Original Article

Breast metastases from primary lung cancer: a retrospective case series on clinical, ultrasonographic, and immunohistochemical features

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Background: Lung cancer metastases to the breast are less common and consequently have received much less attention in clinical practice. The purpose of this study was to provide a better understanding of clinical, ultrasonographic, and immunohistochemical features of breast metastases from primary lung cancer.

Methods: This retrospective case series included patients with breast metastases from primary lung cancer between January 2012 and December 2020. Clinical features, ultrasonographic characteristics, and immunohistochemical findings were evaluated in this analysis.

Results: In all, 7 cases (mean ± standard deviation age: 57.4±8.3 years; range, 49–70 years) were evaluated. The maximum size of breast lesions in 6 cases ranged from 1.2 to 4.5 cm, while 1 case showed a diffused pattern. Ultrasound features of breast metastases from lung cancer were irregular (5/7, 71.4%), indistinct (6/7, 85.7%), hypoechoic (7/7, 100.0%), and parallel (6/7, 85.7%) masses without calcification. Immunohistochemical staining test was positive for thyroid transcription factor 1 (TTF-1) in all patients (7/7, 100.0%), 3 cases (3/5, 60.0%) were negative for p63, 5 cases (5/5, 100.0%) were positive for cytokeratin 7 (CK7), 4 cases (4/5, 80.0%) were positive for napsin A.

Conclusions: The ultrasonographic features of lung metastases to the breast are clinically important to understand. A known history of the primary lung cancer is of great importance when evaluating patients with a breast nodule. The presence of an ipsilateral lung cancer, breast nodule and axillary lymphadenopathy should be considered with pathological and immunohistochemical data to differentiate breast metastases from a primary breast malignancy in this setting.

Keywords: Breast metastases; lung cancer; ultrasonography; immunohistochemistry; case series

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Introduction

Lung cancer is one of the most prevalent cancers around the world, resulting in almost one-quarter of all cancer related deaths (1). Metastases of lung cancer to bone, liver, lung, and brain are frequently observed and has garnered significant interest as the identification of stage IV disease has treatment and prognostic significance (2). Lung cancer metastasis to the breast are less common and consequently have received much less attention in clinical practice (3). Although lung cancer metastasis to the breast can spread via hematogenous and lymphatic routes, classic teaching is that the breast is relatively spared given the relatively poor blood supply in the fibrous breast tissue (4). No specific risk factors related to the development of breast metastasis from lung cancer have been identified.

In patients with a known history of lung cancer, the discovery of breast nodules may result in underutilization of surgery and/or systemic therapy if mis-identification of stage IV disease occurs. There were several reports investigated clinical, or molecular characteristics of breast metastases from extramammary malignancies (5). However, they did not summarize the features of breast ultrasound (US). Breast US is widely utilized in such scenarios to assess the imaging characteristics concerning for malignancy. Although a few case reports have described US features suggestive of breast metastasis versus primary breast malignancy (6,7), breast metastasis from lung cancer still pose a significant diagnostic dilemma in clinical practice. In order to apply the appropriate therapy and avoid unnecessary treatment, there is a need to define specific US features of breast metastases from primary lung cancer. To the best of our knowledge, this is the first report that focus on breast metastases from primary lung cancer and correlate ultrasonographic features with histology to help guide clinical decision making. We present the following article in accordance with the AME Case Series reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-542).

Methods

Trial design

This study is a single-center retrospective case series on clinical, ultrasonographic, and immunohistochemical features of breast metastases from primary lung cancer. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital (No. S2020-354-01), and individual consent for this retrospective analysis was waived.

Patients

From January 2012 to December 2020, pathologically proven cases of primary lung cancer metastases to the breast were searched in Chinese People's Liberation Army General Hospital. All breast pathology was confirmed by biopsy. Patients were excluded if (I) they did not undergo breast and axillary lymph node (LN) US scans, or (II) if clinical, ultrasonography, pathological information was incomplete.

