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Original Article

Solid neuroendocrine breast carcinoma: mammographic and sonographic features in thirteen cases

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Abstract

This study aimed to determine and quantitate the mammographic and sonographic characteristics in 13 cases of solid neuroendocrine breast carcinoma (NEBC) and to analyze the association of radiological findings with the clinical and histopathologic findings. The clinical data and imaging findings of 13 female patients with histologically confirmed solid NEBC were reviewed. Imaging data were evaluated by two radiologists for a consensual diagnosis. All patients presented with one palpable mass; only 1 experienced occasional breast pain, and 5 complained of fluid discharge. In 7 patients, the masses were firm and mobile. Regional lymph node metastasis was noted in only 1 patient. For the 10 patients who underwent mammography, 6 had a mass, 1 had clustered small nodules with clustered punctuate microcalcifications, 2 had asymmetric focal density, and 1 had solitary punctuate calcification. Most of the masses had irregular shape with indistinct or microlobulated margins. For the 9 patients who underwent ultrasonography (US), 9 masses were depicted, all of which were hypoechoic, mostly with irregular shape and without acoustic phenomena. Different types of acoustic phenomena were also identified. One patient had developed distant metastases during follow-up. NEBC has a variety of presentations, but it is mostly observed on mammograms as a dense, irregular mass with indistinct or microlobulated margins. Sonographically, it typically presents as an irregular, heterogeneously hypoechoic mass with normal sound transmission. Histories of nipple discharge and calcification observed using imaging are not rare.

Key words Solid neuroendocrine carcinoma of the breast, mammography, sonography

Neuroendocrine breast carcinoma (NEBC) is a rare tumor with unclear histogenesis. In 1977, 8 cases of breast tumors with argyrophilia and cytoplasmic dense core granules were reported and first classified as NEBC[1]. In 2003, the World Health Organization (WHO) classified neuroendocrine tumors of the breast as those with the immunohistochemical expression of one or more markers [neuron-specific enolase (NSE), chromogranin A (CgA), and synaptophysin (Syn)] in at least 50% of the tumor cells[2]. Neuroendocrine tumors include solid neuroendocrine carcinoma, atypical carcinoid tumor, small cell/oat cell carcinoma, and large cell neuroendocrine carcinoma[2]. Previously reported cases of solid neuroendocrine carcinoma were isolated case reports or small series describing mainly the clinicopathologic and immunohistochemical features of this tumor[3-6]. In this paper, we reported the mammographic and sonographic findings of this rare tumor and related the radiological manifestations with the clinical and histopathologic presentations.

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Materials and Methods

Patient information

Samples of pathologically confirmed solid NEBC

were obtained from Sun Yat-sen University Cancer Center under the institutional review board guidelines and were reviewed. The patients had been treated between March 2004 and July 2010. The disease histories, physical examination results, treatment, follow-ups, initial imaging (mammographic and ultrasonographic) findings, and histopathologic results were analyzed.

Imaging acquisition and analysis

Mammography with two routine positions (craniocaudal and mediolateral oblique) was performed using a Senographe DS (General Electric, USA) or an MUG-100A (Toshiba Cooperation, Japan). All mammograms were reviewed by two radiologists specializing in breast imaging, with the information from the histopathologic diagnoses but not from the physical examination or sonographic records. According to the criteria established by the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS)[7], the following mammographic features were analyzed: parenchymal patterns, mass characteristics (shape, margin, density, size, and location), presence and type of microcalcifications, associated architectural distortion, and skin changes.

Sonography was performed using the Siemens Acuson Sequoia 512 (Siemens Ultrasound, Mountain View, CA) with the 15L8 linear array transducer (7.0–14.0 MHz). The original sonographic prints and records of each patient were reviewed after the mammograms. Each sonogram was assessed for lesion shape, margin, echo texture, echogenicity, and posterior acoustic phenomenon according to the BI-RADS criteria[8].

