



# Metastatic adenocarcinoma to the breast from the lung simulates primary breast carcinoma – a clinicopathologic study

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**Background:** Rare extra-mammary metastases of adenocarcinoma to the breast closely mimic primary invasive breast carcinoma (PBC), and specifically without an aware of clinical history, pose a difficult diagnostic issue.

**Methods:** With the aim to improve differential diagnosis of lung adenocarcinoma metastasis and primary breast carcinoma in the breast, we retrieved 41 breast metastases from lung adenocarcinoma, seven of which were from the archived pathologic files of Cancer Hospital, Chinese Academy of Medical Science (CHCAMS) between 2001 and 2019, and the other 34 cases were collected from the published literatures. Clinicopathological features were collected and analyzed for differential diagnosis of primary lung malignancy, triple negative breast pathology and breast lesions without ipsilateral axillary lymphadenopathy or with contralateral axillary lymphadenopathy. Supplementary breast (GCDFP-15, or GATA-3) and lung-lineage (TTF-1) immunostaining plus genetic alternation analysis were also recorded and analyzed.

**Results:** Among the 41 cases, there were 37 females and four males, with a median age of 63 (range, 40–81) years at diagnosis of the breast lesion. Twenty-four cases (58.5%, 24/41) were detected metachronously to the counterpart of the lung. Strikingly, 13 cases (31.7%, 13/41) were initially misdiagnosed as primary breast cancer, and differential diagnostic factors were compared and analyzed between the correct and misdiagnosed cases, among which a documentation of lung cancer history showed significant difference. Pathologist initially misinterpreted six cases (46.2%, 6/13) as PBC on needle biopsy of breast mass with an unknown lung cancer history. The clinical diagnosis was considered two cases (15.4%, 2/13) to be either a primary breast tumor with lung and pleural metastasis or two synchronous primary tumors. Three cases (23.1%, 3/13) were initially misinterpreted as PBC by breast ultrasonography. TTF-1 immunostaining was found to be critical for a correct diagnosis of metastatic lesion (84.6%, 11/13) from the initially misdiagnosed cases as PBC.

**Conclusions:** Metastatic lung adenocarcinoma to the breast, although rare, should be considered in the differential diagnosis of primary breast carcinoma, especially when the breast lesion exhibits as a “triple-negative invasive carcinoma”. A documented lung cancer history combined with the clinicoradiological assessment and pathological evaluation are essential to make a correct differential diagnosis. TTF-1 immunostaining is crucial in approaching the diagnosis.

**Keywords:** Lung adenocarcinoma; breast metastases; breast carcinoma/secondary; differential diagnosis

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## Introduction

Primary advanced adenocarcinoma of the lung is prone to distant metastasis, with the most common metastatic organs being lung, liver, adrenal gland, brain, bone etc. (1). According to sporadic case reports, the breast was reported as a metastatic site for primary lung adenocarcinomas and the incidence of breast metastases from an extramammary primary tumor can be as low as 0.5–3.0% (2–7). Because of its rarity, even with known history of lung cancer, breast metastases would have been easily misdiagnosed as primary breast cancer and thus leads to unnecessary mastectomies (6,8,9). Due to the distinct biological mechanisms, advanced lung adenocarcinoma and breast cancer are treated with different therapies, such as *EGFR* tyrosine kinase inhibitors (TKIs) for lung cancer, and estrogen receptor (ER), progesterone receptor (PR) related endocrine treatment or human epidermal growth factor receptor 2 (HER-2) related target therapy for breast cancer. Therefore, for patients with lung cancer history who have synchronous or heterochronous breast nodules, it is necessary to fully identify whether it is a metastatic lesion or a secondary primary breast tumor.

The main reason for misdiagnosis lies in the fact that breast metastasis of lung adenocarcinoma shares similar cellular morphology as primary invasive ductal carcinoma of breast, especially in samples from fine needle biopsies.

