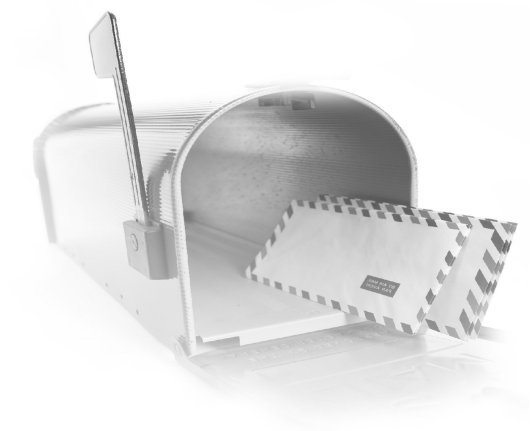

BLOOD RESEARCH
Volume 55 · Number 1 · March 2020

Letters to the Editor

Clinical significance of myeloproliferative neoplasms with *JAK2*V617F mutations and major *BCR-ABL1* translocations: a literature review with case presentation

TO THE EDITOR: It is well known that *BCR-ABL1* translocations and *JAK2*V617F mutations are mutually exclusive events in myeloproliferative neoplasms (MPN) [1]. However, the coexistence of both abnormalities has been reported in several cases [1-6]. Until now, two studies have reported the co-occurrence of *BCR-ABL1* translocation and *JAK2*V617F mutation in Korea [3, 4]. Here, we discuss the clinical significance through a literature review, especially focusing on cases reported in Korea with a case presentation.

A 68-year-old woman was admitted with increased hemoglobin (Hb) and leukocyte count. Complete blood count (CBC) at admission showed the following: white blood cells, 17.06×10^9/L; Hb, 17.3 g/dL; and platelets, 245×10^9/L. Peripheral blood smear demonstrated leukoerythroblastosis with the presence of few tear drop cells. Differential counts of leukocytes were as follows: myelocytes 1%, metamyelocytes 1%, neutrophil 84%, lymphocytes 9%, monocytes 4%, eosinophil 1%, and rare nucleated red blood cells. Her serum lactate dehydrogenase level was elevated (313 IU/L, reference range, 0–250 IU/L) while her serum erythropoietin level was decreased (3.06 mIU/L, reference range, 3.7–37.5 mIU/L). An abdominopelvic computed tomography showed splenomegaly. We could not acquire sufficient information from the bone marrow aspirate, because it was diluted. However, bone marrow biopsy revealed hypercellularity and a slightly increased number of megakaryocytes (3.4/high power field) with dense clustering and certain degree of atypia (Fig. 1). Diffuse myelofibrosis, with bone marrow fibrosis (MF) grade 2, was detected (Fig. 1). Reverse-transcriptase PCR (RT-PCR) assay for the *BCR-ABL1* fusion transcript showed the presence of a major *BCR-ABL1* fusion transcript (b13a2 type), which was confirmed by sequencing (Fig. 1). The fusion transcript level was 1.23% on the international scale (IS). An allele-specific PCR assay for the *JAK2*V617F mutation was positive for a heterozygous type *JAK2*V617F mutation with an allelic burden of 79.20%, which was confirmed by sequencing (Fig. 1). The chromosomal analysis revealed 46,XX karyotype[20]. Interphase fluorescent *in situ* hybridization for *BCR-ABL1* translocation was nuc ish (ABL1, BCR)×2 (ABL1 con BCR×1) [13/500], representing a normal result (below the cutoff level). The final diagnosis revealed MPN, with concurrent *JAK2*V617F mutation and major *BCR-ABL1* translocation. The patient was only treated with hydroxyurea (500 mg, twice a day). After 10 months of treatment, her CBC became normal (5.35×10^9/L white blood cells, a Hb of 14.9 g/dL, and 185×10^9/L platelets) and *BCR-ABL1* transcripts level was 0.016% IS.

Detecting *BCR-ABL1* translocation and *JAK2*V617F mutation simultaneously at the time of diagnosis is a rare event. Recent studies have reported that about 0.2–0.5% of MPN patients are positive for both *BCR-ABL1* and *JAK2*V617F [6, 7]. It has been suggested that most MPN cases with concurrent *BCR-ABL1* and *JAK2*V617F consist of two unrelated clones [2, 6, 8].

