Pregnant woman with acute promyelocytic leukemia delivers healthy twins and is cured successfully: A case report

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Abstract. Acute promyelocytic leukemia (APL) during pregnancy is rare and difficult to treat. To the best of our knowledge, there is little precedent for successful treatment with combined chemotherapeutic agents without affecting delivery. The present study reported the case of a 31-year-old woman pregnant with twins who presented to the antenatal service at 13-week gestational age with complaints of vaginal bleeding, lower abdominal pain, bleeding gums and skin ecchymosis, and was eventually diagnosed with APL. After treatment with all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO)-based induction regimen, the patient achieved a complete remission (CR) and delivered two healthy male infants at 34 weeks of gestation. The use of ATRA and ATO for the treatment of APL is controversial due to teratogenic effects and lethal retinoic acid syndrome. However, the patient demonstrated that the chemotherapy regimen with ATRA and ATO during the second and third trimesters can result in a sustainable remission and successful pregnancy outcome.

Introduction

Acute promyelocytic leukemia (APL) is a curable subtype of acute myeloid leukemia (1). All-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) are first line treatment options for APL (1). Although contemporary combined ATRA and ATO therapy is effective in inducing complete remission (CR) in the majority of patients, the use of this regimen remains controversial in pregnant women. ATO has a significant transplacental transport and is highly embryotoxic (2,3). Therefore, its use in pregnancy is not recommended.

In addition, the management of APL is challenging because of the inherent hyperfibrinolytic state, treatment-induced differentiation syndrome and infection (2). Pregnancy associated with APL is extremely rare and makes its management more difficult (4-6). APL and its treatment during pregnancy may lead to maternal complications, such as coagulopathy and abortions, as well as fetal complications, such as preterm birth and intrauterine growth restriction (3). The current study reported the case of a young patient delivering two healthy infants while undergoing treatment for APL.

Case report

A female patient (31-year-old) had no children for ~5 years after marriage and had two miscarriages within 6 weeks of pregnancy. After *in vitro* fertilization treatment in Zhongshan Boai Hospital Affiliated to Southern Medical University (Zhongshan, China), the patient successfully conceived and the postoperative color Doppler ultrasound showed a twin pregnancy (Fig. 1). In October 2017, the patient presented to the antenatal service of the aforementioned hospital at 13-week gestational age with vaginal bleeding for 4 days and lower abdominal pain for 1 day accompanied by bleeding gums and skin ecchymosis.

Laboratory blood tests showed hemoglobin (HGB) 110 g/l (normal range, 110-150 g/l), white blood cell (WBC) count $1.70x10^9$/l (normal range, 4-$10x10^9$/l), neutrophils $0.86x10^9$/l (normal range, 1.80-$6.30x10^9$/l), platelets (PLT) $77x10^9$/l (normal range, 100-$300x10^9$/l), prothrombin time (PT) 15.20 sec (normal range, 11-13 sec) and D-dimer 8.53 μg/ml (normal range, <0.5 μg/ml). Serum biochemical tests revealed normal renal and hepatic profiles. The blood film showed abnormal promyelocytes. Cytomorphological examination of the bone marrow showed that the proportion of abnormal hypergranular promyelocytes with Auer rods increased to ~62% (Fig. 2). The results of flow cytometry showed that lymphocytes accounted for 6.60%, granulocytes for 90.10%, monocytes for 1.70%, $CD45^{dim}$ cells for 0.80% and $CD45^-$ cells for 0.80%. The immunophenotype of abnormal cell

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Abbreviations: APL, acute promyelocytic leukemia; ATRA, all-trans-retinoic acid; ATO, arsenic trioxide; CR, complete remission; DIC, disseminated intravascular coagulation; HGB, hemoglobin; WBC, white blood cell; PT, prothrombin time

