

Non-acute promyelocytic leukemia variant, acute myeloid leukemia with translocation (11;17)

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Key Clinical Message

t(11;17) is a rare but recognized finding usually found in Acute Promyelocytic Leukemia with variant *RARA* translocation (APLv). We present a case of Acute Myeloid Leukemia with t(11;17) that has different break points than those occurring in APLv. The diagnosis of acute myeloid leukemia, not otherwise specified, acute monoblastic leukemia was reached after a thorough investigation. Reaching the correct diagnosis and distinguishing these two entities are essential as they have different management, prognosis, and overall survival.

KEY WORDS

acute myeloid leukemia, acute promyelocytic leukemia, *KMT2A/SEPT9*, translocation t(11;17), variant *RARA* translocations

1 | CASE REPORT

We present a 21-year-old female who was admitted to our center with one-month history of fatigue, high-grade fever, and generalized skin rash. She sought medical advice for her symptoms before she was seen at our center, and laboratory investigations showed pancytopenia with no definite abnormal circulating cells. Accordingly, she was started on empirical antibiotics and local steroids with no improvement. When she came to our emergency department, initial investigations were requested, including complete blood count (CBC) that reported as white blood cell count (WBC) of $0.49 \times 10^9/L$, red blood cell count (RBC) of $2.98 \times 10^{12}/L$, hemoglobin of 87 g/L, hematocrit (HCT) of 0.258, mean cell volume (MCV) of 86.6 fL, and platelet count of $13 \times 10^9/L$. The white blood cell differential was not performed due to the very low count (differential cut off at our center is $0.5 \times 10^9/L$). Based on the history and CBC findings, the patient was admitted for further assessment and evaluation, that included the following laboratory tests: calcium level: 2.09 mmol/L (low), urea level: 3 mmol/L, creatinine: 106 $\mu\text{mol}/L$ (high), D-dimer 14.91 mg/L (high), fibrinogen level: 3.91 g/L, prothrombin time (PT) 17.9 seconds

(high), international normalized ratio (INR): 1.4 (high), partial thromboplastin time (PTT): 39.5 seconds, and PTT ratio 1.2. Additionally, the patient was scheduled for an urgent bone marrow (BM) examination (which was scheduled in the next morning). An initial peripheral blood smear assessment confirmed the pancytopenia. Moreover, occasional circulating blasts and rare abnormal promyelocytes were seen (Figure 1A-F). Accordingly, the hematology team was informed and the consensus plan based on the rare abnormal promyelocytes seen in the peripheral blood smear and the deranged coagulation profile was to start the patient on all-trans retinoic acid (ATRA) with urgent fluorescence in situ hybridization (FISH) testing on the peripheral blood for assessment of *PML-RARA* translocation, of which the results are discussed later on.

The next day, BM examination showed a diffusely infiltrated BM aspirate by blast cells (about 98%) (Figure 2A,B) and a hyper-cellular BM trephine biopsy (cellularity almost reached 100%) with marked infiltration by blasts (Figure 2C,D). Furthermore, multiparameter flow cytometry (MFC) was performed on the BM aspirate and detected around 78% blasts with positivity for CD45, CD117, MPO, CD33, CD15 (partial positivity), CD4, CD64, CD38, and CD123 (Figure 3).

