Hormozgan Medical Journal

doi 10.34172/hmj.8378

Hormozgan Med J. 2025;29(3):154-157

Case Report

Neuroendocrine Cancer of the Breast: The Report of a Rare but Challenging Entity

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Abstract

Background: Neuroendocrine breast cancer (NEBC) is a rare subtype of breast cancer, accounting for a very small proportion of all breast cancer cases.

Case Presentation: A 41-year-old nonsmoking woman presented with a two-month history of a right breast lump. She had no significant medical or family history of cancer. Mammography showed an abnormal mass with jagged margins located in the upper outer quadrant of the right breast. Subsequent tests with ultrasound demonstrated a complex, dark mass measuring about 2.5 × 1.8 cm, located 3 cm from her right nipple.

Conclusion: Microscopic examination of the excised tissue demonstrated a grade 3 primary neuroendocrine carcinoma of the breast. This is a serious type of cancer. Further tests showed that the cancer cells were sensitive to estrogen and progesterone hormones but negative for HER2, confirming the diagnosis of neuroendocrine breast cancer. After surgery, the patient received additional treatments such as chemotherapy, radiotherapy, and oral tamoxifen.

Keywords: Breast carcinoma, Immunohistochemistry, Neuroendocrine tumor, Rare case

Received: August 21, 2024, **Revised:** October 5, 2024, **Accepted:** October 12, 2024, **ePublished:** July 1, 2025

Background

Breast cancer represents a leading cause of mortality among women in Western societies (1,2). According to the World Health Organization (WHO), primary neuroendocrine breast cancer (NEBC) is an uncommon variant that accounts for 2-5% of all breast cancer cases (3). An epidemiological analysis of 381,644 stage I-IV breast carcinoma cases diagnosed over a six-year period revealed a prevalence of NEBC of less than 0.1% (4). NEBC was first identified as a distinct type of breast cancer by Feyrter and Hartmann in 1963 (5) and was subsequently characterized histopathologically and clinically by Cubilla and Woodruff in 1977 (6).

Neuroendocrine differentiation occurs in approximately 20% of breast carcinoma cases; however, accurate identification can be challenging due to the limited use of neuroendocrine markers in conventional breast tumor evaluation (3). The 2012 WHO Classification of Tumors of the Breast broadened the diagnostic criteria for NEBC, allowing for its diagnosis even when fewer than 50% of tumor cells express neuroendocrine biomarkers (7).

The 2019 WHO Classification of Tumors of the Breast aimed to harmonize the classification, terminology, grading criteria, and tumor-node-metastasis (TNM) staging of neuroendocrine tumors, including NEBC. NEBC was classified with neuroendocrine neoplasms (NENs) from other organ systems due to shared histological characteristics. The updated classification system introduced the umbrella term "neuroendocrine neoplasms" to describe tumors with significant neuroendocrine differentiation. These neoplasms were further classified into well-differentiated neuroendocrine tumors (NETs) or poorly differentiated neuroendocrine carcinomas (NECs), with NECs subdivided into small-cell and large-cell categories, while solid papillary carcinoma and the hypercellular variant of mucinous carcinoma were excluded from this classification. The Nottingham grading system, which assesses glandular/tubular formation, nuclear pleomorphism, and mitotic activity, was retained for grading breast NENs, with mitotic count being the primary determinant for grading assessment (8)

NEBCs typically exhibit a more aggressive clinical course than other invasive breast cancer subtypes, showing a greater risk of both local and distant recurrences (9). However, NEBCs lack distinctive clinical and radiological features, and their optimal management remains under investigation. Current research indicates that these tumors primarily occur in older women, typically in their sixties or seventies (2, 10, 11). The present case involves

a middle-aged woman diagnosed with invasive breast carcinoma displaying neuroendocrine characteristics.

Case Presentation

A 41-year-old nonsmoking woman presented with a two-month history of a lump in her right breast. She had no significant medical or family history of cancer. Upon physical examination, a palpable mass was detected at the 11 o'clock position of the right breast, without evidence of skin edema, thickening, or palpable axillary lymphadenopathy.

Mammography (Figure 1) demonstrated an irregular, spiculated mass in the upper outer quadrant of the right breast, measuring 25 mm in diameter, associated with microcalcifications. Breast ultrasonography further verified the presence of a heterogeneous hypoechoic mass measuring 25 × 18 mm located at the 11 o'clock position, approximately 3 cm from the right nipple. Routine laboratory tests, including hematology, biochemistry analyses, and liver function tests, all yielded normal results. A core needle biopsy of the right breast mass was conducted, confirming malignancy.

The patient subsequently underwent breast-conserving surgery (BCS) with sentinel lymph node biopsy (SLNB) according to National Comprehensive Cancer Network (NCCN) guidelines. Frozen section analysis of the five sentinel lymph nodes demonstrated no evidence of scattered tumor cells, suggesting the absence of lymph node involvement.