Key words: acute promyelocytic leukemia, pregnancy, all-trans-retinoic acid, arsenic trioxide

population was $CD34^-$, $CD117^+$, $CD33^+$, $CD13^+$, HLA-DR^-, $CD64^+$, $CD14^-$, $CD56^-$, $CD19^-$, $CD7^-$, $CD2^-$, $CD5^-$ and $CD20^-$. Immunophenotyping was consistent with APL (Fig. S1). Immunophenotyping was performed on a BD FACSCanto™ Clinical Flow Cytometry (BD Biosciences) using the FCS Express 3.0 (De Novo Software) flow cytometry software. The following reagents and antibodies were used for immunophenotyping: 7-aminoactinomycin D (Beckman Coulter, Inc; cat. no. A07704); CD15 (BD Biosciences; cat. no. 332778); CD14 (BD Biosciences; cat. no. 333951); CD8 (BD Biosciences; cat. no. 335822); CD20 (BD Biosciences; cat. no. 335829); CD2 (BD Biosciences; cat. no. 341024); CD5 (BD Biosciences; cat. no. 341109); CD4 (BD Biosciences; cat. no. 341115); CD10 (BD Biosciences; cat. no. 341102); CD19 (BD Biosciences; cat. no. 3407224); CD7 (BD Biosciences; cat. no. 340656); CD117 (BD Biosciences; cat. no. 339206); CD33 (BD Biosciences; cat. no. 340679); cell-surface immunoglobulin (sIg)-λ (BD Biosciences; cat. no. 555797); sIg-κ (BD Biosciences; cat. no. 555791); CD11b (BD Biosciences; cat. no. 340936); CD13 (BD Biosciences; cat. no. 347406); CD16 (BD Biosciences; cat. no. 335806); CD56 (BD Biosciences; cat. no. 555517); human leucocyte antigen (HLA)-DR (BD Biosciences; cat. no. 642276); CD64 (BD Biosciences; cat. no. 561194); CD3 (BD Biosciences; cat. no. 560176); CD5 (BD Biosciences; cat. no. 555352); CD71 (BD Biosciences; cat. no. 551374); CD34 (BD Biosciences; cat. no. 555823); CD58 (Beckman Coulter, Inc; cat. no. IM1218U); CD123 (Beckman Coulter, Inc; cat. no. B14808); CD9 (BD Biosciences; cat. no. 555372); CD41 (Beckman Coulter, Inc.; cat. no. 6607117); CD45 (Beckman Coulter, Inc; cat. no. IM3548U); CD36 (Beckman Coulter, Inc; cat. no. IM0766U); CD38 (Beckman Coulter, Inc; cat. no. IM0775U); CD138 (Beckman Coulter, Inc; cat. no. A87787); CD200 (BD Biosciences; cat. no. 562126); and CD61 (Beckman Coulter, Inc; cat. no. IM1758U).

Reverse transcription PCR was positive for the L subtype of promyelocytic leukemia- retinoic acid receptor α fusion gene.

A diagnosis of APL was made, and a discussion ensued with the patient regarding termination, the possible adverse effects of the chemotherapy on the fetuses and the risks to the patient in continuing the pregnancy. The patient decided to continue the pregnancy and received induction chemotherapy with ATRA-based regimens.

