BJO
Brazilian Journal of Oncology

CASE REPORTS CLINICAL ONCOLOGY

Small cell neuroendocrine carcinoma of the breast - case series of a common tumour at a rare location

Carcinoma neuroendócrino de pequenas células da mama - série de casos de tumor comum em localização rara

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ABSTRACT

Small cell neuroendocrine carcinoma of the breast is an uncommon primary tumor of the breast with literature limited to case reports and case series. We hereby report 3 cases of small cell neuroendocrine carcinoma of the breast who presented to our institute. One was an elderly lady and the other two were young females. Two of them were of luminal subtype whereas the third was of basal type. One of them occurred in a recurrent setting. The histopathology and immunohistochemistry of all tumors were consistent with neuroendocrine origin. All of them were treated with a combination of chemotherapy, surgery, and radiotherapy. It is important for prognostication as most of them present with a higher grade and stage. Treatment protocols need to be standardized for this rare and aggressive breast tumor.

Keywords: Breast; Carcinoma, Small cell; Primary treatment.

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Financial support: none to declare.
Conflicts of interest: The authors declare no conflict of interest relevant to this manuscript.

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Received on: April 9, 2023 | **Accepted on:** June 18, 2023 | **Published on:** July 31, 2023
DOI: https://doi.org/10.5935/2526-8732.20230415

RESUMO

O carcinoma neuroendócrino de pequenas células da mama é um tumor primário incomum da mama, com literatura limitada a relatos de casos e séries de casos. Relatamos 3 casos de carcinoma neuroendócrino de pequenas células da mama que se apresentaram em nosso instituto. Uma era uma senhora idosa e as outras duas eram mulheres jovens. Dois deles eram do subtipo luminal enquanto o terceiro era do tipo basal. Um deles ocorreu em um cenário recorrente. A histopatologia e a imuno-histoquímica de todos os tumores foram compatíveis com origem neuroendócrina. Todos eles foram tratados com uma combinação de quimioterapia, cirurgia e radioterapia. É importante para o prognóstico, pois a maioria deles apresenta grau e estágio mais elevados. Os protocolos de tratamento precisam ser padronizados para esse raro e agressivo tumor mamário.

Descritores: Mama; Carcinoma de pequenas células; Tratamento primário.

INTRODUCTION

Primary small cell neuroendocrine carcinoma (SCNEC) breast is an uncommon malignancy. In pathology, it shares identical morphology to SCNEC from other sites but the identification of concurrent ductal or lobular in situ or invasive carcinomas favors breast origin. Neuroendocrine carcinomas of the breast are defined as a diffuse expression of neuroendocrine markers in ≥50% of cells.[1] Here we report 3 cases of small cell neuroendocrine carcinoma of the breast that we encountered at our institute.

CASE 1

A 35-year-old lady with a left breast lesion for one month. She underwent an upfront left-modified radical mastectomy (as per patient preference). Histopathology was reported as SCNEC of the breast, staged as *pT2N1* (Figure 1A). Immunohistochemistry (IHC) showed estrogen receptors and progesterone receptors (ER/PR) were weakly positive and human epidermal receptor (HER 2/neu) was negative with positivity for synaptophysin (Figure 1B). She received 6 cycles of adjuvant chemotherapy with cisplatin and etoposide followed by adjuvant radiotherapy. She was on follow-up with tamoxifen. At a disease-free interval of 9 months, she presented with a history of raised intracranial pressure. She was treated with anti-edema measures and magnetic resonance imaging (MRI) brain revealed brain metastasis. She received whole brain radiotherapy. Imaging of the thorax and abdomen revealed multiple liver lesions. She is currently on second-line treatment with irinotecan, cisplatin, and atezolizumab after a discussion in a multidisciplinary tumor board. Response assessment is awaited.

CASE 2

A 55-year-old lady presented with a history of a lump in her right breast for 2 months. She was evaluated at our center with positron emission tomography-computed tomography (PET-CT) scan for staging which showed a non-metastatic disease with the primary in the breast (Figure 2A). The histopathology was reported at SCNEC of the breast with high Ki 67 (Figure 2B) and IHC showed low ER positivity and PR/HER-2 neu were negative. She was started on chemotherapy with cisplatin and

