ACUTE MYELOGENOUS LEUKEMIA IN PREGNANCY IN A 32YR OLD WOMAN

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Abstract

Background: Generally a disease of the elderly, Acute Myelogenous Leukemia (AML) very rarely occurs in pregnancy with an estimated incidence of 1 in 75,000 - 100, 000 pregnancies[1, 2]. There is hardly any data on the difference in its incidence between pregnant women and non-pregnant women in the reproductive age. However, management options are more in the non-pregnant, as they are in the elderly. Because there is yet no globally agreed standard way of managing this clinical dilemma in pregnancy, various institutions have proposed different management protocols depending on the AML type, degree of symptomatology, gestational age at diagnosis and the patient's wishes.
The objective of this publication is to present our experience with this condition at the Korle Bu Teaching Hospital, to bring attention to the possibility of the condition in our environment as part of differential diagnoses of anaemia or coagulopathy in pregnancy.
Case: We report the case of a 32yr old G3P1+1A, at 32weeks 2days gestation diagnosed with and managed for Acute Myeloid Leukemia at the Korle Bu Teaching Hospital, and review of the available literature on this condition in pregnancy.
Conclusion: Acute Myelogenous Leukemia is a very rare condition in pregnancy that lacks universally accepted treatment protocols. Management can pose a challenge to clinicians, patients and their relatives. Early accurate diagnosis is difficult in resource-constrained settings, and management options are limited when trying to save both fetus and mother. Early accurate diagnosis and prompt referral for appropriate interventions are key in improving outcomes, even in the face of other obstetric complications.

Key Words: Acute, Leukemia, Non-Lymphocytic, Promyelocytic, Myelogenous, Myeloid.

Introduction

Acute Myelogenous Leukemia (AML) is also known as Acute Myeloid Leukemia or Acute Non-lymphocytic Leukemia (ANLL). It is a neoplastic proliferation of the myeloid line of blood cells in the bone marrow and is characterized by abnormal growth of white blood cells. These myeloid cells get arrested at one of the early stages of development[3]. Subsequently, the immature cells accumulate in the bone marrow and impair the normal production of blood cells. It is the most common leukemia affecting adults and the incidence increases with age. It is a rare condition with an associated mortality rate of approximately 1.06% in Ghana[4]. Most of the cases detected in pregnancy are acute with less than 10% being chronic[5].

Israel Henig et al, conducted a systematic review of leukemia in pregnancy from 1967 to 2013 during which they reviewed 173 reported cases - 120 (69%) AML and 53 (31%) Acute Promyelocytic Leukemia (APL). They found the median age of diagnosis as 28yrs (range 15-45), thirty-seven women (21%) were diagnosed during 1st trimester, 85 (49%) in 2nd and 47 (28%) in 3rd trimester. The trimester was not reported in 4 (2%) cases. One hundred and twenty-five (72%) of the affected women received chemotherapy during pregnancy across the trimesters while 46 patients had their treatment either after elective abortion or after delivery of a live baby. Delay in therapy beyond 1 week from diagnosis did not affect the overall survival compared to that obtained in women treated promptly. They concluded that the outcome of AML diagnosed during pregnancy appears to be worse than that reported in age-matched non-pregnant women and that survival of fetuses were encouraging with low incidence of birth defects and low birth weights[6].

Known risk factors include ionizing radiation, chemical exposures, genetic predisposition, or other blood dyscrasias.

Symptoms of AML result from replacement of bone marrow cells with malignant cells resulting in a drop in the levels of erythrocytes, thrombocytes, and normal white blood cells. The symptoms include anorexia, fever, fatigue, joint pains, weight loss, dyspnea on exertion, easy bruising, bleeding gums and increased risk of infections, with some masked by pregnancy. Clinical signs are often vague, non-specific and usually associated with those of common cold, anemia, bruised skin or bleeding gums, and petechial hemorrhage. Hepato-splenomegaly are usually mild and asymptomatic. Lymphadenopathy is uncommon[7].

