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Acute myeloid leukemia with *KMT2A-SEPT5* translocation: A case report and review of the literature

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Abstract

Chromosomal rearrangement involving the *KMT2A* gene is one of the most common genetic alteration in acute myeloid leukemia. A total of 135 different *KMT2A* rearrangements have been identified, where 94 translocation partner genes are now characterized at the molecular level. Of these 94 translocation partner genes, 35 translocation partner genes occur recurrently, but only 9 specific gene fusions account for more than 90% of cases. Translocation of *KMT2A* with *SEPT5* gene at 22q11.2 is rare, with few reported cases in the literature. In this report, we are presenting a case of *KMT2A-SEPT5* fusion in de novo acute myeloid leukemia with t(11;22)(q23;q11.2) with a review of the literature.

Keywords

Acute myeloid leukemia, *KMT2A*, *SEPT5*

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease, reflecting the complexities of myeloid cell differentiation. The recent 2016 WHO classification[1] divides AML into four main categories: AML with recurrent genetic aberrations, AML with myelodysplasia-related features, therapy-related myeloid neoplasms, and AML not-otherwise-specified. There are minor refinements related to updates in gene names such as the change from *MLL* to *KMT2A* are also included in 2016 WHO classification.[1] Many of the genetic rearrangements in the myeloid neoplasms disrupt genes that are required for normal myeloid differentiation and create new transcripts that are leukemogenic.[2]

Chromosomal rearrangement of the *KMT2A* gene at 11q23 has been reported in approximately 10% of acute leukemias.[3] This rearrangement results in AMLs with predominantly monocytic or myelomonocytic phenotypes. *KMT2A* rearrangement is also associated with therapy-related myeloid neoplasm, specifically following topoisomerase II inhibitor.[4] The MLL recombinome of acute leukemias in 2017[5] identified 11 novel translocation partner genes (TPGs). Thus, a total of 135 different *KMT2A* rearrangements have been identified, where 94 TPGs are now characterized at the molecular level. Of these 94 TPGs, 35 occur recurrently, but only 9 specific gene fusions account for more than 90% of cases.

Translocation of *KMT2A* with *SEPT5* gene at 22q11.2 is extremely rare with few reported cases in the literature.[6] We are presenting a case of *KMT2A-SEPT5* fusion in AML with t(11;22)(q23;q11.2) and review of the literature.

Case report

A 43-year-old Hispanic female presented to the emergency room complaining of fatigue for 2 months with intermittent

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nose bleeding for 2 weeks. The patient had no family history of hematologic malignancies and no history of previous exposure to chemotherapeutic agents. At the time of presentation, she had pancytopenia with a hemoglobin of 7.2 g/dL, white blood cell count of 3.61 × 10^3/μL, platelet count of 21X10^3/μL, and the absolute neutrophil count of 260 cells/μL. The peripheral blood smear showed increased monocytes with rare immature and atypical monocytes.

Bone marrow biopsy was hypercellular for age (90% cellularity) with decreased trilineage hematopoiesis and involvement by 80% blast cells. The leukemic cells were predominantly formed of myeloblasts, monoblasts, immature, and abnormal monocytes. The monocyte precursors formed 38.4% of all nucleated cells. Leukemic cells showed folded nuclei (Figure 1). No Auer rods were noted. Some of the leukemic cells stained for non-specific esterase (alpha-naphthyl butyrate esterase cytochemical stain). Specific esterase (chloroacetate esterase) was positive in monocytes and other granulocytes. Bone marrow biopsy was consistent with the diagnosis of acute myelomonocytic leukemia (French-American-British (FAB) classification M4). Flow cytometry, cytogenetic analysis, and dual-color fluorescent in situ hybridization (FISH) assay were performed.

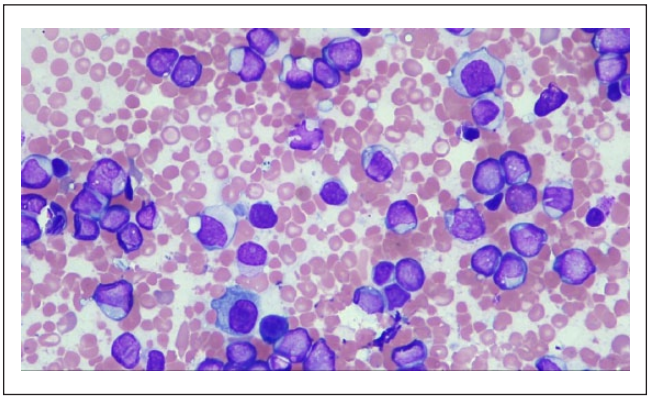

Figure 1. Bone marrow biopsy shows myeloblast population, some with folded nuclei (arrow).

