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# Case Report: A Rare Case of Primary Neuroendocrine Tumour of Breast

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**Abstract:** ***Neuroendocrine tumours of the breast can be primary or secondaries from lung, gastrointestinal tract and pancreas. Primary Neuroendocrine tumours of the breast is a rare entity. It is diagnosed by histopathology, immunohistochemistry and exclusion of primaries elsewhere by imaging. Here we report a case study of a 72 year old lady with left breast lump diagnosed as early breast carcinoma who underwent modified radical mastectomy with axillary dissection. Post operatively the histopathology revealed primary neuroendocrine tumour – mixed type.***

**Keywords:** Neuroendocrine tumours, Primary neuroendocrine tumour, breast cancer, mixed type of neuroendocrine tumours

## 1. Introduction

Neuroendocrine tumours are tumours identified by histopathology and immunohistochemistry with chromogranin, synaptophysin and neuron specific enolase staining. Primary neuroendocrine tumours have an incidence of less than 0.1 percent of invasive breast carcinoma and less than 1 percent of neuroendocrine tumours [1]. They are most common in the sixth and seventh decades of life [2]. Neuroendocrine tumours were first discovered by Feyrter and Hartmann in 1963 [3] and described as a case series by Cubila and Woodruff in 1977 [4] which provided the first descriptive study for diagnosis, investigations and management of neuroendocrine tumours.

## 2. Case Report

A 72 year old lady came with complaints of left breast lump for 3 months which was insidious in onset with gradual progression without mastalgia. She had no prior history of radiation exposure, previous surgery and intake of hormonal therapy. She attained menarche at 13 years of age with regular menstrual periods and attained menopause at 42 years of age. She had four children delivered by normal vaginal delivery. She had no significant family history.

On clinical examination 4x4 cm lump in left breast upper inner quadrant was palpable which was firm in consistency, irregular surface with ill defined margins, moving along with breast tissue and not fixed to the chest wall. There were no axillary lymph nodes palpable in the left side. The contralateral breast, axilla, neck, cranium, musculoskeletal examination were normal. The clinical Staging was T2N0Mx IIA as per AJCC 8$^{th}$ edition.

Bilateral mammogram revealed irregular lesion with spiculated margin and microcalcifications in the left upper inner quadrant. CT CHEST, ABDOMEN, BRAIN, X RAY SKELETAL SURVEY showed no evidence of metastases or primary lesion in Gastroingtestinal tract or lungs.

Preoperative core needle biopsy showed nests, cords, tubules of oval cells with eosinophilic cytoplasm, prominent nucleoli, atypical mitotic figures suggestive of INVASIVE BREAST CARCINOMA – with Immunohistochemistry of ER+ve, PR+ve, Her2neu –ve, Ki67 - 25%

As the tumour was operable early breast carcinoma Left Modified Radical Mastectomy with Axillary Dissection done. Post operatively HPE showed gross features of gray white firm tumour 4x3.2x1.5cm and microscopic appearance of salt and pepper chromatin.

| IHC MARKERS | |
|---|---|
| **ER** | **+ve** |
| **PR** | **+ve** |
| **HER2NEU** | **- ve** |
| **Ki67** | **25%** |

The histology was **Invasive Breast Carcinoma with Ductal - 5%, Neuroendocrine Differentiation - 85%, MUCINOUS - 10 %with 5%NECROSIS** and GRADE 2. All margins were free of tumour.20 lymph nodes were excised and all showed reactive hyperplasia. Perineural invasion was not identified. Nottingham prognostic index was 3.8 and pathological staging – PT2N0Mx

