8p11 Myeloproliferative syndrome with t(8;22)(p11;q11): A case report

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Abstract. The 8p11 myeloproliferative syndrome (EMS), a rare myeloproliferative disease, generally progresses rapidly and is characterized by chromosomal translocations of the fibroblast growth factor receptor 1 (FGFR1) gene. The FGFR1 gene is located at chromosome 8p11 and may fuse with distinct partner genes. The breakpoint cluster region gene located at chromosome 22 is one of these partner genes. The patients' clinical phenotype is primarily dependant on the partner gene that translocates with FGFR1. Of all the available examinations, determination of the chromosome karyotype is most essential for the diagnosis of EMS. In addition, regarding treatment, allogeneic hematopoietic stem cell transplantation is currently the optimal method. The present study presented a case of 8p11 myeloproliferative syndrome with t(8;22)(p11;q11). This represents a total of 8 and 11 chromosomal translocations, which form a BCR/FGFR1 fusion gene in the patient to produce the abnormal karyotype: 46,XY,t(8;22)(p11;q11). The difference between the current case and other EMS incidences is that the patient progressed slowly and the clinical manifestation was similar to chronic myeloid leukemia (CML).

Introduction

The 8p11 myeloproliferative syndrome (EMS) is an infrequent, aggressive hematological disease. At the molecular level, EMS is defined as chromosomal rearrangements of the fibroblast growth factor receptor 1 (FGFR1) gene. Among these karyotypes, there are distinct fusion partners, including the breakpoint cluster region (BCR) gene on chromosome 22. The FGFR1 fusion pattern is correlated with the phenotype and prognosis of the disease (1-3).

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EMS presenting with t(8;22)(p11;q11) is infrequent in clinical practice, with only 14 cases reported to date, as presented in Table I. This type of disease may rapidly progress to acute myeloid leukemia (AML) or, less commonly, to acute lymphoblastic leukemia (ALL) (4-6).

The present study reports on a case EMS with t(8;22)(p11;q11), presenting as chronic myeloid leukemia (CML), as distinguished by its slow progression, which differs from that of other cases presenting as AML, ALL and lymphoma.

Case report

Patient information. A 41-year-old male who had been presenting with progressive leukocytosis and thrombocytosis for 1 year was admitted to Tongji Hospital (Wuhan, China) in October 2016. The patient was formerly physically healthy and exhibited no obvious symptoms. Physical examination indicated no lymph node enlargement or hepatosplenomegaly, which was confirmed by ultrasonography and abdominal computed tomography. The initial complete blood analysis revealed hemoglobin levels of 139 g/l (normal range, 115-150 g/l), a white blood cell (WBC) count of $23x10^9$/l (normal range, 3.5-9.5x10^9/l) and a platelet count of $492x10^9$/l (normal range, 125-350x10^9/l). For the past year, the patient's WBC and platelet counts had been steadily increasing. Bone marrow (BM) cytology smears and BM biopsy indicated myelosis and granulocyte hyperplasia. BM cell differential analysis revealed 92% granulocytes (with a myeloid/erythroid cell ratio of 26:1). Polymerase chain reaction analysis indicated negativity for the BCR-Abelson murine leukemia fusion gene and the Janus kinase 2/Val617Phe mutation. Cytogenetic analysis of the BM was performed with 10 metaphase cells, all of which carried the 46,XY,t(8;22)(p11;q11) mutation. Fluorescence *in situ* hybridization (FISH) further validated this chromosome translocation. These results provided crucial evidence for the diagnosis of EMS, although unlike those of other EMS cases, the patient's clinical manifestations resembled those of CML.

EMS usually progresses rapidly and is associated with a poor prognosis. However, one more year after the initial diagnosis, the patient remained asymptomatic without any treatment, while his leucocytosis and thrombocytosis did not mitigate. According to previous studies, hematopoietic cell transplantation remains the only effective measure to control EMS (7-11). However, the patient refused to receive

Table I. Previous case studies reporting on t(8;22)/breakpoint cluster region-fibroblast growth factor receptor 1 rearrangements.

