

Case Report

Ipsilateral breast metastasis from a pulmonary adenocarcinoma: a case report and a focused review of the literature

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Abstract: Metastases to the breast from extramammary malignancies are extremely rare. Ruling out the diagnosis of primary breast tumor is important in order to decide on clinical management and predict prognosis. We report a case of metastasis to the breast from a pulmonary adenocarcinoma, with extensive micropapillary component, diagnosed concomitantly with the primary tumor. A 52 year-old female patient presented with mammary gland tingling and dyspnea accompanied with fatigued of 4 months duration and a nodular shadows in the front of the upper lobe was found on a chest computed tomography (CT) scan. The original clinical diagnosis was right breast cancer with lung and bone metastasis, or breast and lung double primary cancers. In addition, on physical examination a poorly defined mass was noted in the upper outer quadrant of the right breast. The patient underwent thoracocentesis and breast biopsy. By imageology, cytology, histology and immunohistochemistry, we diagnosed primary lung cancer with metastases to the right breast and bone. The metastatic anatomic sites demonstrated histologically extensive micropapillary component, which is recently recognized as an important prognostic factor. The patient was administered 4 cycles of cisplatin and docetaxel, although no clinical response was seen, the patient is still alive 9 months after diagnosis. The result of immunohistochemistry is a useful supplement in differential diagnosis.

Keywords: Lung neoplasms, breast metastasis, breast neoplasm

Introduction

Breast cancer is one of the most common malignant tumors in women, there is an upward trend in the incidence of this disease. However, metastases to the breast from extramammary malignancies are extremely rare, the prevalence of such lesions ranges from 0.4-1.3% [1-4]. Despite the rarity of metastases to the breast, the diagnosis of it from extramammary malignancies and distinction from primary mammary malignancy, is important for patient appropriate clinical management and outcome.

Sitzentfrey firstly published a case of ovarian carcinoma metastatic to the breast in 1907 [5]. So far, various of malignancies have been reported to metastasize to the breast and according to the literature the most common primary

tumors metastasizing to the breast are melanoma (29.8%), lung carcinoma (16.4%), gynecological carcinoma (12.7%), intestinal carcinoma (9.9%), leukemia and lymphoma (8.4%), rhabdomyosarcoma (7.3%), and renal cell carcinoma (1.5%) [6].

Lung cancer is the most common malignant disease, has widespread metastasis at initial presentation or during treatment course. The most commonly affected metastatic organs are lymph node, bone, lung, brain, liver, and adrenal gland, nevertheless, there have only been a few published cases of pulmonary carcinomas metastasizing to the breast [7-10]. Recently, micropapillary carcinoma has been recognized as a rare but distinctive variant of carcinoma at several anatomical sites, including breast, urinary bladder, lung, and major salivary glands [11].

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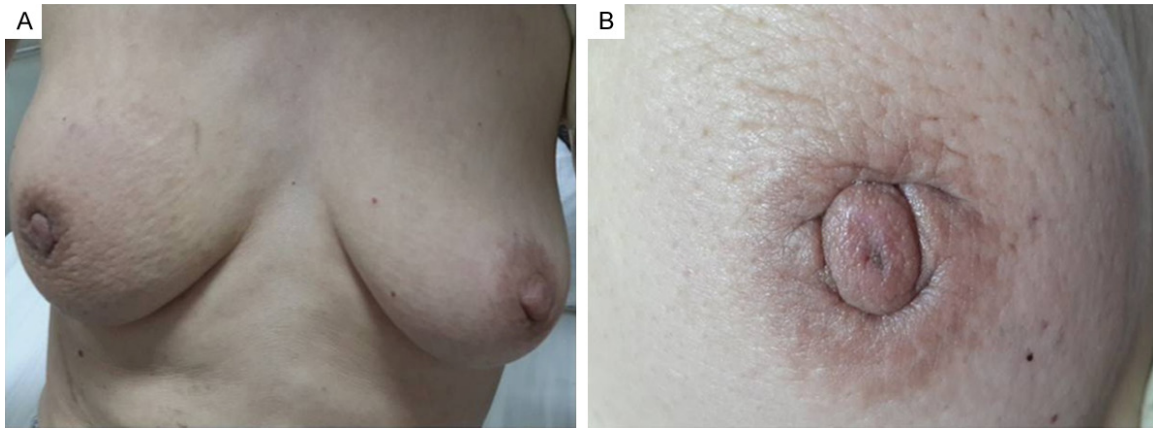


Figure 1. Physical findings of the chest. A. Bilateral breast were symmetrical; B. The lesions caused the skin of right breast to become puffy and pitted, resembling orange peel. Retraction of the nipple has been observed.