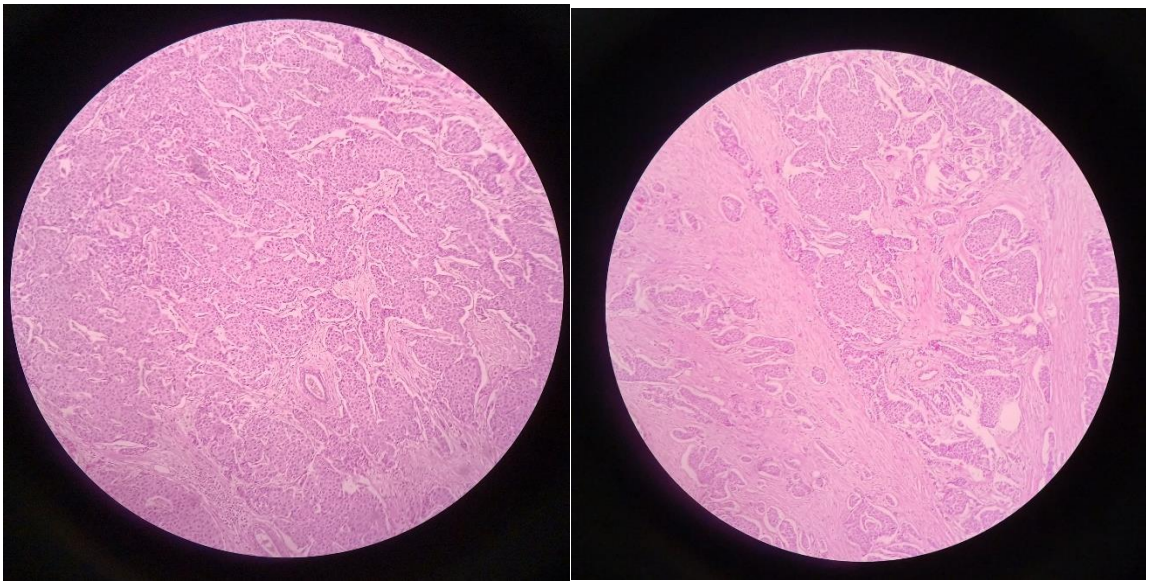


**Figure 1 and 2:** Showing Low Power Histopathological picture with nests, cords, tubules of oval cells with eosinophilic cytoplasm, prominent nucleoli, atypical mitotic figures

Post operatively Adjuvant Hormonal therapy Letrozole was started as per Institutional Tumour Board policy along with bisphosphonates and advised regular followup.

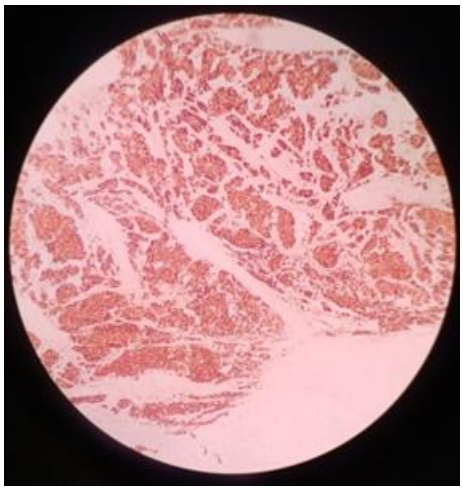
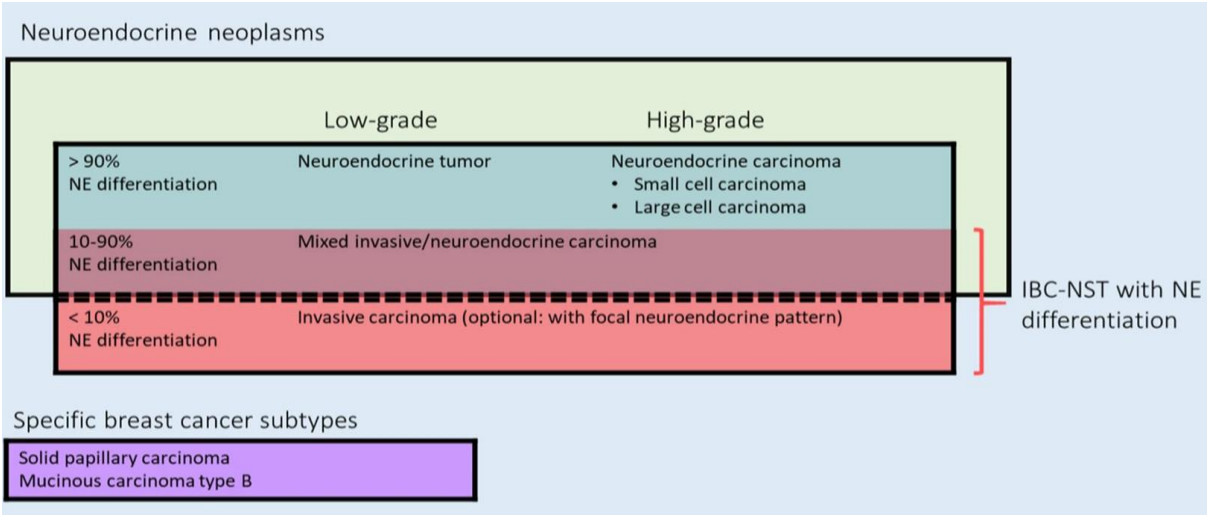


