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Original Article

Breast metastasis from lung cancer: report of two cases of adenocarcinoma with different gene mutation and one case of squamous cell carcinoma

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Abstract: Breast metastasis from extra-mammary malignancy is not common. According to the literature, an incidence of 0.4-1.3% has been reported. We present three cases of metastasis to the breast from two pulmonary adenocarcinoma and one lung squamous carcinoma diagnosed concomitantly or metachronous with the primary tumor. Two pulmonary adenocarcinomas (a 43-year-old female and a 45-year old female) presented with cough and a massive was found on a chest radiograph. One lung squamous carcinoma of a 75-year old male with no clinical symptom and a massive was found on a chest radiograph accidental. Additionally, on physical examination a poorly defined mass was noted in right breast of the three patients. The patient underwent bronchoscopy, excisional breast biopsy and medical thoracoscopy. By cytology, histology and immunohistochemistry primary lung cancer with metastasis to the breast was diagnosed. From our results, we speculate that lung cancer metastasis to the right side of the breast is more than the left side and the mutations should be detected of the breast adenocarcinoma from lung. Both the primary and metastatic anatomic sites demonstrated histologically extensive solid component of the two pulmonary adenocarcinoma patients.

Keywords: Lung cancer, breast, metastasis, ALK, ROS1, EGFR

Introduction

Accurate differentiation of metastatic from primary carcinoma is very important because the treatment and prognosis differ significantly. Although primary breast cancer is the most common malignancy of adult females, metastatic involvement of the breast is rare with a reported incidence of 0.4-1.3% according the literature [1], in addition, the most common primary tumors are melanomas and hematological malignancies [2, 3]. Despite lung cancer is the most malignant cancer worldwide and often metastasizes to the brain, bone, liver, adrenal gland, and contralateral lung [4], breast metastases from non-small cell lung carcinoma are extremely rare. There have only been a few published cases of pulmonary carcinomas metastasizing to the breast [5-8]. We report two cases of female patient with lung adenocarcinoma and one case of male patient with squamous-cell carcinoma metastatic to the breast were described. To our knowledge, this is the first time to report cases of breast metastasis from lung adenocarcinoma with one anaplastic lymphoma kinase (ALK)-rearrangement and another with the c-ros oncogene 1 (ROS1)-rearrangement. As far, there was no previous case reporting squamous cell carcinoma of the lung metastasis in male breast could be found in the literature. Our case reports highlight the usefulness of gene mutation detection for diagnosis and targeted treatment.

Materials and methods

Cases

All cases were sent in consultation to pathology specialists. Clinical and radiologic data of patients were collected from pathologic reports,

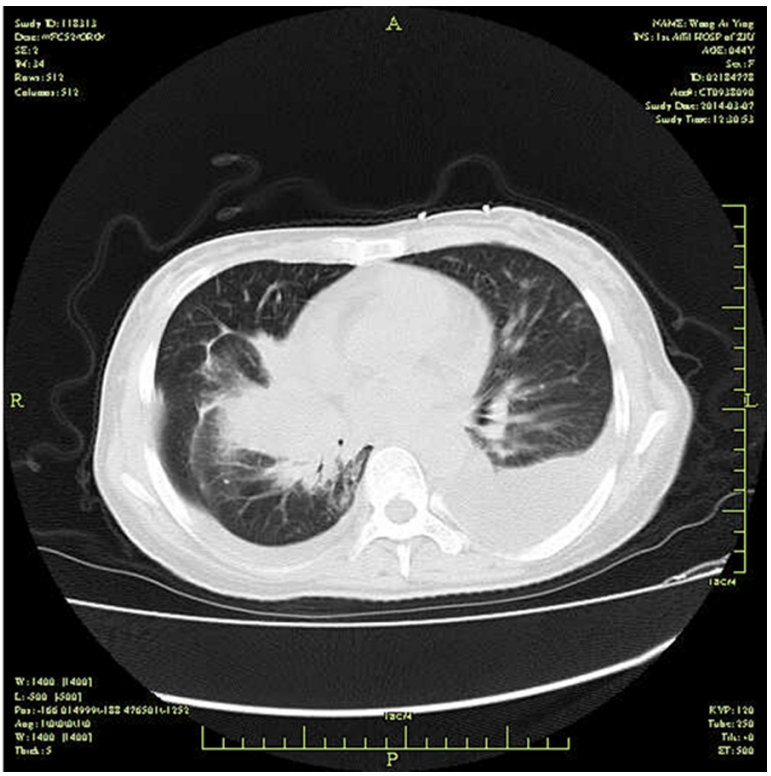

Figure 1. Computed tomography (CT) scan of thorax showed tumor (5 cm × 4 cm) in the hilus of her right lung.