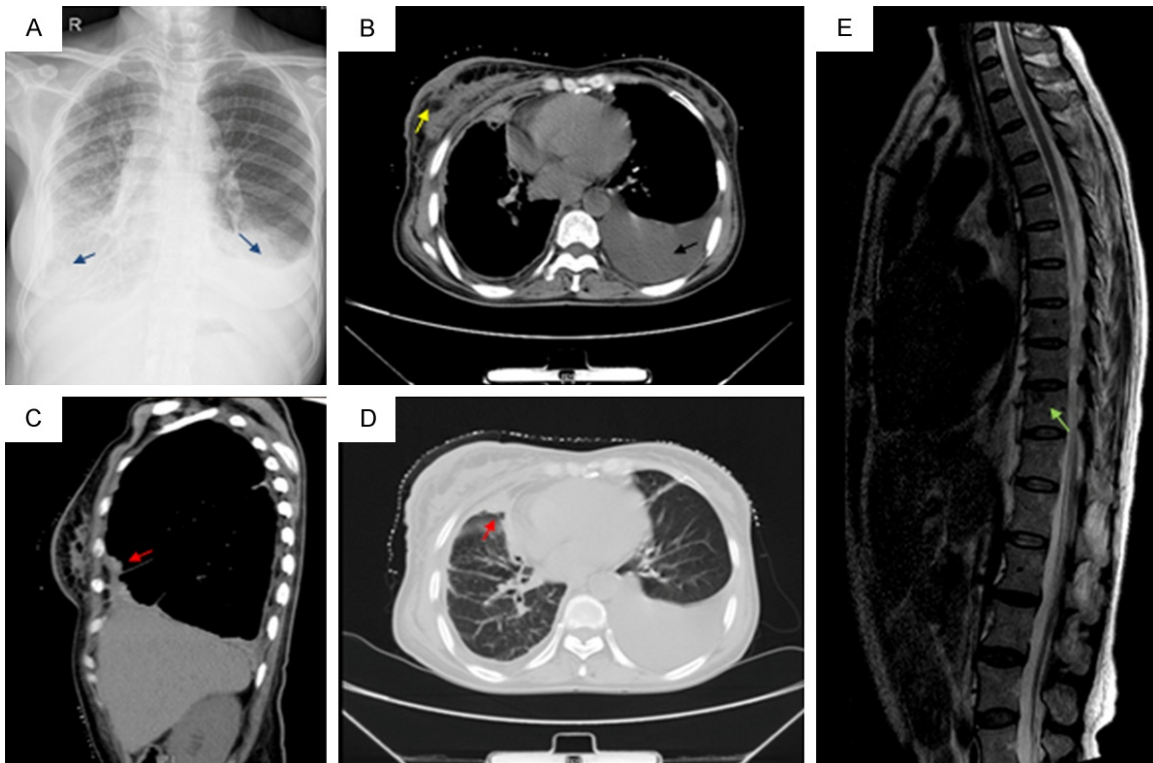


Figure 2. Imaging techniques. A. Chest x-ray: a little pleural effusion occupying the bilateral hemithorax (blue arrow); B. Chest computed tomography: The left lung is atelectatic and compressed by a little pleural effusion (black arrow). Additionally, right breast skin was thickened, a irregular mass with lobular boundary connected to thickening of the skin (yellow arrow); C. Chest computed tomography: Sagittal reformatted CT image demonstrates the presence of a neoplasm in the right parietal pleura (red arrow); D. Chest computed tomography: a nodular shadows in the front of the upper lobe that contact with the splanchnic pleura and approached the parietal pleura, in addition, adjacent pleural was thickened (red arrow); E. Magnetic resonance imaging: a metastasis to the 10th thoracic vertebrae (green arrow).

