CAS CLINIQUE/CASE REPORT

DIFFUSE LARGE B-CELL LYMPHOMA OF THE LUNG IN PREGNANCY
A Case Report

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ABSTRACT • Primary lung lymphoma (PLL) or pulmonary diffuse large B-cell lymphoma (DLBCL) is a rare entity. There is an increase incidence of DLBCL in patients with autoimmune disorders and recurrent or chronic bacterial infection. However, the cause is more complex and involves certain genetic factors for its development. Having lymphoma diagnosed during pregnancy is uncommon, and relatively little information has been available about the management and outcome of lymphoma in pregnant women. Primary pulmonary DLBCL during pregnancy is not even reported in the English medical literature. We are reporting the case of a 34 y/o lady who was diagnosed with DLBCL of the lung during the 19th week of her intrauterine pregnancy. She was treated with R-CHOP combination chemotherapy regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and received a total of six cycles before her delivery. Because of the early presentation during the second trimester, she received most of the planned chemotherapy course during the pregnancy. Follow-up of the mother showed major improvement and serial monitoring of the baby showed no developmental delays or physical abnormalities. At delivery the baby had neither side effects from chemotherapy nor any treatment related complications or developmental defects. FDG staging after delivery confirmed the primary pulmonary nature of the disease. Pulmonary DLBCL may present during pregnancy and poly-chemotherapy treatments should be considered as therapeutic options in such complex scenarios.

Keywords : DLBCL; pregnancy; chemotherapy; pulmonary lymphoma

INTRODUCTION

Hodgkin lymphoma (HL) is one of the most frequent hematologic malignancy reported in pregnant women, largely because the peak incidence of HL coincides with female reproductive age [1-3]. However, non-Hodgkin lymphoma (NHL) is relatively uncommonly reported during pregnancy [1-3]. This low incidence when compared to the age-adjusted general female population is thought to be due to the protective effect of female hormones during their reproductive period [4]. Results of a recent study support the hypothesis that exposures to estrogen and/or other reproductive hormones in women may induce favorable immunologic responses that reduce the risk of developing certain NHL subtypes and may help to explain sex differences in risk across subtypes [5]. The median period of lymphoma occurrence during pregnancy is about 24 weeks of pregnancy and in general impose little side effects on the pregnant patient and her baby [6]. Lymphoma during pregnancy poses multiple medical and ethical considerations best addressed in a multidisciplinary approach. These considerations include the effect of chemotherapy on pregnant women well-being, safety and fetal growth.

CASE REPORT

The patient is a 34-year-old lady, in her 18th week of gestation, presenting with a month history of worsening dyspnea. At presentation the patient was hypoxic with dyspnea at rest. She was suspected on clinical grounds by another clinician to have pulmonary embolism and was started on tinzaparin without clinical improvement. This was her first pregnancy after multiple in vitro fertilization attempts, therefore a precious baby. She was admitted to our institution through the emergency department with respiratory distress, severe pleuritic chest pain and dysphagia.

Her physical examination was noticeable for decreased air entry on the left lung field and dilated superficial veins on the left anterior chest wall. Her oxygen saturation on 4 liters nasal cannula was 94%.

Her blood test results were remarkable for a normocytic normochromic anemia with a hemoglobin of 9.7 g/dL.

A chest X-ray was obtained upon admission (19/4/2016) showing a complete opacification of the left hemithorax and mediastinal shift to the right.

An echocardiogram revealed right-sided shift of the heart, a moderate size pericardial effusion without tamponnade and a left pleural effusion.

A non-enhanced CT scan of the chest shielding the abdomen and pelvis showed a bulky mass completely obstructing the left main stem bronchus with collapse of the left lung and a moderate size effusion (Figure 1).

