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Case Report
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A Case of Primary Large Cell Neuroendocrine Carcinoma of the Breast in a Patient Previously Treated for Invasive Ductal Carcinoma

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Abstract

Neuroendocrine Carcinoma (NEC) of the breast is a very rare entity representing approximately 0.1% of all breast cancers. The clinical or radiological features are not distinguishable from high-grade Not Otherwise Specified (NOS) type invasive breast carcinoma. We present a 53 y/o female patient who had previously been treated for mammary carcinoma with neuroendocrine differentiation recurred with large cell neuroendocrine carcinoma describing detailed imaging findings on mammography, ultrasonography, elastography, and MRI. We present different imaging features of the tumor such as benign morphology in B mode ultrasound, stiffness in elastography, and lack of restricted diffusion on diffusion-weighted MRI.

Keywords: Invasive ductal carcinoma; Neuroendocrine carcinoma; Mammography; Breast MRI; Ultrasound

Introduction

Primary NECs of the breast is a very rare entity. Small Cell NECs (SCNECs) account for approximately 0.1% of all breast cancers and Large Cell NECs (LCNECs) are extremely rare [1]. However, metastatic NEC to the breast is a more common condition. Primary NEC of the breast can be warranted when the presence of a non-mammary primary site is clinically ruled out or an associating in situ cancer component is histologically detected. The disease is more commonly diagnosed in elderly women in their sixth or seventh decade of life [2].

NEC is an invasive carcinoma characterized by high-grade neuroendocrine morphology (small cell or large cell), supported by the presence of neurosecretory granules and a diffuse, uniform immunoreactivity for neuroendocrine markers. According to the 2012 WHO classification, the distinction between Neuroendocrine Tumour (NETs) and grade I or II breast carcinomas of other types that show neuroendocrine differentiation was not so clear. For this reason, the key feature of the 2019 WHO classification is the distinction between well-differentiated NETs and poorly differentiated Neuroendocrine Carcinomas (NECs), and breast neuroendocrine neoplasms are now categorized as NETs, small cell NECs and large cells NECs [1].

It is controversial that neuroendocrine cells are present in normal breast tissue. According to Shin et al. [3] SCNECs originate from mammary cancer stem cells which show a specific line of differentiation towards neuroendocrine/small cell type differentiation rather than originating from specific neuroendocrine cells nesting in the normal breast tissue. This specific line of differentiation may take place at the in situ or a later stage (at the invasive stage) [3]. However, the pathogenesis of LCNEC is obscure [1].

In this paper, we report multi modality imaging findings of primary large cell neuroendocrine breast carcinoma in a patient with previously treated for invasive ductal carcinoma.

Case Presentation

A 53-year-old female patient with a breast cancer history applied for her routine follow-up examinations. She had breast-conserving surgery 5 years ago in an outside center with a diagnosis of invasive ductal carcinoma of the breast which showed neuroendocrine differentiation. Typically, the

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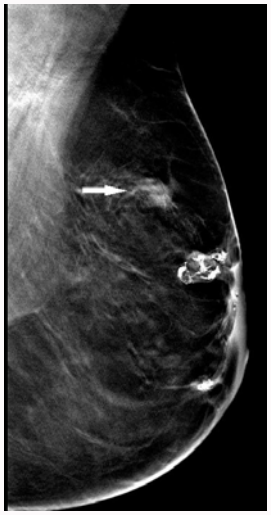

Figure 1a: LMLO tomosynthesis (3D) slice image: Developing ill-defined mass (arrow).

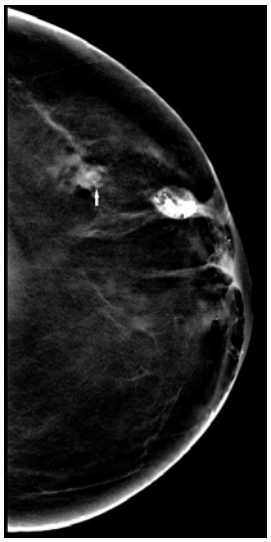

Figure 1b: LCC tomosynthesis slice image: Eccentric microcalcifications (arrow)

tumor presented with ER and PR positivity and Her-2 negative status.

