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Case Report

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Importance of the Third Trimester Complete Blood Count: A Case Report on Aplastic Anemia in Pregnancy

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Abstract

Aplastic anemia (AA) poses a significant threat to maternal and fetal health throughout the perinatal period. Diagnosis is based on complete blood count (CBC) and bone marrow biopsy with treatment varying based on severity of disease. This report highlights a case of AA incidentally identified by the third trimester CBC drawn in the outpatient office. Patient was referred for inpatient management to mobilize a multidisciplinary team of healthcare professionals including obstetricians, hematologists, and anesthesiologists to optimize maternal and fetal outcome. The patient received blood and platelet transfusions prior to delivering a healthy liveborn infant by cesarean section. This case highlights the importance for routine third trimester CBC screening to identify potential complications and decrease maternal and fetal morbidity and mortality.

Keywords: Aplastic anemia; Pancytopenia; Anemia in pregnancy

Introduction

Aplastic anemia (AA) is defined as a disorder of the bone marrow resulting in pancytopenia with acellular marrow in those not previously diagnosed with malignancy or myeloproliferative disease [1]. It poses an increase in both maternal and fetal morbidity and mortality [2]. Ninety percent of maternal mortalities are due to hemorrhage and sepsis while most fetal complications are secondary to maternal anemia [3]. This condition was first described by Ehrlich in 1888 in a pregnant patient and continues to arise in pregnancy. This case highlights an asymptomatic patient who was incidentally found to have pancytopenia with subsequent diagnosis of AA of unknown origin, highlighting the importance of routine third trimester complete blood count (CBC).

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Case Report

Investigations

A 35-year-old woman, gravida 1 para 0, with body mass index 35.4 kg/m^2, at 37 weeks and 5 days of gestation by *in vitro* fertilization, 5-day single embryo transfer presented to labor and delivery, after an abnormal routine third trimester CBC result drawn the day prior. Her values were significant for pancytopenia: hemoglobin of 7.8 g/dL, white blood cell count of $2.75 \times 10^3/\mu L$ and platelet count of $12 \times 10^3/\mu L$. First trimester CBC was within normal limits. Patient endorsed an episode of mild gingival bleeding after brushing her teeth 1 week prior to her CBC; however, she denied history of bruising, episodes of epistaxis, excessive bleeding after dental procedures, known personal or family history of clotting or bleeding disorders and cancer. She also denied recent viral illnesses, fevers, chills, sore throat, myalgias, rashes, cough, shortness of breath and nausea or vomiting. Coronavirus disease 2019 (COVID-19) polymerase chain reaction testing was negative on admission; she had received two doses of the COVID-19 vaccination and denied known recent sick contacts. The pregnancy course was otherwise uncomplicated, and she denied smoking, alcohol, or drug use in pregnancy.

Diagnosis

Upon presentation to triage, the patient denied all complaints and endorsed good fetal movement. Fetal heart tracing was reactive with a reassuring biophysical profile. Repeat CBC confirmed pancytopenia with hemoglobin of 6.9 g/dL, white blood cell count of $2.92 \times 10^3/\mu L$ and platelet count of $10 \times 10^3/\mu L$. Given her gestational age, the decision was made to admit the patient to facilitate multidisciplinary coordination of care including primary obstetrics, maternal fetal medicine, internal medicine and hematology oncology. Infectious etiology including testing for human immunodeficiency virus (HIV), COVID, hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr viral infection and treponema pallidum were

Table 1. Complete Blood Counts

	Hemoglobin (g/dL)	White blood cells ($\times 10^3/\mu L$)	Platelet ($\times 10^3/\mu L$)
Outpatient	7.8	2.75	12
Admission	6.9	2.92	10
Prior to antithymocyte globulin (ATG)	9.6	2.3	26
6 months postpartum	11.9	4	144

The patient's lab results as a function of her disease course were described in the literature.

