CASE REPORT

# Neuroendocrine Carcinoma of the Breast – Real versus Mimic

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**Abstract:**

Primary neuroendocrine carcinoma of the breast is a rare entity and is difficult to differentiate from invasive ductal carcinoma with neuroendocrine differentiation especially on small core biopsy specimens. Here we present one such challenging case of a 69 years old female who presented with invasive ductal carcinoma of the breast with neuroendocrine differentiation. The biopsy specimen showed predominately invasive high grade tumor staining for neuroendocrine markers and negative cytokeratin markers, supporting a diagnosis of neuroendocrine carcinoma. Follow up mastectomy showed in situ and invasive ductal carcinoma with neuroendocrine differentiation. This case highlights the challenges of differentiating between these closely similar entities with overlapping features. Clinical history, thorough morphological examination and immunohistochemistry are needed to accurately classify these tumors as the treatment and prognosis vary significantly.

**Keywords:** Primary Neuroendocrine Carcinoma, Large Cell Neuroendocrine Carcinoma, Breast Core Biopsy vs. Excision

## Introduction:

Primary Neuroendocrine Carcinoma (PNEC) of the breast is a rare tumor of the breast representing less than 0.1% of all breast cancers and less than 1% of all neuroendocrine tumors[1]. It was described as a separate entity in 1963 [2] and formally recognized by World Health Organization (WHO) in 2003 [3]. WHO defined PNEC of the breast as having >50% neoplastic cells expressing neuroendocrine (NE) markers. Stemming from the neuroendocrine cells that are dispersed throughout the body, the neuroendocrine carcinomas commonly originate from the bronchopulmonary system and gastrointestinal tract [4]. however other organs may also be involved. Neuroendocrine origin of these tumours is confirmed with immunohistochemical positivity for Synaptophysin+, Chromogranin+, CD56+ (cluster of differentiation marker), and variable Cytokeratin (CK). Immunohistochemical tests for Estrogen and Progesterone receptors are often performed in order to confirm breast origin of the tumor & differentiate from metastasis originating from lung or gastrointestinal tract tumor.

## Case Report:

A 69 years old female with family history of breast cancer in mother (at age 65) and sister (at age 67) presented with a self palpable mass in the right breast. Mammography revealed a nodular mass with clustered micro-calcifications in the upper outer quadrant of right breast. An ultrasound guided biopsy revealed a high grade carcinoma with infiltrating nests and sheets of tumor cells showing enlarged nuclear cytoplasmic ratio, hyperchromatic nuclei and increased mitotic activity. Immunohistochemistry results were

positive for Chromogranin A, Synaptophysin and negative for CK8/18 and p63. CK5 and CK7 were predominately negative with rare staining cells. Based on these findings a diagnosis of large cell neuroendocrine carcinoma of the breast was made. Follow up mastectomy revealed invasive tumor mixed with areas of ductal carcinoma in situ (~15%). By immunohistochemical analysis, the invasive tumor stained positively for E-Cadherin; negatively for GCDFP-15, Mammaglobin and TTF-1. Prognostic marker study showed Estrogen Receptor positive (95%), Progesterone receptor positive (92%), Her- 2 IHC negative (1+ positivity), Proliferative index by Ki-67 low (0%) and p53 negative (0%). Based on above findings tumor was reclassified as invasive ductal carcinoma with neuroendocrine features, Bloom Richardson Grade 2/3.

