Neuroendocrine carcinoma of the breast with a mucinous carcinoma component: A case report with review of the literature

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Received January 30, 2012; Accepted March 30, 2012

DOI: 10.3892/ol.2012.678

Abstract. Neuroendocrine carcinoma (NEC) of the breast is a rare distinct clinicopathological entity, which, clinically, tends not to be aggressive. Mucinous carcinoma of the breast is also a rare distinct entity and is classified into types A (paucicellular) and B (hypercellular). It is well known that type B mucinous carcinoma frequently shows neuroendocrine differentiation. However, the coexistence of NEC and mucinous carcinoma within the same breast tumor is extremely rare. In the present study, we report a case of solid NEC of the breast with a mucinous carcinoma component and discuss the tumorigenesis of this extremely rare lesion. A 37-year-old Japanese female presented with a right breast tumor. Mastectomy and removal of the right axillary lymph nodes were performed. The resected breast tumor was composed of solid NEC (approximately 85% of the tumor) and type B mucinous carcinoma components. The right axillary lymph nodes had metastatic solid NEC. Three years later, local recurrence of mucinous carcinoma occurred in the operation scar of the right thoracic wall. In addition, seven years after the first surgery, metastatic solid NEC in the liver was observed. Recent molecular studies clearly revealed that no differences in gene expression are present between type B mucinous carcinoma and NEC. Therefore, the present case may represent solid NEC and type B mucinous carcinoma as part of a spectrum with the same genetic background. Moreover, the prognosis of solid NEC is thought to be good, and metastasis is extremely rare. However, metastasis of solid NEC of the breast may occur at a later stage. Therefore, long-term follow-up is required for patients with solid NEC of the breast.

Introduction

Neuroendocrine carcinoma (NEC) of the breast is a rare distinct clinicopathological entity, comprising 0.5-2% of breast carcinomas worldwide (1,2). Since previous diagnostic criteria for NEC of the breast had been contradictory, the World Health Organization Classification of Tumours of the Breast and Genital Organs proposed the following diagnostic criteria for breast NEC in 2003: i) Presence of morphological neuroendocrine features resembling those of neuroendocrine tumors of the gastrointestinal tract and lung, and ii) expression of neuroendocrine markers in more than 50% of tumor cells (1).

Mucinous carcinoma of the breast is also a rare distinct clinicopathological entity, and accounts for approximately 2% of breast carcinomas worldwide (1). It is characterized by a proliferation of clusters of generally small and uniform tumor cells floating in large amounts of extracellular mucus. Pure mucinous carcinoma is not recognized as a single homogenous entity. Capella et al classified it based on structural and cytological features as type A (paucicellular; a tumor showing a ribbon, annular, or cribriform growth pattern with prominent extracellular mucin) and type B (hypercellular; tumor showing clumps or sheet-like structures with less extracellular mucin) (3). It is well known that type B mucinous carcinoma frequently shows neuroendocrine differentiation (3,4).

Solid NEC of the breast with a mucinous carcinoma component is rarely reported (2). In the present study, we report a case of solid NEC of the breast with a mucinous carcinoma component and discuss the tumorigenesis of this rare lesion. The study was approved by the ethics committee of the university and patient consent was obtained.

Patients and methods

Case report. A 37-year-old Japanese female presented with a right breast tumor. A physical examination revealed a relatively well-circumscribed tumor, measuring 3x2.5 cm in diameter, in the right breast and swollen right axillary lymph nodes. No metastatic lesions with the exception of the right axillary lymph nodes were detected by computed tomography (CT). The biopsy specimen of the right breast tumor revealed invasive carcinoma; thus, total mastectomy and removal of the right axillary lymph nodes were performed (cT2N1M0, stage IIB). Chemotherapy and hormonotherapy were adminis-
tered following the surgery. Three years later, local recurrence was observed on the operation scar of her right thoracic wall, and tumor resection was performed again. Seven years after the first surgery, a liver tumor was detected during the follow-up CT. CT and magnetic resonance imaging demonstrated a relatively well-circumscribed tumor, measuring 42x37x30 mm, in S3 (Fig. 1). Metastatic breast cancer in the liver was suspected clinically, resulting in the surgical resection of the liver tumor. The post-operative course was uneventful, and the patient has been free from recurrence for 18 months of medical follow-up.

