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CHRONIC MYELOGENOUS LEUKEMIA TRANSFORMATION INTO ACUTE LYMPHOBLASTIC LEUKEMIA

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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. A 22-year-old male with a history of CML since 2014 and positive BCR-ABL p210 in 2017 came with the complaint of weakness. Physical examination showed hepatosplenomegaly. Complete Blood Count (CBC) showed Hb 7.1 g/dL, WBC 290,620/µL, platelet 434,000/µL. Blood Smear Evaluation (BSE) suggested CML blastic crisis with DD of AML-M5. Patient's condition got worse and the CBC result showed WBC 96,770/µL and platelet 7,000/µL in 2 weeks. Blood smear evaluation was dominated by mononuclear cells with scanty blue cytoplasm, no granules, no Auer rods, loose chromatin, and indistinct nucleoli, suggesting lymphoblasts with a proportion of 60%. The BMA result was dominated by lymphoblast, consistent with ALL. The immunophenotyping result was CD10+, CD34+(0,99%), CD79a+, HLA-DR+, and CD20+. Molecular examination showed positive RUNX1 and NRAS while FLT3, NPM1 and del(5q) was negative. BCR-ABL gene can be found both in CML and ALL. CML transformation into ALL had been reported to be related with deletion of a transcription gene. Diagnosis of ALL can be established by BMA and immunophenotyping. CD34+ expression of lymphoblast in ALL can be varied and found to be minimal in this case. Patient with history of CML showed an ALL picture based on BSE, BMA, and immunophenotyping suggesting CML transformation into ALL although CD34+ expression was minimal.

Key words: Chronic myelogenous leukemia, acute lymphoblastic leukemia, transformation, BCR-ABL

INTRODUCTION

Chronic Myelogenous Leukemia (CML) is a myeloproliferative neoplasm from a pluripotent stem cell in bone marrow consistently related to BCR-ABL gene fusion that found in Philadelphia chromosome. Translocation t(9;22)(q34;q11.2) can be found in 90-95%. This translocation causes gene fusion of the BCR gene on chromosome 22 with the ABL gene on chromosome 9.[1]

Untreated CML could undergo three phases chronic, accelerated and blastic crisis phase. Most patients are diagnosed in the chronic phase. Untreated CML can progress into blastic phase with or without accelerated phase. Most blastic crisis CML has a feature of Acute Myeloid Leukemia (AML), while others rarely have a feature of acute lymphoblastic leukemia (ALL). The researcher will report the case of CML that transformed into ALL.[2,3]

CASE

Twenty-two years old man came to Dr. Soetomo hospital Surabaya Indonesia with main complain of general weakness on December 29, 2017. The patient was also complained about an intermittent fever for about one week before admission. Spontaneous bleeding was denied.

The patient was diagnosed with CML in 2014 based on blood smear evaluation and bone marrow evaluation. Both examinations were done in the Dr. Soetomo Hospital. Because of financial limitation, the CML diagnosis was based on blood smear and bone marrow evaluation only. He had not done a BCR-ABL examination yet in 2014. He routinely controlled in Hematology-Oncology Outpatient Ward in the Dr. Soetomo Hospital. The patient received hydrea since 2014.

In August 2017, the CML diagnosis was confirmed by quantitative BCR-ABL examination. The result showed 5% of BCR-ABL p210 was detected. The therapy was changed into a combination of hydrea and imatinib after since until his recent complaint. He got hospitalization from December 29, 2017, until February 3, 2018, that will be discussed later in the discussion.

Physical examination showed the patient was weak, conscious, looked anemic, with hepatosplenomegaly. The liver was palpable on 2 fingers below the costal

margin, while the spleen was palpable on Scuffner 4 Hacket 5. The extremities were normal, warm and no spontaneous bleeding manifestation.

Serial complete blood counts were done. The complete blood count results were shown in Table 1. The result of BSE on September 27, 2017, was normochromic normocytic anemia, dominated by myeloid series with the proportion of myeloblast 12%, promyelocyte 18%, myelocyte 12%, metamyelocyte 5%, stab neutrophil 18%, segmented neutrophil 28%, eosinophil 2%, basophil 3%, while lymphocyte 2% accompanied with thrombocytosis. The conclusion was the accelerated phase of chronic myelogenous leukemia. The patient's BSE in accelerated phase is presented in Figure 1.

