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A case report of metastatic bilateral ovarian cancer due to non-small cell lung cancer with ALK gene rearrangement

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Summary

Ovarian cancer patients are becoming more and more frequent; a part of them are metastatic ovarian cancer patients ,which mostly come from colon, stomach, appendix, and pancreas, rarely come from lung. The authors report a case of metastatic bilateral ovarian cancer due to non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) gene rearrangement. This female patient was diagnosed with adenocarcinoma of lung (cT3N2M1 Stage IV) and received chemotherapy and targeted drug therapy. She was diagnosed with metastatic ovarian cancer from lung by CT, and puncture biopsy and pathologic examination after surgery. Cancer gene detection confirmed ALK gene rearrangement. ALK gene rearrangement may increase the rate of metastasis of lung cancer, and as the target spot of tumor targeted therapy, it may provide an important treatment method for primary tumor and metastasis.

Key words: Metastatic bilateral ovarian cancer; Non-small cell lung cancer (NSCLC); Adenocarcinoma of lung; ALK gene rearrangement; Crizotinib.

Introduction

About 5-10% of malignant ovarian tumors originate from other parts of the body; the most important include the colon, stomach, appendix, breast, and pancreas. Ovarian cancer due to primary lung cancer accounts for only 0.3-0.4% of metastatic ovarian tumors [1].

Case Report

The patient, female, 42-years-old, with no smoking history, had heavy left pleural effusion displayed by ultrasound examination, with many heterosexual cells which were lung adenocarcinoma cells. CT examination of chest showed lower lobe of left lung with a lesion approximately 3.0×2.3×3.0 cm in size, there was nodule at the distal end of the lateral basal segment and the posterior basal segment of the lower lobe of the left lung, adjacent pleural was pulled, a small amount of effusion was on the left pleural, the left pleura had multiple nodules, and pleural metastasis could not be excluded. On April 15, 2014, CT examination of chest and upper abdomen in another hospital showed that the lower lobe of left lung had a lesion of approximately 2.1×3.0 cm in size. Mixed density soft tissue nodules were found in the lower lobe of the left lung. The maximum cross-section of it was about 1.8×1.9 cm in size, considered a left lung cancer, lymphadenectasis of left hilum and mediastina, metastatic carcinoma of the left pleural, and effusion of left pleural; retroperitoneal nodule lesions considered as lymphadenectasis; the fourth thoracic vertebrae local bone was destructed which could not exclude metastatic cancer. She was diagnosed with adenocarcinoma of the left lung (left lung cancer,left hilar and mediastinal lymph node metastasis, metastatic carcinoma of the pleural cT3N2M1 Stage IV). Then she was treated with chemotherapy (as described in the treatment history). On October 3, 2014, PET-CT examination revealed FDG in left lung lesions was highly metabolized, FDG in left pleural was slightly metabolized; FDG in a part of the mediastinum and left hilar lymph nodes was highly metabolized, FDG in the right ovary was highly metabolized. Pelvic ultrasound showed that there was no representation of tumor. So she did not receive the relevant treatment.

The patient felt abdominal pain. On October 24, 2015, CT examination of chest and abdomen showed that the left lung had multiple nodules (Figures A2 and A3), bilateral adnexal cystic-solid masses (the larger had a size of about 10.1×7.1 cm is on the left). Enhanced scan showed that the solid part of that had uneven signal, and the bladder and small intestine were pushed (Figures B1, B2, and B3). CA-125 was 78.12 U/ml and CA15-3 was 35.21 U/ml. Ultrasound-guided percutaneous biopsy of left ovarian mass showed left ovarian cancer from lung adenocarcinoma metastasis. Immunohistochemical test revealed that: TTF-1+, Napsin A+, CK5/6-, P63 focal +, Ki67+ 15%. Her uterus, double adnexa and greater omentum were excised on October 29, 2015. During the operation the authors noticed that the diameter of the left ovarian tumor was about 10 cm, the root of the mass was twisted in a circle, the tumor capsule was complete, diameter of the right ovarian tumor was about 5 cm, and this tumor capsule was also complete. Pathological examination of the resected tissue showed that bilateral ovarian tumors were consistent with metastatic carcinoma of the lung adenocarcinoma (Figures C1 and C2), there were no significant changes in bilateral fallopian tubes, and there was no obvious abnormality in the greater omentum. Immunohistochemical test displayed TTF-1+ and Napsin A+ (Figures C3 and C4). Cancer gene detection confirmed that there were ALK gene rearrangements in patient's blood and tissue was surgically removed.Then the patient underwent drug therapy which was tumor-targeted with crizotinib. This made the treatment very convenient and the patient was willing to take the prescription.

