

Transformation from chronic myelogenous leukemia to acute lymphoblastic leukemia in children: A case report

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Abstract

Chronic Myelogenous Leukemia (CML) is a myeloproliferative neoplasm that can progress into various conditions. Transformation of CML into Acute Lymphoblastic Leukemia (ALL) is rare. An 8-year-old girl is brought to the hospital because of a fever. physical examination revealed hepatosplenomegaly, the patient had a history of bone marrow morphology examination in 2019 chronic phase CML with blast count <10%. In 2021, an assessment of the bone marrow was carried out again, showing a hypocellular picture, no erythropoiesis cells, and only a few granulopoiesis cells were found, and there were no megakaryocytes. Infiltrating lymphoblasts dominate cells in the bone marrow. The transformation of CML to ALL can occur in 5% of children and 40% of adults. Change can occur due to genetic mutations and inadequate treatment.

Keywords: Chronic myelogenous leukemia, acute lymphoblastic leukemia, transformation.

1. Introduction

Chronic myeloid leukemia is a myeloproliferative neoplasm originating from pluripotent stem cells. The Philadelphia chromosome (Ph) is the result of a translocation between chromosomes 9 and 22, which can be detected in myeloid, erythroid, megakaryocytes, B lymphocytes, and sometimes T lymphocytes. Chronic Myelogenous Leukemia (CML) consists of three phases, namely the chronic phase, acceleration phase, and blast crisis phase. In nearly 85% of patients, CML is chronic phase CML. Confirmation of the diagnosis is obtained by identification of the Philadelphia chromosome or the BCR ABL gene or both, in peripheral blood cells or bone marrow (BM).

2. Case

A pediatric patient aged 8 years came with complaints of fever 10 days before admission to the hospital. Complaints of fever were felt continuously. Complaints accompanied by bleeding gums. The patient in 2019 was diagnosed with Chronic Myeloid Leukemia through a bone marrow puncture examination at Hasan Sadikin Hospital, BCR-ABL has not been tested yet. The patient in this case based on the results of the 2019 bone marrow examination was diagnosed with chronic phase CML because the blast count was < 10%. The patient 3 weeks earlier had been treated at Thamrin Hospital, Jakarta, for 7 days and was given a transfusion of 2 units of Packed Red Cell blood and 6 units of platelet blood. Then the patient was referred to Hasan Sadikin Hospital RSHS) for further treatment. Patients routinely take hydroxyurea 1x1 tablet/day since the

diagnosis of CML in 2019.

Physical examination revealed that the patient was weak, conscious, and anemic, with hepatosplenomegaly. The liver was palpable 3 cm below the costarum arc and the spleen was palpated on Schuffner 2, the extremities were warm. The patient's laboratory results on the first day showed pancytopenia with Hb 6.7 g/dL, leukocytes 980/mm³, and platelets 21,000/mm³. While the results of the type count obtained 4% segment neutrophils, 90% lymphocytes, 4% monocytes, and 2% blasts. Transformation of hematological results and confirmed type count from bone marrow aspiration carried out in 2021 showed a predominance of lymphoid series with lymphoblasts at 24.6%. Figure 1 below shows a bone marrow aspiration with lymphoblast infiltration in 2021