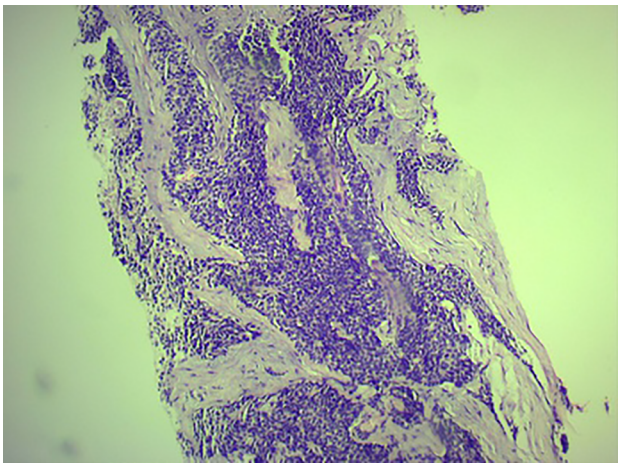

Figure 1.a Low power view of small cell neuroendocrine carcinoma breast in H and E stain.

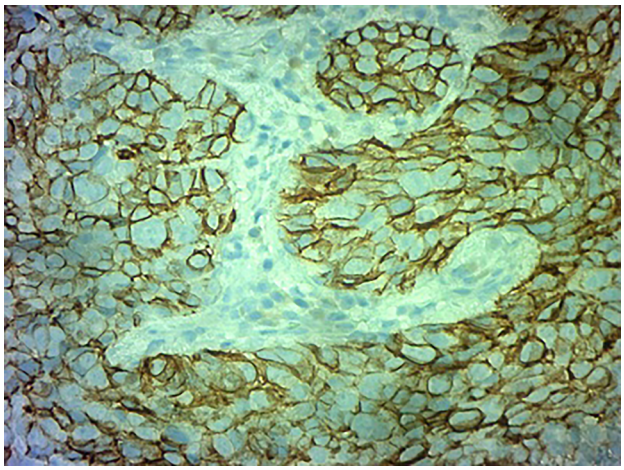

Figure 1.b Small Cell Neuroendocrine carcinoma showing synaptophysin positivity.

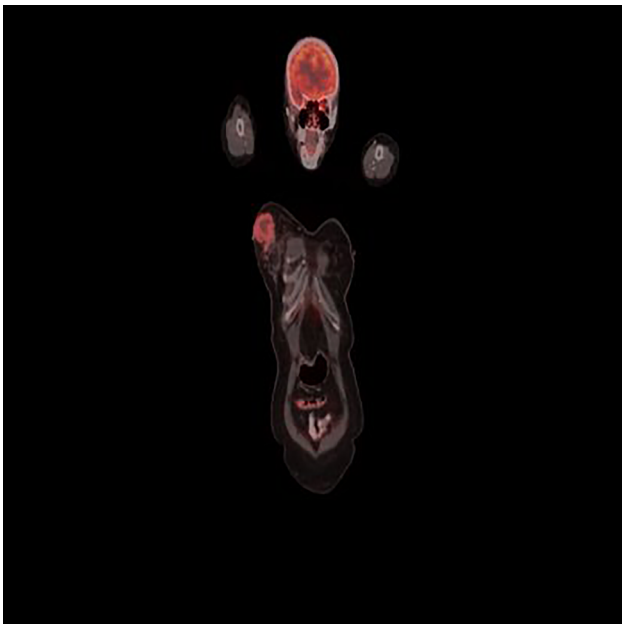

Figure 2.a PET CT Scan showing high-grade uptake in the primary lesion in the breast with no distant metastasis.

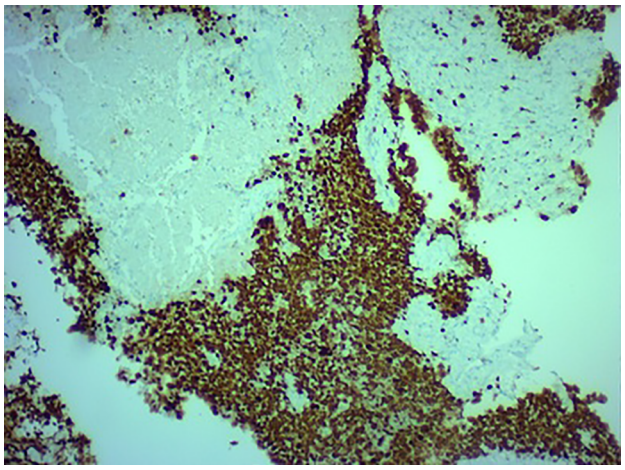

Figure 2.b Low power view of small cell neuroendocrine carcinoma breast showing high Ki 67.

etoposide. She received 4 cycles of the same and underwent a right-modified radical mastectomy. The histopathology post-surgery revealed *ypT2N3a* disease. In view of their poor response to neoadjuvant chemotherapy, she received 4 cycles of docetaxel, after discussion in a multidisciplinary tumor board followed by adjuvant radiotherapy. She is currently on 3 monthly follow up with oral letrozole.

