Received: 2 July 2019 | Revised: 9 July 2019 | Accepted: 10 July 2019

DOI: 10.1111/tbj.13535

The Breast Journal WILEY

CASE REPORT

Primary neuroendocrine carcinoma of the breast: A case report of liver and lymph node metastases after eight years from diagnosis

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Abstract

Primary neuroendocrine carcinoma of the breast (NECB) is one of the rarest subtypes of breast tumor, and for this reason, there are no data from prospective clinical trials on its optimal management. Its incidence is <0.1% of all breast cancers and <1% of all neuroendocrine tumors. The diagnosis of NECB requires the expression of neuroendocrine markers (chromogranin, synaptophysin, NSE) and the lack of simultaneous neuroendocrine carcinoma in extramammary sites. We present a case of a poorly differentiated neuroendocrine carcinoma (PD-NEC) metastasized in liver and lymph node after eight years. Mammography, ultrasound imaging, CT, and pathology findings are described.

KEYWORDS

breast, carcinoma, liver metastases, mammography, neuroendocrine

1 | CASE REPORT

A 69-year-old woman presented in our Breast Unit with clinical evidence of a right retro-areolar palpable mass with Paget-like infiltration of the nipple, which appears eroded and swollen as well as the areolar and peri-areolar region.

Mammography showed (Figure 1A,B) some relatively bright and heterogeneous microcalcifications next to a nodule of tenuous radiopacity with a diameter of about 15 mm, persistent at spot compression.

Breast US (Figure 1 C,D) showed in the superior paracentral area the presence of a 12 mm nodule with shaded and irregular margins with a posterior acoustic shadowing. Nearby, in the retro-areolar area, we founded a further 14 mm nodule with the same characteristics.

Then, the patient was sent to surgery. A central right quadrantectomy with removal of the nipple-areola complex was performed, with complete axillary lymph node dissection, since the sentinel lymph node was positive for neoplastic cells. Final pathology revealed two different tumors: multiple invasive lobular carcinoma (G3; 1.5 cm) (Figure 2A-D) associated with neuroendocrine carcinoma (G3; 2.5 cm) extended to the superficial dermis (Figure 2 E-H).

Multiple focus of peritumoral intraepithelial lobular neoplasia (LIN2-3) was also found. Immunohistochemical characteristics are reported in Table 1.

Two lymph nodes were positive, respectively, for metastasis of neuroendocrine carcinoma and metastasis of lobular carcinoma. Postoperative was regular, and the patient was treated with chemotherapy (fluorouracil\epirubicin\cyclophosphamide followed by docetaxel), radiotherapy, and anastrozole.

Subsequently, 18-Fluorodeoxyglucose PET-CT was performed to exclude a different primary site. Diagnostic findings did not show any high uptake areas in extramammary sites.

After eight years free from disease, subclavicular lymph node enlargement was observed on physical examination. The patient went to the emergency room a few days later in poor general health status. At the CT scan, we found multiple hypodense liver lesions compatible with metastases (Figure 3A) and at chest CT, multiple and confluent subclavicular, and mediastinal lymph nodes enlargement, associated with a solid thickening with C.E infiltrating the first

right intercostal space without secure cleavage planes with pectoralis minor muscle (Figure 3B).

