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Case Report

Small Cell Lung Cancer with Metastasis to the Breast: A Case Report and Review of the Literature

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Abstract

Metastasis to the breast represents 0.4-1.3% of all breast malignancies. In those rare instances, the primary site is usually leukemia, lymphoma, or melanoma. Lung cancer, mostly adenocarcinoma, has been reported to be associated with metastasis to the breast. We report a rare case of a female patient with a rapidly growing breast metastasis from a small cell lung cancer, as a first site of recurrence, misread as a triple negative breast cancer. A full immunohistochemical panel, including ER, PR, Her2/Neu, TTF-1, CK7/CK20, and chromogranin should be employed to confirm the pathology. Differentiating between a newly diagnosed primary breast cancer and metastatic small cell cancer to the breast is important because recurrent small cell lung cancer has a worse prognosis and is treated differently.

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INTRODUCTION

Breast cancer is the most commonly diagnosed non-skin malignancy in women worldwide [1]. Around 1 in 8 women will be diagnosed with breast cancer in their lifetime [2]. Metastasis to the breast is an uncommon phenomenon, occurring in about 0.4-1.3% of all breast malignancies [3]. In those rare instances, the primary site is usually leukemia/lymphoma (48%) or melanoma (38.5%) [4-6]. Other infrequent sites include genitourinary (4.7%), gastrointestinal (7.1%), and lung carcinomas (13%) [4-6]. Among lung cancers metastasizing to the breast, NSCLC has been reported in approximately 30 cases [1-3],while small cell carcinoma reported only in three [7]. We report a female patient with breast metastasis, as the first site of metastasis, originally misdiagnosed as a triple negative breast cancer, confirmed to be originating from a small cell lung carcinoma. We report and discuss clinical, radiological and pathological differential diagnosis.

CASE REPORT

A52 year old woman, 12 pack-year smoker, presented with dyspnea and orthopnea for few months. She also complained of symptoms of upper respiratory tract infection. A CT scan showed an infiltrative anterior mediastinal soft tissue mass. A fine-needle aspirate biopsy revealed primary small cell lung carcinoma. Metastatic work-up at that time was negative. The patient was given4 cycles of cisplatin and etoposide, followed by radiation therapy. A routine follow-up CT scan by her primary physician, after 6 months, showed 3 new left breast lesions, measuring 2.4cm, 2.5cm, and 1.3cm, and a new right breast nodule of 0.9cm, as well as a new 4.3x2.4cm right adrenal mass (Figure 1a). Her interval history was positive for redness and swelling of her left breast. Biopsy of the breast was read as an infiltrating breast cancer with Estrogen Receptor (ER) negative, Progesterone Receptor (PR) negative, and HER2 negative. She did not receive treatment at that time. Two months later, she presented to us for a second opinion and we noted marked swelling and redness overlying more than one-third of the breast along with an inverted nipple. A9x13cm mass was felt in the upper outer quadrant of the left breast, which was fixed to the overlying skin (Figure 2).Two to three lymph nodes were also appreciated in the left axilla. Repeat CT scan showed increase in size of the 3 left breast lesions to 4.5cm, 2.6cm, and 2.2cm, and the right breast nodule to 2cm (Figure 1b). The right adrenal mass also increased to 5.6x2.6cm. There was also evidence

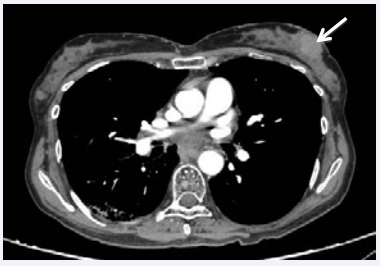

Figure 1a CT scan of the chest showing a 2.5cm lesion in the left breast.