negative. Patient was normotensive, maternal serum and hepatic function were appropriate. Coagulation studies were within normal limits. Lactate dehydrogenase, bilirubin, haptoglobin, reticulocyte count levels and anti-red blood cell antibodies were not consistent with a hemolytic process. Pernicious anemia workup including intrinsic factor antibody and anti-parietal antibody was negative. Paraproteinemia workup including serum protein electrophoresis, quantification of serum free light chain immunoglobulins and serum free light chain ratios were normal. Vitamin B12 was found to be borderline and she was started on vitamin B12 1,000 mg subcutaneously daily. There was an increase in vitamin B12 levels noted on day 5, however no improvement in reticulocyte response suggesting continued impairment of hemopoiesis. Patient was also started on folic acid supplement of 4 mg daily and oral iron. Transabdominal ultrasound was significant for borderline spleen enlargement, otherwise the liver, bilateral kidneys, gallbladder, pancreas, bile ducts, aorta and inferior vena cava were within normal limits with no ascites noted. Bone marrow biopsy was significant for variable cellular marrow ranging from 5% to 40% with an overall of 20-30%. Biopsy consisted of variable cellularity with erythroid predominant maturing trilineage hematopoiesis with no increase in blasts. Megakaryocytes were normal in number with unremarkable morphology. No evidence of megaloblastic change was noted. Cellular genetics were performed and nonsignificant; patient with normal female karyotype of 46 XX and fluorescence *in situ* hybridization analysis of bone marrow did not reveal assay abnormalities.

Treatment

Initially, supportive therapy was provided with transfusion to maintain platelet levels of greater than $10 \times 10^3/\mu L$ and hemoglobin of greater than 7 g/dL. Patient was acutely responsive to initial transfusions, however shortly after platelet and hemoglobin levels began down trending on repeat CBCs. As etiology was unclear in the setting of down trending platelets and increasing transfusion requirements, the decision was made to proceed with a primary cesarean delivery under general anesthesia at 38 weeks and 5 days. Prior to the operating room, the patient was optimized with packed red blood cells, platelet transfusion and tranexamic acid.

A viable male infant was delivered weighing 3,595 g with APGAR (appearance, pulse, grimace, activity, and respiration) score of 9/9. The estimated blood loss was 550 mL. Placental pathology revealed a trivascular umbilical cord without significant histopathologic findings and chorioamniotic membranes without significant histopathologic findings. She had an uneventful post-partum course and was discharged on day 6 with close outpatient follow-up. The infant was also discharged home without hematologic concerns; neonatal hemoglobin of 18.4 g/dL, white blood cell count of $14.19 \times 10^3/\mu L$ and a platelet count of $204 \times 10^3/\mu L$ with minimal bleeding after circumcision.

Follow-up and outcomes

A diagnosis of nonsevere AA was made by outpatient hematology oncology. Twenty-two days after discharge, repeat CBC was significant for hemoglobin of 9.6 g/dL, white blood cell count of $2.3 \times 10^3/\mu L$ and a platelet count of $26 \times 10^3/\mu L$. At this time, she was treated with equine antithymocyte globulin (ATG) 40 mg/kg intravenous (IV), slow infusion for 4 days via central line with 1 mg/kg methylprednisolone given prior to infusion and 1 mg/kg methylprednisolone mixed in with infusion. Tylenol 650 mg and Benadryl 50 mg IV were also given prior to treatment with equine ATG. She was placed on a 2-week steroid taper to prevent serum sickness. Cyclosporine 250 mg every 12 h was initiated after ATG infusion was completed, followed by Eltrombopag (Promacta) 150 mg/day. Upon evaluation 6 months after delivery, her values were improved; hemoglobin of 11.9 g/dL, white blood cell count of $4.0 \times 10^3/\mu L$ and platelet count of $144 \times 10^3/\mu L$.

The laboratory data of the patient are summarized in Table 1.

Discussion

AA in pregnancy is associated with an increased risk for maternal and fetal morbidity and mortality. Maternal complications include hemorrhage, chorioamnionitis, endometritis, placentomegaly, placental abruption, subchorionic hematoma, preterm labor, and preterm birth. Fetal complications include fetal growth restriction, thrombocytopenia, and oligohydramnios [2, 4]. Pregnancy associated with severe AA has worse maternal and fetal outcomes including cases of maternal mortality and intrauterine and neonatal death [2].

