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Successful Treatment of a Patient with Chronic Myelogenous Leukemia with Concurrent Janus Kinase 2 (JAK2) R795S Mutation and Breakpoint Cluster Region-ABL1 (BCR-ABL1) Fusion: A Case Report and Literature Review

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 50-year-old
Final Diagnosis: Chronic myeloid leukaemia
Symptoms: Dizziness • weakness
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Unusual clinical course

Background: Although the V617F mutation in the Janus kinase 2 (JAK2) gene and the breakpoint cluster region-abl1 (BCR-ABL1) oncogene fusion have been considered mutually exclusive in most myeloproliferative neoplasms (MPNs), many recent studies have described patients with both. This report describes a patient with chronic myelogenous leukemia (CML) and the unusual JAK2 R795S mutation and reviews 23 additional patients with JAK2 gene mutations coexisting with myelofibrosis (MF) and CML.

Case Report: A 50-year-old woman with MF experienced rapid disease progression 3 weeks later, accompanied by severe abdominal pain and a white blood cell count of 257.45×10^9/l. Karyotype analysis indicated that she was 46, XY, Philadelphia (Ph) (+) and BCR-ABL1 positive. Bone marrow aspiration after 1 cycle of chemotherapy and treatment with dasatinib showed that her marrow was hypercellular, with an increased number of megakaryocytes and 48.5% myeloblasts expressing the myeloid antigens CD33, CD13, CD34, CD117, and CD71. Next-generation sequencing identified a rare JAK2 R795S mutation. She was diagnosed with CML in blast phase, and was successfully treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Conclusions: JAK2 gene mutations, including the rare JAK2 R795S mutation, can coexist with BCR-ABL1 in patients with MPNs. The clinical course of MPN in patients with both BCR-ABL1 and JAK2 mutations may be different from that in patients with classical MPNs.

MeSH Keywords: Janus Kinase 2 • Leukemia, Myelogenous, Chronic, BCR-ABL Positive • Myelofibrosis

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Background

Myeloproliferative neoplasms (MPNs) are clonal disorders characterized by proliferation of hematopoietic stem cells. Major genetic aberrations include the breakpoint cluster region-abl 1 (BCR-ABL1) fusion gene in patients with Philadelphia (Ph) chromosome-positive chronic myelogenous leukemia (CML) and mutations in the Janus kinase 2 (JAK2), thrombopoietin receptor MPL (MPL), and calreticulin (CALR) genes in patients with Ph chromosome-negative MPN. Since the first report of the absence of JAK2 V617F in patients with Ph^+ CML [1], BCR-ABL1 and JAK2 gene mutation were thought to be mutually exclusive. To date, however, more than 20 BCR-ABL1-positive patients with myelofibrosis (MF) and CML have been reported to have JAK2 gene mutations, with the majority having JAK2 V617F mutations. It is not clear whether the characteristics of patients with concurrent JAK2 gene mutations and BCR-ABL1 differ from those of other patients with MPNs.

This report describes a patient in CML blast phase (CML-BP) who originally presented with MF and was positive for both the BCR-ABL1 oncogene and a rare JAK2 R795S mutation. This patient was effectively treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT). To our knowledge, this is the first such CML patient positive for BCR-ABL1 with a JAK2 R795S mutation. This study also summarized the clinical and laboratory features of an additional 23 patients with concurrent BCR-ABL1-positive CML and JAK2 gene mutations positive MF.

