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Case Report

Neuroendocrine Primary Carcinoma of the Small-cell Breast of High Grade - Case Report and Literature Review

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Abstract

The primary neuroendocrine carcinoma of the small-cell breast of high grade is an extremely rare and aggressive tumor, accounting for less than 1% of cases of malignant tumors of the organ. There are only about 35 cases reported in the literature. The present study aims to report an unusual case of this neoplasm with a description of the clinical characteristics, histopathological findings, immunohistochemical findings and evolution of the disease, as well as a systematic review of the literature. the case of undifferentiated neuroendocrine carcinoma of small breast cells in a female patient of 56 years old was reported, presenting a perceptible QSL nodule of the left breast. The lesion was biopsied, and the pathology confirmed by immunohistochemistry. Patient was submitted to surgical treatment followed by chemotherapy and adjuvant radiotherapy.

Keywords: Neuroendocrine Tumor; Breast Cancer; Small Cell Carcinoma; Extrapulmonary Carcinoma; Immunohistochemistry

Abbreviations

QSL: Super-lateral Quadrant; NNRTIs: Primary Breast Neuroendocrine Tumors; NPT: Primary Neuroendocrine Tumor; G3P2C1A0: 3 Gestations, 2 Natural Birth, 1 Caesarean, No Abortion; CT Scan: Computerized Tomography Scan; EP: Chemotherapy with Cisplatin and Etoposide Protocol; WHO: World Health Organization; SCLC: Small Cell Lung Carcinoma; IHC: Immunohistochemical; CK7: Cytokeratin 7; CK20: Cytokeratin 20; MRI: Magnetic Resonance Imaging

Introduction

The primary neuroendocrine carcinoma of the small-cell breast of high grade is a variant of primary breast neuroendocrine tumors (NNRTIs), the latter representing about 2 to 5% of breast tumors [1]. It is a neoplasm of low prevalence, comprising less than 1% of malignant breast tumors [2]. It presents with an aggressive clinical course and early dissemination, being the worst prognostic variant of the NPT. This tumor presents morphological and immunohistochemical characteristics similar to small cell lung

carcinoma, and it is difficult to differentiate a primary carcinoma of the breast from a metastatic lesion from extramammary sites. Small-cell neuroendocrine carcinoma has been reported in several extrapulmonary sites beyond the breast, such as the larynx, trachea, gastrointestinal tract, prostate, bladder, cervix and ovary, being of clinical course as aggressive as lung carcinoma. Diagnosis should be made by discarding possible extramammary sources and confirmed by immunohistochemistry. There is no consensus regarding the treatment and prognosis of this carcinoma.

Materials and Methods

The information was obtained by reviewing the medical records, interviewing the patient, photographing the diagnostic and therapeutic methods to which the patient was submitted, and reviewing the literature.

Results

A 56-year-old female Caucasian patient, G3P2C1A0, breastfed for three months, menarche at age 14, menopause at age 54, no family history for tumor, non-smoker, non-alcoholic, and having caesarean section and surgery as previous surgeries. She sought an oncologist presenting a noticeable nodule in a super-lateral quadrant of the left breast.

At the physical examination, a palpable nodule was found in the left breast at 2 hours (super-lateral quadrant) 3 centimeters away from the nipple, with dimensions of approximately 1.9 x 1.7 centimeters. No nipple discharge, no palpable lymph node enlargement and free axilla. Due to the strong suspicion of tumor, a mammogram was performed.

Mammography revealed an oval nodular image with irregular contours in the posterior third of the QSL of the left breast, measuring approximately 2.5 cm in diameter, highly suggestive of malignancy with category BI-RADS V, intact nipples and axillary extensions free of lymph node enlargement. Core biopsy of the lesion was ordered revealing undifferentiated neuroendocrine carcinoma of small cells infiltrating breast tissue. Due to the possibility of involvement of extramammary organs, the patient was asked for MRI of the skull, CT scan of the whole abdomen and chest CT with high resolution of the lungs, without focal lesions suggestive of primary site or implantation of neuroendocrine tumors.