of anew infiltrative mass of 5cm in the pancreatic body and tail. A new reading of the prior breast biopsy at our institution showed metastatic small cell lung carcinoma to the breast, and notprimary breast cancer. A PET scan showed hypermetabolic activity in the upper lobe of the right lung, 2 masses in the left breast, left axillary and supraclavicular lymph nodes, right adrenal, and tail of the pancreas. Patient was treated with second line chemotherapy with CAV (Cyclophosphamide, doxorubicin, and vincristine) once every three weeks [8]. Patient had a very good clinical response of her breast metastases, with the three congruent masses in the left breast now decreased to 4x5cm on physical exam. After 4 cycles, a repeat PET scan showed mixed response to treatment; while the breasts, adrenal and pancreas showed decreased FDG metabolic activity, there were an increase in the lung primary site. Patient was then shifted to a third-line chemotherapyregimen with irinote can [9]. However, the patient's course was complicated by pulmonary embolism, and she passed away one month later, seven months after the appearance of breast metastasis, and fifteen months after her first diagnosis (Figure 3).

DISCUSSION

Small cell lung cancer is known to be a very aggressive tumor, with a metastasis rate reaching up to 60% at diagnosis [10]. Lung cancer metastasizes to various organs, mainly the liver and bone (30-50%), brain (15-43%), lung (20-40%), adrenal gland (17-38%), kidney (16-23%), spleen (9%), ovary and pituitary (1%) [11]. Moreover, metastases to other sites have also been reported, including the breast, which per se, is a very rare site of metastasis. In a review of 14,000 breast cancer cases diagnosed between 1907 and 1999 conducted by Georgiannos group, only 0.43% (60 cases) of the total were reported to have metastasized from other sites [6]. Out of those 60 cases, only 5 (0.035% of the 14,000 patients) were found to be small cell lung carcinoma with metastasis to the breast.[6]In another study in 2007, Williams et al. investigated 169 cases of secondary metastasis to the breast, 15 of which had a pathology reading of small cell carcinoma, including extra-pulmonary small cell carcinoma [5]. So far, only few case reports have been published on this topic in the English literature [7,12,13].

The gold standard to differentiate between primary breast cancer and secondary metastasis to the breast is by cytological examination

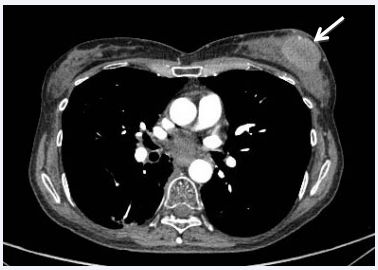

Figure 1b Follow-up CT scan 2 months later showing an increase in size of the left breast lesion to 4.5cm.

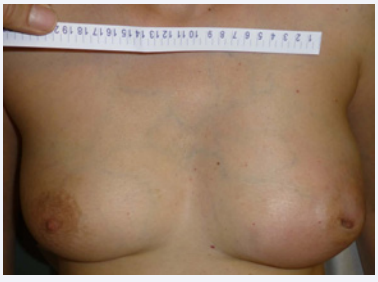

Figure 2 Breast metastasis showing enlargement of the breast, redness of the overlying skin, and edema and retraction of the nipple-areola complex.

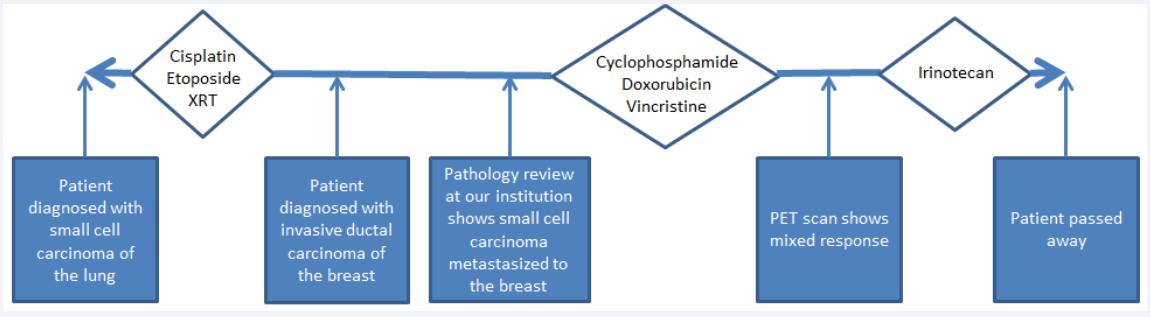

Figure 3 Schematic diagram of the treatment course of the patient.