Case Report

A 50-year-old woman was referred to the Department of Hematology with a 2-month history of dizziness, weakness, and abdominal distension. Her social history and family history were unremarkable. Her medical history was significant for mild anemia, with a medical examination organized by her company one year earlier showing a hemoglobin (Hb) concentration of 9.4 g/dl, a white blood cell (WBC) count of 4.4×10^9/l, a platelet count of 374×10^9/l and a normal spleen. Because she did not have obvious discomfort at that time, she was not further examined. A physical examination at admission to the Department of Hematology showed splenomegaly, with ultrasonography showing a spleen size of 18.5×4.5 cm. Blood tests showed leukocytosis (WBC 13.3×10^9/l), mild anemia (Hb 9.6 g/dl), thrombocytosis with a platelet count of 832×10^9/l and a lactate dehydrogenase (LDH) concentration of 450 U/l. A peripheral blood smear showed many rare blast-like platelets, with a total granulocyte ratio of 78.5% but without teardrop cells. A bone marrow (BM) biopsy showed megakaryocytic hyperplasia with marked fibrosis (Figure 1A, 1B), but BM aspiration failed due to a dry tap. BM fibrosis could not be graded at that time due to the absence of silver-staining for reticulin and collagen. She was examined for several recurrent MPN-related gene mutations, such as JAK2, MPL, and CALR, but none was positive. Neither cytogenetic analysis nor BCR-ABL1 fusion gene test was performed due to a dry tap. Based on the 2016 version of the World Health Organization (WHO) diagnostic criteria, she was diagnosed with an MPN and treated with 3 million units/day of interferon α.

Three weeks later, the patient was admitted to the emergency department due to severe abdominal pain with a markedly increased WBC count of 257.45×10^9/l and an LDH concentration of 1773 U/l. Preliminary examination suggested that the etiology of her severe abdominal pain might be splenic embolism or rupture, visceral thrombosis, or leukostasis. A repeat BM biopsy again demonstrated fibrosis (Figure 1C, 1D). Contrast-enhanced computed tomography (CT) excluded visceral thrombosis and splenic rupture. The concentrations of D-dimer, fibrinogen and fibrin degradation products were not substantially abnormal. The patient had moderate symptoms of chest tightness and shortness of breath. Based on a preliminary diagnosis of leukostasis, she was treated with therapeutic leukapheresis and oral hydroxyurea. To alleviate severe discomfort, she was administered induction chemotherapy with modified idarubicin 10 mg/d on days 1, 3, and 5 and cytarabine 50 mg/d on days 1–7 (IA regimen). Cytogenetic analysis showed an abnormal karyotype of 46, XY, Ph (+), and real-time reverse transcript polymerase chain reaction (RT-PCR) assays for 40 types of leukemia-related fusion genes showed that her cells were positive for BCR-ABL1. She was therefore started on 100 mg/day dasatinib. After 1 week, her peripheral blood cell counts and classification returned to the normal range. BM aspiration still showed a hypercellular marrow with increased megakaryocytes. Flow cytometry showed that 48.5% of myeloblasts were positive for moderate to strong expression of myeloid antigens CD33, CD13, CD34, CD117, and CD71. Quantitative RT-PCR showed that 85% of these cells were positive for BCR-ABL1/ABL1. A sample obtained prior to IA treatment was screened by next-generation sequencing for 42 types of gene mutations characteristic of myeloid neoplasms. A rare mutation was detected in exon 18 of the JAK2 gene (c. 2385 G>T: p.R795S) in 9.27% of BM cells (Figure 2A). Sanger sequencing showed that this mutation was not present in hair and nail samples of this patient (Figure 2B), suggesting that JAK2 (c.2385 G>T: p.R795S) was an acquired clonal somatic mutation, not a germline mutation. Based on the 2016 WHO classification of tumors of hematopoietic and lymphoid tissues, the patient was diagnosed with CML-BP.

A BM smear after 1 month of IA chemotherapy showed 6.0% myeloblasts, with quantitative RT-PCR showing 6.4% BCR-ABL1/ABL1; and her spleen size was 13.0×4.0 cm. She was administered IA reinduction chemotherapy, consisting of idarubicin 10 mg/d on days 1–3 and cytarabine 100 mg/q12 h on