Subsequently, the immunohistochemical profile of the lesion was performed, for complementary therapeutic orientation, which showed positive immunoreaction to the antibodies: Pankeratins clones AE1/AE3; Synaptophysin clone SYPO2 and Chromogranin A clone DAK-A3. Research of estrogen, progesterone and HER-2/NEU were negative. The immunohistochemical profile confirmed the diagnosis obtained by the previous biopsy.

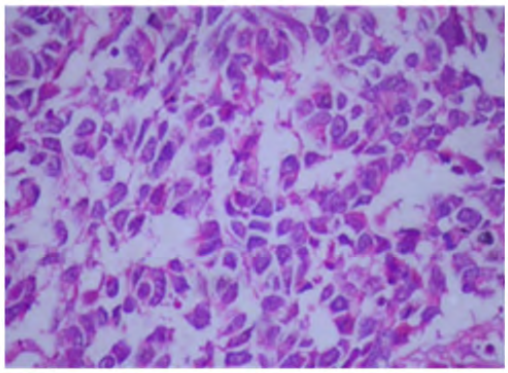

FIGURE 1 - IHC: Hematoxylin-Eosin, 400X, neoplastic cells: rounded or polyhedral nuclei, nuclear molding and rosette outlines; irregularly granular chromatin, salt and pepper pattern, small nucleoli, moderate cytoplasm and acidophilus.

Figure 1

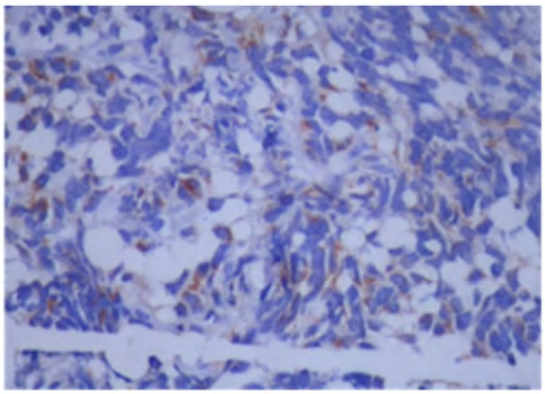

FIGURE 2 IHC: 400X, PANQUERATINS (clones AE1 / AE3) neoplastic cells with staining of cytoplasmic pattern, or Golgi pattern, dot like, characteristic and pathognomonic CNPC.

Figure 2

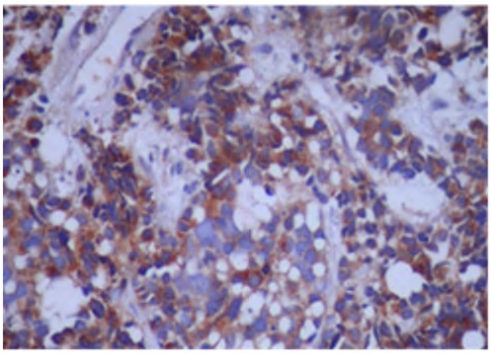

FIGURE 3 - IHC: 400X, CHROMOGRANINE-A (clone DAK-A3) intense and diffuse immunoexpression of cytoplasmic pattern in the vast majority of neoplastic cells.

Figure 3

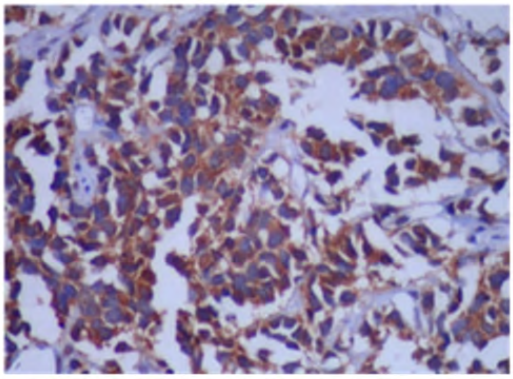

FIGURE 4 - IHC: 400x, SINAPTOFISIN (clone 27G12) Intense and diffuse immunoexpression of cytoplasmic pattern, in large part of neoplastic cells.

