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Abstract

Introduction: Neuroendocrine carcinoma (NEC) occurs mostly in the digestive organs, such as the pancreas and gastrointestinal tract, and the lungs. Primary NEC of the breast is a rare entity. There are not many studies on this disease, and this study was carried out in order to know the clinical pathology of this disease. **Methods**: Of 2354 patients who underwent surgery for breast cancer in our hospital during the period from January 2000 to July 2015, 8 (0.34%) were pathologically diagnosed with NEC of the breast. This study is retrospectively registered. **Result**: The histological types were small cell carcinoma in one patient and invasive ductal carcinoma (IDC) with neuroendocrine differentiation in the remaining 7. The mean patient age was slightly higher than that of patients with usual IDC. On pathological examination, the NEC tumors were more hormone dependent and often HER2 negative, as compared to usual IDC, though there was no significant difference in nuclear grade. The patients with NEC of the breast showed positivity for neuroendocrine markers on immunohistological staining, and had favorable outcomes. **Conclusion**: NEC of the breast is rare, and there is no established consensus regarding the pathological significance, prognosis, and treatment method. Further accumulation of cases is necessary.

Keywords

Breast Cancer, Neuroendocrine Carcinoma

1. Introduction

Neuroendocrine carcinoma (NEC) occurs mostly in the digestive organs, such as the pancreas and gastrointestinal tract, and the lungs. Primary NEC of the breast is a rare entity. In 2012, the WHO divided NECs into three subtypes: well-diffe-

rentiated neuroendocrine tumor, small cell carcinoma, and invasive breast carcinoma with neuroendocrine differentiation [1]. In recent years, the number of case reports of NEC of the breast has been increasing. However, there is no established consensus regarding the pathological significance, prognosis, and treatment method because the reported data are still limited and long-term studies are lacking. We reviewed cases with NEC of the breast in our hospital according to the new classification.

2. Patients and Methods

Of 2354 patients who underwent surgery for breast cancer in our hospital from January 2000 to July 2015, 8 (0.34%) were pathologically diagnosed with NEC of the breast. All 8 patients were female. The mean patient age was 60.4 years, slightly higher than that of total patients undergoing breast cancer surgery (58.6 years). Clinicopathological and immunohistological analyses of each cases were performed.

Ethics approval and consent to participate is not applicable. Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

3. Results

1) Disease condition, treatment, outcome (Table 1): The mean tumor size was 1.99 cm (range of tumor size: 0.5 - 5.0 cm). Three cases were positive for lymph node metastasis.

The disease stage was stage I in 4 patients, stage IIA in 3, and stage IIB in one, indicating relatively early stages. Five patients underwent breast-conserving surgery, and the remaining 3 underwent mastectomy. Primary systemic therapy (FEC (fluorouracil (500 mg/m^2) + epirubicin (110 mg/m^2) + Cyclophosphamide (500 mg/m^2)) followed by DTX (docetaxel (75 mg/m^2)), 8 cycles) was administered to one patient who had been diagnosed with invasive ductal carcinoma (IDC) on preoperative core needle biopsy, but the effect was judged to be grade 0

Table 1. Characteristics of patients with neuroendocrine carcinoma of the breast.

Case	Age	stage	Tumor (cm)	N factor (P/D)	Operation	Adjuvant therapy	Radiation therapy	Outcome
1	85	IIA	3.5	-	Bp	ET (TAM)	-	12Y0M death (other illness)
2	75	IIA	0.8	1/7	Bt + Ax	ET (TAM)	-	11Y3M alive
3	52	IIA	1.5	1/8	Bp + Ax	ET (TAM→AI)	50 Gy	10T0M alive
4	45	I	1.9	0/4	Bp + SN	CT+ET (TAM + LH − THanalogue)	60 Gy (Boost)	7Y8M alive
5	69	I	0.5	0/5	Bt + Ax	No adjuvant therapy	-	4Y11M alive
6	75	I	1.6	0/3	Bt + SN	ET (AI)	-	4Y7M alive
7	36	IIB	5.0	2/27	Bp + Ax	CT + ET (TAM + LH − RH analogue)	66 Gy (Boost)	3Y10M alive
8	46	I	1.2	0/3	Bp + SN	ET (TAM + LH − RH analogue)	60 Gy (Boost)	2Y9M alive

P/D: Positive/Dissection, Bp: breast-conserving surgery, Bt: mastectomy, ET: Endocrine therapy, CT: Chemotherapy (FEC followed by DTX 8cycles) TAM: tamoxifen, AI: Aromatase inhibitor, Boost: Boost irradiation.

of pathological response grade for chemotherapy. Hormone therapy was administered after postoperative adjuvant chemotherapy (FEC followed by DTX, 8 cycles) to a patient with stage IIB disease. A 5-year hormone therapy regimen was given to 6 subjects, after excluding one patient with triple negative disease. One patient with a small cell carcinoma measuring 0.5 cm in diameter was not treated because she declined the procedure. Radiation therapy was performed for those who had undergone breast-conserving surgery with 50 - 66 Gy (boost radiation was additionally performed depending on tumor extension and age). All cases except survival except one case of other illness deaths (case 1), and a median survival time (MST) of 75 months (33 - 144 months), showing favorable outcomes.

