



Primary Neuroendocrine Tumor of the Breast: A Rare Case Report

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Abstract

Primary neuroendocrine tumors of the breast are an uncommon and often overlooked subtype of breast carcinoma primarily affecting postmenopausal women. These rare tumors account for approximately 2-5% of all breast cancers and are classified as well-differentiated Neuroendocrine Tumors (NETs), highly aggressive Neuroendocrine Carcinomas (NECs), and Invasive Breast Cancers of no particular type (IBCs- NST) with neuroendocrine features based on the latest 2019 World Health Organization (WHO) Classification. This case study reports a 54-year-old woman who presented a painless lump on her right breast. The lump was Estrogen Receptor - Positive (ER+), Progesterone Receptor - Positive (PR+), and Human Epidermal growth factor Receptor 2 - negative (HER2-). Further tests revealed the patient was positive with neuroendocrine markers Ki-67, chromogranin-A (CGA), and Synaptophysin (SYN). The principal treatment of Neuroendocrine Breast Cancer (NEBC) is the same as of that of any other invasive carcinomas of the breast - breast conservation or a mastectomy with sentinel lymph node biopsy or axillary dissection; thus, the patient underwent a total mastectomy of the right breast with axillary lymph node dissection. Post-operatively, she was started with hormonal therapy based on her immunohistochemically reactivity. Due to the low incidence, rarity and lack of comprehensive clinical research on primary NETs, the exact origin of these tumors remains unknown. Accurate diagnosis and specific treatment options remain challenging and prognosis of this condition is still uncertain.

Introduction

Neuroendocrine Breast Cancer (NEBC) is an uncommon type of breast cancer [1]. The World Health Organization (WHO), in its 2019 classification of breast cancer explained that NEBC accounts for only 2- 5% of all invasive breast carcinomas and less than 1% of all neuroendocrine tumor [2]. Most patients that were reported typically occur in the postmenopausal age group

[3]. As for most breast cancers, age and family history is a substantial risk, and certain risk factors such as early menarche or late menopause and exposure to estrogens, which are commonly associated with oral contraceptives or Hormone Replacement Therapy (HRT), can increase the risk of this disease [4]. Correspondingly, these tumors appear similar to carcinoid tumors found in other organs and contain argyrophil granules [2].



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According to the latest guidelines provided by the WHO, tumors exhibiting a Hormone Receptor (HR)-positive and Human Epidermal growth factor type 2 (HER2) - negative profile in Immunohistochemistry (IHC) can potentially be treated with hormonal therapy involving Cyclin-Dependent Kinase (CDK)4/6 inhibitors [5]. To diagnose Neuroendocrine Neoplasms (NENs), the WHO recommends analyzing Chromogranin A (CGA) and Synaptophysin (SYN) expressions in whole tissue sections using the IHC method [6]. Survival is influenced by several significant prognostic factors, such as age, grade, metastatic status, lymph node count, and molecular subtype.

Our knowledge regarding this subject is constrained to anecdotal accounts or studies that have been conducted on limited populations. Additionally, the origins, treatment, and prognosis are subjects of ongoing controversy. The low prevalence of this condition, coupled with underreporting, has led to changes in diagnostic criteria over time.

This is the case of a postmenopausal woman who presented with a firm painless lump on the right breast and upon workup, was found to have a primary mammary neuroendocrine tumor. This work is reported in line with the SCARE 2020 Criteria.

Case presentation

A 54-year-old, known hypertensive postmenopausal Filipino woman presented at the clinic with a gradually enlarging painless lump on the right breast, associated with an episode of bloody nipple discharge. She has no family history of breast cancer, no previous breast surgeries nor any allergies. Her physical exam revealed a firm non-tender mass at the 10 o'clock position on the right breast just above the nipple-areola complex with no nipple discharge at the time of examination. The axillary nodes on the right were non-palpable.

Her breast workup included a breast ultrasound which showed a 3.6 x 2.8 x 2.7cm lobulated complex mass, predominantly solid with heterogenous echo pattern at the 10-12 o'clock position at the periareolar area (BIRADS 4B) and a mammogram with tomosynthesis which demonstrated the hyperdense lesion at the said area with no micro calcification nor architectural distortion (BIRADS 4B). The axillary nodes were unremarkable on both imaging studies. A core biopsy of the mass showed atypical polygonal to columnar cells arranged in nests, sheets and rosettes with attempts at papillary formation, and supported by occasional fibrovascular to fibro-hyalinized stroma. On microscopic view, there is no definitive cell necrosis; no significant mitotic activity, lympho vascular and perineural invasion and no involvement of the lactiferous ducts. It also showed the nuclei with speckled salt and pepper chromatin and granular eosinophilic cytoplasm. Subsequent staining confirmed the presence of a neuroendocrine tumor, as it exhibited positive staining for the recommended markers: Ki67, chromogranin, and synaptophysin.

