

Pulmonary Adenocarcinoma Presenting as Bilateral Triple Negative Breast Cancer: Case Report and Literature Review

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Abstract

The vast majority of breast malignancies are primary lesions. However, metastasis to the breast is unusual with melanoma and hematolymphoid malignancies being the most common. In addition, metastasis from lung cancer to breast can occur, with adenocarcinoma being the most common histological subtype to metastasize. We report a 77-year-old female who presented with bilateral breast lesions, initially was thought to be bilateral mammary carcinoma, after thorough imaging workup, it was diagnosed as secondary lesions from lung adenocarcinoma. This diagnosis was confirmed by proper immunohistochemical and molecular studies on the bilateral breast biopsies. The patient was managed by tyrosine kinase inhibitors and responded well. Identification of primary versus secondary breast lesions is a very essential step in inpatient management as treatment lines can differ entirely. Performing a proper immunohistochemical panel is essential in such cases to make this differentiation in addition to the clinical and imaging correlation.

Keywords: Lung cancer; Breast metastasis; Immunohistochemistry; Case report; Non-small cell; Lung; Breast; Metastatic carcinoma

Introduction

Lung cancer is the leading cause of cancer deaths among men and the second among women [1]. Lung cancer has a poor prognosis with a 5-year survival rate of around 15 %, with adenocarcinoma being the most common histological type [2]. Primary breast malignancy is the most common malignancy in women. However, metastasis to the breast from another primary location is quite uncommon with a prevalence of 0.4 %- 1.3 % [3–7]. If we include Malignant melanoma and hematolymphoid malignancies- as they are the most common to metastasize to the breast- the incidence will increase to 3 %. If we include autopsy studies the incidence can reach up to 1.7–6.6 % [8,9]. Agrawal et al. reported an incidence of 7.6 % for all metastatic malignancies of the breast [8,10–13]. Metastasis to the breast from solid organs includes lung, ovary, prostate, kidney, stomach, ileum, thyroid, and cervix [14]. Certainly, metastasis from the contralateral breast is the commonest among all others mentioned earlier [11,15]

followed by ovary then lung [8]. The largest series studied by William between 1983 and 1998 have identified 169 patients. All were confirmed by histopathologic examination to be metastasis to the breast from solid organs, he found that the most common metastasis to the breast is from malignant melanoma [9]

Most patients present with their primary malignancies followed after some time with breast metastasis, in approximately 25 % of patients the metastatic breast mass is the presenting symptom, and it may resemble benign disease of the breast such as fibroadenoma or primary breast malignancies [12,15].

We present a case with bilateral breast metastasis from a primary lung carcinoma, misdiagnosed as triple-negative invasive ductal carcinoma. Identifying the primary lesion in such cases is essential for proper management and to avoid unnecessary procedures.

Case report

We report a 77-year-old lady with negative past medical history for malignancy, presented with bilateral breast lesions. A mammogram revealed highly suspicious masses in both breasts, bilateral BI-RADS 5. Computerized tomography scan (CT Scan) Guided core needle biopsies from both breasts were done, they revealed fibro adipose tissue infiltrated by adenocarcinoma, the

malignant cells are arranged in glands, trabeculae, and cords, no carcinoma in situ is seen and no lymphovascular invasion. No normal residual breast issue is seen in **Figure 1**. Immunohistochemical study showed the adenocarcinoma cells to be reactive for pan-cytokeratin (PCK) and cytokeratin 7 (CK7) While stains for estrogen, progesterone receptors (ER, PR), And Her2 Neu antibodies were all

negative, with low Ki-67 index. The initial impression was triple-negative breast cancer, but when a CT scan chest was performed it revealed left hilar lung mass with a metastatic nodule in the right upper lobe. In addition, a metastatic lytic lesion in the rib was found **Figure 3**. Due to the CT scan findings, a TTF1 immunohistochemical stain was performed on the breast biopsy that turned out to be positive

confirming primary lung adenocarcinoma with breast metastasis. **Figure 2**. A molecular study revealed epidermal growth factor (EGFR) Exon 19 mutation.

