Case Report / Olgu Sunumu

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Epidermal growth factor receptor-mutated lung adenocarcinoma diagnosed from endometrial polyp metastasis: A case report and literature review

Endometrial polip metastazıyla tanısı konulan epidermal büyüme faktörü reseptörü-mutasyonlu akciğer adenokarsinomu: Bir olgu sunumu ve literatür incelemesi

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Abstract

Endometrial metastasis from the lung primary remains is rare. Moreover, the literature only contains case reports of endometrial metastasis from the primary lung cancer. An 83-year-old female patient presented with postmenopausal uterine bleeding and anemia. Endometrial thickening was detected using transvaginal ultrasound and endometrial curettage was performed. Histopathology revealed adenocarcinoma infiltration on an endometrial polyp surface. On histologic examination, high-grade serous carcinoma and clear cell carcinoma diagnoses were initially considered. The tumor cells were immunohistochemically negative for Wilms' tumor 1 and wild-type for p53 expression; however, it was positive for Napsin A. Primary lung adenocarcinoma (LUAD) metastasis was also included in the differential diagnosis. Thyroid transcription factor 1 was positive, whereas paired box gene 8 (Pax8) was negative in tumor cells. Primary LUAD metastasis was diagnosed since a lung mass was radiologically confirmed. Furthermore, epidermal growth factor receptor-exon 19 mutation was detected by molecular analysis. In addition to the clinical and morphological features, this case report emphasizes the importance of multiple immunohistochemical panel applications for the correct diagnosis.

Keywords: EGFR protein, adenocarcinoma of lung, metastasis, endometrium, metrorrhagia

Öz

Akciğer primerinden endometriyuma metastaz literatürde ağırlıklı olarak olgu raporları bildirilmiş olup oldukça nadirdir. Kliniğimize 83 yaşında kadın hasta postmenopozal uterin kanama ve anemi ile başvurdu. Transvajinal ultrason ile endometriyal kalınlaşma tespit edildi ve endometriyal küretaj yapıldı. Histopatolojik incelemede endometriyal polip yüzeyinde adenokarsinom infiltrasyonu saptandı. Histolojik incelemede ilk olarak yüksek dereceli seröz karsinom ve berrak hücreli karsinom tanıları düşünüldü. Tümör hücreleri immünohistokimyasal olarak Wilms tümör 1 proteini için negatif, p53 ekspresyonu için wild tip ve Napsin-A için pozitif olduğundan, primer akciğer adenokarsinomu metastazı da ayırıcı tanıya dahil edildi. Tümör hücrelerinde tiroid transkripsiyon faktör-1'in pozitif, Pax8'in ise negatif çıkması ve de radyolojik olarak akciğerde kitlenin doğrulanması üzerine primer akciğer adenokarsinomu metastazı tanısı konuldu. Ayrıca moleküler analizde epidermal büyüme faktörü reseptöründe ekson 19 mutasyonu tespit edildi. Bu olgu sunumu, klinik ve morfolojik özelliklerin yanı sıra doğru tanı için çoklu immünohistokimyasal panellerin uygulanmasının önemini vurgulamaktadır.

Anahtar Kelimeler: EGFR proteini, akciğer adenokarsinomu, metastaz, endometriyum, metroraji

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Introduction

Postmenopausal uterine bleeding (PUB) accounts for approximately 5% of gynecology outpatient clinic visits[1]. Usual or atypical endometrial hyperplasia and polyps, as well as endometrial cancers, are well-known causes of postmenopausal bleeding in women[2]. Uterine carcinomas are the most common gynecologic cancers in United States accounting for approximately 13,000 annual deaths[3]. Hence, endometrial sampling is a crucial step for evaluating patients who present with PUB.

