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CASE REPORT

A case mimicking chronic myeloid leukemia with t(8;22)(p11;q11) /BCR-FGFR1 and sequential transformation to B-acute lymphoblastic leukemia and acute myeloid leukemia

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Abstract

Myeloid/lymphoid neoplasm is a rare malignancy with an aggressive course and rapid transformation to acute myeloid leukemia (AML), or less frequently to acute lymphoblastic leukemia (ALL). Cases with t(8;22)(p11;q11) *BCR-FGFR1* fusion gene may be misdiagnosed with chronic myeloid leukemia (CML), due to a very similar morphologic and clinical profile. We report a case of 48-year-old woman who complained of weakness and gastric pain. She had splenomegaly, eosinophilia, and elevated white blood cells. Bone marrow (BM) aspiration biopsy was performed with an initial diagnosis of CML. Cytogenetic analysis of the BM showed a 46,XX,t(8;22)(p11.2;q11.2). She was diagnosed with myeloid/lymphoid neoplasm with eosinophilia and rearrangement of *FGFR1* gene. Throughout the chronic phase, the patient was treated with hydroxurea. Additional chromosomal abnormalities developed during therapy. Owing to the (8;22) clone, our patient did not respond to the treatment and rapidly transformed first to B-ALL and then AML. To the best of our knowledge, this is the first MPN patient with rearrangement of *BCR* and *FGFR1* genes with rapid transformation to B-ALL and then to AML.

Keywords FGFR1 gene · FGFR1/BCR fusion · Leukemia

Introduction

Myeloid/lymphoid neoplasm is a rare malignancy with an aggressive course and transformation to acute myeloid leukemia (AML), or less frequently to acute lymphoblastic leukemia (ALL) [1, 2]. Various partner genes have been identified that may fuse to *FGFR1* gene. *BCR* gene (located on chromosome 22q11) is one of these partner genes [1]. Translocation between chromosomes 8 and 22 leads to the formation of a protein similar to the BCR/ABL chimeric protein [3, 4]. Accordingly, the clinical features of the patients with *BCR-FGFR1* fusion gene are similar to chronic myeloid leukemia (CML) and thus may be misdiagnosed as CML [5–7]. These patients are resistant to tyrosine kinase inhibitor (TKI) therapy, so they are generally treated with chemotherapy and allogeneic stem cell transplantation (SCT). Therefore, the patients may achieve long-time survival [6, 8–10].

Clinical history

We report the case of a 48-year-old woman who complained of weakness and gastric pain (2013 January). Physical examination revealed splenomegaly (lower edge 4 cm below arcus costa vertical diameter 160 mm with US). Complete blood count showed a white blood cell (WBC) count of 118×10^3/mL, a neutrophil count of 105×10^3/mL, an eosinophil count of 5.6×10^3/mL, a hemoglobin level of 10.8 g/dL, and a platelet count of 179×10^3/mL. Segmented and band neutrophils were predominated, and granulocytes at all stages of development were presented in the peripheral blood smear. Furthermore, hyposegmentation and pseudo Pelger-Huet anomaly in

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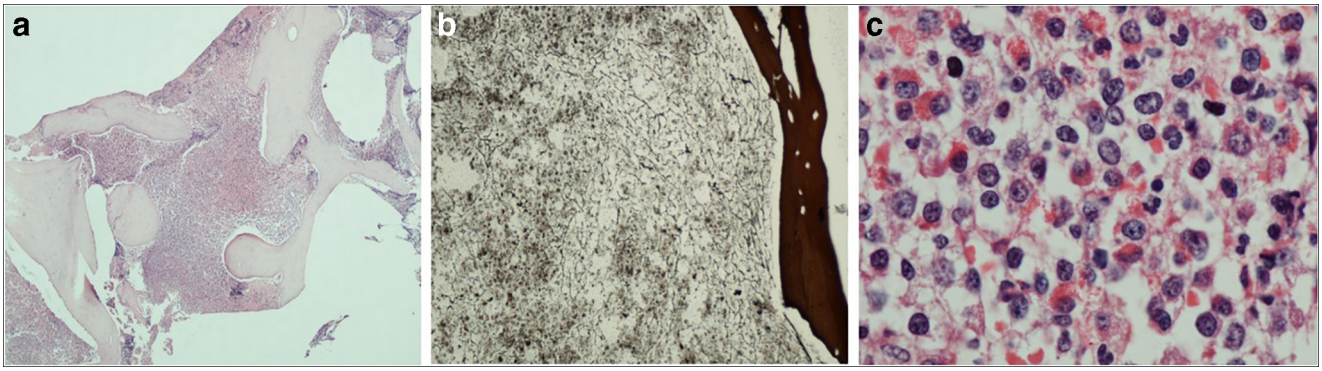

