


Concurrent JAK2-Positive Myeloproliferative Disorder and Chronic Myelogenous Leukemia: A Novel Entity? A Case Report With Review of the Literature

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Abstract

JAK2 V617F mutation and BCR-ABL translocation have been considered to be mutually exclusive. However, many cases where both hits coexisted have been reported. We have personally managed a case too. We believe this hybrid entity is underdiagnosed. Thus, we decided to shed light on this “double hit” disease to improve its diagnosis and optimize its treatment. We reviewed the English literature in PubMed since JAK2 discovery. We found 33 cases reported so far. We summarized patient characteristics and analyzed possible interactions between JAK2 and BCR-ABL clones.

Keywords

myeloproliferative disorder, chronic myelogenous leukemia, JAK2 mutation, BCR-ABL translocation

Introduction

Chronic myelogenous leukemia (CML) and Philadelphia-negative myeloproliferative disorders (MPD) are common hematologic diseases. The prevalence of CML is 1 in 17 000. Polycythemia vera (PV) with a prevalence of 44 to 57 per 100 000 and essential thrombocytosis (ET) with a prevalence of 38 to 57 per 100 000 are much more common than primary myelofibrosis (PMF), which has a prevalence of 4 to 6 per 100 000.¹ In CML, hybrid BCR-ABL gene as a result of translocation (9,22) encodes a fusion protein that leads to activation of ABL tyrosine kinase and subsequent uncontrolled production of mature and maturing granulocytes. In Philadelphia-negative MPD, mutated Janus kinase 2 (JAK2) has increased kinase activity. It leads to proliferation of progenitors independently of cytokine stimulation. JAK2 V617F mutation is present in around 95% of PV and 50% of ET and PMF cases. BCR-ABL translocation and JAK2 V617F mutation have been considered to be mutually exclusive. However, several cases of JAK2 mutation coexisting with CML have been reported. In the pre-JAK2 era, it was difficult to confirm the coexistence of CML and Philadelphia-negative MPD due to lack of a marker for the latter. The discovery of JAK2 V617F mutation in 2005 provided the opportunity to document concomitant Philadelphia-positive and Philadelphia-negative MPD with more certainty. We used PubMed to conduct a review of cases published in English where JAK2-positive MPD and CML coexisted. Obviously, the cases were

published post JAK2 discovery in 2005. We are also reporting a case that we have personally diagnosed and treated.

Results

We found 33 cases of concomitant JAK2-positive MPD and CML. Patient characteristics are shown in Table 1. We have also personally managed a case of PMF and CML.

The patient is a 75-year-old male who presented to our clinic in 2017 with progressive weight loss over prior 2 years, night sweats, pruritus, early satiety, and left upper quadrant pain. Physical examination was pertinent for hepatosplenomegaly. His white blood cell (WBC) count was 23 200 cells/mm³ with 92% neutrophils, hemoglobin 14.3 g/dL, and platelet count 741/mm³. He had no blasts in peripheral blood. Per chart review, we noted that he had started to develop neutrophilia and thrombocytosis in 2013 and 2014, respectively. Quantitative reverse transcription polymerase chain reaction was positive for both b2a2 and b3a2 transcripts at 2.1% and

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Table 1. Patient Characteristics.

