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**Essential Differences in Clinical and Bone Marrow Features in *BCR/ABL*-Positive Thrombocythemia Compared to Thrombocythemia in the *BCR/ABL*- Negative Myeloproliferative Neoplasms Essential Thrombocythemia and Polycythemia Vera**

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According to strict morphological, biochemical, cyto-genetic and molecular criteria, including the Ph1+ chromosome and *BCR/ABL* fusion gene and protein, chronic myeloid leukemia (CML) is a malignant disease with an obligate transition into acute leukemia, whereas essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis form the *BCR/ABL*-negative chronic myeloproliferative neoplasms featured by a benign hyperproliferation of one, two or three hematopoietic cell lines with a normal or near-normal survival [1–6]. The morphology and size of megakaryocytes in bone marrow smears and biopsy are small and mononuclear in *BCR/ABL*-positive thrombocythemia preceding or associated with CML. Georgii et al. [3] distinguished three bone marrow histology types of *BCR/ABL*-positive CML: CML of common type with a predominance of granulopoiesis, CML with megakaryocyte increase, and CML with megakaryocytes predominance. In contrast, in ET the megakaryocytes are large, show hyperlobulated nuclei and are pathognomonic for ET (fig. 1) [4–6].

We present a 47-year-old female patient with antecedents of a carcinoma of the ovarium from 5 years earlier, who was referred to the hematology department of the Antwerp University Hospital because of a massive thrombocytosis ( $>5,000 \times 10^9/l$ ) in the presence of normal Hb (16 g/dl) and borderline high leukocyte count ( $10.6 \times 10^6/l$ ) with a normal formula. The JAK2 mutation proved negative, while *BCR-ABL* was positive. Bone marrow examination showed a myeloproliferative disease with dense clusters of small megakaryocytes and monolobulated nuclei consistent with the diagnosis of *BCR/ABL*-positive thrombocythemia with a predominance of small and monolobulated megakaryocytes (fig. 2) similar to that described for CML with megakaryocyte predominance [3]. Despite repeated thrombocyte apheresis, the thrombocyte count increased again under hydroxyurea treatment while the leukopenia got worse, and the patient developed a toxic rash (fig. 3). She was then started on anagrelide (Xagrid<sup>®</sup>) which resulted in slowly decreasing thrombocyte counts and recuperation of the leukocytes, and a diagnosis of CML was made. Due to the development of thrombocytopenia, anagrelide was stopped after 14 days. Imatinib was started 5 weeks later when thrombocyte counts returned to  $4,244 \times 10^9/l$ . Under this treatment, the thrombocyte count only decreased slowly over a period of 7 months (fig. 3). After these 7 months there was an evolution from chronic-phase CML with high thrombocytosis to an acceleration phase/blast crisis with increased leukocyte counts ( $141 \times 10^6/l$ ), appearance of peripheral blasts, and thrombocytopenia ( $117 \times 10^9/l$ ). Imatinib was switched to a second-generation tyrosine kinase inhibitor (dasatinib). The present study documents the essential differences in the clinical presentation of blood and bone marrow features and poor prognosis of Ph+positive thrombocythemia as compared to the clinical presentations and a favorable prognosis of Ph-negative thrombocythemia in patients with ET or PV.

