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ACUTE MYELOID LEUKEMIA IN PREGNANCY: DIFFICULT JOURNEY FROM DIAGNOSIS TO DELIVERY AND TREATMENT

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Abstract

The incidence of Acute Myeloid Leukemia in pregnancy is about 1 in 75,000 to 1 in 100,000. Owing to the therapy attributable risks to mother and fetus, the management of AML in pregnancy is very challenging, both for the parents and the medical fraternity. Furthermore, the diagnosis of leukemia in pregnancy is very difficult owing to vague presenting symptoms like fatigue and weakness which are confused with physiological changes during pregnancy.

Case Report: Primigravida, 33 weeks 6 days gestation age, with history of weakness and fatigue for 15 days and fever, cough and cold for 3 days was referred to our hospital with blood reports of raised total leucocyte count. The lab reports showed thrombocytopenia, anemia and leukocytosis with increased circulating blasts in the peripheral smear. As she was in her third trimester, plan of induction of labor and delivery followed by chemotherapy was taken. She delivered a live healthy baby. Post-delivery, she was advised chemotherapy. She had an immediate remission after the chemotherapy. The disease relapsed after 10 months and she succumbed to the disease due to unavailability of facilities during the COVID pandemic.

Conclusion: AML during pregnancy is rare. There is no fixed protocol for management of AML during pregnancy. The aim of management should be to take care of the initial concerns regarding fetal well-being according to gestation age and commence chemotherapy as soon as possible. This would give the best survival chances to the mother.

Introduction

The association of leukemia and pregnancy is very rare, rather under-diagnosed and sparsely reported. The prevalence based on diagnosed and reported cases is one in 75,000 to 100,000 pregnancies. Most of the leukemias diagnosed in pregnancy are myeloblastic.

Acute myeloid leukemia (AML) is characterized by excessive proliferation of blast cells of myeloid lineage. This results in hematopoietic insufficiency like anemia and thrombocytopenia. The symptoms are related to complications of the pancytopenia, such as infections or hemorrhagic diathesis. The mentioned initial symptoms of leukemia in pregnancy are easily attributed to physiological changes related to the pregnancy and hence are either missed or diagnosed late. We report a case of Acute Myeloid Leukemia in a pregnant patient, its management and outcome.

Case Presentation

18-year-old primigravida presented at 33 weeks 6 days gestation. She was referred with history of weakness since 15 days and fever, cough, cold since 3 days associated with raised leucocyte count. She belonged to low socioeconomic status, was unbooked and had two antenatal visits during her pregnancy. She visited the facility when she had symptoms of gross weakness.

Her first trimester was uneventful. She was registered at a local hospital but was not compliant. Dating scan, trisomy screening and anomaly scan was not done.

On examination, her pulse rate was 88, blood pressure 100/60, respiratory rate 20 per minute, and temperature 99 degree Fahrenheit. She was pale but there was no jaundice, icterus or edema. She had angular stomatitis, and glossitis indicating malnutrition. Lymph nodes were not palpable.

On per abdomen examination, Uterus was relaxed, 33-34 weeks size and fetal heart 143/min. Ultrasound showed a single live fetus in cephalic presentation with effective fetal weight of 2.4 kg and liquor 12.7cm. Placenta was in upper posterior position. The fetus had overdistended urinary bladder with hydronephrosis of fetal kidneys suggestive of bladder outlet obstruction. Moderate hepatosplenomegaly was present. She was moderately anemic with hemoglobin of 8.3 gm/dl. The leucocyte count was very high 2,66,000/cu mm with neutrophils 4, lymphocytes 1, eosinophils 1 and basophils 1. The blood picture showed marked leucocytosis with blasts cells predominating 86% and 2 myelocytes and 1 metamyelocyte. The blast cells typically showed large nuclei, opened up chromatin, prominent nucleoli and cytoplasmic blebs. This picture raised the suspicion of Acute Myeloid Leukemia in pregnancy. Her platelet count was 96000/cu mm. LDH was raised 995 U/L signifying cell lysis. Liver enzymes were also borderline raised. Dengue serology was found negative. Her blood group was O negative. Serum Creatinine - 1.05 mg/dl and Serum uric acid - 10.9 mg/dl were also raised. The blood picture thus indicated towards normochromic normocytic anemia, thrombocytopenia and leukocytosis. On further examination of the peripheral blood smear, a leukoerythroblastic formula was noted with the presence of predominant blast population (86%) (Figure 1).

