Acute Lymphoblastic Leukaemia in Pregnancy:
A Case Report

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Authors’ contributions

Author CEA designed the case study and made substantial contributions to the concept and writing of the manuscript. Author OOI was involved in the literature search and also ensures that all laboratory data were collated and analyzed author ROO made substantial contributions to the clinical care of the case presented. All authors read and approved the final manuscript.

ABSTRACT

Background: Acute Lymphoblastic leukaemia (ALL) is a malignant disorder which originates in a single B–or T-lymphocytes progenitor as a result of somatic mutation. ALL represents about 15% of all malignancies in 1-15 year olds, 5% in 15-19 year olds, and <10% of malignancy in >20 year olds. This condition is rare in pregnancy and when it occurs, its management and the use of chemotherapy during pregnancy, poses a significant risk to both the mother and fetus.

Aim: To underscore the difficult dilemma physicians are faced with in the management of ALL in pregnancy.

Study Design: Case study.

Place of Study: Obstetrics & Gynaecology Department of the Federal Medical Centre, Bida, Nigeria.

Methods: A review of the index case was conducted at the Obstetrics & Gynaecology Department of the Federal Medical Centre, Bida-a tertiary health care facility in Nigeria. This review took into cognizance the patient’s demographic bio-data, case history, methods of diagnosis and various supportive measures. A comprehensive analysis and account of events during this period were also reviewed.

Results: This case identifies a 26-year old gravida 2, para 1+0, a full term housewife and secondary school leaver, a Muslim background from a tribe of the Nupe part of Niger.

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State. She was on a routine antenatal visit to Obstetrics Unit, when patient was noticed to have purpuric lesions. She was subsequently referred to our unit (Haematology Department) at a gestational age of 22 weeks 4 days along with florid features of bleeding diathesis. A complete blood count, cytochemical, Immunophenotyping and molecular analysis done classified patient as having a Ph Negative, pre B acute lymphoblastic leukaemia in pregnancy. Patient was then offered some supportive measures though inadequate due to the absence of aphaeretic machine in the centre. Patient had early uneventful spontaneous vaginal delivery of a live baby (birth weight; 2.6kg) at 30 weeks gestation thereby making administration of chemotherapy much less worrisome. Meanwhile, mother and baby remain clinically stable while being followed up on the aftermath of remission induction of combination chemotherapy. **Conclusion:** Supportive management for ALL patients with anaemia and thrombocytopenia is a necessary pre-induction workup step, and as in this case, would allow room for fetal growth and lung maturity; when the fetus would be mature enough to cope with extra-uterine life but also without endangering the health of the mother. This patient however, had early spontaneous vaginal delivery precluding the anticipated risk of fetal exposure to cytotoxic agents.

**Keywords:** Acute lymphoblastic leukaemia; pregnancy; supportive management; gestational age; limited facilities.

1. **INTRODUCTION**

Acute Lymphoblastic leukaemia (ALL) is a malignant disorder which originates in a single B – or T-lymphocytes progenitor as a result of somatic mutation in a single progenitor cell at one of several discrete stages of development [1,2].

The incidence in the western countries is about 1.3 per 100,000 with a slight male predominance [2]. In the developed population, ALL represents about 15% of all malignancies in 1-15 year olds, 5% in 15-19 year olds, and <10% of malignancy in >20 year olds [3]. Acute leukaemias were also reported to be the commonest form of leukaemias in Ethiopia, constituting 63.8% of all cases reviewed, acute myeloid leukaemia (AML) being three times more common than ALL [4].

In Ibadan, South-Western Nigeria, the annual incidence for ALL had been reported to be 0.8 per 10^5 per year [5,6] ALL also displays a bimodal distribution with an initial peak incidence between the ages 3 to 5 years followed by falling rates during later childhood, adolescence and young adulthood. The incidence rate rose again, beginning in the sixth decade and reaching a second, smaller peak in the elderly [7]. This pattern is however not seen in African countries (including Nigeria) with no pre-school peak [5,7].

About forty percent of adults achieve remission with modern treatment modalities that are largely lacking in developing countries like Nigeria. Major discoveries in the biology of ALL over the past decades have improved the outcome of the disease. Markers such as the BCR-ABL chimera and CD20 have altered the treatment regimen. The basic principle of ALL treatment of combination therapy with sequential administration of induction, consolidation and maintenance therapy is still the mainstay of treatment [8,19]. This condition is rare in pregnancy and when it occurs, its management and the use of chemotherapy during pregnancy, poses a significant risk to both the mother and the fetus.
Although, there is no standard protocol on when or not to initiate treatment, the use of chemotherapy during pregnancy poses a difficult dilemma to the physician.

