BCR/ABL positive thrombocythemia: a diagnostic dilemma

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Both chronic myeloid leukemia and essential thrombocythemia are part of the spectrum of myeloproliferative neoplasm. Therefore, considerable overlap may occur in the clinical manifestations, and hematological and molecular findings in some patients. We report here a case of a 45-year-old men who presented with thrombocytosis. Bone marrow aspiration yielded small megakaryocytes with hypolobulated nuclei and positive *BCR-ABL* rearrangement. A diagnosis of *BCR-ABL*$^+$ essential thrombocythemia was made and imatinib was advised.

Keywords:
BCR-ABL rearrangement, chronic myeloid leukemia, essential thrombocythemia, myeloproliferative neoplasm

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Introduction

The Philadelphia (Ph) chromosome is a disease-specific marker for chronic myeloid leukemia (CML), which is a myeloproliferative neoplasm and accounts for 15% of newly diagnosed cases of leukemia in adults [1]. The disease is characterized by a balanced genetic translocation, t(9;22)(q34;q11.2), leading to *BCR-ABL1* gene rearrangement, the product of which is a constitutively active tyrosine kinase. The Hannover Bone marrow classification has distinguished three phenotypes of *BCR-ABL*$^+$ CML – CML of common type (CML.CT), CML with megakaryocyte increase (CML.MI), and CML with megakaryocyte predominance (CML.MP) – on the basis of clinical features, peripheral blood smear, and bone marrow (BM) examination [2]. We discuss here a case of a 45-year-old man who was *BCR-ABL*$^+$ with marked thrombocythemia without evidence of CML in peripheral blood smear.

Case report

A 45-year-old man presented to our outpatient department with complaints of fatigue and malaise for previous 2 months. He was a nonsmoker and was not having any chronic disease. His previous medical history was insignificant, but treatment history revealed that he was on hypouricemic agents for last 3 months. His clinical examination was normal with no splenomegaly, and the patient was not having any thrombotic or bleeding manifestations. The complete blood count revealed a hemoglobin level of 12.2 g/dl, hematocrit level of 37.6%, white blood cells count of 23.8×10^3/μl (differential count: neutrophils 80%, lymphocytes 14%, eosinophils 2%, basophils 4%, and monocytes 0%), and platelet count of 589×10^3/μl. Peripheral blood smear showed marked thrombocythemia without any underlying etiology, and also there were no immature cells present. BM aspiration yielded small megakaryocytes with hypolobulated nuclei (Figures 1, 2). His serum biochemistry was as follows: aspartate aminotransferase 28 IU/l; alanine aminotransferase 37 IU/l; total bilirubin 0.4 mg/dl; blood urea nitrogen 10 mg/dl; creatinine 1.0 mg/dl; random blood glucose 119 mg/dl; and serum uric acid 8.7 mg/dl. Ultrasonography of abdomen was normal with no evidence of splenomegaly or hepatomegaly. He was negative for *JAK2V617F* mutation. On the basis of thrombocythemia and BM features, the patient was investigated for *BCR-ABL* rearrangement, which turned out to be positive. Quantitative PCR for BCR/ABL rearrangement showed major translocation, that is, e13a2 and e14a2. Finally, the patient was diagnosed as *BCR-ABL*$^+$ essential thrombocythemia (ET) and was advised imitanib 400 mg/day, and he subsequently responded to treatment (Figure 3).

Discussion

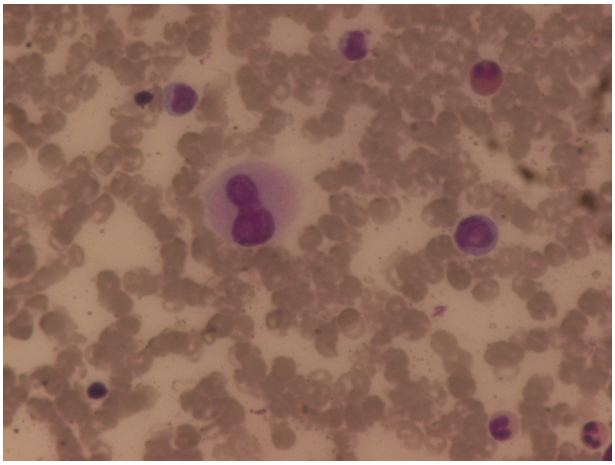
The criteria for diagnosis of CML and ET has been given by Polycythemia Vera Study Group and WHO [3,4]. ET is considered to lack *BCR-ABL* rearrangement whereas its expression is considered diagnostic of CML. However, a gray zone exists between the two entities, as observed in our patient who was *BCR-ABL*$^+$ with marked thrombocythemia, without any evidence of CML in the peripheral blood smear. Michiels *et al.* [5] evaluated cases with similar presentation and concluded that the presence of peripheral blood thrombocythemia, normal hemoglobin, normal white blood cell differential

count, and presence of small megakaryocytes with round or slightly lobulated nuclei in normocellular BM should be diagnosed as Ph^+ ET.

