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Letter to the editor

t(8;22)/*BCR-FGFR1* myeloproliferative disorder presenting as B-acute lymphoblastic leukemia: Report of a case treated with sorafenib and review of the literature

1. Introduction

The 8p11 myeloproliferative syndrome (EMS) is a rare and aggressive hematological neoplasm caused by rearrangements involving fibroblast growth factor receptor 1 (*FGFR1*) gene on chromosome 8p11, and one of 11 identified partner genes. The result is a variety of fusion genes encoding aberrant tyrosine kinases and activating multiple signal transduction pathways [1,2].

Involvement of t(8;22)/*BCR-FGFR1* is exceedingly rare, with only 8 cases reported to date [3]. It usually presents as chronic myelogenous leukemia (CML)-like disease rapidly evolving into acute myeloid leukemia (AML), but one reported case presented as B-acute lymphoblastic leukemia (B-ALL) [3]. Herein, we report the second case of t(8;22) presenting as B-ALL, and the first to be treated with targeted therapy against tyrosine kinase following chemotherapy.

2. Case report

A 43 year-old man presented with weakness, night sweats, and weight loss. Physical examination revealed tender splenomegaly. White blood cell (WBC) count was 53×10^9/L with 18% neutrophils, 9% lymphocytes, 3% monocytes, 3% metamyelocytes, 2% myelocytes, 2% promyelocytes, and 63% blasts. Hemoglobin was 7.6 g/dL and platelet count was 6×10^9/L.

Bone marrow (BM) aspirate and biopsy showed 100% cellularity with virtual replacement by B-ALL. Flow cytometry demonstrated an 84% population of B-lymphoblasts with $CD10^+/CD19^+/CD20^{partial+}/CD22^+/CD38^+/CD34^{subset+}$/surface $Ig^-/Tdt^+/CD79a^+$/myeloid antigens$^-$ immunophenotype. Cytogenetics showed t(8:22)(p11;q11) among other structural abnormalities.

The patient was in remission after cycle 1A of hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, decadron). He completed 8 cycles of intravenous chemotherapy and 16 intrathecal chemotherapy infusions.

His treatment course was intriguingly complicated by severe leukocytosis and painful splenomegaly (21.9 cm spleen on ultrasound) in response to granulocyte colony-stimulating factor therapy (filgrastim). The highest WBC was 233×10^9/L after cycle 3A with 61% neutrophils and 3% blasts. BM examination revealed left-shifted granulopoiesis reminiscent of CML and no evidence of recurrent B-ALL. We investigated the therapeutic option of allogeneic stem cell transplantation but were unable to identify a suitable HLA-matched donor.

At the completion of hyperCVAD, the patient still had no evidence of ALL but displayed characteristics of a CML-like neoplasm. Because of his *BCR-FGFR1* rearrangement, we reasoned that the disease might be driven in part by *FGFR1* tyrosine kinase activity. He was started on hydroxyurea 1000 mg twice a day and the *FGFR1* inhibitor sorafenib 400 mg orally twice a day [4]. Eleven days later, hydroxyurea was discontinued since this therapy was associated with a decrease in WBC count (Fig. 1). BM biopsy at 1 month revealed relapsed B-ALL despite a normal peripheral WBC count and differential. The patient received FLAG-Ida (fludarabine, cytarabine, idarubicin) without filgrastim, while remaining on sorafenib. Day 15 BM showed persistent B-ALL and an expansion of myeloblasts of which further immunophenotypic analysis could not be performed due to low cellularity. The patient deteriorated clinically and died 6 weeks later.

3. Results

3.1. Cytogenetics and FISH

At diagnosis, an abnormal karyotype with translocation (8;22) and additional abnormalities was observed in all 11 metaphases: 45,XY,t(6;11)(q11;p13),−7,t(8;22)(p11.2;q11.2),del(9)(p13p22) (Fig. 2A).

The next cytogenetic studies at CML-like phase showed sole t(8;22)(p11.2;q11.2). FISH using the Vysis LSI BCR/ABL Dual Color, Dual Fusion Translocation Probe (Des Plaines, Illinois 60018) showed 3 signals for BCR in 87% of nuclei examined, consistent with rearrangement of *BCR* but no evidence of *BCR/ABL1* fusion. FISH on G-banded metaphases showed a *BCR* signal on the derivative chromosome 8 (Fig. 2B). FISH studies using the BAC clone RP11-333B24 from Empire Genomics (Buffalo, New York 14203, USA) spanning the *FGFR1* locus showed that 85% of nuclei had evidence of a rearrangement of the *FGFR1*, which was confirmed on previously G-banded metaphases, manifested as the BAC clone RP11-333B24 signal on the normal chromosome 8, the derivative chromosome 8 and the derivative chromosome 22 (Fig. 2C).

