A Rare Breast Tumor Confused with Ductal Carcinoma in Situ, Primary Solid Neuroendocrine Carcinoma

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ABSTRACT

The concept of pure neuroendocrine breast tumors was initially defined by Sapino et al. There are three sub-types of these tumors: solid, small cell/oat cell, and large cell neuroendocrine carcinomas. To diagnose neuroendocrine tumors, more than half of the tumor cells must have neuroendocrine differentiation. The possibility of metastatic neuroendocrine carcinoma must always be excluded in the differential diagnosis. In addition, it should be considered that solid neuroendocrine (NE) carcinomas can be confused with ductal carcinoma in situ due to their similar morphologic appearance. In this article, a patient with primary solid neuroendocrine breast cancer who had been diagnosed with ductal carcinoma in situ at another center was presented along with morphological and immunohistochemical features.

Key words: Neuroendocrine carcinoma, breast, solid

Introduction

Primary neuroendocrine (NE) breast carcinomas are rare tumors (1). These tumors were initially defined by Cubilla and Woodruff and have been categorized into a different group of primary NE breast tumors by the most recent breast cancer classification of the World Health Organization (2, 3). The diagnosis of these rare tumors, which have three sub-types (solid, small cell/oat cell, and large cell NE carcinomas), is made by finding NE differentiation in more than half of the tumor cells (3, 4). When considering primary NE breast carcinoma, the possibility of metastatic carcinoma must be excluded (3). Another condition that must be excluded is solid NE carcinoma and ductal carcinoma in situ (DCIS) cases due to their similar morphologic appearance. In this article, a patient with primary solid neuroendocrine breast cancer who had been misdiagnosed with DCIS at another center was presented along with morphological and immunohistochemical features.

Case Presentation

A 76-year-old female patient was identified with a lesion suspicious for malignancy following mammography and ultrasonography performed by the healthcare organization she was admitted to for the palpable mass in her right breast. The mass was evaluated by aspiration cytology. Because the outcome of aspiration cytology revealed a malignancy, the patient underwent a breast-conserving surgery without an additional diagnostic intervention. No sentinel lymph node biopsy was performed during the surgery. The outside evaluation of patient's pathology was reported to be DCIS. The diameter of the tumor was reported to be 1.5 cm by the pathology report of an outside center. The patient then presented at our hospital for oncologic treatment, and paraffin-embedded blocks were required to revise the pathologic diagnosis. Analysis of H&E sections made of paraffin-embedded blocks revealed a tumoral formation made of atypical cells with uniform appearance infiltrating the breast tissue in solid isles (Figure 1). We noticed that rosette-like structures were generated within the tumor cells and showed palisading at the periphery (Figure 2). Despite positive interior control, in immunohistochemical analysis performed with SMA and P63, no myoepithelial cells were found around tumor isles (Figure 3). Approximately 80% of the synaptophysin tumor cells strongly stained positively (Figure 4). Estrogen and progesterone were 90% and 80% positive, respectively. Cerb B2 stained negatively. The proliferation index was found to be 10% with Ki-67. There was no DCIS focus present. Neither non-breast primary focus nor metastasis was found during systematic scanning performed for metastatic disease. The case was reported to have primary solid NE breast carcinoma. Neither recurrence nor metastasis was present during the 12-month follow-up period with no additional treatment after surgery.

This case was presented as a poster at the 22nd National Pathology Congress, 07 November-11 November 2012, Antalya, Turkey.

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Received: 08.04.2013

Accepted: 31.08.2013

Figure 1. Tumor development is seen in solid isles. Note the similarity to DCIS (H&E, x40)

Figure 3. Common synaptophysin immunoreactivity in tumor cells is observed (DAB, x40)

Figure 2. Tumor cells form rosette-like structures (ring) and they show palisading string on the periphery (arrow) (H&E, x400)

Figure 4. P63 immunoreactivity; while myoepithelial cells in the periphery normal ductus are stained (arrow), the isles of tumor cells in the periphery (right side) are not stained (DAB, x40)

Discussion and Conclusions

The concept of NE breast tumors was initially defined in 1977 (2). In 2000, Sapino et al. (4) defined breast tumors with NE differentiation in which NE indicators were identified in more than 50% of tumor cells as pure NE tumors. In 2003, the World Health Organization (3) categorized those tumors into a different group of breast tumors. These tumors are common in women in their 6th or 7th decades of life. NE differentiation is also defined for male breast tumors. NE tumors do not have specific clinical or radiological characteristics to distinguish them from other breast tumors (1-3).