Ultrasonography

US images were obtained using a 5–12 MHz linear probe and a VISION Ascendus ultrasound system (Hitachi Aloka Medical, Tokyo, Japan), a Voluson E8 Exp (GE Medical Systems, Zipf, Austria), an Apolio 500 platform (Toshiba, Otawara, Japan), a MyLab Twice ultrasound system (Esaote, Genoa, Italia), an iU22 scanner (Philips Ultrasound, Bothell, WA, USA), and an Aixplorer ultrasound system (SuperSonic Imagine, Aix en Provence, France).

Two independent radiologists with more than 10 years' working experience in breast US retrospectively evaluated the sonography features of the lesions using the American College of Radiology breast imaging reporting and data system (ACR-BIRADS) 5th edition. Nodule features including location, multiplicity, size, shape, margin, orientation, echogenicity, calcification, blood flow signal of the lesions, and axillary LN status were recorded. In addition, associated features, including skin thickening, edema, and architectural distortion were also evaluated by ultrasonography. If two radiologists had different opinions, all disagreements were discussed to the point of consensus. If the patients presented with multiple breast nodules, the largest was evaluated.

Immunohistochemical staining

All samples were evaluated by a pathologist and based on morphology on HE-staining, panels of immunohistochemistry staining were selected as deemed suitable in each case. The data on immunohistochemical staining was also collected retrospectively. These indicators included thyroid transcription factor 1 (TTF-1), creatine kinase (CK), p63, cytokeratin 7 (CK7), napsin A, CK5, synaptophysin (Syn), estrogen receptor (ER), progesterone receptor (PR), human epithelial

Table 1 Clinical features

Patients No.	Age	Sex	Interval	Pathology	Location	Metastases	Symptom
1	70	Female	NA	Adenocarcinoma	Left	Spine, brain, muscle, breast	Palpable breast lesion, pain
2	52	Female	33 months	Adenocarcinoma	Left	Supraclavicular, cervical and axillary lymph nodes, Lung, spine, breast	Skin edema, palpable breast lesions
3	49	Female	29 months 17 days	Adenocarcinoma	Left	Axillary and mediastinal lymph nodes, breast	Skin edema, palpable breast lesions
4	53	Female	4 months	Small cell lung cancer	Right	Lung, brain, axillary and mediastinal lymph nodes, breast	No symptoms
5	53	Female	47 months 13 days	Adenocarcinoma	Right	Scapula, rib, brain, axillary lymph nodes, breast	Skin edema, palpable breast lesions
6	57	Male	NA	Adenocarcinoma	Right	Liver, mediastinal and axillary lymph nodes, breast	Palpable breast lesion
7	68	Female	38 months 14 days	Large cell lung cancer	Right	Cervical and retroperitoneal lymph nodes, brain, scapula, breast	Skin edema, palpable lesion

NA, not available.

receptor 2 (HER-2), Ki-67, and others.

Statistical analysis

Statistical analyses were performed with Microsoft Excel 2019 and IBM SPSS Statistics 21. The continuous data was presented as mean with standard deviation and range. The categorical data was presented as numbers with proportion (%). The interval of diagnosis of breast metastases was defined as the interval between the date of the detection of primary lung cancer and the date of detection of breast metastases.

Results

Clinical features

From January 2012 to December 2020, 13 pathologically proven cases of primary lung cancer metastases to the breast were identified in our institution. Six cases were excluded due to incomplete clinical or ultrasonographic information. In total, 6 females and 1 male (mean ± standard deviation age: 57.4±8.3 years; range, 49–70 years) were enrolled. The clinical features of 7 cases are shown in *Table 1*. In this study group, there were 5 cases of lung adenocarcinoma, 1 case with large cell lung cancer, and 1 case with small cell lung cancer. The primary lung cancer was found in the right lung in 4 (4/7, 57.1%) cases and on the left in 3 (3/7, 42.9%) cases. In 5 patients, breast metastases were identified between 4 and 47 months after a diagnosis of lung cancer. These 5 cases received at least one modality of therapy, including surgery, chemotherapy, radiotherapy, and/or immunotherapy. In the remaining 2 patients, breast metastases were discovered before the diagnosis of primary lung cancer. All 7 patients had other distant metastases aside from those in the breast, including the brain, spine, rib, scapula, and cervical LNs.