An abnormal full blood count (FBC) finding of leukocytosis with blasts on differential counts, or peripheral blood smear is usually the initial pointer to a suspected case. It can also present with isolated anemia, thrombocytopenia or even a leukopenia. Although

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peripheral blood smear can lead to a presumptive diagnosis, the definitive diagnosis is clinched with a bone marrow biopsy examination, as demonstrated below:

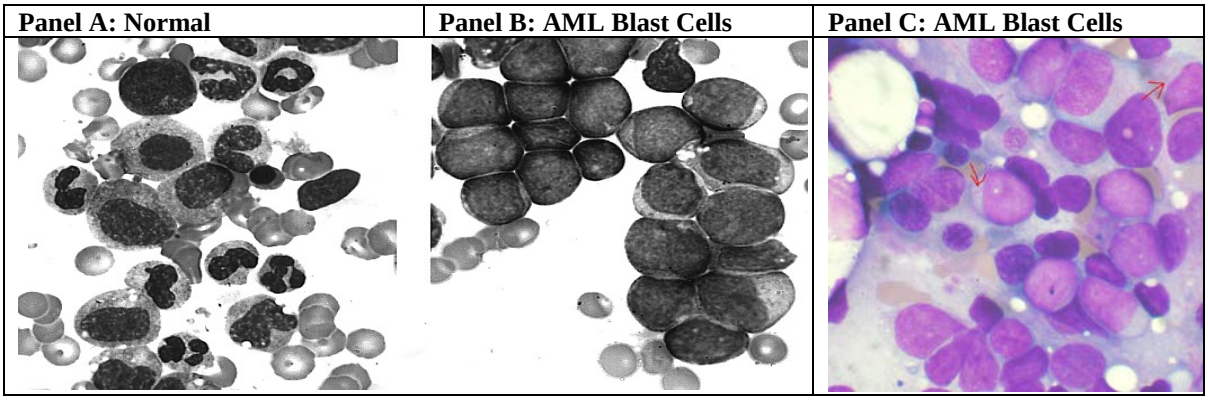

Fig1: Slide showing normal bone marrow (panel A) and AML blast cells (panels B & C). Curtesy: (1)

The disease progresses fast and kills in weeks if untreated. Available data suggest that maternal outcomes for acute myeloid leukemia (AML) following chemotherapy are analogous to nonpregnant patients, and recommend avoiding delays in commencing treatment[8]. AML has several subtypes with the acute promyelocytic leukemia type (M3) in particular having a high curability rate. This subtype also requires a unique form of treatment and so it's important to distinguish subtypes using Fluorescent in situ Hybridization (FISH) techniques[1].

Treatment consists primarily of chemotherapy placed into two phases: induction and post-remission (consolidation) therapy. Induction aims at achieving complete remission by reducing the number of leukemic cells to undetectable levels – cytarabine (200mg/m^2 for seven days) and doxorubicin (60mg/m^2 for three days). Consolidation on the other hand, aims at eliminating any undetectable residual disease to achieve a cure using 3 to 4 cycles of cytarabine given in high doses for 5days at a time in conjunction with Etopocide, Daunorubicin, or Idarubicin. The available evidence suggests that postponing treatment until postpartum is associated with increased maternal mortality[5, 2].

Case Presentation

A 32 years old woman G3P1+1A was referred from a Regional Hospital in Ghana to the Korle Bu Teaching Hospital at 32W2D gestation with complaints of a worsening episodes of total hematuria, sub-conjunctival hemorrhages and bleeding gums of about a week's duration. These had been preceded by generalized weakness, malaise and easy fatigability. She had been admitted and transfused two units of blood for symptomatic severe anemia three weeks earlier.

She had no significant medical or surgical history of note. She attained menarche at 10 years with 28 days regular cycles, coitarche at age 20 with 2 lifetime sexual partners. She has had an elective termination of pregnancy at age 20 years and a spontaneous vaginal delivery at 29 years.

At presentation she looked stable, fully conscious, alert and well oriented. She was moderately pale, anicteric, satisfactorily hydrated, but with sub-conjunctival hemorrhages, bleeding gums, bruises on tongue, and diffuse petechiae as well as ecchymosis over different parts of the skin.

Her cardiorespiratory system findings were normal with a blood pressure of 110/70mmHg, pulse 80bpm and normal heart sounds I and II with no murmurs.