The coexistence of these abnormalities may affect laboratory findings and patient diagnosis. Park *et al.* [3] reported two cases of MPN, with a relative *JAK2*V617F dominancy over *BCR-ABL1* transcripts. Their laboratory findings resembled essential thrombocythemia (ET) and primary myelofibrosis (PMF). Our patient showed a relative dominancy of *JAK2*V617F, with the laboratory diagnosis resembling PMF. In contrast, the case reported by Yi and Kim [4] showed relatively high levels of *BCR-ABL1* transcripts. Laboratory features of both CML and PMF were detected (Table 1). Soderquist *et al.* [8] have reported that coexistence cases show mixed megakaryocytes characteristics that include both dwarf megakaryocytes, seen in CML, and bulbous megakaryocytes, seen in PMF. Therefore, it is essential to perform tests for *BCR-ABL1* and *JAK2*V617F simultaneously with quantitation, in order to avoid misinterpretation and obtain an accurate diagnosis of MPN.

The molecular abnormality profile can influence the

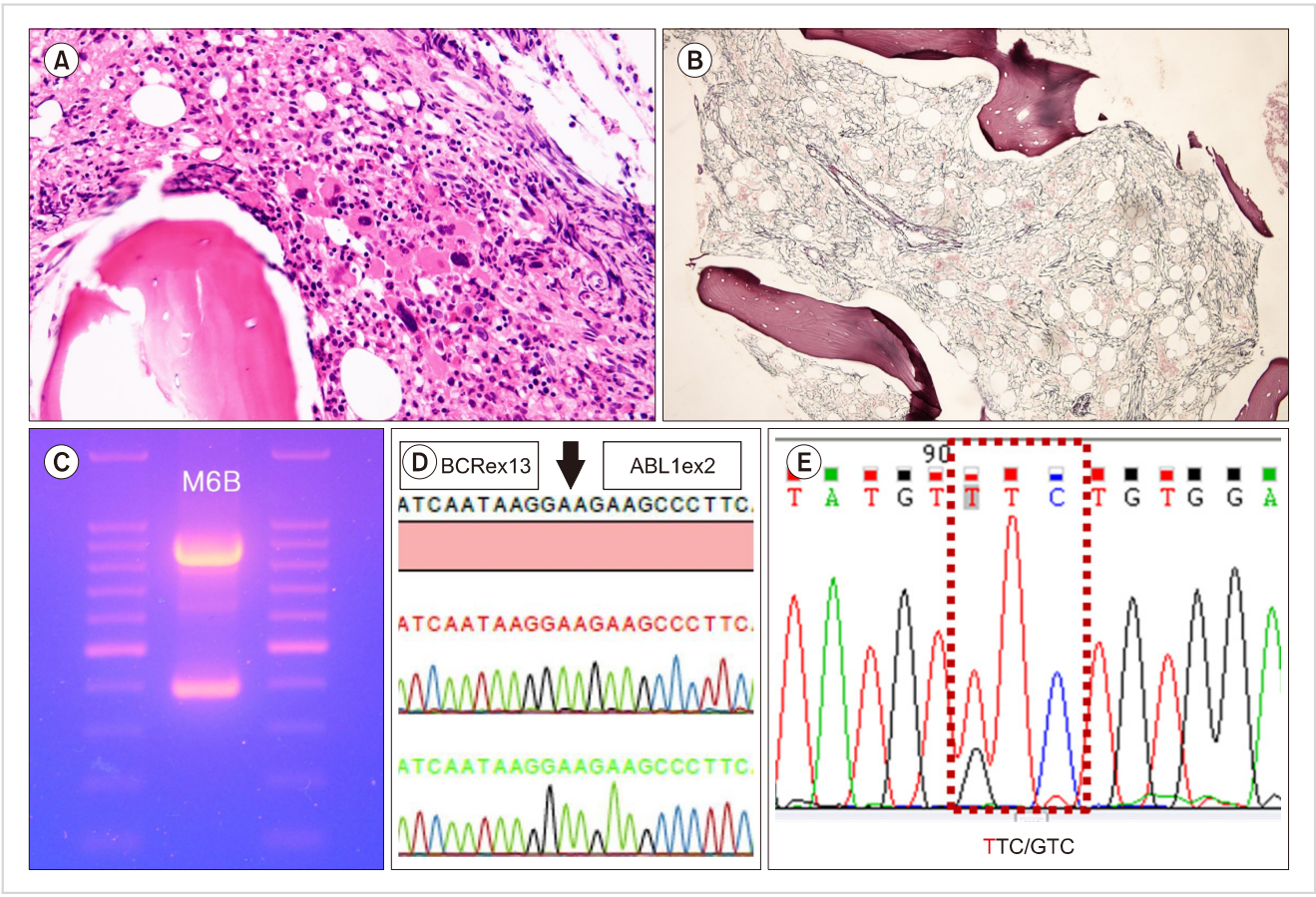

Fig. 1. Bone marrow biopsy showing **(A)** hypercellular marrow with increased megakaryocytes and atypia (H&E stain, ×400) and **(B)** myelofibrosis grade MF-2 demonstrated by reticulin staining (reticulin stain, ×200). Reverse transcriptase (RT)-PCR analysis of *BCR-ABL1* translocation using a HemaVision kit showing a single 397 bp band in the M6B split out PCR, indicating a fusion transcript with *BCR-ABL1* **(C)**. Sequencing analysis of the RT-PCR product showing breakpoint located at exon 13 in the *BCR* gene and exon 2 in the *ABL* gene **(D)**. Sequencing analysis of *JAK2*V617F showing a heterozygous *JAK2*V617F mutation **(E)**.

