Basophilic Crisis of Chronic Myelogenous Leukemia

Michiko OZAKI, Nozomu KANEMITSU, Masaki YASUKAWA and Shigeru FUJITA

An 81-year-old woman with Phi-positive chronic myelogenous leukemia developed blast crisis four years after diagnosis of the disease. In the blast crisis phase, hematological examination disclosed WBC 93,000/μl with basophilia in both the peripheral blood (40.0%) and bone marrow (33.2%), with increased numbers of immature basophils, such as basophilic promyelocytes, myelocytes and metamyelocytes. Electron microscopy of bone marrow cells showed immature and mature types, which contained granules characteristic of basophils. Toluidine blue metachromasia was evident in the basophils. Cytogenetic study revealed the Ph1 chromosome along with additional abnormalities. In view of these findings, it seems likely that basophilic crisis developed in this patient with chronic myelogenous leukemia.

Key words: CML, Blast crisis, Basophils.

Chronic myelogenous leukemia (CML) is a clonal disorder of pluripotent hematopoietic stem cells (1). Blastic transformation of CML can take place at different stages of stem cell development, and thus the condition can appear heterogeneous with respect to cellular expression (2). In this paper, we report a case of CML with blast crisis, in which the numbers of mature and immature basophils increased with emergence of additional chromosome abnormalities. This case seems likely to have been a rare example of CML basophilic crisis.

CASE REPORT

A 77-year-old woman was initially admitted to Ehime University Hospital in November 1982, because of leukocytosis. On physical examination, no hepatosplenomegaly was evident. A bone marrow smear showed hypercellularity with increased myeloid elements. The karyotype was 46,XX,t(9;22) (q34;q11). A diagnosis of CML was made and treatment with busulfan was started. She remained in stable condition until August 1986, when she suffered high fever, general fatigue and hepa-
tomegaly. She was admitted to our hospital for the second time in October 1986.

Physical examination: Pulse rate was 84/min, and regular. The blood pressure was 100/50 mmHg. The conjunctiva palpebrae indicated anemia, but the conjunctiva bulbi was not icteric. The lungs were clear and the heart sounds were pure. The liver was palpable at 4.5 cm below the right costal margin. The spleen was not palpable but splenic dullness was enlarged. No lymphadenopathy was found.

Laboratory data: The results obtained on the second admission are shown in Table 1. Erythrocyte sedimentation rate was 75 mm/h. The urine and stool were normal. CRP and anti-HTLV-1 antibody were positive. The levels of alkaline phosphatase and lactate dehydrogenase were elevated to 272 IU/l and 261 IU/l, respectively. The serum protein concentration was 5.1 g/dl. The vitamin B12 level was greater than 3,200 pg/ml. Histamine levels in both whole blood and plasma were elevated. The serotonin level was within the normal range.

Hematological examination: The results of hematological examination are shown in Table 2.
Table 1. Laboratory data on admission.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>ESR</td>
<td>75 mm/h</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>n.p.</td>
</tr>
<tr>
<td>Occult blood</td>
<td>(-)</td>
</tr>
<tr>
<td>Serological test</td>
<td>(-)</td>
</tr>
<tr>
<td>Anti-HTLV-I Ab</td>
<td>≥20</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td></td>
</tr>
<tr>
<td>GOT</td>
<td>8 IU/l</td>
</tr>
<tr>
<td>GPT</td>
<td>10 IU/l</td>
</tr>
<tr>
<td>AIP</td>
<td>272 IU/l</td>
</tr>
<tr>
<td>LDH</td>
<td>261 IU/l</td>
</tr>
<tr>
<td>γ-GTP</td>
<td>24 IU/l</td>
</tr>
<tr>
<td>T. Protein</td>
<td>5.1 K/dl</td>
</tr>
<tr>
<td>Alb</td>
<td>63.7%</td>
</tr>
<tr>
<td>Stool</td>
<td>α-gt</td>
</tr>
<tr>
<td>Occult blood</td>
<td>β-gt</td>
</tr>
<tr>
<td>CRP</td>
<td>3+</td>
</tr>
<tr>
<td>Anti-HTLV-I Ab</td>
<td>≥20</td>
</tr>
<tr>
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<td>Anti-HTLV-I Ab</td>
<td>≥20</td>
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</table>

At the first admission, the WBC count was 15,000/μl with 1.0% blasts, 68.5% neutrophils and 12.0% basophils. All the basophils were of mature type. A bone marrow smear showed hypercellularity with increased myeloid elements. At the second admission, the hemoglobin level was 6.3 g/dl, and WBC count was 93,000/μl with 13.5% blasts and 40% basophils. At this time, many immature basophils were detected in the peripheral blood. A bone marrow smear showed hypercellularity with 33.2% basophils.

Cytochemical and immunological studies: Cytochemical findings of peripheral blood mononuclear cells at the time when blasts accounted for 67% of WBC are shown in Table 3. Blasts were negative for myeloperoxidase (MPO), α-naphthyl butyryl esterase, naphthol ASD chloroacetate esterase and terminal deoxynucleotidyl transferase (TdT), and weakly positive for periodic acid-Schiff (PAS). The blasts present at the second admission showed the same cytochemical characteristics. The monoclonal antibodies used for surface marker analysis are listed in Table 3. Monoclonal antibody reactivity was determined by direct or indirect immunofluorescence. The percentages of fluorescent cells were determined using a fluorescence-activated cell sorter (Epics C, Coulter, USA). Surface marker analysis was performed when blasts accounted for 67% of WBC. Blasts were negative for CD2 (T11), CD3 (T3), CD10 (J5), CD20 (B1), CD14 (MY4) and LA, weakly positive for CD13 (MY7), CD19 (B4) and CDw41 (glycoprotein IIb/IIIa), and strongly positive for...
for CD11 (Mo1) and CD33 (MY9). These data indicated that the blasts had the characteristics of immature myeloid cells.

