Received: 18 June 2023 | Revised: 29 July 2023 | Accepted: 2 August 2023

DOI: 10.1002/jha2.769

eJHaem

British Society for Haematology

HAEMATOLOGY IMAGES

Acute myelofibrosis superseding B-lymphoblastic leukemia/lymphoma

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KEYWORDS
B-acute lymphoblastic leukemia, B-ALL, primary myelofibrosis

The patient is a 68-year-old man diagnosed with B-acute lymphoblastic leukemia/lymphoma (B-ALL) replacing the bone marrow, without evidence of myelofibrosis by morphology and reticulin stain (Figure 1A–C). By flow cytometry analysis, blasts were positive for CD10, CD19, CD20 (bright), CD22, CD34, cytoplasmic TdT, and cytoplasmic CD79a, while double-negative for both surface, and cytoplasmic, kappa and lambda light chain expression. Cytogenetic analysis revealed a diploid male karyotype. FISH analysis showed copy number gain of the *BCR* (22q11.2) locus; However, no evidence of *BCR/ABL1* gene rearrangement or other cytogenetic lesions was detected. Lumbar puncture analysis was negative for central nervous system involvement by B-ALL.

The patient was enrolled in a Phase III randomized trial of Blinatumomab for newly diagnosed *BCR-ABL* negative B-ALL in adults (ECOG-ACRIN clinical trial E1910). He received 2 cycles of induction therapy with Daunorubicin, Vincristine, Dexamethasone, Rituximab, Cytarabine, and Methotrexate, followed by maintenance with Methotrexate, Pegaspargase, and Leucovorin. He was then randomized to recieve 3 cycles of consolidation with Blinatumumab, followed by maintenance with Daunorubicin, Vincristine, Dexamethasone, Rituximab, Cytarabine, and Methotrexate.

Throughout chemotherapy, patient's complete blood count values fluctuated: His white blood cell count averaged at 6×10^9/L (normal range (NR), 4.2–9.1); hemoglobin and mean corpuscular volume averaged at 11 g/dL (NR, 13.7–17.5) and 110 fL (NR, 79–92), respectively, while his platelets averaged at 70×10^9/L (NR, 150–330). Following cycle two, he was negative for minimal residual disease by flow cytometry analysis, with the following blood count values: white blood cell count of 5×10^9/L (normal range, NR, 4.2–9.1), hemoglobin and mean corpuscular volume of 10.8 g/dL (NR, 13.7–17.5) and 111.3 fL (NR, 79–92), respectively, with platelets of 71×10^9/L (NR, 150–330). A follow-up bone marrow biopsy showed regenerative trilineage hematopoiesis without evidence of myelofibrosis (Figure 1D–F). After completion of chemotherapy 2 years later, the patient was still in complete remission with negative minimal residual disease by flow cytometry analysis and the following complete blood count values: white blood cell count averaged of 1.9×10^9/L, hemoglobin and mean corpuscular volume of 7.3 g/dL and 103 fL, respectively, and platelets of 17×10^9/L. A concurrent bone marrow biopsy was remarkable for dense marrow fibrosis (myelofibrosis (MF)−3 by reticulin stain) with megakaryocytic hyperplasia and dysplasia (Figure 1G–I). Next-generation sequencing interrogating 35 myeloid unique genes with a limit of detection at 5% allele frequency at 500x coverage showed the following pathogenic mutations: *DNMT3A* c.2071dupA p.Thr691AsnfsTer22 and *TP53* c.428T > C p.Val143Al*a* detected with similar variant allele frequency (VAFs) of 25% and 21%, respectively. In addition, the following mutation of unknown significance, *EZH2* c.938G > A p.Arg313GIn was detected with a VAF of 19%. Cytogenetic analysis revealed a diploid karyotype. The patient was managed with supportive care only (transfusion with platelets and packed red blood cells) and was evaluated for potential allogeneic hematopoietic stem cell transplant in the future. The patient stayed in complete remission (negative minimal residual disease by flow cytometry analysis) 4 years after diagnosis of B-ALL, and 2 years after myelofibrosis, until he was found to be positive for