Age/Sex	Diagnosis (+CML)	WBC ($\times 10^3$)	Hb	PLT	Treatment	Course	Clone Interaction
Unknown ²	ET	?	?	?	I	ET, CML 12 years later	?
50/Male ³	MF	93	15	345	I	CML, MF 4 years later	BCR-ABL disappeared, JAK2 constant
43/Male ⁴	PV	?	Hct 49	?	INF, HU then I	CML, PV 6 years later	BCR-ABL decreased, JAK2 constant
82/Female	PV	67	9.8	605	Radioactive P, HU, A then I	PV, CML 16 years later	?
73/Female ⁵	PV	214	10.2	65	HU then I	PV, CML 15 years later	
66/Male ⁶	MF	?	11.3	?	I then HU	Concomitant	?
55/Male ⁷	MF	163	11.5	?	I	CML, MF 2 years later	BCR-ABL decreased, JAK2 increased
43/Male ⁸	PV	100	Hct 36	?	I	PV, CML 16 years later	BCR-ABL decreased, JAK2 increased
49/Male	MF	?	?	?	I then D	CML, MF 2 years later	BCR-ABL and JAK2 decreased
64/Male ⁹	?	?	?	?	I then N	Concomitant	BCR-ABL decreased, JAK2 constant
64/Male ¹⁰	PV	15.3	24	380	I	Concomitant	BCR-ABL decrease, JAK2 increased
52/Female ¹¹	MF	193	10	689	HU then I	Concomitant	BCR-ABL and JAK2 decreased
58/Male ¹²	MF	7.5	13.5	669	I then HU	MF, CML 4 years later	BCR-ABL decreased, JAK2 increased
67/Male ¹³	MF	35	8.9	143	I then HU	Concomitant	?
32/Male	ET	35	?	907	A, HU then I	ET, CML 40 months later	BCR-ABL and JAK2 decreased
58/Female	MF	83	14.5	496	HU, INF	Concomitant	?
63/Male	PV	41	14.4	371	HU then I	PV, CML 15 years later	BCR-ABL decreased, JAK2 increased
45/Male ¹⁴	?	57	14	266	I	Concomitant	?
39/Male ¹⁵	PV	66	20	342	I then D then N	PV, CML 15 years later	Opposite growth
69/Male ¹⁶	?	32.5	10.9	511	I	Concomitant	BCR-ABL and JAK2 decreased
60/Male ¹⁷	PV	121	18.5	152	I then HU	Concomitant	BCR-ABL increased, JAK2 decreased
67/Male ¹⁸	PV	11.9	17.2	507	INF, HU then I	CML, PV 10 years later	BCR-ABL decreased, JAK2 increased
70/Male ¹⁹	?	11.5	15.3	950	INF then I	JAK2, 7 years after CML	?
42/Female ²⁰	?	350	?	498	HU then I then D	JAK2, 5 years after CML	JAK2 increased with CML treatment
53/Female	ET	36.7	12.5	983	HU then INF then I, A	CML, ET 11 years later	?
60/Female ²¹	ET	23	8.3	220	I, A then D	CML, ET 2 years later	?
21/Female ²²	?	73	13.3	440	I	Concomitant	?
67/Male ²³	MF	22.6	Hct 42	652	N then D	MF, CML 3 years later	BCR-ABL decreased, JAK2 constant
77/Male ²⁴	?	6.2	8.7	242	?	Concomitant	?
60/Male ²⁵	?	30	Hct 21	324	I	Concomitant	?
61/Male ²⁶	PV	108	9	95	HU, I	PV, CML 7 years later	JAK2 emerged with decrease in BCR-ABL
36/Male	ET	9.4	13.8	830	HU	Concomitant	BCR-ABL increased
58/Male ²⁷	MF	19.7	13	285	HU, D	Concomitant	?
Our case: 75/Male	MF	23	14.3	741	HU, I	Concomitant	?

Abbreviations: A, anagrelide; CML, chronic myelogenous leukemia; D, dasatinib; ET, essential thrombocytosis; Hb, hemoglobin in g/dL; Hct, hematocrit; HU, hydroxyurea; I, imatinib; INF, interferon; JAK2, Janus kinase 2; MF, myelofibrosis; N, nilotinib; P, phosphorus; PLT, platelet count/mm³; PV, polycythemia vera; WBC, white blood cell count/mm³; ?, unknown or unclear.