Author, year	Age (years), sex	Clinical manifestation prior to EMS diagnosis	Chromosomal abnormalities	Treatment	Outcome	(Refs.)
Fioretos, 2001	75, male	AML	46,XY,t(8;22)(p11;q11) t(9;21)(q34;q22)	Not reported	Not reported	(3)
Demiroglou, 2001	65, female	CML-CP	Not reported	Hydroxyurea, IFNα	Alive on publication	(10)
Demiroglou, 2001	51, female	CML-CP	Not reported	Hydroxyurea, IFNα	Alive on publication	(10)
Pini, 2002	74, female	CML-CP	Not reported	Not reported	Not reported	(12)
Murati, 2005	Not available	CML-CP and B-cell proliferation	Not available	Not available	Not reported	(13)
Agerstam, 2007	58, female	AML	46,XY,t(8;22)(p11;q11)	Not reported	Not reported	(14)
Richebourg, 2008	56, female	CML, evolved to blast crisis	47,XX,t(3;21)(q26;q22) t(8;22)(p11;q11), +der (22)	Hydroxyurea+IFNα, arsenic trioxide, cytarabine, daunorubicin+cytarabine	Death 24 months after presentation	(15)
Baldazzi, 2010	70, female	pre-ALL	45,XX,del (3)(p11p21), del (7)(p12p15), t(8,22) (p11;q11), add (8)(p23), -9	Induction combined chemotherapy	Death 24 months after presentation	(6)
Wakim, 2011	43, male	B-ALL	45,XY,t6;11)(q11;p13), -7, t(8;22)(p11.2;q11.2), del (9) (p13p22)	Hyper-CVAD	Death	(5)
Haslam, 2012	21, male	B-ALL	46,XY,t(8;22)(p12;q11)/45, idem, der (3;9)(q10;q10), dic (7;11)(p11;q13), +r (cp3)	FLAG, HSCT	Alive on publication	(9)
Morishige, 2012	50, male	Trilineage acute leukemia lymphoma	Not available	Cord blood	Alive on publication transplantation	(8)
Matikas, 2013	74, female	AML	46,XX, del (5) q33q35, t(8;22)(p11;q11)	Mitoxantrone+etoposide, interferon, hydroxyurea, flutalazine	Alive on publication	(4)
Dolan, 2012	8, male	Juvenile myelomonocytic leukemia	46,XY, inv (4)(p15.2q13), t(8;22)(p11;q11;q24)	Allogenic HSCT	Alive on publication	(7)
Qin, 2016	26, female	CML	46,XX,t(8;22)(p11;q11)	Hydroxyurea	Alive on publication	(16)

CML-CP, chronic myeloid leukemia in chronic phase; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; IFN, interferon; HSCT, hematopoietic stem cell transplantation; del, deletion; hyper-CVAD, hyperfractionated administration of cyclophosphamide, vincristine, doxorubicin and dexamethasone; idem, chromosomal abnormalities; der, translocation derived; dic, dimeric; FLAG, initial chemotherapy for acute monocytic leukemia; dic, dimeric centromeric; inv, inverted.

