Metachronous bilateral breast metastases of a lung neuroendocrine tumor: A case report

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Abstract. Breast metastases of primary lung neuroendocrine tumors are rarely reported. The current report presents the case of a 41-year old female with no history of smoking who initially underwent surgery for a breast fibroadenoma, during which a neuroendocrine tumor of the right lung was detected via chest X-ray. The patient underwent surgery for the tumor and developed right breast nodules after adjuvant chemotherapy. Histological and immunohistochemical examinations of biopsies from these nodules indicated breast metastasis of the primary lung neuroendocrine tumor. The patient underwent mastectomy of the right breast but subsequently developed metastases in the left breast, for which local radiotherapy was administered. The observed metachronous bilateral breast metastases indicated that the contralateral breast should be considered during an investigation of metastasis.

Introduction

Lung cancer is the most common cause of cancer death worldwide (1). Localized stage of lung cancer represents approximately 15% of lung cancer (2). Estimated new case of non-small cell lung cancer (NSCLC) in the United states is approximately 22,800, with an estimated 13,500 death each year by NSCLC (2). After resection for early-stage NSCLC, 20% of patients developed recurrences (3). NSCLC patients with postoperative recurrence had poor prognosis. Survivals after recurrence were 13% at 5 years in patients who underwent resection for NSCLC (4). The most common sites of lung cancer metastases are the brain, bone, liver, and adrenal glands (5). Previous study showed that the first recurrent site was distant in 78% of patients and patients with distant recurrence had a shorter postrecurrent survival than those with local recurrence (6). There are only few reports that have demonstrated breast metastases of primary lung neuroendocrine tumors (7-10). Here, we report a case of a female patient who developed metachronous bilateral breast metastases of a lung neuroendocrine tumor.

Case report

A 41-year-old woman with no history of smoking underwent surgery for a breast fibroadenoma. An abnormal shadow was observed on a chest X-ray, and subsequent chest computed tomography (CT) revealed nodules on the right lung (Fig. 1). ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT revealed increased tracer uptake that was highly suggestive of lung cancer, with no evidence of metastasis. The patient underwent right lower and middle lobectomy, and immunohistochemistry revealed that the tumor cells were positive for transcription termination factor-1 (TTF-1), CD56, chromogranin A, and synaptophysin (Fig. 2). Additionally, 25.7% of the tumor cells expressed the proliferation marker Ki67. A pathological analysis led to a diagnosis of neuroendocrine tumor.

A regular medical follow-up of the surgical outcomes for breast fibroadenoma revealed nodules in the right breast 3 months after adjuvant chemotherapy (Fig. 3), which were subsequently biopsied. Histological analyses of hematoxylin and eosin (H&E)-stained, paraffin-embedded biopsy sections indicated carcinoma, and positive immunohistochemical staining for CD56, chromogranin A, and synaptophysin confirmed a neuroendocrine origin (Fig. 2). Accordingly, a diagnosis of breast metastasis of primary lung neuroendocrine tumor was made based on cytological and immunohistochemical similarities between the primary and metastatic lesions. The patient underwent mastectomy of the right breast after ^{18}F-FDG-PET/CT revealed no areas of increased tracer uptake. Subsequently, she developed metastases in the left breast, lung, lymph node, and peritoneum at 2 months post-mastectomy (Fig. 4). Systemic chemotherapy and local radiotherapy to the left breast were administered. The patient remained alive 6 months later, with no evidence of a bilateral breast recurrence.

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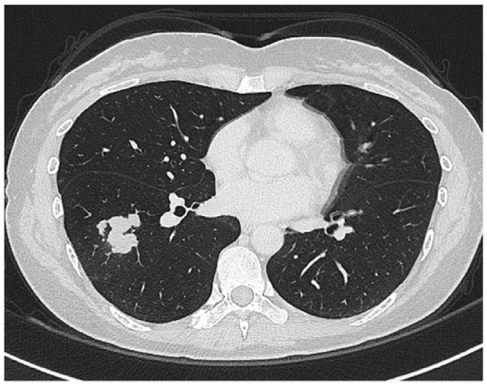

Figure 1. Chest computed tomography revealed nodules on the right lung, leading to a diagnosis of primary lung cancer.

