


CASE REPORT

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The rare case of synchronous bilateral breast metastasis from a lung neuroendocrine tumor (small cell lung carcinoma): a case report and literature review

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Abstract

Background Breast metastasis from small cell neuroendocrine carcinoma (SNEC) is very rare. In the present report, we describe a case of a female patient who was initially diagnosed with triple negative primary bilateral breast cancer, but during systemic examination, the diagnosis was bilateral breast metastasis from SNEC.

Case presentation A 62-year-old woman with no history of smoking presented to the Department of General Medicine with left-sided chest pain, and computed tomography revealed masses in both breasts and left pleural thickening that was further confirmed by mammography and ultrasound of the breasts. A needle biopsy was performed, and triple negative primary bilateral breast cancer was diagnosed. Because progastrin-releasing peptide (ProGRP) 37,300 pg/ml (normal range, 0–81.0 pg/ml) and neuron-specific enolase 35.0 ng/ml (normal range, 0–16.3 ng/ml) levels were elevated, thoracoscopic biopsy was performed, and SNEC was diagnosed. Pathological examinations showed that the bilateral breast masses were also positive for immunohistochemical staining of chromogranin A, synaptophysin, and CD56, leading to a diagnosis of bilateral breast metastasis of neuroendocrine tumor.

Conclusion Although very rare, the possibility of breast metastasis should be considered when malignancy is suspected in other organs.

Keywords Bilateral, Breast metastasis, Small cell carcinoma, Lung neuroendocrine carcinoma

Background

Breast cancer is the most commonly diagnosed cancer worldwide, surpassing lung cancer in 2020. The global cancer statistics 2020 estimate that 2.3 million new breast cancer cases were diagnosed, representing 11.7% of all

cancer cases. Globally, breast cancer kills approximately 680,000 people annually [1].

Breast cancer easily metastasizes to the bones, liver, lungs, and brain. Conversely, metastasis to the breast is very rare, accounting for 0.4–1.3% of all malignant breast tumors [2–4].

Most reported metastases to the breast are from hematologic malignancies, such as leukemia and lymphoma, with some reports from malignant melanoma, lung, ovarian, prostate, renal, stomach, ileum, and thyroid cancers [4, 5].

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In particular, metastasis from small cell neuroendocrine carcinoma (SNEC) is very rare, with few reports in the literature.

In the present report, we describe a case of a female patient who was initially diagnosed with triple negative primary bilateral breast cancer, but during systemic examination, the diagnosis was bilateral breast metastasis from SNEC.

Case presentation

A 62-year-old woman with no smoking history experienced itching on the left side of her chest 16 months before diagnosis. She visited a dermatologist, but no abnormality was found, and she was followed up with. Seven months later, she fell and bruised her chest. Since then, she had left-sided chest pain when coughing and sneezing. She was prescribed painkillers, but the left-sided chest pain gradually became more severe. She thought it was caused by yoga, which she had recently started practicing. She visited a general practitioner who noted multiple masses in both breasts.

Her only medical history was of scoliosis and chronic gastritis, neither of which required treatment.

She had no family history of cancer, no allergies, no alcohol consumption, or no smoking.

A screening mammogram 6 months earlier revealed no abnormalities.

A contrast-enhanced computed tomography (CT) scan revealed slightly irregular pleural thickening from the base to dorsal pleura of the left lung and a more tangential mass-like structure at the base of the left lung. There was no abnormality in the hilum. There were no obvious rib fractures. Since multiple nodules were found in both breasts, a consultation with a breast surgeon was recommended (Fig. 1).

On palpation, an elastic, firm, well-defined, slightly poorly mobile mass of approximately 1–2 cm was palpated on the B region of the right breast and the D region of the left breast. No axillary or supraclavicular lymph nodes were observed.

Mammography revealed a round, well-defined, hyperintense mass in the left breast without calcification. The mass was not clearly visible in the right breast, but there was focal asymmetric density (Fig. 2).

Ultrasonography showed multiple round, well-defined, full, hypoechoic masses with internal pulsatile blood flow signal. Elastography showed relatively uniform firmness. The multiple masses were showed in both breasts' subcutaneous and mammary tissues. The largest masses were 7 mm in the B region of the right breast and 6 mm in the D region of the left breast, and the multiple masses were similar in shape. There were no bilateral axillary lymph node enlargements (Fig. 3).

