A case report and case review: Chronic myeloid leukemia (CML) blast phase with myelomastocytic differentiation

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ABSTRACT

We presented a patient with CML who progressed to unclassical blast phase after Tyrosine Kinase Inhibitors (TKIs) therapy. The patient presented with 2 populations of blasts: one with no cytoplasmic granules and was CD117 weak+/tryptase-/CD34- (typical myeloblasts), and another with metachromatic granules in the cytoplasm and was CD117 strong+/tryptase+/CD25+/CD34 subset+ (myelomastocytic blasts). Almost all the cells were positive for BCR/ABL1 fusion and no KT V816F mutation was detected. The patient was misdiagnosed as having blast phase CML with coexisting mast cell leukemia at an outside institute. Three similar cases and previously described myelomastocytic leukemia are reviewed and discussed.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that is driven by the BCR/ABL1 fusion or Philadelphia chromosome. It presented with granulocytic proliferation with left-shift and possible increase in blasts. CML is clinically classified into chronic phase, accelerated phase, and blast phase with worsening prognosis [1]. CML is diagnosed in the accelerated or blast phase in <5% of patients, and its incidence has been dramatically reduced because of the available effective treatments for chronic phase CML. Blast phase CML is characterized by the presence of >20% blasts in the peripheral blood or bone marrow. In the blast phase, blasts are myeloblasts in 70% of cases and lymphoblasts in 20% to 30% of cases. They are rarely megakaryoblasts, basophilic blasts, monoblasts, or eosinophilic blasts [2, 3]. It has been found that patients treated with TKIs are more likely to show unusual blasts (43.5%) than patients who do not undergo TKI treatment (11.4%) [4]. Blast phase CML with blasts of mast cell phenotype (myelomastocytic blasts) has rarely been reported and could pose a diagnostic challenge and cause treatment confusion [3, 5, 6]. The term myelomastocytic leukemia has previously been described for advanced myeloid neoplasms with blasts showing metachromatic granules in the cytoplasm and mast cell or basophilic phenotypes [7].

We report a patient with a history of CML with disease progressed to blast phase with 2 populations of blasts: one with a morphology and immunophenotype of typical myeloblasts and another with a morphology and immunophenotype of myelomastocytic blasts. The patient was initially misdiagnosed as having blast phase CML with coexisting mast cell leukemia. Other similar reports are also reviewed and the major differential diagnoses are discussed.

Case report

A 74-year-old male was diagnosed with CML in January 2019 following an incidental finding of leukocytosis. He was treated with imatinib, and the treatment was changed to nilotinib because of progressing leukocytosis. In January 2020, he presented with worsening leukocytosis with anemia and thrombocytopenia. Accelerated phase CML was suspected. A bone marrow biopsy was performed at an outside facility and the patient was diagnosed with blast phase CML with coexisting mast cell leukemia. He presented to our institute for a second opinion and treatment.

Blood workup showed marked leukocytosis (25.19 × 10⁹/L), anemia (7.9 g/dl), and thrombocytopenia (94 × 10⁹/L). A peripheral blood differential (Fig. 1A and 1B) showed 4% blasts with no obvious cytoplasmic granules (typical myeloblasts) and 75% cells with metachromatic granules, one third of which showed immature chromatin (myelomastocytic blasts). A bone marrow biopsy was performed. The bone marrow aspirate smears (Fig. 1C) showed 5% blasts with no...
obvious cytoplasmic granules (typical myeloblasts) and 38% immature cells with metachromatic coarse azurophilic granules (myelomastocytic blasts), and some without granules (typical myeloblasts) (A and B). The aspirate smears also show similar blasts with metachromatic granules (myelomastocytic blasts) and some blasts without granules (typical myeloblasts) as well as fewer immature mastocytic cells (promastocytes, metamastocytes) (C and D). The bone marrow is markedly hypercellular (100%; E) with diffuse infiltrate by immature cells with fine chromatin and conspicuous nucleoli (F).

Fig. 2. The Immunophenotype. Immunohistochemical studies showed a diffuse increase in CD117+ immature cells (A), some of which were strong-positive (myelomastocytic blasts) and others weak-positive (typical myeloblasts). The CD117+ myelomastocytic blasts were positive for tryptase, whereas the typical myeloblasts were negative for tryptase (B). CD34 was positive in a very small population of the blasts (C). Flow cytometry (D) showed 2 populations of CD45 dim blasts. One population (the red-colored cluster) was strong-positive for CD117 (myelomastocytic blasts), with a small subset positive for CD34; the other population (the blue-colored clusters) was weak-positive for CD117, compared with the control lymphocytes (the green-colored cluster in green), and negative for CD34. Both populations were positive for CD33 and negative for myeloperoxidase.

obvious cytoplasmic granules (typical myeloblasts) and 38% immature cells with metachromatic granules (myelomastocytic blasts). A few immature mastocytic cells (promastocytes, metamastocytes) were also observed (Fig. 1D). The core biopsy showed markedly hypercellular marrow (approaching 100%; Fig. 1E) with sheets of immature cells (Fig. 1F). Immunohistochemical studies were performed, showing that CD117 (Fig. 2A) was strong-positive in approximately 30% to 35% of the cells (myelomastocytic blasts) and weak-positive in approximately 20% (typical myeloblasts). Tryptase (Fig. 2B) was positive in a subset of the blasts, presumably the myelomastocytic blasts. CD34 was positive
in a small subset of the blasts (Fig. 2C).