The blood and bone marrow presentation of BCR/ABL-positive thrombocythemia without features of CML (fig. 3) is similar to that described for CML with megakaryocyte predominance [3]. The initial peripheral blood findings of the presented Ph<sup>+</sup> thrombocythemia case showed no features of CML. The clinical outcome of BCR/ABL-positive thrombocythemia was poor as compared to near-normal to normal survival in thrombocythemia in BCR/ABL-negative myeloproliferative neoplasms [2]. The platelets in BCR/ABL-positive thrombocythemia patients are small, indolent and non-reactive, and usually remain asymptomatic in terms of platelet-mediated thrombotic manifestations [7]. Evidence that the small platelets in BCR/ABL-positive thrombocythemia are indolent and non-reactive, and that large platelet-hypersensitive activated platelets in thrombocythemia of various myeloproliferative disorders are activated and hypersensitive stems from our platelet kinetic studies in symptomatic ET and PV patients as compared to asymptomatic patients with reactive thrombocytosis (RT) or thrombocytosis associated with Ph-positive thrombocythemia associated with CML [8, 9]. Platelet kinetic studies using <sup>51</sup>Cr-sodium chromate-labeled autologous platelets were performed in 3 groups of patients: group A, 4 healthy controls and 6 asymptomatic thrombocytosis patients (3 Ph<sup>1+</sup> thrombocytosis, 3 RT); group B, 6 patients with asymptomatic ET or PV, and group C, 8 patients with ET or PV complicated by erythromelalgia (table 1). The platelet survival times and disappearance curves in 8 thrombocythemia patients (ET or PV) with erythromelalgia (E+, group C; table 1) are significantly shortened as compared to normal platelet survival times in controls, Ph<sup>1+</sup> thrombocytosis and RT ( $p < 0.01$ , group A; table 1). The shortened platelet survival times demonstrate that ET or PV complicated by erythromelalgia and thrombocythemia (group C; table 1) is indeed featured by platelet consumption caused by arteriolar platelet-mediated thrombosis, as could be seen in skin biopsies from erythromelalgic areas of the same patient [8–10]. The shortened platelet survival times in 4 symptomatic E+ patients could be corrected to normal by 500 mg/day of aspirin, which was associated with the disappearance of erythromelalgia clinically as well as in skin biopsy [8, 9]. The erythromelalgic thrombotic complications, including migraine-like cerebral or ocular ischemic attacks, in ET and PV patients are caused by platelet-mediated inflammation and thrombosis in the end-arterial circulation, which are reversible by aspirin and platelet reduction to normal ( $<350 \times 10^9/l$ ), but not by Coumadin [8–10]. Despite the high platelet count, the presented case of BCR/ABL-positive thrombocythemia showed neither erythromelalgic microvascular ischemic events nor bleeding complications. We conclude that small platelets produced by small mononucleated megakaryocytes in BCR/ABL-positive thrombocythemia (fig. 2) are indolent and non-reactive, and that, in contrast, large platelets produced by large pleomorphic hyperlobulated megakaryocytes (fig. 1) in patients with ET and PV are activated and hyper-reactive [8]. The majority of symptomatic PV and ET patients carry the JAK2 V617F or MPL 515 mutation, in which the megakaryocytes are larger than normal and produce constitutively activated (hypersensitive) platelets as the underlying cause of a high risk of platelet-mediated inflammation and thrombosis in the end-arterial circulation [10].

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**Table 1.** Platelet kinetic studies in the three groups

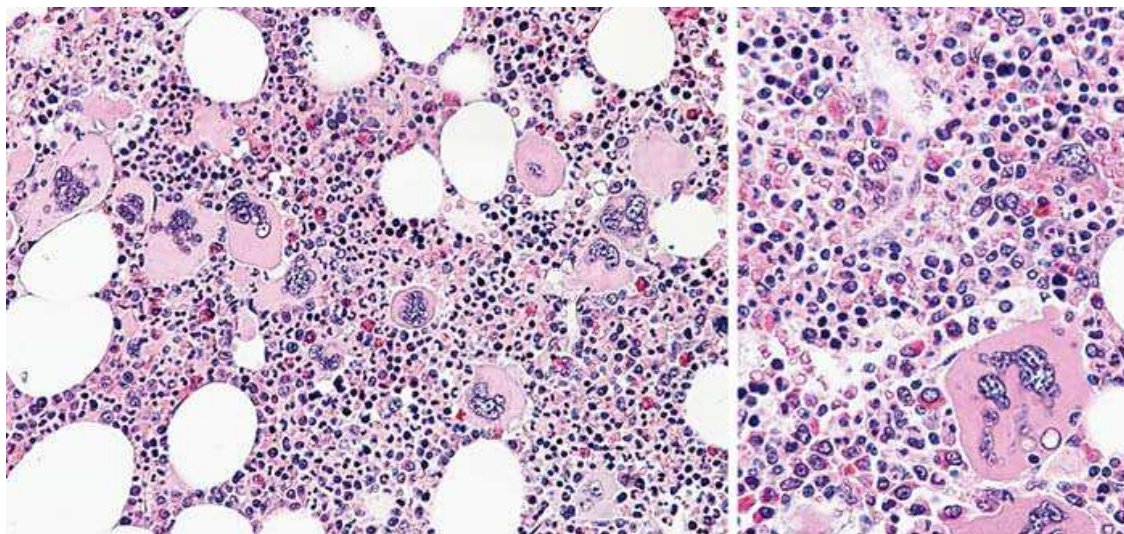
Platelet kinetics:	n	Platelet range, $\times 10^9/l$	Half-life, days	Mean life span, days	Maximal life span, days	Platelet turnover
<i>Group A</i>						
<i>Controls</i>						
Ph1+ CML/RT	6	722 – 2244	4.1 ± 0.4	7.8 ± 1.2	8.9 ± 0.9	203 ± 107

<i>Group B</i>						
E-	6	506 – 1722	3.3 ± 0.3	5.4 ± 0.7	8.0 ± 0.9	335 ± 119
<i>Group C</i>						
E+	8	489 – 1130	2.4 ± 0.4	2.4 ± 0.4	6.6 ± 0.8	572 ± 374

E- = Asymptomatic ET and PV; E+ = symptomatic ET and PV complicated by erythromelalgia.  
Compare results with figure 4 of Michiels et al. [8].

