CASE REPORT

Blast Phase of Chronic Myeloid Leukemia Presenting Lymphoid Phenotype with a Chronic Phase of Extremely Short Duration

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Abstract

Chronic myeloid leukemia (CML) is generally diagnosed in the chronic phase. We have recently encountered two CML-blastic phase (BP) cases, a 71-year-old woman and a 74-year-old man, who resembled de novo acute leukemia. The complete blood count was normal at least 11 and 13 months before the presentation, respectively. The leukemic cells showed predominant lymphoid phenotype. The blasts and granulocytes were positive for BCR-ABL, indicative of CML-BP. Both patients were successfully treated with prednisone and vincristine, followed by Imatinib. Our cases indicate rare presentations of CML-BP with an extremely short chronic phase. Ph-positive de novo acute leukemia should be carefully distinguished from CML-BP.

Key words: CML, blastic phase, BCR-ABL


Introduction

The clinical presentation of chronic myeloid leukemia (CML) is usually insidious, with most patients presenting in chronic phase. Approximately 10% of patients, however, present in blastic phase (BP) (1). It is deduced that it takes 6 years for patients to become symptomatic from the time of the initial chromosomal translocation (2). It takes 19 months (range, 7 to 24 months) for the white blood cell count to increase from 10,000/μL to 100,000/μL (1). Our two cases resembled Ph-positive acute lymphoid leukemia (ALL) associated with cross-lineage nature, however, the demonstration of BCR-ABL fusion gene in the granulocytes and peripheral mononuclear cells even after the leukemic blasts were decreased in the peripheral blood by chemotherapy, strongly suggested CML-BP with unusually short duration of CML chronic phase. These cases highlight the significance of discriminating Ph-positive ALL from CML-BP since therapeutic strategies differ between the two diseases. CML-BP cases with such characteristics have not been reported to the best of our knowledge.

Case Report

(Case 1): A 71-year-old Japanese woman presented with painful swelling of the right leg due to deep venous thrombosis. Laboratory findings revealed prominent leukocytosis and the patient was referred to our hospital. On admission, the leukocyte count reached 131,100/μL (basophils 0%, eosinophils 1%, myeloblast 0%, promyelocytes 0%, myelocytes 1%, metamyelocytes 0%, stab form 2%, segmented form 4%, lymphocytes 3%, atypical lymphocytes 1%, monocytes 1%, blasts 87%). Hemoglobin and platelet count decreased to 8.1 g/dL and 130,000/μL, respectively (Table 1). Bone marrow examination presented hypercellularity with 89.4% of immature blasts (Fig. 1). Flow cytometric analysis using CD45 gating method showed that blast cells expressed both lymphoid (CD10 and 19) and myeloid (CD 13, 33) markers on their surface. Leukemic cells were also positive for surface CD34 and HLA-DR. However, the leukemic cells were positive for cytoplasmic CD79a, while negative for cytoplasmic peroxidase, confirming that the leukemic cells were committed to B-cell lineage according to
Figure 1. Bone marrow pictures of the two cases. The bone marrow samples were stained using the May-Giemsa method. Hypercellular bone marrow was predominantly occupied by immature blasts, and differentiated nucleated cells were seldom seen in either case. (a) Case 1. Nucleated cell count 312,000/μL, Blast 89.4%. (b) Case 2. Nucleated cell count 698,000/μL, Blast 93.2%.

Table 1. Laboratory Data

<table>
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<tr>
<th>Variable</th>
<th>Case 1 11 Months Before Admission</th>
<th>Case 1 On Admission</th>
<th>Case 2 13 Months Before Admission</th>
<th>Case 2 On Admission</th>
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<tr>
<td>RBC (per μL)</td>
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<td>263 × 10⁴</td>
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<td>Hb (g/dL)</td>
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<td>Ht (%)</td>
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<td>41.5</td>
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<tr>
<td>WBC (per μL)</td>
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<td>131,100</td>
<td>7,800</td>
<td>174,300</td>
</tr>
<tr>
<td>PLT (per μL)</td>
<td>27 × 10⁴</td>
<td>13 × 10⁴</td>
<td>24.4 × 10⁴</td>
<td>21.9 × 10⁴</td>
</tr>
</tbody>
</table>

the EGIL scoring system (B cell score 4, myeloid score 2) (3) (Fig. 2a). Cytogenetic study showed t(9;22) (q34;q11.2) in 18 out of 20 analyzed cells without additional abnormality. RT-PCR analysis showed major bcr-abl transcript. Fluorescence in situ hybridization (FISH) study also showed BCR-ABL translocation in blast cells. Interestingly, BCR-ABL fusion gene was also found in the peripheral segmented nuclear cells (83.0%) (4) and mononuclear cells (24.0%) when the peripheral blasts were deceased to 5.0% after the chemotherapy began, suggesting a diagnosis of CML-BP, but not de novo ALL (Fig. 3a). Her annual health check showed normal complete blood count at least 11 months before the presentation (Table 1). In addition, imaging studies showed no evidence of hepatosplenomegaly.

