



Ovarian Metastasis of ALK Translocation-Positive Lung Adenocarcinoma: A Case Report

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SUMMARY

Ovarian metastasis is substantially rare in non-small cell lung cancer (N-SCLC). Driver gene mutations, such as Anaplastic Lymphoma Kinase (ALK), are used in the diagnosis of N-SCLC and its metastases. Demonstration of ALK mutation in N-SCLC patients will be helpful for detecting ovarian metastasis and planning personalized therapy; however, there is a limited number of cases related to this topic. In this case, we present the diagnosis and treatment of ALK-positive non-small cell lung adenocarcinoma patient with ovarian metastasis. Crizotinib is the first-class tyrosine kinase inhibitor using for the treatment of ALK-positive N-SCLC. The ovarian metastasis has been treated with surgery while under Crizotinib treatment. The patient continues to receive crizotinib treatment and no new metastases were detected at the end of a one-year follow-up. The possibility of ovarian metastasis in female N-SCLC patients with ALK rearrangement should be kept in mind.

Keywords: Anaplastic Lymphoma Kinase (ALK); crizotinib; lung adenocarcinoma; metastasis; ovary.

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Introduction

Metastatic tumors of the ovary usually originate from the gastrointestinal tract and the breast. Ovarian metastasis of lung cancer is substantially rare and only 0.4-1% of cases with lung cancer develop ovarian metastasis.[1] Adenocarcinomas account for approximately 34% of these metastases.[2] In the literature, only seven ovarian metastases have been reported in adenocarcinoma histology with ALK gene rearrangement mutation.[3-9] In these patients, surgical resection is often performed to confirm the origin of the ovarian tumor. On the other hand, the role of surgery in diagnosis and treatment is controversial and the management should be individualized.

Case Report

A 37-year-old Gravida 4, Parity 3, Abort 1, the patient was admitted to Kocaeli University Hospital with a prolonged cough complaint. Her medical history was unremarkable, and she had no history of smoking. Computerized tomography scan revealed a 4×5 cm mass in the distal left main bronchus, pleural metastasis, mediastinal lymphadenopathy, and multiple bone metastases. Transbronchial biopsy was performed from the lesion during fiberoptic bronchoscopy, and the pathology report of the biopsy specimen showed lung adenocarcinoma. Real-time PCR analysis (Rotor-Gene Q, Diatech Pharmacogenetics Easy) detected 31% Echinoderm microtubule-associated protein-like

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four (EML-4) ALK mutation and crizotinib therapy was started. The patient's cranial magnetic resonance imaging revealed lesions compatible with metastasis in the right superior temporal gyrus and in the posterior left cingulate gyrus measuring 10×11 mm and 4 mm, respectively (Fig. 1a). The patient received stereotaxic radiotherapy for intracranial metastasis at a dose of 1800cGy. Positron Emission Tomography-Computed Tomography (PET-CT) showed a positive response to treatment for the lung, mediastinum and skeletal metastases at the 5th-month follow-up. However, abdominal ultrasonography revealed a 110×80×130 mm left adnexial multilocular, septate, cystic mass with a solid component and widespread ascites in the abdomen. The serum Ca-125 value was 1789 U/ml. Laparotomic staging surgery was performed. Pathological examination revealed metastasis of lung adenocarcinoma in the left ovary, right external iliac and right internal iliac lymph nodes (Fig. 1b). Immunohistochemical examination demonstrated strong nuclear staining with Thy-

