Unexpected Rapid Growth of Estrogen Receptor Positive Lung Cancer during Pregnancy

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We report a case with lung cancer during pregnancy, which has a very poor prognosis. A 34-year old female at 30 weeks of pregnancy came to us with a cough and right lower chest pain. Chest computed tomography revealed a mass in the right lower lung lobe and the diagnosis of adenocarcinoma cT2aN1M0 was made. We performed a right sleeve pneumonectomy, as the tumor had progressed to the right main bronchus near carina. Histological sections of the specimens revealed a poorly differentiated adenocarcinoma that infiltrated surrounding structures. The pathological stage of lung cancer was T4N2M0 stage IIIB. Immunohistochemistry findings for estrogen receptor β were positive in the nuclei of the adenocarcinoma. She had a rapid recurrence in spite of chemotherapy, and she died 7.5 months after operation. The positive estrogen receptor and hormonal condition during pregnancy might promote cancer and result in her poor prognosis.

Keywords: lung cancer, pregnancy, estrogen receptor

Introduction

This report describes a rare case of lung cancer during pregnancy, which is usually diagnosed at an advanced stage and has a very poor prognosis. In our case, the mass grew very rapidly during pregnancy, which might be explained by the hormonal status of the tumor.

Case Report

A 34-year old female came to our outpatient clinic at 30 weeks of pregnancy complaining of a cough and right lower chest pain. She had never smoked and previously underwent a left ovariectomy due to a borderline malignant ovarian tumor. A chest computed tomography (CT) scan revealed a mass in the right lower lung lobe, surrounding the lower bronchus (Fig. 1A). A previous CT scan obtained 7 months prior during a follow-up examination of the ovarian tumor showed no clear nodule in the lung at that time. Two days after the chest CT scan, the patient developed dyspnea and was admitted for further examination and treatment. Complete blood cell and blood chemistry examinations were performed, which revealed white blood cells at 10600 and CRP at 10.94 mg/dl, while the serum level of carbohydrate antigen 19-9 (CA 19-9) was very high at a concentration of 1620 U/mL (normal: <37). We performed a positron emission tomography (PET) scan, as we considered that the benefits of PET scanning outweighed the radiation exposure. PET imaging showed that the standardized uptake value (SUV) of the mass in the right lower lobe was high at 7.05/8.47 (early phase/late phase), while there was no mediastinal lymph node or distant metastasis detected (Fig. 2). A bronchoscopic examination revealed narrowing of the right lower bronchus. Transbronchial biopsy findings for the
Fig. 2 Positron emission tomography/computed tomography scan showing a high standardized uptake value in the right pulmonary mass of 7.05, along with no evidence of mediastinal lymph node or distant metastasis.

lesion showed adenocarcinoma. Based on these results, we made the diagnosis of resectable T2aN1M0 lung cancer.

Surgical treatment for lung cancer was planned for after delivery. At 32 weeks of gestation, the patient delivered a healthy baby by cesarean section, with a birth weight of 2022g and Apgar score of 8. There was no pathological or cytological metastasis to the placenta or amniotic fluid. An enhanced CT scan was performed the day after delivery, which showed that the tumor had invaded the inferior pulmonary vein (Fig. 1B).

We performed a right sleeve pneumonectomy, as the tumor had progressed to the right main bronchus near the carina. On postoperative day (POD) 1, the patient suffered from an airway obstruction at a left main bronchus in the distal portion of an anastomosis and required reintubation and mechanical ventilation. We applied a self-expanding bronchial metallic stent (Ultraflex®) on POD 6, which made ventilator weaning possible on POD 7. She was discharged on foot on POD 16.

Histological sections of the resected specimens revealed a poorly differentiated adenocarcinoma that had infiltrated the hilar structures, hilar lymph nodes, and extrapulmonary portion of the pulmonary vein and left atrium (Fig. 3A). Multiple upper mediastinal lymph node metastases were evident, while the subcarinal lymph nodes were negative. The lung cancer pathological stage was T4N2M0 stage IIIB. Immunohistochemistry findings for estrogen receptor (ER) β were positive in the nuclei of the adenocarcinoma cells (Fig. 3B), where ER α was negative. Neither EGFR (epidermal growth factor receptor) mutation nor EML4-ALK (echinoderm microtubule-associated protein-like-4-anaplastic lymphoma kinase) gene was positive in the tumor.