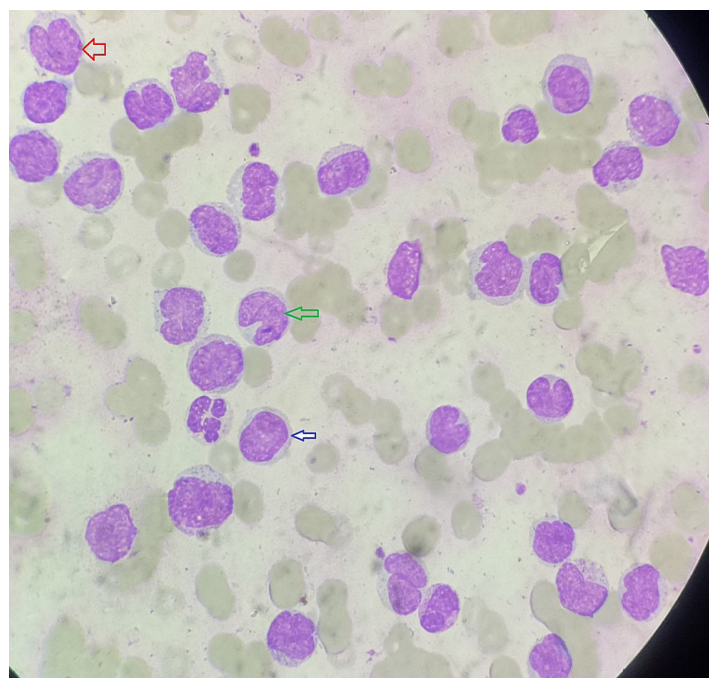


Figure 1: Slide picture of Peripheral smear with predominant blasts.

Peripheral smear showed mostly Monoblasts (red arrow), promonocytes (green arrow) and few myeloblasts (blue arrow) under the oil immersion object 100 X, Leishman stain.

Monoblasts are large cells with abundant cytoplasm, moderately to intensely basophilic, scattered fine azurophilic granules, round nuclei with lacy chromatin and one or more large nucleoli.

Promonocytes have moderate cytoplasm, less basophilic, granulated with occasional large azurophilic granules. Vacuoles are more irregular. Nuclei are delicately folded. Myeloblasts have large nuclei, fine chromatin, 3-4 prominent nucleoli and few Auer rods in the cytoplasm.

In view of suspected Acute Myeloid Leukemia, she was advised Bone marrow aspiration, biopsy and immunophenotyping, flow cytometry and translocation (15:17) study by oncologist.

The obstetrical examination was normal. All cardiotocographies were reactive. She was started on IV antibiotics, Inj Ceftriaxone 1 gm IV BD and steroids, Inj Betamethasone was given for fetal lung maturity. In view of malignancy with pregnancy, the case was discussed in tumor board on 10/9/19 and a decision for delivery followed by chemotherapy was taken.

She was induced with one dose of intracervical dinoprostone gel following which she went into labour and delivered live baby 2.8 kg weight with good apgar. The baby was shifted to nursery in view of premature delivery and mother was planned to transfer to medical oncology department for Induction chemotherapy.

Repeat investigations three days after delivery, haemoglobin decreased to 7 g/dl, TLC increased to 3,81,000 cells per cu mm with neutrophils 2, lymphocytes 5 and myelocytes 5. The abnormal blast cells had increased to 88% and platelets decreased to 21000 per cu mm TABLE 1. Serum creatinine also increased to 1.43 mg/dl and e-GFR decreased to 54 ml/min/1.73 m², indicating compromised renal function. The peripheral picture showed mostly agranuloblasts with moderate to scanty grey blue vacuolated cytoplasmic nuclei showing convolutions and 1-3 nucleoli occasional myelocytes, metamyelocytes seen, findings in favour of Acute myeloid leukemia (M4/M5). On myeloperoxidase staining, only 40 % took up the stain indicating AML-M4 lineage. She was transfused with one packed cell and one single donor platelet, following which her condition improved. She was transferred to medical oncology ward where she received chemotherapy and had immediate remission of the disease.

Table 1: Sequential Investigation Reports during hospital stay

Date	8/9	11/9	12/9	13/9
Hemoglobin	8.3	8.6	7	6.4
TLC	2,66,000	3,22,500	3,81,000	4,02,000
DLC	N-4, L-1, M-2, E-1, B-3	N-1, L-3, M-7, E-0, B-0	N-2, L-5, M-5	N-1, L-1
ABNORMAL CELLS	Blast cells- 86 Myelocyte-2 Metamyelocyte-1	Blast cells-89	Blast cells-88	Blasts-95 Promyelocyte-2 Myelocyte-1
PLATELETS	96000	860000	21000	40000
WBC Morphology	marked leucocytosis with fair no of blast which shows large nuclei open up chromatin, prominent nucleoli, cytoplasmic blebs	Large mostly agranuloblasts with moderate to scanty grey blue vacuolated cytoplasmic nuclei showing convolutions and 1-3 nucleoli occasional myelocytes,metamyelocytes seen, findings are in favour of Acute myeloid leukemia		mostly blasts having large nuclei, fine chromatin, 2-3 prominent nucleoli. Few blasts have indentation

Discussion

The Incidence of Acute Myeloid Leukemia is 1 in 75,000 to 100,000 pregnancies with maximum 40% presenting in third trimester and 23% and 37% in first and second trimester respectively. In a population based study by Nolan et al [1], out of total acute leukaemia cases, two thirds are myeloblastic and one third lymphoblastic leukemia.

