

AML with t(8;21): A Molecularly Defined Entity with Morphological Ambiguities

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August 12, 2025

October 24, 2025

Acute myeloid leukemia (AML) with t(8;21)(q22;q22.1) is well-defined subtype of AML, constituting 1-5% of cases, predominantly affecting children and young adults [1]. In the FAB classification, this cytogenetic abnormality is most often associated with AML-M2. The t(8;21) translocation results in a fusion of ETO (RUNX1T1) gene on chromosome 8 and the AML1 (RUNX1) gene on chromosome 21, resulting in the RUNX1–RUNX1T1 fusion protein, which impairs normal myeloid differentiation and leads to the accumulation of immature myeloid precursors [2]. Patients typically have a favorable prognosis, especially when treated with high-dose cytarabine [3]. However, AML with t(8;21) may present with atypical clinical and morphological features, sometimes mimicking other myeloid neoplasms and complicating diagnosis, as illustrated in the following two cases.

Case 1

A 45-year-old female presented with fatigue, generalized weakness, and abdominal fullness for three weeks. Examination revealed marked splenomegaly (6 cm below costal margin) without lymphadenopathy or hepatomegaly. Laboratory investigations showed a total leukocyte count of $52.6 \times 10^9/L$, hemoglobin of 9.6 g/dL, and platelet count of $21 \times 10^9/L$. Peripheral blood smear demonstrated dysgranulopoiesis and significant shift to left with 44% myelocyte and metamyelocytes, 6% blasts, and 2% basophils (Figure 1A). Bone marrow aspiration revealed myeloid hyperplasia (M:E=10:1) with 8-10% blasts, occasional Auer rods, and prominent dysgranulopoiesis. Differential diagnosis included AML with recurrent cytogenetic abnormality and MDS/MPN (aCML). Flow cytometry showed 6% CD45 dim blasts expressing CD34, CD117, CD33, HLA-DR, CD56, which were negative for CD13, CD123, CD7 and CD11b. Conventional karyotyping revealed t(8;21)(q22;q22), confirmed by RT-PCR. A final diagnosis of AML with recurrent genetic abnormality was made.

Case 2

A 6-year-old male presented with fever, weight loss, and abdominal distension with bilateral proptosis. Examination revealed moderate splenomegaly (4 cm below the costal margin) without hepatomegaly or lymphadenopathy. CBC showed hyperleukocytosis ($101.1 \times 10^9/L$), anemia (9.3 g/dL), and thrombocytopenia ($25 \times 10^9/L$). Peripheral blood showed 8% blasts with few showing Auer rods, marked dysgranulopoiesis, left shift (myelocytes 46%) and thrombocytopenia (Figure 1A). Bone marrow aspirate showed myeloid preponderance with 4% blasts, marked dysgranulopoiesis, and 1% basophils (Figure 1B). Possibilities considered included juvenile myelo-monocytic leukemia (JMML) and AML with recurrent cytogenetic abnormality. Flow cytometry demonstrated blasts positive for CD34, CD117, HLA-DR, CD13, CD33, CD56 and CD38; and negative for CD14, CD64, CD7 and CD10. Cytogenetic studies revealed t(8;21)(q22;q22) and RT-PCR confirmed for RUNX1–RUNX1T1 fusion. A final diagnosis of AML with t(8;21) was made.

According to the WHO 5th edition classification, the presence of certain cytogenetic aberrations is sufficient for the diagnosis of AML regardless of blast count [4]. This reflects a shift toward a genomics-driven classification of myeloid neoplasms, emphasizing the primacy of molecular events over strict morphological thresholds [5,6]. Notably, AML with t(8;21) may present with low blast percentages, particularly when there is prominent granulocytic dysplasia [4,7]. Such presentations can be mistaken for MDS/MPN overlap syndromes, especially if cytogenetic data are unavailable or delayed [4,7], a misclassification that carries profound therapeutic implications. AML with t(8;21) can exhibit low blast counts, granulocytic hyperplasia, and dysplasia, closely mimicking MDS/MPN entities such as aCML or JMML. While morphological overlap can be misleading, accurate diagnosis requires integrating morphological assessment with cytogenetic and molecular data, particularly the identification of

Auer rods and recurrent genetic abnormalities. These cases highlight the critical role of comprehensive cytogenetic and molecular work-up in leukemias with overlapping features and underscore the need to integrate clinical, morphological, immunophenotypic, cytogenetic, and molecular findings. Awareness of these atypical presentations is essential to avoid misdiagnosis and ensure timely, appropriate treatment.

