

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

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ABSTRACT

Despite the high rate of lung cancer among other primary tumors, metastasis of this common malignancy to the breast is very rare. We report 3 new cases of lung cancer with breast metastases and discuss radiological and clinical findings. Radiologically each case displayed different features. First one of them had bilateral superficially and deeply located irregular lesions. The second patient presented with findings similar to inflammatory breast cancer. The third case had a circumscribed mass, resembling a benign complicated cyst. Radiologists should be aware of the spectrum of typical and atypical imaging findings of metastatic involvement of the breast to guide the clinicians for appropriate patient management.

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

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Introduction

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

Differentiation of primary from secondary malignancies of the breast is important because therapeutic approaches and outcomes are very different. Various radiologic findings have been described in the literature. Detailed imaging reports of metastatic breast lesions from lung cancer are few. We report 3 cases of metastases to the breast from primary lung cancer, each with different radiological findings. We also present a systematic review of the literature covering all cases published up to 2019 in English language.

Case Presentations

Written informed consent was obtained from nearest relatives (spouses and children) of the patients.

Case 1

One year after diagnosis of small cell lung cancer, a 52 years-old female patient felt a lump in her right breast. The mammograms performed 6 months ago were unremarkable, therefore bilateral whole breast ultrasound (US) was performed as the first line of imaging. US revealed 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). The lesion showed central and peripheral vascularization on Doppler imaging and resembled a primary tumor. However, there were two additional irregular 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 measured 10 mm, 3 mm and 6 mm respectively. One was superficially located in the subcutaneous fat and the other two were deep inside the parenchyma. One of them was a heterogeneous hyperechoic lesion, and the small lesion had an echogenic rim (Figure 1b). Because of these additional lesions with unusual appearances, the possibility of bilateral breast metastases was considered and mammography was performed. Mammograms (Figure 2a-b) demonstrated additional small nodules with microlobulated and indistinct margins in both breasts which were not detected with US.

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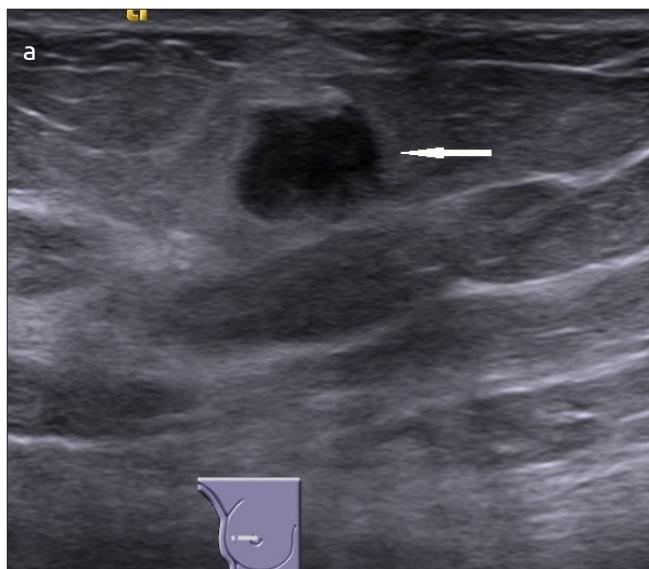


Figure 1. a, b. US examination: (a) superficially located irregular solid nodular lesion with echogenic halo at 9 o'clock position in the right breast (arrow). (b) Hyperechoic lesion (in calipers) and a deeply located heterogeneous nodule with an echogenic halo (arrow) at 12 o'clock position in the right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