Pathologic and immunohistochemical analysis

Tumors and lymph node tissue sections from these patients were reviewed by two pathologists for a consensual diagnosis. Tissues were fixed in 10% formaldehyde and routinely processed. Histological and immunohistochemical examinations were performed on paraffin-embedded sections following the WHO criteria for diagnosing NEBC: more than 50% of invasive tumor cells had cytoplasmic immunoreactivity for NSE, Syn, or CgA. The immunohistochemical markers in this study included NSE, Syn, CgA, estrogen receptor (ER), progesterone receptor (PR), HER2 (CerbB-2), and Ki-67. The Ki-67 index was obtained by calculating the percentage of positive tumor cells. Ki-67 scoring was determined as nil ($\leqslant$10%), low (10%–25%), middle (25%–50%), and high ($\geqslant$50%). The positive results of NSE, Syn, or CgA were defined as a proportion of more than 50% of tumor cells with positive staining. The mammographic and sonographic findings were then compared with histopathologic findings. Information on lymph node status was obtained from postoperative pathologic reports.

Follow-up

Tumor marker (CEA and CA153) examinations, breast mammography, chest X-ray radiography, abdominal and pelvic ultrasonography were conducted every three months in the first two years after initial therapy, every six months in the next two years, and every year thereafter until August 2011. Brain magnetic resonance imaging (MRI) and whole body computed tomography (CT) were not performed routinely.

Results

Clinical characteristics

Samples from 13 patients with NEBC were collected. The clinical characteristics of the 13 patients are summarized in Table 1.

All patients were women. Their age varied from 36 to 78 (median, 53) years at the time of diagnosis. All patients denied most of the breast cancer risk factors, such as a family history of breast cancer, nulliparity, early menarche (age < 12 years), late menopause (age > 55 years), or late pregnancy (age > 30 years). The length of symptom history ranged from 1 week to 5 years. Every patient had a palpable mass. Only 1 experienced occasional breast pain, and 5 complained of bloody fluid discharge; the others denied any discomfort.

Physical examinations showed that 7 patients had a mobile firm mass, 3 had an immobile firm mass, 1 had a mobile tenacious mass, 1 had a immobile tenacious mass, and 1 had a mobile soft mass. Of the 13 masses, 5 located in the left upper outer quadrant, 2 in the right upper outer quadrant, 2 in the left lower inner quadrant, 2 in the retro-areola area, 1 in the right upper inner quadrant, and 1 in the left upper quadrant. Among the 13 patients, 4 underwent mammography, 3 underwent ultrasonography, and 6 patients underwent both. The locations of the lesions were confirmed by the mammography and ultrasonography.

All patients underwent a modified radical mastectomy with endocrine therapy. Axillary lymph node clearance was performed in 7 patients. For patients younger than 60 years, adjuvant chemotherapy was also administered.

Mammographic features of NEBC

The mammographic findings of the solid NEBCs in 10 patients are listed in Table 2. On mammography, the

Table 1. The clinical information of 13 woman patients with neuroendocrine breast carcinoma

Patient No.	Age (years)	Clinical presentation	Regional lymph nodes	Treatment	Outcome	Follow-up (months)
1	39	Painless mass and bloody nipple discharge for 1 week	0/0	MRM+C+E	MFS	73
2	74	Painless mass for 3 months	0/16	MRM+E	MFS	81
3	75	Painless mass for 1 year	0/0	MRM+E	MFS	63
4	47	Painful mass for 10 days	0/6	MRM+C+E	MFS	48
5	78	Painless mass and bloody nipple discharge for 1 year	0/9	MRM+E	MFS	48
6	44	Painless mass for 1 month	0/16	MRM+C+E	MFS	54
7	37	Painless mass for 1 month	0/16	MRM+C+E	MFS	81
8	53	Painless mass for 1 week	1/9	MRM+C+E	Dead of metastasis	46
9	36	Painless mass for 5 years, bloody nipple discharge for 3 years	0/0	MRM+C+E	Unclear	Unclear
10	65	Painless mass for 10 days	0/0	MRM+E	MFS	89
11	40	Painless mass for 2 weeks	0/7	MRM+C+E	MFS	72
12	66	Painless mass for 3 months, bloody nipple discharge for 10 days	0/0	MRM+E	MFS	72
13	66	Painless mass and bloody nipple discharge for unknown duration	0/0	MRM+E	MFS	41

MRM, modified radical mastectomy; C, chemotherapy; E, endocrine therapy; MFS, metastasis-free survival. The data of regional lymph nodes are presented as the number of positive lymph nodes / the number of lymph nodes resected by lymphadenopathy. Six patients did not undergo lymphadenopathy.

