



# Three Cases of Breast Metastases from Lung Cancer and Systematic Review of the Literature

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## ABSTRACT

Despite the high prevalence of lung cancer among other primary tumors, metastasis of this particular malignancy in the breast is very rare. We report three new cases of lung cancer with breast metastases and discuss radiological and clinical findings. Radiologically, each case displayed different characteristics. First, one of them had bilateral superficially and deeply located irregular lesions. Second, the patient presented with findings similar to inflammatory breast cancer. The third case had a circumscribed mass, resembling a benign complicated cyst. To guide clinicians for proper patient management, radiologists should be aware of the scope of typical and atypical imaging findings of metastatic involvement of the breast.

**Keywords:** Breast neoplasm, breast metastasis, lung cancer, breast ultrasound

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## Key Points

- Metastatic tumors in the breast have a wide array of radiological manifestations.
- For pathological confirmation, needle biopsy should be performed for interval lesions in a patient with a known history of lung cancer, even with a probably benign appearance.
- Radiologists should be aware of the range of typical and atypical imaging findings of metastatic involvement of the breast to guide clinicians for proper patient management.

## Introduction

The incidence of metastatic spread from extramammary sites to the breast varies between 0.4% and 1.3% of all breast malignancies in clinical series (1-6). The breast is considered to be resistant to metastasis because it contains large areas of fibrous tissue with a relatively low supply of blood (7, 8). Most common malignancies that metastasize into the breast are lymphoma, leukemia, and melanoma. Some of the less common primary tumors are carcinomas of the ovary, stomach, and lung, and very rare sources are carcinoid tumors, hypernephromas, and carcinomas of the liver, thyroid, tonsil, pleura, pancreas, cervix, perineum, endometrium, and bladder (7, 9).

It is important to differentiate primary from secondary breast malignancies because therapeutic approaches and outcomes are very different. In the literature, various radiological findings have been described. Moreover, there are few detailed imaging reports of metastatic breast lesions from lung cancer. We report three cases of breast metastases from primary lung cancer, each with different radiological findings. We also present a systematic review of the literature covering all cases published in English until 2019.

## Case Presentations

### Case 1

A year after she was diagnosed with small-cell lung cancer, a 52-year-old female patient felt a lump in her right breast. The mammograms performed 6 months ago were unremarkable, so the first line of imaging was bilateral whole-breast ultrasound (US). Further, US showed a

superficially located 9-mm round solid mass with irregular margins and an echogenic halo at 9 o'clock position in the right breast (Figure 1a). On Doppler US imaging, the lesion showed central and peripheral vascularization, which resembled a primary tumor. However, there were two additional irregular Breast Imaging-Reporting and Data System (BIRADS 4) lesions with indistinct margins at 12 o'clock position in the right breast and a well-defined nodule at 9 o'clock position in the left breast. The widths of these lesions, respectively, were 10 mm, 3 mm, and 6 mm. One was superficially located in the subcutaneous fat, and the other two were deep within the parenchyma. One of them was a heterogeneous hyperechoic lesion, and the small lesion had an echogenic rim (Figure 1b). Due to these additional lesions with unusual appearances, the possibility of bilateral breast metastases was considered, and mammography was performed. Mammograms (Figures 2a and 2b) revealed additional small nodules with microlobulated and indistinct margins that were not detected in the US.

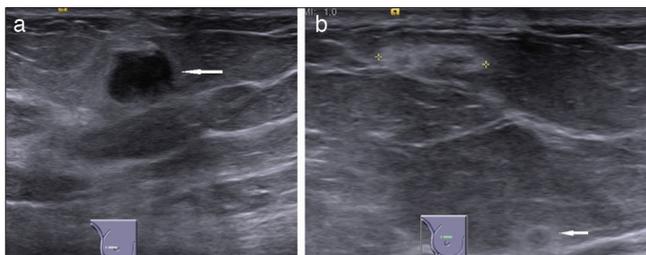
Tumor infiltration by small-cell carcinoma was demonstrated by ultrasound-guided core needle biopsy of the index lesion (Figure 3). Moreover, immunohistochemical analysis showed tumor cells positive for synaptophysin, chromogranin, and TTF-1. The tumor displayed high Ki-67 (90%) proliferation index.