An ultrasound-guided needle biopsy was performed on the B region of the right breast and the D region of the left breast. Both breast masses were diagnosed as solid-type invasive ductal carcinoma of the breast. Furthermore, both had the same immunostaining characteristics of triple negative type, with negative estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor2 (HER2) status. The pathology confirmed the diagnosis of triple negative primary bilateral multiple breast cancer (Fig. 4).

Contrast-enhanced MRI showed multiple masses with rim enhancement and hypo-diffusion in both breasts' subcutaneous and mammary tissues. The largest masses were 13 mm in the B region of the right breast and 10 mm in the D region of the left breast, and all masses, including these masses, showed similar contrast patterns (Fig. 5).

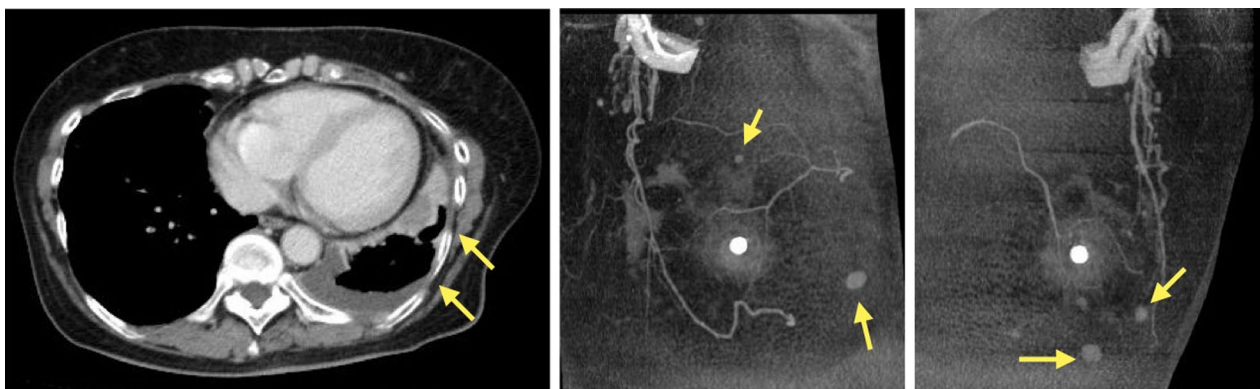


Fig. 1 A contrast-enhanced computed tomography (CT) scan revealed irregular pleural thickening and a more tangential mass-like structure at the base of the left lung. Multiple nodules were also revealed in both breasts

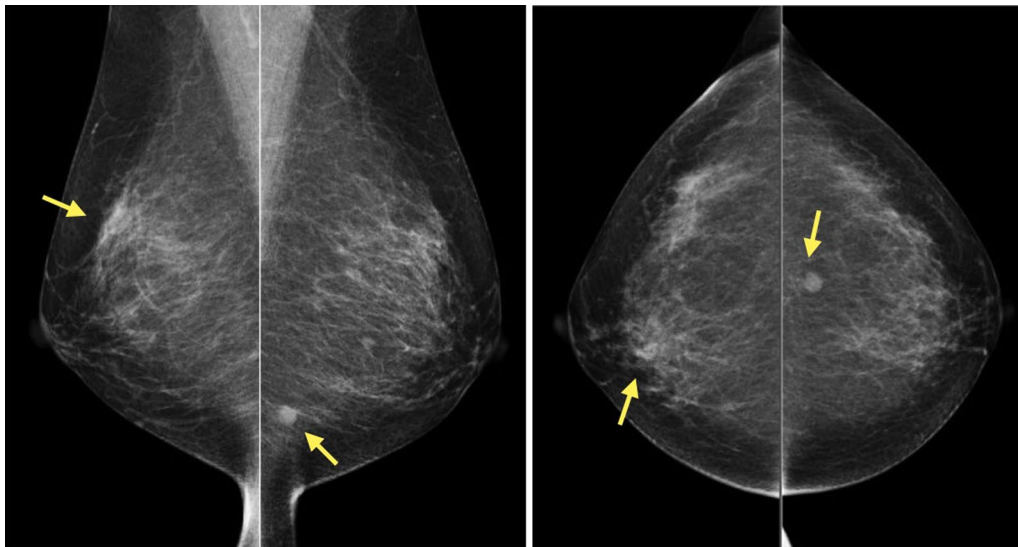


Fig. 2 Mammography revealed a round, well-defined, hyperintense mass in the left breast. There was focal asymmetric density in the right breast

