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Case Series

Neuroendocrine Breast Carcinoma: A Case Series

Rabeeta Sheikh, Irfan Haider, Muhammad Sohaib Nadeem*, Jawad Latif, Kiran Inam, Muhammad Fawad UL Qamar**

Department of Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Peshawar Pakistan, *Department of Oncology, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, **Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Peshawar Pakistan,

ABSTRACT

Neuroendocrine breast carcinoma (NEBC) is histologically a rare type of invasive breast cancer. It constitutes only 0.2–0.5% of all invasive breast cancers. In this case series, we are presenting five cases having primary neuroendocrine breast cancers that had been reported at a high-volume cancer centre in Pakistan. In this study, neuroendocrine breast cancer patients at Shaukat Khanum Memorial Cancer Hospital and Research Centre Peshawar were evaluated. We had retrospectively collected information on demographic characteristics of our patients, physical examination, radiological findings, surgical procedures with their outcomes, histopathological and immuno-histochemical characteristics, systemic adjuvant/neoadjuvant therapy and follow-up.

Keywords: Hypoechoic masses, Invasive breast cancer, Neuroendocrine breast carcinoma.

How to Cite This Article: *Sheikh R, Haider I, Nadeem MS, Latif J, Inam K, Qamar MFU. Neuroendocrine Breast Carcinoma: A Case Series. Pak Armed Forces Med J 2023; 73(5): 1549-1551. DOI: https://doi.org/10.51253/pafmj.v73i5.9418*

INTRODUCTION

Breast cancer is reported to be one of the major causes of cancer-related deaths among women. Neuroendocrine breast carcinoma (NEBC) is histologically a rare type of invasive breast cancer, constituting only 0.2–0.5% of all invasive breast cancers, as per the World Health Organization (WHO).[1,2] In 1963, Feyrter and Hartmann had, for the first time, mentioned NEBC. In the mid-seventies of the twen+-tieth century, Cubilla *et al*. presented a case series comprising eight cases of NEBC. They had also classified these tumours, seeing their histopathological characteristics. They also proposed diagnostic criteria for this rare group of diseases in the year 2002. NEBC, by definition, is "A carcinoma that has key features morphologically comparable to neuroendocrine neoplasms found in other tissues and organs. These tumours breed by establishing trabeculae and nests of tumour cells in the fibrovascular stroma. Palisade cells, rosettes, and solid-papillae formation can be morphologically seen". [3,4]

CASES

We are enlisting five patients diagnosed and treated by us. We had their short-term follow-up recorded. The demographic characteristics of these patients, their clinical features, histological and immune-histochemical properties, management and follow-up are summarized in Tables-I & II.

Correspondence: Dr Muhammad Sohaib Nadeem, Department of Oncology, SKMCH & RC, Peshawar Pakistan

Received: 23 Oct 2022; revision received: 29 Nov 2022; accepted: 30 Nov 2022

The median age at diagnosis was 52 years (34–56 years). The mean tumour size, which we found in the NEBC group, was 3cm. The median duration of symptoms ranged between 20 days to 12 months. X-ray mammogram image showed asymmetrical, structurally distorted breast with hyper-density masses with micro-lobulated and speculated margins. Common sonographic findings were hypoechoic masses. Tumor sizes noted in our patients were between 2-5 cm.

Regarding the receptor status, 3 out of 5 patients (60%) were hormone receptor-positive and did not over-express HER 2 neu receptors. Metastatic workup was negative for all the cases. All of them received platinum-based chemotherapy and surgery, and four received adjuvant external beam radiotherapy as well. All patients are alive with follow-up time ranging between 1-6 years with no evidence of recurrence or metastasis.

DISCUSSION

NEBCs are a rare entity of breast cancer. The first-ever case series was reported by Cubilla and Woodruff and included eight cases of primary NEBC2. Ever since there have been a few small case series,[3,4,5] or individual case reports,[6,7] about this entity. Of all invasive breast cancers, 0.27-0.51% of cases belong to the NEBC category. A median age of 63 years for NEBC patients has been mentioned by Lopez-Bonet *et al*. Most of the patients were above the age of 50 years, except one patient in mid thirties.[2] The percentage of patients who were post-menopausal was 90%. The mean age of 70 years was reported by Rovera *et al*. The age amongst

Table-I: Clinical Features of Patients with Neuroendocrine Breast Carcinoma (NEBC)