The patient continued chemotherapy, and magnetic resonance imaging (MRI) (Figures 4a and 4e) of the breast revealed progression in the diameter and number of lesions after 6 months. Almost all of them were hyperintense in fat-saturated T2-weighted images (Figures 4a and 4b). In contrast-enhanced images, most of the lesions showed rim enhancement and type-3 enhancement kinetics (Figures 4c and 4d). On the other hand, in diffusion-weighted images, they showed restricted diffusion (Figure 4e).

Following the development of multiple brain metastases, the patient died 18 months after the diagnosis of primary lung cancer and 6 months after the diagnosis of breast metastases.

## Case 2

A 70-year-old female patient who had a strong family history of lung cancer presented with dyspnea. Chest X-ray and consequent computed tomography (CT) scan of the thorax revealed a 26-mm spiculated mass in the anterior segment of the upper lobe of the left lung, followed by bilateral mediastinal and left hilar lymphadenopathies and left pleural effusion. Furthermore, tissue diagnosis of the lung tumor was adenocarcinoma of the lung. Pleural effusion also demonstrated malignant cytology. In addition, brain magnetic resonance imaging

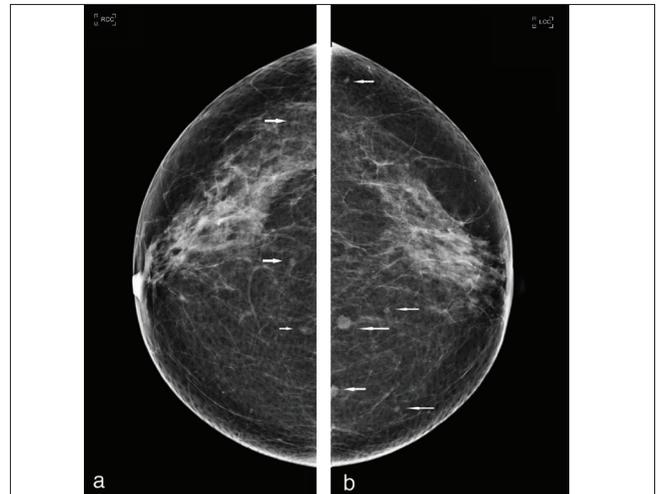


**Figure 1.** US examination: (a) superficially located irregular solid nodular lesion with echogenic halo at 9 o'clock position in the right breast (arrow). (b) Hyperechoic lesion (in calipers) and a deeply located heterogeneous nodule with an echogenic halo (arrow) at 12 o'clock position in the right breast

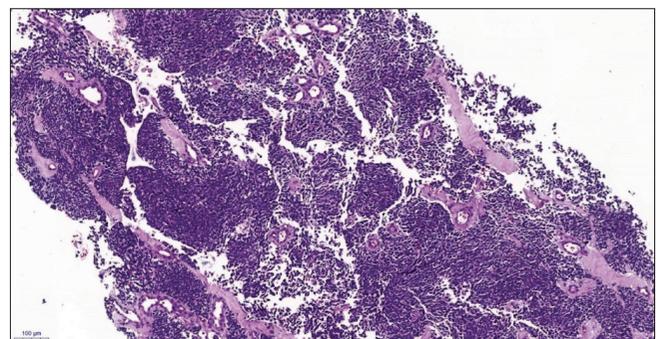
US: Ultrasonography

(MRI) revealed additional metastatic lesions in the brain and the left frontal bone. For the brain lesion, she received systemic chemotherapy and stereotactic radiotherapy.

