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Small Cell Neuroendocrine Carcinoma of Bilateral Breasts in a Young Female - A Case Report and Literature Review

Jogamaya Pattnaik[1], Ponraj Madasamy[2], Murali Paramanandhan[3], ,, Srinivas Bh[4] Smita Kayal[5], Naresh Jadhav[6], Jagdeep Singh[7]

Senior Resident,[1,2,3,,6,7] and Associate Professor[5], Department of Medical Oncology, Associate Professor[4], Department of Pathology, RCC, JIPMER, Pondicherry

Corresponding Author: Murali Paramanandhan, Department of Medical Oncology, RCC, JIPMER, Dhanvantri Nagar, Pondicherry 605 006, Email: josh.messi19@gmail.com

ABSTRACT: Primary neuroendocrine carcinoma of breast is an extremely rare entity. According to the literature its incidence ranges from 0.3 to 0.5% of all breast cancers. As per WHO definition more than 50% of the breast cancer cells should express neuroendocrine markers to be defined as neuroendocrine carcinoma (NEC) of breast. An 18 year old female, probably one of the youngest reported till date presented with a lump in the left breast with overlying ulceration for 2 months. On examination she had an ill-defined lump and induration in the right breast. The Clinical TNM staging of right and left breast were cT3N2M0, cT4bN3M0 respectively. The biopsy from left and right breasts was suggestive of NEC, small cell variant. The metastatic work up was negative. She received 6 cycles of chemotherapy (Cisplatin and Etoposide), which resulted in clinically complete response (CR). Somatostatin receptor scintigraphy showed increased uptake in bilateral breasts breast and small subcarinal node. Prior to surgery, she developed local recurrence in left breast and axilla. The recurrent disease was inoperable and hence planned for palliative chemotherapy.She received 4 lines of chemotherapy later on and died after 15 months due to disease progression.

KEYWORDS: Carcinoma Breast, Neuroendocrine Carcinoma, Metastasis, Palliative

INTRODUCTION:

Neuroendocrine carcinomas (NEC) arise from neural crest cells. Some of them are treated like invasive breast cancer and some cases having small cell type of histology are treated like small cell carcinoma of lung. Neuroendocrine differentiation in case of infiltrating ductal carcinoma occurs in 7 to 18 percent cases and the literature is not in favor of much prognostic significance. [1,2] The most important part of the treatment decision is always to diagnose it correctly and label it as primary or secondary.

CASE SUMMARY:

An 18 year old female, presented with history of progressive increase in size of a lump in the left breast with ulceration and pain for 2 months, associated with loss of appetite and weight (loss of 4 kg in 2 months). She had attained menarche and had no family history of breast or ovarian carcinoma. Clinically a 15 x 20 cm hard lump involving the entire left breast, fixed to the skin and underlying muscles with multiple ulceration, 3cmx4cm fixed left axillary node and 2 x 2 cm left supraclavicular node. Right breast had induration of 6 x 8 cm with multiple skin nodules. The right axilla had a 4 x 6 cm hard matted node. Systemic examination was unremarkable.

The biopsy of left and right breast showed sheets of small to medium size cells with marked nuclear atypia and high mitotic figures with no evidence of in-situ ductal component. IHC was negative for LCA, pan CK, CK 7, CD 20 & GCDFP, chromogranin, CD56 with ER, PR and Her2 neu negative. NSE and Synaptophysin was positive in >50% the tumor cells. Ki67 index was 70% suggestive of small cell neuroendocrine carcinoma breast. The imaging study

in form of USG breast revealed irregular hypoechoic thickening in the right breast with multiple axillary lymph nodes with largest SAD of 2cm and the left breast showed irregular lump with subcutaneous edema and inflammatory changes. CT scan of chest and abdomen was showing heterogeneously soft tissue lesion 8.1 x 7.6 x 8.5 cm in the lower inner quadrant of the left breast infiltrating the skin and underlying muscles with bilateral axillary multiple enhancing nodes. There was no hepatic, pulmonary or osseous metastasis. Tc99 bone scan was negative for skeletal metastasis. Baseline somatostatin scintigraphy or PET scan was not done.

