

Management of primary neuroendocrine tumour of the breast

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Introduction

Primary neuroendocrine tumour (NET) of the breast is a rare entity and constitutes less than 1% of all breast cancers [1]. The World Health Organization (WHO) defined mammary neuroendocrine carcinoma (NEC) as a separate entity in 2003 and revised the term NEC in 2012 to carcinoma with neuroendocrine differentiation [2]. Unlike infiltrating duct carcinoma (IDC), clinical features, and biological behaviour of NET of the breast is not well understood. In the absence of any large series, the optimal treatment is uncertain and they are treated as other invasive tumours of the breast. Therefore, this study aimed to analyze the outcome of surgery among patients with NET of breast.

Methods

We retrospectively analysed patients with breast carcinoma who received treatment between January 2012 to December 2018 in the Departments of Surgery (unit III) and Radiation Oncology at Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh. Four female and one male patients were diagnosed and treated as primary NET of the breast. Records of patients with primary NET of breast were analysed (Table 1). Patients presenting to surgery OPD with complaints of unilateral painless gradually increasing breast lump and were investigated with bilateral sonomammography and fine-needle aspiration cytology (FNAC). NET was missed on pre-operative FNAC in four cases and they were diagnosed to have NEC on final histopathology after mastectomy. Positron emission tomography (PET) scan was done using 150 MBq of ⁶⁸Ga-DOTATATE for patients once the histological diagnosis came as NET of the breast to rule out the presence of primary elsewhere in the body.

On suspicion of the neuroendocrine tumour on histopathology, immunohistochemical markers were studied. Patients were diagnosed to have NET of the breast based upon

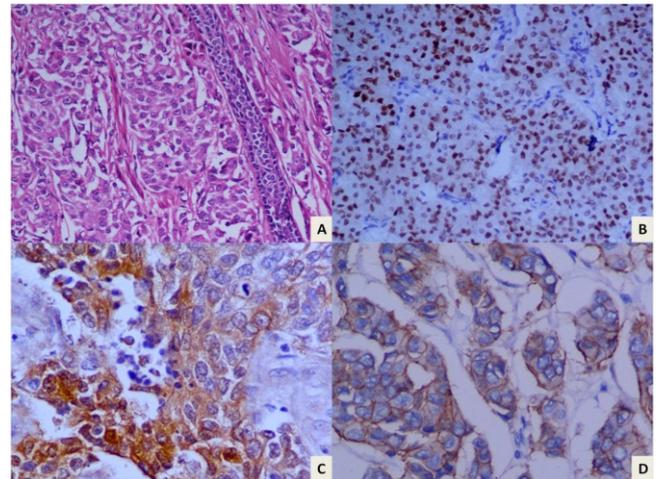


Figure 1 A: photomicrograph of the tumour showing round to oval tumour cells with monomorphic nuclei moderate amount pale eosinophilic cytoplasm. Tumour cells are arranged in clusters separated by fine fibrous septa. A benign duct is seen entrapped by the tumour cells. (H &E, X250).

Figures B, C and D. Panel of photomicrographs showing Positive immuno-histochemistry staining.

Figure 1B. Nuclear estrogen receptor positive cells.

Figure 1C. Cytoplasmic positivity for neuron specific enolase.

Figure 1D. Cytoplasmic membrane positivity for e cadherin. (Peroxidase anti-peroxidase).

WHO criteria. Immunohistochemical analysis for estrogen receptors (ER), progesterone receptors (PR), HER 2 neu was also performed (Figure 1). All patients received six cycles of chemotherapy (Cisplatin and Etoposide for 3 days, every 21 days).

Radiotherapy was given in doses of 35Gy/15#/3wks to the chest wall and 40 Gy to the supraclavicular fossa in similar fractions. Patients who were hormone receptor-positive were administered tamoxifen 20 mg or letrozole 2.5 mg once a day based on their menopausal status. Patients were followed up 3 monthly in an outpatient clinic as per department protocol.

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Table 1. Characteristics of patients with neuroendocrine tumour of the breast

Age/gender	Preoperative diagnosis	Postoperative diagnosis	Surgery	Chemo therapy	Radio therapy	Hormone Treatment	DFS (months)	OS (months)
35 / F	IDC	NET	TMAC	PE	Yes	Yes	30	30
61/ F	IDC	NET	TMAC	PE	Yes	Yes	39	39
61 / F	NET	NET	L+AC	PE	Yes	Yes	9	9
35/ F	IDC	NET	TMAC	PE	Yes	No	59	59
55/M	IDC	NET	TMAC	PE	Yes	Yes	45	45

[IDC= infiltrating ductal carcinoma, NET= neuroendocrine tumour, TMAC=total mastectomy axillary clearance, L+AC=lumpectomy and axillary clearance, P=Cisplatin, E= Etoposide, DFS=disease free survival, OS=overallsurvival]