On physical exam, 4 cases (4/7, 57.1%) had breast manifestations of skin edema and a palpable lesion, 1 case (1/7, 14.3%) presented with a palpable breast lesion and pain, 1 case (1/7, 14.3%) presented with only a palpable lesion, and the remaining was asymptomatic. None of the 7 cases showed other clinical symptoms associated with breast malignancies, such as orange peel-like skin changes, nipple discharge, or nipple depression.

US features

The US features of the 7 included patients are shown in *Table 2*. All cases showed single-side breast metastases. Among the 7 cases, 6 (6/7, 85.7%) had ipsilateral breast

Table 2 Ultrasonography characteristics

Patients No.	Lesions number	Location	Size (cm)	Shape	Margin	Echogenicity	Internal echogenicity	Orientation	Posterior features	Microcalcification	vascularity	Axillary lymphadenopathy	BI-RADS	Associated secondary signs
1	Single	Left	2.3	Irregular	Indistinct	Hypoechoic	Heterogeneous	Not parallel	Enhancement	No	Absent	No	4C	No
2	Multiple	Left	4.2	Irregular	Indistinct	Hypoechoic	Heterogeneous	Parallel	Enhancement	No	Present	Both side	4C	Edema, skin thickening
3	Multiple	Left	2.7	Irregular	Indistinct	Hypoechoic	Heterogeneous	Parallel	No	No	Present	Left side	4C	Skin thickening
4	Single	Right	1.2	Oval	Indistinct	Hypoechoic	Homogeneous	Parallel	No	No	Absent	Right side	4A	No
5	Diffused	Right	NA	Irregular	Indistinct	Hypoechoic	Heterogeneous	Parallel	Shadowing	No	Absent	Right side	5	Skin thickening
6	Single	Left	4.5	Irregular	Indistinct	Hypoechoic	Heterogeneous	Parallel	Enhancement	No	Absent	Left side	4B	Skin thickening
7	Multiple	Right	1.5	Oval	Circumscribed	Hypoechoic	Homogeneous	Parallel	No	No	Absent	Right side	3	Edema, skin thickening

NA, not available.

metastases, 1 (1/7, 14.3%) case had contralateral breast metastasis, 3 (3/7, 42.9%) cases showed single breast lesions, while the other 4 (4/7, 57.1%) cases had multiple or diffused lesions. Metastatic lesions were found on the right breast in 3 (3/7, 42.9%) cases and on the left breast in 4 (4/7, 57.1%) cases. Additionally, in 5 (5/7, 71.4%) cases, metastases concurrently were found in axillary LN's on the same side, bilateral axillary LN's in 1 (1/7, 14.3%) case, and in 1 (1/7, 14.3%) case presented with no axillary lymphadenopathy was identified.

In our study, the maximum size of breast lesions in 6 cases ranged from 1.2 to 4.5 cm, and 1 case with a diffused breast lesion was identified (*Figure 1*). The shape of breast metastases in 5 (5/7, 71.4%) cases was irregular, with the other 2 (2/7, 28.6%) cases having an oval shape (*Figure 2*). The margin of metastases in 6 (6/7, 85.7%) cases was indistinct, while in the remaining case the margin was noted to be well circumscribed. The lesions were hypoechoic in all cases (7/7, 100.0%) and had heterogeneous internal echogenicity in 5 (5/7, 71.4%) cases, while homogeneous internal echogenicity was found in 2 (28.6%) cases. The lesion orientation of 6 (6/7, 85.7%) cases was parallel (wider than tall), 3 (3/7, 42.9%) cases showed enhancement posterior feature (*Figure 3*), and 1 (1/7, 14.3%) case had a feature of posterior acoustic shadowing. Microcalcification was not observed in any patient. Color Doppler US detected blood flow in 2 (2/7, 28.6%) cases. Associated secondary signs, including edema and skin thickening, were found in 5 (5/7, 71.4%) cases. The final BI-RADS assessment categories were BI-RADS 3 in 1 (1/7, 14.3%) case, BI-RADS 4A in 1 (1/7, 14.3%) case, BI-RADS 4B in 1 (1/7, 14.3%) case, BI-RADS 4C in 3 (3/7, 42.9%) cases, BI-RADS 5 in 1 (1/7, 14.3%) case.