CASE 3

A 35-year-old premenopausal lady presented with a lesion in her left breast. She had a personal history of luminal-type carcinoma in the right breast which was treated in 2010 and on hormonal therapy. Biopsy was done and histopathology was reported as SCNEC of breast, basal type (Figure 3A). Staging done with positron emission tomography-computed tomography (PET-CT) showed no evidence of distant metastasis (Figure 3B). She was started on neoadjuvant chemotherapy with

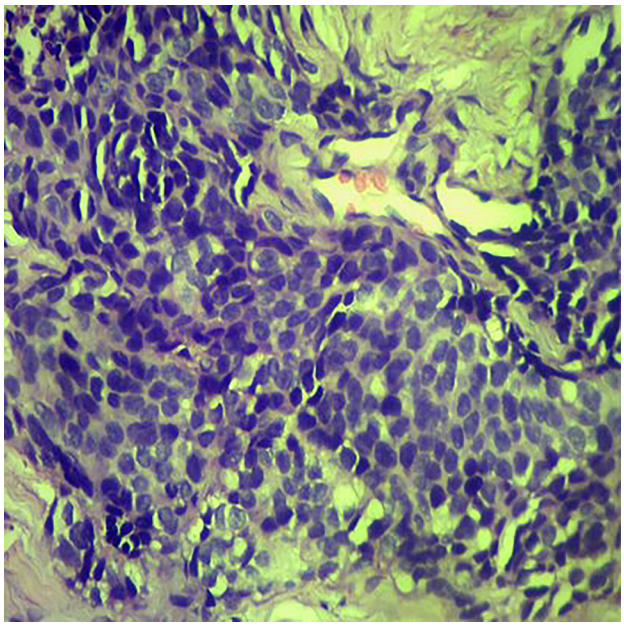

Figure 3.a Small Cell Neuroendocrine Carcinoma high power view in H and E stain.

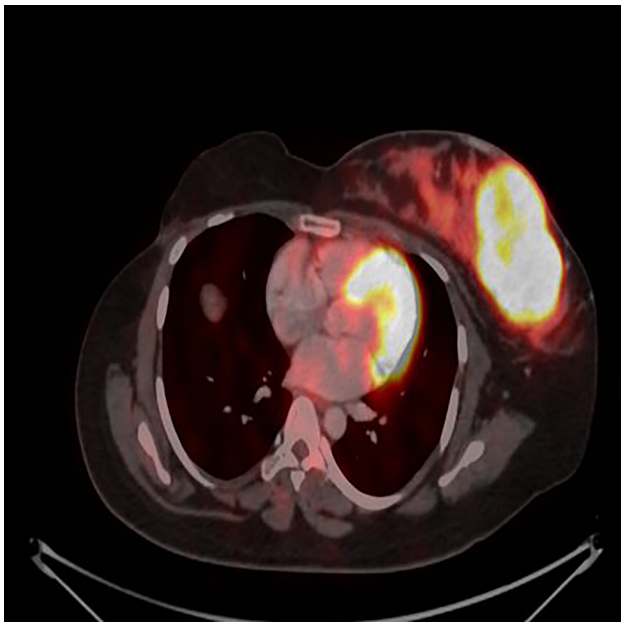

Figure 3.b PET CT scan showing primary lesion in the breast.

5-fluorouracil-epirubicin-cyclophosphamide (FEC) for 3 cycles followed by docetaxel for 3 cycles. She underwent breast conservation surgery and histopathology was reported as *ypT2N0* disease. A breast cancer (BRCA) germline test was sent in view of bilateral breast cancer, and it was positive for BRCA 2 exon 25 mutation. She is currently on adjuvant radiotherapy and is on capecitabine maintenance. She has been counseled for adjuvant olaparib, but logistic issues hinder the treatment with the same.

