**TITLE:**  LEUKEMIA IN PREGNANCY MASQUERADING AS HELLP SYNDROME

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**INTRODUCTION:** The occurrence of cancer in pregnant women ranges from 0.07% to 0.1%. Acute leukemias rank third after breast and cervical cancer in association with pregnancy. Leukaemia in pregnancy is a rare event with an estimated incidence range of 1 in 75 000 to 1 in 100 000 pregnancies.[1,2 ] Acute leukaemia accounts for the vast majority of these presentations of which acute myeloblastic leukaemia (AML) accounts for two-thirds of cases and Acute lymphoblastic leukaemia (ALL ) representing one third of cases.[ 3,4]

The rarity of acute leukemia during pregnancy precludes prospective controlled clinical trials and the literature regarding the management is restricted largely to retrospective case reports, case series & few meta-analysis[5].

The diagnosis of leukemia in pregnancy is challenging as the initial features of leukemia are non- specific and often masked by pregnancy like fatigue, dyspnoea, weakness and pallor. Additionally, anaemia and thrombocytopaenia are relatively common laboratory findings in pregnancy. Taken together these can either miss or cause delay in the diagnosis of leukaemia. [5,6] Besides these features might produce diagnostic dilemma with the relatively more common medical disorders of pregnancy, creating a diagnostic dilemma and this is further complicated by the fact as acute leukaemia often presents as medical emergency.

Herein we present a case of 31 years multigravida with history of severe preeclampsia in her previous pregnancy , referred to us as a case of severe anaemia ,neutropenia, thrombocytopaenia ,modestly elevated liver enzymes and new onset ecchymotic patches all over body and deranged prothrombin and activated thrombin time ; proteinuria with presence of 70 percent blasts cells in peripheral blood smear creating a diagnostic dilemma of AML, HELLP, TTP, pregnancy associated haemolytic uremic syndrome (HUS) in this covid pandemic.

**CASE DESCRIPTION:** Thirty one years, gravida three with previous cesarean section done 5years back in view of severe preeclampsia ,followed by one spontaneous abortion was referred to our institute on 12.06.2020 evening with term pregnancy; 39 weeks ( calculated from her last menstrual period ,corresponding well with first trimester scan) with singleton pregnancy and HELLP ( **H**emolysis **E**levated **L**iver Enzyme **L**ow **P**latelets) syndrome with coagulopathy with history of bleeding from multiple sites.

After initial stabilization, a detailed evaluation was undertaken to find the underlying cause to guide directed optimal management. The patient revealed she was a booked case at private center and the pregnancy was uneventful till approximately 8-10 days before admission with us, when she developed gradually progressing pedal edema, decreased urine output followed by high grade fever (101F) with diarrhea. She was symptomatically managed with intravenous antibiotics, where during 2nd inpatient day she developed ecchymotic patches all over body and also 2-3 episodes of gum bleeding followed by mild vaginal bleeding.

On examination there was severe pallor, regular pulse at a rate of 100/min, normovolemic, Blood pressure of 110/80 millimeters of mercury, Respiratory rate of 14/minute. No lymphadenopathy no thyromegaly, no sternal tenderness, edema upto knees was present. CVS, respiratory and CNS examination was normal, urine output was decreased and was cola colored.

Per abdomen revealed abdominal edema, hepatosplenomegaly, fundal height corresponding to 32-34 weeks, cephalic presentation normal fetal heart rate of 150 beats per minute, low transverse scar with no scar tenderness, 2-3 contractions lasting for 20-30 seconds present.

Per vaginal examination revealed soft cervix, central, 1.5-2cm dilated, 60-70% effaced, well applied to head, membranes flat, vertex at -3 station , mild bleeding present with pelvis adequate for baby size. Ultrasound done revealed upper segment placenta with no evidence of retroplacental clot or thickening of the same, also suggesting small for gestational age baby with parameters of 34 weeks and decreased liquor (AFI 4cm). This USG finding, in the backdrop of DIC, the vaginal bleeding was attributed to abruption.

