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Case report

Acute promyelocytic leukemia during pregnancy: A case report and 10-year institutional review of hematologic malignancies during pregnancy

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ABSTRACT

Acute promyelocytic leukemia (APL) manifesting during pregnancy is a very rare but highly challenging gestational complication in part due to its associated profound coagulopathy. We present the case of a 23-year-old Gravida 3 Para 2002 woman admitted to our hospital at 26 weeks of gestation for severe pre-eclampsia with documentation of intrauterine fetal demise (IUFD), thrombocytopenia, and placental abruption. A peripheral blood smear revealed promyelocytes with azure granules, highly concerning for APL. Additional peripheral blood studies confirmed APL. Placental examination also revealed circulating blasts in decidual vessels and scattered blast entrapment in diffuse perivillous fibrinoid deposits, but none in the chorionic villi. Treatment for APL was initiated immediately and she is in complete molecular remission. Our case underscores the importance of close collaboration among obstetric, hematology, and pathology teams in the care of patients with pre-eclampsia, thrombocytopenia, and postpartum coagulopathy. We also describe five additional cases of gestations complicated by hematologic malignancies identified upon a 10-year institutional retrospective review.

1. Introduction

The incidence of acute leukemia during pregnancy is estimated at approximately 1 in 75,000–100,000 pregnancies [1,2]. Acute leukemia during pregnancy is associated with severe, life-threatening, maternal peripartum infection and hemorrhage, making prompt diagnosis and treatment extremely important. To date, only about 70 cases of acute promyelocytic leukemia (APL) during pregnancy have been reported, making APL in pregnancy a very rare event [3].

APL accounts for 10–15% of acute myeloid leukemias (AML) and is an aggressive hematologic malignancy characterized most commonly by the t(15;17)(q24;q21) translocation involving the retinoic acid receptor-α gene on chromosome 17 (*RARA*) and the promyelocytic leukemia gene (*PML*) on chromosome 15. This leads to generation of a chimeric PML-RAR-α transcription factor which blocks retinoic acid induced myeloid differentiation [4,5]. APL is associated with a profound coagulopathy which is multi-factorial, still incompletely understood, and the most common underlying cause of early mortality [6].

Here we report a case of APL diagnosed on the second postpartum day in a woman without previous history of hematological abnormality. Our aim is to emphasize the importance of suspecting, investigating, and treating the APL patient in the peripartum setting.

2. Case report

A 23-year-old Gravida 3 Para 2002 (term births 2, living children 2) woman with a history of gestational hypertension, morbid obesity, pseudotumor cerebri (PTC) status post ventriculoperitoneal shunt placement, and deep vein thrombosis (DVT) was admitted to our hospital at 26 weeks of gestation for pre-eclampsia with severe features and vaginal bleeding. Examination revealed intrauterine fetal demise (IUFD) and placental abruption. On admission, she had leukopenia and thrombocytopenia (white blood cell count [WBC]:3.51 × 10^3/uL; hemoglobin level [Hb]: 12.0 g/dL; and platelet count [Plt]: 63.9 × 10^3/uL). She also had coagulopathy which was initially attributed to pre-eclampsia and complications of placental abruption (prothrombin time [PT]: 14.8 s, normal range: 12–14.5 s; activated partial thromboplastin time [aPTT]: 38 s, normal range: 25–35 s; fibrinogen: 160 mg/dL, normal range: 220–498 mg/dL). She received 2 units of packed red blood cells, 1 unit of platelets, 1 unit of fresh frozen plasma, and 10 units of cryoprecipitate. However, despite these transfusions, on postpartum day (PPD) 2, her CBC showed persistent leukopenia (WBC: 2.07 × 10^3/uL), anemia (Hb 9.5 g/dL) and thrombocytopenia (Plt: 37.9 × 10^3/uL). Peripheral blood smear showed 11% promyelocytes with bi-lobed nuclei and azure granules, some with cytoplasmic Auer rods; findings highly suspicious for APL (Fig. 1). Her coagulation

