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Case Report

Primary lung cancer with metastasis to the ipsilateral breast-a case report

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ABSTRACT

The metastasis of extra-mammary malignancy to breast is extremely rare; literature reports the incidence between 0.4-1.3%. Primary sites include the contralateral breast, leukaemia, lymphoma, malignant melanoma, sarcoma, lung, prostate, ovary, colon and the stomach. Here we present a rare case in which lung cancer was found to metastasise to the breast. Initially the patient presented with chest symptoms and a left breast lump was detected clinically. The radiological and histological investigations confirmed the diagnosis of primary lung cancer with breast metastases. Prognosis of such cases is generally poor.

Keywords: Breast cancer, Cytokeratin 7, Lung adenocarcinoma, TTF-1

INTRODUCTION

Metastasis to the breast from extra-mammary sites is rare. Leukaemia, lymphoma and malignant melanoma are the most common sites of the primary. Other sites have been reported as lung, rhabdomyosarcoma, renal adenocarcinoma, leiomyosarcoma, cervix, vulva, stomach, endometrial adenocarcinoma and plasma cell myeloma.[1-10] Clinical symptoms from the breast metastatic focus may be the first presentation of the disease. Differentiation of primary breast cancer from a metastatic auxiliary source is essential to decide on best management. It is not always easy to distinguish between a metastatic tumour and a synchronous or metachronous primary cancer, especially when the metastatic focus is asymptomatic. A systemic and palliative approach is usually required for metastatic disease; accurate diagnosis may avert unnecessary surgery. In this paper we present a case of an 84-year old female with breast metastases, secondary to lung cancer.

CASE REPORT

An 84-year-old female presented to the emergency department with a recent history of progressive shortness of breath, fatigue, cough and chest pain. Her past medical history included hypertension, atrial fibrillation on warfarin and childhood intraabdominal tuberculosis. No significant medical family history was noted but she was an ex-smoker with a significant pack-year history. Clinically, there was dullness on percussion and reduced air entry in the left hemithorax. In addition to chest signs, she had a discrete mobile lump in the left breast upper outer quadrant, measuring about 25mm. Chest x-ray and chest CT scan revealed a soft tissue attenuation of the left

lung lower lobe mass associated with a large left-sided hydropneumothorax (Figures 1,2). Mammogram showed a suspicious soft tissue mass in the left breast upper outer quadrant (Figure 3). The left breast ultrasound scan detected a 21x20x13mm hypoechoic suspicious lesion with slightly irregular margins (Figure 4); this was graded as M4/U4 in BIRADS [Breast Imaging-Reporting and Data System].

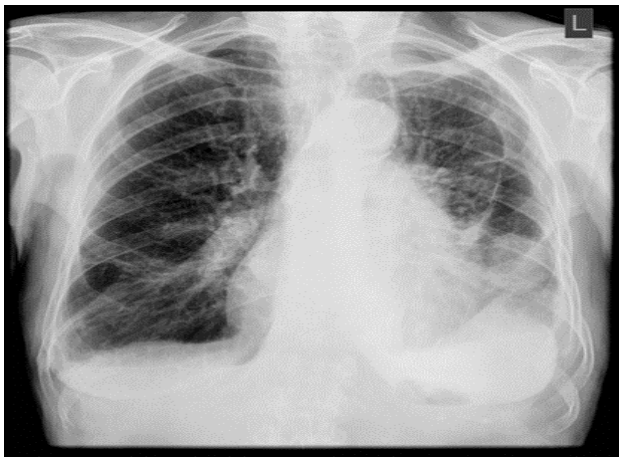

Figure 1: chest x-ray. left side hydro-pneumothorax with lesion in the left lung lower lobe.

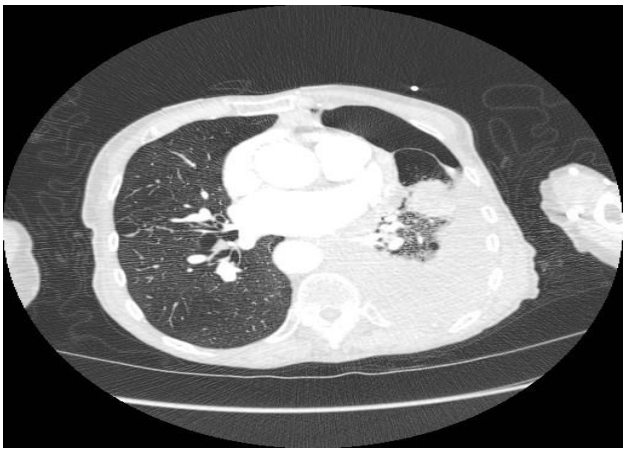

Figure 2: Axial view chest CT scan. Mass lesion in left lung lower lobe with left sided hydro-pneumothorax.

