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Primary breast carcinomas with neuroendocrine features: Clinicopathological features and analysis of tumor growth patterns in 36 cases

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ABSTRACT

Primary breast carcinoma with neuroendocrine features (NEBC) is an uncommon tumor. In the classification of WHO 2012, these tumors were categorized as: 1- neuroendocrine tumor, well-differentiated; 2- neuroendocrine carcinoma, poorly differentiated/small cell carcinoma; and 3- invasive breast carcinoma with neuroendocrine differentiation. In this study, we reviewed NEBC except poorly differentiated/small cell carcinoma variant in order to define the morphological growth patterns and cytonuclear details of these tumors. All breast surgical excision materials between 2007 and 2016 were re-evaluated in terms of neuroendocrine differentiation. Thirty-six cases showing positive staining for synaptophysin and/or chromogranin A in ≥50% of tumor cells were included in the study. All cases were female with a mean age of 67.4. Mean tumor diameter was 26 mm. Multifocality was noted in 5 cases. Grossly, they were mostly infiltrative mass lesions. T stages, identified in 34 cases, were as follows: 13 cases with pT1; 19 pT2 and 2 pT3. We described schematically 4 types of patterns depending on predominant growth pattern, except one case: 1) Large-sized solid cohesive groups (6 cases), 2) Small- to medium-sized solid cohesive groups with trabeculae/ribbons and glandular structures (6 cases), 3) Mixed growth patterns (20 cases), 4) Invasive tumor with prominent extracellular and/or intracellular mucin (3 cases). The tumor cells were mostly polygonal-oval with eosinophilic/eosinophilic-granular cytoplasm. The nuclei of tumor cells were mostly round to oval with evenly distributed chromatin. Only 5 cases showed high grade nuclear and histological features. Molecular subtypes of the cases were as follows: 33 luminal A, 2 luminal B, and 1 triple negative. NEBC should come to mind when a tumor display one of the morphological patterns described above, composed of monotonous cells with mild to moderate nuclear pleomorphism and abundant eosinophilic/eosinophilic granular or clear cytoplasm, especially in elderly patients.

1. Introduction

Primary breast carcinoma with neuroendocrine features is an uncommon tumor that was first recognized in 1963 by Feyrter and Hartmann as carcinoid growth pattern in two cases with invasive breast carcinoma [1]. Later, in 1977, Cubilla and Woodruff described eight cases of breast carcinoma also as carcinoid tumor [2]. Initially, the presence of neurosecretory granules within these tumors was revealed by modified silver stain and/or electron microscopy. However, after immunohistochemistry became routine practice in the 1980s, many markers such as NSE (neuron-specific enolase), synaptophysin, chromogranin, PGP9.5 and CD56 (N-cellular adhesion molecule) have been used to show neuroendocrine differentiation in these tumors.

Initially, the reported incidence of these tumors changed from < 1% to 20%, mostly due to lack of clear diagnostic criteria [3-9]. In 2003, the World Health Organization (WHO) classification of tumors of the breast and female genital organs defined neuroendocrine carcinoma (NEC) of the breast as a specific histological type of invasive breast carcinoma in which > 50% of the tumor cells express at least one of neuroendocrine markers [10]. According to the 2003 WHO classification, the reported incidence of these tumors was limited between % 2 and 5% [10]. In 2012, however, the WHO classification was revised and the minimum percentage of cells exhibiting positive immunostaining for neuroendocrine markers was removed. It has been defined that 'all

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tumors that express neuroendocrine markers to a greater or a lesser degree' were in this group [11]. These tumors were categorized under the following three major headings: 1-neuroendocrine tumor, well-differentiated; 2- neuroendocrine carcinoma, poorly differentiated/small cell carcinoma; and 3- invasive breast carcinoma with neuroendocrine differentiation [11].

Neuroendocrine tumors in other sites such as the gastrointestinal tract and lungs could easily be recognized by their classical growth patterns (solid - alveolar - nested growth patterns, ribbons-cords-trabeculae and rosette formation) and cytonuclear features (salt and pepper chromatin distribution). Based on the `breast carcinomas with neuroendocrine features` section in the WHO 2012 classification, the 'neuroendocrine tumor, well-differentiated' subgroup resembles carcinoid tumors and the 'neuroendocrine carcinoma, poorly-differentiated/small cell carcinoma' subgroup has a similar morphology to classical small cell carcinomas; therefore, NE features are easier to recognize in these two groups. The third group, which is more overlooked, is `invasive breast carcinoma with NE differentiation`. This group might not have the typical morphological features of NE tumors. Recognition of this group by pathologists would help to determine the actual frequency of this tumor and its effect on prognosis.

The data regarding prognosis remain contradictory. Some studies show that these tumors are clinically aggressive [9,12], whereas other studies report good prognosis [5,13,14]. There are also studies indicating no prognostic differences [3,4,15]. However, among these studies, there are some differences in terms of the number of reported cases, follow-up period, type of immunohistochemical markers and antibody clone selected for diagnosis as well as the threshold value for positive staining within the tumor with these antibodies.

