

Case Report

Cases of chronic myeloid leukemia presenting with isolated thrombocytosis: case reports and review of the literature

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Abstract: Chronic myeloid leukemia (CML) is generally diagnosed through findings such as marked leukocytosis at full blood count or splenomegaly at physical examination, while isolated thrombocytosis is not an expected condition. This paper examines hematological values, clinical findings, cytogenetic and molecular genetic data from 3 cases of CML presenting with isolated thrombocytosis. In addition, potentially significant differences between cases of CML presenting with isolated thrombocytosis and typical CML were investigated. No splenomegaly was present in these patients, peripheral leukocyte numbers and formulae were normal, LDH and uric acid levels were lower than in classic CML, while hemoglobin levels were higher. BCR/ABL levels were similar. In terms of CML risk scoring, since the EUTOS scoring system is based solely on peripheral blood basophil percentage and splenic dimension it was not considered appropriate for these patients.

Keywords: Chronic myeloid leukemia, isolated thrombocytosis, leukocytosis, case report

Introduction

Chronic myeloid leukemia (CML) is a hematological malignancy deriving from reciprocal t(9, 22) in primitive hematopoietic stem cells. Myeloid cells predominate at all series of maturation, and there may be an increase in erythroid and thrombocyte numbers at peripheral blood count; leukocytosis is the main finding, however. An increase in myeloid precursors, eosinophils and basophils are present at peripheral smear. Marked splenomegaly, and an increase in myeloid series at bone marrow examination are typical [1, 2]. More than 30% of megakaryocytes in the chronic stage of CML are smaller than normal, with hypolobulated nuclei. Nonetheless, there are instances of Philadelphia chromosome positive (Ph+) CML with isolated thrombocytosis (CML-T) or slightly elevated granulocyte numbers. This special CML group is described as Ph chromosome + essential thrombocytemia, and the condition is more frequent in women. It is characterized by absence of splenomegaly, and smaller than normal megakaryocytes with hypolobulated nuclei in bone marrow [3, 4].

This paper presents hematological parameters, clinical findings and cytogenetic and molecular genetic data from three cases of CML presenting with isolated thrombocytosis. It also seeks to identify potentially significant differences between patients with CML presenting with isolated thrombocytosis and patients with typical CML.

Case reports

Case 1

A 77-year old woman had been followed for approximately 20 years in another hospital due to hypertension, diabetes mellitus and cerebral ischemic attack. She was referred to our hematology clinic when thrombocytosis was determined during routine checks. Her physical examination in our clinic revealed no specific finding, and she did not have splenomegaly. Hematological and some biochemical parameters at the time of diagnosis among Case 1 are presented in **Table 1**. Full blood count revealed thrombocytes: $711 \times 10^9/L$, hemoglobin: 13.8 g/dL, white cell count: $5.2 \times 10^9/L$. In peripheral

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Table 1. Full blood counts and some biochemical parameters among the cases at the time of diagnosis

	Case 1	Case 2	Case 3	Normal Range
Full blood count				
Thrombocytes (number/L)	711×10 ⁹	1.853×10 ⁹	1.277×10 ⁹	150-450×10 ⁹
Hemoglobin (g/dL)	13.8	13	15.7	12-17
White cell count	5.2×10 ⁹	9.2×10 ⁹	11.1×10 ⁹	5-10×10 ⁹
Peripheral blood smear leukocyte formula				
Neutrophil %	60.9	77.9	73.1	40-60
Lymphocytes %	31.8	17.3	21.4	25-35
Eosinophils %	1.5	2.4	2.6	1-5
Basophils %	0.3	1.2	1.3	0-1
Monocytes %	5.5	0.4	1.6	5-10
Selected Biochemical Parameters				
Lactate dehydrogenase (U/L)	223	184.4	419	<248
Uric acid (mg/dL)	4.4	3.7	4.9	2.6-7.2

