Case Report

Adenocarcinoma of the lung with positive epidermal growth factor receptor mutation in pregnancy

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ABSTRACT

Lung cancer during pregnancy is a rare condition. We report a case of 28-year-old nonsmoker female, who was admitted to our hospital with massive left pleural effusion in the 21st week of gestation. Chest radiograph showed total left hemithorax opacity with contralateral mediastinal deviation. Pleural biopsy and cytological examination of pleural fluid revealed adenocarcinoma invasion with positive epidermal growth factor receptor mutation status. Cesarean section was performed at 32 weeks of pregnancy, and targeted therapy was given to this patient after delivery. Computed tomography of the thorax showed a mass lesion in the left hemithorax with liver metastases. Unfortunately, the patient died 10 days after delivery.

KEY WORDS: Adenocarcinoma, lung cancer, mutation, pleural effusion, pregnancy

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INTRODUCTION

Lung cancer is the most commonly diagnosed malignancy worldwide in 2012, both in term new cases (1.8 million cases, 12.9% of total) and deaths (1.59 million deaths, 19.4%). In women, lung cancer is the third most common cancer (580.000 cases) after breast cancer (1.6 million cases) and colorectal cancer (614.000 cases), and it is the second leading cause of death (491.000 deaths) after breast cancer (522.000 deaths).[1-3]

Cancer during pregnancy occurs one in every 1000 gestations. The most frequent types of malignancy diagnosed during pregnancy are breast cancer, cervical cancer, lymphoma, melanoma, and leukemia. Lung cancer during pregnancy is a rare situation, and there are no data about its real incidence.[4-6] There were sixty cases of lung cancer in pregnancy that have been published in English literature between 1952 and 2012. Forty-eight patients were nonsmall cell lung cancer (SCLC) with the predominant type was adenocarcinoma, and there were only three cases which were related to epidermal growth factor receptor (EGFR) mutation. In general, most cases were diagnosed at advanced stages, and the prognosis is quite dismal.[4,7]

Diagnostic procedures and treatment for the patient with lung cancer in pregnancy are challenging because it provokes medical, ethical, moral, and psychosocial conflicts. Giving treatment for lung cancer patient during gestation is also a dilemma. It may pose serious risk for the fetus while postponing it would be dangerous for the maternal condition, thus increases poor prognosis for maternal survival. Priority and rational management

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should consider some aspects, including the clinical condition of maternal and fetus, staging of cancer, and choice of treatment.[4,5]

Here, we present a case of 28-year-old nonsmoker pregnant woman with adenocarcinoma of the lung and positive mutation of the EGFR status. We report this case since lung cancer accompanying pregnancy is a very rare coincidence.

CASE REPORT

A 28-year-old woman experienced progressing dyspnea with a dry cough since 4 months before admission. She was diagnosed at district hospital with massive pleural effusion in the left hemithorax, and cytological examination of pleural fluid showed reactive mesothelial cell. Then, she was referred to respiratory hospital. When admitted, she was in the 21st week of her second pregnancy. There was not a history of cancer in her family, and she has never smoked before.

On the physical examination, the patient was in a moderately good general condition with the performance status (PS) score of 2. Pulmonary auscultation revealed the reduction of the breath sounds in her left hemithorax. We did not find lymph node enlargement and any abnormality in the thyroid glands, breast, and gynecologic status. Laboratory results revealed leukocytosis: 13.810/mm^3 (N: 5–10.0 10^3/mm^3), increase of serum lactate dehydrogenase: 343 U/L (N: 135–225 U/L), and decrease of serum albumin: 3.2 g/dl (N: 3.4–5 g/dl). The tumor markers: cancer antigen 125 and alpha-fetoprotein were nonspecifically increased and carcinoembryonic antigen was normal. Chest X-ray showed total left lung opacity with contralateral mediastinal deviation. Computed tomography (CT) of the thorax was not performed to reduce ionizing radiation exposure to the fetus. The cytological of pleural fluid and histopathological of pleural biopsy examination showed adenocarcinoma invasion to pleura with positive EGFR status in terms of exon 21 mutation. We diagnosed adenocarcinoma of the lung for this patient at 25 weeks of gestation. This patient was managed with a chest tube connected to the water-sealed drainage catheter to evacuate massive pleural effusion continuously [Figure 1].

