Primary neuroendocrine tumors of the breast: a case report

Sinou Nikoleta[1,2], Milonaki Despina[3], Sinou Natalia [1,2], Filippou Dimitrios [1,2], Provatas Ioannis [4]

1: Medical school, National and Kapodistrian University of Athens, Medical School, 2: Research and Education Institute of Biomedical, Science, 3: Consultant breast surgeon, 1st medical department, 4: Consultant B', department of pathology

ABSTRACT

Primary neuroendocrine tumors (NETs) of the breast are a very rare type of tumors, originated from cells that make up the neuroendocrine system and produce peptides and amines. This type of tumor consists of a rare subtype of breast carcinoma, representing less than 1% of breast cancers, and occur mainly in postmenopausal women. NETs are graded as G1, G2 or as an invasive neuroendocrine carcinoma (NEC), small or large cells. Neuroendocrine carcinomas affect usually the gastrointestinal and the pulmonary system. We present a rare case of an 88-years old-woman who presented with a mass in the right breast. The patient reported mild pain and localized tenderness throughout the day. The pathological identification revealed histologic sections of neoplastic mammary gland tissue exhibiting neuroendocrine immunomorphological features, consistent with well-differentiated grade.
This case highlights the rarity of primary neuroendocrine tumors of breast and the importance of their early diagnosis. Further studies and treatment strategies are needed to be made to discover the biological behavior of the tumor and more optimal therapies to maximize patient's outcome.

CONTACT

Nikoleta Sinou
NKUA
nikoletta.sinou@gmail.com

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a heterogeneous group of epithelial tumors characterized by morphological and immunohistochemical evidence of neuroendocrine differentiation [1]. They originate from the diffuse endocrine system, and their behavior depends on the differentiation of the tumor. They can occur in almost every organ system, most commonly the gastro-entero-pancreatic (GEP) and broncho-pulmonary systems. Primary neuroendocrine tumors of breast (NETs) are a very rare, heterogenous group of tumors, representing less than 0.5-1% of all breast cancers and 1% of all neuroendocrine tumors [1-4].
The first tumor of the breast with neuroendocrine features was first described in 1963 by Feyrter and Hartmann, who observed a "carcinoid" growth pattern in 2 cases of invasive breast carcinoma. Later, in 1977, 8 additional cases with similar patterns were reported [5,6]. Breast neuroendocrine carcinoma (NEC) was first recognized as a distinct entity in the 2003 WHO Breast classification system The term was later refined in 2012 and subsequently harmonized with the general framework for NENs in the 2019 fifth edition and 2022 "Blue Book". According to the WHO Classification, NENs can be stratified based on their histological differentiation into a) well-differentiated: low grade (G1), intermediate (G2), where G1 and G2 have a low proliferation index Ki-67, and high grade (G3), b) poorly differentiated (small or large cells, G3) that have a high proliferation index Ki-67 and, typically, a very aggressive behavior, and c) invasive breast carcinomas of no special type (IBC–NST) with neuroendocrine features. The Nottingham System is a method for grading breast cancer by evaluating its aggressiveness based on three factors: the degree of tubule formation, nuclear pleomorphism, and mitotic count. Clinically, breast NETs, in most reported cases, concern postmenopausal women and over more than 50% of cells express neuroendocrine markers, typically chromogranin A and Synaptophysin. Most of these tumors are well or moderately differentiated and most of the poorly differentiated express estrogen and progesterone receptors [6,7]. There are no standardized guidelines for diagnosis and treatment of breast NETs, due to their rarity. The aim of this report is to highlight and analyze a rare case of a primary neuroendocrine tumor (NET) of the breast, providing detailed macroscopic, microscopic, and immunohistochemical findings.

Case Presentation

An 88-years-old woman presented with a medical background of hypertension and chronic venous insufficiency. She reports no allergies, does not smoke, and does not consume alcohol. She has been vaccinated against COVID-19 (Table 1).
The patient was scheduled for admission to the hospital in December 2022 for surgical treatment of a right breast mass, which was identified 1,5 months prior. The patient reports episodes of mild breast pain, during the day. Digital mammography conducted in November demonstrates a density measuring approximately 1.5 × 1.0 cm, with ill-defined margins and lobulated contour, located in the central region of the right breast. Histological analysis of breast gland tissue samples with a core biopsy revealed Breast tissue fragments of a well-differentiated neuroendocrine tumor, predominantly solid, low mitotic activity, no necrosis, ER/PR +++ (~95%), Ki-67 ~5%, HER2 negative (1+), with surrounding fibrosis and duct-lobular atrophy.
Right breast: mild tenderness above and medial to the nipple. No palpable lump or skin changes noted.
The patient underwent a right breast lumpectomy for a palpable mass located in the upper inner quadrant, 1.5 cm from the nipple, extending from the 1 o'clock to 3 o'clock position, measuring approximately 2 × 1.5 cm. She declined to undergo a sentinel lymph node dissection and refused adjuvant radiotherapy and chemotherapy.
Histopathological findings
The right breast specimen, weighing 59 g and measuring 7 × 5 × 3 cm, included a spindle-shaped section of skin (5.3 × 1.8 cm) and contained a 1.7 × 1.5 × 1.4 cm irregular tumor. the tumor is of intermediate differentiation (Nottingham Grade II), Immunohistochemistry revealed diffuse membranous E-cadherin positivity, diffuse nuclear GATA-3 positivity, negative TTF-1 and p63, diffuse synaptophysin positivity, focal chromogranin positivity, INSM-1 positivity in several cells, preserved YAP-1 in few areas, RB-1 loss, and negative serotonin and CD56. Somatostatin receptors SSTR2a and SSTR5 were ++ positive (Volante score 2, <50% of tumor cells).