Material and methods

Flow cytometry analysis

Flow cytometry was conducted on the suspended cells utilizing the Beckman Coulter FC500 instrument. Briefly, 100 mL of suspended cells were incubated with 20 mL of the antibody for 15 min, then lysed with fluorescence-activated cell sorting (FACS) solution for 10 min, and finally washed with a phosphate buffer saline (PBS) solution. The data were acquired on the Beckman Coulter FC500 Flow Cytometer and analyzed using the Beckman CXP software.

Cytogenetic analysis

A representative sample of the bone marrow was received for cytogenetic analysis. Standard culture and harvest procedures were performed. Briefly, the tissue was disaggregated and cultured in RPMI 1640 media supplemented with 20% fetal bovine serum for 24–48 h. The cells were exposed to colcemid for 45 min (0.02 μg/mL), were treated with hypotonic solution (0.075M KCl for 20 min), and fixed with methanol and glacial acetic acid (3:1). Metaphase cells were banded with Leishman stain.

Dual-color FISH assay

In an attempt to identify the putative genes involved in t(11;22)(q23;q11.2) translocation, *KMT2A* dual color, break-apart probe (Cytocell, Tarrytown, NY, USA) and *SEPT5* aqua color probe (Empire Genomics, Buffalo, NY, USA) were used. FISH probe set was designed in such a way that the two probes flank both sides of the *MLL* breakpoint region without overlap. The *MLL* (*KMT2A*) product consists of an 87kb probe, labeled in red, covering a region telomeric to the *MLL* (*KMT2A*) gene including the marker D11S3207 and a green probe covering a 168kb region centromeric to the *MLL* (*KMT2A*) gene spanning the *CD3G* and *UBE4A* genes. The *SEPT5* FISH probe was labeled in aqua, looking for 22q11.21 rearrangements. These two probes were commercially procured and mixed in equal proportions, and this probe mix was used to confirm the *MLL*/*SEPT5* rearrangement.

FISH analysis was performed on both interphase and metaphase cells. FISH procedures were carried out on fixed bone marrow cells. Briefly, the slides was prepared and incubated in 2 SSC for 10 min at 37°C, followed by an alcohol series of dehydration. Co-denaturation was carried out at 75°C for 5 min, followed by overnight hybridization at 37°C using the HYBrite instrument (Vysis). Post-hybridization, the slides were washed with 2× SSC/0/3% NP-40 working solution at 70°C for 2 min and counterstained with 4′,6-diamidino-2-phenylindole (DAPI II; Vysis). Evaluation of the FISH signals was performed using the Olympus BX51 fluorescent microscope under 100× magnification. In total, 400 interphase nuclei and 10 metaphase cells were evaluated. Images were acquired by use of the CytoVision Image Analysis System (Applied Imaging, Santa Clara, CA, USA). The FISH results were interpreted in the context of routine G-banded karyotypes, and metaphases were used to verify the interphase FISH pattern as well as to confirm the chromosomal position of the rearrangement.[7]

The 2016 edition of the International System for Human Cytogenomic Nomenclature (ISCN 2016)[8] was used for the nomenclature that is used to describe any genomic rearrangement identified by karyotyping to FISH techniques.

Results

Concurrent flow cytometry analysis was performed on the entire population of cells. Aberrant population of monocytes