Neuroendocrine (NE) breast carcinomas morphologically have three sub-types: solid, small cell/oat cell, and large cell NE carcinomas (3). Cellular uniformity, peripheral nuclear palisades, and pseudo-rosette formation are basic histological features that permit diagnosis. However, NE immune determinants must be expressed in more than half of tumor cells to make a diagnosis (3, 4).

The grade of histological differentiation in NE tumors is considered the most important factor for prognosis (5). Solid NE carcinomas are well-differentiated tumors. On the contrary, small cell/oat cell and large cell NE carcinomas are poorly differentiated (6). From this

point, some researchers have suggested that solid NE carcinomas have a better prognosis than small cell/oat cell and large cell NE carcinomas (6). Receptor positivity of estrogen and progesterone and the presence of mucinosis differentiation are defined as good prognostic factors as well (5). It is important to differentiate these tumors from NE tumor metastases located on the other organs, as it will affect treatment and thus prognosis (7).

Making an accurate differential diagnosis is very important because NE breast tumors morphologically and immunohistochemically resemble NE carcinomas of other organs such as the gastrointestinal system and lungs (8). The presence of ductal carcinoma in situ within a tumor strongly suggests that the breast is the primary focus (8). However, patients with primary NE breast carcinomas that do not include DCIS have been reported in the literature (9). Although receptor positivity of estrogen and progesterone initially suggests that the breast is the primary focus, it has been reported for some non-breast NE tumors as well, such as the lungs (8). Thus, this positivity supports the diagnosis of primary breast tumors, but it does not necessarily confirm it. In this context, it is important to scan patients through imaging methods on a regular basis to rule out other diagnoses. This can increase the likelihood of obtaining a more accurate diagnosis, accompanied by pathological and radiological findings (9).

Our case was morphologically and immunohistochemically parallel with data in the literature. As defined in many cases of primary NE breast carcinoma, there was a higher receptor positivity of estrogen and progesterone. Cerb B2 was negative, supporting previous findings. DCIS focus was not present, which is commonly defined in the literature and considered quite important for diagnosis. To exclude the possibility of metastatic NE carcinoma, positron emission tomography / computed tomography (PET/CT) scanning was also performed. As no secondary focus was detected, the case was considered a primary solid NE breast carcinoma.

Another issue requiring attention is the need to differentiate solid NE carcinomas from DCIS due to their similar morphological characteristics, as in our case the solid NE carcinoma could easily be confused with DCIS. In addition, morphological characteristics such as the formation of pseudo-rosette viewed in NE carcinomas should draw the attention of the pathologist during diagnosis. Furthermore, immunohistochemical negativity of myoepithelial cell markers around the tumor islands could help eliminate a diagnosis of DCIS. However, it is not enough to demonstrate the invasive nature of the tumor in some cases such as solid papillary carcinomas. In this case, immunohistochemical tests can be useful for basal membrane components such as laminin and collagen type IV. Positivity of basal membrane components is considered in favor of DCIS (10). Apart from that, the existence of cases of pure or focal invasive in situ NE carcinomas should be taken into consideration (11). In this sense, immunohistochemical methods evaluated with morphology will be a guide for the differential diagnosis.

Consequently, primary NE breast carcinomas can be identified by proving that a tumor is not metastatic as well as by a careful histopathological examination. Furthermore, one should bear in mind the possibility that solid neuroendocrine carcinomas may be confused with DCIS due to similar morphological features. We should bear in mind that the treatment will be delivered according to the type of tumor; therefore, accurate diagnosis is critical for patient survival.

Ethics Committee Approval: Ethics committee approval was obtained from Samsun Education and Research Hospital EPK.

Conflict of Interest: No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Informed Consent: Written informed consent was obtained from patients who participated in this case.

Author Contributions: Concept - O.A.; Design - O.A., S.K.A.; Supervision - O.A., S.K.A.; Funding - O.A.; Materials - O.A., S.K.A.; Data Collection and/or Processing - O.A., S.K.A.; Analysis and/or Interpretation - O.A., S.K.A.; Literature Review - O.A.; Writer - O.A.; Critical Review - O.A., S.K.A.

Financial Disclosure: The authors declared that this study has received no financial support.

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