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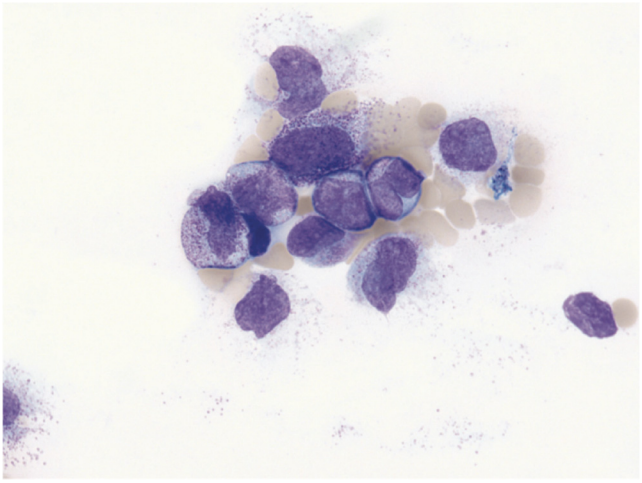

Figure 1. Acute promyelocytic leukemia in peripheral blood smear. Abnormal promyelocytes shows "bilobed" nuclei and abundant cytoplasmic granules.

laboratory tests revealed continued prolongation of PT (21.1 s) and aPTT (62 s), decreased fibrinogen levels (124 mg/dL; normal range 220–498 mg/dL), and markedly increased D-dimer levels (> 20,000 ng/mL; normal range: 0–240 ng/mL). In addition to ongoing vaginal bleeding, she developed spontaneous oral bleeding. Treatment for suspected APL was immediately initiated with all-trans retinoic acid (ATRA) (45 mg/m^2/day in two divided doses). Bone marrow biopsy was precluded due to possible DIC. On PPD 3, peripheral blood flow cytometry revealed a dysplastic population of blasts comprising 59% of the total cells with an APL immunophenotype (CD34-, CD117 + /lo, CD13 +, CD33 +, CD64 +, CD123 + CD38 + /lo, CD15 + /lo, CD14 −, HLA-DR −, CD7 −, CD56 −) and a heterogeneous side scatter. Arsenic trioxide (ATO) (0.15 mg/kg/day) was added promptly. Fluorescence *in situ* hybridization (FISH) for the *PML/RARA* fusion showed 85.5% of cells had the t(15;17)(q22;q21) translocation resulting in *PML/RARA* gene fusion. Chromosome analysis also showed that 20/20 cells had the 46,XX, t(15;17)(q22;q21). The placental examination revealed features of acute IUFD and massive perivillous fibrinoid deposits that contained scattered, entrapped leukocyte blasts with morphologies compatible with the patient's clinical history of APL and associated coagulopathy. There was no chorionic villous stromal infiltration or evidence of circulating blasts in the villous capillaries (Fig. 2). These findings were superimposed upon those of maternal malperfusion of the placental bed (preeclampsia); the placenta was small for 26 weeks of gestation and showed chronic chorionic villous ischemic changes, decidual arteriopathy (mural fibrinoid necrosis and atherosis, the presence of intramural lipid-laden macrophages and smooth muscle cells), and excessive numbers of circulating nucleated fetal erythrocytes indicative of a reactive left shift to chronic hypoxemia. ATRA was discontinued after 22 days due to worsening vision secondary to PTC despite presence of shunt, probably related to shunt thrombosis based on a heard computed tomography (CT) venogram. Other complications during her hospitalization included development of methicillin resistant *Streptococcus*