The patient was given a tyrosine kinase inhibitor and in spite of her high clinical stage of primary lung cancer she did well, however, after 6 months she was lost for follow-up due to travel outside the country.

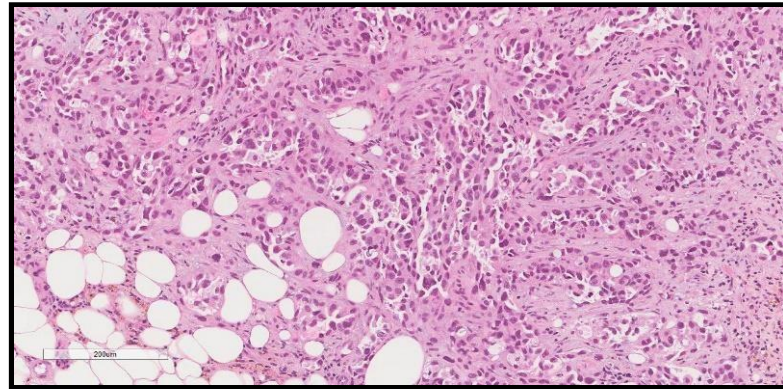


Figure 1. H&E stained section showing malignant glandular formation consistent with adenocarcinoma. The power is 200X.

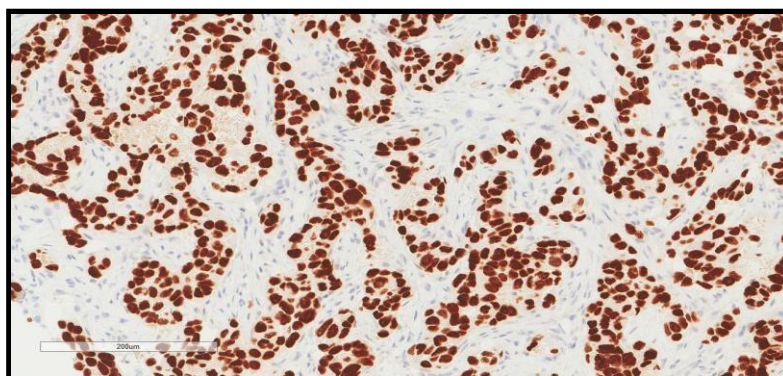


Figure 2. TTF-1 immunohistochemical stained section showing positive nuclear stain within malignant cells confirming lung adenocarcinoma. The power is 200X.