Eight months later, positron emission tomography (PET) scan demonstrated left axillary lymphadenopathy as an interval finding. Two months after this finding and 10 months after the diagnosis of her primary tumor, she detected a lump in her left breast. Mammography revealed skin thickening and trabecular thickening in the lower outer quadrant of the left breast (Figure 5a). On the other hand, US revealed subcutaneous tissue edema, parenchymal distortion, and multiple small vertically oriented irregular hypoechoic non-mass lesions in the lower outer quadrant of the left breast, covering an area of approximately 4 cm in diameter (Figure 5b). Further, there was evidence of primary inflammatory breast cancer. Ultrasound-guided core needle biopsy of the lesions was then performed. Moreover, hematoxylin-eosin (H&E) stained paraffin sections of the breast needle biopsy revealed adenocarcinoma (Figure 6a). The tumor cells demonstrated immunoreactivity for TTF-1 and CK7 and negative immunostain with GATA3, estrogen receptor, and progesterone receptor (Figure 6b). The histopathological findings were consistent with metastasis of pulmonary adenocarcinoma and diffuse intralymphatic spread. Mutational analysis of the tumor in the breast core biopsy specimen demonstrated an L858R mutation in Exon 21 of the *EGFR* gene. Later on, the patient died 15 months after diagnosis of primary lung cancer and approximately 7 months after breast metastasis was diagnosed.

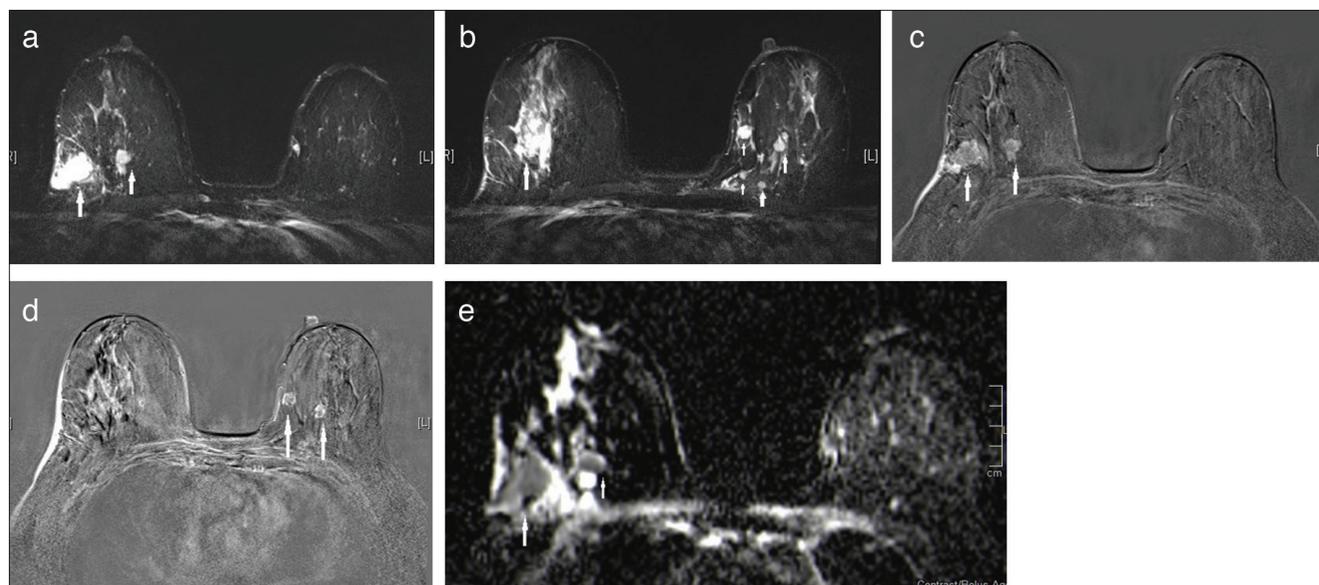


**Figure 2.** (a,b) Mammography (craniocaudal views) shows multiple nodules smaller than 1 cm with indistinct/microlobulated margins (arrows)