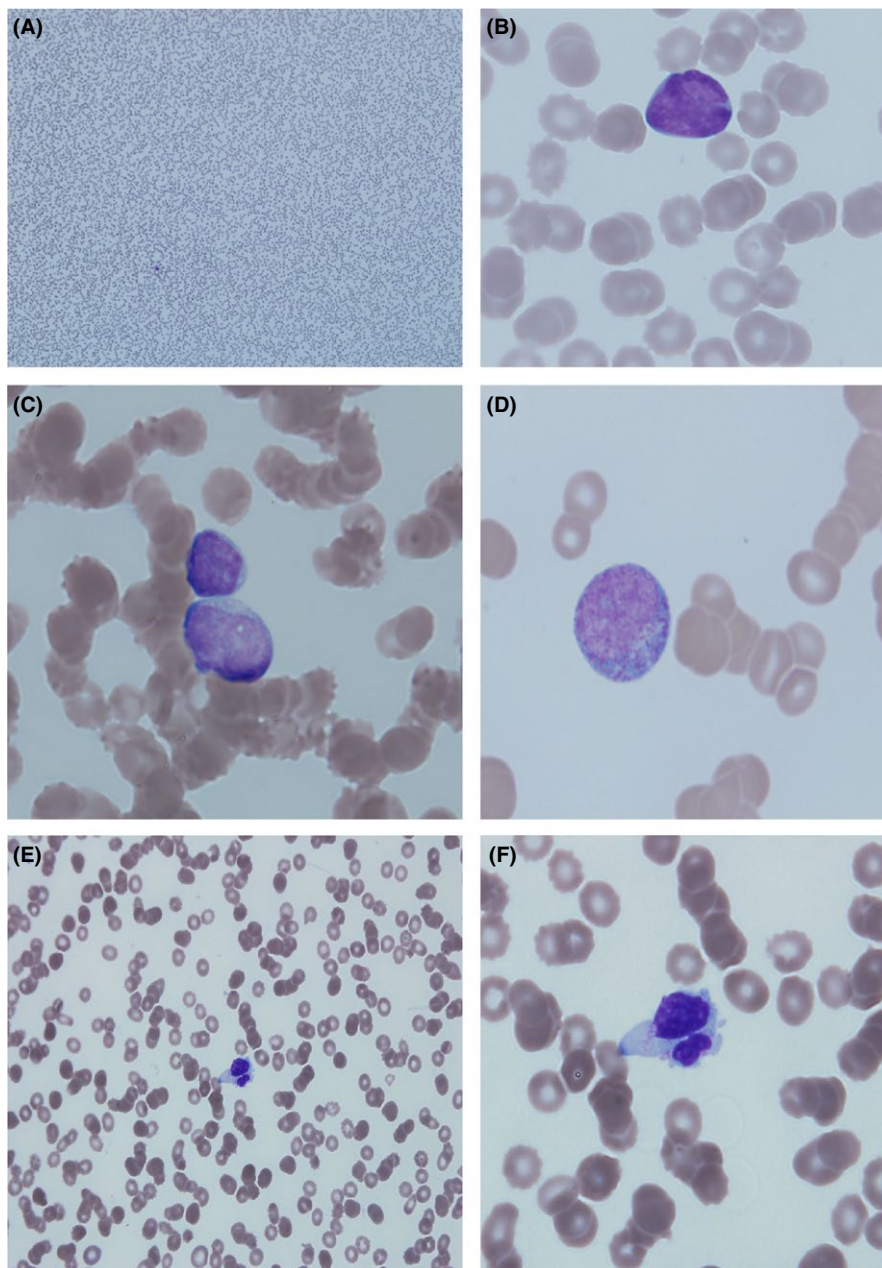


FIGURE 1 Peripheral blood smear showing: (A) marked pancytopenia. (B and C) Rare blasts. (D) occasional promyelocytes. (E and F) low- and high-power images of very rare binucleated (suspicious-looking) cells with sparse cytoplasmic granules

FISH was done on the BM aspirate using five specific probes designed to detect the most common cytogenetic abnormalities and translocations associated with acute myeloid leukemia including the following: *KMT2A* gene at 11q23 rearrangement, which was detected in 96% of nuclei (Figure 4), *RUNX1/RUNX1T1* t(8;21) which showed gain of *RUNX1* signal at 21q22 in 22% of cells. However, the probe showed no evidence of *RUNX1T1/RUNX1* fusion. Interestingly, *PML/RARA* t(15;17) was negative (Figure 5). Lastly, the remaining two probes used to detect *CBFβ* rearrangement at 16q22 and *RPNI/MECOM* t(3;3) or inversion 3 were negative.

Urgent request for molecular *PML_RARA* fusion gene detection by reverse transcription polymerase chain reaction (RT-PCR) was sent and reported to be negative.

The above-mentioned morphological, immunophenotypic, cytogenetics, and molecular findings led to the diagnosis of AML, NOS; acute monoblastic leukemia and the exclusion of suspected APL. As a result, the initial treatment of ATRA started per protocol was aborted after one day and the patient was started on ICE induction protocol (Idarubicin, Cytarabine, and Etoposide).

Other molecular studies including search for *NPM1*, *FLT3*, *IDH1*, and *IDH2* mutations were also done, and all were reported as negative.

Later on, karyotype report was released that detected two related clones: The first clone was 46,XX,t(11;17)(q23;q25)[35] as the sole abnormality, and the second major clone was 47,XX,t(11;17)(q23;q25),+21[45%] (Figure 4).