Table 2. Mammographic findings of neuroendocrine breast carcinomas in 10 patients

Patient No.	Location	Size (mm)	Parenchymal pattern	Mass category	Margin	Shape	Calcification
1	L, UOQ	23	Scattered fibroglandular density	Focal asymmetry[a]	–	–	No
2	L, LIQ	10	Fatty	Focal asymmetry[a]	–	–	A few, punctuate
3	R, UIQ	27	Scattered fibroglandular density	Solitary mass	Indistinct	Irregular	No
4	L, RETRO	40	Scattered fibroglandular density	Clustered several nodules (3–5 mm each)	Indistinct	Round-ovoid	Clustered, punctuate
5	L, RETRO	25	Scattered fibroglandular density	Solitary mass	Indistinct	Round-ovoid	No
6	R, UOQ	35	Heterogeneous density	None[b]	–	–	Solitary, punctuate
7	L, UQ	40	Scattered fibroglandular density	Solitary mass	Indistinct	Irregular	No
10	L, UOQ	10	Fatty	Solitary mass	Microlobulated	Round-ovoid	No
12	L, UOQ	10	Scattered fibroglandular density	Solitary mass	Microlobulated	Irregular	No
13	L, UOQ	35	Scattered fibroglandular density	Solitary mass	Microlobulated	Irregular	No

The numbers of all cases are identical to those in Table 1. L, left; R, right; UOQ, upper outer quadrant; LIQ, lower inner quadrant; UIQ, upper inner quadrant; RETRO, retro-areola area; UQ, upper quadrant. [a]Focal asymmetry is defined as asymmetry of tissue density with similar shape on two views but completely lacking borders and the conspicuity of a true mass[7]. [b]Mammography only detected a solitary calcification in patient No. 6.

parenchymal patterns of the breast were scattered fibroglandular density in 7 patients, almost entirely fatty in 2 patients, and heterogeneous density in 1 patient. Mammography identified that 6 patients had solitary masses [4 were irregularly shaped, and 2 were round to ovoid (Figure 1A); 3 with indistinct margins, and 3 with microlobulated margins]; 1 had clustered small nodules, with indistinct margins and punctuate calcification (Figure 2A); 2 had focal asymmetry (1 with punctuate calcification) with no evidence of solid mass; and 1 had isolated calcification with no evidence of solid mass. All lesions had high densities. The size varied between 10 and 40 mm (mean, 26 mm).

Sonographic features of NEBCs

The sonographic findings of the solid NEBCs in 9 patients are listed in Table 3. On sonography, all