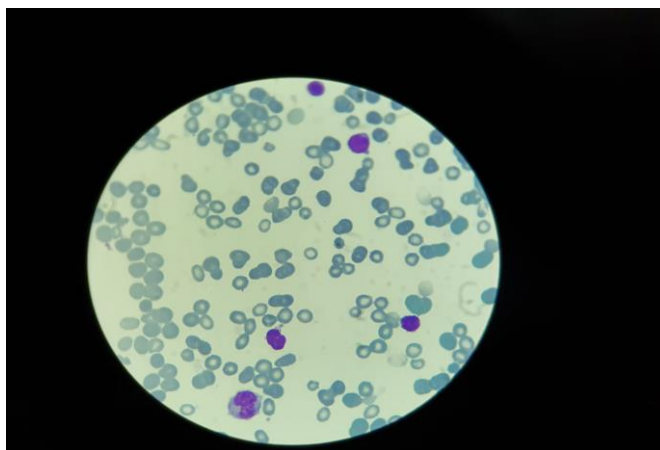


Figure 1. Lymphoblast infiltration

3. Discussion

Chronic myeloid leukemia is a myeloproliferative neoplasm originating from pluripotent stem cells. The Philadelphia chromosome (Ph) is the result of a translocation between chromosomes 9 and 22, which can be detected in myeloid, erythroid, megakaryocytes, B lymphocytes, and occasionally T lymphocytes.¹ The ABL gene (Abelson Murine Leukemia Viral Oncogene Homolog 1) is normally expressed in all cells and has a role in signal transduction of adhesion receptors and cell surface growth factors to regulate the cytoskeleton structure of chromosome 9.² Although not yet fully elucidated. Functions of ABL proteins are known to be involved in cell cycle regulation, cell growth, gene transcription, stress response, and signal transduction.²

The BCR (Breakpoint Cluster) gene was also normally expressed in all cells. Fusion of the BCR-ABL gene causes impaired adhesion to stromal cells and the extracellular matrix, constitutively active mitogenic signaling pathways, and results in decreased apoptosis. CML transformation is associated with mutations such as gene deletion, insertion, or point mutation.³

Philadelphia chromosome is a chromosomal abnormality encoded BCR-ABL1 is a hallmark lesion of CML disease and a subset of ALL.⁴ The Philadelphia (Ph) chromosome has a reciprocal translocation between the ABL gene on chromosome 9 and the BCR gene on chromosome 22. The Philadelphia chromosome (Ph) is

found in 95% of adult CML patients and 5% of pediatric CML patients.³ The Ph chromosome is not only specific for CML but also can be found in patients with acute leukemia, either ALL or AML. Philadelphia chromosomes are also found in adult Acute Lymphoblastic leukemia (ALL) (10%-20%) and 2%-5% of pediatric ALL, lymphoma, myeloma, and Ph-positive Chronic Neutrophilic Leukemia (CNL) patients.³

In the chronic phase of CML, the patient is stable for several years and is usually responsive to chemotherapy. Peripheral blood smear examination in patients with chronic phase of CML can find blasts with a small number, namely 10%. In the accelerated phase, CML patients can experience various clinical manifestations that lead to worsening, namely the patient has a fever, significant weight loss, splenomegaly, bone, and joint pain, bleeding, and is prone to infection.¹ On hematological examination, a very progressive leukocytosis will be found, persistent thrombocytopenia ($1000 \times 10^9/L$), and on examination of the peripheral blood smear and/or bone marrow smear, 10-19% blasts can be found, and an increase in the basophil count 20% on the peripheral blood smear.¹

The patient in this case based on the results of a bone marrow examination in 2019 was diagnosed with chronic phase CML because the blast count was <10%. The patient in June 2021 came to the hospital and underwent a bone marrow evaluation. Bone marrow results showed hypocellular cellularity, no erythroid cells were found, only a few granulocytes were found, and 24.6% lymphoblast infiltration was found with scanty cytoplasm, fine nuclear chromatin, and 1-2 nuclear daughter so the results of BM are thought to resemble acute lymphoblastic leukemia (ALL) these conditions indicate a transformation towards lymphoblastic. Acute leukemia can occur at any age, but several studies have shown that 75% of cases of ALL occur in children with a peak incidence at the age of 2-9 years and 80% of cases.¹ The cause of leukemia is still not known with certainty.⁵ Genetic factors, namely the presence of translocations, fusions, and gene mutations in hematopoietic progenitor cells can cause disturbances in the expression of oncogenes and tumor suppressor genes so that regulation of cell proliferation and differentiation is disrupted.⁵

Acute Lymphoblastic Leukemia (ALL) consists of a group of disorders characterized by chromosomal abnormalities, translocations, trisomies, and deletions.^{2,6} BCR-ABL1-positive in acute lymphoblastic leukemia is found in 5% of children and about 40 of adults.^{6,7}