Also noted was an enlarged left axillary lymph node. An ultrasound guided pleural tap yielded 1600 ml of clear pleural fluid. It was exudative (Protein: 4.5, LDH: 1647)

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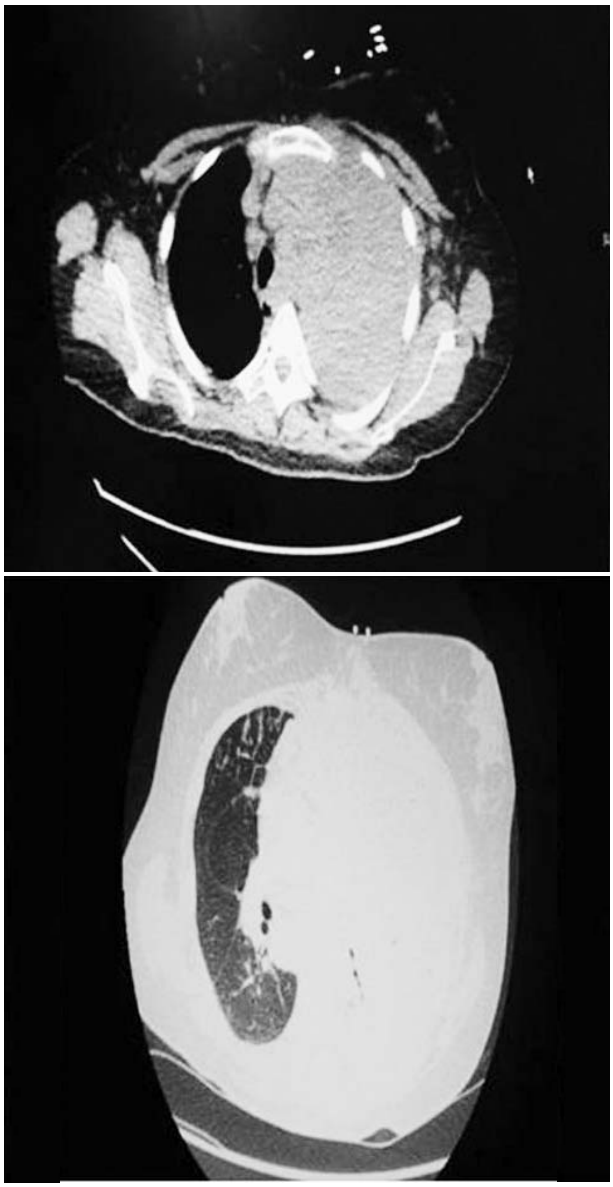


Figure 1. CT scan of the chest showing a bulky mass completely obstructing the left main stem bronchus with collapse of the left lung.

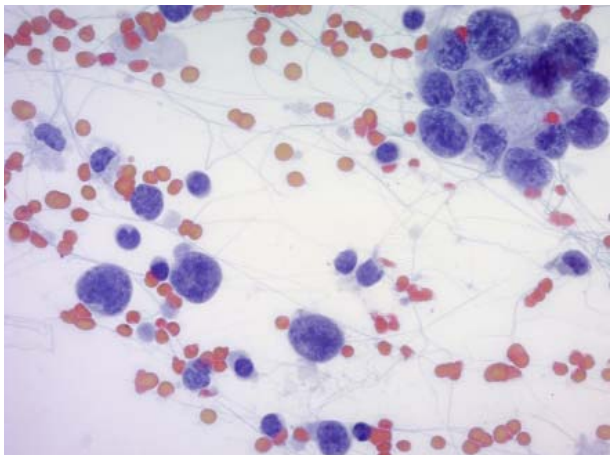


Figure 2. Pleural fluid showing large atypical cells in a background of RBCs and small lymphocytes

with lymphocytic predominance (Lymphocyte: 52%).

The cellular examination of the pleural fluid was highly suspicious for a lympho-proliferative disorder (Figures 2, 3). A biopsy of the enlarged lymph node showed evidence for a diffuse large B-cell lymphoma involving the lung (Figures 4,5).

