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CASE REPORT

A rare presentation of BCR-ABL1 and RUNX1-MECOM rearrangement in a pediatric patient with acute myeloid leukemia

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Key Clinical Message

In a patient with de novo AML, co-existing *BCR::ABL1 p190* isoform and *RUNX1::MECOM* rearrangement is accompanied by a very poor prognosis including limited response to treatment and no molecular remission. It is essential to develop a consensus on the therapeutic modalities different from the current regimen.

Abstract

Acquisition of *BCR::ABL1* fusion as a primary or secondary event and *RUNX1::MECOM* fusion independently is reported in de novo and therapy-related MDS/AML, albeit with low frequency (<0.5%). Coexistence of *BCR::ABL1* and *MECOM* translocation is known to cause leukemogenesis in animal models and progression towards blast crisis CML but not AML. Here we report a unique case of pediatric AML with concomitant BCR::ABL1 and RUNX1::MECOM fusion. Routine diagnostic work-up included WBC manual differential, immunophenotype, morphology, qPCR, FISH, and NGS-based CNV analyses. The patient presented with history of fever, dizziness, fatigue, gingival bleeding, and epistaxis associated with ecchymosis in right hand and heavy, prolonged menstrual period. At presentation, her hemoglobin was 5.3 g/dL, WBC 52.1(10*9/L), PLT 10(10*9/L), ESR 5 mm/h and LDH 2658 U/L. Bone marrow was hypercellular with 71% blasts, and flow cytometry showed myeloid markers including CD11c, CD33, CD34, and CD45 among others indicating AML with monocytic differentiation. FISH analyses showed variant t(9;22) (q34.1;q11.1), one additional copy each of chromosome 8 and *Runx1* gene, while NGS-based CNV analyses revealed a terminal and proximal pathogenic gain within 9q34.12q34.3 and 22q11.1q11.23, respectively, and gain of entire chromosome 8 and 12 in mosaic state. qPCR confirmed the presence of *p190* and also revealed *RUNX1::MECOM* fusion. Patient received ADE (cytarabine, daunorubicin, and etoposide) induction regimen but required multiple ICU admissions due to sepsis, cardiac shock, acute myocarditis,

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and thyroiditis. Coexisting *BCR::ABL1* and *RUNX1::MECOM* fusion is suggestive of poor prognosis, and a need for consensus on the treatment modalities other than the current regimen is warranted.

KEYWORDS
acute myeloid leukemia, *BCR::ABL1* fusion, chronic myeloid leukemia, *RUNX1::MECOM*

1 | INTRODUCTION

Acute myeloid leukemia (AML) with *BCR::ABL1* fusion, also known as AML with t(9;22)(q34.1;q11.2) was a provisional entity in the WHO 2016 classification[1] but is an established new AML type with defining genetic abnormalities in the WHO 2022 version.[2] Clinical findings supporting the diagnosis of de novo AML with *BCR::ABL1* include a lack of history of CML, absence of splenomegaly, and absence of peripheral blood basophilia at diagnosis. AML with *BCR::ABL1* is considered a high-risk disease with poor response to traditional AML therapy or tyrosine kinase inhibitor therapy alone.[3]

The AML is associated with other prognostically significant recurrent genetic abnormalities in the form of isolated chromosomal translocations such as t(8;21)(q22;q22) generating *RUNX1::RUNX1T1*, t(16;16)(p13;q22) generating *CEFB::MYH11* or coexisting rearrangements such as *RUNX1::RUNX1T1*;*BCR::ABL1*.[4] *MECOM* rearrangement and other coexisting genetic abnormalities were reported in elderly patients,[5] and the rearrangement is a well-established entity in WHO 2022 classification with t(3;21)(q26;q22) generating *RUNX1::MECOM* occurring mostly in therapy-related myeloid neoplasm, CML with blast or accelerated phase, and rarely in de novo AML.[6,7] *RUNX1::MECOM* fusion transcript has also been reported in AML secondary to acute promyelocytic leukemia.[8] We report a pediatric AML patient with monocytic differentiation who presented with coexisting *BCR::ABL1 p190* isoform and *RUNX1::MECOM* rearrangement. The patient did not respond well to the AML regimen used suggesting poor prognosis and a need for consensus on the treatment modalities other than the current regimen is warranted.

