Case Report

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# Mammographic, Sonographic, and MRI Features of Primary Neuroendocrine Carcinoma of the Breast: A Case Report

## 원발성 신경내분비 유방암의 유방촬영술, 초음파, 자기공명영상 소견: 증례 보고

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Primary neuroendocrine carcinomas of the breast are a rare, distinct category of breast carcinomas that require immunohistochemical staining for diagnosis. Currently, there is not enough evidence on the clinical pattern, prognosis, and proper management of the disease. Only few case series have described the imaging findings of neuroendocrine carcinomas of the breast. We herein present a case of a primary neuroendocrine carcinoma of the breast (small cell) presenting as a locally aggressive tumor with metastatic disease, and describe the radiologic findings.

**Index terms** Breast Neoplasm; Carcinoma; Carcinoma, Neuroendocrine; Breast Neoplasms; Diagnostic Imaging

## INTRODUCTION

Primary neuroendocrine tumors of the breast is a rare histologic type of breast carcinomas, which accounts for less than 0.1% of breast carcinomas (1). Neuroendocrine breast carcinoma was first included in the 2003 World Health Organization (WHO) classification of tumors of the breast and female genital organs. In 2012, WHO classification divided carcinomas with neuroendocrine features into three categories: well-differentiated neuroendocrine tumor, poorly differentiated neuroendocrine/small cell carcinoma, and invasive breast carcinomas with neuroendocrine differentiation. In 2019, newly revised WHO classification adopt the term "neuroendocrine neoplasm" as a term for all tumors with dominant neuroendocrine differentiation, dividing into 1)

neuroendocrine tumor, including G1 and G2, and 2) neuroendocrine carcinoma, including small cell and large cell. Invasive carcinomas without dominant neuroendocrine features (< 10% neuroendocrine morphology) are classified as invasive carcinoma, no special type (NST). Tumors with ≥ 10% neuroendocrine morphology are included in the category of neuroendocrine neoplasm, and further divided into neuroendocrine tumor and carcinoma (2). Diagnosis requires neuroendocrine markers of immunohistochemistry, such as synaptophysin and chromogranin A, neuron-specific enolase (3). As it is a rare entity, clinical behavior, radiologic findings and prognosis of neuroendocrine breast carcinomas are not well known. We describe the clinical, radiologic and pathologic findings in a case of primary neuroendocrine breast carcinoma.