Following a multidisciplinary discussion, we completed our staging using the above CT scan and a bone marrow biopsy.

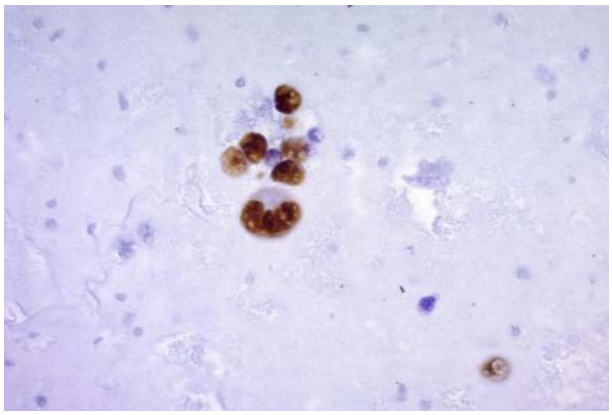


Figure 3. The large atypical cells are positive for PAX5 (nuclear B cell marker)

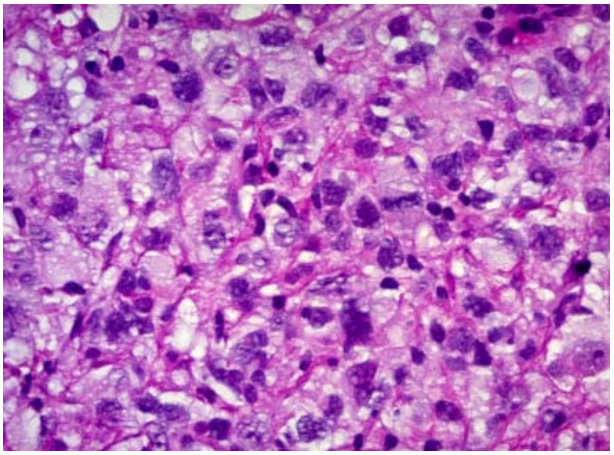


Figure 4. Axillary lymph node showing diffuse sheets of large atypical cells with mitotic figures

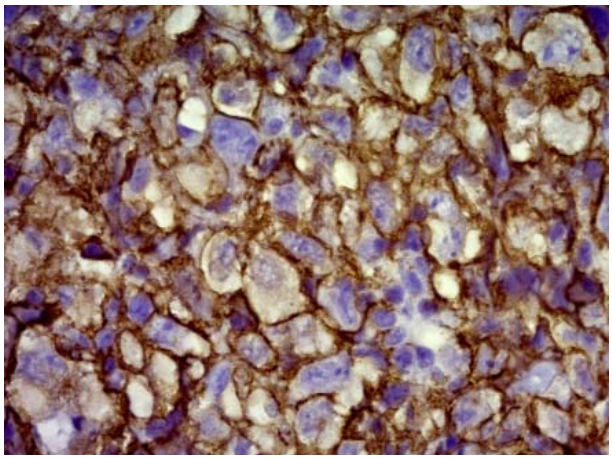


Figure 5. Axillary lymph node
The large atypical cells are positive for CD20.

The patient was staged as a IIAE DLBCL and started on treatment with standard doses of R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) given every three weeks. A total of six cycles were administered all during pregnancy. Her treatment started during week 19. Serial follow-ups showed excellent improvement of the patient's dyspnea, dysphagia and gas exchange.

Chest X-ray done one month after chemotherapy (31/5/2016) showed an improvement of the left lung aeration with left hemi-diaphragmatic elevation.

A fetal ultrasound was done at weeks 19, 21, 23, 26 and 29. No evidence of any structure or functional abnormalities was discovered. The patient completed her treatment with no major complications. She complained of grade 2 fatigue. From week 32 till week 35 of pregnancy, our obstetrician noted oligoamnios and in utero growth restriction. At 35 weeks + 3 days of pregnancy, she delivered through C-section a healthy baby with no obvious abnormalities.

