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Lung Cancer Metastasis to the Breast: Consideration of an unusual Presentation

Keywords: Lung cancer metastases; Metastases to the breast; EML4-ALK fusions; Bioanalysis for targeted mutations

Abstract

Background: The EML4-ALK fusion oncogene is found in 2 to 7% of all non-small cell lung cancers, most of which are adenocarcinomas. These rare ALK-positive lung malignancies represent approximately 4% of all adenocarcinoma non-small-cell lung cancer; metastatic spread to the breast is exceedingly rare, with an incidence between 0.2-3% of reported cases. Here we present a case of ALK-positive lung cancer metastasizing first to the breast and then to the spine.

Case Report: A 60-year-old female with a left upper lobe pulmonary lesion suspicious for malignancy underwent a wedge resection; pathology revealed pulmonary adenocarcinoma with positive nodes. While an EML4-ALK fusion was identified, the patient refused adjuvant therapy. One month later, a 7mm lesion in the right lower mid-breast was identified; a biopsy identified poorly differentiated carcinoma consistent with lung origin. Pemetrexed, Cisplatin, and Carboplatin were initiated. Two months later, with new onset of back pain, a PET scan revealed a hypermetabolic bony lesion in the third lumbar vertebral body. A biopsy revealed metastatic adenocarcinoma from the lung. The patient began radiation therapy and, given the EML4-ALK fusion, transitioned from standard chemotherapy to targeted therapy. Currently, following the completion of radiation therapy, the bony metastasis has resolved, and the patient continues to tolerate targeted therapy well.

Conclusion: Metastases to the breast from other primary locations account for only 0.2-1.3% of all breast malignancies, but most often, these are lung cancer. EML4-ALK fusions are found in 2-7% of pulmonary adenocarcinomas, but indicate the use of targeted therapy which portends a high and durable response rate. This is the fifth EML4-ALK fusion oncogene identified in lung cancer metastasis to the breast that is managed with targeted therapy, emphasizing the importance of bioanalysis in management.

Abbreviations

EML4-ALK: (echinoderm microtubule-associated protein-like 4)-(anaplastic lymphoma kinase); ALK: anaplastic lymphoma kinase; ED: emergency department; CT: computed tomography; PET: positron emission tomography; ER: estrogen receptor; PR: progesterone receptor; Her-2: human epidermal growth factor receptor-2; GATA3: transcription factor important in the differentiation of breast epithelia

TTF-1: thyroid transcription factor 1; SOS-10: son of sevenless-10; developmental protein that stops DNA repair; TKI: tyrosine kinase inhibitor; Napsin-1: functional aspartic proteinase that is a new marker for lung cancer.

Introduction

Lung cancer is the most commonly diagnosed cancer, with over 238,000 cases and over 127,000 deaths expected in 2023 [1]. Lung cancer is classified into two categories: small-cell lung cancer, representing 15% of cases, and the more prevalent non-small cell lung cancer representing 85% of cases [1].

The EML4-ALK fusion oncogene is found in 2 to 7% of all non-small cell lung cancers, most of which are adenocarcinomas. These gene rearrangements are more prevalent in females, young patients, and non-smokers, as well as in Asian and Western populations [2]. Metastases typically present in the liver, adrenals, bone, and brain. While there are treatments with molecularly targeted therapy, which have been noted to increase survival [3], the prognostic significance of the EML4-ALK oncogene is controversial [4].

Breast metastases from extramammary locations are rare, representing 0.2%-1.3% of all breast malignancies [5], typically portending a poor prognosis given that, in most cases, widely diffuse metastases of the primary cancer are often present at the time of the breast metastasis discovery [5]. However, in the limited reports of patients with EML4-ALK-positive lung cancer metastasizing the breast, patients have demonstrated favorable outcomes to targeted therapy. Here we present a case of ALK-positive lung cancer metastasizing first to the breast and then to the spine.

Clinical Case

A 60-year-old female presented to the ED for dyspnea and tachycardia. A CT angiogram of the chest incidentally revealed a left upper lobe spiculated pulmonary lesion (1.4 cm) that was suspicious for malignancy; no mediastinal hilar lymphadenopathy was noted. CT/PET demonstrated a single hypermetabolic left upper lobe lesion with no other evidence of disease. A robotic wedge resection and left upper lobectomy were completed; pathology revealed an invasive pulmonary adenocarcinoma that invaded the visceral pleura, as confirmed on elastin stain, with negative margins; 1/12 nodes were positive for metastatic carcinoma (T2aN1; Figure 1).

