CASE REPORT

Differential diagnosis of lung lesion in breast carcinoma: a metachronous neoplasm or metastasis?

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SUMMARY

A 34-year-old woman—a diagnosed case of pT1N1M0, stage IIa, estrogen and progesterone receptor positive (ER, PR) positive, Her2 negative carcinoma of the left breast—was managed with modified radical mastectomy and adjuvant chemotherapy. While planning for radiotherapy, she was found to have a well-defined enhancing lesion with spiculated margins in the superior segment of the right lower lobe along with a heterogeneously enhancing right hilar lymph node on CT. Histopathological evaluation of the lesion was suggestive of adenocarcinoma. The lesion was negative for ER, PR receptors, mammoglobin and gross cystic disease fluid protein. Thyroid transcription factor 1 (TTF-1) was positive, suggesting a primary lung adenocarcinoma rather than metastatic lesion from the breast. This case clearly signifies the importance of histopathological diagnosis of suspicious metastatic lesions in the setting of early breast cancer. We would also like to highlight the importance of TTF-1 in differentiating primary lung malignancy from metastasis.

BACKGROUND

Lung metastases in breast carcinoma are often a manifestation of widespread dissemination of malignancy indicating poor prognosis with a median overall survival approaching 2 years.¹ However, metastasis in a patient with early breast cancer is rare. We present an interesting case of early breast cancer with suspicious metastatic lung lesion that—after histopathological confirmation—turned out to be primary lung cancer.

CASE PRESENTATION

A 34-year-old woman presented with history of a palpable breast mass and sanguineous nipple discharge. She had no history of smoking. On examination, a 1×1 cm hard, non-tender, mobile mass was felt in the upper outer quadrant of the left breast, without palpable lymph nodes. Systemic examination was unremarkable. Fine-needle aspiration cytology of the breast mass was suggestive of infiltrating ductal carcinoma of the breast. The patient underwent left-sided modified radical mastectomy. Histopathological evaluation of the resected specimen showed infiltrating ductal carcinoma. Two of 13 dissected nodes showed metastasis (pT1N1M0). The tumour was positive for estrogen and progesterone receptors (ER and PR); Ki67 was 28% (figure 2). Fluorescence in situ hybridisation analysis on formalin fixed paraffin embedded sections

was negative for HER2/neu gene amplification. Adjuvant chemotherapy with four courses of doxorubicin and cyclophosphamide at three weekly intervals followed by four courses of paclitaxel at three weekly intervals was administered. The patient was found to have a well-defined enhancing lesion with spiculated margins in the superior segment of the right lower lobe along with a heterogeneously enhancing right hilar lymph node on CT (figure 1), while planning for adjuvant external beam radiotherapy. Five fluorodeoxyglucose positron emission tomography with CT (FDG-PET CT) showed a lobulated, metabolically active soft tissue lesion in the apical segment of the right lower lobe of the lung, with a 2.9×2.9 cm right hilar lymph node. CT-guided biopsy of the lesion revealed it to be adenocarcinoma. The lesion was negative for mammoglobin and gross cystic disease fluid protein (GCDFFP). The biopsy was positive for Thyroid Transcription Factor-1 (TTF-1) (figure 3). Thus a diagnosis of metachronous primary lung malignancy was made and the patient started on chemoradiotherapy for primary lung malignancy.

INVESTIGATIONS

The complete blood picture, renal function tests, liver function tests and thyroid function tests were within normal range. Chest X-ray was within normal limits.

Fine-needle aspiration cytology of the left breast mass carried out at an outside hospital was suggestive of infiltrating ductal carcinoma of the breast.

Figure 1 CT scan of the chest without contrast (axial view), showing well-defined lesions with spiculated margins in the superior segment of the right lower lobe.

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Figure 2 Primary breast cancer with positivity for ER, PR and 2+ staining for Her2 neu. ER, PR, estrogen and progesterone receptor.

Mammography of both breasts showed them to be composed of dense fibroglandular tissue with no evidence of focal lesions on the right. A multilobulated mass with indistinct margins was noted in the upper and outer quadrant of the left breast.

Histopathological examination of the resected specimen was suggestive of infiltrating ductal carcinoma with 2 of 14 dissected lymph nodes showing metastasis. Immunohistochemistry and immunofluorescence showed ER, PR receptor-positive status. Ki67 was positive in 28% of cells (figure 2).

Fluorescence in situ hybridisation analysis on formalin fixed paraffin embedded sections was negative for HER2/neu gene amplification.

CT of the thorax showed a well-defined enhancing lesion with spiculated margins in the superior segment of the right

lower lobe and a heterogeneously enhancing right hilar lymph node (figure 1).

Postadjuvant chemotherapy, positron emission tomography with CT (PET CT) showed left postmastectomy with no obvious metabolically active local recurrence; a lobulated metabolically active 2.1×1.8 cm soft tissue lesion in the apical segment of the right lower lobe lung parenchyma along the right oblique fissure; and a metabolically active 2.9×2.9 cm soft tissue lesion in the right hilar region.

The histopathology of the CT-guided biopsy of the lung lesion was suggestive of adenocarcinoma. Immunohistochemical and immunofluorescence were negative for ER, PR, mammoglobin and Gross Cystic Disease Fluid Protein (GCDFFP), and were positive for TTF (figure 3), suggestive of primary lung

Figure 3 Malignant cells beneath respiratory epithelium, which were negative for ER, PR and positive for TTF-1 on IHC. ER, PR, estrogen and progesterone receptor; IHC, immunohistochemical; TTF-1, thyroid transcription factor.

adenocarcinoma. This lung lesion was negative for EGFR and ALK mutation.