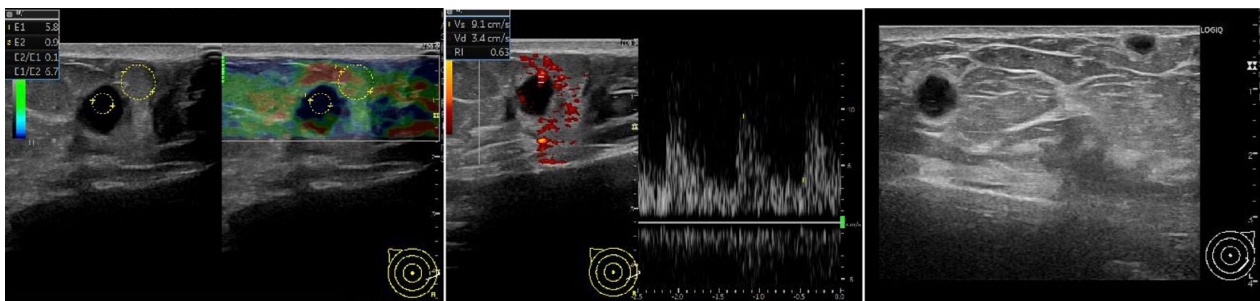


Fig. 3 Ultrasonography revealed multiple round, well-defined, full, hypoechoic masses with internal pulsatile blood flow signal in both breasts. Elastography showed relatively uniform firmness

18F-fluorodeoxyglucose (FDG) positron emission tomography-CT showed a nodule with FDG accumulation (SUVmax=11.42) in the left lower lobe. In addition, multiple other nodules were also found in the bilateral breasts, such as a 1.1 cm nodule (SUVmax=6.27) in the left D region and a 1.1 cm nodule (SUVmax=5.75) in the right B region in the breast subcutaneous tissue. Multiple FDG accumulations were also observed in the left pleura, diaphragm, supraclavicular fossa lymph node, and left parasternal lymph node. Notably, no significant FDG accumulations were observed in subcutaneous tissue other than the breasts (Fig. 6).

Blood tumor markers were high: progastrin-releasing peptide (ProGRP) 37,300 pg/ml (normal range, 0–81.0 pg/ml) and neuron-specific enolase (NSE) 35.0 ng/ml (normal range, 0–16.3 ng/ml). Carcinoembryonic antigen (CEA), carbohydrate antigen 15–3 (CA15-3), squamous cell carcinoma (SCC), sialyl Lewis X-i

antigen (SLX), and cytokeratin fragment (CYFRA) were within the normal ranges.

Based on high ProGRP levels, we considered the possibility of primary lung cancer and performed a thoracoscopic biopsy. Pathological examination revealed atypical epithelial cells in a full or sporulated fashion, small cells with a high N/C ratio, and slightly larger cells with eosinophilic cytoplasm. ChromograninA (+), synaptophysin (+), CD56 (+), thyroid transcription factor-1-TTF-1 (+), and p40 (–) were the immunostaining characteristics of the cancer. Based on the above findings, the diagnosis of SNEC was made (Fig. 7).

Additional immunostaining was performed on needle biopsies of bilateral breast masses (chromograninA (+), synaptophysin (+), CD56(+), thyroid transcription factor-1-TTF-1 (+), cytokeratin AE1/AE3 (+), LCA(–), E-cadherin (+), napsin A (–), ER=0%, PgR=0%, HER2=0, Ki-67=30%). The immunostaining results of the bilateral breast masses were the same. Furthermore,