Blood smear evaluations were also done during this recent hospitalization. The result of the blood smear evaluations was presented in Table 2, while the pictures were presented in Figure 2 and 3.

The transformation of the BSE result was then confirmed with bone marrow aspiration examination and immunophenotyping. The bone marrow aspiration examination was performed on January 17, 2018, and followed with immunophenotyping on January 18, 2018. The bone marrow examination picture was dominated with lymphoid series and the conclusion was consistent with acute lymphoblastic leukemia. The bone marrow examination result is presented in Table 3, while the picture is presented in Figure 4.

Table 1. The dynamics of complete blood count examination

Parameters	29 Dec 2017	4 Jan 2018	11 Jan 2018	25 Jan 2018	27 Jan 2018	2 Feb 2018	Reference range
Hb (g/dL)	7.1	9.8	8.8	8.4	10.4	10.8	L:13.3-16.6 P:11.0- 14.7
RBC (106/µL)	2.72	3.91	3.2	4.2	3.85	4.13	3.69-5.46
HCT (%)	21.8	30.8	27.1	25.2	24.8	30.1	L:41.3-52.1 P:35.2- 46.7
MCV (fL)	80.1	78.8	82.6	79.7	78.2	72.9	86.7 – 102.3
MCH (pg)	26.1	25.1	26.8	26.6	27	26.2	27.1 – 32.4
MCHC (g/dL)	32.6	31.8	32.5	33.3	34.6	35.9	29.7 – 33.1
RDW (%)	18.8	17.7	16.9	16.0	16.1	16.8	12.2 – 14.8
Platelet (103/µL)	434	165	7	7	8	12	150 – 450
WBC (103/µL)	290.62	149.67	96.77	14.57	1.27	0.15	3.37 – 10
Diff count* (%)	0/0/ 9/84/7	0/0/2/ 75/23	0/0/0/78/ 22	0/0/2/82/ 6	0/0/16/7 6/8	0/0/20/73 /7	-

Hb, Hemoglobin; RBC, Red Blood Cell Count; HCT, Hematocrit; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration, RDW, Red Cell Distribution Width; WBC, White Blood Cell Count; diff count, differential white blood cell count

*: Baso/Eo/Neut/ Lympho/Mono

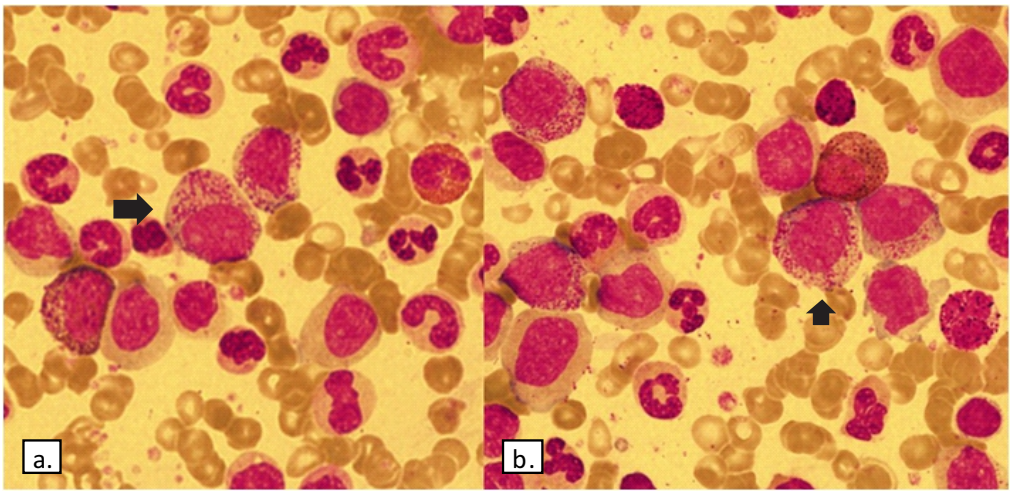

Figure 1. Patients blood smear evaluation picture was done in September 2017. Pictures a. and b. showed the accelerated phase of chronic myelogenous leukemia, blue arrow showed myeloblast. (Wright staining, 1000x magnification)

