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Breast metastasis and lung large-cell neuroendocrine carcinoma: first clinical observation

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Abstract

Background and Aims: The lung large-cell neuroendocrine carcinoma (LCNEC) is a very rare aggressive neuroendocrine tumor with a high propensity to metastasize and very poor prognosis. We report an atypical presentation of lung LCNEC was diagnosed from a metastatic nodule on the breast.

Methods: Our patient is a 59-years-old woman that presented in March 2014 non-productive cough. A CT scan showed multiple brain, lung, adrenal gland and liver secondary lesions; moreover, it revealed a breast right nodule near the chest measuring 1.8 cm. The breast nodule and lung lesions were biopsied and their histology and molecular diagnosis were LCNEC of the lung. To our knowledge, this is the first documented case of breast metastasis from LCNEC of the lung.

Results: Furthermore, breast metastasis from extramammary malignancy is uncommon and its diagnosis is difficult but important for proper management and prediction of prognosis. Therefore, a careful clinical history with a thorough clinical examination is needed to make the correct diagnosis. Moreover, metastasis to the breast should be considered in any patient with a known primary malignant tumor history who presents with a breast lump. Anyhow, pathological examination should be performed to differentiate the primary breast cancer from metastatic tumor.

Conclusion: Therefore, an accurate diagnosis of breast metastases may not only avoid unnecessary breast resection, more importantly it is crucial to determine an appropriate and systemic treatment.

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Key words
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Authorship and contributorship
Papa Anselmo and Rossi Luigi wrote the paper under the supervision of Tomao Silverio; Verrico Monica collected data about the case; Di Cristofano Claudio and Moretti Valentina provided histopathological details; Strudel Martina and Zoratto Federica analyzed data from literature; Minozzi Marina reviewed language. All authors read and approved the final manuscript.

Ethics
This work was created in accordance with the ethical standards of the Declaration of Helsinki.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Background

Neuroendocrine tumor of the lung is classified into four subtypes according to the recent World Health Organization Classification: typical carcinoid, atypical carcinoid, small cell carcinoma, and large-cell neuroendocrine carcinoma (LCNEC) (1). LCNEC is now recognized as a histologically high-grade nonsmall cell carcinoma by WHO (2).

The diagnosis of LCNEC is based on recognition of both neuroendocrine morphology (organoid pattern) and the immunohistochemical demonstration of specific neuroendocrine markers (2), such as