In this study, we aim to improve the differential diagnosis criteria of primary breast nodules and breast nodules metastasized from lung adenocarcinoma by retrieving and analyzing 41 cases of metastatic adenocarcinoma from the lung to breast. We made a comparative analysis from the perspective of the accuracy of the first diagnosis in order to explore which factors affect the accuracy of pathological diagnosis. A documented lung cancer history combined with the clinicoradiological assessment and pathological evaluation are essential to make a correct differential diagnosis. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-2250>).

## Methods

Metastatic cases of lung adenocarcinoma to the breast were retrieved both from Department of Pathology in Cancer Hospital, Chinese Academy of Medical Science (CHCAMS) and published literatures from 2001 to 2019. Computerized literature searches were performed using PubMed databases. MeSH terms and free words were all used. The search

terms were as follows: “breast cancer”, “lung cancer”, “lung carcinoma”, “adenocarcinoma”, “metastasis”, “lung cancer/primary”, “breast cancer/secondary”, “metastasis to the breast” and “extramammary primary”. We also screened the reference lists of all relevant articles for potentially suitable studies. In this way, we collected seven archived cases from CHCAMS and 34 counterparts from literatures, respectively. The clinicopathological related features were collected and recorded, including gender, age at diagnosis of the breast lesions, possible prior history of a lung primary before the breast disease, solitary or multicentric masses, lymphadenopathy region, concomitant metastases to other organs than breasts, etc. Specially, the archived pathology reports and slides of the selected cases from CHCAMS were reviewed by two pathologists (XW and LY) to confirm the diagnosis and clarify the pathological features for differential diagnosis. Immunohistochemical markers were also collected and analyzed in which lineage-specific stains for lung carcinoma [thyroid transcription factor-1, TTF-1 (SP141, Roche Diagnostics, China)] and those for the breast [gross cystic disease fluid protein, GCDFFP-15 (23A3, Maixin, China) or transcription factor, GATA-3 (EP368, Zhongshan, China)] as well as ER (SP1, Roche Diagnostics, China), PR (1E2, Roche Diagnostics, China) and HER-2 (4B5, Roche Diagnostics, China). Genetic alternation status (*EGFR* mutation, *ALK* gene rearrangement, etc.), if available, was also collected. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital (NCC-004409) and individual consent for this retrospective analysis was waived.

## Statistical analysis

The Chi-square test was performed to clarify the various significances of the above factors among initial misdiagnosis cases or no misdiagnosis cases.  $P < 0.05$  was considered as a statistically significant result.

## Results

### *Clinicopathological features of lung adenocarcinomas to the breast, retrieved from CHCAMS and literatures*

In totally, we collected 41 cases of metastatic lung adenocarcinomas to the breast, seven of which were from the archived files of the Department of Pathology in CHCAMS; the other 34 cases were from 21 published

case reports or mini-review between 1992 and 2019. The clinicopathological features for all 41 cases were listed in *Table 1*. Among the 41 cases, there are 37 females and 4 males, with a median age of 63 (range, 40–81) years at diagnosis of the breast lesion. Twenty-four cases (58.5%, 24/41) were metachronous to the primary lung tumors, while 17 (41.5%, 17/41) were detected synchronously. Thirty-one (75.6%, 31/41) cases were detected as a solitary metastatic nodule, and ten (24.4%, 10/41) were detected multifocal nodules including three with bilateral breast involvement. Tumor border on radiographical examination was recorded in *Table 1*, among which 31 cases (75.6%, 31/41) showed an irregular border, while ten cases (24.4%, 10/41) showed a regular border. Twenty of the 41 cases were documented with a previous treatment for primary lung cancer, 17 cases of which received systemic chemotherapy and/or radiation, compared with three instances of

segmental mastectomy. Forty (97.6%, 40/41) patients had lymph node involvement at the time of diagnosis, in which 28 patients had axillary lymph node metastasis, eight with bilateral axillary lymph nodes involvement, and 24 with hilar/mediastinal lymph node involvement. Twenty-four (58.5%, 24/41) patients showed distant metastases to other organs at the time of the breast mass detection. The metastasized organs were bone (n=13), liver (n=6), pleura (n=5), brain (n=5), adrenal gland (n=4), subcutaneous (n=4), pancreas (n=2), and choroid plexus (n=1).