Demography			Clinical Features						Histological and Immuno-histochemical features				
Age	Gender	Month of Diagnosis	Diagnosis	Latera-lity	Family Hx	Tumor size (cm)	Axillary Nodes	Mets	Grade	Intrinsic Subtype	Ki67	Transcription Factors	Immuno-histochemistry
56	F	AUG-21	High grade neuroendocrine carcinoma of breast	RIGHT	+	1.4	2/27	Mo	G2	ER+,PR+, Her2neu-	-	GATA 3+	Synaptophysin+, INSM1+, CK7-
37	F	JUN-21	Invasive carcinoma favors high grade Neuroendocrine carcinoma	RIGHT	-	3.2	0/1	Mo	G2	ER+,PR+, Her2neu-	5%	GATA 3+	Synaptophysin+, E-cadherin+
55	F	JAN-21	Neuroendocrine tumor, WHO grade-II	RIGHT	-	2.8	0/3	Mo	G3	ER+,PR+, Her2neu-	15%	-	E-cadherin+, Synaptophysin+, INSM1+
52	F	OCT-20	High grade Neuroendocrine tumor of the breast	LEFT	-	4.5	4/34	Mo	G3	-	70%	-	Synaptophysin+, INSM1+, CD56+
34	F	JUN-16	Poorly Differentiated Neuroendocrine carcinoma	LEFT	-	4	1/3	Mo	G3	ER-,PR-, Her2neu-	50%	-	Synaptophysin+, Chromogranin+, Cytokeratin+, LCA-

Table-II: Management and Duration of follow-up of our NEBC Patients

Surgery	Radiotherapy	Hormone Therapy	Chemotherapy	Follow Up
Local wide excision and biopsy of sentinel lymph node, Completion Mastectomy (R)	No	Yes	4 cycles of docetaxel+cyclophosphamide	Alive at 01 year
Wide local excision, sentinel lymph node biopsy	Yes (5 fractions)	Yes	6 cycles of cisplatin+Etoposide	Alive at 01 year
Bilateral Modified Radical Mastectomy (B/L)	Yes (15 fractions)	Yes	4 cycles of doxorubicin+cyclophosphamide (Dose-Dense regime), 12 cycles of Taxol (80mg/m^2)	Alive at 1.5 years
Lumpectomy (B/L), sentinel lymph node biopsy	Yes (15+3 fractions)	No	Carboplatin+paclitaxel for 3 cycles followed by CMF (cyclophosphamide, methotrexate and 5-Fluorouracil) for 3 cycles	Alive at 02 years
Wide local excision, Axillary lymph node dissection	Yes (18 fractions)	No	6 cycles of cisplatin+Etoposide	Alive at 06 years

our patients ranged between 34-56 years and was analogous to previously reported cases.[3] Signs and symptoms of NEBC are analogous to invasive breast cancers without any distinguishing clinical features. The typical presenting complaint in these patients is a mass felt in some part of their breast.[6] Only one patient in the literature had breast carcinoma involving most parts of the breast with inflammatory features (T4d cancer), and similar clinical findings were present in one of our patients.

Imaging of NEBC is rarely found in case reports. If we do an ultrasound examination, the primary neuroendocrine carcinomas of the breast may appear as either a lesion with some cystic component or as solid lesions having morphologically speculated, radiating or ill-defined margins and amplified vascularity.[7] Needle-like, speculated, radiating and irregular margins were found in tumours being reported in our case series.

There are no special unique properties based on whom we can radiologically differentiate these cancers.[8] However, on a difference with common breast carcinomas, sharply circumscribed masses can be found in NEBC without any associated micro-calcifications on mammography so that it may mimic a benign tumor. Another study on invasive NEBC of the breast reported 74 cases that were found to have inferior prognosis as compared to patients of invasive carcinoma that were stage- and age-matched controls.[9] In literature, 87% of patients had survived for over ten years. NEBC has similar prognostic factors as in other invasive cancers. As proposed in a study, the lymph node status, T-stage, and mitotic count define the overall survival.[10]

Primary NEBC is a rare cancer and can be classed as a subtype of breast carcinoma. On histopathology, it has many distinctive features. Modern discoveries in molecular genetics and immunohistochemistry make its diagnosis possible. New oncological treatments, including the development of targeted therapies, have revealed that knowing the molecular biology of tumour cells is vital to treatment planning. Experts still need to agree on any single protocol of management. Due to the scarcity of evidence on treatment methods and the absence of randomized data, they are still being managed like invasive breast carcinoma. We would like to know more about its features and targets in the coming days with the advent of radiologically and histologically defined discrete features.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

RS & IH & MSN: Conception, study design, drafting the manuscript, approval of the final version to be published.

JL & KI & MFUQ: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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