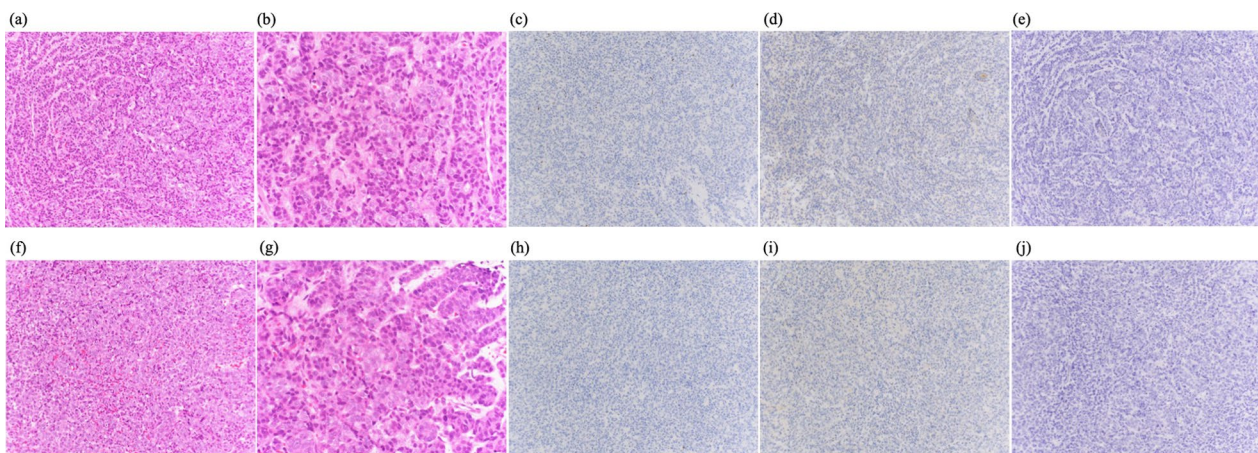


Fig. 4 Photomicrographs of the biopsied breast tumor sections. **a–e** are the right breast tissue, **f–j** are the left breast tissue. **a, f** Hematoxylin and eosin (H &E) -staining (magnification $\times 20$), **b, g** (magnification $\times 40$), **c, h** Immunohistochemistry of ER (magnification $\times 20$), **d, i** PgR (magnification $\times 20$), **e, j** HER2 (magnification $\times 20$)

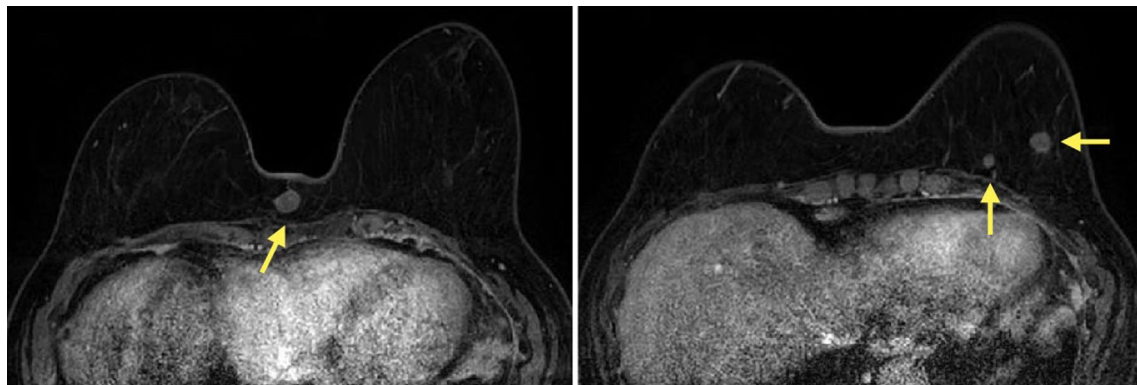


Fig. 5 Contrast-enhanced MRI showed multiple masses with rim enhancement and hypo-diffusion in both breasts' subcutaneous and mammary tissues

the lung tissue from thoracoscopic biopsy also showed the same findings (Fig. 8).

The patient was finally diagnosed with bilateral breast metastases of primary SNEC. The patient was started on cisplatin, etoposide, and atezolizumab in the Department of Respiratory Medicine to treat stage IV small cell lung cancer.

Discussion

Small cell lung cancer is common in smokers but rare in nonsmokers. Small cell lung cancer is a high-grade neuroendocrine tumor known to be more aggressive than other lung cancers. Approximately 70% of cases have distant metastases, mainly to the liver, brain, bones, and adrenal glands [3]. Thyroid, ovary, pancreas, stomach, intestine, and pituitary gland metastases have also been reported, although rarely [6].