***Clinicopathological features of initial diagnosis retrieved from CHCAMS and literatures***

Thirteen cases (31.7%, 13/41) were initially misdiagnosed as primary breast cancer. The clinical diagnosis was considered cases of No. 37 and 39 (15.4%, 2/13) in *Table 1*

**Table 1** Clinicopathological features of lung adenocarcinomas to the breast, retrieved from CHCAMS and literatures (n=41)

Source	No.	Age/gender	M/S	Time	Breast mass	Misinterpreted	Border of breast mass	Treatment/outcome
CHCAMS	1	40/F	S	0	Solitary	No	Irregular	Navelbine and cisplatin
	2	68/F	S	0	Solitary	No	Irregular	Docetaxel and cisplatin
	3	56/F	Me	8 m	Solitary	No	Irregular	Gemcitabine
	4	63/F	S	0	Solitary	No	Irregular	Pemetrexed and cisplatin
	5	62/F	Me	18 m	Multiple	No	Diffuse	Gemcitabine and cisplatin
	6	46/F	Me	3 m	Solitary	No	Irregular	Paclitaxel and cisplatin
	7	66/F	Me	32 m	Solitary	Yes <sup>§</sup>	Irregular	Partial mastectomy and etoposide + cisplatin
Verger <i>et al.</i> , 1992 (10)	8	63/M	Me	18 m	Solitary	No	Irregular	NR
Yeh <i>et al.</i> , 2004 (11)	9	44/F	Me	NR	Solitary	No	Irregular	NR
Rimner <i>et al.</i> , 2007 (12)	10	81/F	Me	7 m	Multiple	No	Irregular	Palliative radiation
Ucar <i>et al.</i> , 2007 (13)	11	63/M	Me	NR	Solitary	No	Irregular	NR
Klingen <i>et al.</i> , 2009 (14)	12	79/F	Me	1 m	Solitary	No	Diffuse	Dead
	13	70/M	Me	24 m	Solitary	No	Well-defined	Dead
Yoon <i>et al.</i> , 2010 (15)	14	42/F	Me	36 m	Multiple	No	Well-circumscribed	Gemcitabine and cisplatin
Fukumoto <i>et al.</i> , 2011 (8)	15	65/F	Me	72 m	Solitary	Yes*	Irregular	Partial mastectomy
Nasit Jitendra <i>et al.</i> , 2011 (16)	16	42/F	Me	18 m	Bilateral/multiple	No	Diffuse	Dead
Branica <i>et al.</i> , 2012 (17)	17	55/F	S	0	Multiple	No	Well-defined	NR
Ko <i>et al.</i> , 2012 (18)	18	47/F	Me	3 m	Solitary	Yes*	Irregular	Erlotinib

**Table 1** (continued)

Table 1 (continued)