We report a case of ALL diagnosed during pregnancy. The aim is to highlight the constraints confronting the Specialist in managing this condition in a pregnant woman.

In line with ethical standards and principle of 1964 Helsinki declaration, a written informed consent was obtained from patient and spouse for the purpose of this case publication.

2. CASE REPORT

A 26- year old, booked gravida 2, para 1, 1 alive, a full term housewife and secondary school leaver, a Muslim background from a tribe of the Nupe part of Niger State, was on a routine antenatal visit to Obstetrics Unit, Federal Medical Centre, Bida, Nigeria - a tertiary health care facility, when she was noticed to have bleeding diathesis. She was subsequently referred to our unit (Haematology Department) at 22 weeks 4 days of gestation with a 3-week history of generalized body pain and weakness, bleeding gums and purpuric skin lesions. There was no history of similar features or bleeding in her previous pregnancy. History of trauma or use of drugs and herbal concoctions could not also be established. General and Physical examination revealed swollen gums, discrete bleeding spots on the upper & lower gums, as well as purpuric lesions around her upper arms and thighs. There was neither fever (Temp; 37°C) nor any significant lymphadenopathy. Respiratory rate was 20/min; breath sounds were vesicular globally, while pulse rate was 100bpm. Average blood pressure was 110/70mmHg and Heart sounds were S1 & S2 only. Electrocardiography showed normal sinus rhythm (QRS +30°, P-wave+30°, T-Wave 30°).

Abdominal examination showed a distended abdomen with a fundal height of 20 weeks but no palpable organ enlargement. This finding on physical examination was reaffirmed by an abdominal Ultrasound which revealed a single live fetus at 22 weeks 5 days, cephalic presentation with regular cardiac activity. There was no sonographic evidence of hepatosplenomegaly or intra-abdominal lymph nodes enlargement.

A complete blood count (CBC) done revealed a white cell count (WBC) of 48.6x10^9/l, lymphoblast of 68%, Neutrophils of 21%, lymphocyte of 11%, haemoglobin concentration (Hb) of 9.0g/dl, and platelet count (PLT) of 8x10^9/l. Peripheral blood film show leucocytosis with immature lymphoid cells predominance; lymphoblast are heterogeneous, small, intermediate to large size, abundant basophilic cytoplasm with irregular nuclear outline, and an open lacy nuclear chromatin pattern containing 1 to 2 nucleoli, and severe thrombocytopenia. Bone marrow aspiration revealed Hypercellularity with >70% lymphoblast. Based on the above CBC counts and morphologic findings, a diagnosis of Acute Lymphoblastic Leukaemia (L2; FAB Morphological classification) in Pregnancy was made. However, further investigations to characterize ALL type was carried out and the following results were obtained; cytochemistry was negative for myeloperoxidase (MPO) and periodic acid Schiff (PAS), Immunophenotyping by Flow cytometry and Immunocytochemical analysis was positive for CD 19, CD 20, CD34, CD 38, Tdt, and negative for CD3, CD10, CD57 and PAX 5. (Figs. 1 to 5)

A single Multiplex Real Time Polymerase Chain Reaction-TaqMan Chemistry did not detect any BCR-ABL transcript for p210 BCR-ABL or p190 BCR-ABL. Other investigations conducted are as shown in Table 1.
A diagnosis of Philadelphia Negative precursor B cell ALL in pregnancy was made based on the clinical features and laboratory results.

