Case report

Chronic myelogenous leukemia showing biphenotypic blast crisis followed by lineage switch to B lymphoblastic leukemia

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1. Introduction

Chronic myelogenous leukemia (CML) is a common myeloproliferative disease that is characterized by the clonal expansion of marrow stem cells, and is associated with the Philadelphia chromosome [1]. As the disease progresses, the indolent chronic phase may convert to a more aggressive accelerated phase or, finally, blast crisis (BC). In this final stage (BC), the marrow is infiltrated by blasts, which are more frequently of myeloid lineage than of lymphoid lineage [2]. Due to its heterogeneity, bilineage crisis is sometimes found in the blastic phase of CML [3,4], and biphenotypic crisis has also been reported to account for 14% of BC [5]. Treatment options have been selected according to the phenotype of blasts and recently renewed by the introduction of the Abi kinase inhibitor imatinib mesylate (IM) [6,7]. Here, we report a novel case of imatinib-resistant CML-BC, in which the blast lineage switched from biphenotypic to B-lymphoid.

2. Case report

A 14-year-old boy was admitted to our hospital in July 2007 because of persistent epistaxis for 5 days. His initial complete blood count (CBC) showed a hemoglobin level of 8.9 g/dL, a platelet count of 676,000/μL, and a WBC count of 263,200/μL, with 4% blasts. A bone marrow study revealed hypercellular marrow, with 5.2% blasts (Fig. 1). A chromosome study revealed a 46,XY,t(9;22)(q34;q11.2) in all 20 cells analyzed. A fluorescence in situ hybridization (FISH) study using a BCR/ABL1 probe (Abbott Molecular/Vysis, Des Plaines, IL) showed two fusion signals in 89% of the cells analyzed, consistent with the result of “nuc ish (ABLx3)(BCRx3)(ABL con BCRx2)[178/200].” Reverse transcriptase-polymerase chain reaction (RT-PCR) analysis identified the p210 isoform of the BCR/ABL1 fusion transcript (b2a2 type). The patient was diagnosed with CML in the chronic phase; however, treatment with IM was delayed due to economic reasons. Instead, hydroxyurea was started and he responded well. After 6 months, his peripheral blood showed an increased leukocyte count, with 13% blasts and 4% basophils. His marrow showed hypercellularity and was infiltrated by medium-to-large sized blasts, with fine nuclear chromatin, distinct nucleoli, and limited basophilic cytoplasms. Immunophenotyping by flow cytometry revealed that the blasts were positive for myeloperoxidase (MPO), CD13, CD19, CD20, CD10, CD22, and TdT (Fig. 2). A diagnosis of biphenotypic blast crisis (myeloid and B-lineage) from CML was made. Despite chemotherapy with cytarabine and fludarabine, in combination with IM, he did not achieve complete remission. After receiving continuous administration of IM for 4 months, his marrow was replaced by lymphoblastic leukemic cells showing CD19, CD20,
Fig. 1. Bone marrow aspirate ($1000\times$) and FISH findings. (A) Chronic myelogenous leukemia at the initial diagnosis. (B) Acute biphenotypic leukemia at the blastic phase. (C) Acute lymphocytic leukemia at the relapse. (D) FISH using BCR/ABL probe showed dual fusion signals: nuc ish (ABLx3)/BCRx3/ABL con BCRx2[/178/200].

CD10, CD22, and TdT, but not CD13 or MPO. During the patient’s clinical course, no additional chromosome aberration other than the Philadelphia chromosome was detected. After being diagnosed with lymphoid BC, he is now awaiting allogeneic hematopoietic stem cell transplantation after ALL-type induction chemotherapy.

3. Discussion

There are several previous reports of lineage switch in acute leukemia [8–10]. Many cases of lineage switch have occurred in Philadelphia chromosome-positive acute leukemia [11–15]. Blast lineage switch was characterized by clonal selection or transformation of multipotential progenitor cells during intensive chemotherapy [9]. However, lineage switch is a very rare event in CML-BC. To our knowledge, only three cases of lineage switch between lymphoid/myeloid lineages have been reported [16–18]. Only one case of lineage switch from mixed (myeloid/B-lineage) to myeloid was reported [19]. On the other hand, our case underwent a lineage switch from biphenotypic to lymphoid. In the previous cases, lineage switch occurred during the course of treatment with conventional chemotherapeutic agents, but our patient’s switch occurred during the administration of imatinib. The biphenotypic and bilineage presentation of blasts suggested that the origin was multipotent progenitor cells [12]. Thus, our case suggests that blasts in CML-BC have the potential to commit to other phenotypes, which may be subject to factors such as treatment modality. To our knowledge, this is the first case report of biphenotypic blast crisis with successive lymphoblastic lineage switch in CML. Further studies are needed to survey the frequency, prognosis, and treatment response of such lineage switching CML patients.

Contributions

Drs. Seung Hwan Oh and Tae Sung Park conducted study design and preparation of the manuscript. These two authors contributed equally to this work as first authors. Dr. Hae Ran Kim interpreted chromosome study and Drs. Ja Young Lee, Jae Hyun Kim, and Jeong Hwan Shin reviewed the case and the manuscript. Dr. Jeong Nyeo Lee, as the corresponding author, interpreted bone marrow pathology, and she reviewed the manuscript.
Fig. 2. Immunophenotype results of the present study. (A) It showed a positive result for MPO and CD13 markers (biphenotypic blast crisis). (B) It showed a negative result for MPO and CD13 at relapse (lineage switch to lymphoid leukemia).
Conflict of interest

No financial support or conflicts of interest are reported by the authors.

References