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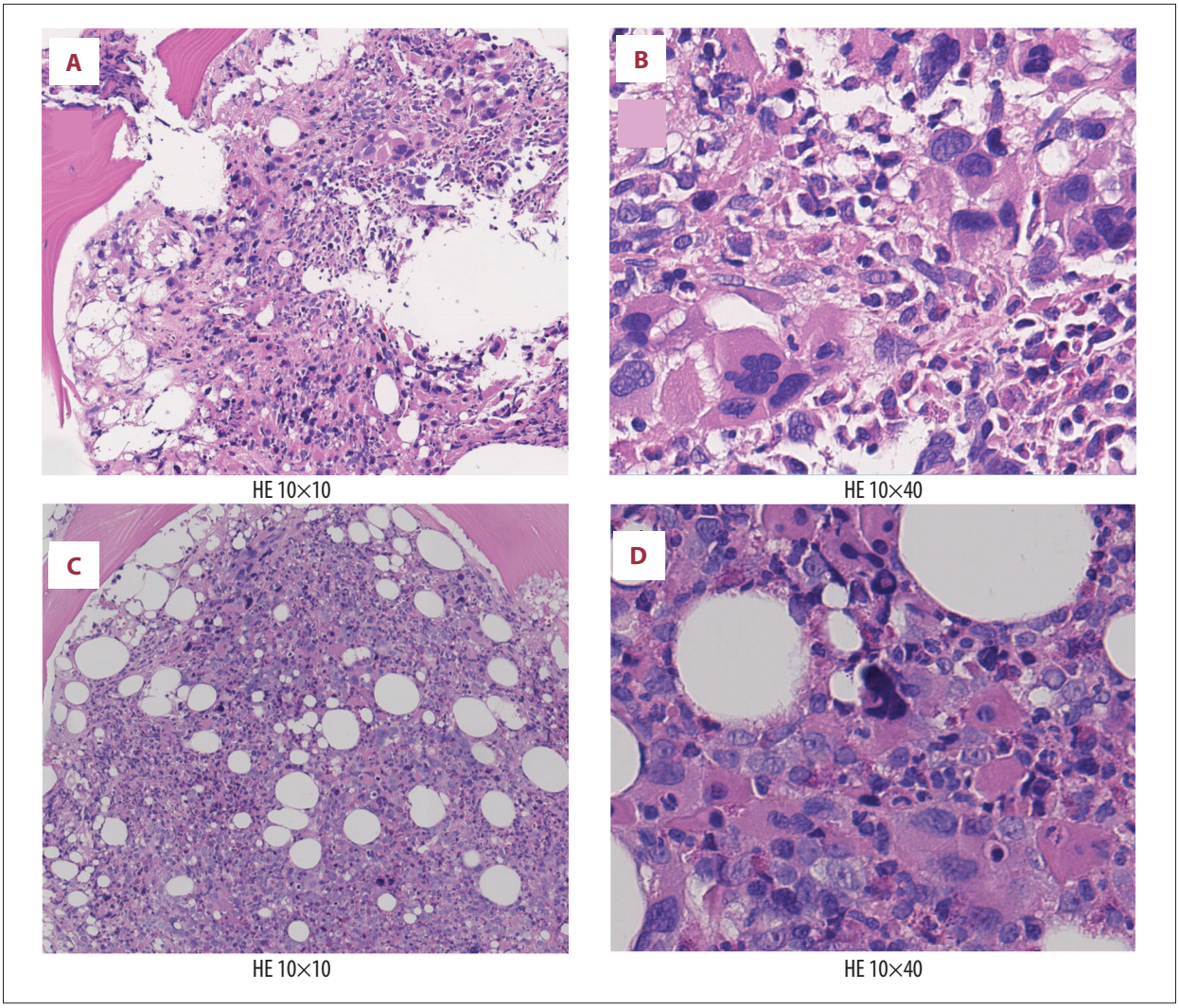

Figure 1. Bone marrow histology showing severe fibrosis with large and clustering megakaryocytes at the first (**A, B**) and second (**C, D**) admissions.

days 1–7. A subsequent BM smear showed 2.0% myeloblasts, and the cells had a karyotype of 46, XX(19)/46, XX, Ph(+). Quantitative RT-PCR showed 0.17% BCR-ABL1/ABL1; and her spleen size was 12.8×4.5 cm. Dasatinib was also administered during this period. Cytogenetic and molecular biologic analyses showed that this patient did not attain complete remission (CR) after 2 courses of the IA regimen combined with dasatinib.