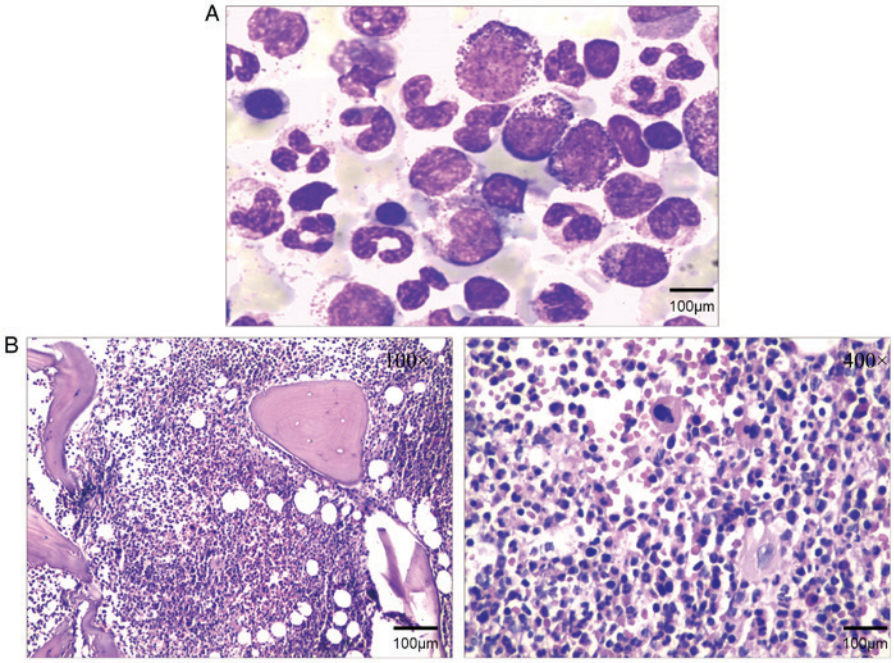

Figure 1. (A) Bone marrow cytology stained with Swiss-stain, revealed active bone marrow hyperplasia, and proliferation of mostly granulocytes, while erythroid and megakaryocytic proliferation was inhibited. (B) Bone marrow biopsy indicated primarily granulocyte hyperplasia and active bone marrow hyperplasia.

hematopoietic cell transplantation and was only followed up and monitored WBC count once a month for 2 years.

Examination results

BM cytology smears and biopsy. To analyze the myeloproliferative status, BM cytology smears and BM biopsy were performed at a hematology laboratory. The cytology and biopsy results indicated that the BM was hypercellular with granulocytic hyperplasia, as presented in Fig. 1A and B.

Cytogenetics. Sufficient sample material obtained via BM aspiration was available to examine the BCR gene, which is located at 22q11. The initial analysis indicated that in the present case, FGFR1 crosses the breakpoint located on chromosome 22q11. Following initial diagnosis, 10 BM cells in metaphase were analyzed, and all of them were clonally abnormal karyotypes, while the abnormalities were 8 and 11 chromosomal translocations, forming a BCR/FGFR1 fusion gene in the patient. The abnormal karyotype 46,XY,t(8;22)(p11;q11) was observed in all of the cells, with no other abnormal karyotypes. The BCR-FGFR1 fusion gene is the characteristic chromosome karyotype in 8p11 myeloproliferative syndrome. At 2 months after the initial diagnosis, the karyotype remained identical, as indicated in Fig. 2. Although karyotype analysis is a simple and basic technology, it is of great significance for the diagnosis of EMS.

FISH. Once the gene has been cloned and characterized, FISH analysis may be performed. In the present study, the rearrangement of the FGFR1 gene was verified by FISH. A total of 200 interphase nuclei were examined for each probe, and no abnormal signals regarding the platelet-derived growth factor receptor (PDGFR)A (4q12) gene and PDGFRB (5q32) rearrangements were detected (Fig. 3A and B, respectively).

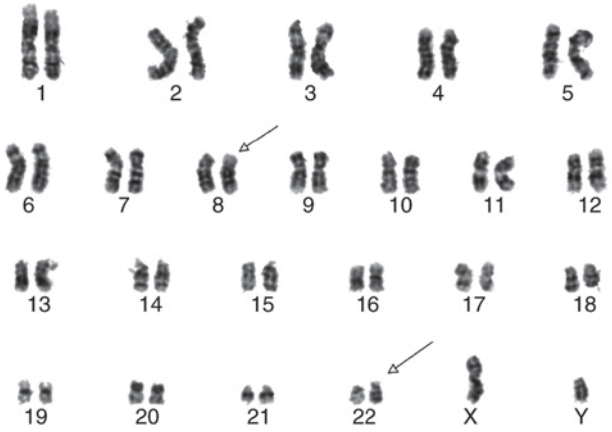

Figure 2. A total of 10 bone marrow cells in metaphase were subjected to karyotype analysis. All of them were clonal abnormal karyotypes with 8 and 11 chromosomal translocations, forming a breakpoint cluster region-fibroblast growth factor receptor 1 fusion gene in the patient (arrows).