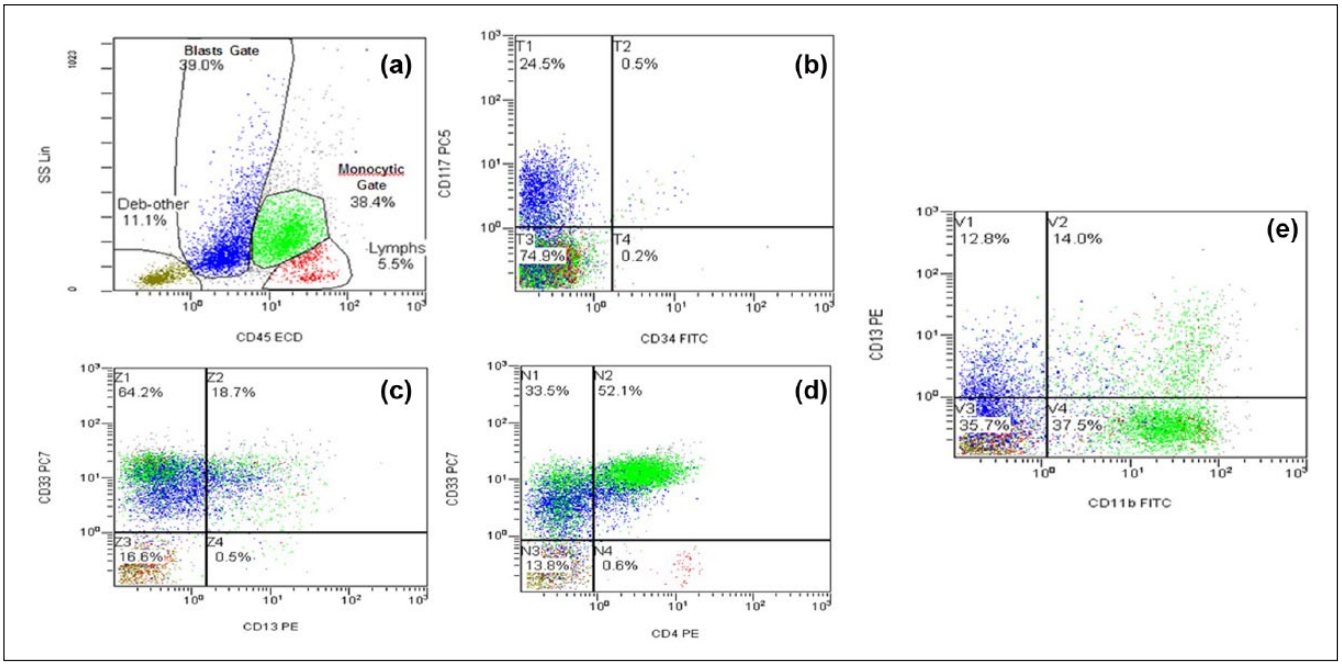

Figure 2. Flow cytometry analysis show 2 prominent populations in blast and monocyte gates (a). These 2 populations are negative for CD34 (b) and positive for CD33 (c). Blast population is positive for CD117 (b), and weakly for CD4 (d), and the monocytic population is positive for CD4 (d) and CD11b (e).

forming 38.4% of cells expressed CD4, CD11b, CD13 (partial), CD14 (partial), CD15, CD33, and HLA-DR, CD64, CD36, and MPO (partial). On the lymphoid gate that represented 11.0% of total cells, B-lymphocyte population showed a polyclonal phenotype expressing CD19 and CD20. The ratio of Kappa to Lambda was normal at 1.45. The T-lymphocyte population had a normal mature phenotype expressing CD2, CD3, CD5, and CD4: CD8 ratio of 0.69. (Figure 2(a)). Both populations were negative for CD34. The cells in the monocyte gate (38.4% of total cells) expressed CD4, CD11b, CD13 (partial), CD14 (partial), CD15, CD33 and HLA-DR. (Figure 2).

Chromosomal analysis showed an abnormal female karyotype with a balanced translocation between 11q23 and 22q11.2 in all 20 metaphase cells; 46, XX, t(11;22)(q23;q11.2) (Figure 3(a)). Molecular analyses were negative for *NPM1, CEBPA, FLT-3 ITD*, and *FLT-3 TKD* mutations. FISH on the metaphase cells of the patient using *KMT2A* break-apart probe (red and green) and *SEPT5* probe (aqua) showed that the 3′*KMT2A* segment was translocated to the derivative chromosome 22, and the breakpoint on chromosome 22 was located near the *SEPT5* gene at 22q11.2. The rearrangement of *KMT2A* with *SEPT5* resulting in der(11) and der(22) chromosomes is shown in (Figure 3(b)). The patient was given induction chemotherapy using anthracycline and cytarabine; patient's condition deteriorated rapidly, and she was transferred to the ICU. The patient developed ventricular tachycardia, then pulseless electrical activity, and unfortunately, she succumbed to the disease in 2 months.