The TNM staging of right and left breast was T3N1M0 and T4b N3 M0 respectively. The final diagnosis was neuroendocrine carcinoma of bilateral breast was confirmed. Patient was planned for chemotherapy with Cisplatin + Etoposide. After 4 cycles of chemotherapy she had clinically partial response. Post 6 cycles of chemotherapy, clinically only a small ulceration of 2 x 2 cm was present in the left breast which gradually healed. She was planned for surgery followed by radiation. Prior to surgery, somatostatin receptor scintigraphy was done which showed increased tracer uptake in bilateral breast and mediastinal area with 15 x 17 mm lesion in right breast, 50 x 14 mm lesion in left breast and subcarinal node 27 x 14 mm. Within few days, patient developed a progressive disease in the left breast with a 8 x 8 cm lump with multiple satellite nodules and a left axillary node of 2 x 2 cm therefore was planned for second line palliative chemotherapy with single agent Gemcitabine. After 1 cycle, new skin nodules were noticed suggestive of disease progression. Third line chemotherapy Irinotecan and Carboplatin was started, but she progressed after 2 months with multiple extensive bilateral chest wall nodules. Then Temzolomide and Capecitabine as fourth line chemotherapy was started on which after 3 cycles she progressed further with left sided massive pleural effusion which was cytology positive for neuroendocrine carcinoma cells. Patient was kept on best supportive care, and finally succumbed to die after 15 months of the diagnosis.

DISCUSSION:

The Literature suggested the origin of neuroendocrine carcinoma from breast is either from neuroendocrine cells present in breast or form breast stem cells by "divergent differentiation" to give rise to both epithelial and neuroendocrine cells. [1,3] Sapino et al in 2001, defined that breast tumors expressing 50% or more of neuroendocrine markers can be considered as neuroendocrine carcinoma of breast. [4] The proper definition of neuroendocrine tumors of breast was included in 2003 WHO classification of breast tumors as a separate entity.

Most of the primary NEC breast is hormone receptor positive and HER2 negative confirming the origin from breast tissues itself. Molecular analysis of these tumors often presents a luminal type picture. [5] Morphologically NEC can be solid neuroendocrine tumors, small cell or large cell types. They express one or more of the neuroendocrine markers like synaptophysin, chromogranin or neuron specific enolase (NSE) in more than 50% of cells. Small cell variant often resembles small cell carcinoma of lungs (SCLC), but they are CK 7 positive and CK20 negative. In contrast SCLC is negative for both. [6] NEC breast needs core needle biopsies for diagnosis and cytology alone is insufficient. The incidence is 0.3%-0.5% as per the WHO definition. [7,8] The age incidence ranges between 20-83 years, majority being e"50 years. Our case is 18 year old female with a bilateral breast mass at presentation which is lesser than the data available in literature.

The 2012 WHO classified primary NEC breast into 3 categories: (a) Neuroendocrine tumor, well differentiated (Like carcinoids) (b) Neuroendocrine carcinoma, poorly differentiated / small cell carcinoma and (c) Invasive carcinoma with neuroendocrine differentiation. [9] NEC breast is classified as primary and secondary. Prognosis and management of NEC breast is different for primary

and secondary; therefore distinction between them is important. Points in favor of primary are : presence of in situ component, small tumor, hormone receptor positive, and presence of axillary lymphadenopathy and absence of disease anywhere else. [10] In our patient, biopsy of breast showed small cell NEC, IHC negative for LCA, pan CK, CK 7, CD 20 & GCDFP, chromogranin and CD 56, along with ER, PR and HER 2 neu also negative. NSE and synaptophysin was stained positive in >50% the tumor cells. We had dilemma about the disease being primary or secondary though ER, PR negativity, absence of in situ component and CK 7 and CK20 both negative were suggesting towards a secondary NEC.

