Case report

Breast Neuroendocrine Neoplasms (BNEN): a case report

ABSTRACT

Primary neuroendocrine carcinoma of the breast (NECB) is a rare tumour with an incident rate of 0.3–0.5%. Breast Neuroendocrine carcinoma is rare and no treatment guidelines are present. This current case report describes a 60-year-old female patient with NECB, 5x3cm hard mass in the upper outer quadrants of the left breast with no axillary lymphadenopathy or metastasis in initial presentation. She underwent Lumpectomy and histopathological examination disclosed the diagnosis of primary breast neuroendocrine tumours with negative surgical margins. The tumour cells were positive for neuroendocrine markers, a highKi67 proliferation index and negative ER/PR and negative for Her2neu. She received adjuvant chemotherapy with cisplatin/etoposide. On follow up she showed recurrence after 6months with FDG-PET showing left breast, Multiple enlarged lymph nodes with metastasis to superior and anterior mediastinum and right iliac bone.
Conclusion: Primary breast neuroendocrine carcinoma is a rare entity; thus, no treatment guidelines exists and the prognosis remains difficult to determine. This calls for further research on BNEN.

Keywords*: Neuroendocrine carcinoma, Breast cancer, Case report, Chromogranin, Immunohistochemistry*

1. INTRODUCTION

Neuroendocrine neoplasms have been documented in various organs, such as the lungs, bronchi, the gastrointestinal tract and on rare occasions, the breast. The categorization of NENs primarily hinges on tumor grade and differentiation. NENs are categorized into neuroendocrine tumors and neuroendocrine carcinomas.[1,2] Breast neuroendocrine neoplasms are the least common type of NENs. The exact occurrence rate is not well-established due to the lack of routine immunohistochemical staining for Br-NENs, as well as multiple changes in the WHO classification of these tumors over the past decade. In 2003, the World Health Organization (WHO) classification of neuroendocrine tumours of the breast established that the immunohistochemical expression of one or more markers (neuron specific enolase, chromogranin A, and synaptophysin) in at least 50% of the tumour cells.[2] It was later revised and the term changed into carcinomas with NE features in the 2012 WHO Classification of Tumours of the Breast , with the 50% threshold for NE marker positivity considered arbitrary and therefore removed.[3] 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).

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); highgrade (G3). All poorly differentiated NECs are G3 but not all G3 NENs are poorly differentiated.

The incidence of Br-NEN is reported to range from 0.3% to 0.5%.[4,5] Therefore, there is no consensus on the clinical significance, treatment strategy, or prognosis of Br-NENs. Herein, we report a case of Breast Neuroendocrine Neoplasm and review the literature on Br-NENs.

Case presentation

60year old elderly female came with history of self-detected left breast lump in the last 2 years which 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. No axillary lymph node 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 with large left axillary node (BIRADS IVC) *(Figure 1).*

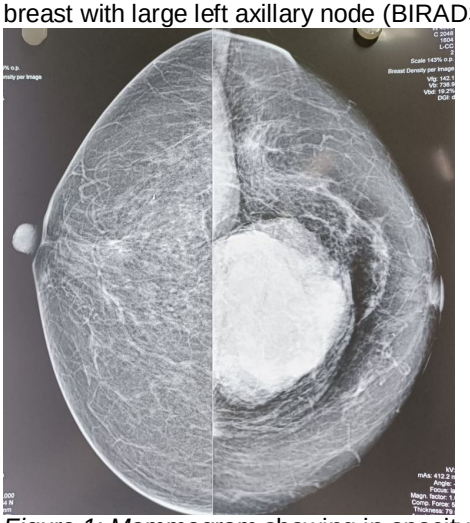

Figure 1: Mammogram showing in opacity in left breast

A core needle biopsy of the mass reported cellular 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 is seen. Tumor cells had scant eosinophilic to clear cytoplasm. Salt and pepper chromatin is appreciated at many places. A thoracoabdominal computed tomography (CT) scan ruled out any other primary disease or metastasis.
Lumpectomy with adequate margins was performed. Excised specimen, on gross examination was10x5x4cm in size, homogenous grey white with necrotic centre.
Pathological examination:
It was moderately pleomorphic, diffusely infiltrating the fibrofatty 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. *(figure 2).*
Markers
The tumour cells are positive for SYNAPTOPHYSIN, CK (weak) and were negative for CK, CD45, NKX2.1, GATA3, ER, PR, HER2.KI-67 proliferation index is 70%. Based on these histological findings the tumour was classified as a small cell neuroendocrine carcinoma of Breast

