

Megakaryocytic Blast Crisis as First Presentation of Chronic Myeloid Leukemia

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We describe an extremely rare case of megakaryocytic blast crisis as first presentation of chronic myeloid leukemia. The patient had a very high platelet count and developed an ischemic stroke with seizures. She was treated with hydroxyurea, platelet apheresis, ARA-C, and idarubicin in order to obtain a prompt reduction of thrombocytosis and then with imatinib 600 mg/die PO. The therapy induced a complete hematological remission with a resolution of neurological signs within 4 weeks. *Am. J. Hematol.* 82:231–233, 2007.

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INTRODUCTION

Blast crisis as first presentation of chronic myeloid leukemia (CML) accounts for 5–10% of all cases [1]. The presence of translocation 9-22 (q34; q11), detected by cytogenetic study or reverse transcription-polymerase chain reaction (RT-PCR) is the hallmark to distinguish between CML blast crisis and acute myeloid leukemia. CML blast phase may be diagnosed when at least one of the followings is found: blasts $\geq 20\%$ of peripheral blood white cells or nucleated bone marrow cells; extramedullar blast proliferation; large foci or clusters of blasts in the bone marrow. As far as we know, a megakaryocytic blast phase in CML occurs very rarely, with only few cases reported [1,2]: at the diagnosis almost all these patients had thrombocytosis, but no one presented thrombotic complication. Therefore we thought it was useful to describe an unusual presentation of CML: a woman with a megakaryocytic blast phase associated with marked thrombocytosis and seizures caused by ischemic stroke.

CASE REPORT

A 60-year-old woman was admitted to our department for thrombocytosis and syncopal episode. At physical examination no abnormalities were detected. An abdominal echography showed a mild splenomegaly (diameter 12 cm). Laboratory tests revealed the presence of anemia (hemoglobin 9.4 g/dl), marked thrombocytosis ($4,100 \times 10^9/l$), and mild leukocytosis

($9.9 \times 10^6 l^{-1}$) with 57% neutrophils, 30% lymphocytes, 2% monocytes, 2% eosinophils, 7% basophils, 1% myelocytes, and 1% blast cells. Plasma D-dimer level was normal. Hepatic and renal tests were normal. Plasma LDH was 1120 mg/dl. Bone marrow aspiration showed a diffuse massive infiltration of displastic megakaryocytes with platelet aggregates, blast cells were 20% (Figs. 1 and 2). At the admission patient was treated with hydroxyurea 3 g/die PO associated with daily platelet apheresis. During the first 48 hr the patient had two episodes of seizures associated with left facial paralysis. Computed tomography was negative for cerebral lesion, but magnetic resonance imaging showed little ischemic lesions in the left frontal lobe and in the left temporal lobe. During EEG registration abnormalities were present in left frontal area and in left temporal area. Subsequently immunophenotyping studies performed on bone marrow blood demonstrated the presence of 56% of blasts CD33, CD13, HLA-DR, CD45, CD34 positive with a co-expression

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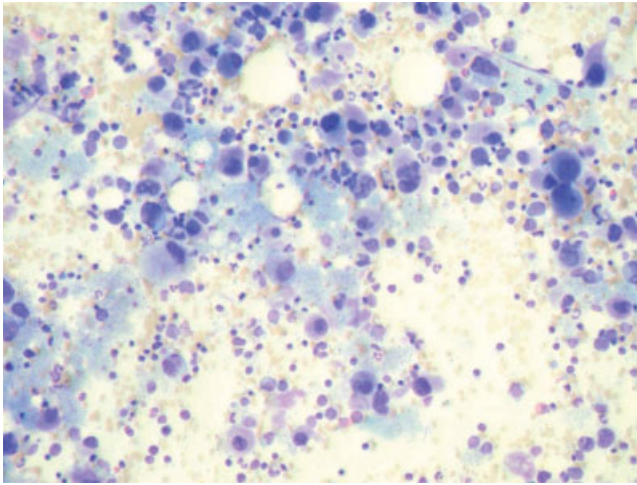


Fig. 1. Diffuse bone marrow infiltration of small displastic megakaryoblasts. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

