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PRIMARY MYELOFIBROSIS

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ABSTRACT

A 55-year-old male was admitted to hospital with chief complaint of abdominal distention since one year before admission, and it became more prominent than before. The physical examination showed splenomegaly with schuffner line S5, and it was confirmed with ultrasonography. The routine blood test showed a hemoglobin level of 9.2 g/L, leukocyte count of 14.690/µL and thrombocyte count of 115 x 103/µL. From the peripheral blood smear results, the suspected diagnosis of chronic myeloid leukemia with differential diagnosis of a leukemoid reaction was made. However, bone marrow aspiration revealed hypoplastic marrow of primary myelofibrosis. The patients with primary myelofibrosis need early diagnosis and treatment to manage the symptoms of splenomegaly, stop fibrosis process and extramedullary hematopoiesis. Early treatment, in this case, can decrease poor prognosis and mortality rate.

Key words: Primary myelofibrosis, chronic myeloid leukemia, hypoplastic marrow

INTRODUCTION

Myelofibrosis (MF) is one of the Myeloproliferative Neoplasm (MPN) which is categorized by the World Health Organization (WHO). This disease is characterized by an increased fibrotic tissue in the bone marrow. Myelofibrosis is also defined as a stem cell hematopoietic disorder which is related to other chronic myeloproliferative diseases.[1-4] This rare disorder was first described in 1879 by Heuck as peculiar leukemia and until now has been described in 30 names including primary myelofibrosis, osteomyelofibrosis, agnogenic myeloid metaplasia, idiopathic myelofibrosis.[5,6] Myelofibrosis is described as bone marrow hypocellularity, extramedullary hematopoiesis, splenomegaly and leukoerythroblastic pictures of theperipheral blood smear.[7] Myelofibrosis is divided into primary and secondary myelofibrosis. Secondary myelofibrosis may be caused by the progression of Polycythemia Vera (PV) and Essential Thrombocythemia (ET), but now the term post-PV or post-TE myelofibrosis is more commonly used than secondary myelofibrosis.[8]

Primary Myelofibrosis (PMF) is a stem cell proliferative disorder that ultimately results in ineffective erythropoiesis, megakaryocyte dysplastic hyperplasia, reactive myelofibrosis, and extramedullary hematopoiesis which commonly occur in the liver and spleen. The incidence rate of this disease is about 1 case per 100,000 populations in the age of 65 in general and under 45 years of age in 11% of cases. Death by this disease is caused by complications of cytopenia, thrombosis, congestive heart failure or myeloid leukemia.[9]

The clinical symptoms of myelofibrosis are usually anemia or signs of chronic inflammation such as fatigue, asthenia, abdominal bloating, and discomfort in the upper abdomen and early satiety which is caused by enlarged spleen that pressures the stomach and adjacent organs. Fever and night sweats are caused by inflammation or infection. Weight loss and malnutrition, pruritus, easy bleeding and bruising caused by decreased thrombocytes or disorders of coagulation factors, joint pain or gout that is caused by increased production of uric acid. Portal hypertension, extramedullary hematopoiesis, and some patients get no symptoms.[10]

Based on the laboratory results of myelofibrosis disease, the hemoglobin level is usually low or normal (<10g/dL) in 60% of cases and normocytic normochromic. Leukocyte count may be decreased, normal, or increased (rarely> 100 x 109/L) while thrombocyte count may decrease or normal but usually increases. In the peripheral blood smear, leukoerythroblastic anemia is found in the form of nucleated erythrocytes and teardrop cells (96% of cases), polychromasia (Figure 1). Myelocytes, giant thrombocytes, and megakaryocyte fragments are also found. However, bone marrow aspiration is not usually successful (dry tap).

