Int J Clin Exp Pathol 2020;13(7):1880-1885
www.ijcep.com /ISSN:1936-2625/IJCEP0113602

Original Article

Clinical and molecular characteristics of secondary breast metastases from primary lung cancer: a study of 22 Chinese cases

Yue Zhu[1], Wei-Wei Liu[2], Qiong Wu[3], Jing-Hao Yao[1], Zheng-Guang Zhou[1], Yan Yang[1]

Departments of [1]Medical Oncology, [2]Otolaryngology, [3]Pathology, The First Affiliated Hospital of Bengbu Medical College, Bengbu 233004, Anhui, People's Republic of China

Received April 30, 2020; Accepted June 11, 2020; Epub July 1, 2020; Published July 15, 2020

Abstract: Background: To analyze the clinical and molecular characteristics, as well as pathologic diagnosis and treatment of lung tumors that spread to the breast in 22 Chinese patients. Materials and methods: A systematic literature search of PubMed, Embase, ScienceDirect, Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technology Journal Database and Wanfang Databases was conducted to identify the related studies published before March 31, 2020. A case of a 64-year-old man who underwent pneumonectomy and who was eventually diagnosed with a breast lump 5 years after surgery at our hospital, was also included in the present study. We analyzed the clinical and immunohistochemical characteristics from these case reports. Results: The analysis totally incorporates 21 case reports and our own case, covering 22 subjects. Among all cases we found 11 adenocarcinomas, 7 small-cell carcinomas, and 4 squamous carcinomas. In addition, most of metastatic breast masses were located below or near the nipple, rather than in the outer quadrant. The results of immunohistochemistry mostly showed triple negative breast cancers. Conclusion: A lung cancer patient with a breast tumor should suggest the possibility of metastasis. It is extremely difficult to distinguish secondary breast cancer from primary simply through medical observation and pathologic testing. Additional immunohistochemical examinations are necessary to avoid delays in diagnosis and treatment.

Keywords: Secondary breast cancer, metastasis, lung cancer, immunohistochemical

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of cancer death among females worldwide. According to available statistical data, 1.7 million new cases of BC and 521,900 deaths occurred in 2012 worldwide [1]. In recent years, the incidence of BC in China has rapidly increased, accounting for 11.2% of all new cases and 9.6% of all cancer-related deaths among all BC cases worldwide [2].

Metastases to the breast from extramammary carcinoma are rare, especially those deriving from lung cancer [3, 4]. In the following study we performed a secondary analysis of baseline data collected from 21 cases with secondary breast metastasis deriving from lung cancer that have been reported in China, including one additional case from our medical record. Furthermore, we analyzed the clinical and molecular characteristics of those tumors, which were different from primary breast carcinoma.

Materials and methods

This study was based on a secondary analysis of baseline data collected from cases with secondary breast metastasis that have been reported in China. All cases were retrieved from PubMed, Embase, ScienceDirect, Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technology Journal Database and Wanfang Databases. The following texts and keywords were searched: "lung cancer", "lung tumor", "lung carcinoma", "lung neoplasm", "breast cancer", "metastatic to breast", "secondary breast cancer", "malignant tumor of

breast". Cases of lung carcinoma that had metastasized to the breast were selected. Finally, twenty-two cases were retained, including a case of 64-year-old man who underwent pneumonectomy and who was eventually diagnosed with a breast lump 5 years after surgery at our hospital.

Previous reports provided information about the disease, including age, sex, mass size, metastasis of lymph nodes, tumor location, and histologic type of lung cancer. Additionally, some reports provided immunohistochemical analysis, which included lineage-specific immunohistochemical markers for lung carcinoma and breast cancer biomarkers, like thyroid transcription factor-1 (TTF-1), estrogen receptor (ER), and progesterone receptor (PR). The clinical features, hormone receptor status and HER2 status were analyzed in a total of 22 patients individually and as a group.

