A Life-Threatening Complication During the Fourth Pregnancy Due to Acute Promyelocytic Leukemia: A Case Report

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ABSTRACT

Incidents of leukemia in pregnancy are infrequent with only one case found from 75,000 to 100,000 pregnancies. The pathophysiological mechanism of leukemia during pregnancy is still unclear. Leukemia which occurs in pregnancy is usually acute and predominantly the myeloid type.

A 35-year-old woman in her fourth pregnancy with a gestational age of 38-39 weeks, came to the emergency department (ED) with complaints of contractions since 4.5 hours before admission. The contraction was not accompanied by discharge, mucus, or blood, and fetal movements was still active. She denied complaints of fever, nausea, vomiting, dizziness, shortness of breath, weakness, fatigue, lethargy, and bleeding. Physical examination results, both palpebral conjunctiva were pale. Laboratory examination results of a complete blood count, white blood cell count were 2,930/uL, hemoglobin 8.3 g/dL, Hct 24.10%, erythrocytes 2.78x10^6/µL, platelets 62,000/µL. Bone Marrow Aspiration (BMA) revealed Acute Promyelocytic Leukemia (APL).

APL is a subtype of Acute Myelogenous Leukemia (AML). Persistent fatigue, recurrent infections, and bleeding are common manifestations of APL. The diagnosis of APL is made by bone marrow aspiration examination, and it is safe for pregnancy. APL therapy in pregnancy uses All-Trans Retinoic Acid (ATRA) and Arsenic Trioxide (ATO). ATRA and ATO are highly teratogenic, but recent studies have reported no fetal abnormalities.

Accuracy and speed in diagnosing and initiating APL therapy in pregnancy are essential in preventing serious complications.

Keywords *Acute promyelocytic leukemia, pregnancy.*

INTRODUCTION

Incidents of cancer in pregnancy are about 0.07% to 0.1%.[1] Cancer during pregnancy is relatively rare but may lead to maternal mortality.[2] Acute leukemia is a malignancy in the third rank after breast cancer and cervical cancer associated with pregnancy.[3] Leukemia in pregnancy is rare and only found in one in 75,000 to 100,000 pregnancies.[1,3] Leukemia which occurs in pregnant women is usually acute and dominated by the myeloid type. During pregnancy, the incidence of acute leukemia in

the first trimester is 23%, in the second trimester is 37%, and in the third trimester is 40%.[1] Acute promyelocytic leukemia (APL) is a subtype of acute myelocytic leukemia (AML) which is a fatal hematological malignancy. APL is a potential threat to both the mother and the fetus and can cause abortion, premature delivery, intrauterine growth retardation, and death of the fetus and mother if not managed properly. Therefore, APL in pregnancy requires prompt and appropriate diagnosis and therapy.[4,5] However, the diagnosis of leukemia in pregnancy is still quite difficult because the symptoms caused are non-specific and resemble the symptoms that commonly occur during pregnancy. The symptoms that can arise are in the form of weakness, fatigue, shortness of breath, pallor, anemia, thrombocytopenia, and leukocytosis.[1] In addition, APL therapy in pregnancy is challenging and requires attention. The main therapy of APL is chemotherapy, but chemotherapy can also cause teratogenic effects if given during pregnancy.[6]

CASE ILLUSTRATION

A 35-year-old woman in her fourth pregnancy complained of contractions for 4.5 hours before coming into the RSPAL emergency department (ED) on November 27, 2021, at 4:30 a.m. The complaints are felt without being accompanied by her water breaking, mucus, and blood. The patient still felt active fetal movement. The patient denied any complaints of fever, nausea, vomiting, headache, and shortness of breath. A history of bleeding and recurrent infections was also denied. There was no history of hypertension, diabetes mellitus, asthma, or heart disease in the patient, but the patient's mother had a history of hypertension. The patient is taking pregnancy vitamins and iron tablet supplements regularly during this pregnancy. There is no history of drug or food allergies. The patient was married once for thirteen years. The patient had menarche at the age of 13 years with irregular cycles, and the duration of one menstrual period was about 5 days without dysmenorrhea. The first day of the patient's last menstrual period (LMP) is March 6, 2021, and the estimated due date of birth is December 13, 2021. The patients routinely receive antenatal care every month in Surabaya Islamic Hospital. In the first pregnancy, the baby was born full term by cesarean section with an indication of high myopia helped by a doctor in Surabaya Medical Service Hospital. The baby was born male had a birth weight of 3,500 grams and is now 12 years old. In the second pregnancy, the baby was born full term by cesarean section with an indication of high myopia helped by a doctor in Surabaya Medical Service Hospital. The baby was born female with a birth weight of 3,500 grams and is now 9 years old. In the third pregnancy, the baby was born full term by cesarean section with an indication of high myopia helped by a doctor in Surabaya Medical Service Hospital. The baby was born female with a birth weight of 3,500 grams, and now she is 5 years old. Now the patient is pregnant for the fourth time. The patient used a Depoprovera contraceptive injection and then switched to a contraceptive pill but was not consumed regularly.

