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【 CASE REPORT 】

Ovarian Metastases from *ALK*-rearranged Lung Adenocarcinoma: A Case Report and Literature Review

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Abstract:
We herein report a 37-year-old woman with lung adenocarcinoma with brain metastases and an asymptomatic ovarian tumor. Immunohistochemistry and a fluorescent *in situ* hybridization analysis of the biopsied lung tumor revealed anaplastic lymphoma kinase (*ALK*) gene rearrangement. Although the origin of the ovarian tumor remained unclear, alectinib administration was initiated, and radiological responses were observed in all lesions, which confirmed that the ovarian tumor was a metastasis from lung cancer. Although differentiating the origin of an ovarian tumor is difficult in lung cancer patients due to the rarity of ovarian metastases, alectinib therapy can replace an invasive biopsy, especially in *ALK*-rearranged lung cancer patients.

Key words: Alectinib, *ALK*-rearranged lung adenocarcinoma, metastatic ovarian tumor

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Introduction

Determining the status of driver gene mutations is a well-accepted way of deciding on the most appropriate therapeutic strategy. In addition, some reports have clarified the relationship between driver gene mutations and distant metastases in non-small-cell lung cancer (1-3). Although ovarian metastases of lung cancer are reportedly rare, some reports have shown that anaplastic lymphoma kinase (*ALK*)-rearranged lung cancer metastasizes to the ovary (4-9). However, because of the rarity of ovarian metastases from lung cancer, surgical resection has often been performed to confirm the origin of the ovarian tumor (4-7, 9).

We herein report a patient with *ALK*-rearranged lung cancer-derived ovarian tumor that was diagnosed and treated with alectinib without an invasive procedure, along with a review of the pertinent literature.

Case Report

A 37-year-old woman with no history of smoking was admitted to the Japanese Red Cross Ise Hospital in November 2015 with a one-week history of headache, nausea, and appetite loss. Contrast-enhanced computed tomography (CT) revealed brain tumors (the largest tumor in the basal ganglia had a diameter of 30 mm) and remarkable cerebral edema. A 27×31 mm nodule at the lower lobe of the left lung, pulmonary hilar and mediastinal lymph node enlargements, and a left ovarian tumor of 90×58 mm were also detected (Fig. 1). Gadolinium-enhanced magnetic resonance imaging (MRI) of the ovarian tumor showed an admixture of enhanced solid components and cysts (Fig. 2).

Because her brain metastases were neurologically symptomatic with an Eastern Cooperative Oncology Group scale of performance status (ECOG-PS) score of three, betamethasone at a dose of six mg daily and glycerol at a dose of 200 mg daily were administered before a definitive diagnosis could be reached. After a few days of this treatment, the ECOG-PS score improved to one. A transbronchial biopsy of the lung nodule confirmed lung adenocarcinoma showing an acinar pattern and several signet-ring cells. Stereotactic radiosurgery was performed to treat the brain tumor. Immunohistochemistry and a fluorescent *in situ* hybridization

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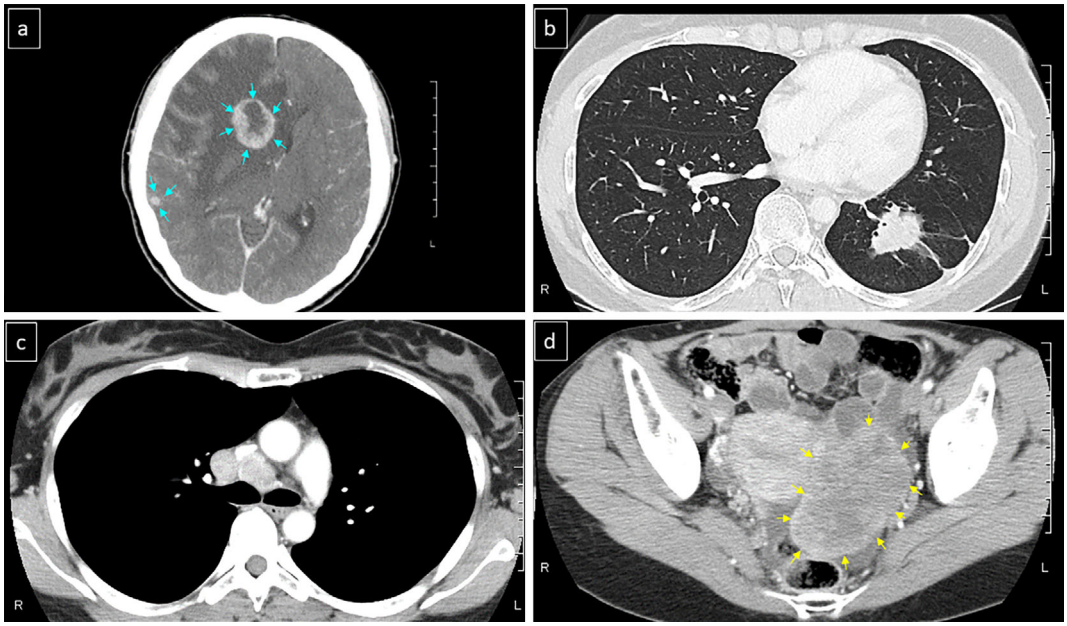