Results

Among the presented tumor types, we found 11 adenocarcinomas, 7 small-cell carcinomas, and 4 squamous carcinomas. The age at diagnosis of the breast lesion ranged between 30 and 79 with a mean age of 51 years. Seventeen cases were female and 5 were male. The clinical features of patients are analyzed and shown in **Table 1**. Breast masses at presentation ranged between 1.0 and 5.0 cm in size. Eighteen cases had some solitary metastatic deposits in the breast, while only 4 had bilateral breast involvement. Unlike primary breast cancer, the tumors of secondary breast cancer were mostly located in the superficial part and around the nipple, but not in the most common area, i.e. upper quadrant. Two patients showed inflammatory breast cancer. Lymph node metastasis were observed in 10 cases; among these patients, 8 presented with axillary metastasis. In addition, most patients had non-lymph node involvement. Twelve cases presented with a breast lump with no history of lung malignancy. Sixteen of 22 patients had extensive metastasis to bone, brain, liver and other multiple organs around the time of discovery of the breast mass.

Since different treatment methods are used for primary and secondary breast cancer, their prognosis is also different [5]. Eleven of 22 patients had data related to survival period from breast metastasis to death (11 patients had no available information on survival period in their case reports). The outcome in secondary breast cancer was poor and all 11 patients died within 1 year of presentation. Median survival time was 4.0 months (range: 0.5-11.8). Multiple factors such as metastasis to other organs around the time of discovery of the breast mass and the lack of correct and effective treatments, all led to the extremely negative prognosis.

Discussion

Primary lung cancer can cause development of distant metastasis. The most common sites include liver, bone, and brain. However, establishing an accurate diagnosis for lung tumors that spread to the breast is extremely challenging [6-9]. Since they are so rare, breast examination such as ultrasonic testing and mammography are not used as a review index for lung cancer, which might result in misdiagnosis [10]. The presence of breast mass in the superficial area around the areola, and non-axillary lymph node involvement with or without prior lung malignancy, should direct the pathologist to consider a metastasis.

It is not possible to distinguish secondary breast cancer solely by clinical manifestations, clinical signs, and imaging examination. Nevertheless, in most instances, pathology and immunohistochemistry are required to identify a secondary lump and confirm the primary site of the tumor [11, 12]. Patient 22 (**Table 1**) was diagnosed with a breast lump 5 years after surgery. Briefly, his upper left lobectomy and lymph node were surgically removed, and histopathologic analysis showed a level 2 adenocarcinoma, 3.0 cm*2.5 cm in size. Two lymph nodes of the carina were shown to be associated with cancer. Five years later, the patient sought medical attention for a mass in the left breast. Breast lump pathological analysis showed (poorly differentiated) carcinoma (**Figure 1A** and **1B**). Next, the immunohistochemical analysis of the breast tumor was conducted to identify the source and molecular phenotype of cancer. Immunohistochemistry showed EMA (+) (**Figure 1C**) CEA (+) (**Figure 1D**), and CK7 (+) (**Figure 1E**), which indicated that the breast tumor was the source. CKH (-) (**Figure 2A**) and TTF-1 (+) (**Figure 2B**) are used for the diagnosis

