BCR/ABL-1-Positive Myeloproliferative Neoplasm Presenting with Isolated Remarkable Thrombocytosis with Atypical Clinicopathological Features: Discussion from Management Point of View

Dina Sameh Soliman1,2,4*, Mohammad A Abdulla1, Ahmad Al Sabbagh1,4, Susanna Akiki1, Feryal Ibrahim1, Afraa Mustafa1 and Mohamed Yassin2,4

1Department of Laboratory Medicine and Pathology, National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar
2Department of Hematology and Medical Oncology, National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar
3Department of Clinical Pathology, National Cancer Institute, Cairo University, Cairo, Egypt
4Department of Clinical Pathology, Weill Cornell Medical College, Qatar

Abstract

Chronic Myeloid Leukaemia can rarely present in essential thrombocythaemia-like picture. Apart from the genetic defining marker (BCR-ABL fusion), these cases lack almost all typical features of CML.

Here, we highlight the response of these patients to different therapeutic approaches and to emphasize that although the proliferation is solely limited to the platelets, this group of patients did not show any response except after initiation of Tyrosine kinase inhibitors which highpoints the essentiality of excluding CML by performing BCR/ABL-1 in all cases with features of myeloproliferative neoplasms in order to avoid delayed management and adverse outcome. Apparently, many hematologists have not been persuaded to always test for BCR/ABL-1 when there are no features suggesting CML.

Unlike what was previously reported, upon literature review, we found no significant difference in disease prognosis in this group of patients compared to classic CML, provided TKI was started early in disease course.

Keywords: Chronic myeloid leukaemia; Isolated thrombocytosis; Ph positive thrombocythaemia; Tyrosine kinase inhibitor

Abbreviations: MPN: Myeloproliferative Neoplasms; CML: Chronic Myeloid leukaemia; PB: Peripheral Blood; BM: Bone Marrow; CBC: Complete Blood Count; WBCs: White Blood Cells; Hb: Hemoglobin; PLTs: Platelets; ECG: Electrocardiogram; ET: Essential Thrombocythaemia; M/E: Myeloid/Erythroid; TKI: Tyrosine Kinase Inhibitor; CAD: Coronary Artery Disease; OR: Optimal Response; Hyper: Hypercellular BM; N: Normal; N/P: Not Provided; VC: Vascular Complications; US: Ultrasound; E: Physical Exam; MI: Myocardial Infarction; PE: Pulmonary Embolism; Allo SCT: Allogenic Stem Cell Transplant.

Introduction

Although myeloproliferative neoplasms (MPN) are an overlapping group of myeloid neoplasms that may share a common pathogenetic and phenotypic features; yet accurate classification and particularly exclusion of chronic myeloid leukemia (CML) is essential from both therapeutic and prognostic point of views. The WHO classification of hematopoietic neoplasms relies on genetic features to distinguish between Philadelphia positive (CML) and Philadelphia negative MPN. CML is a stereotypic disease with almost always straight forward diagnosis in vast majority of patients. In a few cases, atypical clinical or morphologic manifestations may obscure or delay the diagnosis. Typical clinical features of classic CML include splenomegaly, which is almost always present and may be massive, and pallor from associated anemia. The peripheral blood smear (PB) smear in CML is usually diagnostic as it consistently shows leucocytosis [ranges, 12,000-1,000,000/µL (12-1,000 × 10³/L)] owing to neutrophils in different stages of maturation [1,2].

Bone marrow (BM) sections are usually hypercellular owing to granulocytic proliferation with markedly increased myeloid/erythroid (M/E) ratio, erythroid islands are usually reduced in number and in size. Megakaryocytes commonly exhibit distinguishing morphologic features as they are smaller than normal with hypolobated nuclei (“dwarf megakaryocytes”) [3,4].

Average platelet count in CML at diagnosis ranges from normal to less than 1,000 × 10³/µL [1]. Although thrombocytosis is a relatively common presenting feature, it rarely exceeds >1000 × 10³/L.

CML can rarely present in ET-like picture with no initial features to raise the specter of CML, specifically, no splenomegaly, no leukocytosis, and no immature myeloid cells on peripheral smear.

Here we describe a rare case of CML case with a classical Philadelphia translocation and common BCR-ABL1 fusion transcript but an unusual clinical and pathological presentation which illustrates the underlying genetic heterogeneity of MPNs. The aim of this report is to emphasize on the importance of excluding CML by testing for BCR/ABL-1 in all cases with features of myeloproliferative neoplasms in order to avoid delayed management and adverse outcome. Early initiation of a specific inhibitor of the BCR/ABL tyrosine kinase in these patients probably could have more readily controlled blood counts, prevented thrombotic complications, and spared drug toxicities.

Case Presentation

A 46 years old gentleman, heavy smoker, known case of type II Diabetes Mellitus on Insulin, presented with complaint of intermittent
Bone marrow (BM) aspirate smear showed trilineage hematopoiesis (Figure 2A) with moderate erythroid hyperplasia with increased early forms and some megaloblastoid changes (Figure 2B).