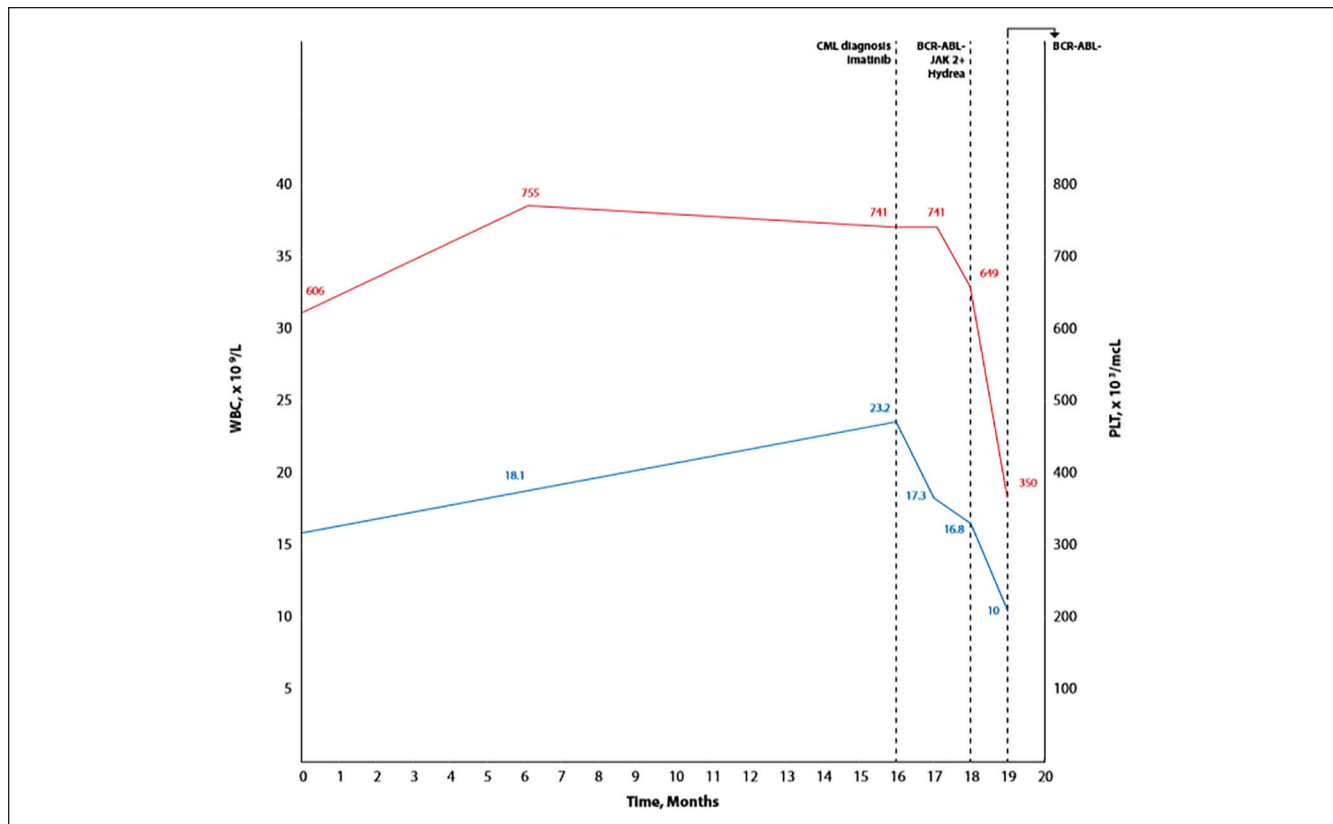


Figure 1. Clinical course.

1.2%, respectively. Imatinib was started. Eight weeks later, WBC count was 16.8 cells/mm³, hemoglobin 14.5 g/dL, platelet count 649/mm³, and reverse transcription polymerase chain reaction negative for BCR-ABL transcripts. The fact that the patient had complete molecular response without hematologic response triggered further workup. JAK2 V617F mutation was checked in peripheral blood and was positive. Erythropoietin was low at 1.3 mIU/mL. Examination of the bone marrow showed hypercellularity (90%) with myeloid/erythroid ratio of 7.7, proliferation of atypical megakaryocytes, <1% blasts, and widespread grade 2 reticulin fibrosis. No BCR-ABL translocation was detected by fluorescence in situ hybridization. DIPSS (Dynamic International Prognostic Scoring System) Plus score was 1. Myelofibrosis mutational profile analysis was not available. Hydroxyurea was added on top of imatinib (Figure 1).

Including our case, 11 patients had PMF, 10 had PV, and 5 had ET. In 8 cases, the exact nature of the myeloproliferative disorder was not clear. MPD preceded CML in 10 cases, CML preceded MPD in 9 cases, and both were diagnosed concomitantly in 15 cases. Interestingly, when MPD preceded CML, the mean time interval between the diagnoses of the 2 entities was 10.6 years compared with 5.4 years when CML preceded MPD. Interaction between JAK2 mutation and BCR-ABL transcripts levels varies. In most cases, JAK2 and BCR-ABL levels moved in opposite directions. In the

remaining cases, JAK2 level decreased or remained constant while BCR-ABL level decreased.

