Case Report

Diffuse large B-cell lymphoma in a patient with chronic myelogenous leukemia on accelerated phase with bilateral pleural effusion: a case report

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ABSTRACT

Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder of pluripotent stem cells. The pathogenesis of CML is known to be related to mutations in the form of Philadelphia chromosomes. The incidence of CML constitutes 20% of all cases of leukemia in adults. The current gold standard for CML therapy is using tyrosine kinase inhibitors (TKI), Imatinib. Non-Hodgkin Lymphoma (NHL) is a malignancy that develops from lymph nodes. In NHL the formation of malignant cells is in the form of lymphocytes that are at one of the differentiation levels of either T lymphocytes or B lymphocytes. Diffuse large B cell lymphoma is the most common NHL, representing about 40% of all lymphoma cases. NHL management is targeted chemotherapy using rituximab combined with cyclophosphamide, doxorubicine, vincristine and prednisone. A Thirty-four year-old female patient has been reported with the main complaint of fatigue and pale weakness accompanied by an enlarged abdomen. Complaints are also accompanied by a lump in the right neck, fever, productive cough and shortness of breath. The patient has been known to suffer from CML with BCR-ABL (+) since five years ago and received Imatinib therapy, but then the patient stopped treatment himself. On physical examination found anemic, multiple enlargement of the neck lymph nodes, wet crackles soft and loud in the basal of both lungs and splenomegaly. On investigations found severe anemia, thrombocytopenia and blast 13%, increased d-dimer, bronchopneumonia-compliant infiltrate and bilateral pleural effusion on chest x-ray, results of exudate pleural fluid analysis with the cytology of a malignant smear metastasis of lymphoma to the pleura, histopathology of the neck lymph nodes with chest x-ray, analysis of exudate pleural fluid with the cytology of a malignant smear metastasis of lymphoma into the pleura, histopathology of the neck lymph nodes with the results of diffuse large B-Cell lymphoma, as well as enlargement of paraaortic lymph nodes, hepatosplenomegaly and chronic pancreatitis on abdominal ultrasound. Patients were given antibiotics, transfusion of packed red cells and platelets, pleural tap and chemotherapy. The patient was planned to undergo chemotherapy for 6 cycles of 21 days, and a CD20 examination was performed. The incidence of NHL in patients with good CML in imatinib therapy is not yet certain whether there is a direct relationship.

Keywords: Chronic myelogenous, Imatinib, Non-hodgkin's lymphoma

INTRODUCTION

Chronic Myelogenous leukemia (CML) was the first leukemia that found and discovered its pathogenesis.
CML is a myeloproliferative disorder in pluripotent stem cells and with the presence of Philadelphia (Ph) chromosome. Translocation of chromosomes 9q34 and 22q11 occurs in patients with CML. Ph chromosome has a unique gene fusion called Bcr- Abl, and it is now believed to be the main cause of CML.1

CML representing 20% of all leukemia cases affecting adults. CML was the second most common leukemia in adults after chronic lymphocytic leukemia. The incidence of CML reaches 1.5 per 100,000 population per year and happens more common in men than women (2:1.2), typically occurring in middle age with a peak at 40-50 years. In Japan, the incidence increased after the atomic bombings in Nagasaki and Hiroshima, and in Russia after the Chernobyl atomic reactor exploded.2

The BCR-ABL gene on the Ph chromosome causes extreme proliferation of pluripotent stem cells in hematopoiesis system. The Bcr-abl gene is anti-apoptosis so the clones can survive longer than the normal cells. The formation of these abnormal clones suppresses other hematopoiesis systems.3

The BCR gene functions as a heterodimer of the ABL gene that has tyrosine kinase activity, so the fusion of these two genes can auto-phosphorylation which activates several proteins in the cytoplasm of cells through the SRC-homology 1 (SH1) domain that causes deregulation of cell proliferation, decreasing adherent’s cells to bone marrow stroma and reduced apoptotic response. The fusion of the BCR-ABL gene will interact with various proteins in the cytoplasm that occurring oncogenic signal transduction. This signal will cause activation and repression of the transcription process in RNA, so there will be dysfunction in the process of apoptosis.4

CML is divided into 3 phases, namely: the chronic phase, the acceleration phase, and the blast crisis phase. In general, when the first diagnosis is made, the patient is still in the chronic phase, often even the diagnosis of CML is found by chance. Most CML do not provide clinical symptoms. If found, there were not typical such as fever, lots of sweating, night sweats, bone pain, fatigue, anorexia, and weight loss. In the chronic phase, patients often complain of enlarged spleen, or feel full quickly due to spleen pressure on the stomach. Sometimes pain arises like squeezing in the upper right abdomen due to stretching of the spleen capsule.5