To further explore whether this patient had other molecular biological abnormalities, whole-exome and transcriptome sequencing were performed. Five 5 genetic mutations were detected, including mutations in the androgen receptor (AR) gene (c.234_239del p.Gln79_Gln80del); the DEAD-box helicase 41 (DDX41) gene (c.1649C>T p.Ala550Val); the major histocompatibility complex, class I, B (HLA-B) gene (c.277_283delinsACCAACA p.Ala93_Ala95delinsThrAsnThr); the mitogen-activated protein kinase 8 interacting protein 1 (MAPK8IP1) gene (c.1864G>A p.Val622Ile); and the roundabout guidance receptor 1 (ROBO1) gene (c.1837A>C p.Asn613His). In addition, a fusion gene of ornithine decarboxylase antizyme 1 (OAZ1)/ATPase H+ transporting V0 subunit c (ATP6V0C) was detected. The clinical significance of these genetic abnormalities in hematologic malignancies has not been determined. Interestingly, neither JAK2 R795S nor BCR-ABL1 was observed by whole-exome and transcriptome sequencing. Her cells were negative for mutations in the ABL kinase region, with quantitative RT-PCR showed 0.16% BCR-ABL1/ABL1.

Based on her young age and the short period of transformation from CML with MF to acute myeloid leukemia (AML), allo-HSCT was recommended. The patient had a younger brother with a complete HLA-match who could serve as a peripheral blood stem cell donor. After providing written consent, the patient underwent modified total body irradiation (TBI) and was

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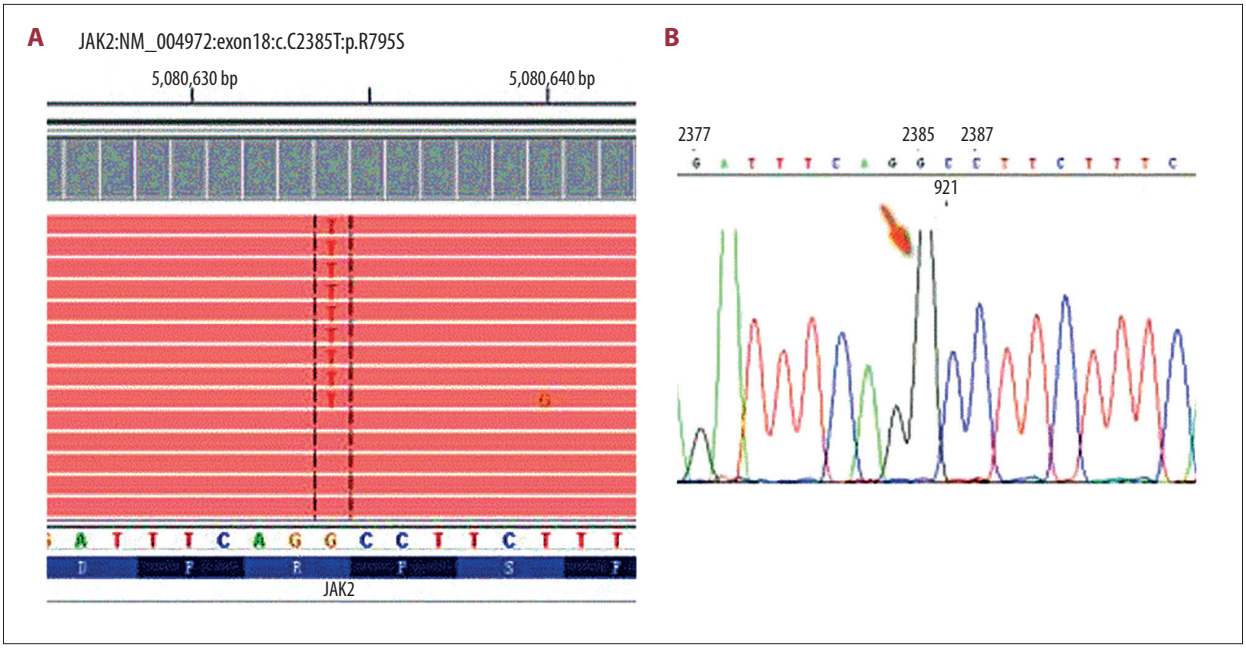

Figure 2. Molecular findings before the first round of induction chemotherapy with modified IA. (**A**) Next-generation sequencing showing a JAK2 gene mutation in exon 18 (c. 2385 G >T: p.R795S). (**B**) Sanger sequencing showing the absence of the JAK2 R795S gene mutation in hair and nails of the same patient.

treated with busulfan, cladribine, and an ATG intensive conditioning regimen beginning on day –10. On day 0, she received a peripheral blood stem cell transfusion from her HLA10/10-matched brother, which resulted in molecular CR. She continues to receive maintenance therapy with dasatinib, and maintains molecular CR without obvious graft-versus-host disease.

