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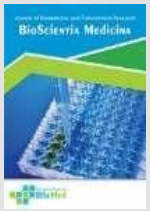

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Atypical Chronic Myeloid Leukemia in Pregnancy

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A B S T R A C T

Background: Atypical chronic myeloid leukemia was first depicted as a subtype of myeloid neoplasm that closely resembles chronic myeloid leukemia but does not have the pathognomonic Philadelphia chromosome. Chronic myeloid leukemia can also be found in pregnant and fertile women, which means pregnancy can happen at the time of diagnosis or during the treatment of this disease. **Case presentation:** A 32-year-old woman came to the hemato-oncology polyclinic at M. Djamil General Hospital Padang with the main complaint of weakness and fatigue. The patient was pregnant with a gestational age of 23-24 weeks. On physical examination, the conjunctiva was anemic, and the spleen was palpable S4 (18 cm). On routine blood laboratory examination, the results of anemia, leukocytosis, and on the peripheral blood picture, severe normochromic normocytic anemia was found with pathological cells of 3% myelocytes and 1% metamyelocytes. Conclusion bone marrow puncture (BMP) results follow the description of chronic myeloid leukemia in the chronic phase. **Conclusion:** During pregnancy, chronic myeloid leukemia has a better prognosis compared to acute leukemia. However, atypical chronic myeloid leukemia still has the potential of leukostasis, causing uteroplacental deficiency and eventually leading to fetal growth restriction, premature birth, and an increase in perinatal mortality.

1. Introduction

Chronic myeloid leukemia (CML) was the first leukemia whose pathogenesis was known.[1] Chronic myeloid leukemia is chronic leukemia originating from the transformation of myeloid stem cells with slowly developing symptoms and is one of the myeloproliferative disorders.[2] The incidence of CML is 1-2 cases per 100,000 cases. This incidence is about 15% of newly diagnosed leukemia cases in adults.[3]

Chronic myeloid leukemia is characterized by the presence of the Philadelphia chromosome (Ph). Chromosomes are formed as a result of a reciprocal translocation between the long arms of chromosomes 9 and 22 (t9:22). As a result, most of the ABL oncogenes on the long arm of chromosome 9 have merged with the BCR oncogene on the long arm of chromosome 22, which then forms a new oncogene, the BCR-ABL oncogene.[2]

Atypical chronic myeloid leukemia belonged to the group of myeloproliferative neoplasms and was originally described as a subtype of myeloid neoplasm that closely resembles CML but lacks the Philadelphia chromosome. Atypical CML is very rare, with approximately 100 times less incidence than positive BCR-ABL CML.[4] Atypical CML has a high risk of transformation to acute myeloid leukemia and a poor prognosis. The management of atypical CML is a

challenge in itself due to the variety of clinical manifestations, the absence of specific markers, and standard therapy.[5]

Chronic myeloid leukemia can occur in women of childbearing age, which means pregnancy can occur at diagnosis or during treatment. The incidence of chronic myeloid leukemia in pregnancy is about 0.6-2 per 100,000. The global incidence and prevalence of CML tend to increase from year to year.[6] Leukostasis can occur in CML, causing uteroplacental insufficiency and increasing the risk of impaired fetal growth, preterm delivery, and increased perinatal mortality. In addition, CML therapy in pregnancy should also be given care by considering the effect on the fetus. Chronic myeloid leukemia that occurs during pregnancy is also a challenge because of the adverse effects of CML treatment on the mother and fetus.[7]

2. Case Presentation

A 32-year-old woman came to the hemato-oncology polyclinic at M. Djamil General Hospital Padang with the main complaint of weakness and fatigue 1 month before being admitted to the hospital. The patient looks pale and complains of abdominal discomfort. The patient was pregnant with a gestational age of 23-24 weeks.

On physical examination, the conjunctiva was anemic, and the sclera was not icteric. On abdominal examination, it was found that the abdomen was bulging, the liver was not palpable, the spleen was palpable S4 (18 cm), and the uterus was palpable according to the gestation period. On routine blood laboratory examination, the results were hemoglobin 5.6 g/dl, leukocytes 18.410/mm^3, platelets 359.000/mm^3, and the leukocyte count found 0% basophils, 4% eosinophils, 6% rod neutrophils, 73% segment neutrophils, lymphocytes 10%, monocytes 3%. On the peripheral blood picture, severe normochromic normocytic anemia was found with pathological cells of 3% myelocytes and 1% metamyelocytes. Other laboratory tests, including kidney and liver function, were within normal limits. The Sokal score of this patient was found to be an intermediate risk.