AA is considered a hypoproliferative anemia, or a lack of adequate red blood cell production within the bone marrow. Hypoproliferative anemia can range from common nutritional deficiencies, chronic inflammation, renal disease to more rare bone marrow failure syndromes and AA [5]. AA can be classified as nonsevere, severe, and very severe based on CBC results. Severe AA (SAA) is diagnosed using Camitta's criteria

of bone marrow cellularity < 25% and at least two of the following: absolute neutrophil count of < 0.5×10^9/L, a platelet count of < 20×10^9/L, or a corrected reticulocyte count of less than 1%. Patients with absolute neutrophil count of < 0.2×10^9/L meet criteria for very severe. As in our case, patients with hypocellular bone marrow not meeting criteria for severe or very severe are considered nonsevere [6].

Anemia and thrombocytopenia in pregnancy are common physiologic changes in pregnancy. According to the American Congress of Obstetrics and Gynecology (ACOG), screening for anemia in pregnancy with routine CBC should be ordered in the first trimester and again at 24 weeks 0 days - 28 weeks 6 days [7]. This allows for early diagnosis and management of hematologic diseases such as iron deficiency, thalassemia, or sickle cell disease. As seen in our case, AA may develop at any gestational age, which suggests the need for routine near term CBC screening to identify blood cell disorders, thereby allowing opportunities for early intervention and medical optimization prior to delivery. Furthermore, anemia of pregnancy most commonly develops in the third trimester, therefore routine CBC in the third trimester would have maternal and neonatal benefits for those without AA as well [8].

Antepartum management of AA involves an interdisciplinary team of obstetricians, hematologists, and anesthesiologists. In the non-pregnant patient, treatment options vary based on severity of disease. In cases of nonsevere AA, the combination of ATG with cyclosporine has been shown to have an earlier, better quality and higher probability hematologic response in comparison to cyclosporine alone [9]. In cases of severe AA, triple immunosuppressive therapy is used with the addition of eltrombopag, however bone marrow transplant has been shown to be the most effective [10]. In pregnant patients, treatment options are limited due to desire to avoid further immunosuppression and fetal toxicity [11]. Supportive therapy consisting of blood and platelet transfusions has been found to have favorable maternal and fetal outcomes in pregnancy complicated by AA [12]. Frequent maternal blood counts and fetal growth surveillance should be performed. Transfusions are suggested to achieve a hemoglobin > 8 g/dL and platelet count > 20×10^9/L [13]. Treatment for those requiring repeated transfusions can be augmented with cyclosporin and/or granulocyte-macrophage colony-stimulating factor (GM-CSF). These agents have no reported fetal effects; however, teratogenicity is currently unknown [3, 14]. Expanded CBC screening guidelines throughout the perinatal period would allow for early intervention and coordination of all subspecialities to enhance maternal and fetal care and delivery outcomes.

Vaginal delivery is preferred over cesarean delivery at appropriate platelet levels of > 20×10^9/L and > 50×10^9/L, respectively [15]. The risk of spinal epidural hematoma with a platelet count > 70×10^9/L is very low; however, the decision to proceed with regional anesthesia is at the digression of the anesthesiologist and hospital protocol [16]. General anesthesia should be considered if undergoing cesarean section [4].

Learning points

Pregnancy-associated AA is a serious condition that can result in maternal and fetal morbidity and mortality. Routine third trimester CBC evaluation and increased CBC monitoring throughout the course of the pregnancy will allow for prompt detection and management of abnormalities, including rare diseases such as AA, which may negatively affect maternal and fetal outcomes. A multidisciplinary team approach, early recognition amongst providers, and preparation to optimize delivery is necessary to improve care for patients with AA in pregnancy.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed patient consent was obtained.

Author Contributions

Jaclyn Del Pozzo wrote the manuscript. Insaf Kouba contributed to literacy search and drafting of the manuscript. Theodore Goldman contributed to revisions of the manuscript. Jolene Muscat contributed to revisions and final approval of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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