

BCR-ABL Positive Essential Thrombocythaemia: A Variant of Chronic Myelogenous Leukaemia or A Distinct Clinical Entity: A Special Case Report

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ABSTRACT

A 37-year-old Malay man presented initially with the clinical picture of essential thrombocythaemia (ET) without the extreme leukocytosis, marked splenomegaly and low neutrophil alkaline phosphatase characteristic of chronic myelogenous leukaemia (CML). Bone marrow examination showed massive megakaryocytic hyperplasia; cytogenetic studies showed the presence of Philadelphia chromosome. The patient was treated with hydroxyurea that resulted in reduction in the platelet count. Seventeen months later, he presented with fever associated with tender massive splenomegaly. Bone marrow finding was consistent with chronic phase CML. The presence of a rearrangement involving the major breakpoint cluster region (M-bcr) on chromosome 22 was confirmed by reverse transcriptase - polymerase chain reaction. The clinical importance of finding the Philadelphia chromosome in patients who seem to have ET is in assessing prognosis. ET generally follows a chronic, indolent course. However, this patient who had Philadelphia chromosome underwent clinical transition to chronic phase CML 17 months and blast crisis 29 months after presentation.

Keywords: Chronic myelogenous leukaemia, essential thrombocythaemia, Philadelphia chromosome, BCR-ABL fusion protein

Singapore Med J 2000 Vol 41(12):595-598

INTRODUCTION

Essential thrombocythaemia (ET) is a myeloproliferative disorder characterized by a prolonged clinical course and episodes of thrombosis or haemorrhage if the disorder is left untreated. In contrast to ET, chronic myelogenous leukaemia (CML) has a brief course because of the development of accelerated phase and blast crisis after a median interval of 3-4 years. Bone marrow karyotype is normal in most instances. Some cases are Philadelphia positive and frequently progress to typical CML⁽¹⁾. They are commonly regarded as CML variants. Whether they should be treated as Philadelphia positive CML or

a distinct disease entity remain uncertain. In this report, we describe a patient who meets the five basic criteria for ET (according to the criteria of the Polycythaemia Vera Study Group (PVSG) but have the Philadelphia chromosome in his marrow karyotype.

CASE REPORT

A 35-year-old Malay man presented in February 1996 with headache, marked thrombocytosis and absence of splenomegaly. The haemoglobin was 13.2 g/dL, white cell count $13.5 \times 10^9/L$ with 5% basophils and occasional immature granulocytic forms and platelet count $2520 \times 10^9/L$. The neutrophil alkaline phosphatase (NAP) activity was normal. Sections of an iliac crest biopsy showed hypercellular marrow with megakaryocytic hyperplasia. The megakaryocytes showed cytological atypia, abnormal sizes and were distributed in clusters (Fig. 1). Granulopoiesis appeared normal and erythropoiesis was reduced. There was no collagen fibrosis noted and the iron stores were reduced. Bone marrow karyotype demonstrated the Philadelphia chromosome. The patient was treated with hydroxyurea. This controlled his platelet count and he remained haematologically stable until July 1997, when the leucocyte count rose to $165 \times 10^9/L$ with 32% neutrophilia, 38% bands, 5% metamyelocytes, 10% myelocytes, 2% promyelocytes, 4% blasts, 5% basophils, 4% lymphocytes and 3% nucleated red cells. The platelet count was $348 \times 10^9/L$ and haemoglobin 10.3 g/dL. He also had high-grade fever and massive tender splenomegaly. The NAP score was 0 per 100 neutrophilia. Bone marrow specimen showed markedly increased granulopoiesis with full maturation, normal megakaryopoiesis (Fig. 2). A reverse transcription-polymerase chain reaction (RT-PCR) revealed the presence of major BCR-ABL fusion protein. The RT-PCR was performed according to the method described by Chomczynski and Sacchi⁽²⁾. A diagnosis of chronic phase CML was made. Subcutaneous cytosine arabinoside, interferon-alpha and hydroxyurea were administered. There was haematological remission without cytogenetic response. In August 1998, the

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Table I. Differentiating factors between Ph positive ET and Classical CML patients.

	Ph positive ET	Classical CML
1. Sex predilection	Female	Male
2. Splenomegaly	None, mild	Massive
3. Thrombotic or hemorrhagic events	Frequent	Rare
4. NAP score	Normal	Low
5. Time to blastic transformation	5 to 7 years	3 years or less
6. Blast cell morphology	Megakaryoblastic differentiation	Myeloid differentiation

patient developed blast crisis and palliative chemotherapy with low-dose cytosine arabinoside was instituted. He is still alive 3 months after diagnosis of blast phase of CML.