Left lung mass biopsy showed several fragments of soft tissue infiltrated by sheaths of relatively large epithelial cells with round-oval nuclei, vast eosinophilic cytoplasm of distinct limits (Figure 5), and frequent mitosis and apoptosis bodies. Tumour cells expressed high levels of CK7 (Figure 6) and TTF-1 (Figure 7), but were negative for CK5, P63, oestrogen receptor (ER) (Figure 8) and GCDF-15 (Figure 9). Lung ALK was negative in immuno-histochemistry. The left breast biopsy was similar to the lung biopsy in morphology (Figure 10) and biopsy was completely negative for ER (0/8) and PR (0/8), with Ki67 proliferative index of approximately 60%. Her-2 was also negative by both IHC and ISH. The left breast biopsy was also similar to the lung biopsy in the immunophenotype. Screening for both lung ALK-IHC and EGFR mutation was negative. These features were in keeping with an adenocarcinoma of the lung, predominantly solid type. The patient was referred to the oncological team for further management.

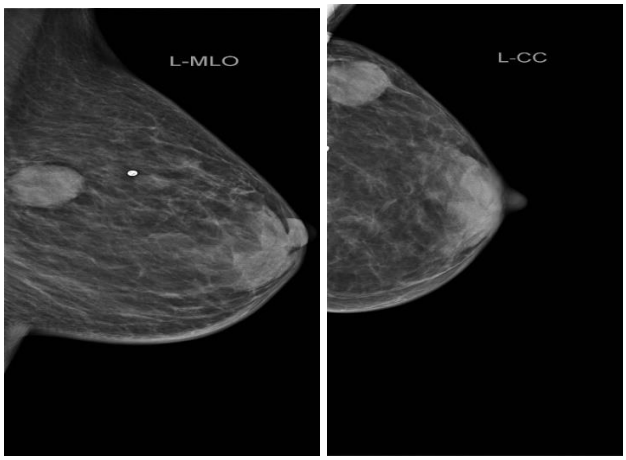

Figure 3: Left mammogram [MLO and CC] views. Soft tissue mass in outer upper quadrant (M4).

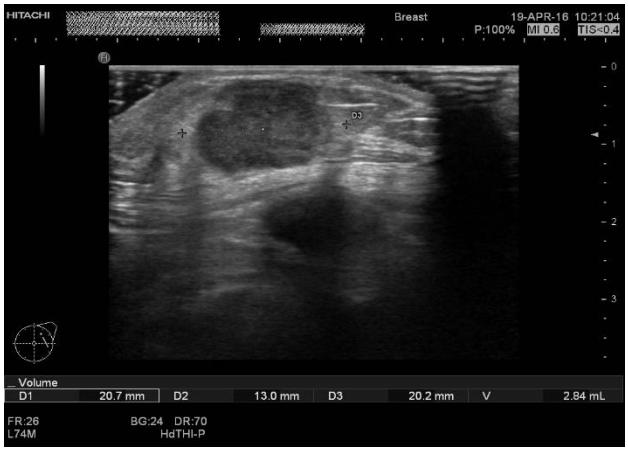

Figure 4: Left breast US. 21x20x13 mm hypoechoic lesion with slightly irregular margins (U4).

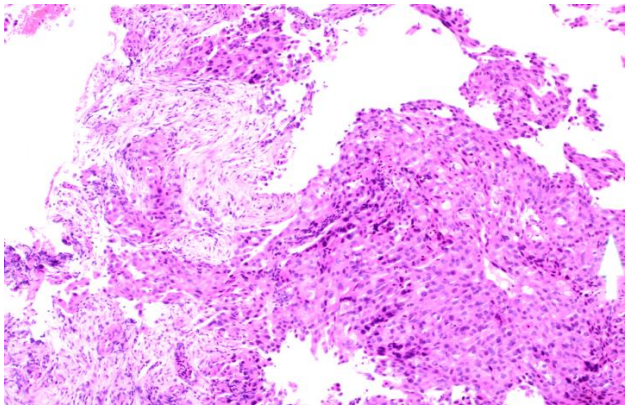

Figure 5: Fragments of tissue from lung biopsy sample infiltrated by poorly differentiated carcinoma (H and E).