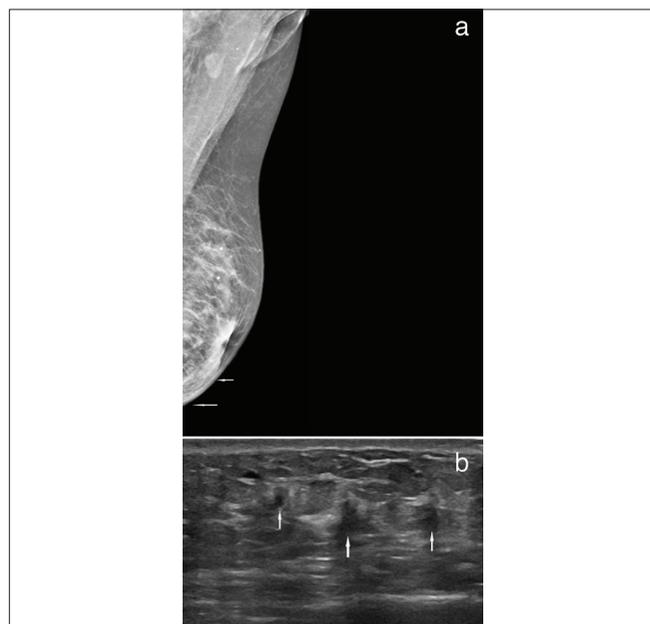
**Figure 3.** Breast biopsy. Small-cell carcinoma (H&E)

H&E: Hematoxylin-eosin



**Figure 4.** Breast MRI examination. **(a-b)** Fat-saturated T2-weighted images show bilateral multiple irregular hyperintense nodular lesions (arrows). **(c-d)** Contrast-enhanced T1-weighted subtraction images: most of the lesions displayed rim enhancement (arrows). **(e)** Diffusion-weighted images ADC map: lesions showed restricted diffusion (arrows)

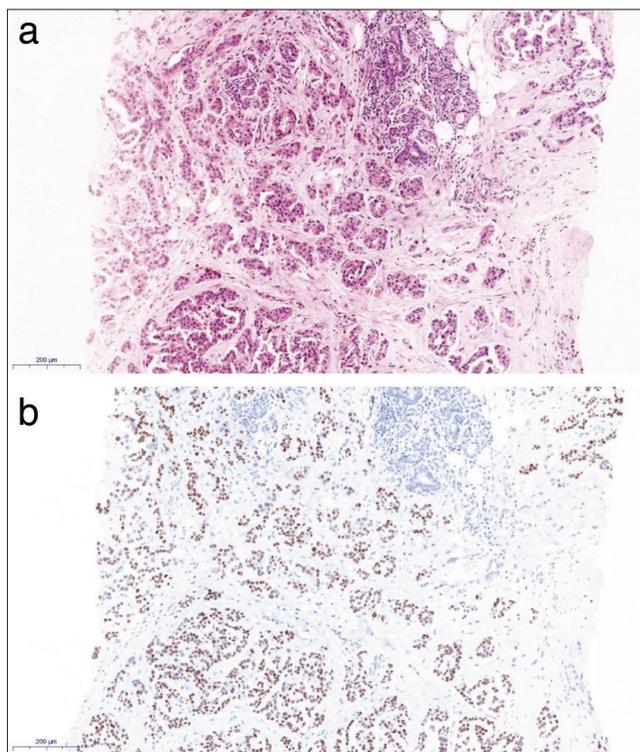
MRI: Magnetic resonance imaging; ADC: Apparent diffusion coefficient



**Figure 5.** **(a)** Mammography (left mediolateral oblique view) demonstrates trabecular thickening and skin thickening (arrows) in the lower outer quadrant of the left breast. Retraction of both nipples is noted as incidental finding. **(b)** Ultrasound of the left breast: irregular, vertically oriented, non-mass lesions (arrows) are seen