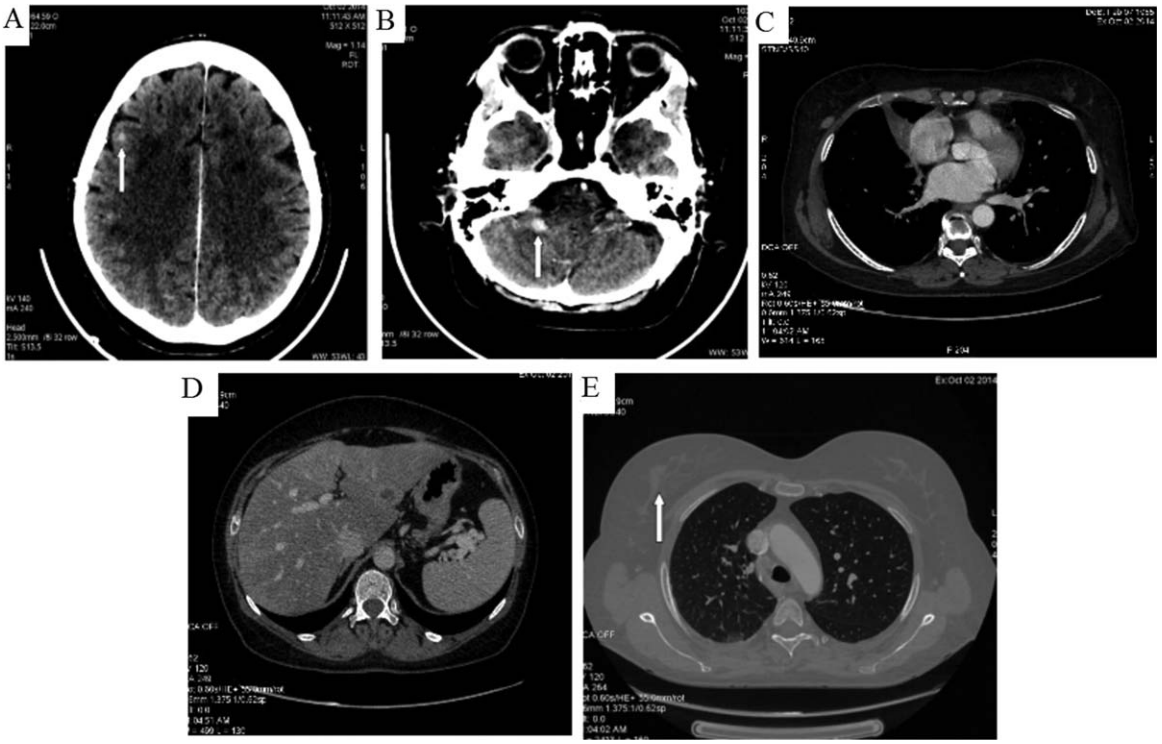

Figure 1. CT scan showing brain lesions (A, B), middle lobe lung lesion and atelectasis (C), liver lesions (D) and right breast nodule (E).

chromogranin, synaptophysin, and neural cell adhesion molecule, also known as CD56. To confirm the neuroendocrine origin in the tumor cells, at least one such marker must be positive.

The lung LCNEC is an aggressive and rare neoplasm and one of the most challenging diseases to diagnose and treat. It accounts for approximately 1.6%–3.1% of all lung cancer (3) categorized as a variant of large cell carcinoma. The lung LCNEC has a distant metatasize rate of 65% (4) and poor prognosis even in early stages, with survival rates similar to small-cell lung cancer (SCLC) (5). The life expectancy of stage IV lung LCNEC with distant metastasis was estimated at around 6 months (6).

In this article, we present an atypical case of LCNEC with metastasis to the brain, liver, and breast.

The clinically observed rate of breast metastases from extramammary malignancies is rare, ranging from 0.5% to 1.3%, due to the late appearance of extramammary malignancies in the course of malignant disease (7).

Typically, most patients are in a preterminal condition with systemic metastases outside the breast (8).

In literature, 31 reported cases of non-small-cell lung carcinoma (NSCLC) metastasized to the breast were identified, along with eight cases of small-cell lung carcinoma (9).

Furthermore, the most common sources of extramammary metastases to the breast are lymphomas/leukemias and melanomas. Some of the less common sources include carcinomas of the lung, ovary, and stomach, and infrequently, carcinoid tumors, hypernephromas, carcinomas of the liver, tonsil, pleura, pancreas, cervix, perineum, endometrium and bladder (10). Usually, breast metastasis indicates disseminated metastatic disease and carries a poor prognosis (11).

Due to the fact that patients with lung LCNEC are less likely to present with pulmonary symptoms such as cough, hemoptysis or postobstructive pneumonia (12), the early detection and diagnosis represent hard challenges.

Case report

We report the rare case of a 59-years-old female patient that presented nonproductive cough in March 2014. Pertinent social history includes 10 cigarettes/day from 40 years history of tobacco smoking. In May 2014, she had a bronchopneumonia episode and she was hospitalized. During hospitalization a chest X-ray and an ultrasound abdomen were performed. Ultrasound (US) revealed liver lesions suspected to be metastatic.