Table 2. Pathological characteristics

Patients	Tumour Size (cm)	LN metastasis	Bone metastasis	ER (%)	PR (%)	Her 2neu	Ki 67 (%)	Neuroendocrine markers
35 F	2.5x2	Yes	Yes	+	+	-	20	Chromogranin, E-Cadherin
61 F	3x2	Yes	No	+	+	-	-	NSE and E-cadherin
61 F	2x2	Yes	No	+	+	-	-	Chromogranin, E-Cadherin
35/F	6x5	No	No	-	-	-	-	NSE and E-cadherin
55/M	3x3	Yes	No	+	+	-	30	NSE and E-cadherin

[NSE=neuron specific enolase, ER=estrogen receptor, PR=progesterone receptor, LN=lymph node]

Results

NET was diagnosed in four female (three pre and one postmenopausal) and one male patients. All patients underwent surgery and had high-grade NET on histopathology. Tumour details of the pathological examination are mentioned in Table 2. Presence of lymph node metastasis and ER, PR positivity was seen in 4 patients and all five patients were HER 2-neu negative.

On PET scan, there was no definite evidence of abnormal somatostatin receptor (SSTR) expressing lesion anywhere in the body in three patients. One patient had FDG avid lytic skeletal lesions in D8 and D 11 (SUV 3.7). Bone metastasis was confirmed by whole-body bone scan using Tc-99m MDP. PET was not performed in one patient.

Follow up

Follow up time range was from 9 to 59 months. A patient who presented with bone metastasis is having stable disease. DOTA-PET scan at 2 years was negative for any recurrent disease. She is now 39 months postoperative and doing well on follow up with no further progression of her bone lesions on follow up scan.

Discussion

Diagnosis of primary NET of the breast requires exclusion of NET at non-mammary sites and the presence of histological evidence of intraductal or in situ component [3]. It is a rare entity with a reported incidence of < 1% in postmenopausal females (97%) in the 6th-7th decade of life [1,4,5]. However, Bogina *et al* have reported neuroendocrine differentiation in 10.4% of breast carcinoma patients in a retrospective analysis of 1232 patients of breast cancer when immunohistochemistry staining was performed with synaptophysin and chromogranin A [6]. Therefore, true incidence of this disease is questionable as immunochemistry with neuroendocrine markers is not a routine for histopathological diagnosis of breast cancer. The incidence in males is even less as there are only a few case reports or small series in the literature due to the rarity of this condition.

Clinical presentation and radiological findings are similar to those of other IBC. Diagnosis of NET requires the expression of neuroendocrine markers (synaptophysin, chromogranin A). Authors suggest these markers should be checked customarily in carcinoma breast especially in mucinous and

solid papillary carcinoma to decrease the incidence of missing NET of the breast. Most NEC is estrogen and progesterone receptor-positive (92% and 69% respectively) and HER 2 neu negative (91%) [4, 5].

Tumour biology of this entity has not been studied in detail because of infrequent occurrence. Lymph node metastasis was observed in 43% and distant metastasis (liver, bones, lungs, brain and pancreas) was present in 8% [4, 5]. It is recommended that surgical management be based on tumour location and stage. The choice of chemotherapy should be based on the stage of tumour and histological differentiation. It is suggested that well-differentiated NEC should receive anthracycline and taxane-based regimens similar to conventional breast cancer, and poorly differentiated NET should receive platinum compounds and etoposide as small cell carcinoma of the lung. As the majority of these tumours are ER/PR positive; there is a definite role of endocrine treatment. Patients who received endocrine treatment had a better prognosis and longer overall survival than who did not (156 vs 50 months) [2]. Although the role of radiotherapy in this entity is questionable it was reported that patients who received radiotherapy had better results than chemotherapy although this did not reach statistical significance [4].

Neuroendocrine differentiation was an independent adverse prognostic factor for both overall and disease-specific survival ($p < 0.0001$) in a population-based study [5]. Differentiated tumours have a better prognosis than small and large cell variant which are poorly differentiated.

All authors disclose no conflict of interest. The study was conducted in accordance with the ethical standards of the relevant institutional or national ethics committee and the Helsinki Declaration of 1975, as revised in 2000.

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Learning Points:

- Primary neuroendocrine tumour (NET) of the breast is a rare entity and diagnosis requires exclusion of NET at non-mammary sites and the presence of histological evidence of intraductal or breast in situ component.
- NET is commonly observed in postmenopausal females during the 6th-7th decade of life.
- Majority of NET are estrogen and progesterone receptor-positive and HER 2 neu negative.
- Surgery with adjuvant chemo-radiotherapy and hormone treatment appears as an acceptable treatment option with satisfactory survival.