CORRESPONDENCE

BCR-ABL and JAK2V617F Mutation Co-existence, Rare or Just Unexplored

H. S. Darling¹ · Rajiv Kumar¹ · Rajan Kapoor¹ · Jasjit Singh¹ · Tarun Verma¹

Received: 14 October 2016 / Accepted: 18 January 2017 / Published online: 1 February 2017
© Indian Society of Haematology & Transfusion Medicine 2017

Abstract Current hematology practice distinguishes chronic myeloid leukemia (CML) and other major chronic myeloproliferative neoplasms as different entities classically characterized by positivity of BCR-ABL fusion gene and JAK2V617F mutations. These are different in clinical presentation, molecular genetics, therapy and response to present treatments. Nevertheless, there have been occasional case reports of detection of both mutations in the same patient. Although some of these had been incidentally detected, most have manifested clinically while being treated for one disease. Here, we present two cases of co-existence of BCR-ABL and JAK2V617F positivity. The first one was initially managed as CML. On obtaining adequate molecular and hematological response, thrombocytosis persisted. Hence she was tested for JAK2V617F mutation. In the second case, when we noticed upfront very high platelet counts along with a clinical picture of CML, we tested her for both and was found to be positive for both. Till to date, no such clinical case has been reported from India. The current status and approach to BCR ABL and JAK2 coexistent mutations has been reviewed and discussed.

Keywords Chronic myeloid leukemia · BCR-ABL · JAK2V617F · Essential thrombocythemia · Myeloproliferative neoplasm

Introduction

The study of medicine is a science but its clinical application is an art. This is how we evolve in research when we try to explain the uncommon presentation of diseases. Although thrombocytosis may be a part of the phenotypic presentation of CML, co-existence of CML and an another JAK2V617F positive MPN is a rare phenomenon. We came across two such cases, the first from India.

Case 1

A 69 year old lady presented in May 2012 as a diagnosed case of CML, initially managed by a general practitioner. She carried a few clinical notes which mentioned her to have presented with fever and leucocytosis in Jun 2011. In Jan 2012, while on Imatinib, she had no hepatosplenomegaly and had Hb 12.2 g/dL, TLC 11,160/mm³, Platelet count 9,60,000/mm³ and an RQ-PCR BCR-ABL of 0.0%. On evaluation her Hb was 12.4 g/dL, TLC-8300/mm³ and Platelets of 11 lacs/mm³. A repeat RQ PCR BCR-ABL was reported as *borderline positive*. She refused bone marrow studies and she was continued on Imatinib. Her BCR-ABL ratio was 0.05% in Sep 12 and 0.00% in Jan 13 and 0.00% in Feb 14. On follow up she had persistent thrombocytosis between 7 lakhs to 11 lacs/mm³. Her BM studies were re-advised which showed a cellular marrow with panmyelosis and megakaryocytes clustering. Her JAK2V617F qualitative RT-PCR turned out to be positive. In the absence of a definite BCR-ABL PCR report her diagnosis was changed to Essential Thrombocythemia and Imatinib was stopped and she was started on hydroxyurea and ecosprin. Her quantitative BCR-ABL ratio remained undetectable till May 14 and platelet count normalised. RQ-PCR BCR-ABL in Aug

✉ Rajiv Kumar
k.rajiv76@gmail.com

¹ Department of Hematology, Army Hospital (R&R),
Dhaura Kuan, New Delhi 110010, India

Table 1 Laboratory and clinical characteristics of patients

Pt	Age	Sex	At diagnosis of other mutation		Features of Ph negative MPN	At diagnosis of CML				
			CML duration (m)	CML phase		Karyotype	Transcript	WBC (/mm ³)	Hb (g%)	Plt (lac/mm ³)
1	69	F	31	CP	Thrombocytosis	Not known	P210	135,000	Not known	Not known
2	57	F	0	CP	Thrombocytosis	100% Ph+	P210	30,100	11.6	12.25

14 was reported as *low positive*. Hence, she was restarted on Imatinib and hydroxyurea continued. In Jan 15 and April 15 she had two episodes of pancytopenia necessitating short withdrawal of both drugs. In May 15, BCR-ABL ratio further increased to 6.14% and repeat qualitative JAK2V617F was positive. Hence, Imatinib was restarted at 400 mg OD and HU reduced to 500 mg OD. Her last RQ PCR BCR-ABL (IS) in Mar 16 is 0.00% (Table 1).