Her laboratory investigations revealed a rapidly progressing normocytic normochromic (normal MCV,MCH,MCHC) anemia ; drop in hemoglobin from 9.6gram/dL (4.06.2020) to 6.8mg/dl (12.06.2020) within a week, severe thrombocytopaenia 10,000/cumm, leucopoenia 1700cell/cumm with significant neutropenia of less than 10% on differential count, with evidence of microangiopathic hemolysis as suggested by raised total bilirubin of 3.32mg/dl due to raised indirect fraction bilirubin of 2.84 mg/dl and markedly elevated LDH (lactate dehydrogenase ) of 2997 U/L, modest elevation of liver transaminases with AST125U/L ALT 57U/L), markedly raised prothrombin and activated prothrombin time each > 200 , with raised D-Dimer 13,675 μg/mL suggesting Disseminated intravascular complication ( DIC) with normal HPLC ( High Performance liquid Chromatography) .RT-PCR testing for covid-19 was done and was found to be negative.

Most striking was the presence of 70% blast cells and few nucleated Red blood corpuscles in the peripheral blood film owing to which among the various differential diagnosis a provisional diagnosis of Acute leukaemia was made most likely Acute Myeloid Leukaemia (AML) as acute leukaemia is relatively more common during pregnancy, two thirds of which is accounted by AML.

But in view of the above features suggesting microangiopathic hemolytic anemia, elevated liver enzymes, thrombocytopaenia, coagulopathy and urine dipstick albumin 4+ ( >1000mg/dl) other differential diagnosis of HELLP syndrome, pregnancy associated thrombotic thrombocytopenic Purpura ( TTP) and Pregnancy associated atypical Hemolytic syndrome ( a-HUS) were made in the order respectively, however neither of them have presence of blast cells hence favoring the clinical presentation more in favor of acute leukaemia.

In view of the diagnostic and therapeutic dilemma and suspected oncologic and medical emergency multidisciplinary team was immediately involved comprising of Medicine, medical Oncologist, Anesthetist and pediatrician. The medicine consultants confirmed the provisional diagnosis of AML, specifically one of its variant acute Promyelocytic leukaemia (APL) which is specifically chacterized by features Of DIC and Infection and carries a high mortality if immediate induction chemotherapy delayed.

Since the patient was already term with 39weeks, in established labor, abruption with no scar tenderness and reassuring fetal heart pattern on cardiotocography (CTG), after informing the relatives and in continuous consultation of medicine and medical oncologists , decision for contemplating vaginal delivery was taken, keeping preparation for cesarean section for obstetrics indication; in the backdrop of DIC and severe thrombocytopenia and markedly deranged PT,aPTT.

Meanwhile patient was symptomatically managed with Platelets, fresh frozen plasma, cryoprecipitate and packed red blood cells. Strict monitoring of vitals , oxygen saturation , input output was done, she progressed well with the delivery of healthy female baby of 1.990 kg with APGAR score of 7 and 8 by VBAC and was shifted to NICU in view of severe respiratory distress.

Keeping a Low threshold for postpartum hemorrhage in this patient, it was managed with balloon tamponade along with uterotonics. Despite giving intravenous Lasix boluses as advised by anesthetist with ongoing packed cell transfusion her oliguria progressed to complete anuria (two hours) till she delivered.

Her BP increased to 150/100mm of mercury, she was confused, dizzy and her saturation dropped immediately and was put on high oxygen flow. Anesthesia consultation was done for the same, intubation done, but soon bleeding from various sites viz intravenous canula, urinary catheter was found along with subconjunctival haemmorhage, her pupils were semi dilated non reacting to light. There was sudden shoot of her BP to 200/100mm of mercury, became agitated and unconscious, following which CPR was started in view of cardiorespiratory arrest and then soon she succumbed to death, most likely due to DIC induced sudden intracranial haemmorhage.