Invasive micropapillary components are being increasingly recognized as prognostic predictors in lung adenocarcinomas, many studies

repeatedly find that it may be a manifestation of aggressive behavior [12, 13]. Here we report a case of a female patient who presented a

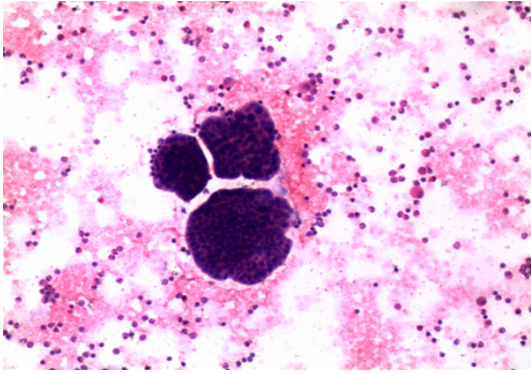


Figure 3. Pleural effusion aspiration smears. Hematoxylin and eosin (H&E)-stained smears prepared from the pleural effusion demonstrating low differentiated adenocarcinoma (H&E; 10 \times).

mass in the upper outer quadrant of right breast that had been detected through self-examination. After further systematic examinations, the patient was diagnosed with primary lung cancer that had metastasized to the right mammary gland with extensive micropapillary carcinoma in pathology. Written informed consent was obtained from the patient for publication of this case report and the corresponding images.

Case presentation

A 52-year-old, non-smoking peasant woman presented to the emergency department with mammary gland tingling and dyspnea accompanied with fatigued of 4 months duration. She had not identified chronic medical conditions history and remarkable family medical history. Physical examination revealed a pain, poorly defined, firm, and non-tender mass located in the upper outer quadrant of her right breast. It was measured 5 centimeter in diameter approximately, and had some adhesion with adjacent tissue. In addition, the lesions caused the skin of right breast to become puffy and pitted, resembling orange peel. Retraction of the nipple has been observed (**Figure 1**). Palpable bilateral axillary lymph nodes were also noted. Examination of the chest revealed reduced breath sounds and percussion dullness at the lower left hemithorax.

Imaging tests

A chest radiograph showed a little pleural effusion occupying the bilateral hemithorax (**Figure**

2A). A chest computed tomography (CT) scan showed nodular shadows in the front of the upper lobe. The nodular was in contact with the splanchnic pleura and approached the parietal pleura and adjacent pleural was thickened (**Figure 2C, 2D**). Additionally, the right breast skin was thickened, a irregular mass with lobular boundary connected to thickening of the skin (**Figure 2B**). A thoracolumbar magnetic resonance imaging (MRI) showed metastasis to the 10th thoracic vertebrae (**Figure 2E**). The original clinical diagnosis was right breast cancer with lung and bone metastasis, or breast and lung double primary cancers.

Cytologic and immunocytochemical findings

Moreover, the patient underwent ultrasound-guided thoracentesis, by examination of the pleural effusion and a diagnosis of adenocarcinoma was made (**Figure 3**). Immunocytochemistry performed on the smears prepared from the pleural effusion sample presented the tumor cells to be strongly immunoreactive for thyroid transcription factor-1 (TTF-1), cytokeratin (CK)7, and Napsin A. Tumor cells were negative for CK20, CK 5/6, gross cystic disease fluid protein (GCDFP)15.

Histopathological and immunohistochemical findings

Finally, a breast biopsy guided by ultrasound was performed. Hematoxylin-Eosin (H&E) stained paraffin sections of the breast biopsy demonstrated poorly differentiated adenocarcinoma was infiltrated (**Figure 4A**). Compared with pleural effusion smear, the cells morphology are similar. In addition, within the stroma, sharply demarcated nodules of a high-grade adenocarcinoma with solid and micropapillary pattern was demonstrated (**Figure 4B**), and no evidence of in situ carcinoma or elastosis was observed. Immunohistochemical analysis showed tumor cells diffusely positive for cytokeratin (CK)7, NapsinA and thyroid transcription factor-1 (TTF-1) (**Figure 4C-F**). Moreover, the tumor cells lacked expression of Estrogen receptors (ER), progesterone receptors (PgR), Mammaglobin and gross cystic disease fluid protein 15 (GCDFP-15). Proliferation index using Ki-67 was 30%. Thus, the final diagnosis was metastatic pulmonary adenocarcinoma.