Physical examination results showed both conjunctiva palpebrae were pale, there was no icterus, cyanosis, or dyspnea. The lymph nodes are within normal limits. Thorax, abdomen, and extremities examination are within normal limits. Then the patient was given a complete blood test on November 27, 2021, the result showed a white blood cell count of 2,930/µL, hemoglobin 8.3 g/dl, Hct 24.10%, erythrocyte $2.78x10^6$/µL, thrombocyte 62,000/µL.

A complete blood count and a peripheral blood smear were carried out on November 29, 2021, at 07:45 p.m., the result showed a white blood cell count of 21,120/µL, hemoglobin 7.4 g/dl, Hct 21.10%, erythrocyte $2.63x10^6$/µL, thrombocyte 20,000/µL. The results of the patient's peripheral blood smear concluded that "suspicious of an APL (*Acute Promyelocytic Leukemia*)" with the suggestion to do Bone Marrow Aspiration (BMA), and *Immunophenotyping*.

The patient received two bags of Packed Red Cell (PRC) transfusion before the active phase of labor on November 29, 2021, and then got an emergency C-section. The baby was born alive with a birth weight of 3,200 grams. After the C-section was performed, the patient was treated in the intensive care unit for recovery caused by heavy bleeding during surgery (1,000 cc). Once stable, the patient is transferred to the puerperal room.

Table 1. The results of hematology analysis (November 29, 2021) with scattergram.

Para.			Result	Unit	Ref. Ranges	
1	WBC	H	50.48	10^3/µL	4.00 - 10.00	Flag
2	Neu#	RH	9.85	10^3/µL	2.00 – 7.00	
3	Lym#	eH	6.46	10^3/µL	0.80 – 4.00	WBC Scattergram Abn
4	Mon#	eH	34.07	10^3/µL	0.12 – 1.20	Blasts?
5	Eos#	RL	0.01	10^3/µL	0.02 – 0.50	Abn Lymph/blast?
6	Bas#	RH	0.12	10^3/µL	0.00 – 0.10	Immature Gran?
7	Neu%	RL	19.5	%	50.0 – 70.0	Atypical Lymph?
8	Lym%	EL	12.8	%	20.0 – 40.0	Leucocytosis
9	Mon%	EH	67.5	%	3.0 – 12.0	Anemia
10	Eos%	RL	0.0	%	0.5 – 5.0	PLT Histogram Abn
11	Bas%	R	0.2	%	0.0 – 1.0	Thrombocytopenia
12	IMG#	R	0.18	10^3/µL	0.00 – 999.99	
13	IMG%	R	0.4	%	0.0 – 100.0	Note:
14	RBC	L	2.56	10^6/µL	3.50 – 5.00	Lym# 13,66; Mon# 5,71;
15	HGB	L	7.1	g/dl	11.0 – 15.0	Lym% 64,7; Mon% 27,0
16	HCT	L	20.2	%	37.0 – 47.0	
17	MCV	L	78.9	fL	80.0 – 100.0	
18	MCH		27.7	Pg	27.0 – 34.0	
19	MCHC		35.1	g/dl	32.0 – 36.0	
20	RDW-CV	H	20.3	%	11.0 – 16.0	
21	RDW-SD	H	57.8	fL	35.0 – 56.0	
22	PLT	RL	32	10^3/µL	100 – 300	
23	MPV	R	8.7	fL	6.5 – 12.0	
24	PDW	R	15.7		15.0 – 17.0	
25	PCT	RL	0.028	%	0.108 – 0.282	
26	P-LCC	RL	9	10^3/µL	30 – 90	
27	P-LCR	R	29.5	%	11.0 – 45.0	
*28	HFC#		****	10^3/µL		
*29	HFC%		****	%		