Table 2. Blood smear evaluation results of recent hospitalization

Parameter	Date	
	December 29, 2017	**January 11, 2017**
Erythrocyte	Normochromic normocytic, no normoblast	Normochromic normocytic, normoblasts were present
Leukocyte	The count seemed to be increased. Dominated by mononuclear cells with bluish cytoplasm, no granule, no Auer rod, irregular-regular nuclei, loose chromatin, 1 - 4 nucleoli suggesting monoblast with a proportion of 80%. There were also promonocyte 4%, myelocyt e 2%, stab neutrophil, segment neutrophil 7%, and other cells 3%	The count seemed to be increased. Dominated by mononuclear cells with bluish cytoplasm no granule, no Auer rod, irregular-regular nuclei, loose chromatin, 1-2 nucleoli suggesting lymphoblast with a proportion of 60%. There were also prolymphocyte 27%, and lymphocyte 13%,
Thrombocyte	The count seemed normal, no giant platelet	The count seemed to be decreased, no giant platelet
Conclusion	Suggesting blastic crisis CML differential diagnosed with AML-M5	Patient with CML history currently presents anacute lymphoblastic leukemia picture.
Suggestion	-	Bone marrow aspiration and immunophenotyping

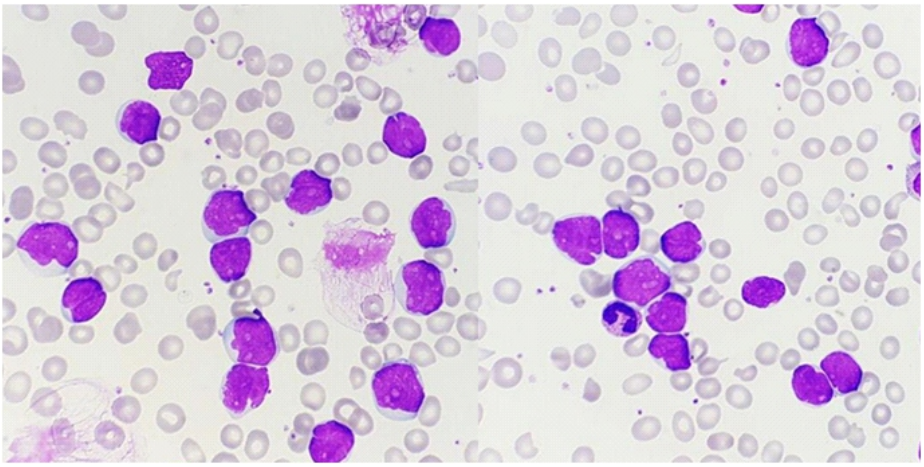

Figure 2. Blood smear evaluation picture of the patient on December 29, 2017, suggested blastic crisis CML differential diagnosed with AML-M5. (Wright staining, 1000x magnification)

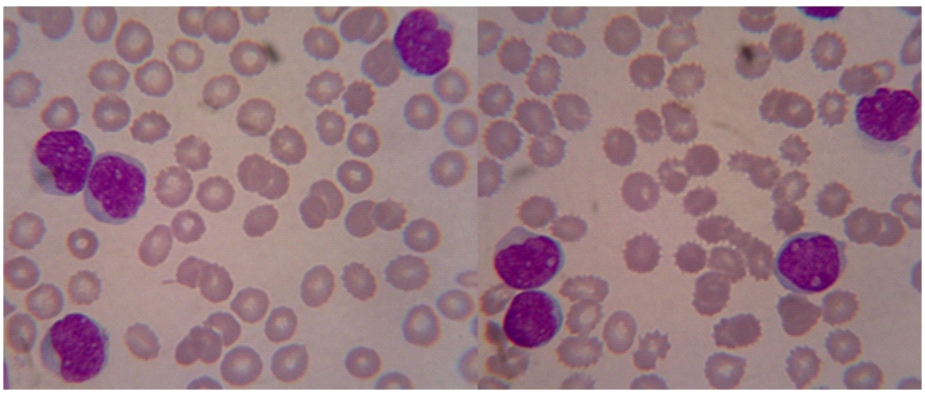

Figure 3. Blood smear evaluation picture of the patient on January 11,2018, was dominated by lymphoid series suggested acute lymphoblastic leukemia picture in the patient with CML history. (Wright staining, 1000x magnification)

Table 3. Bone marrow aspiration evaluation result on January 11,2018

Parameter	Bone marrow aspiration evaluation
Cellularity	Hypercellular
M:E ratio	1:1
Erythropoiesis system	Decreased activity
Granulopoiesis system	Decreased activity
Megakaryopoiesis system	Decreased activity, megakaryocyte was difficult to be found
Other cells	The nonhematopoietic cell was not found. Increase in lymphoblast proportion as many as 50%.
Conclusion	Bone marrow aspiration picture of a patient with chronic myelogenous leukemia history currently was consistent with an acute lymphoblastic leukemia picture