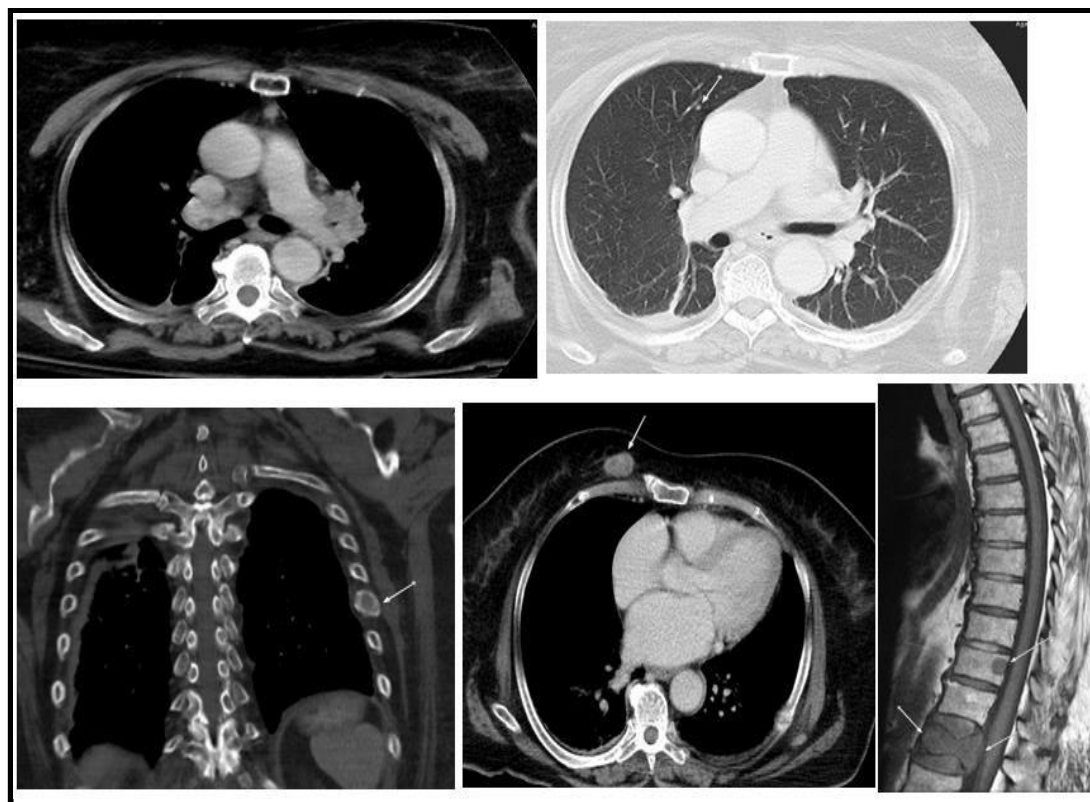


Figure 3: Metastatic disease including the left hilar mass, right upper lobe nodule, left rib lytic lesion, right anterior chest wall enhancing deposit and spinal deposits with lumbar vertebral collapse (MRI T1 weighted image)

Discussion

The most common malignancy worldwide is lung cancer with a high mortality rate of ¹⁶. Around 20 % of patients with primary lung cancer present with distant metastasis, the most frequent sites are brain, bone, liver, and adrenal glands. Breast metastasis is rare from a primary lung malignancy [3–6].

In breast metastasis, the lesion tends to be superficial within the subcutaneous fat without nipple or skin retraction, unlike the deep embedded primary breast lesions [6,17]. Mammographic features in breast metastasis usually demonstrate well-defined lesions that lack to express microcalcifications and speculations as is the primary breast malignancy, moreover the size of the lesion on physical exam

is similar to the size on mammography due to lack of scars, this is opposite to primary breast cancer where the size of the primary lesion is smaller on mammography than on physical exam due to marked fibrosis [18,19]. The most commonly described mammographic presentation is usually single but may sometimes present as multiple well-circumscribed lesions with smooth margins [3,8,20]. Besides primary mammary carcinomas, microcalcifications are reported in metastatic serous ovarian papillary carcinoma [7].

Rola et al have searched for metastatic lung cancer to breast between the years 1996 and 2017. Within the 21 years search, she has found 16 cases in their hospital files. Adenocarcinoma was the most common histologic type to metastasize to the breast. She summarized some histologic and prognostic points that help in suspecting or diagnosing these lesions; A triple-negative tumor with low-grade morphology, a tumor that lacks an in-situ component, with the absence of elastosis [3,5,6,14,21,22]. More features include a tumor presenting with the high stage but has negative axillary lymph node involvement and or not responding to standard breast cancer therapy [7,8]. More morphologic features on imaging studies include superficial location in subcutaneous tissue immediately adjacent to glandular breast, presence of multiple lymphatic tumor emboli, well-circumscribed tumor, smooth contour with multiple satellite foci, lack of architectural distortion, speculations and microcalcifications [14,23]. A predilection for the upper outer quadrant is noted by many authors [3,7,9,15]. An even very rare presentation reported by some authors is lung metastasis presenting as inflammatory carcinoma (IBC) of the breast [7,13,24,25].