Her current mammography showed a developing round mass with indistinct margins and eccentric heterogenous microcalcifications (Figure 1a, 1b). US examination revealed a 7 mm circumscribed microlobulated, hypoechoic solid mass with internal septations (Figure 2a) and an adjacent 3 mm round-shaped hypoechoic lesion with ill-defined margins. Shear wave elastography of the index lesion showed stiffness of the lesion (194 kPa) (Figure 2b). Breast MRI displayed initial fast contrast uptake, washout kinetics with intralesional non-enhancing areas representing cystic-necrotic changes (Figure 3a). Diffusion-Weighted Imaging (DWI) did not show diffusion restriction and the ADC was calculated at 1.512 $mm^2/s \times 10^{-3}$ mm^2/s (Figure 3b) as detailed in Table 1. US-guided core needle biopsy revealed invasive cancer of the breast but final tissue diagnosis after surgery revealed a neuroendocrine tumor without axillary metastasis. FDG-PET and DOTA- PET did not show any extramammary activity.

Skin sparing mastectomy was performed. Macroscopically

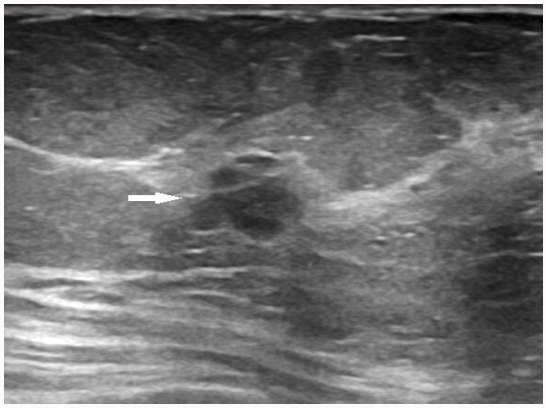

Figure 2a: US image: circumscribed lobulated solid mass with internal septations (arrow).

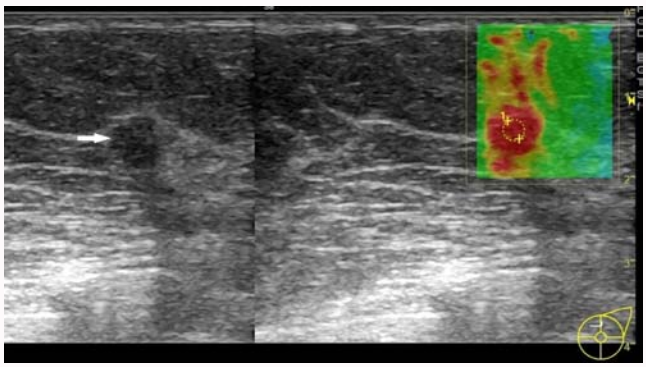

Figure 2b: Shear wave elastography image: The B-mode image and the color-coded elasticity map. Lesion elasticity was measured 194 kPa.

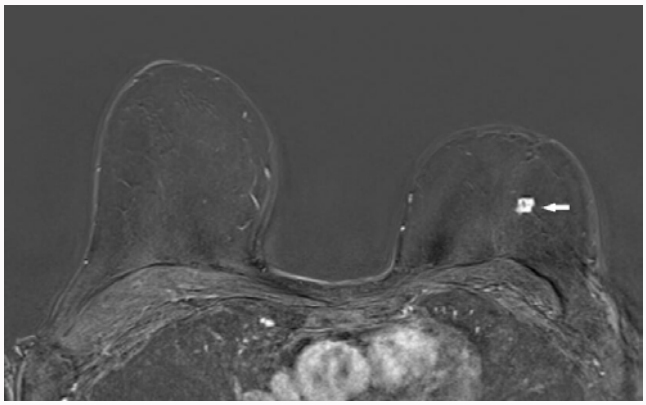

Figure 3: a). Contrast-enhanced MR image: heterogeneous enhancement with intralesional cystic-necrotic changes. b). Apparent Diffusion Coefficient (ADC) map: Lesion is hyperintense indicating no restricted diffusion.

