



## Case Report

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# A Case of a Primary Small-Cell Neuroendocrine Carcinoma of the Breast



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## Abstract

The primary neuroendocrine tumor of the breast is a rare neoplasm, representing less than 1% of primary breast cancers. The diagnosis can only be made if non mammary sites are excluded along with the presence of characteristic immunohistochemical markers. The treatment is controversial, with no established protocol. The combination of treatments used in more common histologies, can be employed in cases of localized disease. The chemotherapy regimens most commonly used are those based on platinum (as in neuroendocrine tumors of the lung) or anthracyclines (as in breast neoplasms). The prognosis is variable, it depends on the subtype of neuroendocrine tumor and its staging; those with small-cell histology have a worse outcome. We report the case of a 55-year-old woman diagnosed with primary small-cell breast cancer and the evolution.

**Keywords:** Small cell; Neuroendocrine tumour; Breast cancer; Treatment; Pathology; Prognosis; Management

**Abbreviations:** WHO: World Health Organization; TTF: Thyroid Transcription Factor; MR: Magnetic Resonance; PET: Positron Emission Tomography; SUV: Standard Uptake Values; AJCC: American Joint Committee on Cancer; IMRT: Intensity Modulated Radiation Therapy; CT: Computed Tomography

## Introduction

Neuroendocrine carcinomas can occur in a variety of sites throughout the body, especially in the lungs, the gastrointestinal tract and the pancreas [1]. Primary neuroendocrine carcinoma of the breast is a rare entity, comprising 0.3 to 0.5% of all breast cancers. The first case was described by Wade et al in 1983 and only about 100 cases have been reported until now [2,3]. Most articles are clinical cases with the longest series of cases published by Shin with nine patients [4]. According to the classification of tumors of the World Health Organization (WHO), neuroendocrine carcinomas can be divided into three categories: well differentiated, poorly differentiated/small cell carcinoma, invasive breast carcinoma with neuroendocrine features. Immunohistochemical staining with neuroendocrine patterns represents the gold standard for diagnosis. The most sensitive and specific neuroendocrine markers are: chromogranin A, chromogranin B and synaptophysin. Hormone receptors (progesterone and estrogen) cannot confirm the diagnosis but they can be present in some cases; this fact is important as a prognostic factor and therapeutic target [5].

The diagnosis of a primary neuroendocrine tumor of the breast is confirmed if:

- i. More than 50% of the histological sample expresses neuroendocrine features;
- ii. Intraductal component coexists and/or
- iii. Extra-mammary locations of the primary tumor are excluded by imaging tests [2].

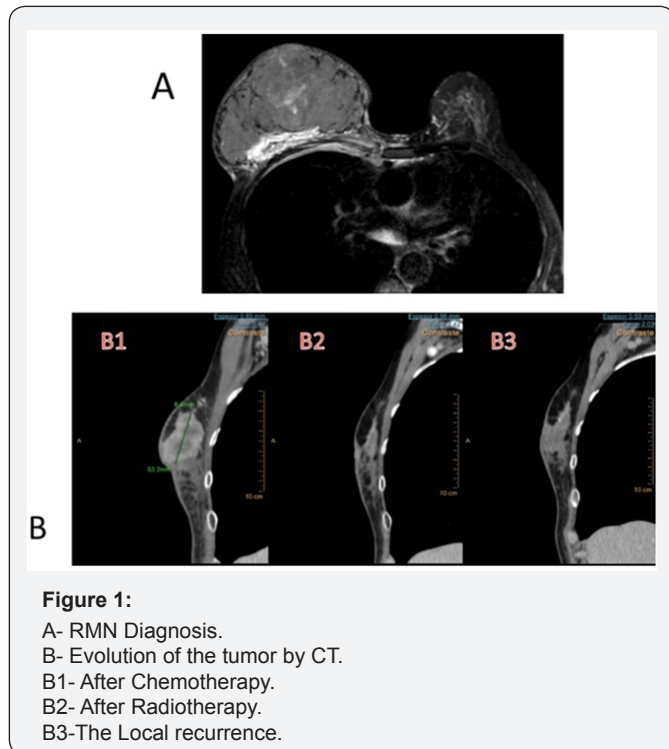
Treatment includes different options (surgery, chemotherapy and radiotherapy), which depend on the clinical stage and the presence or absence of distant metastases. At this moment, an established protocol does not exist, due to the rarity of this disease. Here, we describe a case of a primary breast neuroendocrine tumor in a 55-year old woman and its therapeutic management.