Lung and bronchial cancers are the second most common cause of cancer-related death in both women and men and the most common type of cancer in both groups[3]. Lung adenocarcinoma (LUAD) is the most frequent subtype of lung carcinomas[4]. Most patients with LUAD are at an advanced stage at the time of diagnosis and lose the best chance of surgical resection due to the relatively insidious early symptoms of LUAD[5]. Tobacco smoking accounts for most lung cancer etiology, except for LUAD. The Swedish Cancer Registry (involving approximately 18,000 patients with lung cancer) revealed that the nervous system, bone, liver, respiratory system, and adrenal gland as the most common sites for metastasis[6]. An autopsy study involving 175 patients with primary lung cancer showed 0.6% metastasis to the ovary[7]. Metastasis from primary lung cancer to the female genital tract remains rare.

This report presents a primary LUAD case with uterine bleeding. The definitive pathological diagnosis was received from endometrial curettage material. Molecular study analyses were performed and epidermal growth factor receptor (EGFR)-exon 19 deletion was detected. Additionally, this study also includes a literature review of endometrial metastasis that originates from primary lung carcinomas.

Case Report

An 83-year-old female patient came to the outpatient gynecology clinic presenting vaginal bleeding, which lasted for one week. She had a similar vaginal bleeding complaint six years ago, and the biopsy specimen was diagnosed as an endometrial polyp. Her past medical history included pulmonary emboli, hypertension, osteoarthritis, gout, and cardiac pacemaker. Physical examination revealed active bleeding from cervix. Transvaginal ultrasound showed a 13 mm endometrial thickness, multiple cystic degeneration foci, and endometrial polyp formations. However, both ovaries were atrophic and without mass lesions.

Diagnostic hysteroscopy, polypectomy, and endometrial curettage were performed. Histologic examination revealed an adenocarcinoma infiltration on the endometrial polyp surface. The tumor was sharing papillary and micropapillary formations with eosinophilic cytoplasm (Figure 1). No necrosis was seen. "High-grade serous carcinoma" and "clear cell carcinoma" diagnosis was considered for the first morphological evaluation. Immunohistochemical (IHC) stains were negative for Wilms' tumor 1 (WT1) and wild-type for p53 (30% of the tumor cells were positive with p53), thus high serous carcinoma was ruled out (Figure 2). However, Napsin A was diffusely positive, which was requested for clear cell carcinoma (Figure 2). Napsin A is simultaneously a strong predictor of primary LUAD[8]. The medical reports were retrospectively reviewed from the hospital information system. The previous thoracic computed tomography (CT) reported a lung mass lesion at the right lower lobe and multiple additional metastatic lesions, which were consistent with primary lung carcinoma, with mediastinal lymph node and bone metastasis. However, the patient did not previously receive a pathological diagnosis of lung lesion. Therefore, "LUAD metastasis" is also included in the differential diagnosis and the IHC panel was expanded. Clear cell carcinoma was excluded by negative paired box gene 8 (Pax8) staining (Figure 2). Moreover, thyroid transcription factor 1 (TTF1) staining was performed for LUAD diagnosis, which was positive (Figure 2). Thereafter, the diagnosis of "LUAD metastasis to endometrial polyp" was determined.

Chemotherapy was the first treatment option due to the advanced stage, thus molecular testing studies were conducted from the curettage material. Deoxyribonucleic acid (DNA) isolation was performed using the "AmoyDx® FFPE DNA Kit." DNA quantity and quality were measured using the "Nanodrop 2000" device. The A260/A280 value of the DNA sample ranges

