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Case Report Primary Neuroendocrine Carcinoma of Breast

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Abstract
Introduction: Primary neuroendocrine carcinoma (PNEC) of the breast is a rare subtype of breast cancer, often diagnosed in postmenopausal women and typically associated with aggressive clinical behavior. Histological features and the immunohistochemistry expression of neuroendocrine markers constitute the basis for the diagnosis. Due to its rarity, standardized treatment protocols are lacking.
Case Presentation: We report a case of a 38-year-old premenopausal female who presented with a painless left breast mass. Imaging revealed a suspicious lesion, and core biopsy confirmed invasive mammary carcinoma with neuroendocrine differentiation. Immunohistochemistry was positive for chromogranin, synaptophysin, and NSE, confirming the diagnosis. The patient underwent neoadjuvant chemotherapy (dose-dense AC followed by Taxane), followed by breast-conserving surgery and sentinel lymph node biopsy. Due to close surgical margins, she later underwent a nipple-sparing mastectomy with implant reconstruction. Despite systemic therapy, the patient developed liver metastases with a Ki-67 index of 100%, necessitating platinum-based chemotherapy.
Conclusion: This case highlights the aggressive nature of PNEC, particularly in younger patients, and underscores the need for heightened clinical suspicion, multidisciplinary management, and further research to guide treatment strategies for this rare malignancy.

Keywords: Neuroendocrine tumor, breast carcinoma, diagnosis, immunohistochemistry, metastases

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors that include well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). These tumors can arise in various organs, most commonly in the gastrointestinal tract, pancreas, and lungs, and less frequently in the bladder, breast, larynx, prostate, and cervix (1).

Primary neuroendocrine carcinoma (PNEC) of the breast is a rare and underdiagnosed subtype of breast cancer, characterized by histological heterogeneity and diagnostic ambiguity. It primarily affects postmenopausal women in their sixth or seventh decade of life (2). PNEC accounts for less than 1% of all NENs (3) and up to 5% of breast cancer (BC) cases (4).

According to the most recent WHO classification, PNEC of the breast diagnosis is still complicated and is now reliant upon the expression of neuroendocrine markers, notably chromogranin and synaptophysin, in over 90% of tumor cells (5).

In this article, we present the case of a 38-year-old female patient diagnosed with invasive mammary carcinoma exhibiting neuroendocrine features, with a focus on clinical presentation, diagnostic workup, and differential diagnosis.

Case presentation

A 38-year-old female presented to our clinic with a painless lump in her left breast, noticed approximately three months prior to consultation. The mass had gradually increased in size without associated skin changes, nipple discharge, or systemic symptoms such as weight loss, fatigue, or fever. No previous medical history of any chronic diseases, but she had an appendectomy before. There was no significant personal or family history of breast or other cancers, no previous breast surgery, nor any allergy. She had no history of smoking.

Physical examination revealed a firm, non-tender, irregularly shaped lump in the left breast's upper outer quadrant that measured around 3 cm. Nipple retraction and involvement of the surrounding skin were absent. In the left axilla, palpable, movable lymph nodes were noticed.

Mammography and breast ultrasonography diagnostic imaging showed an oval, dense mass in the upper outer quadrant of the left breast, measuring about 3.3 × 1.3 cm, at 2 o'clock that extended toward the axilla. The lesion demonstrated surrounding architectural distortion and contained foci of calcification. There was ductal dilatation prominent on the right breast posterior to the nipple. Figure 1

The breast ultrasonography revealed a heterogeneous echotexture with posterior acoustic shadowing in both breasts, accompanied by scattered minute cysts and conspicuous ducts. In the left breast, a hypoechoic mass with calcifications was noted, associated with architectural distortion and possible extension into a dilated adjacent duct, with invasion of the underlying muscle. No anomalous lesions were seen in the right breast. Bilateral axillary lymphadenopathy was observed, with lymph nodes showing a prominent cortex and preserved fatty hilum. One lymph node in the left axilla had modest cortical thickening but retained its fatty hilum. The lesion was classified as BI-RADS 6 (biopsy-proven malignancy). An ultrasound-guided core needle biopsy was performed for histopathological evaluation. Figure 2

