A Case of a Pregnant Woman Diagnosed as Having ALK-rearranged Lung Adenocarcinoma

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Abstract. A 28-year-old woman who was 34 weeks pregnant was admitted with complaints of cough and blood-stained sputum. After delivery of the baby at 37 weeks gestation, computed tomography and magnetic resonance imaging revealed a tumor in the right lung and a 15-mm brain metastasis. A diagnosis of lung adenocarcinoma was made, cT4N3M1b (stage IV disease) by pleural fluid cytology. Additional testing for anaplastic lymphoma kinase (ALK) fusion protein showed a strongly positive result, which was then confirmed by fluorescence in situ hybridization. The patient was started on treatment with alectinib, and the tumor and brain metastasis had almost vanished by 2 months after the start of this treatment. In the literature, there are 59 reports of lung cancer diagnosed during pregnancy, including two cases of cancer with expression of ALK fusion protein and five cases showing epidermal growth factor receptor mutation. The type of mutation should be taken into consideration while selecting for the appropriate therapeutic strategy.

Lung cancer is leading cause of cancer-related death worldwide. Recent findings of genetic alteration, including of epidermal growth factor (EGFR) and anaplastic lymphoma kinase (ALK), have brought about fundamental changes in survival benefit to certain populations of patients with lung cancer. Nonetheless, there are still many problems in the treatment of patients with lung cancer. Lung cancer during pregnancy is rare and one of the major obstacles to deal with. We have been treating patients with lung cancer detected during pregnancy and diagnosed as having ALK rearranged lung adenocarcinoma.

Case Report

A previously healthy 28-year-old woman who was 34 weeks pregnant was admitted to the Gynecologic and Obstetric Department of our hospital with complaints of cough and blood-stained sputum. A plain chest X-ray showed infiltrative opacities in the lower lobe of the right lung. There were no other symptoms, and her baby was delivered by Caesarean section at 37 weeks of gestation. After delivery, a chest computed tomographic (CT) examination was performed, which revealed a tumor in the right pulmonary hilum with enlargement of the mediastinal lymph nodes, atelectasis of the lower lobe of the right lung, and modest pleural effusion (Figure 1A-C). Magnetic resonance imaging of the brain showed a 15-mm brain metastasis in the right parietal lobe (Figure 1D). Cytological and immunohistochemical examination of the pleural fluid revealed the diagnosis of lung adenocarcinoma [positive for cytokeratin 7 (CK7), human epidermal growth factor receptor type 2 (HER2) and thyroid transcription factor-1 (TTF1) (Figure 2B-D); negative for CK20, estrogen receptor (ER), progesterone receptor (PgR) and tumor protein 63 (p63) (Figure 2G-J)]. Based on further examinations to determine the disease stage, the patient was diagnosed as having primary lung adenocarcinoma, cT4N3M1b, stage IV disease (UICC seventh edition).

To determine the optimal therapeutic strategy, additional immunohistochemistry testing of the tumor specimen was conducted. The test yielded a negative result for mutation of EGFR, but a strongly positive (3+) result for presence of ALK fusion protein, which was subsequently confirmed by fluorescence in situ hybridization (FISH) (Figure 2E and F). After gamma knife therapy for the brain metastasis, the
Patient was started on treatment with alectinib, a novel highly selective inhibitor of ALK translocation. In response to this treatment, the tumor began to shrink dramatically. By 2 months after the start of alectinib treatment, the tumor had almost vanished on CT images (Figure 3A-C), and the brain metastasis also became smaller in size (Figure 3D). At the time of writing, over 12 months have passed since the start of treatment, the efficacy of alectinib against both the primary lung tumor and brain metastasis remains sustained, the patient is raising her child as normal and is back at work.

Although there is a concern about metastasis of lung cancer to the fetus, the removed placenta only showed the effects of moderate hypoxia and ischemia with no evidence of malignancy. The baby has remained well, with normal developmental milestones so far.

**Discussion**

Lung cancer is the leading cause of cancer-related death worldwide. Nevertheless, lung cancer in pregnant women is exceptionally rare. According to the available statistics, only 0.1% of pregnant women are diagnosed as having cancer, with breast, ovarian, or endometrial cancer accounting for most of the cases (1, 2).

