KMT2A-CBL Fusion Gene Resulting from del(11)(q23.3q23.3) Identified by Chromosome Microarray Analysis - second report in AML

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Abstract

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Clinics

Age and sex: 18 years old female patient.
Previous history: no preleukemia, no previous malignancy; no inborn condition of note
Organomegaly: no hepatomegaly, no splenomegaly, no enlarged lymph nodes, no central nervous system involvement

Blood

WBC: 1.3 (neut 0.1x10^9/L);X 10^9/l
HB: 7.4g/dl
Platelets: 55X 10^9/l

Note

The marrow smears showed heavily infiltrated with medium sized cells, which are round, have minimal lightly basophilic agranular cytoplasm and inconspicuous nucleoli, with partially clumped nuclear chromatin. Some of the nuclei appear cleaved or folded. A minority of the cells has very immature chromatin and/or prominent nucleoli, and are more classically blasts. There are no Auer rods in either population. Very minimal evidence of maturing granulopoiesis and erythropoiesis is seen. Granulopoiesis appears to have normal granulation. Erythropoiesis appears normoblastic and not grossly dysplastic. Some of the mature neutrophils appear dysplastic with abnormal nuclear stranding. Megakaryocytes are not seen.

Cyto-Pathology Classification

Phenotype AML with 'recurrent cytogenetic translocations'

Immunophenotype CD45lo/ SSClo blasts account for 61.2% of total BM intact single cells. Positive for: CD34, CD33, CD15, CD38, CD56, HLADR. By intracellular staining, these cells were entirely cCD34+ and 45% were cMPO+. These cells were negative for: TdT, cCD3- and cCD79a-.

Rearranged Ig Tcr Not performed
Pathology Not performed
Electron microscopy Not performed
Diagnosis Common Acute Myeloid Leukaemia.

Survival

Date of diagnosis 05-2017
Treatment according to FLAG-Ida chemotherapy protocol.
Complete remission: Complete remission was obtained on 06/2017
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**Treatment related death:** no  
**Relapse:** no  
**Status:** Alive  
**Last follow up:** 08-2019  
**Survival:** 26 months +

### Karyotype

**Sample** Bone marrow  
**Culture time** 24h  
**Banding** GTG  
**Results** 46,XX[20] - All 20 G-banded metaphase cells analysed showed a female karyotype with no apparent cytogenetic abnormalities.

**Other molecular cytogenetics techniques**  
1. FISH analysis was performed screening for cryptic chromosome rearrangements using the commercial dual colour break apart KMT2A (MLL) and dual colour dual fusion CBFB-MYH11 probes (both Cytocell, Cambridge, UK) following routine protocol to look for aberrations involving 11q23.3 and for the presence of inv(16)/t(16;16) respectively.  
2. Chromosome microarray analysis (CMA) was performed using 8x60K oligonucleotide arrays (Agilent) analyzed with Agilent Genomic Workbench v 7.0 (settings: ADM2, threshold 6, 3 consecutive probes) at an average resolution of 50Kb. The patient's DNA was hybridized against commercially available same-sex control DNA (Promega) as done before (Nacheva et al., 2013).  
3. The target myeloid gene panel TruSight on a MiSeq platform (Illumina, USA) was used to screen mutational hotspots of 54 cancer-related genes relevant in myeloid malignancy as before (Boneva et al., 2017). Gene variances were reported at allele frequencies (VAF) >10% and at minimum read depth of 300 as per manufacturers criteria. We used the Catalogue of Somatic Mutations In Cancer (COSMIC), dbSNP and 1000 genome (>2%) to classify gene variants as either drivers, variants of unknown significance and/or germline polymorphisms (SNPs). Genome addresses are given according to hg19 (GRCH37)

![Image of FISH and CMA analysis of AML with normal G banding karyotype](image_url)
Other molecular cytogenetics results

**FISH:** nuc ish1q23(5'KMT2Aex2,3'KMT2Aex1) (5'KMT2Acon3'KMT2Aex1)[92/100], 16p13.11(MYH11x2),16q22.1(CBFBx2)[100]. Out of the 100 cells analysed, 92 showed an abnormal signal pattern for KMT2A indicative for interstitial deletion of the 3’ site of the KMT2A gene probe [figure 1a]. All 100 cells analysed were negative for CBFB-MYH11 rearrangement.

**CMA:** arr[GRCh37] 11q23.3 (118355060_119103310)x1 (748Kb). Whole genome scan identified a female genome with two SNP polymorphic markers reported in normal individuals at the Database of Genomic Variants (DGV; http://dgv.tcgac.ca) and a 748Kb deletion within the 11q23.3 region, commencing at chr11:118,355,060 and terminating at chr11:119,103,310 [figure 1b-d]. The genome loss includes 47.855bp from the 5’ part of KMT2A and 26.324bp from the 3’ part of the CBL gene likely resulting in formation of a KMT2A-CBL fusion as described before (Huret et al., 2013; Meyer et al., 2018).

**Variants:** The only mutation identified in this sample is a missense variance of the RUNX1 gene (NP_001745.2:p.Gly372Ser at 36164761) which is predicted to be tolerated’ (http://cancer.sanger.ac and http://www.ncbi.nlm.nih.gov/SNP) and therefore considered indicative for disease only in the presence of cell morphology and immunophenotyping evidence (Genovese et al., 2014; Cargo et al., 2015 and reviewed in Steensma, 2018).

**Comments**

The most common rearrangements of the KMT2A gene are reciprocal chromosome translocations and their prognostic relevance is well established, but deletions of the same region leading to KMT2A fusion rearrangements are rare and little is known about their prognostic significance. We describe the second case of AML with extremely rare 5’KMT2A-3’CBL fusion gene resulting from interstitial cryptic loss (748Kb) within the 11q23.3 chromosome region identified by FISH and CMA analysis. The first case of adult AML, which was reported in 2003, affected a 29-year-old female patient (Fu et al., 2003; also reported in Shih et al., 2006 and in Huret, 2013). In the previous report, the authors demonstrated that the hybrid gene (5’KMT2A-3’CBL) is the result of loss of 3’of KMT2A with breakpoint in exon 9 and fusion whit exon 8 of CBL gene. In present case, we used FISH and CMA to demonstrate interstitial deletion of the 3’ region of the KMT2A gene. We therefore assume that the loss of 3’ part of KMT2A gene leads to 5’ KMT2A -3’CBL fusion as described. What is the prognostic impact of this fusion gene is still unclear. Our patient has achieved complete remission with chemotherapy for 26 months. In both previous and present cases, the fusion 5’ KMT2A - 3’CBL gene results from a cryptic genome loss, the detection of which is beyond G banding resolution and leaves the chromosome 11 banding pattern intact. Of a note, the KMT2A-CBL fusion was also described in T-ALL resulting form t(11;11)(q23;q23). The presented case provides further support to the investigative power of CMA and a reminder for the existence of rare and possibly recurrent 5’ KMT2A - 3’CBL fusion gene in adult AML.

**References**


Fu JF, Hsu JJ, Tang TG, Shih LY. Identification of CBL, a proto-oncogene at 11q23 3, as a novel MLL fusion partner in a patient with de novo acute myeloid leukemia Genes Chromosomes Cancer