Breast metastasis of SNEC is very rare. There are very few reports of it in the literature. Furthermore, reports of bilateral breast metastasis are especially rare [3].

One school of thought is that breast metastasis from small cell lung cancer occurs to the ipsilateral breast via lymphatic vessels [7]. The other is that the metastasis is hematogenous since it may also metastasize to the contralateral breast or both breasts [5]. According to Jose et al., only 16% of patients had bilateral metastasis, while the rest had metastasis on only one side [8]. In our case, multiple metastasis were showed in the subcutaneous and mammary tissues in both breasts. No significant masses were observed in subcutaneous tissue other than the breasts. Similar findings have also been reported [9, 10]. We consider that the cancer cells can metastasize to breasts close to the primary tumor through the hematogenous route or a retrograde axillary lymphatic drainage.

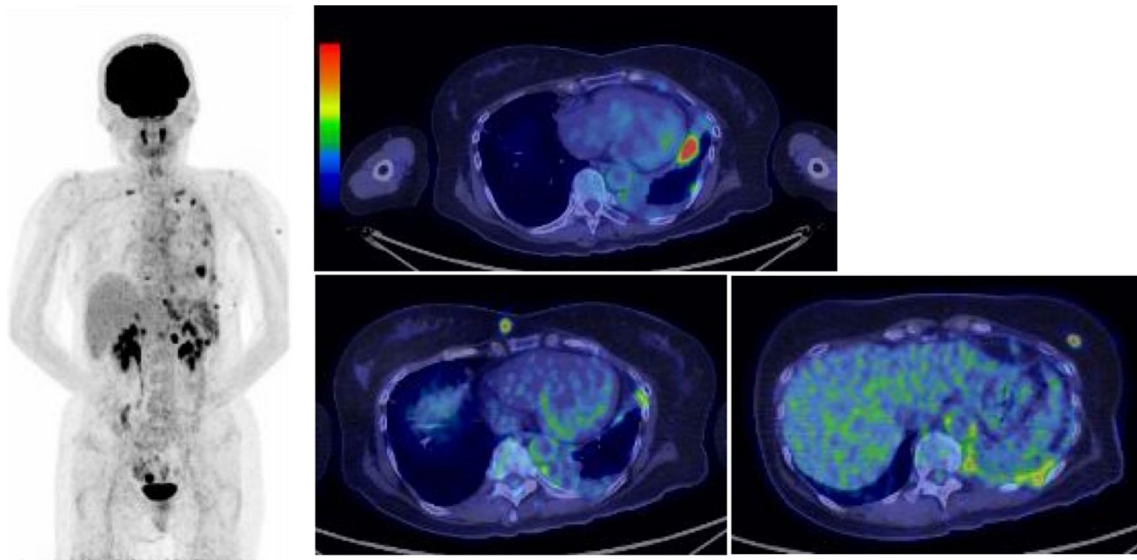


Fig. 6 18F-fluorodeoxyglucose (FDG) positron emission tomography-CT showed a nodule with FDG accumulation (SUVmax = 11.42) in the left lower lobe. Multiple FDG accumulations were also observed in the bilateral breasts