### Table 1. Laboratory data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference range [9,10]</th>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood counts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (x10^9/L)</td>
<td>2.5–7.5</td>
<td>48.6</td>
<td>57.4</td>
<td>47.6</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.5–13.5</td>
<td>9.0</td>
<td>12.0</td>
<td>12.7</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>34-40</td>
<td>28</td>
<td>37</td>
<td>39</td>
</tr>
<tr>
<td>Platelets(x10^9/L)</td>
<td>100-350</td>
<td>8.0</td>
<td>4.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Lymph (x10^9/L)</td>
<td>1.5–3.0</td>
<td>39.4</td>
<td>33.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Neutrophils (x10^9/L)</td>
<td>1.5–7.5</td>
<td>6.9</td>
<td>16.4</td>
<td>12.5</td>
</tr>
<tr>
<td>CD3 cell count (cells/μl)</td>
<td>1381-2311</td>
<td>-</td>
<td>1035</td>
<td>-</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTTK (secs)</td>
<td>36–56</td>
<td>36.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PT (secs)</td>
<td>11–17</td>
<td>17.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>INR</td>
<td>0.9–1.1</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>Not available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP</td>
<td>Negative</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HCV</td>
<td>Negative</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HIV I &amp; II</td>
<td>Negative</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: 1PTTK=Partial thromboplastin time with kaolin; 2PT=Prothrombin time; 3INR=International normalized ratio; 4EBV=Epstein-Barr Virus 5TP=Treponema Pallidum 6HBsAg=Hepatitis B surface antigen; 7HCV=Hepatitis C virus; 8HIV=Human immunodeficiency virus; 9DCT/ICT=Direct/Indirect coombs’ test; 10LDH=lactate dehydrogenase

Following the clinical evidence of mucosal bleeding and thrombocytopenia, the patient was transfused with a unit (500mls) of fresh whole blood in addition to other supportive measures which included, adequate bed rest, counselling and psychological support, barrier nursing, avoidance of intramuscular injections, maintenance of haemodynamic balance through intravenous infusion of 0.9% normal saline alternating with 5% dextrose saline at the rate of 1litre 8 hourly, Intravenous infusion of Augmentin 625mg 12 hourly, and adequate oral hygiene using oral mouth wash, soft toothbrush and cotton wool.

The patient was noticed to be passing coca-cola colored urine on the third day of admission. It became frank haematuria by the fifth day. There were new purpuric lesions and fresh gum bleeds. A complete blood count done on the same day revealed Hb conc. of 12.0g/dl and platelet count of 4x10^9/l while direct and indirect antiglobulin / coombs’ test were negative. She was subsequently transfused with two units of fresh whole blood. The bleeding subsided at Hb conc. of 12.7g/dl and platelet count of 29x10^9/l. Platelets transfusion support, which this patient really required, could not be provided at the Centre hence necessitated the need to refer her to a Hospital where aphaeresis was available. At the point of referral, bleeding had subsided significantly and the fetus remained very active. Eight weeks after, Patient had an uneventful spontaneous vaginal delivery of a live baby (birth weight; 2.6kg) at 30 weeks of gestation. Mother is clinically stable and being worked up for chemotherapy.
3. DISCUSSION

The occurrence of cancer in pregnancy is relatively rare. The most commonly diagnosed in the western world and developing countries such as Nigeria are breast and cervical cancer, followed by melanoma, leukemia and lymphoma [11,12].

Acute leukaemia and chronic lymphocytic leukaemia are rare during pregnancy. Donegan W reported 1 in 1000 pregnancies while Terek M et al. stated that approximately about 1 in 75,000 pregnancies are affected [11,13]. In 2005, Joseph D.E et al. reported the first AML case in two Nigerian pregnant women [14]. From available records, ALL in Pregnancy has not been reported in Nigeria, the index case representing the first case to be reported. Acute lymphoblastic leukaemia (ALL) accounts for about 28% of all leukemia during pregnancy; while acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) accounts for the remainder [11]. Diagnosis is usually made during the second and third trimesters, though it may present earlier in the first trimester.

Management of ALL in pregnancy is quite challenging in resource poor countries. The demand therefore, to successfully manage these patients is a daunting task given the manpower and resources available in developing nations, notwithstanding the multidisciplinary approach to the management. Several therapeutic roles and decision on approaches to management including supportive, monitoring of mother and the fetus / gestational age, institution of chemotherapy, immunotherapy and possible stem cell transplantation are employed by a team of medical personnel (haematologist, obstetrician, neonatologist, nutritionist, intensive care nurse etc).

