Asian Journal of Case Reports in Surgery

Volume 7, Issue 2, Page 360-366, 2024; Article no.AJCRS.118540

Primary Neuroendocrine Breast Carcinoma (NEBC): A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/118540

Case Report

Received: 25/04/2024
Accepted: 28/06/2024
Published: 06/07/2024

ABSTRACT

Primary Neuroendocrine Breast Carcinoma (NEBC) is a rare tumor with an incident rate of <0.1% of Breast Cancers and <1% of all neuroendocrine neoplasms. This case report describes a 60-year-old female patient with NEBC of the left breast with no axillary lymphadenopathy or metastasis at initial presentation. The tumor cells were positive for neuroendocrine markers, a highKi67 proliferation index and negative for ER/PR and Her2neu. Breast neuroendocrine tumors are a rare heterogenous group of tumors and further studies are needed to understand its' presentation and establish effective management strategies.

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Cite as: *Gayatri, Rangra, Singhal Basant Mohan, Kewlani Vishal, and Yadav Dev Kumar. 2024. "Primary Neuroendocrine Breast Carcinoma (NEBC): A Case Report". Asian Journal of Case Reports in Surgery 7 (2):360-66. https://journalajcrs.com/index.php/AJCRS/article/view/550.*

Keywords: Neuroendocrine neoplasms; neuroendocrine carcinoma; breast cancer; NEBC; NECB.

1. INTRODUCTION

"Neuroendocrine neoplasms (NEN) have been documented in various organs, such as the lungs, bronchi, the gastrointestinal tract and on rare occasions, the breast" [1]. Feyrter and Hartmann in 1963 for the first time identified neuroendocrine differentiation in a breast carcinoma. "Cubila and Woodruff in 1977 reported the first case of primary NEBC and gave clinical and histological classification for this rare subtype of breast cancer" [1].

The categorization of NENs primarily based on tumor grade and differentiation. NENs are categorized into neuroendocrine tumors (NET) and neuroendocrine carcinomas (NEC). NETs are well-differentiated while NECs are poorly differentiated neoplasms. Well differentiated NETs are further classified into 3 categories: low-grade (G1), intermediate-grade (G2), high grade (G3). "All poorly differentiated NECs are G3 but not all G3 NENs are poorly differentiated" [2,3].

Breast neuroendocrine neoplasms are the least common type of NENs. "The exact occurrence rate is not well established, due to the lack of routine immune-histo-chemical staining for Breast NENs, absence of uniform histological and immunohistochemical (IHC) diagnostic criteria as well as multiple changes in the WHO classification of these tumors over the past decade" [1].

"World Health Organization (WHO) classification of neuroendocrine tumours of the breast in 2003 established that, there should be immune-histo-chemical expression of one or more markers (neuron specific enolase, chromogranin A, and synaptophysin) in at least 50% of the tumour cells" [4]. "Later on, it was revised and the term changed into carcinomas with NE features in the 2012 WHO Classification of Tumours of the Breast and the 50% threshold for NE marker positivity was considered arbitrary and therefore removed. Breast neuroendocrine neoplasms were catagorized into three major groups: well differentiated NET, poorly differentiated NEBC/small cell carcinoma, and breast carcinoma with NE features determined by IHC" [5].

Again it was redefined in 2019, as tumours in which >90% of cells show histological evidence of NE differentiation, including NETs (low-grade tumours) differentiation NEC (high-grade) [2]. Breast NEN is a rare entity among neuendocrine neoplasm. Therefore, there is no consensus on the clinical significance, treatment strategy, or prognosis of Breast NENs.

Herein, we are reporting a case of Primary Neuroendocrine Breast Carcinoma (NEBC) along with a brief review the literature.

2. CASE REPORT

A 60 year old elderly female came with history of self-detected left breast lump, which for the last 2years grew progressively in size. Physical examination revealed a 5x3cm hard mass in the upper outer quadrants of the left breast, which was not adhered to the chest wall. clinically axillary lymph nodes were not palpable. The right breast and right axilla were normal. Mammography revealed a large, oval, irregular radio dense lesion in supero-medial quadrant of left breast which was BIRADS IVC (Fig. 1).

A core needle biopsy of the mass reported malignant blue round cell tumor arranged in sheets, cords, and pseudoalveolar pattern, separated by variably thick bands of fibrous tissue with coagulative tumor cell necrosis. Tumor cells had scant eosinophilic to clear cytoplasm. Salt and pepper chromatin was appreciated at many places. HPE was highly suggestive of lymphoma. A thoracoabdominal computed tomography (CT) scan ruled out any other primary disease or metastasis.

