ACCSCIENCE PUBLISHING

Tumor Discovery

CASE REPORT

Challenges in the diagnosis and management of primary neuroendocrine carcinoma of the breast: A case report

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Abstract

Neuroendocrine carcinoma of the breast (NECB) is a rare and aggressive malignancy, accounting for <1% of all breast cancer cases. This report describes the case of a 60-year-old postmenopausal woman who presented with a painless mass in her left breast. Clinical examination and imaging revealed an irregular lesion classified as Breast Imaging Reporting and Data System V. The patient underwent breast-conserving surgery along with axillary lymph node dissection. Histopathological examination and immunohistochemistry confirmed the diagnosis of invasive neuroendocrine carcinoma (pT2N1a). The tumor cells were positive for estrogen receptor, progesterone receptor, synaptophysin, and GATA binding protein 3 but negative for human epidermal growth factor receptor 2 (HER2/neu). Adjuvant treatment included chemotherapy, radiotherapy, and hormonal therapy. This case highlights the diagnostic challenges and management strategies associated with this rare condition, emphasizing the critical role of histopathological and immunohistochemical evaluations in achieving an accurate diagnosis. Due to the rarity of NECB, treatment protocols are typically extrapolated from those used for invasive ductal carcinoma, underscoring the need for further research to establish optimal management strategies.

Keywords: Neuroendocrine neoplasm; Breast cancer; Invasive carcinoma

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1. Background

Neuroendocrine neoplasms (NENs) are epithelial tumors composed of cells that predominantly exhibit neuroendocrine (NE) differentiation. These tumors represent a rare and heterogeneous group, characterized by the presence of hormone-secreting endocrine cells and nerve cells. They can arise in various organs, including the intestines, pancreas, lungs, and breasts.[1,2] NENs of the breast are particularly uncommon, accounting for <1% of all NENs.[3] According to the fifth edition of the World Health Organization classification, breast NENs are categorized as follows: (i) cancers with over

90% NE pattern, which include neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs). NECs are further subdivided into small cell carcinomas and large cell NECs. (ii) Cancers with <90% NE pattern, which are further classified into tumors with 10–90% NE pattern (mixed invasive tumor of no special type [NST] and NET/NEC) and those with <10% NE pattern (invasive NST with a note on focal NE pattern). In addition, solid papillary carcinoma and the hypercellular variant of mucinous carcinoma are excluded from this classification.[2,4] Neuroendocrine carcinoma of the breast (NECB) is considered more aggressive than invasive ductal carcinoma (IDC), with a higher propensity for local recurrence and distant metastasis.[5] However, due to its rarity, there are no randomized controlled trials to establish standardized management strategies. Consequently, treatment protocols are generally adapted from those used for IDC.[6] This report presents a rare case of invasive NECB in a postmenopausal woman, highlighting the diagnostic process, treatment approach, and a review of current literature.

2. Case presentation

A 60-year-old female patient presented with a non-painful mass in her left breast. Clinical examination identified a hard, non-tender mass in the left lower inner quadrant, characterized by irregular margins and non-adherence to the underlying muscles or chest wall. In addition, a non-tender, firm level I left axillary lymph node was palpable. Bilateral mammography revealed an irregular, spiculated mass lesion in the lower central quadrant classified as Breast Imaging Reporting and Data System (BI-RADS) V. Sonographic evaluation demonstrated an irregular hypoechoic mass located at the 6 O'clock position of the left breast, with internal vascularity and central microcalcifications, also classified as BI-RADS V. Core needle biopsy of the breast mass revealed the presence of invasive breast carcinoma with grade 2 NE differentiation. Immunohistochemistry (IHC) analysis showed strong positive expression for estrogen receptor (ER), progesterone receptor (PR), and synaptophysin while negative for human epidermal growth factor receptor 2 (HER2)/neu. A whole-body 18-fluorodeoxyglucose positron emission tomography (PET)-computed tomography (CT) scan revealed a metabolically active, spiculated soft tissue lesion measuring 2.1 × 1.3 × 1.3 cm in the lower inner quadrant of the left breast (SUVm-5.89). In addition, mildly enlarged level I axillary lymph nodes (SUVm-3.2) were observed (Figure 1). The patient was diagnosed with carcinoma of the left breast, classified as cT2N1M0 (stage IIB).

She underwent breast-conserving surgery with axillary lymph node dissection. Histopathological analysis identified an infiltrative tumor arranged in nests, islands, and sheets, with individual cells infiltrating the surrounding stroma. The tumor cells exhibited pleomorphism, moderate eosinophilic cytoplasm, a high nuclear-to-cytoplasmic ratio, salt-and-pepper chromatin, and inconspicuous nucleoli. The stroma showed an inflammatory infiltrate composed of lymphoplasmacytic cells with mitotic activity (Figure 2). No lymphovascular or perineural invasion was observed. The tumor measured 2 × 1.8 × 2 cm, with all margins clear, and 3 out of 19 lymph nodes were positive for tumor deposits. IHC analysis revealed that the tumor cells were positive for ER and PR and negative for HER2/neu. The cells exhibited a Kiel-67 (Ki-67) proliferation index of 20% and were positive for synaptophysin and GATA binding protein 3 (GATA3) (Figure 3). The sample could not be assessed for chromogranin A or other markers for NETs, such as neuron-specific enolase and cluster of differentiation (CD) 56, due to their unavailability at the authors' institute at the time. Based on pathological and IHC findings, a diagnosis of NECB (pT2N1a) was established.