blood smear leukocyte formula: neutrophil 60.9%, lymphocytes 31.8%, eosinophils 1.5%, basophils 0.3%, and monocytes 5.5%. In terms of biochemical parameters, LDH was 223 U/L (normal range: <248) and uric acid 4.4 mg/dl (normal range: 2.6-7.2). JAK2 V617F mutation was negative, BCR/ABL (P210)-major % IS 60.44 (+) positivity was determined. Bone marrow biopsy revealed normocellularity. Myeloid/erythroid series ratio was normal, and an increased number of small megakaryocytes with hypolobulated nuclei were observed. Philadelphia chromosome positivity was determined at conventional bone marrow aspiration chromosome analysis. Risk classification was performed at the time of diagnosis which revealed high Sokal, moderate Hasford and low Eutos risk scores. A diagnose of Philadelphia chromosome positive CML was established, and imatinib (400 mg/day) therapy was initiated. Complete hematological response was achieved on the 3rd month of therapy. BCR/ABL (P210)-major level % IS from peripheral blood on the 3rd month was measured as 0.5658 (+) positive. The patient was considered as optimal responsive; and the imatinib therapy was continued.

Case 2

A 70-year-old woman had been under follow-up because of cerebral ischemic attack and coronary artery disease. At a routine check-up involving full blood count thrombocytosis was determined and the patient referred to our hematology clinic. Physical examination revealed

no specific finding. And, she had no splenomegaly. Hematological and some biochemical parameters at the time of diagnosis among Case 2 are presented in **Table 1**. Full blood count analysis revealed thrombocytes: 1.853 ×10⁹/L, hemoglobin: 13 g/dl, white cell count: 9.2×10⁹/L. Peripheral blood smear revealed that leukocyte formula: neutrophil 77.9%, lymphocytes 17.3%, eosinophils 2.4%, basophils 1.2% and monocytes 0.4%. Levels of serum LDH was 184.4 U/L and uric acid of 3.7 mg/dl. JAK2 V617F mutation negative and BCR/ABL (P210)-major % IS: 262.6 (+) positivity was determined. Bone marrow biopsy revealed increased number of small megakaryocytes with hypolobulated nuclei. Myeloid/erythroid series ratio was within normal limits. Philadelphia chromosome positivity was determined at conventional bone marrow aspiration chromosome analysis. At the time of diagnosis, risk classification was performed which revealed high Sokal, high Hasford and low Eutos risk scores. Imatinib therapy (400 mg/day) was initiated and a complete hematological response was achieved on the 3rd month of therapy. BCR/ABL (P210)-major % IS was negative. Treatment response parameters were compatible with optimal response in controls at the 3rd, 6th and 12th months of therapy which is still continuing.

Case 3

A 30-year-old male patient presented to our hematology clinic when thrombocytosis was determined at full blood analysis, performed at

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another center due to findings of flu-like infection. Physical examination revealed no specific findings, and he had no splenomegaly. Hematological and some biochemical parameters at the time of diagnosis among Case 3 are presented in **Table 1**. Full blood count values were hemoglobin: 15.7 g/dl, thrombocytes: $1277 \times 10^9/L$, leukocytes: $11.1 \times 10^9/L$. Peripheral blood smear revealed neutrophil 73.1%, lymphocytes 21.4%, eosinophils 2.6%, basophils 1.3% and monocytes 1.6%. The levels of serum LDH and uric acid was 419 U/L and 4.9 mg/dl, respectively. JAK2V617F mutation was negative and BCR/ABL (P210) major % IS: 42.1 (+) positive. Bone marrow biopsy revealed hypercellularity with an increased number of megakaryocytes, micromegakaryocytic appearance with hypolobulated nuclei. Myeloid/erythroid series ratio was within normal range. Philadelphia chromosome positivity was determined at conventional bone marrow aspiration chromosome analysis. At time of diagnosis, risk analysis revealed high Sokal, moderate Hasford and low Eutos risk scores. Imatinib therapy (400 mg/day) was initiated and complete hematological response was obtained at 3rd month of the treatment, while BCR/ABL (P210)-major % IS: 2.4 (+) positivity and cytogenetic findings were compatible with major cytogenetic response. The patient was considered non-responsive to imatinib therapy, because complete cytogenetic response was not achieved at the end of the 1st year of treatment. Mutation analysis was performed, and no BCR/ABL gene mutation was determined. The patient was switched to nilotinib (2×400 mg/day) therapy. But, no response was achieved. Then, dasatinib therapy was prescribed, and donor screening was performed.