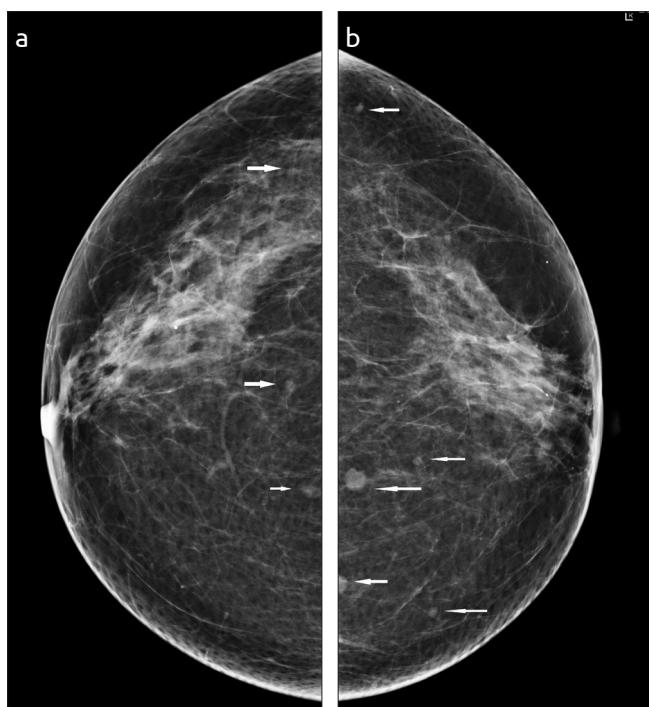
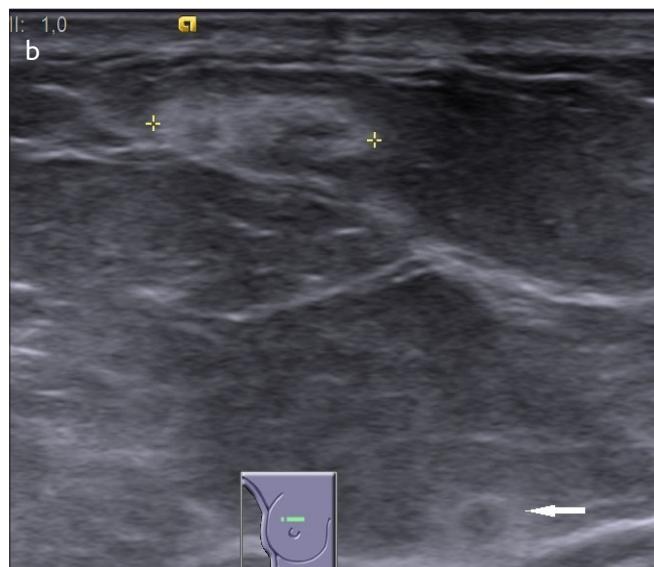


Figure 2. a, b. Mammography (craniocaudal views) shows multiple nodules smaller than 1 cm with indistinct/microlobulated margins (arrows)

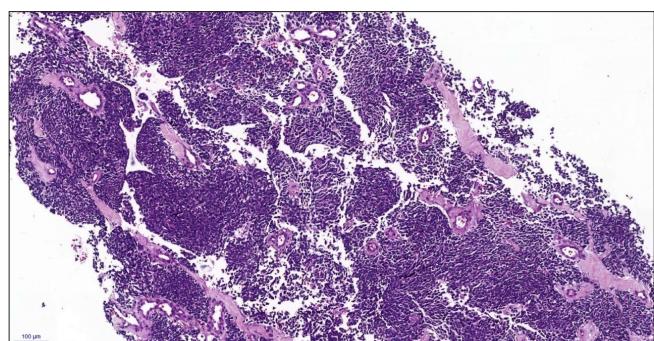


Figure 3. Breast biopsy. Small cell carcinoma (H&E)

Ultrasound-guided core-needle biopsy of the index lesion demonstrated tumoral infiltration by a small cell carcinoma (Figure 3). Immunohistochemical analysis showed tumor cells positive for Synaptophysin, Chromogranin and TTF-1. The tumor showed high Ki-67 (90%) proliferation index.

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

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

Key Points

- Metastatic tumors in the breast have a wide range of radiologic appearances.
- An interval lesion in a patient with a known history of lung cancer, even with a probably benign appearance should undergo needle biopsy for pathologic confirmation.
- Radiologists should be aware of the spectrum of typical and atypical imaging findings of metastatic involvement of the breast to guide the clinicians for appropriate patient management.

Case 2

Seventy years-old female patient who had a strong family history of lung cancer presented with dyspnea. Chest x-ray and consequent CT scan of the thorax revealed a 26 mm spiculated mass in the anterior segment of the upper lobe of the left lung, accompanied with bilateral mediastinal and left hilar lymphadenopathies and left pleural effusion. Tissue diagnosis of the lung tumor was adenocarcinoma of the lung.