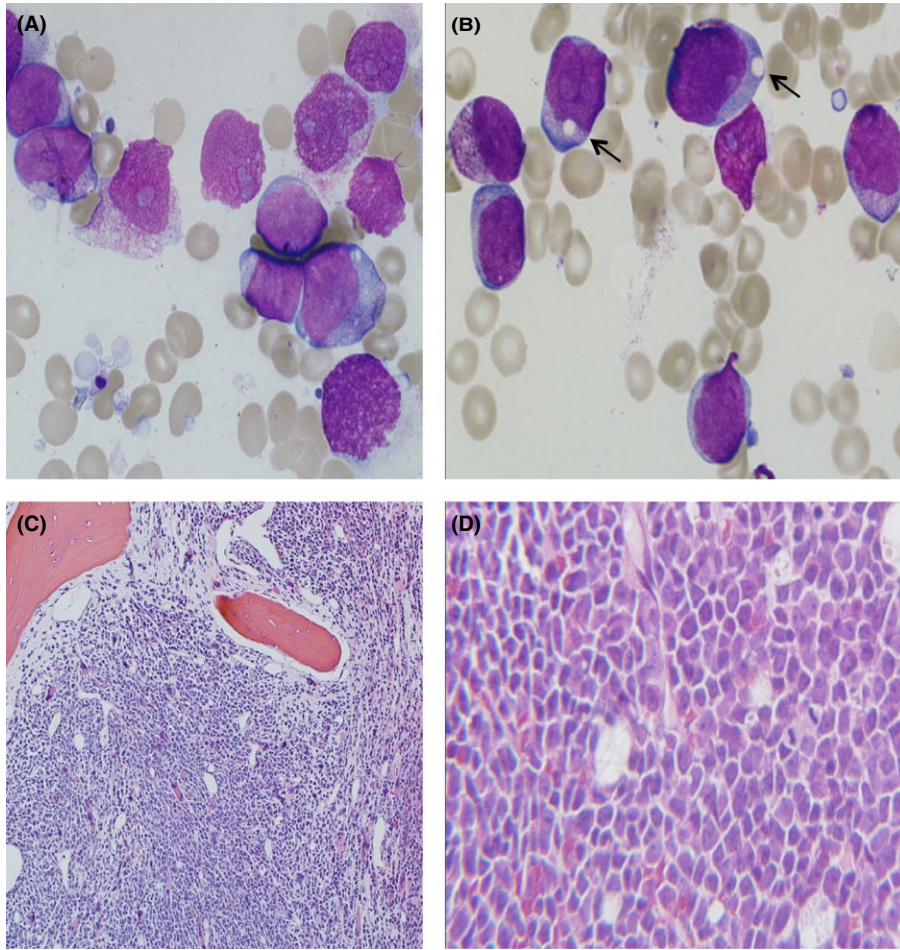


FIGURE 2 (A and B) Bone marrow aspirate showing diffuse infiltration by medium to large blasts with delicately convoluted nuclei, fine lacy chromatin, and multiple prominent nucleoli. The cytoplasm is moderately basophilic with some scattered azurophilic granules and vacuoles (arrows). (C and D) low- and high-power images showing bone marrow trephine biopsy packed with blasts

