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clinical practice

Non small cell lung cancer metastasized to the breast and treated with modified radical mastectomy: a case report

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SUMMARY: **Non small cell lung cancer metastasized to the breast and treated with modified radical mastectomy: a case report.**

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Breast metastasis from extra-mammary malignancy is extremely rare with an incidence from 0.4% to 1.3%. Several types of malignancies that most commonly metastasize to the breast include leukemia, lymphoma, and melanoma.

Aim. *We report a case of a 57-year-old male with a history of non-small cell lung cancer (NSCLC) who manifested a left breast mass, two years and four months after the initial diagnosis and treatment of NSCLC.*

Method. *Physical examination revealed a poorly defined mass in the upper outer quadrant of the left breast, suspicious for breast cancer. After mammography results, the patient underwent Fine Needle Aspiration that was indicative of cancer. He underwent then modified radical mastectomy and axillary lymph node dissection. Histology and immunohistochemical analyses were conducted, that revealed a NSCLC that metastasized to the left breast.*

Results. *Finally, the prognosis of the patient was poor, as NSCLC relapsed from IIB to stage IV.*

Conclusions. *An accurate differentiation of metastasis to the breast from primary breast cancer is of paramount importance because the therapeutic approach and prognosis of the two differ significantly.*

KEY WORDS: Lung cancer - NSCLC - Breast metastasis - Immunohistochemistry - Thyroid transcription factor-1 (TTF1) - Ker7 - Ker20.

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Histologically, NSCLC is divided into adenocarcinoma, squamous cell carcinoma (SCC) and large cell carcinoma. Patients with NSCLC require a complete staging workup to evaluate the extent of disease, because accurate staging plays a major role in determining the choice of treatment.

Breast cancer still remains the most frequent female malignant neoplasm in the Western population (1, 2). Metastases to the breast represent approximately 0.4 to 1.3% of malignant neoplasms in the breast in current clinical series of the literature (3). Despite the rarity of this clinical entity, metastatic breast disease is a significant diagnostic clinical problem because its therapeutic approach differs fundamentally from that of primary breast cancer.

Sitzentfrey was the first to publish a case of ovarian carcinoma that metastasized to the breast (1). Different type of malignancies, from hematological to malignant melanomas, lung tumors, renal cell carcinomas, ovarian cancers, thyroid carcinomas and small bowel carcinoids, may metastasize to the breast (1, 4). Lung cancer is one of the most frequent malignancies, as far as incidence and mortality concerns; however, cases of lung carcinomas (small cell, non small cell, large cell, oat cell anaplastic squamous, lung neuroendocrine) that give metastasis to the breast have also been published in various series and case reports (1).

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The molecular profile of lung cancer is also crucial. Recently, the fusion between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) otherwise an EML4-ALK chimeric gene product from translocation of ALK in 2p23 has been found to be expressed in 2-15% of non-small cell lung cancers (NSCLCs) (5). *EML4-ALK* is most often detected in non smokers with lung cancer and has unique pathologic features. *EML4-ALK* is oncogenic both *in vitro* and *in vivo* and there are targeted therapies with ALK kinase inhibitors like crizotinib PF0234-1066. When this chimeric gene is proved to be positive these targeted therapies are quite effective in pre-clinical model systems. More recently ALK inhibitors have entered clinical development and remarkably clinical efficacy has been observed in NSCLC patients harbouring *EML4-ALK* translocations (6).

We report a patient with left breast metastasis from non-small cell lung carcinoma. To our knowledge, this article is the first to report lung cancer cells infiltrating into the contralateral breast parenchymal tissues, as a single mass lesion, two years and four months after the initial diagnosis of NSCLC. We also performed a differential diagnosis by using a panel of immunohistochemical markers.

Written informed consent was obtained from the patient for publication of this case report.

Case report

A 57-year-old man with a history of smoking (25 pack years), presented with a right lung mass three years ago. Transbronchial Needle Aspiration Biopsy revealed non-small cell lung cancer (NSCLC), adenocarcinoma that was negative for Ker20(-), positive for Ker7(+) and TTF1(+). The stage of the disease after complete work up was T2aN1M0 (stage IIB).

The molecular profile of the tumor was checked for gene mutations in exons 18,19,20,21 of EGFR gene that were negative. Also, there was no mutation in exons 2,3,4 of kras gene.

The patient was given three cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel and then underwent lobectomy of the right lower lobe and radiotherapy. The postoperative course of the patient was uncomplicated.

In two years follow-up, the disease remained therefore stable and in two years and four months, the patient developed a palpable mass in the left breast. Physical examination of the mass and mammography were indicative of breast cancer. Fine Needle Aspiration of the breast lesion was indicative for adenocarcinoma. Modified left radical mastectomy and axillary lymph node dissection was performed.