Source	No.	Age/gender	M/S	Time	Breast mass	Misinterpreted	Border of breast mass	Treatment/outcome
Sato <i>et al.</i> , 2012 (19)	19	57/F	Me	12 m	Solitary	No	Irregular	CBDCA + pemetrexed + bevacizumab
Mirrielees <i>et al.</i> , 2014 (20)	20	58/F	Me	36 m	Solitary	Yes <sup>#</sup>	Irregular	Erlotinib
Ali <i>et al.</i> , 2018 (9)	21	64/F	Me	36 m	Solitary	Yes <sup>§</sup>	Circumscribed	NR
	22	59/F	Me	NR	Solitary	No	Irregular	NR
	23	45/F	Me	NR	Solitary	No	Irregular	NR
	24	70/F	Me	NR	Solitary	Yes <sup>*</sup>	Circumscribed	Partial mastectomy
	25	69/F	Me	NR	Solitary	Yes <sup>§</sup>	Infiltrative	NR
	26	64/F	Me	NR	Solitary	No	Irregular	NR
	27	70/F	S	0	Multiple	Yes <sup>§</sup>	Circumscribed	NR
	28	72/F	S	0	Solitary	No	Infiltrative	NR
	29	63/F	S	0	Bilateral/two	Yes <sup>§</sup>	Infiltrative	NR
	30	65/F	S	0	Solitary	No	Circumscribed	NR
31	65/F	S	0	Solitary	Yes <sup>§</sup>	Irregular	NR	
Sadikot <i>et al.</i> , 1997 (21)	32	47/F	S	0	Multiple	No	Well-circumscribed	Dead
Babu <i>et al.</i> , 2009 (6)	33	51/F	S	0	Solitary	Yes <sup>§</sup>	Irregular	Wide local excision and axillary node clearance
Maounis <i>et al.</i> , 2010 (22)	34	73/F	S	0	Solitary	No	Irregular	Bevacizumab, cisplatin and docetaxel
Ji <i>et al.</i> , 2012 (23)	35	49/F	S	0	Solitary	No	Well-defined	Dead
	36	40/F	S	0	Solitary	No	Irregular	Gefitinib
Sanguinetti <i>et al.</i> , 2013 (24)	37	43/F	S	0	Solitary	Yes <sup>**</sup>	Irregular	Bevacizumab, cisplatin and docetaxel
Malek <i>et al.</i> , 2019 (25)	38	80/F	Me	36 m	Solitary	No	Irregular	NR
Wu <i>et al.</i> , 2019 (26)	39	49/F	S	0	Multiple	Yes <sup>**</sup>	Well-defined	Crizotinib
	40	63/F	Me	15 m	Bilateral/multiple	No	Irregular	Crizotinib
Erhamamci <i>et al.</i> , 2016 (27)	41	74/M	S	0	Solitary	No	Irregular	Dead

<sup>§</sup>, Pathologist initially misinterpreted as PBC on needle biopsy of breast mass with an unknown lung cancer history, until the patient came back with a supplementation of a 32 months' lung cancer history. Later on, TTF-1 immunostaining was applied and the diagnosis was corrected to be a metastatic one. <sup>\*</sup>, Initially misinterpreted as PBC by breast ultrasonography. Case 24 had a solitary circumscribed 2-cm mass in the right breast that appeared benign on ultrasound and mammography with the differential diagnosis of a cyst vs. fibroadenoma. <sup>\*\*</sup>, The clinical diagnosis was considered to be either a primary breast tumor with lung and pleural metastasis or two synchronous primary tumors. <sup>§</sup>, This patient had a left breast mass with contralateral enlarged axillary lymph nodes and mediastinal lymphadenopathy. Nine years earlier, she had a history of right mastectomy for ductal carcinoma. This case was referred to the cancer agency and TTF-1 was later found to be positive. <sup>#</sup>, This patient's family history was significant for a sister diagnosed with breast cancer in her forties and her mother's diagnosis of breast cancer in her sixties. Later, a repeat pathologic evaluation of the slides from the patient's breast biopsy was requested. Immunolabeling for TTF-1 demonstrated the tissue to be more consistent with a metastatic lung adenocarcinoma. M, male; F, female; Me, metachronous; S, synchronous; Time, interval time; Misinterpreted, initially misinterpreted as PBC; NR, not retrievable; PBC, primary invasive breast carcinoma.

**Table 2** Clinicopathological features of initial diagnosis retrieved from CHCAMS and literatures (n=41)

Features	Misdiagnosis* (n=13), n (%)	No misdiagnosis (n=28), n (%)	$\chi^2$	P
Source			1.183	0.277
CHCAMS	1 (7.7)	6 (21.4)		
Literature	12 (92.3)	22 (78.6)		
Known tumor history			15.138	<0.001
Yes	7 (53.8)	28 (100.0)		
No	6 (46.2)	0 (0.0)		
Time interval			0.173	0.678
Synchronous	6 (46.2)	11 (39.3)		
Metachronous	7 (53.8)	17 (60.7)		
Lesion foci			0.018	0.894
Solitary	10 (76.9)	21 (75.0)		
Multiple	3 (23.1)	7 (25.0)		
Specimen type			1.086	0.297
Biopsy	10 (76.9)	25 (89.3)		
Mastectomy	3 (23.1)	3 (10.7)		
Ipsilateral axillary <sup>#</sup>			2.342	0.126
Yes	11 (84.6)	17 (60.7)		
No	2 (15.4)	11 (39.3)		
Distant <sup>**</sup>			0.777	0.378
Yes	8 (61.5)	21 (75.0)		
No	5 (38.5)	7 (25.0)		