At 10 days post delivery an FDG PET CT scan was obtained and revealed a complete resolution of all lymphadenopathies in the mediastinum and left hilum, with post obstructive loss of parenchymal lung volume, and residual FDG avid mass lesion with a standardized uptake value (SUV) max of 24.1 confirming the lung origin of the disease as previously suspected and the further need of additional therapy (Figures 6,7).

DISCUSSION

Diffuse large B-cell lymphoma (DLBCL) of lung is a rare intermediate to high grade B-cell non-Hodgkin lymphoma affecting most commonly the elderly. It is also the least common subtype of lung lymphoma. Secondary pulmonary involvement by DLBCL is more common but remains very rare [7-9]. Symptoms depend on the organ involved, along with systemic symptoms such as fatigue, pains, fever, weight loss, loss of appetite, anorexia and cachexia.

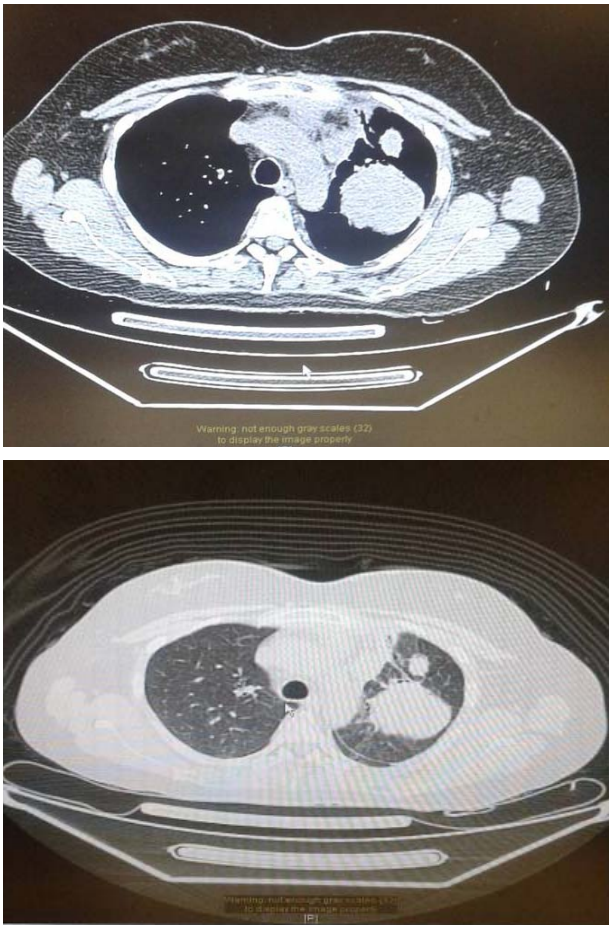
Primary pulmonary non Hodgkin lymphoma (NHL) accounts only for 0.4% of all lymphomas. The most common primary pulmonary lymphoma being the mucosa-associated lymphoid tissue type (MALT) lymphoma, which represents 70-90% of all primary pulmonary NHL [7-8] and 10% of the pulmonary lymphoma are DLBC type [9]. Most patients with primary pulmonary NHL are initially asymptomatic. When symptoms do develop, they are non specific respiratory symptoms, such as dyspnea.

Diffuse large B-cell lymphoma (DLBCL) is classified as an aggressive lymphoma. Survival is less than one year if untreated [10]. The disease typically presents as a rapidly growing nodal or extranodal mass with occasional systemic symptoms. DLBCL affects extranodal sites in around 40% of the cases. Sites involved are typically the bones, salivary glands, lungs, kidneys, liver and GI tract, particularly the stomach and less frequently the CNS [11].

A study investigating the characteristics of 855 NHL patients reported gastric involvement in more than 80% of all cases. Of note, most of gastrointestinal cases are MALT [12]. Pulmonary involvement is seen in 38% of HL and 24% of NHL. An open lung biopsy is typically needed to confirm the diagnosis [13,14].