choice of treatment modalities. Cases reported by Park *et al.* [3] and our patient showed acceptable responses to hydroxyurea. However, the case reported by Yi and Kim [4] showed treatment responses to dasatinib (a tyrosine kinase inhibitor), hydroxyurea, and ruxolitinib (a JAK1/2 tyrosine kinase inhibitor) (Table 1). Other studies [6, 9] have reported successful responses to the simultaneous use of tyrosine kinase inhibitors and hydroxyurea or ruxolitinib in patients with concomitant *BCR-ABL1* and *JAK2*V617F. Therefore, detection of molecular abnormalities is important for appropriate treatment, especially when a decision must be made in the event of therapeutic failure and drug replacement.

Another issue is the impact of molecular abnormalities on patient outcomes. Soderquist *et al.* [8] have reported that seven of 11 MPN patients with concurrent *BCR-ABL1* and *JAK2*V617F showed progression to myelofibrosis, suggesting that these patients are more prone to disease progression. The coexistence of two molecular abnormalities might accelerate the progression. Nevertheless, cases reported in Korea have shown successful responses without death, at the time of publication [3, 4]. However, data concerning the progression rate and survival of patients with concomitant *BCR-ABL1* and *JAK2*V617F mutations are currently insufficient.

In summary, it is important to recognize the possibility of the coexistence of a *BCR-ABL1* translocation and *JAK2*V617F mutation in MPN, because they can affect hematologic features and treatment strategy. However, it is unclear if MPNs with concomitant *BCR-ABL1* translocations and *JAK2*V617F mutations reflect a novel clinical entity with distinct features and outcomes. Further investigation with a large cohort is needed.

Bohyun Kim[1], Kyu Taek Lee[2], Young Ahn Yoon[1], Young-Jin Choi[1]

[1]Department of Laboratory Medicine, [2]Division of Hematology & Oncology, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Korea

Table 1. Clinical and hematologic features in Korean MPN patients with concurrent *BCR-ABL1* translocation and *JAK2*V617F mutation.