Discussion

BCR-ABL transcripts have been detected at very low levels in healthy persons without clinical features of CML. The amount of BCR-ABL mRNA present in healthy individuals ranged from 5 to 20 copies/5 × 10⁷ to 10⁸ WBCs.²⁸ Our patient had BCR-ABL transcripts level well above this threshold. We believe he had concomitant PMF and CML. As mentioned above, JAK2 mutation and BCR-ABL translocation have been considered to be mutually exclusive. However, several cases of coexistence of both hits have been reported. The prevalence of this “dual disease” is unknown. However, we think this entity is underdiagnosed since it is rarely suspected and checked. Few studies showed surprisingly elevated proportion of this “double hit” in CML patients. In one study, 314 patients with CML were screened for the presence of JAK2 V617F mutation. The latter was present in 8 patients accounting for 2.5%.²⁹ Two studies done in Karachi, Pakistan, showed proportions of CML patients harboring JAK2 V617F mutation as high as 26.7% and 44%.^{30,31}

Clinically, emergence of MPD in CML patients may be mistaken for relapse or drug resistance. MPD must be suspected in

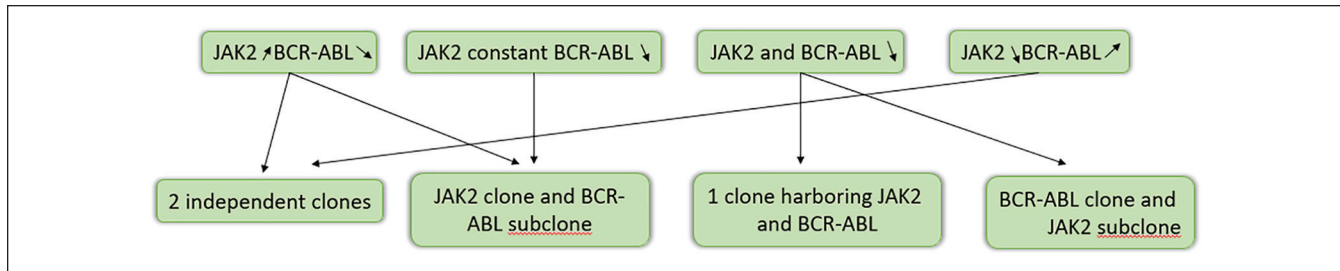


Figure 2. Possible JAK2 and BCR-ABL interactions and clones.

CML with atypical course such as erythrocytosis or progressive or persistent thrombocytosis or neutrophilia while CML is in remission. Development of CML must be considered in cases of JAK2-positive MPD with CML-like features such as leukocytosis or progressive splenomegaly years after clinical stability.

In Figure 2, we show possible interactions between JAK2 mutation and BCR-ABL transcripts levels and corresponding clonal origin. The model where BCR-ABL clone is a subclone of JAK2 one was demonstrated in a patient with CML and PV. BCR-ABL translocation and JAK2 mutation were present in most erythroid and myeloid colonies. Few colonies harbored JAK2 mutation only, and none had BCR-ABL transcripts alone.⁸ In another case, JAK2 mutation was present in CFU-GM and CFU-E compartments. However, BCR-ABL translocation was present in few CFU-GM colonies and absent in CFU-E.⁶ In 2 patients with PV and CML³² and a patient with PMF and CML,²³ all hematopoietic colonies had JAK2, some had both JAK2 and BCR-ABL, and none had BCR-ABL alone. The model where JAK2 clone is a subclone of BCR-ABL one was also demonstrated. A patient with CML with positive JAK2 was treated with imatinib. Both JAK2 and BCR-ABL disappeared with treatment.¹⁶ The model where JAK2 and CML clones are distinct was also shown. BCR-ABL was absent in endogenous erythroid colonies formed without erythropoietin. Progressive decrease in BCR-ABL was associated with JAK2 clone expression.¹⁰

As mentioned above, it took around a decade in average for CML to occur after MPD. However, MPD followed CML in about 5.4 years in average. The difference between time intervals is not clear.