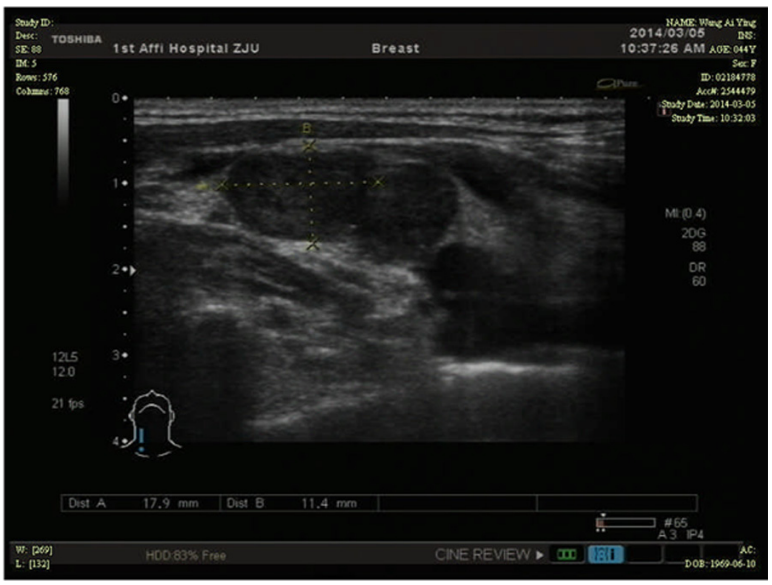

Figure 2. Breast ultrasonography showed a mass (1.8 cm × 1.1 cm) in the right breast.

clinical charts, referring physicians, or directly from the patient's families. In each case, hematoxylin and eosin-stained slides and paraffin tissue blocks were available for immunohistochemistry, PCR and FISH as described below.

Immunohistochemistry

The standard streptavidin biotin immunoperoxidase method was performed for immunostaining with TTF-1 (ZM-0270, Leica, 1:500), napsin-A (ZM-0473, Invitrogen, 1:200), CK7 (M-0332, LabVion, 1:100), G15 (M-0278, LabVion, 1:100), mammaglobin (ZM-0388, Invitrogen, 1:80), human epidermal growth factor receptor 2 (Her-2, 4B5, Roche, 1:1000), estrogen receptor (ER, M0241, LabVion, 1:200)) and progesterone receptor (PR, M-0448, LabVion, 1:200), CK5/6 (M-0745, LabVion, 1:200), and p63 (M-0654, LabVion, 1:300) and GATA-3 (ZM-0498, Invitrogen, 1:300) antibodies. Immunohistochemical labeling concluded ALK (D5F3, Roche,) and Ros1 (D4D6, Roche, 1:80) were also performed on the Benchmark XT autostainer (Ventana Medical Systems Inc, Tucson, AZ) using the I-View detection kit. Positive and negative controls were included in each test. A tumor was considered positive if more than 10% of the neoplastic cells reacted, with a moderate (2+) or strong (3+) intensity, in the relevant subcellular localization.

Molecular analysis

We examined epidermal growth factor receptor (EGFR) mutations in exons 18 to 21 and ROS1 rearrangement using a PCR-based pyrosequencing assay. Sequence analysis was performed using the PyroMark ID system

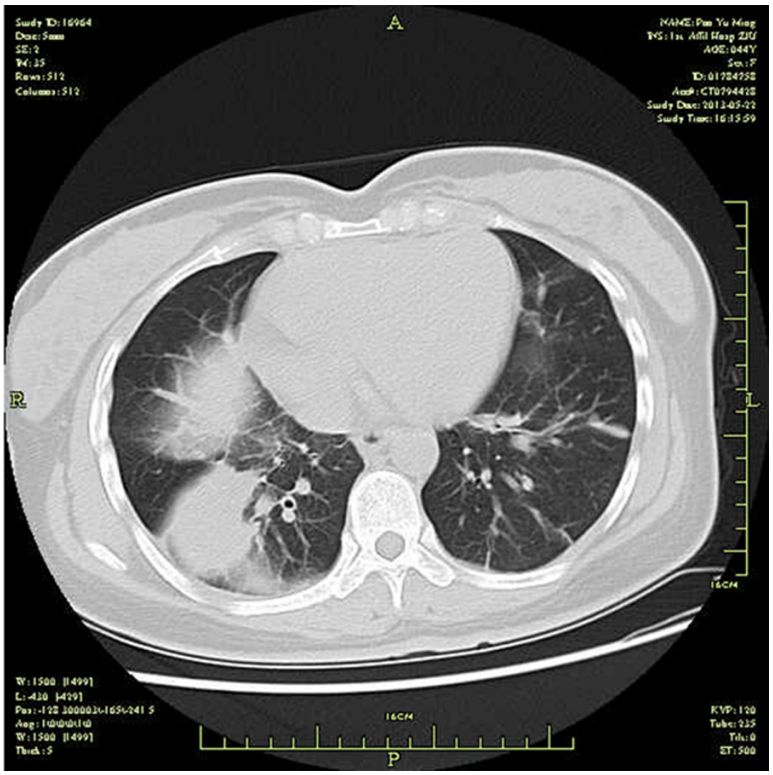

Figure 3. Chest CT showed a poorly defined mass (4.8 cm × 3.9 cm) in the lower lobe of her right lung.

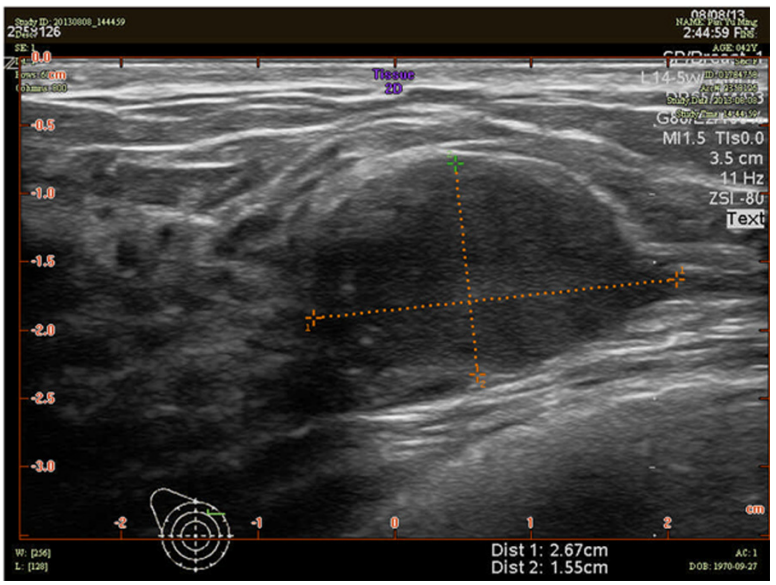

Figure 4. Breast US reveal ed a mass (2.7 cm × 1.6 cm) in the lower outer quadrant of the right breast.