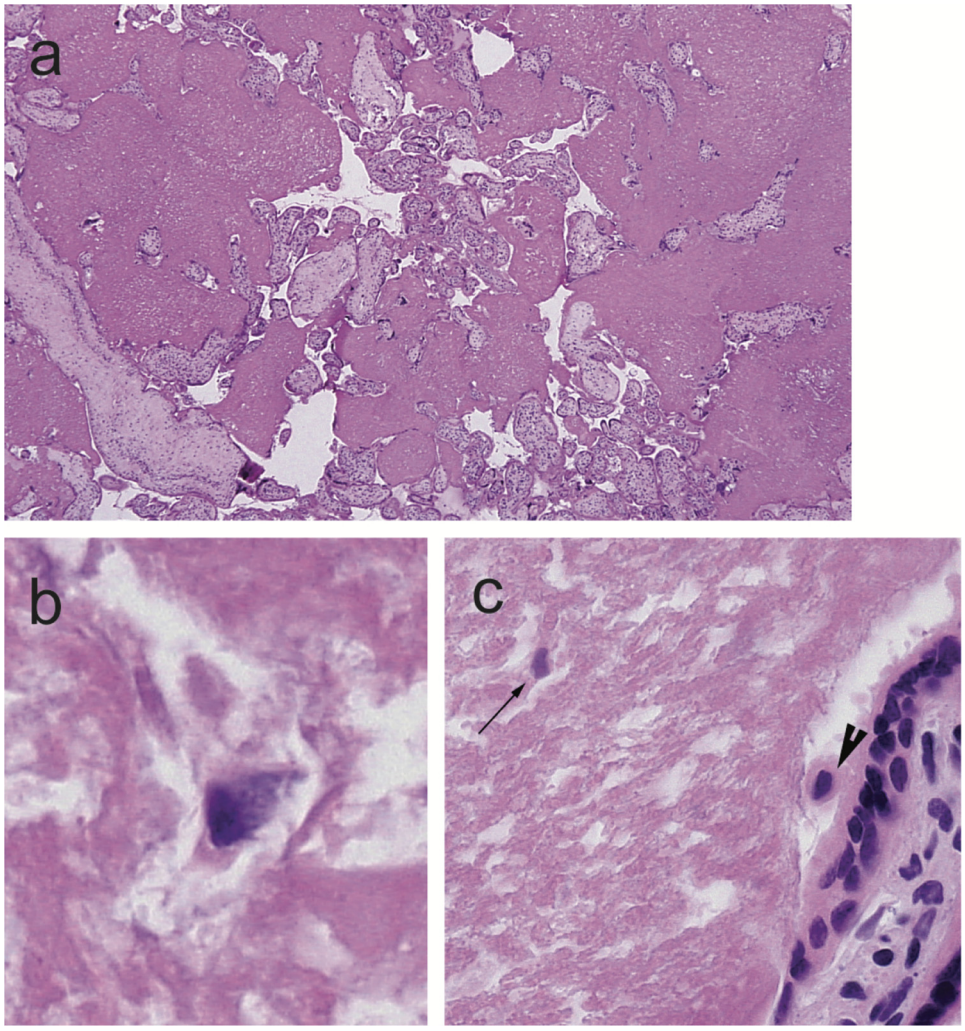

Figure 2. Evidence of APL in the placenta. 2a.Low power (100×) Diffuse deposition of pink amorphous fibrinoid material cloaks branches of the chorionic villous tree and broadly separates them from one another in many areas. Normally, the perivillous space consists of fluid maternal blood, not fibrinoid material, and this extensive deposition interferes with normal transfer of oxygen and nutrients to the fetus. In this case, these diffuse depositions are consistent with sequelae of the maternal coagulopathy. Entrapped APL cells cannot be seen at this low magnification. 2b-1, 2b-2. These two images show degenerating blasts (500×). 2b-1 shows a blast with scant light blue cytoplasm entrapped in fibrinoid material (arrow) and an adjacent portion of a chronic villus shows a detached syncytiotrophoblast cell for comparison of size and staining intensity (arrowhead). 2b-2 shows a "smudge cell" (disrupted, fragile blast) with faintly discernable cytoplasmic granules, surrounded by fibrinoid material.

Table 1
Patient characteristics and outcomes.