Two months later when the patient was still in CML-like phase, cytogenetic analysis again showed t(8;22)(p11.2;q11.2) as the sole abnormality. FISH suggested an additional rearrangement of *FGFR1* (Fig. 2D).

Follow-up cytogenetic studies at recurrence of B-ALL showed the abnormalities detected in the initial clone at diagnosis: t(8;22)(p11.2;q11.2), t(6;11)(q11;p13), del(9)(p13p22) with additional structural abnormalities including inv(2)(p11.2q31), t(3;7)(q23;q11.2), add(7)(p13), der(9)t(7;9)(p15;p22), inv(17)(p11.2q21), and an extra copy of der(8)t(8;22)(p11.2;q11.2).

4. Discussion

We report the second case of t(8;22)/*BCR-FGFR1* presenting as B-ALL [3], and the first to be treated with the multi-tyrosine kinase

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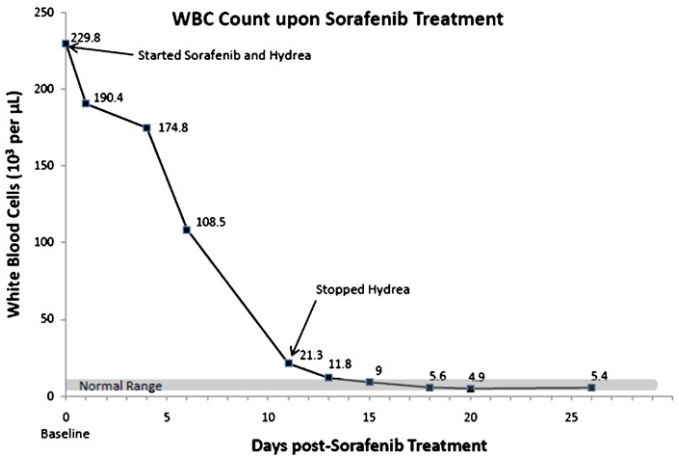

Fig. 1. Representative curve of white blood cell (WBC) count upon sorafenib treatment (patient received hydroxyurea from day 0 to day 11).

inhibitor sorafenib following chemotherapy. Our case reaffirms several important clinicopathologic and biologic aspects of EMS.

First, in contrast with other *FGFR1* rearrangements frequently presenting with eosinophilia and lymphadenopathy, patients with t(8;22)/*BCR-FGFR1* display leukocytosis and neutrophilia in a clinical syndrome resembling CML, as did our patient. This distinct clinical presentation suggests a special role of *BCR* in the expression of the disease [5]. This is thought to be the case for all *FGFR1* partner genes, each wielding a different effect on the malignant phenotype, even if activation of *FGFR1* remains the most significant oncogenic step [2].

Second, our case supports that EMS derives from a multipotent hematopoietic stem cell [1,2], by demonstrating *BCR-FGFR1* fusion in the B-lymphoid lineage at initial presentation of B-ALL, and in the myeloid lineage at the CML-like phase. It is currently believed that normal hematopoiesis involves the generation of myeloid/T-lymphoid and myeloid/B-lymphoid progenitor cells at the early stages of development [6]. Therefore, the cell origin of EMS may be a very early progenitor cell retaining the potential for both myeloid and lymphoid differentiation.

Third, this case illustrates the importance of cooperating oncogenic pathways in the pathogenesis of neoplastic phenotypes in EMS. Our case harbored additional chromosomal abnormalities comparable to the previously reported case of t(8;22)/*BCR-FGFR1* rearranged B-ALL: −7 and del(9)(p13p24), and del(7)(p12p15) and −9, respectively [3]. Interestingly, *PAX-5* and *IKZF1* are located in 9p13 and 7p12, in that order, and recurrent genomic deletions of both genes have been identified and implicated in the pathogen-