Immunohistochemical features

Immunohistochemical staining test results from 7 cases were collected. All 7 (7/7, 100.0%) cases were TTF-1 positive; 5 cases underwent p63 staining, among which 2 (2/5, 40.0%) cases were p63 partially positive and 3 (3/5, 60.0%) were p63 negative; 5 cases received CK7 and napsin A staining, among which 5 (5/5, 100.0%) cases were CK7 positive, 4 (4/5, 80.0%) were napsin A positive (*Figure 4*). Other staining indicators are shown in *Table 3*.

Discussion

Lung cancer metastasis to the breast is an extremely rare

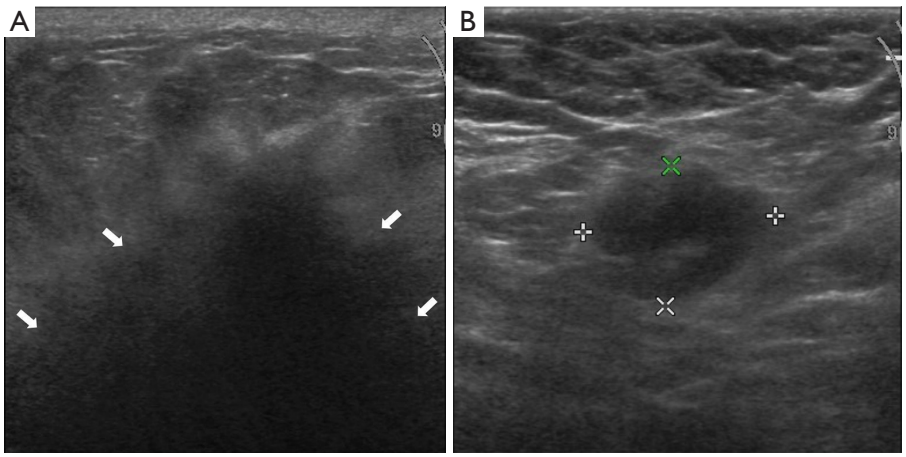

Figure 1 Ultrasonography for breast metastases from primary lung cancer. Patient No. 5: a 53-year-old female with adenocarcinoma of right lung. Ultrasonography shows a diffused irregular indistinct and heterogeneous hypoechoic mass in the right breast with the long axis parallel to the skin, shadowing posterior features (white arrow) (A), and ipsilateral axillary lymph adenopathy (cross symbol) (B).

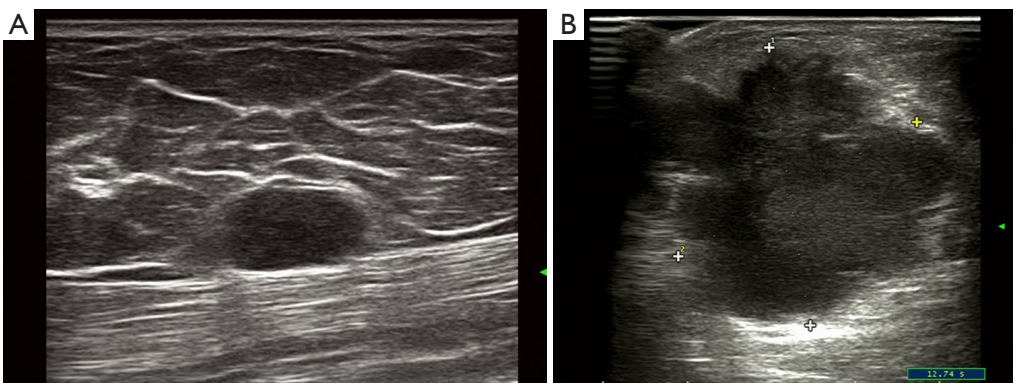

Figure 2 Ultrasonography for breast metastases from primary lung cancer. Patient No. 4: a 53-year-old female with small cell lung cancer of right lung. Ultrasonography shows an oval indistinct and homogeneous hypoechoic mass in the right breast with the long axis parallel to the skin (A), and ipsilateral axillary lymph adenopathy (cross symbol) (B).