After extensive reviews and consultations with the specialists of fetomaternal medicine and neonatologist in our hospital, we planned to do Cesarean section at 32 weeks of gestation. Serial obstetric ultrasonography and fetal lung maturation were performed toward 32 weeks of pregnancy. Targeted therapy would be given after delivery because it was toxic for the fetus. The patient was discharged from the hospital with good condition (PS 1) and used pigtail catheter to drain pleural effusion. She was planned to control her disease in district hospital until the time of performing Cesarean section.

At 32 weeks of gestation, she was admitted to our hospital with poor (PS 3) and enlargement of supraclavicular and axillary lymph nodes. Cesarean section was performed, and she delivered a boy with 1650 g of birth weight, and Apgar score was 8/9. The child was low birth weight and small gestational age. There was no any congenital anomaly, and placental examination did not reveal any metastasis. He was hospitalized in the Neonatal Intensive Care Unit (NICU) until complete recovery, and nowadays, he is a healthy male child.

After delivery, this patient was administered targeted therapy: gefitinib (Iressa®) 250 mg/day. CT of the thorax with contrast was performed and showed a mass lesion in the left hemithorax, extending to the chest wall and mediastinum, with bilateral pleural effusion and left pleural thickening. It also showed multiple metastatic nodules in the liver [Figure 2]. CT of the brain showed no metastases. Her condition became worst (PS 4), and unfortunately, the patient died 10 days after delivery.

DISCUSSION

Cancer and pregnancy have parallel immune modulation. Mechanism of immune tolerance that happened during pregnancy supports developing of cancer cells. Maternal and fetal immunomodulatory factors have an important role for adequate placental invasion and have similarities to the tumor microenvironment. The uterine natural killer (uNK) cells are the major immune cells which present at the fetomaternal interface. It is different from peripheral blood NK cells. The uNK cells are more immunomodulatory than cytotoxic. During pregnancy, T helper (Th)-2 cells are predominant and influence the immunologically tolerant. The other cells, such as macrophage, regulatory T-cell, and dendritic cell, are also infiltrating to decidua in pregnancy. Their function is maintaining Th-2 polarized, immunosuppressive, and

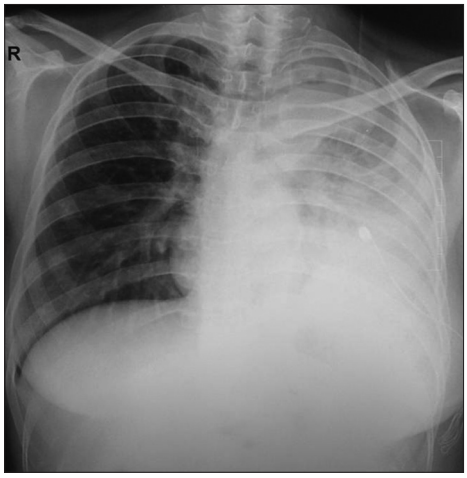

Figure 1: Chest X-ray: Nonhomogeneous consolidation in the left hemithorax with pleural effusion. No mediastinal deviation after inserting water-sealed drainage catheter

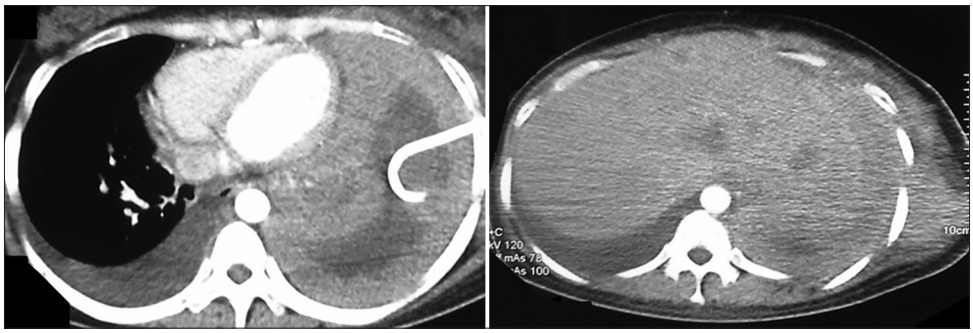

Figure 2: Computed tomography of the thorax with contrast: (Left) a mass lesion in the left hemithorax, extending to the chest wall and mediastinum with bilateral pleural effusion and left pleural thickening. (Right) multiple metastatic nodules in the liver