R-CHOP, the most common treatment regimen used in NHL, consists of anti-CD20 antibody rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone every 21 days and occasionally as a dense regimen every 14 days [15].

The occurrence of cancer in general and lymphomas in particular during pregnancy is a serious problem concerning the safety of the therapy during this period and the possibility of fetal malformations. This debate requires good communication between the oncologist, the obstetrician and the couple. NHL is a rare hematological disease during pregnancy and our case is one of the very rare cases of pulmonary lymphomas that occur in this critical period. Here, we report a pregnant women at 19 weeks of pregnancy presenting with suffocating dyspnea associated with marked respiratory distress and



Figures 6 & 7. Left lung apex shows markedly hypermetabolic mass measuring 66 mm largest axial diameter with SUV max = 24 with complete resolution of all lymphadenopathies in the mediastinum and left hilum, with post obstructive loss of parenchymal lung volume.

dysphagia. All these symptoms abated after initiation of R-CHOP protocol and most interestingly the baby was delivered in an excellent health.

The difficulty stems from the fact that chemotherapy agents can cross the placenta and can potentially cause fetal malformations [16].These agents as they cross the placenta [16] during the first trimester can cause fetal death,spontaneous abortions and major malformations, as chemotherapy would interfere with organogenesis [17,18]. More specifically, administration of chemotherapy during the first trimester affect embryogenesis leading to heart defects, limbs deformities or agenesis as well as neural-tube abnormalities [19]. After week 10 of gestation, the ear or palate can be involved with functional defects [19].

The placenta plays a pivotal role in drug transfer [20]. Chemotherapy inadvertently administered prior to the development of the placenta in the first two weeks of pregnancy is generally less teratogenic [21]. In comparison, single agent and combination chemotherapy administered in the remainder of the first trimester result in a risk of congenital malformations of approximately 10 to 25% of cases [21].

Adverse effects of chemotherapy on the fetus are often more subtle during the second and third trimesters [22] and the administration of chemotherapy can be considered relatively safe [23]. The possible toxic effects are low birth weight, intrauterine growth restriction, premature birth, stillborn fetus, impaired functional development, intellectual disability (mental retardation), and diminished learning capability. Still chemotherapy used for NHL has been administered successfully during the second and third trimesters with good outcomes for both the mother and the fetus [24].

Radiation therapy can offer local disease control, but is associated with teratogenesis and an increased risk of childhood malignancy. Irradiation should be delayed until the second or third trimester, the whole body fetal dose should be limited to 0.10 Gy or less and the aim is for local response and disease control until delivery. As uterine fundal height increases we will note an increased dose exposure to radiation therapy administered to the chest from internal radiation scatter [25].

Most NHL during pregnancy data consist of case reports or small case series. Data on 50 patients with NHL during pregnancy compiled from the literature showed that standard chemotherapy regimens administered during the second and third trimesters, including as early as 13 weeks gestation in some cases, was associated with minimal maternal complications or fetal detriment [26].

Through our review of the literature we noted the following:

A case of bony lymphoma during pregnancy presenting with cruralgia in a 40-year-old lady with multifocal bone DLBCL who was diagnosed at 21 weeks of gestation was reported in 2014. Following a multidisciplinary discussion between rheumatologists, orthopedic surgeons, gynecologists and hematologists, a therapeutic interruption of pregnancy was realized at the 24th week of amenorrhea followed by tubal ligation [27].

An unusual case of DLBCL with cavernous sinus syndrome in a 24-year-old pregnant lady was also recently reported in the Chinese literature [28]. The patient was at week 30 of pregnancy, and was admitted with the chief complaint of sudden onset diplopia. She was diagnosed with cavernous sinus syndrome, inflammation, thrombosis of venous sinus and malignant cancer infiltration. A complete response was achieved after six cycles of R-CHOP chemotherapy. At 32 weeks of gestation the patient underwent a cesarean section. A viable baby weighing 1,700 g was delivered. The baby was initially treated in the neonate intensive-care unit for two weeks and discharged home in good health.