Additionally, the tumor tested positive for Estrogen and Progesterone Receptors (ER and PR) and showed a negative result for human epidermal receptor-2 (HER2/neu).

Further investigation yielded no extramammary tumor, particularly in the chest and the gastrointestinal tract by a multi-slice contrast computed tomography of the chest and abdomen. The patient underwent a total mastectomy with axillary lymph node dissection. The rest of the hospital course was unremarkable. Final histopathology showed a 3.5x2.6cm well-differentiated neuroendocrine tumor with all 18 lymph nodes

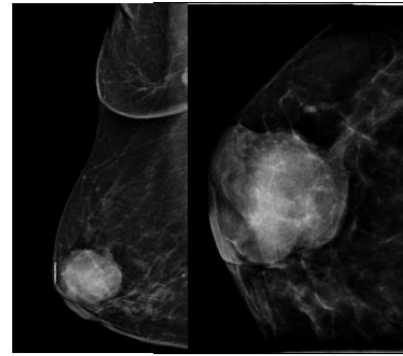


Figure 1a: Sonomammogram: A lobulated complex mass predominantly solid with a heterogeneous echo pattern at 10 to 12 o'clock positions at the periareolar area.

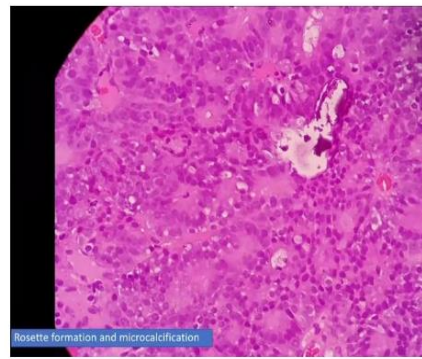


Figure 1b: Histopathologic result from core needle biopsy of the breast mass: Shows atypical polygonal to columnar cells arranged in nests, sheets, and rosettes, with attempts at papillary formation and supported by occasional fibrovascular to fibro-hyalinized stroma.

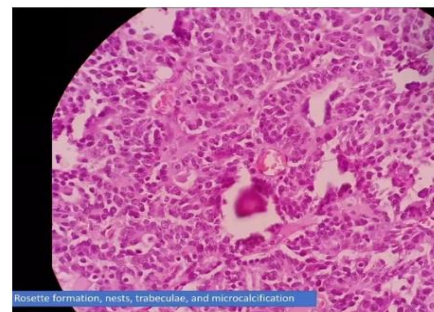


Figure 1c: Microscopic findings of the right breast mass: Described as no definitive cell necrosis, significant mitotic activity, lymph vascular and perineural invasion, and no involvement of the lactiferous ducts.

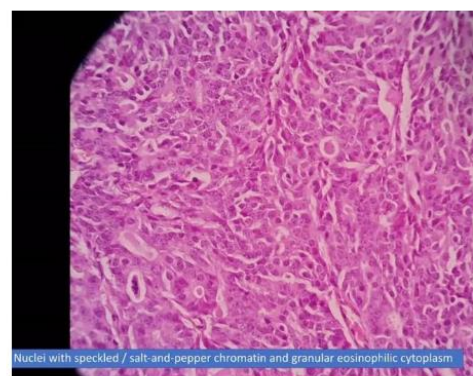


Figure 1d: Microscopic finding of the right breast mass: Showing nuclei with speckled/salt and pepper chromatin and granular eosinophilic cytoplasm.

negative for metastasis. All margins of resection were clear. She was maintained on tamoxifen 20mg once a day based on her breast biomarker results. Patient is disease-free at two years.

Discussion

Neuroendocrine Neoplasia (NEN) encompasses a rare and diverse spectrum of tumors that arise from the diffuse endocrine system, exhibiting varying clinical behaviors contingent upon the tumor's degree of differentiation. Mammary origin accounts for less than 1% among neuroendocrine tumors [7]. Their incidence among breast cancer has been reported to range from 0.1% to 5% [8]. A diagnosis of primary neuroendocrine breast tumors is typically reached through exclusion. To rule out alternative primary sites, octreoscan and Positron Emission Tomography (PET) scans should be conducted, focusing on areas like the Ears, Nose, and Throat (ENT), lungs, digestive tract, and skin. Notably, there are no specific clinical signs that point directly to these tumors. These tumors tend to progress slowly, and the most common reason for seeking medical consultation is the presence of an isolated breast nodule or a breast nodule accompanied by other symptoms. There is no specific clinical or radiological sign to diagnose a neuroendocrine carcinoma; a histological examination is the only way to confirm the diagnosis of this tumor [9].