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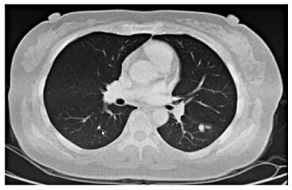
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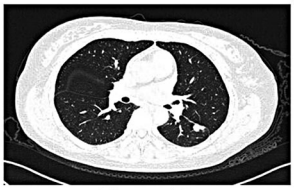
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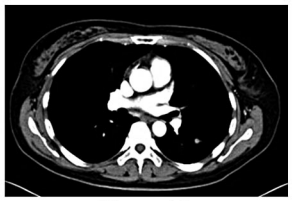
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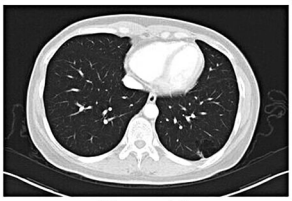
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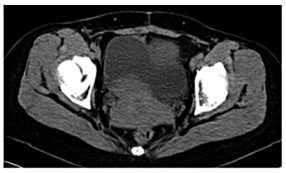
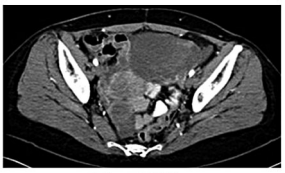


Figure B1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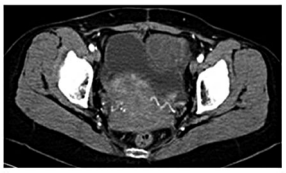
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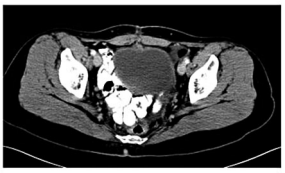
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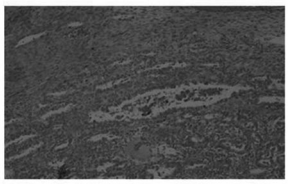
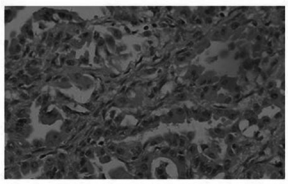


Figure C1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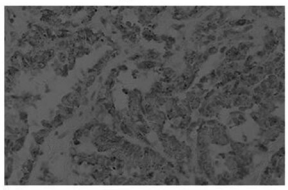
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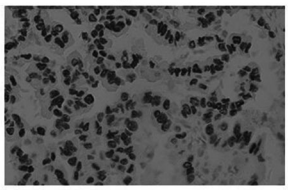
Figure C4

On April 13,2016, CT examination of chest and abdomen showed that the tumor was significantly reduced and there was no obvious signs of metastasis (Figures A4 and B4).

Figures A2 and A3 compared with CT on September 28, 2015 (Figure A1) showed multiple nodules with different sizes and densities in the oblique fissure of the left lung and diaphragmatic pleura increased compared with the previous, the lower left lung lobe basal segment had a new small lesion, the size of left lower lobe cavitary lesion also increased compared to before, and the solid component was larger.

Figures B1, B2, and B3 showed that the uterine volume was increased, density was uneven, included intrauterine liquid density, bilateral adnexal cystic-solid masses (the largest with a size of about 10.1×7.1cm on the left), and enhanced scan showed that the solid part had uneven signals, the bladder and small intestine were pushed, and the Douglas pouch had a small amount of liquid density. Figure C1: ovary HE ×100. Figure C2: ovary HE ×400. Figure C3: ovary with Napsin A+ ×400. Figure C4: vary with TTF-1+ ×400.

From April 2014 to October 2014, bevacizumab+nedaplatin+pemetrexed disodium was administered six times. The left lung achieved complete remission and pleural metastasis was stable. On August 12, 2014 CT examination of chest revealed that the left lung had no specific nodules, left hilar and mediastinal lymph nodes had metastasis. On June 9, 2014 left pleural metastasis was improved, and fourth thoracic vertebrae local bone destruction which could not be excluded from the transfer remained unchanged. From October 2014 to March 2015 bevacizumab+pemetrexed disodium was administered five times. CT examination remained unchanged from before. CEA, NSE, and Cyfra21-1 were normal. From March 2015 to August 2015 pemetrexed disodium was administered three times. From September 2015 to November 2015 iressa was administered. From October 29, 2015 the uterus, was excised, together with bilateral adnexectomy and greater omentectomy. Crizotinib is currently being adminstered from November 2015.

