

## CASE REPORT

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# Extrapulmonary small cell carcinoma of the breast. Case report

## Carcinoma de células pequeñas extrapulmonar de mama. Comunicación de caso

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### ABSTRACT

Small cell carcinoma accounts for 20% of lung cancers; it rarely occurs at other sites. Extrapulmonary small cell carcinoma is aggressive, with a propensity for regional and distant spread. This type of carcinoma is a rare breast neoplasm. Although the clinical appearance is nonspecific, it often responds well to therapy and has a good prognosis of survival. We present the case of a 50-year-old woman with extrapulmonary small cell carcinoma of the breast. Physical examination showed a 4 x 3 x 3 centimeters lesion confirmed by magnetic resonance imaging of the left breast. The diagnosis was made by biopsy showing characteristic small, round, lymphocyte-like cells with hyperchromatic nuclei and scant cytoplasm, compatible with small cell carcinoma of the breast. The patient was treated with chemotherapy before undergoing total mastectomy and lymph node resection.

**Key words:** Breast; Breast neoplasms, extrapulmonary small cell carcinoma.

### RESUMEN

El carcinoma de células pequeñas representa 20% de los cánceres de pulmón; raramente ocurre en otros sitios. El carcinoma de células pequeñas extrapulmonar es agresivo, con propensión a la diseminación regional y a distancia. Este tipo de carcinoma es una neoplasia poco frecuente en mama. Aunque la apariencia clínica es inespecífica, a menudo responde bien a la terapia y tiene buen pronóstico de supervivencia. Se presenta el caso de mujer de 50 años con carcinoma de células pequeñas extrapulmonar de mama. El examen físico mostró lesión de 4 x 3 x 3 centímetros confirmada por resonancia magnética de la mama izquierda. El diagnóstico se realizó mediante biopsia que mostró las características células pequeñas, redondas, similares a linfocitos con núcleos hiper cromáticos y escaso citoplasma, compatible con carcinoma de células pequeñas de mama. La paciente fue tratada con quimioterapia antes de ser sometida a mastectomía total y resección de los ganglios linfáticos.

**Palabras clave.** Mama, Neoplasias de la mama, extrapulmonar de células pequeñas.

### INTRODUCTION

Small cell carcinoma (SCC) is a tumor usually located in the lung<sup>(1)</sup>. Extrapulmonary SCC is a rare malignant neoplasm that was first described in 1930 as a clinical pathologic entity distinct from that of the lung<sup>(2,3)</sup>. It has an incidence of 0.1% to 0.4% in general neoplasms and 2% to 5% in SCCs. There are reports of numerous sites of occurrence, the most frequent being head and neck, digestive tract and genitourinary system. Occasionally cases have been reported in breast, thyroid, skin and thymus, presenting both a diagnostic and therapeutic challenge<sup>(3)</sup>.

PCC is one of the least frequent types of breast cancer (less than 1%). The natural history of this carcinoma has not yet been fully discovered and, therefore, there is little data on its clinical behavior and optimal treatment<sup>(2,4)</sup>. A case of extrapulmonary small cell carcinoma of the breast is presented.



## CLINICAL CASE

This is a 50-year-old female patient who presented with a continuous and progressive increase in volume of the left breast, which did not improve with any type of medication, of approximately 9 months of evolution. The patient denied a personal history of hypertension, diabetes mellitus, tuberculosis or any chronic disease or significant family history. She also denied a history of tobacco, alcohol or recreational drug use.

Physical examination revealed a retroareolar lump in the left breast of approximately 6 centimeters associated with enlargement of the ipsilateral axillary lymph nodes. The rest of the physical examination was normal. Ultrasonography and mammography showed the presence of a 4 x 3 x 3 centimeter nodule located in the retroareolar region of the left breast. Also, a satellite nodule of 1.5 centimeters and two enlarged axillary nodes (2.5 and 1.9 centimeters, respectively). No pulmonary lesions suggestive of possible primary lung tumor, mediastinal lymphadenopathy or metastases in other regions were found, evaluated by total body computed tomography and bone scintigram.

In view of the clinical picture, it was decided to perform a core needle biopsy of the lesion, which showed the presence of small, round or oval, lymphocyte-like cells with hyperchromatic nuclei, scant cytoplasm, frequent mitoses and small nucleoli, compatible with PCC. The cells were strongly positive for cytokeratins, synaptophysin and chromogranin A and negative for p53, Her2/Neu and estrogen and progesterone receptors. The Ki67 index was 80%. Blood bio-

FIGURE 1. MAGNETIC RESONANCE IMAGE OF THE LEFT BREAST SHOWING THE RETROAREOLAR NODULE.

