The Carcinoembryonic Antigen as a Potential Prognostic Marker for Neuroendocrine Carcinoma of the Breast

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Abstract. Aim: Primary neuroendocrine carcinomas of the breast (PNCB) are very rare and tumor markers for this indication are not well defined. We aim at reporting a case and providing a marker useful for prognosis and prediction of tumor recurrence for patients with PNCB. **Case Report:** A 75-year-old woman presented with a slight painful lump in her left breast of more than 6 months duration. Prior to surgery, the serum level of carcinoembryonic antigen (CEA) (54.4 ng/ml；normal limit <5.0 ng/ml) was significantly elevated. Ultrasonography identified a hypoechoic lesion. Mammography revealed a hyperdense lesion with a well-circumscribed margin. The patient underwent a modified radical mastectomy with axillary lymph node dissection. Pathology showed tumor cells with neuroendocrine features , with diffuse immunopositivity for chromogranin and synaptophysin. The tumor cells were also strongly positive for progesterone and estrogen receptor, but negative for HER-2/neu expression. The CEA value gradually decreased to the normal range within one month after surgery. Neither recurrence nor distant metastasis has been detected at 20 months after surgery and hormone therapy with letrozole. The serial CEA levels were within normal limits in the follow-up period. **Conclusion:** The serum CEA level after surgery

may be a potential marker for evaluating tumor recurrence or prognosis of patients with PNCB.

Primary neuroendocrine carcinomas of the breast (PNCB) are very rare and have been reported mainly occurred in elderly women (1). They were first described by Cubilla and Woodruff in 1977 (2) and the incidence rate ranged from 0.27-0.5% in breast carcinomas (3, 4). Due to its rarity, tumor detection, treatment and prognosis of patients having PNCB is not well defined. We report the case of PNCB in a 75-year-old woman in Taiwan and make a comprehensive review of tumor detection, treatment and prognosis of patients having PNCB.

Case Report

A 75-year-old woman presenting with a slight painful lump in her left breast of more than 6 months duration visited our hospital. Upon examination, an ill-defined hard lump measuring about 4.0 cm was felt in central portion of her left breast, near the nipple-areolar complex. There was no axillary lymphoadenopathy. Ultrasonography showed a 4.0 cm hypoechoic lesion with a slightly irregular contour and heterogenous content (Figure 1). Mammography revealed a hyperdense lesion with a

well-circumscribed margin, without microcalcification (Figure 2). Ultrasound-guided core needle biopsy for the mass demonstrated a mucinous carcinoma. Prior to surgery for removal of the lesion, the serum level of the tumor marker carcinoembryonic antigen (CEA), 54.4 ng/ml, was significantly elevated (normal limit <5 ng/ml), while the cancer antigen (CA) 15.3 value was within the normal range.

The patient underwent a modified radical mastectomy of the left breast with axillary lymph node dissection. Grossly, the breast tumor was a well-circumscribed, tan to grayish, firm mass, measuring 4.0×3.0×3.0 cm. Upon microscopic examination, the tumor was composed of round to oval neoplastic cells arranged in a solid-nested, trabecular or ribbon growth pattern and separated by a delicate fibrovascular stroma, with abundant extracellular mucin production (Figure 3). These tumor cells contained relatively uniform nuclei, with fine chromatin and moderate granular eosinophilic cytoplasm. There was evidence of increased mitotic activity, with 5 mitotic features per 10 high-power fields, marked tumor necrosis and hemorrhage. No lymph node metastasis was noted. Immunohistochemical staining of tumor cells revealed a diffusely cytoplasmic positivity for chromogranin and synaptophysin (Figure 4),

which are neuroendocrine markers. Tumor cells were also strongly positive for progesterone and estrogen receptors but negative for HER-2/neu expression. We had examined the head, neck, lung, gastrointestinal tract and bone in order to exclude possible nonmammarian primary sites or distant metastasis. The breast tumor pathology was revised to PNCB, solid type, of histological grade 1 and stage IIA (pT2N0M0).

The patient received adjuvant hormone therapy with letrozole after surgery. The CEA value was decreased to 20.5 ng/ml at 8 days after surgery, and then decreased to within the normal range (CEA value 4.38 ng/ml) at one month after surgery. There was no evidence of recurrence or distant metastasis 20 months after surgical treatment and hormone therapy with letrozole. The serial serum CEA levels were within normal limits in the follow-up period.