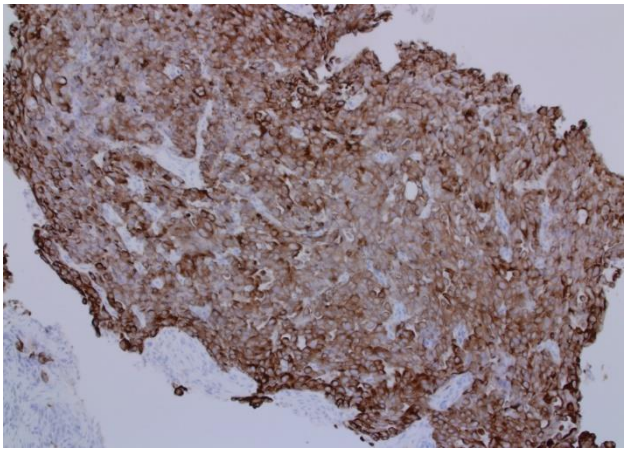

Figure 6: The neoplastic cells are positive for CK7.

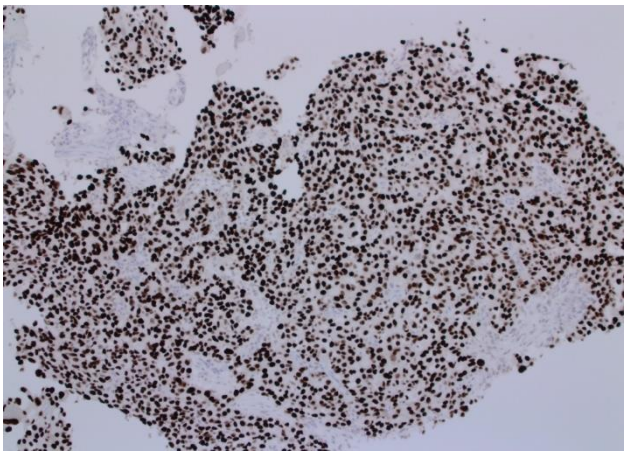

Figure 7: The lung biopsy tumour is strongly positive for TTF-1.

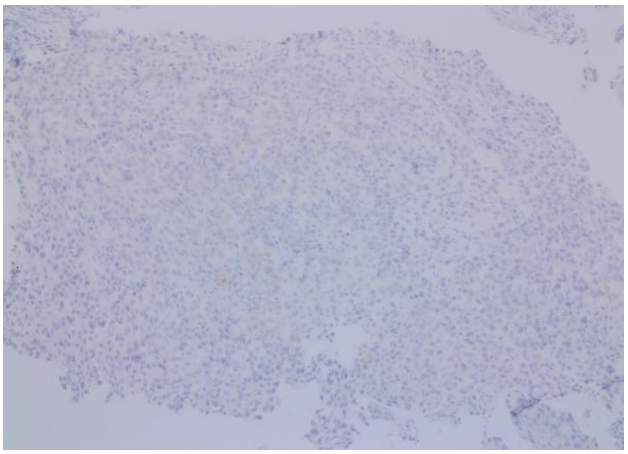

Figure 8: ER negative.

DISCUSSION

WHO classifies lung cancer into epithelial origin [adenocarcinoma, squamous carcinoma], lymphohistiocytic, ectopic origin, neuroendocrine, mesenchymal and metastatic.[11] The neuroendocrine tumours are subdivided into small cell carcinoma (SCC), large cell carcinoma, carcinoids and sarcomatoid carcinoma.[11] Primary lung cancer is the most common malignancy after non-melanocytic skin cancer, and the leading cause of human cancer deaths worldwide, with an overall 5-year survival rate of 10% to 15%.[12,13] Non-small-cell lung cancer (NSCLC) accounts for 80-85% of lung cancers, it is subdivided into three distinct histological subtypes: adenocarcinoma, lung squamous cell carcinoma (SQCC) and large cell carcinoma.[14,15] Studies have shown that smoking is the main risk factor of lung cancer, accountable for 80% of cases.[16] The most common sites of small cell carcinoma is the lung, but it can also occur in extra-pulmonary sites such as the gastrointestinal, genitourinary or gynaecological tracts, head and neck.[17]