Case 2

A 57 year old obese lady was being evaluated for non-specific pain abdomen of 01 month duration. Clinically she had no palpable lymphadenopathy or splenomegaly. She was detected to have leucocytosis and thrombocytosis and referred for evaluation by Hematologist. Her Hb was 11.6 g/dL, TLC 30,100/mm³, (DLC—P89, L06, Baso03%), Plt 12.25 lac/mm³. PBS showed neutrophilic leucocytosis, basophilia and thrombocytosis and no blasts. BM aspirate and biopsy showed hypercellularity with myeloid hyperplasia and megakaryocytic hyperplasia. Megakaryocytes were grouped together in relation to marrow fragments with most of them showing immature morphology. RQ-PCR for BCR-ABL translocation was 38.51% in bone marrow aspirate and peripheral blood RT PCR was positive for JAK2V617F mutation. She was diagnosed as a case of CML with ET and started on Imatinib and Ecosprin.

Discussion

We did a literature search and found that about 68 clinical cases of coexistence of BCR-ABL and JAK2V617F mutations have been reported so far. No clinical case has been reported from India. Except for those detected in mass specimen analysis, most isolated cases have been unearthed during an atypical clinical scenario, where while on treatment for one myeloproliferative neoplasm (MPN) and its molecular marker decreasing or undetectable, the patient had developed another clinical or laboratory abnormality.

The JAK2V617F mutation has been detected before, simultaneous to, or after the detection of BCR-ABL fusion

transcript. Controversy exists between the origin of both genetic changes from different cells or a common stem cell acquiring JAK2V617F and the BCR-ABL fusion gene at different time points. There are three possible mechanisms. *Firstly*, the two mutations might have arisen independently from susceptible polyclonal stem cells [1]. Zhou et al. demonstrated a significant decrease in BCR-ABL ratio on treatment with ABL TKI, with a concomitant rise in JAK2V617F allele burden, suggesting that the two disorders arose from independent clones. On adding Ruxolitinib JAK2V617F clone also reduced [2]. *Secondly*, BCR-ABL clone may be a sub-clone of JAK2V617F mutated cell achieving a growth advantage at initial diagnosis. It is seen that JAK2V617F is initially detectable at a very low level when BCR-ABL ratio is 100% [3]. Possibly, JAK2V617F exists in all the myeloid progenitor cells while BCR-ABL is limited to a small compartment. Imatinib induces suppression of the BCR-ABL clone but not the JAK2V617F clone and the latter remains at previous level or even higher than before. Bornhauser and Cambier proved that JAK2V617F mutation was found in granulocytic and erythroid colonies, whereas BCR-ABL fusion in granulocytic colonies but not in erythroid colonies. *Thirdly*, both these mutations may follow another independent founder mutation predisposing to their acquisition [4]. Most recently, Inokuchi and Koiti reported Dasatinib successfully repressed both BCR-ABL and JAK2V617F clone in the patient who was resistant to Imatinib.

Certain questions should definitely surface out of our discussion. For example, which patients should be tested for JAK2V617F/BCR-ABL double positivity; if detected whether both of these are clinically important; do both require treatment and what should be the treatment modality; does this co-existence impact the prognosis. Further large volume prospective studies are needed to answer these questions. A recently published study found the incidence of 0.2% of BCR-ABL1/JAK2V617F double positive cases in a large cohort of 10,875 cases as compared to previously reported frequency of 2.55% [5].

Compliance with Ethical Standards

Conflict of interest Authors Dr. Harry S. Darling, Dr. Rajiv Kumar, Dr. Rajan Kapoor, Dr. Jasjit Singh and Dr. Tarun Verma declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Tefferi A, Levitt R, Lasho TL, Knudson RA, Ketterling RP (2010) Post- Imatinib therapy emergence of a new JAK2V617F clone and subsequent development of overt polycythemia vera in a patient with chronic myelogenous leukaemia. *Eur J Haematol* 85:86–87
2. Zhou A, Knoche EM, Engle EK et al (2015) Concomitant JAK2 V617F-positive polycythemia vera and BCR-ABL-positive chronic myelogenous leukemia treated with ruxolitinib and dasatinib. *Blood Cancer J* 5:e351
3. Pastore F et al (2013) Impressive thrombocytosis evolving in a patient with a BCR-ABL positive CML in major molecular response during dasatinib treatment unmasks an additional JAK2V617F. *Exp Hematol Oncol* 2:24
4. Nadali F, Ferdowsi Sh, Karimzadeh P, Chahardouli B, Einollahi N, Mousavi SA et al (2009) JAK2-V617F mutation and Philadelphia positive chronic myeloid leukemia. *IJHOSCR* 3(3):43–45
5. Martin-Cabrera P, Haferlach C, Kern W, Schnittger S, Haferlach T (2016) BCR-ABL1-positive and JAK2 V617F-positive clones in 23 patients with both aberrations reveal biologic and clinical importance. *Br J Haematol*. doi:[10.1111/bjh.13932](https://doi.org/10.1111/bjh.13932)