We gave carboplatin and pemetrexed as adjuvant chemotherapy. However, the patient developed right malignant pleural effusion during that treatment. Thus, we gave her cisplatin and irinotecan in combination as second-line chemotherapy, while resulted in no symptomatic or radiologic improvement. The patient died 7.5 months after operation.

Discussion

Cancer occurs in approximately 1 of 1000 gestations, and the most frequently diagnosed types are cancers that occur during reproductive age, such as breast cancer, uterus cervical cancer, Hodgkin’s disease, and melanoma. On the other hand, only 0.5% of patient with lung cancer are younger than 40 years old; thus that during pregnancy is very rare. Most pregnant women with lung cancer are in advanced stages and median survival is generally poor at approximately 4.5 months (range, 1–42 months).

There are various factors related to the high risk of a poor outcome. Pregnant women or their physicians might tend to consider lung cancer-related symptoms, such as general fatigue, dyspnea, and cough, to be related to pregnancy. Also, physicians generally hesitate to subject a pregnant patient to radiological assessment due to radiation exposure, which might be related to a delay in diagnosis. Nevertheless, even after diagnosis, there are limitations to available treatments for lung cancer. Surgery or radiation during pregnancy should generally not be applied, and, in some cases, early termination is necessary when lung cancer is detected during an early gestational stage. Chemotherapy during pregnancy is potentially toxic, though the risk can be avoided if given after the first trimester. In recent reports, anticancer drugs (carboplatin, cisplatin, paclitaxel, and vinorelbine) were administered with good tolerance and normal fetal growth.

There are an increasing number of reports about the relationship between lung cancer and estrogen. A Women’s Health Initiative trial revealed that treatment with estrogen plus progesterone in postmenopausal women increased the number of deaths from lung cancer, though it did not increase the incidence of lung
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Fig. 1 Chest computed tomography scan showing a pulmonary mass surrounding the right lower bronchus (A). Enhanced chest computed tomography scan showing a tumor invading the left atrium (B).

Fig. 3 Microscopic findings with hematoxylin eosin staining showing a poorly differentiated adenocarcinoma infiltrating the surrounding components (A). Positive immunohistochemistry findings for estrogen receptor β (B).

cancer. Nose, et al. reported that a strong cytoplasmic expression of ER α or nuclear expression ER β was detected in half of human primary lung adenocarcinoma specimens investigated. Using in vitro examinations, Niikawa, et al. showed that estradiol significantly increased cell proliferation of ER-positive lung cancer cell lines. From these findings, it is speculated that lung cancer in pregnant women, whose estrogen levels are extremely high, might be largely promoted by the hormone. In the present case, lung cancer grew very rapidly and advanced to N2 disease within only 7 months. Indeed, immunohistochemistry of the resected lung cancer specimens showed ER β immunoreactivity in the nuclei of the tumor cells. Thus, hormonal status might have been the cause of mortality in this case.

From these results as described above, ER could be a therapeutic target in ER-positive lung cancer as in breast cancer. Indeed, a recent study has demonstrated that an anti estrogen (fulvestrant), which reduces estrogen receptor protein, inhibits cell proliferation in ER-positive lung cancer cells. Fulvestrant was already tested as a pilot study in the treatment of postmenopausal women with advanced non-small cell lung cancer. However, we did not apply an anti-estrogen agent to our patient because there were no clinical trial results at that time, showing efficacy of the anti-estrogen drug in human lung cancer treatment.
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**Conclusion**

This report describes a rare case of lung cancer during pregnancy, which grew very rapidly. The characteristics of the tumor might be best understood by hormonal status, as there was evidence of ER β in the adenocarcinoma specimens.

**Disclosure Statement**

None declared.

**References**