Fig. 1 **a** Hypercellular bone marrow for age. **b** Reticulin fibrosis by a silver impregnation stain. **c** Granulocytic proliferation and increase in the eosinophilic lineage

neutrophils, anisocytosis and poikilocytosis in erythrocytes, erythroblasts, and extensive tear drops were seen. Bone marrow (BM) aspiration and biopsy were performed with an initial diagnosis of CML. The BM was markedly hypercellular (95% cellularity) primarily because of granulocytic hyperplasia. Mild hyperplasia was seen in megakaryocytes, and reticulin fibrosis grade was 1–2. The morphological findings were evaluated to be compatible with chronic phase CML (Fig. 1). Cytogenetic analysis of the BM revealed a reciprocal translocation between chromosomes 8 and 22 [t(8;22)(p11.2;q11.2)[20]] (Fig. 2a). The rearrangement of the BCR and FGFR1 genes was detected in FISH analysis (Fig. 2c). qRT-PCR was performed for the analysis of *BCR/ABL*, but the suspected *BCR/ABL* fusion was not detected. However, *BCR-FGFR1* fusion was detected with

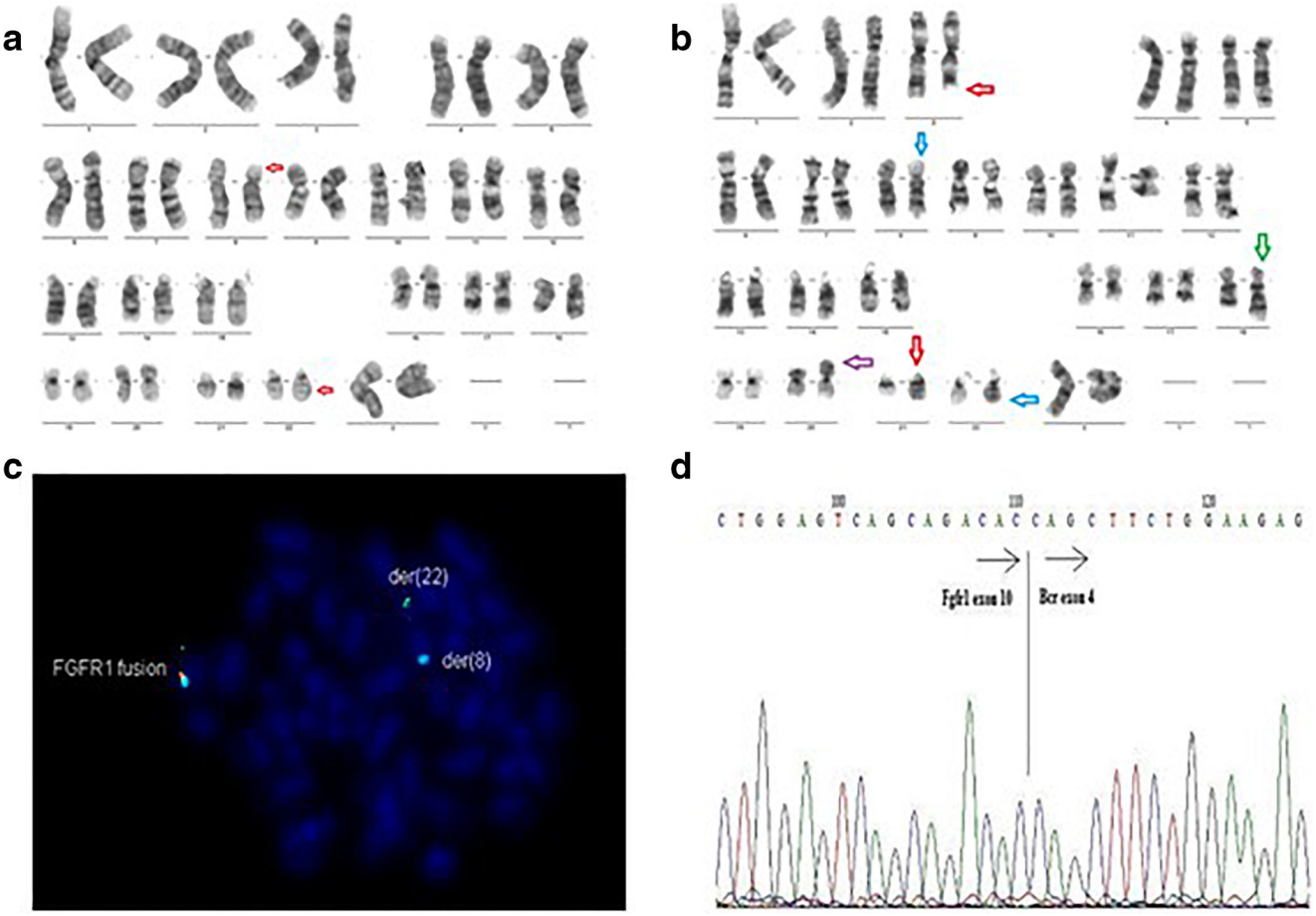

Fig. 2 **a** Karyotype analysis showing 46,XX,t(8;22)(p11;q11)[20]. **b** Karyotype analysis showing t(8;22)(p11;q11) and additional abnormalities. Abnormal chromosomes were indicated by arrows. **c** Three-color break-apart probe metaphase FISH for FGFR1 gene rearrangement (1G1F2A). **d** Sanger sequencing diagram showing an in-frame fusion between BCR exon 4 and FGFR1 exon 10

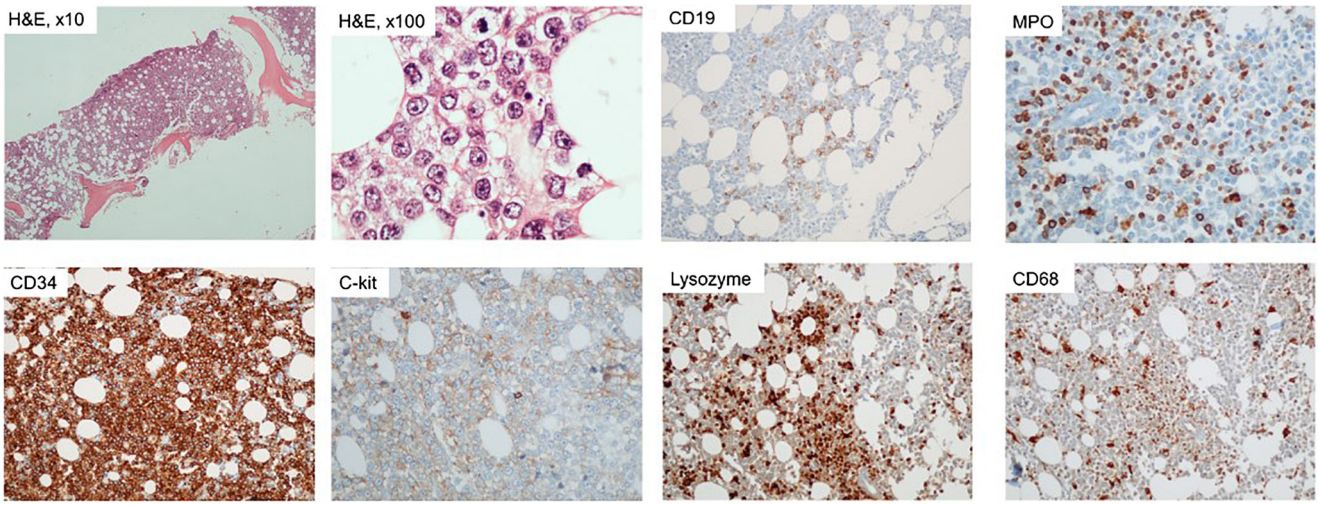

Fig. 3 Histologic and immunohistochemical findings in bone marrow biopsy compatible with AML