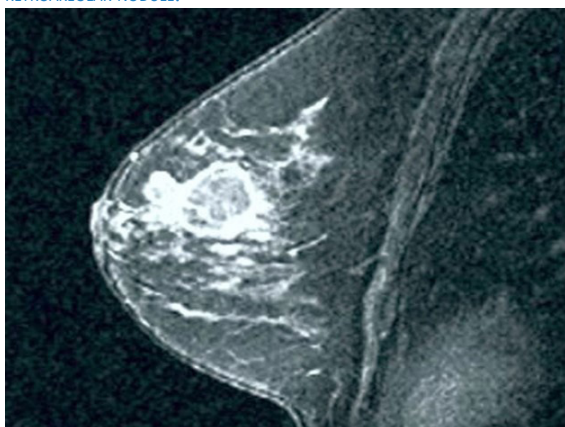
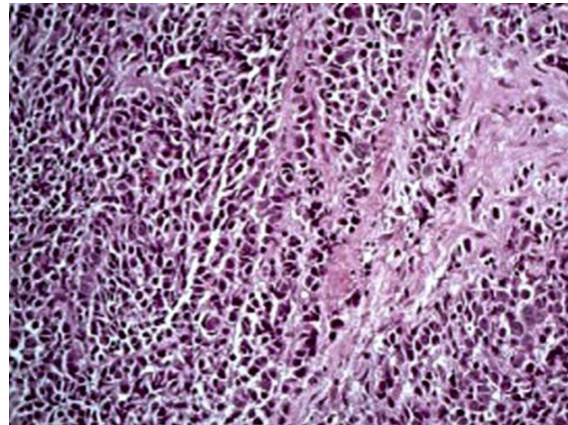


FIGURE 2. SMALL, ROUND OR OVAL, LYMPHOCYTE-LIKE CELLS WITH HYPERCHROMATIC NUCLEI, SCANT CYTOPLASM, FREQUENT MITOSES AND SMALL NUCLEOLI, COMPATIBLE WITH SMALL CELL BREAST CARCINOMA. HEMATOXYLIN-EOSIN STAINING.



chemical tests, electrocardiogram, and carcinoembryonic antigen and CA 19-9 values were all within normal limits, ruling out the possibility of paraneoplastic syndrome. These findings led to the diagnosis of extrapulmonary breast PCC with extension to lymph nodes.

Due to the locally advanced stage of the disease, the patient initially underwent chemotherapy with intravenous cisplatin (75 mg/m<sup>2</sup>) and etoposide (100 mg/m<sup>2</sup>), every 21 days for 5 cycles. Magnetic resonance imaging performed at the end of chemotherapy showed 90% regression of the tumor. Thirty days after the end of treatment, total mastectomy with ipsilateral lymph node dissection was performed. Anatomicopathologic evaluation confirmed chemotherapy-responsive breast PCC, with no evidence of residual disease in the breast parenchyma and axillary nodes. Adjuvant radiotherapy of the chest wall and supraclavicular lymph nodes was performed together with prophylactic brain irradiation. After 21 months, post-treatment controls have shown no evidence of local or systemic disease recurrence.

## DISCUSSION

PCC accounts for about 20% to 25% of all bronchogenic carcinomas and only 2.5% to 4% arise in extrapulmonary sites, and is considered an aggressive neoplasm<sup>(1)</sup>. Its occurrence has been reported most frequently in paranasal sinuses, nasal cavity, salivary glands, thyroid gland, larynx and trachea; rarely in ovaries, prostate, urinary bladder, cervix and breast<sup>(3)</sup>. There are few studies on extrapulmonary PCC located in the



breast. The average age of onset is 55 years (between 41 and 70 years), appearing as a clinically palpable tumor, and two thirds of patients have lymph node invasion at the time of diagnosis<sup>(4-6)</sup>.

Although various theories have been postulated, the origin of PCC is unclear. It is considered to originate from pre-existing neuroectodermal cells, pluripotent epithelial stem cells or adenocarcinoma precursor cells. It has also been proposed that these tumors originate from primitive totipotent cells that may lead to dual or multiple differentiation, including a mixture of small neoplastic cells, squamous cells and adenocarcinomatous cells. Some cytogenetic abnormalities, such as microsatellite instability, loss of heterozygosity, and chromosome deletion or loss, have also been reported in extrapulmonary HCC of the gastrointestinal tract, gallbladder, cervix, urinary bladder, and breast<sup>(3)</sup>.