Literature review results

To date, JAK2 R795S has not yet been reported in patients with MF, polycythemia vera (PV), or any other hematologic or other diseases. A single-nucleotide polymorphism (SNP) was ruled out. A literature review identified 23 other patients with MF and CML who were found to have both BCR-ABL1 translocations and concomitant JAK2 gene mutations since 2005. The characteristics of these 24 patients, including ours, are shown in Table 1 [2–15]. The other 23 patients all had the JAK2 V617F mutation. MF preceded CML in 11 patients, CML preceded MF in 3, and both were diagnosed concomitantly in 10. Interestingly, when MF preceded CML, the mean time between the 2 entities was 9.9 years, but when CML preceded MF, the mean time was 2.67 years. The changes in JAK2 gene mutation and BCR-ABL1 transcript levels varied. JAK2 gene mutation and BCR-ABL1 levels moved in opposite directions in 3 patients. JAK2 gene mutation level decreased or remained constant while BCR-ABL1 levels declined in another 9 patients. Our patient remained positive for BCR-ABL1 after the JAK2 gene mutation disappeared. Changes in JAK2 gene mutations and BCR-ABL1 levels were not reported for the other patients. Twenty-one patients were administered tyrosine kinase inhibitor (TKI) therapy, with most showing reductions in BCR-ABL1 levels. JAK2 gene mutation levels were reduced in 2 patients treated with ruxolitinib. At the outset, most of the 24 patients were in CML chronic phase, with only 2 in CML accelerated phase. Our patient was in CML-BP and was the only patient among the 24 to undergo allo-HSCT.

Discussion

To date, dozens of patients have been reported with concomitant JAK2 gene mutations and BCR-ABL1 translocation, accounting for 2.55% of patients with CML and 0.2–0.4% of those with MPNs [15–17]. Because of their relative rarity, management of this patient subgroup remains challenging. This report describes a patient with CML-BP who had a rare JAK2 R795S mutation and was BCR-ABL1 positive. The findings in this patient, along with findings in previous patients, may increase understanding of the clinical presentation, method of diagnosis, and treatments of this unusual condition.

Within 1 year, the mild anemia and normal spleen in our patient progressed to CML-BP with conspicuous fibrosis. Although a subgroup of Ph^+-CML mimics ET or primary MF by presenting with marked thrombocytosis or myelofibrosis, concomitant JAK2 gene mutations and BCR-ABL1 are rare. Although results suggested that the presence of the JAK2V617F mutation in CML may be associated with early disease progression [18], that

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Table 1. Characteristics of patients with MF and CML with coexisting JAK2 gene mutations and BCR-ABL1 translocations since 2005.