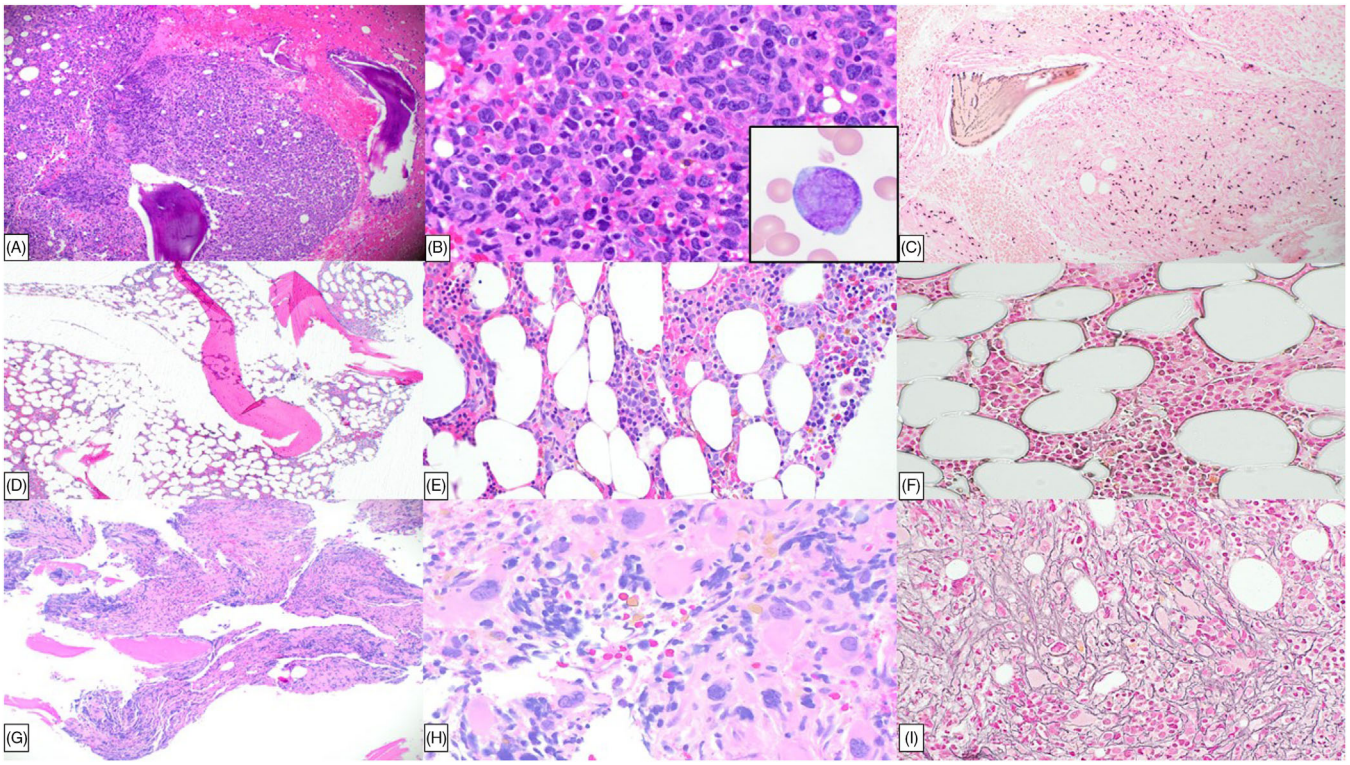

FIGURE 1 **(A)** Bone marrow biopsy at diagnosis, showing a hypercellular marrow for age **(B)** involved by sheets of immature cells, with irregular nuclear contours, open chromatin and prominent nucleoli (inset), **(C)** without increased reticulin fiber deposition. **(D)** Bone marrow biopsy performed following cycle two chemotherapy shows a normocellular marrow for age (30%) with **(E)** trilineage hematopoiesis and **(F)** absence of increased reticulin fiber deposition. **(G)** Bone marrow biopsy 2 years later after completion of chemotherapy, demonstrates a hypercellular marrow for age **(H)** with increased clusters of dysplastic megakaryocytes **(I)** and markedly increased reticuloin fiber deposition.

minimal residual disease and was started on Blinatimumab. Following Blinatumumab, his blood count values averaged as follows: white blood cell count of 4.3×10^9/L (normal range, NR, 4.2–9.1), hemoglobin and mean corpuscular volume of 7.6 g/dL (NR, 13.7–17.5) and 88 fL (NR, 79–92), respectively, with platelets of 23×10^9/L (NR, 150–330).

Acute myelofibrosis is a distinct clinicopathological entity characterized by the sudden onset of pancytopenia, extensive bone marrow (BM) fibrosis, megakaryocytic hyperplasia with or without dysplasia, leucoerythroblastic blood picture, absence of hepatosplenomegaly (HSM), and no tear drop cells. Myelofibrosis, preceding [1–5] or coexisting [6–9] with B-ALL, have been reported before. However, to our knowledge, this is the first report of acute myelofibrosis superseding B-ALL, 2 years after remission. In the case we illustrate, signs pointing at marrow failure included inexplicable and persistent decreased blood counts. A bone marrow core biopsy was helpful in unraveling underlying fibrosis and dysplastic megakaryocytes, findings that were absent in the bone marrow biopsy after cycle 2 chemotherapy, arguing against the possibility of evolution of B-ALL from an established (pre B-ALL) or concurrent myeloproliferative neoplasm with fibrosis (namely, primary myelofibrosis). A question that may be raised is whether the evolving myelofibrosis with pathogenic mutations in *DNMT3A* and *TP53* during complete remission could have started in clonal hematopoiesis to support homeostasis in a regenerative marrow. Another question that remains unclear is whether the myelofibrosis constituted an early sign of B-ALL relapse (which occurred 2 years after the morphologic and molecular diagnosis of myelofibrosis). The relationship between these 2 processes remains to be determined, although we favor that these are 2 unrelated diseases with divergent pathobiology. Nevertheless, this case highlights the possibility of acquired myelofibrosis as a rare cause of decreasing blood counts in cases of B-ALL in remission, in the setting of treatment with Blinatumumab. Furthermore, it argues in favor of performing bone marrow biopsies in similar scenarios to assess for the presence of an evolving new hematologic process.

AUTHOR CONTRIBUTIONS

SEH conceptualized and wrote the initial draft of the manuscript with valuable comments from JMB and KMO.

CONFLICT OF INTEREST STATEMENT

None of the authors declares conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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How to cite this article: El Hussein S, O'Dywer KM, Bennett JM. Acute myelofibrosis superseding B-lymphoblastic leukemia/lymphoma. eJHaem. 2023;4:1179–1181. https://doi.org/10.1002/jha2.769