Table 1. Clinical features of 22 cases of lung tumors that spread to the breast

NO.	Sex/Age (years)	Histology of lung cancer	As the first symptom	Location of the breast mass	Size (cm)/Boundary	Lymph node metastasis	Unilateral or Bilateral	Other metastaticsites	Immunohistochemistry	Survival time after breast metastasis (months)
1	Female/32	Adenocarcinoma	Yes	Below the nipple	3.0×3.0/Not clear	Supraclavicular lymph nodes	Unilateral	Bone	NA	4.0
2	Male/74	Squamous carcinoma	Yes	NA	5.0×5.0/Clear	(-)	Unilateral	(-)	NA	0.5
3	Female/49	Adenocarcinoma	Yes	Non-apparent mass	Inflammatory breast cancer	NA	Unilateral	Mediastinal, Pleural	NA	3.6
4	Female/54	Adenocarcinoma	No	Near the nipple	1.9×3.8/Not clear	Axillary lymph nodes	Unilateral	Lung	ER (-) PR (-) HER2 (3+) Ki67 (+20%)	NA
5	Female/45	Squamous carcinoma	Yes	Near the nipple	4.0×4.0/Not clear	Supraclavicular lymph nodes	Unilateral	(-)	NA	NA
6	Female/48	Small-cell carcinoma	Yes	Left: Near the nipple Right: Near the nipple	Right: 5.0×5.0/Clear	(-)	Bilateral	Waist subcutaneous	NA	NA
7	Female/46	Adenocarcinoma	Yes	NA	NA/Clear	(-)	Unilateral	Bone	ER (+) PR (-) TTF-1 (+)	4.6
8	Female/68	Adenocarcinoma	Yes	NA	NA/Clear	Axillary lymph nodes	Unilateral	Bone	ER (-) PR (-) HER2 (-) TTF-1 (+)	4.9
9	Female/37	Small-cell carcinoma	No	Upper quadrant	1.1×1.2/Clear	Axillary and Supraclavicular lymph nodes	Unilateral	Mediastinal	NA	NA
10	Female/38	Small-cell carcinoma	No	Below the nipple	3.0×4.0/NA	Axillary and Supraclavicular lymph nodes	Unilateral	Mediastinal, Ovary	NA	NA
11	Male/79	Adenocarcinoma	Yes	Upper quadrant	2.0×2.0/Not clear	Axillary lymph nodes	Unilateral	Bone	NA	NA
12	Female/37	Small-cell carcinoma	No	Right: Near the nipple Left: Upper quadrant	Left: 1.9×1.6/Not clear	Axillary lymph nodes	Bilateral	(-)	NA	4.0
13	Female/30	Adenocarcinoma	Yes	Near the nipple	3.0×2.0/Not clear	(-)	Unilateral	Bone, Liver	ER (-) PR (-) HER2 (-) TTF-1 (+++)	10.5
14	Female/38	Small-cell carcinoma	Yes	Extramammary inferior quadrant	3.0×3.0/Not clear	(-)	Unilateral	(-)	ER (-) PR (-) HER2 (-)	NA
15	Male/53	Small-cell carcinoma	Yes	Right: Upper quadrant Left: Upper quadrant	Right: 1.0×1.0/Not clear Left: 3.0×3.0/Not clear	Axillary lymph nodes	Bilateral	Bone, Brain	NA	NA
16	Female/63	Squamous carcinoma	No	Near the nipple	3.0×2.0/Clear	(-)	Unilateral	Brain	NA	NA
17	Male/62	Squamous carcinoma	No	Near the nipple	3.3×3.0/Clear	(-)	Unilateral	(-)	ER (-) PR (-) HER2 (-) CKH (+)	NA
18	Female/55	Small-cell carcinoma	No	Near the nipple	Left: 1.0×1.0/Not clear Right: 3.0×4.0/Not clear	NA	Bilateral	(-)	NA	NA
19	Female/46	Adenocarcinoma	No	Non-apparent mass	Inflammatory breast cancer	(-)	Unilateral	Bone	ER (-) PR (-) HER2 (-) TTF-1 (+)	3.0
20	Female/56	Adenocarcinoma	No	NA	NA/Clear	Axillary lymph nodes	Unilateral	Bone, Pleural	ER (-) PR (-) HER2 (-) TTF-1 (+)	0.8
21	Female/63	Adenocarcinoma	Yes	NA	NA/Clear	(-)	Unilateral	Pancreas	ER (-) PR (-) HER2 (-) TTF-1 (+)	11.8
22	Male/64	Adenocarcinoma	No	Near the nipple	2.0×2.0/Clear	(-)	Unilateral	Bone, Lung	ER (-) PR (-) HER2 (+) TTF-1 (+) Ki-67 (10%+)	1.3

NA: not available (not provided or unknown).