## Case Report

A 55-year-old Spanish female smoker, with 10 packs-years, and no significant past medical history. In November 2013, the

patient presented with increased volume of the breast. During the physical examination, an enlarged and swollen right breast was observed. A single, mobile and bilobate right axillary lymph node was palpated. A breast ultrasound and mammography were performed. In the right breast, a solid lesion that occupied the entire breast, compatible with neoplasia, was observed. Histopathological sample was obtained, resulting in neuroendocrine small-cell carcinoma with poor differentiation, grade 3 (Hormone receptors: negative; Her2Neu: 0; p53: 95%; CK19: negative; Ki67: 70%; Synaptophysin: positive; Chromogranin: positive; CD56: positive, CK20: negative; Thyroid transcription factor (TTF)-1: positive, Bombesin: negative), with deep dermis infiltrated.

In the mammary magnetic resonance (MR), a much enlarged right breast was seen, which was occupied by a mass of 12.5 cm with a central area with a hemorrhagic and necrotic component. Suspicious axillary lymph nodes were observed, the greater with 3 cm in its major axis. Because of the rarity of these kinds of breast tumors, a Positron Emission Tomography (PET) was performed as an extension study and to discard a possible primary tumor in another location. A hyper metabolic breast mass was observed, with 14 cm in diameter and an 8.49 Standard Uptake Values (SUV), lymph node involvement was detected in the right axillary region (levels I and II) and right parasternal space without other lesions suggestive of malignancy at any other level. Considering stage cT4bcN3bcM0, concordant with stage IIIC, according to the classification of the American Joint Committee on Cancer (AJCC), the patient initiated systemic treatment (Figure 1).

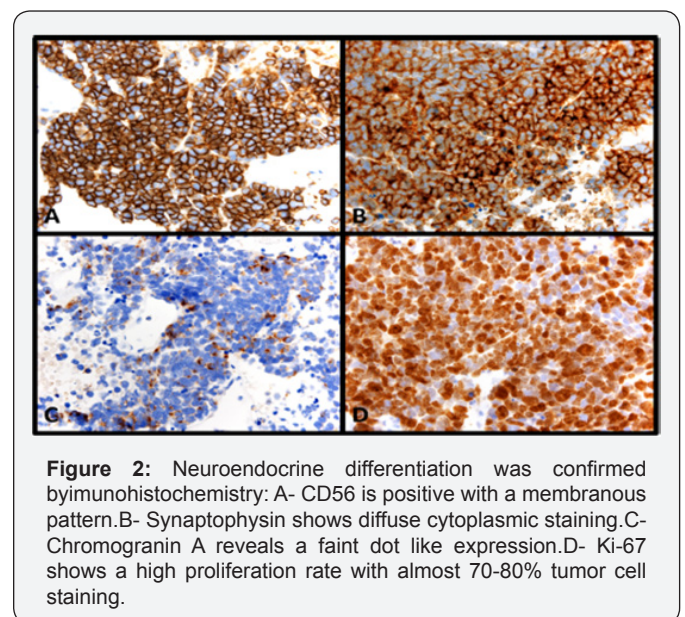


It was decided to start treatment with Cisplatin 75mg / m<sup>2</sup> day 1 and Etoposide 100 mg / m<sup>2</sup> days 1, 2 and 3 every 21 days