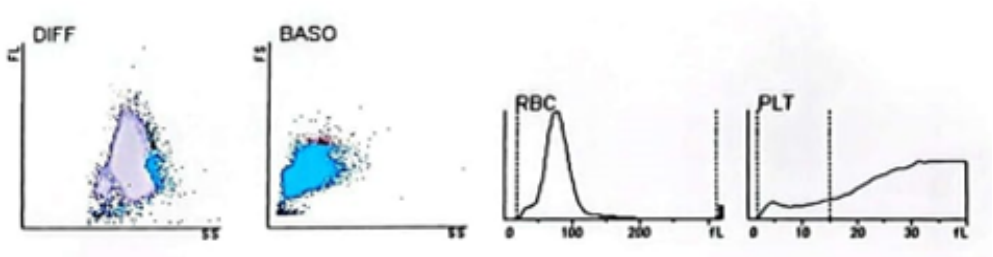

Table 2. Serial complete blood count.

	11/27/2021 at 05:11 a.m	11/29/2021 at 05:10 a.m	12/01/2021 at 07:45 p.m	12/04/2021 at 06:25 p.m	12/05/2021 at 05:20 p.m	12/07/2021 at 06:00 a.m	Unit
White Blood Cell	2,900	9,410	21,120	86,570	118,950	148,760	/µL
Hb	8.30	8.1	7.4	8.0	6.8	9.4	g/dL
Hct	24.10	23.70	21.10	23.50	20.10	27.30	%
Erythrocyte	2.78	2.78	2.63	2.96	2.53	3.33	10^6/µL
Thrombocyte	62,000	46,000	20,000	29,000	36,000	37,000	/µL