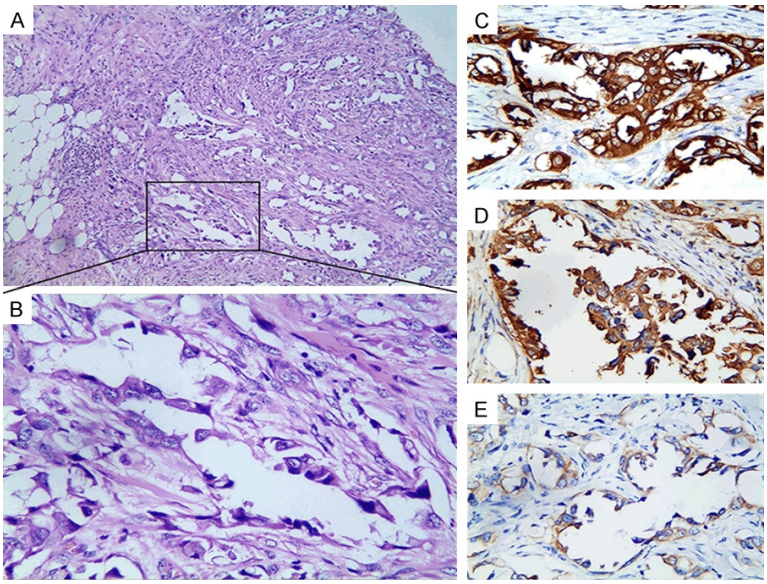

Figure 1. Histopathologic features of metastatic breast tumor from case 22. (A, B) Hematoxylin and eosin staining of breast tumor tissues confirmed the presence of (poorly differentiated) carcinoma (100× magnification and 400× magnification, respectively). (C-E) Positive expression of EMA (C), CEA (D), and CK7 (E) in the cytoplasm; 400×.

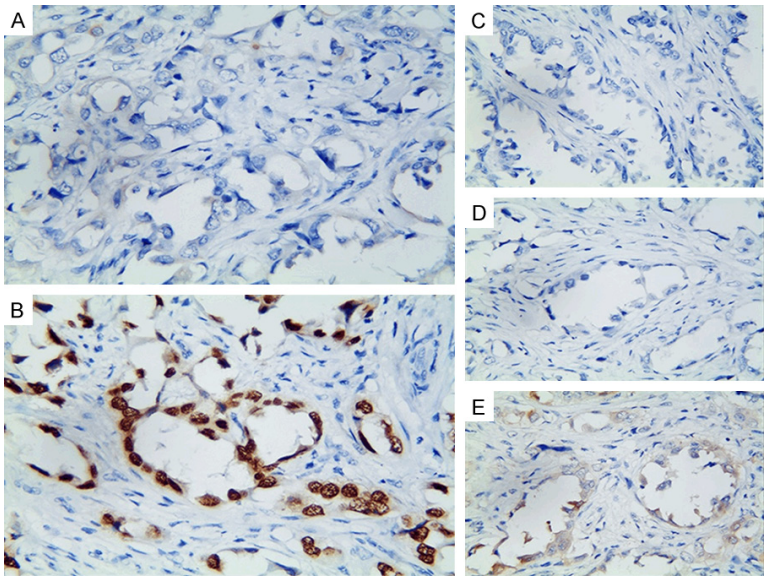

Figure 2. Molecular characteristics of metastatic breast tumor from case 22. A. Negative staining for CKH. B. Positive expression of TTF-1. C. Positive expression of ER. D. Negative staining for PR. E. Weak but positive expression of HER2. 400×.

of metastatic adenocarcinoma. As a molecular marker for breast, immunohistochemistry revealed that tumor was ER negative (**Figure 2C**), PR negative (**Figure 2D**), and HER2 (+) (**Figure 2E**). 1.3 months from the discovery of the breast metastases, the patient died of heart failure caused by severe pulmonary infection. It was not possible to exclude tumor-related death.