Discussion

Although thrombocytosis is an expected finding in CML, cases of CML presenting with isolated thrombocytosis are very rare. And, CML patients presenting with isolated thrombocytosis have different clinical and laboratory characteristics. Splenomegaly or hepatomegaly, the common findings of CML (at 48-80% and 10-20%, respectively), are typically absent in these patients. Consistently, our cases, consisting of two women and one man, did not have splenomegaly or hepatomegaly. Isolated thrombocytosis was present in our cases, but there were

no leukocytosis, low hemoglobin, eosinophilia or basophilia, which are among to the common laboratory findings in classic CML cases. In addition, while LDH and uric acid elevations are expected findings in classic CML, our patients' LDH and uric acid levels were within normal limits. Hypercellularity, another finding of typical CML, was determined in one of the patient not in the other two, and myeloid/erythroid ratio elevation seen in typical CML was not present in any of our cases.

Michiels *et al.* described the biological and histopathological characteristics of Philadelphia chromosome (+) thrombocythemia cases that without typical peripheral blood characteristics of CML [3]. In their study, they reported three new cases (all women) and analyzed reported cases of Philadelphia chromosome (+) thrombocythemia. And, they indicated that majority of the analyzed cases from literature consisted of female gender which had no splenomegaly. They documented that the major difference between essential thrombocytosis and the thrombocytic form of CML is the presence of small megakaryocytes with hypolobulated nuclei in thrombocytic form of CML, resembling of typical CML [3]. Girodon *et al.* described four cases with Philadelphia chromosome (+) thrombocythemia without the typical characteristics of CML [4]. Three of those patients were male, with no splenomegaly, referred to hospital due to thrombocytosis. They determined only thrombocytosis, with no findings suggestive of CML at full blood count. However, the presence of bone marrow hypercellularity and absence of giant megakaryocytes was interpreted in favor of CML rather than essential thrombocytosis. Cytogenetic and molecular genetic analyses were also performed, and Philadelphia chromosome (+) BCR/ABL fusion gene was identified. In contrast to Michiels *et al.*, male gender predominated in the latest small patient group [4]. In another study, a woman with isolated thrombocytosis diagnoses with follicular lymphoma was reported as JAK2 V617F mutation negative and Philadelphia chromosome positive [5]. Kim *et al.* performed a study intended to differentiate a single case with leukocyte number elevation from essential thrombocytosis due to thrombocytosis and other myeloproliferative diseases, and described that patient as a case of CML with elevated thrombocyte numbers [6]. By reporting a

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single case with leukocyte number elevation from essential thrombocytosis due to thrombocytosis and other myeloproliferative diseases, Kim *et al.* performed a study intended to differentiate a single case with leukocyte number elevation from essential thrombocytosis due to thrombocytosis and other myeloproliferative diseases, and described that patient as a case of CML with elevated thrombocyte numbers [6]. Emilia *et al.* examined 112 patients with essential thrombocytosis. They identified BCR/ABL fusion gene in only one patient, in whom acute leukemia had developed 1 year later [7].

In contrast to the classic CML patients, the majority of the patients in our CML group presenting with isolated thrombocytosis were female, and our patients were similar in terms of gender distribution to those of Michiels *et al.* [3]. Similar to other case reports, no splenomegaly, leukocytosis, basophilia, eosinophilia, anemia, LDH elevation or uric acid elevation were observed in our patients.

The Sokal, Hasford and Eutos risk classification systems are used for risk scoring in cases of CML, and there are no recommendations for which scoring system should be preferred. In cases of CML presenting with isolated thrombocytosis, since basophil levels are normal and no splenomegaly is present, as in our patients, all patients can be classified as low-risk under the Eutos scoring system despite registering as moderate or high risk under the other risk scoring systems. Indeed, one patient in our small series was resistant to imatinib and nilotinib despite being in the Eutos low risk group.

Conclusion

CML should clearly be considered in all cases of isolated thrombocytosis, even in the absence of leukocytosis. And Philadelphia chromosome or BCR/ABL analysis must be performed. And, from the data presented it could be suggested that the use of the Hasford and/or Sokal risk scoring systems, rather than Eutos, for initial risk scoring is more appropriate for risk screening when diagnose of Philadelphia (+) CML-T is made.

Disclosure of conflict of interest

None.

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