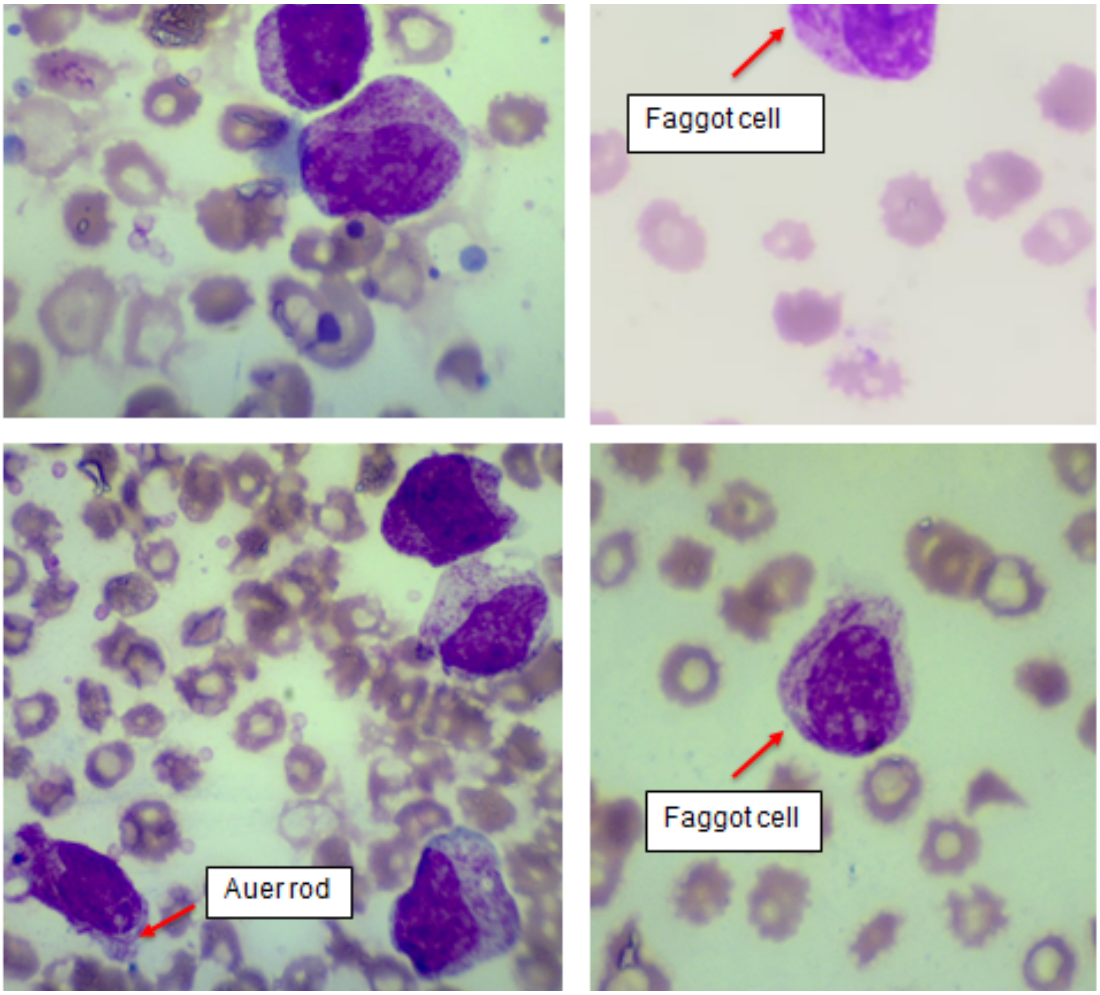

Figure 1 The peripheral blood smear shows promyelocytes, Auer rods (+), and phaggot cells (+).

Then the patient is suggested for bone marrow aspiration (BMA). The BMA was performed on December 2, 2021, with hypercellular results; erythropoiesis system activity was decreased by 2% proportion. Granulopoiesis system activity was increased, the proportion of myeloid series 96%, dominated by hyper granular promyelocytic with proportion 87%, Auer rod (+), faggot cell (+); megakaryopoiesis system activity was decreased. Bone marrow image supported the diagnosis of acute promyelocytic leukemia (APL).

The patient planned to receive chemotherapy but the patient is only able to perform minimal self-care and is confined to a bed or chair for >50% in 24 hours (ECOG 3), so the administration of chemotherapy was postponed. On December 5, 2021, the patient complained of fatigue, fever, and chills. After observing the vital signs at 05:00 p.m., the blood pressure was 98/51 mmHg, pulse 120 beats per minute, temperature 39 ^{0}C, and oxygen saturation was 87%. Then the patient got nasal oxygen 4 liters per minute and oral therapy with folic acid, paracetamol, omeprazole, and myotonic while monitoring the vital signs. At 06:10 p.m., the blood pressure was 100/70 mmHg, pulse 114 beats per minute, temperature 38.2^{o} C, and pulse oximetry showed 92% with oxygen supplementation 4 liters per minute using nasal cannula. On the following day, the patient was transferred to the intensive care unit. The patient died two days later due to sepsis.

DISCUSSION

Leukemia occurred due to the uncontrolled proliferation of white blood cells.[7] Clinically and pathologically, leukemia is classified into four major groups, namely acute myelogenous