Sanger sequencing (Fig. 2d). Identification of the translocation changed the diagnosis to myeloid/lymphoid neoplasm with eosinophilia and rearrangement of the *FGFR1* gene. The patient was treated with hydroxyurea and allopurinol. After a month of the treatment, the size of the spleen was found to be normal, and WBC count decreased to 3.1×10^3/mL. One week later, she started to complain about bilateral lower extremity pain. On MR scan of the lower extremities, T1 hypo- and T2 hyperintense nodular images were observed in femur, tibia, and patella. The new complete blood count showed a WBC count of 30×10^3/mL, a hemoglobin level of 7.9 g/dL, and a platelet count of 49×10^3/mL. The peripheral blood smear was repeated and 66% blastic cells with scant, agranular cytoplasm; round nuclei; and frequently inconspicuous nucleoli were detected. Immunophenotyping was performed which supported the diagnosis as B-ALL (CD45 99%, CD10 79%, CD19 81%, CD20 88%, CD22 83%, HLA-DR 95%, CD34 2%, surface light chains (−)). After beginning GMALL protocol, the patient achieved remission. Radiotherapy, including cranial prophylactic radiotherapy, was applied to the bones where activity was observed and the patient was followed up under maintenance treatment with methotrexate and purinethol. In February 2014, bone marrow examination was performed again to assess the patient's remission status. There was no blasts infiltration in the BM aspiration and biopsy (immunophenotyping: CD3(−), CD20(−), pax-5(−), TdT(−)). Cytogenetic analysis of the BM showed new structural abnormalities [46,XX,t(3;21)(q26.2;q22),t(8;22)(p11;q11),der(18)t(9;18)?,der(20p)] (Fig. 2b). The patient was hospitalized, and consolidation treatment was started in accordance with GMALL protocol, after which the patient developed long-term pancytopenia and pneumonia. In March 2014, BM aspiration, biopsy, immunophenotyping, and cytogenetic analysis were performed due to unresolved thrombocytopenia and blasts seen on peripheral blood smear. Diffuse neoplastic blast infiltration was seen in the BM. Widespread and strong CD34 antigen positivity was present in the blasts. Monocytic cell antigens such as CD68 and lysozyme were positive in the cell population of relatively small size, more compact and scant cytoplasm. On the other hand, myeloid antigens such as CD117 and CD33 were positive in relatively larger cells (Fig. 3). A diagnosis of AML was established (immunophenotyping: CD34 75%, CD33 62%, HLA-DR 81%, CD13 43%, CD117 27%). FLAG-IDA regimen was applied as a treatment. However, the patient died due to the infections in the cytopenic period. The laboratory, histopathological, cytogenetic, FISH, and molecular findings of the patient during the treatment process are shown in Table 1.

Material and methods

Conventional cytogenetic Cytogenetic study was carried out after 24- and 48-h BM cultures. Harvesting, slide making, and G-banding were done according to standard procedures. Metaphases were analyzed using the Lucia Cytogenetic Analysis System (Lucia Cytogenetics, Czech Republic). At least 20 metaphases were evaluated. Details of the karyotype are reported in accordance with the International System for Human Cytogenetic Nomenclature (ISCN 2016).

FISH In FISH studies, 200 metaphases were analyzed using the Isis Fluorescent Imaging System (Metasystems, Germany). FISH for *BCR-ABL* was performed with dual color dual fusion probes (Cytocell, UK) according to the manufacturer's instructions. Two red and 3 green signals pointed out rearrangement of *BCR* gene. FISH for *FGFR1* was performed with triple-color combined fusion/break-apart probes (Cytocell, UK) according to the manufacturer's instructions. It has been

Table 1 Laboratory, histopathologic, cytogenetic, FISH, and molecular findings of the patient