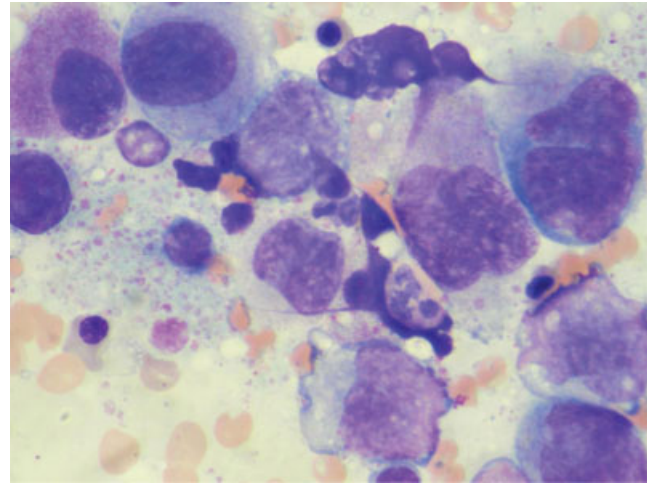


Fig. 2. Displastic micromegakaryoblasts with platelet aggregates. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of CD41 and CD61. Bone marrow biopsy did not show fibrosis and G-banding karyotype showed 46, t(9-22) (q34, q11) in 17 metaphases. The presence of BCR-ABL transcript was demonstrated by reverse transcription-polymerase chain reaction (RT-PCR) on bone marrow blood. Moreover RT-PCR gave rise to product with a size corresponding to a 210-kDa protein (p210) b2a2. All these data supported the diagnosis of chronic myeloid leukemia (CML) megakaryocytic blast crisis: hydroxyurea and plateletpheresis were stopped and a short cycle of chemotherapy with idarubicin 10 mg/m² Day 1 and cytarabine 200 mg/m² Days 1-2-3 was administered, followed by a therapy with imatinib mesylate 600 mg/die PO. Platelet count declined below $2,000 \times 10^9 \text{ l}^{-1}$ within the first week. Within 4 weeks the therapy induced a complete hematological remission. After 4 months the patient, still treated with imatinib (600 mg/die PO), feels well, has not showed any drug-related adverse event and a new cytogenetic analysis showed a major cytogenetic response. We are evaluating the feasibility of a reduced intensity bone marrow allogeneic transplantation with a HLA sibling brother.

DISCUSSION

CML is a clonal myeloproliferative disorder with an incidence of 1 case per 10⁵ people in Western countries. The hallmark of CML is the Philadelphia chromosome which derives from a translocation between chromosome 9 and 22, t(9,22)(q34, q11). This aberration gives rise to a fused BCR/ABL gene and transcriptions of an abnormal protein of 210 kDa. Variant of the Philadelphia chromosome with a 190 kDa protein occurs in few cases of acute myeloid leukemia and in adult acute

lymphoblastic leukemia [3]. Blast crisis with clinical features quite similar to acute leukemia, is the first presentation of CML in 5–10% of patients. To our knowledge only three cases of megakaryoblastic crisis have been described as first presentation of CML and none of these patients showed symptomatic thrombocytosis [1,2]. In our case the differential diagnosis of a megakaryoblastic crisis of CML with a “de novo” acute megakaryocytic leukemia is based on the presence of a transcription BCR/ABL with a protein of 210 kDa together with the expression of platelet-specific antigens CD41, CD61 on blast surface, the slight basophilia and left-shifted leukocytes. In asymptomatic CML marked thrombocytosis is seen in 41% of cases with only 0.9% experiencing evidence of thrombosis [4]. A literature search reveals that there is only one case report with digital cyanosis, headache, vertigo, and malaise due to extreme thrombocytosis during CML [5]. Specific platelet defects have been identified in myeloproliferative disorders (abnormal platelet morphology, platelet membrane abnormalities, abnormal arachidonic acid metabolism) but causal relationship between these abnormalities and microvascular thrombosis has not been clearly identified [6]. In our patient immediate cytoreduction was required to relieve neurological symptoms, so we treated her with hydroxyurea and plateletpheresis before a definitive diagnosis was established. Therapeutic plateletpheresis can be aid to chemotherapy in order to control the platelet counts and symptoms until chemotherapy is effective in symptomatic thrombocytosis [7]. Therefore, a rapid cytoreduction with platelet removal by apheresis can be important to prevent or reduce thrombosis. An other possible therapeutic option to obtain a relatively rapid reduction of platelet count is the use of radioac-

tive phosphorus (^{32}P) in addition to the cytochemical agents and platelet phoresis [8]. But in many countries it is difficult to obtain ^{32}P and there are no studies about association of ^{32}P and imatinib in patients affected by CML. After making the diagnosis of CML a 3-days chemotherapy cycle with idarubicin and cytarabine was begun in order to obtain a more intense cytochemical reduction and then we started a therapy with imatinib. In blast crisis therapy with imatinib is less toxic and produces a higher response rate in comparison with standard cytarabine combination [9]. During treatment of patients in blast crisis with imatinib severe cytopenias are frequent and represents the main reason for drug discontinuation. Most cytopenias are probably due to the direct pharmacological effect of imatinib on leukemic cells and the poor normal bone marrow reserve in patients with blast-phase disease [9]. The time interval between the diagnosis of blastic crisis and the beginning of imatinib therapy associated with the absence of additional cytogenetic abnormalities are the only significant prognostic factors for the event free survival and the overall survival of these patients [10]. Imatinib therapy produces a high percentage of sustained hematological remission in patient with CML in blast crisis, a minority of the patients also obtain some degree of cytogenetic response [9]. These responses are transient and additional therapy should be offered [10]. In conclusion, CML is a disease that originates in an abnormal pluripotent bone marrow stem cell and can reveal itself with rare and atypical syndromes. Nevertheless the diagnosis of an atypical presentation of

CML is essential for the treatment choice; therefore we considered it of interest to present this case of a very unusual CML presentation.

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