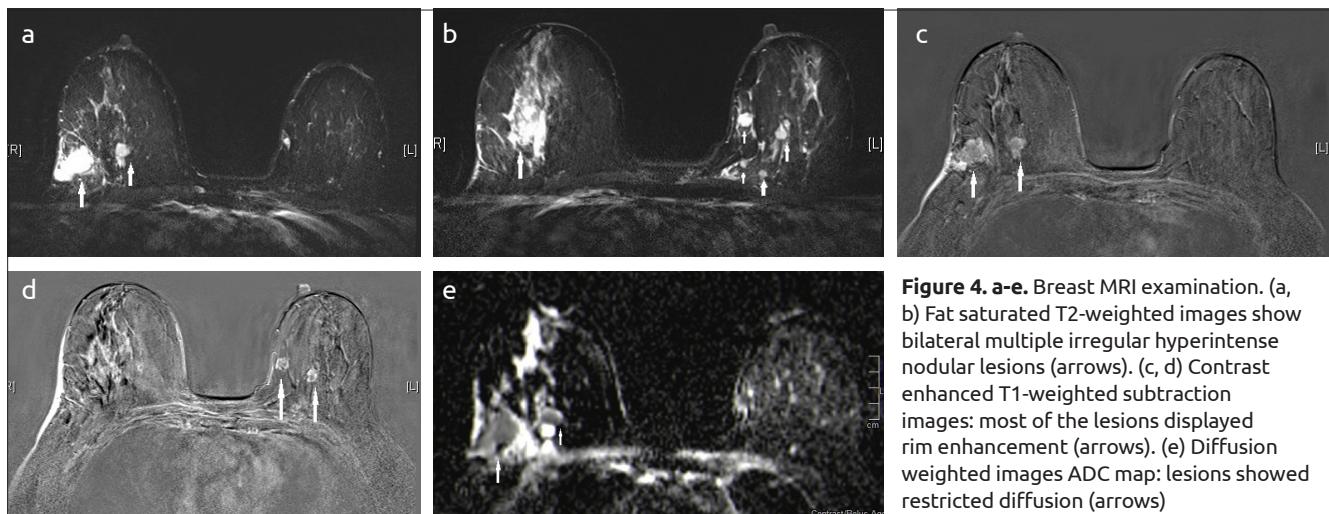


Figure 4. a-e. Breast MRI examination. (a, b) Fat saturated T2-weighted images show bilateral multiple irregular hyperintense nodular lesions (arrows). (c, d) Contrast enhanced T1-weighted subtraction images: most of the lesions displayed rim enhancement (arrows). (e) Diffusion weighted images ADC map: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

Pleural effusion demonstrated malignant cytology. Brain MRI revealed additional metastatic lesions in the brain and the left frontal bone. She received systemic chemotherapy and stereotactic radiotherapy for the brain lesion.

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 demonstrated skin thickening and trabecular thickening in the lower outer quadrant of the left breast (Fig 5a). 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). Primary inflammatory breast cancer was suspected. Ultrasound-guided core needle biopsy of the lesions was performed. 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 (ER) and progesterone receptor (PR) (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. The patient died 15 months after diagnosis of primary lung cancer, approximately 7 months after diagnosis of breast metastasis.

Case 3

Sixty-four years-old heavy smoker female patient who had smoked for forty years and suffered from dyspnea was diagnosed to have 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. Pathologic diagnosis was small cell lung cancer. Ten months after the diagnosis of the primary tumor, a PET scan was performed. Right adrenal metastasis, multiple intraabdominal lymphadenopathies and a hypermetabolic nodular lesion in the upper inner quadrant of the left breast were detected. Bilateral breast US examination was performed, which revealed a circumscribed hypoechoic round lesion, 8 mm in size at 9 o'clock position in the left breast (Figure 7a). It resembled a complicated cyst at first examination which showed 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). US-guided core needle biopsy demonstrated tumoral infiltration by small cell carcinoma (Figure 8). Immunohistochemical analysis showed tumor cells positive for Synaptophysin, Chromogranin, pan-cytokeratin and TTF-1. The tumor showed high Ki-67 (95%) proliferation index. The patient died 26 months after the diagnosis of lung cancer and 16 months after diagnosis of breast metastasis.