Histopathological examination of the core biopsy revealed features consistent with invasive mammary carcinoma exhibiting neuroendocrine differentiation. The tumor was graded as Elston and Ellis grade 3/3, with a combined score of 8/9, indicating a high-grade malignancy. Immunohistochemical staining demonstrated strong positivity for chromogranin A, synaptophysin, and neuron-specific enolase (NSE), confirming neuroendocrine differentiation. Estrogen receptor (ER) expression was weakly positive in 1% of the invasive tumor cells, while progesterone receptor (PR) expression was positive in 25% of cells, with both strong and intermediate intensities. HER2 was negative. The Ki-67 proliferation index was 25%, indicating intermediate proliferative activity. Additional markers showed scattered positivity for GATA3, while TTF-1 and GCDFP-15 were negative, helping exclude a non-mammary primary origin. MNF116 was positive, supporting epithelial origin. Figure 3

A whole-body bone scan using Technetium-99m methylene diphosphonate (Tc-99m MDP) revealed no evidence of skeletal metastases. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis showed a 6 mm lesion in the liver's segment IVB and a small, uncharacteristic lesion in segment VIII. The left liver lobe appeared elongated. Additionally, mild intrapelvic free fluid was noted. Additionally, an intrauterine contraceptive device (IUCD) had been identified on-site. The hepatitis panel was negative, indicating no evidence of active or prior hepatitis A, B, or C infection.

The patient was referred to a multidisciplinary tumor board, after which she was managed by the team and received neoadjuvant dose-dense doxorubicin and cyclophosphamide (DD-AC) followed by a taxane-based chemotherapy regimen.

A referral for breast surgery was made after the patient received four months of neoadjuvant chemotherapy. Surgical management included a left wide local excision (WLE) and sentinel lymph node biopsy (SLNBx) performed using a dual tracer technique (radioisotope and blue dye). Histopathological examination of the WLE specimen revealed residual neuroendocrine carcinoma involving the medial surgical margin, with the tumor located 1 mm from the anterior margin and 2 mm from the deep margin. The axillary dissection revealed multiple involved nodes, and the pathologic stage was reported as ypT2 ypN2a, indicating residual tumor measuring between 2 and 5 cm with metastases to 4-9 axillary lymph nodes.

Two weeks later, the patient underwent a left breast margin re-excision biopsy, which revealed residual small cell neuroendocrine carcinoma measuring 20 mm, involving deep and lateral margins, and located less than 1 mm from the medial margin. Due to persistent positive/close margins, the patient underwent left breast completion nipple-sparing mastectomy (NSM) with implant-based reconstruction three weeks later. Final histopathological examination indicated residual small cell neuroendocrine carcinoma measuring 16 mm, positioned 1 mm from the deep margin and less than 1 mm from the anterior margin, left breast superolateral margin was negative for invasive malignancy, left axillary lymph node biopsy showed that 8 lymph nodes examined, with 2 positive for metastatic neuroendocrine carcinoma (2/8) and periareolar tissue biopsy: benign breast tissue with no evidence of malignancy.

Postoperatively, the patient was started on hormonal therapy with anastrozole (Arimidex) in combination with goserelin (Zoladex) for ovarian suppression. After one month, she was switched to tamoxifen due to treatment protocol adjustment. Subsequently, the patient developed abdominal pain, persistent vomiting, and a cutaneous nodule at the surgical site, prompting further evaluation. A contrast-enhanced CT scan of the

abdomen revealed an enlarged, heterogeneous liver measuring 19 cm with an irregular contour. Multiple hypodense lesions of varying sizes were identified, consistent with hepatic metastases. An ultrasound-guided liver biopsy confirmed the presence of metastatic neuroendocrine carcinoma, with chromogranin positivity and a Ki-67 proliferation index of 100%, indicating a highly proliferative tumor. Laboratory tests showed an elevated AST level of 202 U/L. The patient was subsequently admitted for systemic chemotherapy and initiated on Cycle 1 of etoposide and cisplatin.

