**ALK rearrangement in lung adenocarcinoma with concurrent cervix and breast metastases: A case report**

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**Abstract**

Distant metastases of pulmonary adenocarcinoma are regularly observed in the bones, brain, adrenal gland, and liver, but rarely in the breast or cervix. In this report, we describe a novel case of concurrent cervix and breast metastases from lung adenocarcinoma, with ALK rearrangements that were strongly consistent between the primary and metastatic cancers. A 44-year-old Chinese woman with a chief complaint of abdominal discomfort was referred to our hospital. Based on diagnostic imaging, pathology, immunohistochemistry, and next-generation sequencing, the patient was diagnosed with lung adenocarcinoma with breast and cervical metastases, and ALK rearrangements were found in all three lesions. The patient was prescribed crizotinib as first-line treatment, which showed a steady reduction of the lung lesion. To our knowledge, this is the first report of concurrent breast and cervical metastases from lung adenocarcinoma. We conclude that physicians should consider that metastases may invade the breast and cervix uteri when making a diagnosis.

**Introduction**

ALK fusion gene rearrangements are observed in approximately 5% of patients with advanced lung adenocarcinoma. Metastases in non-small cell lung cancer (NSCLC) generally occur in the bones, brain, adrenal gland, and liver. When primary tumors metastasize to the female reproductive system, the most common sites are the ovaries and vagina. Herein, we report a rare case of cervical and breast metastases concurrent with lung adenocarcinoma and ALK rearrangements in all three sites.

**Case report**

A 44-year-old woman with no history of smoking was referred to our hospital in July 2017 with a chief complaint of abdominal discomfort, which had lasted for a month. Transvaginal sonography suggested cervical carcinoma. Cervical smear cytology showed poorly differentiated adenocarcinoma of the cervix uteri (Fig 1a). Moreover, immunohistochemistry (IHC) revealed expression of CK7, TTF-1, and Ki-67 (25%) without GATA-3, P16, or P63 (Fig 1b–g). Mammography revealed a mass in the upper outer quadrant of both breasts, highly suggestive of category 4 malignancy, according to the Breast Imaging Reporting and Data System (BI-RADS). Ultrasound-guided breast puncture biopsy revealed poorly differentiated adenocarcinoma, which also suggested lung metastatic adenocarcinoma (Fig 2a). IHC staining showed positivity for TTF-1 and Ki-67 (25%) and negativity for GATA-3, ER, PR, and Her-2 (Fig 2b–g). Meanwhile, chest computed tomography (CT) showed a lesion in the upper lobe of the left lung and mediastinum, plus left hilar lymphadenopathy (Fig 3a). Computed tomography (CT)-guided percutaneous lung puncture biopsy revealed pulmonary adenocarcinoma (Fig 4a), and IHC staining showed positivity for CK7, TTF-1, and Ki-67 (< 10%) and negativity for ER, PR, Her-2, and GATA-3 (Fig 4b–e). We chose these as potential markers of malignant disease: TTF-1 is the most valuable specific antibody for identifying primary or metastatic lung adenocarcinoma; ER, PR, Her-2, and GATA-3 expression has great significance in diagnosing metastases of primary
breast cancer; and Ki-67 is used to determine the proliferative activity of tumor cells. Thus, the patient was eventually diagnosed with lung adenocarcinoma with breast and cervical metastases. Subsequently, next-generation sequencing of DNA from the tumor biopsy specimens revealed consistent ALK rearrangements (EML4-ALK) between the primary lung lesion and metastases. As shown in Figure 5, there was mutant abundance among the different tissues.

Mutant abundance is an important indicator of tumor heterogeneity. There are various tumor cells in the tumor tissue, and different tumor cells carry different mutant genes, thus mutant abundance between the primary lesion and metastases will vary by heterogeneity.

The patient was prescribed crizotinib (250 mg orally, twice daily) in August 2017, and experienced no obvious drug-related adverse effects during or following treatment.
Follow-up CT scans taken at one week and at two months after treatment commenced demonstrated that the lung lesion was markedly diminished and was assessed as stable disease (Fig 3b,c). In addition, an ultrasound revealed that the metastases in the cervix and breast were obviously reduced after crizotinib treatment. Unfortunately, encephalic magnetic resonance imaging revealed multiple bilateral intracerebral metastases; therefore, the patient has received radiotherapy for the brain metastases while continuing oral crizotinib therapy to date.

**Discussion**

Lung carcinomas predominantly metastasize to the brain, bones, and adrenal glands, whereas metastases in the breast and cervix uteri are rare. Breast metastases from
extragenital cancers are very rare, occurring in just 0.5–6% of patients with breast cancer. In a study of 6668 oncology patients, Surov et al. estimated that the risk of breast metastasis from non-mammary sources was approximately 0.76%: 16% from primary lung tumors and 31% from melanoma. Sauer surveyed 6334 patients with breast cancer, identifying only 45 breast metastases from non-mammary sources (0.56%), and the most common primary sites were...
lung cancer (33.3%) and lymphoma (20%). Moreover, metastasis to the female genital tract from sources other than genital tract cancers is rare, most often affecting the ovary and vagina, but seldom invading the cervix. The rarity of this phenomenon is probably explained by poor blood flow at the cervix, the prevalence of fibrous tissue, and the small cervical body, which make the growth and proliferation of malignant tumor cells difficult. Accurately differentiating metastases from primary lesions is essential, especially in cases with atypical secondary lesions, in order to choose the appropriate therapeutic regimen and significantly improve prognosis.

In the present case, we found high concordance of ALK rearrangement between the primary tumor and both distant metastatic sites. The patient was prescribed with crizotinib as first-line treatment, which showed a steady reduction of the lung lesion.

In conclusion, in our case, lung adenocarcinoma metastasized to both breasts and the uterine cervix concurrently, which is extremely rare. Nevertheless, based on evidence from the literature, doctors should be vigilant for breast or cervical metastases from lung cancer. Early diagnosis and appropriate therapeutic regimens can relieve symptoms and significantly prolong survival. In addition, more attention should be paid to the homogeneity of ALK rearrangements between primary and metastatic tumors to promote accurate diagnosis and personalized, precise medicine in clinical practice.

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**Disclosure**

No authors report any conflict of interest.

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