Biomarker analysis (FoundationOne; Cambridge, MA) identified EML4-ALK fusion; the patient refused oral targeted therapy. Adjuvant

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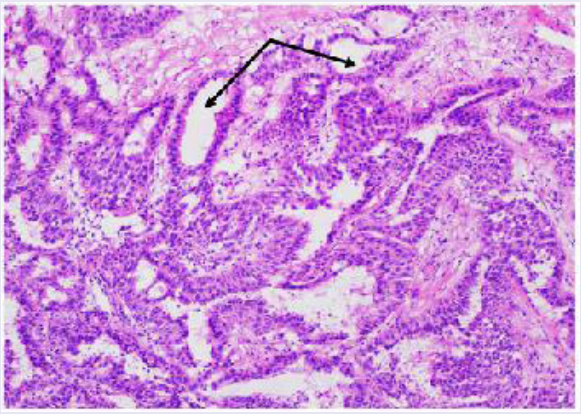

Figure 1: Lung adenocarcinoma histology. The nested pattern with nuclear hyperchromasia (100x) is consistent with adenocarcinoma. Note the glandular lumen (black arrows) characteristic of adenocarcinoma.

cisplatin/pemetrexed was initiated; however, the patient terminated therapy after one cycle due to nausea and facial swelling. Carboplatin/pemetrexed was initiated, but after two cycles, was terminated by the patient due to nausea.

Upon a routine screening mammogram one month later, a new 7mm lesion in the right lower mid -breast, which had not been visualized at the previous year's screening, was identified and felt to be suspicious. Subsequent ultrasound of the lesion revealed posterior acoustic shadowing consistent with a solid lesion; a biopsy was recommended and completed at an outside institution. Outside pathology reviewed at our institution noted a poorly differentiated carcinoma inconsistent with a breast primary (Figure 2a) with a non-breast immunohistochemical profile (11% ER +, PR-, Her-2-); cells were negative for GATA3 and mammoglobin, but were positive for TTF-I (Figure 2b) and Napsin A (Figure 2c), suggesting a lung origin.

Concordance with the lung adenocarcinoma confirmed that the breast lesion was consistent with metastatic lung cancer (GATA-, mammoglobin -, TTF-1+, Napsin A+, SOS-10+). A staging PET/CT scan revealed no uptake in the lung, minimal uptake in the right breast lesion, and a concerning lesion at L3. MRI of the brain was negative for intracranial metastatic disease. An interventional radiology vertebral biopsy revealed metastatic adenocarcinoma diffusely positive for CK7, TTF-1, and Napsin A consistent with the lung primary (ER and GATA3 negative; Figure 3).

Breast lumpectomy was completed; pathology identified metastatic pulmonary adenocarcinoma forming a 0.8cm mass which stained positive for TTF-1 and Napsin. All margins were negative, with the closest margin being 1.2 cm

Radiation therapy for the bony lesion was initiated (stereotactic body radiation to the L3 vertebral body; 700Gy for 5 days; total dose 3500Gy). Once the radiation was completed, and given the EML4-ALK fusion, the patient was transitioned to, and continues to take, targeted therapy (alectinib; Tyrosine Kinase Inhibitor; TKI). Serial follow-up CT chest/abdomen/pelvis at three months for a year and then every six months, along with brain MRIs every six months, have revealed stable findings with no evidence of new or recurrent disease 18 months postdiagnosis.