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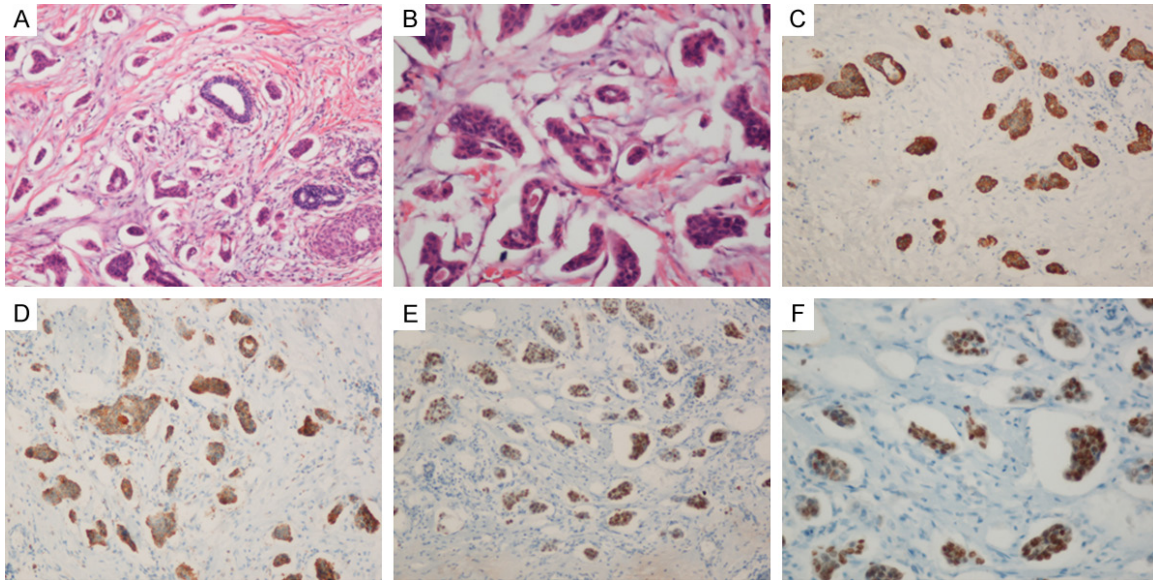


Figure 4. Histological findings. A. Infiltration by poorly differentiated adenocarcinoma with micropapillary pattern (Hematoxylin-eosin, $\times 100$); B. An extensive micropapillary component was identified. (Hematoxylin-eosin, $\times 200$); C. The tumor cells were CK-7 positive. ($\times 100$); D. The tumor cells were NapsinA positive. ($\times 100$); E. Immunohistochemical nuclear TTF-1 positivity of adenocarcinoma with solid and micropapillary component. ($\times 100$); F. Immunohistochemical nuclear TTF-1 positivity of micropapillary component ($\times 200$).

Discussion

Frequency and types of secondary breast tumours

According to Virchow's concept, the mammary gland is a rare site of involvement by metastatic disease from extramammary malignancies [14]. The reason may be that it contained large areas of fibrous tissue with a relatively poor blood supply [15]. From clinical and autopsy cases, malignant tumors metastasizing to the breast comprise only 0.2-1.3% and 2-7% respectively [10]. Geogiannos group in a retrospective review contain more than 14000 cases with breast malignancies diagnosis from 1907 to 1999 (with the exception of carcinoma in situ) found that only 60 cases originated from non-breast malignancies, the majority of metastasis to the breast are caused by contralateral breast cancer [3]. Williams et al reported that among extramammary solid tumors metastatic to the breast, the most common histological type was disseminated malignant melanoma in the largest published series of 169 cases [16]. Other tumor types include small cell carcinoma of the lung (SCLC), sarcoma, neuroendocrine tumors, squamous cell carcinoma.