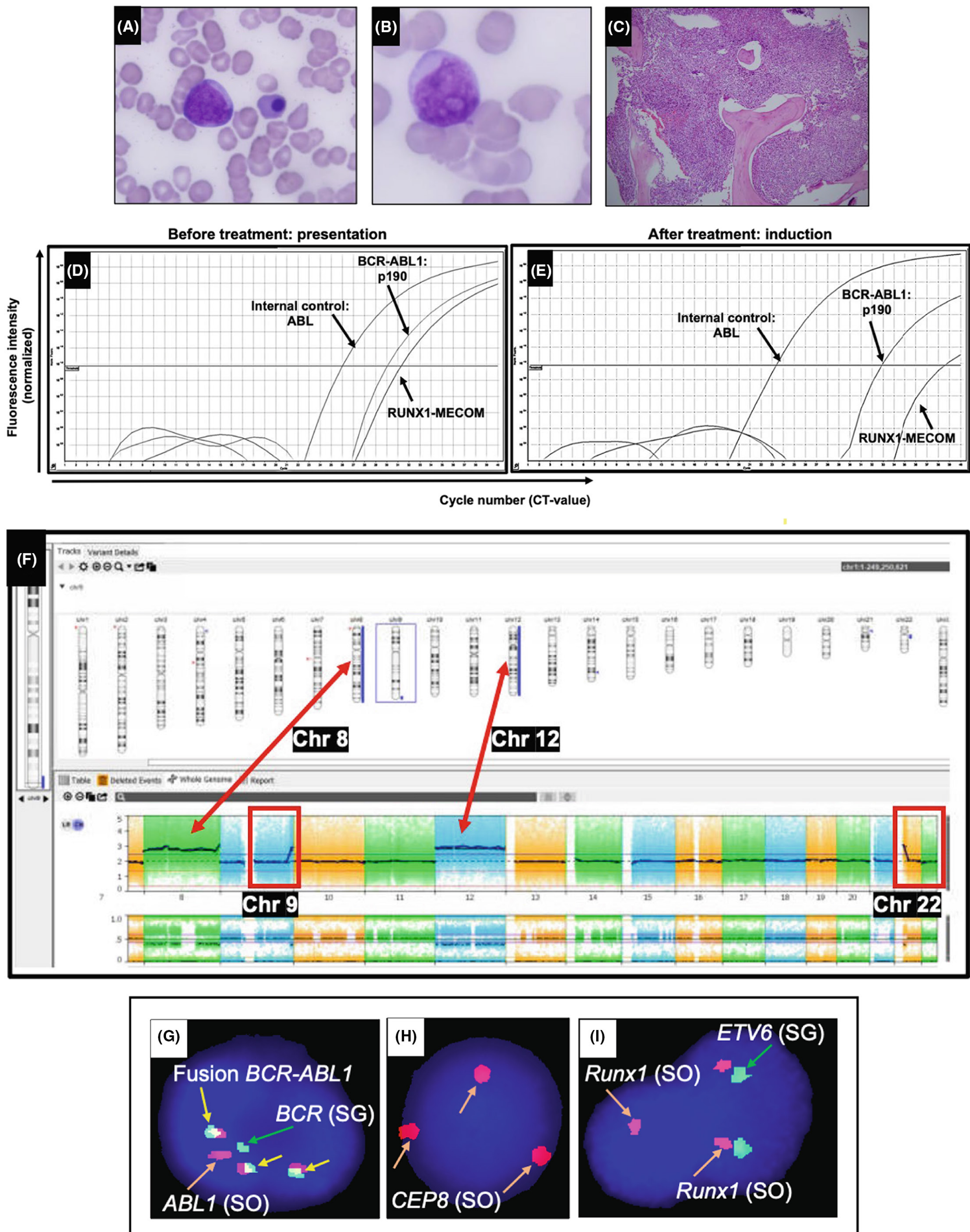
2 | CASE HISTORY

A 13-year-old female patient was presented to emergency department (ER) and referred from another hospital as a suspected case of leukemia. She had no past medical history on file, no surgical history, no known allergies, and no history of tobacco, alcohol, or drug use. Initial investigations at the previous hospital had revealed high white blood cell (WBC) count 52.1 × 109/L, hemoglobin (Hb) 5.3 g/dL, platelets (PLT) 10 × 109/L, potassium 4.3 mol/L, sodium 133 mol/L, BUN 2.5, and uric acid 450 mol/L. The coagulation profile and renal and liver function tests were unremarkable. Blood, urine, and throat cultures were negative. On admission in the ER, patient had fever, vomiting, and diarrhea. Initial work-up showed high WBC count 65.70 × 109/L, Hb 5.3 g/dL, and PLT 12×10^9/L.

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT)

Routine diagnostic workup was initiated with manual WBC differential that revealed more than 60% circulating blasts. The differential diagnosis was malignancy involving leukocytes and AML. Immunophenotyping on the peripheral blood by multi-parameter flowcytometry was

FIGURE 1 Morphology, qPCR, NGS-based CNV and FISH analyses in a patient with *BCR::ABL1* and *RUNX1::MECOM*. (A–B), Bone marrow aspirate showing blast infiltration (71%), cells are medium to large in size with high nuclear/cytoplasmic ratio, prominent nucleoli, cytoplasm is agranular, scant, and moderately basophilic; (C) bone marrow biopsy showing hypercellular marrow (100%), a sheet of blasts which markedly suppressed the trilineage hematopoiesis; (D) qPCR data obtained before treatment at presentation showing amplification curves of *BCR::ABL1 p190* isoform and *RUNX1::MECOM* (see arrows) including *ABL1* gene as internal control on RotorGene instrument using commercially available kit (Hemavision 28Q, Denmark); (E) qPCR data obtained after treatment post-induction showing amplification curves of *BCR::ABL1 p190* isoform and *RUNX1::MECOM* (see arrows); (F) NGS-based CNV analysis showing scatter view and full chromosomal view using Illumina platform (Centogene, Germany) with the arrows indicating gain of entire chromosome 8 and 12, and boxes indicating the a terminal and proximal pathogenic gain within 9q34.12q34.3 and 22q11.1q11.23, respectively; (G) FISH image showing the presence of *BCR::ABL1* fusion (see arrow) using Vysis Abbott Molecular probes for *BCR* (spectrum green or SG) and *ABL1* (spectrum orange or SO); (H) CEP8 probe for trisomy 8 (spectrum orange or SO), and (I) *ETV6::RUNX11* probes (SG or SO respectively) for extra RUNX1 copy.



followed by morphological assessment of the bone marrow aspirate and biopsy was performed. Polymerase chain reaction (qPCR), fluorescence in situ hybridization (FISH), and NGS-based CNV analyses were used for confirmation of diagnosis and prognostification. Patient was started on antibiotics before initiating chemotherapy protocol.

4 | CONCLUSIONS AND RESULTS (OUTCOME AND FOLLOW-UP)

Bone marrow aspirate showed infiltration by 71% of leukemic cells. These cells are medium to large in size with high nuclear/cytoplasmic ratio, delicate lacy chromatin, and prominent nucleoli. The cytoplasm is agranular, scant, and moderately basophilic (Figure 1A–C). Bone marrow biopsy revealed hypercellular marrow, whose cellularity is almost 100%. It shows a sheet of blasts that markedly suppressed the trilineage hematopoiesis (Figure 1A–C).