DISCUSSION

Patients with ET usually have a normal bone marrow karyotype. Clonal chromosomal changes have been reported in few cases but no specific chromosomal alteration has been suggested for this disorder. Recently, a small group of patients with the clinical picture of ET with Philadelphia chromosome in their karyotype has been described⁽³⁻⁵⁾. The Ph translocation, characteristic of CML, consists of a reciprocal exchange of genetic material between chromosome 9 and 22, allowing the *abl* proto-oncogene to move from chromosome 9 to the major breakpoint cluster region (*M-bcr*) in chromosome 22. Since the latter segment includes two main break regions (5' and 3'), the genetic exchange can result in the transcription of two different chimeric BCR-ABL mRNA types (b2a2 or b3a2), depending on whether exon b2 or b3 of *M-bcr* is spliced to exon a2 of the *abl* proto-oncogene⁽⁶⁾. Based on the above molecular differences, a correlation was suggested between b3a2 hybrid BCR-ABL mRNA type and higher platelet counts in CML^(7,8), but this was not confirmed by subsequent studies^(6,7). On the other hand, a few CML patients mimicked ET at presentation, due to marked predominance of the megakaryocytic proliferation^(3-5,11,12). Of note, the results of BCR-ABL mRNA in such patients indicate an association between this special form of CML and b3a2 type of mRNA^(5,12). However, the available information on this issue is still scarce.

Cases of ET that are Ph negative have a favorable long-term prognosis with a low incidence of transformation to leukaemia. In 37 cases of ET without the Philadelphia chromosome followed up by the Polycythaemia Vera Study Group (PVSG), no instance

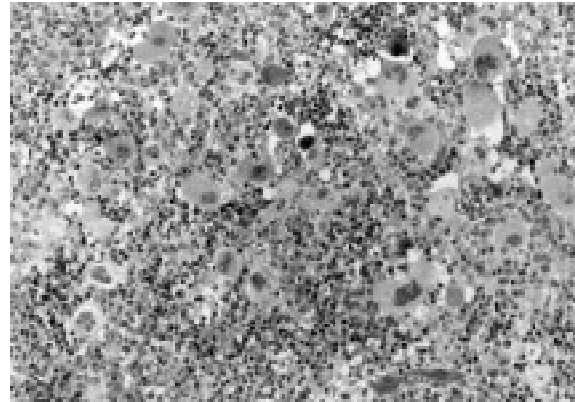


Fig. 1 Bone marrow biopsy specimen upon initial presentation showing increased and abnormal megakaryopoiesis. Megakaryocytes are pleomorphic and atypical. May-Grunwald-Giemsa, x 40.

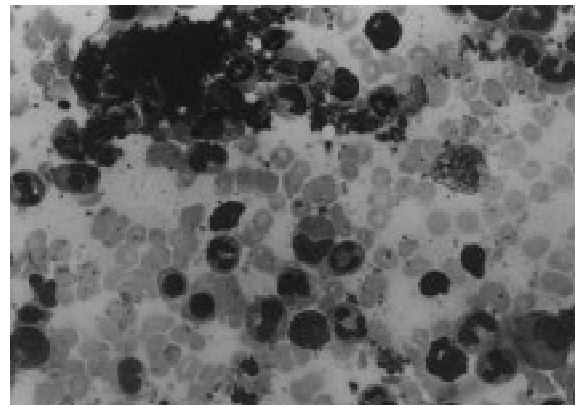


Fig. 2 A repeat bone marrow aspirate showing marked granulopoiesis with full maturation which is characteristic of chronic phase of CML. May-Grunwald-Giemsa, x 40.

of seroconversion to CML or blastic leukaemia has been seen as yet⁽¹³⁾. Other large series with long-term follow-up have confirmed this relatively benign course. The prognosis is worse when the Philadelphia chromosome is present. Most patients die within 5 to 7 years, having developed the accelerated phase of CML or blast crisis⁽¹⁴⁾. It has been proposed that the diagnosis in this latter group should be regarded as CML. However, important differences exist between Ph positive ET and typical CML (Table I).

Our patient showed the clinical picture of ET and the cytogenetic abnormality of CML. The clinical importance of finding the Philadelphia chromosome in an otherwise typical case of ET is primarily in assessing prognosis. Six women presented with the clinical picture of ET without the anaemia, marked splenomegaly, and extreme leukocytosis characteristic of CML⁽⁴⁾. All had the Philadelphia chromosome on karyotype analysis of the bone marrow. Peripheral basophilia was present in four cases, providing a clinical clue that the Philadelphia chromosome might be present. Marrow biopsy showed granulocytic hyperplasia and either small megakaryocytes or sheets of megakaryocytes with marked atypia, findings that are more typical of CML than ET. Five of these six

Table II. Characteristics at Diagnosis and clinical course of Ph Positive ET patients.

