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Original contribution

# Myeloproliferative neoplasms with t(8;22)(p11.2;q11.2)/*BCR-FGFR1*: a meta-analysis of 20 cases shows cytogenetic progression with B-lymphoid blast phase☆

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**Summary** Rearrangements of *FGFR1* result in the 8p11 myeloproliferative syndrome, a group of rare diseases that features a myeloproliferative neoplasm (MPN) that commonly progresses to lymphoblastic leukemia/lymphoma or acute myeloid leukemia. The most common partner of *FGFR1* is *ZMYM2*, and patients with the *ZMYM2-FGFR1* fusion often present with MPN and T-lymphoblastic lymphoma. There are 14 other partners that can fuse with *FGFR1*, and of interest is the *BCR-FGFR1* fusion that results from t(8;22)(p11.2;q11.2). Patients with t(8;22) often show leukocytosis and present with an MPN resembling chronic myeloid leukemia or very rarely, with B-lymphoblastic leukemia (B-ALL). In this study, we analyzed the clinicopathological, cytogenetic, and molecular features of 2 new patients with the t(8;22)(p11.2;q11.2)/*BCR-FGFR1* who presented with B-ALL. An underlying MPN became apparent when a morphologic remission of B-ALL was achieved after chemotherapy. We subsequently reviewed the literature and identified 18 additional cases reported with B-ALL in a background MPN or with the MPN as a chronic phase. Our data suggest that the t(8;22)(p11.2;q11.2)/*BCR-FGFR1* may arise from a myeloid/B progenitor cell. It is important to recognize that neoplasms carrying the t(8;22)/*BCR-FGFR1*, although rare, can commonly with B lymphoblastic leukemia at the initial diagnosis, which could distract one from recognizing a possible underlying 8p11 myeloproliferative syndrome.


## 1. Introduction

The term *8p11 myeloproliferative syndrome* was coined by Macdonald and colleagues [1] to describe neoplasms

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associated with 8p11/*FGFR1* rearrangements. Patients with these neoplasms commonly present with features of a myeloproliferative neoplasm (MPN) and often a concomitant acute lymphoblastic leukemia/lymphoma of T-cell lineage. The 2008 World Health Organization classification used the umbrella designation of "Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* and *FGFR1*" in 2008 [2] to encompass neoplasms that share activation of tyrosine kinases, present with eosinophilia, and interestingly, the neoplasms associated with *PDGFRA/B* groups responded to tyrosine kinase inhibitors, whereas those associated with *FGFR1* rearrangements were resistant to tyrosine kinase inhibitors [2].

The most common partner of *FGFR1* is *ZMYM2,* formerly known as *ZNF198*, that results from the translocation t(8;13)(p11.2;q12), representing approximately half of all cases. It is considered that patients with *ZMYM2-FGFR1* usually present with a disease that resembles an MPN that is often associated with or subsequently develops a blastic neoplasm of T lymphoblasts with myeloid blasts [3-5]. 14 fusion partners have been identified for the *FGFR1* gene (Supplementary Table 1). We recently identified cases with the translocation t(8;22)(p11.2;q11.2) that resulted in *BCR-FGFR1* fusion gene, and patients who presented with leukocytosis and an MPN resembling chronic myeloid leukemia (CML) [5]; and in contrast with cases with *ZMYM2-FGFR1*, patients appeared to develop a B-lineage blast phase.

In this study, we analyzed the clinicopathological, cytogenetic, and molecular features of 2 new patients with t(8;22)(p11.2;q11.2)/*BCR-FGFR1* who presented with B-lymphoblastic leukemia (B-ALL) at the initial diagnosis. We also reviewed the literature and identified 18 additional cases and performed a meta-analysis of these cases.

## 2. Materials and methods

### 2.1. Case selection

We retrospectively reviewed the cytogenetic database in the Department of Hematopathology at The University of Texas MD Anderson Cancer Center from January 2001 to December 2015 for cases diagnosed with hematologic malignancies showing the t(8;22)(p11.2;q11.2). We extracted clinical, laboratory, and hematologic data, and cytogenetic/molecular findings from the medical records at diagnosis as well as at follow-up. We reviewed the morphologic findings in peripheral blood and bone marrow specimens whenever possible, along with patients' clinical management and outcomes. This study was approved by the institutional review board at MD Anderson Cancer Center.

### 2.2. Immunophenotyping

Bone marrow aspirates were analyzed by standard 4- or 8-color flow cytometry immunophenotypic analysis as described previously [6]. The panel included antibodies directed against the following: CD3, CD4, CD5, CD7, CD9, CD10, CD13, CD19, CD20, CD22, CD25, CD33, CD34, CD38, CD52, CD79a, CD117, HLA-DR, TdT, myeloperoxidase, IgM (cytoplasmic), and kappa and lambda light chains. All antibodies were obtained from Becton-Dickinson Biosciences (San Jose, CA), except for TdT (Supertechs, Bethesda, MD). Additional histopathologic and immunohistochemistry examinations were evaluated (Fig. 1) following standard laboratory procedures.

### 2.3. Cytogenetic and fluorescence in situ hybridization analyses

Conventional cytogenetic analysis was performed on metaphase cells prepared from bone marrow aspirate specimens cultured overnight without mitogens. We analyzed 20 Giemsa-banded metaphases and reported the results using the 2016 International System for Human Cytogenomic Nomenclature [7].

Fluorescence in situ hybridization (FISH) analysis for *BCR-ABL1* was performed on interphase nuclei using the *ASS/BCR/ABL1* tricolor translocation probe (Abbott Molecular, Des Plaines, IL). A minimum of 500 interphase nuclei were analyzed for each case. The *FGFR1* FISH testing was performed using a dual-color *FGFR1* break-apart probe (Kreatech/Leica Biosystems, Buffalo Grove, IL), and a minimum of 200 interphase nuclei obtained from bone marrow cultures were analyzed. Additional metaphase FISH using the same probe sets for *BCR-ABL1* and *FGFR1* was also performed. All specimens obtained at our institution during follow-up were also assessed by conventional cytogenetic and/or FISH analyses.

Overall survival was calculated from the date of initial diagnosis to the date of death or last follow-up for all reviewed cases in the literature. Event-free survival was calculated from the date of initial diagnosis to the date of disease progression, relapse, or death.

## 3. Results

There were 3 patients with the t(8;22)(p11.2;q11.2) identified from our database, including 2 women and 1 man. One patient, a 55-year-old woman, was reported previously [8]. The clinicopathological features of the 2 patients are summarized in Table 1 and Fig. 1. In brief, both patients presented with B-ALL in the bone marrow with blast counts of 90% and 17%, respectively.

Patient 1, a 41-year-old woman, diagnosed as having B-ALL had hypercellular marrow at diagnosis (Fig. 1A). FISH analyses performed outside on her initial diagnostic bone marrow showed no evidence of *BCR-ABL1* fusion or *KMT2A* (*MLL*)