Age (years)	Sex	Diagnosis (+CML)	Treatment	Course	Phase	Clone interaction	Reference number
50	M	MF	HU then I	CML, MF 4 years later	CP	BCR-ABL disappeared, JAK2 constant	[2]
66	M	MF	I then HU	Concomitant	CP?	?	[3]
55	M	MF	I	CML, MF 2 years later	AP	BCR-ABL decreased, JAK2 increased	[4]
49	M	MF	I then D	CML, MF 2 years later	CP	BCR-ABL and JAK2 decreased	[5]
64	M	MF	I then N	Concomitant	AP	BCR-ABL decreased, JAK2 constant	[5]
52	F	MF	HU then I	Concomitant	CP	BCR-ABL and JAK2 decreased	[6]
58	M	MF	I then HU	MF, CML 4 years later	?	BCR-ABL decreased, JAK2 increased	[7]
67	M	MF	I then HU	Concomitant	CP	?	[8]
58	F	MF	HU, INF	Concomitant	CP?	?	[9]
67	M	MF	N then D	MF, CML 3 years later	CP	BCR-ABL decreased, JAK2 constant	[10]
58	M	MF	HU, D	Concomitant	?	?	[11]
75	M	MF	I then HU	Concomitant	CP?	?	[12]
54	F	MF	I\N\D	Concomitant	CP	BCR-ABL decreased, JAK2 constant	[13]
56	M	PV/MF	HU then R	PV/MF, CML? 16.1 years later			[14]
73	F	ET/MF	HU then R	ET/MF, CML? 9.6 years later		BCR-ABL and JAK2 decreased	[14]
44	F	PV/MF	INF, R then I	PV/MF, CML 5.0 years later			[14]
40	F	ET/MF	R, I then B	ET/MF, CML 33 years later	CP		[14]
76	F	ET/MF	A, I, P, R, Ara-c	ET/MF, CML 10 years later	CP-AP-BP		[14]
48	F	MF	N, HU, R	PMF, CML 10.75 years later	CP	BCR-ABL and JAK2 decreased	[15]
66	F	ET/MF	HU, R, I, B	ET/MF, CML 3.75 years later	CP		[15]
48	F	PV/MF	Phleb, HU, INF, I, R	PV/MF, CML 4.83 years later	CP		[15]
60	F	PV/MF	HU, Th, R, I	PV/MF, CML 8.9 years later			[15]
70	M	MF	I, N, D, HU	Concomitant		BCR-ABL increased, JAK2 decreased	[15]
50	F	MF	IA/D	Concomitant	BP	BCR-ABL and JAK2 decreased	Our case

A – anagrelide; AP – accelerated phase; Ara-c – cytarabine; B – bosutinib; BP – blast phase; CML – chronic myelogenous leukemia; CP – chronic phase; D – dasatinib; ET/MF – myelofibrosis secondary to essential thrombocytosis; F – Female; HU – hydroxyurea; I – imatinib; INF – interferon; IA – idarubicin and cytarabine; M – Male; MF – myelofibrosis; N – nilotinib; PV/MF – myelofibrosis secondary to polycythemia vera; P – ponatinib; Phleb – therapeutic phlebotomy; R – ruxolitinib; Th – thalidomide.

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study included few patients. The JAK2 R795S mutation disappeared when our patient achieved CR based on bone marrow cell morphology, suggesting that this mutation may be associated with the early presentation of myelofibrosis and may have contributed to the rapid progression to CML-BP.

JAK2 V617F is the most common mutation site in MPNs. The JAK2 R795S mutation results in the replacement of arginine by serine. Whole-exome sequencing showed that this patient was negative for the JAK2 R795S mutation after 2 cycles of the IA regimen and dasatinib, whereas quantitative RT-PCR showed that this patient was positive for BCR-ABL1. These 2 gene abnormalities may have derived from different progenitor cell clones or the JAK2 clone may have been a subclone of the BCR-ABL1 clone. Alternatively, the JAK2 R795S mutation may have been below the analytical sensitivity of whole-exome sequencing. The review of the 24 patients with concomitant JAK2 gene mutations and BCR-ABL1 translocations found no common pattern for their origin, with some studies reporting that these anomalies originated from 2 independent clones and others reporting that one was a subclone of the other.

Currently, there is no uniform standard on the treatment of MPN patients with both JAK2 gene mutations and BCR-ABL1 translocation. TKIs are the major treatment options for these patients. If TKIs alone are not sufficiently effective, they can be combined with other regimens, such as Hu, INF, ruxolitinib, and chemotherapy. The combination of ruxolitinib and dasatinib was reported safe and effective in the treatment of a patient with concomitant PV and CML [19]. A multi-institutional study of a JAK2 V617F+ BCR–ABL1+ CML accelerated phase patient found that both JAK2 V617F and BCR–ABL1 were negative after allo-HSCT [15]. Similarly, JAK2 R795S and BCR-ABL1 disappeared in our patient after allo-HSCT. At present, our patient is still in CR. Most of the 24 patients were diagnosed in chronic stage and could be controlled with TKI or combination therapy. Allo-HSCT was feasible if the disease progressed.

Conclusions

JAK2 gene mutations, including JAK2 R795S, can coexist with the BCR-ABL1 translocation in MPNs. The clinical course of MPN patients with both anomalies may differ from that in patients with classic MPNs.

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Conflict of interest

None.

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