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Endometrial Metastasis of Lung Adenocarcinoma: A Report of Two Cases

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Data Collection B
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Conflict of interest: None declared

Case series
Patient: Female, 55 • Female, 51
Final Diagnosis: Metastatic lung adenocarcinoma
Symptoms: Neck swelling
Medication: Erlotinib
Clinical Procedure: Lymph node biopsy
Specialty: Oncology

Objective: Unusual clinical course

Background: The female genital tract is an uncommon site of involvement for extragenital malignancies. Ovarian, vaginal, and cervical metastasis has been described in the literature. Uterine corpus and, particularly, endometrial involvement are exceedingly rare. As the incidence of lung cancer is rising in the female population, metastatic uterine involvement by lung cancer is also being reported in the medical literature. Here, we report two cases of endometrial metastasis from primary lung adenocarcinoma.

Case Report: The first case is a 55-year-old woman diagnosed with stage III lung adenocarcinoma who received initial treatment with sequential chemotherapy and radiotherapy, which resulted in complete response to treatment. However, patient was found to have recurrence soon after completion of initial treatment. Biopsy of a hypermetabolic lesion confirmed endometrial metastasis. The second case is a 51-year-old woman who presented with stage IV lung adenocarcinoma with metastasis to the uterus. EGFR mutation analysis of the lung mass and endometrial biopsy revealed epidermal growth factor receptor L858R mutation in exon 21. She had a positive response to EGFR-directed treatment of all areas of disease, including the uterus.

Conclusions: Uterine metastasis from lung adenocarcinoma is uncommon and difficult to differentiate from primary uterine cancer. The possibility of lung cancer metastasis should be considered in patients who have adenocarcinoma on biopsy of uterine lesions.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung • Urogenital Neoplasms • Uterine Neoplasms

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/892495

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Background

The incidence of lung cancer is increasing in women [1]. Regional lymph nodes, liver, adrenal gland, bones, and brain are considered the most frequent sites of metastasis from lung adenocarcinoma. Metastatic involvement to female genital tract by lung cancer is rare. Ovarian and vaginal involvement are the most common gynecological metastatic sites for both extra-genital and genital primary malignancies [2]. The ovaries are relatively common sites of metastasis from primary lung adenocarcinoma [3]. Endometrial metastasis is extremely rare for primary lung malignancies. To the best of our knowledge, there have been only 2 reports of primary lung adenocarcinoma with metastatic involvement of the endometrium [4,5]. Here, we report 2 cases of histopathologically proven primary lung adenocarcinoma metastasizing to the endometrium.

Case Reports

Case report 1

A 55-year-old woman initially noticed a swelling on the right side of her neck. The needle biopsy result was consistent with adenocarcinoma of the lung. Tumor cells were positive for cytokeratin 7, TTF-1, and Napsin, and negative for cytokeratin 20, cytokeratin 5/6, and CDX2. A staging CT scan confirmed stage IIIB disease. The patient was started on chemotherapy with Cisplatin and Etoposide, with a plan for sequential radiation treatment. Chemotherapy was later switched to Carboplatin, Abraxane, and Bevacizumab. Chemotherapy resulted in a partial response after 2 cycles. The patient completed radiation treatment to her chest and received 2 more cycles of consolidation chemotherapy afterwards. A restaging scan after completion of treatment showed a complete radiologic response by PET/CT scan.

A PET CT scan was performed 5 months after treatment, due to development of new pulmonary symptoms, which showed hypermetabolic activity in the left hilum and in the endometrium (Figure 1). Because it was assumed that the endometrial lesion was likely a second primary lesion the, patient underwent mediastinal lymphadenectomy for local disease recurrence. Pathology results confirmed disease relapse in left hilar lymph nodes, consistent with the initial diagnosis. An endometrial biopsy was also performed, which showed adenocarcinoma morphologically identical to the left hilar lymph node biopsy. Tumor cells were positive for cytokeratin (AE1/AE3), cytokeratin-7, and