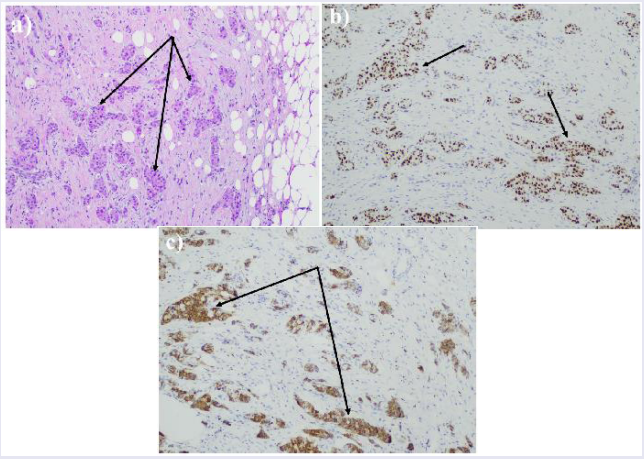

Figure 2: Breast biopsy histology. a) Infiltrating nests (black arrows) of adenocarcinoma within the desmoplastic stroma (100x); b) immunohistochemical staring for TTF-1 demonstrating positive nuclear staining (examples identified by black arrows) and c) immunohistochemical staining for Napsin-A demonstrating positive cytoplasmic staining (black arrows), indicative of lung adenocarcinoma.

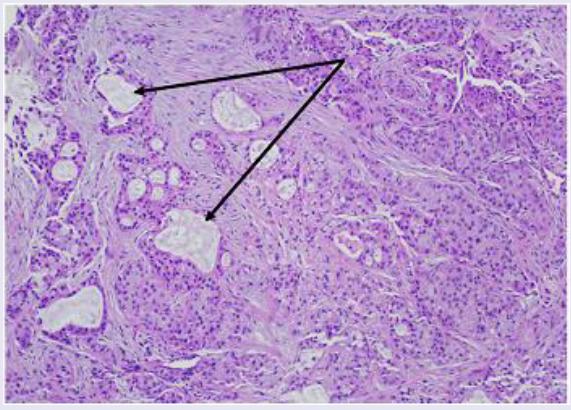

Figure 3: Bone biopsy histology. a) Adenocarcinoma infiltrating within the bone marrow (100x), forming glandular structures indicative of lung adenocarcinoma.

Discussion

Breast cancer accounts for 30% of all cancers in women [6]; however, metastases to the breast from other primary locations accounts for only 0.2-1.3% of all breast malignancies [5]. Tumors most often metastatic to the breast are lung cancer (22% of cases), lymphomas (15%), melanoma (13%), gastrointestinal cancers (8%), and papillary serous carcinomas (4%) [7]. Typically, tumors metastatic to the breast portend a poor prognosis as most patients have widely disseminated disease [5].

Histologic analysis and immunohistochemical evaluation of breast lesions can differentiate between primary and metastatic disease. In the case presented here, the IHC of the breast lesion indicated low ER expression with absent PR and Her-2, negative GATA3 and mammaglobin [8,9], inconsistent with a breast primary; the positive expression of TTF-1 and Napsin A, characteristic of 75% and 84% of lung adenocarcinomas, respectively suggested lung origin

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[10,11]. While TTF-1 is one of the most commonly utilized IHC markers in diagnosing lung cancers, it can also distinguish primary lung adenocarcinoma from tumors of other sources, substantiating the breast and spine lesions as lung metastases [12,13].

A comprehensive review of the literature noted 179 reports of lung carcinoma metastases to the breast between 1965 and 2013. In 2013, a systematic review of 31 previously published cases (1989-2013) identified that 87% of patients with lung metastases to the breast were female, 62% were nonsmokers, and the median age of diagnosis was 54. Pathologically, 58% of the tumors were adenocarcinomas, none of which expressed ER, PR, or HER-2 positivity [14]. In the case presented here, the presence of the EML4-ALK fusion in both the lung primary and the breast and spine lesions not only suggested metastatic disease, as EML4-ALK fusions are found in only 2-7% of pulmonary adenocarcinomas [2,15,16], but also indicated use of a targeted therapy that inhibits this fusion kinase and demonstrates high and often durable response [17].

To date, there are only three other reports identifying the EML4-ALK fusion oncogene in lung cancer metastasis to the breast and one widely metastatic breast cancer with this genetic profile.

All patients were eventually managed with TKIs that showed tumor regression [18,19,20].

Conclusion

Metastasis to the breast is an uncommon phenomenon but must be considered upon discovery of a breast mass in a woman with a history of cancer, especially primary lung cancer. Management of the breast is not the primary concern in such cases, as is evidenced by the current case where the additional systemic disease was discovered and thus identified the need for effective systemic therapy. The current management of non-small cell lung cancer demands an evaluation of possible actionable mutations. Typically, biomarker assessment is performed with nextgeneration sequencing panels looking for an ever-growing number of mutations that indicate targeted therapy, often oral agents with a high degree of initial disease control. As noted in our case, targeted therapy allows for effective management of a disease that would typically portend a poor prognosis.