Characteristics of the acceleration phase are leukocytosis, which is difficult to control by myelosuppressive drugs, peripheral myeloblasts reaching 15-30%, promielocytes >30%, and platelets <100,000/mm³. Clinically, this phase can be suspected if the spleen that was already shrinking with enlarged therapy, worsening anemia, petechial, ecchymosis arise. If accompanied by fever, usually there is an infection.6

In the blast crisis phase, more than 30% of immature cells are found in the peripheral region or bone marrow. In this phase, CML cells begin to behave like acute leukemia. Sufferers often have fever, malaise, enlarged spleen, weight loss, and other symptoms that mimic acute leukemia. Generally within 3-5 years, CML chronic phase will progressively become a phase of acceleration and blastic crisis which is fatal.7

The diagnosis of CML is confirmed by the finding of clinical manifestations and supported by the finding of anemia and severe leukocytosis with blast cells in peripheral blood. The definitive diagnosis of CML is hyper-cellular bone marrow biopsy with dominant myeloid system.8

**CASE REPORT**

A 34-year-old woman was hospitalized in the internal medicine ward of M. Djamil Hospital Padang, with the chief complaints of fatigue that has increased since 1 week before being hospitalized. The patient looked pale since 1 week ago. The patient also complained of an enlarged abdomen 8 years ago. The patient has been known to suffer from CML since 8 years ago, received hydroxurea 1x500 mg for 3 years, then received Imatinib 1x400 mg therapy after BCR-ABL examination was positive.

The patient also complained of a lump in the right neck since 3 weeks ago. Initially one with the size of a marble and then followed by 5 small lump as big as peanuts. Next lumps appear on the head, left and right fold of thighs, upper middle abdomen, left neck and finally fold the armpits. The lump felt increasingly enlarged, felt chewy. There was no pain in the lump.

The patient also complained of cough since 1 week ago accompanied by yellowish-white phlegm accompanied with fever since 2 days ago. Patient felt decreased appetite and weight since 1 week ago. The patient was treated at M. Djamil Hospital 2 weeks ago with complaints of a lump in the right neck. A biopsy has been done on the right neck lump, but it is still waiting for the results. The patient is a housewife, lives in a permanent home with her husband and 2 children with good ventilation and adequate lighting. History of smoking, exposure to radiation, malignancy in the family was denied. History of contact with chronic coughing patients is absent. A history of blood transfusion was present. The last blood transfusion was 2 units of packed red cell in the previous treatment.

At the time of treatment, the patient was fully alert, with blood pressure of 110/70 mmHg, respiratory rate 20 x / minute, heart rate 92x/minute and body temperature 37.5°C. Physical examination showed anemic on conjunctiva, enlargement of multiple lymph node in the neck region of the right hand with varying sizes, with a springy consistency, fixed, without tenderness and fluctuations. On physical examination of the lungs, there
was a soft wet crackle in both lung bases. On abdominal physical examination hepatosplenomegaly is obtained.

The results of right neck lymphadenopathy biopsy was for mofa diffuse large B-cell lymphoma. Patient was treated with antibiotics, packed red cell and platelet transfusions, pleural fluid puncture. Furthermore, patient is given chemotherapy with cyclophosphamide, vincristine, and prednisone. Chemotherapy is planned to be carried out for 6 cycles between 21 days. Patient was followed upon clinical and laboratory responses to chemotherapy for NHL and monitoring Sokal scores for CML prognosis.

Laboratory Investigations showed Hemoglobin was 5.6 gr/dl, leukocytes 6,500/mm³ with diff count 0/1/4/40/20/10, blast 13%, promielocytes 6%, myelocytes 6%, platelets 20,000/mm³, Reticulocytes 0.67. MCV/MCH/MCHC80/27/36, an D-dimer 1403 ng/mL. The peripheral blood film obtained erythrocytes normochromic anisocytosis. LDH was 1340 u/L, uric acid 10.3 mg/dL, direct bilirubin 0.2 mg/dL, indirect bilirubin 0.3 mg/dL.

Hbs Ag, anti HCV was non-reactive. Chest X-ray showed bronchopneumonia with bilateral pleural effusion. Pleural fluid analysis was performed with result exudate impression and pleural fluid cytology with the result of malignant smear possibly a lymphoma metastasis in pleura. Abdominal ultrasound showed hepatosplenomegaly and paraaortic lymphadenopathy.

DISCUSSION

A 34-year-old woman with a final diagnosis of acceleration phase of CML, diffuse large B cell lymphoma stage 3B, hospital acquired pneumonia, bilateral pleural effusion due to malignancy, bicytopenia because of leukemia cell infiltration, a high risk of VTE and chronic pancreatitis was treated.