Conclusion

Several cases of concomitant JAK2 MPD and CML have been reported. This hybrid disease is probably more frequent than expected because it is underdiagnosed. Providers must suspect this hybrid disease in atypical clinical course to optimize treatment and avoid transformation to acute leukemia. The World Health Organization's MPD diagnostic criteria must probably be revised to account for the possibility of this "double hit" disease, which might be a novel clinical entity.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases.

Informed Consent

Verbal informed consent was obtained from the patient for his anonymized information to be published in this article.

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References

1. Mehta J, Wang H, Iqbal SU, Mesa R. Epidemiology of myeloproliferative neoplasms in the United States. *Leuk Lymphoma*. 2014;55:595-600.
2. Scott LM, Campbell PJ, Baxter EJ, et al. The V617F JAK2 mutation is uncommon in cancers and in myeloid malignancies other than the classic myeloproliferative disorders. *Blood*. 2005;106:2920-2921.
3. Krämer A, Reiter A, Kruth J, et al. JAK2-V617F mutation in a patient with Philadelphia-chromosome-positive chronic myeloid leukaemia. *Lancet Oncol*. 2007;8:658-660.
4. Inami M, Inokuchi M, Okabe M, et al. Polycythemia associated with the JAK2V617F mutation emerged during treatment of chronic myelogenous leukemia. *Leukemia*. 2007;21:1103-1104.
5. Mirza I, Frantz C, Clarke G, Voth AJ, Turner R. Transformation of polycythemia vera to chronic myelogenous leukemia. *Arch Pathol Lab Med*. 2007;131:1719-1724.
6. Bornhäuser M, Mohr B, Oelschlaegel U, et al. Concurrent JAK2(V617F) mutation and BCR-ABL translocation within committed myeloid progenitors in myelofibrosis. *Leukemia*. 2007;21:1824-1826.
7. Hussein K, Bock O, Seegers A, et al. Myelofibrosis evolving during imatinib treatment of a chronic myeloproliferative