Breast metastasis from lung adenocarcinomas

In terms of non-small cell type lung cancer (NSCLC), metastasis spread to unusual sites is less frequent and the incidence of metastasis to the breast is even rare. According to the literature, the most common metastatic organs are liver (33-40%), adrenal glands (18-38%), brain (15-43%), bone (19-33%), kidney (16-23%) and abdominal lymph nodes (29%) [17]. To the best of our knowledge, by reviewing the literatures of similar case reports between 1992 and 2012, which gave detailed clinical data regarding the primary lung cancer and breast metastasis. Only 12 cases of breast metastasis from adenocarcinomas in the PubMed database (**Table 1**) [4, 7-9, 14, 18-22]. It included 8 female, their average age was 58.5 years. Moreover, 4 of them also showed ipsilateral breast metastases as ours.

Clinical manifestation of secondary breast cancer

Previous studies have shown that the most common features of breast metastases present as palpable, rapidly growing, well-circumscribed and painless breast masses with predilection to the upper outer quadrant [1, 10, 14,

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Table 1. Clinical characteristics of patients with lung adenocarcinoma and breast metastasis in previous reports

Author, year	Age/sex	Breast tumor size/location	Primary tumor location	IHC of breast	Skin change	Follow-up (months)
Verger E et al., 1992 [18]	63/male	4 cm×3.5 cm/left breast	Right lung	Not available	Not available	Not available
Ramar K et al., 2003 [8]	56/male	Not available right breast	Right lung	CK7 (-) ER (-) PR (-)	Not available	Not available
Masmoudi A et al., 2003 [7]	54/female	8 cm in diameter/left breast upper quadrant	Right lung	Not available	Not available	Not available
Yeh CN, et al., 2004 [14]	44/female	4 cm×3 cm/medial lower quadrant of right breast	Not available	Not available	Not available	Not available
Gomez-Caro et al. 2006 [9]	65/male	Not available/left breast	Left lung	CK4 (-) CK7 (-) TTF-1 (-)	Negative	6 AWD
Ucar et al., 2007 [19]	63/male	4 cm×2 cm/left breast	left lung	TTF-1 (+) CK7 (+)	Not available	Not available
Fulciniti F et al., 2008 [20]	59/female	Not available/ upper inner quadrant of right breast	Right lung	TTF-1 (+)	Positive	14 AWD
Klingen TA et al., 2009 [4] (2 cases)	79/female	8 cm indiameter/subareolar tumor in left breast	Not available	TTF1 (+) CK7 (+)	Not available	1 DFD
	70/female	0.9 cm in diameter/subareolar tumor in right breast	Not available	TTF1 (+) CK7 (+)	Positive	4 DFD
Maounis N et al., 2010 [21]	73/female	4.5 cm×3.5 cm/upper outer quadrant of left breast	Left lung	TTF-1 (+) SP-A (-) GCDFP-15 (-) ER (-) Mammaglobin (-)	Positive	6 DFD
Fang-Fang Ji et al., 2012 [22] (2 cases)	49/female	3.2 cm×3.1 cm/lower inner quadrant of the left breast	Right lung	TTF-1 (+) ER (-) GCDFP-15 (-) Mammaglobin (-)	Negative	5 DFD
	40/female	1.0 cm in diameter/upper inner quadrant of right breast	Left lung	TTF-1 (+) ER (-) GCDFP-15 (-) Mammaglobin (-)	Negative	8 DFD

AWD: alive with disease; DFD: dead from disease.

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16, 23]. Unlike primary breast cancer, the retraction of skin or nipple do not demonstrate in the majority of metastases, despite their superficial location [2, 4]. However, in our patient, the lesion was poorly defined. The retraction of the skin and nipple was also observed.