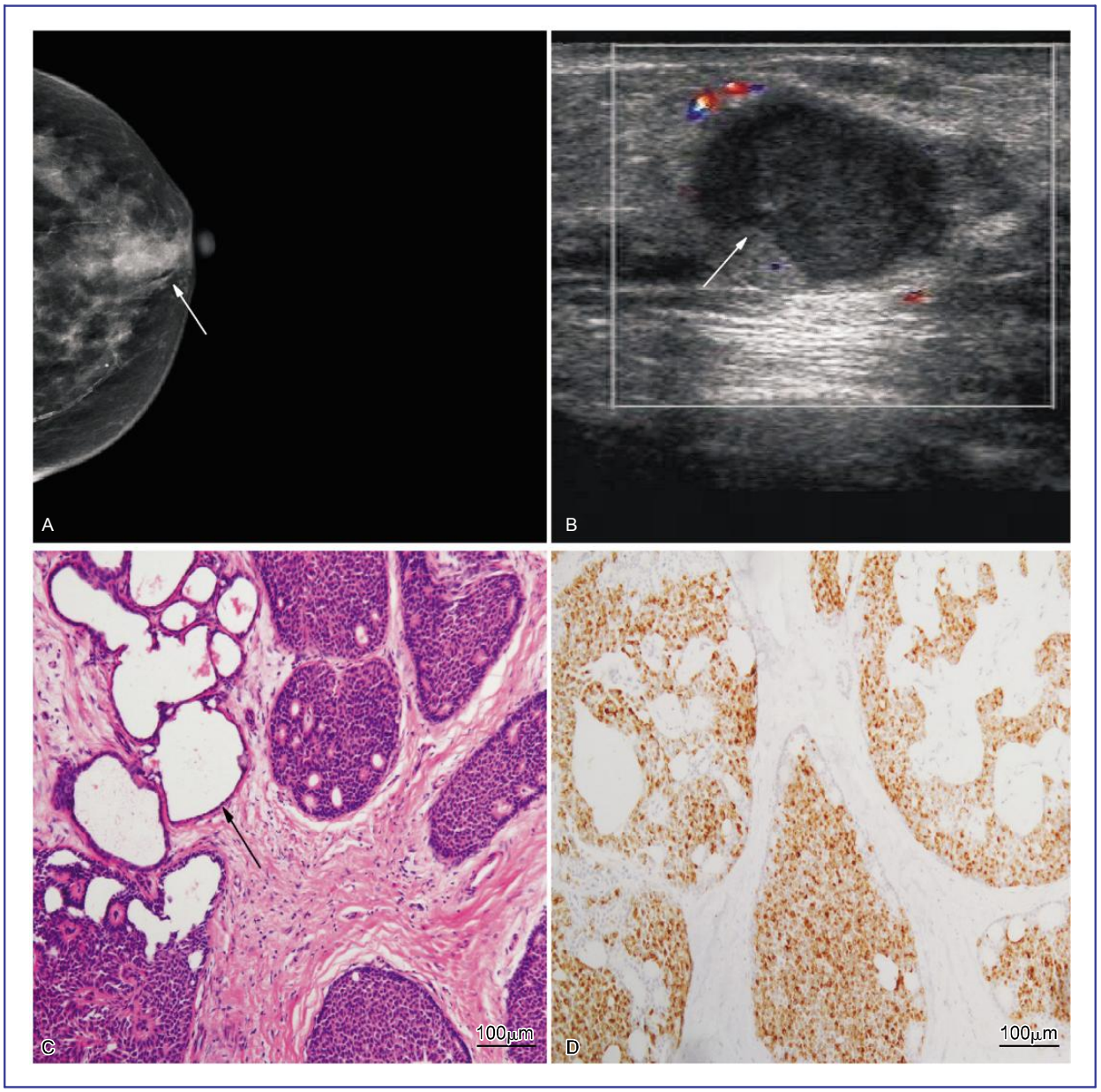

Figure 1 **A 78-year-old woman (patient No. 5) with a soft, mobile mass in the left breast.** A, a craniocaudal mammogram of the left breast shows a 20-mm round mass with indistinct margins (*arrow*). B, a transverse plane sonographic scan shows an 18-mm, round, hypoechoic, solid mass with posterior enhancement (*arrow*). C, a photomicrograph (HE) shows multiple rosette formations and duct dilation (*arrow*) of *in situ* components and invasive components with intervening fibrovascular tissue. D, a photomicrograph (anti-CgA) shows prominent chromogranin A positivity.

