



Pleural Effusion in Blast Crisis Phase of Chronic Myeloid Leukemia: An Unusual Extramedullary Manifestation

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Abstract

Pathogenesis of pleural effusion in Chronic Myeloid Leukemia (CML) is poorly understood and rarely reported in the literature. Extramedullary involvement has been reported in 10% of CML cases and mostly affects lymph nodes and spleen. Extensive pleural involvement of leukemia cells is rarely reported in CML. Here we report a 44-year-old Indonesian male having severe pleural effusion due to extramedullary manifestation of blast crisis CML. He had prior diagnosis of CML since August 2019, with positive Philadelphia (Ph) chromosome. Cytological examination of the pleural fluid revealed cells with the morphological features of myeloblasts. Initially the patient had a significant response to imatinib, but later he died because of poor adherence and disease progression.

Keywords: Pleural effusion; Chronic myeloid leukemia; Philadelphia chromosome; Extramedullary blast crisis

Introduction

Pleural and peritoneal involvements are rare in leukemia's. Both complications are most commonly seen in solid hematological tumors such as lymphomas. Extramedullary involvement in Chronic Myeloid Leukemia (CML) is reported in 10% of cases, mainly affects lymph nodes and spleen. Whereas pleural and peritoneum involvement are rare. Among the hematologic and lymphoid malignancies, pleural involvement is commonly seen in Hodgkin's and non-Hodgkin's lymphomas, with a frequency of 20% to 30%, especially if accompanied by mediastinal involvement [1,2]. We report an interesting case of a 44-year-old Indonesian male who presented with massive left-sided pleural effusion in the setting of blast crisis phase of CML.

Case Presentation

A 44-year-old Indonesian male with six months history of CML was presented to our hospital with shortness of breath. He had experienced mild dyspnea on exertion for a few weeks, but more recently it was worsening in the last five days. It was not associated with cough, hemoptysis, fever, or any form of bleeding manifestation. He was not a diabetic or hypertensive and there was no history of contact with tuberculosis. Although he had been diagnosed with CML since August 2019, he received no medical care until he presented to our hospital.

On admission, he was conscious and oriented (GCS 15), tachycardia (heart rate 130 bpm), tachypneic (respiratory rate 28 per min), blood pressure 130/80 mmHg, and afebrile. He was thin (body mass index: 16.53 kg/m²) and pale. Chest examination showed restricted chest movement, dullness percussion and diminished breath sound were noted in areas below the second left intercostal space. Abdominal examination revealed hepatomegaly, 3 cm below the costal margin, soft, non-tender, with a smooth edge and Schuffner-three splenomegaly, firm in consistency, smooth surface, and non-tender. There was no evidence for ascites or stigmata of chronic liver disease. The other physical examination was unremarkable.

Complete blood count revealed marked leukocytosis $114.6 \times 10^9/L$ (20% blasts, 44% neutrophils, 3% bands, 8% basophils, 4% eosinophils, 18% lymphocytes, 2% monocytes, 3% metamyelocytes, and 6% myelocytes), hemoglobin of 80 g/L and platelet count of $1030 \times 10^9/L$. The other laboratory studies only significant for low albumin (20 g/L). Peripheral blood smear revealed a left shift with abundant of blast cells (Figure 1). The BCR-ABL examination was positive (9.73%).

Since he was reporting a dyspnea in the setting of CML myeloid blast crisis, he underwent a chest CT which revealed massive left-sided pleural effusion, also partial atelectasis and a consolidation area in the anteroposterior segment of the left lung (Figure 2).

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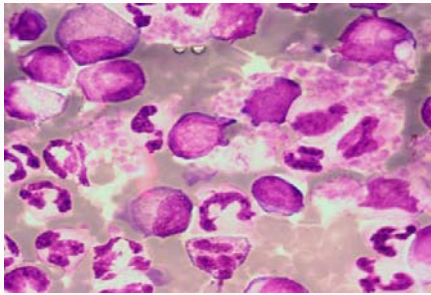


Figure 1: Peripheral blood leukocytosis with granulocytes at all stages of maturation (myeloblast predominant).

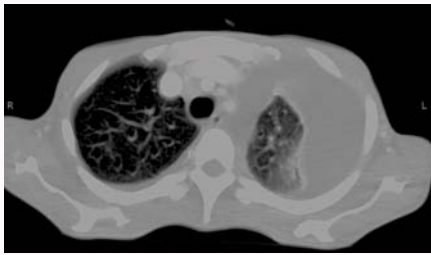


Figure 2: CT showed massive left pleural effusion with a consolidation area in the anteroposterior segment of the left lung.

Based on the imaging result, he was subjected to a diagnostic thoracentesis, which revealed an exudate with cells count $1.98 \times 10^9/L$ (86.5% mononuclear cells and 13.5% polymorphonuclear cells), 52 g/L protein (normal: 10 to 20 g/L), glucose was 4.7 mmol/L (normal <3.3 mmol/L) and Lactate Dehydrogenase (LDH) concentration was 636 U/L (more than two thirds of upper limits from normal serum LDH). We ruled out tuberculosis with a negative result of Xpert MTB/RIF and other bacterial infection with a sterile result of pleural fluid gram stain. Meanwhile, the pleural fluid cytological examination showed a lymphocyte predominant effusion with dispersed abnormal large cell which were morphologically (oval-shaped, pleomorphic and hyperchromatic) identical to a blast cell (Figure 3).