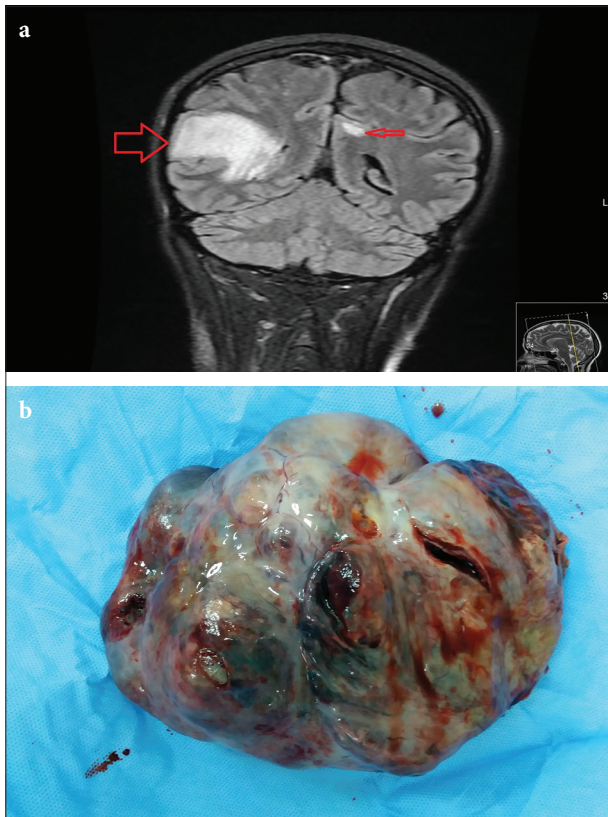


Fig. 1. (a) Cranial magnetic resonance imaging. Thick arrow indicates right temporal metastasis; thin arrow indicates metastasis in the left posterior cingulate gyrus. (b) Macroscopic view of the left ovarian mass.

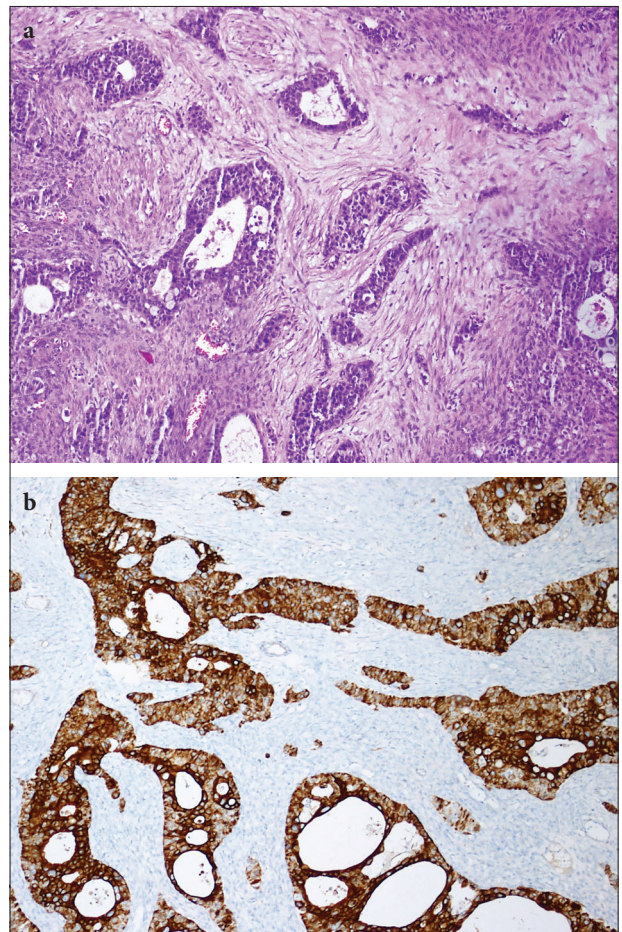


Fig. 2. (a) Focal strong nuclear positive immunostaining with TTF-1 for lung carcinoma (100x). (b) Diffuse strong cytoplasmic staining with cytokeratin (CK)-7 (100x).

roid Transcription Factor-1 (TTF-1) (Fig. 2a), Caudal Homeobox 2 (CDX2) and strong cytoplasmic staining with cytokeratin-7 (CK-7) (Fig. 2b) despite negative staining with p53, WT-1, cytokeratin-20 (CK-20) and Napsin-A. The patient is still on crizotinib therapy with no evidence of new metastases at the end of a one-year follow-up.

Discussion

Driver mutations may occur in the genes of signal transduction proteins. The presence of these mutations provides a growth advantage to cancer cells, and generally, more than one driver mutation is not detected in a tumor at the same time. Detection of driver gene mutations in non-small cell lung cancer (N-SCLC) has been implicated in the diagnosis and selection of appropriate treatment.[10]

EGFR mutations have been associated with brain metastasis,[11] also ALK gene rearrangement has been associated with liver and pleural metastasis.[12] In addition, EML-4 ALK mutations are less common than EGFR mutations in N-SCLC.[13] Ovarian metastasis has been reported in seven ALK-positive N-SCLC patients in the literature. Ovarian metastasis developed during follow-up in four of the seven patients and it was detected at the first presentation in the remaining three patients. Five patients underwent ovarian resection and one patient received adjuvant alectinib therapy, and five patients started to receive crizotinib treatment. One patient refused to receive treatment and was lost to follow-up. Except for this patient, all patients had a mean follow-up time of 27.5 months. Resection of the metastatic tumor is controversial. Some authors claim that ovarian metastasis can be eradicated completely with alectinib or crizotinib treatment. Also, they advocate that attempts that increase morbidity should be avoided.[9] However, in our patient, ovarian metastasis developed under crizotinib therapy and treated with surgery, which is contrary to this view. Considering that the treatment given for primary ovarian cancer does not provide a benefit on N-SCLC metastasis, it is essential to perform surgery for diagnosis and therapy. Crizotinib is a first-class ALK tyrosine kinase inhibitor and has been shown to be superior compared to standard chemotherapy in two phase-3 studies.[14,15]