We first treated the patient with vincristine and prednisone (VP) because the lymphoid markers were predominant according to EGIL scoring system (3). Imatinib was begun after the diagnosis of CML was fixed. Combinational therapy of VP and Imatinib was effective, leading to complete hematological response (CHR) and major cytogenetic response (Major CyR; residual Ph chromosome 5%) within 2 months. The patient is currently treated with single use of Imatinib as the maintenance therapy.

(Case 2): A 74-year-old Japanese man had hypertension, and was regularly checked by his physician. His complete blood count was normal at least 13 months prior to the presentation (Table 1). Three days before the admission to our hospital, leukocytosis was found by his physician although he did not show any symptoms such as hepatosplenomegaly. The laboratory test on admission showed 174,300/μL (basophil 0%, eosinophil 1%, myeloblast 0%, promyelocytes 0%, myelocytes 0%, metamyelocytes 0%, stab form 2%, segmented form 4%, lymphocyte 2%, monocyte 1%, blasts 90%) without anemia or thrombocytopenia (Table 1). Flow cytometric analysis of blastic cells showed almost identical results as seen in case 1 (Fig. 2b). Bone marrow examination presented hypercellularity with 93.2% of immature blasts (Fig. 1). Also, cytogenetic study of bone marrow cells showed t(9;22) (q34;q11.2) without additional abnormality in all analyzed 20 cells. RT-PCR analysis showed minor BCR-ABL transcript and FISH study showed BCR-ABL translocation in blast cells. BCR-ABL fusion genes were also demonstrated in both the peripheral segmented nuclear cells (74.0%) (4) and mononuclear cells (83.0%) when the peripheral blastic cells were decreased to 8.0% after the chemotherapy began, again suggesting a diagnosis of CML-BP (Fig. 3b).

Imatinib was administered 15 days after the beginning of
Figure 2. Leukemic cells expressed both lymphoid and myeloid markers on their surfaces. Bone marrow mononuclear cells were gated on \(CD45^{int}\) \(SSC^{low}\) population (leukemic cells), and analyzed for the surface expression of each marker by flow cytometric analysis. The leukemic cells expressed CD13, CD33 and CD19, with substantial biphenotypic blast population (CD19\(^+\)CD13\(^+\)) in both cases (case 1: 68\%, case 2: 32.9\%). Cytoplasmic staining of CD79a was positive while that of myeloperoxidase (MPO) was negative, indicating the commitment to B-cell lineage. The leukemic cells also expressed CD34 and HLA-DR, possibly reflecting the immature characteristics.

Figure 3. FISH analysis of segmented nuclear cells. BCR:22q11.2/ASS-ABL (ABL1):9q34 probe was used for the FISH. Arrows indicate the fusion signal of BCR-ABL fusion genes. One hundred interphase cells were analyzed for each experiment. (a) Case 1. BCR-ABL was positive in 83.0\% of segmented nuclear cells and 24.0\% of round nuclear cells (data not shown). An extra small red signal derived from ASS on chromosome 9 was lost, indicating the deletion of this region. This pattern was also found in the blast cells (data not shown). (b) Case 2. BCR-ABL was positive in 74.0\% of segmented nuclear cells, and 83.0\% of round nuclear cells (data not shown). A small fusion signal derived from minor BCR-ABL was also shown (upper arrow).

VP therapy. CCyR was obtained 3 months after the initiation of treatment. However, interstitial pneumonia occurred 3 months after the administration, necessitating the cessation of Imatinib. Pneumonitis was successfully treated with corticosteroid. The leukemic blasts, however, increased in the peripheral blood during the absence of Imatinib, which had been already refractory against chemotherapy including Imatinib and VP therapy. The patient died due to the bone
marrow failure 15 months after the initiation of treatment.