The abdomen had a palpably gravid uterus, moved with respirations, with no scars or scarifications, but had petechiae and ecchymosis, linea nigra from umbilicus to symphysis pubis with a flat umbilicus. The symphisio-fundal height measured 33cm, with the fetus in a longitudinal lie, cephalic presentation, descent 5/5, and fetal heart rate of 140bpm, which was regular.

The full blood count that accompanied her referral note revealed: Hemoglobin 10.1g/dl, Platelet count 3 x10^9/L, and white blood cell count 10.1x101^9/l. The patient had been started on oral Amoxicillin/Clavulanic acid 625mg BD prior to referral. Her laboratory results on admission revealed: Hemoglobin 7.7g/dl, Platelet count 1 x10^9/L. Her renal and liver function parameters were all within normal limits, as well as urine analysis. A routine obstetric ultrasound scan detected a placenta previa type 1A. She was subsequently reviewed by the Hematologists who performed bone marrow biopsy that confirmed the diagnosis of Acute Myelogenous Leukemia, and then managed by a multi-disciplinary team comprising the Obstetricians, Hematologic-Oncologists, Anesthesiologists and Neonatologists. She was planned to have chemotherapy following delivery at 34weeks. Patient was therefore continued on routine prenatal supplements, transfused 12 units of platelet concentrate, two units of whole blood and a 48 hour course of intramuscular dexamethasone injections for fetal lung maturation.

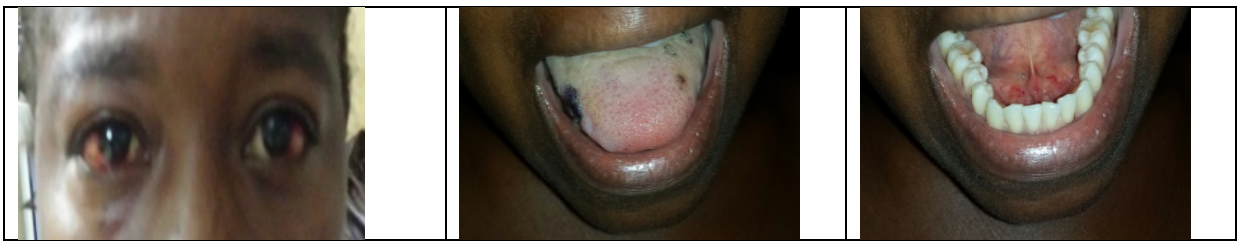

Fig 2: Photographs of patient showing sub-conjunctival hemorrhage, bleeding gums and oral mucosal petechiae

She was delivered through an elective Caesarean section at 34 weeks with findings of a live male in cephalic presentation, weighing 2.1kg, Apgar scores of 6/10 and 7/10 at one and five minutes respectively. Amniotic fluid was clear and normal in volume, placenta previa type1A was confirmed. Her tubes and ovaries looked normal and she lost approximately 300mls of blood intra-operatively. She received routine prophylactic intravenous antibiotics and was transfused a further 8 units of platelet concentrate post delivery.

She was nursed at the intensive care unit post-operatively and was stable on the first day post surgery, but developed a fever (temperature 38.4^0 C) with a significant serosanguinous wound and vaginal discharge, and followed with vaginal bleeding with clots (estimated 800ml) in the morning of the second day post surgery. She was pale, anicteric, and well hydrated. Chest examination revealed basal crepitation, but with normal oxygen saturation. There was a moderate abdominal distension that was soft, non-tender with a palpable splenomegaly (about 6cm below the left costal margin). Uterus was 22weeks in size and firmly contracted, with a heavy lochia but no active bleeding per vaginam subsequently. She had received 4,310mls of intravenous fluid but made only 2,008mls of urine. Her antibiotic cover was scaled up to intravenous ceftriaxone 2g daily and metronidazole 500mg tid, intravenous anti-malarial course started with transfusion of 3 units of packed red blood cells. She was started on intravenous paracetamol 1g tid, 2 liters of intravenous crystalloids in 24hours, rectal misoprostol 800mcg inserted, and she started on graded oral sips, her wound dressing was changed twice daily.