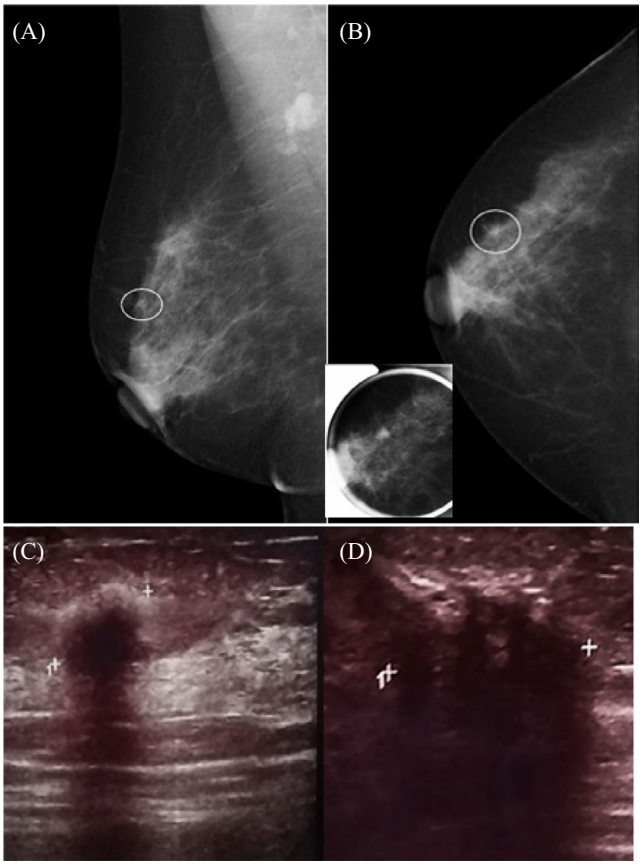

FIGURE 1 A, B - Mammography shows nodule persistent at spot compression. C,D - Hypoechoic and irregular nodules at breast US

TABLE 1 Immunohistochemical characteristics

	Neuroendocrine carcinoma (G3; 2.5 cm)	Invasive lobular carcinoma (G3; 1.5 cm)
Chromogranin	+++	/
NSE	+++	/
CK CAM 5.2	–	+
CK HMW	–	+
ER	–	100%
PGR	–	100%
CERB-B2	–	–
KI67	90%	40%

2 | DISCUSSION

Primary neuroendocrine carcinoma of the breast (NECB) is one of the rarest subtypes of breast cancer. Its incidence is <0.1% of all breast cancers and <1% of all neuroendocrine tumors.

Carcinomas with neuroendocrine features are subclassified into three groups: well-differentiated neuroendocrine tumor (WD-NET), which are low-grade tumors that architecturally resemble carcinoid tumors of other sites; poorly differentiated neuroendocrine carcinoma (PD-NEC) or small-cell carcinoma, which is identical to its pulmonary counterpart; and invasive breast carcinoma with neuroendocrine differentiation (IBC-NED).[1-3]

The diagnosis of NECB requires the expression of neuroendocrine markers (chromogranin, synaptophysin, and NSE) and the lack of simultaneous neuroendocrine carcinoma in extramammary site. Neuroendocrine differentiation has been demonstrated in >30% of invasive ductal carcinomas, but it is important to note that, less

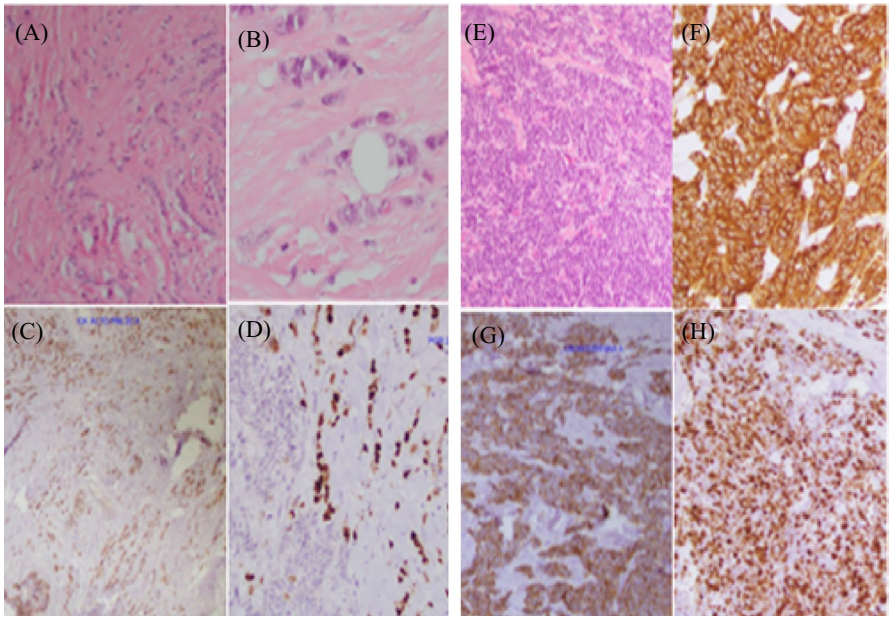

FIGURE 2 A-D- Invasive lobular carcinoma (A,B) with CK HMW positivity (C) and PGR 100% (D). E-H- Poorly differentiated neuroendocrine carcinoma (E) with neuron specific enolase positivity (F), chromogranin positivity (G) and KI67 90% (H)

