Cytogenetic Evolution Associated With Disease Progression in Hematopoietic Neoplasms With t(8;22)(p11;q11)/BCR-FGFR1 Rearrangement

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Abstract
Hematopoietic neoplasms with FGFR1 rearrangements are rare. Clinically, patients often present with a chronic myeloproliferative neoplasm with eosinophilia and an increased risk of transformation to acute leukemia. We report a patient who initially presented with B-cell acute lymphoblastic leukemia (B-ALL) with t(8;22)(p11.2;q11.2) and an additional derivative chromosome 22 [der(22)t(8;22)]. After induction chemotherapy, B-ALL blasts were eradicated; however, a chronic myeloproliferative process emerged showing persistent t(8;22)(p11.2;q11.2) but not der(22)t(8;22). Combined morphologic and fluorescence in situ hybridization revealed that both lymphoblasts and myeloid cells harbored t(8;22)(p11.2;q11.2); but only lymphoblasts carried the additional der(22)t(8;22). This case provides direct evidence to illustrate the clonal relationship of chronic phase and blast phase in myeloid neoplasms with FGFR1 rearrangement, and demonstrates that clonal cytogenetic evolution plays an important role in disease progression.


Background
Fibroblast growth factor receptor 1 (FGFR1)–associated myeloid and lymphoid neoplasm, also known as 8p11 myeloproliferative syndrome, is a rare hematopoietic neoplasm molecularly characterized by reciprocal translocations involving FGFR1 and one of its multiple partner genes. The most common fusion partner is ZMYM2 (ZNFI98) on chromosome 13q12, detected in approximately 50% of cases. Clinically, patients often present with a chronic myeloproliferative neoplasm with eosinophilia but have an increased risk of transformation to acute leukemia. Blasts are often of a myeloid lineage in the bone marrow (BM), or T lymphoblasts in nodal and extranodal sites, or rarely, a B-lymphoid lineage. In contrast to t(8;13)(p11;q12), the t(8;22)(p11.2;q11.2) translocation with the product of BCR-FGFR1 fusion is extremely rare. Its clinicopathologic features and the mechanisms underlying disease progression are not well characterized. Here we report a patient with t(8;22)(p11.2;q11.2) who initially presented with B-cell lymphoblastic leukemia (B-ALL). After induction therapy, a chronic myeloproliferative process emerged. We performed combined morphologic and fluorescence in situ hybridization (FISH) to illustrate that cytogenetic evolution with the development of additional genetic abnormalities may be one of the mechanisms mediating disease progression and transformation.

Case Report
A 55-year-old woman presented with 48 x 10^9/L WBCs and 22% circulating blasts. Her past medical history was
significant for stage I invasive breast ductal carcinoma, treated with excision and localized radiation therapy 10 years earlier. At admission, she underwent BM biopsy, which demonstrated a hypercellular marrow with 52% blasts. Flow cytometry showed a typical B-ALL immunophenotype with blasts positive for CD19, CD22, CD34, CD10, and TdT. They were uniformly positive for CD25, and negative for CRLF2, CD3, and MPO. The concurrent conventional cytogenetic analysis revealed an abnormal karyotype: 46,XX,t(8;22)(p11.2;q11.2)[9]/47,XX,t(8;22)(p11.2;q11.2),+der(22)t(8;22)[10]/46,XX[1] (Figure 1). FISH analysis was negative for BCR/ABL1 fusion, but it showed BCR rearrangement.

The patient received induction therapy with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and ofatumumab alternating with methotrexate and cytarabine. She achieved complete remission after induction therapy. Her BM was negative for B-ALL by morphology and by assessment of minimal residual disease (MRD) using flow cytometry; however, the BM showed an 80% cellularity with an increased myeloid:erythroid (M:E) ratio at 9:1. The latter features were suggestive of a myeloproliferative neoplasm. The detailed differential counts for this BM were: blasts, 1%; progranulocytes, 1%; myelocytes, 13%; metamyelocytes, 20%; granulocytes, 46%; eosinophils, 2%; lymphocytes, 3%; plasma cells, 1%; monocytes, 4%; and normoblasts, 9%.