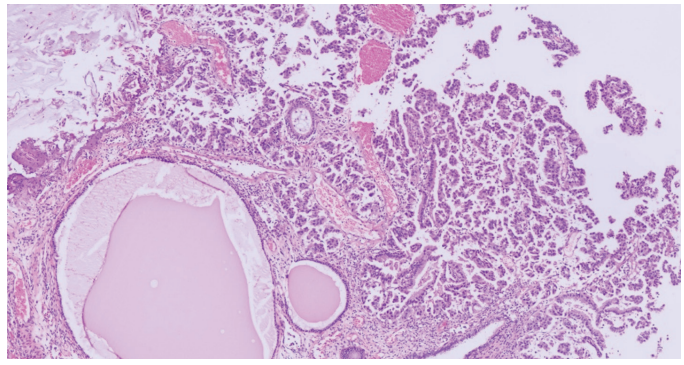

Figure 1A. Adenocarcinoma infiltration is seen on the endometrial polyp surface in papillary and micropapillary architecture (4x; hematoxylin and eosin)

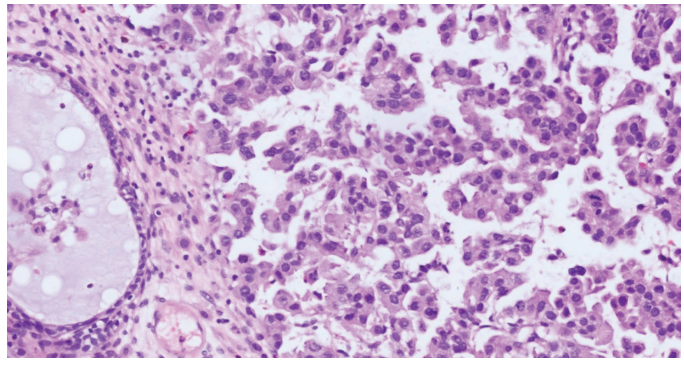

Figure 1B. Tumor cells that constitute the adenocarcinoma have mild to moderate nuclear atypia and eosinophilic cytoplasm without significant pleomorphism (hematoxylin and eosin)

from 1.8 to 2.0. The polymerase chain reaction was performed using the "BIO-RAD CFX96 Real-Time Detection System + C1000 Touch Thermal Cycler" device and the "AmoyDx® EGFR 29 Mutations Detection Kit" as specified in the kit protocol. Internal and external positive and negative controls were used in each study. Twenty-nine different mutations frequently seen in *EGFR* gene were evaluated, and exon 19 deletions of the EGFR were detected, which is known to be associated with the susceptibility to anti-EGFR-acting tyrosine kinase inhibitors in the tumor. T790M mutation was also evaluated but no mutation was found. Ventana ALK (D5F3) IHC antibody was used for the anaplastic lymphoma kinase (ALK) mutation analysis.

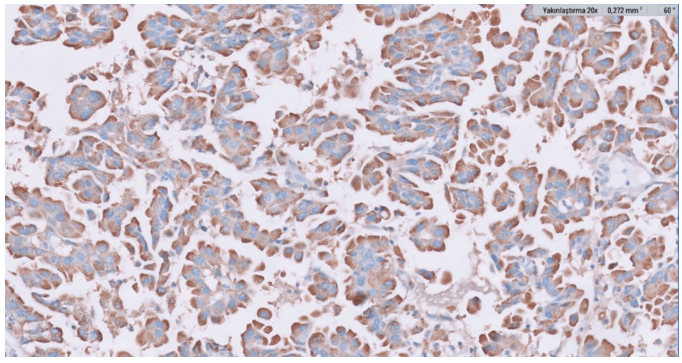

Figure 2A. Tumor cells diffuse granular cytoplasmic positivity with Napsin A

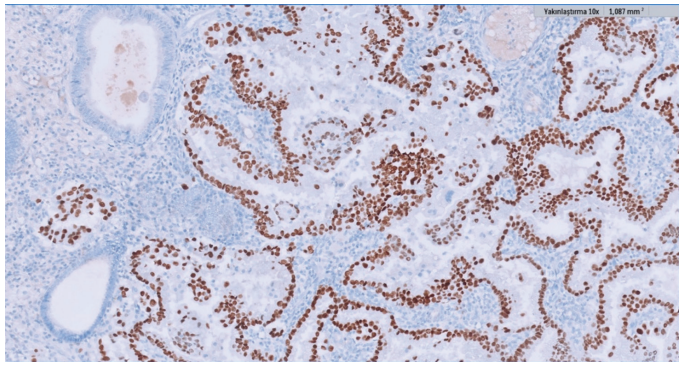

Figure 2B. Tumor cells diffuse nuclear positivity with thyroid transcription factor-1 (TTF1)