In bone marrow biopsy (Bone Marrow Punction/BMP), hypocellular hematopoietic and varied reticulin fibrosis and an increase in

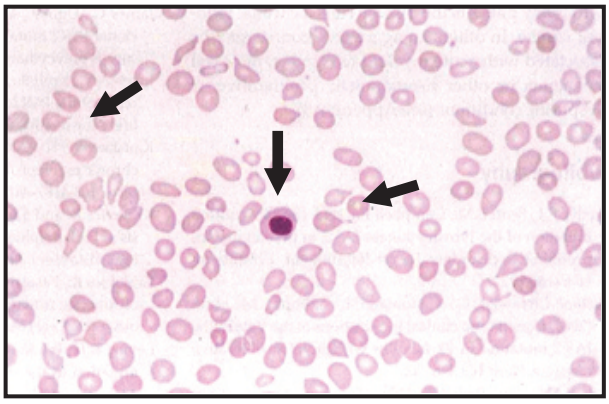

Figure 1. Peripheral blood smear images:Blasts cell and many tear drop cells

megakaryocyte size are usually found. In the blood clotting test, there are a platelet aggregation disorder and a disturbance of coagulation. On cytogenetic examination, abnormalities are found up to 75% of cases, i.e. 13q-, 20q-, and 1q + chromosomes are more common. Abnormalities found in blood chemistry test are hyperbilirubinemia (40% of cases), increased alkaline phosphatase and transaminase (50% of cases) and increased uric acid (60% of cases). In magnetic resonance imagery, it is very easy to distinguish bone marrow fibrosis from normal. [6,11] There is increased bone density on X-ray and in 50% of cases, mutation is found in Janus Kinase (JAK2) and an increase in Neutrophil Alkaline Phosphatase (NAP) score is also found. [6]

CASE REPORT

A 55-year-old man came to the internal medicine center in the hospital with a history of abdominal distention since one year ago, and it was getting bigger, with a two-day fever only at night and shivering. A good history of urination. There was a history of diabetes mellitus for three years, and regular medication was not taken. There was no bleeding history, no difficulty in urinating, and no history of hematoma. Patients felt full quickly after eating only one spoon of food.

The impressions were moderate illness, lack of nutrition, compos mentis Glasgow Coma Scale (GCS) score of 15, and body weight of 53 kg. Blood pressure was 120/70 mmHg, heart rate was 80x / minute, respiratory rate was 20x / minute, and the body temperature was 37°C.

Physical examination results showed signs of anemia, bronchovesicular breathing, rhonchi, and wheezing were not found. In auscultation examination, regular pure I/II heart sound was found. Abdomen examination results showed a normal