clinical presentation with an incidence of just 0.2–1.3% (8). On the contrary, 21–32% of breast cancer patients with distant metastases have lesions in the lung (9). In lung cancer cases where a concurrent breast nodule is identified, one should include metastatic lung cancer within the differential. However, some patients may present with a breast nodule as the first clinical manifestation of metastatic lung cancer, confusing the clinical workup of these patients. Under these circumstances, comprehensive understanding both pathologic features associated with lung cancer metastasis and ultrasonography features of nodules that are metastatic to the breast is particularly important.

Selection of appropriate therapy depends on accurate diagnosis of the breast lesions, and is significant for the effective management and life quality of the patients. Patients with primary breast cancer and breast metastasis from lung cancer have different therapy sections and clinical consequences. It has been documented that patients with late-stage lung cancer have a very poor prognosis, while patients with primary breast cancer present with relatively good prognosis (1,10). In clinical practice, it is very challenging to distinguish breast metastasis from primary breast cancer, as metastatic cancer can mimic malignant breast lesions or even benign lesions. The symptoms of orange peel-like skin changes, nipple discharge, or depression are uncommon in breast metastasis (11). In

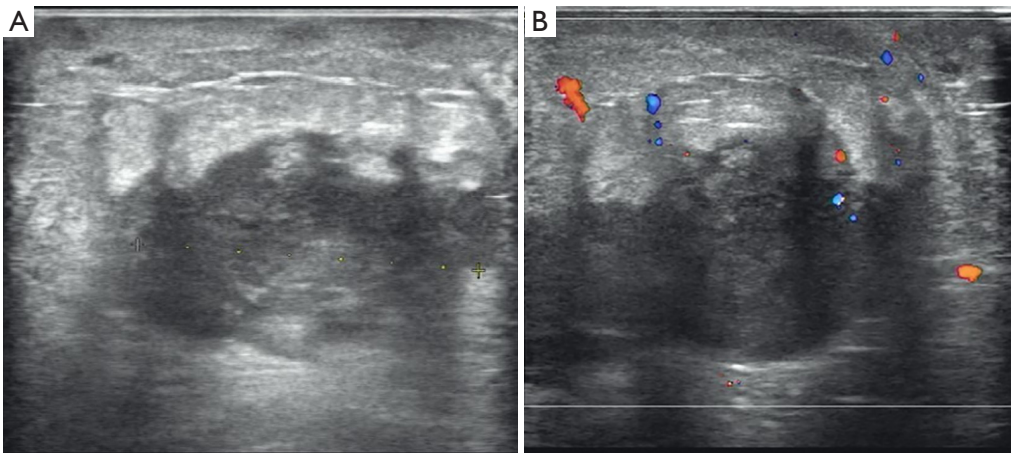

Figure 3 Ultrasonography for breast metastases from primary lung cancer. Patient No. 2: a 52-year-old female with adenocarcinoma of left lung. (A) Ultrasonography shows an irregular indistinct and heterogeneous hypoechoic mass in the left breast with the long axis parallel to the skin, enhancement posterior features (cross symbol); (B) color Doppler flowing imaging shows blood flow signals inside the mass.