Mullighan's study found that the cause of the transformation of CML into ALL was due to a mutation in the form of a deletion of the Ikaros transcription factor 1 (IKZF) gene. IKZF1 gene deletion was found in 90.9% of adult patients, and 76.2% of pediatric patients with BCR ABL ALL.⁷ The deletion of IKZF1 in the transformation of CML to ALL leads to loss of Ikaros. Ikaros is important for hematopoiesis and tumor suppressor activity. IKZF1 deletion containing Ikaros causes a lymphoblast-type blast crisis, resulting in the transformation from CML to ALL. The mutation is said to occur due to inadequate treatment of CML. The pathomechanism of the mutation is not clearly understood.⁷

Tyrosine Kinase Inhibitor (TKI) is an effective and selective therapy for CML with positive BCR-ABL. Tyrosine Kinase Inhibitor therapy plays an important role in modulating growth factor signaling. The active form of this enzyme can lead to increased proliferation and growth of tumor cells, induce anti-apoptotic effects, and promote angiogenesis and metastasis. In the CML presence of the BCR-ABL gene, tyrosine kinase causes cellular transformation. Thus BCR-ABL is an ideal target as molecular target for the treatment of CML.⁸

Imatinib is the first generation TKI used for the treatment of chronic phase CML. Imatinib is a 2-phenyl amino pyrimidine derivative that functions as a specific inhibitor of the tyrosine enzyme. Imatinib is the first

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Dasatinib is a second-generation TKI with 350 times the strength compared to imatinib with an initial dose of 100 mg once daily. Side effects of dasatinib in the form of neutropenia and thrombocytopenia occur in the majority of patients with chronic phase CML who were initially treated with dasatinib. Nilotinib is a TKI in the form of a capsule that is given orally and has a structure analogous to imatinib. Nilotinib is intended for patients who fail to provide a hematological or cytogenetic response to imatinib.⁸

The patient regularly takes hydroxyurea. Hydroxyurea or Hydroxycarbamide is a ribonucleotide reductase inhibitor. Hydroxyurea was first synthesized in 1869 and is used in myeloproliferative diseases. This hydroxyurea is well tolerated and effective in suppressing leukocytosis in CML patients until a diagnosis of CML can be established. Since 2019, patients have been advised to do a BCR-ABL examination but it has not been done so it is not known whether the patient has a Ph chromosome or not. Treatment of ALL with Ph chromosomes can use a tyrosine kinase inhibitor (TKI) but even after treatment with TKI or stem cell transplantation, relapse can still occur.⁹

The patient used hydroxyurea from 2019 to 2021 because the ABL BCR had not been examined and leukocytosis was obtained in 2019. Hydroxyurea was used as palliative therapy in this patient to reduce leukocytes. Hydroxyurea used for the treatment of malignancies can cause bone marrow suppression in the form of leukopenia followed by thrombocytopenia and anemia.¹⁰ Leukocytes in patients with acute leukemia can also vary with the incidence of hyperleukocytosis ($> 100,000/\text{mm}^3$) occurring in approximately 15% of patients. Leukopenia in ALL can occur especially if the patient is already on chemotherapy.¹ On day 5 of treatment in 2021 the patient was diagnosed with febrile neutropenia. Neutropenia was defined as an absolute neutrophil count less than $500/\text{mm}^3$. Febrile neutropenia (FN) is defined as a temperature above 38.3°C in one temperature measurement or a temperature obtained at 38.0°C in a period of more than 1 hour with an absolute neutrophil count less than $500/\text{mm}^3$ or an absolute neutrophil count less than $1000/\text{mm}^3$ with predicted absolute neutrophil decline to $500/\text{mm}^3$ within 48 hours.¹¹

This patient had an absolute neutrophil of $300/\text{mm}^3$ since the 1st day of treatment and had a continuous fever with a temperature $>38^\circ\text{C}$, so it was included in the criteria for febrile neutropenia. The causes of neutropenia vary, including infection, drugs, radiotherapy, chemotherapy, hypersplenism, bone marrow replacement, anemia, bone marrow failure, hypoplastic anemia, nutritional deficiency, vitamin B12, and folate deficiency.^{11,12} In this case, febrile neutropenia was probably due to the effect of hydroxyurea chemotherapy. Hydroxyurea can cause febrile neutropenia in 5% of cases, and cause thrombocytopenia in 1-5% of cases.¹³

4. Conclusion

The transformation of CML to ALL can occur in 5% of children and 40% of adults. Transformation can occur due to genetic mutations and inadequate treatment.

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