Discussion and Conclusion

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 disseminates to other organs but very rarely metastasizes to the breast. A few reviews about lung cancer metastasizing to the breast have been reported previously (3, 4, 10-13). Alva et al. (12) reported 78 cases in their literature review from 1855 to 1998. The most recent and largest review that was published in 2018 has reported 169 cases from 1999 to 2017 (13). We have found 180 cases of metastatic lung tumors to the breast in addition to the cases of Alva et al. (12) and made a summary of a total of 258 cases reported in the English language up till 2019. We could reach the histologic type of lung tumor in 111 cases. Nine of them were reported as non-small cell lung cancer. Among the rest 102 cases 61 adenocarcinomas, 14 neuroendocrine tumors, 12 small-cell carcinomas, 9 squamous cell carcinomas, 2 carcinoid tumors, one each of anaplastic carcinoma, large cell cancer, pleomorphic carcinoma, adenosquamous carcinoma were reported.

Metastatic tumors in the breast have a wide range of radiologic appearances. Some of them may mimic a probably benign lesion whereas some resemble primary breast carcinomas (3, 9). Lee et al. (14) have reported that in their series of 33 cases of breast metastases, only 2 were classified as BIRADS 3. The rest were 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 reported that around 75% of cases have irregular margins. Superficial location can be a clue, because primary cancers, which arise from the ductal or lobular tissue tend to be located deep in the parenchyma (1). Although superficially located, they do not cause skin or nipple retraction contrary to primary masses. Spiculation, posterior

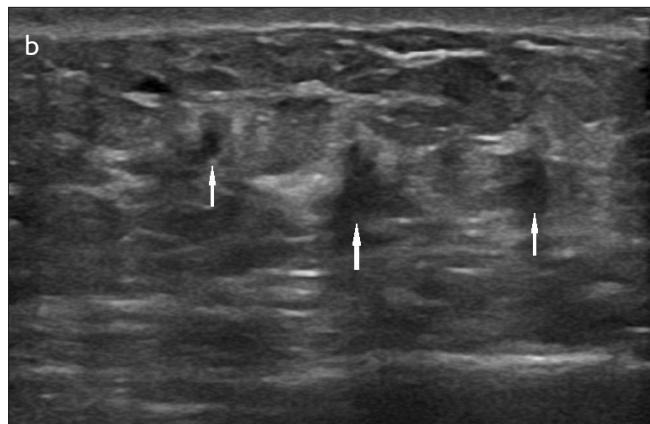
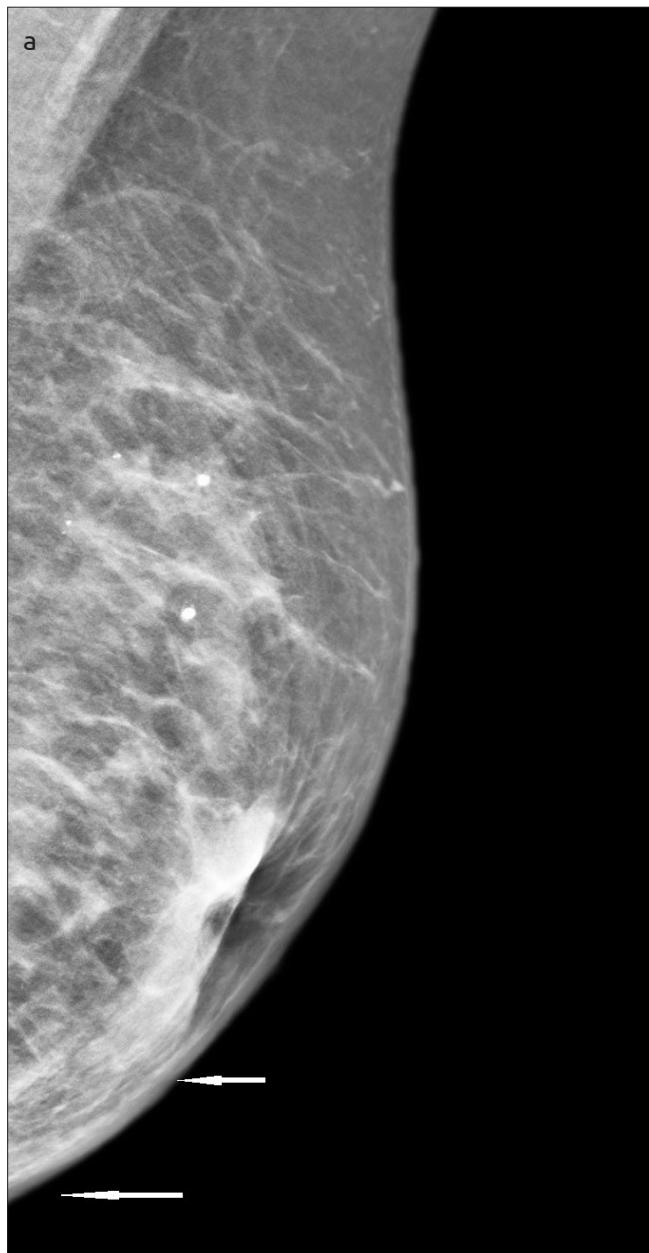