Discussion

The chronic phase of CML generally lasts for 3 to 5 years, followed by an accelerated phase of 3 to 18 months, leading to BP (1). The present two CML-BP cases showed quite similar clinical courses resembling de novo ALL. They did not show any abnormality in the CBC almost 1 year before the prominent leukocytosis (>100,000/μL) was found. The lack of thrombocytopenia and expression of both lymphoid and myeloid markers on the blastic cells prompted us to examine the presence of BCR-ABL transcript. The presence of the BCR-ABL translocation not only in blastic cells, but also in normal granulocytes and mononuclear cells indicated the change in common hematopoietic progenitor cells with multi-lineage differentiation potential, supporting the diagnosis of CML-BP. Neutrophil-FISH is a useful method to demonstrate BCR-ABL-positive leukemic cells in the peripheral blood as real-time quantitative RT-PCR analysis (4). However, it is difficult to strictly distinguish Ph-positive ALL from Ph-positive CML in lymphoid crisis because the significance of BCR-ABL fusion genes in granulocytes of Ph-positive ALL patients has been controversial. It was reported that the Ph-positive ALL cells with cross-lineage nature showed the potential to differentiate into granulocytes in the presence of GM-CSF or G-CSF in a colony assay, indicating that the Ph-positive common progenitors preserved the potential for granulocyte differentiation (5). On the other hand, the differentiated granulocytes in colonies from mononuclear cells of Ph-positive ALL patients showed a normal karyotype, while those in colonies from Ph-positive CML patients showed Ph chromosome (6), indicating that the Ph-positive ALL leukemic progenitor cells did not preserve the potential to differentiate granulocytes in this report. We also encountered the absence of BCR-ABL gene in normal granulocytes in some Ph-positive ALL patients (data not shown). It is possible that some Ph-positive ALL progenitors retain the potential for multi-lineage differentiation. In the present two cases, the BCR-ABL gene was present in the normal granulocytes and mononuclear cells even when the peripheral blastic cells were prominently decreased following chemotherapy, indicating that abnormal hematopoietic progenitors, but not ALL progenitor cells, contributed to these populations, supporting the diagnosis of CML-BP. We deduce two possibilities for the atypical clinical presentation of these two CML-BP cases. One is the lack of leukocytosis during the chronic phase. It is unclear whether the patients were in the chronic phase of CML almost 1 year before the presentation when the CBC appeared normal. Second is the short duration of chronic phase of less than 1 year and lack of an accelerated phase.

“Lymphoid” BP is reported to contain a biphenotypic subgroup (3, 7). The frequency of biphenotypic BP in the “lymphoid” BP varies from 4/17 (23.5%) (7) to 6/7 (85.7%) (3). Patients with “lymphoid” BP have a better response to chemotherapy regimens including vincristine and prednisone and survived longer, and seldom have an accelerated phase prior to BC than non-lymphoid BC (7). No significant difference in the length of chronic phase was found between “lymphoid” and non-lymphoid BC (51.3±10 vs 49±4.9 months) (7). Although the present cases shared several clinical features of “lymphoid” BC, it is not clear whether the atypical clinical course of our cases is a unique feature of “lymphoid” BC with cross-lineage nature.

The second case showed minor BCR-ABL transcript by RT-PCR, which is frequent in Ph-ALL, but exists as a very rare fusion type in CML (8). The minor BCR-ABL may represent some similarity to Ph-ALL in the second case. However, it will require large numbers of similar cases to conclude that the minor BCR-ABL is typical for the CML with short chronic phase.

In BP, additional cytogenetic changes are found in 70-80% of cases beyond the Ph chromosome (1). The common abnormalities are: +8, +Ph, i(17q), +19, -Y, +21, +17, monosomy (9). The underlying molecular changes are various: over-expression of BCR-ABL, increased Evi 1 expression, increased telomerase activity, mutations of p53, RB1, or p16INK4A. Chromosomal translocation, t(3;21) (q26;q22) and t(7;11) (p15; p15) resulted in the fusion genes, AML1-MDS1/EVI1 and NUP98-HOXA9 respectively, which interferes with the differentiation of hematopoietic cells (10, 11). The present two CML-BP cases showed no additional cytogenetic changes upon the Ph chromosome. The underlying molecular changes characterizing these CML-BC cases are unknown at present.

The clinical presentation of our two CML-BP cases could not be differentiated from de novo ALL without the demonstration of BCR-ABL in normal nucleated and mononuclear cells. To our knowledge, such an atypical presentation of CML-BP has not been reported. It may indicate the presence of a clinical subgroup of CML, which will require further study with larger numbers of CML-BP cases. The surface markers representing the hallmark for such rare cases should be investigated. It may be possible that some CML-BP has been recognized as Ph-positive ALL. Acute leukemia should be carefully diagnosed not to misdiagnose CML-BP. It is necessary to reveal the difference of clinical outcomes between de novo ALL and CML-BC, and the appropriate therapy should be investigated in a large number of cases.

References

2. Kamada N, Uchino H. Chronologic sequence in appearance of clinical and laboratory findings characteristic of chronic myelo-