Positive expression of CEA, EMA, and CK7 suggested that the metastatic lesion is the source of epithelial tissue. Nevertheless, negative CKH, which labelled as squamous cell tumor, excluded squamous epithelium as a source. TTF-1 is a tissue-specific transcription factor expressed in lung and thyroid epithelial cells [13, 14]. TTF-1 can distinguish lung adenocarcinoma from squamous cell carcinoma, and thus is very useful for the diagnosis of metastatic adenocarcinoma. Among 22 cases included in this study, only 10 had IHC done at the time of diagnosis, and 9 patients were ER and PR negative. Adenocarcinoma was found in one ER (+) patient. In addition, there were 8 HER2 negative or weak positive cases, which further suggested that most of the secondary breast metastases from lung cancer have a triple negative breast cancer phenotype. The above results are consistent with previous findings [15]. Most of these patients were non-hormone dependent, and had different clinical features and molecular phenotypes from primary breast cancer, which is an important theoretical basis for creating treatment strategies for patients with secondary breast metastases, since there is no clinical evidence to indicate that this group can benefit from systemic chemotherapy for primary breast cancer [16].

Patients with secondary breast cancer can benefit from systemic comprehensive treatment for primary tumors. Preclinical studies

have suggested that surgical removal of a primary tumor may accelerate the progress of metastasis, so intervention could even be detrimental. Evidence shows that routine use of surgery for the primary lesion in patients with demonstrable metastatic disease does not result in prolonged survival [17]. Nevertheless, can patients with metastatic tumor benefit from the surgical removal of the metastatic mass? Studies have shown that radical surgery for secondary breast cancer does not lead to prolonged survival, while local excision or radiotherapy can lead to local control and improvement of symptoms [18, 19]. It is essential to avoid unnecessary mastectomy and to proceed with timely systemic treatment according to the histologic type of primary tumor [20, 21]. Among these case reports, 2 patients were treated with chemotherapy based on platinum; one received pemetrexed and cisplatin, while the other one received a chemotherapy regimen of cyclophosphamide, doxorubicin and cisplatin. Results of scans demonstrated breast target lesions PR. The total survival period was not reported. Conversely, the patient died 1.3 months from the discovery of the breast metastases, since he did not receive an effective systemic treatment after the operation, which may also be related to the lack of timely cure.

Conclusion

Lung cancer rarely metastasizes to the breast. Though rare, it should not be ignored, especially in large populations. The imaging and pathologic examination of the breast mass are essential to avoid an incorrect diagnosis and unnecessary surgery. Accordingly, immunohistochemistry is valuable. Early diagnosis and correct treatment are very important for prolonging the survival time of patients with breast metastases.

Acknowledgements

This work was supported by the grants from Bengbu Medical College Key Project of Translational Medicine (No. BYTM2019009), Bengbu Medical College Nature and Science Fund (No. BYKY1885), and the internal grant from Leading New Technology Project of the First Affiliated Hospital of Bengbu Medical College (No. 2018126).

Disclosure of conflict of interest

None.

Abbreviations

BC, breast cancer; CNKI, China National Knowledge Infrastructure; ER, estrogen receptor; HER2, human epidermal growth factor receptor; PR, progesterone receptor; TTF-1, transcription factor-1.

Address correspondence to: Dr. Yan Yang, Department of Medical Oncology, The First Affiliated Hospital of Bengbu Medical College, Bengbu 233004, Anhui, People's Republic of China. Tel: +86-552-3086178; Fax: +86-552-3086178; E-mail: qiannianhupo@163.com

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, Chen WQ, Shao ZM and Goss PE. Breast cancer in China. Lancet Oncol 2014; 15: e279-289.

[3] Barber Z and Kosti A. Breast metastases from primary lung cancer. BMJ 2017; 357: j1203.

[4] Maounis N, Chorti M, Legaki S, Ellina E, Emmanouilidou A, Demonakou M and Tsiafaki X. Metastasis to the breast from an adenocarcinoma of the lung with extensive micropapillary component: a case report and review of the literature. Diagn Pathol 2010; 5: 82.