After 3 days from admission, the coagulation function (PT, 27.60 sec; PT-international normalized ratio, 2.58; activated partial thromboplastin clotting time, 46.90 sec; fibrinogen, <0.30g/l; thrombin time, 32.0 sec; D-dimer, 25.83 μg/ml) suggested that the patient was at risk of disseminated intravascular coagulation (DIC), therefore fresh frozen plasma (4 units) were used for treatment. Significant improvement in coagulation parameters was observed after 5 days of treatment. Induction chemotherapy with ATRA [10 mg/m^2 *ter in die* (tid) day (D)1-D28] + ATO (5 mg/m^2 D1; 10 mg/m^2 D2-D28) regimen commenced on the 4th day of admission. On day 17 after the commencement of induction chemotherapy, laboratory data showed HGB 70 g/l, WBC $6.39x10^9$/l, neutrophils $2.76x10^9$/l, PLT $101x10^9$/l and D-dimer 1.52 μg/ml. A total of two units of suspended red blood cells were transfused to improve anemia on D21 and D24 after admission. After the first course of induction chemotherapy (D34), laboratory data showed that the patient's HGB remained stable (HGB, 85 g/l), the WBC count was significantly reduced ($3.63x10^9$/l, of which neutrophils were $1.38x10^9$/l) and the PLT count increased ($330x10^9$/l), whereas fibrinogen (3.86 g/l) and D-dimer (0.83 μg/ml) returned to normal levels (Fig. 3). Moreover, liver and kidney function were normal. Bone marrow cytomorphology (data not shown) and flow cytometry (lymphocytes accounted for 19.70%, granulocytes for 67.90%, monocytes for 4.40%, $CD45^{dim}$ cells for 1.60% and $CD45^-$ cells for 6.40%) showed that the patient achieved CR (Fig. S2), and no promyelocyte of abnormal immunophenotype was found. At the same time, the color Doppler ultrasound (data not shown) showed that the fetuses were normal, and the rash on the patient's extremities subsided.

The patient then underwent four successive courses of induction chemotherapy with ATRA + ATO regimen at the hospital of admission (Table I). During the third induction chemotherapy, color Doppler ultrasonography of both lower extremities showed venous thrombosis in the left lower extremity (data not shown) and anticoagulation therapy with low molecular weight heparin (200 U/kg) was administered. In addition, the patient was infected with the influenza B virus and developed herpes zoster on the left chest wall with hypoalbuminemia during the fourth induction chemotherapy. The patient was transferred to the intensive care unit for respiratory isolation, antiviral therapy with oseltamivir phosphate (75 mg q12h D1-D5) and intermittent albumin supplementation (5-10 g iv).

At 34 weeks gestational age, the patient developed edema, increased blood pressure (138-170/85-98 mmHg) and proteinuria. The obstetrician recommended ending the pregnancy and two healthy male infants (Apgar score of 10) were successfully delivered by cesarean section. Subsequently, the patient underwent consolidation therapy for ~27 months (the therapeutic procedures are shown in Table I), their medical condition was stable and they continued to be in CR. During the ~4-year follow-up period, the two infants were not found to have any health problems.

Discussion

Cases of APL in pregnancy are rare. The risks of APL in pregnancy include sequelae of abortion, perinatal mortality, intrauterine growth retardation, preterm delivery (7), high risk of bleeding, infection, inflammation and placental abruption (8). Therefore, timely treatment of maternal leukemia is necessary. The current management of APL in pregnancy is a challenge, as it cannot be based on evidence from well-designed trials, but instead relies on data from historical cases and discussions with individual patients. The present patient presented to the hospital at 13 weeks gestational age and elected to continue with the pregnancy and receive induction chemotherapy for her leukemia after an informed discussion.

A retrospective study by Santolaria *et al* (3) showed that among pregnant patients with APL, most of them were treated with ATRA alone (32%) or combined with chemotherapy (cytarabine or daunorubicin) (43%), while the remaining patients received chemotherapy alone and a small number of patients were treated with ATO-based regimens after delivery. ATRA is controversial during pregnancy owing to the teratogenicity and fatal retinoic acid syndrome, especially in the first 3-5 weeks of gestation (9,10). Other complications include craniofacial alterations, neural tube defects, cardiovascular