To arrive at a definitive diagnosis, Lumpectomy with adequate margins was performed. The excised specimen, on gross examination was10x5x4cm in size, homogenous grey white with necrotic centre and all margins were free of tumour by >1 cm. On HPE, it was moderately pleomorphic, with diffusely infiltrating the fibro-fatty stroma, mostly in sheets and at some places in cords and trabeculae. Cells display high N:C ratio, open chromatin, single conspicuous nucleoli, scanty cytoplasm and ill defied cell borders. At some foci, the nuclei appeared to be angulated and hyperchromatic with negligible cytoplasm. The central part of tumour showed extensive necrosis admixed with dense infiltration by lymphoid cells, mostly small to medium size with occasional large cells.. The

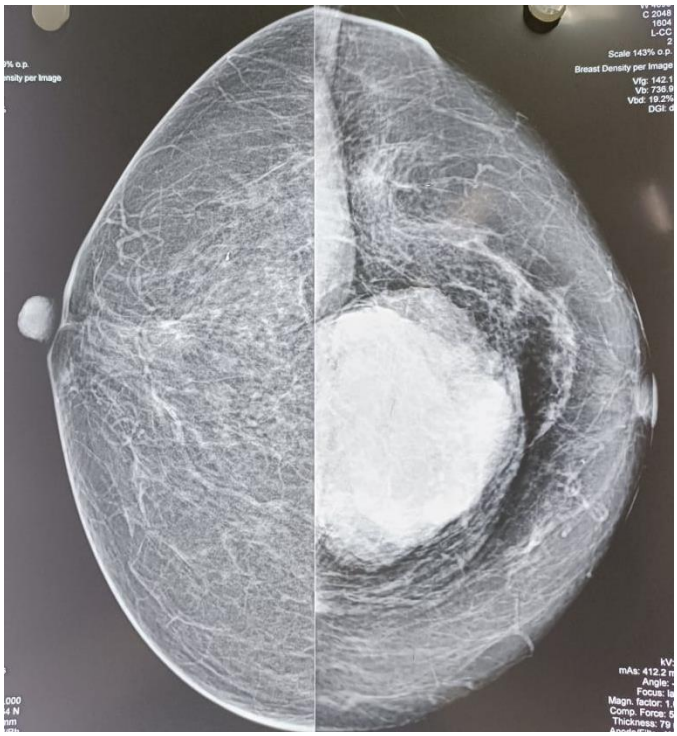

Fig. 1. Mammogram MLO view

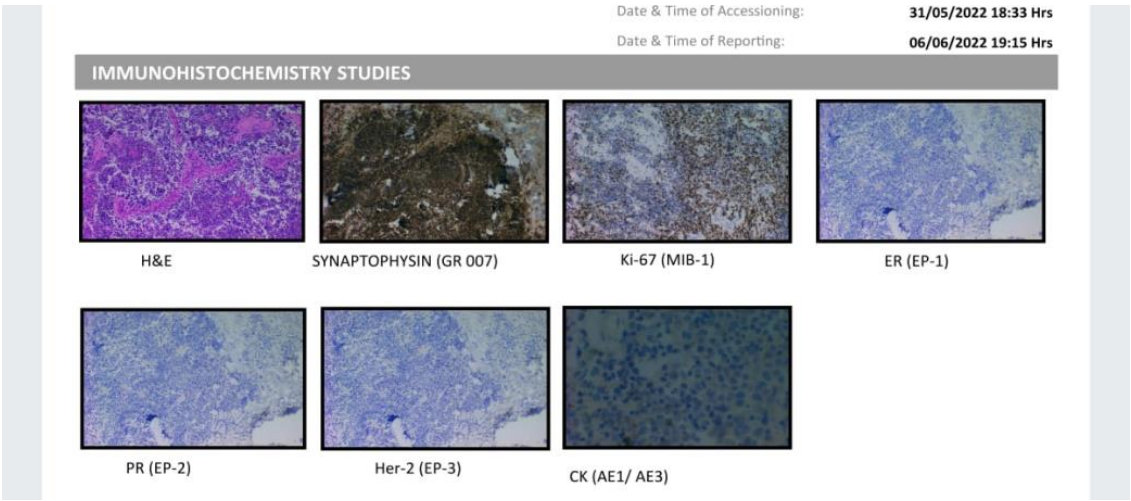

Fig. 2. Immunohistochemistry (ICH): neuroendocrine tumor of the breast

tumour cells were positive for SYNAPTOPHYSIN, CK (weak) and were negative for CK, CD45, NKX2.1, GATA3, ER, PR, HER2 and KI-67 proliferation index was 70%. Based on these histo-pathological findings the tumour was classified as a small cell neuroendocrine carcinoma of Breast (NEBC). (Fig. 2).