2) Histological grade (Table 2): The histological type was small cell carcinoma in one patient and IDC with neuroendocrine differentiation in the remaining 7. The histological grade was of nuclear grading system I in 3 patients, II in 3, and III in 2. Ki-67 expression was measured in cases 4 - 8, and the percentage of Ki-67 expression was at least 20% in these 5 patients. Lymphovascular invasion was observed in only 2 patients. Regarding biological characteristics, the 7 patients with IDC with neuroendocrine differentiation were estrogen receptor (ER)-positive and progesterone receptor (PgR)-positive, and one was strongly positive for human epidermal growth factor receptor 2 (HER2). One patient with small cell carcinoma had triple negative disease. Immunological staining revealed the patient with small cell carcinoma to be positive only for neuron specific enolase (NSE), while the other patients were positive for synaptophysin and/or chromogranin. Figures 1-3 show histopathological images of representative cases: case 4, IDC with neuroendocrine differentiation; case 5, small cell carcinoma; and case 7, NEC + mucinous carcinoma.

Table 2. Pathological characteristics of the patients with neuroendocrine carcinoma.

Case	Pathological diagnosis	Grade	LVI	Ki-67	ER	PgR	HER2	Synop.	Chrom.	NSE
1	IDC with neuroendocrine differentiation	II	−	−	+	+	1+	+	−	−
2	IDC with neuroendocrine differentiation	I	+	−	+	+	1+	+	−	−
3	IDC with neuroendocrine differentiation	II	+	−	+	+	−	+	−	−
4	IDC with neuroendocrine differentiation	I	−	24%	+	+	1+	−	+	−
5	Small cell carcinoma	III	−	60%	−	−	−	−	−	+
6	IDC with neuroendocrine differentiation	I	−	5%	+	+	3+	+	+	−
7	IDC with neuroendocrine ca+ mucinous ca	III	−	37%	+	+	1+	+	+	−
8	IDC with neuroendocrine differentiation	II	−	96%	+	+	−	+	−	−

ER: Estrogen Receptor, PgR: Progesterone Receptor, HER2: Human epidermal growth factor receptor, LVI: Lymphovascular invasion Synop.: Synoptophysin, Chrom.: Chromogranin, NSE: Neuron-specific enolase, IDC: Invasive ductal carcinoma.

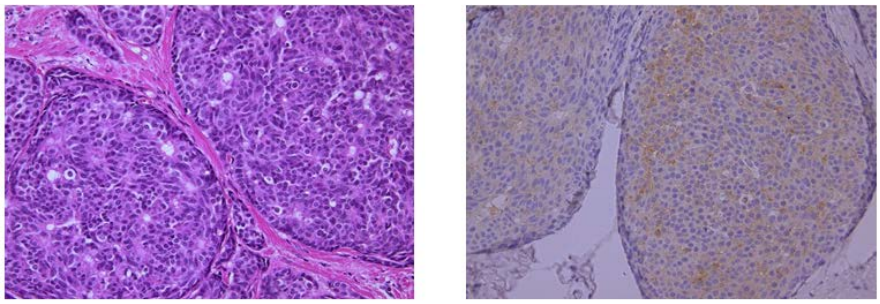

Figure 1. Case 4: invasive ductal carcinoma with neuroendocrine differentiation. HE staining (×200): Accept solid cell proliferation. Immunohistological staining (×200): synaptophysin positive.

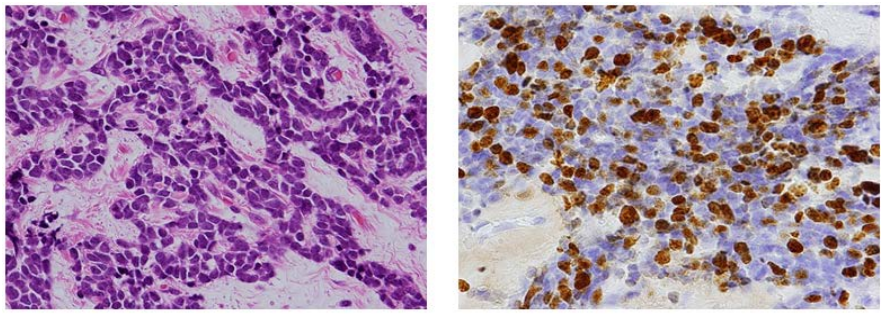

Figure 2. Case 5: small cell carcinoma. HE staining (×400): Tumor cells with a high N / C and chromatin-rich nucleus grow densely. Neuron-specific enolase（NSE）staining (×400): Immunohistochemical neuroendocrine marker was positive.