The patient received adjuvant chemotherapy, consisting of four cycles of adriamycin and cyclophosphamide, followed

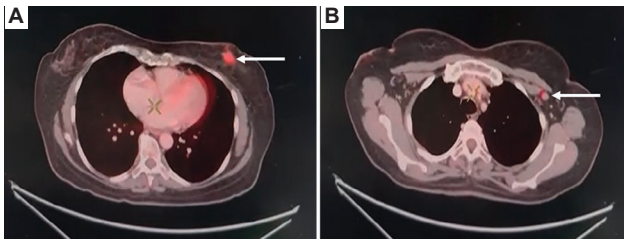

Figure 1. Whole-body 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography scan. (A) A 2.1 × 1.3 × 1.3 cm metabolically active, spiculated soft tissue lesion is observed in the lower inner quadrant of the left breast (SUVmax 5.89). (B) Enlarged left axillary level I lymph nodes with increased FDG uptake (SUVmax 3.2).

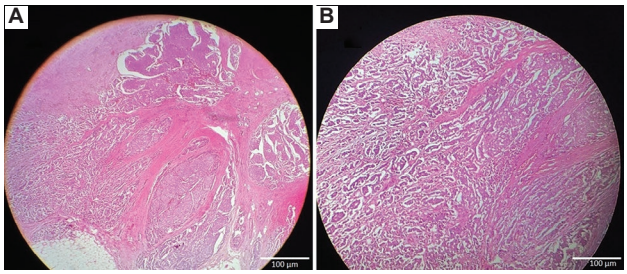

Figure 2. Histopathological examination of the tumor (hematoxylin and eosin staining). (A) Infiltrative tumor composed of nests, islands, sheets, and singly dispersed tumor cells infiltrating the adjacent stroma (40× magnification; scale bar = 100 μm). (B) Tumor cells exhibit pleomorphism, moderate eosinophilic cytoplasm, a high nuclear-to-cytoplasmic ratio, salt-and-pepper chromatin, and inconspicuous nucleoli. The stroma shows a lymphoplasmacytic inflammatory infiltrate with mitotic activity (magnification = 100×; scale bar = 100 μm).

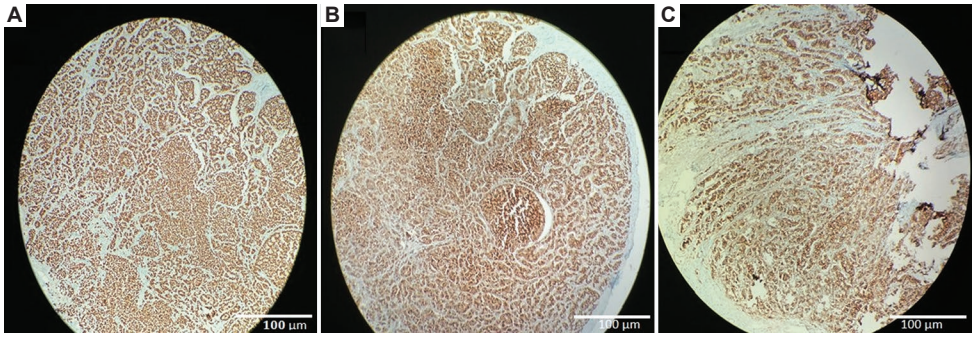

Figure 3. Immunohistochemical staining of the tumor (magnification = 100×; scale bar = 100 µm). (A) Estrogen receptor (ER) immunostaining: Tumor cells show strong and diffuse nuclear positivity for ER. (B) Progesterone receptor (PR) immunostaining: Tumor cells also exhibit nuclear positivity for PR. (C) Synaptophysin immunostaining: Tumor cells show cytoplasmic positivity for synaptophysin.

by 12 cycles of paclitaxel. She subsequently underwent adjuvant locoregional radiation therapy targeting the entire breast and left supraclavicular lymph nodes, with a total dose of 40 Gy in 15 fractions. This was followed by a boost to the lumpectomy site with an additional 12.5 Gy in five fractions. Given the hormone receptor-positive status, she was started on aromatase inhibitors (anastrozole 1 mg once daily). The patient remained disease-free at the 6-month follow-up. Considering the aggressive nature of NECB, extended surveillance is warranted. She will remain under close follow-up with clinical assessments every 3–6 months for the first 2 years, followed by annual evaluations. Imaging and additional investigations will be performed as clinically indicated.