(Qiagen, Hilden, Germany). Each case was identified as positive or negative by comparison with the wild-type sequence. EML4-ALK rearrangements were examined by FISH with a break-apart ALK probe (Vysis LSI Dual Color, Break Apart Rearrangement Probe; Abbott Molecular, Abbott Park, IL, USA). EML4-ALK rearrangements were classified as positive if greater than 15% of the tumor cells displayed split signals or isolated signals containing a kinase domain.

Results

Case histories

Case 1: A 45-year-old, non-smoking housewife presented to the general surgery clinic complaining a painless mass in her right breast for 3 weeks and a cough of 5 months' duration. Physical examination revealed a painless, well defined mass between the upper inner and lower inner quadrant of the right breast. Palpable right Clavicle lymph nodes were also noted. Chest computed tomography (CT) (**Figure 1**) showed a poorly defined mass (5 cm × 4 cm) in the hilus of her right lung. A few lymph nodes were identified in the mediastinum and a number of paratracheal lymph nodes were also observed. MRI revealed a metastasis to the lumbar vertebrae. Breast ultrasound revealed a mass in the right breast (**Figure 2**). The bronchoscopy brush and alveolar lavage fluid found the non-cell carcinoma cell. The right breast biopsy was performed, and the following pathology analysis revealed poorly differentiated adenocarcinoma. At first, patients received pemetrexed and cisplatin. No significant improvement in symptoms was found, and the disease progress was found after 1-month. It was chosen to further treat the patient with crizotinib and received radiation

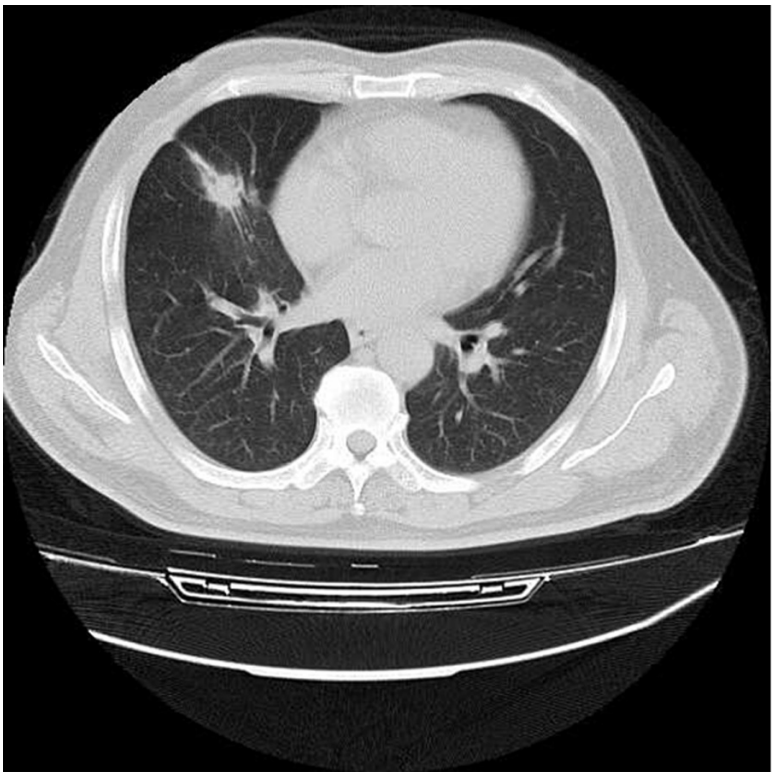

Figure 5. Chest CT scan showed a poorly defined mass (1.8 cm × 1.6 cm) in the middle lobe of his right lung.

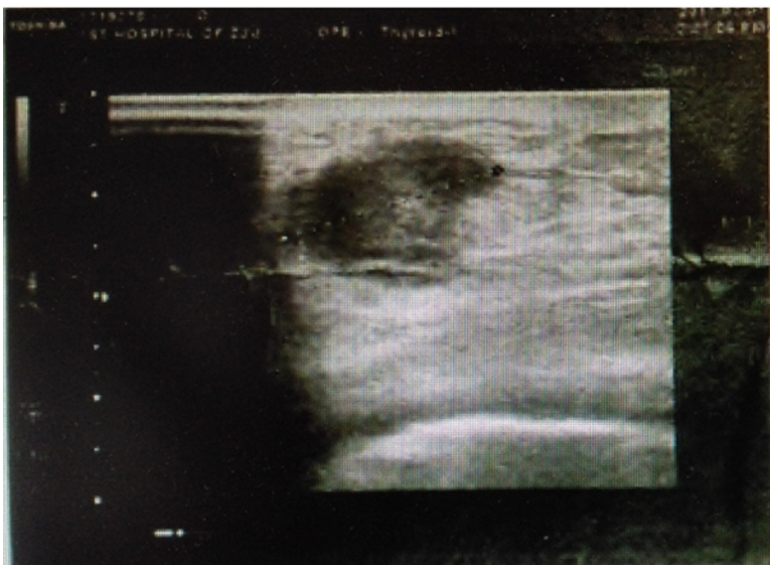

Figure 6. Breast ultrasound revealed a poorly defined mass (1.8 cm × 2.2 cm) in the lower outer quadrant of the right breast without skin involvement and a number of axillary lymph nodes were also observed.

treatment three times. The patient had lived for 5 more months since the diagnosis and then loss of follow up.