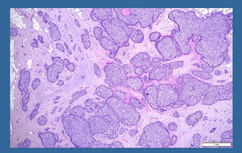

Figure 1: Hematoxylin- Eosin staining (H&E)

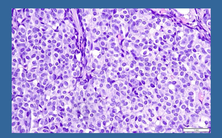

Figure 2: Hematoxylin- Eosin staining (H&E)

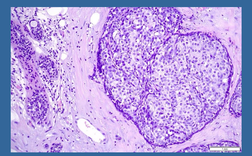

Figure 3: Hematoxylin- Eosin staining (H&E)

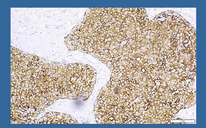

Figure 4: synaptophysin positivity

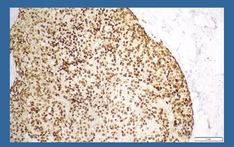

Figure 5: estrogen positivity

DISCUSSION

neuroendocrine carcinomas of the breast represent a very rare subtype of breast cancer. Namely, they compose less than 0.1% of all breast cancers and less than 1% of all neuroendocrine tumors. Most patients are women, 60-70 years of age. However, they have also been reported in younger female patients and in men [3]. NECBs (Neuroendocrine Carcinomas of the Breast), usually present as palpable and painless masses located in the retro-areolar area. Secondary symptoms, such as nipple retraction, fixation to adjacent structures, bloody nipple discharge, skin ulceration and lymphadenopathy have also been reported.
Radiological findings on mammography include an irregularly demarcated, round and hyperdense mass. Breast ultrasound depicts a hypoechoic solid mass with cystic components, rich vascularity and obscure borders, whilst MRI shows homogeneous, low signal intensity on T1-weighted images [7,8]. It should be noted that PET-CT with 68 gallium-labelled somatostatin analogues can be used for well differentiated tumors, while 18-Fluorodeoxyglucose (FDG) PET-CT is reserved for NECBs with poor differentiation or those with high metabolic activity. Most common metastatic sites include the bones, liver, lungs, brain, bone marrow and pleura. Skin involvement has also been reported. There are a variety of potenital diagnoses that need to be ruled out first, in order for NECBs to be diagnosed. The diagnosis is based on the morphology and the immunohistochemistry: Synaptophysin (+), Chromogranin A (+), INSM1 (+) and hormone receptors: usually ER+/PR+, HER2−. The Ki-67 index determines grade and aggressiveness.Specifically, these tumors present similarly to metastases from extra-mammary locations. Breast metastasis of a neuronendrocrine tumor of an extra-mammary location is the most significant diagnosis that needs to be ruled out.

Regarding treatment, there are no specific guidelines for the therapy of NECBs, owing to their extreme rarity and heterogeneity. Current evidence suggests treatment strategies that are very much alike to those of classic, invasive breast carcimoma. According to tumor localization and staging, treatment mostly constists of total or partial mastectomy. In some instances, axillary lymph node dissection and metastasectomy are also performed. Adjuvant radiotherapy following mastectomy is also an integral compoment of treatment, especially for tumors with good or moderate differentiation. Chemotherapy in the form of neoadjuvant or adjuvant treatment is usually reserved for locally advanced and metastatic disease, or for tumors with a high risk of recurrence. The exact prognosis for NECBs has yet to be estabilished, as most studies do not take into consideration each and every specific subtype of NECB. Prognosis generally depends on the stage and histological grade of the tumor. Reportedly, five year survival rates exceed 80% for all forms.

CONCLUSIONS

Primary neuroendocrine tumors of the breast consist of a very rare and a heterogeneous group of epithelial tumors characterized of breast malignancies and concern postmenopausal women. Due to their rarity, there are no specific guidelines for the therapy of NECBs, and heterogeneity. Treatment strategies follow protocols to those of classic, invasive breast carcinoma, mastectomy.

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