Flow cytometry immunophenotyping (Fig. 2D) also showed 2 distinct populations of immature cells or blasts. The first population (the red-colored cluster) expressed very bright CD117 (myelomastocytic blasts), with a small subset positive for CD34. The second population (the blue-colored cluster) showed weaker positive CD117 (typical myeloblasts), as compared with the control lymphocytes (the green-colored cluster), and was negative for CD34. Therefore, 2 populations of blasts, myelomastocytic blasts and typical myeloblasts, were identified in this patient.

An interphase fluorescence in situ hybridization (FISH) study showed BCR/ABL1 rearrangements in 93% of the cells. Reverse transcription polymerase chain reaction for BCR-ABL1 fusion transcript p210 was detected at 4.5149% international scale (IS). Karyotyping showed the following complex karyotype in all 20 cells: 51,XY,+8,t(9;22)(q34;q11.2),+17,+19,+21,+der(22)t(9;22)(q34;q11.2) [20]. Next generation sequencing using a 54 myeloid–targeted gene panel was positive for ABL1 T315I mutation, which is associated with resistance to early generation ABL1 kinase inhibitors, and ASXL1 G646W*12 and RUNX1 R162M mutations. No KIT D816V mutation was detected.

Because the majority of the cells (93%) were positive for BCR/ABL1 fusion, all 20 metaphase cells showed t(9;22), and no KIT D816V mutation was detected, the patient was diagnosed with blast phase CML with partial myelomastocytic differentiation, rather than coexisting mast cell leukemia. The patient was treated with ponatinib and showed great clinical improvement.

Discussion

The incidence of blast phase CML has been greatly decreased after the introduction of TKI therapy. The unclassical presentation of blast phase CML is even rarer, and its diagnosis and classification may be challenging in clinical practice. In this report, we presented a patient with CML who progressed to blast phase with 2 populations of blasts: challenging in clinical practice. In this report, we presented a patient with CML and should be treated as having this disease rather than coexisting mast cell leukemia. Soler et al. reported a patient with blast phase CML, showing blasts with coarse azurophilic cytoplasmic granules and was CD117 weak+/tryptase−/CD34+ (typical myeloblasts), and another had metachromatic granules in the cytoplasm and was CD117 strong+/tryptase+/CD25−/CD34 subset+ (myelomastocytic blasts). The patient was misdiagnosed as having blast phase CML with coexisting mast cell leukemia at an outside institute. Almost all the cells (93%) were positive for BCR/ABL1 fusion, all 20 metaphase cells showed the same karyotype with t(9;22) translocation, and no KIT V816F mutation was detected, thereby indicating that both populations were the same clone and CML-related. Coexisting mast cell leukemia was less likely to be the correct diagnosis. The patient achieved complete remission after undergoing treatment with TKI therapy, further confirming that the patient had blast phase CML and should be treated as having this disease rather than coexisting mast cell leukemia.

So far, there have been only 3 case reports on this atypical presentation of blast phase CML. Soler et al. reported a patient with blast phase CML, showing blasts with coarse azurophilic cytoplasmic granules and vacuoles that resembled basophils or mast cells [5]. However, neither detailed immunohistochemical studies nor a C-KIT mutation study were performed. Martinez-Cordero et al. [3] reported a CML patient in blast phase with 29% myeloblasts and 46% of immature cells with basophilic or mast cell characteristics (CD117+, CD25−, CD123+, CD34 partial+, myeloperoxidase−, and tryptase not reported). Serum tryptase and Kit mutations were not tested. Vigel et al. reported a patient with blast phase CML that showed blasts with metachromatic cytoplasmic granules that were CD117−, tryptase−weak−, CD25+, and CD34− in 15% of the cells in the orbital wall lesion [6]. In the left femur, the cells were CD117−, tryptase−strong−, and CD34−. BCR/ABL1 was found to be positive in all the CD117+ cells by FISH studies, whereas the karyotype was found to be normal. No KIT D816V or JAK2 V617F mutations were detected. The patient was treated with dasatinib and low-dose Ara-C. Both the orbital mass and the bone lesion resolved thereafter.

A novel subtype of myeloid leukemia (myelomastocytic leukemia) was previously described [8], in which immature myelomastocytic cells with coarse metachromatic granules and expressing CD117 and tryptase are diffusely increased (>10% in the bone marrow or peripheral blood). This diffuse increase can be seen in many myeloid neoplasms, including myelodysplastic syndrome, myeloproliferative neoplasm, and acute myeloid leukemia. The metachromatic cells show a phenotype of CD117+, tryptase−+, CD11b−, CD123+, CD2+, and CD25−. A subset of the metachromatic cells may represent basophils (CD117−, CD25+, and CD11b+) [8-10]. The major differentials of myelomastocytic leukemia are mast cell leukemia, systemic mastocytosis, systemic mastocytosis with associated hematopoietic neoplasm (SM-AHN), and basophilic leukemia. Systemic mastocytosis and SM-AHN show mostly mature mast cells that form dense clusters, whereas mast cell leukemia shows mostly immature mast cells. The neoplastic mast cells in these mast cell disorders usually not only express CD117 and tryptase but also show aberrant expression of CD2 and/or CD25, and most of patients with this disease have a k-KIT D816V mutation. In comparison, myelomastocytic leukemia cells usually do not form dense clusters, are CD2+, CD25−, and contain no k-KIT mutation.

In summary, CML blasts phase with myelomastocytic differentiation is rare and a combination of morphology, immunophenotyping, genetic, and molecular studies are necessary and important to distinguish it from a coexisting mast cell neoplasm to avoid misdiagnosis and mistreatment.

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Authors’ contributions

Jinming Song and Hailing Zhang: Acquisition of data and drafting of the manuscript.

Javier Pinilla-Ibarz: Editing and approval of the manuscript.

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