\*, Initially misdiagnosed as primary breast carcinoma. <sup>#</sup>, Ipsilateral axillary lymphadenopathy to the breast mass. <sup>\*\*</sup>, Distant lymphadenopathy (including contralateral axillary).

to be either a primary breast tumor with lung and pleural metastasis or two synchronous primary tumors. In *Table 1* cases of No. 15, 18 and 24 (23.1%, 3/13) were initially misinterpreted as primary invasive breast carcinoma (PBC) by breast ultrasonography. Cases of No. 25 in *Table 1* had a left breast mass with contralateral enlarged axillary lymph nodes and mediastinal lymphadenopathy. Nine years earlier, she had a history of right mastectomy for ductal carcinoma. This case was referred to the cancer agency and TTF-1 was later found to be positive. The other patient's family history which was cases of No. 20 in *Table 1* was significant for a sister diagnosed with breast cancer in her forties and her mother's diagnosis of breast cancer in her sixties. Later, a repeat pathologic evaluation of the slides from the patient's breast biopsy was requested. Immunolabeling for TTF-1 demonstrated the tissue to be more consistent with a metastatic lung

adenocarcinoma. Pathologist initially misinterpreted cases of No. 7, 21, 27, 29, 31 and 39 (46.2%, 6/13) in *Table 1* as PBC on needle biopsy of breast mass with an unknown lung cancer history, until the patient came back with a supplementation of lung cancer history. Later on, TTF-1 immunostaining was applied and the diagnosis was corrected to be a metastatic one. A comparative analysis was made in *Table 2* to clarify the associated clinicopathological features with respect to misdiagnosis. A history of lung cancer showed significant difference between initial correct diagnosis and misdiagnosis (28/28, 100% vs. 7/13, 53.8%;  $P < 0.001$ ) (*Table 2*).

#### ***Immunohistochemistry (IHC) of initial diagnosis retrieved from CHCAMS and literatures***

Available IHC staining for differential diagnosis were

**Table 3** IHC of initial diagnosis retrieved from CHCAMS and literatures (n=41)

IHC markers	Misdiagnosis* (n=13), n (%)	No misdiagnosis (n=28), n (%)
ER (+)	0	0
PR (+)	0	0
HER-2 (+)	0	0
Mammaglobin, GCDFP-15, GATA-3 (+)	0	0
TTF-1 (+)	11 (84.6) <sup>#</sup>	27 (96.4)

\*, Initially misdiagnosed as PBC. #, TTF-1 was found to be positive after the 11 cases of 13 cases were initially misdiagnosed as PBC. The other two cases of 13 cases initially misdiagnosed as PBC (cases of No. 21 and 31) were found to be negative for TTF-1 which compounded the problem. In view of the known lung cancer history that preceded the development of a breast mass, widespread disease, and negative breast markers and hormone receptors, the breast tumor was considered a TTF-1 negative metastatic adenocarcinoma of lung. ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; TTF-1, thyroid transcription factor-1; GCDFP-15, gross cystic disease fluid protein; GATA-3, transcription factor; PBC, primary invasive breast carcinoma.

shown in *Table 3*. No positive staining of ER, PR, HER-2, mammaglobin, GCDFP-15, or GATA-3 was found in all confirmed metastatic cases. The positive rate of TTF-1 in initially correct diagnosis cases was 96.4% (27/28). Besides, TTF-1 was found later to be positive in 11 cases of the 13 initially misdiagnosed as PBC (11/13, 84.6%) and thus helped correcting the initial misdiagnosis. Cases of No. 21, 26 and 31 were considered a TTF1-negative metastatic adenocarcinoma of the lung in view of the known lung cancer history that preceded the development of a breast mass, widespread disease, and negative breast markers and hormone receptors. There were nine cases with reported genetic detections, including two p.L858R in *EGFR* exon 21, four *EGFR* exon 19 deletion, two with *ALK* rearrangement, and one with *ROS1* rearrangement.