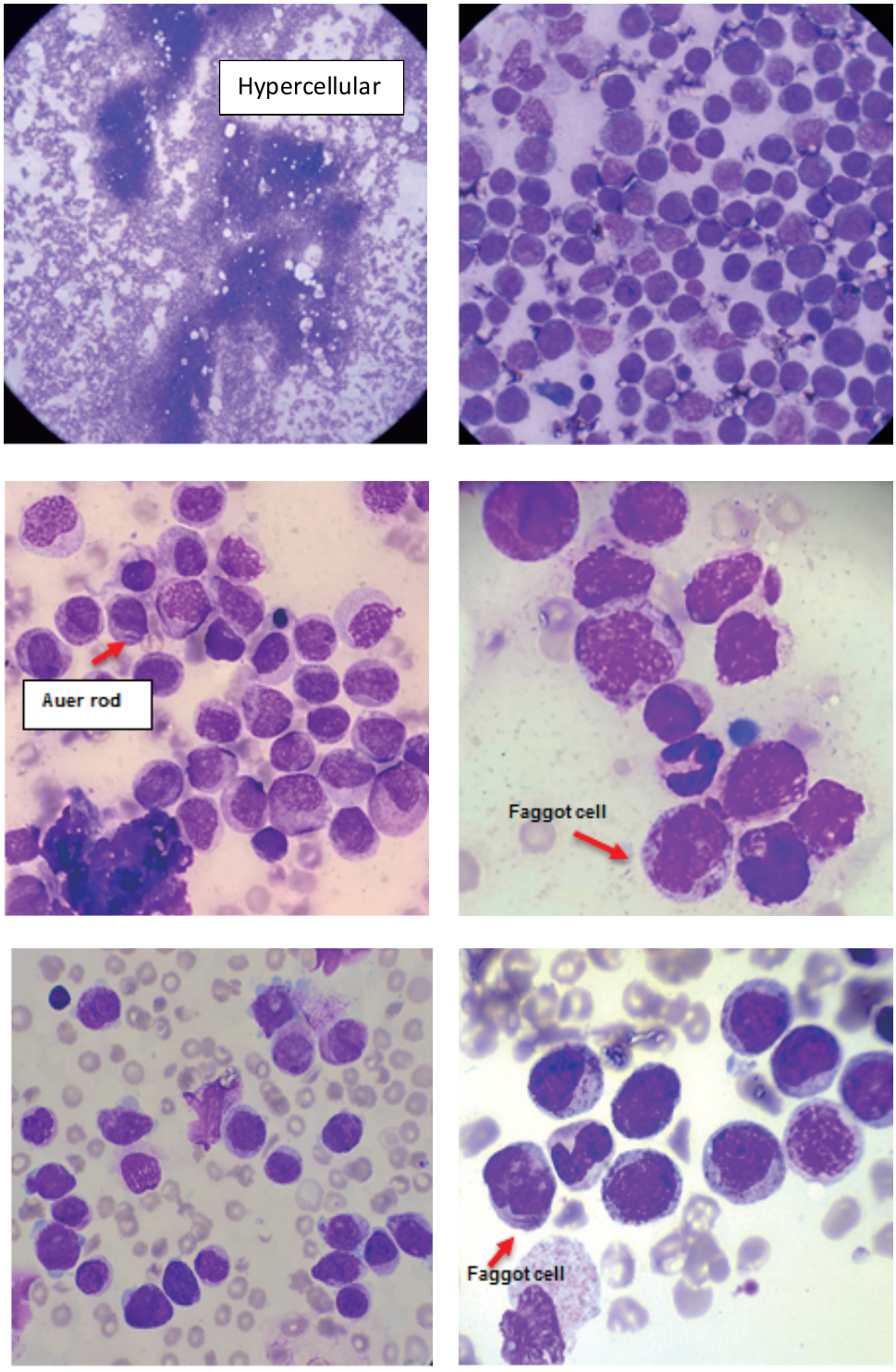

Figure 2. The result of BMA.

leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). ALL and AML are the most harmful types.[8] According to French-American-British (FAB), AML is divided into 8 subtypes, namely minimally differentiated AML (M0), minimally maturing AML (M1), maturing AML (M2), APL (M3), acute myelomonocytic leukemia (M4), acute monocytic leukemia (M5), acute erythroid leukemia (M6), and acute megakaryoblastic leukemia (M7).[9] APL (M3) itself is a unique subtype of AML.[5] APL occurs

due to a translocation between chromosomes 15 and 17 [t(15;17)], resulting in the fusion of the PML-RARA gene. This translocation will stop the development of promyelocytes (immature white blood cells) so that there will be an accumulation of immature white blood cells in the bone marrow.[6]

According to The American Cancer Society, in 2018 there were 19,520 new cases and 10,670 deaths due to AML in the USA and 5-15% of the total cases were APL type. APL is a medical emergency because 17.3% of cases experienced premature death within one month of diagnosis, primarily due to intracranial or severe pulmonary hemorrhage.[10] Cases of acute leukemia in pregnancy are rare, i.e., 1 in 100,000 pregnancies. APL is curable but requires prompt and appropriate diagnosis and therapy.[11] Prognosis in the fetus is strongly related to gestational age; the incidence rate of abortion in the first, second, and third trimesters is 87%, 33%, and 7%, respectively.[6]

The clinical manifestations of APL may include recurrent infections, persistent fatigue, and signs of bleeding. In addition, coagulopathy and petechiae are the most common clinical manifestations of APL. To prevent complications, a fast and precise diagnosis is needed. The diagnostic procedure for APL in pregnancy is no different from that in non-pregnant patients, namely bone marrow aspiration and trephine biopsy can be performed; these procedures are safe during pregnancy. The diagnosis of APL is confirmed when >30% promyelocytic cells are found in the bone marrow peripheral blood smear.[4] In the above case, the patient did not experience obvious manifestations, which the manifestations of her pregnancy may also mask, so the patient came to the hospital not because of complaints about her APL but about her pregnancy. Then it was suspected that she had leukemia when a complete blood test showed abnormalities. Complete blood count errors were denied by re-examination which showed the same result.