The rarity of disease during pregnancy, might also be due to very low reporting in view of confusing diagnosis. The symptoms of AML can easily be confused with symptoms of anaemia like malaise, easy fatigueability, low grade fever. Thrombocytopenia and anaemia are relatively common findings in pregnancy. Although, Neutropenia is rare and merits further investigation or close monitoring. But in the developing country like India, it is majorly missed. Thus, whenever there is presence of circulating blasts in a blood film, it suggests a diagnosis of haematological malignancy and is an indication for bone marrow biopsy. The other differential diagnosis that should be kept in mind are Thrombotic microangiopathy, HELLP syndrome and Cytopenias of deficiency or immune origin [2].

The tests to be done before bone marrow aspiration are Full blood count, blood film examination, Vitamin B12, folate and ferritin measurement, Coagulation screen, Renal and liver function tests. All these were done for our patient and further bone marrow aspiration was suggested with studies directed at Immunophenotypic, cytogenetic and molecular analysis for accurate subtyping and understanding of prognostic features.

Once diagnosed, a Multidisciplinary approach comprising of hematologists, obstetricians, anesthetists and neonatologists is the key to appropriate management. Consideration should be given to health of both mother and baby. The woman should be fully informed about

the diagnosis, treatment of the disease and possible complications during pregnancy , clearly implying that any treatment delays might result in compromised maternal outcome without improving the outcome for the fetus [3].

The risks of Leukemia, disease per se, to pregnancy is miscarriage, foetal growth restriction, perinatal mortality, premature labour and Intrauterine fetal death [4].

Due to the high risk of the disease, there are different recommendations for management of AML in pregnancy in the three trimesters owing to the urgent need of chemotherapeutic agents and the adverse effects of the drugs involved .

If it is diagnosed in the first trimester, the patient should be counselled for elective abortion, medical/surgical and starting of chemotherapy. Between 13- 24 weeks, the Induction chemotherapy should be started while pregnancy is continued [5]. Preterm termination of pregnancy is indicated after fetal viability. Similar conclusions were derived by Nicola et al and Farhadfar in a single centre study of 5 and 23 case of AML diagnosed during pregnancy respectively [6,7].

Between 24 - 32 weeks, chemotherapy exposure to the fetus must be balanced against risks of prematurity following elective delivery at that stage of gestation (Grade 1C). At gestation age more than 32 weeks, the fetus should be delivered prior to Induction chemotherapy.

Chemotherapy with anthracycline based regimens are favored. According to a meta-analysis done by Natanel A Horowitz et al, anthracycline based regimens were associated with maximum remission but overall maternal survival was very low (30%)[8]. Even in our case, although the mother immediately had remission with chemotherapy. There was a recurrence after disease free 10 months and

she succumbed to the disease during the COVID pandemic. Quinolones, tetracyclines and sulphonamides are better avoided in pregnancy(Grade 1B).

In one case report by Abdullah et al, a trial of 5-azacytidine has shown promising results [9]. The antifungal of choice in pregnancy is Amphotericin B or lipid derivatives (Grade 2C). If blood transfusion is needed, the blood should be screened for Cytomegalovirus (Grade 1B). Supportive therapy like a course of Corticosteroids given if delivery is between 24 and 35 weeks gestation (Grade 1A) [10]. Magnesium sulphate should be considered 24 h prior to delivery before 30 weeks gestation (Grade 1A).

Delivery should be planned for a time when the woman is at least 3 weeks post-chemotherapy to minimize risk of neonatal myelosuppression (Grade 1C). Planned delivery is preferred, like Induction of labour (Grade 2C). Caesarean section is indicated only for obstetric indications. Epidural analgesia is better avoided.

The Dose of chemotherapy is calculated on their actual body weight with dose adjustments for weight gain during pregnancy owing to various pregnancy changes.

The Chemotherapy agents have a MW of 250-400 KDa and hence can cross the placenta resulting in detrimental teratogenic effects on developing fetus. Sunny J. Patel et al have done a comprehensive analysis on outcomes in hospitalized pregnant patients with acute myeloid leukemia and come to conclusion that a multidisciplinary, holistic approach leads to quick remission of the disease [11]

After delivery, histopathologic examination of placenta to rule out placental transfer to fetus is advisable. Cytologic examination should be performed in both maternal and umbilical cord blood and neonates should be clinically examined for palpable skin lesions, organomegaly or other masses. If the baby is found to be healthy, a follow up after every six months for two years is recommended. In each visit, physical examination, chest x-ray and liver function tests should be done.

Conclusions

Acute myeloid leukemia in pregnancy is a Rare diagnosis and even rarely reported. With the trend for delaying pregnancy into the later reproductive years, we expect to see more cases of cancer complicating pregnancy. Presently, there are no clear management guidelines to

address timing and dosing of anthracycline/cytarabine based regimens especially in pregnancy. The potential drug toxicity to mother and fetus and transplant considerations in intermediate and highrisk patients during pregnancy has not been addressed.

What we also need today is a National registry for leukemia patients, treated in pregnancy. This will help us to answer many unanswered queries and improve maternal and fetal overall survival rates. Although we have few comprehensive studies, but further studies and references are needed. Finally, a Multidisciplinary team is needed to provide comprehensive care to patients.

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