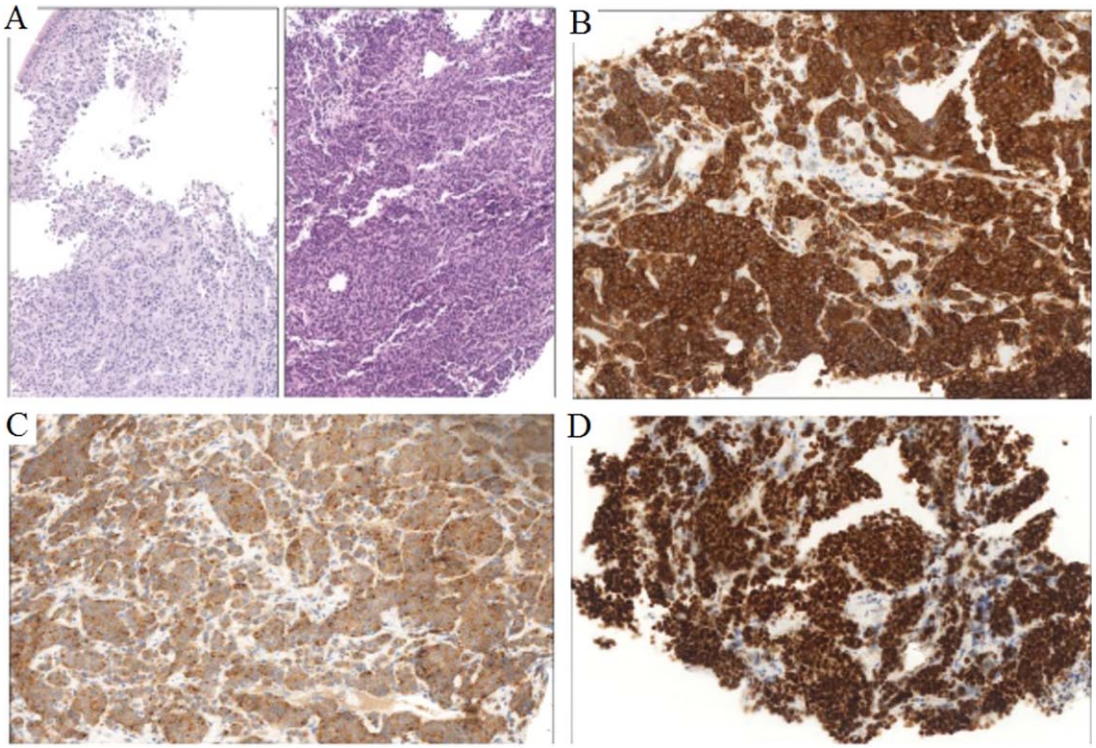

Figure 2. Pathology report slides: hematoxylin/eosin slide (A), positive stain of synaptophysin (B), positive stain of chromogranine A (C), breast's nodule cells, positive for TTF-1 (D).

The patient came to our observation on July 2014 and she had a total body CT scan (Fig. 1) and bone-scan. The CT scan showed multiple secondary brain lesions (Fig. 1A, B), a consolidation of the right lung measuring 3.9 cm, due to a middle lobe lesion associated with atelectasis (Fig. 1C); hilar and mediastinal lymphadenopathy were also described, as well as multiple focal liver metastases (Fig. 1D) and two lesions, respectively, to the left and right adrenal gland. Moreover, CT scan revealed a breast right nodule near the chest, measuring 1.8 cm (Fig. 1E).

A biopsy of the breast nodule and a biopsy of the lung lesion were performed.

Morphologically, both samples show tumor cells arranged in nests and cords solids, often with trabecular growth pattern. Neoplastic cells are large with rounded nuclei, often irregular and with moderate eosinophilic cytoplasm. Mitotic counts exceed 10 per 10 high power field (HPF). These features are evident in the pathology report slides (Fig. 2A, hematoxylin/eosin). The positive stain of synaptophysin (Fig. 2B) and chromogranine A (Fig. 2C) confirmed the neuroendocrine origin. The neoplastic cells of breast's nodule were positive also for thyroid transcription factor 1 (TTF-1) (Fig. 2D).

Subsequently, patient received three cycles of cisplatin–etoposide and on October 2014, CT scan revealed progression disease. A second-line treatment with topotecan was performed; unluckily a CT scan evaluation after 2 months of treatment showed a new progression disease. Considering progression and clinical conditions worsening, the patient underwent best supportive care; after 4 weeks the death occurred.

Discussion

LCNEC of the lung is a variant of a large cell carcinoma which exhibits neuroendocrine architectural features and immunohistochemical or ultrastructural evidence of neuroendocrine differentiation (4, 5). It is one of the most challenging diseases to diagnose and treat. The incidence is approximately 1.6%–3.1% of all lung cancer (2).

Particularly, the diagnosis of LCNEC is defined as: microscopical neuroendocrine morphology, large tumor cells, low nuclear-cytoplasmic coarse chromatin and a lot of nucleoli, mitotic rate more than 10 mitoses per 10 high power fields, tumor necrosis; immunohistochemical positivity to Cromogranine A and/or other specifical neuroendocrinal markers (13).

Breast metastasis from extramammary malignancy is uncommon and often presents hard diagnostic challenges. The overall incidence of extramammary metastasis to the breast is 0.2%–1.3% of all malignant breast tumors. Patients with non-Hodgkin lymphoma, melanoma and carcinoma of the lung, stomach, ovary, kidney and colorectum in adults and children with rhabdomyosarcoma, have a higher risk of metastasis to the breast (14).