Patient	Hb (g/dL)	WBC ($\times 10^9/L$)	Basophil (%)	Platelet ($\times 10^9/L$)	Palpable Splenomegaly	NAP Score	Clinical Course	Survival from Diagnosis
1 ⁴	12.2	15.3	5	2881	Absent	120 (NR:10-70)	BT after 6 years	6 years
2 ⁴	12.3	14.8	2	1380	Present	78 (NR:13-130)	BT after 7 years	7 years
3 ⁴	13.7	8.0	9	1714	Absent	Not done	AP after 4 years	6 years
4 ⁴	14.4	32.6	6	2007	Absent	11 (NR:30-175)	BT after 5 years	6 years
5 ⁴	10.0	25.3	10	2850	Absent	66 (NR:30-175)	No change after 5 years	5 years (died due to unrelated cause)
6 ⁴	11.6	17.7	2	2590	Absent	16 (NR:15-125)	BT after 4 years	4 years
7 ¹⁵	10.3	17.3	4.5	1442	Absent	264	No change after 1 year	Still alive after 1 year
8 ¹⁶	12.4	38.6	4	3.225	Absent	Normal	Died of pneumonia and septic cholangitis 9 months after diagnosis	
This case	13.2	13.5	5	2520	Absent	80 (NR:30-100)	BT after 2.5 years	Still alive after 2.5 years

BT = blastic transformation; AP = accelerated phase of CML; NR = normal range

patients underwent clinical transition to the accelerated phase of CML or blastic leukaemia in 4-7 years. The summary of the haematological features and clinical course for Ph positive ET patients as described by different workers^(4,15,16) is shown in Table II. Our patient developed chronic phase CML within 18 months of presentation despite myelosuppressive therapy with moderate doses of hydroxyurea.

In contrast to classical Ph positive CML, the molecular characteristics of Ph positive ET is not well defined. There are scarce data on BCR-ABL transcript in CML patients in whom the disease mimics ET at presentation. Seven patients with Ph positive ET were investigated for the presence of a rearrangement within the major breakpoint cluster region (*M-bcr*) using the Southern blot technique and, in six cases, for the presence of the hybrid *bcr-abl* mRNA using the PCR⁽⁵⁾. The molecular studies showed rearrangement of *M-bcr* in all cases; there was evidence of the *b2a2* mRNA junction in one case and of *b3a2* junction in five cases. These findings are identical to what might have been expected in Ph positive CML. These features may explain the poor prognosis of Ph positive ET in comparison with cytogenetically normal cases. In agreement with the findings reported by Martiat et al, Cervantes et al⁽¹⁷⁾ found a high percentage (5 of 6 patients) of *b3a2* type of BCR-ABL transcript among CML patients with thrombocytopenic onset. From the

molecular point of view; this distinct CML subtype appears to be associated with the *b3a2* type of BCR-ABL transcript. Others have also suggested that the *abl* portion of the hybrid *bcr-abl* gene may differ in Ph positive ET and CML⁽¹⁸⁾. Because the clinical picture of Ph positive ET is fundamentally different from that of Ph positive CML, other undefined molecular changes must play an important role in determining the phenotype of the disease.

One of the diagnostic criteria of ET is the absence of the Philadelphia chromosome. On the molecular level, Ph negative ET may carry BCR-ABL transcript. The natural history of BCR-ABL positive Ph negative ET is undetermined. Blinckstein et al⁽¹⁹⁾ found that 12 (48%) of the 25 Ph negative ET patients showed positivity for BCR-ABL transcript. The BCR-ABL positive and negative patients had similar clinical and laboratory characteristics, except for a significant increased patients' age and decreased polymorphonuclear cell count in the BCR-ABL positive group. During a median follow-up of 20 and 22.5 months for the BCR-ABL negative and positive groups, respectively, there was neither blastic transformation nor unrelated death in both groups. They concluded that these cases were best regarded as a new variant of ET on the basis of their benign clinical course. On the contrary, Marasca et al⁽²⁰⁾ found BCR-ABL transcript only in one (5%) among 20 Ph negative ET patients and this patient

progressed to blastic crisis 12 years after diagnosis. They suggested that the presence of BCR-ABL transcript is diagnostic of CML, even in those cases that are Ph negative at cytogenetic level and that BCR-ABL positive Ph negative patients are CML variants. In view of lack of agreement about the diagnostic value of BCR-ABL transcript among Ph negative ET patients, the so-called BCR-ABL positive ET, need a longer follow-up period in order to better understand the natural history of this entity.

CONCLUSION

In summary, a minority (less than 10%) of patients with the clinical picture of ET may have the Philadelphia chromosome in their marrow karyotype. The karyotypic abnormality predicts the progression to accelerated phase and blast crisis just as it does in classical CML; therefore should be used to guide therapy. We suggest that Ph positive ET with M-*bcr* rearrangement should be considered an entity separate from either classic CML or Ph negative ET and that BCR-ABL status should be examined in all ET patients. Larger studies with longer follow-up are needed to better define the relation between BCR-ABL transcript and clinical outcome in patients with ET onset.

ACKNOWLEDGEMENT

We would like to thank Dr. Roswati Mohd Nor for performing the RT - PCR test.

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