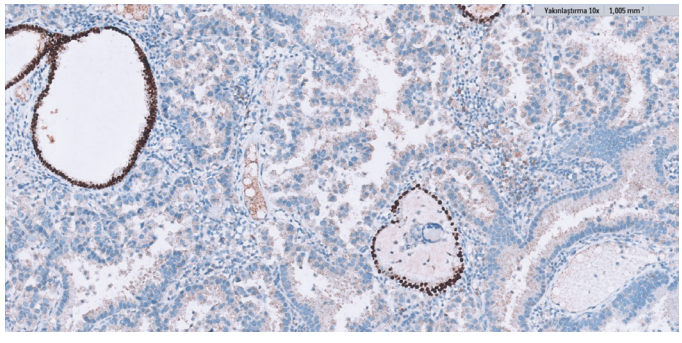

Figure 2C. Tumor cells are negative with paired box gene 8 (Pax8). As an internal control, the endometrial glandular cells are positively stained with Pax8

Ventana ROS (SP384) IHC antibody was used for reactive oxygen species (ROS) mutation analysis. The study was automatically conducted using the OptiView DAB IHC Detection Kit and the OptiView Amplification Kit on the Ventana Benchmark XT device. Appropriate staining was observed in the control tissue. No staining was observed with either ALK or ROS IHCs in the tumor.

Positron emission tomography-CT and brain CT showed metastatic mass lesions other than the endometrium. The patient received first-line erlotinib therapy for one month and currently has been using osimertinib for two months. Regression was not detected with these anti-EGFR therapeutic agents yet.

Discussion

Metastasis from the primary lung cancer to the female genital tract, including ovaries, myometrium, endometrium, vagina, cervix, and vulva is rare. Here, we present a case of EGFR-mutated LUAD with endometrial metastasis.

A literature search of endometrial metastasis from primary lung cancer yielded 11 case reports (Table 1)[9-18]. The patients' age ranged from 37 to 73 years. Most reported cases (81.82%) were non-small cell lung cancer. Endometrial biopsy due to abnormal vaginal bleeding (n=5, 45.46%) [9,11,12,14,17] and abnormal uterine or endometrial imaging during lung cancer follow-up (n=5, 45.46%)[10,14-16,18] were the leading causes for endometrial metastasis detection in this small cohort. Five cases (45.46%) were investigated for EGFR mutation status, where one case was negative[11], one case has had EGFR L858R and T790M mutation[14], one case was positive with E746_A750del mutation in exon 19 and T790M mutation in exon 20[16], and two cases were wild-type for EGFR mutation[17,18]. The EGFR status of the other cases is unknown. The ALK was detected in two cases and was treated with ALK inhibitors[16,18]. One of the ALK mutated cases sequentially had EGFR mutation[16].

Thyroid transcription factor-1 (TTF-1) and Napsin A are highly sensitive and specific markers for LUAD diagnosis, especially when used together[8]. Evaluation of 1,674 cases of lung cancer revealed that Napsin A was more sensitive (87% vs. 64%; p<0.001) and more specific (p<0.001) marker than TTF-1 in the differential diagnosis of LUAD[19]. TTF-1-positive