Case	Age at diagnosis	wk G at diagnosis	Disease subtype	Cytogenetics	Molecular genetics	Treatment	Pregnancy/infant outcome	Placenta report	Disease outcome	Patient outcome
1	26	35.6	γσ T-ALL	46 XX	N/A	Post-delivery: ECOG 2993 CNS intensification Relapse: FLAG-IDA BMT: MUD	IVD at 36 wk G BW: 2855 g Apgar: 8^1, 9^5 Discharged to home, 36.2 cwk GA without complications.	Third trimester, 560 g (372-542 g expected) placenta. - Trivascular umbilical cord with eccentric insertion.	CR1 then relapsed CR2 then BMT with CR	Alive Skin and gut GVHD
2	27	27	cHL (nodular sclerosing)	46 XX	N/A	Post-delivery: ABVD x 6 cycles	Triplet C/S at 29 wk G BWs and Apgar scores: Baby A: 1280 g; Apgar 9^1, 8^5 Baby B: 1335 g; Apgar 8^1, 8^5 Baby C: 1190 g; Apgar 7^1, 8^5 Treatment for complications of prematurity, eg: apnea of prematurity & respiratory distress; nutritional needs; patent ductus arteriosus (B,C); isolated perforated bowel & sepsis (B). Discharged to home at 38-40 cwk GA and pediatric followup	Third trimester, fused triamniotic trichorionic, 572 g (516–697 g expected for triplet placenta at 28 weeks) placentas with clinically designated umbilical cords. - Maternal history of Hodgkin's lymphoma: No tumor seen. - Triplet 1 (single cord clamp) Trivascular umbilical cord, eccentric insertion. - Triplet 2 (double cord clamps) Trivascular umbilical cord, eccentric insertion. - Triplet 3 (triple cord clamps) Trivascular umbilical cord, eccentric insertion.	Clinical CR	Alive Remains in clinical CR
3	29	18	CML-CP	46, XX, t(9;22)(q34;q11.2) [8]/ 46, idem, t(1;11)(q21;q23) [12]	t(9;22)(q34;q11.2)	Pre-delivery: IFN-σ Post-delivery: Hydroxyurea, dasatinib, FLAG-Ida, ponatinib, decitabine	C/S at 37.4 wk G BW: 3230 g Apgar: 1^1, 7^5 Treated for respiratory distress at birth. Discharged to home, 38 cwk GA without complications.	Third trimester, 584 g (391–566 g expected) placenta. - Trivascular umbilical cord, eccentric insertion. - Acute subchorionitis, membranes and chorionic plate, with chorionic vasculitis. - Acute funisitis, phlebitis.	CML-blast crisis (AML) after delivery BCR-ABL with T315I mutation	Disease unresponsive to treatment; transferred to hospice care 7 mo post delivery. Deceased
4	18	39	APL	46, XX	FLT3 ITD mutation PML/ RARA fusion	Post-delivery: ATRA, Arsenic, Idarucibin, Dexamethasone Consolidation: Tretinoin/ Arsenic trioxide x 4 cycles	IVD at 39 wk G BW: 3355 g Apgar: 9^1, 10^5 Did well at birth. Discharged to home, without complications.	Third trimester, 463 g (426–611 g expected) placenta. - Three vessel umbilical cord with eccentric insertion. - Mild chorionic meconiosis. - Abnormal cells in maternal space consistent with history of leukemia.	Negative for the PML/ RARA fusion Negative for FLT3 ITD mutation	Alive Remains in clinical CR

(*continued on next page*)

Table 1 (*continued*)

Case	Age at diagnosis	wk G at diagnosis	Disease subtype	Cytogenetics	Molecular genetics	Treatment	Pregnancy/infant outcome	Placenta report	Disease outcome	Patient outcome
5	21	28	cHL (nodular sclerosing)	N/A	N/A	Post-delviery: ABVD x 6 cycles	C/S at 28.5 wk G BW: 1250 g Apgar: 3^1, 7^5 Treatment for complications of prematurity, eg: apnea of prematurity & repiratory distress; nutritional needs; anemia. Discharged to home at 37 cwk GA and pediatric follow up.	Third trimester, 290 g (210–331 g expected) placenta. - Trivascular umbilical cord, eccentric insertion. - No diagnostic histopathology seen; specifically, no atypical lymphoid cells or other cells suspicious-appearing for malignancy seen in maternal space or decidua tissue or vessels	Clinical CR	Alive Remains in clinical CR

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; cHL, classic Hodgkin Lymphoma; CML-CP, chronic myeloid leukemia - chronic phase; BMT, bone marrow transplant; MUD, matched unrelated donor; GVHD, graft-versus-host disease; wk G, weeks gestation; wk GA weeks of gestational age; cwk GA, corrected weeks of gestational age; IVD, induced vaginal delivery; SVD, spontaneous vaginal delivery; C/S, cesarean section; BW, birth weight; Apgar scores reported at one[1] and five[5] min, respectively; CNS, central nevous system; CR, complete remission; min, minutes; mo, months; N/A, not applicable.

aureus (MRSA) bacteremia and renal insufficiency for which she was treated successfully by switching vancomycin to daptomycin. A follow-up bone marrow aspirate and biopsy specimen obtained after four weeks of treatment indicated no morphologic or phenotypic evidence of APL; however, FISH analysis *PML/RARA* fusion showed 33% of cells had the *PML/RARA* gene fusion. Consolidation therapy with ATO only was pursued due to PTC-related visual abnormalities. At the time of this report, she is in complete molecular remission after two consolidation cycles of ATO.