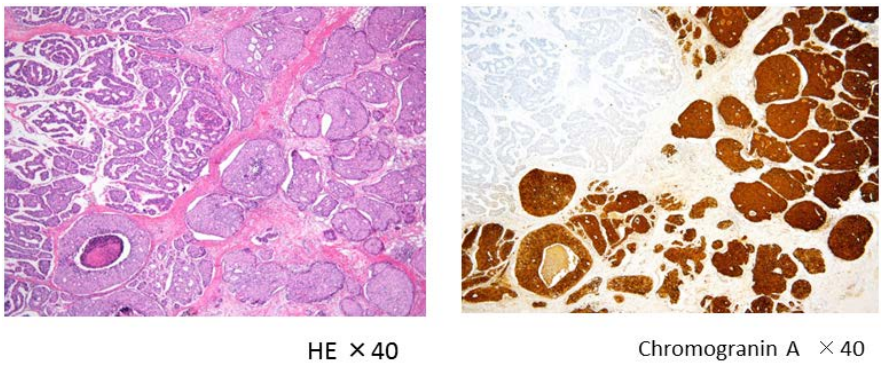

Figure 3. Case 6: NEC and mucinous carcinoma coexisted. HE staininig (×40): The NEC part forms (right side) the lamina cribrosa, some with comdedo necrosis. On its left side, cancer cells form papillary agglomerates and are floating in the mucus lake. Myxoid nodules are destroying the surrounding stroma. Immunohistological staining (×40): In the NEC part, Chromogranin A was positive and negative in the mucinous cancer part.

4. Discussion

NEC of the breast is a rare entity, comprising <1% of all NECs and <0.1% of breast carcinomas [2]. It was first reported as carcinoid mammary tumor, and then the tumors with high nuclear grade and high malignancy grade were sepa-

rately recognized as neuroendocrine tumors of the breast [3]. A major hypothesis regarding pathogenesis is that cancer cells undergo neuroendocrine differentiation [4]. The most common form is IDC of the breast, and a palpable mass is a common clinical presentation, although there are patients in whom cancer is detected based on bloody nipple discharge or who have non-invasive cancer [5] [6]. In the present cases, all tumors had been detected by palpation of a mass.

NECs of the breast are usually seen in mature women, around the seventh or eighth decade of life, and the tumors tend to be larger (measuring ≥20 mm in diameter), higher grade, and more advanced than usual breast cancers. Studies have found both progression free survival and overall survival to be shorter than those of patients with usual IDC [7] [8]. However, in the present study, the patients with NEC had survival rates similar to those of patients with usual IDC and had favorable outcomes (MST of 75 months). According to the literature, the histological characteristics are: expression of neuroendocrine markers (synaptophysin, chromogranin A, CD56, NSE, etc.) in more than 50% of tumor cells; presence of carcinoid-like structures such as pseudorosettes, cord-like arrangement, small tubules, and alveolar components; and the presence of numerous neuroendocrine granules on micro-morphological observation. Regarding the biological characteristics, most tumors are reportedly hormone dependent and HER2 negative [9]. In the present study, one patient was HER2 positive and the one with small cell carcinoma had triple negative disease.

Reports on treatment of NEC of the breast are limited, and the optimal treatment method and therapeutic effect predictors have not been established. Currently, treatment is conducted according to the regimen for usual IDC. Regarding the effects of chemotherapy, one study demonstrated the use of conventional agents for breast cancer [10], and another found that cisplatin/etoposide followed by paclitaxel/carboplatin was effective [11]. One patient in the present study was diagnosed with IDC, T2N1 on preoperative core needle biopsy and underwent primary systemic therapy (FEC followed by DTX, 8 cycles) but the effect was judged to be grade 0, raising the possibility that conventional chemotherapy is relatively ineffective for this type of cancer. Further investigation of this issue is needed. In addition, we had planned to treat the patient with small cell carcinoma according to the regimen for treating small cell carcinoma of the lung but she refused.

Reported outcomes are variable. One study found that patients with NEC of the breast reportedly had outcomes similar to those of IDC patients [12]. Another study found that patients with NEC of the breast, especially those with small cell carcinoma, tended to have more advanced disease and poor outcomes [13]. The patients in the present study had favorable outcomes. Further accumulation of cases is needed to clarify disease status. A registration system for this disease, like the registration system for NETs of the digestive organs, is needed to achieve this aim.

5. Conclusion

We conducted a clinicopathological study of 8 patients with NEC of the breast.

These patients were slightly older than those with usual IDC and but there was no significant difference in malignancy grade between the two groups. The NEC tumors were more hormone dependent and were often HER2 negative. The 8 patients with NEC of the breast in the present study had favorable outcomes. Further accumulation of ceases is needed to establish the optimal treatment method for this rare breast cancer.

Consent to Publish

I have obtained consent to publish from the participant. A copy of the written consent is available for review by the Editor-in Chief of this journal.

Authors Contribution

MK have operated this case and analyzed all data. SY and NT, SO, KI, SH did the assistant of the operation.

Competing Interests

I confirm that I have read BioMed Central's guidance on competing interests and have included a statement indicating that none of the authors have any competing interests.

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Not applicable, the authors declare that there is no competing interest.

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