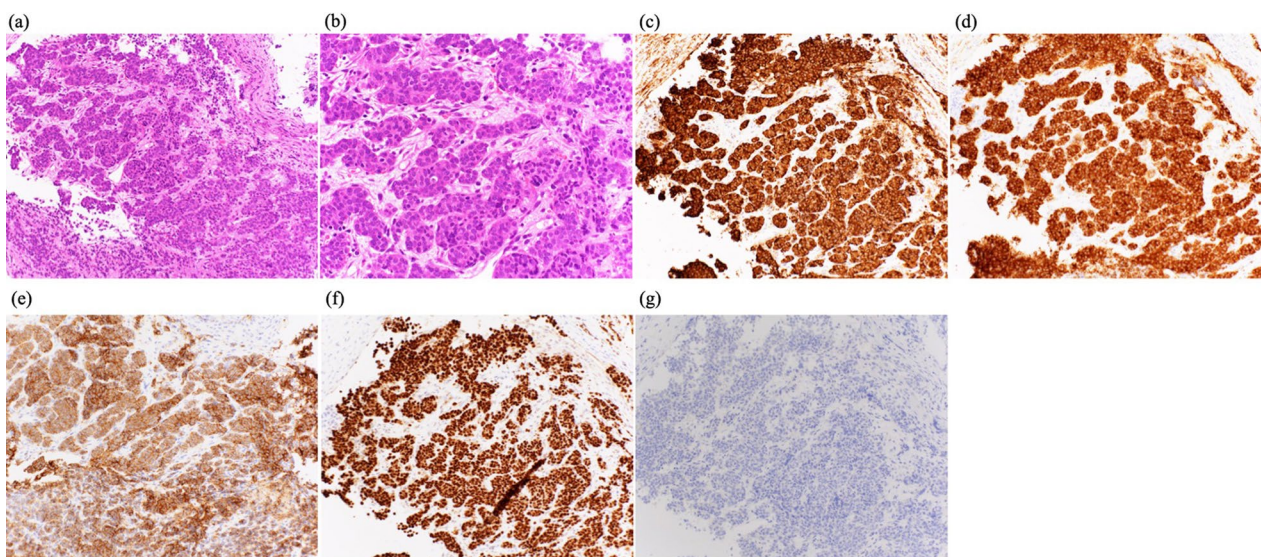


Fig. 7 Photomicrographs of the biopsied lung lesion. **a** Hematoxylin and eosin (H & E) -staining (magnification $\times 20$), **b** (magnification $\times 40$), **c** Immunohistochemistry of Chromogranin A (magnification $\times 20$), **d** Synaptophysin (magnification $\times 20$), **e** CD56 (magnification $\times 20$), **f** thyroid transcription factor-1-TTF-1 (magnification $\times 20$), **g** p40 (magnification $\times 20$)

A review paper by Joakim Crona et al. reported that breast metastases of neuroendocrine tumors could be identified in 85% of cases by mammography and 100% of cases by ultrasound [7]. The imaging findings of breast metastases are characterized by a round, well-defined, hyperintense mass on mammography without calcification, spicula, or architecture disorganization. On ultrasound, many hypoechoic masses are full or cystic and may be diagnosed as benign. Therefore, they may

not proceed to a full pathological examination and are instead followed up with, delaying the diagnosis [3, 4].

Pathological findings of breast metastases are often negative for ER, PgR, and HER2 status, so cases of triple negative breast cancer are often diagnosed differently [5, 7, 9–14].

Immunohistochemical markers such as chromogranin A, synaptophysin, and CD56 are neuroendocrine tumors' most common positive markers. TTF1 is also

