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PERINATAL/NEONATAL CASE PRESENTATION

Metastatic non-small-cell lung cancer and the use of gemcitabine during pregnancy

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We present a case of metastatic non-small-cell lung malignancy diagnosed in the mother in her 24th week of pregnancy and illustrate the obstetric, oncology, neonatal and ethical issues involved. This is the second reported case on the use of gemcitabine for lung cancer in human pregnancy.
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Case report

A 38-year-old Caucasian female presented at 24 weeks gestation to the medical unit with a 7-week history of severe dyspnea, pyrexia and intermittent hemoptysis. She was in her second pregnancy with no known antenatal or medical problems. She did not smoke nor drink alcohol.

A chest radiograph demonstrated right upper lobe collapse and multiple 'cannon-ball' metastatic lesions in both lung fields (Figure 1). Blood test revealed a normochromic anemia (hemoglobin 6.5); CK7 was positive but CK20, TTF1, Ca125, ER, EMA, neuroendocrine and Vimentin were all negative. Bronchoscopy and biopsy were carried out and histology showed poorly differentiated carcinoma with hints of squamoid differentiation.

Clinical examination and mammography did not reveal the breast as the primary cancer. Abdominal ultrasound showed a viable fetus and multiple liver lesions consistent with metastases. No gynecological tumor was seen on transabdominal scan. A CT/MRI scan was not carried out as it was unlikely to affect the outcome or management. Tumor markers did not help in identifying a primary site of disease. Her AFP, HCG, Ca15-3, CEA, all of which were within normal limits for pregnancy. Nonspecific levels of Ca19-9 = 237(eight times normal), Ca12-5 = 131 (four times normal) were found.

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A working diagnosis of primary lung cancer with multiple liver metastases was made and the patient was transferred to a tertiary unit for specialist management. At this point, she was 25 weeks pregnant, when the expected survival rate for a baby delivered electively by cesarean, after a course of steroids, would be perhaps 50 to 60%, with significant neurodevelopment disability in 40 to 50% of survivors.[1]

The patient and her partner were seen by obstetricians, neonatologists, anesthetists and oncologists. After multidisciplinary team discussions with the couple, it was planned to prolong the pregnancy until 28 to 29 weeks gestation with steroids being given at 26 weeks. It was hoped that this would improve survival for the baby to perhaps 90% with only 10 to 20% neurodevelopmental disability if the baby survived. It was felt that this benefit would offset any potential harm done to the baby by chemotherapy, although the latter could only be guessed at in the absence of controlled trials.

The patient consented to palliative chemotherapy as aggressive chemotherapy in such a late stage was not considered appropriate and she received one cycle of gemcitabine at 1000 mg m^{-2} (days 1 and 8) and carboplatin AUC 5 (day 1) when she was at 25 weeks gestation. Carboplatin and gemcitabine were a familiar combination in our unit. The patient was very frail and there was concern that other combinations of chemotherapy may have led to respiratory symptoms and volume overload. There was some improvement in her follow-up chest radiograph and her condition stabilized while pregnant.

Fetal growth, liquor volume and end-diastolic flow on ultrasound at 26 weeks were normal.

A baby girl weighing 1.04 kg was delivered by elective cesarean at 28 + 4 weeks gestation (Apgar score 7 and 9 at 1 and 5 min). Delivery by vaginal route at such an early gestation was not considered appropriate due to the lie of the fetus and after discussion with the parents. The placenta showed no signs of metastatic spread. Postoperative recovery was uneventful from the obstetric point of view.

A postpartum staging CT scan demonstrated a large 10 cm right upper lobe lung lesion as the likely primary tumor, multiple cannon ball pulmonary metastases, liver metastases

involving both lobes and an incidental 8 cm ovarian dermoid.

The patient underwent one further cycle of gemcitabine and carboplatin 1-week postpartum. She remained dyspneic with a WHO performance status of 3, requiring oxygen and salbutamol nebulizers. After a meeting with the Macmillan palliative care team, she was discharged home with community team support.

Her breathing deteriorated. The chest radiograph showed disease progression the following week, and a provisional diagnosis of pulmonary embolism was made. She was subsequently fully anticoagulated and dexamethasone 4 mg was commenced for control of her dyspnea. She died at home 2 weeks postpartum.

The newborn baby girl was anemic at birth with hemoglobin of 7.5 g per 100 ml and required blood transfusion. The maternal Kleihauer test done on day 6 after birth was positive with estimated 17 ml of fetomaternal hemorrhage. The white cell and platelet counts were normal at birth. The lowest neutrophil count was 1.95×10^9 per liter, white cell count was 6.19×10^9 per liter and platelet count was 168×10^9 per liter during her entire stay.

The baby needed three doses of surfactant and was on conventional ventilator for a total of 29 days. She failed extubation on days 2 and 17. She had copious secretions from her endotracheal tube. She also had right upper lobe consolidation between days 9 and 13 that was treated with antibiotics. At this stage all her endotracheal secretions, blood cultures and surface swabs did not grow any pathogens.