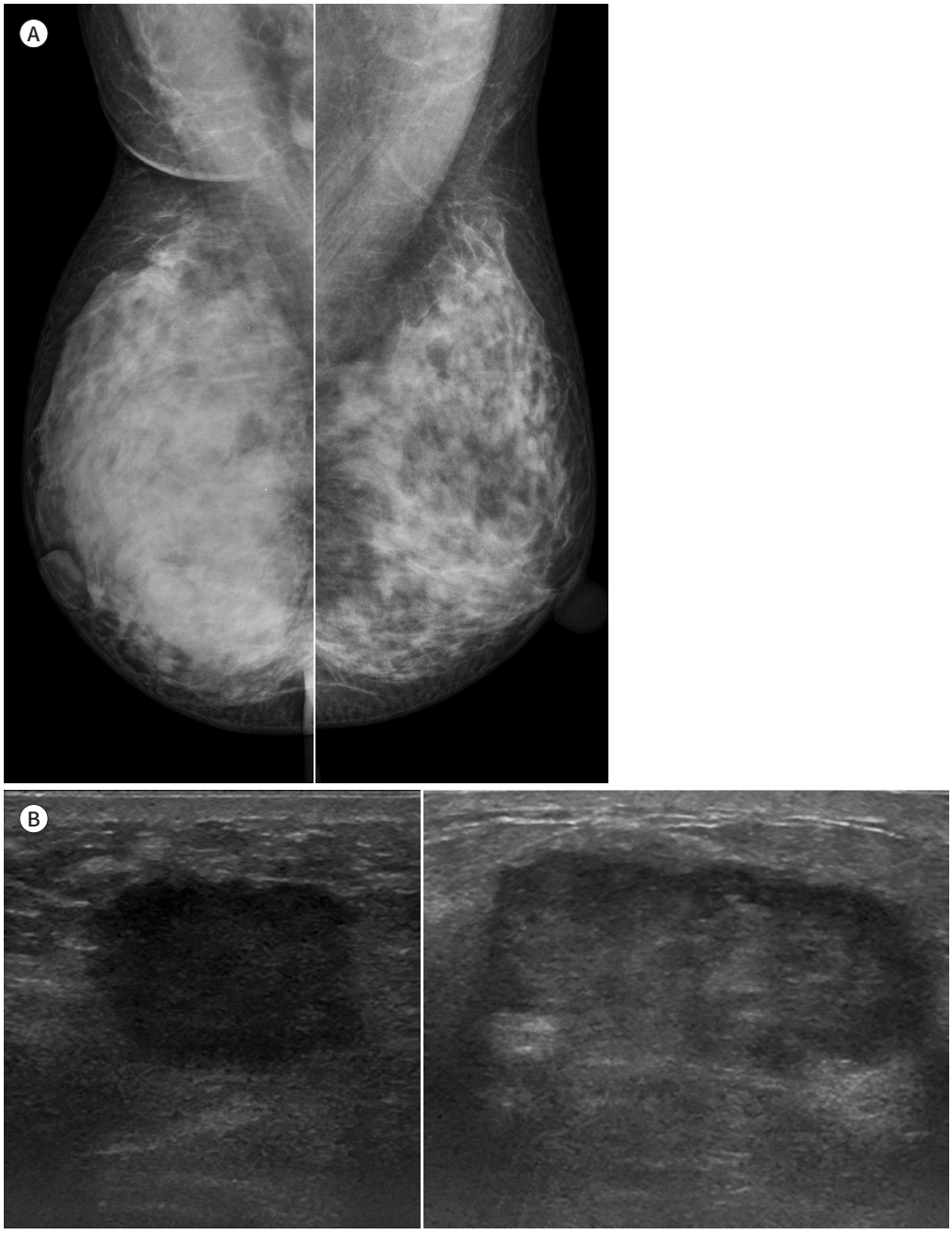
## CASE REPORT

A 37-year-old female presented with palpable mass in right breast with breast pain and nipple discharge. Mammography showed large, irregular shaped high density mass with obscured margin, occupying almost entire right breast. Right breast showed mild thickening of skin and trabecula due to edema (Fig. 1A). Several benign punctate calcifications were present. Ipsilateral axillary lymphadenopathy with cortical thickening was also seen on mammography. Breast sonography revealed multiple hypoechoic masses with irregular shape and indistinct margin (Fig. 1B). On MRI, multiple masses of right breast showed irregular shape and margin with rim enhancement, with early fast enhancement and delayed washout kinetics. Ipsilateral axillary lymph nodes and internal mammary lymph nodes were enlarged (Fig. 1C). These imaging findings were highly suspicious of malignancy, corresponding to Breast Imaging-Reporting and Data System (BI-RADS) category 5. Sonography-guided core biopsy was performed in right breast mass. Microscopically, a heavy diffuse infiltration of small round cells with scant amount of cytoplasm was observed (Fig. 1D). The tumor cells had irregular hyperchromatic nuclei with fine granular chromatin and occasional molding appearance and showed inconspicuous nucleoli (Fig. 1E). On immunohistochemical staining, tumor cells were positive for neuron specific enolase, chromogranin A, synaptophysin (Fig. 1F) and Ki-67 labeling index was about 30–40%. The patient underwent neoadjuvant chemotherapy and radiotherapy for 4 months, and had modified radical mastectomy. Histopathologic results revealed multifocal residual small cell carcinoma, with extension to chest wall and involvement of resection margin. 10 regional lymph nodes had metastasis. About 6 months after, tumor recurrence was suspected in right internal mammary chain, and showed gradual growth with destruction of sternum. During 6 years of postoperative follow-up, distant metastasis in right adrenal gland, liver and lung occurred. The patient received adjuvant radiotherapy, hormonal therapy, and is currently on palliative chemotherapy.

## DISCUSSION

Neuroendocrine tumors occur most commonly in the lung and gastrointestinal tracts. However, neuroendocrine tumors can rarely develop in various other sites, such as breast, larynx, prostate, bladder, ovary and cervix (4). Primary neuroendocrine tumors of the breast accounts