This mode of presentation confirms that the tumor has reached the breast via the lymphatic route, a predilection for the ipsilateral breast, and upper outer quadrant have been noticed by many authors. Moreover, in patients with bilateral metastasis, both breasts can be affected again due to extensive lymphatic spread [7,14,24].

Ota et al described a 69 years old patient who underwent left lower lobectomy for primary adenocarcinoma of the lung that was epidermal growth factor (EGFR) exon 21 mutated. Initially, she responded well to tyrosine kinase inhibitors (TKI). But she had a recurrence 2 years later in the form of IBC. CT- Guided core needle

biopsy from breast, confirmed lung primary as the tumor was TTF1 positive and harbour the same EGFR mutation. He also postulated that when metastatic tumor reaches the breast through blood supply it will form a single mass, but when it reaches the breast through lymphatics it tends to form multiple nodules [13].

Metachronous and synchronous presentation of metastasis are correlated with histologic type, initial staging at diagnosis, treatment histories, and outcomes, therefore it has clinical relevance [7,23].

Jennifer et al reported 39 cases of breast metastasis from lung cancer, 31 were adenocarcinoma, and 8 of which are small cell carcinoma (SCC), while 80 % of the SCC metastasized synchronously only 33 % of the adenocarcinoma did so [23].

In most situations, metastatic disease to the breast occurs after the diagnosis of the primary tumor i.e., metachronous. In approximately 25 % of patients, a breast mass is a cause for the initial presentation just like our patient. In these patients, metastases to the breast can mimic benign disease or primary breast malignancies. In the study by Babu all of his three cases, a breast mass was the initial mode of presentation [15]. This is further supported by the study of Williams who mentioned that 88.2 % of patients who presented with breast metastasis had a prior history of known malignancy [9].

Nicoletta et al reported a micropapillary adenocarcinoma that presented synchronously. This histologic type of primary lung adenocarcinoma is a high grade with a poor prognosis, so such a presentation is expected [24].

In Jennifer's study 8/31 cases of metastatic lung cancer to the breast were SCC, 80 % of them presented synchronously, a similar observation noted by Alessandro and Nicoletta [7,23,24].

As the prognosis and management of primary mammary carcinoma versus metastatic carcinoma to the breast are different, all authors have agreed that an immunohistochemical panel is needed for differentiation between them; the recommended panel is displayed in **Table 1**. [8,13,14,26].

It is evident that the TTF-1 antibody is the most reliable antibody, it is positive in up to 85 % of lung carcinoma, the other tumor that can be positive is thyroid carcinoma, but breast metastasis of primary thyroid cancer is extremely rare [27]

Table 1: List the proper immunohistochemical panel that is recommended to differentiate between primary mammary carcinoma from metastatic lung adenocarcinoma

Antibody	Lung adenocarcinoma	Breast mammary carcinoma
TTF1	73 %–88 %	3 % weak and focal
Napsin A	80 %-90 %	less than 3 %
CK7		
Mammoglobin		48 % to 72.1 %
ER	7.6 % to 27.2 %,	80 %
PR	negative	60 %
Her2 Neu		
GCDFP-15	5.2 % to 15 %	45 %-53 %
GATA 3	less than 10 %	67 %-95 % (43 %–73 %) In triple-negative cases

The primary lung adenocarcinoma with metastasis to the breast in the series reported by Rola has unilateral metastasis in 11/13 while only 2 presented with bilateral metastasis [8]. Li Wang et.al have reported 2 patients with bilateral metastasis to the breast, but his patients had neuroendocrine carcinomas and not adenocarcinomas, moreover, his patients were found to have synchronous breast and lung masses at the time of presentation, unlike our patient who was found to have the lung mass discovered by CT-Scan later [28].