References

1. https://www.cancer.org/cancer/lung-cancer.html; accessed 1/2/2023.
2. Solomon B, Varella-Garcia M, Camidge DR (2009) ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. J Thorac Oncol 4: 1450-1454.
3. Pacheco JM, Gao D, Smith D, Purcell T, Hancock M, et al. (2019) Natural history and factors associated with overall survival in stage IV ALK-rearranged nonsmall cell lung cancer. J Thor Onc 14: 691-700.
4. Liu Y, Ye X, Yu Y, Lu S (2019) Prognostic significance of anaplastic lymphoma kinase rearrangement in patients with completely resected lung adenocarcinoma. J Thorac Dis. 11: 4258-4270.
5. Lee AHS (2007) The histological diagnosis of metastases to the breast from extramammary malignancies. J Clin Pathol 60: 1333-1341.
6. Siegel RL, Miller KD, Fuchs HE, Jemal A (2021) Cancer Statistics, 2021. CA Cancer J Clin 71: 7-33.
7. Lee AHS, Hodi Z, Soomro I, Sovani V, Abbas A, et al. (2020) Histological clues to the diagnosis of metastasis to the breast from extramammary malignancies. Histopathology 77: 303-313.
8. Cimino-Mathews A, Subhawong AP, Illei PB, Sharma R, Halushka MK, et al. (2013) GATA3 expression in breast carcinoma: utility in triple-negative, sarcomatoid, and metastatic carcinomas. Hum Pathol 44: 1341-1349.
9. Baker E, Whiteoak N, Hall L, France J, Wilson D, et al. (2019) Mammaglobin-A, VEGFR3, and Ki67 in Human Breast Cancer Pathology and Five Year Survival. Breast Cancer (Auckl) 13: 1178223419858957.
10. Stenhouse G, Fyfe N, King G, Chapman A, Kerr KM (2004) Thyroid transcription factor 1 in pulmonary adenocarcinoma. J Clin Pathol 57: 383-387.
11. Suzuki A, Shijubo N, Yamada G, Ichimiya S, Satoh M, et al. (2005) Napsin A is useful to distinguish primary lung adenocarcinoma from adenocarcinomas of other organs. Pathol Res Pract 201:579-586.
12. Schilsky JB, Ni A, Ahn L, Datta S, Travis WD, et al. (2017) Prognostic impact of TTF-1 expression in patients with stage IV lung adenocarcinomas. Lung Cancer 108: 205-211.
13. Kim JH, Kim HS, Kim BJ, Han B, Choi DR, et al. (2018) Prognostic Impact of TTF-1 Expression in Non-Squamous Non-Small-Cell Lung Cancer: A Meta-Analysis. J Cancer 9: 4279-4286.
14. Mirrielees JA, Kapur JH, Szalkucki LM, Harter JM, Salkowski LR, et al. (2014) Metastasis of primary lung carcinoma to the breast: a systematic review of the literature. J Surg Res 188: 419-31.
15. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, et al. (2010) Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363: 1693-1703.
16. Pikor LA, Ramnarine VR, Lam S, Lam WL (2013) Genetic alterations defining NSCLC subtypes and their therapeutic implications. Lung Cancer 82: 179-189.
17. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, et al. (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371: 2167-2177.
18. Liu C, Ding L, Sun B, Wu S (2016) Bilateral breast adenocarcinomas with EML4-ALK fusion in a patient with multiple metastases successfully treated with crizotinib: is lung the primary site?. Onco Targets Ther 9: 3589-3593.
19. Kelly AD, Wiklund T, Kononen J, Creeden J (2021) STRN-ALK Fusion-Positive Case of Breast Cancer With Response to Alectinib. JCO Precis Oncol PO.21.00142.
20. Wu X, Wang H, Fang M, Li C, Zeng Y, et al. (2019) ALK or ROS1-rearranged breast metastasis from lung adenocarcinoma: a report of 2 cases. Tumori 105: NP67- NP71.