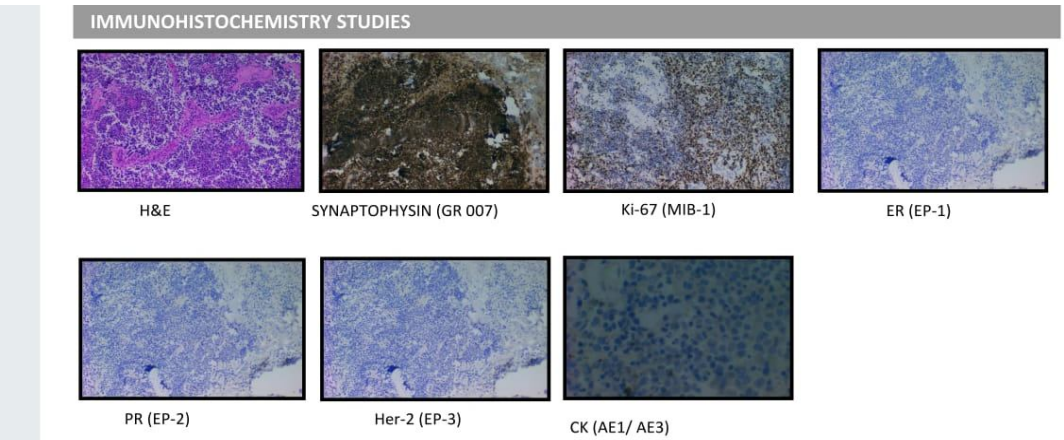

*Figure 2: Immun*ohistochemistry (ICH): neuroendocrine tumor of the breast.

Final diagnosis was primary neuroendocrine carcinoma of the right breast. Patient received adjuvant chemotherapy (etoposide and cisplatin).
Postoperatively, after 6months the patient developed recurrence and underwent PET scan 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 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 is seen in right iliac bone (*Figure 3).*