Smoking and alcoholism have been postulated as risk factors, but this association has not been verified. Most patients present with a palpable breast tumor and/or axillary lymphadenopathy and may be accompanied by paraneoplastic syndromes (inappropriate secretion of adrenocorticotropic or antidiuretic hormone)<sup>(6)</sup>. Mammographic, ultrasound and MRI features have been described as non-specific, as they are similar to those of other breast carcinomas, so the final diagnosis is made only by biopsy<sup>(2)</sup>. In order to establish the diagnosis of breast PCC, it must be taken into account that it is not metastatic. The evaluation should include brain imaging studies and bone scintigraphy to exclude central nervous system involvement and bone metastases. Bone marrow aspirate is suggested, especially in those patients with cytopenia<sup>(6)</sup>.

PCCs, regardless of site of origin, share similarities in their morphological characteristics. The cells are small round or oval, with dense nuclei, discrete nucleoli and scant cytoplasm. They have a high mitotic index, with lamellar growth, trabecular patterns and may contain areas of necrosis<sup>(5,7)</sup>. Generally, they can be associated with histologic evidence of ductal carcinoma in situ and areas of ductal, lobular or papillary differentiation. Immunohistochemistry, as well as histology, is considered the hallmark of pathologic diagnosis. Not surprisingly, the cells stain positive for common neuroendocrine markers,

such as neuron-specific enolase, synaptophysin, and the specific marker of neuroendocrine differentiation, chromogranin-A. About 50% of tumors are hormone receptor positive. HER2/Neu overexpression has not been described<sup>(7)</sup>.

Differential diagnoses include: Metastatic PCC, Merkel cell tumor, primary or secondary lymphoma, carcinoid tumor, and metastatic malignant melanoma<sup>(6)</sup>. Merkel cell carcinoma is morphologically similar, but shows characteristic immunohistochemical staining of perinuclear CK-20. Melanoma and lymphoma can be easily identified by their specific markers S-100, HMB-45 and CD45<sup>(6-8)</sup>.

Lung PCC is a very fast-growing tumor with potential for distant metastasis, even in the early course of the disease<sup>(1)</sup>. It usually metastasizes to bone, lymph nodes, adrenal gland, liver, oral cavity, tongue, gum, parotid gland and brain. Extrapulmonary PCC is a clinicopathologic entity with an aggressive clinical course similar to that of the lung and, because it is recurrent in nature, it has a poor prognosis<sup>(9)</sup>. However, a distinction should be made between cases with localized disease that have a survival of more than 8 to 22 months. Patients with disseminated disease have lower survival rates, from 3 to 8.5 months<sup>(5)</sup>. Patients with extrapulmonary breast PCC have a more favorable prognosis, especially if diagnosed in early stages, with 3-year survival rates of 60%, while only 7% of patients with gastrointestinal origin remain alive<sup>(2,5)</sup>.

There is no consensus regarding treatment regimens and there are differences between cases with localized and disseminated disease. Surgery plays a more important role in extrapulmonary PCC than in pulmonary PCC, especially in patients with breast disease, but should be supported by chemotherapy and radiotherapy. Treatment has evolved from radical surgery to chemotherapy treatments with schemes similar to lung PCC. Multimodality therapy with the combination of radical surgery or chemotherapy is preferred, even in early stages. The most effective chemotherapy scheme for treatment is the combination cisplatin plus etoposide, with a response rate of 69%<sup>(10)</sup>, as shown in this case. The association of doxorubicin does not improve the survival rate<sup>(11)</sup>. Since resolution is possible in limited disease, intensive multimodality treatment is recommended.



Radiation therapy should cover the primary lesion and include regional lymph nodes. The use of prophylactic cranial radiotherapy in patients with PCC of the lung has been shown to be beneficial for overall survival, as well as for reducing the number of brain metastases. The small number of breast PCC cases published to date makes it impossible to offer recommendations on the role of prophylactic cranial radiotherapy in this group of patients<sup>(12)</sup>. In contrast to what has been done in this case, most published cases have opted not to use prophylactic radiotherapy. Perhaps this could have specific indications in patients with advanced disease at the time of diagnosis.

In conclusion, breast PCC is a neoplasm for which no effective treatment protocol has been established due to the small number of reported cases. Based on clinical stage, surgery and chemotherapy with or without prophylactic radiotherapy appear to be the treatment of choice.

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