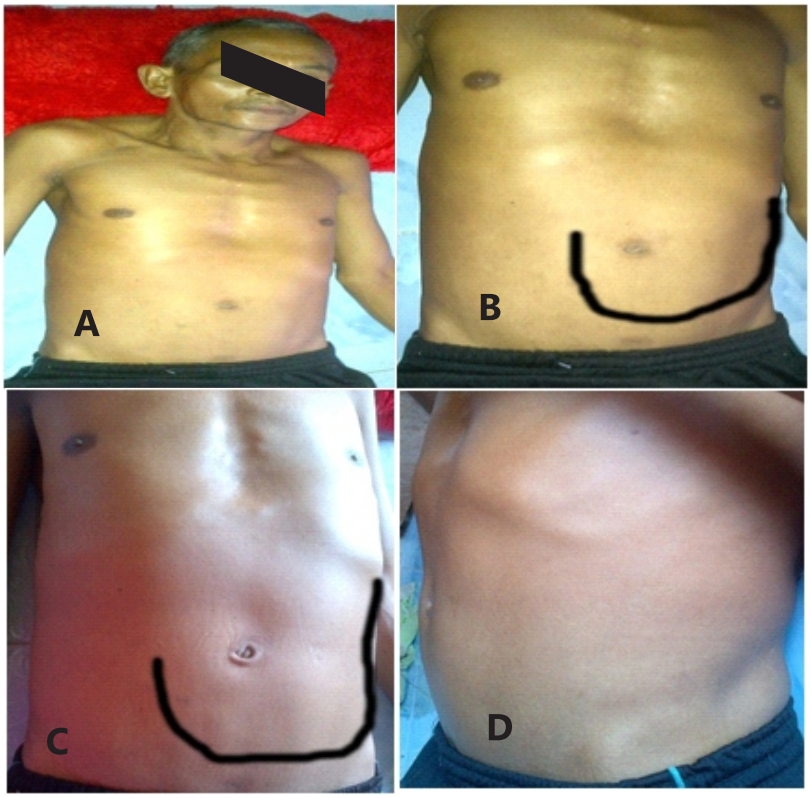

Figure 2. Enlargement of the patient's abdomen A,B,C: Front view. D: Left view

peristaltic; the liver was detected 1 cm below the arcus costa, with elastic consistency, flat surface, no pain on palpationsharp outline (Figure 2). Splenic examination showed congestion impression on the spleen with a Schuffner S5 size with no pain on palpation.

Laboratory test results showed the hemoglobin level of 9.2 g/dL, leukocyte count of 14,690/µL, thrombocyte count of 115 x 103/µL. Hemostasis examination was performed, including Prothrombin Time (PT) of 16.6 seconds and Active Partial Thromboplastin Time (APTT) of 38.7 seconds. Blood chemistry examination results showed patients with 46 mg/dL urea level, 0.9 mg/dL creatinine, 25 mg/dL Aspartate Aminotransferase (AST), 28 mg/dL Alanine Aminotransferase (ALT), and 141 mg/dLfasting blood sugar. HBsAg test showed positive values and other variables had values within thenormal range. Based on the anamnesis, physical examination,and the additional examinations, clinician made a provision diagnosis which is splenomegaly caused by suspected chronic myeloid leukemia. On the following day, a complete blood count test was performed resulting hemoglobin level of 9.6 g/dL, leukocyte count of 16,550/µL, and thrombocyte count of 120 x 103/µL. The peripheral blood smear examination showed a variety of erythrocytes in the form of theteardrop, eosinophils were found in the maturation stage of myeloid series, myeloblasts and giant thrombocytes were also present. Chronic myeloid leukemia with dd/leukemoid reactions was suspected, and BMP examination is recommended.

Ultrasonography (USG) results of the abdomen, liver, gallbladder, pancreas, right and left kidney, urinary tract are the within thenormal condition, but the enlarged spleen was found. The thorax image showed animage of anormal condition.

From examination of bone marrow aspiration, some findings were found such as a hypocellular impression, a decreased activity of erythropoietic, presence of myeloid precursors, 9% of myeloblast, with sufficient activity of thrombopoietic, presence of megakaryocytes, absence of plasma cells and mitosis, and ratio of myeloid and erythroid was 4:1. The aspiration impression of hypoplastic bone marrow fits with the characteristic of primary myelofibrosis.

DISCUSSION

The case of a 55-year-old male has come to the polyclinic with a complaint of abdominal distention since one year ago, and it was getting bigger, with the two-day fever which occurred only at night, and shivering was reported. The patient feels full quickly after eating only one spoon of food.

Physical examination showed anemic impression with laboratory resulting the hemoglobin level of 9.2 g/dL, leukocyte count of 14,690 µ/L, thrombocyte count of 115 x 103/mm. There is no history of