with clinical and radiological data of response to it. A total of 6 cycles were administered, keeping partial response of primary tumor. Regarding toxicity, she presented symptoms of grade 2 CTCAE sensitive neuropathy. The patient received a sequential treatment by Intensity Modulated Radiation Therapy (IMRT); a total dose of 50 Gray (Gy), in 25 fractions of 2 Gy given in 5 weeks. The treated volumen included right breast and ipsilateral lymph nodes (axilla, supraclavicular and internal-mammary). The Chemotherapy/Radiation treatment was finished in April 2014. At the reappraisal by PET, post-radiotherapy treatment, complete response was observed, describing a lesion of 7 cm in the breast with a 5.86 SUV. In December 2014, Computed Tomography (CT) confirmed a recurrence of the disease, showing a hyper intense lesion in the breast with a diameter greater than 10 cm at that time, satellite nodule and a left axillary adenopathy; no findings relevant to other levels. Combination scheme of chemotherapy with Carboplatinum-Etoposide was initiated as a second line. The patient responded unfavorably with new signs of progression, receiving consecutive chemotherapy lines, four lines in the aggregate. The patient died in January 2016.

**Discussion**

The primary neuroendocrine tumor of the breast is a real challenge to face in the clinical practice, although it is not uncommon to find isolated cells with neuroendocrine differentiation in the assessment of more common cell types (up to 50% of breast tumors). Even without considering the difficulty that diagnosis represents, the absence of established standards to guide the appropriate management of this kind of neoplasm generates a great challenge about the most suitable treatment scheme [6]. The diagnosis of this entity mainly depends on histological analysis of the sample; the clinical and radiological presentation is quite similar to other more frequent tumors (Figure 2).



Neuroendocrine neoplasms present a tendency to appear in more advanced stages, as in the presented case. Regarding immunohistochemical aspects, an important variability related to hormone receptor expression and the presence/absence of neuroendocrine markers is reported among the published cases. It is not usual to find cases with over expression of HER2 receptor in these neoplasms [2]. Moreover, the exclusion of an extra-mammary origin is an unavoidable criterion. Although we did not identify an intraductal component in our sample which would have reinforced the mammary origin of the neoplasm, the complete study did not show an alternative origin for the primary tumor [5,7]. Concerning the current management, in the localized disease, the initial approach is based on surgery (both lumpectomy and mastectomy) associated with adjuvant radiotherapy including the standar volumes, with favorable evolution described in a series of cases 2.

Hormone therapy could be biologically feasible in cases where estrogen/progesterone receptors are expressed; there is not much data about it; similar cases related to somatostatin analogs are described in sensitive cells to this molecule [8]. There is insufficient information about adjuvant chemotherapeutic schemes to establish a preferential option above the rest. Similarly, there is no standard therapy in the locally advanced/metastatic context. Positive results have been reported with the usual protocols of other more frequent breast neoplasms (taxanes and anthracyclines based); as well as with cytotoxic agents normally used in high-grade neuroendocrine tumors such as small-cell lung cancer (platinum doublets, especially associated with etoposide or irinotecan).

In terms of prognosis, these tumors have a more aggressive evolution in comparison with invasive ductal carcinoma (the most common subtype), more prone to local and distant recurrence. These tumors are usually more dedifferentiated, and this may act as a confounding factor; however, in cases of localized disease, its behavior seems to be similar to the most common carcinomas, even small-cell tumors [9-11]. Studies are needed with more patients and longer follow-up to document such statements. Nevertheless, neuroendocrine tumors are a heterogeneous group with defined characteristics and different prognoses, with small-cell tumors having the worst expectation [12]. In our case, the aggressive behavior of the disease, with significant loco regional involvement and the histological and immunohistochemical characteristics

conditioned the chemotherapeutic scheme chosen; equivalent to that used in small-cell lung cancer. With the subsequent association of external beam radiation focused on the affected area, we got a partial response with a progression-free interval of approximately eight months. During this time, the patient had an acceptable quality of life, without significant toxicity. Once we verified the progression of the disease, we used successive lines of cytotoxic agents, based on histology.

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