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Case Report

A Case Report of *BCR-ABL-JAK2*-Positive Chronic Myeloid Leukemia with Complete Hematological and Major Molecular Response to Dasatinib

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Keywords
BCR-ABL1 · *JAK2*-positive chronic myeloid leukemia · Chronic myeloid leukemia · Dasatinib

Abstract
Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) that harbors the Philadelphia chromosomal translocation resulting in the uncontrolled production of mature granulocytes. Commonly, patients are diagnosed with CML during blood work for other reasons or enlarged spleen. The diagnosis is based on WHO criteria that require the demonstration of Philadelphia chromosome. Typically, *JAK2* mutation is not found in *BCR-ABL1*-positive MPN (CML). Most patients with CML are *JAK2* negative. It is rare for CML Philadelphia-positive patients to have a coexisting *JAK2* mutation. Little is known regarding the effect of *JAK2* mutation on the disease course of CML, the complications, and the response to treatment. We report the case of a 57-year-old man with no previous medical illness who presented with elevated white blood cell count on perioperative assessment for hernial repair; on further workup, he was diagnosed with Philadelphia-positive CML. He was found to have *JAK2* mutation and was started on treatment with dasatinib and achieved hematological and cytogenetic remission with loss of the *JAK2* mutation. Patients with *JAK2*-positive *BCR-ABL*-positive CML had a good hematological and cytogenetic response to dasatinib. In such rare coexistence of *JAK* and *BCR-ABL*, dasatinib is a good option due to multi-kinase activity.

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Introduction

Myeloproliferative neoplasm (MPN) is a group of hematological disorders characterized by he uncontrolled production of myeloid cell expansion, resulting in erythrocytosis, leukocytosis, thrombocytosis, or a rise in the count of more than one type together. They are divided into *BCR-ABL1*-positive chronic myeloid leukemia (CML) [1] and *BCR-ABL1*-negative MPN (essential thrombocytosis, polycythemia vera, and primary myelofibrosis). *BCR-ABL1*-negative MPN has characteristic mutations, including *JAK2, CALR, MPL,* and others [2]. Classically, *JAK2* mutation does not coexist with *BCR-ABL1*-positive MPN (CML).

CML is an uncommon MPN with an incidence of 1–2% per 100,000 per year [3]. It is diagnosed with blood and bone marrow findings of mature granulocytes confirmed by demonstration of the Philadelphia chromosome [4]. The defect in CML is a reciprocal translocation between chromosomes 9 and 22, resulting in the *BCR-ABL1* fusion gene [5]. It is the product of this gene that has an uncontrolled tyrosine kinase activity which plays the central role in the pathogenesis of CML and is the primary target for treatment [1]. Classically, CML is *BCR-ABL1* positive, unlike other MPNs. The presence of mutations (like *JAK*) is seen in *BCR-ABL1*-negative MPN, but its presence with CML is a rare finding; only a few cases have been reported. We present a 57-year-old man diagnosed with *BCR-ABL1*-positive and *JAK*-positive CML who had a good clinical response to treatment with dasatinib.

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A 57-year-old man not known to have any chronic illness was referred to hematology due to a high white blood cell count discovered during preoperative blood work for hernial repair. White blood cell count was 65.6 × 10^3/μL; other blood work is shown in Table 1. On physical examination, there was no pallor, jaundice, palpable lymph nodes, or organomegaly. Body weight was 88.6 kg, and body mass index was 28.15 kg/m^2. Peripheral blood smear picture showed normocytic normochromic red cells with marked leukocytosis with marked neutrophilia, eosinophilia, and basophilia. Karyotype study showed 46,XY,t(9;22)(q34; q11.2), *JAK2* V617F mutation-positive. Interphase fluorescence in situ hybridization (iFISH) showed *BCR-ABL1* rearrangement, t(9;22) in 96% of cells analyzed. Bone marrow aspiration showed marked hypercellularity (~100%) with marked granulocytic hyperplasia. He was initially started on hydroxyurea for 1 week, then he was started on dasatinib 100 mg daily after the result of the bone marrow. The *BCR-ABL1* turned negative 3 months after starting therapy.

After 1 year of treatment, he developed shortness of breath; a chest X-ray showed evidence of pleural effusion. He received furosemide 20 mg for 5 days, and the dose of dasatinib was reduced from 100 to 50 mg daily. *BCR-ABL* was repeated 3 months later and showed that he was on major molecular response, *BCR-ABL1*-positive with a *BCR-ABL1* to *ABL1* percentage ratio of 0.03% (IS), consistent with previous data about the safety and efficacy of 50 mg [6] (Fig. 1). Twenty-four months after treatment, repeated *JAK* mutation showed loss of the *JAK* mutation. The patient is under regular follow-up and reported no major complications.