Megakaryocytes are markedly increased; showing anisocytosis; mostly represented by small hypolobated forms (micromegakaryocytes) with some atypical megakaryocytes showing abnormal nucleocytoplasmic ratio and abnormal nuclear lobulation/chromatism (Figure 2C).

Granulopoiesis was mildly suppressed with decreased myeloid/erythroid (M/E) ratio at 0.9:1 with orderly maturation, increased basophils (3%) and increased blasts (5%) (Figure 2D).

BM biopsy was normocellular for age (~ 50-60%) with prominent erythropoiesis, relatively decreased granulopoiesis and marked megakaryocytic hyperplasia, mostly small hypolobated forms with some small clusters and no prominent atypia noted (Figure 3).

CD34 immunostain highlighted increased vasculature with intrasinusoidal hematopoiesis and increased CD34-positive blasts (roughly estimated by 7-10% with few adjacent cells) (Figure 3G). No significant increase in reticulin fibers.

There is an atypical lymphoid aggregate composed of mixed T and B-cells.

Based on peripheral blood counts and BM findings, ET was preferentially considered over other MPNs. However, JAK2 V617F mutation, JAK exon 12-15 mutation, and CALR exon 9 mutations, were reported as negative. Surprisingly, karyotype analysis showed the Philadelphia chromosome without any additional cytogenetic abnormalities 46,XY,t(9;22)(q34;q11.2) [13]/46,XY [7].

Subsequently, BCR/ABL1 fluorescence in situ hybridization (FISH) analysis confirmed a BCR-ABL1 gene fusion and Reverse transcriptase- polymerase chain reaction (RT-PCR) analysis for BCR/ABL1 rearrangement revealed a common e13a2 breakpoint. A diagnosis

Figure 1: Peripheral blood smear (P.S) shows extreme thrombocytosis. No leukocytosis (500 ×). (A) Basophilia (black arrow); (B) No shift to left (1000 ×).

Figure 2: (A) BM aspirate smear (500 ×) shows trilineage hematopoiesis; (B) Erythroid hyperplasia; (C) Marked megakaryocytic hyperplasia with many dwarf forms (micromegakaryocytes) and (D) Increased blasts.
of CML, chronic phase associated with extreme thrombocytosis was reported. In view of marked thrombocytosis with increased CD34 immunostain positivity, these findings were considered as presumptive evidence of impending acceleration.

During the initial diagnostic period, the patient was started on Hydroxyura for more than one month; however thrombocytosis was refractory with no significant response in counts (Figure 4A).

Following the diagnosis of CML, Tyrosine kinas inhibitor (TKI) therapy (Dasatinib 70 mg twice daily) was started and the platelets dropped dramatically (Figure 4B). Follow-up at 3 months interval showed complete haematological response with normalization of platelets counts and the patient achieved complete cytogenetic response at 6 months. Dasatinib dose was reduced to 70 mg daily and BCR-ABL1 transcript levels were monitored throughout treatment following the ELN expert recommendations [5]. The patient has sustained a major molecular response for more than 2 years after diagnosis.

Discussion

Since 2001 WHO diagnostic criteria for ET mandate that BCR-ABL1 should be negative to exclude CML diagnosis (3). But lack of specific guidance for rare Ph+ cases and atypical presentations mean opportunities to make an accurate diagnosis can be missed affecting treatment.

Unusual presentation in this case

The case presented with quite unusual pathologic and clinical findings as CML diagnosis was obscured and totally unexpected except after the cytogenetics result. Clinically, the patient was asymptomatic with no splenomegaly that is reported in the great majority of CML patients. Pathologically, absence of neutrophilic leukocytosis, shift to left together with absence of bone marrow hypercellularity. An additional unusual finding in this case is the presence of unexplained erythroid hyperplasia with decreased M/E ratio, which is not reported in previous similar cases.

The overall findings were more convincing of ET. The dwarf megakaryocytes with almost absent large hyperlobulated forms together with marked basophilia were the only morphologic keys to CML.

Figure 3: (A) Bone marrow biopsy (H&E) 40 ×; (B) BM shows normal cellularity (~50-60%); (C) With prominent erythropoiesis; (D) Glycophorin immunostain highlighted erythroid hyperplasia; (E) MPO immunostain shows relatively decreased granulopoiesis; (F) vWF immunostain highlights marked megakaryocytic hyperplasia, mostly small hypolobated forms with some small clusters; (G) CD34 immunostain highlighted increased vasculature with intrasinusoidal hematopoiesis and increased CD34-positive blasts (~7-10%) with tiny clusters (upper right corner insert.)
CML was a very remote possibility that was not suspected although the case was examined by three experienced hematopathologists and would definitely be missed if screening for Philadelphia was not performed. In our lab we follow WHO recommendations to perform BCR/ABL-1 routinely in any case with myeloproliferation. In view of marked thrombocytosis and increased CD34 positivity (appreciated in biopsy), accelerated phase of CML was suggested.

