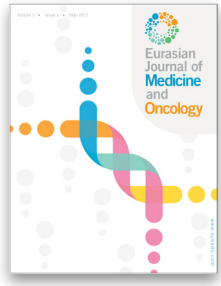
EJMO

DOI: 10.14744/ejmo.2018.0028
EJMO 2018;2(4):258–260



Case Report

Acute Promyelocytic Leukemia Diagnosed at the End of First Trimester with a Successful Outcome

Mehmet Baysal,[1] Elif G. Umit,[1] Ali Caner Ozdover,[1] Havva Sutcu,[2] Isil Uzun Cilingir,[2] Onur Kirkizlar,[1] Cenk Sayın,[2] Ahmet Muzaffer Demir[1]

[1]Department of Hematology, Trakya University Faculty of Medicine, Edirne, Turkey
[2]Division of Perinatology, Department of Obstetrics & Gynecology, Trakya University Faculty of Medicine, Edirne , Turkey

Abstract

The treatment and management of patients with acute promyelocytic leukemia (APL) diagnosed in pregnancy can involve a wide range of difficulties and limitations. Thus, these cases are each unique and present challenges to physicians. The aim of this study was to present the case of a 24-year-old patient who was diagnosed with APL in the 14th week of pregnancy who was treated successfully with all-trans retinoic acid and chemotherapy.

Keywords: Acute promyelocytic leukemia, disseminated intravascular coagulation, hemorrhagic diathesis, pregnancy, remission induction chemotherapy

Cite This Article: *Baysal M, Umit E, Ozdover A, Sutcu H, Cilingir I, Kirkizlar O, Sayin C, Demir A. Acute Promyelocytic Leukemia Diagnosed at the End of First Trimester with a Successful Outcome. EJMO. 2018; 2(4): 258-260*

Acute promyelocytic leukemia (APL) is a unique subtype with the PML-RARA fusion gene that occurs due to a translocation [t(15; 17) (q22; q21)]. All-trans retinoic acid (ATRA) therapy has revolutionized the treatment of APL. It is now over 90% of full remission rates with ATRA and anthracycline-based treatments, which are the standard approaches in the guidelines.[1] However, treatment of APL in pregnancy is complicated and challenging because of the potential teratogenic effects of ATRA and anthracycline therapies. Knowledge regarding the optimal APL treatment in pregnancy is limited to case reports. We aimed to present a patient who was diagnosed with APL in the second trimester of pregnancy and treated successfully with ATRA and anthracycline.

Case Report

A 24-year-old, gravida 1 para 0 woman at the 14th weeks of pregnancy was referred because of abnormal laboratory test results. Physical examination was unremarkable except for the petechial bleeding which was detected in the lower extremity. Whole blood count showed a hemoglobin level 8.3 gr/dl, leucocyte 2700/mm^3 and platelets 81.000/mm^3. Atypical cells were observed with promyelocytic morphology on her peripheral smear. Prothrombin time was 15.6 sec, fibrinogen136 mg/dL and D-dimer 16.42 µg/ml. Bone marrow aspiration revealed atypical morphologic cells with irregular contours with promyelocytic morphology. Flow cytometry examination revealed a blastic population with MPO, CD33 and CD117 positivity and HLA-DR negativity. Cytogenetic and FISH studies showed the translocation t(15; 17) (q22; q21), which constitutes the PML-RARA fusion gene. According to leucocyte and platelet count, the patient was regarded as low risk APL. According to the detailed first trimester obstetric ultrasound examination fetal development was consistent with 14 weeks of gestation, without any anomaly. Since organogenesis was completed, remission induction therapy was started with ATRA 45 mg/m^2 and Idarubicin 12 mg/m^2 day for 4 days. Supportive

Address for correspondence: Mehmet Baysal, MD. Trakya Universitesi Tip Fakultesi, Hematoloji Bilim Dali, Balkan Yerleskesi, 22030 Edirne, Turkey
Phone: +90 284 235 76 41 - 2687 **E-mail:** drmehmetbaysal@gmail.com
Submitted Date: May 08, 2018 **Accepted Date:** July 24, 2018 **Available Online Date:** October 11, 2018

measures such as to maintain fibrinogen level above 150 mg/dl and thrombocyte count ≥50.000 mm³ were carried out. Neutropenic fever was treated with piperacillin tazobactam, followed by meropenem and amphothericin B for probable invasive fungal infection. Blood counts and coagulation tests improved, maturation arrest in bone marrow cells was resolved and [t(15; 17) (q22; q21)] turned to negative.