Discussion

Neuroendocrine carcinomas, including carcinoid tumors are malignant tumors with neuroendocrine differentiation, which arise mainly from endocrine organs and non-endocrine organs, such as the gastrointestinal

system and lungs (5), but rarely from breast. Unlike such lesions in gastrointestinal tract or lungs, benign neuroendocrine tumors have, to our knowledge, never been reported in breast; therefore, all breast neuroendocrine lesions have previously been considered as carcinomas (6).

PNCB was first described by Cubilla and Woodruff in 1977, and only eight cases of breast carcinoid tumors with argyrophilic granules were identified (2). In 1988, chromogranin and secretogranin were found to be localizedly expressed in some argyrophilic breast carcinomas (7). In 2000, Sapino *et al*. firstly defined differentiated neuroendocrine breast carcinomas as tumors with specific morphological features which expressed neuroendocrine markers in more than 50% of the tumor cells (8), compatible with the 2003 WHO classification of PNCB based on two characteristics: morphologic features and neuroendocrine differentiation (9). Chromogranin and synaptophysin have been identified as specific markers for neuroendocrine differentiation (10, 11). By definition, breast carcinomas showing neuroendocrine differentiation only in scattered or some tumor cells are not included in PNCB. Accordingly, the incidence of PNCB is very low. For instance, the incidence in the report of

Gunhan-Bilgen *et al*. was only 0.27% in 1,845 cases of breast carcinoma (3). The incidence in the report of López-Bonet *et al*. was about 0.5% in a series of 1,368 histopathologically proven breast carcinomas (4). Moreover, the disease occurrs mainly in elderly women in sixth to seventh decades of life (1, 12, 13).

Miremadi and colleagues observed that the amount of neuroendocrine differentiation in breast carcinomas bears no relation to prognostic factors or patient outcome (14). Histological grade is one of the most important prognostic factors (15). Solid neuroendocrine carcinoma and atypical carcinoids are regarded as well-differentiated tumors, with better prognosis with adequate surgical and adjuvant therapy (16); in contrast, small cell and large cell neuroendocrine carcinomas are poorly differentiated, giving a negative prognosis (17, 18). Since our patient was a case of solid neuroendocrine carcinoma of the breast with strong positivity for progesterone and estrogen receptors and a lack of lymph node involvement, we believe the patient should have a good prognosis, which is supported by no evidence of recurrence or distant metastasis at 20 months after surgery and hormone therapy.

Several tumor markers can be detected in the serum of patients

with malignancy. The concept of serum tumor marker represents a quantifiable assessment of the tumor burden at that time. The use of tumor markers concern several different aspects, such as determination of cancer risk, screening, diagnosis, prognosis, prediction of response to therapy, and monitoring the course of disease (19-21). The most common serum markers used for postoperative monitoring of breast cancer are CEA and CA15-3 (21, 22). The European Group on Tumor Markers suggests that CEA and CA15-3 testing should be performed even in asymptomatic women despite the impacts of the lead time on patients' survival not being clear (23). Nobels and colleagues analyzed 211 patients with neuroendocrine tumors and 180 controls with nonendocrine tumors, and stated that chromogranin is the best general neuroendocrine serum marker available. Unfortunately, it is not a very sensitive marker (24). Until now, the association between PNCB and tumor markers has not been well investigated because of its rarity. In this case, because of the significantly elevated CEA value in serum before surgery and into gradually reduction to normal within one month after surgery, we propose that the change of CEA levels may be a potential marker in the follow-up of treatment of patients and their prognosis.

In our present case, the specimen of core biopsy was initially misdiagnosed as a mucinous adenocarcinoma due to florid extracellular mucin production over the stroma. But in considering the whole specimen of this tumor, the extracellular mucinous stroma did not fit the criterion of mucinous adenocarcinoma that more than 50% of the tumor should contain extracellular mucinous pools (9). In a previous report, about 26% of neuroendocrine carcinomas exhibited either intracellular or extracellular mucin, or both (13). Therefore, the amount of extracellular mucin production may reveal a limitation for making a correct diagnosis of neuroendocrine carcinoma of the breast based on small core biopsies.