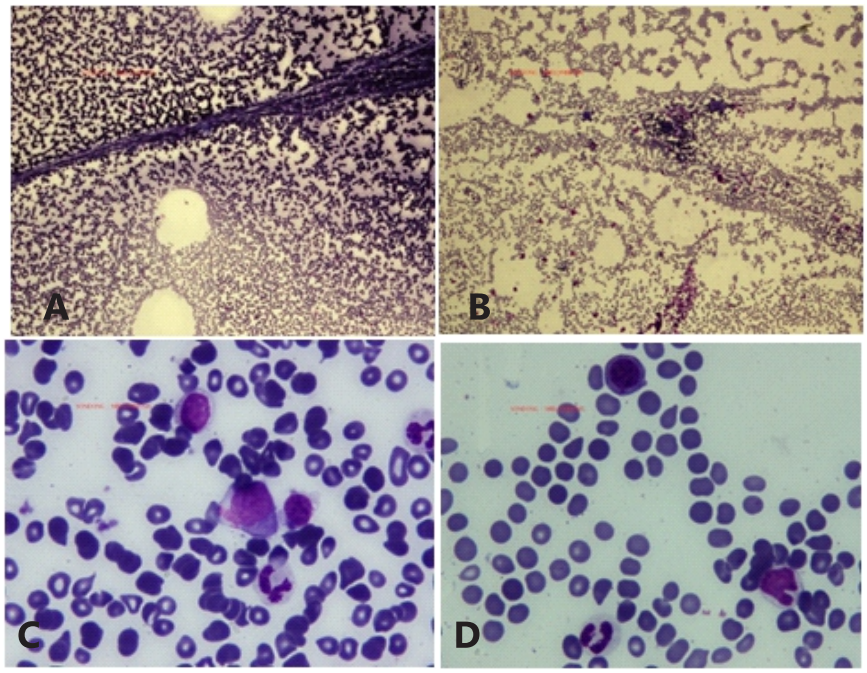

Figure 3. Image of the peripheral blood smear in bone marrow
Fibrin fibers on the smear, decreased erythropoietic activity (A,B). Large numbers of myoblast cells (C,D).

bleeding, but there is a prolonged PT for 16.6 seconds and prolonged APTT for 38.7 seconds. Spleen examination showed the presence of an enlarged spleen with a S5schuffner size with no pain on palpation. The peripheral blood smear examination showed a suspected Chronic Myeloid Leukemia (CML) DD/leukemoid reaction with the evidence of erythrocyte variation in the form of teardrop cells, eosinophils in the myeloid series maturation stage, and myeloblasts and thrombocytes were present. The enlarged spleen was also detected during abdominal ultrasonography examination.

From examination of bone marrow aspiration, some findings were found such as a hypocellular impression, a decreased activity of erythropoietic, presence of myeloid precursors and 9% of myeloblast, sufficient activity of thrombopoietic, presence of megakaryocytes, absence of plasma cells and mitosis cell, and ratio of myeloid and erythroid was 4:1. The aspiration impression of hypoplastic bone marrow fitted the characteristic of primary myelofibrosis.[12]

Primary myelofibrosis is a very rare disease in Indonesia. Tefferi *et al*. showed the incidence of myelofibrosis was only 1 in 100,000 individuals which occurred at the age of 50 to 70 years in the United States. Nwannadi *et al*. showed only 0.9 to 2.2% of the 100,000 populations and cases of myelofibrosis at the age of 40-80 years were found in European countries.[2,13] Common clinical symptoms in this disease were based on anamnesis of the patient, which then confirmed by the laboratory test results of hemoglobin 9.2 g/dL, fever at the times, and early satiety due to the pressure of the spleen against the stomach. Physical examination and ultrasonography examination of these patients showed an enlarged spleen that was used as a basis for strengthening the diagnosis of myelofibrosis.

In peripheral blood smear examination, teardrop cells can be found (in 96% of cases); eosinophils are found in the stage of myeloid maturation and myeloblasts are also found.[6,12,14] It is usually rather difficult to do BMP examination because of the fibrosis in bone marrow tissues which results in difficulties in obtaining the aspiration result (dry tap). In this patient, hypoplastic marrow which was caused by a massive fibrotic process in the bone marrow was also found. The fibrotic process caused by stimulation of Platelet-Derived Growth Factor (PDGF) with other cytokines formed by thrombocytes which act as mitogens in connective tissue, causes an increase in fibroblast proliferation and tunica intima of smooth muscles. This patient's BMP result strengthened the diagnosis of PMF and eliminates the diagnosis of CML.[6,12,15] Cytogenetic examinations such as JAK2 gene mutations could be performed but was aborted due to the limited supply of tools and materials in the hospital which was one of the shortcomings in treating this case.