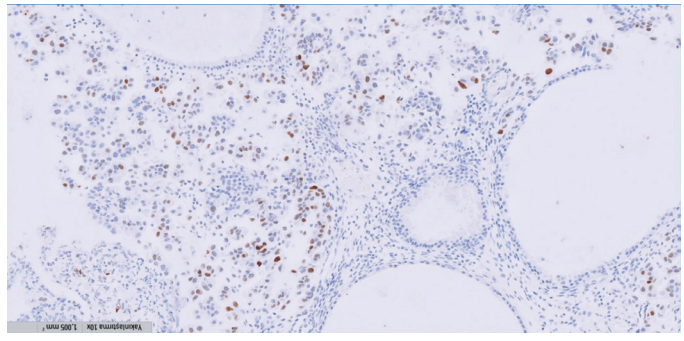

Figure 2D. Tumor cells with a wild-type pattern p53 staining

Table 1. Summary of the case reports with lung cancer metastasis to endometrium

Case no.	Age (years)	Race	Menopause	Smoking status	Discovery of metastasis to endometrium	Primary cancer	IHC findings (Lung)	IHC findings (Endometrium)	Report
1	68	NR	Yes	NR	Endometrial biopsy due to postmenopausal bleeding	well-differentiated neuroendocrine lung carcinoma (SCLC)	NR	NR	Jordan et al.[9]
2	56	NR	NR	No	After the diagnosis of lung cancer, hysterectomy was performed due to suspected mass that was detected in imaging	Small cell lung carcinoma (SCLC)	Chromogranin (+) Synaptophysin (+) TTF-1 (+)	Chromogranin (+) Synaptophysin (+) CD56 (+)	Chargari and Vedrine[10]
3	50	NR	NR	Yes	After the diagnosis of lung cancer, endometrial biopsy due to metrorrhagia	Lung adenocarcinoma (NSCLC)	TTF-1 (+) CEA (+) SPA (–)	TTF-1 (+) CEA (+) SPA (–) ER (–) PR (–)	Hibi et al.[11]
4	58	Caucasian	NR	Yes	After the diagnosis of lung cancer, endometrial biopsy due to vaginal bleeding	Lung adenocarcinoma (NSCLC)	TTF-1 (+) cytokeratin 7 (+) cytokeratin 20 (–) thyroglobulin (–) S100 (–) HMB-45 (–) melan A (–) ER (–)	TTF-1 (+) cytokeratin 7 (+) cytokeratin 20 (–) myogenin (–) S100 (–) ER (–)	Tiseo et al.[12]
5	70	White	Yes	NR	After the diagnosis of lung cancer, endometrial biopsy due to abnormal thickening of the endometrium	Pulmonary carcinoid tumor (NSCLC)	TTF1 (+) Chromogranin (+) Synaptophysin (+) Cytokeratin AE1/AE3 (+)	TTF1 (equivocal) Chromogranin (+) Synaptophysin (–) Cytokeratin AE1/AE3 (–)	Momeni et al.[13]
6	55	NR	NR	NR	Endometrial biopsy due to PET-CT showing hypermetabolic activity in the endometrium	Lung adenocarcinoma (NSCLC)	TTF-1 (+) cytokeratin 7 (+) Napsin (+) cytokeratin 20 (–) cytokeratin 5/6 (–) CDX2 (–)	TTF-1 (+) cytokeratin 7 (+) Cytokeratin AE1/AE3 (+) Vimentin (+) cytokeratin 20 (–) ER (–) PR (–)	Ahmad et al.[14]
7	51	NR	NR	No	After the diagnosis of lung cancer, endometrial biopsy due to heavy vaginal bleeding	Lung adenocarcinoma (NSCLC)	TTF-1 (+) Napsin A (+) cytokeratin 7 (+) MOC-31 (+) cytokeratin 5/6 (–) WT-1 (–) ER (–) PR (–) CDX-2 (–) cytokeratin 20 (–)	TTF-1 (+) ER (–) PR (–)	Ahmad et al.[14]