The clinical and imaging features of neuroendocrine carcinoma of the breast mimic other types of breast carcinoma in many ways without any specificity (9). Neuroendocrine tumors often present as dense round or irregular masses with a spiculated or lobulated margin in mammography (3, 25, 26). On ultrasonography, neuroendocrine tumors are hypoechoic with cystic or no cystic component (26, 27). Hence it is difficult to diagnose neuroendocrine tumors based on these image findings alone. The ultrasonographic and mammographic examinations in our present case revealed a focal lesion with indistinctive margin in the

left breast. The image studies and clinical features were not specific for diagnosis of PNCB.

The best treatment for patients with PNCB is still unknown (28). In general, surgery is regarded as the major treatment among the strategy choices (6). The surgical choice includes lumpectomy and modified radical mastectomy with axillary lymph node dissection, or sentinel lymph node biopsy based on the tumor size, location and stage. Chemotherapy or hormone therapy may be given according to clinical tumor status and biomarkers (6, 28, 29). Our case surgery operation and then received adjuvant hormone therapy with letrozole thereafter. There was no evidence of recurrence or distant metastasis at 20 months after operation.

In conclusion, PNCB is very rare in incidence. Tumor histological grade is a known prognostic factor. Long-term prognosis and tumor behavior are not well known because of its rarity. The only index in the present case is the significantly altered CEA level before and after surgery. We propose that the change of CEA levels may be a potential marker for clinical application in follow-up, in addition to its was in detection. Further studies recruiting larger patient populations with long-term

follow-up may lead us to clearly understand this new concept.

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References

1 Papotti M, Macri L, Finzi G, Capella C, Eusebi V and Bussolati G: Neuroendocrine differentiation in carcinomas of the breast: a study of 51 cases. Semin Diagn Pathol *6*: 174-188, 1989.

2 Cubilla AL and Woodruff JM: Primary carcinoid tumor of the breast: A report of eight patients. Am Surg Pathol *1*: 283, 1977.

3 Gunhan-Bilgen I, Zekioglu O, Ustun EE, Memis A and Erhan Y: Neuroendocrine differentiated breast carcinoma: imaging features correlated with clinical and histopathological findings. Eur Radiol *13*: 788-793, 2003.

4 Lopez-Bonet E, Alonso-Ruano M, Barraza G, Vazquez-Martin A, Bernado L and Menendez JA: Solid neuroendocrine breast carcinomas: incidence, clinico-pathological features and immunohistochemical profiling. Oncol Reports *20*: 1369-1374, 2008.

5 Maluf HM and Koerner FC: Carcinomas of the breast with endocrine differentiation: a review. Virchows Archiv *425*: 449-457, 1994.

6 Lee YC, Chen YL, Chan SE, Tseng HS and Chen DR: Neuroendocrine Carcinoma of the Breast: Case Report and Literature Review. Breast Care *4*: 324-327, 2009.

7 Ooi A, Ohta T, Mai M, Nakanishi I and Takahashi Y: Primary breast carcinoma with extensive endocrine differentiation: an immunohistochemical and immunoelectron microscopic study. Surg Pathol *1*: 277-284, 1988.

8 Sapino A, Righi L, Cassoni P, Papotti M, Pietribiasi F and Bussolati G: Expression of the neuroendocrine phenotype in carcinomas of the breast. Semin Diagn Pathol *17*: 127-137, 2000.

9 Tavassoli FA and Devilee P: World Health Organization Classification of Tumours. Pathology and Genetics of Tumors of the Breast and Female Genital Organs. IARC Press, Lyon, 2003.

10 Gould VE, Lee RV, Wiedenmann B, Moll R, Chejfec G and Franke WW: Synaptophysin: a novel marker for neurons, certain neuroendocrine cells, and their neoplasms. Hum Pathol *17*: 979-983, 1986.

11 Lloyd RV: Immunohistochemical localization of chromogranin in normal and neoplastic endocrine tissues. Pathol Annu *22*: 69-90, 1987.