Immunohistochemistry (IHC) is an important adjunct tool in distinguishing ovarian metastatic tumors. Positive TTF-1 and CK-7, and negative CK-20 immunohistochemical staining is required for differentiating lung carcinoma metastasis from primary ovarian malignancy.[16] Also, Napsin-A is a good marker for the diagnosis of lung adenocarcinoma because it could only be detected in alveolar macrophages and pneumocytes.[17]

Further research is needed to analyze the correlation between ALK rearrangement and the metastatic behavior to the ovary or the adnexal area. ALK driver mutations will be more important in the near future for diagnosis and patient-based individualized treatment of N-SCLC metastases.

Conclusion

Ovarian metastasis of N-SCLC is substantially rare. Using driver gene mutations, such as ALK, will be more important in the patient-based individualized treatment of N-SCLC and its metastases. However, there is a need for more case series due to the limited number of ovarian metastasis of ALK-positive N-SCLC in the literature.

Informed consent: Informed consent was obtained from the patient in this study.

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References

1. Fujiwara K, Ohishi Y, Koike H, Sawada S, Moriya T, Kohno I. Clinical implications of metastases to the ovary. *Gynecol Oncol* 1995;59(1):124–8.
2. Irving JA, Young RH. Lung carcinoma metastatic to the ovary: a clinicopathologic study of 32 cases emphasizing their morphologic spectrum and problems in differential diagnosis. *Am J Surg Pathol* 2005;29(8):997–1006.
3. 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(2):302–4.
4. Lee KA, Lee JS, Min JK, Kim HJ, Kim WS, Lee KY. Bilateral Ovarian Metastases from ALK Rearranged Non-Small Cell Lung Cancer. *Tuberc Respir Dis (Seoul)* 2014;77(6):258–61.
5. Mushi RT, Yang Y, Cai Q, Zhang R, Wu G, Dong X. Ovarian metastasis from non-small cell lung cancer with ALK and EGFR mutations: A report of two cases. *Oncol Lett* 2016;12(6):4361–66.
6. Wang W, Wu W, Zhang Y. Response to crizotinib in a lung adenocarcinoma patient harboring EML4-ALK translocation with adnexal metastasis: A Case Report. *Medicine (Baltimore)* 2016;95(30):e4221.
7. Jing X, Li F, Meng X, Liu Z, Yu J, Liu B. Ovarian metastasis from lung adenocarcinoma with ALK-positive rearrangement detected by next generation sequencing: A case report and literatures review. *Cancer Biol Ther* 2017;18(5):279–84.
8. West AH, Yamada SD, MacMahon H, Acharya SS, Ali SM, He J, et al. Unique metastases of ALK mutated lung cancer activated to the adnexa of the uterus. *Case Rep Clin Pathol* 2014;1(2):151–4.
9. Sasano H, Sekine A, Hirata T, Iwamoto K, Itou Y, Itani H, et al. Ovarian Metastases from ALK-rearranged Lung Adenocarcinoma: A Case Report and Literature Review. *Intern Med* 2018;57(22):3271–75.
10. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. NCCN 2017 v3. Accessed 10 Feb-

- ruary 2019. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
11. Sekine A, Kato T, Hagiwara E, Shinohara T, Komagata T, Iwasawa T, et al. Metastatic brain tumors from non-small cell lung cancer with EGFR mutations: distinguishing influence of exon 19 deletion on radiographic features. *Lung Cancer* 2012;77(1):64–9.
 12. Doebele RC, Lu X, Sumey C, Maxson DA, Weickhardt AJ, Oton AB, et al. Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer. *Cancer* 2012;118(18):4502–11.
 13. Soda M, Choi YL, 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(7153):561–6.
 14. Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013;368(25):2385–94.
 15. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014;371(23):2167–77.
 16. Yeh KY, Chang JW, Hsueh S, Chang TC, Lin MC. Ovarian metastasis originating from bronchioloalveolar carcinoma: a rare presentation of lung cancer. *Jpn J Clin Oncol* 2003;33(8):404–7.
 17. Suzuki A, Shijubo N, Yamada G, Ichimiya S, Satoh M, Abe S, et al. Napsin A is useful to distinguish primary lung adenocarcinoma from adenocarcinomas of other organs. *Pathol Res Pract* 2005;201(8-9):579–86.