Discussion

To our knowledge to this date, nine cases of AML with t(11;22)(q23;q11.2) translocation resulting in *KMT2A-SEPT5* fusion transcripts have been reported (Table 1); three of the cases were infants, four were in adults, and two cases were unknown (article in Chinese).[9] All cases including ours were diagnosed as AML. The overall incidence of AML with monocytic differentiation in *KMT2A-SEPTIN* cases is 54%, higher with the *KMT2A-SEPT9* and lower with the *KMT2A-SEPT6* translocations.[10] In the AMLs with *KMT2A-SEPT5*, less than half of the reported cases including the current case demonstrate monocytic or myelomonocytic phenotype (Table 1). Tatsumi et al. detected the expression of *SEPT5* in 13 AML and 14 acute lymphoblastic leukemia (ALL) cell lines and found that its expression is significantly higher in AML cell lines than in ALL. This might indicate the importance of *KMT2A-SEPT5* fusion in the leukemogenesis of AML with t(11;22)(q23;q11.2).

The overall survival of the AML patients with *KMT2A-SEPT5* varied according to the therapy protocol. Cases who received allogenic bone marrow graft showed the longest survival. One case survived 2 years[12] and the other is in remission till the date of publication in 2016.[12] All cases listed in Table 1 are de novo, and none were therapy-induced leukemia.

KMT2A translocation can be divided into four distinct categories: fusion with nuclear proteins, fusion with cytoplasmic proteins, fusion to histone acetyltransferases, and fusion to septin family members.[10] Septins belong to GTP-binding proteins that are associated with cell membrane and

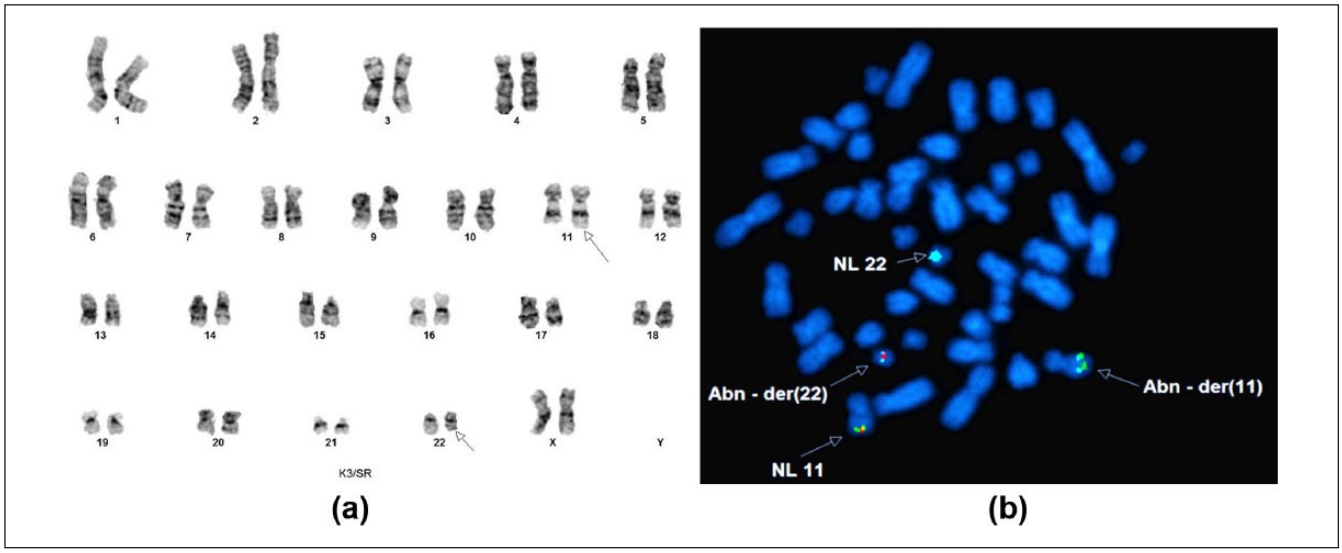

Figure 3. (a) Balanced translocation between the long arm of chromosome 11 and the long arm of chromosomes 22, with breakpoints at 11q23 and 22q11.2. (b) Metaphase FISH analysis confirmed that the 3′ end of *KMT2A* (red) has translocated to chromosome 22 and bind to *SEPT5* (aqua), and part of *SEPT5* (aqua) has fused to the 5′ end region (green) of *KMT2A* on the derivative 11.

