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 68 Ga-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

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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 immunohisto-chemistry 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

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

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Preoperative diagnosis</th>
<th>Postoperative diagnosis</th>
<th>Surgery</th>
<th>Chemo therapy</th>
<th>Radio therapy</th>
<th>Hormone Treatment</th>
<th>DFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 / F</td>
<td>IDC</td>
<td>NET</td>
<td>TMAC</td>
<td>PE</td>
<td>Yes</td>
<td>Yes</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>61 / F</td>
<td>IDC</td>
<td>NET</td>
<td>TMAC</td>
<td>PE</td>
<td>Yes</td>
<td>Yes</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>61 / F</td>
<td>NET</td>
<td>NET</td>
<td>L+AC</td>
<td>PE</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>35 / F</td>
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<td>NET</td>
<td>TMAC</td>
<td>PE</td>
<td>Yes</td>
<td>No</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>55 / M</td>
<td>IDC</td>
<td>NET</td>
<td>TMAC</td>
<td>PE</td>
<td>Yes</td>
<td>Yes</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

[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=overall survival]

Table 2. Pathological characteristics

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

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

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.

References


