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Case Report

An obstetric challenge in the management of lymphoma in pregnancy

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ABSTRACT

Non-Hodgkin lymphoma (NHL) comprises of heterogeneous group of lymphoid malignancies originating from lympho-reticular tissues and is quite uncommon in pregnancy (0.8 cases per 1,00,000 women). Anaplastic large cell lymphoma (ALCL) is a large-cell neoplasm with anaplastic morphology classified under NHL. Here, a 31 year old primigravida diagnosed with NHL of ALCL subtype in third trimester, started on chemotherapy which resulted in severe pancytopenia during which she had to undergo emergency caesarean section for fetal indication. This patient was transfused with blood products and managed in isolated intensive care unit. She had a good outcome in postnatal period and went on to complete her chemotherapy and ended with remission of lymphoma.

Keywords: Pregnancy, Lymphoma, Pancytopenia, Non-Hodgkins lymphoma

INTRODUCTION

Cancer is the second leading cause of death during reproductive years, complicating approximately 1 in 1000 pregnancies.[1,8] Lymphoma is the fourth most common cancer in pregnancy with an estimated prevalence of 1 in 6000 pregnancies.[1,9] Compared to Hodgkin's Lymphoma, the occurrence of NHL complicated by pregnancy is very rare as the peak incidence of NHL occurs after child bearing age.[2,4]

Many challenges are faced in diagnosing and treating lymphomas in pregnancy. There can be delay in the diagnosis and treatment due to many factors like symptoms mimicking those of normal pregnancy, hesitation in doing imaging studies, complications of chemotherapy (CT).

Decisions regarding timing of delivery and CT regimens are made based on staging, type of tumor, immunohistochemistry, gestational age of pregnancy. Here, we have presented a case of NHL diagnosed in third trimester who developed bone marrow suppression in the first cycle of CT and delivery had to happen during nadir of the pancytopenic phase.

CASE REPORT

31 years old, primigravida at 31 weeks gestation was admitted at our hospital after prior inpatient evaluation in three hospitals in view of intermittent fever with chills of 25 days duration for further evaluation and management. Her pregnancy was uneventful until 28 weeks. She was investigated for fever including dengue, COVID and urinary infection. All these tests found to be negative. She was given multiple antibiotics other than antipyretics before admission in our hospital.

She was admitted after ensuring her repeat COVID RTPCR report was negative. Clinical examination revealed generalized lymphadenopathy (cervical, axillary and inguinal lymph nodes). No other positive relevant clinical findings. Differential diagnosis of infectious and noninfectious causes were considered. Blood investigations performed for scrub typhus, leptospira,

brucella, infections and ANA profile which turned out to be negative.

Stool test for clostridium difficile was negative. Other blood investigations showed mild anemia, normal leucocyte and platelet count, mildly raised liver enzymes. Urine and blood cultures showed no growth. Ultrasound (USG) abdomen revealed hepatomegaly. Fetal USG and non- stress test were normal. On admission, she was started on IV antibiotics, antipyretics and other supportive measures including low molecular weight heparin for thromboprophylaxis.

USG guided left cervical and right axillary lymph node biopsy was performed. Samples were sent for gram stain, acid fast bacilli stain, Gene xpert plus (MTB PCR plus tuberculosis culture) and fungus KOH staining, which were all turned out to be negative. Histopathological examination of the biopsy tissue revealed NHL, with ALCL subtype (Figure 1). Immunohistochemistry studies showed anaplastic lymphoma kinase marker positive (ALK) (Figure 2) and CD30 marker positive (Figure 3).

MRI scan was deferred as it is poor modality for staging even though plain MRI is safe during third trimester. The staging was assigned to IIIB. Prophylactic steroids for fetal lung maturity was completed at 31 weeks 5 days.

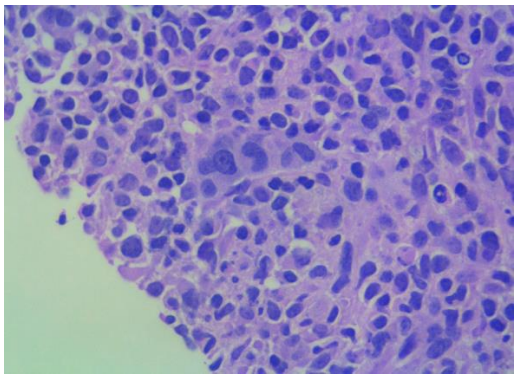

Figure 1: Hematoxylin and eosin stained slide showing anaplastic large cells.

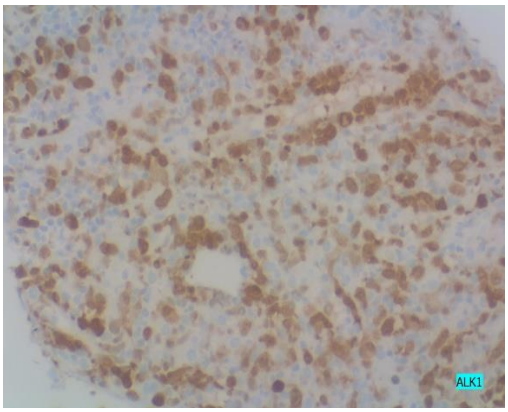

Figure 2: Shows immunohistochemistry staining positive for anaplastic lymphoma kinase (ALK).