Imageological and pathological differential diagnosis

In the distinctiveness of a breast metastasis from a primary mammary adenocarcinoma, the clinical history, the cytopathological picture and the immunocytochemical profile of the neoplasm may be the most meaningful factors. Because the wide range of imaging manifestations of the metastatic lesions, only based on mammographic findings, it may be extremely difficult to distinguish them, and metastasis can even mimic a benign breast tumor [3, 4, 24]. On the ultrasonographic manifestations, the metastatic breast lesion has also been reported as a large hypoechoic without ascoustic shadows [25, 26]. Occasionally, the ultrasound images showed variable internal echoes, ranging from homogeneous hypoechogenicity to heterogeneous hypoechogenicity to homogeneous hyperechogenicity [25]. Instead, histological indicators may aid in the recognition of secondary tumors. As sited in the literature, the absence of in situ carcinoma strongly supports a metastatic tumor, although this may not be present in all primary invasive carcinomas [21]. Other clues to a metastatic malignancies rather than primary origin are often sharply circumscribed from the surrounding breast tissue [3]. Furthermore, elastosis is common in primary tumors but rare in secondary tumors [1]. Most researchers agree that calcifications are rarely seen in metastases to the breast but common in mammary carcinomas [2, 10, 21]. Invasive micropapillary components have been described at several anatomical sites including the breast, urinary bladder, ovary and salivary glands. With micropapillary components are being increasingly recognized as prognostic predictors in lung adenocarcinomas and it may be a manifestation of aggressive behavior [11-13]. Histologically, the micropapillary component is characterized by small papillary tufts lying freely within alveolar spaces or encased within the thin walls of connective tissue. These small, cohesive nests lack fibrovascular con-

nective tissue cores [12]. In the present case, breast biopsies examined demonstrated tumor lesions are composed of irregular and solid malignant glands infiltrating the dense, fibrohyalinized stroma. In addition, an extensive micropapillary component has been found. No evidence of in situ carcinoma or elastosis was observed. The current case also showed metastasis to the bone, may suggesting that primary lung cancer had an aggressive behavior consistent with previous researchs. It is a significant diagnostic dilemma to distinguish between metastasis from lung adenocarcinoma, particularly with an extensive micropapillary pattern, and primary mammary adenocarcinoma. The result of immunohistochemistry is a useful supplement in differential diagnosis. TTF-1 has been reported expressed in 93% of primary pulmonary small cell carcinomas, and in 63% of adenocarcinomas [27], it has not been reported positively in breast adenocarcinoma [28-30]. ERs are expressed in 80% and GCDFP-15 in 45-53% of breast carcinomas [29, 31]. Occasionally, tumors from extramammary malignancies also express ER, but usually it is weak and local [32]. GCDFP-15 is expressed in 45-53% and mammaglobin in 48-72% of breast carcinoma, but mammaglobin stains negatively in pulmonary adenocarcinomas [29, 31, 33]. In addition, CK7 is frequently immunoreactive in lung cancer, and also in metastatic breast cancer and thyroid cancer [34]. The TTF-1, Napsin-A and CK7 is considered to be a useful marker for primary adenocarcinoma of the lung, a study involving various of immune indexes showed that the simultaneous determination of CK7 and TTF-1 contributes to distinguish between metastasis from lung adenocarcinoma and primary mammary adenocarcinoma [29]. In our case, immunohistochemical analysis showed all the tumor cells (pleura and breast) positive for TTF-1, CK7, Napsin-A and lack expression of GCDFP-15.

Treatment and outcome

The prognosis of metastasis to the breast is generally poor as most patients have widely disseminated disease [2, 23]. Even though longer survival is well recognised if there is effective systemic treatment, the overwhelming majority patients die within a year of diagnosis [1, 35-37]. Accurate diagnosis can prevent unne-

essary mutilating surgery. In many patients, systemic treatment or palliative care is more appropriate than extensive surgery. Surgical treatment of metastases should be as conservative as possible, and excision with or without radiotherapy is considered adequate, additionally, mastectomy is only advised for very painful or deeply seated tumours. In our patient, she was administered 4 cycles of cisplatin and docetaxel, although no clinical response was seen, the patient is still alive 9 months after diagnosis.

Conclusions

Our patient illustrates that the possibility of metastasis to the breast from lung adenocarcinoma. Despite its rarity, it should be considered in the differential diagnosis of a primary mammary carcinoma because the treatment and prognosis differ significantly. It can mimic primary breast cancer in biological behavior. The result of immunohistochemistry is a useful supplement in differential diagnosis.

Disclosure of conflict of interest

None.

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