Histological analysis (Figure 2) identified a grade III primary neuroendocrine breast carcinoma according to the Nottingham grading system, with scores of 3 for tubular differentiation, 3 for notable nuclear pleomorphism, and 2 for mitotic activity, resulting in a cumulative score of 8. No necrosis was observed. The tumor appeared as a solitary focus of invasive carcinoma, with no evidence of ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), or involvement of the skin, nipple, or skeletal muscle. Surgical margins were free of invasive carcinoma, and the adjacent non-tumoral tissue exhibited fibrocystic changes with adenosis.

Lymphovascular invasion, including dermal lymphovascular invasion, was identified. A total of five sentinel lymph nodes were examined, with one positive for micrometastasis. Extranodal extension was not identified. The treatment effect in the breast was assessed as absent, as no presurgical therapy had been administered. TNM staging was PT2cN1miMx, corresponding to at least stage IIB. Cut sections revealed an ill-defined, whitish mass measuring 3.2 × 2.4 × 2.2 cm, located approximately 0.7 cm from the nearest deep margin.

Immunohistochemical analysis revealed strong

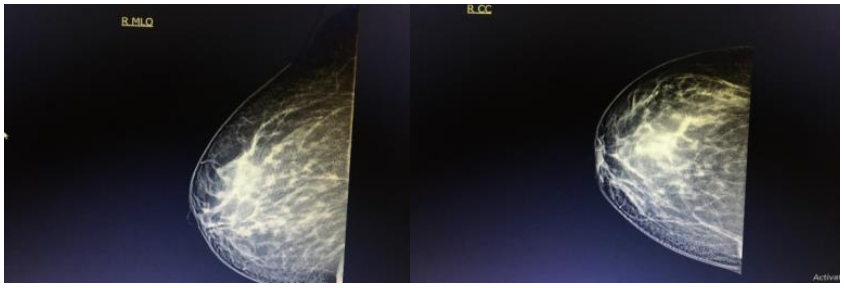

Figure 1. Mammographic Profile Showing An Opacity Above the Nipple in the Right Breast

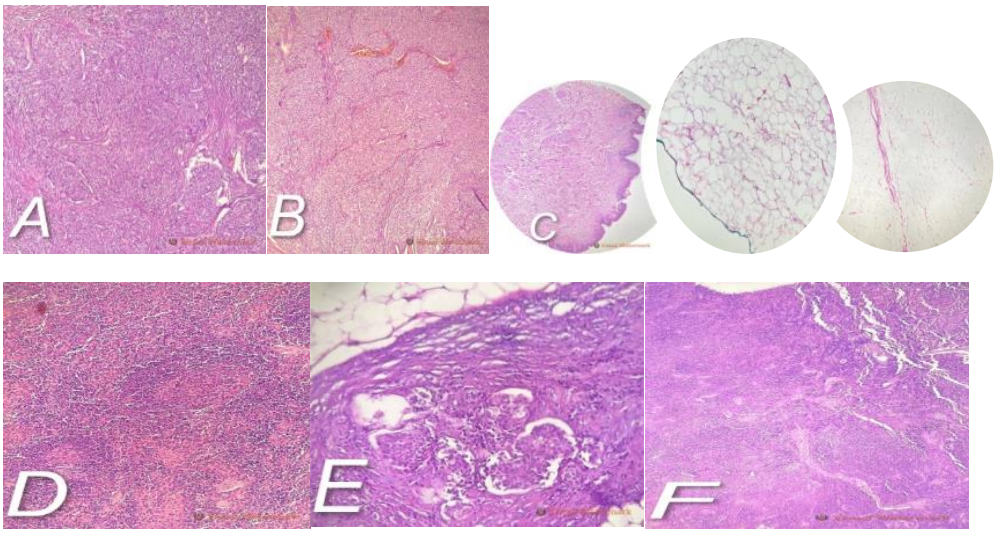

Figure 2. Pathological Findings in a Large-cells Neuroendocrine Carcinoma of the Breast: (A and B): Tumoral tissue; (C) Margins; (D, E, and F) Lymph nodes

estrogen receptor (ER) positivity in 90% of tumor cells and progesterone receptor (PR) positivity in 40% of tumor cells. HER2 expression was negative. Additionally, the tumor exhibited positive immunoreactivity for synaptophysin and chromogranin A, confirming its neuroendocrine phenotype, while CD56 expression was negative. The Ki67 proliferation index was 70%. Postoperative computed tomography revealed no evidence of metastatic disease. The patient received adjuvant chemotherapy, radiotherapy, and oral tamoxifen. Moreover, there was no evidence of recurrence six months following surgery.

Discussion

The presented case involves a patient diagnosed with invasive breast carcinoma exhibiting neuroendocrine characteristics, aligning with the 2019 WHO classification. This classification is based on the immunohistochemical expression of neuro-specific enolase (NSE) and the distinctive morphology of the tumor cells.