**Figure 2:** Showing Low Power ImmunoHistoChemistry picture

## 3. Discussion

Neuroendocrine tumours are tumours arising from neural crest cells. They most commonly arise from lungs, gastrointestinal tract and pancreas. WHO classification of neuroendocrine tumours of breast 3rd Edition (2003) defined neuroendocrine tumours are tumours with more than 50 percent cells staining positive of neuroendocrine markers. The histological classification of breast carcinomas shows neuroendocrine tumours under epithelial neoplasms and are further subdivided into Solid, Atypical carcinoid, Small cell carcinoma and large cell carcinoma. WHO Classification 4th Edition (2012) stated that the criteria of more than 50 percent cells staining positive with neuroendocrine markers was arbitrary. Based on the latest WHO Classification 5th Edition (2019) [5]

- <10% - Invasive Breast Carcinoma NST with focal Neuroendocrine differentiation
- **10 - 90% - mixed NE/IBC – this pt**
- >90% - NE tumour



The clinical features of neuroendocrine tumours vary based on the functioning and non functioning type of neoplasms. The non functioning type is asymptomatic and treated similar to invasive breast carcinoma. The functioning type of tumours may present with features of carcinoid syndrome such as flushing, diarrhoea, sweating and palpitations.

Radiological evaluation requires bilateral mammogram, metastatic evaluation using CT brain, chest, abdomen, xray skeletal survey/DEXA scan. Mammographic findings of neuroendocrine tumours are round/oval/lobular mass with non spiculated margins [6]. Metastatic carcinoma needs PET CT for whole body evaluation. Somatostation receptor scan GALLIUM 68 PETCT can also be taken for specific localisation but their usefulness is still being debated.

Initial histopathological evaluation done by core needle biopsy which reveals nests, cords, tubules of oval cells with eosinophilic scanty cytoplasm, prominent nucleoli, atypical mitotic figures, granular salt and pepper chromatin and necrosis [7]. Immunohistochemical staining with Neuron Specific Enolase (NSE) is positive in all types [8]whereas Chromogranin A and Synaptophysin is positive in specific types. NET of breast are most commonly ER +VE, PR+VE, Her2Neu - VE – Luminal type A

Management of primary neuroendocrine tumours of the breast is based on the stage whereas secondaries are treated palliatively. Early NET are treated with surgery followed by adjuvant chemo or radiotherapy. Locally advanced tumours require neoadjuvant chemaotherapy followed by surgery [4] [9]

Chemotherapy includes anthracyclines, taxanes and platinum compounds. Metastatic NETs are treated by palliative chemotherapy. If non responsive targeted therapy with cyclin dependent kinase 4/6 inhibitors, PI3K inhibitos, PDL1 inhibitors, multipurpose tyrosine kinase inhibitors and FGFR inhibitors can be used [10]. Somatostatin radionuclides like 90YDOTATOC, Antiangiogenic factors and monoclonal antibodies – Bevacizumab can also be given but their usage is still under trials.
Prognostic factors include Tumour grade and Ki67 for determining overall Disease Free Survival; age and ER for determining Overall survival. Ki 67>14 percent and high grade tumors denote worse prognosis [11].

This postmenopausal patient was diagnosed with early breast cancer T2N0M0 Luminal A molecular type [12]and so Modified Radical Mastectomy with axillary dissection was done. Post operatively HPE revealed primary Mixed type of neuroendocrine/invasive breast carcinoma as per WHO 5$^{th}$ Edition with IHC synaptophysin and chromogranin positive. She was advised adjuvant hormonal therapy.

## 4. Conclusion

Neuroendocrine tumours are most commonly seen as secondaries in breast whereas primary tumour is rare. The treatment differs for secondaries in breast and primary Neuroendocrine tumour and so their diagnosis is of utmost importance. The diagnosis of primary neuroendocrine tumour of the breast is mainly by histopathology and immunohistochemistry. Primary tumour if operable surgery is the mainstay of treatment followed by adjuvant hormonal therapy. Locally advanced tumours need neoadjuvant Chemotherapy followed by surgery with adjuvant chemotherapy or radiotherapy. Metastatic tumour is treated by palliative chemotherapy and targeted therapy. Other therapies such as Somatostatin radionuclides, Antiangiogenic factors, targeted therapy and monoclonal antibodies are being considered as alternative therapy. Due to paucity of cases being reported and no detailed protocol for investigation, management of primary neuroendocrine tumours of breast, there is need for further research and standardisation [13] [14] [15].

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**Conflict of Interest:** None declared

**Ethical Approval:** Not needed

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