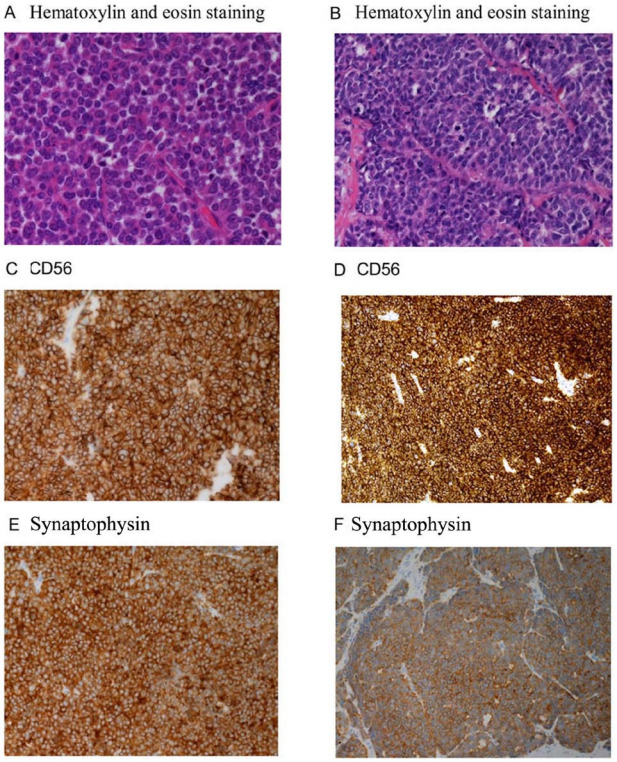

Figure 2. Photomicrographs of tumor sections. (A) Hematoxylin and eosin staining of the surgically excised lung lesion (magnification, x400). (C) Immunohistochemistry of the tumor cells revealed CD56 (magnification, x400) and (E) synaptophysin positivity (magnification, x200). (B) Hematoxylin and eosin staining of a biopsy specimen from the right breast (magnification, x100). (D) Immunohistochemistry also revealed tumor cells that were positive for CD56 (magnification, x200) and (F) synaptophysin (magnification, x100).

Discussion

Breast metastasis of lung cancer is rarely reported. Particularly, a few reports have described breast metastasis from lung neuroendocrine tumors, which account for approximately 3% of lung cancers in surgical series (7-11). Overall, breast metastases of all extramammary malignancies are very rare, accounting for 0.4-1.3% of all mammary malignancies (12,13). These generally arise from primary hematological malignancies, melanoma, rhabdomyosarcoma, lung tumors, renal cell carcinoma, thyroid and cervical carcinomas, intestinal carcinoid, epidermoid carcinoma of the head and neck, and leiomyosarcoma (12,13).

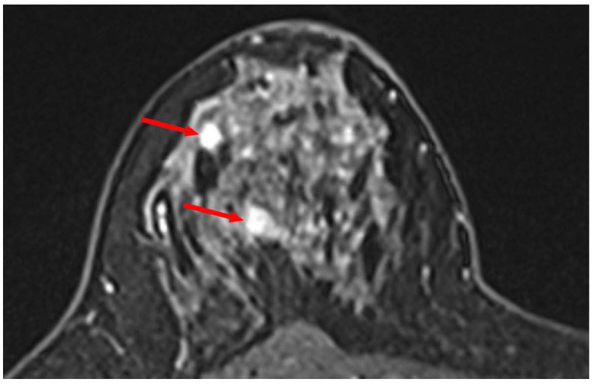

Figure 3. Magnetic resonance imaging revealed nodules (red arrows) in the right breast.