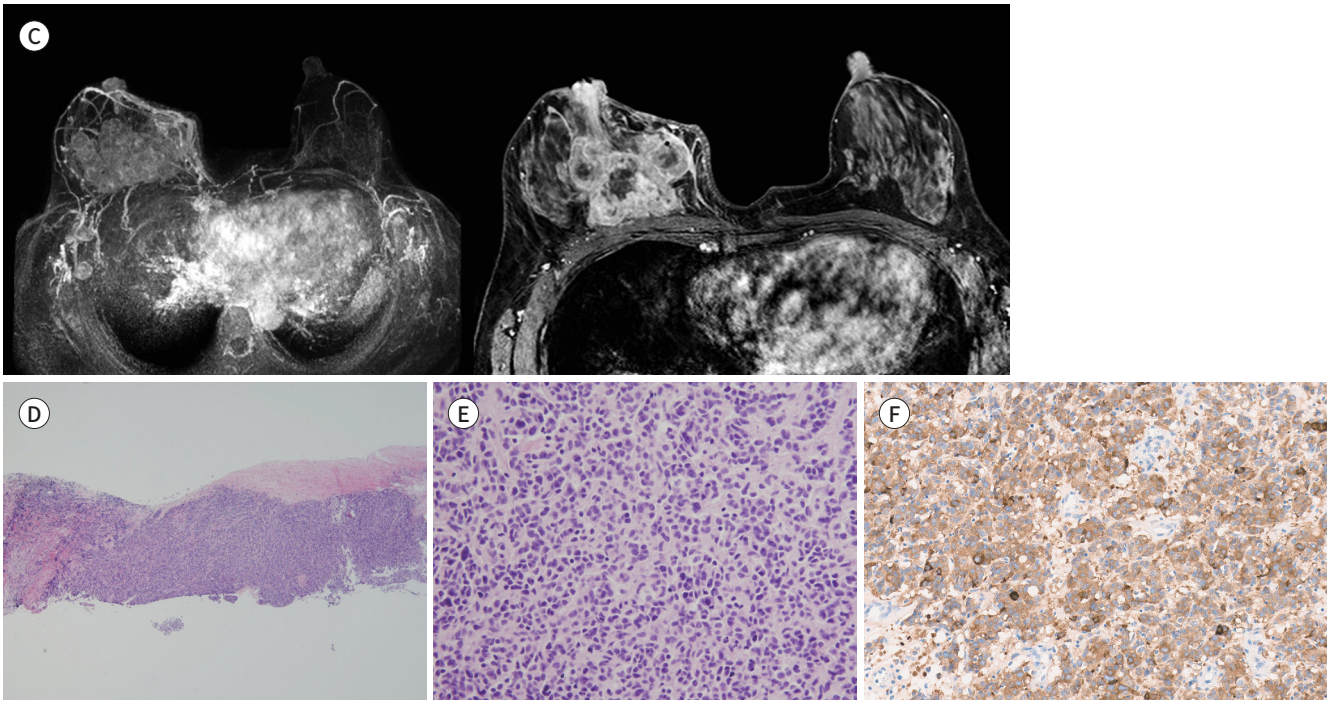
Fig. 1. Neuroendocrine carcinoma (small cell) of a 37-year-old female.
A. Mammography shows a large, irregular high-density mass with ill-defined margins, occupying almost the entire right breast. Mild skin and trabecular thickening in the right breast and ipsilateral axillary lymphadenopathy with cortical thickening are present.
B. Breast sonography shows multifocal irregular shaped hypoechoic masses with ill-defined margins.




for less than 0.1% of breast carcinomas (1) and most of the affected patients are postmenopausal female.

Commonly reported symptoms of neuroendocrine breast carcinoma are palpable mass and nipple discharge (5, 6). Imaging features of neuroendocrine breast carcinomas are only described in a few case reports. In the largest case series, mammographic findings of neuro-

Fig. 1. Neuroendocrine carcinoma (small cell) of a 37-year-old female.
C. On MRI, there are multiple irregular rim enhancing masses in the right breast. In dynamic studies, these masses showed a fast enhancement in the early phase and washed out in the delayed phase (not shown). The ipsilateral axillary lymph nodes and internal mammary lymph nodes are enlarged.
D. At low magnification power, diffuse infiltration of small-sized tumor cells with ill-defined margins are observed (H&E stain, × 40).
E. At high magnification power, tumor cells show irregular hyperchromatic nuclei with inconspicuous nucleoli and fine granular chromatin (H&E stain, × 400).
F. On immunohistochemical stain, tumor cells are diffusely positive for synaptophysin (× 400).
H&E = haemotoxylin and eosin




endocrine carcinomas showed difference from typical invasive ductal carcinomas (IDCs). As compared with IDC, neuroendocrine carcinomas most commonly presented as masses on mammography (7). Calcifications were infrequent finding (4, 6). Larger proportion showed nonspiculated margin, and they often appeared as circumscribed, round or oval mass mimicking benign mass or triple-negative breast cancer (5). Bergstrom et al. (8) reported a case demonstrating large mass with skin thickening and axillary lymphadenopathy on mammography, likewise locally aggressive tumor in our case. Most common sonographic findings were irregular hypoechoic mass with indistinct margin (5, 6). MRI usually showed highly suspicious features of malignancy, such as masses with irregular shape and noncircumscribed (irregular, spiculated, indistinct) margin. Most of the reported cases had washout kinetics, and were classified as BI-RADS category 5 (5, 6). Park et al. (6) reported imaging findings of 87 patients with primary neuroendocrine carcinoma of the breast. Multiplicity was occasionally observed in this study: 6.9% had multifocal, and 9.2% had multicentric disease.