The patient underwent bone marrow puncture (BMP) examination with hypercellular cellularity, and granulopoiesis activity found 5% myeloblasts, 7.5% promyelocytes, 10% myelocytes, 5.5% metamyelocytes, 11.5% rod neutrophils, 17.5% segment neutrophils, and 1 basophil. .5%, eosinophils 6.5%. Conclusion BMP results follow the description of chronic myeloid leukemia in the chronic phase (figure 1). Furthermore, a BCR-ABL examination was performed with the result that no gene fusion was detected. Obstetric ultrasound revealed a gestational age of 23-24 weeks for a single live intrauterine fetus.

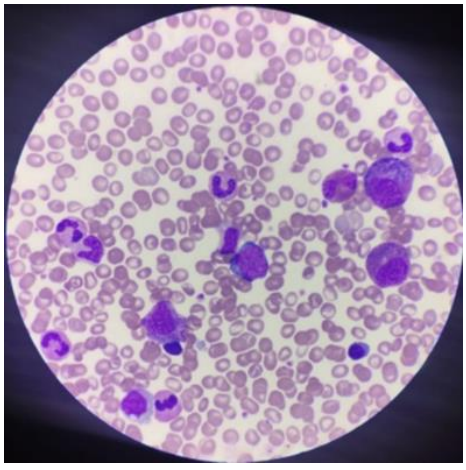

Figure 1. Patient BMP results

3. Discussion

It is reported that a 32-year-old female patient was admitted to the internal medicine ward of Dr. M. Djamil General Hospital with a diagnosis of atypical chronic myeloid leukemia in pregnancy. The diagnosis of chronic leukemia in the patient was established from the history, physical examination, and investigations.

The patient comes with the chief complaint of weakness, fatigue, and looking pale. Physical examination revealed anemic conjunctiva and splenomegaly. Confirmed by laboratory examination, routine blood results with severe normochromic normocytic anemia, leukocytosis, and found pathological cells from immature granulocyte series in the form of myelocytes and metamyelocytes. The patient underwent a BMP examination with the results following the description of the CML chronic phase.

Anemia is a symptom that often occurs in CML patients. Amer et al. (2017) found that the main type of anemia in chronic leukemia was mild-moderate normochromic normocytic anemia, and leukocytosis was more common in CML compared to chronic lymphocytic leukemia (CLL). Amer et al. investigated changes in basic hematological parameters in chronic leukemia patients. Leukocytosis was found in all CML patients. Anemia was found in 92.5% of CML patients. The degree of anemia in CML depends on the CML phase, wherein the chronic phase severe anemia occurs in 1.25% of patients, moderate anemia in 37.5% of patients, mild anemia in 42.5% of patients, and anemia does not occur in 7.5% of patients.[8]

Munir et al. (2019) found that anemia, leukocytosis, and thrombocytopenia are characteristics of all leukemias, except in CML, thrombocytosis can occur. Changes in the bone marrow due to leukemia are reflected in a complete peripheral blood count. Leukemic cells grow uncontrollably in the bone marrow and replace normal hematopoietic cells. The replacement of bone marrow with malignant cells causes a decrease in erythropoiesis, which manifests as anemia. Anemia is a significant finding in almost all leukemias, both acute and chronic.[9]

The CML disease course consists of 3 phases, namely the chronic phase, the accelerated phase, and the blast crisis phase.[10] Approximately 50% of CML patients in the United States are asymptomatic. The diagnosis of CML is often found on routine physical examination and laboratory examination. In general, the diagnosis of CML is made in the chronic phase and is often found incidentally.[1] General signs and symptoms of the CML chronic phase are symptoms of anemia and splenomegaly in the form of weakness and fatigue, pallor, weight loss, and a feeling of fullness in the left upper quadrant of the abdomen. Splenomegaly is one of the typical signs on physical examination found in about 20-40% of cases.[11]

The diagnosis of chronic phase CML on hematological laboratory examination is leukocytosis accompanied by basophilia and immature granulocytes, namely promyelocytes, myelocytes, and metamyelocytes, and most of them show blast presentation, normochromic normocytic anemia, and the platelet count may be normal, decreased, or increased.[12] Blast in the chronic phase less than 10%. The progression of the chronic phase of CML is very slow, requiring several months to years to enter the next phase. Compared to other phases, this chronic phase has a better response to therapy.[13]

The second phase of CML is called the acceleration phase. In this phase, the number of myeloblasts will increase from normal, as well as leukocytes, while the number of platelets in the blood decreases.[13] The hallmark of the accelerated phase is leukocytosis which is difficult to control by myelosuppressive drugs. Myeloblasts in the periphery reach 15-30.[10]

The third phase is the blast crisis phase. In this phase, more than 30% of young cells are found either in the periphery or in the bone marrow. CML cells begin to behave like acute leukemia. Symptoms often include fever, malaise, enlarged spleen, weight loss, and other symptoms resembling acute leukemia.[14]