DISCUSSION

Small cell carcinoma is an aggressive tumor most commonly found in the lung but can arise in non-pulmonary sites, such as the gastrointestinal tract,

breast, larynx, bladder, and ovary. Primary SCNEC of the breast is a very rare type of breast cancer, with a reported incidence of <0.1% to 1-5% of all breast cancers.[2] SCNEC has been recognized as a distinct breast cancer subtype and this is based on case reports and small series.[3]

Histogenesis of SCNEC of the breast is not clearly defined yet with theories of multiplication of constitutive neuroendocrine cells and divergent differentiation of breast cancer stem cells into both neuroendocrine cells existing.[4] The diagnosis requires the presence of over 50% of neoplastic cells expressing neuroendocrine markers of immunohistochemistry, excluding primary extra-mammary tumors, and the identification of a concomitant component in situ in the breast.[5] A comprehensive genetic characterization of NEC of the breast revealed that p53 and retinoblastoma (Rb) pathway alterations are highly prevalent.[3] Analysis of gene expression profiles revealed that SCNEC of the breast mostly belongs to the luminal subtype.[4] Moreover, SCNEC of the breast has a significantly lower frequency of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation, around 7 to 33%.[6]

Despite the luminal phenotype, many studies have reported an aggressive clinical course of SCNEC given the age, size, degree, and state of the estrogen receptor while some have reported a prognosis similar to that of invasive breast cancers depending on staging and molecular classification.[7,8] Roininen et al. (2019)[9] assessed the immunohistochemical expression of gastroenteropancreatic neuroendocrine tumors (GEP-NET) and found a striking similarity between the two entities.

Due to the rare occurrence and limited reports, there is no standard approach to the treatment for SCNEC of the breast. Treatment regimens in the literature include combinations of surgery, chemotherapy, radiation therapy, and endocrine therapy, as per standard breast cancer treatment guidelines. Surgery is the mainstay of the treatment with alternatives of both modified radical mastectomy and breast conservation surgery. Various chemotherapy regimens have been employed including the standard adriamycin-based chemotherapy used in invasive breast tumors and platinum-based chemotherapy for small-cell lung cancers. Chemotherapy may be given as a neoadjuvant or adjuvant, but a neoadjuvant is recommended in view of the aggressive nature of the disease. There has also been a concept of utilizing Ki67 to decide the chemotherapy regimen – for tumors with Ki67 >15%, a platinum-based regime was used, and for Ki67 <15%, an adriamycin-based regimen was given.[10,11] Postoperative radiotherapy is warranted as per standard breast cancer treatment guidelines although conflicting evidence is present. Immunotherapy has also been suggested to have benefits in SCNEC of the breast (because of its similarity with small cell lung cancer), even though studies are lacking.

A surveillance, epidemiology, and end results (SEER) database analysis of 323 patients of SCNEC breast from 1975 to 2018 was published. The overall incidence after adjustment for age between 1990 and 2018 was 0.14 per million per year and the disease was more common in older women aged >60 years. The 5-year disease-specific survival and overall survival were 61.6% and 53.1%, respectively. The patients with SCNEC breast had poorer survival than patients with other uncommon types of invasive ductal carcinoma.[12]

To summarise, in our series of 3 cases, two of the cases were young when compared to already reported literature and one of the cases occurred in a relapsed setting. Two of them were of luminal type while the third was a basal type. We used platinum-based chemotherapy for two cases and an adriamycin-based regimen for the third case. Neoadjuvant chemotherapy was given in two of the cases. One of the cases relapsed and is on palliative chemo-immunotherapy.

CONCLUSION

Primary SCNEC of the breast is an uncommon and aggressive variant of breast cancer. It has similar pathological features when compared to small-cell lung cancer. A diagnostic evaluation must include a workup to rule out metastasis from another primary site, especially the lung. Due to its rarity, no standard guidelines for treatment exist. More research is required for improving prognosis and systematizing treatment.

ABBREVIATIONS	FULL NAMES
SCNEC	Small cell neuroendocrine carcinoma
IHC	Immunohistochemistry
ER/PR	Estrogen receptor/ Progesterone receptor
Her 2/neu	Human epidermal receptor (HER-2/neu)
MRI	Magnetic resonance imaging
PET CT	Positron emission tomography-computed tomography
FEC	5-fluorouracil-epirubicin-cyclophosphamide
BRCA	Breast cancer gene
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
GEP-NET	Gastroenteropancreatic neuroendocrine tumors
SEER	Surveillance, epidemiology, and end results

AUTHORS' CONTRIBUTIONS

DHV	Collection and assembly of data, Final approval of manuscript, Manuscript writing
TB	Collection and assembly of data, Manuscript writing, Provision of study materials or patient
SPS	Final approval of manuscript, Manuscript writing, Provision of study materials or patient
SVMK	Manuscript writing, Provision of study materials or patient
TNTK	Manuscript writing, Provision of study materials or patient
NW	Final approval of manuscript, Manuscript writing

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