Figure 1. **Contrast-enhanced computed tomography at the initial assessment. Contrast-enhanced computed tomography revealed a) brain tumors and remarkable cerebral edema (blue arrows), b) a 27×31 mm nodule at the lower lobe of the left lung, c) mediastinal lymph node enlargement, and d) a left ovarian tumor of 90×58 mm (yellow arrows).**

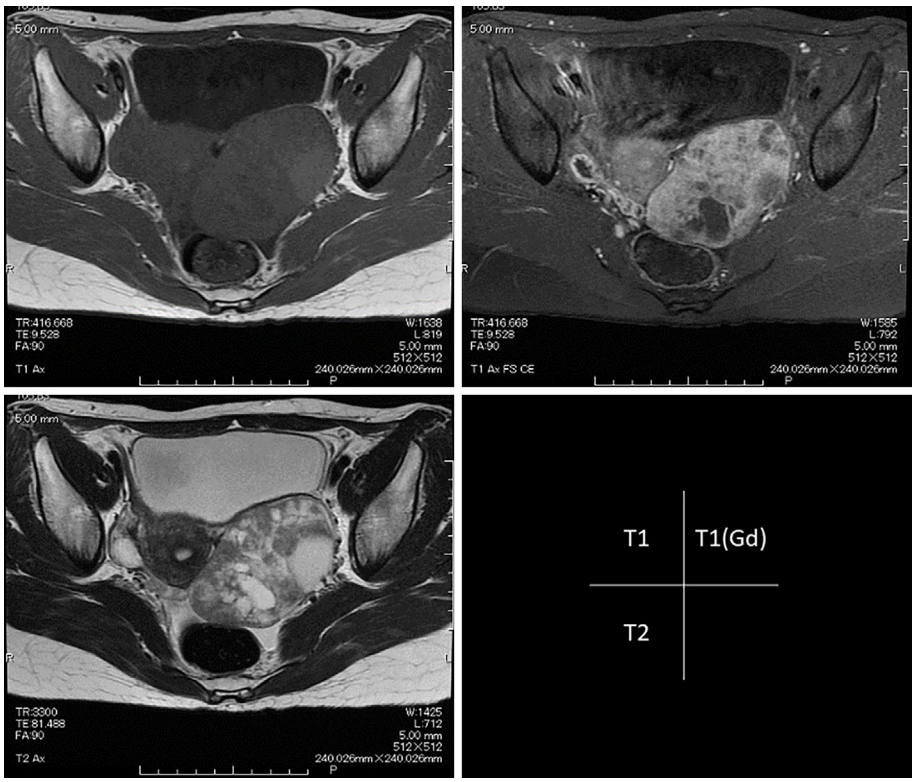

Figure 2. **Gadolinium-enhanced magnetic resonance imaging of the ovarian tumor. The left ovarian tumor contains a solid component exhibiting a higher signal than the muscle on T1- and T2-weighted imaging. Gadolinium-enhanced imaging showed an admixture of enhanced solid components and cysts.**

analysis of the biopsied lung tumor tissue revealed *ALK* gene rearrangement. Thus, a diagnosis of lung adenocarcinoma with positive *ALK* gene rearrangement (cT2aN3M1b, stage IV) was made according to the seventh edition lung