Case 2: A 43-year-old, non-smoking housewife presented to the general surgery clinic complaining paroxysmal cough of 5 months. Chest computed tomography (CT) showed a poorly defined mass (4.8 cm × 3.9 cm) in the lower lobe of her right lung (**Figure 3**). A few lymph nodes were identified in the mediastinum and a number of paratrachea lymph nodes were also observed. Whole body bone image showed bone metastasis. Breast ultrasound revealed a mass in the lower outer quadrant of the right breast (**Figure 4**). Puncture of right lung tumor and right breast tumor all confirmed adenocarcinoma. Patients received Alimta and cisplatin for 6 cycles, and then accepted radiotherapy 5 times. The patient still alive two years without progress after the diagnosis of both the primary lung tumor and the breast metastasis.

Case 3: A 75-year-old man presented to our hospital because of the mass in his middle lobe of right lung found in the annual physical examination. He was in good health with no specific family or past medical history. Chest computed tomography (CT) showed a poorly defined mass (1.8 cm × 1.6 cm) in the middle lobe of his right lung (**Figure 5**). He refused bronchoscopy and underwent radical operation of lung cancer. The following pathology analysis revealed moderately differentiated squamous cell carcinoma. Two months later, Breast ultrasound revealed a poorly defined mass (2.2 cm × 1.8 cm) in the lower outer quadrant of the right breast without skin involvement and a

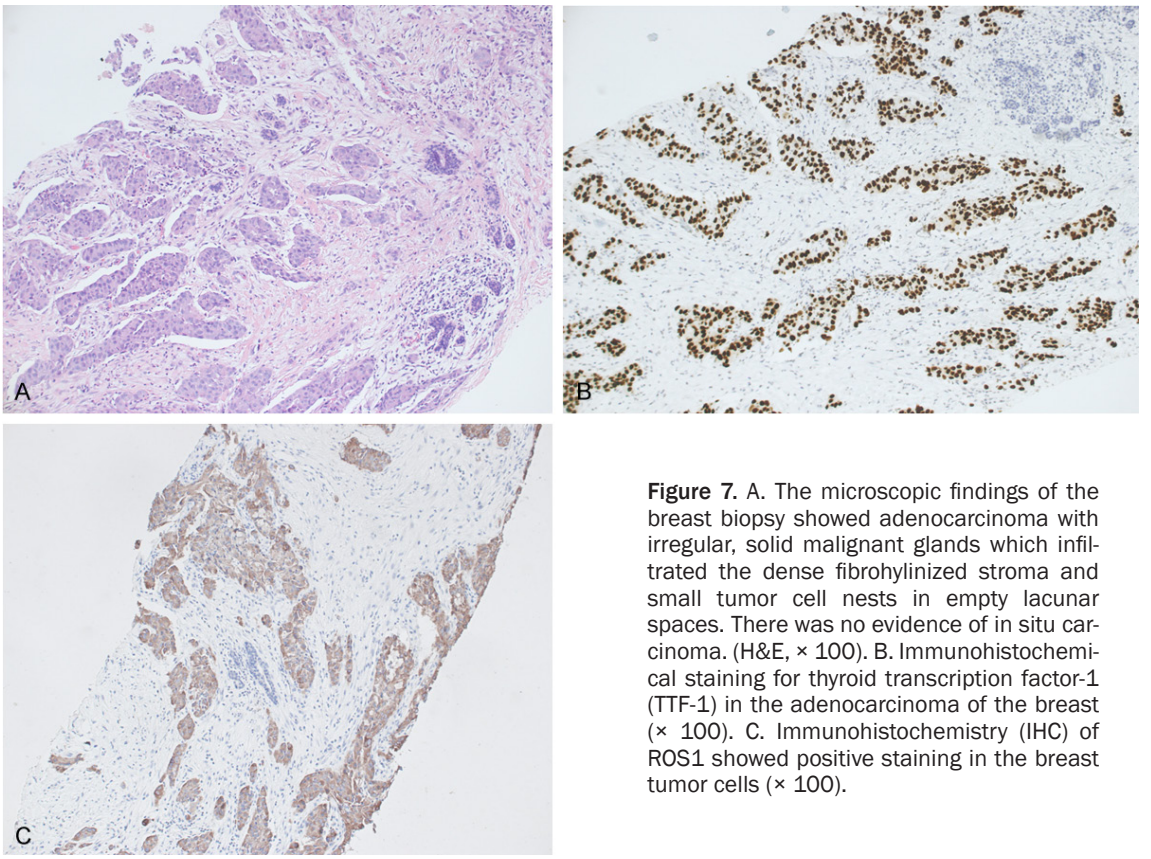

Figure 7. A. The microscopic findings of the breast biopsy showed adenocarcinoma with irregular, solid malignant glands which infiltrated the dense fibrohylinized stroma and small tumor cell nests in empty lacunar spaces. There was no evidence of in situ carcinoma. (H&E, × 100). B. Immunohistochemical staining for thyroid transcription factor-1 (TTF-1) in the adenocarcinoma of the breast (× 100). C. Immunohistochemistry (IHC) of ROS1 showed positive staining in the breast tumor cells (× 100).

number of axillary lymph nodes were also observed (**Figure 6**). A right simple mastectomy was performed and confirmed squamous cell carcinoma. The patient refused chemotherapy and loss of follow up.