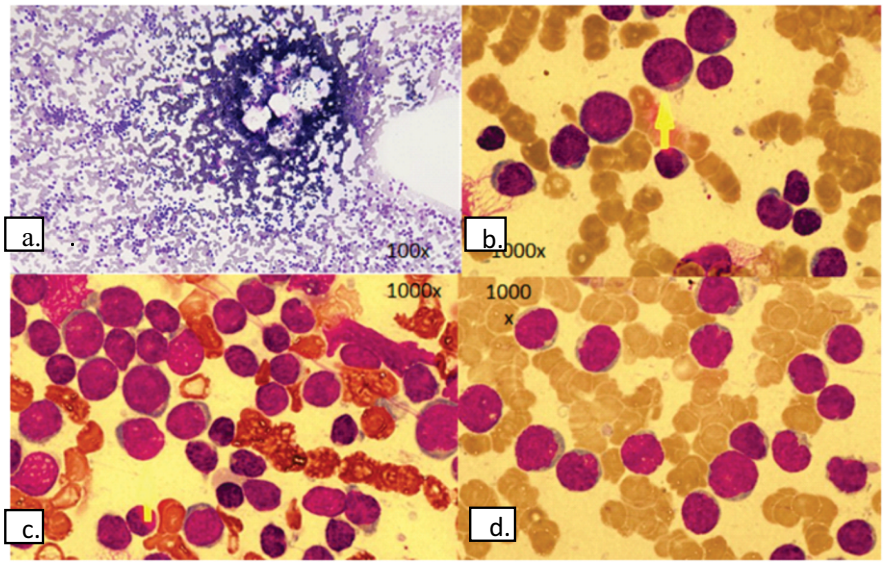

Figure 4. Bone marrow aspiration picture of the patient with chronic myelogenous leukemia currently was dominated with lymphoid series; a. cellularity of the bone marrow; b, c, and d. bone marrow aspiration pictures were dominated with lymphoid series, yellow arrow showed lymphoblast. (Wright staining, 1000x magnification, except upper left picture was 100x magnification)

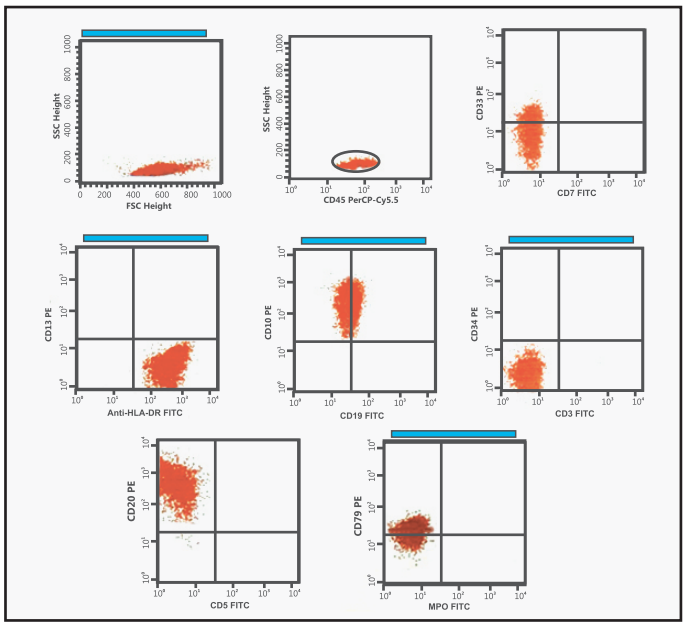

Figure 5. The result of immunophenotyping examination done on January 18, 2018

Immunophenotyping examination of peripheral blood results were as follow CD10+, CD34+(0,99%), CD79a+, HLA-DR+, and CD20+. This immunophenotyping result suggested the cells were lymphocytic series (Figure 5).

The molecular examination was done in order to know any mutation happened in this transformation. The results showed positive for RUNX1 and NRAS while negative for FLT3, NPM1 and del(5q). The molecular RUNX1, FLT3, NRAS, and NPM were tested using Polymerase Chain Reaction (PCR), while del(5q) was tested using Fluorescence In Situ Hybridization (FISH).