However, ~79% of the nuclei had signals indicative of the FGFR1 (8p11) gene rearrangement (Fig. 3C). The results further confirmed the formation of the BCR-FGFR1 fusion gene.

Discussion

EMS is characterized by the following: i) Myeloproliferative neoplasm associated with eosinophilia; ii) Lymphadenopathy; iii) High tendency toward converting to AML; and iv) Reciprocal translocations involving 8p11 (2).

To the best of the author's knowledge, the present study reports on the 15th published case of t(8;22)/BCR-FGFR1 rearrangement. All other cases are presented in Table I. The

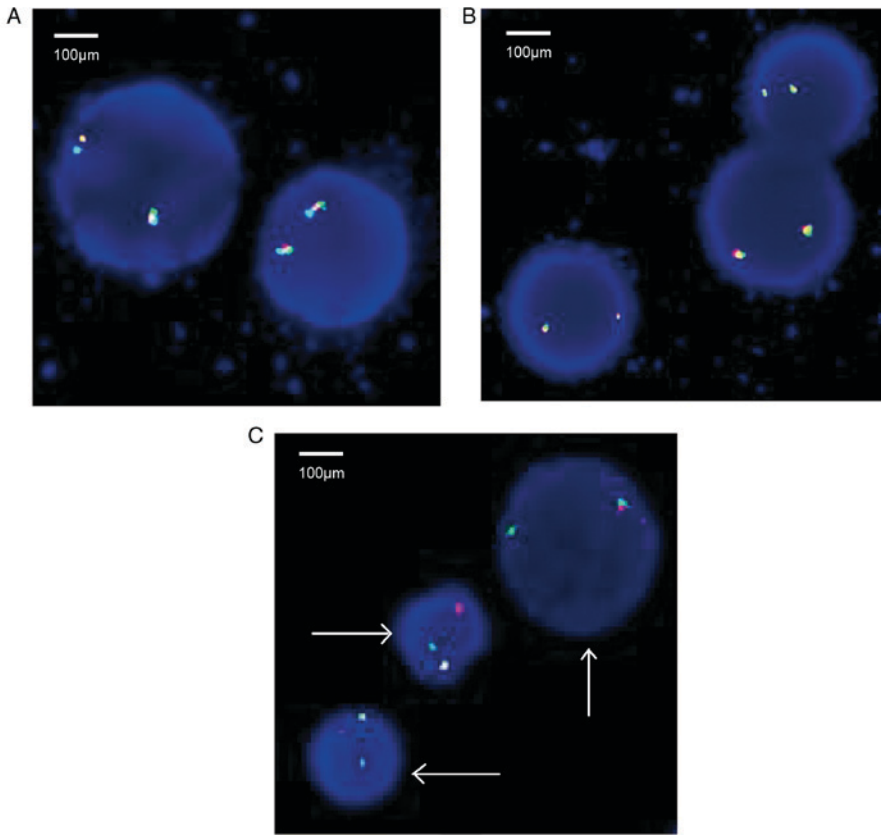

Figure 3. Rearrangement of the FGFR1 gene was also demonstrated by fluorescence *in situ* hybridization. A total of 200 cells in interphase were counted using three sets of probes. (A) Two fusion genes exhibiting red, green and blue staining. No abnormal signals of PDGFRA (4q12) gene rearrangement were detected; (B) two fusion genes exhibiting red, green and blue staining. No abnormal signals of PDGFRB (5q32) gene rearrangement were detected; (C) cells with red, green and blue fusion gene signals, indicating the presence of the FGFR1 (8p11) gene rearrangement using FISH analysis. The derivative chromosomes are indicated by arrows. FGFR1, fibroblast growth factor receptor 1; PDGFR, platelet-derived growth factor receptor.