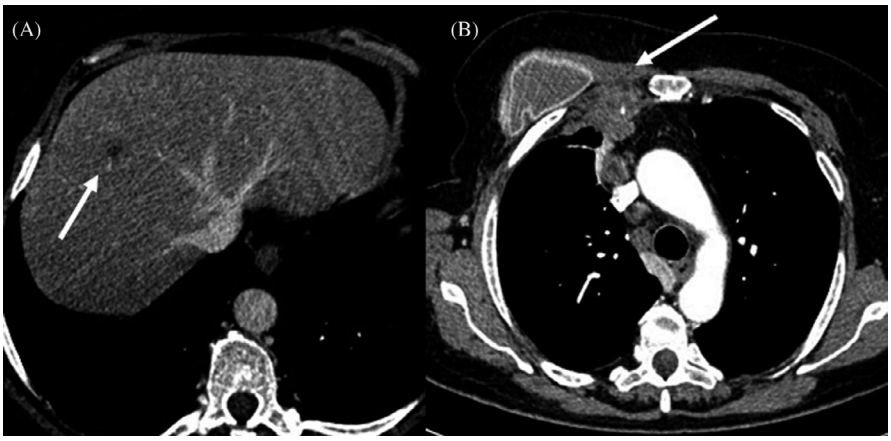

FIGURE 3 A- Liver metastases at CT scan. B- Multiple and confluent subclavicular and mediastinal lymph nodes enlargement associated with solid thickening

frequently, invasive lobular carcinoma can also demonstrate neuroendocrine differentiation.[4]

Neuroendocrine carcinoma of the breast mammographic characteristics are a high-density mass with spiculated margins. At breast US, it appears as a hypoechoic mass with enhanced posterior echo. RM shows homogeneous low-signal intensity with heterogeneous rapid initial enhancement on the T1-weighted image. These features are unspecific, and biopsy is required for diagnosis.

Neuroendocrine carcinoma of the breast can metastasize to multiple sites even years after the treatment for primary tumor, and therefore, a long-term follow-up is advisable. Metastatic sites include liver, bones, lung, pancreas, soft tissues, and brain.[5]

Somatostatin receptor scintigraphy (SRS) or positron emission tomography (PET)-CT with 68-Gallium-labeled somatostatin analogs also may be useful to exclude a different primary site in the case of well-differentiated neuroendocrine carcinomas, whereas 18-fluorodeoxyglucose PET-CT could be used with the same purpose in the case of poorly differentiated neuroendocrine carcinoma with a high proliferation rate.[6] There are no specific guidelines for treatment of primary NECB.

Surgical management, like conventional breast cancer, is based on tumor location and stage. Adjuvant chemotherapy can be used in patients with high risk of relapse. Patients with hormone receptors positive NECB are candidates to receive adjuvant endocrine therapy. Several chemotherapy regimens are reported in literature, for example, fluorouracil/epirubicin/cyclophosphamide followed by docetaxel,[7] The prognosis for this rare carcinoma is controversial because several studies have been published with mixed results [6]

In patients with NECB larger tumor size (>20 mm), higher stage, KI67 > 14%, and negative hormone receptor status were associated with shorter overall survival.[6] When specific histologic subgroups were introduced in 2012, small-cell carcinoma (PD-NEC) was significantly associated with a worse prognosis in comparison whit other subtypes.[6]

Imaging features of NECB are suspicious for malignancy, but are not specific. NECB can metastasize to multiple sites even years after the treatment for primary tumor, and therefore, a long-term follow-up is advisable.

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How to cite this article: Valente I, Tringali G, Martella EM, Pallavera L, D'Aloia C. Primary neuroendocrine carcinoma of the breast: A case report of liver and lymph node metastases after eight years from diagnosis. *Breast J*. 2019;00:1–3. https://doi.org/10.1111/tbj.13535