**DISCUSSION:** The first description of leukemia in pregnancy was done by Virchow dating back in 1845 [1], since then a rising number of similar cases have been reported due to the advancing age at gestation. More than two-third of these cases are accounted to AML [2 ].The diagnosis usually occurs during second and third trimester of pregnancy, median age at diagnosis is 32 years ,similar to our patient who was 31 years with 39 weeks pregnancy [3]

Although the diagnostic criteria is same for both pregnant and non- pregnant women , the diagnosis during pregnancy is challenging and is often delayed or missed as the initial non-specific features of Acute leukemia like dyspnoea, fatigue, weakness and pallor are often masked due to the physiological changes of pregnancy and are commonly described symptoms of the patient. To add further anemia, thrombocytopenia, leukocytosis are also common laboratory findings during gestation. This was the similar presentation seen in our patient who gave history of dyspnoea, weakness and pallor initially which she ignored and found it trivial to consult her doctor.

The features of pancytopenia specifically neutropenia which is rare in pregnancy, severe thrombocytopaenia, severe anemia, hemolysis, recurrent infection and bleeding complications usually suggest a precarious cause, might be indicative of bone marrow clonal expansion by leukemic cells and needs detailed evaluation .The presence of Blasts cells > 20 % is strongly suggestive of hematological malignancy and needs confirmation by Bone marrow, immunophenotype or cytochemistry analysis in liaison with the hematologists [4]

 Acute promyelocytic leukaemia (APL) one of the subtypes of AML is seen in relatively higher proportions in young adults, compared to other subtypes of AML, hence more commonly seen during pregnancy compared to the general population and is characterized by pancytopenia, DIC, fibrinolysis, infection which presents as medical emergency in pregnancy. To add the sequalae of DIC often leading to abruption and bleeding complications often results in high maternal and perinatal loss [5,6] .

 The above features corroborated with our case too, created a diagnostic dilemma and medical emergency. Though AML was the first diagnosis in view of the presence of 70percent blast cells in the peripheral blood film but other differential diagnoses were also considered viz HELLP syndrome, thrombotic thrombocytopenic purpura (TTP)and pregnancy associated hemolytic syndrome (HUS) in view of features suggestive of microangiopathic hemolytic anemia, raised liver enzymes, and thrombocytopaenia.

 HELLP represents a severe form of preeclampsia , but the relationship between the two disorders remains controversial and HELLP may be a separate disorder from preeclampsia because approximately 15-20 percent of patients with HELLP syndrome do not have antecedent hypertension or proteinuria [7,8] this was consistent with our case where hypertension was not present ,though urine albumin of 4+ present and with history of preeclampsia in her previous pregnancy.

The distinction of TTP with the above clinical features was difficult but there was absence of neurological features; and atypical haemolytic syndrome is usually more common in postpartum period, not associated with purpura and deranged liver function test, The presence of Blast cells is characteristically absent in the other diagnoses [9,10].

 The diagnosis of acute leukaemia poses a challenge and an ethical dilemma because the mother needs optimal cancer therapy for survival and the developing foetus who could potentially be affected by the disease and/or the teratogenicity of antineoplastic agents. Many recently published literatures and the recent haematological guidelines suggests that immediate induction chemotherapy after the confirmed diagnosis significantly improves the maternal survival and perinatal outcome relatively. Also, they state vaginal delivery is preferable and chemotherapy should not be given after 36 weeks.

Therefore we decided for TOLAC ( which resulted in vaginal delivery) followed by confirmation of the diagnosis with Bone marrow Biopsy or cytochemical or immunophenotype analysis and institution of induction chemotherapy to achieve complete remission in liaison of the haematologist , but despite our aggressive treatment with antibiotics , blood and blood products the patient succumbed to the complications of DIC probably intracranial haemorrhage.

**CONCLUSION:** Leukemia in pregnancy is rare event and no single person can be expert hence the involvement of multidisciplinary team is imperative and also often they are diagnosed later and present as medical and oncologic emergency; which if not optimally managed carries high risk of maternal and perinatal mortality.

The initial features of leukemia are non-specific and often mimics the common symptoms of pregnancy. But Most important is that Anemia in pregnancy is multifactorial and should always be evaluated in detail regarding the type of anemia, the severity and cause of anemia. Even our simple blood films may reveal hints towards the underlying precarious condition which if ignored and not timely detected would cost as maternal and fetal mortality.

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