Key words: Acute Myeloid Leukemia, t(8;21)(q22;q22), RUNX1–RUNX1T1 Fusion, Atypical Chronic Myeloid Leukemia, Juvenile myelomonocytic leukemia, Cytogenetics, Molecular Diagnostics

Conflict of Interest: All the authors declared that they have no conflict of interest.

Authorship Contributions

Concept and supervision: S.G.; Data Collection or Processing: R.S, L.G.; Analysis or Interpretation: S.G.; Writing: S.G, R.S., L.G.

Patient consent: Informed consent has been obtained from the patient.

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Short running title: AML with t(8;21) mimicking MDS/MPN

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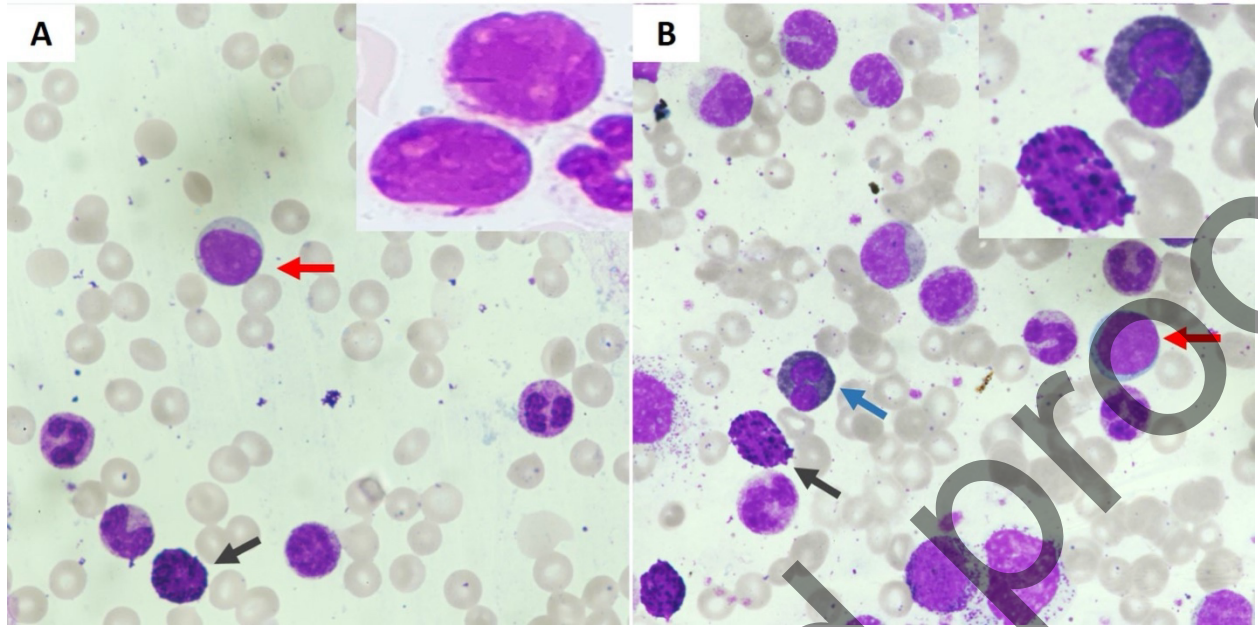


FIGURE. 1. **A** Peripheral blood smear showing blasts (red arrow) and basophils (black arrow) (Jenner- Giemsa stain, X1000) **B.** Bone marrow aspirate smear showing blasts (red arrow), eosinophils (blue arrow) and basophils (black arrow) (Jenner- Giemsa stain, X1000)