Over the next 4-6 hours, the patient's fever worsened with temperatures above 38.8^{o}C, and pallor became severe, but she remained alert and well oriented with only complaints of dizziness. She was started on intravenous Meropenem 500mg tid, blood transfusion continued and seven units of platelet concentrates transfused. She was also started on intravenous Hydroxyurea 1.5g daily.

In the morning of the third post-operative day, she still complained of dizziness. She was fully conscious and alert, now afebrile (T 37.2^0), mildly pale, with a tinge of jaundice, and mild bilateral pedal edema. She was tachypnoeic, had adequate air entry, coarse crepitation in both lung bases with $Sp0_2$ of 97% on room air. Her blood pressure had risen to 163/100mmHg, with a low-grade diastolic murmur. Abdominal distension had worsened with tympanitic percussion notes and no free fluid demonstrable. Her repeat laboratory findings were Hb 7.5g/dl, Platelet 3x10^9/L and WBC 21.81x10^9/L. She was transfused a unit of platelet concentrate and further intravenous fluids withheld while the blood pressure was controlled with intravenous hydralazine infusion and maintained at 148/84mmHg.

By the evening of the third post-operative day, the patient started desaturating with $Sp0_2$ 73-86% and so was immediately started on intranasal oxygen by facemask, which did not improve her oxygen saturation. She was subsequently intubated and given oxygen at 6litres per minute, transfused 2 units of blood, given intravenous calcium gluconate and furosemide and blood pressure now monitored through the radial artery.

Her saturation however persistently declined overnight while on oxygen via the endotracheal tube, until her blood pressure begun dropping around 3:00am on the fourth post-operative day (not responding to interventions). She had a cardiac arrest with attempts at resuscitation unsuccessful till she was declared clinically dead at 4:00am.

Discussion

Acute Myelogenous Leukemia is a very rare condition in pregnancy and the paucity of data, as well a lack of internationally accepted clear-cut management guidelines make the management a real clinical dilemma.

The proposed guideline by The British Committee for Standards in Hematology's, appears to be the most comprehensive one available. It recommends that a multidisciplinary team that includes hematologists, obstetricians, neonatologists and anesthetists should manage pregnant women with the condition as was done in our case presented above[9].

As per the WHO guidelines, bone marrow is required in order to confirm the diagnosis of AML, and our patient did have same after admission in the teaching hospital. This is applicable in both pregnant and non-pregnant patients[4].

There is the general principle to treat pregnant women diagnosed with AML promptly without delays. Patients diagnosed of AML in the first trimester usually carry considerable risk for spontaneous pregnancy loss. The recommendation would therefore be to discuss reasons for and against elective termination with the patient[4]. Between 24 and 32 weeks, risks of fetal chemotherapy exposure must be balanced against risks of prematurity following elective delivery at that stage

of gestation. This would pose another challenge in our setting where preterm babies below 1000g have very minimal chance of survival. In cases of patients presenting beyond 32 weeks gestation, it may be reasonable to deliver the fetus prior to commencement of chemotherapy. The management plan for our patient, in agreement with this recommendation, was to deliver at 34 weeks before commencing chemotherapy.

In managing AML in pregnancy, the risk-benefit ratio must be carefully considered before using any of the chemotherapeutic agents. Where AML induction chemotherapy is delivered, a standard Daunorubicin, Cytarabine 3+10 schedule is the strongly recommended regime. The British Committee for Standards in Hematology's guidelines further recommend that doses should be worked out based on the patients' actual body weight and adjustments made for weight changes during treatment. While it is recommended to avoid the use of Quinolones, Tetracyclines and Sulphonamides in pregnancy, Amphotericin B or lipid derivatives are the antifungal of choice in pregnancy. Cytomegalovirus (CMV)-negative blood products should be administered during pregnancy regardless of CMV sero-status. Even though our patient did not get screened for CMV, this did not prevent her from being transfused when the need arose. Our patient was given a course of steroids for fetal lung maturation in line with the Royal Infirmary recommendation that a course of corticosteroids should be considered if delivery is anticipated between 24 and 35 weeks gestation, given over a 48-h period during the week prior to delivery[9].