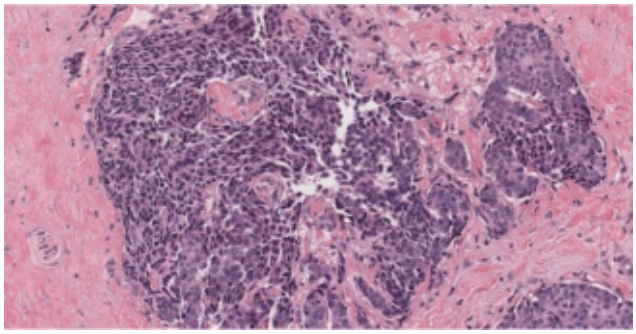

**Fig.1: H&E staining (Grade 3) of Large Cell Neuroendocrine Carcinoma of the Breast**

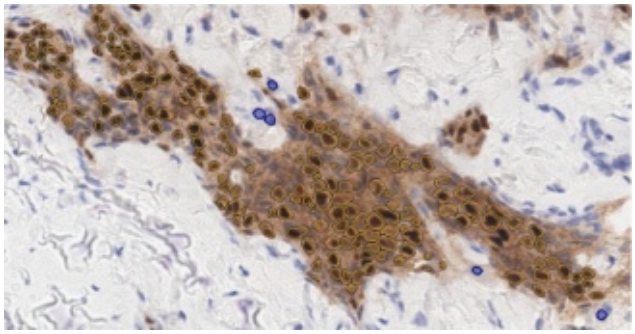

**Fig. 2: Estrogen Receptor: Positive (95%)**

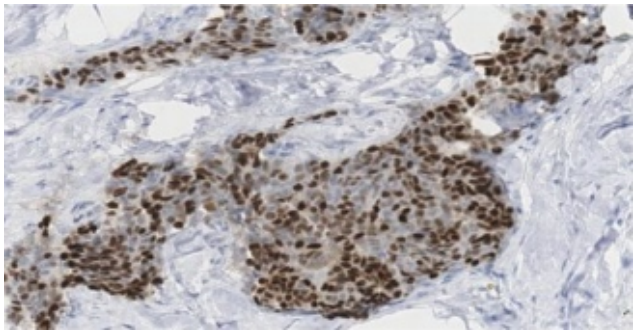

**Fig. 3: Progesterone Receptor: Positive (92%)**

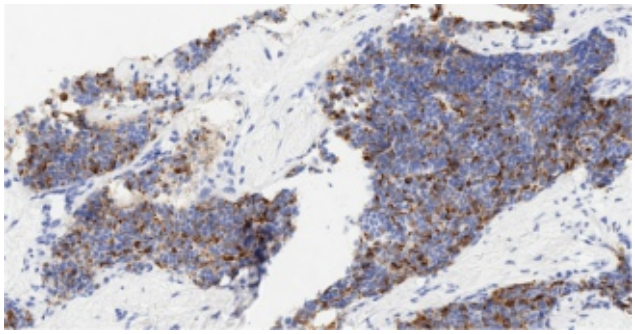

**Fig. 4: Chromogranin- A: Positive**

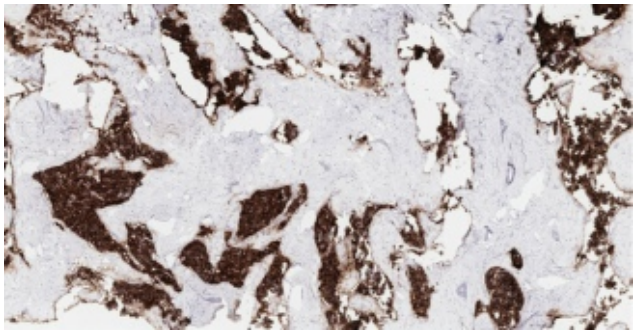

**Fig.5: Synaptophysin: Positive**

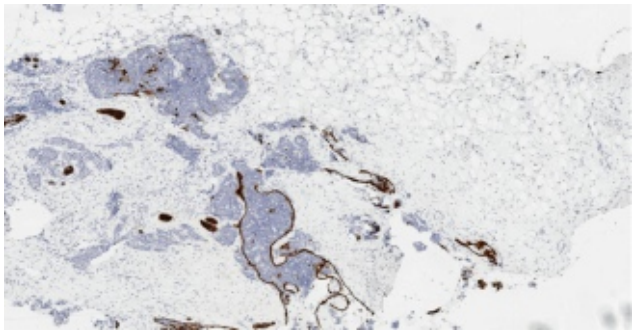

**Fig.6: Cytokeratin 7: Rare Positive Staining Cells**

**Discussion:**

Our case describes a not so uncommon situation in Pathology practice where a breast tumor exhibits specific (in this case neuroendocrine) differentiation features. The differential diagnosis is between invasive ductal carcinoma with those specific (neuroendocrine) features and primary neuroendocrine carcinoma of the breast. This situation becomes more challenging due to the small size of core biopsies available for primary diagnosis and the wide panel of stains and markers required for accurate categorization. Primary biopsy of this patient revealed a neuroendocrine carcinoma of the breast. This was supported by the absence of in situ component, positive staining of neuroendocrine markers and predominately negative cytokeratin staining. There was no history of lung mass or any other primary in this patient. However, the mastectomy specimen had larger quantity of tumor making it easier to evaluate. Also, the mastectomy specimen showed multiple foci of ductal carcinoma in situ and classical invasive ductal carcinoma (pure neuroendocrine carcinoma was <50%). Case was referred to a tertiary level hospital (Beth Israel Deaconess Medical Center, The teaching hospital of Harvard Medical School) and was confirmed as invasive ductal carcinoma with neuroendocrine features. Beth Israel Deaconess Medical Center additionally performed Cytokeratin (AE1/AE3) stain, which showed positive staining whereas CK 8/18 and CK5 were negative.