Final diagnosis was primary NEBC of the Left breast. Postoperatively the patient received adjuvant chemotherapy (etoposide and cisplatin) 4 cycles, which were tolerated relatively well by the patient. After 6 months the patient developed recurrence in left breast. A PET scan was done, which showed FDG avid heterogenous enhancing lesion, seen in upper inner quadrant of left breast, abutting the pectoralis major muscle-primary. Multiple enlarged lymph nodes with increased FDG uptake were seen in left axillary, subpectoral and interpectoral regions. Few mildly enlarged lymph nodes with increased

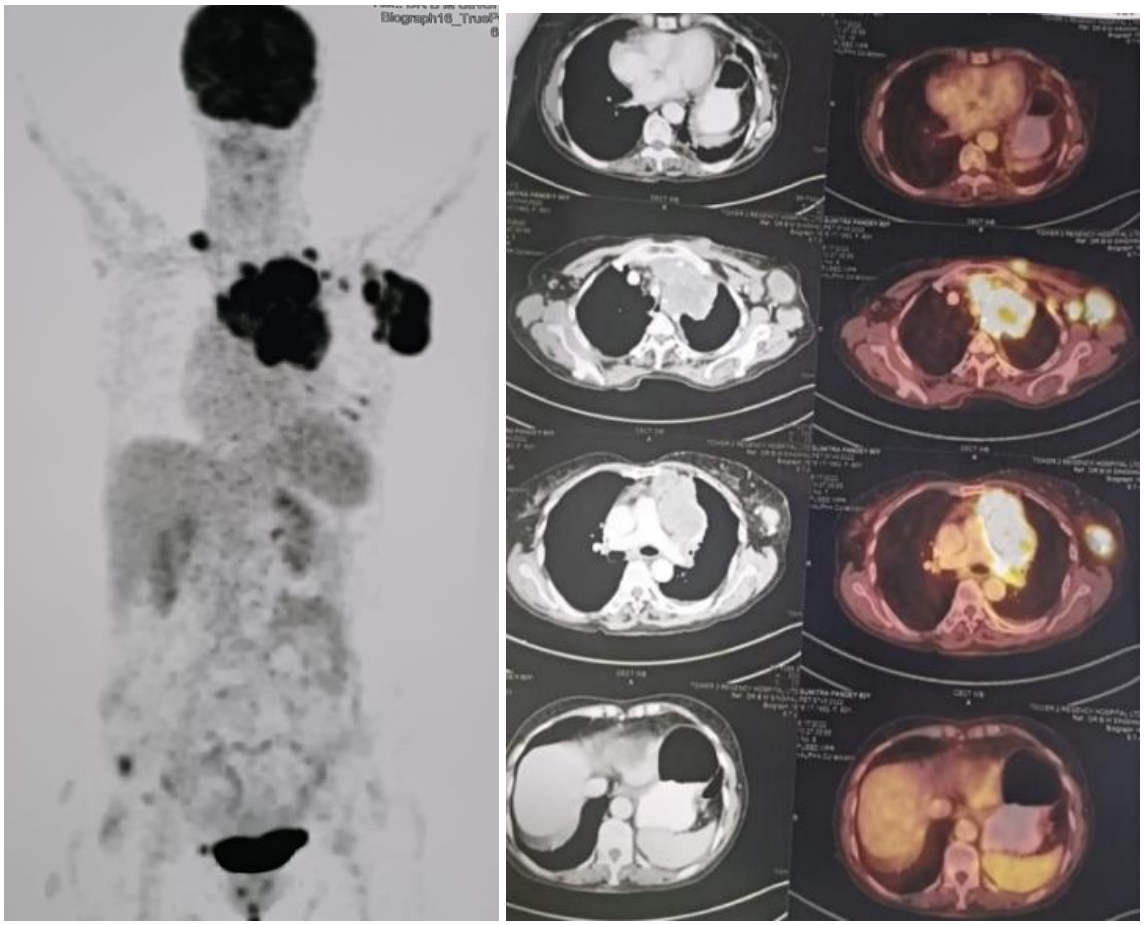

Fig. 3. FDG-PET

FDG uptake were seen in bilateral supraclavicular regions. A large heterogenous enhancing lobulated mass lesion with increased FDG uptake was seen in superior and anterior mediastinum, medially extending into AP window region, and abutting mediastinal vessels. A lytic lesion with focal increased FDG uptake was also seen in right iliac bone (Fig. 3).