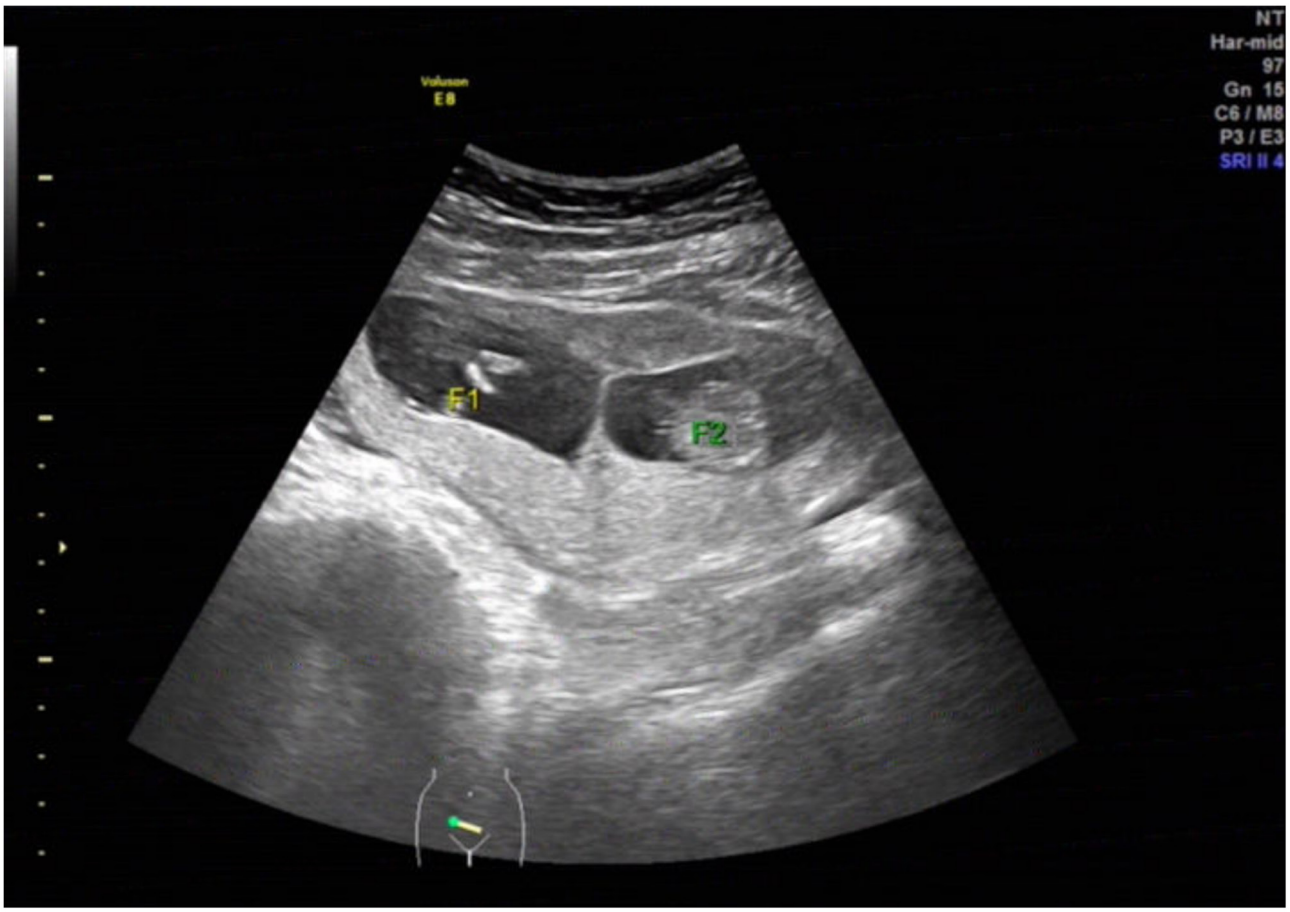

Figure 1. Doppler ultrasound reveals twin pregnancy in the present patient.