Histopathology and immunohistochemistry revealed metastasis from adenocarcinoma grade II, from NSCLC with molecular pattern Ker7(+), Ker20(-), TTF-1(-), Napsin(-), ER(-), PR(-), Mammoglobin(-). 13 lymph nodes that were harvested from the axilla were free from metastatic disease. At that time**,** tumor markers in serum were Carcinoembryonic Antigen: 90.97 ng/ml (<3.8 ng/ml), Alpha-Fetal Protein: 5.55 ng/ml (<7 ng/ml), Cancer Antigen 19-9: 0.60 U/ml (<34 U/ml).

The breast biopsy specimen was compared to the biopsy specimen of the lung mass and they were histologically identical, with molecular pattern CH 20, CAM 5.2, ER, PR, and CDP being negative.

After six months (three years from the initial diagnosis of NSCLC), our patient developed bone metastasis in the right orbital bone and in the right humerus bone. There was also detected a right supraclavicular lymph node, that was proved to be infiltrated with NSCLC, when Fine Needle Aspiration was performed.

The current staging of the disease with chest Computer Tomography, revealed a partial filling defect in the superior vena cava, enlarged lymph nodes in the right and in the central compartment of the mediastinum. Also, a 11 mm nodular lesion was detected in the right posterior upper lobe. Other nodular lesions with radial distortion were found in the upper segment of the right upper lobe up to 17 mm and a similar 5 mm lesion in the posterior segment of the left upper and lower lobe.

The abdominal Computer Tomography revealed that there were lymph nodes detected in the continuum of the splenic, the common hepatic and the left gastric artery. Peritoneal nodular disease up to 21 mm and a 13 mm nodule was detected in the right gluteal muscle.

Due to disease progress to stage IV, the patient was subjected to palliative chemotherapy and also

underwent radiotherapy in the right orbital bone and in the mediastinal lymph nodes that were detected in chest Computer Tomography.

The patient subsequently received six cycles of chemotherapy with cisplatin and vinorelbine. He had a partial clinical and radiological response according to RECIST criteria (Response Evaluation Criteria In Solid Tumors) that lasted for 6 months. The patient presented again with recurrence of his disease. This time he was treated with three cycles of gemcitabine. The patient had a stable clinical and radiological response. The patient underwent two cycles of the single agent topotecan. Thereafter, our patient is enrolled in our palliative care programme.

Discussion

The rate of metastasis at the time of diagnosis of NSCLC varies from 11 to 36%. Most common sites of metastasis are the liver (33-40%), adrenal glands (18-38%), brain (15-43%), bone (19-33%), kidney (16-23%), and abdominal lymph nodes (29%) (7, 8). Metastatic spread to less common sites include stomach, pancreas, small bowel, arteriovenous hemangioma, choroid plexus, muscle, umbilicus, and the penis.

Metastatic solid tumors to the breast comprise 0.3-0.8% of breast cancer (7, 9, 10). The incidence of metastatic lung cancer to the breast is very low (<0.5% of all metastatic disease). The most common primary sources for metastatic breast cancer are malignant melanoma, lymphoma, and leukemia.

Metastasis to breast may be lymphatic or hematogenous. Lymphatic may be due to initial pleural infiltration with chest wall lymphatic involvement which drains to ipsilateral axillary lymph nodes and retrograde dissemination to the breast. In hematogenous metastasis a solitary discrete lesion is more common as in our case (11).

Patients with breast metastasis from lung cancer usually present with a rapidly growing, painless, firm, well circumscribed and palpable mass with a predilection to the ipsilateral upper outer quadrant. Unlike primary tumors, the clinical image of metastases do not often demonstrate skin or nipple retraction, despite their superficial infiltration. Distinguishing breast metastasis from primary mammary adenocarcinoma based on mammographic findings may be very difficult because of the wide range of imaging manifestations of metastatic lesions. Thus, metastasis can mimic a primary malignancy or even a benign breast tumor.

Immunohistochemistry plays a crucial role in differentiation. TTF-1 is expressed in 68-80% of lung adenocarcinomas and never reported in primary breast tumors. ER is expressed in 80% of breast carcinomas. Lung adenocarcinoma may show low ER 7.6-14.1% expression. Mammaglobin is expressed in 48-72.1% of mammary adenocarcinomas but stains negatively in pulmonary adenocarcinoma (11).

In addition, many cases of primary and metastatic breast adenocarcinomas (including ductal and lobular) are K7+/K20–/K5/6–, which exhibit an important diagnostic value in combination with ER, PR and GCDFP-15 immunohistochemistry in differentiating a primary breast adenocarcinoma from an adenocarcinoma at another primary site.

Lung adenocarcinomas are K7+ whereas lung squamous cell carcinomas are usually K7–, as expressed in our case. Consequently, it is important to use a panel of antibodies, as no single marker is completely sensitive or specific.

In addition to histopathologic diagnosis and immunohistochemistry, Positron Emission Tomography (PET) can be useful to identify distant or unusual sites of metastasis from lung cancer. However, PET scanning would not be able to differentiate a metastatic lesion from a primary breast tumor, similarly to our case.