Cytological, histopathological and immunohistochemical findings

In case 1, by examining bronchial brush (BB) s and bronchial washing (BW) specimens the diagnosis of adenocarcinoma was made. The lung mass puncture biopsy of the case 2 showed low differentiated adenocarcinoma. In case 1 (**Figure 7A**) and case 2 (**Figure 8A**), the breast tumor lesion is composed of irregular, solid malignant glands which infiltrated the dense fibrohylinized stroma. There was no evidence of in situ carcinoma in both cases. The tumor cells of both cases showed positive immunoreactivity for TTF-1 (**Figures 7B** and **8B**), napsin A and CK7. Moreover, the both tumors were negative for gross cystic disease fluid protein 15 (GCDFP-15), mammaglobin, human epidermal growth factor receptor 2 (Her-2), estrogen receptor (ER), progesterone receptor (PR), P63, CK5/6 and GATA-3. The tumor cells of case 1 and case 2 demonstrated respectively positive immunoreactivity for ROS1 (**Figure 7C**) and ALK (**Figure 8C**). In case 3, Hematoxylin and eosin (H&E)-stained paraffin sections of the pulmonary lobectomies showed moderately differentiated squamous cell carcinoma with in situ carcinoma of bronchial mucosal. Latter simple mastectomy revealed the diagnosis of Lung squamous cell carcinoma metastasis to the male breast without evidence of skin infiltration (**Figure 9A** and **9B**). The tumor cells of both places showed positive immunoreactivity for P63 (**Figure 9C**), CK5/6 (**Figure 9D**) and negative immunoreactivity for TTF-1.

Molecular analysis findings

No epidermal growth factor receptor (EGFR) mutations were disclosed in all three cases detected by PCR analysis, while breast lesion of case 1 showed ALK rearrangement on fluorescent in-situ hybridization (FISH) testing (**Figure 10**) and case 2 showed ROS1 rearrangement detected by PCR analysis (**Figure 11**).