**Case 3**

A 64-year-old heavy smoker female patient, who had smoked for 40 years and suffered from dyspnea, was diagnosed with a mass in the upper lobe of the left lung. CT scan revealed a centrally located tumor with mediastinal invasion as well as pleural effusion and multiple mediastinal lymphadenopathies. Moreover, the pathological diagnosis was small-cell lung cancer. Ten months after the diagnosis of the primary tumor, a PET scan was performed. In the upper inner quadrant of the left breast, right adrenal metastasis, multiple intraabdominal lymphadenopathies,



**Figure 6.** **(a)** Breast biopsy. Adenocarcinoma (H&E). **(b)** Tumor cells positive with TTF-1 immunostain

H&E: Hematoxylin-eosin

and hypermetabolic nodular lesion were detected. A bilateral breast US examination was performed, showing an 8-mm circumscribed hypoechoic round lesion at 9 o'clock position in the left breast (Figure 7a). At first examination, it resembled a complicated cyst that displayed no internal vascularization. However, a second examination revealed the solid nature of the nodule and an echogenic halo around it, when

window levels were adjusted (Figure 7b). In addition, US-guided core needle biopsy demonstrated tumor infiltration by small-cell carcinoma (Figure 8). Immunohistochemical analysis showed tumor cells positive for synaptophysin, chromogranin, pan-cytokeratin, and TTF-1. The tumor had a high Ki-67 (95%) proliferation index. Later on, the patient died 26 months after lung cancer was diagnosed and 16 months after the diagnosis of breast metastasis.

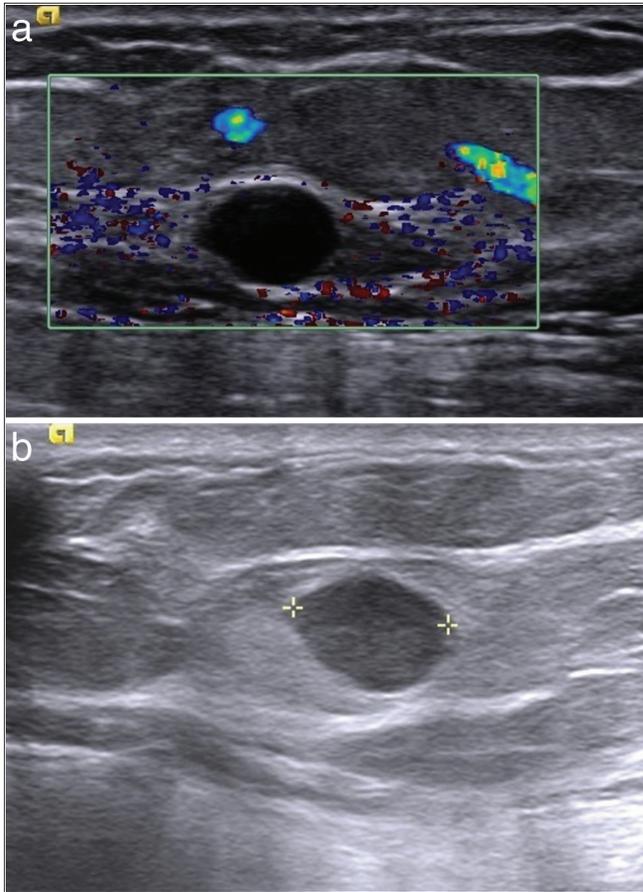
## Discussion

Breast metastases from extramammary sites are very rare. Lung cancer, which is a common malignancy and one of the leading cancer-related