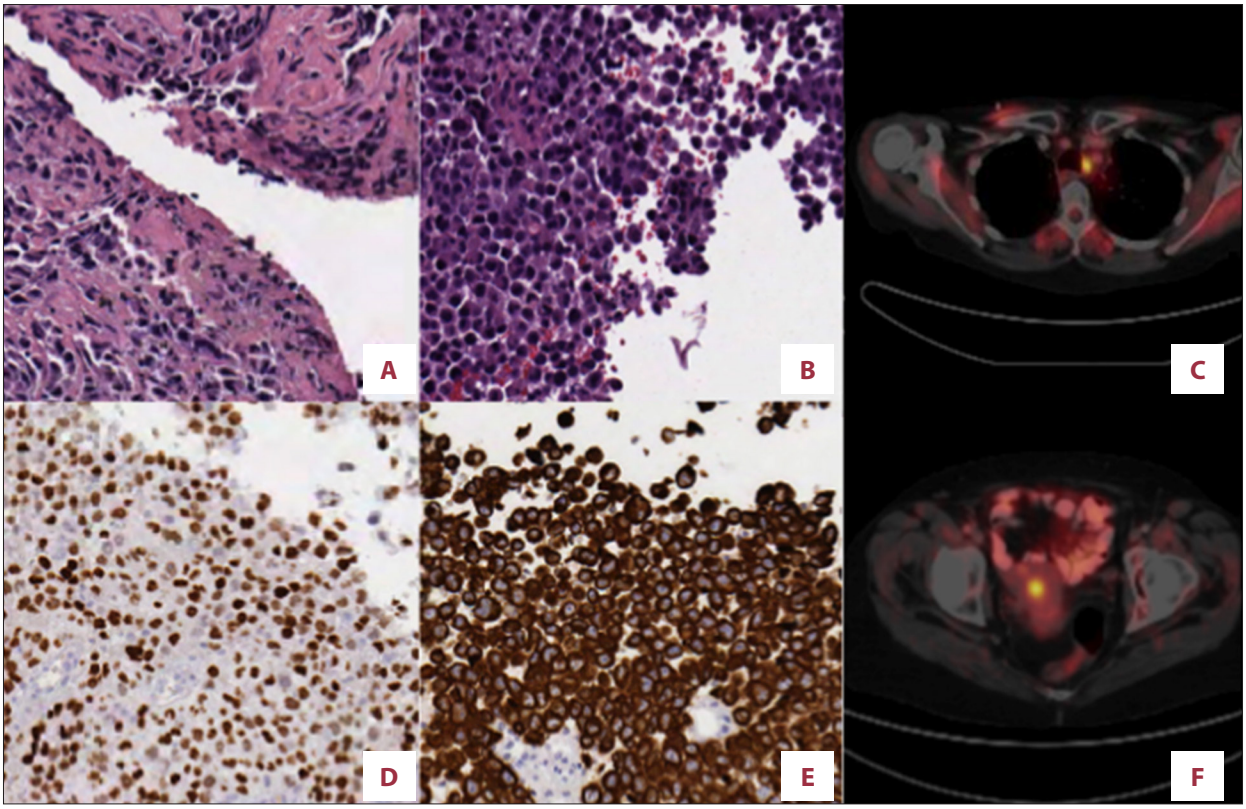

Figure 1. Case report 1. (**A**) Left hilar lymph node biopsy H&E; (**B**) Endometrial biopsy H&E stain which was morphologically identical to left hilar lymph node biopsy; (**C**) PET CT image showing FDG uptake in left hilum; (**D**) Endometrial biopsy TTF-1 stain; (**E**) Endometrial biopsy CK-7 stain; (**F**) PET CT image showing FDG uptake in uterus.

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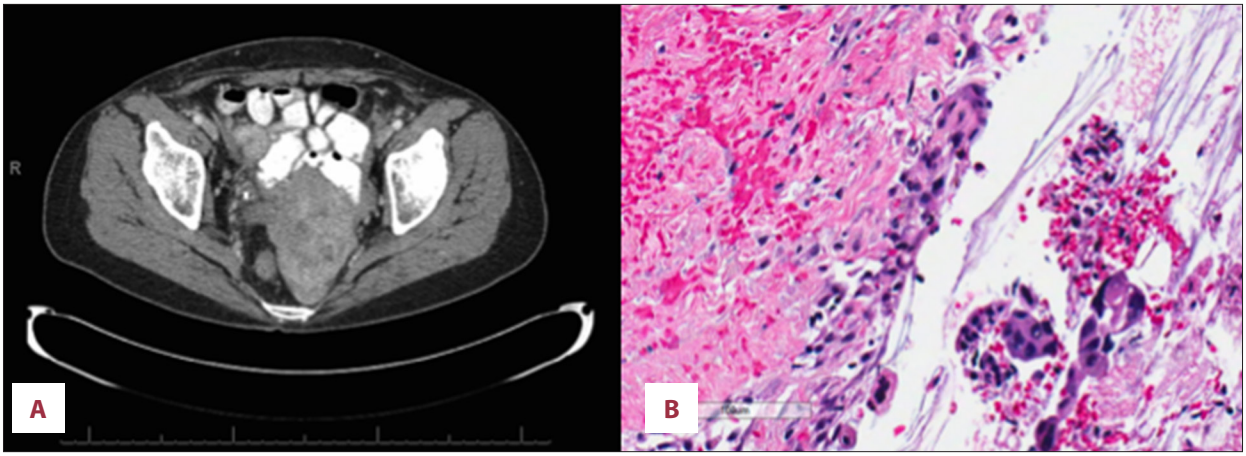

Figure 2. (**A**) CT scan image showing uterine metastasis; (**B**) Endometrial biopsy H&E stain, which was morphologically identical to lung cancer primary tumor.