Discussion

MPNs are classified into Philadelphia-positive (CML) and Philadelphia-negative MPN (essential thrombocytosis, polycythemia vera, idiopathic primary myelofibrosis, and profibrotic myelofibrosis) [2]. The WHO classification 2008 has incorporated molecular genetics

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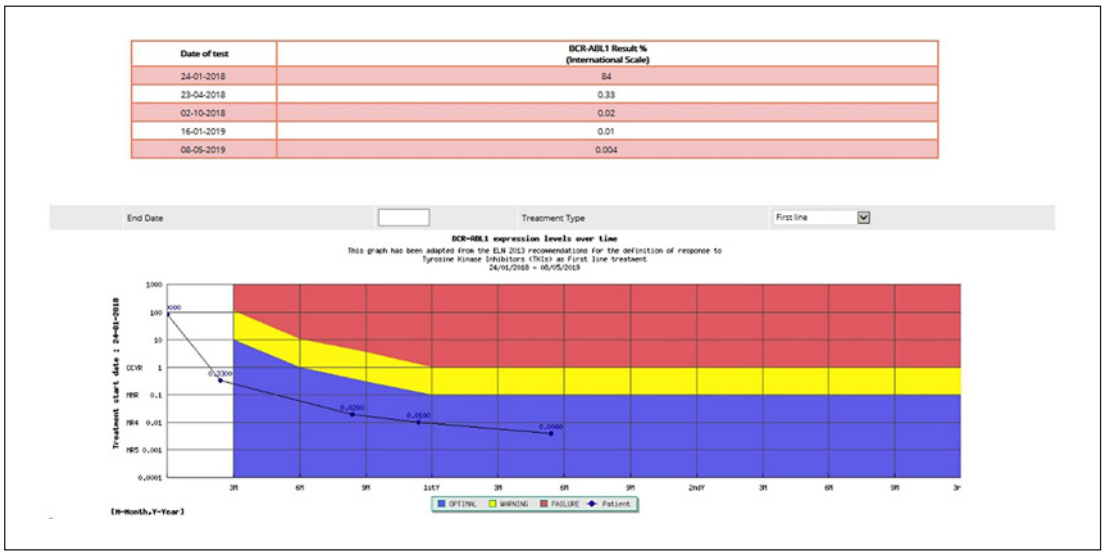

Fig. 1. BCR-ABL percentage in the course of the disease.

Table 1. Shows complete blood count at the time of the diagnosis

Parameter	Result	Normal range
White blood cells	65.6 $\times 10^3/\mu L$	4–10 $\times 10^3/\mu L$
Platelets	181 $\times 10^3/\mu L$	150–400 $\times 10^3/\mu L$
Hemoglobin	14.0 g/dL	13–17 g/dL
Absolute neutrophil count	59.9 $\times 10^3/\mu L$	2–7 $\times 10^3/\mu L$
Lymphocytes	3.3 $\times 10^3/\mu L$	1–3 $\times 10^3/\mu L$
Basophils	0.40 $\times 10^3/\mu L$	0–0.10 $\times 10^3/\mu L$
Eosinophils	0.5 $\times 10^3/\mu L$	0–0.5 $\times 10^3/\mu L$

in the diagnosis of Philadelphia-negative MPN and requires the presence of *JAK2* 3617F CALR MPL or other clonal abnormalities. *BCR-ABL*-negative MPN is usually sporadic; however, familial cases can occur in a different part of the world [7, 8]. The classification is applied worldwide, and it is well understood that patients with *BCR-ABL*-negative MPN can progress to MF CML and other hematological and nonhematological malignancies [9]. It was thought that *BCR-ABL* positive and *JAK* mutation could not exist together [10]. However, it is rarely found among patients with *BCR-ABL*-positive CML [11]. This disease with positive *JAK* and positive *BCR-ABL* may be thought of as a separate entity, and there is a need to revise the diagnostic criteria [12].

Patients with CML with *JAK2* mutation had a weak response to imatinib [13]. This is a point of significance as our patient had a good hematological response with dasatinib [14]. Imatinib inhibits the *BCR-ABL1* pathway and is a more specific inhibitor for tyrosine kinase acting by competitively inhibiting the inactive *BCR-ABL1* protein tyrosine kinase by blocking the ATP binding site and thereby preventing the conformational switch to the active form [15]. On the other hand, dasatinib is a second-generation tyrosine kinase inhibitor with a much broader mechanism of action; in addition to inhibiting the *BCR-ABL1* like imatinib, it inhibits other signaling pathways like SRC kinases. This may allow dasatinib to have additional therapeutic effects that can include the *JAK2* mutation. Our patient was treated with dasatinib, and on follow-up repeated *JAK2* mutation was not detected. This could mean that

the *JAK2* mutation is not the driving mutation and has little effect on the CML course. Moreover, the patient did not develop any other complication related to CML.

It is still unclear whether *JAK2*-mutant clones and *BCR-ABL*-positive clones are different or share a common stem cell origin. Because the *JAK2* clones responded well to broad-spectrum dasatinib but did not respond to the more specific tyrosine kinase inhibitor imatinib [16], this suggests that they have a different origin. This leads to a vital clinical point that patients with positive clones for *JAK2* and *BCR-ABL* have a better response with a multi-kinase inhibitor like dasatinib.

Conclusion

Patients with *JAK2*-positive BCR-ABL-positive CML had a good hematological and cytogenetic response to dasatinib. In such rare coexistence of *JAK2* and *BCR-ABL*, dasatinib is a good option due to multi-kinase activity.

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Statement of Ethics

The case report was approved by the medical research center MRC-04-20-849. The patient has provided written informed consent for the publication of this case report.

Conflict of Interest Statement

All authors have no conflicts of interest.

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Author Contributions

Elrazi A. Ali: writing, editing, final approval. Susanna Al-Akiki: writing, editing, final approval. Mohamed A. Yassin: writing, editing, final approval.

Availability of Data and Material

Data is available on request.

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