12 Azzopardi JG, Muretto P, Goddeeris P, Eusebi V and Lauweryns JM: Carcinoid tumours of the breast: the morphological spectrum of

13 Sapino A, Righi L, Cassoni P, Papotti M, Gugliotta P and Bussolati G: Expression of apocrine differentiation markers in neuroendocrine breast carcinomas of aged women. Modern Pathol *14*: 768-776, 2001.

14 Miremadi A, Pinder SE, Lee AH, Bell JA, Paish EC, Wencyk P, Elston CW, Nicholson RI, Blamey RW, Robertson JF and Ellis IO: Neuroendocrine differentiation and prognosis in breast adenocarcinoma. Histopathology *40*: 215-222, 2002.

15 McIntire M, Siziopikou K, Patil J and Gattuso P: Synchronous metastases to the liver and pancreas from a primary neuroendocrine carcinoma of the breast diagnosed by fine needle aspiration. Diagn Cytopathol *36*: 54-57, 2008.

16 Stita W, Trabelsi A, Gharbi O, Mokni M and Korbi S: Primary solid neuroendocrine carcinoma of the breast. Can J Surg *52*: E289-290, 2009.

17 Tsai WC, Yu JC, Lin CK and Hsieh CT: Primary alveolar type large cell neuroendocrine carcinoma of the breast. Breast *11*: 487, 2005.

18 Berruti A, Saini A, Leonardo E, Cappia S, Borasio P and Dogliotti L: Management of neuroendocrine differentiated breast carcinoma.

19 Bartsch R, Wenzel C, Pluschnig U, Hussian D, Sevelda U, Altorjai G, Locker GJ, Mader R, Zielinski CC and Steger GG: Prognostic value of monitoring tumour markers CA 15-3 and CEA during fulvestrant treatment. BMC Cancer *6*: 81, 2006.

20 Stearns V, Yamauchi H and Hayes DF: Circulating tumor markers in breast cancer: accepted utilities and novel prospects. Breast Cancer Res Treat *52*: 239-259, 1998.

21 Lumachi F and Basso SM: Serum tumor markers in patients with breast cancer. Exp Rev Anticancer Ther *4*: 921-931, 2004.

22 Duffy MJ: Serum tumor markers in breast cancer: Are they of clinical value? Clin Chem *52*: 345-351, 2006.

23 Molina R, Barak V, van Dalen A, Duffy MJ, Einarsson R, Gion M, Goike H, Lamerz R, Nap M, Soletormos G and Stieber P: Tumor markers in breast cancer–European Group on Tumor Markers recommendations. Tumor Biol *26*: 281-293, 2005.

24 Nobels FR, Kwekkeboom DJ, Coopmans W, Schoenmakers CH, Lindemans J, De Herder WW, Krenning EP, Bouillon R and Lamberts SW: Chromogranin A as serum marker for neuroendocrine

25 Mariscal A, Balliu E, Diaz R, Casas JD and Gallart AM: Primary oat cell carcinoma of the breast: imaging features. Am J Roentgenol *183*: 1169-1171, 2004.

26 Wade PM, Jr., Mills SE, Read M, Cloud W, Lambert MJ, 3rd and Smith RE: Small cell neuroendocrine (oat cell) carcinoma of the breast. Cancer *52*: 121-125, 1983.

27 Jundt G, Schulz A, Heitz PU and Osborn M: Small cell neuroendocrine (oat cell) carcinoma of the male breast. Immunocytochemical and ultrastructural investigations. Virchows Archiv *404*: 213-221, 1984.

28 Deveci U, Manukyan MN, Kebudi A, Gokce K, Midi A and Atasoy MM: Primary neuroendocrine carcinoma of the breast: case report. J Surg Arts *2*: 22-27, 2010.

29 Yalcin B, Zengin N, Tekuzman G and Kucukali T: Primary neuroendocrine tumor of the breast. Med Oncol *14*: 121-123, 1997.

Figure Legends

Figure 1. Ultrasonography showing a hypoechoic lesion with slightly irregular contours and heterogenous content.

Figure 2. Mammography revealing a hyperdense focal lesion with circumscribed margins and without microcalcification：(A) medial-lateral oblique view, (B) caudal-coronal view.

Figure 3. Histopathology showing ribbons and nests of tumor cells within the mucinous stroma. Haematoxylin-eosin stain (×200).