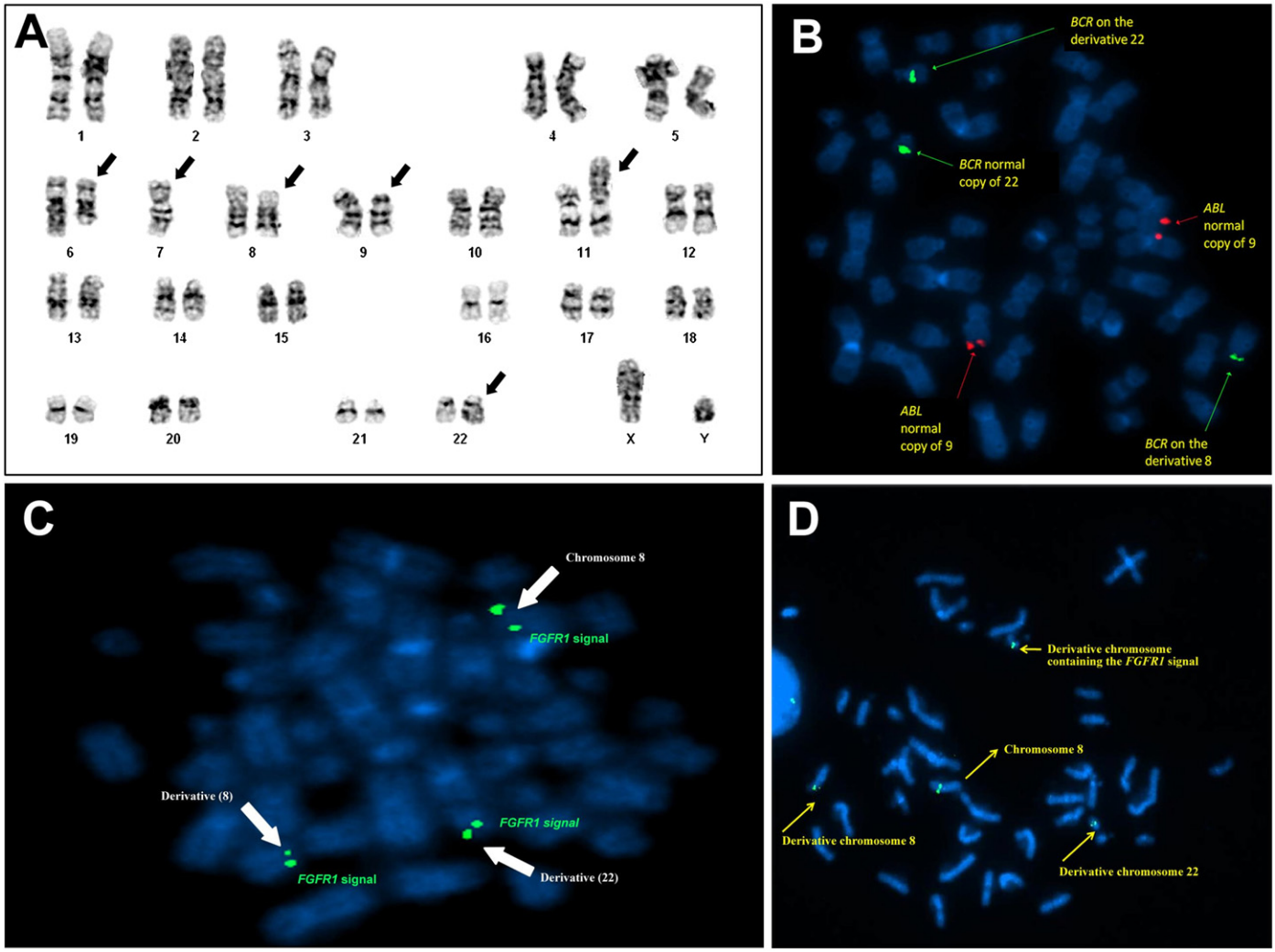

Fig. 2. (A) Representative karyotype at initial diagnosis shows abnormalities including t(8;22)(p11;q11). (B) FISH shows 3 *BCR* signals (using the LSI BCR/ABL). (C) FISH shows 3 *FGFR1* signals (using the RP11-33B24 BAC) in 92% of the cells examined. (D) FISH using the BAC clone RP11-333B24 shows *FGFR1* rearrangement in 91.8% (179/195) of nuclei. 73 of these 179 cells (41%) had an extra RP11-333B24 signal, suggesting an additional rearrangement of *FGFR1* with a different chromosome, which was also confirmed with FISH on metaphases.

esis of t(9;22)/*BCR-ABL1* rearranged B-ALL [7,8]. It is tempting to speculate that the disruption of *PAX5* and *IKZF1* may play a role in the transformation of CML-like disease to B-ALL in *BCR-FGFR1* rearranged neoplasm, in a manner similar to *BCR-ABL1* rearranged B-ALL. On the other hand, alteration of *RUNX1* has been previously suspected to play a role in the transformation of both t(9;22)/*BCR-ABL1* CML and t(8;22)/*BCR-FGFR1* neoplasm to AML [9].