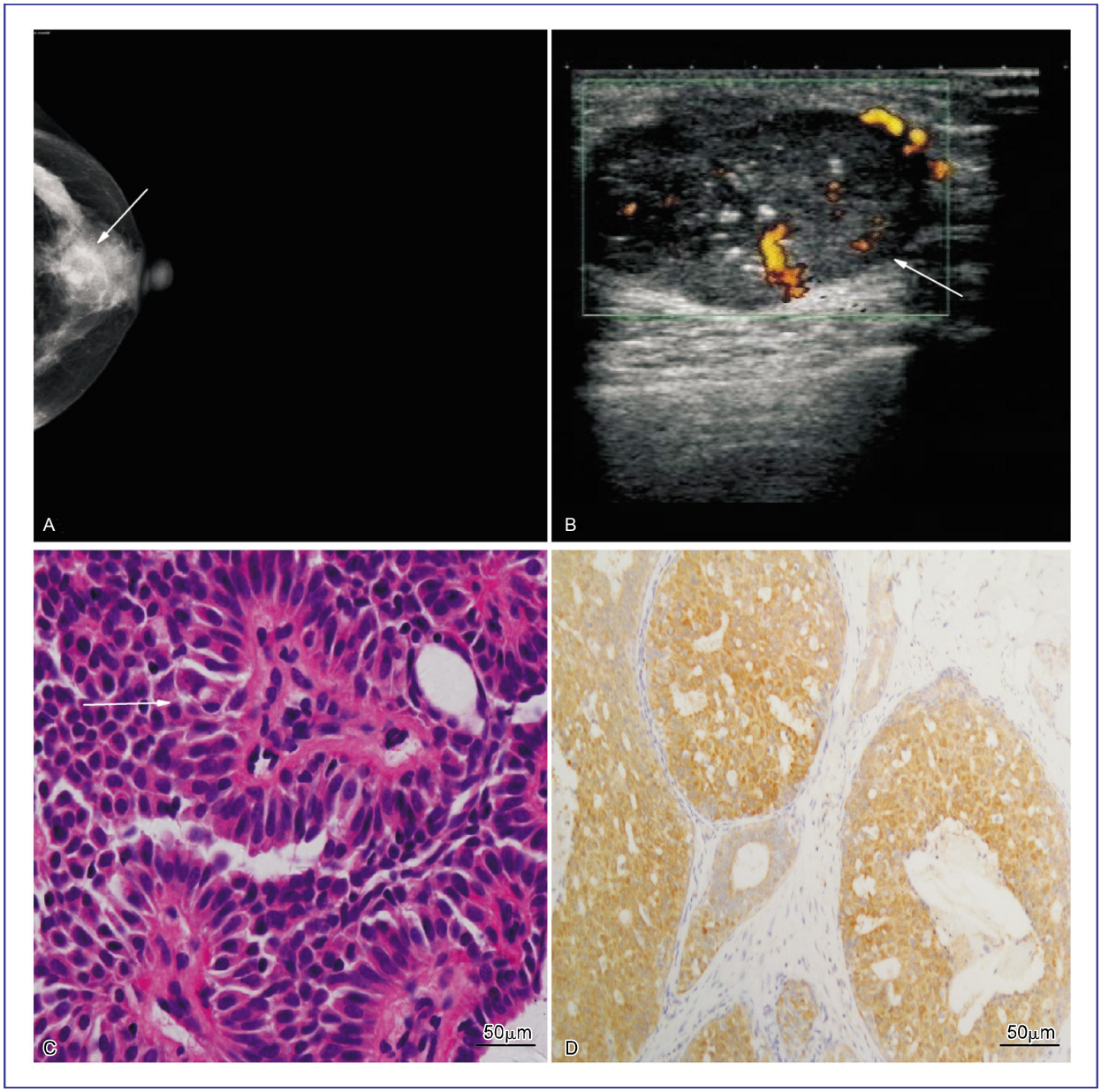

Figure 2 **A 47-year-old woman (patient No. 4) with a tenacious mass in the right breast.** A, a craniocaudal mammogram of the right breast shows an abnormal density (*arrow*) consisting of several clustered nodules with indistinct margins and clustered punctuate calcifications. B, a transverse plane sonographic scan shows an irregular, hypoechoic, solid mass with heterogeneous echo texture and normal sound transmission (*arrow*). C, a photomicrograph (HE) shows clear rosette formation (*arrow*) consisting of impacted arranged cells with uniform size and round or spindle nuclei. D, a photomicrograph (anti-NSE) shows prominent NSE positivity.

masses were hypoechoic (Figures 1B, 2B). Seven were irregularly shaped: 4 with indistinct margins and no acoustic phenomena; 1 with spiculate margins and no acoustic phenomena; 1 with microlobulated margins and posterior acoustic shadow; 1 with circumscribed margins and no acoustic phenomena. Two had a round-ovoid shape with circumscribed margins and posterior acoustic enhancement. Five masses had heterogeneous echo texture: 4 had calcifications, whereas 1 had a cystic change. The other 4 masses had homogeneous echo texture.

Fine needle aspiration biopsy results

A preoperative fine needle aspiration (FNA) biopsy was performed in 5 patients. One was suspicious for

Table 3. Sonographic findings of neuroendocrine breast carcinomas in 9 patients

Patient No.	Size (mm)	Margins	Shape	Echogenicity	Echo texture	Acoustic phenomena
1	20	Circumscribed	Irregular	Hypoechoic	Homogeneous	None
2	8	Indistinct	Irregular	Hypoechoic	Heterogeneous	None
4	43	Indistinct	Irregular	Hypoechoic	Heterogeneous	None
5	18	Circumscribed	Round-ovoid	Hypoechoic	Homogeneous	Enhancement
6	28	Indistinct	Irregular	Hypoechoic	Heterogeneous	None
8	19	Microlobulated	Irregular	Hypoechoic	Heterogeneous	Shadowing
9	27	Spiculated	Irregular	Hypoechoic	Heterogeneous	None
11	14	Circumscribed	Round-ovoid	Hypoechoic	Homogeneous	Slight enhancement
12	27	Indistinct	Irregular	Hypoechoic	Homogeneous	None

The numbers of all cases are identical to those in Table 1.

intraductal carcinoma, 1 was suspicious for ductal carcinoma, 1 was negative, and 2 were considered invasive ductal carcinoma. All patients underwent a modified radical mastectomy with endocrine therapy. Axillary lymph node clearance was performed in 7 patients. For patients younger than 60 years, adjuvant chemotherapy was also administered.