These tumors are thought to arise from endocrine differentiation of breast carcinoma rather than from pre-existing endocrine cells with malignant transformation [10]. The 2012 WHO classification of breast carcinomas classifies neuroendocrine tumors into three subtypes: well-differentiated neuroendocrine tumors; poorly differentiated neuroendocrine carcinomas or small cell carcinomas; and invasive breast carcinomas with less neuroendocrine features of 50% of cancer cells [11,12].

In 2019, there was a radical change in the WHO classification of neuroendocrine tumors/carcinomas to create a common way of classification across sites to reduce inconsistencies and contradictions among the various systems currently in use. Neuroendocrine neoplasm is intended as a definition that comprises all tumor classes with predominant neuroendocrine differentiation including both well differentiated and scarcely differentiated types. Neuroendocrine tumor is an invasive tumor characterized by: Low/intermediate grade, neuroendocrine morphology, and supported by the presence of neurosecretory granule and diffuse, uniform immunoreactivity for neuroendocrine markers. The main prognostic parameters used are tumor stage and histological grade, which include mitotic counts [13].

On macroscopic examination, primary neuroendocrine carcinomas of the breast are round or multilobulated, yellowish-colored, and have a firm consistency, or, rarely, they are gelatinous if associated with a mucinous component [14]. Upon histological examination, the neuroendocrine differentiation of these tumors can be inferred based on their morphological characteristics, however the gold standard for diagnosis of these types of breast tumors are immune histochemical analysis of neuroendocrine biomarkers. The most sensitive and specific markers are CGA and SYN [15]. In this case, the patient tested positive for both markers, along with hormone receptors estrogen and progesterone. The use of tamoxifen alone was common in premenopausal women, combining it with luteinizing hormone-releasing hormone analog is also a standard treatment. Adjuvant hormonal therapy was carried out for 5-10 years for HR-positive Br-NEN. HER2 expression was absent, which was consistent with previous literature [16].

According to reports, there is limited evidence for treating this type of neuroendocrine tumor, prognostic or predictive factors should be considered before initiating treatment [17].

The primary approach to treating breast neuroendocrine tumors predominantly involves surgical interventions, which typically encompass mastectomy, axillary dissection, and metastasectomy. It should be noted that a mastectomy is often the preferred treatment option for Breast Neuroendocrine Neoplasias (Br-NENs) due to their potentially aggressive nature, even though breast conservation surgery is still an option [18]. This patient typically underwent a mastectomy with axillary lymph node dissection. Indications for chemotherapy and radiotherapy align with those for other types of breast cancers clinicopathologic factors such as tumor size, nodal status, nuclear grade, and tumor subtype identified through immunohistochemical staining for ER, PR, HER2, and Ki67 index [16]. Additionally, the use of an anti-aromatase agent targets the mammary component of the tumor. The neuroendocrine component usually escapes within a few months but can be controlled by anthracycline-based chemotherapy [19]. There are no established guidelines for using hormone therapy and immunotherapy due to the uncertainty surrounding their effects [20].

There are still conflicting data about prognosis due to the rarity of these heterogenous tumors and still changing classification criteria. But these tumors carry a relatively better prognosis than other high-grade neuroendocrine neoplasms [21]. The 5-year survival of breast primary neuroendocrine tumors exceeds 80% in all combined tumor subtypes [22]. The main prognostic factors are the age, the field, the capacity of tumor secretion, the tumor size, and the existence or not of distant metastases [23-25].

Conclusion

Breast tumors with neuroendocrine differentiation represent a rare and heterogeneous group, often sharing histological features with invasive breast cancers. While Neuroendocrine Carcinomas (NECs) of the breast exhibit distinct morphological and clinical characteristics, diagnosis of Neuroendocrine Tumors (NETs) based solely on morphological criteria can be challenging. Currently, there is limited evidence to guide specific treatment strategies for breast cancers with neuroendocrine differentiation, which are typically managed as invasive breast cancers. Further research is essential to define and categorize this tumor group and establish effective management approaches. Neuroendocrine breast tumors, whether primary or secondary, require accurate diagnosis through histopathological analysis with appropriate immune histochemical staining. A comprehensive understanding of their biological behavior necessitates further studies involving larger patient cohorts. This case contributes valuable insights to the limited literature on NEBC, emphasizing the importance of individualized treatment in achieving a favorable outcome.

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