Discussion

The ovary is a rarely metastatic location for lung cancer. Commonly metastatic sites from lung cancer include bone, liver, adrenal gland, and brain. A study of 32 cases of lung cancer patients with ovary metastasis showed that 14 cases were small cell lung cancer (SCLC), 11 cases were adenocarcinoma of lung, five cases were large cell lung cancer, and one case was squamous cell carcinoma [1]. The probability of ALK gene rearrangement in patients with non-small cell lung cancer is about 6.7% (5/75) [2]. ALK gene rearrangements appear to be more common in patients with lung adenocarcinoma with the wild type of EGFR and KRAS gene [3]. It can be stated that metastatic ovarian cancer from non-small cell lung cancer with ALK DNA rearrangement is unusual. One retrospective study reported that ALK gene rearrangement in non-small cell lung cancer patients may increase the risk of pericardial and pleural metastases [4]. Ovarian metastasis in lung cancer patients with ALK gene rearrangement may not be accidental. The molecular expression and behavior of metastatic ovarian tumors are the same as those of primary tumors [5]. The EML4-ALK fusion gene which is composed of the 19th intron of ALK gene and 20th intron of EML4 gene was detected in the patient's blood and tumor tissue samples. The fusion gene is composed of expressed region 1-20 of EML4 and expressed region 20-29 of ALK gene. The fusion mutation may activate ALK kinase, promote cell proliferation

and migration by activating the downstream signaling pathway, and participate in tumor genesis and development. It may increase the response of tumor cells to ALK kinase inhibitors such as crizotinib, ceritinib etc. Therefore, targeted therapy of ALK fusion gene can inhibit cell proliferation and migration, and reduce tumor metastasis and recurrence rates. The treatment for ALK+ lung cancer patients with ovarian metastasis, include the traditional treatments such as surgical treatment, chemotherapy, etc., and can also include targeted drug therapy. It cannot only improve the therapeutic effect on metastatic ovarian cancer, but also reduce the probability of metastasis to the abdominal cavity and other parts. Actually, the PET-CT of the present patient revealed signs of ovarian metastasis. Active treatments such as pathological examination, CT examination, prophylactic resection of ovary, etc should be undertaken. The present patient did not undergo any early treatment for ovarian metastasis. One year later, bilateral ovarian metastasis was removed by surgery.

In conclusion, targeted therapy for ALK gene rearrangement is helpful to cure metastatic ovarian cancer from lung cancer, and improve therapeutic effect, and reduce the risk of recurrence. It is practically and theoretically significant for the diagnosis and treatment of metastatic ovarian cancer, in order to investigate whether the ALK gene rearrangement increases the chance of NSCLC metastasis and the chance of metastasis to the ovary.

References

[1] Irving J.A., Young R.H.: "Lung carcinoma metastatic to the ovary: a clinic pathologic study of 32 cases emphasizing their morphologic spectrum and problems in differential diagnosis". *Am. J. Surg. Pathol.*, 2005, *29*, 997.

[2] Soda M., Choi Y.L., Enomoto M., Takada S., Yamashita Y., Ishikawa S., *et al.*: "Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer". *Nature*, 2007, *448*, 561.

[3] Solomon B., Varella-Garcia M., Camidge D.R.: "ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung.cancer". *J. Thorac. Oncol.*, 2009, *4*, 1450.

[4] Lee K.A., Lee J.S., Min J.K., Kim H.J., Kim W.S., Lee K.Y.1.: "Bilateral Ovarian Metastases from ALK Rearranged Non-Small Cell Lung Cancer". *Tuberc. Respir. Dis. (Seoul)*, 2014, *77*, 258.

[5] Fujiwara A., Higashiyama M., Kanou T., Tokunaga T., Okami J., Kodama K., *et al.*: "Bilateral ovarian metastasis of non-small cell lung cancer with ALK rearrangement". *Lung Cancer*, 2014, *83*, 302.

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