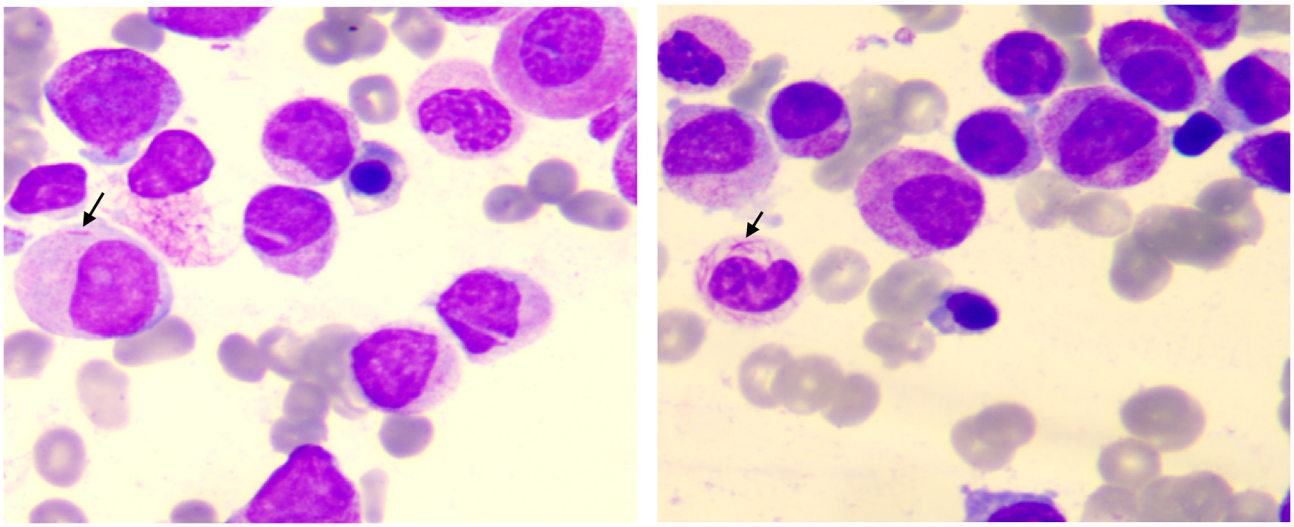

Figure 2. Two representative examples of bone marrow cytomorphological examination of the patient. Wright staining (magnification, x1,000). The black arrows point to Auer rods.

malformations, thymic aplasia and psychological impairments (9,11). However, there are currently data showing that ATRA appears to be reasonably safe and well tolerated if given outside the first trimester (12). In the present case, the patient received an ATRA-based induction chemotherapy regimen at 13 weeks of gestational age and achieved CR status. It should be noted that clinical bleeding problems were more marked before the introduction of ATRA, therefore continued vigilance during induction therapy was required to monitor and prevent fatal bleeding. Throughout the course of treatment, the occurrence of DIC was successfully prevented through blood infusion and continuous monitoring of coagulation factors.

Table I. Procedure for induction chemotherapy.

Course no.	Chemotherapy regimen
1-5	ATRA (10 mg/m^2 tid D1-D28) + ATO (5 mg/m^2 D1, 10 mg/m^2 D2-D28)
6	Cytarabine (100 mg/m^2 D1-D5) + Pirarubicin (30 mg/m^2 D1-D3)
7	ATO (10 mg/m^2 D1-D15) + Intrathecal chemotherapy (Methotrexate + Cytarabine + Dexamethasone, D14) + ATRA (10 mg/m^2 tid D16-D30)
8	ATO (10 mg/m^2 D1-D15)
9	ATO (10 mg/m^2 D1-D15) + ATRA (10 mg/m^2 tid D16-D30)
10	ATO (10 mg/m^2 D1-D15)
11-13	ATO (10 mg/m^2 D1-D15) + ATRA (10mg/m^2 tid D16-D30)
14-18	ATO (10 mg/m^2 D1-D15)

D, day; *tid, ter in die*; ATRA, all-trans-retinoic acid; ATO, arsenic trioxide.