The cause of PMF is still unknown. Chromosomal abnormalities usually occur at 9p, 20q, 13q, trisomy 8, trisomy 9, or partial trisomy 1q with no specific disorders. In several studies, it was mentioned that the mutations in the Janus Kinase 2 gene (JAK2V617F) occurred in approximately 50% of myelofibrosis cases resulting in erythrocytosis, extramedullary hematopoiesis, and bone marrow fibrosis in this myeloproliferative disease.[2,8,16,17]

Strengthening diagnosis of myelofibrosis is based on the WHO diagnostic criteria. The diagnosis of myelofibrosis requires at least three major criteria and two minor criteria, namely:[2,8,9] Major criteria were megakaryocyte and atypical proliferation accompanied by reticular fibrosis and/or collagen. There are no WHO criteria for polycythemia vera (including Fe deficiencies), chronic myeloid leukemia, myelodysplasia syndrome, and other myeloid malignancies, presence of JAK2617V or other marker mutation, with no inflammatory-caused diseases or other malignancies when no markers are present. Minor criteria were leukoerythroblastosis, increased blood serum lactate dehydrogenase, anemia, splenomegaly.[2,8,9]

From the discussion, it can be concluded that this patient might suffer from a primary myelofibrosis despite initially having clinical symptoms, physical examination, and laboratory result similar to CML, however, the diagnosis of PMF was strengthened by BMP results and even supported by the diagnosis determination based on the WHO diagnostic criteria. Early diagnosis is very essential for early treatment and reduction of risk of a poor prognosis due to delayed treatment.[2,8,9]

The prognostic rate in myelofibrosis varies depending on several factors. Based on The International Prognostic Scoring System (IPSS), the patient's prognosis is estimated by 55-year old age factor, hemoglobin level, clinical symptoms, and the presence of blast cells. This patient is categorized as intermediate-2 risk (two or three factors) that can survive in an average of 2.9 years with anemia in Hb level of <10 g/dL (9.2 g/dL) and presence of blast cells in peripheral blood was 1% (9%), with common symptoms of myelofibrosis. So that treatment is based on age and risk of prognosis and these patients need to be treated early to prevent a poor prognosis. However, the International Working

Group for Myeloproliferative Neoplasms (MPN) Research and Treatment (IWG-MRT) developed a new prognosis assessment from the modified IPSS, which is called Dynamic International Prognostic Scoring System (DIPSS) by adding three other factors, such as the needs for transfusion of red blood cells, thrombocyte count of <100 x 109/L, and karyotype results.[2,8,9]

The most effective myelofibrosis therapy nowadays is Allogenic Stem Cell Transplantation (ASCT), but there is a high risk of side effects from this therapy. Supportive treatment can also be done if treatment of anemia is needed in these patients such as transfusion of red blood cells to increase red blood cells level and reduce symptoms of asthenia and fatigue. Androgen therapy, erythropoietin, glucocorticoids, chemotherapy (hydroxyurea), immunomodulatory treatment can also be done to treat anemia. Splenomegaly could be treated with splenectomy, chemotherapy, immunomodulatory therapy, JAK inhibitors, and radiotherapy to reduce the size of enlarged spleen.[9,18]

The differential diagnosis that is closest to myelofibrosis is polycythemia vera and essential thrombocythemia. Despite having bone marrow fibrosis and JAK2V617F mutations, a patient with polycythemia vera has a high hemoglobin level which is around 18.5 g/dL (male) and > 16.5 g/dL (female). While essential thrombocythemia is also caused by JAK2V617F mutation and megakaryocyte proliferation, it also has a large size and more mature morphology when compared with myelofibrosis, with thrombocyte count of 50450 x 109/L (Figure 4).[2]

CONCLUSION

A case of a 55-year-old male with a primary myelofibrosis diagnosis had been reported. In this patient, there were symptoms such as abdominal distention, fever, abdominal bloating, anemia with ahemoglobin level of 9.2 g/dL. The ultrasonography examination detected an impression of splenomegaly while the peripheral blood smears showed the presence of teardrop cells, the maturation of myeloid series, and myeloblasts. In the bone marrow aspiration test, hypoplastic marrow was found, and it fits the characteristic of primary myelofibrosis. This case should be treated early with supportive treatment for anemia and curative treatment to overcome the symptoms of splenomegaly and stop the progression of bone marrow fibrosis and extramedullary hematopoiesis. Early treatment on this case will decrease the level of poor prognosis and mortality rate.

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