

# ***BCR::ABL1*-Positive Secondary B-Acute Lymphoblastic Leukemia Mimicking Acute Megakaryoblastic Leukemia Following Multiple Myeloma**

Multipl Miyelom Sonrasında Gelişen, Akut Megakaryoblastik Lösemiye Taklit Eden *BCR::ABL1* Pozitif Sekonder B-Akut Lenfoblastik Lösemi

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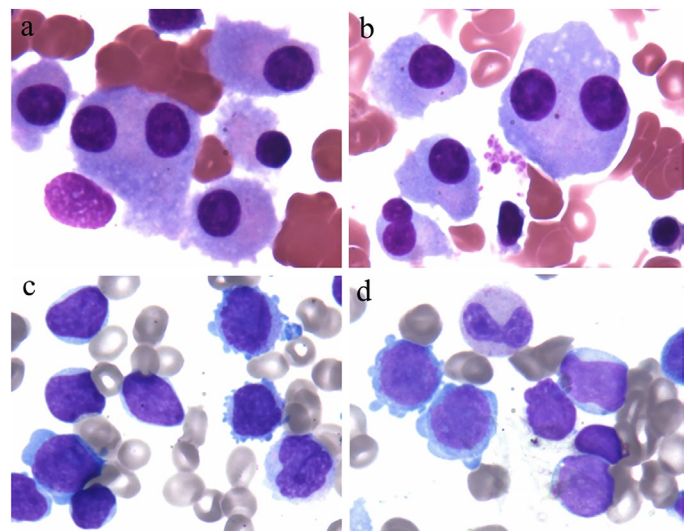
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## To the Editor,

A 63-year-old woman was diagnosed with IgG-kappa multiple myeloma (MM) in January 2021, confirmed by 71% abnormal plasma cells on bone marrow smears (Figures 1a and 1b) and aberrant plasma cells with a CD45-CD19-CD38<sup>+</sup>CD138<sup>+</sup>BCMA<sup>+</sup>kappa<sup>+</sup>lambda<sup>-</sup> phenotype demonstrated by flow cytometry. She received bortezomib- and lenalidomide-based regimens followed by allogeneic hematopoietic stem cell transplantation (HSCT) in July 2021 and lenalidomide maintenance from September 2022. She then remained in remission until January 2025, when she developed fatigue and dizziness. Bone marrow smears revealed 76% blasts with medium to large cell size, irregular nuclei, and basophilic cytoplasm with occasional cytoplasmic blebbing or pseudopod formation, resembling a megakaryoblastic morphology (Figures 1c and 1d). Myeloperoxidase staining was negative. Flow cytometric analysis revealed that 71% of the blasts were positive for CD10, CD19, CD22, CD99, cCD79a, HLA-DR, CD38 (partial), CD13 (partial), CD33 (partial), and CD7 (partial) and negative for cCD3, MPO, CD34, CD117, CD4, CD56, and CD41. Quantitative reverse transcription polymerase chain reaction identified the *BCR::ABL1*<sup>p190</sup> transcript. Karyotyping revealed t(9;22)(q34;q11)[10]. Next-generation sequencing detected no additional mutations. Given the patient's history, a diagnosis of secondary Philadelphia chromosome-positive (Ph<sup>+</sup>) B-cell acute lymphoblastic leukemia (B-ALL) with *BCR::ABL1* fusion following MM was made. She was initiated on vincristine-prednisone chemotherapy combined with flumatinib, a second-generation tyrosine kinase inhibitor (TKI). However, the treatment course was complicated by recurrent fungal infections, severe cytopenia, and fatigue. Due to progressive disease and financial constraints, she discontinued treatment and was discharged against medical advice.

MM is a clonal plasma cell malignancy with significantly improved survival in the era of proteasome inhibitors, immunomodulatory drugs (IMiDs), and HSCT. However, long-term survivors are increasingly susceptible to second primary malignancies (SPMs), with therapy-related myeloid neoplasms being the most frequently reported [1]. Secondary acute lymphoblastic leukemia (sALL), particularly B-ALL harboring *BCR::ABL1* fusion and mimicking acute megakaryoblastic leukemia (AMKL), is exceedingly rare and only a few cases of secondary B-ALL following treatment for MM have been reported



**Figure 1.** Initial diagnosis: bone marrow aspirate smears showed 71% abnormal plasma cells (a, b: Wright-Giemsa staining, 1000<sup>x</sup> magnification). Current presentation: bone marrow smears revealed 76% blasts with medium to large cell size, regular nuclei, and basophilic cytoplasm with occasional cytoplasmic blebbing or pseudopod formation, resembling a megakaryoblastic morphology (c, d: Wright-Giemsa staining, 1000<sup>x</sup> magnification).

[1,2,3,4]. Miller et al. [3] reported a 71-year-old man with a history of MM who developed B-ALL after chemotherapy; the Philadelphia chromosome was cryptic and *BCR::ABL1* fusion was detected by molecular testing. Due to the extreme rarity of such presentations, we report our unusual case to highlight that morphology can sometimes be misleading and accurate diagnosis requires a comprehensive approach integrating flow cytometric immunophenotyping and molecular testing. Diagnosis of such cases can be particularly challenging when blast morphology is heterogeneous or mimics other hematologic malignancies such as monoblastic or megakaryoblastic leukemia. Accurate classification requires an integrated approach combining morphology, immunophenotyping, cytogenetics, and molecular diagnostics.

The pathogenesis of sALL is multifactorial. IMiDs like lenalidomide may drive clonal evolution by modulating immune surveillance. Additionally, prior exposure to alkylating agents and high-dose chemotherapy can cause genotoxic stress, further increasing the risk of leukemic transformation. Disruption of the bone marrow microenvironment and underlying genetic susceptibility may also contribute to malignant clonal progression [5]. Although Ph+ ALL often shows an initial response to TKIs, outcomes in the context of secondary disease remain suboptimal. Our case emphasizes the importance of heightened clinical vigilance for lymphoid SPMs in MM survivors, particularly in those receiving IMiD maintenance or presenting with unexplained cytopenia. Early diagnostic evaluation, including molecular screening, may facilitate timely intervention and potentially improve outcomes.

In summary, we report a rare case of secondary Ph+ B-ALL with *BCR::ABL1* fusion, morphologically mimicking AMKL and arising after successful MM treatment and lenalidomide maintenance. This case underscores the importance of long-term surveillance and a comprehensive diagnostic approach in MM patients and raises important questions regarding the leukemogenic risk of maintenance therapies and the optimal management of sALL in this unique clinical setting.

**Keywords:** *BCR::ABL1* fusion, B-acute lymphoblastic leukemia, Acute megakaryoblastic leukemia, Multiple myeloma, Medical history

**Anahtar Sözcükler:** *BCR::ABL1* füzyonu, B-akut lenfoblastik lösemi, Akut megakaryoblastik lösemi, Multipl miyelom, Tıbbi öykü

### Ethics

**Informed Consent:** Informed consent was obtained from this patient.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: F.L., H.W., Z.S., J.Y.; Concept: F.L., H.W., Z.S., J.Y.; Design: F.L., H.W., Z.S., J.Y.; Data Collection or Processing: F.L., H.W., Z.S., J.Y.; Analysis or Interpretation: F.L., H.W., Z.S., J.Y.; Literature Search: F.L., H.W.; Writing: F.L., H.W.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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