Typical CML with extreme thrombocytosis

Thrombocytosis above 2,000,000/µL is extremely rare in CML unless the patient is splenectomized. Rare case reports with classic CML presented with extreme thrombocytosis, [6-9] and those cases are often associated with the e19a2 BCR-ABL1 transcript type [7]. These exceptional cases have otherwise typical clinical and pathological features of CML and although platelets count exceeds 1000 × 10^9/L, hemorrhagic or thromboembolic complications is far less common than ET patients who are associated with similar degree of thrombocytosis.

BCR/ABL-1 testing delayed or ignored

Upon review of literature we found that many of the patients who had this presentation had suffered from delayed management as they were misdiagnosed as ET and managed accordingly which had led to disease progression, vascular complications and transformation into accelerated or blast phases [9-12]. Rice and Popat [10] had reported two women presented with findings typical of ET with severe thromboembolic complications and absolutely no initial features raising the possibility of CML. Philadelphia chromosome testing was delayed or ignored in all aspects of CML. No concurrent JAK2 mutation in old reports but also in some recent articles after release of World Health Organization classification of hematopoietic tumors release in 2001. The authors had described cases with isolated thrombocytosis in absence of leukocytosis as a distinct disease entity that has female predilection with no splenomegaly and poor prognosis. Of note, these patients were not tested for Ph/BCR-ABL-1 at their initial presentation and managed as ET and were all refractory to therapy or show high tendency of transformation, progression to myelofibrosis and blast crisis after few to several years [11,13-17].

Possibility of concurrent mutations and investigations performed

The possibility that some atypical manifestations may be due to specific genetic lesions present concurrently with the BCR-ABL1 fusion gene should also be considered. A detailed genetic analysis to look for clonal drivers may be warranted in these cases. Recently, a number of reports have described the coexistence of the JAK2V617F mutation in patients with CML, BCR-ABL1+. In some cases, the mutated JAK2 was detected after treatment of CML with TKI [18,19] but retrospective analyses of the initial specimen in those cases demonstrated that the mutated JAK2 was present at the time of the initial diagnosis of CML. In our case JAK-2 was performed initially at diagnosis and retested after treatment of CML and found to be negative. In addition, Next generation sequence (NGS) performed to look for other clonal markers associated with MPN but no additional variants identified [20].

Literature review of similar cases

Less than 20 cases had been reported in the English literature for BCR/ABL1 positive CML presenting in ET like picture. Table 1 includes 13 cases who presented with isolated thrombocytosis and at the same time lacking all other classic features of CML (no leukocytosis and no shift to left). Unlike what was previously reported, we found males and females are equally affected (M/F: 1:1). Except for one case, no anemia was reported within this group. These cases usually present with extreme thrombocytosis, above one million in 9 out of 13 cases.

Interestingly, almost all reported cases in this context had classic BCR/ABL with p210 b3/a2 break point. No concurrent JAK-2 mutation was reported in any of these cases.
Vascular complications/symptoms had been frequently reported within this group particularly as a complication when TKI therapy was delayed.

Conclusion

Rare cases of CML can present in a manner absolutely typical for ET and this may briefly challenge categorization. These cases usually present with extreme thrombocytosis, hence masking CML picture.

Screening for Ph or BCR/ABL-1 is crucial in any atypical myeloproliferation regardless of the degree of neutrophilia or thrombocytosis. Although it is required by WHO to exclude BCR/ABL-1 before making a diagnosis of ET, many hematologists have not been persuaded to always check cytogenetic tests when there are no other features suggesting CML. Upon literature review of similar cases, it was found that whenever BCR/ABL-1 testing is missed or ignored the cases are mislabeled as ET, mismanagement led to poor response and CML acceleration. Unlike what was previously reported, we found no significant difference in disease prognosis and response to therapy in this group of patients compared to classic CML, provided TKI was started early in disease course with no delay.

Declarations

Statement of ethics

The manuscript has been approved by Medical research centre, Hamad Medical Corporation.

Consent for publication

Not applicable. No patient personal identifiers/images were included in our report. A waiver of consent form had been accepted by my institution.

Conflict of interest

“The authors have no conflicts of interest to declare.”

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Author Contributions

DS: Performed hematopathologic diagnosis, major contributor in writing the manuscript including literature review. AS: Agreed with hematopathologic diagnosis and reviewed the manuscript. MA: Performed clinical diagnosis, patient’s monitoring and contributed to the literature review. SA: Performed molecular genetics testing. FI: Agreed with hematopathologic diagnosis and contributed in writing the manuscript. AM: Performed clinical diagnosis, patient management, monitoring and contributed by writing the Clinical section. MY: Performed clinical diagnosis, patient monitoring and reviewed the manuscript. All authors read and approved the final manuscript.

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