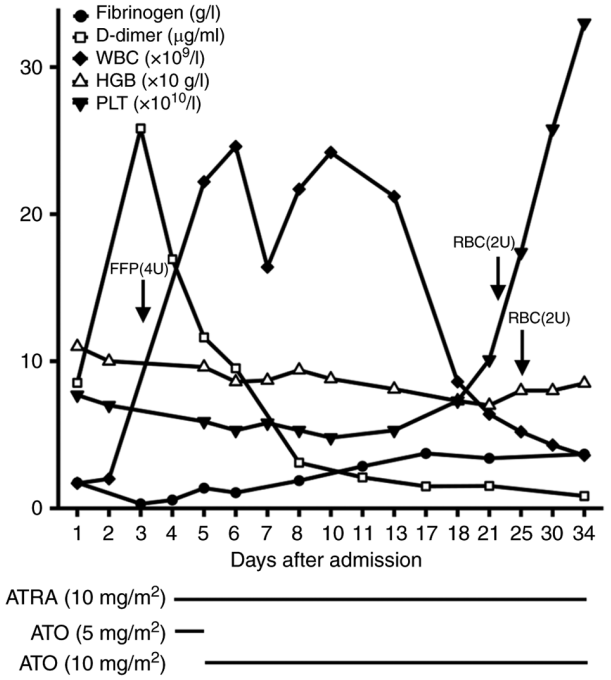

Figure 3. Procedure of first induction chemotherapy and time course of changes in fibrinogen, D-dimer, WBC count, HGB and PLT in the patient after admission. Different parameters were measured at different time points as per the medical requirements. WBC, white blood cells; HGB, hemoglobin; PLT, platelets; ATRA, all-trans-retinoic acid; ATO, arsenic trioxide; FFP, fresh frozen plasma; RBC, red blood cells; U, unit(s).

Once initial chemotherapy had been administered and remission had been achieved, the subsequent course was simpler. The present study showed that CR is likely to be achieved with maintenance chemotherapy and ATRA.

Over the last two decades, single administration or combination of ATO with other agents have been successfully used for the treatment of APL and several other myeloid tumors, such as non-APL acute myeloid leukemia (13). However, as stated in the European LeukemiaNet recommendations and other published guidelines for the treatment of APL, its use in pregnant women should be avoided due to its teratogenic effects (2,14). In animal studies, arsenic has been reported to cause anencephaly, cranial neural tube defects, that affect embryonic growth by altering the glucocorticoid signaling system during embryonic development and several different maternal toxicities (15). In the present case, the decision of treating the patient with ATO was taken due to their strong desire to protect the fetuses in the womb and the fact that the pregnancy was in the second trimester. Considering a large amount of trivalent arsenic excretion in breast milk and the possible fetal complications caused by ATO (16), strict feto-maternal surveillance and withheld breastfeeding were performed. It has been reported that the sequel of arsenic exposure to the fetus in pregnancy has been based on long-term exposure to high doses, mostly from environmental sources, such as drinking water (17,18). To the best of our knowledge, pregnant women that have received APL and were cured without affecting delivery in previous cases were relatively rare (2) and very few patient cases were treated with ATO + ATRA regimen (19-21), which is what makes the present case special.

In conclusion, the present study reports the case of successful treatment of APL in a pregnant woman of 13-week gestational age with an ATRA + ATO-based induction regimen, without any feto-maternal complications, provided the patient is managed strictly clinically. In-depth research to verify this observation is necessary.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

WN and KD confirm the authenticity of all the raw data. WN, KD, YC, LL, JL, WJ and LW collected and analyzed cell

morphology and Doppler ultrasound images, complete blood count and serum biochemical data, flow cytometry data, and other clinical information. WN wrote the manuscript. JL, YC and LL revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Zhongshan Boai Hospital Affiliated to Southern Medical University (Zhongshan, China). Written informed consent was obtained from the patient.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the data and images in this case report.

Competing interests

The authors declare that they have no competing interests.

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