Immunophenotyping revealed 30% of all gated events were located in the blast gate (dim CD45 and low side scatter). These cells were positive for CD34, CD117, HLA-DR, CD33 (partial), CD13, CD4, CD11c (partial), and CD58. These cells are negative for CD14, CD15, MPO, and all other B/T-cell lineage markers. Thus, morphology and flow cytometry were highly suggestive of AML with monocytic differentiation.

The qPCR confirmed the presence of *BCR::ABL1 p190* isoform and revealed the presence of *RUNX1-MECOM* transcript as an additional finding (Figure 1D,E). As a routine work-up for AML, no mutations were detected in *FLT3* and *NPM1* genes (data not shown). Next generation sequencing (NGS)-based copy number variant (CNV) analysis revealed arr[GRCh37] 9q34.12q34.3(133701970_141068637)×2~3, arr[GRCh37] 22q11.1q11.23(16052962_23571642)×2~3 indicating a terminal pathogenic gain of 7.3 Mb within 9q34 chromosomal cytobands, partially encompassing the *ABL1* gene, and a proximal pathogenic gain of 7.5 Mb within 22q11 chromosomal cytobands, partially encompassing the *BCR* gene in mosaic state. The gain of entire chromosomes 8 and 12 was also identified as arr(8)×2~3 and arr(12)×2~3 (Figure 1F). Fluorescence in situ hybridization (FISH) using the AML panel also revealed variant t(9;22) representing fusion BCR-ABL1 (Figure 1G, see arrows), one additional copy each of chromosome 8 (Figure 1H, see arrows) and *Runx1* gene (Figure 1I, see arrows).

The patient had a spike of fever and positive blood culture for staphylococcus haemolyticus. She was given antibiotics, and after 5 days following a negative blood culture, she was started on induction regimen (ADE 10 + 3 + 5), which consisted of cytarabine, daunorubicin, and etoposide. A week after induction, the patient developed acute myocarditis with severe chest pain and significantly elevated troponin I (>3107, reference range <10) and BNP (>70,000). Patient was shifted to the intensive care unit, intubated, and required an inotropic support. Echocardiogram revealed a depressed ejection fraction (EF of 44%). Later, she developed hyperinflammatory syndrome showing high creatinine, liver enzymes, and inflammatory markers indicating acute kidney injury. During that time, chemotherapy was put on hold and then resumed after the patient was stable. EEG showed evidence of diffuse, nonspecific moderate-severe cerebral dysfunction and no epileptiform discharges or recorded electrographic seizure. Medical Resonance Imaging (MRI) revealed bilateral superficial watershed MCA zone acute/subacute infarcts with a few petechial hemorrhage. Computerized Tomography (CT) brain showed bilateral multiple small hyperdense focus possibly representing a micro hemorrhagic focus with surrounding mild vasogenic edema. This raised the possibility of therapy-related demyelination and leukoencephalopathy versus embolic infarcts. Patient required another ICU admission due to cardiogenic shock with multi-organ failure. Follow-up bone marrow showed hypocellularity (30%–40%), reduced trilineage hematopoiesis, and no immune-morphological evidence of residual disease. However, patient did not achieve cytogenetic or molecular remission till the last assessment (Figure 1E).

5 | DISCUSSION

We report a rare case of de novo AML with concomitant *BCR::ABL1 p190* isoform and *RUNX1::MECOM* rearrangement at presentation. There are no previous reports in the literature describing similar patients with *p190* and *MECOM* rearrangement. The patient needed intubation several times and had many complications including myocarditis, renal injury, elevated liver enzymes, and septic shock, which led to many interruptions for chemotherapy treatment indicating a very poor prognosis. This case highlights the need of developing a consensus on treatment modalities and guideline for AML patients with concomitant *BCR::ABL1 p190* isoform and *RUNX1::MECOM* rearrangement additional to other genetic abnormalities.