Figure 5. a, b. (a) Mammography (left mediolateral oblique view) demonstrates trabecular thickening and skin thickening (arrows) in the lower outer quadrant of the left breast. Retraction of both nipples are noted as incidental findings. (b) Ultrasound of the left breast: irregular, vertically oriented,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

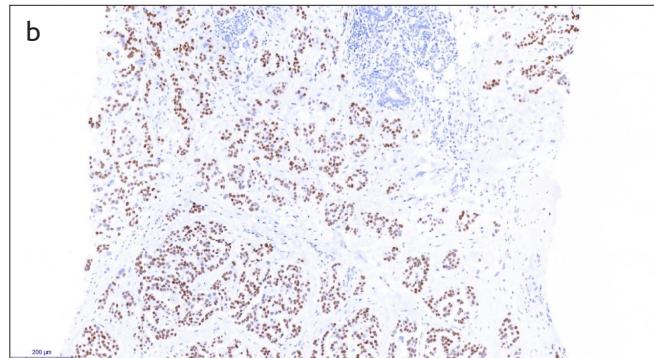
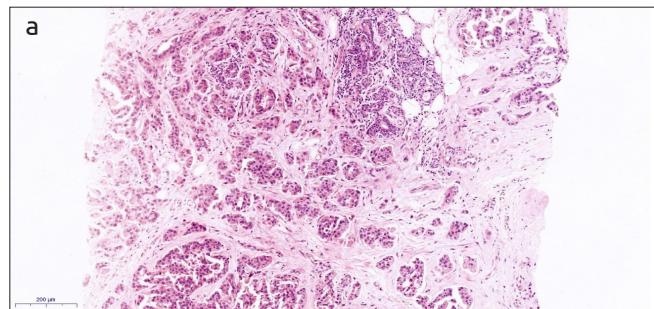


Figure 6. a, b. (a) Breast biopsy. Adenocarcinoma (H&E). (b) Tumor cells positive with TTF-1 immunostain

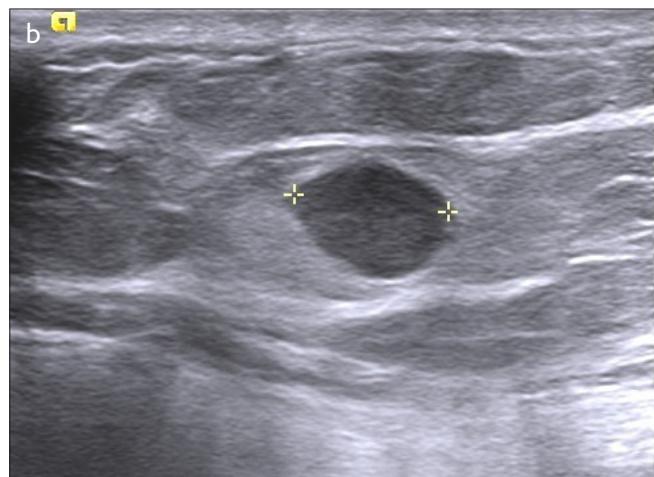
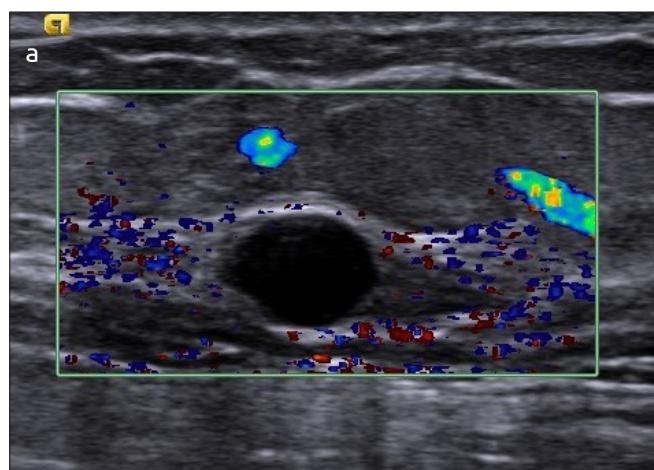