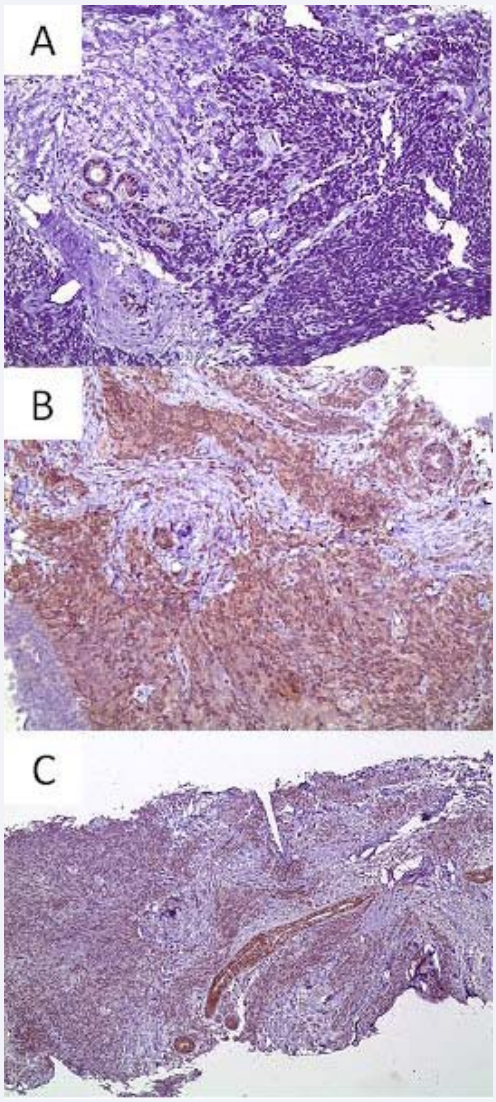

Figure 4 A. Negative staining for ER; B. Negative staining for PR; C. Negative staining for HER2.

of the tumor cells [7,13]. Other techniques that may help to reach the proper diagnosis include physical examination, radiological findings, and immunohistochemistry. In general, on physical exam, breast metastasis patients have been reported to present with well circumscribed firm masses that are very mobile [3,13]. Also, they tend to be rapidly-growing, painless lesions that are usually located in the subcutaneous tissues rather than glandular tissue [14]. In contrast, primary breast cancer is most commonly adenocarcinoma, hence arising from glandular tissue [6]. Moreover, they have a predilection to the upper outer quadrant of the breast, without causing skin or nipple retraction [1-3,14]. However, in our patient, the presentation was quite misleading. The tumor was rapidly-growing but fixed to the skin and associated with nipple inversion.

Radiologically, microcalcifications and speculations are usually absent in breast metastasis patients [13-15]. On mammography, the metastatic breast lesion appears roughly the same size as that on physical examination. This is in contrast to primary breast lesions, which frequently appear smaller on mammography [15]. Our patient did not undergo mammography since she was diagnosed with breast metastasis incidentally upon follow-up CT scan for her primary lung cancer.

For further confirmation of the diagnosis of metastasis versus primary breast cancer, immunohistochemical panel should be employed. Small cell carcinomas usually stain positive for synaptophysin, chromogranin and CD56 [4]. Thyroid Transcription Factor-1 (TTF-1) was shown to be positive in 93% of small cell lung carcinoma [3], while it stains negative in breast adenocarcinomas [1]. In addition, CK7 is consistently negative in small cell lung carcinoma, while it is mostly positive in primary breast small cell carcinoma and lung adenocarcinoma [16]. Markers that favor breast adenocarcinoma include estrogen receptor (ER), progesterone receptor (PR), gross cystic disease fluid protein 15 (GCDFP-15), and mammaglobin [3]. ER and PR are expressed in 80% and 60% of breast adenocarcinomas, respectively. However, negativity in ER and PR does not rule out breast adenocarcinoma [3]. As for GCDFP-15 and mammaglobin, both markers can help differentiate between breast adenocarcinoma