Previously reported cases of neuroendocrine carcinomas had similar immunohistochemistry results. Most were positive for estrogen, progesterone receptor (ER, PR) and negative for human epidermal growth factor receptor type 2 (HER-2) (3, 6), and classified as luminal A or B type. Same immunohistochemical findings of ER, PR, HER-2 were noted in our case. Al-

though the prognosis of neuroendocrine breast carcinoma is controversial, in recent studies, presence of neuroendocrine differentiation appeared to be a worse prognostic factor independent of ER, PR status, nuclear grade. Therefore, neuroendocrine carcinomas tend to be more aggressive with higher recurrence rate than IDC, NST (3, 9). In a study of 199 patients with primary small cell carcinoma of breast, 42% had localized disease, 39% had regional and 19% had distant disease (10). Currently, there is no standard treatment for neuroendocrine carcinomas of the breast. Same as other invasive carcinomas, surgical removal and adjuvant chemotherapy, hormonal therapy are considered as management options, according to the disease stage and molecular characteristics. Chemotherapy regimen used in small cell lung cancer, such as combination of platinum compounds and etoposide, can be used in cases of metastatic disease (2).

In this report, we present a case of primary neuroendocrine carcinoma, small cell, of the breast with mammographic, sonographic and MRI findings. Due to its low incidence, it is hard to generalize the radiologic findings and prognosis of neuroendocrine breast carcinomas. In this case, clinical and imaging findings are not specific, and differential diagnosis with other common types of breast cancer (such as IDC) is challenging. Further studies may be needed for better understanding of this rare disease entity, and better diagnosis, treatment decision.

### Author Contributions

Conceptualization, C.K.R.; investigation, P.S.E.; methodology, C.K.R.; writing—original draft, P.S.E.; and writing—review & editing, all authors.

### Conflicts of Interest

Kyu Ran Cho has been an Editorial Board Member of Journal of the Korean Society of Radiology since 2013; however, she was not involved in the peer reviewer selection, evaluation, or decision process of this article. Otherwise, no other potential conflicts of interest relevant to this article were reported.

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## REFERENCES

1. Ogawa H, Nishio A, Satake H, Naganawa S, Imai T, Sawaki M, et al. Neuroendocrine tumor in the breast. *Radiat Med* 2008;26:28-32
2. Pareja F, D'Alfonso TM. Neuroendocrine neoplasms of the breast: a review focused on the updated World Health Organization (WHO) 5th edition morphologic classification. *Breast J* 2020;26:1160-1167
3. Lavigne M, Menet E, Tille JC, Lae M, Fuhrmann L, Bonneau C, et al. Comprehensive clinical and molecular analyses of neuroendocrine carcinomas of the breast. *Mod Pathol* 2018;31:68-82
4. Yoon YS, Kim SY, Lee JH, Kim SY, Han SW. Primary neuroendocrine carcinoma of the breast: radiologic and pathologic correlation. *Clin Imaging* 2014;38:734-738
5. Jeon CH, Kim SM, Jang M, Yun BL, Ahn HS, Kim SW, et al. Clinical and radiologic features of neuroendocrine breast carcinomas. *J Ultrasound Med* 2014;33:1511-1518
6. Park YM, Wu Y, Wei W, Yang WT. Primary neuroendocrine carcinoma of the breast: clinical, imaging, and histologic features. *AJR Am J Roentgenol* 2014;203:W221-W230
7. Chang ED, Kim MK, Kim JS, Whang IY. Primary neuroendocrine tumor of the breast: imaging features. *Korean J Radiol* 2013;14:395-399
8. Bergstrom C, Porembka J, Fang Y, Sarode V, Syed S. Primary neuroendocrine carcinoma of the breast. *Breast J* 2019;25:519-520

9. Wei B, Ding T, Xing Y, Wei W, Tian Z, Tang F, et al. Invasive neuroendocrine carcinoma of the breast: a distinctive subtype of aggressive mammary carcinoma. *Cancer* 2010;116:4463-4473
10. Hare F, Giri S, Patel JK, Hahn A, Martin MG. A population-based analysis of outcomes for small cell carcinoma of the breast by tumor stage and the use of radiation therapy. *Springerplus* 2015;4:138

# 원발성 신경내분비 유방암의 유방촬영술, 초음파, 자기공명영상 소견: 증례 보고

박상은[1] · 조규란[1]* · 송성은[1] · 우옥희[2] · 서보경[3] · 이정현[4]

신경내분비 유방암은 드물게 발생하며 고유한 특징을 가진 원발성 유방암의 아형으로서, 정확한 진단을 위해서는 면역조직화학염색법이 필요하다. 현재까지는 이 질환의 임상적 특징이나 예후, 올바른 치료에 대한 정확한 이해가 부족한 상태이며, 원발성 신경내분비 유방암의 영상의학적 소견은 소수의 증례에서만 보고되었다. 본 증례에서는 국소적 진행과 전이를 보인 원발성 신경내분비 유방암의 영상 소견을 보고하고자 한다.

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