Distant metastasize rate is 65% (4). In literature, many cases revealed abnormal locations of metastases of lung LCNEC.

In 2010, Tsimpas *et al.* reported a rather uncommon metastatic case to the cauda equina and to the lumbar spine causing foot drop (15).

In 2011, Tadashi reported a case with a man who had quadruple carcinomas; esophageal squamous cell carcinoma, prostatic well differentiated adenocarcinoma, gastric moderately differentiated adenocarcinoma and lung LCNEC diagnosed in a brain metastasis (16).

In 2012, Shimizu *et al.* describes a 77-years-old man with LCNEC of the lung and metastases from this primary cancer in prostate (17).

In 2014, Mitsuaki *et al.* documented the first case of metastatic LCNEC of the lung in the scalp (18).

Also in 2014, Cai Yuan *et al.* elucidates the unusual case of cutaneous metastasis site from LCNEC (19).

In this report, we describe the first documented case of metastatic LCNEC of the lung in the breast. Anyhow, because LCNEC is rare, the optimal treatment including chemotherapy has not been defined (20). Usually, the most used schedule is platinum-based chemotherapy, however, the outcome remains poor. Recent studies showed that LCNEC responds to cisplatin-based chemotherapy, like those used for SCLC (21). Regarding this controversy palliative chemotherapy for LCNEC, Sun *et al.* in their study evaluated whether advanced lung LCNEC should be treated similarly to SCLC or non-small-cell lung cancer (NSCLC); he concluded that treatment similar to SCLC is more appropriate than NSCLC (21).

The outcome of advanced LCNEC treated with cisplatin-etoposide doublets is poor, similar to those of patients with advanced SCLC (22). The life expectancy of stage IV LCNEC with distant metastasis is around 6 months (6). Furthermore, its prognosis is poor even in early stages.

The majority of previous studies reported that LCNEC is associated with poor survival compared to stage-matched NSCLC, approaching the very poor prognosis of SCLC (12, 23).

Therefore, new therapeutic options are needed. Tyrosine kinase inhibitors (TKI) have demonstrated greater efficacy and better tolerability than standard chemotherapy in nonsmall-cell lung cancer harboring epidermal growth factor receptor (EGFR) mutations (24). The research of EGFR mutations is not performed routinely on LCNEC because it is not commonly present in this subtype (22), like our case; already today at least two cases of lung LCNEC positive for EGFR mutation it has been reported in the literature, and then treated with TKI showing a good sensitivity to the same. (24, 25).

In the end, the diagnosis of metastasis to the breast from extramammary malignancies is difficult but important for proper management and prediction of prognosis; therefore, a careful clinical history with an accurate clinical examination is needed to make the correct diagnosis.

References

1. Brambilla E, Pugatch B, Geisinger K, *et al.* Large cell carcinoma. In: Travis WD, Bramblilla E, Muller-Hermelink HK, Harris CC, editors. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus, and Heart.* Lyon, IARC Press, 2004: 45–50.
2. Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. Eur Respir J. 2001;18: 1059–68.
3. Travis WD, Linnoila RI, Tsokos MG, Hitchcock CL, Cutler GB Jr, Nieman L, Chrousos G, Pass H, Doppman J. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol. 1991;15: 529–53.
4. Swarts DR, Ramaekers FC, Speel EJ. Molecular and cellular biology of neuroendocrine lung tumors: evidence for separate biological entities. Biochim Biophys Acta. 2012;1826: 255–71.
5. Graziano SL, Mazid R, Newman N, Tatum A, Oler A, Mortimer JA, Gullo JJ, DiFino SM, Scalzo AJ. The use of neuroendocrine immunoperoxidase markers to predict chemotherapy response in patients with non-small-cell lung cancer. J Clin Oncol. 1989;7: 1398–406.
6. .Bhamidipati PK, Ribbeck A, Liaghati-Nasseri G, Kumar R, Babu Paidipaty B, Bartnik J. An atypical presentation with diagnostic challenge of a large cell neuroendocrine cancer of lung: a case report and review of the literature. Lung Cancer Int. 2011;2011: 1–6.
7. Bohman LG, Bassett LW, Gold RH, Voet R. Breast metastases from extramammary malignancies. Radiology. 1982;144: 309–12.
8. Surov A, Fiedler E, Holzhausen HJ, Ruschke K, Schmoll HJ, Spielmann RP. Metastases to the breast from non-mammary malignancies: primary tumors, prevalence,