Figure 4. Immunohistochemistry showing diffusely synaptophsin-positive staining (brown color, ×200).

Figure 1

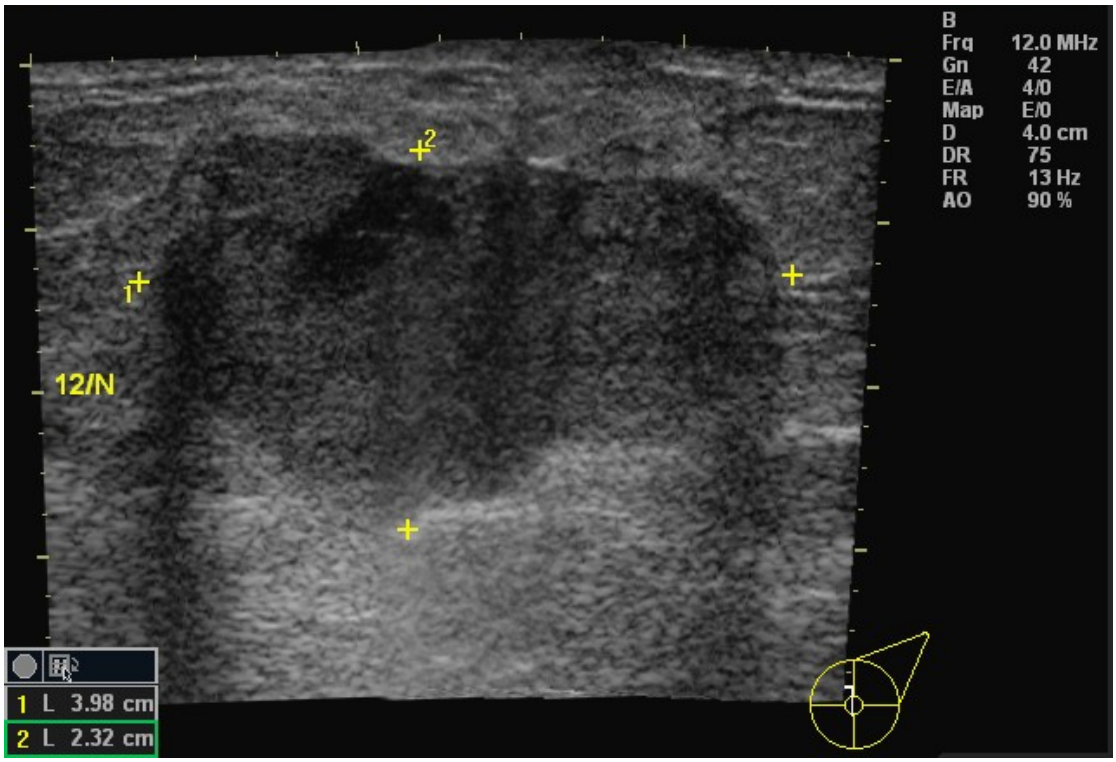
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Figure 2