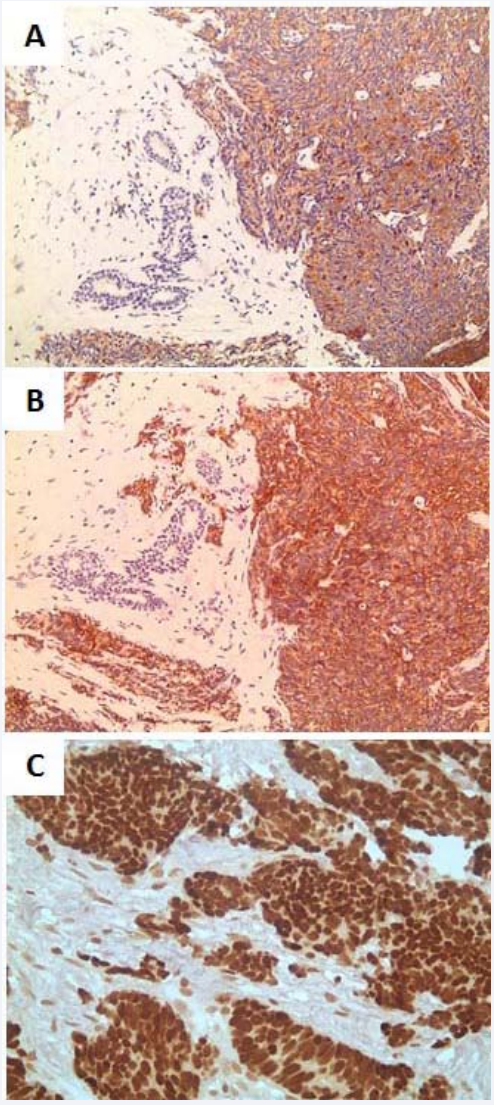

Figure 5 A. Positive staining for Synaptophysin in metastatic tumor; B. Positive staining for CD56 in metastatic tumor; C. Positive stainig for TTF-1 in metastatic tumor.

(positivity rate of 45-53% and 48-72.1%, respectively) and lung adenocarcinoma (positivity rate of 5.2-15% and null, respectively) [1]. Consequently, a single biomarker is insufficient to reach the proper diagnosis; thus, a panel of immunohistochemistry is recommended.

Although small cell carcinoma most commonly occurs in the lung, one should not overlook the possibility of it originating from the breast. The absence of in situ component is essential in diagnosing metastatic tumor, although it does not confirm it [4]. Moreover, elastosis is usually present in primary tumors but is rarely seen in secondary tumors [3]. In our patient, histological findings revealed small malignant cells with high nuclear-cytoplasmic ratio that were identical to the fine needle aspirate from the mediastinal mass, with no in situ component detected. The ER, PR, and HER2 were all negative (Figure 4). Also, the tumor stained positive for TTF-1, CD56, and synaptophysin, thus confirming the diagnosis of primary small cell lung carcinoma with breast metastasis (Figure 5).

Attention to above different features helps to differentiate between primary breast adenocarcinoma and small cell lung carcinoma with secondary metastasis to the breast in order to determine the proper course of treatment, including different chemotherapeutical and surgical options [4,7]. Furthermore, breast metastasis carries a much worse prognosis than breast adenocarcinoma with an estimated survival period of less than a year after diagnosis [5].

CONCLUSION

We report the first case of a rapidly growing breast metastasis from a small cell lung cancer with breast being its first clinical site of metastases, initially misread as a triple negative breast cancer. Metastasis to the breast, although a rare diagnosis, should be kept on the differential of a patient with primary small cell lung cancer. Physical examination, radiological findings, and immunohistochemistry are very helpful in reaching the proper diagnosis. This, in return, has a significant impact on the patient's treatment modalities and prognosis.

CONFLICT OF INTEREST STATEMENT

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from nagi.saghir@aub.edu.lb.

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