Sokal score on CML is used to assess the prognosis of patients with CML. The Sokal score uses simple clinical and hematological data and is used to estimate survival risk. The Sokal score was assessed based on age, spleen size, platelet count, and blast count. The patient obtained a Sokal score with intermediate risk. The Sokal score with intermediate-risk has a 10-year overall survival of 81% and a 6-year leukemia-related death of about 4%.[15]

The criteria for the pathognomonic diagnosis of CML, according to WHO in 2016, is to find a BCR ABL gene fusion or a positive Philadelphia chromosome on cytogenetic examination.[10] However, in this patient, no BCL-ABL gene fusion was found. Cases of CML without BCR-ABL gene fusion are very rare. Chronic myeloid leukemia without BCR-ABL gene fusion is known as atypical chronic myeloid leukemia.[16]

Atypical chronic myeloid leukemia is a rare hematologic malignancy with an aggressive course and poor prognosis. The overall incidence of atypical CML is 1 per 100,000 or less, with approximately 1-2 cases per 100 cases of positive BCR-ABL CML. The molecular pathogenesis of atypical CML remains elusive, and no specific molecular or genetic markers have been identified.[16]

Atypical CML belongs to the group of myeloproliferative neoplasms. Changes in the diagnostic criteria and the rarity of cases with a 100-fold lower incidence compared with positive ABL-BCR CML lead to limited knowledge about atypical CML.[4] Atypical CML is a subtype of myeloid neoplasm but in the absence of pathognomonic signs such as the Philadelphia chromosome or BCR-ABL negative. The diagnostic criteria for atypical CML based on WHO 2016 are persistent leukocytosis (≥ 13 x 10^9/L), presence of immature myeloid precursors (≥ 10% leukocytes), dysgranulopoiesis, absence of basophilia (<2%), none/minimal monocytosis (< 10% leukocytes), hypercellular bone marrow with myeloid proliferation and myeloid dysplasia, with or without dysplasia in the erythroid line or megakaryocytes, <20% blast cells in both blood and bone marrow, absence of BCR-ABL gene fusion, and whom criteria for BCR-ABL positive, primary myelofibrosis, polycythemia vera, or essential thrombocytopenia are not met.[17]

The prognosis of CML changes after the use of Tyrosine kinase inhibitors (TKI). CML patients with positive BCR-ABL were given tyrosine kinase inhibitors. Patients treated with imatinib achieve an estimated overall survival of 89%. With the introduction of 2nd and 3rd- generation TKI and the selection of drugs according to the patient's condition, the percentage will be higher.[18] However, from the results of the BCL-ABL gene fusion examination, the patient did not find BCL-ABL gene fusion, so treatment with TKI was not an option.

The incidence of chronic myeloid leukemia accounts for about 20% of all leukemias in adults. Chronic myeloid leukemia can occur at a young age with more progressive disease. However, it is generally found in the age range of 40-50 years.[1]. So that patients can be diagnosed during pregnancy or treatment. The patient, in this case, was diagnosed during pregnancy. The diagnosis is usually made in the second or third trimester of pregnancy because the symptoms that appear are often not typical and are similar to early pregnancy symptoms. Pregnancy does not affect CML, but there is a risk of leukostasis and placental insufficiency with the consequences of low birth weight babies, premature delivery, and increased mortality.[19]

Management of CML in pregnancy is still a dilemma, referring to the many reports of successful delivery in CML patients but what should be considered is the teratogenic effect of therapy. In patients with atypical CML, tyrosine kinase inhibitor therapy cannot be given. Other treatment options that can be given are busulphan and hydroxyurea, but these drugs inhibit DNA synthesis and can cause abortion and congenital malformations.[20]

The optimal management of atypical CML patients remains unclear. Treatment options can range from monitoring in asymptomatic patients to Hematopoietic stem cell transplantation (HSCT). Indications for therapy include a desire to achieve curative therapy, a high-risk disease condition, the presence of

constitutional symptoms of leukocytosis or splenomegaly, the need for transfusion, or worsening of anemia or thrombocytopenia. Starting chemotherapy in stable asymptomatic patients is not known to improve overall survival. In eligible young patients, HSCT may be the best potentially curative option. In older patients, especially those with low-risk diseases, monitoring or palliative chemotherapy may be an option.[16]

4. Conclusion

Atypical CML is a myeloproliferative neoplasm with negative BCR-ABL. Atypical chronic myeloid leukemia is a rare disease. Management of atypical CML in pregnancy is monitored in asymptomatic patients. Indications for therapy include a desire to achieve curative therapy, a high-risk disease condition, the presence of constitutional symptoms of leukocytosis or splenomegaly, the need for transfusion or worsening of anemia, or thrombocytopenia.

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