Patient was referred to Medical Oncology unit for further 2nd Line chemotherapy.

3. DISCUSSION

The diagnosis of primary neuroendocrine tumors, is concluded with expression of neuroendocrine marker (Chromogranin and or synaptophysin) [6,7,8]. The WHO estimates that NEBC incidence varies between 0.3% and 0.5% [6,7,9]. Wang et al. analysed the Surveillance, Epidemiology, and End Results (SEER) registries during 2003–2009 and reported 142 cases of primary Breast NEBC, accounting for no more than 0.1% of total breast cancers, much less than the rate reported by the WHO [9]. Nevertheless, authors have used the 2003 WHO criteria in their study.

The modifications in the WHO classification criteria for Breast NEBC over the years may explain the large differences in the incidence rate between one study and another. The latest WHO diagnostic criteria for NEBC stress the obligation to exclude the probability of metastatic neuroendocrine tumours from other organ systems because ≥97% of all neuroendocrine carcinomas originate from the gastrointestinal tract or lungs. “If there is associated DIC (Ductal Carcinoma *in situ)*, it favours origin from the breast” [10].

It is believed, that small cell NEBC may be due to the specific differentiation line of mammary cancer stem cells toward the neuroendocrine/small cell type, which can occur at the in-situ stage or later (at the invasive stage), rather than the malignant transformation of specific neuroendocrine cells in the normal

breast tissue. Small cell NEBC shows an infiltrative growth pattern [6].

Neuroendocrine markers may come positive for both invasive mammary carcinoma with neuroendocrine differentiation and metastatic neuroendocrine neoplasm, thus make it difficult to differentiate histologically. In our case tumour was positive for SYNAPTOPHYSIN, CK (weak) and were negative for CD45, NKX2.1, GATA3, ER, PR, HER2, TTF-1, GCDFP-15 and Mammoglobin. “However, in previous literature Breast NENs are associated with high hormonal receptor positivity” [11-13].

The panel of site-specific lineage markers are, TTF-1 for pulmonary origin, CDX2 for gastrointestinal tract origin, PAX8/PAX6 for gastro-pancreatic and duodenal origin, and ER/PR, mammaglobin, GCDFP-15 and GATA3 for mammary origin. “These may be helpful in distinguishing metastatic neuroendocrine neoplasms (particularly well-differentiated neuroendocrine tumours) from invasive mammary carcinomas with neuroendocrine differentiation” [14]. However, in this case all markers come negative for any specific location. There are no clinical reports of Breast NEN as manifesting with clinical syndromes related to ectopic production of any hormones, such as carcinoid syndrome. Our case also did not exhibit any endocrine syndrome.

“Due to the low incidence as well as their complexity, there are few reports of specific clinical trials for Breast NENs” [8]. And there are no current guidelines at present for the management of NEBc.

“Surgery is the recommended treatment for patients with resectable NEBc, it can be a Breast conserving surgery (BCS) or mastectomy with or without adjuvant therapy” [15]. It is important to differentiate between primary NEBCs and metastatic NET from other organs to determine the optimal surgical approach. There is little reported evidence for the optimal extent of resection for primary early NEBC. “Tumour size and nodal status are also the major predictors of recurrence in patients with NEBCs. Use of radiotherapy is debatable” [16,17]. Chemotherapy is used as adjuvant therapy in high-risk patients or as neo-adjuvant in Local advance cases. “The survival benefit of adjuvant etoposide plus cisplatin or carboplatin (EP) is based on studies on SCLC as there is no exclusive data on patients with NECB” [1]. “Endocrine therapy in hormone receptor positive cases and other chemo-regimes similar to Breast Intra-ductal carcinoma- not otherwise specified (IDC-NST) can be used depending on the receptor positivity” [8,11-13]. “In Metastatic NEBC, etoposide plus platinum (Cisplatin or Carboplatin) is the standard chemotherapy regimen for palliation” [1]. Prognosis of breast cancers with NE differentiation is matter of great speculation due to rarity of these heterogeneous tumors and changing classification criteria. “Yang L et al showed 26% median survival and 53.6% five-year overall survival for NEBC, as defined according to the WHO 2019 classification, which is worse than corresponding stage or grade IDCs-NST” [9,18].

4. CONCLUSION

Neuroendocrine Neoplasm of the Breast are very rare heterogenous group of tumours and further studies of NEBC, are needed to understand their presentation and to establish effective management strategies.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/118540