tumor measured 16 mm in diameter with poorly circumscribed, fleshly, solid, and gray to pink cut surfaces. Primary NECs have no gross features distinct from those of other types of high- grade breast cancer [1]. Light microscopy revealed a tumor predominantly composed of solid nests, lobular pattern, and large areas of necrosis. The tumor cells were large, with moderate to abundant cytoplasm, showed highly pleomorphic nuclei, and often prominent nucleoli (Figure 4). High numbers of mitotic figures and lymphatic tumor emboli were encountered. The tumor presented neither carcinoma in situ nor conventional-type mammary carcinoma component.

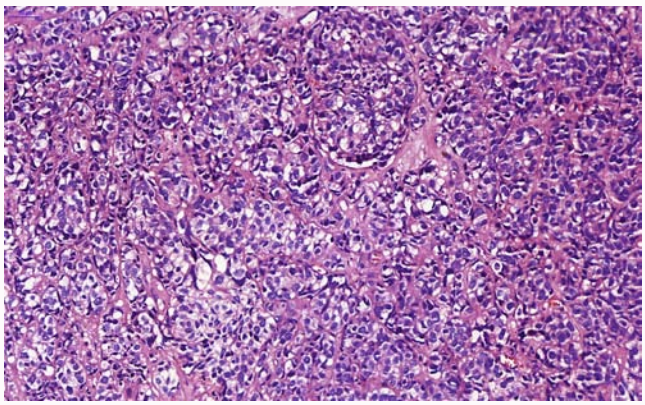

Figure 4: Large Cell Neuroendocrine Carcinoma (LCNEC) of the breast; mastectomy specimen; (H&E x200).

Metastatic disease was not detected in the axillary sentinel lymph node biopsy. Immunohistochemical analysis showed diffuse uniform staining for Cytokeratin, GATA3, Estrogen Receptor (ER), neuroendocrine markers (Synaptophysin, Chromogranin) (Figure 5a, 5b). Ki-67 proliferation index was 70%. Tumor cells were negative for ERBB2 (HER2), Progesterone Receptor (PR), and TTF1 (Thyroid Transcription Factor). The case was signed out as a large cell NEC of the breast.

Discussion

NECs of the breast show similar morphological features with their counterparts in the lung and gastrointestinal system. Accurate differentiation of metastasis of extramammary NEC to the breast from primary breast neuroendocrine cancer is very important because the treatment and prognosis of the two differ significantly. Clinical examination and/or radiological evaluation should be performed to exclude the possibility of metastasis. The presence of in situ component is evidence for primary breast carcinoma. In addition to that, it might be helpful to distinguish primary and secondary NECs utilizing a panel of site-specific lineage markers. The origination of these tumors from the breast tissue per se is supported with the positive immunohistopathologic staining for hormone (ER, PR) receptors, GATA-3, GCDFP-15, and mammaglobin. Particularly, GATA3 expression of the tumor is reported as an important indicator of NEC originating from the breast as it is not expressed in metastatic NEC cells [4]. However, current literature data is limited, and further research is needed to depict the molecular profile of the tumor and sustain targeted therapeutic strategies.

This case differs from previously reported cases in many ways. First; the patient had invasive ductal carcinoma of the same breast located in the same quadrant 5 years ago. Second, to our knowledge, there is no report in the literature describing distinctive imaging findings including elastography and diffusion-weighted MRI. In a study of 87 patients NEC was commonly characterized with high-density, round or oval, or lobular mass without spiculation on mammograms and an irregular, hypoechoic mass, with indistinct margins, with no or enhanced posterior acoustic features on US [5]. Lack of posterior acoustic shadowing was also supported by other studies [6,7]. Cystic changes on ultrasound are rarely reported [6,7]. Park et al. [6] reported that NECs are less likely to demonstrate calcifications (5). However, Wu et al. stated that calcification was not a rare finding in their study of 13 cases [6].

