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# Primary Neuroendocrine Carcinoma of the Breast – A Review

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**Abstract:** *Primary neuroendocrine carcinoma of the breastis a rare tumor, only a few caseshave beenreported in literature. The clinical presentation and imaging characteristics mimic invasive ductal carcinoma of the breast and hence diagnosis is often difficult.Immunohistochemistry has aided in achieving the diagnosis of this cancer. Due to the rarity of this condition no standard treatment protocols have been established.A brief review of literature on primary neuroendocrine breast carcinoma is presented.*

## 1. DISCUSSION

### 1.1. Definition

Neuroendocrine carcinoma (NEC) of the breast is a rare tumour accounting for less than 0.5% of primary breast cancers(1).It was first described in 1963 by Feyrter et al(2). PrimaryNEC of the breast is thought to arise from endocrine differentiation of a breast carcinoma rather than from pre-existing endocrine cells in the breast(3). Focal neuroendocrine differentiation can be found in different histological types of breast cancers, however the term neuroendocrine carcinoma is applied when more than 50% of the neoplastic cells express neuroendocrine markers (chromogranin A, synaptophysin andneuron-specific enolase)(4).

### 1.2. Clinical Features and Investigation

Primary NEC of the breastcommonly occur in women in their sixth and seventh decades of life(5–7). The clinical presentation of primary NEC is similar to that of other more common types of breast cancer, the most common presentation being a painless lump in the breast.Imaging in the form of mammogram and ultrasound of the breast also have been reported to have similar features to that of invasive ductal carcinoma(7).However, Park et al in a study of 74 patients with primary NEC breast found that they presented more frequently as masses on mammograms with non-spiculated margins and also calcifications were infrequent compared with their occurrence in invasive mammary cancer. They concluded that primary neuroendocrine carcinoma of the breast has mammographic features that differ from those of invasive mammary carcinoma(8). The preoperative diagnosis of NEC of the breast is based on core biopsy.

### 1.3. Pathology

The histological characteristics that suggest endocrine differentiation in a breast carcinoma are: low nuclear grade, palisading of nuclei at the periphery of tumor islands and dense sparsely cellular collagenous stroma surrounding it(6).Histologically NEC of the breast were classified into four subtypes: (i) small cell carcinoma (ii) large cell carcinoma (iii) solid neuroendocrine carcinoma and (iv)atypical carcinoid tumour(4).In 2012, WHO revised the category and divided neuroendocrine carcinomas into three subtypes: neuroendocrine tumor, well-differentiated; neuroendocrine carcinoma, poorly differentiated/small cell carcinoma; and invasive breast carcinoma with neuroendocrine differentiation(9).Solid neuroendocrine carcinoma and atypical carcinoids are considered to be well-differentiated tumours. However, small cell or oat cell carcinoma and large cell neuroendocrine carcinoma are poorly differentiated.

### 1.4. Primary Vs Secondary NEC Breast

NEC can metastasise to the breast from primaries in the lung or gastrointestinal tract. These comprise less than 1% of malignant breast lesions. They can mimic primary NET of the breast in their presentation and histopathological features(10). A good clinical history along with appropriate imaging is important to make this differentiation. The presence of an intraductal component is helpful in confirming the breast as the origin of the neuroendocrine carcinoma. Immuno-phenotyping with a panel of tissue specific antibodiesaids in thediagnosis.Primary NEC of breast are more likely to be estrogen receptor(ER)/ progesterone receptor(PR) positive and human epidermal growth factor

receptor (HER-2) negative, unlike metastatic NEC to breast, in whom ER/PR/HER-2 would be negative. A significant number of metastatic NEC are positive for tissue specific markers of the lung (TTF-1, 60%) or gastrointestinal tract (CDX-2, 100%)(10). Imaging in the form of a CT scan of the thorax and abdomen may help exclude a primary lung or GI tumour. An octreotide scan may be helpful in identifying possible other primary sites(11).

### 1.5. Bilateral Breast Carcinoma

In patients with bilateral breast carcinoma the dilemma faced isto differentiate a second primary from contralateral breast metastasis. Chaudary et al have proposed criteria to differentiate a second primary breast carcinoma from a metastatic lesion(12). These are:

1. Demonstration of insitu change in contralateral tumor. This was absolute proof of a second primary.
2. A histologically different lesion in contralateral breast.
3. The degree of histological differentiation distinctly greater than that of the lesion in first breast.
4. In absence of definite histological difference, a carcinoma in the breast was considered to be a second primary provided there was no evidence of local, regional or distant metastasis from cancer in ipsilateral breast.

### 1.6. Treatment

There is no consensus on the treatment of these tumours. Most patients have been treated in a similar manner to invasive ductal carcinoma of the breast with surgery (mastectomy or wide local excision - breast conservation surgery can be offered if technically feasible), adjuvant radiotherapy and chemotherapy. The role of radiotherapy is not well known. Similarly, the optimal chemotherapeutic regimen is also not known. Cisplatin and carboplatin have been used in some centres (based on the efficacy seen in treatment of neuroendocrine carcinomas of the lung) with some benefit(13). Others have used doxorubicin, cyclophosphamide,adriamycin, etoposide and cisplatin in various combinations(14). Patients who have ER/PR positive tumours may be given adjuvant tamoxifen.

### 1.7. Prognosis

There is contrasting literature regarding the prognosis of these tumours. Earlierreportshave shown NEC of breast to behave aggressively. Wei et al in a study of 74 patients with NEC breast have reported a five year local recurrence rate of 15%, five year distant recurrence rate of 34% and25% patients presenting with distant metastasis. Factors predicting a poorer prognosis were larger size,high grade of the tumor and axillary lymph node status(15). Wang et al, in a population based study of 142 patients with NEC of the breast showed that neuroendocrine differentiation itself was an independent adverse prognostic factor for both overall survival and disease specific survival(5). However, there are a few recent reports of patients with early small cell neuroendocrine carcinoma who have responded well to adjuvant therapy(13). Other recent reports also suggest a good prognosis for these tumours(1,16). Studies with larger numbers and long term follow up data are needed to resolve this question.

## 2. CONCLUSION

Primary neuroendocrine carcinoma of the breast is a rare disease. Clinical presentation is similar to other more common types of breast cancer and diagnosis is made on core biopsy. Majority are ER/PR positive. Their behaviour and prognosis are not well known although it is believed that they are more aggressive. In patients with bilateral breast carcinoma it is important to differentiate a second primary from a metastatic lesion as prognosis for both are very different.They are presently being treated similar to the more common types of breast cancers.The role of targeted therapy as used in other neuroendocrine tumours needs to be explored.

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