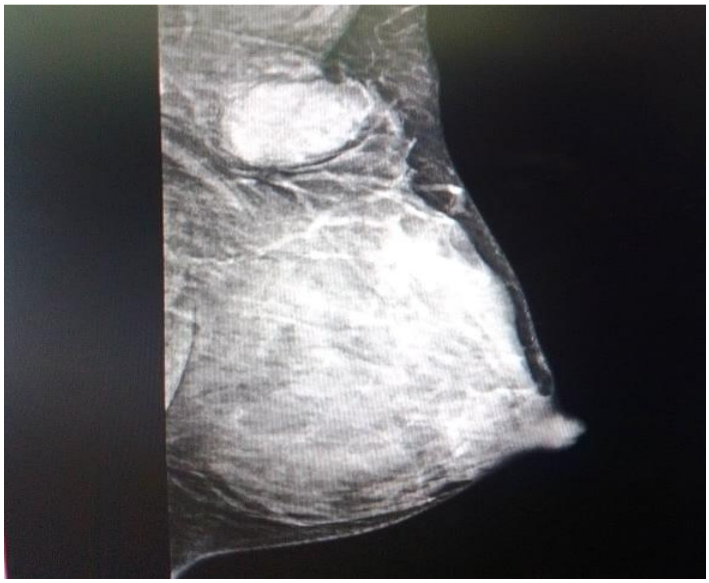

Figure 1. Mammography of the left breast: oval dense mass in the left breast upper toward the axilla measuring 3.3cm surrounding architectural distortion containing foci of calcification.

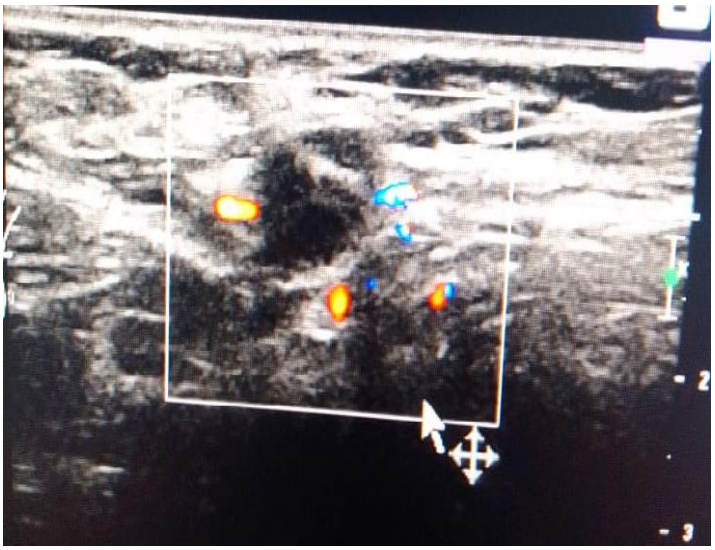

Figure 2. Left breast ultrasound: hypoechoic mass containing foci of calcification surrounding architectural distortion with possible extension into an adjacent dilated duct invading underlying muscle.