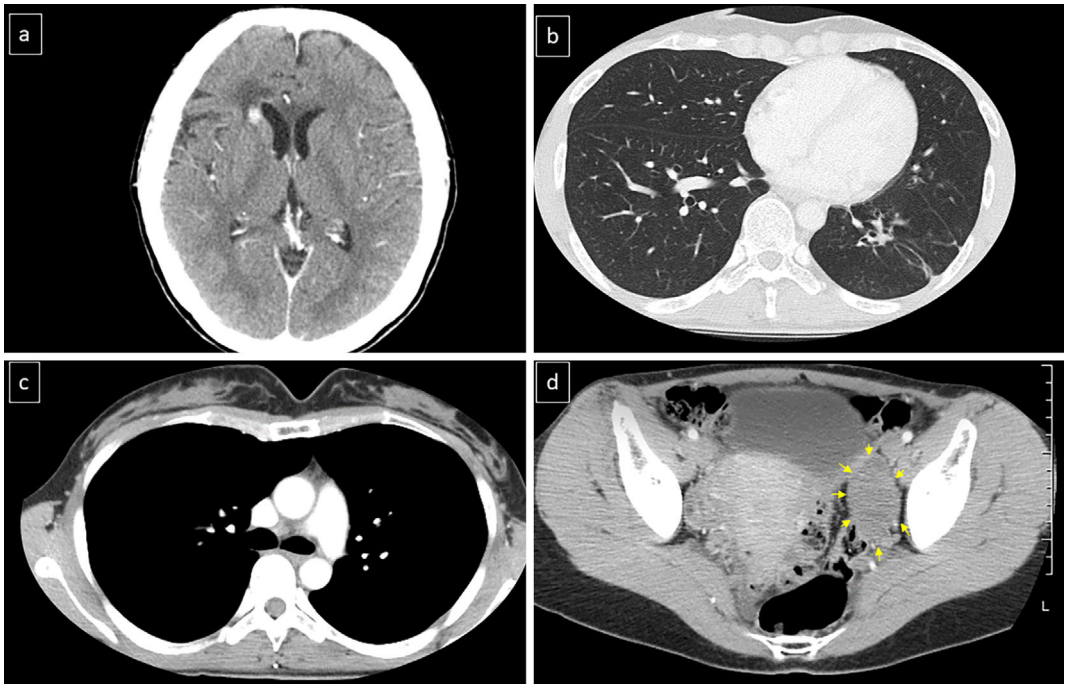

Figure 3. **Contrast-enhanced computed tomography at 20 months after the initiation of alectinib treatment. The volume of each tumor was remarkably reduced: a) brain , b) lung, c) mediastinal lymph node, and d) left ovary (yellow arrows).**

cancer stage classification (10).

However, positron emission tomography-CT detected disseminated pelvic metastasis, and transvaginal ultrasonography revealed that her left ovary included both solid and multiple cystic lesions. Based on these findings, an experienced gynecologist diagnosed the ovarian tumor as a metastatic one. However, no abnormal findings were found by gastrointestinal endoscopy or colonoscopy, and the origin of the ovarian tumor remained unclear.

The oral administration of alectinib (300 mg, twice daily) was started in January 2016, and radiological responses were observed in all of the disease lesions, including the ovarian tumor, two months after the treatment initiation. Based on the response to alectinib, the ovarian tumor was diagnosed as metastatic lung adenocarcinoma. Currently, at the 20-month follow-up, the patient status is "complete response", with no evidence of progression at any lesion site (Fig. 3).

Discussion

A relationship between driver gene mutations and distant metastases in non-small-cell lung cancer (NSCLC) has frequently been reported, and the diagnostic value of the driver gene mutation status in optimizing treatment regimens is now well accepted. Lung cancers with epidermal growth factor receptor (*EGFR*) gene mutations (EGFR-LC) frequently result in miliary metastases in the lung or the brain (2, 3). In addition, NSCLC with *ALK* gene rearrangement (ALK-LC) might present with pleural disease, pericardial effusion, and liver metastases (1). However, ovarian metastasis of lung cancer with a positive driver gene mutation status has rarely been described.