In this case, mammography showed that the tumor had indistinct margins without spiculations in line with the given literature data and few eccentric heterogenous calcifications were detected in the mass. However, on ultrasound, the index lesion showed a circumscribed round mass with internal septations, mimicking a benign lesion. The lack of posterior acoustic features was in line with the literature data. But the presence of cystic changes within the mass was a remarkable feature.

MR imaging of these lesions is reported as mass enhancement, irregular margins, and washout kinetics with a rim enhancement, or heterogeneous internal enhancement pattern. Early intense contrast uptake has been described in different studies [5,8-10]. In this case, the dynamic contrast enhancement features were similar. However, despite these pathognomonic features for malignancy we have observed lack of restriction of diffusion in DWI which presented

Table 1: Summary of imaging findings.

Mammography	Round mass, indistinct margins, few eccentric microcalcifications
Ultrasound	Round, circumscribed microlobulated, hypoechoic solid mass with internal septations and cystic changes
Elastography	stiff (194 kPa on shear wave elastography)
MRI	initial fast contrast uptake, washout kinetics with intralesional non-enhancing areas representing cystic-necrotic changes, no diffusion restriction (ADC value 1.512 × 10–3 mm^2/s)

*kPa: Kilopascal; ADC: Apparent Diffusion Coefficient

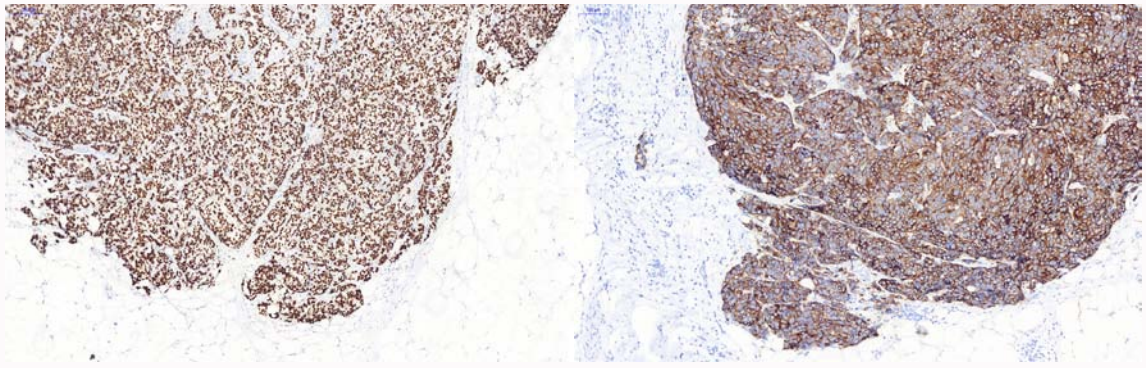

Figure 5: The carcinoma was positive for synaptophysin. (a). GATA 3. (b). (IHC x100).

with a high ADC value. No literature data could be reached about the diffusion imaging characteristics of the NEC. Lack of restricted diffusion on MRI conflicts with the stiffness detected on elastography. Satake et al. [11] studied the elastography and DWI features of 115 suspicious breast lesions. They found that the elasticity score was a significant predictive of malignancy, whereas the ADC value was not independently predictive in BIRADS 4 lesions. They suggested that sensitivity of DWI to some subtle histologic conditions such as Mucin Lake, tissue structure, necrosis, extracellular space, fibrosis and cellularity would result in different values of ADC [11].

Conclusion

Primary NEC of the breast is a very rare entity. Clinical, radiological and immunohistochemical studies are necessary for an accurate diagnosis. A previous history of infiltrating ductal carcinoma of the same breast and the presence of microcalcifications and cystic changes, lack of restricted diffusion on MRI, benign morphology on ultrasound with malignant elastography features are remarkable points in this case. The presence of both benign and malignant imaging features detected on different imaging modalities is confusing but may be discriminating in the radiologic diagnosis of this rare tumor.

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