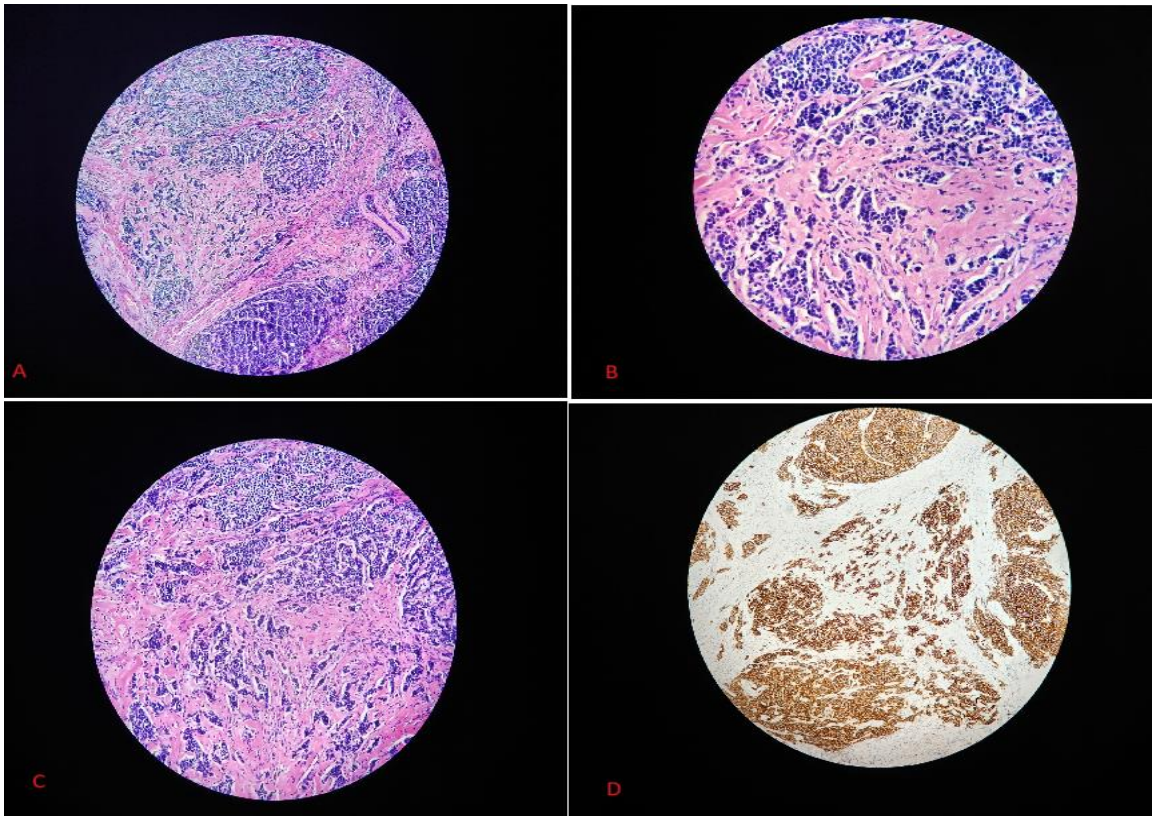

Figure 3. Brest biopsy: cores of breast tissue showing an invasive mammary carcinoma with Neuroendocrine differentiation. IHC stains showed ER weakly positive in 1%, PR positive in Strong and intermediate intensities in 25% of invasive tumor cells. Synaptophysin, chromogranin, and NSE were positive. MNF was positive.

Discussion

The uncommon subtype of breast cancer known as primary neuroendocrine carcinoma of the breast (PNEC) presents diagnostic and treatment challenges because of its histological overlap with other breast and non-mammary neoplasms. According to the WHO classification, PNEC is defined by the expression of neuroendocrine markers (chromogranin, synaptophysin) in more than 90% of tumor cells, in the absence of a non-mammary primary (5).

A palpable, painless lump in the retroareolar area is the most common clinical manifestation of PNEC of the breast (6). Additional signs may include nipple retraction, skin changes, and bloody nipple discharge (6). Notably, nipple discharge has been observed in 54.5% of cases (7), making it a potential clinical indicator of underlying PNEC of the breast. A painless lump was the sole clinical sign in this case.

The majority of documented cases of PNEC of the breast occur in postmenopausal women, usually in the sixth or seventh decade of life, making this case of a premenopausal woman in her third decade highly unusual (8-11). Premenopausal patients have been reported to account for up to 15% of primary PNEC of the breast cases (Wei et al., 2010). To the best of our knowledge, Murthy et al. (2013) remains among the few prior reports documenting PNEC of the breast in a patient within this age group (12).

The tumor in our patient exhibited small cell morphology, high-grade histology (Elston-Ellis grade 3), and a moderately elevated Ki-67 index (25%), all of which are indicative of aggressive biological behavior. According to immunohistochemistry, it was HER2-negative and hormone receptor-low (ER 1%, PR 25%), which corresponds to either a triple-negative neuroendocrine phenotype or a luminal B-like neuroendocrine phenotype, both of which are often linked to poor outcomes (13).