3. Discussion

Neuroendocrine carcinoma of the breast is an uncommon and aggressive form of breast cancer, representing <1% of all cases, with reported incidence rates varying from under 0.1% to 5.4%.[2,7] According to Dasari *et al.*,[8] there has been a significant rise in the occurrence of NENs in recent decades, largely due to advancements in disease understanding, diagnostic methods, and screening processes. However, the increased incidence is particularly notable in gastrointestinal sites such as the stomach and rectum.[8] It is plausible that the incidence of breast NENs may also be rising. Nevertheless, owing to the extreme rarity of breast NENs and limited population-based data, there is currently insufficient evidence to confirm a true epidemiological trend in this subset.

We presented a 60-year-old postmenopausal woman, who falls within the age group most commonly affected by this tumor type, with peak incidence in the seventh decade.[7,9,10] The clinical and radiological characteristics of NECB are similar to IDC, making it nearly impossible to distinguish between the two based on imaging and clinical characteristics. The predominant clinical manifestations include a solitary breast lump, skin ulceration, bloody nipple discharge, skin retraction, a palpable axillary mass, and breast discomfort.[2,6,11,12] NECB is generally more aggressive than IDC, as these tumors tend to be high-grade and present at more advanced stages. They also have a higher metastatic potential, reported to range from 19% to 30%.[2,6,9,13] In our case, the clinical presentation mimicked that of IDC, with the patient presenting with a breast lump with axillary lymph node involvement. Histopathological and IHC evaluation of the core needle biopsy revealed invasive breast carcinoma with NE differentiation. Tumor cells showed strong positivity for synaptophysin, ER, and PR and were negative for HER2/neu.

The case was discussed by a multidisciplinary tumor board, and the patient subsequently underwent breast-conserving surgery along with axillary lymph node dissection. Histopathological and IHC analysis of the lumpectomy specimen confirmed NE differentiation, with strong positivity for synaptophysin, GATA3, ER, and PR, HER2/neu negativity, as well as a high Ki-67 index of 20%. Based on these characteristics, the patient was diagnosed with NECB. The diagnosis of NECB involves histopathological evaluation, which typically reveals a high-grade tumor with more than 90% NE differentiation, along with expression of immunohistochemical markers such as chromogranin, synaptophysin, neuron-specific enolase, and CD56.[1,2] These markers are generally absent in invasive breast carcinomas.[6,14] However, the diagnosis of a primary breast NEN requires exclusion of other potential primary sites.[6,15] In this case, the patient underwent a PET-CT scan before surgery to accurately stage the tumor and rule out metastatic disease from a primary NE tumor elsewhere.

Due to the rarity of this disease, no standardized management guidelines exist. Consequently, treatment strategies for localized NEBC are not based on prospective clinical trials but rather on retrospective studies and case reports. Surgical removal remains the cornerstone of

treatment for localized disease, following principles akin to those used for ductal and lobular breast cancers.[10] Our literature review revealed that anthracycline- and taxane-based chemotherapy regimens have been utilized in both adjuvant and neoadjuvant settings, with reports of partial to complete responses.[16,17] Based on these data, our patient received adjuvant chemotherapy with adriamycin/cyclophosphamide followed by paclitaxel. As with other types of breast cancer, the decision to administer adjuvant chemotherapy and/or radiotherapy following curative surgery depends on factors such as tumor size, lymph node involvement, and the presence of distant metastasis.[2,6,9,10,18]

In our case, the tumor was detected at an early stage and was hormone receptor-positive but demonstrated a high Ki-67 index. As reported in most studies, poor prognostic outcomes are typically associated with larger tumor size (>20 mm), advanced stage (stage III/IV), high Ki-67 index (>14%), and hormone receptor-negative status.[6,19] While our patient had an elevated Ki-67 index, the early-stage disease and hormone receptor positivity may confer a more favorable prognosis compared to patients with multiple adverse factors.

4. Conclusion

Primary invasive NECB is an extremely uncommon and diagnostically complex cancer that necessitates a high level of suspicion and verification through IHC analysis. Given its overlapping clinical and radiological features with more common breast cancer subtypes, definitive diagnosis relies on histopathology and the expression of NE markers. Due to the lack of prospective data, treatment strategies are generally extrapolated from standard breast cancer protocols. This case highlights the importance of multidisciplinary evaluation and individualized management for these rare entities. Further studies and case series are essential to better understand the behavior, optimal treatment, and prognostic factors of this rare tumor type.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Prabhjeet Singh Bathla, Sankalp Singh
Investigation: Surjeet K. Dwivedi, Ayjaz Hussain, Malvika Shaji
Writing- Original draft: All authors
Writing-review & editing: All authors

Ethics approval and consent to participate

Ethical approval was obtained from the Institutional Review Board of Command Hospital Air Force, Bangalore, under approval number CHAF/IRB/25/18. Written informed consent to participate was obtained from the sole participant before inclusion in the study.

Consent for publication

Written informed consent for the publication of data was obtained from the sole participant.

Availability of data

The data related to this study are available from the corresponding author upon reasonable request through email.

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