In this study, we reviewed the primary breast carcinomas showing NE features with positive immunostainings (synoptophysin and/or chromogranin) in at least 50% of the tumor volume for the purpose of defining the morphological growth patterns and cytonuclear details. Although the current (2012) WHO criteria do not require a threshold for neuroendocrine marker positivity for the diagnosis of this tumor, we intended to define the growth patterns and cytonuclear findings in tumors that had already proven to have extensive neuroendocrine expression.

2. Materials and methods

Invasive breast carcinoma cases diagnosed in excision materials between 2007 and 2016 in three different centers were collected. Among all cases, the ones in which NE markers (synaptophysin, chromogranin A) were applied were retrieved from the slide archive and evaluated. Cases which had ≥50% tumor cells staining positive for synaptophysin and/or chromogranin A were included in the study. Cases suspicious for primary breast carcinoma (metastasis to breast), small cell carcinoma or immunopositivity for only NSE, CD56 or PGP9.5 were excluded.

A total of 36 breast surgical excision materials, all from female patients were re-evaluated. Twenty-four, 8 and 4 cases were diagnosed in Istanbul Training and Research Hospital, Istanbul University Cerrahpasa Faculty of Medicine and Bezmialem University Faculty of Medicine, respectively. Two out of 8 cases from Istanbul University were consultation cases.

Immunohistochemical staining for the neuroendocrine markers synaptophysin (antibody polyclonal, dilution: 1:500, CellMarque Sigma-Aldrich Co, Rocklin, CA, USA) and chromogranin A (antibody LK2H10, dilution: 1:500, CellMarque Sigma-Aldrich Co, Rocklin, CA, USA) was performed on all cases morphologically suggesting neuroendocrine differentiation. Some of the cases also showed positive immunostaining for CD56, NSE (neuron-specific enolase) and/or PGP9.5. Herein, we included the cases showing positive staining for synaptophysin and/or chromogranin A in ≥50% of tumor cells in their excisional materials. Cases suspicious for primary breast carcinoma (metastasis to the breast), small cell carcinoma or immunopositivity for only NSE, CD56 or PGP9.5 were excluded.

3. Results

3.1. Clinical features

All cases were female with an age distribution between 40 and 88 years, median age of 69.5 and mean age of 67.4. Five cases were premenopausal (age < 50, 13.8%), and 31 cases were postmenopausal (age > 50, 86.2%). Breast-conserving surgery was performed in 18 cases, modified radical mastectomy in 14 cases, simple mastectomy in 1 case and breast lesion excision system (BLES) in 1 case. Two cases were composed of consultation blocks. Sentinel lymph node biopsy (SLNB) was performed in 7 cases. One case had a history of neoadjuvant chemotherapy.

Out of 26 cases with SLNB and/or axillary dissection, 16 (61.5%) did not have metastasis, whereas 10 cases (38.5%) had lymph node metastasis (1–14 lymph nodes). In terms of N staging, 16 cases were N0 (61.5%), 4 cases were N1 (15.4%), 4 cases were N2 (15.4%), and 2 cases were N3 (7.7%).

3.2. Gross pathological features

The tumor diameter ranged from 4.5 mm to 60 mm (median: 25 mm, mean: 26 mm). Multifocality was noted in 5 of 36 cases (13.8%). Grossly, they were mostly infiltrative mass lesions with a solid appearance and a grey-tan color. They were noted as well-circumscribed tumor nodules in 3 cases (3/36, 8.3%), of which 2 were cellular mucinous carcinoma, and 1 was solid papillary carcinoma with invasion. Four cases had mucoid/flaccid appearance in large or focal areas (2 cellular mucinous carcinomas and 2 mixed IDC-mucinous carcinomas). Necrosis was not detected on gross examination.

3.3. Histopathological features

After microscopic examination, the pathological T stages of tumors were noted as the following: pT1: 13 cases; pT2: 19 cases; and pT3: 2 cases. pT stage could not evaluate in 2 consultation cases. DCIS was present in 28 cases (77.7%), with the most frequent patterns being solid, cribriform, papillary and micropapillary. Comedo necrosis was seen in 7 cases. Microcalcification was identified in 4 of 36 cases (11%) and was associated with DCIS in 3 cases and invasive carcinoma in 1 case.

We described mainly 4 types of patterns – in invasive tumor depending on predominant growth pattern (composed of > 50% of tumor volume) and/or features of the tumor, described below.

3.3.1. Large-sized solid cohesive groups of tumor cells (n = 6 cases) (Pattern 1)

This pattern was composed of large solid nests that appeared to complement each other (puzzle-like appearance) and were separated by a small amount of collagenized stroma. The contours of these nests could be angular (Fig. 1A) or could have a rounder, worm-like appearance (Fig. 1B). A thin vascular network was always present in tumor cell groups, either focally or extensively (Fig. 1C–F). An accompanying focal cribriform pattern was also seen (Fig. 1G). Rosette structures were noted focally (Fig. 1H).

3.3.2. Small- to medium-sized solid cohesive groups of tumor cells as well as trabeculae/ribbons and glandular structures (n = 6 cases) (Pattern 2)

This growth pattern was mainly observed in two ways. The first way consisted of small- to medium-sized solid nests with irregular contours and cordons, trabeculae, single cells and occasionally small glandular structures surrounding them (Pattern 2A; Fig. 2A–D). Because of the mixture of growth patterns, this type of tumor was previously described