Although mucinous carcinoma may occasionally exhibit neuroendocrine differentiation, it generally carries a more favorable prognosis (12). Patients with mucinous carcinoma exhibiting neuroendocrine differentiation are often older and typically present with tumors of lower nuclear grades, reduced axillary lymph node involvement, elevated progesterone receptor expression, and decreased HER2 expression (13). In contrast, the case presented in this study involved a middle-aged patient with axillary lymph node micrometastases and negative HER2 status. Additionally, consistent with Park et al's observations, NEBCs are often associated with a low frequency of microcalcifications on mammography (9), aligning with the imaging findings in this patient.

Diagnosing NEBC can be difficult due to the absence of distinctive clinical features. Some histological subtypes, including hypercellular neuroendocrine carcinoma and solid-papillary carcinoma, may display neuroendocrine differentiation (9). As reported by Cloyd et al, the histological subtype of NEBC has prognostic implications, with advanced-stage tumors generally associated with unfavorable prognoses (14). Clinically, NEBCs resemble other high-grade breast carcinomas, often presenting as palpable or non-palpable masses detected through imaging modalities. Hormonal syndromes associated with NEBC are uncommon (15), although serological tests, such as chromogranin A, may aid in detecting circulating neuroendocrine markers (16).

NEBC lacks specific radiological features, necessitating a histological diagnosis based on adequate tissue samples (17). Immunohistochemical staining for neuroendocrine markers is critical to confirm the diagnosis in instances with indicative histological features. A review by Gallo et al summarized imaging features reported in multiple NEBC cases, emphasizing that the most frequent mammographic presentation is a hyperdense, irregularly shaped solitary mass with indistinct, micro-lobulated, or spiculated margins (18). Calcifications are generally uncommon in NEBC; however, in the present case, multiple microcalcifications were observed. Due to the reliance on morphological characteristics and neuroendocrine markers, a biopsy was necessary. Consequently, the patient underwent breast-conserving surgery with sentinel lymph node biopsy.

Histologically, NEBC is characterized by alveolar structures with peripheral palisading (18). Consistent with previous reports (7, 9, 11, 15), the presented case involved a luminal subtype of NEBC, showing positivity for ER and PR expression, and negativity for HER2. Tumor staging and histological grading, including mitotic counts, are critical prognostic indicators. However, the prognostic impact of neuroendocrine differentiation in breast carcinoma remains unclear, largely due to the absence of standardized diagnostic criteria (19). This uncertainty complicates the reliable evaluation of tumor aggressiveness and treatment response.

Currently, neuroendocrine differentiation in breast neoplasms does not warrant distinct therapeutic strategies, and patients are typically managed using standard treatment regimens for invasive breast cancer (20). While surgery remains the primary treatment for most breast neoplasms, individualized decisions regarding adjuvant radiotherapy and systemic therapy are essential. Anthracyclines and/or taxanes are frequently recommended as part of chemotherapy regimens (21). Breast-conserving surgery (BCS), with or without subsequent adjuvant therapy, is considered a feasible treatment option; however, mastectomy may be preferred for early-stage NETs due to their aggressive behavior (22). Consistent with these guidelines, BCS was performed on the patient in the present case.

Recent studies have explored targeted therapies for lung NEC and other breast carcinoma subtypes, which may have potential implications for NEC management. Vranic et al have identified various promising therapeutic targets, including farletuzumab, mirvetuximab soravtansine (FOLR1), sacituzumab govitecan (TROP-2), and histone deacetylase (HDAC) inhibitors (H3K36Me3). These targeted agents may provide novel treatment options for NEBC in the future.

Limitation of the Study

This case report provides valuable insights into a rare tumor diagnosis in a middle-aged patient without significant comorbidities. One drawback of this case report is the lack of detailed information concerning the management of the case within the oncology department and her response to treatment. The management of this case was challenging due to the uncommon nature of the pathology, necessitating careful consideration of

treatment options and effective communication with the patient.

Conclusion

Neuroendocrine tumors of the breast are rare and often difficult to diagnose due to the absence of unique clinical or imaging characteristics. Given the low frequency of these tumors and the scarcity of prospective clinical trial data, insights into optimal management and prognosis predominantly stem from case reports and series. This case report underscores the significance of recognizing this uncommon cancer subtype and highlights the need to address existing knowledge gaps regarding its prognosis and therapeutic approaches.

Acknowledgments

The authors would like to express their gratitude to the Clinical Research Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, for assistance with English editing.

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Competing Interests

The authors declare no conflict of interests.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approval by the Ethics Committee of Urmia University of Medical Sciences (No.: IR.UMSU.HIMAM.REC.1402.033).

Funding

This research did not receive any specific grant from the public, commercial, or not-for-profit funding agencies.

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