Figure 4

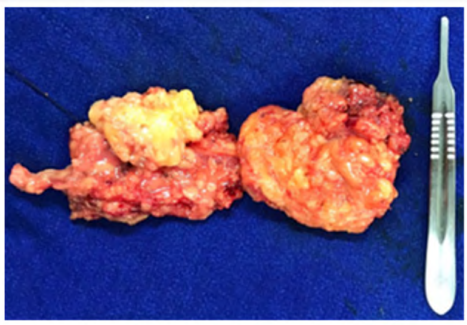

FIGURE 5: Macroscopic aspect of the lesion after left breast quadrantectomy and axillary emptying.

Figure 5

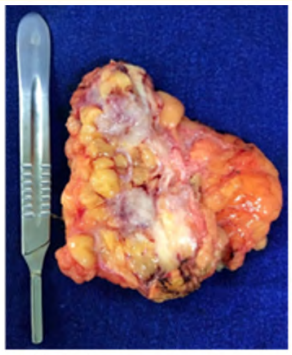

FIGURE 6: Macroscopic aspect of the lesion after left breast quadrantectomy.

Figure 6

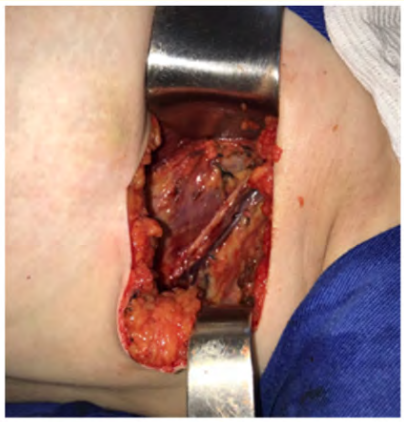

FIGURE 7: Macroscopic aspect of the lesion during left breast quadrantectomy and axillary emptying.

Figure 7

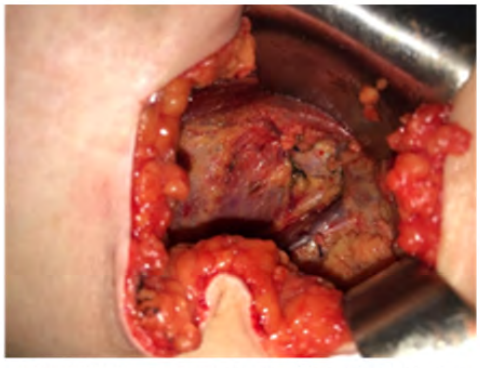

FIGURE 8: Macroscopic aspect of the lesion during the surgical procedure.

Figure 8

Patient was submitted to the super-lateral quadrantectomy of the left breast with axillary lymph node dissection. The pathological anatomy of the procedure revealed free peripheral surgical margins measuring at least 5 mm in the closest deep margin to surgical resection, focal perineoplastic angiolymphatic infiltration present, perineural infiltration present, focal desmoplastic reaction and absence of perineoplastic inflammatory infiltrate. Of 14 lymph nodes removed, 2 were affected by metastases. Patient was submitted to the super-lateral quadrantectomy of the left breast with axillary lymph node dissection. The pathological anatomy of the procedure revealed free peripheral surgical margins measuring at least 5 mm in the closest deep margin to surgical resection, focal perineoplastic angiolymphatic infiltration present, perineural infiltration present, focal desmoplastic reaction and absence of perineoplastic inflammatory infiltrate. Of 14 lymph nodes removed, 2 were metastasized.

O Pathological staging occurred in pT2N1aMx. After quadrantectomy, the patient was followed up with adjuvant therapy of four cycles of combined chemotherapy with cisplatin and etoposide, EP protocol, between June and September 2017. She completed the four cycles without major complaints, delays or significant intercurrences. Adjuvant radiotherapy was indicated, which occurred between October and December 2017 at the dose of 5040cGy directed to the breast and supraclavicular fossa with BOOST of 1000cGy, without intercurrences. One year after the end of treatment, the patient was free of tumor activity, no evidence of relapse of the disease by clinical imaging (tomography) or biochemical methods (tumor markers).