We present a patient who developed metastasis to the breast from NSCLC. This is a very rare occurrence and the prognosis for such patients is poor.

It is remarkable, that six months after the diagnosis and treatment of breast metastasis, NSCLC relapsed form IIB to IV stage. It is also important to distinguish a primary breast cancer from metastasis to the breast, as the therapy offered would be markedly different with considerably different outcomes (7).

Currently, local excision and systemic treatment are recommended for breast metastasis. Mastectomy, still has a role in very selected subgroup of patients.

There are in the literature similar cases of patients with breast metastases from pulmonary adenocarcinoma. In general, metastasis to the breast has been associated with poor prognosis in patients who die within a year of diagnosis.

Wang et al. reported (1) two patients who remained alive for 7 and 8 months after they were diagnosed with primary lung tumor and breast metastasis, respectively. Hence, patients should be followed up continually.

A combination of clinical history, imaging data and pathology may provide effective modalities for disease diagnosis than any single examination. A detailed evaluation of the breast mass and specific immunohistochemical analysis are necessary to distinguish a primary breast cancer from metastasis to the breast, to avoid unnecessary mastectomy and provide appropriate systemic treatment modalities, because the recommended therapy is possibly different with considerably varying outcomes.

The diagnostic work-up may include fine-needle aspiration, core needle biopsy, as well as surgical biopsy which offer an accurate as possible pre-mastectomy diagnosis for patients with breast lumps.

In our presented case, since the diagnosis from Fine Needle Aspiration was indicative of adenocarcinoma, the possible primary site (lung) was suspected after the therapeutic surgical therapy was decided. Modified radical mastectomy and axillary lymph node dissection was selected as a reasonable choice of procedure under this condition.

If the diagnosis of lung lesion is definite before detecting the breast lump, avoiding any operation or performing a conservative operation could be considered as therapeutic management. Small cell carcinomas, either from pulmonary or extrapulmonary site, are aggressive in their molecular characteristics and require combined modalities of treatments including chemotherapy. Neoadjuvant chemotherapy followed by resection has been considered for selective cases without evidence of distant metastasis by Jakovljević et al. (12).

Conclusions

To conclude, the clinical message of this case report is to emphasize the importance to distinguish extra-mammary metastasis from a primary breast carcinoma according to clinical and imaging features. If a breast lump is noted, the possibility of metastasis should always be considered (13). In such cases, the role of surgery and radiation therapy must be incorporated in clinical practice.

Finally, immunohistochemistry might be the principal diagnostic tool to prove that metastasis is the same type of cancer as the primary tumor.

Conflict of interest

None.

References

1. Wang L, Wang SL, Shen HH, Niu FT, Niu Y. Breast metastasis from lung cancer: a report of two cases and literature review. Cancer Biol Med. 2014;11:208-215.
2. Hajdu SI, Urban JA. Cancers metastatic to the breast. Cancer. 1972;29:1691-1696.
3. Klingen TA, Klaasen H, Aas H, Chen Y, Akslen LA. Secondary breast cancer: a 5-year population-based study with review of the literature. APMIS. 2009;117:762-767.
4. Williams SA, Ehlers RA, Hunt KK, Yi M, Kuerer HM, Singletary SE, et al. Metastases to the breast from nonbreast solid neoplasms: presentation and determinants of survival. Cancer. 2007;110:731-737.
5. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, Bando M, Ohno S, Ishikawa Y, Aburatani H, Niki T, Sohara Y, Sugiyama Y, Mano H. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448:561-566.
6. Sasaki T, Rodig SJ, Chirieac LR, Jänne PA. The biology and treatment of EML4-ALK non-small cell lung cancer. Eur J Cancer. 2010;46:1773-1780.
7. Ramar K, Pervez H, Potti A, Mehdi S. Breast metastasis from non-small-cell lung carcinoma. Med Oncol. 2003;20:181-184.
8. Quint LE, et al. Distribution of distant metastases from newly diagnosed non-small cell lung cancer. Ann Thorac Surg. 1996;62:246-250.
9. Sandison AT. Metastatic tumors in the breast. Br J Surg. 1959;47:54-58.
10. Hajdu SI, Urban JA. Cancers metastatic to the breast. Cancer. 1972;29:1691-1696.
11. Venkatesulu BP, Mallick S, Singh A, Julka PK. Non small cell carcinoma of lung with metachronous breast metastasis and cardiac tamponade: Unusual presentation of a common cancer. J Egypt Natl Canc Inst. 2015;27:165-169.
12. Jakovljević B, Stevanović O, Bacić G. Metastases to the breast from small-cell lung cancer: MR findings. A case report. Acta Radiol. 2003;44:485-488.
13. Luh SP, Kuo C, Tsao TC. Breast metastasis from small cell lung carcinoma. J Zhejiang Univ Sci B. 2008;9:39-43.