causes of death worldwide, frequently spreads to other organs but metastasizes to the breast very rarely. A few reviews have previously been published on lung cancer metastasizing to the breast (3, 4, 10-13). Alva and Shetty Alva (12) reported 78 cases in their literature review from 1855 to 1998. The most recent and largest review published in 2018 has reported 169 cases from 1999 to 2017 (13). In the cases of Alva and Shetty Alva (12), we have found 180 additional cases of metastatic lung tumors in the breast and made a summary of a total of 258 cases published in English until 2019. Moreover, we could reach the histologic type of lung tumor in 111 cases. Nine of these were identified as non-small-cell lung cancer. The remaining 102 cases were also reported: 61 adenocarcinomas, 14 neuroendocrine tumors, 12 small-cell carcinomas, nine squamous cell carcinomas, two carcinoid tumors, and one each of anaplastic carcinoma, large-cell cancer, pleomorphic carcinoma, and adenosquamous carcinoma.

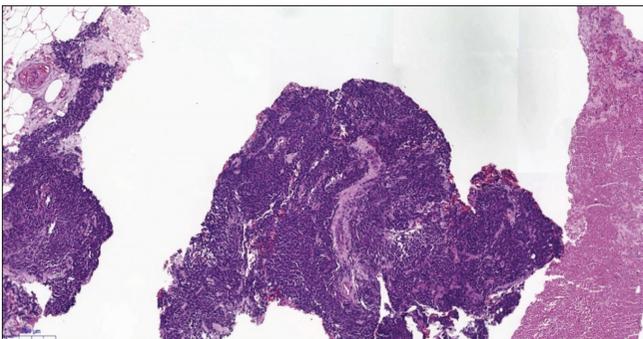
Metastatic tumors in the breast have a wide variety of radiological appearances. Some may mimic a probably benign lesion, whereas some may be similar to primary breast carcinomas (3, 9). Lee et al. (14) also reported that only 2 were classified as BIRADS 3 in their series of 33 cases of breast metastases, the rest being categorized as BIRADS 4b or higher. They are usually unilateral and unifocal with a predilection for the upper outer quadrant, but it has been reported that around 33% can be multifocal and 15% can be bilateral (15). The most common radiological appearance is a round or oval mass with uncircumscribed margins located superficially in the subcutaneous tissue (10). Lee et al. (16) have stated that around 75% of cases have irregular margins. Superficial location can be an indication, as primary cancers that arise from the ductal or lobular tissue tend to be deeply located in the parenchyma (1). Although superficially located, unlike primary masses, they do not cause skin or nipple retraction. In secondary tumors, spiculation, posterior shadowing, and calcifications usually detected in primary breast cancers are very rare (2, 3, 7, 16). Calcifications have been identified in metastases of ovarian, gastric, thyroid, and mucin-producing gastrointestinal cancers (14). Metastatic lesions tend to develop rapidly and lack desmoplastic response, which is a typical finding of primary breast cancer (9). Therefore, contrary to primary tumors, an echogenic halo around the mass and parenchymal distortion is not typical characteristics of breast metastases. Nevertheless, two of our cases had an echogenic halo. Moreover, the differential diagnosis of benign and malignant lesions is made easier by the echogenic halo. In case number three, it was evident only after the window level was adjusted, which highlights the significance of meticulous imaging. Echo patterns of metastatic lesions can be homogeneous or heterogeneous (7). Masses may contain cystic areas due to hemorrhage or necrosis. This is more frequently detected in lymphoproliferative lesions as well as gastric, hepatocellular, and ovarian cancers (17). Due to high cellular proliferation, metastatic tumors may also present with a pseudocystic appearance at US. Thus, they may resemble complicated cysts as in one of our cases or triple-negative breast carcinomas (9). As seen in the third case, radiologists should be very cautious before calling these lesions cysts, especially in patients with primary malignancies. Color Doppler US imaging may also be helpful in differentiation.