	Park *et al.* [3] – Patient #1	Park *et al.* [3] – Patient #2	Yi *et al.* [4]	This patient
Sex and age	Male, 36-year-old	Male, 58-year-old	Male, 68-year-old	Female, 68-year-old
White blood cells ($\times 10^9$/L)	9.4	19.7	28.7	17.1
Hemoglobin (g/dL)	13.8	13.0	10.4	17.3
Platelets ($\times 10^9$/L)	830	285	244	245
Peripheral blood smear	Marked thrombocytosis	Tear-drop cells, immature granulocytes with blasts	Excess myelocytes and metamyelocytes	Tear-drop cells, rare myelocytes
Splenomegaly	Not mentioned	Detected	Detected	Detected
Bone marrow study	Increased number of clustered megakaryocytes without dysplasia	Extensive myelofibrosis, increased number of dysplastic megakaryocytes	Prominent granulopoiesis with hypercellularity, myelofibrosis and an increased number of megakaryocytes with atypia	Extensive myelofibrosis with hypercellularity and slightly increased numbers of megakaryocytes with atypia
Chromosomal analysis	46,XY [20]	46, XY,t(9;22)(q34;q11.2)[4] /46,XY [16].	46, XY,t(9;22)(q34;q11.2)[9] /46,XY [15].	46,XX [20]
FISHfor *BCR-ABL1* rearrangement	Fusion signal (30.5%)	Not mentioned	Fusion signal (61.5%)	No fusion signal
Type and quantity of *BCR-ABL1* fusion transcripts from real-time PCR at diagnosis	b3a2/0.02 NCN	b3a2/1.0 NCN	Not mentioned/65.7% IS	b2a2/1.51 NCN (1.2% IS)
Allelic burden of *JAK2*V617F mutation at diagnosis	27.91%	69.66%	Not mentioned	79.2%
Hematologic diagnosis	ET with a major *BCR-ABL1* fusion transcript	Not mentioned	CML	MPN with concurrent *JAK2*V617F mutation and major *BCR-ABL1* translocation
Treatment	Hydroxyurea	First 6 mo: hydroxyurea After 6 mo: dasatinib	First 3 mo: dasatinib After 3 mo: dasatinib+ hydroxyurea After 6 mo: dasatinib and ruxolitinib	Hydroxyurea
Clinical course	In the 1st yr: a decrease in the number of fusion transcripts (0.005–0.01 NCN) In the 2nd yr: increase in the number of fusion transcripts (up to 5.0 NCN)	In the first 6 mo: similar numbers of fusion transcripts (1.0–1.6 NCN) After 6 mo: decreased numbers of fusion transcripts(NCN was not mentioned)	In the first 3 mo: major molecular response, newly developed leukocytosis and anemia At 6 mo: complete molecular response, worsened anemia After 6 mo: major molecular response and improvement in clinical findings	In the 1st yr: decrease in the level of fusion transcripts (0.1% IS), normalized blood cell counts, and symptom improvement

Abbreviations: CML, chronic myeloid leukemia; ET, essential thrombocythemia; FISH, fluorescence *in situ* hybridization; IS, international scale; MPN, myeloproliferative neoplasms; NCN, normalized copy number; PCR, polymerase chain reaction.

Correspondence to: Bohyun Kim
Department of Laboratory Medicine, Soonchunhyang University Cheonan Hospital, 31 Suncheonhyang 6-gil, Dongnam-gu, Cheonan 31151, Korea
E-mail: bhkim@schmc.ac.kr

Received on Nov. 29, 2019; Revised on Jan. 10, 2020; Accepted on Jan. 13, 2020
https://doi.org/10.5045/br.2020.55.1.62

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Xiao X, Zhang Y, Zhang GS, Zheng WL, Xiao L, Liu SF. Coexistence of JAK2V617F mutation and BCR-ABL1 transcript in two Chinese patients with chronic myelogenous leukemia.

Acta Haematol 2012;127:47-9.
2. Martin-Cabrera P, Haferlach C, Kern W, Schnittger S, Haferlach T. BCR-ABL1-positive and JAK2 V617F-positive clones in 23 patients with both aberrations reveal biologic and clinical importance. Br J Haematol 2017;176:135-9.
3. Park SH, Chi HS, Cho YU, et al. Two cases of myeloproliferative neoplasm with a concurrent JAK2 (V617F) mutation and BCR/ABL translocation without chronic myelogenous leukemia phenotype acquisition during hydroxyurea treatment. Ann Lab Med 2013;33:229-32.
4. Yi JH, Kim HR. Coexistence of BCR/ABL1-positive chronic myeloid leukemia and JAK2 V617F-mutated myelofibrosis successfully treated with dasatinib and ruxolitinib. Blood Res 2019; 54:77-9.
5. Bader G, Dreiling B. Concurrent JAK2-positive myeloproliferative disorder and chronic myelogenous leukemia: a novel entity? A case report with review of the literature. J Investig Med High Impact Case Rep 2019;7:2324709619832322.
6. Lewandowski K, Gniot M, Wojtaszewska M, et al. Coexistence of JAK2 or CALR mutation is a rare but clinically important event in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. Int J Lab Hematol 2018;40:366-71.
7. Agarwal R, Blombery P, McBean M, et al. Clinicopathological differences exist between CALR- and JAK2-mutated myeloproliferative neoplasms despite a similar molecular landscape: data from targeted next-generation sequencing in the diagnostic laboratory. Ann Hematol 2017;96:725-32.
8. Soderquist CR, Ewalt MD, Czuchlewski DR, et al. Myeloproliferative neoplasms with concurrent BCR-ABL1 translocation and JAK2 V617F mutation: a multi-institutional study from the bone marrow pathology group. Mod Pathol 2018;31:690-704.
9. Zhou A, Knoche EM, Engle EK, Fisher DA, Oh ST. Concomitant JAK2 V617F-positive polycythemia vera and BCR-ABL-positive chronic myelogenous leukemia treated with ruxolitinib and dasatinib. Blood Cancer J 2015;5:e351.