TTF-1, and focally positive for vimentin. Stains were negative for cytokeratin-20, estrogen receptors, and progesterone receptors (Figure 1). These results are consistent with metastasis of lung adenocarcinoma to the endometrium.

Case report 2

A 51-year-old Taiwanese woman who had never smoked was diagnosed with metastatic adenocarcinoma of the lung. Biopsy of lung lesion revealed positive expression of Napsin A, TTF-1, cytokeratin 7, and MOC-31, and was negative for cytokeratin 5/6, WT-1, estrogen and progesterone receptors, CDX-2, and cytokeratin 20, consistent with adenocarcinoma of lung origin. Testing for epidermal growth factor receptor (EGFR) revealed L858R mutation in exon 21. Her initial PET scan showed lung lesions, as well as a uterine mass that was presumed to be a uterine fibroid; however, this was not biopsied at the time of initial diagnosis. She was initially started on erlotinib, which is an EGFR tyrosine kinase inhibitor (TKI), but after about 10 days she developed a severe skin rash; erlotinib was discontinued and she was treated with gefitinib. A repeat PET scan after 4 months showed a partial response to therapy. Of note, the uterine mass also decreased in size. The patient developed 2 liver lesions almost 7 months after treatment, for which she received CyberKnife radiotherapy, as well as receiving CyberKnife radiotherapy to her primary lung lesion. She was then restarted on erlotinib at a lower dose. She subsequently had disease progression resulting in pleural effusion and pericarditis and was switched to afatinib almost 18 months after the diagnosis.

Twenty-two months after her initial diagnosis, she developed abdominal pain and heavy vaginal bleeding. A CT abdomen revealed enlarged right uterine mass, right hydronephrosis, and hydroureter. An endometrial biopsy was performed, which showed adenocarcinoma positive for TTF-1, negative for ER and PR, and morphologically similar to her primary lung cancer (Figure 2). Tissue was sent for EGFR mutation analysis, which showed the same L858R mutation, but also the presence of the EGFR TKI resistance mutation, T790M. This confirmed metastasis of EGFR mutant lung adenocarcinoma to the uterus with subsequent development of T790M mutation. This represents another rare case of uterine endometrial metastasis from primary adenocarcinoma of the lung.

Discussion

Metastatic involvement of the female genital tract from lung adenocarcinoma is rare, and we are aware of only 2 prior published case reports of uterine metastasis. Other uncommon sites of metastasis of non-small cell lung cancer are the pancreas, spleen, and placenta, which can sometimes be challenging to diagnose [6–8].

Pathologically, endometrial metastatic lesions can be difficult to differentiate from primary uterine cancers in some circumstances. TTF-1 nuclear expression is the most highly sensitive and specific marker to differentiate primary adenocarcinoma of lung from adenocarcinomas of other sites [9]. Between 74% and 92% cases of lung adenocarcinoma exhibit TTF-1 nuclear expression [10–12]. However, TTF-1 has also been reported in 6% to 32% of endometrial adenocarcinoma [13,14]. Almost 100% of patients diagnosed with endometrial adenocarcinoma and 90% of patients with lung adenocarcinoma are CK-7-positive and CK-20-negative [15]; thus, a combination of expression of TTF-1+, CK-7+, and CK-20- immunophenotype is highly suggestive of primary adenocarcinoma of the lung (specificity 100%) [16]. The immunohistochemical profiles in the 2 cases we describe here are indicative of metastatic lung adenocarcinoma rather than primary uterine cancer. Between 35% and 90% of endometrial adenocarcinomas also express estrogen and progesterone receptors (ER and PR, respectively) [17,18].

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Though ER/PR positivity can also be observed in lung adenocarcinomas [19], the absence of ER and PR expression in our 2 cases also support the diagnosis of lung cancer metastasis to the endometrium. The finding of the classic L858R EGFR mutation observed in the second case with the most common EGFR TKI resistance mutation, T790M, are also highly suggestive of lung metastasis. EGFR mutations are rarely observed in endometrial cancers, but none of those reported wee similar to mutations commonly seen in lung cancer [20].

These 2 cases highlight the importance of recognizing hematogenous metastasis, as it could impact care. Our first patient died of complications following mediastinal lymphadenectomy, which was only performed under the assumption of local recurrence rather than hematogenous metastasis. Although the patient described in case report 2 remains alive, her treatment course might have been altered, as she most likely would not have received local therapy for liver lesions under the described circumstances. Moreover, if recognized earlier as a metastatic lesion, it could have been addressed with local treatment early on for palliation.

Conclusions

Uterine metastasis from lung adenocarcinoma can present a diagnostic dilemma. The possibility of lung cancer metastasis should be considered in patients found to have adenocarcinoma on biopsy of a uterine mass. Appropriate immunohistochemical staining should be used, considering the possibility of adenocarcinoma of lung origin in appropriate clinical settings.

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