anti-inflammation. All of these components support not only fetal development but also cancer cell growth.[8,9] This theory explains that gestational lung cancer represents more aggressive disease and has a poor prognosis for the patient. Boussios *et al*. reviewed 60 cases of lung cancer during pregnancy and found that 58 patients were diagnosed at advanced stage (Stage III and IV). Thirteen percent death cases happened in 1-month postpartum, and only 10% patients were alive in 12 months or more.[7] In our case, the patient was diagnosed at Stage IV, and the patient died <1-month postpartum.

Delay in lung cancer diagnosis is the major problem in pregnant women. Most of the respiratory symptoms are misinterpreted because they are often related to infection.[10] The hesitancy in performing both invasive diagnostic procedures and radiological investigation may also contribute to a late diagnosis of lung cancer in pregnancy.[7] Azim *et al*. reviewed 43 lung cancer patients with pregnancy and found that the median of gestational age at diagnosis was 27 weeks (range 12–37) and the median of gestational age at delivery was 32 weeks (range 27–42) in 34 patients.[4] In our patient, the diagnosis was established at 25 weeks of gestational age, and it was related to diagnostic procedure's obstacles. Cesarean section was decided to perform at 32 weeks of gestation, 7 weeks after diagnosis established. Lack of NICU facilities in our hospital, time needed for the family to make a decision, and maternal survival based on the stage of cancer was some considerations to perform Cesarean section at that time. Limited experience in the management of lung cancer in pregnancy is also a problem of this case.

Though chemotherapy is used in most of the lung cancers in pregnancy, there is only limited experience of using chemotherapy in these cases.[7] Chemotherapy administration during the first trimester of gestation may be harmful to the fetus. It will be safe in the second and third trimester, but it still has the risk of stillbirth, intrauterine growth retardation, and premature delivery.[7,11,12] Targeted therapy improves patient with lung adenocarcinoma significantly,[13,14] but it is not recommended for pregnant women. EGFR is involved in either early conception and implantation phase or proliferation and differentiation of embryonic cells. In an animal model, inhibition of EGFR is to impaired epithelial growth in the lung, skin, and intestine organs of the fetus.[14] There are five cases of using EGFR-tyrosine kinase inhibitor (TKI) during pregnancy for lung cancer patients and there is no congenital malformation in all the children.[11,15] In our patient, we postponed the administration of targeted therapy until this patient delivery because only few data are available on EGFR-TKI safety for the fetus.

Vertical transmission of cancer cells to the placenta and fetus is uncommon. Boussios *et al*. reported three cases of fetal metastases in sixty cases of gestational lung cancer. One newborn had scalp metastasis, another had brain metastasis, and the third had liver and lung spread. They also found 11 cases of placental metastasis. Most of the fetal and placental metastasis were found in SCLC patients. So that, it is important to examine both palpable skin lesion and organomegaly of neonates and should be followed up for 2 years. Histopathological examination of placenta is also recommended.[4,7]

CONCLUSION

Lung cancer is uncommon in pregnancy, and published data about this case are limited. Cancer cells grow aggressively in pregnant women, so most cases of lung cancer during gestation are found at advanced stage. Delay in diagnosis will impact in mortality rate, and cancer treatment during pregnancy can induce detrimental effects to the fetus. Before taking the decision, patient and family should be explained properly about the clinical condition, prognosis, risk, and benefit of cancer treatment. Since lung cancer can occur in pregnancy, the physician should be aware of this coincidence, especially when we find pleural effusion or consolidation which does not respond to initial treatment. Until now, there are only a small number of data on teratogenicity and fetal toxicity of chemotherapy, both cytotoxic and targeted therapy for lung cancer in pregnancy. Further research or report is needed to confirm the safety of these drugs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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