The patient completed induction and consolidation chemotherapy for B-ALL, followed by single-agent blinatumomab maintenance therapy. Approximately 11 months after the initial B-ALL diagnosis, the patient presented with a rising WBC count up to 44 x 10^9/L and thrombocytopenia. BM biopsy showed no evidence of B-ALL, as confirmed by flow cytometry MRD study, but BM repeatedly showed a hypercellularity with an increased M:E ratio. The patient received ponatinib plus hydroxyurea that resulted in leukoreduction but not a cytogenetic response.
Of note, chromosomal analyses were performed on 5 follow-up BM biopsies that were negative for B-ALL MRD, and all showed the persistent presence of t(8;22)(p11.2;q11.2) as the sole abnormality. Derivative chromosome der(22)t(8;22) detected at the time of initial diagnosis was not detected. She finally underwent a matched unrelated stem cell transplant (SCT) 1 year after B-ALL diagnosis. Post SCT, her BM showed a normal male karyotype, 46,XY[20]. Currently, the patient is 5 months after SCT with no clinical evidence of relapse. Her clinical course and treatment regimens are also illustrated in Figure 2.

We performed combined morphologic-FISH analysis using FGFR1 dual-color breakapart DNA probe (Kreatech/Leica Microsystems Inc., Chicago, IL). On the BM smear at initial B-ALL diagnosis, 3 patterns of FISH signals were identified (Figure 3A, B): the small lymphocyte shows a normal pattern (2 fusion signals); mature myeloid cells show FGFR1 rearrangement; and the lymphoblasts show not only FGFR1 rearrangement but also an additional red signal, corresponding to der(22)t(8;22). One month after induction therapy, when the patient’s BM was negative for B-ALL blasts (Figure 3C), FISH showed persistence of FGFR1 rearrangement in a subset of myeloid cells and a normal pattern in the remaining cells. No cells carrying additional red signal of der(22)t(8;22) were detected (Figure 3D).

### Discussion

Our results demonstrate the clonal relationship between B-ALL lymphoblasts and the background
myeloid cells, as both types of cells harbored t(8;22) (p11.2;q11.2)/FGFR1 rearrangement; however, only lymphoblasts had the additional copy of der(22) t(8;22), indicating clonal evolution. These findings suggest that both myeloid and lymphoblast components originated from the same multipotent hematopoietic stem cells, and the acquisition of an additional cytogenetic abnormality played a critical role in the progression to lymphoblastic phase. In this case, the additional cytogenetic abnormality, der(22) t(8;22), was analogous to the effect of an additional copy of Philadelphia chromosome in chronic myelogenous leukemia (CML). Acquisition of an extra copy of Philadelphia chromosome has been shown to correlate with CML progression to accelerated or blast phase.3

To determine whether the association between clonal cytogenetic evolution and disease progression was also evident in other similar cases, we reviewed the literature for cases with t(8;22)(p11.2;q11.2). Cases with available conventional cytogenetic results were included.4-19 Indeed, 82% (9 of 11) of cases in blast phase had additional cytogenetic abnormalities. In contrast, only 18% (2 of 11) of cases in chronic phase had additional cytogenetic abnormalities (Table 1). These findings indicate that when neoplastic cells have t(8;22)(p11.2;q11.2) as the sole abnormality, they most likely manifest as a chronic myeloproliferative neoplasm; however, when the stem cells or progenitor cells gain additional cytogenetic abnormalities or molecular events, they have a tendency to undergo progression to acute leukemia.

In contrast to myeloid and lymphoid neoplasms with PDGFRα and PDGFRB rearrangements, diseases with FGFR1 rearrangement are aggressive and tend to be resistant to tyrosine kinase inhibitor (TKI) treatment. Recent studies have demonstrated that the third-generation TKI ponatinib may be effective in treating these patients.20 In our case, intensive chemotherapy eradicated the transformed leukemic clones, but the clone with sole t(8;22)(p11.2;q11.2) was resistant to high-dose chemotherapy. Ponatinib may have some effect on the latter clone, leading to a decreased WBC count (Figure 2), but the patient also received hydroxyurea at the same time, so the definitive effect of ponatinib is unknown. SCT effectively eradicated abnormal clones and, to the last follow-up (5 months post SCT), the patient showed no clinical evidence of disease relapse.

References