- disease with coexisting BCR-ABL translocation and JAK2 V617F mutation. *Blood*. 2007;109:4106-4107.
8. Bocchia M, Vannucchi AM, Gozzetti A, et al. Insights into JAK2-V617F mutation in CML. *Lancet Oncol*. 2007;8:864-866.
 9. Kim YK, Shin MG, Kim HR, et al. Simultaneous occurrence of the JAK2V617F mutation and BCR-ABL gene rearrangement in patients with chronic myeloproliferative disorders. *Leuk Res*. 2008;32:993-995.
 10. Cambier N, Renneville A, Cazaentre T, et al. JAK2V617F-positive polycythemia vera and Philadelphia chromosome-positive chronic myeloid leukemia: one patient with two distinct myeloproliferative disorders. *Leukemia*. 2008;22:1454-1455.
 11. de Conchon MRM, Costa JL, Novaes MMY, et al. Simultaneous detection of JAK2 V617F mutation and BCR-ABL translocation in a patient with chronic myelogenous leukemia. *Int J Hematol*. 2008;88:243-345.
 12. Jallades L, Hayette S, Tigaud I, et al. Emergence of therapy-unrelated CML on a background of BCR-ABL-negative JAK2V617F-positive chronic idiopathic myelofibrosis. *Leuk Res*. 2008;32:1608-1610.
 13. Pardini S, Fozza C, Contini S, et al. A case of coexistence between JAK2V617F and BCR/ABL. *Eur J Haematol*. 2008;81:75-76.
 14. Hussein K, Bock O, Theophile K, et al. Chronic myeloproliferative diseases with concurrent BCR-ABL junction and JAK2V617F mutation. *Leukemia*. 2008;22:1059-1062.
 15. Pingali SR, Mathiason MA, Lovrich SD, Go RS. Emergence of chronic myelogenous leukemia from a background of myeloproliferative disorder: JAK2V617F as a potential risk factor for BCR-ABL translocation. *Clin Lymphoma Myeloma*. 2009;9:E25-E29.
 16. Campiotti L, Appio L, Solbiati F, Ageno W, Venco A. JAK2-V617F mutation and Philadelphia positive chronic myeloid leukemia. *Leuk Res*. 2009;33:e212-e213.
 17. Bee PC, Gan GG, Nadarajan VS, Latiff NA, Menaka N. A man with concomitant polycythemia vera and chronic myeloid leukemia: the dynamics of the two disorders. *Int J Hematol*. 2010;91:136-139.
 18. Tefferi A, Levitt R, Lasho TL, Knudson RA, Ketterling RP. Postimatinib therapy emergence of a new JAK2V617F clone and subsequent development of overt polycythemia vera in a patient with chronic myelogenous leukemia. *Eur J Haematol*. 2010;85:86-87.
 19. Caocci G, Atzeni S, Orrù N, et al. Response to imatinib in a patient with chronic myeloid leukemia simultaneously expressing p190 BCR-ABL oncoprotein and JAK2 V617F mutation. *Leuk Res*. 2010;34:e27-e29.
 20. Pastore F, Schneider S, Christ O, Hiddemann W, Spiekermann K. Impressive thrombocytosis evolving in a patient with a BCR-ABL positive CML in major molecular response during dasatinib treatment unmasks as additional JAK2V617F. *Exp Hematol Oncol*. 2013;2:24.
 21. Lee YJ, Moon JH, Shin HC, et al. Two CML patients who subsequently developed features of essential thrombocyto-penia with JAK2-V617F mutation while in complete cytogenetic remission after treatment with imatinib mesylate. *Int J Hematol*. 2013;97:804-807.
 22. Xu W, Chen B, Tong X. Chronic myeloid leukemia patient with co-occurrence of BCR-ABL junction and JAK2 V617F mutation. *Int J Hematol*. 2014;99:87-90.
 23. Yamada O, Mahfoudhi E, Plo I, et al. Emergence of a BCR-ABL translocation in a patient with the JAK2V617F mutation: evidence for secondary acquisition of BCR-ABL in the JAK2V617F clone. *J Clin Oncol*. 2014;32:e76-e79.
 24. Maerki J, Katava G, Siegel D, Silberberg J, Bhattacharyya PK. Unusual case of simultaneous presentation of plasma cell myeloma, chronic myelogenous leukemia, and a Jak2 positive myeloproliferative disorder. *Case Rep Hematol*. 2014;2014:738428.
 25. Hassan A, Dogara LG, Babadoko AA, Awwalu S, Mamman AI. Coexistence of JAK2 and BCR-ABL mutation in patient with myeloproliferative neoplasm. *Niger Med J*. 2015;56:74-76.
 26. Ursuleac I, Colita A, Adam T, Jardan C, Ilea A, Coriu D. The concomitant occurrence of JAK2V617F mutation and BCR/ABL transcript with phenotypic expression—an overlapping myeloproliferative disorder or two distinct diseases? Case report. *J Med Life*. 2013;6:34-37.
 27. Park SH, Chi HS, Cho YU, et al. Two cases of myeloprolif-erative neoplasm with a concurrent JAK2 V617F mutation and BCR/ABL translocation without chronic myelogenous leuke-mia phenotype acquisition during Hydroxyurea treatment. *Ann Lab Med*. 2013;33:229-232.
 28. Biernaux C, Loos M, Sels A, Huez G, Stryckmans P. Detection of major BCR-ABL gene expression at a very low level in blood cells of some healthy individuals. *Blood*. 1995;86:3118-3122.
 29. Pieri L, Spolverini A, Scappini B, et al. Concomitant occur-rence of BCR-ABL and JAK2V617F mutation. *Blood*. 2011;118:3445-3446.
 30. Pahore ZA, Shamsi TS, Taj M, et al. JAK2V617F mutation in chronic myeloid leukemia predicts early disease progression. *J Coll Physicians Surg Pak*. 2011;21:472-475.
 31. Tabassum N, Saboor M, Ghani R, Moinuddin M. Frequency of JAK2 V617F mutation in patients with Philadelphia posi-tive chronic myeloid leukemia in Pakistan. *Pak J Med Sci*. 2014;30:185-188.
 32. Wang X, Tripodi J, Kremyanskaya M, et al. BCR-ABL1 is a secondary event after JAK2V617F in patients with polycy-themia vera who develop chronic myeloid leukemia. *Blood*. 2013;121:1238-1239.