Our patient was admitted with initiation of imatinib 400 mg po q12H, along with other supportive therapy, including albumin transfusion. Pleural effusion was treated with insertion of small-bore pigtail catheter for periodic pleural fluid withdrawal. He showed a good response in the beginning of the treatment, after six days of therapy his leukocyte count was reduced to $42.66 \times 10^9/\mu L$ (blasts 5%). He was finally discharged after eight days of hospitalization. Unfortunately, the patient died one month later due to poor adherence and disease progression.

Discussion

Extramedullary blast crisis of CML is defined by infiltration of leukemic blasts in areas other than bone marrow, which has been reported in only 4% to 16% of CML cases during the disease course [3]. In our case, even though there was a hypoalbuminemia, the presence of myeloblasts in pleural fluid examination convinced that leukemia infiltration was the etiology for the underlying pleural effusion.

A study reported the cytomorphologic feature of extramedullary disease in 18 patients with CML could be sorted into three types, depending on the proportion of the blast to the mature-differentiated granulocyte cells [1]. These three categories were (1) Blastic, which

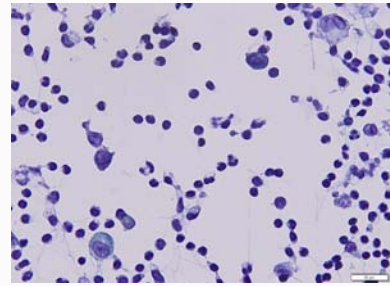


Figure 3: Pleural fluid cytology examination showed abundance of lymphocyte and blasts cell.

showing a predominance of blasts (5 patients, 28%), (2) Immature, with a predominance of blasts and other non-blastic myeloid precursor (8 patients, 54%), and (3) Mature, with a full spectrum of granulocytic maturation from blasts to granulocytes (5 patients, 28%) [1]. Based on the cytological examination, our case was the blastic type.

Several possible mechanisms of pleural effusion in patients with CML have been proposed as follows:

1. Leukemic infiltration into the pleura that usually occurs at the time of or just prior to bone marrow evolution to blast crisis phase. The most common site are lymph node, bone and nervous system, while infiltration of the brain, testis, skin, breast, soft tissue, synovial, gastrointestinal tract, ovaries, kidneys and pleura occur less frequent. Involvement of pleura has been rarely documented and isolated pleural blast crisis in the absence of medullary transformation is extremely rare [4].

2. Second possible cause of pleural effusion in CML is extramedullary hematopoiesis, although the pleura are a rare site for this mechanism. Unlike pleural leukemic infiltration, extramedullary hematopoiesis includes hematopoietic cells of the erythroid, myeloid and megakaryocytic cells, although one lineage can predominate [4,5].

3. Third mechanism of development of pleural effusions in CML is the possible obstruction of pleural capillaries or infiltration of interstitial tissue by leukemic cells during uncontrolled leukocytosis and increased capillary permeability due to cytokine production. Predisposing factors such as leukostasis and platelet dysfunction may have a role in hemorrhagic effusion of CML. Leukostasis can induced a plugging of blood vessels with secondary hemorrhage. Marked thrombocytosis and abnormal platelet function in CML may aggravated it [4,5].

4. Non-malignant causes like infection and hypoproteinemia have also been postulated as the cause of effusion. Therefore, this possibility must be excluded by identification of microorganisms by special stain and/or presence of necrotic debris [5].

5. The last possible cause of pleural effusion in CML is drug induced. Dasatinib and imatinib are tyrosine kinase inhibitor with significant anti-leukemic activity in CML patients. Their use has been associated with pleural effusion in 15% cases in one study [4,5]. The pathophysiology of dasatinib induced pleural effusion was not clear, but off-target Tyrosine Kinase Inhibitor (TKI) effect on the immune system was suggested by an observation [6]. Several risk factors such as, older adults, a history of cardiac disease, hypertension, hypercholesterolemia, and autoimmune diseases and skin rash

during or prior to treatment had been associated with dasatinib and imatinib induced pleural effusion [7,8].

Based on the literature and clinical findings, leukemic infiltration was suggested as the cause of pleural effusion in our patient. The median time from diagnosis to extramedullary blast crisis is four months, and the median survival after development of extramedullary transformation is around five months. Extramedullary disease in CML is considered as an indicator of poor prognosis, which should lead to a change in therapy and to the institution of treatments usually reserved for blast crisis [5].

Currently there is no effective standard treatment of pleural effusion associated CML, periodic pleural fluid withdrawal along with the treatment of underlying CML are the best clinical management [5]. The treatment for blast crisis in CML is depends on existence of the previous therapy and on the type of blast crisis, with the goal of the therapy is to restore the chronic phase of the disease. Patients with CML blast crisis can be treated with TKI alone or in combination with myelosuppressive chemotherapy. The dose of TKI in the setting of blast crisis phase is usually higher than appropriate dose for the chronic phase, and the second or third generation TKI is recommended for the initial therapy. However, hematologic remission rate of imatinib at a dose of 400 to 600 mg/day was superior than 400 mg to 600 mg of nilotinib (52% and 21%, respectively), but nilotinib showed superior complete remission than imatinib (40% and 16%, respectively). Meanwhile, the optimal dose of TKI in blast crisis phase of CML regarding the efficacy has not been established and individualized dose according to the treatment goal and patient's condition is recommended [9-11].

Conclusion

We report a rare case of severe pleural effusion in the setting of blast crisis CML. Patients with CML can experience several extramedullary manifestations, which commonly occurred in the blast crisis phase. It is important to note that the extramedullary blast crisis phase can occur at any time in the course of the disease, with poor prognosis. Although very rare, pleural leukemic infiltration should be considered as a cause of pleural effusion in CML patient, especially in blast crisis phase.

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