DIFFERENTIAL DIAGNOSIS

Synchronous double primary adenocarcinoma of the lung and infiltrating ductal carcinoma of the breast.

Infiltrating ductal carcinoma of the breast, with lung metastasis.

TREATMENT

The patient was treated with a modified radical mastectomy followed by chemotherapy (adriamycin and cyclophosphamide for four cycles followed by paclitaxel for four cycles) for breast carcinoma. She was diagnosed with carcinoma of the lung stage cT1bN2 and adenocarcinoma of the lung and was planned for concurrent chemoradiotherapy.

OUTCOME AND FOLLOW-UP

The patient was, at writing, undergoing chemoradiotherapy for lung carcinoma and had completed two weeks of treatment.

DISCUSSION

Breast cancer has metastatic capacity as an inherent feature. Predictors of metastasis in breast cancer are not well established. Some of the confirmed prognostic markers of metastasis in breast cancer include tumour size, lymph node involvement and histological grade.² Young age and premenopausal age groups are found to have early visceral metastasis.³ About one-third of breast cancers without lymph node involvement have a distant metastasis (Cardoso *et al*, 2011; De Vita *et al*, 2008). About 10–15% of cases with breast cancer develop early distant metastasis. About one-third of the breast metastases are visceral metastases either to the lung or liver.

Lung cancer is also one of the most common malignancies in the world. Lung cancers account for 5% of second primary cancers after breast cancer.⁴ It is also a common site of metastasis for cancers such as breast, gastric, colon, renal cell carcinoma, etc. Even though breast cancers are inherently metastatic irrespective of the size of primary or lymph node status, initial assessment and staging of early breast cancer is purely clinical and histopathological. Imaging is not indicated unless in the presence of clinical symptoms as per National Comprehensive Cancer Network guidelines. Our case—which was staged as an early breast cancer but turned out to have a suspicious metastatic lung lesion incidentally picked up on CT of the thorax—ultimately turned out to be a lung primary. Thus, in light of the above facts, a suspicious metastatic lung lesion found in a case of breast malignancy, irrespective of the stage of the primary, should be histopathologically identified, to differentiate it from a second primary, as it may dictate a prognosis and treatment plan that differs significantly for each scenario. Also, it suggests the importance of imaging even in asymptomatic cases, to identify an occult metastasis or a second primary that may go unnoticed.

Malignancies of similar histological types have similar histological features, thus differentiating a primary from a metastatic lesion based only on morphological features is difficult. Immunohistochemical analysis of these lesions helps in differentiating them. Thyroid transcription factor-1 is a member of the NKX-2 gene family of the homeodomain-containing nuclear transcription factors expressed selectively by thyroid follicular and parafollicular C-cells, type II pneumocytes and non-ciliated bronchiolar epithelium (Clara cells) of the lung. It plays an important role in the early differentiation and morphogenesis of the lung and thyroid gland. In the lung, it regulates the

expression of surfactant apoproteins. TTF 1 is positive in small cell carcinomas (85–90%) and in adenocarcinoma (75–80%).⁵ It is a reliable indicator of primary lung malignancy, provided a thyroid primary has been excluded. It has a sensitivity of 61.53% and specificity of 100% in identifying primary lung malignancy.⁶

Moldvay *et al* showed TTF 1 positivity in 46 of 50 primary lung adenocarcinomas; and of 50 metastatic adenocarcinomas studied all but two were negative.⁶ Yue-Chiu Su *et al* showed TTF-1 positivity in 73% of primary lung adenocarcinomas.⁷ While it was negative in all non-pulmonary adenocarcinomas. Discordance in the expression of ER, PR and Her2/neu of primary and metastatic breast cancers has been shown,^{8,9} so they cannot be relied on in differentiating primary and metastases. Mammaglobin has a sensitivity of 42.3% and that of GCDPF-15 is 31.6% in detecting cancers of breast origin. Combined usage of mammaglobin and GCDPF increased sensitivity to 53.0% for primary tumours and 69.0% for nodal metastases.¹⁰ In our case, histopathological examination of this suspicious lung lesion was suggestive of adenocarcinoma as the primary breast cancer was also an adenocarcinoma. Immunohistochemical analysis of lung lesions, with TTF-1, mammaglobin and GCDPF, is used to establish the diagnosis of metachronous primary lung malignancy. Thus histological examination combined with immunohistochemical analysis of metastatic lesions, with tissue-specific markers such as TTF-1, mammaglobin and GCDPF, helps in differentiating primary lung neoplasm from metastases in known cases of malignancy, thus helping in planning appropriate therapy for the patient and avoiding catastrophic sequelae. Our case has clearly shown the importance of biopsy in suspected metastatic lesions in cases of early breast cancer, as a new primary lesion should not be missed.

Learning points

- ▶ A diagnosis of metastatic disease should always be made with a confirmatory biopsy, as it would affect the further management and prognosis, and alter the outlook for the patient.
- ▶ CT of the thorax is advisable in early breast cancer even if the patient is asymptomatic, as most lung lesions are indolent in the early stages.
- ▶ Immunohistochemistry helps in differentiating primary from metastatic malignancies with identical histological features.

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Competing interests None declared.

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Reminder of important clinical lesson

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