Pathologic and immunohistochemical results

Histopathologic examination showed both *in situ* and invasive components in all patients. On gross pathologic examination, the tumors were pale-gray or brownish and hard or brittle, with mostly irregular margins. Histologically, the tumor cells were medium sized, mostly plasmacytoid or spindle with abundant eosinophilic cytoplasm, and had round to ovoid nuclei. The size of the cells was relatively homogeneous. Cells were arranged in nest, adenoid-like, and cribriform formations. Pseudorosettes were observed in most tumors (Figures 1C, 2C).

Immunohistochemical examination showed high (≥ 50%), middle (25%–50%), low (10%–25%), and no (≤ 10%) Ki-67 immunostaining in 2, 3, 5, and 3 NEBCs, respectively. Seven patients were highly positive for all three neuroendocrine markers, 3 for NSE and Syn, 1 for CgA and Syn, 1 for NSE, and 1 for CgA (Figures 1D, 2D). All patients were positive for ER and PR and negative for CerbB-2. Only one patient demonstrated regional lymph node metastasis.

Follow-up

By August 2011, 12 patients were followed for 41 to 89 months, with a median of 67.5 months; 1 was lost after she finished her initial therapy. No recurrence was found. CEA was changed from negative to weakly positive in 1 patient who had metastases detected in the liver and bones by PET-CT 21 months after treatment. This patient died of liver dysfunction 25 months after the diagnosis of liver metastasis. The other 11 patients were all alive and free of metastasis.

Discussion

Primary NEBC was recently recognized as a distinct entity and was thought to arise from endocrine differentiation of a breast carcinoma rather than from pre-existing endocrine cells in the breast[9]. However, the histogenesis remains unclear. In 2003, the World Health Organization established the diagnostic criteria for primary NEBC as tumors that exhibit morphologic features similar to those of neuroendocrine tumors of both the gastrointestinal tract and lung and that express neuroendocrine markers in more than 50% of tumor cells[2]. Due to these newly defined criteria, it is difficult to determine the actual prevalence of NEBC by reviewing the literature. Guenhan-Bilgen *et al.*[10] have stated that the prevalence was only 0.27% in a series of 1845 histopathologically proven breast carcinomas. Neuroendocrine tumors include solid neuroendocrine carcinoma, atypical carcinoid tumors, small cell/oat cell carcinoma, and large cell neuroendocrine carcinoma[2]. NEBC is more common in elderly women, and most patients are in their 60s or 70s[3]. The disease was also reported in males[11]. Our patients were all women, with a median age of 53 years (range, 36 to 78 years) at the time of diagnosis. All patients had 1 palpable mass; 1 complained of occasional breast pain, and 5 had concurrent bloody nipple discharge. All patients denied most of the breast cancer risk factors and carcinoid syndrome.

Histologically, except for small cell NEBC, most NEBCs typically consist of a uniform population of cells

with abundant eosinophilic cytoplasm and round nuclei with stippled (salt-and-pepper) chromatin. They may appear to grow in nests and resemble ductal breast carcinomas or to grow in strands and resemble lobular breast carcinomas [12]. Neuroendocrine markers were reported to be the most important feature for diagnosis [4]. In addition, the resemblance of the morphology of NEBCs to neuroendocrine tumors from other cells of origin makes it challenging to distinguish them from metastases from other sites [4]. However, intraductal components can support the possibility of breast origin[13,14]. All our cases had *in situ* components, which confirmed the diagnosis of primary NEBC.

Although the diagnosis of NEBC is possible or can be suspected by FNA biopsy[4], FNA is often inadequate, and the findings can be misinterpreted as adenocarcinoma[12]. Moreover, a carcinoid crisis has been reported to be provoked by FNA [15]. In our cases, FNA biopsies were obtained in 5 patients. None showed signs of inspired carcinoid crisis, and no one was identified as NEBC by FNA.