Discussion

Primary neuroendocrine tumors of the breast account for approximately 2 to 5% of cases of organ tumors [1,3]. Its variant, the neuroendocrine Carcinoma of small cells of high degree, is characterized by being a rare and aggressive tumor, representing less than 1% of the carcinomas of breast [4]. This rare tumor had its first case described in 1963 by Feyrter and Hartmann [2], when only 35 cases were found in the literature [3]. Only in 2003 the World Health Organization (WHO) recognized the need to classify neuroendocrine carcinomas into three well-described subtypes: high-grade small cell, large cell, and carcinoid or solid [3,5], according to the expression of markers being precise criteria for histological diagnosis [1]. In 2012, a review of the tumor classification was performed, establishing the subdivision for neuroendocrine tumors in: well differentiated, poorly differentiated (small cell carcinoma) and carcinomas with neuroendocrine differentiation [5].

High-grade small cell neuroendocrine carcinoma presents morphological and immunohistochemical characteristics similar to small cell lung carcinoma (SCLC), generating difficulty in differentiating a primary breast carcinoma from a metastatic lesion from extramammary sites [4]. This tumor, morphologically similar to SCLC, has been reported in distinct extrapulmonary sites beyond the breast as in the larynx, trachea, stomach, small intestine, prostate, bladder, cervix and ovary [3,6,7], with extrapulmonary carcinomas being as aggressive as lung cancer.

The reported incidence of this tumor varies between 40 and 70 years of age, being more common in women around the age of 60 [6]. Small cell carcinoma is characterized by early dissemination, rapid and aggressive clinical course [3] and presents the worst prognosis among the other histologies of the primary neuroendocrine tumors of the breast [8-11].

The diagnosis of small cell neuroendocrine carcinoma begins by discarding lesion from extramammary site or demonstrating component *in situ* [12], based on clinical, radiological, pathological and immunohistochemical data (IHC) [3]. The expression of the neuroendocrine markers evidenced in the IHC does not yet present a consistent characteristic for the small cell carcinomas, however, they should be carefully researched. The positivity will aid in the differentiation between the possible diagnoses and the negative expression should not be an exclusion criterion [6]. Small cell carcinoma shows positivity for cytokeratin 7 (CK7) and negativity for cytokeratin 20 (CK20), and small cell lung carcinoma presents negativity for CK7 and CK20, allowing the differentiation [2,6]. There may also be reactivity to enolase and cytokeratins, synaptophysin, serotonin and chromogranin A or B in these tumors, and the expression of cromagranin and synaptophysin represents neuroendocrine differentiation [13]. Reactivity to the HER-2 receptor is typically negative. Expression of the estrogen and progesterone receptor is related to the degree of differentiation, since well differentiated tumors express more receptors [4]. The present case presented positive immunoreactions to cytoplastmal

pankeratin receptors, synaptophysin and chromogranin A, whereas the estrogen and progesterone receptors, HER-2/NEU receptor and CD-45 receptor were negative.

Neuroendocrine carcinomas of the breast, although presenting nonspecific findings to the imaging tests, should be included in the differential diagnosis of nodular lesions without associated microcalcifications found in mammography and of hypoechogenic mass with irregular contours to the ultrasonography [5].

Due to the rarity of this subtype of carcinoma, there is no consensus regarding its treatment and prognosis, explaining the fact of the diversity of conducts found in the works published until then. The treatments described include surgical procedures, chemotherapy, radiotherapy and hormone therapy. Surgical treatment will be defined according to the clinical stage of the patient, and radical mastectomy may be performed in cases of large tumors (3 cm or more) or in lymph node metastases in the lymph node. Quadrantectomy is another option, and it may be performed on small tumors (less than 3 cm) and in the absence of lymph node metastases and muscular-skin involvement [2]. In some reported cases, chemotherapy, radiotherapy and adjuvant hormone therapy [1,3,6], but the benefits of adjuvant are not proven by the literature [2]. In the present case, the patient received adjuvant therapy with chemotherapy cycles combined with cisplatin and etoposide, a behavior similar to some reported cases [6,14].

Conclusion

Reporting the rarity of the case of high-grade small cell primary neuroendocrine breast cancer and the procedures performed had the objective of elucidating the advantages in the patient's outcome, as well as helping other professionals in similar cases, since there are few cases described. The expression of neuroendocrine markers by immunohistochemistry is not entirely clear yet, but it was concluded that it helps in the differentiation of diagnoses. The absence of consensus about the treatment to be used was evidenced and the divergent behaviors and prognoses present in the literature demonstrate the need for new research on this tumor.

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