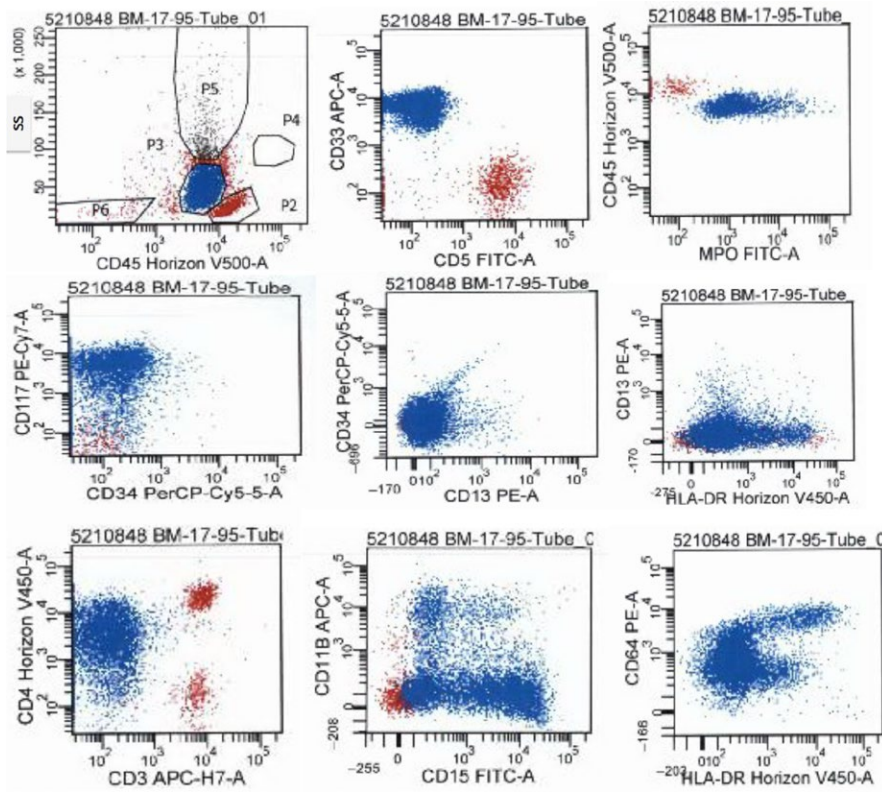


FIGURE 3 Multiparameter Flow cytometry (MFC) scattergram of the diagnostic bone marrow aspirate. Events acquired at the blast gate with dim CD45 and low to intermediate side scatter were analyzed (dark blue population); They are positive for CD33, MPO, CD117, HLA-DR, and CD15 (partial). As well as monocytic markers, including: CD4 and CD64. SS, side scatter; APC, allophycocyanin; FITC, fluorescein isothiocyanate; PE, phycoerythrin; PE-Cy7, phycoerythrin-cyanine5; PerCP-Cy5, peridinin-chlorophyll-protein complex-cyanine

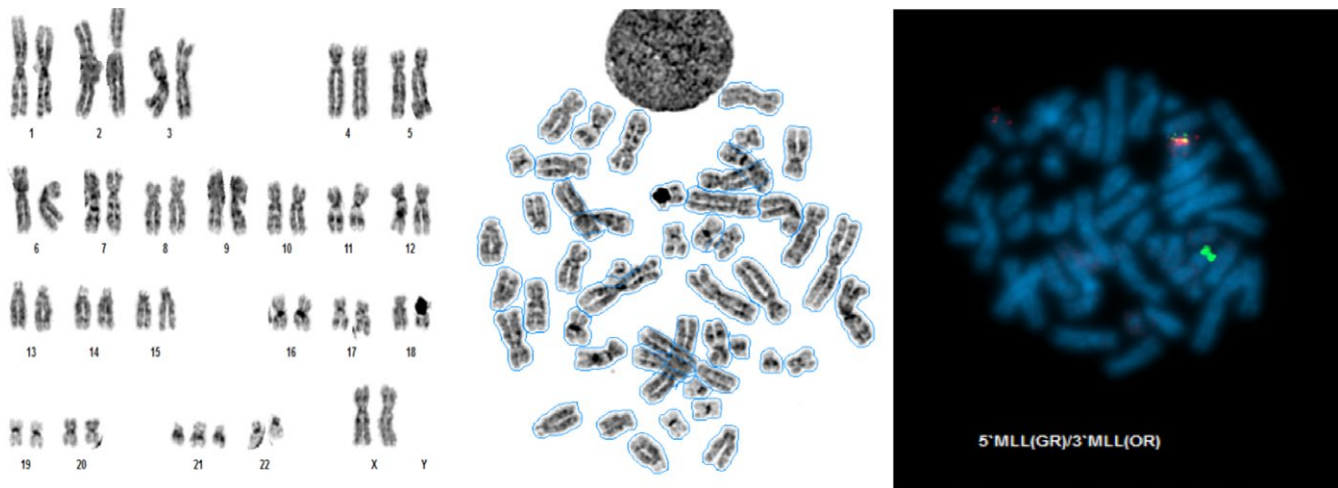


FIGURE 4 karyotype analysis on bone marrow aspirate showing 46,XX,t(11;17)(q23;q25)[7]/47,idem,+21[9]/46,XX[4], and FISH analysis done on bone marrow aspirate interphases, showing positive KMT2A(MLL) gene rearrangement

Per protocol, BM examination was further repeated on day fourteen and day thirty of her induction therapy, which reported as a markedly hypocellular bone marrow with no morphological evidence of residual disease and a mildly hypocellular bone marrow with regenerating trilineage hematopoiesis, respectively. Additionally, MFC and FISH were done on day thirty and showed no evidence of minimal residual disease.

After achieving complete remission (CR),¹ the patient received a myeloablative therapy that was followed by an allogeneic hematopoietic stem cell transplantation (allo-HSCT). Currently, almost one year after the initial diagnosis, the patient is in clinical remission and is following up regularly as an outpatient with the Adult Oncology team at our center and was doing fine with no active issues in her last appointment.