We found 59 reports of lung cancer in pregnant women in the English literature. Among these, there were two reports of cancer harboring ALK fusion protein (3, 4) and five of cancer harboring EGFR mutation (5-9) (Table I). At our hospital, to date we have encountered two cases of lung cancer diagnosed during pregnancy, including the present case. The other patient died, as she was seen prior to the...
approval of ALK inhibitor use for lung cancer and received only cytotoxic chemotherapies. Out of the 59 reported cases, in seven (11.8%), the lung cancer harbored mutations; thus, it would seem that mutations are more frequent in lung cancer diagnosed during pregnancy, although not all reported cases had been checked for mutations. A previous study at our hospital also showed a higher likelihood of tumor mutations in young patients with lung cancer, regardless of whether they were pregnant or not (10). Thus, genetic screening is of substantial significance in young pregnant women with lung cancer, and treatment with tyrosine kinase inhibitors (TKIs) is often selected.

Cancer diagnosis is undoubtedly life-threatening for pregnant women and their fetus. Moreover, initiation of cancer treatment poses great problems, in terms of the potential adverse influence of cancer treatment, especially chemotherapy, on the fetus. Among the cases reported previously, three of the patients were treated with EGFR-TKIs during pregnancy because their general condition was sufficiently poor as to be potentially harmful for the fetus (5-
Figure 3. Radiological findings 2 months after the initiation of alectinib therapy. A: Chest X-ray showing lower lobe of the right lung to be clear of tumor. B: Computed tomography showing tumor of right hilar area to have shrunk. C: CT showing atelectasis and pleural effusion had disappeared. D: CT showing brain metastasis still present as a small nodule.

Table I. List of patients reported to have lung cancer with epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) fusion.

| Country   | Age, years | Timing of diagnosis | Delivery, weeks | Genetic alteration | TKI treatment | Author (Ref) |
|-----------|------------|---------------------|-----------------|-------------------|---------------|--------------|
| Italy     | 30         | Before pregnancy    | 42              | EGFR mutation     | Erlotinib     | Zambelli et al. 2008 (9) |
| Malaysia  | 38         | 26 Weeks            | 36              | EGFR mutation     | Gefitinib     | Lee et al. 2011 (6)   |
| Colombia  | 40         | Before pregnancy    | 33              | EGFR mutation     | Erlotinib     | Rivas et al. 2012 (7) |
| Turkey    | 34         | After delivery      | 28              | ALK fusion        | Crizotinib    | Sariman et al. 2013 (4) |
| France    | 33         | 26 Weeks            | 35              | EGFR mutation     | Gefitinib     | Gil et al. 2014 (5)   |
| Portugal  | 36         | 27 Weeks            | 29              | ALK fusion        | Crizotinib    | Neves et al. 2014 (3) |
| Australia | 29         | 29 Weeks            | 31              | EGFR mutation     | Gefitinib     | Holzmann et al. 2015 (8) |
| Japan     | 34         | 27 Weeks            | 27              | ALK fusion        | None          | Previous case of our hospital |
| Japan     | 27         | After delivery      | 39              | ALK fusion        | Alectinib     | Current case          |

TKI, Tyrosine kinase inhibitor.
7). In the absence of any reports on their adverse effect on the fetus in women receiving TKI therapy during pregnancy, the appropriate timing of initiation of treatment is difficult, not only in terms of the effect on the fetus and mother, but also in terms of consideration of the advantages and disadvantages of the medication by the doctor. In our case, in which the tumor was positive for ALK fusion protein, fortunately, both the patient and fetus remained in a highly satisfactory condition, and we were able to postpone further examination and treatment until the fetus had grown sufficiently to be delivered safely.

Conclusion

Diagnosis of lung cancer in pregnant women entails a host of serious problems, both physical and mental, for the patient. TKI treatment is relatively harmless for these patients compared to cytotoxic chemotherapies. The possibility of specific mutations should be taken into consideration when selecting the appropriate treatment strategy.

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