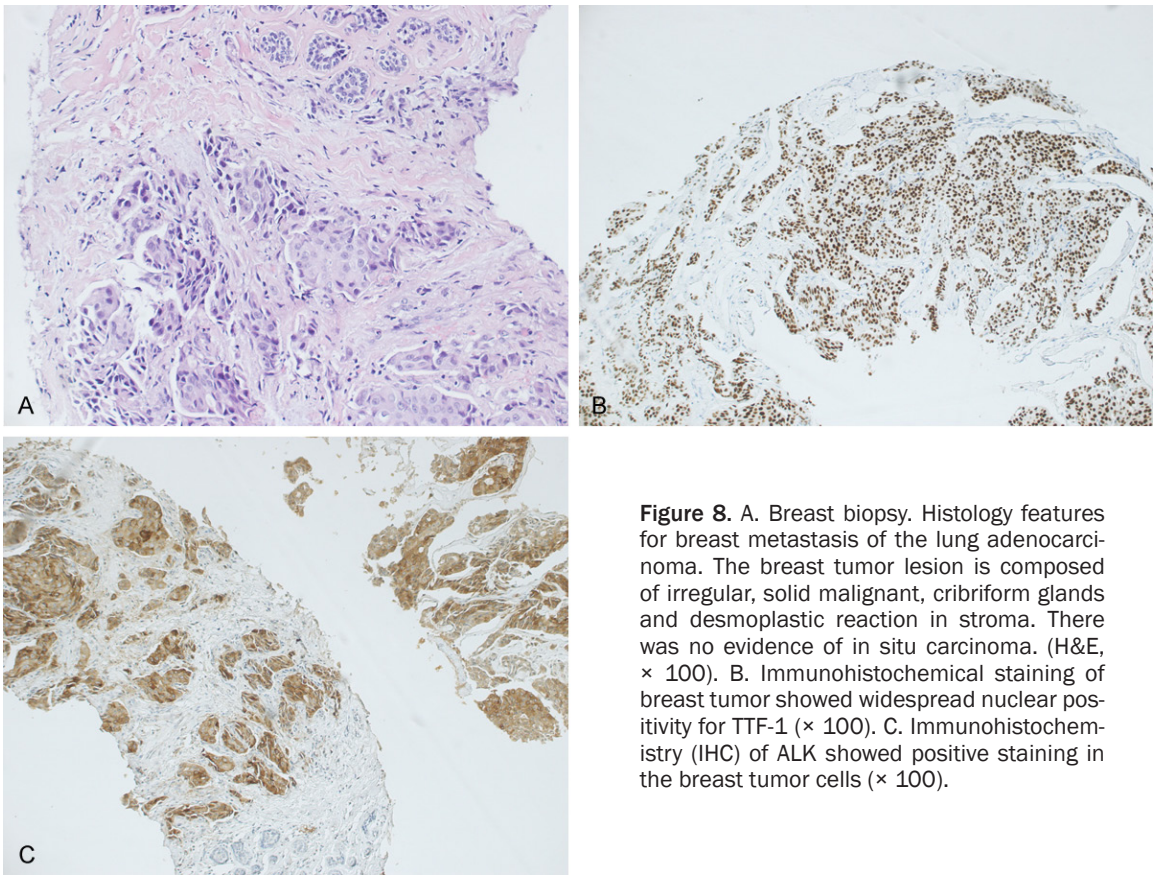

Figure 8. A. Breast biopsy. Histology features for breast metastasis of the lung adenocarcinoma. The breast tumor lesion is composed of irregular, solid malignant, cribriform glands and desmoplastic reaction in stroma. There was no evidence of in situ carcinoma. (H&E, × 100). B. Immunohistochemical staining of breast tumor showed widespread nuclear positivity for TTF-1 (× 100). C. Immunohistochemistry (IHC) of ALK showed positive staining in the breast tumor cells (× 100).

Discussion

Lung cancer is the most malignant cancer according both incidence and mortality worldwide and always metastasizes to the brain, bone, liver, adrenal gland, and contralateral lung. However autopsy series have demonstrated that NSCLCs may metastasizes to virtually any organ.

Breast metastases from extra-mammary malignancies are very rare. Most cases are hematological malignancies including leukemias, lymphomas malignant melanoma according to the international literature. Unlike primary tumors, in the most of metastases retraction of the skin or nipple is not demonstrated despite their superficial location [2, 9]. Except two reports of the lesion were poorly defined and skin redness was observed [1, 10]. In our report, the lesion of all three patients didn't involve skin or nipple.

Based on mammographic findings to distinguish a breast metastasis from a primary mammary lesion, may be extremely difficult because of the diversification of imaging manifestations of the metastatic lesion. So, metastasis may make us confused by mimicking a primary malignancy or even a benign breast tumor [2, 11, 12]. Histological features may aid in the recognition of secondary tumors. Metastases typically do not have an invasive ductal or in situ component when examined microscopically, although it may not be present in all primary invasive carcinomas. In all our three patients, there were absence of in situ carcinoma in the lesion of breast and can be found in lung lesion. Additionally, metastatic malignancies are often sharply circumscribed from the surrounding breast tissue. Furthermore, elastosis is common in primary tumors but rare in extramammary malignancies [10]. Nevertheless, many extramammary malignancies such as NSCLC of the lung lack specific histological features. Patients with breast metastases from lung cancer always present multiple, superficial, and well-circumscribed lesions. This diagnosis should be considered if morphological charac-