She developed chronic lung disease and required a 9-day course of dexamethasone starting on day 27 to aid her extubation on day 29. She required nasal CPAP until day 44. She was also treated with chlorthiazide and spironolactone diuretics for chronic lung disease. Her cranial ultrasound scans on multiple occasions were normal.

She developed staphylococcus aureus sepsis on day 36 with raised CRP (184 mg l^{-1}) and white cell count with neutrophilia from which she recovered well.

She went home on 0.3 l per minute oxygen at 100 days of age. At 8 months (chronological age) of follow-up, she has now weaned off of oxygen therapy and is on high-calorie formula milk, domperidone and lactulose. Her neurodevelopment is age appropriate.

Discussion

Cancer develops in 1 of 1000 pregnant women.[2] Lung cancer is the most common cancer worldwide and the incidence is now higher than breast and cervical cancer in females.[3] With the increasing incidence, increased smoking rates in female teenagers and the later age of conception, there is an increasing need for earlier recognition and improved management of pregnant patients with lung cancer.[3] Non-small-cell lung cancer accounts for approximately 75% of all lung cancer. However, most lung cancers are diagnosed at an advanced stage with a poor prognosis.

Malignant disease arising during pregnancy presents a difficult situation for all involved. Investigation and treatment options for mother such as chemotherapy, CT scans and radiotherapy have to be carefully weighed against the potential toxicity to the developing fetus. When delaying chemotherapy; the effect on maternal survival should be weighed against the risk to the fetus.[2] Our patient's prognosis with extensive metastatic lung cancer was very poor and clinically she was rapidly deteriorating symptomatically at the time of her presentation. Palliative chemotherapy in pregnancy initially stabilized her symptoms of dyspnea, enabling a longer gestation and as a result a survival benefit for the baby.

With the increasing incidence of lung cancer worldwide, coupled with increased smoking rates and later age of conception, it seems that lung cancer complicating pregnancy may become more common and treatment of this condition will be a more frequent problem as a consequence.

Literature on the use of chemotherapy in lung cancer during pregnancy, and its potential effects on the fetus is limited. One case report describes the use of cisplatin and vinorelbine at 26-week gestation. The baby was delivered at 27 weeks and no chemotherapy-related adverse effects were noted in the baby.[4]

Gemcitabine used in combination with carboplatin is well tolerated, and effective in palliation of NSCLC.[5,6] Gemcitabine has been used in gestational choriocarcinoma with the combination of surgery after a full-term pregnancy.[7]

There has recently been one published report on the use of gemcitabine in unrecognized human pregnancy[8] and we now

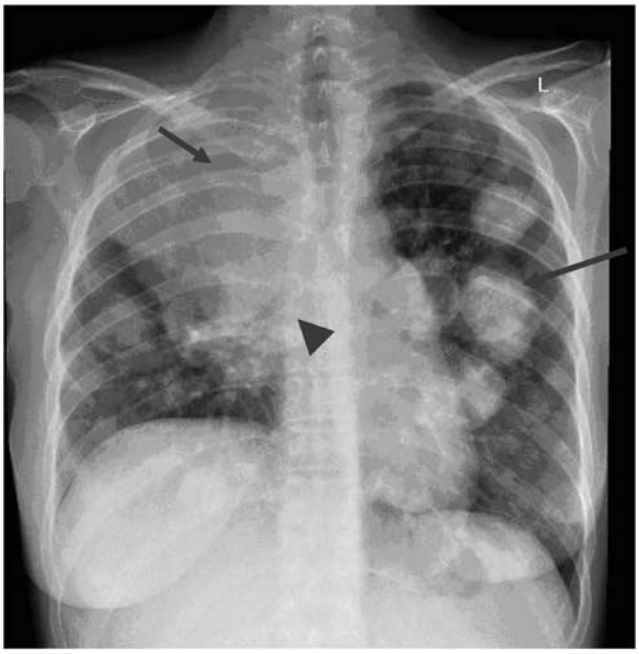

Figure 1 Chest radiograph posterior anterior (PA) view shows multiple nodular lesions in the left lung (long arrow) as well as at the lower zone of the right lung. There is right upper lobe collapse (short arrow) with large mass lesion at right hilum (arrowhead).

report the second case in the literature. The main risks to the fetus seem to be growth restriction, preterm labor associated with poor nutrition and anemia secondary to bone marrow suppression.

The unusual features in our case were the severity of chronic lung disease in the baby and excessive secretions from her lungs. We speculate that this might be related either to exposure to chemotherapy or to some effect of the malignancy itself in the mother. In our case, the baby did not seem to have any evidence of bone marrow suppression.

This case demonstrates the heart-wrenching conflict between improving maternal outcome by early delivery and aggressive chemotherapy; and reducing fetal adverse effects by delaying in aggressive chemotherapy to the mother. The clinical management of such a case requires a truly multidisciplinary approach, with intricate involvement of the patient and her family in the decision-making process.

We believe that we have increased the chances for this baby to live a healthy life, in a situation where the mother was almost certain to die. As cases such as these are rare, we hope that this case adds useful information to help future decision making in lung cancer in pregnancy.

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