Figure 7. a, b. (a) Ultrasound of the left breast: Superficially located well defined cyst-like avascular round lesion. (b) Second US examination revealed the solid nature of the nodule and an echogenic halo

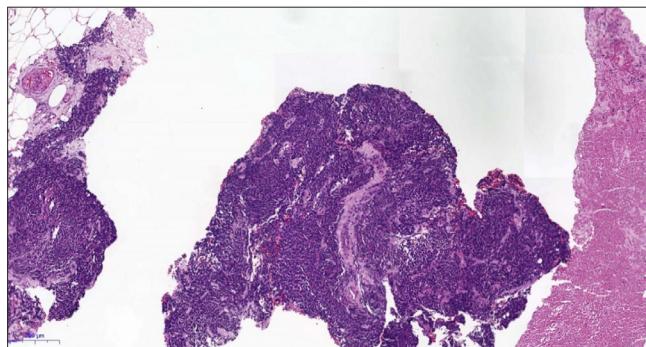


Figure 8. Breast biopsy. Small cell carcinoma with necrosis (H&E)

shadowing, and calcifications, which are commonly detected in primary breast cancers are very rare in secondary tumors (2, 3, 7, 16).

Calcifications have been reported in metastases from ovarian, gastric, thyroid and mucin-producing gastrointestinal cancers (14). Metastatic lesions tend to grow 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 are not common features of breast metastases. However, there was echogenic halo in two of our cases. Echogenic halo makes the differential diagnosis between benign and malignant lesions easier. In case number three, it was apparent only after window level was adjusted, which stresses the importance 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 detected more frequently in lymphoproliferative lesions as well as gastric, hepatocellular and ovarian cancers (17). Metastatic tumors may also present with a pseudocystic appearance at US due to high cellular proliferation. 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 careful before calling these lesions cysts, especially in patients with primary malignancies. Color Doppler US imaging may also be helpful in differentiation.

Reports on MRI findings of breast metastases are very few in literature. As in the first case, metastatic lesions mostly demonstrate rim enhancement, type III enhancement curve and restricted diffusion on breast MRI, demonstrating their malignant nature clearly (17). They can be hypo or hyperechoic on T2 weighted images depending on the presence of necrosis. Mun SH et al have also defined some atypical imaging features such as non-mass lesions and segmentally or ductally distributed micronodules in their series of breast metastases similar to the findings in our second case (9).

Clinical and radiologic findings of breast metastases may vary depending on the route of dissemination of the disease (4, 10, 16-18). Hematologically disseminated lesions tend to appear as single or multiple, round to oval-shaped, circumscribed or irregular masses commonly located superficially in subcutaneous tissue or immediately adjacent to the breast parenchyma that is relatively rich in blood supply (9, 16). Axilla is less commonly involved (9). Our first case represents a good example. There were multiple lesions located superficially in the subcutaneous fatty tissue and additional lesions deep in the parenchyma. Tumors which disseminate via lymphatic route, tend to manifest as skin thickening, subcutaneous edema and trabecular thickening due to tumor emboli in the subcutaneous lymphatic channels (2). There may or may not be an apparent mass (9, 17). Mammography usually shows an asymmetric

opacity and MRI may demonstrate non-mass enhancement and edema. Clinically peau d'orange and redness over the skin may be detected rarely. These cases can be falsely diagnosed as mastitis or inflammatory breast cancers (2, 4). Ovarian, gastric and lung cancers have been reported to lead to this type of breast metastases (4, 16, 19, 20). Huang et al. (11) have reported that in lung cancers which disseminate via the lymphatic route to the breast, pleural effusion, pleural thickening, and ipsilateral axillary lymphadenopathy precede the development of the breast lesion. They have suggested that breast is affected in a retrograde fashion after the involvement of axilla. In our second case, radiologic findings are probably consistent with this type of dissemination. In lung cancer patients with pleural effusion, axilla and the breast should be closely examined. Another way of dissemination of lung cancer to the breast can be through direct chest wall invasion but this is not a frequent finding.

There are no clear predisposing factors related to the occurrence of breast metastases. It has been postulated that estrogen may have a role as a predisposing factor in the development of metastasis by increasing the vascularity of the breast. This has been suggested as a reason 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 PET CT.

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

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