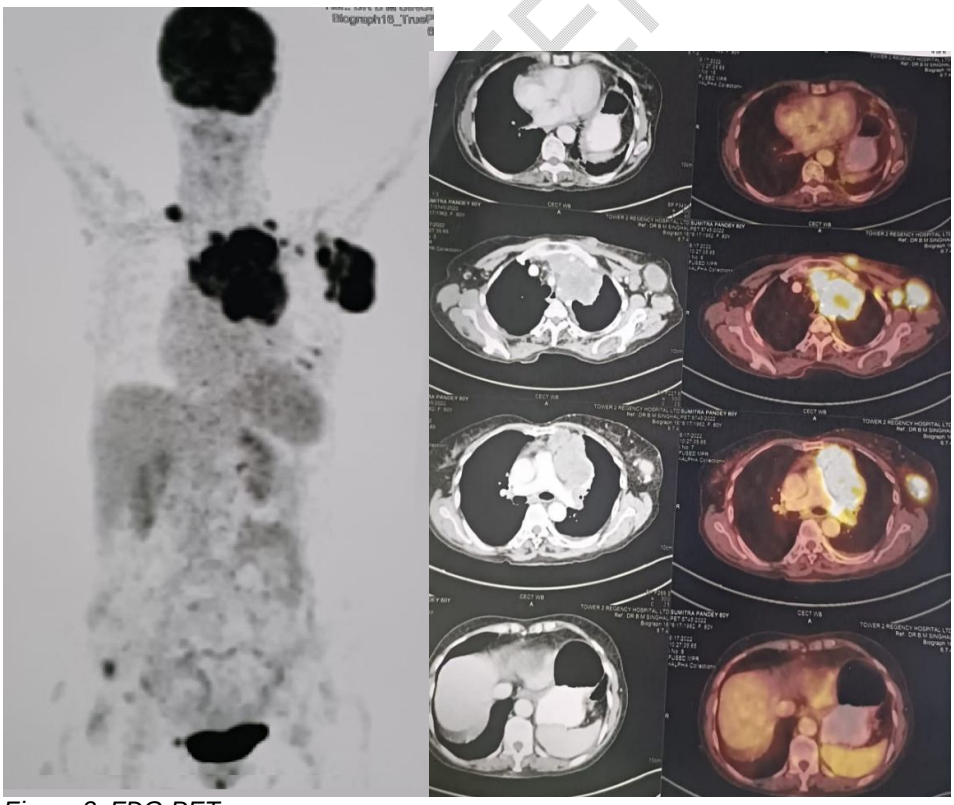

Figure 3: FDG-PET

Discussion

The WHO estimates that NECB incidence varies between 0.3% and 0.5%[6-10] Wang et al. analysed the Surveillance, Epidemiology, and End Results (SEER) registries during 2003–2009 and reported 142 cases of primary BNEN, accounting for no more than 0.1% of total breast cancers, much less than the rate reported by the WHO [9,10]. However the included 2003 WHO criteria. The relevant changes in the WHO classification criteria for BNEN over the years may explain the large differences in the incidence rate between one study and another.
The latest WHO diagnostic criteria for NECB 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. The diagnosis of primary neuroendocrine tumors is concluded with expression of neuroendocrine marker (Chromogranin and or synaptopysin) [4,5,9,11]

Histologically neuroendocrine tumours are characterized by uniform cells (round- or spindle-shaped), nuclear pallisading, abundant finely granular eosinophilic cytoplasm, and nuclei with "salt and pepper" chromatin.[6] It is thought that small cell NEC may be caused by 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 NEC shows an infiltrative growth pattern.[6] Immunohistochemistry (IHC) of breast tumours with NE differentiation usually shows a hormone receptor (HR)-positive and human epidermal growth factor type 2 (HER2)-negative profile. 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 BNENs are associated with high hormonal receptor positivity. [12,13,14,15]

The panel of site-specific lineage markers (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) may be helpful in distinguishing metastatic neuroendocrine neoplasms (particularly well-differentiated neuroendocrine tumours) from invasive mammary carcinomas with neuroendocrine differentiation.[17] However, in this case all markers come negative for all specific location, thus requiring further evaluation to determine tumour origination.
The clinical presentation of patients with Br-NENs is like IBC-NSTs. This disease is more commonly diagnosed in postmenopausal or older women.[8] There are no clinical reports of Br-NEN as manifesting with clinical syndromes related to ectopic production of any hormones, such as carcinoid syndrome. SCNECs have been reported to be diagnosed at a more advanced stage than other types of cancers, and the reported distant metastasis rate is 19–30%.[7,12,13]

Gallo et al. reported that the most common mammographic appearance was a hyperdense, irregularly shaped solitary mass without calcifications.[9] Similar imaging details can be seen in our case.
Due to the low incidence as well as their complexity, there are few reports of specific clinical trials for Br-NENs.[7] No current guidelines are present to dictate the management. Surgery is the recommended treatment for patients with respectable Br-NENs. Breast conserving surgery (BCS) with or without adjuvant therapy and mastectomy (aggressive potential at early stage of NETs).[16] It is important to differentiate between primary NENs and metastatic NE tumors from other organs to determine the optimal surgical approach. There is little reported evidence for the optimal extent of resection for primary early Br-NENs. Tumour size and nodal status are also the major predictors of recurrence in patients with Br-NENs. Use of radiotherapy is debatable. Hare et al. reported no benefit from radiotherapy in small cell carcinoma of the breast [18]. Wei et al. instead reported a benefit of adjuvant radiotherapy on survival, although not statistically significant[19]. Chemotherapy is used as adjuvant therapy in high risk patients or as neo-adjuvant in Local advance cases. Endocrine therapy in hormone recpter positive cases and other chemoregimes similar to Breast Intra-ductal carcinoma-not otherwise specified (IDC-NST)can be used depending on the recepter positivity [12,13,14,15]

Prognosis of breast cancers with NE differentiation is matter of great speculation due to rarity of these heterogeneous tumors and changing classification criteria. In the WHO 2019 classification, solid papillary carcinoma and the hypercellular-subtype mucinous carcinoma were excluded from NENs, whereas these tumors were included in the WHO 2003 and 2012 classifications.[3,4] These tumors carry a relatively better prognosis than other high-grade NENs, which could cause discrepancies in

the reported prognoses.[7] Yang L et al showed a five-year disease-specific survival rate and five-year overall survival of NEC of the breast, as defined according to the WHO 2019 classification, worse than corresponding stage or grade IDCs-NST.[18]

Conclusion

In conclusion, Breast neuroendocrine tumours are rare heterogenous group of tumours and need more studies to be better understood. This case needs to be further evaluated for its primary tumour and followed up for further recurrence. Further studies of Breast Neuroendocrine are needed to understand the presentation and establish effective management strategies.

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