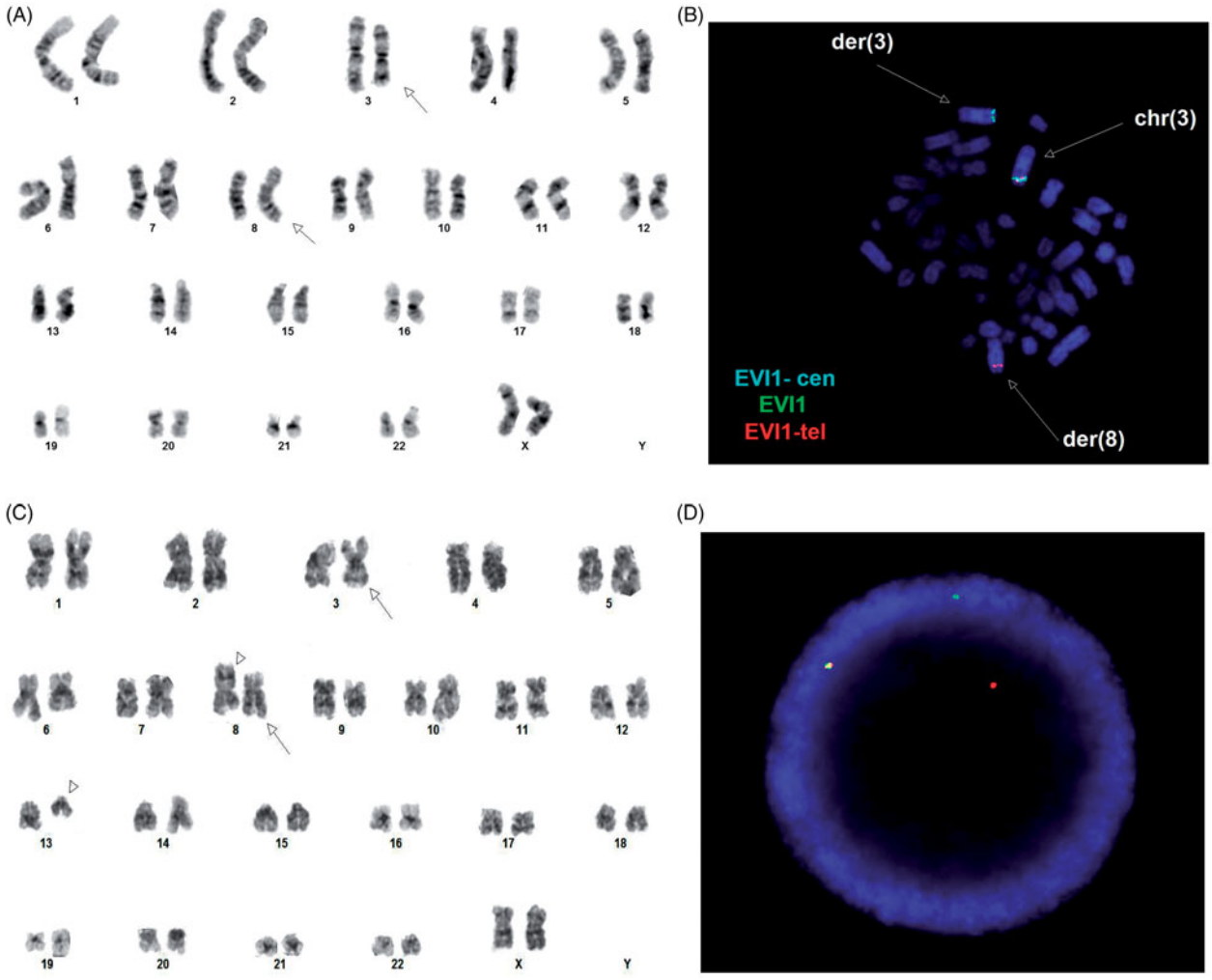

Figure 1. Karyotype and FISH assays detected *MECOM* rearrangement in the initial clone and both *MECOM* and *FGFR1* rearrangement in the subsequent subclone. (A) GTG banding showed translocation between chromosomes 3 and 8 (arrow) as a cytogenetic sole change. (B) FISH analysis showed translocation of the telomeric *MECOM* fragment (red) from chromosome 3 to chromosome 8. (C) GTG banding at time of disease acceleration showed (8;13) (arrowheads) in addition to the t(3;8) (arrows). (D) FISH analysis with *FGFR1* split apart probes confirmed *FGFR1* rearrangement (arrow; red for 5'*FGFR1* and green for 3'*FGFR1*).

Table 1. Karyotype, blasts (%) and therapy history at various times of the disease.

Time	Karyotype	Blasts (%)	Therapy
day 0	46,XX,t(3;8)(q26.2;q24.2)[13]/46,idem,t(X;2)(q13;q13)[2] .ish t(3;8) (RP11-637O11,RP11-82C9+; RP11-362K14+)	70%	7 + 3
day 14	46,XX,t(3;8)(q26.2;q24.2)[10]/46,XX[5]	30-40%	
day 26			HiDAC
day 47		10%	
day 137	46,XX,t(3;8)(q26.2;q24.2)[5]	40-50%	
day 153			Decitabine
day 352	46,XX,t(3;8)(q26.2;q24.2)[7]	30-40%	
day 376	46,XX,t(3;8)(q26.2;q24.2)[5]/46,idem,t(8;13)(p11;q12)[4] .nuc ish (RP11-637O11,RP11-82C9,RP11-362K14x2) (RP11-637O11,RP11-82C9 sep RP11-362K14x1) [83/100],(FGFR1x2)(5'FGFR1 sep 3'FGFR1x1)[17/100]	80-90%	

of all *FGFR1* rearranged cases [4]. The different *FGFR1* fusion partners have clinicopathological associations: for example, *ZMYM2-FGFR1* is associated with T-cell lymphoblastic leukemia/lymphoma, compared to other *FGFR1* rearrangements [8], whereas *BCR-FGFR1* is associated with CML-like disease [9]. Recent studies have also demonstrated oncogenic FGFR1 activation in lung, breast, prostate, and bladder cancers. In these solid tumors, the *FGFR1* genomic aberrations have included gene fusions, point mutations, and gene amplification [10]. While tyrosine kinase inhibitors are effective in treating many tumors, FGFR1 inhibitors have not been very successful in treating tumors with FGFR1 activation. Our initial clinical trial of PKC412 was effective in a patient with progressive myeloproliferative disorder with (8;13) [11]; however, subsequent studies with the FGFR1 inhibitor ponatinib were less successful [12]. Novel FGFR1 inhibitors are currently being tested in clinical trials for solid tumors with FGFR1 activation [13]. Recently a novel FGFR

kinase inhibitor INCB054828 induced complete resolution of eosinophilia, complete hematologic, cytogenetic and molecular remission in a patient with *FGFR1* rearranged MPN [14]. Hopefully these new FGFR1 inhibitors can be helpful in treating myeloid/lymphoid neoplasms with *FGFR1* rearrangements, given that these remain diseases with dismal prognosis.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at https://doi.org/10.1080/10428194.2018.1493733.

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