PNEC of the breast is rare and only about 30 cases have been reported to this date [5]. The WHO categorizes neuroendocrine tumors into three histological categories – 1) solid carcinoid like, 2) large cell type, and 3) small/oat cell type [3]. The neuroendocrine tumors of the breast occur most often in older women who display positivity for Estrogen Receptor [6]. diagnosis of primary neuroendocrine carcinoma of the breast is supported by the absence of an in situ component. Also important is to exclude the possibility of metastatic neuroendocrine carcinoma from the more common pulmonary or gastrointestinal sites. There is always the discrete possibility of the large cell neuroendocrine breast carcinoma to be metastatic rather than primary and computerized tomography is recommended to completely rule out the presence of an extra-mammary primary sites [7, 8].

Targeting these neuroendocrine lesions by means of immunohistochemical stains should always be done to support the diagnosis. It is a common practice to use cytokeratins (AE1/AE3, CAM 5.2 or CK7) and neuroendocrine differentiation indicators such as grimelius stain, synaptophysin, CD56, Leu 7, serotonin, bombesin and chromogranin A or B [9-12]. Small cell/oat type carcinoma shows positive staining for TTF-1 (nuclear staining) and CAM5.2 (perinuclear dots). Carcinoid is usually negative for keratin. For invasive ductal carcinoma with neuroendocrine differentiation, very helpful findings include 1) presence of in situ ductal carcinoma which can be highlighted with basal (CK5/6) and/or myoepithelial markers (p63 and SMMHC) and 2) presence of diffuse cytoplasmic cytokeratin staining. Estrogen and progesterone receptors (ER and PR) are positive in the vast majority of well-differentiated tumor cells and in >50% of poorly differentiated/ small cell carcinomas. To perform all studies on a small core biopsy specimen is difficult which may not show representative areas at all times. In such situations, it is reasonable to discuss the above-mentioned possibilities with the clinician and recommend further studies on the excision specimen.

## References


1. Ogawa H, Nishio A, Satake H, Naganawa S, Imai T, Sawaki M, et al. Neuroendocrine tumor in the breast. *Radiat Med* 2008; 26(1):28-32.
2. Feyrter F, Hartmann G. On the carcinoid growth form of the carcinoma mammae, especially the carcinoma solidum (Gelatinosum) mammae. *Frankf Z Pathol* 1963; 73:24-39.
3. Tavassoli FA, Devilee P. Pathology and genetics. In: Tumors of the Breast and Female Genital Organs. WHO Classification of Tumors Series. Lyon, France: IARC Press; 2003: 32-34.
4. Singh S1, Aggarwal G, Kataria SP, Kalra R, Duhan A, Sen R. Primary Neuroendocrine Carcinoma of Breast. *J Cytol* 2011; 28 (2): 91–92.
5. Akhtar K, Zaheer S, Ahmad SS, Hassan MJ. Primary neuroendocrine carcinoma of the breast. *Indian J Pathol Microbiol* 2009; 52:71–3.
6. Maluf HM, Koerner FC. Carcinoma of the breast with endocrine differentiation: a review. *Virchows Arch* 1994; 425:449–57.
7. Kelly C, Henderson D, Corris P: Breast lumps: rare presentation of oat cell carcinoma of lung. *J Clin Pathol* 1988; 41: 171-172.
8. Jochems L, Tjalma WAA: Primary small cell neuroendocrine tumour of the breast. *Eur J Obstetr Gynecol Rep Biol* 2004; 115:231-233.
9. Papotti M, Gherardi G, Eusebi V, Pagani A, Bussolati G: Primary oat cell (neuroendocrine) carcinoma of the breast. Report of four cases. *Virchows Arch A Pathol Anat Histopathol* 1992; 420: 103-108.
10. Rosen PP: Rosen's Breast Pathology. Philadelphia, Lippin-cott-Raven 1997:437-439.
11. Shin SJ, DeLellis RA, Rosen P. Small cell carcinoma of the breast: additional immunohistochemical studies. *Am J Surg Pathol* 2001; 25: 831-832.
12. Francois A, Chatikhine VA, Chevallier B, Ren GS, Bery M, Chevrier A, et al. Neuroendocrine primary small cell carcinoma of the breast: report of a case and review of the literature. *Am J Clin Oncol* 1995; 18: 133-138.


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