Ph^+ ET is a myeloproliferative disorder and a separate entity from both Ph^+ CML and Ph^- ET. Ph^+ ET is characterized by small hypolobated megakaryocytes in BM caused by *BCR-ABL*-induced maturation defect of hematopoietic stem cells, in contrast to clustered and enlarged mature megakaryocytes with hyperploid nuclei because of growth advantage caused by constitutively activated JAK2V617F or MPL515 mutation in Ph^- ET [6]. The small and indolent platelets in *BCR-ABL*$^+$ ET are nonreactive, that is, they do not have platelet-mediated erthromelalgic microvascular events or bleeding complications similar to *BCR-ABL*$^+$ CML [7,8]. These complications are due to platelet-mediated inflammation and thrombus in end arteries [8–11]. These erythromelelgic thrombotic manifestations are present in *BCR-ABL*$^-$ ET due to the presence of platelets that are large and hypersensitive [10,11].

Ph^+ ET also differs from CML. These include the predilection of Ph^+ ET for women, the absence of splenomegaly, and no features of CML in the peripheral blood or BM [5]. The BM in *BCR-ABL*$^+$ ET is featured by predominant and pronounced mononucleated megakaryopoiesis with initial none, minor, or overt granulocytic hypertrophy consistent with CML.MP [6]. Although the risk for thrombotic or hemmorhagic events is low, the prognosis of *BCR-ABL*$^+$ ET is poor. It may develop features of classic Ph^+ CML with a high risk for blastic transformation and progression to myelofibrosis after a follow-up of a few to several years [5,12].

Figure 1

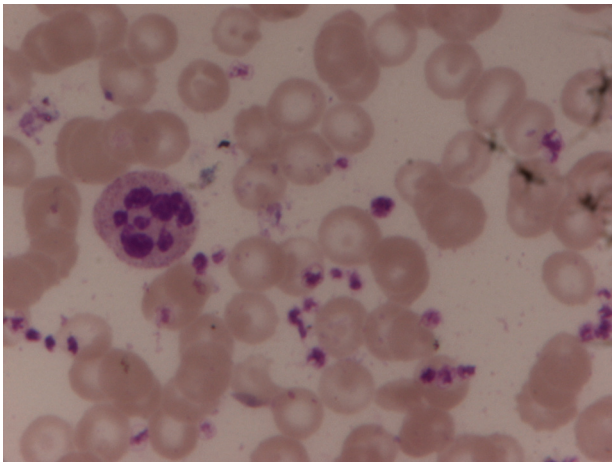


Bone Marrow Aspirate showing small hypolobated megakaryocytes (×400 Leishman's Stain

The *BCR-ABL*$^+$ ET may be considered a third variant of CML, known as CML. megakaryocyte predominant (CML.MP) [6], as suggested in the Hannover BM classification [2], the other two being CML of common type (CML.CT), in which granulocytic hypertrophy is predominant, and CML with megakaryocyte increase (CML.MI), which is characterized by megakaryocytic hypertrophy in addition to granulocytic hypertrophy in BM biopsy.

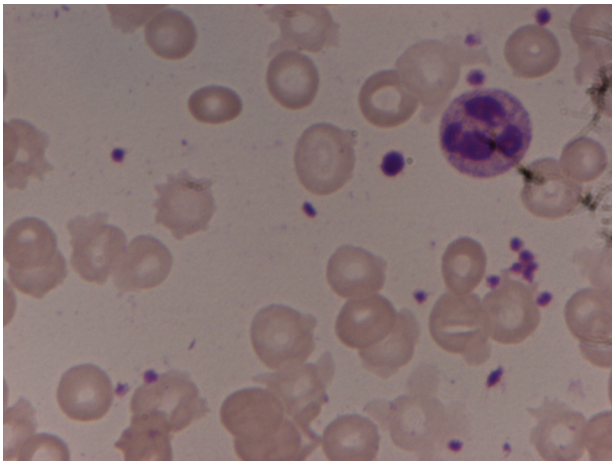
The *BCR-ABL* fusion gene produces protein that has a tyrosine kinase activity. Imatinib mesylate (tyrosine kinase inhibitor) by binding to *BCR-ABL* protein tyrosine kinase and inhibiting the *BCR-ABL* pathway reduces selective proliferation of *BCR-ABL*$^+$ cells and also induces apoptosis of these cells [13]. As TKI are targeting cells that are *BCR-ABL*$^+$, their use as treatment agents in BCR/ABL$^+$ ET is justified.

Figure 2



Pre- treatment peripheral blood smear showing thrombocythemia (×1000 Leishman's stain)

Figure 3



Post Imatinib therapy peripheral smear showing decreased platelets (×1000 Leishman's stain)

Conclusion

This is perhaps the first documented case of a man diagnosed as *BCR-ABL*$^{+}$ ET, which is a neoplastic disorder with specific peripheral blood and BM features and should be confirmed by using karyotyping. This demands a heightened suspicion in any case of thrombocythemia for early diagnosis and prompt treatment.

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Conflicts of interest

There are no conflicts of interest.

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