Daratumumab in dialysis-dependent multiple myeloma

TO THE EDITOR: Daratumumab is an IgG1 kappa monoclonal antibody against CD38, overexpressed by myeloma cells. It acts by several mechanisms, including triggering complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis [1]. The combination of daratumumab, lenalidomide, and dexamethasone has demonstrated remarkable overall response rates (92.9%) in patients with relapsed myeloma [2]. Daratumumab clinical trials have excluded patients with a creatinine clearance <20 mL/min [3]. Data on daratumumab therapy in renal failure patients requiring dialysis are scarce, even though pharmacokinetic data suggest that it can be safely used without dose modification in patients with creatinine clearance <30 mL/min [4]. Here, we present our experience with daratumumab in two patients with severe renal impairment.

A 36-year-old female with no previous comorbidities, presented with anemia and renal failure (serum creatinine, 8.4 mg/dL; urine output, 700 mL/d). The M component was 0.22 g/dL, serum kappa (κ) light chain was 3,650 mg/L, and the lambda light chain (λ) was 7.41 mg/L. The difference in free light chain (dFLC) was 3,642 mg/L. Bone marrow evaluation demonstrated 50% clonal plasma cells. The myeloma fluorescence in-situ hybridization (FISH) panel was negative. The patient was diagnosed with IgG kappa multiple myeloma R-ISS stage III with severe renal impairment requiring dialysis and started on a cyclophosphamide, bortezomib, dexamethasone (CyBorD) regimen. After 2 weeks of CyBorD therapy, the patient developed hyperemesis due to cyclophosphamide. Cyclophosphamide was replaced with thalidomide. Bortezomib, thalidomide, and dexamethasone (VTD) were administered for 2 weeks, following which thalidomide was discontinued owing to severe myalgia. Next, the ABCD regimen, comprising liposomal doxorubicin, bortezomib, cyclophosphamide (100 mg D1-D15), and dexamethasone (40 mg weekly), was initiated. The patient tolerated the ABCD therapy well, and disease evaluation performed after two ABCD cycles presented stable disease (κ>3,650 mg/L; λ, 7.41 mg/L and M spike of 0.24 g/dL), with a continuing need for dialysis. As no disease response was observed, daratumumab (16 mg/kg/dose weekly ×8 doses, followed by 2-weekly ×8 doses, then monthly), lenalidomide (5 mg), and dexamethasone were administered. To avoid fluid overload, the daratumumab infusion was administered after the dialysis session, and the infusion rate did not exceed 100 mL/h. No infusion reactions or cytopenia were observed. The patient was dialysis-independent after the fourth daratumumab dose, reporting a serum creatinine stabilized at 4.3 mg/dL. After the ninth daratumumab dose, disease evaluation demonstrated a Very Good Partial Response (VGPR) including M band of 0.12 g/dL, κ–22.1 mg/L, λ–12.9 mg/L (κ/λ ratio 1.73), and dFLC of 9.2 mg/L. The patient underwent an autologous stem cell transplant with high dose melphalan (140 mg/m^2). Hematopoietic stem cell (HSC) mobilization was performed with the granulocyte colony-stimulating factor and upfront plerixafor. The total HSC dose collected after two sessions of apheresis was 1.52×10^6 cells/kg. Neutrophil engraftment was achieved on day 12, and platelet engraftment was achieved on day 14. The patient was restarted on monthly daratumumab injections from day 60 post-transplant, indicating a stringent complete response (κ, 2.8 mg/L; λ, 1.8 mg/L and ratio 2.1) on the day 100 evaluation, with continuing complete remission observed 21 months post-transplant on monthly daratumumab.

The second patient, a 53-year-old female, with no previous comorbidities, was diagnosed with λ light chain myeloma RISS-III with renal failure requiring hemodialysis (serum creatinine, 7.9 mg/dL; urine output, 200 mL/d). The