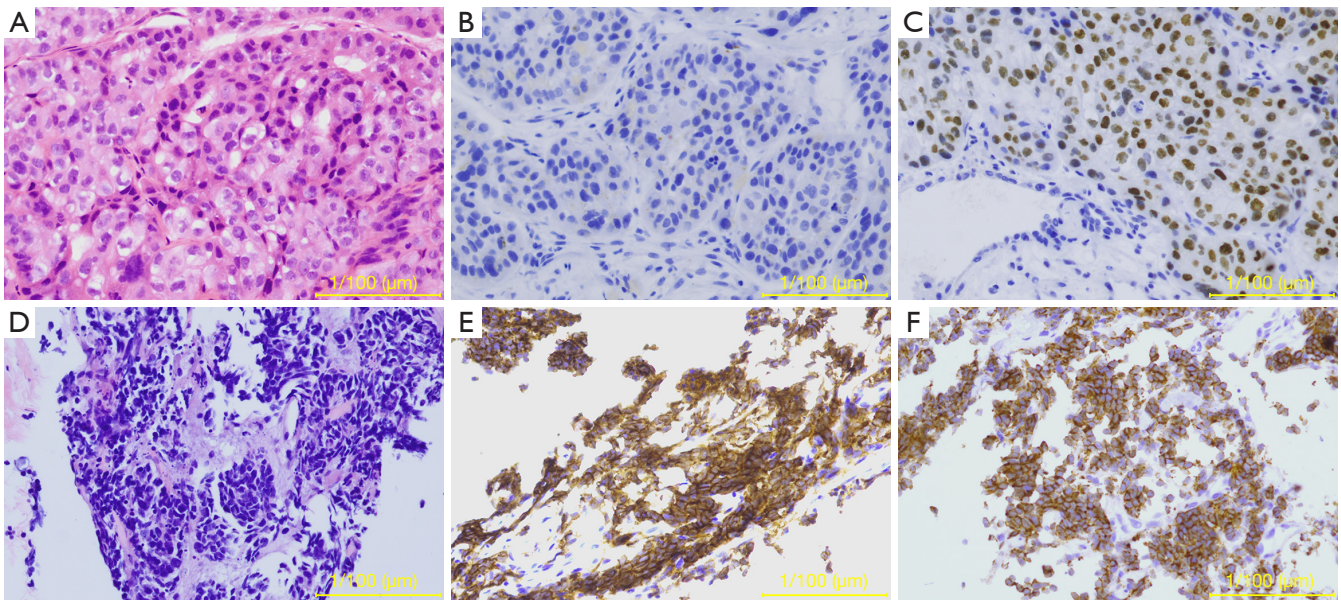

Figure 4 Histological features of breast metastases from primary lung cancer. Patient No. 1: metastasis from lung adenocarcinoma (A, H&E 200×), napsin A (B, immunostain 200×) and thyroid transcription factor 1 (C, immunostain 200×); Patient No. 4: metastasis from small cell lung cancer (D, H&E 200×), synaptophysin (E, Immunostain 200×) and cluster of differentiation 56 (F, immunostain 200×). The scale bar is 100 μm for A-F.

our study, the most common symptoms were skin edema and painless breast lesions. Edema of the skin may be due to the rapid growth of metastatic cancer, which could be misdiagnosed as inflammatory breast carcinoma (12).

Both single and multiple lesions of unilateral breast were found in our study. The ipsilateral breast metastasis from lung cancer was more prevalent than contralateral metastasis in this study. One study has reported metastasis to bilateral breasts (13). In addition, most of the patients in our study had ipsilateral axillary lymphadenopathy. This is similar to other studies, which report cases of lung cancer with ipsilateral breast metastasis (14-16); metastasis to the contralateral

Table 3 Immunohistochemistry staining

Patient No.	TTF-1	p63	CK7	Napsin A	Others
1	Positive	Partially positive	Positive	Negative	CK5(–), Syn(–), PR(–), ER(–), HER-2(2+), Ki-67(+60%), GCDFP-15(–), GATA-3(–), CgA(–), CD56(–)
2	Positive	Partially positive	Positive	Positive	CK5(–), CK(+), CD68(–)
3	Positive	NA	Positive	Positive	CK20(–), Ki-67(+20–30%), EGFR(+), P53(+), ALK(+), D2-40(–), Calretinin(–/+)
4	Positive	Negative	NA	NA	CK(weakly +), Syn(+), CgA(–), CD56(+), LCA(–), Ki-67(+70%)
5	Positive	Negative	Positive	Positive	CK5(–), CK20(–), CEA(+), CR(–), CK6(–)
6	Positive	NA	Positive	Positive	CD56(–), GPC-3(–), GCDFP-15(–), Syn(–), CgA(–), PR(–), ER(–), HER-2(focally+), Ki-67(+15%), GATA-3(–)
7	Positive	Negative	NA	NA	CK(+), Syn(+), PR(–), ER(–), HER-2(2+), CD30(–)