[5] Marshall EM, Bertaut A, Desmoulins I, Darut-Jouve A, Ponnelle T, Poillot ML, Beltjens F and Arveux P. Prognostic factors of survival among women with metastatic breast cancer and impact of primary or secondary nature of disease on survival: a French population-based study. Breast J 2017; 23: 138-145.

[6] Riihimäki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J and Hemminki K. Metastatic sites and survival in lung cancer. Lung Cancer 2014; 86: 78-84.

[7] Arinc S, Gonlugur U, Devran O, Erdal N, Ece F and Ertugrul M. Prognostic factors in patients with small cell lung carcinoma. Med Oncol 2010; 27: 237-241.

[8] Valan CD, Slagsvold JE, Halvorsen TO, Herje M, Bremnes RM, Brunsvig PF, Brustugun OT, Fløtten Ø, Levin N and Sundstrøm SH. Survival in limited disease small cell lung cancer according to n3 lymph node involvement. Anticancer Res 2018; 38: 871-876.

[9] Kang EJ, Lee SY, Kim HJ, Min KH, Hur GY, Shim JJ, Kang KH, Oh SC, Seo JH, Lee SY and Kim JS. Prognostic factors and skeletal related events in patients with small cell lung cancer with bone metastases at the time of diagnosis. Oncology 2016; 90: 103-111.

[10] Matos JC, Pelloso SM and Carvalho MD. Factors associated with secondary breast cancer prevention in Maringa, Parana State, Brazil. Cad Saude Publica 2011; 27: 888-898.

[11] Ko K, Ro JY, Hong EK and Lee S. Micropapillary lung cancer with breast metastasis simulating primary breast cancer due to architectural distortion on images. Korean J Radiol 2012; 13: 249-253.

[12] Leighl NB. Treatment paradigms for patients with metastatic non-small-cell lung cancer: first-, second-, and third-line. Curr Oncol 2012; 19: S52-58.

[13] Vollmer RT. Primary lung cancer vs metastatic breast cancer: a probabilistic approach. Am J Clin Pathol 2009; 132: 391-395.

[14] Zhao L, Mao C, Xiao H, Fu P, Xiao H, Chen C and Wang G. Simultaneous expression of TTF1 and GATA3 in a lung biopsy sample: confusion in diagnostic pathology. Int J Clin Exp Pathol 2019; 12: 3613-3619.

[15] Ali RH, Taraboanta C, Mohammad T, Hayes MM and Ionescu DN. Metastatic non-small cell lung carcinoma a mimic of primary breast carcinoma-case series and literature review. Virchows Arch 2018; 472: 771-777.

[16] Criscitiello C, André F, Thompson AM, De Laurentiis M, Esposito A, Gelao L, Fumagalli L, Locatelli M and Minchella I. Biopsy confirmation of metastatic sites in breast cancer patients: clinical impact and future perspectives. Breast Cancer Res 2014; 16: 205.

[17] Cameron D. Removing the primary tumour in metastatic breast cancer. Lancet Oncol 2015; 16: 1284-1285.

[18] Ben Hassouna J, Slimene M, Bouzaiene H, Khomsi F, Chargui R, Kochbati L, Mtaallah MH, Gamoudi A and Benna F. Secondary breast cancer after treatment for Hodgkin's disease. About seven cases. Gynecol Obstet Fertil 2007; 35: 536-540.

[19] DeLair DF, Corben AD, Catalano JP, Vallejo CE, Brogi E and Tan LK. Non-mammary metastases to the breast and axilla: a study of 85 case. Mod Pathol 2013; 26: 343-349.

[20] Danesh M, Belkora J, Volz S and Rugo HS. Informational needs of patients with metastatic breast cancer: what questions do they ask, and are physicians answering them? J Cancer Educ 2014; 29: 175-180.

[21] Babu KS, Roberts F, Bryden F, McCafferty A, Downer P and Hansell DT. Metastases to breast from primary lung cancer. J Thorac Oncol 2009; 4: 540-542.