Introduction of chemotherapy in any such patient must be guided by certain criteria to avoid chemotherapy related toxicity. However, this challenge becomes even more tasking in pregnancy, regardless of the trimester. Given the haematological parameters of the index case, at presentation, the decision for supportive therapy was much more plausible than to commence chemotherapy. This, in effect was aimed at preventing further depletion of the patient’s haematological parameters envisaged by the myelosuppressive effects of cytotoxic agents and also avoiding unnecessary fetal exposure to chemotherapy and toxicity. These supportive measures included management of septic spots, swollen gums, anaemia, and thrombocytopenia. These were achieved through provision of transfusion of fresh whole blood, prophylactic broad spectrum antibiotics. The transfusion of fresh whole blood is not the standard practice in resource rich countries where blood products transfusion is the norm rather than the exception. However; fresh whole blood transfusion is continually used or embarked upon in the developing countries, to provide a little quantity of platelets where blood products such as platelet concentrates are scarcely available.

Supportive management for ALL patients with anaemia and thrombocytopenia is a necessary pre-induction workup step, and in this case, would allow room for fetal growth and lung maturity (from 34 weeks gestation) when the fetus would be mature enough to cope with extra-uterine life but without endangering the health of the mother.
This patient did fairly well on various supportive measures but her platelet level was not appreciating significantly based on clinical signs and platelet value on CBC. It therefore became necessary to refer her to a Centre equipped with an affordable aphaeresis facility.
It is important to note that aphaeresis machines are not widely available in majority of the tertiary health institutions in Nigeria or other similar developing countries. This fact makes the provision of essential blood components (platelet concentrate) highly unavailable for patients requiring such. Time and money could be saved in caring for such patients if this among other necessary facilities is available, accessible and affordable.

There are different treatment protocols study available for the management of ALL and these protocols include UKALL (United Kingdom Acute Lymphoblastic Leukaemia), LALA (Leucemie Aigue Lymphoblastique de l’Adulte), CALGB (Cancer and Leukaemia Group B), and Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, adramycin and dexamethasone) [15-18]. In some instances, hyper-CVAD are used and has been successfully and safely administered in the third trimester to manage ALL in pregnancy as highlighted in a similar report by Ticku et al. [18].

In a study involving a total of 17 patients, anthracyclines, vincristine and steroids were administered between the gestational ages of 15 to 33 weeks. Although this chemotherapy was mainly given during the second and third trimesters, the result in the review shows that half of the women attained remission while the other half either relapsed or died from disease progression. Some adverse effects noticed among the infants delivered, range from transient pancytopenia, respiratory distress, gonadal and endocrinological disorders, to developmental problems [19,20].

In the index case, patient was sustained on supportive measure, given the low haematological parameters. She however, had early uneventful spontaneous vaginal delivery of a live baby (birth weight; 2.6kg) at 30 weeks of gestation thereby making consideration for administration of chemotherapy much less worrisome. Meanwhile, mother and baby remain clinically stable while being followed up on an aftermath of remission induction of combination chemotherapy.

4. CONCLUSION

Leukaemia in pregnancy poses a difficult challenge to the Clinicians, the unborn fetus and mother. In this case report, chemotherapy could not be instituted because of the challenge of providing adequate platelet support; one of the drawbacks faced in most tertiary health institutions in Nigeria. In the milieu of these challenges, appropriate referral aimed at ensuring overall survival of mother and the unborn baby should be discussed and embarked upon if and when necessary.

This patient had early spontaneous vaginal delivery precluding the anticipated risk of fetal exposure to cytotoxic agents. Given this scenario, institution of chemotherapy for the mother as well as long term follow-up of this child and children born to mothers under similar circumstances remain very important.

5. RECOMMENDATION

The provision of an appropriate guideline / standard protocol on ways of handling such rare condition of acute lymphoblastic leukaemia in pregnancy would be an essential step.

Aphaeresis and other facilities are in critical need in most tertiary health institutions in the developing world. The provision of these facilities at a highly subsidised rate in every tertiary
health institutions, particularly in Nigeria, would create the enabling environment for adequate healthcare for many patients needing such services.

Donor countries and agencies should sustain the unique role of continued assistance to developing economies by making essential healthcare tools available to the disadvantaged population.

In the milieu of inadequate facilities in the developing countries as opposed to developed countries, supportive management remains an essential part of the managing such patients before remission induction cytotoxic treatment.

Adequate long term follow-up of children born to mothers who had ALL during pregnancy should be conducted and incorporated in the guidelines for management of ALL in Pregnancy.

CONSENT

All authors declare that 'written informed consent was obtained from the patient and spouse for publication of this case report.

ETHICAL APPROVAL

All authors hereby declare that this case report has been examined and approved by the Hospital Ethics Committee and therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