During his hospitalization, he got imatinib and hydrea for the therapy. Unfortunately, his condition became worse accompanied by a drastic decrease in white blood cell and thrombocyte counts. The imatinib and hydrea therapy was then stopped after the bone marrow aspiration and immunophenotyping result was released. Therapy was changed into vincristine. However, the patient condition did not get better. The leukocyte and thrombocyte continued to decline. The patient was passed away on February 3, 2018.

DISCUSSION

Besides in CML, BCR-ABL gene fusion caused by t(9;22) translocation can also be found in ALL and AML. Diseases caused by this fusion gene are depended on the breakpoint location on the BCR gene. The most common breakpoint location in CML is in the major cluster M-BCR that produces p210 protein. Breakpoint in the minor area m-BCR will produce ap190 protein that mostly related to ALL cases with positive Philadephia chromosome.[4]

CML is characterized by the Philadelphia chromosome resulting from t(9;22)(q34;q11) reciprocal chromosomal translocation which leads to the formation of BCR/ABL fusion gene. This chromosome can be found in more than 90% of CML patients. This abnormality results from translocation of the ABL gene, located in the long arm of chromosome 9, into the BCR gene located in the long armof chromosome 22. This results in a shortened chromosome 22 and formation of the chimericgene BCR/ABL on chromosome 22.[1-3]

Depending on the breakpoint in the BCR gene, there are three main types of BCR-ABL protein produce by this chimeric gene.[4] The majority of CML patients have a breakpoint in the major breakpoint cluster region (M-bcr) of BCR gene and intron 1 or 2 of ABL gene which results in the production of 210kDa fusion protein (p210 BCR-ABL). A minor case with p190 can be found in CML with monocytosis.[3]

Patient with CML chronic phase can progress into an accelerated phase or directly into blastic phase without tyrosine kinase inhibitor treatment in a period of 5 years. CML patients in chronic phase or accelerated phase usually have a good response to tyrosine kinase inhibitor therapy, while blastic crisis CML patient usually resistant to tyrosine kinase therapy.[2,5]

The patient-controlled routinely in Hematology-Oncology Clinic and got hydrea therapy for 2.5 years. However, the definitive treatment for CML that is the tyrosine kinase inhibitor was not given for more than two years after diagnosis. The quantitative BCR-ABL examination was done after 2.5 years of CML diagnosis and hydrea therapy. The p210 BCR-ABL was detected with a proportion of 5%. Directly after BCR-ABL was confirmed, the therapy was changed into imatinib and continued the use of hydrea. The therapy went on for about six months before his recent hospitalization. The delay of tyrosine kinase inhibitor therapy might play a role in this uncontrolled transformation of CML.

Blastic crisis mechanism in CML is still poorly understood. Some of the blastic crises (75-80%) have myeloblastic phenotype while others (20%) have a lymphocytic phenotype. Chronic myelogenous leukemia transformation into blastic crisis is related to additional mutation such as gene deletion, insertion or point mutation. An additional mutation in p53 tumor suppressor gene and run related transcription factor gene (RUNX1) can be found in 20-38% blastic crisis patient with myelocytic phenotype. These additional mutations are stated to be responsible for tyrosine kinase inhibitor resistance. The RUNX1 mutation mostly found in AML but rarely found both in CML and ALL.[2,5,6]

Mutation locus in Cyclin-Dependent Kinase Inhibitor 2A/2B (CDKN 2A/B) and Ikaros Transcription Factor (IKFZ) can be found in 50% and 55% of ALL case respectively. The decrease in Ikaros activity was also reported to have a correlation with the occurrence of the blastic crisis in CML.[7]

In this case, based on the morphology of peripheral blood smear evaluation and the BCR-ABL examination result, the patient firstly diagnosed as CML accelerated phase. The immunophenotyping result in lymphoid phenotype blastic crisis mostly has the feature of B cell ALL, which usually has a positive expression of CD19, CD 79a, CD22, and CD10. CD 20 and CD34 expression can be variable, while CD45 commonly negative. Co-expression with any myeloid antigen such as CD13 and CD33 do not

exclude B cell ALL.[3,7]

CONCLUSION

Chronic myelogenous leukemia chronic phase can transform into a blastic crisis which most of it has AML feature, less commonly ALL feature. Most of CML patients with lymphocytic phenotype blastic crisis have B cell ALL feature based on immunophenotyping. In this case, we found a CML transformation into B cell ALL with RUNX1 and NRAS mutation.

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