NA, not available; TTF, thyroid transcription factor; CK, creatin-kinase; Syn, synaptophysin; CD, cluster of differentiation; ER, estrogen receptor; PR, progesterone receptor; HER, human epithelial receptor: GCDFP, gross cystic disease fluid protein; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; LCA, leucocyte common antigen; GPC, glypican.

breast has also been previously reported (3), but this finding is less common than ipsilateral metastasis. Indeed, only 1 patient in our study had contralateral breast metastasis. Similarly, in Huang *et al.*'s (17) review of 19 patients with primary lung adenocarcinoma, 3 had contralateral breast metastases, while the remaining 16 patients had ipsilateral metastases. The mechanism of primary lung cancer metastasis to the ipsilateral breast is still unclear. The lymphatic drainage of the mediastinal LNs through the intercostal or supraclavicular lymph vessels may lead to ipsilateral axillary LN metastasis and breast metastasis (18). Another possibility is lymphatic drainage from the chest wall, which may be involved by the lung cancer cells either via direct extension or seeding by a malignant pleural effusion or the parietal pleura (17). The findings of enlarged ipsilateral axillary LNs may represent evidence for these mechanisms. Thus, an ipsilateral lung cancer, breast lesion and axillary lymphadenopathy should raise one's suspicion of a metastatic lung cancer process. A hematogenous route is also another possible way by which extramammary malignancies metastasize to the breast, and may explain why metastasis can also occur in the contralateral breast. Although stage IV lung cancer to the breast is rare, clinicians should carefully examine the axillary LN and breast when evaluating patients with primary lung cancer.

The common US features of primary breast cancer are irregular, not parallel, indistinct, irregular, hypoechoic, homogeneous masses with microcalcification and posterior acoustic shadowing (19). The common US features of breast metastases from lung cancer are nodules that are irregular, indistinct, hypoechoic, and parallel masses without calcification. The maximum size of breast metastases from lung adenocarcinoma was larger than that of large cell and small cell lung cancer. In addition, internal echogenicity was homogeneous in patients with large cell and small cell lung cancer, while it was heterogenous in patients with adenocarcinoma. Most lesions were parallel to the skin. Posterior acoustic enhancement was also observed in our study. This is different from the US feature of primary breast cancer, where posterior acoustic shadowing is most typical (20). However, we still observed 1 patient with a diffused breast metastasis featuring posterior acoustic shadowing, which, to our knowledge, is the first report of these features in breast metastases. Calcification, which is rarely observed in metastasis to the breast, may be helpful in distinguishing stage IV disease from a primary breast cancer. Only 1 prior study has reported a case of calcifications in lung cancer metastatic to the breast (13). Color blood flow signal was detected in 2 patients, which is different from the abundant vascularity of primary breast carcinoma (21). Sippo *et al.* (20) and Moreno-Astudillo *et al.* (22) reported that the US manifestation of other cancer metastases to the breast were round or oval hypoechoic lesions, which could be diagnosed as benign nodules. This study also observed a case of metastatic small cell lung cancer to the breast, which demonstrated an oval shape and indistinct margin, and homogeneous internal echogenicity. In contrast, Luh *et al.* (23) reported 2 small lung cancer masses with a distinct

margin and heterogeneous internal echogenicity.

All lesions in this study could be easily identified in US imaging. However, Mun *et al.* (4) also reported a case of breast metastasis from lung cancer manifesting as non-mass-like lesion with segmental and ductal distribution of multiple small hypoechoic masses and axillary LN enlargement, which could be easily confused with ductal carcinoma *in situ* or papillary lesions. However, only 1 study has thus far reported non-mass-like breast metastatic lesions from lung cancer in US.