## Discussion

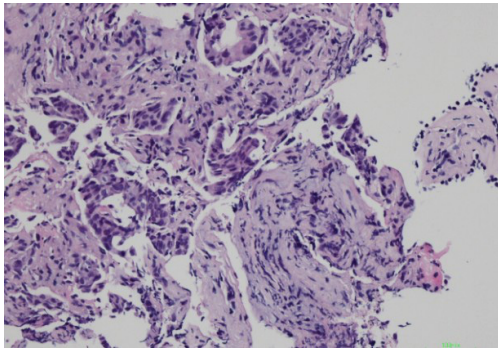
In female patients, lung adenocarcinoma and breast carcinoma are two most common types of malignancies. They share similar organs of distant metastasis, including bone, liver and the brain. Unlike the lung, the breast rarely raises concern as a metastatic site. Rarity of breast

involvement by metastatic tumors is reported due to large areas of fibrous tissue, relatively poor blood supply and anatomically non-connected locations (5).

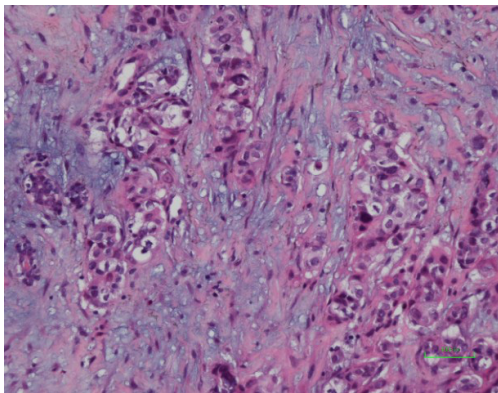
Unlike lung squamous cell carcinoma or small cell lung cancer, pulmonary adenocarcinoma metastasis to the breast is more difficult to be distinguished from primary breast cancer due to the similar morphological features they shared. Moreover, the inadequate sample size from the commonly applied fine needle biopsy may lead to lack of specific histological images such as comedo necrosis in breast carcinoma. Thus, there is a big challenge in differential diagnosis.

Since the imaging manifestations or clinical symptoms of the metastatic lesion are heterogenous between patients, it is hard to make a correct diagnosis from these aspects other than a pathological one (28,29). This was exemplified by cases of No. 15, 18 and 24, which were initially misinterpreted as PBC by breast ultrasonography. Furthermore, case No. 24 had a solitary circumscribed mass with a diameter of 2.0 cm in the right breast that appeared benign on ultrasound and mammography, favoring of a clinical diagnosis of a cyst or fibro adenoma. Besides, case No. 37 and 39 were initially misinterpreted to be primary breast tumor from the clinical perspective. Therefore, the final of differential diagnosis should be decided by the pathologists with additional documentation on lung cancer history provided by responsible physicians.

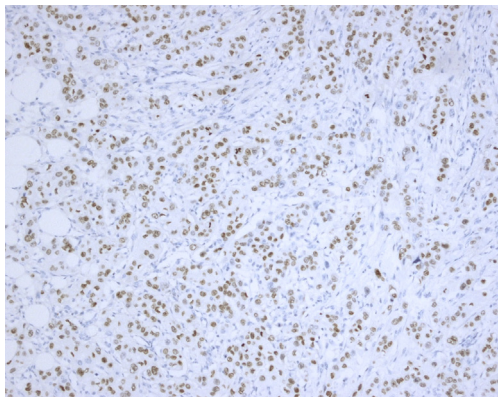
Histologically, some indicators may help to identify the metastatic adenocarcinomas and PBCs. First, elastosis is a consistent indicator of primary neoplasm but is rarely observed in secondary tumors (3). Other studies described a sharp transition at the border of the lesion and the tumor presence in the subcutaneous, rather than parenchymal breast tissue (30,31). Also noted in our series, metastatic tumors to the breast frequently showed irregular tumor borders and commonly present as a solitary (rather than multicentric) breast mass. The absence of *in situ* carcinoma strongly supports a metastatic tumor, although it may not occur in all primary invasive carcinomas (22,32). Most researchers agree that calcifications and micro-calcifications except for ovarian serous carcinoma are extremely rare and observed only in the patients with metastatic papillary carcinoma with psammoma bodies (32-34). However, for samples from fine needle aspiration, a correct differential diagnosis is more challenging, especially for those patients without a documented history of lung cancer (33-35). The authors experienced one such case (No. 7 in *Table 1*), which was a needle biopsy