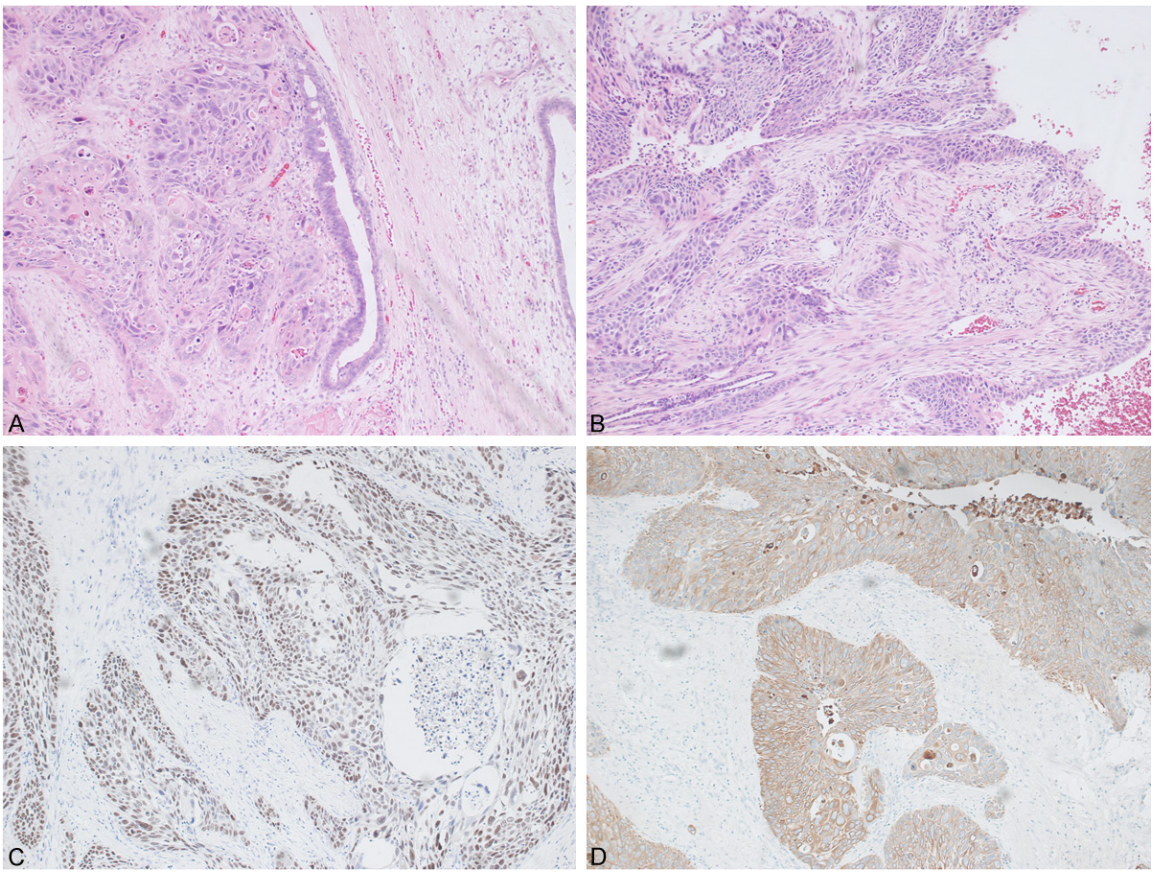

Figure 9. A. Showed the section of breast tissue infiltrated by a moderately differentiated squamous cell carcinoma. The overlying epidermis is focally infiltrated by the tumor (H&E, × 100). B. Showed the section of lung tissue infiltrated by a moderately differentiated squamous cell carcinoma, morphology similar to breast tissue. C. Immunohistochemical staining of breast tumor showed widespread nuclear positivity for P63 (× 100). D. Immunohistochemical staining of breast tumor showed widespread nuclear positivity for CK5/6 (× 100).

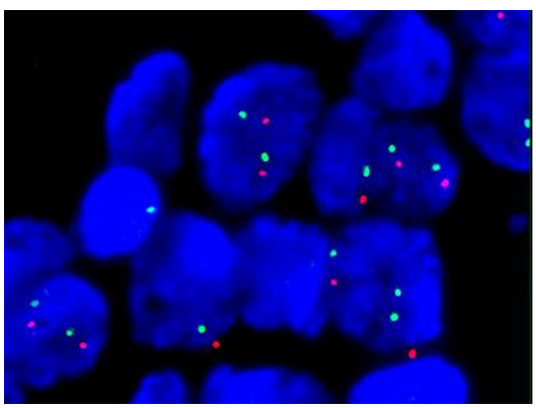

Figure 10. FISH study demonstrating ALK rearrangement with split signals.

teristics are unusual for a primary breast tumor. In one-third of the cases, medical history of lung cancer is useful for the pathologist to review slides from the primary tumor and compare the primary histology with that of the suspicious breast lesion. About two-thirds of such cases possibly show histological characteristics indicative of possible metastasis from lung [13].

Sometimes, metastasis from pulmonary adenocarcinoma might be particularly difficult to be distinguished from primary breast carcinomas. Hence, the contribution of immunehistochemistry to a correct diagnosis is crucial. For example, TTF-1 has been reported positive in 68-80% of lung adenocarcinomas; however, TTF-1 has not been reported to stain positively in breast adenocarcinoma [14-16] except a single case published by Klingen et al [14]. Napsin A and surfactant apoprotein A were positive in pulmonary adenocarcinomas with 77 and 45% [15]. The mammary origin is supported by the expression of ER, PR, GCDFP-15 and

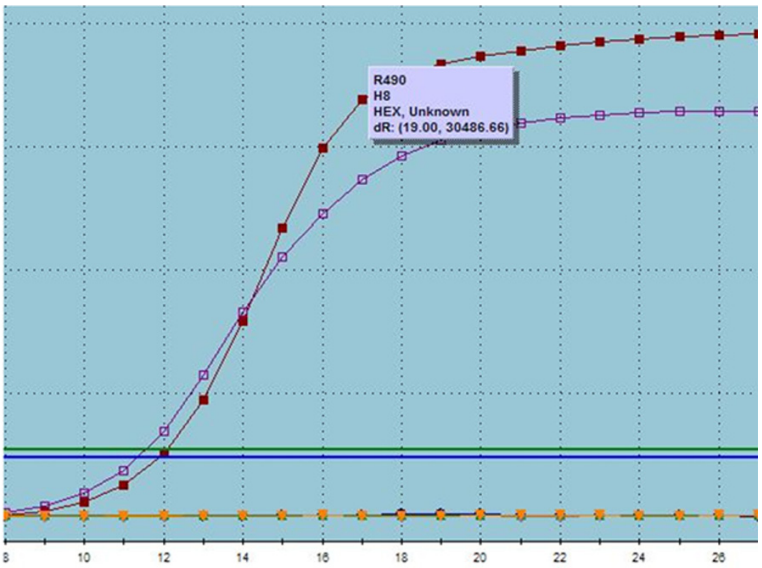

Figure 11. RT-PCR study demonstrating the tumor cells with ROS1 rearrangement.

MG. ER, GATA-3, GCDFP-15 and MG are expressed in 80%, 72%, 45-53% and 48% to 72% of breast carcinoma, respectively. Whereas studies have revealed ER expression in lung adenocarcinoma was 7.6% to 14.1% [15, 17]. The frequency of GATA3 expression in adenocarcinomas of lung was < 10% [18]. Furthermore, GCDFP-15 is expressed in 5.2% to 15% of lung adenocarcinoma [19, 20], but MG stained negatively in pulmonary adenocarcinoma [15, 19]. Among squamous cell carcinomas, the expression was highest in the skin (81%) and lower pulmonary tumors (12%) [18]. All the tumor specimens cases 1 and case 2 showed positive nuclear staining for TTF-1 and cytoplasmic staining for napsin A and SP-A. The neoplastic cells stained negative for GCDFP-15, ER and mammaglobin. All three cases lacked expression of GATA3.