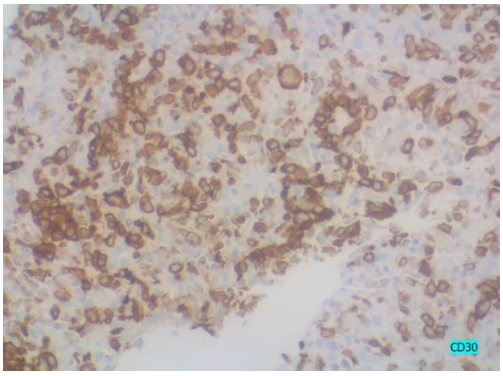

Figure 3: Shows immunohistochemistry staining positive for CD-30.

Decision was made to give CHOEP regimen of chemotherapy with one cycle during pregnancy and to deliver her 3 weeks later at 36 weeks, followed by completion of remaining 5 cycles of chemotherapy in the postnatal period. She was discharged after receiving first cycle and re-admitted 8 days later at 33 weeks with threatened preterm labour during which she was diagnosed with severe pancytopenia. She was treated in low count ward, started on Granulocyte Colony stimulating factor (G-CSF), broad spectrum intravenous antibiotics and blood products were transfused. Two days later, she had febrile spikes with delirium and preterm premature rupture of membranes (PPROM) with grade III meconium stained liquor with persistent fetal tachycardia. Emergency caesarean section was performed under general anesthesia due to meconium stained liquor and abnormal fetal heart tracing and unfavorable Bishop score after taking high risk consent in view of pancytopenia [platelets of 13,000 per µl and total white blood cell (WBC) count of 300 per µl]. Birth weight was 2 kg with Apgar of 6 and 7 at 1 and 5 minutes respectively.

Intraoperatively, 2 single donor platelets, 3 random donor platelets with 1 cryoprecipitate and 2 fresh frozen plasmas transfused. Patient developed transfusion associated lung injury (TRALI) and so she could not be extubated in view of desaturation at the end of the procedure. She was shifted to intensive care unit (ICU) and gradually weaned off from ventilator to nasal prongs by post-operative day 3. Granulocyte-colony stimulating factor (G-CSF) was continued in post-operative period till leukocyte count improved. Her general condition improved on 5th post-operative day and so transferred to ward. She developed urinary retention on 3rd post-operative day and managed by re-catheterization and alpha blockers as advised by urologist. After 4 days of continuous bladder catheterization the same was removed and had normal voiding. She was discharged in good condition on 9th post caesarean day. Her blood counts at the time of discharge showed haemoglobin- 8 g, total count- 4060 per µl, platelets- 45,000 per µl. Her wound healed well in the subsequent postnatal visits. She completed her 5 cycles of chemotherapy without major complications. PET CT scan done after completion of 6 cycles of chemotherapy which

showed complete metabolic remission. Infant at 10 months follow up is doing well in terms of neuro-developmental outcome.

DISCUSSION

Current clinical practice of treating lymphoma during pregnancy is based largely on case reports and small case series.[3,5,8] Diagnosis of such malignancies may be missed or delayed as their symptoms are similar to those encountered during normal pregnancy.[8] As in this case, patient was given empirical treatment for fever initially, and then had to be referred to a higher centre after which underwent thorough evaluation for fever with generalised lymphadenopathy. Diagnosis is usually made by examination of lymph node biopsy sample which does not cause additional fetal or maternal risk when done with local or general anaesthesia.[9] Many imaging studies may be hazardous during pregnancy.[8] The recommendations for imaging studies in pregnancy are mentioned in Table 1. Positron Emission Tomography (PET) scans should not be performed for staging due to the risk of radiation exposure to the fetus.[8] In this report, NHL diagnosis was confirmed at 32 weeks of pregnancy and a plan for radiological evaluation by PET was made to do after delivery.

Table 1: Recommendation for imaging studies during pregnancy.[3]

Non-abdominal or pelvic X-ray examination with abdominal shielding might be used during all trimesters of pregnancy.
There are no limitations for ultrasound examination.
MRI without gadolinium administration might be used in the second and third trimesters.
CT scan should be avoided.
Iodine-based contrast agent is contraindicated during all stages of pregnancy.
Gadolinium should not be used during all stages of pregnancy.