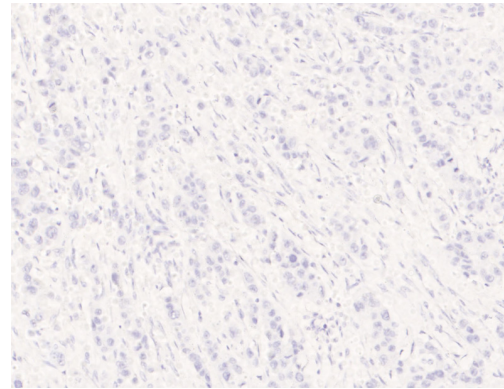
**Figure 1** Lung biopsy of case 7 (H-E,  $\times 20$ ). Primary lung adenocarcinoma is indicated by red arrow, as compared with the normal alveolar epithelium (seen in black arrow).



**Figure 2** Breast biopsy of case 7. (H-E,  $\times 20$ ). The red arrow indicates adenocarcinoma. The black arrow indicates normal mammary duct.



**Figure 3** Breast segmental resection of case 7. Nuclear positivity for TTF-1 (IHC,  $\times 20$ ). IHC, immunohistochemistry.



**Figure 4** Breast segmental resection of case 7. Negativity for GCDFP-15 (IHC,  $\times 20$ ). IHC, immunohistochemistry.

sample from a solitary mass in a 66-year-female patient (representative images of ultrasonography of case 7 seen in [Figure S1](#)). Microscopically, this patient exhibited a poorly differentiated adenocarcinoma, with scattered irregular adeno ducts in mammary parenchymal, which featured a diagnosis of primary breast cancer (seen in [Figure 1](#)). However, the patient subsequently came to consult the pathologist and provided a history of lung adenocarcinoma for 3 years and presented the original pulmonary biopsy for consultation (seen in [Figure 2](#)). Subsequently, this patient was corrected to a final diagnosis of metastatic lung adenocarcinoma to the breast by immunostaining of TTF-1 (seen in [Figure 3](#)). In this scenario, the documentation of a lung cancer history would have great importance for alerting the pathologist to exclude metastatic lesions.

All of the 13 misdiagnosed cases from the enrolled 41 cases in this study were analyzed and compared in [Table 2](#). It was found that history of prior non-mammary malignancy was of paramount importance in this context to be aware of by both clinicians and pathologists. Similarly, DeLair *et al.* (31) also demonstrated that the failure of recognizing the metastatic nature of the lesion by pathologist is mostly due to the absence of a prior cancer history provided by the clinician at the time of initial interpretation. The diagnostic issue becomes more prominent once a primary lung carcinoma hides behind the breast lesion. This was exemplified by case No. 7, 21, 27, 29, 31 and 33. Even though a history of primary lung tumor was known, immunohistochemical staining was considered essential for differential diagnosis. Namely, a panel of markers were essential, including ER/GCDFP-15 (seen in [Figure 4](#)), or GATA-3 for breast carcinoma (36-39), and TTF-1, NapsinA