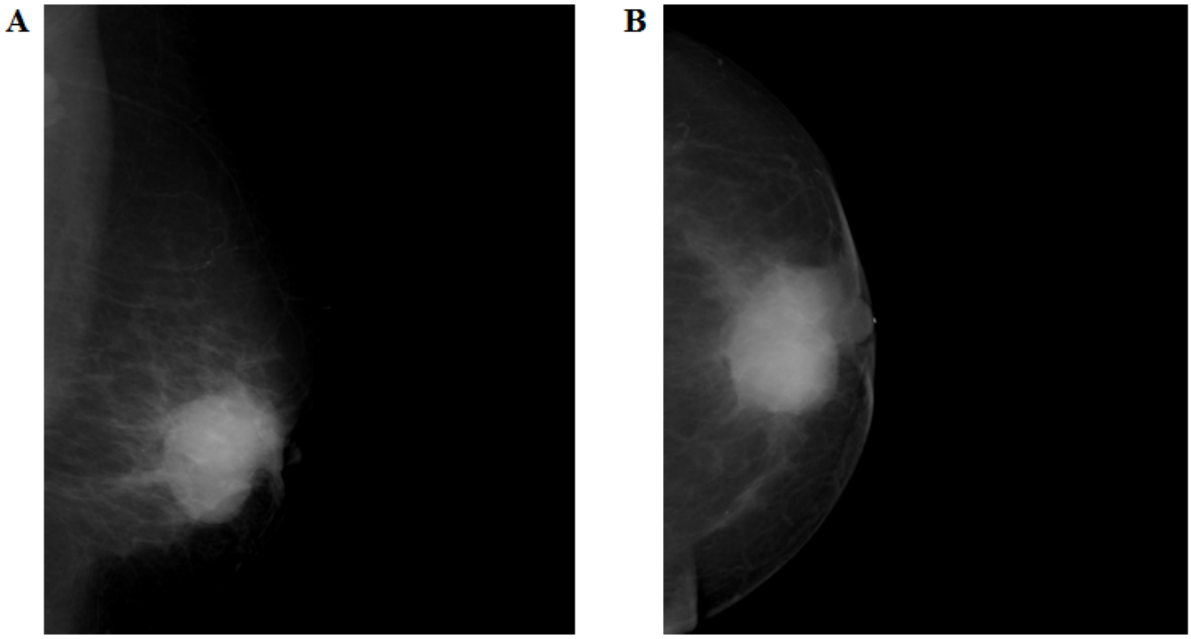

Figure 3

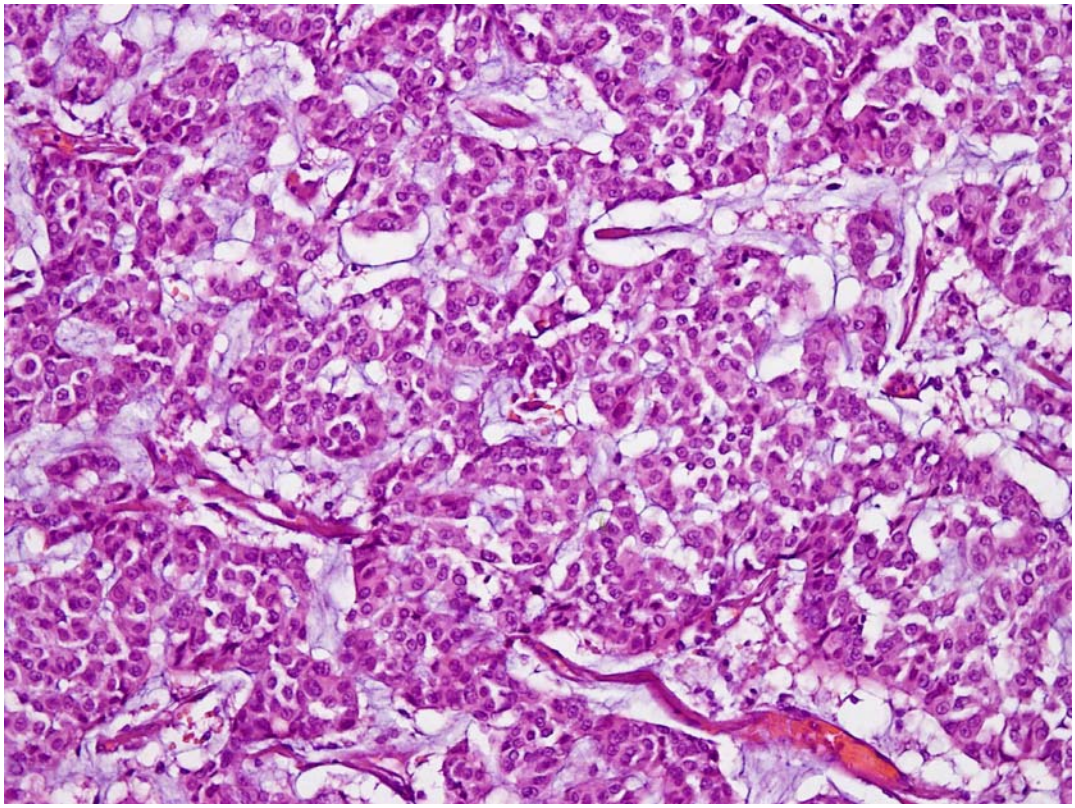

Figure 4