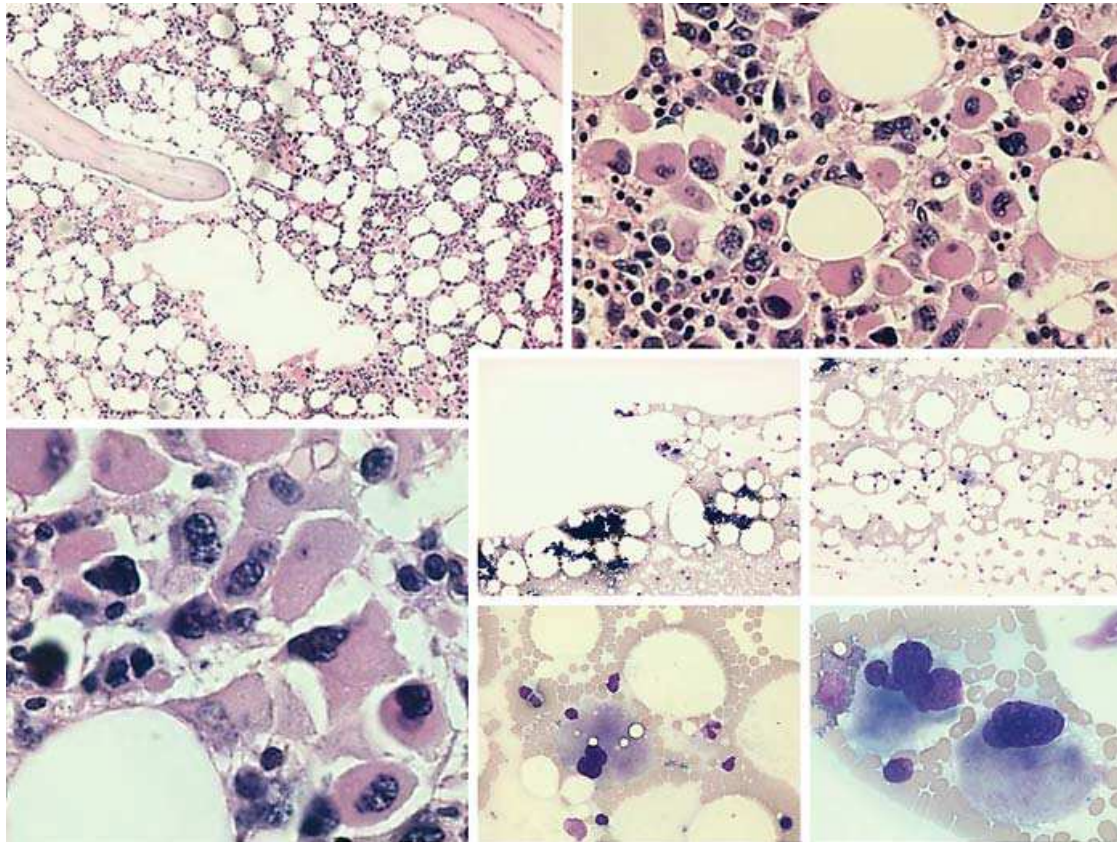
**Fig. 1.**

JAK2V617F-positive ET in a 65-year-old man with RBC  $5.37 \times 10^{12}/l$ , Hb 15.8 g/dl, MCV 89, leukocytes  $12 \times 10^9/l$ , platelets  $517 \times 10^9/l$ , lactate dehydrogenase 600 IU/l (JAK2V617F mutation allele burden: 20% on peripheral blood). Hypercellular bone marrow, with mild erythroid hyperplasia, moderate myeloid hyperplasia and marked hyperplasia of large hyperlobulated megakaryocytes. No reticulin fibrosis. EE  $\times 20$  (a),  $\times 40$  (b).



**Fig. 2.** Dense clusters of small mononucleated/ binucleated megakaryocytes in a normocellular bone marrow biopsy (a–c) and bone marrow smear (d) in a female with BCR/ABL-positive thrombocythemia (original observations, 2012, by Dr. Gadisseur, Department of Hematology University Hospital, Antwerp).





**Fig. 3.** Effect of sequential treatment with hydroxyurea, anagrelide and imatinib on platelet number in a female with BCR/ABLpositive thrombocythemia (original observations by Dr. Gadisseur, Department of Hematology, University Hospital, Antwerp)