3. Institutional case review

We performed a retrospective review from January 2009 through December 2018 at our institution to identify cases of hematologic malignancies newly diagnosed during pregnancy. We identified five additional cases, including one other APL, two classic Hodgkin Lymphomas, one chronic myeloid leukemia (CML), and one T cell acute lymphoblastic leukemia (γδ T-ALL). Table 1 summarizes the details of these patients, disease characteristics, and maternal and fetal outcomes. All patients received postpartum chemotherapy. Four patients achieved complete remission (CR), and are alive. One patient, diagnosed with CML in chronic phase during the second trimester, was treated with IFN-α until delivery. However, in the postpartum period, the patient's disease progressed to AML, which exhibited poor response to treatment, and, due to severe complications of her disease, she was referred to hospice care seven months after delivery.

4. Discussion

The incidence of APL during pregnancy is exceedingly rare, estimated to be approximately one per million pregnancies [7]. Whether the pathogenesis of APL in pregnancy differs from that in nongravid patients is unclear. However, some reports indicate that alterations in hormonal levels and immunological responses during pregnancy may play an important role in the development of malignancies [3,8]. APL is characterized by several distinctive clinical features, especially DIC and associated early hemorrhagic demise. Thus, rapid diagnosis and treatment are of paramount importance to prevent early death.

Here, we describe a case of APL diagnosed on the second postpartum day. The patient was at 26 weeks of gestation and presented with IUFD secondary to pre-eclampsia and placental abruption. Initially, her coagulopathy was considered a complication of these disorders, but her condition worsened despite delivery and transfusion of multiple blood products. Notably, Celsing, et al. found that in some pregnant patients later diagnosed with APL, hematologic abnormalities were initially interpreted as representing components of pre-eclampsia and/or HELLP syndrome (constellation of Hemolysis, Elevated Liver enzyme tests, and Low Platelets.) In addition, some patients had severe complications including IUFD, as seen in our case [7]. Verma et al., in their review of 71 reported cases of APL during pregnancy, found that 32 out of 54 cases of the leukemia occurred in instances of spontaneous or therapeutic abortion, IUFD, or neonatal complications. About one-third of patients had obstetric complications, other than preterm birth or need for cesarean section delivery [3]. Thus, the diagnosis in the setting of pregnancy may be very challenging.

Currently, ATRA and ATO based regimens are the standard treatment for patients with APL. Successful second and third trimester postpartum treatment with ATRA is also reported [3,9–11]. Verma et al. found that among 58 evaluable patients, 93.1% achieved CR after initial induction therapy and the median time to reach CR was 30 days. Infection is the most common complication during induction. In our case, the patient achieved morphologic CR 28 days after her initial induction, but her hospital course was complicated by MRSA infection and acute kidney insufficiency due to the administration of vancomycin. She also developed vision problems secondary to ATRA-related PTC – a rare complication that occurs in 3% patients undergoing ATRA

therapy [12].

We also performed histopathologic examination of the placenta and found scattered entrapped leukocytes with cytomorphology consistent with blasts in masses of perivillous fibrinoid. About 100 cases of placental metastasis are reported, and there is greater risk of tumor metastasis to the placenta with disseminated maternal disease [13–19]. The most common malignancy that may metastasize to the fetus is melanoma, followed by lymphoma, leukemia, and lung cancer [13]. The true occurrence of placental involvement may be underestimated due to the fact that placental examinations are not routinely performed; placental involvement may be not be grossly appreciable; and microscopic detection may be sample dependent due to focal distributions of malignant cells [20]. Of note, our prior case of APL had leukemic localization in the placenta in the perivillous space. Therefore, it is very important that a thorough microscopic examination of the placenta is performed for all patients with pregnancy-associated malignancies, since the findings can guide treatment of the mother and evaluation of the infant. Thus, placental examination in these types of cases may merit more extensive sampling.

In conclusion, our case emphasizes the importance of considering the possibility of APL in a pregnancy complicated by pre-eclampsia, thrombocytopenia, or antepartum or postpartum hemorrhage with DIC. While gestational APL is rare, its diagnosis and management require close collaboration among obstetric, hematology, and pathology teams. Furthermore, it is important to perform a thorough histopathologic examination of the placenta for patients with pregnancy-related malignancies, and this may involve additional sampling.

Declaration of Competing Interest

None.

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