Metastatic ovarian tumors account for 4.2% of malignant ovarian tumors (11). Some 60-80% of metastatic ovarian tumors originate from the stomach, colon, and breast (12, 13). CT and MRI findings of metastatic ovarian tumors vary, generally presenting as bilateral, lobulated, solid, and/or cystic masses, as was observed in the present case. However, no examinations have been able to detect a primary site aside from the lung.

Ovarian metastases of lung cancer are rare, accounting for 0.4-1.0% of all metastatic ovarian tumors (12-14). Small cell carcinoma and adenocarcinoma reportedly account for 44% and 34% of all lung cancers with ovarian metastases, respectively (14). Notably, 64% of those adenocarcinomas were reported to present as the acinar type or solid with mucin-type histology, and these features are often associated with an ALK-LC status (14, 15). To date, there have been only seven reported cases of ovarian metastases of lung adenocarcinoma with driver gene mutations. Six of those cases were ALK-LC, as in the present case, whereas the remaining case was EGFR-LC (4-9) (Table). Given that the echinoderm microtubule-associated protein-like 4-ALK (*EML4-ALK*) fusion gene mutation is less common than *EGFR* gene mutations (3-7% vs. 12-47%, respectively) in NSCLC patients (16, 17), ovarian metastasis may be a characteristic of ALK-LC, although a publication bias may be present.

In the clinical setting, invasive procedures such as laparoscopy are often needed to confirm whether an ovarian tumor is primary or metastatic in lung cancer patients, since the incidence of ovarian metastasis of lung cancer is low.

Table. Patients with Lung Adenocarcinoma Positive for *ALK* Gene Rearrangement (ALK-LC), and Ovarian Metastasis.

year	reference numbers	age (years)	ovarian metastasis		*ALK* gene rearrangement detection		ALK inhibitor	follow up period (months)	final status
			diagnosis	resection	diagnosis	site			
2014	6	54	at initial assessment	+	at initial assessment	lung	not used	NA	NA
2014	4	39	during follow up	+	at initial assessment	lung	crizotinib*	48	alive
2014	9	50	during follow up	+	during follow up	ovary	crizotinib*	46	alive
2016	7	47	during follow up	+	during follow up	breast	crizotinib*	37	alive
2017	5	41	during follow up	+	during follow up	ovary	crizotinib*	24<	alive
2016	8	33	at initial assessment	-	at initial assessment	lung	crizotinib**	4	alive
2017	Present case	37	at initial assessment	-	at initial assessment	lung	alectinib**	20	alive

ALK: anaplastic lymphoma kinase, NA: not assessed, *: ALK inhibitors were administered after the resection of the ovarian tumor. **: ALK inhibitors were started as first-line therapy.

However, based on the findings of our case study, ALK-LC status may be predictive of lung cancer metastasis to the ovary and thus can aid in the accurate diagnosis without the need for invasive procedures. In addition, in the present case, alectinib treatment led to a complete response with no adverse effects or disease progression (at 20 months after treatment initiation). Recently, two randomized phase III trials demonstrated the superiority of alectinib over crizotinib in ALK-LC patients in terms of the progression-free survival and response rate, with a favorable safety profile. The reported progression-free survival was 25.9 months in one (18) and "not reached" in the other (95% confidence interval: 17.7 months to "not estimated") (19), and the overall response rate is reportedly 83-93.5% (19-21). However, the median survival time of metastatic ovarian tumors from the gastrointestinal tract ranges from 8-30 months (22, 23). Our case study implies that, in ALK-LC patients with ovarian tumors, invasive ovarian biopsies may not always be necessary, and response to alectinib may help clarify whether the ovarian tumor is metastatic or primary, although some examinations, such as gastrointestinal endoscopy and colonoscopy, remain important for determining the primary site of the metastatic ovarian tumors.

In conclusion, we present a case of ALK-LC-derived metastatic ovarian tumor. Because the ALK-LC dramatically responds to alectinib treatment and may characteristically metastasize to the ovary, alectinib therapy can replace an invasive biopsy for determining the origin of an ovarian tumor, especially in ALK-LC patients. An additional case series will be necessary to confirm our results.

The authors state that they have no Conflict of Interest (COI).

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