Lung carcinoma is an uncommon source for breast metastasis. To the best of our knowledge, from 1991 to 2015 about 26 metastasis were classified as adenocarcinomas and squamous cell carcinoma in the PubMed database, however, So far cases of breast metastasis from pulmonary adenocarcinoma almost didn't detect gene mutation except two reports, are both EGFR-mutated lung adenocarcinoma [1-3, 5-10, 21-36] (**Table 1**). ROS1 fusion genes have recently been identified in 1-2% of NSCLC [37, 38]. The prevalence of ALK rearrangements in the general population with NSCLC is reported to range from 3% to 6%. In our reports are the two cases of breast from lung adenocarcinoma with one harbored ROS1 fusion and another harbored ALK rearrangements. So, most of the breast adenocarcinoma from lung may be harbored gene mutations.

Cases of metastasis to the mammary gland had been associated with poor prognosis due to late diagnosis [3, 10]. For our patient, case 2 survived for two years and without progress now following the diagnosis of both the primary lung tumor and the breast metastasis. Case 1 and case 3 were lost of follow up.

Here, we presented three patients who developed metastasis to the breast from lung cancer. Two rare cases of metastasis to the breast from an adenocarcinoma of the lung harbored ALK and ROS1 rearrangements respectively. Another rare case was a squamous-cell carcinoma of the lung metastases to the male breast. Metastatic disease from lung to the breast should be considered in the differential diagnosis of a primary mammary carcinoma because the treatment and prognosis differ significantly. Furthermore, the distinction between metastasis from lung adenocarcinoma and primary breast adenocarcinoma may cause a significant diagnostic dilemma. A combination of clinical history, image data and morphology may provide effective and robust measures for disease diagnosis than any single modality. The contribution of immunohistochemistry and gene nutation detected to the correct diagnosis and targeted treatment is essential.

Disclosure of conflict of interest

None.

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Table 1. Breast metastasis from lung adenocarcinoma and SCC: review of the literature (1992-2015)

Author, year	Age/sex	Breast tumor size	Molecular analysis	The type of lung cancer	Follow-up
Verger E et al., 1992 [21]	63/male	4 cm × 3.5 cm	Not available	Adenocarcinoma	Not available
Lee SH et al., 2000 (3 cases) [22]	Not available/female	Not available	Not available	2 Adenocarcinoma and 1 SCC	Not available
Masmoudi A et al., 2003 [5]	54/female	8cm in diameter	Not available	Adenocarcinoma	Not available
Ramar et al., 2003 [6]	56/male	not mentioned	Not detected	Adenocarcinoma	not mentioned
Yeh CN, et al., 2004 [9]	44/female	4 cm × 3 cm	Not available	Adenocarcinoma	Not available
Komorowski AL et al., 2005 [23]	48/not available	Not available	Not available	Adenocarcinoma	Not available
Gomez-Caro et al., 2006 [7]	65/male	NR	Not available	Adenocarcinoma	18 months
Lee AH et al., 2007 (2 cases) [8]	64, 83/ female	Not available	Not available	Adenocarcinoma, SCC	Not available
Ho et al., 2007 [24]	71/male	2 cm × 2.2 cm	Not available	Adenocarcinoma	not mentioned
Ucar et al., 2007 [25]	63/male	4 cm × 2 cm	Not available	Adenocarcinoma	Not available
Williams et al. 2007, 41 cases [3]	Not available	Not available	Not available	Not available	Not available
Fulciniti F et al., 2008 [26]	59/female	Not available	Not available	Adenocarcinoma	alive 14 months after diagnosis
Hsu et al. 2008 [35]	48/female	Not available	Not available	Squamous cell lung carcinoma	Not available
Wood et al. 2008 [36]	8 case				
Klingen TA et al., 2009 [2]	79/female	8 cm in diameter	Not available	Adenocarcinoma	Died 1 month after metastasis
	70/female	0.9 cm in diameter	Not available	Adenocarcinoma	Died 4 month after metastasis
Maounis N et al., 2010 [10]	73/female	4.5 cm × 3.5 cm	Not available	Adenocarcinoma	Died 6 month after metastasis
Lee et al. 2010 [27]	5 case	Not available	Not available	Not available	Not available
Yoon et al. 2010 [28]	42/female	1.2 cm and 0.8 cm in diameter	Not available	Non-small cell lung carcinoma	Alive nine years
Maounis N et al. 2010 [10]	75/female	Not available	Not available	Adenocarcinoma	Died 6 months
Fang-Fang Ji et al. 2012 [29]	49/female	3 cm in diameter	Not available	Adenocarcinoma	Died 5 months after discharge
	40/female	1 cm in diameter	EGFR was detected by IHC.	Adenocarcinoma	Died 8 months after the diagnosis
Ko et al. 2012 [30]	47/female	1 cm in diameter	Not available	Adenocarcinoma	Alive after 8 month
Sanguinetti A, et al. 2013 [1]	43/female	not mentioned	Not detected	adenocarcinoma	succumbed 8 months after diagnosis.
Liam CK, et al. 2013 [32]	70/female	not mentioned	EGFR +ALK-	adenocarcinoma	Died 2 months after metastasis
Hachisuka A et al., 2014 [31]	60/male	3 cm × 4 cm	Not detected	Adenocarcinoma	Died on the 11th day after fifth cycle
Dharmshaktu P, et al. 2014 [33]	65/female	3 × 3 cm 2 × 2 cm	Not detected	squamous cell carcinoma	Succumbed to her illness
Dansin E et al. 2015 [34]	52/female	2.6 cm in diameter	ERFR-mutated	Adenocarcinoma	Not available

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