Methods. The formalin-fixed, paraffin-embedded tissue blocks of the tumors of the breast, local recurrence on the operation scar, and liver were cut into 3-µm sections, deparaffinized and rehydrated. Each section was stained with hematoxylin and eosin, and then used for immunostaining. Immunohistochemical analyses were performed using an autostainer (XT system Benchmark, Ventana Medical System, Tucson, AZ, USA) according to the manufacturer's instructions. The primary antibodies used were: a mouse monoclonal antibody against CD56 (clone CD564, Novocastra Laboratories, Ltd., Newcastle upon Tyne, UK), a mouse monoclonal antibody against chromogranin A (clone DAK-A3, Dako Cytomation, Glostrup, Denmark), a mouse monoclonal antibody against estrogen receptor (ER) (clone 6F11, Novocastra), a mouse monoclonal antibody against gross cystic disease fluid protein-15 (GCDFP-15) (clone 23A3, Novocastra), a mouse monoclonal antibody against progesterone receptor (PgR) (clone PgR636, Dako), and a mouse monoclonal antibody against synaptophysin (clone 27G12, Novocastra). In addition, immunohistochemistry for the c-erbB-2 (HER2) oncoprotein was performed using a Dako kit.

Results

Breast tumor. The tumor was relatively well-circumscribed, however, it had invaded into the surrounding fatty tissue. Most of the tumor comprised variable-sized solid nests with or without central necrosis separated by delicate fibrovascular stroma (Fig. 2A and B). The solid nests consisted of uniform tumor cells which had slightly enlarged oval nuclei and inconspicuous nucleoli with slightly eosinophilic cytoplasm (Fig. 2B, inset). Mitotic figures were easily detected (45/10 high power fields).

Immunohistochemical analyses revealed that these tumor cells were diffusely (>95% of the tumor) positive for chromogranin A (Fig. 3), although CD56, synaptophysin and GCDFP-15 were not expressed. Therefore, this component was considered to be solid NEC of the breast. In addition, ER and PgR were diffusely expressed (100% of the tumor), and the HER2 score was 1+.
Approximately 85% of the tumor belonged to the above-mentioned solid NEC component. However, areas with proliferation of clusters or sheets of uniform tumor cells with mildly enlarged nuclei and slightly eosinophilic cytoplasm floating in extracellular mucin, which are characteristic histopathological features of mucinous carcinoma, were present at the periphery of the tumor (Fig. 2A and C). According to the classification by Capella et al. (3), this mucinous carcinoma was classified as type B. Results of the immunohistochemical analysis revealed that certain tumor cells of the mucinous carcinoma component were positive for chromogranin A, but negative for CD56, synaptophysin and GCDFP-15. In addition, ER and PgR were diffusely expressed (100% of the tumor) in this mucinous carcinoma component and the HER2 score was 0.

According to these histopathological and immunohistochemical findings, an ultimate diagnosis of solid NEC with type B mucinous carcinoma component was made. In addition, the right axillary lymph nodes had metastatic solid NEC (3/28).

Local recurrent tumor. The tumor was located in the dermis to superficial subcutis and was composed of clusters of uniform tumor cells with slightly enlarged nuclei floating in extracellular mucin (Fig. 4). These histopathological features were consistent with local recurrence of mucinous carcinoma of the breast. No NEC component was present.

Liver tumor. The tumor was relatively well-circumscribed from surrounding liver tissue and separated by delicate fibrovascular
Weigelt et al analyzed the molecular characteristics of mucinous carcinoma and NEC of the breast using genome-wide oligonucleotide microarrays (7). The study clearly revealed that no differences in gene expression were present between type B mucinous carcinoma and NEC, whether or not type A mucinous carcinoma exhibited differences compared with type B mucinous carcinoma and NEC (7). Taking these results into consideration, the present case may represent NEC and type B mucinous carcinoma as part of a spectrum with the same genetic background.

The prognosis of solid NEC is thought to be better than invasive ductal carcinoma, since in one report, none of the investigated solid NEC (35 cases) had distant metastasis (5). In another study, only one of seven cases of solid NEC demonstrated metastasis (soft tissue of the cheek; the patient is alive with metastatic disease) (2). In addition, both patients with solid NEC with mucinous carcinoma component reported by López-Bonet et al are free from tumor recurrence (2). However, the present patient had liver metastasis seven years after the surgery. Therefore, long-term follow-up is necessary for patients with solid NEC of the breast due to metastatic potential at a later stage.

References