FGFR1 gene encodes a receptor tyrosine kinase transmembrane protein. It consists of the following three parts: The extracellular domain, the transmembrane domain and the intracellular domain. Under normal circumstances, FGFR1 is in the form of oligomers, where binding of FGFR1 to its ligands, e g BCR, results in FGFR1 homodimerization and autophosphorylation, thus activating multiple effectors, including RAS/mitogen-activated protein kinase/phosphoinositide-3 kinase/phosphoinositide phospholipase C-γ, and providing proliferative and survival signals. BCR is one of the 15 fusion partners of FGFR1. The 15 rearrangement karyotypes are as follows: Myosin XVIIIA (MYO18A; 17q23), tripartite motif containing 24 (TIF1; 7q34), FGFR1 oncogene partner 2 (FGFR1OP2; 12p11), human endogenous retrovirus group K member (HERV-K; 19q13), BCR (22q11), centriolin (CEP110; 9q33), FGFR1 oncogene partner (FOP/FGFR10P; 6q27), zinc finger protein 198 (ZNF198; 13q11-12), cleavage and polyadenylation specific factor 6 (CPSF6; 12q15), tripartite motif containing 24 (TRIM24; 7q34), nucleoporin 98 (NUP98; 11p15), cut like homeobox 1 (CUX1; 7q22), translocated promoter region, nuclear basket protein (TPR; 1q25), RAN binding protein 2 (RANBP2; 2q12) and LPR binding FLII interacting protein 1 (LRRFIPI; 2q37). Among these translocations, t(8;13) is the most common (1-3).

Unlike other cases of FGFR1 rearrangement, which frequently manifest as eosinophilia and lymphadenopathy, the clinical presentation of the case of the present study was as CML. This particular clinical manifestation suggests a specific role of BCR during the development of the disease. FGFR1 has a critical role in the oncogenesis of EMS, and each FGFR1 fusion partner exerts a different influence on the malignant phenotype (2,4).

In other studies reporting on cases of EMS, which appear as leukemia or lymphoblastic lymphoma, accompanying chromosomal abnormalities frequently exist; however, in the present case, the only abnormal karyotype was t(8;22)(p11;q11). The unique clinical features of this patient may be attributed to the absence of any additional chromosomal abnormalities.

As for the treatment of EMS, numerous studies have reported that patients benefited from allogeneic hematopoietic stem cell transplantation (7-9). The application of FGFR1 inhibitors has also been reported in certain cases, but the clinical outcome was not improved (5). Therefore, allogeneic hematopoietic stem cell transplantation remains the primary treatment. In addition, chemotherapy is not ideal for patients who present with acute leukemia or lymphoblastic lymphoma. EMS has a rapidly progressing clinical course with a median survival time of <1 year (4,5).

The present study emphasizes the importance of accurate molecular diagnosis in FGFR1 rearrangement cases. In cases of non-classical clinical manifestations, accurate molecular diagnosis may avoid misdiagnoses. Conceivably, early diagnosis provides patients with the opportunity to adopt allogeneic hematopoietic stem cell transplantation in an

early phase of the disease and may thus improve the clinical outcome of the patients.

Of note, EMS is a type of disease that may be misdiagnosed. In the present case report, a 41-year-old patient with a misdiagnosis of CML due to an increase in the number of white blood cells was subsequently diagnosed with EMS after undergoing a karyotype test. The present study may contribute to the improvement of the diagnosis of EMS in patients, which may first appear to have CML. EMS should be considered in patients with symptoms similar to those of the case of the present study.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JJL analysed and interpreted the patient data. LM analyzed the hematological data. JJL and LM drafted and revised the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

The current case report was published with informed consent of the patient, whose anonymity was preserved.

Competing interests

The authors declare that they have no competing interests.

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