More recently the literature reports a case of primary mediastinal large B-cell lymphoma (PMBCL) (a rare variant of DLBCL) diagnosed at 12 weeks of gestation [29,30]. The patient delivered prematurely a healthy baby at 34 weeks gestation after receiving R-CHOP from week 13 to 31 of her pregnancy.

Our Medline search of the English literature for DLBCL and pregnancy yielded only 4 cases from 2006 to 2013, none of which was a primary pulmonary lymphoma. In our analysis of the reported cases (Table I) and the above cases, chemotherapy during pregnancy for DLBCL was not associated with major complications except for preterm birth, and intrauterine growth restriction [31]. In 2006, the authors reported the diagnosis of nodal DLBCL in a pregnant women successfully treated with R-CHOP. She was diagnosed at 15 weeks of gestational age and delivery occurred at 33 weeks [32].

Staging is difficult in such scenarios as we might jeopardize the healthy development of the fetus. Our patient presented with severe dyspnea, so we had to find a way to deal with this urgency as she was rapidly deterioriating and becoming distressed. She was treated as advanced stage NHL. We originally planned a total of 8 cycles and we are unable to assess the extent or the response by repeating CT scan or obtaining FDG PET CT scan. The goal of staging in this setting is to provide the clinician and patient with the information needed to guide management while limiting the risks to the fetus. Evaluation of the abdomen with MRI is safe and preferred to ultrasound, as it can evaluate nodes, liver and spleen with good accuracy [33,34]. In contrast, computed tomography (CT) scan of the abdomen exposes the fetus to potentially harmful radiation and therefore is rarely performed if MRI and abdominal ultrasound are available. ^{18}F-2-fluoro-2-deoxy-D-glucose injection (FDG) used in positron emission tomography (PET) is generally contraindicated in the pregnant patient [35].

When the treatment cannot be delayed until delivery as in our case, chemotherapy can be administered as multiple case reports showed the safety of the CHOP in the second and third trimesters [19,36]. Adding rituximab to

TABLE I REPORTED CASES OF DIFFUSE LARGE B-CELLL LYMPHOMA (DLBCL) DURING PREGNANCY

Year	Journal	Study Location	Age (year)	Location of the tumor	Diagnosis	Therapy R-CHOP	Result	Gestational age at diagnosis	Chemotherapy before delivery	Gestational age at delivery	Type of delivery	Infant APGAR score	Complication
2014	*Pan African American J*	Africa	40	Multifocal bone	NHL DLBCL	NA	NA	21	NA	Interruption of pregnancy	Interruption of pregnancy	Interruption of pregnancy	Interruption of pregnancy
2013	*J Can Res Ther*	China	24	Cavernous sinus	NHL DLBCL	6 cycles	CR	30	6 cycles	32 weeks	CS	1700 g weight at birth	Preterm birth
2012	*Geburtshilfe Frauenheilkd*	Germany	17	Ovary	Burkitt's lymphoma	7 months of BNHL protocol	CR	11	7 months of BNHL protocol	Interruption of pregnancy at	Interruption of pregnancy	Interruption of pregnancy	Interruption of pregnancy
2006	*Lancet Oncol* [32]	United Kingdom	31	Supraclavicular	NHL DLBCL	6 cycles	CR	15	6 cycles	33 weeks	VD	Weight within 50-90 percentile	Preterm birth
2011	*Korean J Med* [44]	Korea	33	Mediastinum (12 cm)	NHL PMLBCL	8 cycles	CR	22	3 cycles	34 weeks	CS	1935 g [8,9]	Preterm birth
2012	*Case Reports Hematol.* [45]	USA	22	Mediastinum (11 x 13 cm)	NHL PMLBCL	6 cycles	CR	12	6 cycles	34 weeks + 4 days	VD	Not reported	Preterm birth
2013	*Obstetrics & Gynecol Sci.*[46]	Korea	24	Palatine tonsil & level IIa neck	NHL DLBCL	6 cycles	CR	22	4 cycles	34 weeks + 5 days	CS	2560 g (7/9)	Preterm birth