Lastly, our case underscores the importance of accurate molecular diagnosis in patients with *FGFR1* rearrangement who can misleadingly present as B-ALL. These patients have aggressive courses and are resistant to conventional management but might be amenable to treatment with specific *FGFR1* inhibitors. Following the success of imatinib in neoplasms with rearrangement of *PDGFRA* and *PDGFRB* [10], the *FGFR1* inhibitor PKC412 was used in a patient with *ZNF198-FGFR1*, resulting in improved leukocytosis and lymphadenopathy but persistent cytogenetic abnormality [11]. We are the first to apply this strategy in a patient with t(8;22)(p11;q11) and *BCR-FGFR1*, using the *FGFR1* inhibitor sorafenib [4]. The response was of short duration as our patient relapsed with B-ALL nearly a month later. Our patient's malignancy had undergone extensive clonal evolution. Certain clones causing CML-like manifestations may have retained sensitivity to sorafenib treatment, while clones manifesting as B-ALL were clearly resistant. Conceivably, earlier treatment or the use of more potent *FGFR1* inhibitors might be more effective in EMS, but allogeneic stem cell transplantation remains the treatment of choice [1,2].

Conflict of interest statement

All authors have no conflict of interest to declare.

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References

[1] Macdonald D, Reiter A, Cross NC. The 8p11 myeloproliferative syndrome: a distinct clinical entity caused by constitutive activation of FGFR1. Acta Haematol 2002;107(2):101–7.
[2] Jackson CC, Medeiros LJ, Miranda RN. 8p11 myeloproliferative syndrome: a review. Hum Pathol 2010;41(April (4)):461–76.
[3] Baldazzi C, Iacobucci I, Luatti S, et al. B-cell acute lymphoblastic leukemia as evolution of a 8p11 myeloproliferative syndrome with t(8;22)(p11;q11) and BCR-FGFR1 fusion gene. Leuk Res 2010;34(October (10)):e282–285.
[4] Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64(October (19)):7099–109.
[5] Demiroglu A, Steer EJ, Heath C, et al. The t(8;22) in chronic myeloid leukemia fuses BCR to FGFR1: transforming activity and specific inhibition of FGFR1 fusion proteins. Blood 2001;98(December (13)):3778–83.
[6] Kawamoto H, Katsura Y. A new paradigm for hematopoietic cell lineages: revision of the classical concept of the myeloid-lymphoid dichotomy. Trends Immunol 2009;30(May (5)):193–200.
[7] Iacobucci I, Storlazzi CT, Cilloni D, et al. Identification and molecular characterization of recurrent genomic deletions on 7p12 in the IKZF1 gene in a large cohort of BCR-ABL1-positive acute lymphoblastic leukemia patients: on beh*alf of Gruppo Italiano Malattie Ematologiche dell'Adulto Acute Leukemia Working Party (GIMEMA AL WP). Blood 2009;114(September (10)):2159–67.
[8] Iacobucci I, Lonetti A, Paoloni F, et al. The PAX5 gene is frequently rearranged in BCR-ABL1-positive acute lymphoblastic leukemia but is not associated with outcome. A report on b*ehalf of the GIMEMA Acute Leukemia Working Party. Haematologica 2010;95(October (10)):1683–90.
[9] Richebourg S, Theisen O, Plantier I, et al. Chronic myeloproliferative disorder with t(8;22)(p11;q11) can mime clonal cytogenetic evolution of authentic chronic myelogeneous leukemia. Genes Chromosomes Cancer 2008;47(October (10)):915–8.
[10] David M, Cross NC, Burgstaller S, et al. Durable responses to imatinib in patients with PDGFRB fusion gene-positive and BCR-ABL-negative chronic myeloproliferative disorders. Blood 2007;109(January (1)):61–4.
[11] Chen J, Deangelo DJ, Kutok JL, et al. PKC412 inhibits the zinc finger 198-fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder. Proc Natl Acad Sci U S A 2004;101(October (40)):14479–84.

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