The diagnosis of accelerated phase of CML was made because the patient has been known to suffer CML since 8 years ago based on bone marrow puncture examination and has received hydroxyurea therapy followed by imatinib. At present, anemia and thrombocytopenia were found in the patient after imatinib therapy for 4 years. According to research, hematological toxicity of red blood cells can be caused by imatinib. 78 patients (80.4%) experienced anemia after two years of therapy. This was the side effect of imatinib as a tyrosine-kinase inhibitor of BCR-ABL. Imatinib also inhibits C-KIT proto-oncogenes that involved in hematopoiesis. Therefore, myelosuppression may be the result of unexpected suppression of progenitorcells.9

The diagnosis of NHL in this patient was made based on the history of a lump appearing on the right neck. On physical examination, there were lumps that felt supple without pain in several lymph node regions, which is bilateral colli, bilateral inguinal, bilateral axilla, temporal and occipital. The histopathological examination of
lymph nodes biopsy obtained diffuse large B cell lymphoma.

Diffuse large B cell lymphoma is the most common NHL, representing about 40% of all lymphoma cases. A CD20 examination was performed for targeted rituximab chemotherapy and still waiting for the results. The patient was treated with chemotherapy combination of COP regimen; cyclophosphamide, vincristine and prednisone, followed by a good response of therapy. The rituximab and COP regimens will increase overall survival rates in 3 years from 49% to 62% when compared to only COP.10

In this patient, CML has been found since 8 years ago and has received imatinib therapy. Non-Hodgkin lymphoma was the second malignancy found in this patient. It has been reported the incidence of secondary malignancy in patients receiving imatinib therapy for 5 years with the age of 30-88 years. Ten percent of secondary events are non-Hodgkin lymphoma.11

The acceleration phase and blast crisis phase are related to extra medullary disease, 17-29% involve lymph nodes. In another study from a randomized controlled trial about the effects of long- term tyrosine kinase inhibitors showed patients with imatinib therapy had a higher risk of NHL 3.33 times in men and 4.29 times in women. The effect of imatinib on the mechanism of DNA repair may be the mechanism of secondarily malignancy.12,13

The hospital-acquired pneumonia was obtained based on history taking which revealed a cough with phlegm and fever. On physical examination, bronchovesicular breath sounds and crackles found on both lung bases. Diagnosis of hospital-acquired pneumonia is based on history of hospitalized for more than 2 days in the past 90 days.13

Pneumonia infection in patients with malignancies was due to a decreased immune system, but the environment can also worsen the patient. The most common causes of infection are Aspergillus (59.2%) and Staphylococci (44.2%).14

The patient had a sputum culture examination before given antibiotics with “no growth” results. This can occur due to the poor quality of sputum or the patient’s mistake when discharging phlegm which contains more saliva. The patient was given cefepime and levofloxacin antibiotic therapy, which showed a good response known by the loss of pneumonia.15 In a study of 13,096 inpatients, 1,745 adult patients were treated for more than 48 hours (13.3%), and among them, 166 patients were treated with a diagnosis of HAP (9.52%).16

After several days of treatment, the patient complained of dyspnea. From the physical examination found a pleural effusion. There was no complaint of shortness of breath and signs of effusion pleura from chest x-ray on the first day of treatment. Pleural effusion occurs in 18.4% (41/223) of patients with non-Hodgkin lymphoma. Malignant effusion is defined as direct infiltration by tumor cells or metastasis. The appearance of effusion is a sign of poor prognosis inpatients.17

In this patient, a reddish pleural fluid evacuation was performed. The patient clinically improved after evacuation. The pleural fluid analysis result was given the impression of exudate, which indicates this effusion was caused by malignancy. Pleural fluid cytology also showed that the fluid was a metastasis from lymphoma cells into the pleural space.18

The diagnosis of a high risk of venous thromboembolism (VTE) in patients is based on Padua scoring the total score of 9. This patient should be given prophylactic heparin but considering that the patient has thrombocytopenia so it cannot be given. The risk of heparin in this patient is bleeding, because heparin can worsen the state of thrombocytopenia.19

The patient also performed an abdominal ultrasound examination and showed an enlargement of the pancreas. This can occur due to suppression due to enlargement of the paraaortic lymph nodes against the pancreas by lymphoma malignum. In this patient the diagnosis of chronic pancreatitis is made but there are no complaints in the patient at this time so only an observation is made.20

**CONCLUSION**

The incidence of non-Hodgkin lymphoma in patients with CML in imatinib therapy is not yet certain whether there is a direct relationship.

Based on Sokal index Scoring This patient had a score 2.1 which is a high risk. The 2 years survival rate is only 65% and the median survival is 2.5 years. The prognosis in patients is worsened by two malignancies, which is non-Hodgkin lymphoma.

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