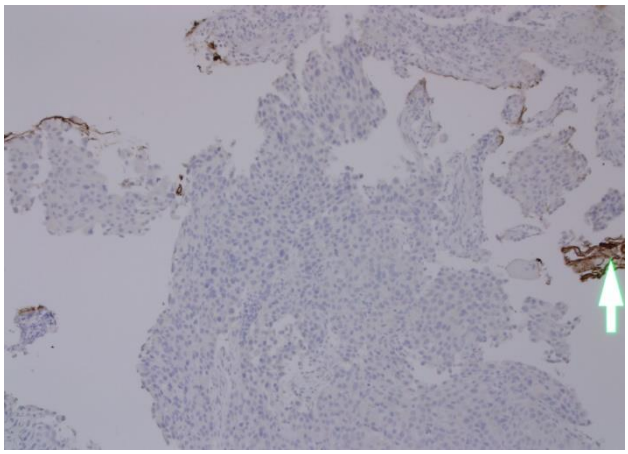

Figure 9: GCDFP15 negative.

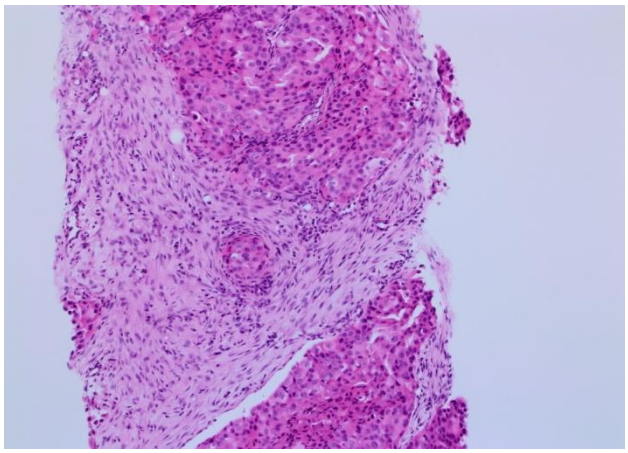

Figure 10: Cores of breast tissue biopsy infiltrated by Invasive carcinoma.

Small cell lung cancer (SCLC) presents as a highly aggressive malignant disease that displays poorly differentiated neuroendocrine features.[18] Nearly all cases of SCLC are attributable to cigarette smoking, accounting for 15% of all cases. In the UK, lung cancer is the third (13%) most commonly diagnosed cancer after breast (15%) and prostate (13%) and before bowel cancer

(11%). These four cancers together account for more than half (53%) of all new cases in the UK (2014).[19] The recent researches showed that the incidence of SCLC has been decreasing in frequency over the last two decades.[20]

About 20% of newly diagnosed lung adenocarcinomas present with remote metastatic disease. The most frequent sites of metastasis in descending order are brain, bone, liver, and adrenal glands.[21] The Autopsy studies revealed that non-small cell lung cancer (NSCLC) can spread to any organ.[22] Breast invasion by metastatic solid extra-mammary tumours is uncommon due to the large areas of fibrous tissue and relatively poor blood supply in the breast.[23] Breast metastases from an extra-mammary primary tumour, including lung cancer, is rarely reported and has an incidence of 0.5% to 3% for all breast malignancies. The most commonly reported sites of primary malignancies which metastasise to the breasts are leukaemia/lymphoma (48%), or malignant melanoma (38%). Other less common sites are lung (13%), colon, rhabdomyosarcoma, renal adenocarcinoma, leiomyosarcoma, cervix, vulva, stomach, endometrial adenocarcinoma and plasma cell myeloma.[1-10,24,25]