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone **APGAR**: activity, pulse, grimace, appearance and respiration **NHL**: non-Hodgkin's lymphoma
DLBCL: diffuse large B-cell lymphoma **CR**: complete remission **VD**: vaginal delivery **PMLBCL**: primary mediastinal large B-cell lymphoma (a variant of DLBCL) **CS**: cesarean section

the CHOP protocol improves the outcome as reported in a recent study involving young non-pregnant DLBCL patients [23]. The review of 231 cases of pregnant women exposed to rituximab showed that most pregnancies resulted in uncomplicated live births. Two congenital malformations (2.2%; clubfoot in a twin, and cardiac malformation in a singleton birth) were reported [22], which is similar to the risk of the general population. The risk of preterm labor was higher in the rituximab group and was estimated at 19% [22,37]. It was concluded that rituximab is relatively safe during pregnancy [22,38].

The placental transfer of rituximab can therefore lead to depletion of neonatal B cells and may also explain the low neonatal B cell counts in several reported cases [32, 39-41]. Of the 21 cases of antenatal rituximab, there are 11 reported cases of neonatal cytopenias that include B cell depletion, low white blood cells, neutropenia, lymphopenia, thrombocytopenia and anemia [42,43]. Most cytopenia cases appeared to be transient and recovered spontaneously within 12-16 weeks in follow-up studies [42,43]. Despite the high incidence of hematological disturbance and significant reduction in B cell counts in neo-nates, there has been no report of infections associated with these cytopenia cases.

Effects of prenatal exposure to chemotherapy on the neurological outcome

During the second and third trimester of pregnancy, administration of chemotherapy is considered relatively safe in the short term [47,48]. However, reliable data on the long-term outcome of children after prenatal exposure to chemotherapy are lacking. To date, available data on long-term follow-up of the children are poor. Aviles *et al*. described a series of 84 children from mothers with haematological malignancies who received chemotherapy during pregnancy [49]. The children were examined for physical health, growth, general development and hematological, cytogenetic, neurological, psychological and learning disorders. However, no details on the neurological and psychological tests were provided. They reported that all children, including 12 second-generation children, had a normal birth weight, a normal learning and educational performance, and no congenital, neurological or psychological abnormalities.

Consequently, questions arise on the possible long-term effects of prenatal exposure to chemotherapeutic agents on the neurological development, fertility and carcinogenesis [47,50,51].

Our patient underwent serial fetal monitoring twice weekly. Intrauterine growth restriction was noted at week 32 to week 35 of pregnancy. Although oligoamnios was reported at week 32, the patient was monitored with a fetal ultrasound till week 35 when she started to have fetal extraction and absence of the fetal growth which led to her delivery through C/section. She delivered a healthy baby with normal cardiac function and APGAR score 8-10-10. A low birth weight of 1920 g was also noted.

CONCLUSION

We report a patient with primary pulmonary DLBCL diagnosed at 19 weeks gestation, successfully treated with R-CHOP chemotherapy and successfully delivered through cesarean section of a healthy unaffected baby. The mother and the baby remain to date in good health. To our knowledge this is the first primary pulmonary NHL successfully treated during pregnancy. As we compile our case report with other case reports, it seems that R-CHOP combination chemotherapy is safe to use for the treatment of DLBCL during pregnancy. Because of the rarity of such conditions, we encourage reporting all isolated cases in the literature as it may allow for meta-analyses to elaborate stronger conclusions and allow other physicians to extrapolate from such reports which will assist them in treatment planning.

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