CT in the first trimester increases the risk of spontaneous abortion, fetal death and 10-20% risk of major fetal malformations.[10] Due to the low molecular weight of the cytotoxic agents, fetus gets exposed to the same as it crosses the placenta easily.[10] CT after the first trimester is likely to be safe and results in acceptable maternal and fetal outcomes.[5,6] However, it increases the risk of fetal or neonatal death, fetal growth restriction, PROM, induction of labour, caesarean delivery, preterm delivery and low birth weight.[1,5] Preterm delivery and not fetal chemotherapy exposure has been shown to be the most strong predictor of neurocognitive impairment.[6] A critical aspect in the management of cancer in pregnancy is timing of delivery with maternal-fetal conflicts.[1,5] Thus, an important goal should be prolonging the pregnancy so as to avoid preterm birth.[3,5-7] It appears that if the diagnosis is that of a poor prognostic type of lymphoma, prompt initiation of CT, regardless of the stage of pregnancy is the only treatment that can offer any hope of survival.[2]

Consideration should be given to postpone delivery for 2-3 weeks following CT to allow bone marrow recovery as well as fetal drug elimination via the placenta since preterm babies have limited capacity to metabolise and eliminate drugs due to liver and renal immaturity.[1,12] A natural vaginal birth is usually favoured whenever possible and importantly, mother's platelet levels should be above 50,000/µl before attempting delivery.[3] Unfortunately, this patient had to undergo caesarean delivery during the pancytopenic phase with febrile delirium in view of PPROM with meconium stained liqour and unfavourable cervix, remote from vaginal delivery. Hence, the need for prolonged ICU stay, need for blood products transfusion with its consequences like TRALI. Figure 4 and 5 shows the serial count estimation of WBC and platelet count depicting the timing of delivery at the nadir of counts. G-CSF is found to be safe for the fetus if administered during pregnancy.[7]

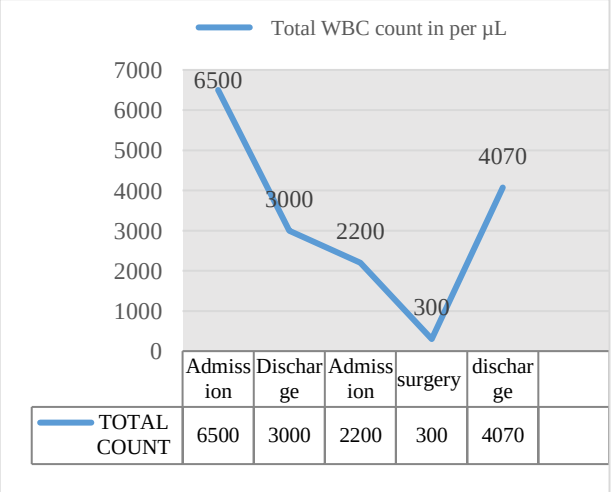

Figure 4: Total WBC count trend in relation to the time of surgery.

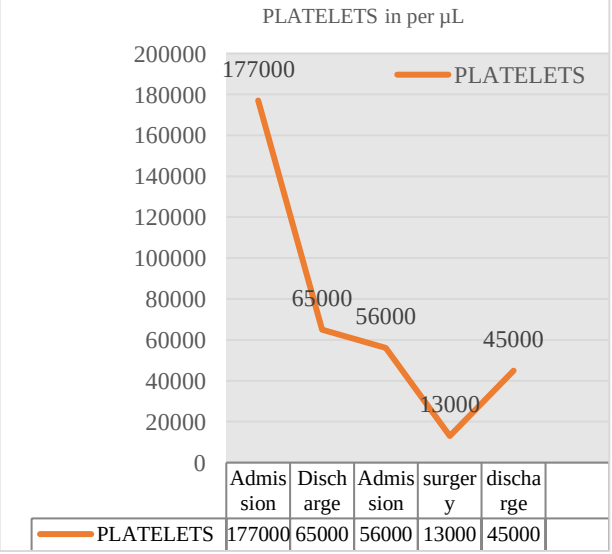

Figure 5: Platelet count trend in relation to the time of surgery.

The reproductive organs (breast, ovaries, cervix and uterus) are commonly involved in pregnancy associated NHL than in age matched patients diagnosed with a similar subtype.[9] Placental and fetal involvement is rare.[9] However, microscopic assessment of the placenta is highly recommended and in case metastases are present, a follow-up of the infant for the development of lymphoma is indicated.[3] Placenta was not sent for histopathology in our case as it was missed out, but it was structurally a normal looking placenta.

Diffuse large B-cell lymphoma is the most common lymphoma seen in pregnancy.[10] ALK-positive ALCL reported to be associated with a better prognosis than ALK-negative ALCL.[11] Most authorities consider cancer CT to be incompatible with breastfeeding.[1]

CONCLUSION

NHL is rare type of lymphoma seen during pregnancy. Management of lymphoma in pregnancy is very challenging in terms of diagnosis and treatment. Treatment decision requires a multidisciplinary approach involving obstetrician, oncologist, haematologist and neonatologist, and on a case to case basis balancing the maternal and fetal risks posed by the disease and its therapy. With limited available studies, the maternal and fetal outcomes for most women diagnosed during pregnancy are excellent and standard curative therapies are well tolerated usually.

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