Table 1. All the reported cases of AML with *KMT2A-SEPT5* fusion.

Reference	Age/sex	Diagnosis (FAB)	Karyotype	*KMT2A* break-apart probe FISH	*SEPT5* FISH	Prognosis
Current case	43/F	AML-M4	t(11;22)(q23;q11.2)	Positive	*KMT2A-SEPT5*	OS: 2 months
Gao et al.[6]	32/M	AML-M2	t(11;22)(q23;q11.2)	Positive	ND	OS: 7 months
Megonigal et al.[11]	11.5 months/F	AML-M2	t(11;22)(q23;q11.2)	Positive	ND	NR
Megonigal et al.[11]	13 months/F	AML-M1	t(11;22)(q23;q11.2)	Positive	ND	NR
Launay et al.[12]	23 months/F	AML-M5	t(11;22)(q23;q11)	Positive	MLL-*SEPT5*	Survived >2 years after allograft
Tatsumi et al.[13]	39/M	AML-M2	t(11;22)(q23;q11)	Positive	*SEPT5* Split Signals	OS: 12 months
Wang et al.[9]	Not available	AML-M2	t(11;22)(q23;q11.2)	Not available	Not available	CR after induction but died during the consolidation therapy
Wang et al.[9]	Not available	AML-M5	t(11;22)(q23;q11.2)	Not available	Not available	CR by induction chemo
Wang et al.[14]	21/M	AML-M1	t(11;22)(q23;q11.2)	Positive	ND	CR by induction chemo and BM transplant. In remission to date.
Wang et al.[14]	22/F	AML-M4	t(11;22)(q23;q11.2)	NR	ND	NR

AML: acute myeloid leukemia; CR: complete remission; FISH: fluorescent in situ hybridization; ND: not done; NR: not recorded; OS: over all survival.

cytoskeleton.[15] There are at least 13 septin genes throughout the human genome that are expressed in almost all types of tissue; however, expression of some is higher in certain tissues.[15] They have a role in cytokinesis, apoptosis, vesicle trafficking, cell motility, and possibly cell DNA damage checkpoint.[16] Alterations in septin expression have been reported in many malignancies including colorectal,[17] breast,[18] ovarian,[19] urogenital, and brain tumors,[20] as well as non-malignant conditions such as Alzheimer[21] and Parkinson diseases.[22]

Among the septin family genes, rearrangement of *SEPT2, SEPT5, SEPT6, SEPT9*, and *SEPT11* with *KMT2A* have been reported; the majority of them in patients with myeloid neoplasm.[10] The breakpoints in all the septin genes happen between exon 2 and exon 4, creating a fusion gene with *KMT2A* that contains almost the entire open reading frame of the septin genes.[10] Interestingly, the majority of the translocation involving *SETP6* happens in pediatric AML[23] and the ones with *SEPT2* in therapy-related myeloid neoplasms.[24] There have been two reports of *KMT2A-SEPT11*, one in a patient with chronic neutrophilic leukemia[25] and the other in ALL.[26]

Santos et al.[16] have shown that expression of septin genes such as *SEPT2* and *SEPT6* are down-regulated in *KMT2A-SEPT2*- and *KMT2A-SEPT6*-related myeloid neoplasms.[16] Moreover, they demonstrated that down-regulation of septin

genes, including septin 5, is not limited to the myeloid neoplasms with *KMT2A-SEPTIN* and can be detected in other neoplasms including AML with *PML-RARA*.[16] However, the significance of this observation is still unclear and requires additional studies.

In conclusion, we report here a new case of de novo AML with *KMT2A-SEPT5* fusion. Up to date, there are only reported nine cases with the same fusion. The prognosis of the cases varied where our case survived for 2 months since the first induction chemotherapy, while others survived for >2 years after allogenic transplantation. Further studies are required to explore the role of septins in leukemogenic. And, the effect of *KMT2A-SEPTIN* fusion transcripts on the prognosis and response to treatment.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Texas Tech University Health Science Center does not require ethical approval for reporting individual cases or case series.

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Informed consent

Informed consent for patient information to be published in this article was obtained.

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