Light microscopic examination: Leukemic cells showing various degrees of basophilic differentiation found in peripheral blood at the second admission are shown in Fig. 1. Blasts that did not contain any cytoplasmic granules had a high nucleocytoplasmic ratio. Their nuclei possessed some nucleoli with fine chromatin (Fig. 1A). Some immature cells contained several basophilic granules in the cytoplasm (Fig. 1B and C). These granules showed metachromasia for toluidine blue stain (Fig. 2). The basophils in peripheral blood at the second admission comprised 2.6% basophilic promyelocytes, 12.0% basophilic myelocytes, 2.6% basophilic metamyelocytes and 22.8% mature basophils. Immature basophils showed morphological abnormalities such as an irregular nuclear shape or coarse granules.

Ultrastructural examination: An electron micrograph of an immature basophil is shown in Fig. 3. Immature basophils possessed granules containing fine particles specific to basophils. Unit membrane enclosed the particles. Some these granules had a myelinoid structure.

Chromosome analysis: The results are summarized in Table 4. Twenty bone marrow cells were analyzed, and the Ph1 chromosome was detected in all of them, in addition to two other types of chromosome abnormality, i.e., 6p deletion and 11p deletion in 16 cells, and 6p deletion, 11p deletion and translocation between 5p and 22q in 4 cells.

Clinical course (Fig. 4): After the diagnosis of blast crisis, treatment with vincristine 2 mg and prednisolone 30 mg (VP) was started. Although the patient was treated with VP intermittently, remission was not achieved and she died of pulmonary mycosis on 30 January, 1987. The final examination of peripheral blood revealed a WBC count of 163,000/μl with 67% blasts and 1% basophils. During her clinical course, hyperhistaminemic syndrome did not develop. At autopsy, the weights of the liver and spleen were 1,030 g and 440 g, respectively. There were some indurations in the bilateral lungs, which were histopathologically diagnosed as pulmonary aspergillosis. The bone marrow was hypercellular. Leukemic infiltrations were observed in many organs including the bone marrow, liver, spleen, pancreas, lungs, kidneys, adrenals, uterus, ovaries and lymph nodes.

**Table 4. Chromosome analysis**

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Number of metaphases</th>
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<tbody>
<tr>
<td>46, XX, del(6) (p21), del(11) (p11p13), t(9; 22) (q34; q11)</td>
<td>16</td>
</tr>
<tr>
<td>46, XX, del(6) (p21), del(11) (p11p13), t(9; 22) (q34; q11) t(5; 22) (p12; q11)</td>
<td>4</td>
</tr>
</tbody>
</table>

Fig. 1. Leukemic cells found in peripheral blood (May-Grünewald-Giemsa stain, ×1,000). A. Blast, B. Basophilic promyelocyte, C. Basophilic myelocyte, D. Basophilic metamyelocyte, E. Mature basophil.

Fig. 2. Toluidine blue staining of an immature basophil (×1,000).
Fig. 3. An immature basophil in the bone marrow (x 10,800). The arrow indicates a typical basophilic granule containing fine particles.

Fig. 4. Clinical course.
DISCUSSION

In the present case, at chronic phase, there was no marked basophilia, and immature basophils did not increase. Karyotype analysis revealed only 46,XX,t(9;22)(q34;q11) and no additional chromosomal abnormalities were found. Four years after the diagnosis of CML, the patient developed a clinical picture of blast crisis, and basophils including immature types with morphological abnormalities increased up to 40% with the emergence of additional chromosomal abnormalities. Additional changes in the chromosomes were found in all cells analysed. On the basis of these findings, we made a diagnosis of basophilic crisis of CML.

Most cases of CML terminate in blast crisis typically resembling acute myelocytic leukemia. In addition to myeloblastic crisis, approximately one-third of blast crisis cases show the lymphoblastic type. Furthermore, less commonly, erythroblastic (3), monocytic (4) and basophilic (5) transformations have been described. There have also been some cases of a single blast type simultaneously expressing different cell lineage antigens (6), or of two distinct blasts being found in a single patient (7). Such heterogeneity of blast crisis suggests that CML has a clonal origin in a pluripotent hematopoietic stem cell (1).

It is not clear whether the blasts in the present case originated from a basophilic precursor cell or a more immature uncommitted cell. When blast crisis occurred, very immature basophils were observed, and morphologically these cells appeared likely to have differentiated from the blasts. Electron microscopy revealed cytoplasmic granules specific to basophils in these immature cells. The light microscopic morphology of the blasts, that increased in the peripheral blood immediately before the patient’s death looked likely to have been the same as that of the blasts observed at the second admission. A phenotypic study performed when only the blasts were increased in the peripheral blood indicated that these cells were of immature myeloid lineage. On the basis of these findings, we speculated that the blasts and the basophils in the present case were derived from the same immature myeloid precursor cell, which had a capacity for differentiation into the basophilic lineage.

So far, only about 30 cases of basophilic crisis of CML have been reported. Previous cytochemical studies on such CML basophilic crisis have indicated that blasts were negative or positive for MPO, PAS and Sudan black B, and positive for toluidine blue and astra blue (5, 8). The blasts in the present case were negative for MPO, weakly positive for PAS, and positive for toluidine blue. These results are identical to those for blasts previously reported in CML basophilic crisis.

No cytological markers specific to basophilic precursors have yet been found. Therefore, it is expected that markers determining immature cells committed to the basophilic lineage will be found, enabling clarification of basophilic differentiation.

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REFERENCES