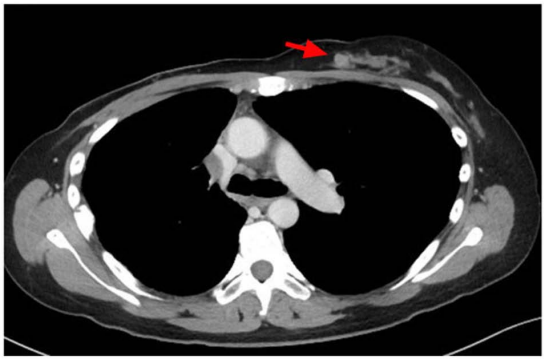

Figure 4. Chest computed tomography revealed nodules (red arrows) in the left breast.

Previous reports have demonstrated the benefits of local therapy for a subset of patients with stage IV non-small cell lung cancer and a small number of metastases (14,15). Vaughan *et al* described three cases of breast metastases of neuroendocrine tumors of the lung, of which two were treated with surgery. One patient developed a breast metastasis 38 months after her original diagnosis, for which she underwent a lumpectomy and remained free of a breast recurrence 7 months later. The second patient presented with a breast metastasis 8 months after her original diagnosis and underwent an excisional biopsy. She subsequently developed another breast metastasis 4 months after the first excision and underwent radiation treatment (10). The patient in our case achieved good local control with a right mastectomy, but subsequently developed metastases in the left breast. However, she maintained good local control of the left-sided breast nodules after radiation therapy.

A search of the PubMed database between 2007 and 2017 identified 13 cases of breast metastases from neuroendocrine tumors of the lung (Table I). Despite the rarity of this condition, the possibility of metastasis to the breast from a lung neuroendocrine tumor should be considered in the differential diagnosis of a primary mammary carcinoma in patients postoperatively discovered to have a breast lesion. One of 13 patients had bilateral breast metastases during the initial diagnostic evaluation (Table I). This finding and our observa-

Table I. Characteristics of previously reported cases of breast metastases from lung neuroendocrine tumors.

Patient no.	Age, years/sex	Interval, from NET diagnosis to breast tumor (months)	Vital status	Secondary survival (months)[a]	Breast laterality	Breast surgery/ radiotherapy	Chemotherapy
1 (9)	44/F	0	NR	NR	NR	Mastectomy	NR
2 (9)	60/F	22	NR	NR	NR	Lumpectomy	NR
3 (9)	44/F	37	NR	NR	NR	Lumpectomy	NR
4 (9)	28/F	87	NR	NR	NR	Lumpectomy	NR
5 (9)	42/F	69	NR	NR	NR	Lumpectomy	NR
6 (9)	62/F	20	NR	NR	NR	Lumpectomy	NR
7 (9)	45/F	36	NR	NR	NR	Not performed	NR
8 (9)	72/F	20	NR	NR	NR	Not performed	NR
9 (10)	30/F	38	Alive	7	Left	Lumpectomy	NR
10 (10)	35/F	0	Alive	9	Bilateral	Not performed	NR
11 (10)	28/F	8	Dead	17	Right	Lumpectomy, radiotherapy	NR
12 (8)	49/F	6	Dead	7	Left	Radiotherapy	Not performed
13 (7)	59/F	0	Dead	NR	Right	Not performed	Cisplatin + etoposide, topotecan
The current case	41/F	12	Alive	18	Bilateral	Mastectomy, radiotherapy	Performed

[a]Time interval between the diagnosis of breast metastasis and death or study follow-up. NR, not reported; F, female.

tion of metachronous bilateral breast metastases in the present case leads us to suggest that the contralateral breast should be considered in an investigation of metastasis.

In summary, we report herein a rare case of a patient with metachronous bilateral breast metastases of a primary lung neuroendocrine tumor. The present case suggests that local therapy provides good control of these metastatic lesions.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

MK, HI and KM designed the current study. MK, HI, RO, AF, TF, YY, YN, MI and KM acquired and analyzed the data. YN and MI performed histological examinations of the tumor specimens. MK and HI drafted the manuscript and constructed the figures. TH advised the study and analyzed the data. All the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication.

Competing interests

The authors declare that they have no competing interests.

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