APL can occur in all trimesters or during postpartum.[12] APL in pregnancy can create complications for both the mother and the fetus. Infant complications include a higher risk of abortion, perinatal mortality, intrauterine growth restriction (IUGR), preterm delivery, and infection. While the mother bears the risk of perinatal, intranatal, or postnatal mortality. In this case, the patient's condition worsened postnatally and required intensive care. Prior studies consist of a comparison between two cases of APL in pregnancy, those who were immediately treated and those who refused therapy due to the worsening of the condition after being given the first therapy. Patients who resist therapy have a poor prognosis, but patients who receive initial therapy with close monitoring of the mother and baby have a better prognosis.[4] Meanwhile, in our case the patient was diagnosed with APL during his fourth pregnancy and was not recognized early, despite having regular antenatal care. APL symptoms appear during term and in-partum pregnancy and are diagnosed immediately after birth, unlike in prior studies, the patient was detected and diagnosed at 34 weeks gestation. In another prior study, the patient came with secondary postpartum bleeding for 6 days and there was bleeding in the gums and hematemesis. The patient was planned for chemotherapy with ATRA but the patient's condition worsened and finally died.[13] This case was almost the same as our case, the patient was just diagnosed postpartum and was planned for chemotherapy but the patient got worse and eventually died. The explanation for why APL appeared at the fourth postpartum is not known in our case.

Treatment of leukemia during pregnancy requires multidisciplinary collaboration. Chemotherapy is the primary treatment for leukemia. Chemotherapy uses cytotoxic chemicals which have numerous adverse effects on both the mother and the fetus, particularly in the first trimester (2-8 weeks). Physiological changes in the mother during pregnancy such as increased plasma volume, the presence of amniotic fluid, hepatic oxidation, and changes in renal clearance, might impact drug metabolism, distribution, and excretion.[14] Treatment of APL in adults is divided into induction and post-remission (consolidation and maintenance) therapy. Induction therapy was administered for four weeks using a combined regimen of ATRA (All-Trans Retinoic Acid) and ATO (Arsenic

Trioxide). As an alternative, anthracycline, cytarabine, and hydroxyurea can be used. Consolidation therapy using a combination of ATRA and ATO for 7 months, and maintenance therapy using a combination of ATRA with 6-mercaptopurine and methotrexate for 2 years.[5]

ATRA is highly teratogenic causing fetal retinal damage, neural tube defects, cardiovascular malformations, craniofacial deformities, renal diseases, psychological disorders, and thymus gland aplasia. This can happen if ATRA is utilized during the first trimester. Therefore, avoid using ATRA in the first trimester and start it in the second and third trimesters, while keeping tight control of the baby's heart rate.[15] However, no congenital problems were found in several previous studies on the use of ATRA in APL pregnancies. Pregnant women get the same dose of ATRA as other patients, specifically 40-45 mg/m^2/day. ATO, like ATRA, is extremely teratogenic and should be avoided during all trimesters of pregnancy. However, prior studies reported the birth of babies without any abnormalities from APL mothers who were treated with a combination of ATRA and ATO. The ATO dosage reported that does not induce fetal abnormalities is 8 mg/day.[5]

Chemotherapy for APL in pregnancy can be started when the gestational age is above 10 weeks because the 10th week of gestation is the time of the most active growth and development of the fetus. If APL is identified in the second or third trimester, chemotherapy can begin immediately.[5] However, if APL is identified during postpartum, chemotherapy can begin immediately, however, it is ensured that the patient is not breastfeeding her child.[15] However, if the mother's condition is critical, chemotherapy can begin in combination with other supportive symptomatic care, and the pregnancy can be terminated after her condition has stabilized.[5] In determining the patient's condition, ECOG (Eastern Cooperative Oncology Group) Performance Status can be used, which consists of grade 0 (very active, the patient can do all activities without limits) to grade 5 (the patient died). Chemotherapy can only be given to patients with ECOG grades 0-2.[16] In our case, the patient was diagnosed with APL during postpartum, and the patient's condition worsened with the patient's ECOG performance status of 3, so chemotherapy administration had to be postponed.

CONCLUSION

Dealing with APL cases during pregnancy is challenging since getting a diagnosis requires speed and precision. On the other hand, the clinical manifestations may be nonspecific. Furthermore, in this type of APL, precision and quickness in initiating therapy are required to prevent complications.

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