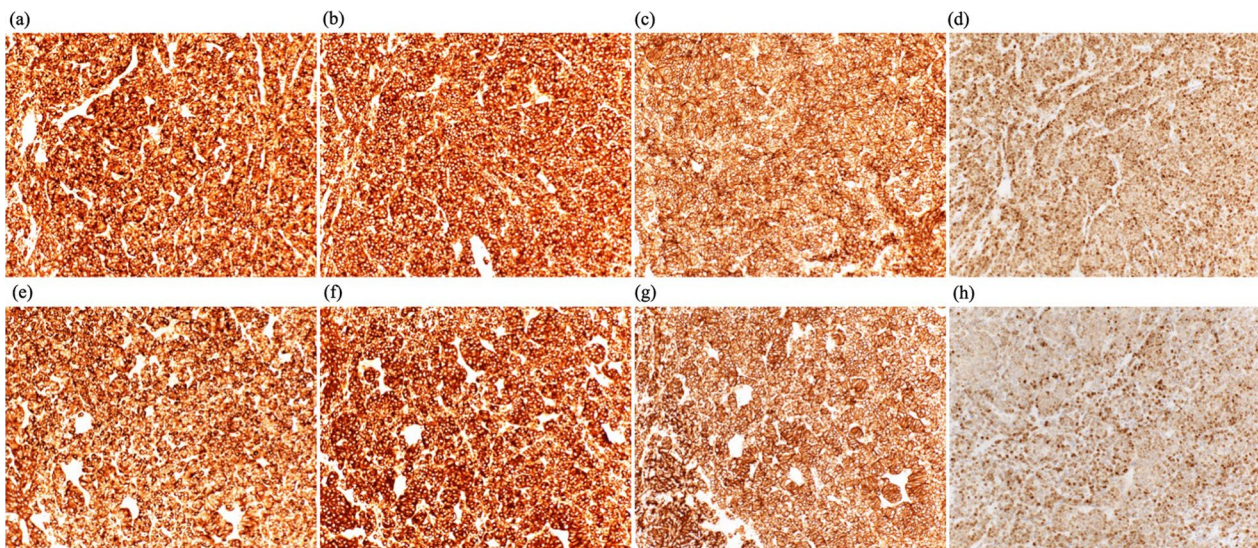


Fig. 8 Photomicrographs of the biopsied breast tumor sections. **a–d** are the right breast tissue, **e–h** are the left breast tissue. **a, e** Immunohistochemistry of ChromograninA (magnification $\times 20$), **b, f** Synaptophysin (magnification $\times 20$), **c, g** CD56 (magnification $\times 20$), **d, h** thyroid transcription factor-1-TTF-1 (magnification $\times 20$)

an important marker positive in 80% of lung cancers, although it may also be positive in thyroid tumors [4, 15]. In particular, in small cell lung cancer, TTF1 is more likely to be expressed in the peripheral type than in the central type, and is attracting attention as a factor for poor prognosis [16]. However, it is rarely stained routinely in the diagnosis of breast cancer. In our case, chromogranin A, synaptophysin, CD56, and TTF1 were not stained initially, and the diagnosis was triple negative primary bilateral breast cancer. Since ProGRP 37300 pg/ml (normal range, 0–81.0 pg/ml) was abnormally high, a lung biopsy was performed, and a diagnosis of small cell lung cancer was made. The possibility of double carcinoma of the breast and lung remained, but because of the multiple bilateral breast masses, additional staining for neuroendocrine tumor markers was performed, and a diagnosis of breast metastasis was made. A similar diagnosis might not have been made if the breast mass had been unilateral and solitary.

Vaughan et al. reported three cases of breast metastasis from neuroendocrine lung cancer, and surgery was performed in two of them [17]. Similar to the present case, Kotake et al. also reported bilateral breast metastases from neuroendocrine lung cancer in a non-smoker who underwent mastectomy and radiation for local control [2]. The breast mass was not resected in the present case, but local control was good with chemotherapy.

It has been proven that primary resection of breast cancer with distant metastases does not prolong prognosis [18]. However, the benefit of surgical resection of breast metastases has not been established. Some

reports suggest that removal of most metastases may be associated with a better prognosis than otherwise [19]. Small cell lung cancer has a very poor prognosis, with a 2-year survival rate of only 8.5% [4]. Therefore, it is essential to diagnose it and initiate treatment at an early stage. In case there is bleeding, pain, or other problems that may reduce quality of life, surgical resection should be limited to local control purposes.

Recently, reports of breast metastasis of neuroendocrine cancer have been increasing. We believe this is due to the increasing awareness of specialists and advances in imaging. Some have suggested that cases of mammary metastasis may have been misdiagnosed as primary breast cancer in the past [13]. Carreras et al. reported a retrospective analysis of metastatic sites of neuroendocrine tumors in 4210 cases using 68 Ga-PET/CT. Their results showed breast metastases in 21 cases (0.5%), which may be the fifth most frequent after liver, lymph node, bone, and heart metastases. Furthermore, they suggested that breast metastasis of neuroendocrine tumors is not rare [20]. Jose et al. summarized 116 cases of breast metastasis from neuroendocrine tumors. The most common primary sites were gastrointestinal (63%), lung (27%), ovarian (3%), renal (1%), cervical (1%), endometrial (1%), and thymic (1%) [8].

In particular, when a triple negative malignancy is found in another organ, the possibility of breast metastasis, although rare, should be taken into consideration, and further examination should be conducted.

Conclusions

We observed a very rare case of bilateral breast metastasis from SNEC. Although the diagnosis was difficult to make, we were able to provide appropriate treatment after a series of thorough examinations.

Abbreviations

SNEC	Small cell neuroendocrine carcinoma
ProGRP	Progastrin-releasing peptide
CT	Contrast-enhanced computed tomography
ER	Estrogen receptor
PgR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
FDG	Fluorodeoxyglucose
NSE	Neuron-specific enolase
CEA	Carcinoembryonic antigen
CA15-3	Carbohydrate antigen 15-3
SCC	Squamous cell carcinoma
SLX	Sialyl Lewis X-i antigen
CYFRA	Cytokeratin fragment

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Author contributions

All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the principles of the Declaration of Helsinki.