The administration of magnesium-sulphate in the 24hr prior to delivery before 32 weeks gestation has been found to be beneficial. Since the patient in our case had gone past 32 weeks, this was not considered. In women receiving chemotherapy prior to delivery, it is recommended to plan delivery for at least 3 weeks post-chemotherapy to minimize risk of neonatal myelosuppression from the chemotherapeutic agents[4]

Planned delivery is beneficial compared to spontaneous labour. Even though induction of labour is usually advised, our patient's placenta previa precluded her from being suitable for induction and hence the choice for Caesarean delivery. This is because elective caesarean delivery is to be considered if there are obstetric indications. Epidural analgesia should be avoided in a woman who is significantly thrombocytopenic (platelet count <80 x 109/l) and / or neutropenic (white blood cell count <1 x 109/l). Antibiotic administration is recommended during and after premature rupture of membranes and delivery as was done in the case presented, and further upgraded when the patient developed worsening fever[9].

The two-weeks spent by the patient in our facility before delivery afforded us the chance to investigate and also mobilize the needed blood and blood products. There was an extensive consultation and team approach in managing this patient with remarkable support from the laboratory department that facilitated her management. It is still unclear whether a splenectomy at the time of elective caesarean section would have benefitted the patient in this case. It is also our view and recommendation that patients (especially pregnant women) who present with sudden onset of severe anaemia be investigated thoroughly and appropriately referred promptly so that any serious diagnoses such as AML are confirmed early for appropriate interventions in a timely manner to avert mortality. In our patient the disease had advanced before referral and this, compounded by the stress of surgery (definite indication for Caesarean) most likely accounted for her grave outcome.

Conclusion

AML is a very rare condition in pregnancy that lacks universally accepted treatment protocols. Management can pose a challenge to clinicians, patients and their relatives. Early accurate diagnosis is difficult in resource-constrained settings, and management options are limited when trying to save both fetus and mother. Prompt referral for appropriate interventions is key in improving outcomes, even in the face of other obstetric complications.

Ethical Considerations

Consent was sought from the deceased's husband (the next of kin) before writing up this case for publication.

Acknowledgements

Our sincere appreciations to the staff of the Korle Bu Teaching Hospital at the departments of Anesthesiology and ICU, Hematology, Oncology, Pediatrics / Neonatology, Laboratory Medicine, and General Surgery for all their tireless efforts in attempting to save this woman's life. Even though we lost her we came out of this stronger, more experienced, closer and just more ready to serve our patients together.

References

1. DeGennaro, Louis J. (AML-Guide L& LS. The AML Guide. 2012; 1–40.
2. Thomas X. Acute Myeloid Leukemia in the Pregnant Patient. Eur J Haematol [Internet]. 2014; 95(33): n/a-n/a. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25409600\n http://doi.wiley.com/10.1111/ejh.12479
3. Seiter, Karen; Talavera, Francisco; Sachle RA. Acute Myelogenous Leukemia. Medscape. 2015;
4. WHO (World Health Organization). Worl Health Ranking, Leukemia Death Rate. 2014;
5. Latifi. Syheda; Ademi, Vlora; Brovina, Ahment; Hoxha, Mynevre; Lulaj S. Refusal of treatment for acute leukemia in pregnancy: a case report. J Med Case Rep. 2013; 7:148(DOI: 10.1186/1752-1947-7-148).
6. Israel Henig, Liat Vidal, Oryan Henig, Noam Benyamini IA. Acute Myeloid Leukemia

Diagnosed During Pregnancy: Facing Challenges. Systematic Review and Analysis of 174 Reported Cases. Blood. 2013; 122:1421.
7. Hoffman; Ronald (2005). Dohner, H ; Weisford, DJ (2015). Abeloff M (22004). Acute Myeloid Leukemia.https://en.wikipedia.org/wiki/Acute_myeloid_leukemia. 2016;
8. Dragana Milojkovic JFA. How I treat leukemia during pregnancy. Blood. 2014; 123:974-998.
9. Ali S, Jones GL, Culligan DJ, Marsden PJ, Russell N, Embleton ND. Guidelines for the diagnosis and management of acute myeloid leukaemia in pregnancy. 2015:487–495.