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CML-like biology is a unifying feature of myeloid/lymphoid neoplasms with tyrosine kinase fusions in lymphoid blast phase. Comment on: Multilineage involvement in ABL-class fusion–positive pediatric B-cell acute lymphoblastic leukemia: CML-like biology

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In a recent issue of *Haematologica*, van Outerstep et al. reported a pediatric patient who initially presented with typical B-lymphoblastic leukemia (B-ALL).[1] At relapse, the patient displayed immunoglobulin heavy chain (*IGH*)/T-cell receptor gene rearrangements distinct from those detected at diagnosis. Notably, the *CCDC88C::PDGFRB* fusion identified at relapse was also detectable retrospectively in the diagnostic sample. Furthermore, the *PDGFRB* rearrangement was present in both myeloid and lymphoid cells in bone marrow (BM) samples obtained after the first and second complete remissions. An accompanying Editorial by Zuna raised a series of questions with important clinical implications.[2]

Here, we briefly present three of our cases with similar clinical presentations and courses.

Case 1.

A 66-year-old woman was diagnosed with B-ALL in September 2014. Conventional karyotyping revealed 46,XX,t(8;22)(p11.2;q11.2)[9]/47,idem,+der(22)t(8;22)(p11.2;q11.2)[10]/46,XX[1], and fluorescence *in situ* hybridization (FISH) demonstrated a *BCR* rearrangement in 79.8% of cells. She achieved negative measurable residual disease (MRD) for B-ALL by flow cytometric immunophenotyping (FCI) analysis after one cycle of Hyper-CVAD plus Ofatumumab. Following the third cycle of chemotherapy in February 2015, FCI and *IGH* gene rearrangement studies confirmed no residual B-ALL; however, karyotyping continued to show persistent t(8;22). FISH analysis demonstrated *FGFR1* rearrangement (54.5%). Despite negative B-ALL MRD by FCI, t(8;22) was persistent (13-20 metaphases) across four subsequent BM samples from April to September 2015. Interestingly, the extra copy of der(22)t(8;22) observed at diagnosis was absent in all five follow-up samples. The patient underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) in October 2015 and has remained disease-free for approximately 10 years at the most recent follow-up.

Case 2.

A 53-year-old woman was diagnosed with B-ALL in May 2014 and achieved negative MRD by FCI after induction chemotherapy at an outside hospital. The initial cytogenetic evaluation at

diagnosis was inconclusive due to insufficient metaphases. She received five cycles of Hyper-CVAD plus Ofatumumab at our institution, during which FCI and *IGH* gene arrangement testing consistently showed no residual B-ALL. However, starting with the second chemotherapy cycle, karyotyping analysis revealed a persistent t(8;22)(p11.2;q11.2) in three consecutive BM samples in over a five-month period, despite negative B-ALL MRD by FCI. FISH analysis confirmed *BCR* rearrangement, suggesting a *BCR::FGFR1* fusion. Subsequently, the patient underwent allo-HSCT and has remained disease-free for 11 years at the last follow-up.

Case 3.

A 69-year-old man was diagnosed with B-ALL in November 2017. At diagnosis, conventional karyotyping demonstrated 45,XY,-7,t(8;9)(p22;p24)[15]/45~46,idem[cp5], and FISH confirmed a *JAK2* rearrangement in 92% of cells. After one cycle of mini-HyperCVD plus Inotuzumab and Rituximab, he achieved morphologic remission. Six subsequent BM samples collected between January and September 2018 after chemotherapy demonstrated discordances in the MRD assessment when comparing FCI and *IgH* PCR results with karyotyping and/or FISH analyses. In the first four follow-up samples, B-ALL MRD by FCI ranged from 0-0.13%, *IGH* rearrangement was negative in one of these four samples, but *JAK2* rearrangement by FISH ranged from 7-41%. In the final two samples, both FCI and *IGH* rearrangement were negative, whereas *JAK2* rearrangement was detected in 45% and 8.5% of cells, respectively. Notably, monosomy 7 observed at diagnosis was absent in all six follow-up samples. The patient died of relapse in March 2019 at an outside facility.

Despite remission of B-ALL, the tyrosine kinase fusion levels remained high, suggesting myeloid lineage involvement in all three cases presented here. The question remains how to classify these cases that lack obvious features of myeloid neoplasms, initially and after therapy. van Outerstep et al. proposed the concept of *ABL*-class fusion B-ALL with multilineage involvement, analogous to *BCR::ABL1*-positive B-ALL with multilineage involvement.[1,3] However, according to the International Census Classification, such cases are categorized as myeloid/lymphoid neoplasms with tyrosine kinase fusions (MLN-TK). The clinical manifestations of MLN-TK are

heterogeneous.[4,5] Although eosinophilia or other myeloproliferative features are common they are not required for diagnosis. Notably, up to 50% of patients with MLN-TK lack eosinophilia, defined as peripheral blood eosinophils ≥0.5 × 10^9/L. Likewise, eosinophilia (or basophilia) is not universally present in patients with CML.

The absence of myeloid neoplasm features following chemotherapy for B-ALL may be attributable to the suppressive effects of ongoing therapy. By analogy, patients with *BCR::ABL1*-positive ALL with multilineage involvement rarely develop chronic myeloid leukemia (CML) features while on tyrosine kinase inhibitor (TKI) therapy, despite persistent *BCR::ABL1* in some patients. However, CML features may emerge in the absence of treatment or in the setting of ineffective therapy. We previously reported a case of *BCR::ABL1*-positive B-ALL without prior evidence of CML that later evolved into typical CML-chronic phase (CML-CP) following prolonged treatment cessation.[6] Historical data also extensively document that patients with *BCR::ABL1*-positive ALL could develop CML-CP after achieving ALL remission in the pre-TKI era, when effective therapy for CML was unavailable.[7,8] Vardiman et al. reported that most *BCR::ABL1*-positive B-ALL cases with multilineage involvement reverted to a typical CML-CP before the advent of TKIs.[8] Even in the TKI era, some patients with established CML may achieve hematologic remission without cytogenetic remission—maintaining high-level *BCR::ABL1* without exhibiting typical CML features in the peripheral blood.[9,10]

Except case #2, which lacked an initial karyotype, another notable observation is the presence of additional chromosomal alterations (ACAs) at the initial diagnosis of B-ALL: extra copy of der(22)t(8;22) in our case #1, monosomy 7 in case #3, extra copy of der(22)t(9;22) in above-mentioned CML,[6] and multiple ACAs in the case reported by van Outerstep et al.[1] These ACAs were not detected when initial B-ALL was in remission, although the translocations encoding the TK fusions persisted, suggesting that these ACAs have contributed specifically to the lymphoblastic transformation at initial presentation.

BCR::ABL1 was the first TK fusion identified to be associated with cancer. If cases of non-

BCR::ABL1 TK fusion-positive B-ALL with multilineage involvement are classified as MLN-TK according to the International Census Classification, the rationale for maintaining a separate category for *BCR::ABL1*-positive ALL with multilineage involvement becomes unclear. A unifying classification scheme is therefore needed. We believe that *BCR::ABL1*-positive ALL with multilineage involvement represents blast-phase CML, and other TK fusion-positive B-ALL with multilineage involvement should be grouped under the umbrella of MLN-TK, the biological counterpart of CML.

Regardless of the classification or terminology, these diseases, including CML, MLN-TK, and B-ALL with TK and multilineage involvement, originate from pluripotent hematopoietic stem cells or multipotent progenitor cells. It is essential to recognize these “stem-cell” leukemias, as they possess both myeloid and lymphoid differentiation potential, which carries important therapeutic and prognostic implications.

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