Consent for publication

The patient's guardian consented to publication of the images in this article.

Competing interests

The authors declare no competing interests and did not receive support for the submitted work from any organization.

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References

- Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–49.
- Kotake M, Imai H, Onozato R, et al. Metachronous bilateral breast metastases of a lung neuroendocrine tumor: a case report. *Mol Clin Oncol.* 2020;13(5):53.
- Bannon M, Marak C, Ashraf A, et al. Unusual presentation of a small cell lung cancer with bilateral breast metastases: case report and a brief review of the literature. *Respir Med Case Rep.* 2022;38: 101693.
- Byon JH, Kim KM, Choi EJ. Radiological and histological clues in the diagnosis of solitary and synchronous breast metastasis from small cell lung carcinoma. *J Breast Cancer.* 2023;26(2):201–6.
- Economopoulou P, Chrysikopoulou A, Goula K, et al. Breast metastasis from neuroendocrine carcinoma of the lung: a case report and review of the literature. *Case Rep Oncol.* 2020;13(3):1281–4.
- Zhao H, Lin C, Jiao B, et al. Case report of 18F-fluorodeoxyglucose positron emission tomography-computed tomography imaging of a patient with multiple endocrine gland metastases from small cell lung cancer. *Thorac Cancer.* 2018;9(1):167–70.
- Crona J, Granberg D, Norlén O, et al. Metastases from neuroendocrine tumors to the breast are more common than previously thought. A diagnostic pitfall? *World J Surg.* 2013;37(7):1701–6.
- Urrego Diaz JA, González M, Romero-Rojas AE et al. Neuroendocrine tumor metastases to the breast: a case report and review of the literature. *Cureus.* 2023;15(6):e40703.
- Ramwani R, Wernberg J. Three cases of atypical breast metastasis from lung adenocarcinoma. *Clin Med Res.* 2022;20(4):231–5.
- Zinzuwadia S, Olivieri J, Zhang C, et al. Bilateral breast metastases from small cell lung carcinoma: case report and review of the literature. *Radiol Case Rep.* 2021;16(7):1718–26.
- Lin Q, Cai G-P, Yang K-Y, et al. Case report: small cell transformation and metastasis to the breast in a patient with lung adenocarcinoma following maintenance treatment with epidermal growth factor receptor tyrosine kinase inhibitors. *BMC Cancer.* 2016;16:593.
- Zhu Y, Liu W-W, Qiong W. Clinical and molecular characteristics of secondary breast metastases from primary lung cancer: a study of 22 Chinese cases. *Int J Clin Exp Pathol.* 2020;13(7):1880–5.
- Zagami P, Kandaraki E, Renne G, et al. Case report: the rare entity of bilateral and unilateral neuroendocrine metastases to the breast: a case series and literature review. *E cancer.* 2020;14:1123.
- Vranic S, Senarathne W, Stafford P, et al. Biomarkers of targeted therapy and immuno-oncology in cancers metastatic to the breast. *Appl Immunohistochem Mol Morphol.* 2020;28(9):661–8.
- Lee AHS. The histological diagnosis of metastasis to the breast from extramammary malignancy. *J Clin Pathol.* 2007;60(12):1333–41.
- Miyauchi E, Motoi N, Ono H, et al. Distinct characteristics of small cell lung cancer correlate with central or peripheral origin. *Medicine.* 2015;94(51): e2324.
- Vaughan A, Dietz JR, Moley JF, et al. Metastatic disease to the breast: the Washington university experience. *World J Surg Oncol.* 2007;5(5):74.
- Cameron D. Removing the primary tumour in metastatic breast cancer. *Lancet Oncol.* 2015;16(13):1284–5.
- Aboud GJ, Go A, Malhotra D, et al. The surgical and systemic management of neuroendocrine tumors of the pancreas. *Surg Clin N Am.* 2009;89(1):249–66.
- Carreras C, Kulkarni HR, Baum RP. Rare metastases detected by (68)Ga-somatostatin receptor PET/CT in patients with neuroendocrine tumors. Recent results. *Cancer Res.* 2013;73(19):5799–804.

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