			Clinical diagnosis	Therapy
January 2013 (at the time of initial presentation) results				
Complete blood count	WBC	118×10^3/mL	Myeloid/lymphoid neoplasm with eosinophilia and rearrangement of *FGFR1* gene (CML mimicking)	Hydroxyurea and allopurinol
	Neutrophil	105×10^3/mL		
	Eosinophil	$5{,}6 \times 10^3$/mL		
	Hemoglobin	10.8 g/dL		
	Platelet	179×10^3/mL		
Peripheral blood smear	Segmented and band neutrophils (hyposegmentation and pseudo Pelger-Huet anomaly), increased granulocytes, erythrocytes (anisocytosis and poikilocytosis), erythroblasts, extensive tear drops			
Bone marrow	Hypercellular (95% cellularity) primarily because of granulocytic hyperplasia			
	Mild hyperplasia in megakaryocytes and reticulin fibrosis grade 1–2			
Cytogenetic	46,XX,t(8;22)(p11.2;q11.2)[20]			
FISH (bcr/abl)	Negative, rearrangement for the BCR gene			
FISH (bcr/FGFR1)	Positive			
qRT-PCR (bcr/abl)	Not detected			
Sanger sequencing	BCR/FGFR1			
February 2013 results (5 weeks after diagnosis)				
Complete blood count	WBC	30 × 103/mL	B-ALL	GMALL protocol maintenance treatment with methotrexate and purinethol
	Hemoglobin	7.9 g/dL		
	Platelet	49 × 103/mL		
Peripheral blood smear	66% blasts with scant, agranular cytoplasm; round nuclei; and frequently inconspicuous nucleoli			
Immunophenotyping of peripheral blood	CD45 99%, CD10 79%, CD19 81%, CD20 88%, CD22 83%, HLA-DR 95%, CD34 2%, surface light chains (−)			
February 2014 results				
Bone marrow	No blasts infiltration		B-ALL	GMALL protocol consolidation treatment
Immunophenotyping of bone marrow	CD3(−), CD20(−), pax-5(−), TdT(−)			
Cytogenetic	46,XX[46]/46,XX,t(3;21)(q26.2;q22),t(8;22)(p11;q11), der(18)t(9;18)?,der(20p)[4]			
March 2014 results				
Peripheral blood smear	Large blasts with basophilic cytoplasm and 1–2 nucleoli, thrombocytopenia		AML	FLAG-IDA
Immunophenotyping	CD34 75%, CD33 62%, HLA-DR 81%, CD13 43%, CD117 27%			
Cytogenetic	47,XX,t(3;21)(q26.2;q22),der(4q),t(8;22)(p11;q11), der(18)t(9;18)?,der(20p),+mar[20]			

shown the split of one of the two fusion signals along with a blue centromere to enumerate chromosome 8.

qRT-PCR Reverse transcription quantitative polymerase chain reaction (qRT-PCR) for *BCR-ABL* fusion transcripts was performed with a commercial kit based on TaqMan technology (Ipsogen® *BCR-ABL1* Mbcr IS-MMR DX Kit-Qiagen, Germany). RNA was extracted from the BM sample and reversely transcribed into cDNA (QIAamp RNA Blood Mini Kit; QuantiTect Reverse Transcription Kit-Qiagen, Germany).

Sanger sequencing A multiplex PCR with four forward *BCR* primers was performed for the detection of *BCR-FGFR1*. Primers used for the detection of *BCR-FGFR1* and the reciprocal fusion were Exon 11: 5′-AGATCTGGCCCAACGATGACGA-3′, Exon 5-6: 5′-GAAATCTCCGAGAACCTGAGAG-3′, Exon 12: 5′-GAGCGTGCAGAGTGGAGGGAGAACA-3′, and Exon 19: 5′-GAGGTCCAAGGTGCCCTACAT-3′ forward primers for bcr and a single reverse primer 5′-GAGGGTCTTCGGGAAGCTCATA-3′ for FGFR1. A 890 base pair (bp) long product was observed in the patient sample, but not in samples from control patients with Ph-positive CML. The sequencing was performed using the BigDye Terminator v3.1 Cycle Sequencing Kit and analyzed with ABI Prism 3500xl Genetic Analyzer (Applied Biosystems, USA). Sequencing of these products revealed an in-frame fusion between *BCR* exon 4 and *FGFR1* exon 10 in the patient.