There are very few studies in the literature on MRI findings for breast metastases. As in the first case, metastatic lesions mostly demonstrate rim enhancement, type-3 enhancement curve, and restricted diffusion on breast MRI, clearly indicating their malignant nature (17). Depending on the presence of necrosis, they can be hypo- or hyperechoic on T2-weighted images. In their series of breast metastases, Mun et al. (9)



**Figure 7. (a)** Ultrasound of the left breast: superficially located well-defined cyst-like avascular round lesion. **(b)** Second US examination revealed the solid nature of the nodule and an echogenic halo

US: Ultrasonography



**Figure 8.** Breast biopsy. Small-cell carcinoma with necrosis (H&E)

H&E: Hematoxylin-eosin

have also defined some atypical imaging features, such as non-mass lesions and segmentally or ductally distributed micronodules, similar to the results in our second case.

Depending on the route of disease transmission, clinical and radiological findings of breast metastases may vary (4, 10, 16-18). Hematologically disseminated lesions tend to appear as single or multiple, round to oval, circumscribed, or irregular masses commonly superficially located in subcutaneous tissue or immediately adjacent to the breast parenchyma, which is relatively rich in blood supply (9, 16). Furthermore, axilla is less commonly involved (9). Our first case represents a good example. There were multiple lesions superficially located in the subcutaneous fatty tissue and additional lesions deep in the parenchyma. Tumors that spread through the lymphatic route tend to manifest in the subcutaneous lymphatic channels as skin thickening, subcutaneous edema, and trabecular thickening due to tumor emboli (2). An apparent mass may or may not be present (9, 17). Mammography usually indicates asymmetric opacity, and MRI may demonstrate non-mass enhancement and edema. Clinically, peau d'orange and redness on the skin may occasionally be observed. These cases can be falsely diagnosed as mastitis or inflammatory breast cancers (2, 4). It has been documented that ovarian, gastric, and lung cancers lead to this type of breast metastases (4, 16, 19, 20). Huang et al. (11) reported that pleural effusion, pleural thickening, and ipsilateral axillary lymphadenopathy precede the development of breast lesions in lung cancers that spread through the lymphatic route to the breast. They have also indicated that the breast is affected in a retrograde fashion after the intervention of the axilla. In our second case, radiological findings are probably consistent with this type of dissemination. In lung cancer patients with pleural effusion, the axilla and the breast should be closely examined. Another means of spreading lung cancer to the breast can be through direct chest wall invasion, but this is not a common finding.

There are no specific predisposing factors associated with breast metastases. It has been postulated that by increasing the vascularity of the breast, estrogen may have a role as a predisposing factor in the development of metastasis. This has been proposed as an explanation for the relatively higher incidence of breast metastases in young women (9, 16). In contradiction to this hypothesis, all of our patients were postmenopausal women. Clinically, the presenting symptom was palpable breast lump in two of our three cases in accordance with the literature (2). In one case, the breast mass was an incidental finding in the PET-CT.

In conclusion, breast metastases from lung cancer are very rare, but it is clinically very important to distinguish primary from metastatic breast lesions. It is also important to apply the necessary chemotherapeutic regimens for metastatic patients and to guide them correctly in their disease prognosis while avoiding unnecessary surgical treatments. In this article, we present a literature review as well as three new cases, each with distinct radiological appearances. These cases support other studies of breast metastases, demonstrating a variety of radiological findings. Due to the lack of specific radiological features, immunohistochemical studies are important to reach an accurate diagnosis.

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**Peer-review:** Externally-peer reviewed.

## Authorship Contributions

Concept: N.G.; Design: N.G., G.E.İ.; Supervision: G.E.İ.; Materials: N.G., G.E.İ., F.T., B.T., H.K., T.K., B.O.U., G.D.; Data Collection and/or Processing: N.G., F.T., B.T., H.K., T.K., B.O.U., G.D.; Analysis and/or Interpretation: N.G., G.E.İ., F.T.; Literature Search: N.G., G.E.İ.; Writing Manuscript: N.G., G.E.İ., F.T.; Critical Review: G.E.İ.

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