Biyuan reported a female patient who was discovered late to have primary lung adenocarcinoma with bilateral breast metastasis and skin deposits after being managed with many treatment lines [29]. Moreover, Xiao Wu reported two cases of primary adenocarcinoma with breast metastasis one of them had bilateral breast metastatic deposits [30]. Assi also reported a metastatic small cell carcinoma of the lung in a 52 years old smoker female patient, who presented with respiratory symptoms rather than breast mass, she received chemotherapy, after 6 months, at follow up visit she was found to have bilateral breast metastasis, manifesting as Inflammatory breast cancer with fixed breast mass, the left breast showed swelling redness and inverted nipple, the right breast had smaller masses [25].

Among the histologic types of primary lung cancer, adenocarcinoma is the commonest to metastasize to the breast. However, all histological subtypes may metastasize to the breast especially small cell carcinoma which tends to spread early, extensively through lymphatics, and is more likely to be synchronous with breast lesion in 80 % of cases [23]

The observation of bilateral breast metastasis from solid organ cancer is described in the Toombs review. He reported 21 metastatic lesions from solid organ cancer, he found 26 % of cases presenting initially with bilateral breast lesions [31].

The case presented by Dansin is very much similar to our patient in many aspects. She is a 52 years old patient who presented with IBC,

diagnosed initially as triple-negative primary breast cancer. She received chemotherapy and progressed, later she was discovered to have a primary lung cancer during workup for cancer progression and examination of the pleural fluid proved a TTF-1 positive primary lung cancer with Exon 19 EGFR mutation. [32] This is the same as our patient’s scenario, however, our patient was found to have a lung mass on CT- Scan during workup for her disease progression, we did not have additional tissue, but we applied TTF-1 and Napsin on the first biopsy from the breast and it proved to be positive for these markers with even Exon 19 EGFR mutation. Breast carcinoma can acquire EFGR mutation, particularly the triple-negative type; an incidence of 1.4 % and 11.4 % is described in two Asian studies. Therefore, not all triple-negative breast cancer with EGFR mutation should be suspected to be metastasis from the lung, IHC panel confirmation is the gold standard [32]. Other case reports of breast metastasis from lung adenocarcinoma with EGFR mutation are available in the literature [23,33,34].

The age range of metastatic lung cancer to the breast as seen in the literature is 40-77 years. The two young patients below 30 years reported in the literature are for Diego & Wang SC [14,26]. Diego reported a 29-year-old patient, diagnosed with breast and lung cancer at the same time, she survived for 20 months after first and second-line chemotherapy for lung cancer, in his literature search since 2000 he found 62 cases, eight of them were for male patients (12.7 %) [14]. Kannan et al. Reported a male patient with lung cancer metastasized to the breast after 4 years [35]. This literature review showed approximately seven hundred cases **Table 2.** [23,7,9,8] More individual case reports are available that are not included in those big series, which means more cases are available and attention to this problem has to be paid when dealing with patients known to have malignancy and presenting with breast lesion.

Table 2: Summary of major literature reviews [23,7,9,8]

Author	Search Years	Cases Found	Number of Cases with Known Histology	Histologic Type			
				Adenocarcinoma Lung	Other NSCLC*	Others including SCC**	other primaries
Alvaetal	1855- 1998	78					
William	1983-1998	169					
Ali	1999- 2017	159	99	36	33	30	
Ali	1996-2017	14	14	11	2	1	
Mirrielees	1965-2013	179	41	18	10	13	
Alessandro	(1990-2010	83	30	12	18		
	Total	682					

NSCLC: Non-small cell lung cancer, **SCC:** Small cell carcinoma

Conclusion

Metastasis to the breast is a rare incidence, in a patient with a known history of malignancy presenting with breast mass, it is important to rule out metastasis before initiating any treatment. With the advancement of imaging studies more cases of metastatic breast lesions are being reported, in good, experienced hands mammography can distinguish breast metastasis from primary breast cancer. However, the best way to reach a final diagnosis is by applying a comprehensive IHC panel on the tissue or cytology samples that are available rather than getting a new biopsy, this will expedite the

Disclaimer

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