2 | DISCUSSION

During the late seventies, AML was classified into different entities according to the French-American-British (FAB) classification system. However, with the advancements achieved in this field, this classification has been almost completely overcome by a new classification from the World Health Organization (WHO) that was majorly based on the cytogenetic and molecular features of each entity. Translocation t(11;17) is a rare and a well-recognized entity as a variant of acute promyelocytic leukemia (APL_v).² APL_v is an AML subset where the *RARA* (Retinoic Acid Receptor α) gene at the long arm of chromosome 17, region 2, band 1 (17q21) is translocated to different partner genes, including *ZBTB16* (formerly called *PLZF*) at 11q23 and *NUMA1* (Nuclear Mitotic Apparatus Protein 1) at 11q13.4.³

KMT2A gene, (previously termed *MLL* gene, mixed-lineage leukemia gene) is a protein-coding gene that is located at the long

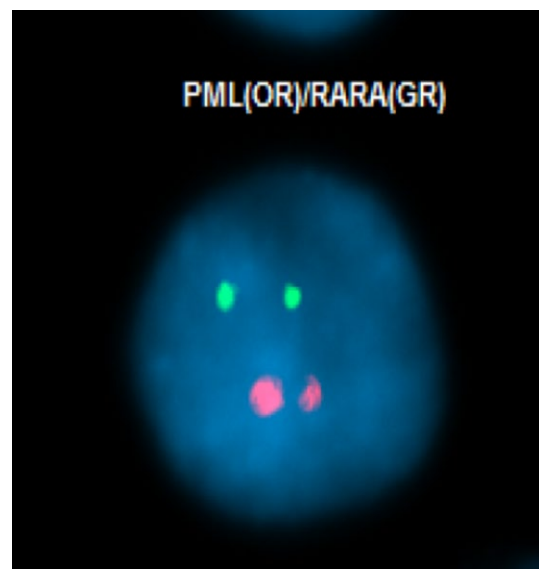


FIGURE 5 Dual-color dual-fusion FISH with probes for PML (15q22), orange signal and RARA (17q12), green signal. As shown: The presence of four separate signals with no fused (and resultant yellow color) signals confirms the absence of PML/RARA translocation (Oncor, Gaithersburg, MD, USA)

arm of chromosome 11, region 2, band 3 (11q23).^{4,6} *KMT2A* gene rearrangements include a wide range of mutations, such as translocations, inversions, insertions, and partial tandem duplications that result in the production of chimeric oncoproteins.^{7,8} These oncoproteins cause a gain of function of the *KMT2A* gene that upregulates the expression of the *HOX* (homeotic gene complex), which has a major role in the regulation of early hematopoiesis.^{9,10} These rearrangements occur in heterogeneous groups of lymphoid, myeloid, and mixed-lineage leukemias.^{4,6} Moreover, they occur in around 5% of newly diagnosed AML and are especially more common in AML with monocytic differentiation like M4, M5a, and M5b; 4.7%, 33.3%, and 15.9%, respectively.⁷

More than 100 different partner genes to *KMT2A* have been described in adults and pediatric AML. Of them, more than 64 genes have been thoroughly studied at the molecular level. These partner genes include the Septin genes family like *SEPT9* gene at 17q25 which is a very rare fusion partner of *KMT2A* that has been reported in a few case reports of acute monocytic leukemia. Some of these cases were associated with adverse or very adverse prognosis.^{11,12} For instance, Kurosu et al reported a de novo acute monocytic leukemia with *KMT2A/SEPT9* that had an aggressive clinical course even after treating the patient with allo-HSCT.¹³

KMT2A gene rearrangements are important adverse prognostic factors in AML. In their presence, AML cases are stratified as intermediate or high risk in most widely used cytogenetic stratification systems.^{9,14,15} Allo-HSCT offers a favorable outcome for these cases when received in early phase.⁸

Although t(11;17) is usually seen with APLv where it occurs between the *RARA* gene at 17q21.2 and different partners including: *ZBTB16* and *NUMA1*,^{2,16} in this case, it occurred at different break points which are t(11;17)(q23;q25), harboring the *KMT2A* and *SEPT9* genes, respectively. The diagnosis of APLv was excluded by the negative results of FISH for *PML/RARA*, as this probe can detect an aberrant *RARA* gene, hence a variant *RARA* translocation. Additionally, all other investigations conducted, including morphological assessment of the BM, immunophenotyping by MFC, cytogenetics, and molecular tests ruled out APLv. Establishing the correct diagnosis, which is acute monoblastic leukemia, is critical as it has different treatment protocols, prognosis, and overall survival than APLv.^{2,3,16-19}

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CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTION

AR: literature review, image collection, writing of the manuscript, and assistance in reaching the diagnosis for the case. AS: thorough editing and feedback on the manuscript. KS: diagnosis of the bone marrow, immunophenotypic and cytogenetic findings of the case, critical review, and supervising of writing of the manuscript.

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