After a successful remission induction therapy, the patient followed with ATRA therapy for 90 days. During this period, the patient developed a HSV-esophagitis confirmed with HSV DNA of endoscopic tissue biopsy and received acyclovir. After remission induction treatment and ATRA completion of 90 days, the patient was followed up with frequent blood count and coagulation tests and [t(15; 17) (q22; q21)] every 3 months. The patient gave birth to a healthy boy with caesarean section on the 34th weeks of gestation. Starting after 3 months of breast feeding, while the patient was still on remission, consolidation therapy with 3 cycles of idarubicin and ATRA followed by maintenance treatment internationally recommended as methotrexate, 6-mercaptopurin and ATRA 14 days every 90 days.

Discussion

Acute myelocytic leukemia (AML) is the mostly observed leukemia type in adult patients, but APL accounts for 10-15% of AML cases.[2] During pregnancy, leukemia is not a common condition, observed in one in 75.000 to 1 in 100.000 pregnant women. Two thirds of acute leukemia cases in pregnancy is AML while one third is acute lymphoblastic leukemia.[3] Because of the characteristic biology and pathophysiology of the disease, prompt decision making and effective treatment modalities must be utilized. There are some reports regarding APL in pregnancy.[4] Coagulation abnormalities, disseminated intravascular coagulation, placental abnormalities, premature delivery, and obstetric complications may be observed at presentation or during the course of disease.[5–7] Urgent and competent management with ATRA may ameliorate coagulation parameters and bleeding, as in our patient.

APL may develop in all trimesters of gestation, but the anticipated presentation is at the third trimester.[8] ATRA is the backbone of treatment of APL. In non-pregnant patients, ATRA is combined with anthracyclines.[9] However, ATRA, anthracyclines and cytosine arabinoside have high teratogenic potential in the first trimester, but in the second and in the third trimesters they rarely cause malformations.[10] Therefore, pregnancy is usually terminated if APL is encountered in the first trimester. Use of chemotherapeutic agents in the second or in the third trimesters causes fetal complications such as developmental delay in the fetus and preterm birth.[3,5,10] Anthracyclines may lead to fetal death, fetal malformations, spontaneous abortions and fetal complications. Moreover, retinoic acid in the first trimester of pregnancy may cause severe malformations. In the second and in the third trimesters ATRA exposure is reported rarely to cause fetal harm and it is suggested to be relatively safe. Therefore, in our patient we have preferred ATRA, and observed no significant complication other than iatrogenic premature delivery. In a recent meta-analysis, 71 pregnant patients diagnosed with APL (first, n=16; second=20; and third trimester, n=28) were evaluated, but none in the first trimester resulted in birth.[8] In another analysis with 14 pregnant women, 12 received induction therapy and 11 had complete remission.[4] Likewise, none <25 weeks of gestation, ended with a healthy birth. Our case was diagnosed at the 14th weeks of pregnancy. To the best of our knowledge, this is the first case with APL diagnosed at the end of the first trimester treated successfully with ATRA and idarubicin, and delivered a healthy infant. Our patient delivered by a planned caesarean section on the 34th weeks, while in the aforementioned meta-analysis, iatrogenic preterm delivery rate was reported as 46.2% (25 of 54).[8]

On the other hand, for antifungal treatment we have used amphothericin B, in our case. Formerly, amphothericin B has been rated as category B by Food and Drug Administration (FDA) with no teratogenesis attributed to this drug, though liposomal structure allows trans placental transfer. We have administered amphothericin B in liposomal form for febrile neutropenia. Since the patient was pregnant, we could not perform thoracic tomography. Also, the patient's fever responded after amphothericin B. As recommended in a meta-analysis, we also endorse amphothericin B as the drug of choice for antifungal treatment in pregnant patients.[10]

In pregnancy, although APL has a high CR rate (above 90% with ATRA and idrarubicin), the disease has high risks in terms of both fetal and obstetric complications and coagulation abnormalities.[1,7,11] Fetal death, spontaneous or therapeutic abortions are reported in first trimester patients. Even the management of patients with APL is complicated and challenging, pregnancy brings another compelling burden to the picture.[9,10] Besides informing patients and their relatives, a multidisciplinary approach, namely collaboration with perinatology and social support departments is essential for the management of this challenging group of patients.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declared that no conflict of interest.

Authorship Contributions: Concept – M.B., E.G.U.; Design – H.K.O., C.S., E.G.U.; Supervision – H.K.O., C.S., A.M.D.; Materials – H.U., I.U.C.; Data collection &/or processing – M.B., A.C.O., E.G.U., H.U.; Analysis and/or interpretation – E.G.U., H.K.O., C.S., A.M.D.; Literature search – M.B., E.G.U., I.U.C., C.S.; Writing – M.B., E.G.U., C.S.; Critical review – C.S., A.M.D.

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