LETTER TO THE EDITOR
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BCR::ABL1-Positive Secondary B-Acute Lymphoblastic Leukemia Mimicking Acute Megakaryoblastic Leukemia Following Multiple Myeloma

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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 (Fig.1a-b) and aberrant plasma cells with $CD45^{-}CD19^{-}CD38^{+}CD138^{+}BCMA^{+}kappa^{+}lambda^{-}$phenotype 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. The patient 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 megakaryoblastic morphology (Fig.1c-d). Myeloperoxidase staining was negative. Flow cytometric analysis revealed 71% 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 *BCR::ABL1*^{p190} transcript. Karyotyping revealed t(9;22)(q34;q11)[10]. Next-generation sequencing detected no additional mutations. Given the history, a diagnosis of secondary Philadelphia chromosome-positive (Ph+) 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 cytopenias, and fatigue. Owing 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 the *BCR::ABL1* fusion and mimicking AMKL, is exceedingly rare, only a few cases of secondary B-ALL following treatment for MM have been reported [1-4]. Miller K et al. 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 [3]. Due to the extreme rarity of such presentations, we present this 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 remains 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-positive 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 cytopenias. 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, 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

Declarations

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Authors' contributions All authors contributed to the paper conception and design. Clinical and histological data were collected by Haiyang Wang, Zengtian Sun and Jiulian Yuan. The draft of the manuscript was written by Fang Long, and all authors read and approved the final manuscript.

Conflict of Interest The authors that they have no conflicts of interest.

Informed consent Informed consent was obtained from this patient.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication Informed consent was obtained from the publication.

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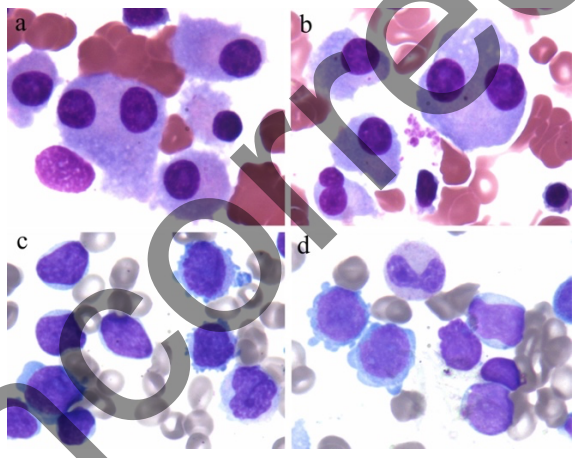

Fig. 1

Initial diagnosis: Bone marrow aspirate smears showed 71% abnormal plasma cells (a-b, Wright-Giemsa staining ×1000 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 megakaryoblastic morphology (c-d, Wright-Giemsa staining ×1000 magnification).