Despite being primarily seen in the lungs, small cell carcinomas have also been found in the stomach, small intestine, uterus, cervix, pancreas, larynx, prostate, and breast, among other extrapulmonary regions (5,14).

Distinguishing PNEC of the breast from metastatic neuroendocrine tumors is crucial, as each requires a distinct treatment strategy (2,15). Positive immunostaining for ER and PR receptors, as well as imaging characteristics including a round, oval, or lobular mass with non-spiculated margins, can support a diagnosis of PNEC of the breast (16). Additionally, immunohistochemical markers such as GATA3, mammaglobin, and GCDFP15 are typically negative in metastatic tumors (17). In the present case, ER, PR, and GATA3

were positive, supporting a diagnosis of PNEC of the breast. However, many previously documented breast PNEC patients lack these diagnostic markers (18, 19), emphasizing the difficulty in discriminating between primary and metastatic diseases.

Approximately 50% of PNEC of the breast cases are classified as having a luminal B phenotype, defined as hormone receptor-positive with a high proliferative index (Ki-67 > 14%) (20). While HER2 expression is typically negative, rare cases of HER2-positive PNEC of the breast have been reported (21). An analysis of a retrospective pathology database encompassing 84 patients with PNEC of the breast found that 98.9% were ER positive, whereas 77% were PR positive (16). Overall, PNEC of the breast tumors tend to retain hormone receptor positivity, though often at low levels.

The patient exhibited residual tumor burden at surgery and needed multiple margin excisions despite previous neoadjuvant chemotherapy with dose-dense AC and Taxane. The final pathology continued to show residual small cell NEC with lymph node involvement, warranting a nipple-sparing mastectomy (NSM). Despite the presence of close margins in prior resections, NSM with implant reconstruction was performed rather than total mastectomy, as there was no clinical or pathological evidence of nipple-areolar complex involvement. A periareolar biopsy confirmed the absence of malignancy, supporting the oncologic safety of NSM (22,23). The decision was made by the multidisciplinary tumor board, considering the patient's young age, lack of nipple involvement, and desire for breast preservation.

Although hormonal therapy was initiated postoperatively, rapid disease progression with liver metastasis was observed, underscoring the aggressive nature of high-grade neuroendocrine carcinomas (NECs). This highlights the importance of close follow-up after treatment initiation. In PNEC of the breast, the liver is one of the most frequently metastasized organs (10,24).

The metastatic lesion showed a Ki-67 index of 100%, consistent with small cell neuroendocrine carcinoma and supporting the use of etoposide-cisplatin, a regimen adapted from pulmonary small cell carcinoma protocols (25). Literature on optimal management is sparse, and most cases are treated with a combination of breast cancer protocols and extrapulmonary neuroendocrine guidelines (26).

This case underscores several key challenges including young age of presentation, high-grade, small cell variant with rapid recurrence, lack of specific guidelines for breast NECs and the need for early recognition, aggressive multimodal therapy, and possibly molecular profiling to guide targeted treatment.

To further understand the biology, best practices for therapy, and prognostic variables for this uncommon and aggressive subtype of breast cancer, more research and pooled case series are needed.

Conclusion

Primary neuroendocrine carcinoma (PNEC) of the breast is an exceptionally rare and aggressive subtype of breast cancer, often presenting significant diagnostic and therapeutic challenges. This case highlights an unusual presentation in a young, premenopausal woman with a high-grade, small cell neuroendocrine carcinoma exhibiting rapid disease progression despite aggressive multimodal therapy. Diagnosis was confirmed through immunohistochemical profiling and exclusion of a non-mammary primary. Despite an initial favorable response to neoadjuvant chemotherapy and surgical resection, early hepatic metastasis with high proliferative activity underscores the tumor's aggressive nature. This case highlights the importance of accurate histopathological diagnosis, early multidisciplinary intervention, and the necessity of customized treatment plans. Given the rarity of PNEC of the breast, further research and collaborative case series are essential to establish standardized management protocols and enhance patient outcomes.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article.

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