for lung adenocarcinoma, as no single immunostaining is entirely specific to this situation (40). TTF-1, a tissue-specific transcription factor expressed in lung and thyroid epithelial cells, is expressed in approximately 72.5% (for clone SPT24) of pulmonary adenocarcinomas (41). Breast carcinoma rarely positively expresses TTF-1 (42-44), which is reported highly specific for lung adenocarcinoma, although not 100% sensitive (76-81%) (45). Napsin-A, an aspartic proteinase, has been reported as a surrogate marker for TTF-1 in some cases (46). However, monoclonal Napsin-A strong immunoreactivity was demonstrated in 14.6% of cases of breast carcinomas with apocrine changes only (47). Thus, sole immunostaining of Napsin-A recommended for explanation of a breast metastatic lesion from the lung. In our study, three cases (3/41, 73.2%) showed TTF1-negative staining, which were diagnosed as metastatic lesion based on clinical information, such as a known lung cancer history, widespread disease situation, and negative breast markers and hormone receptors. ER, is a signature of luminal type of breast carcinoma, with a reported highly positive rate up to 80% (48). Although lung adenocarcinomas were also reported stained with as a wide range of ER positivity depending on different staining protocols (41,49,50), combined breast-specific markers (GCDFP-15, or GATA-3) would be helpful to confirm the breast origin of the specimen. None of our cases expressed GCDFP-15, or GATA-3 in keeping with the non-mammary origin. However, the triple negative entities for breast carcinoma (ER, PR negative and HER-2 negative) were reported a lower positive percentage of breast lineage markers (Mammaglobin 17-18%, GCDFP-15 10-33%, GATA-3 43-66%) (41,42,51,52), which also renders a diagnostic pitfall. On the other hand, GATA-3, the most sensitive immunostaining markers for breast origin, was also reported positive staining in 8-12% of lung adenocarcinomas (53). So, a combined panel of both breast- and lung-origin would be superior to a single biomarker for making a correct differential diagnosis.

In addition to morphological and IHC methods, genetic alterations for lung adenocarcinoma may also play a role in difficult differential diagnosis. In advanced lung adenocarcinoma, *EGFR* mutation, *ALK* rearrangement, *ROS1* fusion were routinely tested in diagnostic settings, and it is reported that these molecular subtypes are highly consistent in the primary and metastatic lesions. Thus, the detection of these molecules from the biopsy samples of suspected breast metastases and the comparison with the primary lung lesions will support the diagnosis of

metastatic cancer (26). This was exemplified by cases No. 5, 7, 39 and 40.

In conclusion, we retrospectively reviewed a relatively large sample of metastatic adenocarcinoma from the lung to the breast, and analyzed the diagnostic dilemma. The pathogenesis of lung cancer metastasis to breast has not been reported. It is difficult to distinguish a metastatic breast mass only based on macroscopy, mammography, ultrasonography, or CT scan. Pathological examination remains gold standard for differentiation diagnosis. Also noted in our cohort, breast lesions with contralateral or no ipsilateral axillary lymphadenopathy, triple negative breast pathology, and *de novo* metastatic breast cancers resistant or refractory to conventional primary breast carcinoma therapeutics may add metastatic consideration to the differential diagnosis list. A documented history of lung cancer or a thorough detection of lung is essential for making a correct diagnosis. Additional breast- and lung-lineage immunostaining plus genetic alternation analysis may confirm the diagnosis and guide precise treatment.

#### ***Compliance with ethical standards***

All individuals listed as authors have contributed to the conception and design of the work, data acquisition, analysis, and interpretation of data. All authors had input in drafting the work and revising it critically for important intellectual content as well as approved the final version herein.

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#### **Footnote**

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-2250>). The authors have no conflicts of interest to declare.

*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 board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital (NCC-004409) and individual consent for this retrospective analysis was waived.

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Supplementary

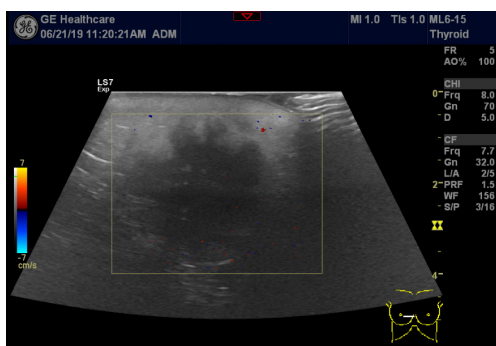


Figure S1 Representative images of ultrasonography for PBC of case 7. PBC, primary invasive breast carcinoma.