The primary breast imaging modalities like mammogram, Ultrasound breast cannot distinguish between infiltrating ductal carcinoma not otherwise specified (IDC NOS) and NEC breast. FDG PET CT and somatostatin receptor scintigraphy (SRS) are important to distinguish primary from secondary NEC. In our case a baseline USG bilateral breast Contrast Enhanced Computer tomography (CECT) and Tc99 bone scan done at baseline were negative.

There are no clear cut guidelines available for treatment of NEC breast. With the available literature, it is being treated like IDC NOS with surgery, adjuvant chemotherapy and adjuvant hormone therapy or anti HER 2 agents. Chemotherapy agents tried include anthracyclines, taxane, platinum and etoposide. The decision to treat with anthracyclines based chemotherapy or platinum and etoposide has been based on the Ki-67 index. In a small series patients with higher Ki-67 (e”15%) were treated with cisplatin and etoposide and lower Ki-67 patients were treated with anthracyclines based chemotherapy. [11] In our case the Ki-67 index was 70% and hence was a high grade, and treated like a small cell variant with first line cisplatin+etoposide.

MD Anderson’s SEER data of 142 patients of NEC breast from 2003-09 shows the disease specific and overall survival is poorer compared to stage matched IDC NOS. Tumor size >2cm, higher histologic grade, and higher clinical stage confer poorer outcome. Hormone receptor (HR) negativity, higher Ki-67 (>14%) and small cell histology are associated with lower disease specific survival. [12,13] Mucin producing tumors and apocrine differentiation are associated with good prognosis. [4,14] Our case had high risk features: younger age at presentation (18 years), bilateral breast mass at presentation, higher clinical stage, small cell variant on histology, HR negative, Ki-67 -70%.

The SEER data reports suggest median survival in NEC is about 26 months. Our case was a highly aggressive disease after the patient completed 6 cycles of first line chemotherapy, there was near complete response, but progressed quickly. She received multiple lines of palliative chemotherapy , but succumbed to die after 15 months from diagnosis.

In NEC breast novel mutations like PIK3CA and VEGFR2 have been reported in tissue polymerase chain reaction-mass spectroscopy which can be targets for novel therapies in future which may help patients to live longer. [15]

FIGURES:

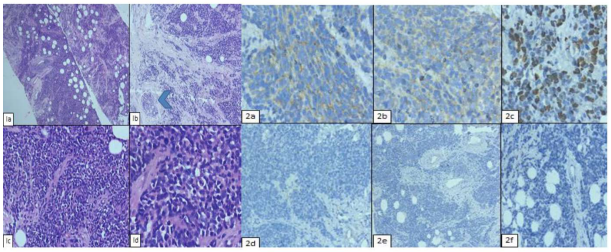

Fig 1: Photomicrographs of hematoxylin and eosin stained section demonstrating 1a. Highly cellular neoplasm (H&EX40): 1b sheets of neoplastic cells arranged around normal ducts (arrow head) (H&EX100): 1c. Shows marked degree of nuclear atypia(H&EX200): 1d. With increased mitotic figures (arrow)(H&EX400).

Fig 2: Photomicrographs of immunohistochemistry (IHC) stained section shows: positive for Neuron specific enolase, NSE (2a: IHCX400) and

synaptophysin (2b: IHCX400). Ki-67 reveals 80% tumor cells shows nuclear positivity (2c: IHCX400). Tumor cells are negative for pancytokeratin (2d: IHCX200), Leukocyte common antigen, LCA (2e: IHCX100) and Estrogen receptor (2f: IHCX200).

CONCLUSION:

NEC breast is a rare, aggressive entity and therefore very limited data exists regarding its diagnosis, classification, prognosis and management. Our case is unique in the sense the presentation was bilateral and age was 18 years; one of the youngest reported. After multiple lines of therapy the disease progressedaggressively. In future, with the development of novel therapies the prognosis of the disease may improve.

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