The morphological and immunophenotypic assessments were highly suggestive of AML with monocytic differentiation. CD34 and CD117 expression by flow cytometry although rare in AML, were found to be positive for both the blastic markers in the current patient. NGS-based CNV analysis revealed a terminal gain within 9q34 and a proximal gain within 22q11 chromosomal cytobands, suggesting a possible t(9;22) translocation. FISH analysis and qPCR on bone marrow specimen confirmed the presence of *BCR::ABL1* fusion and revealed additional complex genetic abnormalities. While *BCR::ABL1* fusion is the genetic hallmark of CML, it is also detected in about 3% of de novo AML.[9] *BCR::ABL1* fusion as a secondary event in AML is rare and has been reported in therapy-related MDS/AML or in relapse post-BM transplant.[10] AML with *BCR::ABL1* fusion is considered as high-risk with a poor prognosis that is dependent upon other coexisting genetic

aberrations. The diagnosis of AML with *BCR::ABL1* fusion requires more than 20% blasts expressing a myeloid immunophenotype in the bone marrow or peripheral blood.[11] and distinguishing AML with *BCR::ABL1* from initial myeloid blast phase of CML can be challenging.[12] The patient showed more than 20% blasts expressing a myeloid immunophenotype in the bone marrow and peripheral blood, showed *BCR::ABL1* at initial diagnosis, and lack of features of CML prior to or at diagnosis or after therapy. Given that the patient's medical history was negative for any hematologic disease, no history of chemotherapy, absence of splenomegaly, and absence of peripheral blood basophilia at diagnosis support the diagnosis of de novo AML with *BCR::ABL1*.

In addition to the presence of *BCR::ABL1* fusion transcripts, the patient also revealed the presence of t(3;21)-generating *RUNX1::MECOM* fusion, rarely reported in de novo AML but in APL, which relapsed as secondary AML.[8] It is interesting to note that while NGS-based CNV analysis suggested a possible *BCR::ABL1* fusion through a terminal and a proximal gain within 9q34 and 22q11 chromosomal cytobands, respectively, we did not observe any gain within chromosomes 3 and 21 to suggest *RUNX1::MECOM* fusion. This could be possibly due to technical limitation of NGS to detect translocation in general and also due to the coverage in the regions encompassing the breakpoint involved. Coyle and Najfeld et al. reported *RUNX1::MECOM* fusion transcripts in CML prior to the onset of blast crisis.[13] Recent WHO classification of myeloid neoplasm also recognized rearrangements involving *MECOM* as a new AML type with poor prognosis.[1] It is now thought that the *RUNX1::MECOM* fusion transcript contributes directly to leukemogenesis or leukemic transformation.[14–16]

Although the BM examination post-induction showed morphological remission, the aspirate was hemodiluted. Additionally, patient did not achieve cytogenetic or molecular remission till date. Several studies demonstrate that *MECOM* rearranged AML regardless of therapy has a poor prognosis with significantly lower overall survival, event-free survival, and higher cumulative incidence of relapse.[14–16] *BCR-ABL1* rearranged cases are also reported to be associated with poor prognosis, and there is a need for aggressive treatment[17] for achieving optimal outcome. This will also hold true when both *BCR::ABL1* and *RUNX1::MECOM* coexist. Additionally, multiple complex genetic abnormalities in the patient seem severe with very little chance of complete recovery.

In conclusion, the presence of coexisting *BCR::ABL1* and *RUNX1::MECOM* rearrangements in de novo AML indicates a poor disease course and prognosis. A need for consensus on the treatment guidelines and modalities other than the current regimen is warranted.

AUTHOR CONTRIBUTIONS

Ragdah Alamri: Data curation; writing – original draft. **Maryam Alanazi:** Data curation; writing – original draft. **Rajeh AlRajeh:** Methodology. **Suha A. Tashkandi:** Formal analysis; investigation. **Azizah Alswayyed:** Investigation; methodology. **Manar A. Samman:** Project administration; writing – review and editing. **Abdul Ali Peer-Zada:** Conceptualization; writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy. Institutional Review Board (IRB Log No. 23-692) was obtained after patient's consent.

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