As mentioned above, the differentiation between primary cancer and breast metastases from lung cancer poses a diagnostic dilemma. Immunohistochemical staining is essential in patients with breast nodules. In general, no single marker can reach 100% specificity or sensitivity, so confirmation through a set of antibodies is essential (24). Choosing a panel for immunohistochemical staining depends on the pathologist assessment of morphology and knowledge of clinical features including earlier malignancy. Some of the antibodies chosen is used to broadly guide when differentiate origin of tumor cells, e.g., CK7 and CK20 can be used to differentiate between origin from lower gastrointestinal tract from, e.g., lung and breast, but not to differentiate between lung and breast (8). Others are chosen to confirm more specific organs and a commonly used panel for lung tumors include TTF-1 and napsin A. TTF-1 is a common marker for the identification of the origin of metastatic mass from lung cancer (25). It is expressed in 70% to 80% of small cell carcinomas and lung adenocarcinomas, and is rarely expressed in other types of lung cancer (26). Napsin A, which is positive in 80–90% of lung adenocarcinomas, is typically reported to be negative in breast cancer (27,28), napsin A is an alternative biomarker for the diagnosis of lung adenocarcinoma. The combination of TTF-1 and napsin A can provide maximum benefit in clinical practice. In the cases presented in this study, differentiation between origin of tumor in either lung or breast is crucial and common markers for breast cancer include PR, ER, HER-2 and GATA-3. PR, ER and HER-2 are usually negative in breast metastases from lung cancer (29). It is reported that HER-2 mutations are identified in about 2% of NSCLCs and 2% to 6% of lung adenocarcinomas (30,31). In this study, we also identified that 2 cases with primary lung adenocarcinoma had positive HER-2 staining, and 1 case with large cell lung cancer had focally positive HER-2 staining. In our study, 2 of 5 cases had a partially positive p63 staining, while the other 3 cases were p63 negative. According to the study of Provenzano *et al.* (32), 97% of lung squamous cell carcinomas show a high expression level of p63, while only 7% of lung adenocarcinomas show a high expression level of p63. Thus, p63 is a helpful indicator to distinguish between squamous cell carcinoma and adenocarcinoma (33,34). p63 positive has been reported to be present in 94–100% of squamous cell carcinomas with diffused staining in most cases, while 9–32% of lung adenocarcinomas tend to show focal staining (32). Moreover, focal p63-positive staining can be seen in about 22% of triple-negative breast cancer cases (35-37). As most breast metastases are from lung adenocarcinoma, p63 may be of limited use in the differentiation of primary and secondary breast cancer. Therefore, in cases with atypical clinical and US features, or in cases without a known primary cancer history, a group of markers is recommended to provide optimal diagnostic accuracy.

This retrospective case series summarized the features of breast metastases from lung cancer by reviewing cases in our center. There are, however, a few limitations to this study. First, the sample size was small and all from one single institution. Second, we did not include elastography or contrast-enhanced US in this study. Thus, we will endeavor to further investigate these issues in future study using cases from multiple centers and a greater variety of techniques. Additionally, this study was not powered to statistically define associations between imaging or pathologic features with risk for metastatic lung cancer, such that these results are more consistent with observations rather than direct correlations.

Conclusions

Form this observational, retrospective case series, we analyzed the clinical, ultrasonographic, and immunohistochemical features of breast metastases from lung cancer. We conclude that the common US features of breast metastases from lung cancer are nodules that are irregular, indistinct, hypoechoic, and parallel masses without calcification. We believe that these features can help guide clinical decision-making including staging and treatment options. A known history of the primary lung cancer is also of great importance when evaluating a patient with breast nodules suspicious for primary versus metastatic disease. The presence of an ipsilateral lung cancer, breast lesion and axillary lymphadenopathy should prompt the clinician to including metastatic lung cancer within the differential diagnosis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital (No. S2020-354-01), and individual consent for this retrospective analysis was waived.

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