The secondary malignant lesions in the breast are most often freely mobile, well-circumscribed, round oval masses. There is also frequently an absence of skin involvement. These features may mimic a benign tumour.[23] Mammogram could be useful in the differential diagnosis of primary and metastatic breast neoplastic lesions. The typical mammographic presentation of metastatic breast malignancy is a round and dense mass. Speculation, distortion of the adjacent architecture and micro calcifications are usually not seen, except in the rare case of metastasis from ovarian carcinoma.[3,23,26-27] The imaging and histology of both primary and metastatic sites can confirm the diagnosis. Hormone receptor status and immuno-histochemistry are necessary to exclude the primary breast cancer. The tissue-specific transcription factor (TTF-1) is expressed in lung epithelial cells and thyroid cells, including C cells. It is also positive in certain areas of the brain. TTF-1 is found to be positive in approximately 70% of pulmonary adenocarcinomas, both primary and metastatic.[28,29]

The majority of primary breast cancers are TFF-1 negative; only a few cases of breast primary small-cell carcinoma express positivity.[30,31] TTF-1 immunohistochemical study in our case was positive. Careful immunohistochemical analysis, including ER, PR, Her2, which may be positive in breast cancer, is needed to confirm the origin. ER, PR and Her2 analysis in our case was negative. Cytokeratin 7 (CK7) is a 5-kDa basic protein, which shows strong expression in different epithelia including the breast, upper gastrointestinal tract, endometrium, urinary bladder, pancreas, biliary tract, and lung.[32,33] CK7 expression was significantly more frequent in pulmonary adenocarcinoma and breast adenocarcinoma than adenocarcinoma of gastrointestinal (GI) origin.[34] In our case CK7 test expressed positivity. CK20 is a 46-kDa acid protein found in the epithelium of the intestine, bladder, pancreas and biliary tract as well as in Merkel cells.[35] CK20 is essentially negative in breast cancer, lung adenocarcinoma and ovarian cancer.[36] It is reported that CK20 expression was significantly more prevalent in adenocarcinoma that originated in the GI tract than that of pulmonary or breast origin.[34] Despite this fact, CK20 may express positivity in lung adenocarcinoma.[34,37-39] Adenocarcinoma originating in the lungs is typically CK7 positive and CK20 negative. However, this immuno-histochemistry profile is not specific to pulmonary adenocarcinomas; it may also be seen in breast cancer, thyroid cancer, upper gastrointestinal or gynaecological carcinoma, biliary tracts, and pancreatic cancer.[40]

Our case was CK7 positive. Gross cystic disease fluid protein 15 (GCDFP-15), which is regulated by the androgen receptor (AR), is a marker of value in differentiation of breast originated tissue. Its expression is higher in tumours with favourable prognostic features.[41] GCDFP-15 was not detected in our case.

The other useful marker is EML4-ALK (echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase). It is a fusion gene which has been identified as a potent oncogenic driver in non-small-cell lung cancer, in particular adenocarcinoma (ADC). It defines a unique subgroup of lung ADC, which may be responsive to ALK inhibitors.[42] Cytokeratin 5 is a protein marker which defines a basal-like subtype of invasive ductal carcinoma of the breast that is usually CK5/6+, ER-, PR-, HER2-.[43] CK5 was negative in our case. P63 (transformation-related protein 63) is a protein that is encoded by the TP63 human gene. This marker is used for squamous differentiation, it rarely stains adenocarcinoma.[44]

This was not expressed in our case. Epidermal Growth Factor Receptor (EGFR) is a transmembrane protein, its function is a membrane receptor for the epidermal growth factor family. Overexpression of this marker has been identified in NSCLC (41%) and up to 89% in lung squamous carcinoma.[45] Chemotherapy remains the standard of care for the majority of patients with metastatic lung cancer and a new treatment approach based on immunomodulation is in place. Program Death-1 (PD1) protein is a co-T-cell regulatory receptor that controls the immunosuppression mechanism by binding to the PD-L1 ligand present on stromal and tumour cells. Current clinical trials revealed that blocking this receptor-ligand interaction results in an enhanced T-cell response and significant tumour cell death.[46] The outcomes of patients with breast metastases are poor, and 80% of these patients die within 1year of presentation.[23]

CONCLUSION

Although metastases to breast from other sites are rare, a secondary lesion should be considered in the differential

diagnosis of breast cancer if the morphology is unusual for primary breast cancer. This is especially the case if there is a previous or current history of malignancy. Accurate diagnosis to distinguish a primary breast carcinoma from a metastatic one is crucial. This needs effective communication between the clinician, radiologist and pathologist, to ensure the most appropriate therapeutic plan is put in place.

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