As described above, NEBCs have typically been reported based on clinicopathologic features[3-6]. Until now, only single cases or small series of solid NEBC have been reported with their imaging characteristics [10,14,16]. Fujimoto *et al.* [16] have described a case in which the lesions were relatively homogeneous on sonograms but had an irregular shape and partially ill-defined margins. Slight posterior acoustic enhancement was also documented. Gunhan-Bilgen *et al.* [10] have reported 5 cases of solid papillary NEBC, with a mean lesion size of 22 mm. Mammographically, the shape of the masses was round in 4 patients and irregular in 1. The margins were spiculate in 2 patients, indistinct in 1 patient, microlobulated in 1 patient, and partially obscured in 1 patient. Sonographically, 4 patients had hypoechoic masses with homogeneous echo texture and no acoustic phenomena.

Here, we describe the imaging features of 13 cases of solid NEBC. To our knowledge, this is the report with the largest series of this very rare tumor with comprehensive mammographic, sonographic, and clinicopathologic data. Mammographically, our patients typically appeared with an irregular mass with indistinct or microlobulated margins. When the breast tissue is either heterogeneously or extremely dense, mammography has a relatively low accuracy. The mammogram of patient No. 6 only showed a solitary calcification, whereas sonography revealed a mass in this patient. Sonographically, they had irregular or round-ovoid hypoechoic masses that showed mostly heterogeneous echo texture with circumscribed margins and normal sound transmission.

The sonographic and mammographic findings of the same patients were largely consistent. These findings may partially relate to the intraductal growth pattern and invasiveness of NEBCs in the surrounding tissue, which were identified histopathologically. Calcification was detected in 4 of 13 patients, which was similar to prior reports[3,17]. In 1983, Wade *et al.*[18] reported the first case with described imaging features, in which the lesion had both solid and cystic components on ultrasonograms. Cystic changes were also detected in 1 of our patients. Further, posterior acoustic shadow was detected in 1 patient, which has not been reported previously.

Radiologically, NEBC needs to be differentiated from various invasive breast carcinomas, such as invasive lobular carcinoma (ILC) and invasive ductal carcinoma, not otherwise specified (IDC-NOS). These types of breast carcinomas display an irregular or angular mass with ill-defined margins that is hypoechoic with a heterogeneous internal echo on ultrasonograms. For ILC, the differentiation features may include multifocality, difficulty of clinical detection, posterior acoustic shadow and isodensity or hypodensity [19]. For IDC-NOS, spiculate margins are a key feature[20], whereas this feature was not prominent in the NEBCs in this study. Nevertheless, in this study, with a limited number of cases, NEBC did not show a specific appearance that could distinguish it from other types of breast cancers.

NEBC has been reported to display strong ER and PR positivity and CerbB-2 negativity [6,21], which was consistent with our observations. Ki-67 has been extensively reported as an important prognostic factor in other breast cancers and gastroenteropancreatic neuroendocrine tumors[22,23]. In our study, Ki-67 immunostaining was observed in 10 NEBCs. However, neither the number of patients nor the follow-up period of our study was enough to draw reliable conclusions on this issue.

Earlier studies concluded that NEBC did not differ from other breast carcinomas with regard to its prognosis[5,6]. One recent cohort study of invasive breast carcinoma selected to pair with NEBC reported that NEBC showed a more aggressive course than invasive ductal carcinoma and that regional lymph node metastasis showed a trend for predicting poor overall survival[24]. All cases in our series were the solid subtype, which was considered to be a well-differentiated tumor[4]. In our series, except for the patient we lost contact with and the patient who died of distant metastases, the patients were alive and free of clinical evidence of other metastases or co-existing tumors during the follow-up period of at least 41 months (the longest was 89 months). The patient who died 25 months after the diagnosis of liver metastasis was the only one who had lymph node metastasis at the time of initial diagnosis with NEBC.

Conclusion

In conclusion, NEBC has a variety of presentations, but it is typically observed on mammograms as a dense, irregular mass with indistinct or microlobulated margins. Sonographically, it typically presents as an irregular, heterogeneously hypoechoic mass with normal sound transmission. Moreover, our study suggests that NEBC might not have a unique appearance to distinguish it from other types of breast cancer solely via mammographic or sonographic screening.

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