Table 1. Continued

Case no.	Age (years)	Race	Menopause	Smoking status	Discovery of metastasis to endometrium	Primary cancer	IHC findings (Lung)	IHC findings (Endometrium)	Report
8	73	NR	NR	NR	Uterus curettage due to PET/CT showing hypermetabolic activity in the uterus and spotting	Lung adenocarcinoma (NSCLC)	NR	TTF-1 (+) ER (–) PAX-8 (–)	Patel et al.[15]
9	37	NR	No	NR	After PET/CT showing uterine uptake, endometrial curettage was performed	Lung adenocarcinoma (NSCLC)	CK-7 (+) TTF (+) ER (–) PR (–) HER2 (–) NEU (–) GCDFP-15 (–)	TTF1 (+) (clone 8G7G3/1)	Anjali et al.[16]
10	47	NR	NR	No	Endometrial biopsy due to vaginal bleeding	Lung adenocarcinoma (NSCLC)	TTF1 (+) ALK (+) PDL1 (+)	TTF1 (+) CK7 (+) PAX-8 (+) ALK (+) PDL1 (+) CK20 (–) ER (–)	Sevinyan et al.[17]
11	54	NR	NR	NR	After abdominal CT revealing uterine mass, endometrial curettage was performed	Lung adenocarcinoma (NSCLC)	NR	NR	Kobayashi et al.[18]
12	83	White	Yes	NR	endometrial biopsy due to AUB	Lung adenocarcinoma (NSCLC)	NR	TTF-1 (+) Napsin A (+) WT-1 (–) p53 (+) PAX-8 (–)	Bulutay et al. (Current Case)

AUB: Abnormal uterine bleeding, CEA: Carcinoembryonic antigen, CT: Computed tomography, ER: Estrogen receptor, IHC: Immunohistochemistry, PET: Positron emission tomography, NR: Not reported, NSCLC: Non-small cell lung cancer, PR: Progesterone receptor, SCLC: Small cell lung cancer, SPA: Surfactant protein A, TTF-1: Thyroid transcription factor-1

tumoral infiltration in extrapulmonary tissues is accepted as a primary LUAD metastasis if the possibility of thyroid primary is not clinically predicted. TTF-1 is considered a relatively specific marker for lung and thyroid neoplasms; however, TTF-1 positivity was reported in a subset of endometrial carcinomas and this rate was much lower, especially in well-differentiated types[20]. Therefore, occasional TTF-1 expression of endometrial and endocervical carcinomas should be kept in mind when evaluating neoplasms of uncertain origin, especially on the gynecological tract. Napsin A is a highly sensitive marker for LUADs, thus studies showed that tumors as ovarian clear cell (71.7%), endometrial clear cell (42.8%), papillary renal cell (40.2%), clear cell (tubular) papillary renal cell (16.7%), endometrial serous (9.3%), papillary thyroid (9.3%), and clear cell renal cell carcinomas (8.2%) can similarly express Napsin A[21]. Therefore, studying multiple markers as a panel for targeted tumors would be beneficial, particularly if a tumor of unknown primary origin is seen. In this case, both TTF-1 and Napsin A positivity, as well as Pax8 negativity with radiologically defined lung mass lesions, were strong indicators of the endometrial metastasis of the primary LUAD.

Conclusion

The endometrium is a rare site for primary lung cancer metastasis; however, an increasing number of cases of endometrial metastases from lung cancer could be reported due to the increasing incidence of primary lung cancer. In addition to the endometrial-originating lesions in patients with abnormal uterine bleeding, clinicians should keep in mind the metastatic tumors. Furthermore, while evaluating tumors that are observed in endometrial curettage materials by pathologists, the possibility of metastatic tumors should always be considered.

Ethics

Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.Y., B.A., Concept: P.B., E.B., Ş.Y., B.A., Design: P.B., E.B., Ş.Y., B.A., Data Collection or Processing: P.B., E.B., Ş.Y., Analysis or Interpretation: P.B., E.B., B.A., Literature Search: P.B., E.B., Writing: P.B., E.B., Ş.Y.
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