clinical signs, and radiological features. Acad Radiol. 2011; 18: 565–74.
9. Mirrielees JA, Kapur JH, Szalkucki LM, Harter JM, Salkowski LR, Strigel RM, Traynor AM, Wilke LG. Metastasis of primary lung carcinoma to the breast: a systematic review of the literature. J Surg Res. 2014;188(2): 419–31.
10. Vergier B, Trojani M, de Mascarel I, Coindre JM, Le Treut A. Metastases to the breast: differential diagnosis from primary breast carcinoma. J Surg Oncol. 1991;48: 112–116.
11. Toombs BD, Kalisher L. Metastatic disease to the breast: clinical, pathologic, and radiographic features. AJR Am J Roentgenol. 1977;129: 673–6.
12. Takei H, Asamura H, Maeshima A, Suzuki K, Kondo H, Niki T, Yamada T, Tsuchiya R, Matsuno Y. Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty-seven cases. J Thorac Cardiovasc Surg. 2002;124: 285–92.
13. Hage R, Seldenrijk K, De Bruin P, Van Swieten H, Van den Bosch J. Pulmonary large-cell neuroendocrine carcinoma (LCNEC). Eur J Cardiothorac Surg. 2003;23: 457–60.
14. Lee A, Sahin A. World Health Organization classification of tumours of the breast. In: Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. *Metastases of Extramammary Malignancies to the Breast*. Lyon, IARC Press, 2012: 162–3.
15. Tsimpas A, Post NH, Moshel Y, Frempong-Boadu AK. Large cell neuroendocrine carcinoma of the lung metastatic to the cauda equina. Spine J. 2010;10(6): 1–5.
16. Tadashi T. Pulmonary large cell neuroendocrine carcinoma diagnosed in a brain metastasis. Int J Clin Exp Pathol. 2012; 582: 159–62.
17. Shimizu K, Goto T, Maeshima A, Oyamada Y, Kato R. Prostatic metastasis of pulmonary large cell neuroendocrine carcinoma. J Cancer. 2012;3: 96–9.
18. Mitsuaki I, Muneo I, Akiko K, Nozomi I, Hidetoshi O. Cutaneous metastasis from pulmonary large cell neuroendocrine carcinoma in the scalp. Int J Clin Exp Pathol. 2014; 7(5): 2701–6.
19. Yuan C, Keating B, Farricielli LA, Zhang K. Large-cell neuroendocrine carcinoma (LCNEC) without pulmonary symptoms diagnosed in a cutaneous metastasis. Am J Case Rep. 2014;15: 97–102.
20. Tanaka Y, Ogawa H, Uchino K, Ohbayashi C, Maniwa Y, Nishio W, Nakao A, Yoshimura M. Immunohistochemical studies of pulmonary large cell neuroendocrine carcinoma: a possible association between staining patterns with neuroendocrine markers and tumor response to chemotherapy. J Thorac Cardiovasc Surg. 2013;145: 839–46.
21. Sun JM, Ahn MJ, Ahn JS, *et al.* Chemotherapy for pulmonary large cell neuroendocrine carcinoma: similar to that for small cell lung cancer or non-small cell lung cancer? Lung Cancer. 2012;77: 365–70.
22. Le Treut J, Sault MC, Lena H, Souquet PJ, Vergnenegre A, Le Caer H, Berard H, Boffa S, Monnet I, Damotte D, Chouaid C. Multicentre phase II study of cisplatin-etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: the GFPC 0302 study. Ann Oncol. 2013;24: 1548–52.
23. Battafarano RJ, Fernandez FG, Ritter J, Meyers BF, Guthrie TJ, Cooper JD, Patterson GA. Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer. J Thorac Cardiovasc Surg. 2005;130(1): 166–72.
24. Aroldi F, bertocchi P, Meriggi F, Abeni C, Ogliosi C, Rota L, Zambelli C, Bnà C, Zaniboni A. Tyrosine kinase inhibitors in EGFR-mutated large cell neuroendocrine carcinoma of the lung? A case report. Case Rep Oncol. 2014;7: 478–83.
25. De Pas TM, Giovannini M, Manzotti M, Trifirò G, Toffalorio F, Catania C, Spaggiari L, Labianca R, Barberis M. Large-cell neuroendocrine carcinoma of the lung harboring EGFR mutation and responding to gefitinib. J Clin Oncol. 2011;29: e819–22.