Immunophenotyping Immunophenotyping was performed on bone marrow on an eight-color flow cytometry platform (BD FACSCanto II, BD Biosciences, USA). The antibodies for CD3, CD10, CD13, CD19, CD20, CD22, CD33, CD34, CD45, CD117, HLA-DR, surface light chains, pax-5, and TdT were included, and their expression was analyzed for the classification of leukemia. The analysis was performed using a hierarchical gating method.

Discussion

The *FGFR* gene family involves proto-oncogenes which are activated by mutations, overexpression, and chromosomal translocations in various cancers. Translocations including the *FGFR1* gene which is a member of this family cause stem cell leukemia/lymphoma syndrome (SCLL), also known as myeloid/lymphoid neoplasm [11]. This chromosomal translocation provides a fused dimerizing partner to the kinase domain of *FGFR1* and leads to structural phosphorylation [12]. Due to the aberrant expression of the *FGFR1* kinase, different transcription factors in the STAT family and in the MAPK pathway are abnormally phosphorylated and lead to excessive cellular proliferation, differentiation, survival, anti-apoptosis, and angiogenesis, suggesting that *FGFR1* fusions play a very important role in leukemogenesis [13].

Myeloid/lymphoid neoplasm has a severe clinical course and progress rapidly to AML and infrequently to ALL in 1–2 years after diagnosis. Differences in the clinical presentation of the disease may be due to the fact that different partner genes affect different pathways. Therefore, allogeneic stem cell transplantation (ASCT) may provide long-term remission and recovery in patients with *FGFR1* rearrangements [7, 8]. As for that, in 2016 WHO classification, myeloid/lymphoid neoplasm was identified according to rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2* [14]. Among these, myeloid/lymphoid neoplasm with rearrangement of *FGFR1* gene is quite rare [5–7, 15]. Due to clinical and laboratory features similar to CML, these patients are usually misdiagnosed. So, cytogenetic analysis and accurate molecular diagnosis is crucial [16]. The mechanisms that trigger B cell differentiation among patients with *FGFR1* rearrangements is not well understood [17]. *FGFR1* gene has many fusion partner genes; the most frequent is the *BCR* gene. This new fusion protein activates tyrosine kinases and induces development of several hematologic malignancies [5]. Patients with *FGFR1-BCR* fusion transform frequently to AML and infrequently to ALL and lymphoid neoplasms after a short period of chronic phase [2]. In the literature, cases with t(8;22) were reported as CML-like disease or AML, T or B lymphoblastic lymphoma/leukemia, or a mixed phenotype acute leukemia. This mixed phenotype may imply that the disease might have derived from early progenitor cells that are capable of differentiating to both myeloid and lymphoid cells [18]. Patients carrying the *BCR-FGFR1* fusion gene develop resistance to chemotherapy or TKIs treatments. However, it was reported that those patients may benefit from treatment with multi-tyrosine kinase inhibitors (e.g., ponatinib) [5, 15], FGFR1 inhibitors [3, 19], or allogeneic SCT [1].

Montenegro-Garreaud et al. reported a patient with the (8;22) translocation, who achieved complete morphologic, immunophenotypic, and cytogenetic remission after allogeneic SCT, with no *FGFR1* rearrangements at the last follow-up. Although chemotherapy for the blastic phase is effective on secondary chromosomal abnormalities, t(8;22) is not affected [20]. In our patient, resistance to treatment and rapid transformation to ALL and AML may be due to the existence of the (8;22) clone. So, ASCT may be the best treatment choice for this disorder due to the high risk of transformation to AML or ALL [1, 19].

The secondary abnormality t(3;21)(q26.2;q22) which developed following therapy in our patient is a rare abnormality and occurs in < 1% of cases with AML/MDS, primarily t-MDS/AML or in the blast phase of CML. It has been reported that these abnormalities occur particularly after chemotherapy and are associated with a poor prognosis [21, 22].

To our knowledge, this is the first report of a MPN patient with rearrangement of *BCR* and *FGFR1* gene (located on chromosome 8p11) who transformed to ALL and then rapidly to AML. This case showed that the identification of *FGFR1-BCR* translocation is very important in rapid decision-making and may guide the clinician with respect to treatment and patient management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent The consent of the patient is included in the hospital clinical documents.

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