

A Rare Solid Variant of Primary Neuroendocrine Carcinoma of Breast

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Keywords: *Neuroendocrine Carcinoma; Chromogranin; Synaptophysin; Tumor.*

ABSTRACT

Solid Primary Neuroendocrine Carcinoma of Breast (NECB) is an extremely rare tumor of breast. Much less is known about it because of only few reported cases. Immunohistochemical examination showing expression of chromogranin and/or synaptophysin in more than 50% of cell population confirms evidence of neuroendocrine carcinoma. Here, we describe a case of 70-years old patient with brief review of clinopathological features, treatment and prognosis of solid NECB. Microscopy Solid islands of tumor cells are separated by fibrovascular stroma. Tumor cells are round to oval, polygonal with finely granular (stippled) nuclear chromatin with eosinophilic cytoplasm and immunohistochemistry reveal strong and cytoplasmic positivity for synaptophysin in >50% tumor cell population.

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Introduction

Primary Neuroendocrine Carcinoma of Breast (NECB) is a rare tumor, which was first recognized by Feyrter et al in 1963¹, one of the earliest cases was presented by Cubilla and Woodruff in 1977². Morphological similarities are evident between NECB and neuroendocrine carcinoma of the lung and gastrointestinal tract. Less than 5% of all cancers arising from breast are of primary neuroendocrine type³. Formal criteria for NECB were established by The WHO in 2003. In 2012³, WHO revised the category and divided neuroendocrine carcinomas into three subtypes: 1) neuroendocrine tumor, well-differentiated; 2) neuroendocrine carcinoma, poorly differentiated/small cell carcinoma; and 3) invasive breast carcinoma with neuroendocrine differentiation. Solid NECB is one of the types of NECB. Here we report a case in a 70 year old female, where most of the areas were having solid type of neuroendocrine differentiation on tissue section with intraductal component suggesting its origin as primary NEC in breast.

Case Report

A 70 year old female patient was admitted in hospital for complain of left sided breast swelling for 5 months. Swelling was gradually increased in size up to present size and was associated with pain. On examination single, hard, slightly mobile lump approximately 2x2cm in size was present in upper and outer quadrant of left breast. It was neither fixed nor associated with nipple retraction or skin changes. USG was done, showing approximately 2.5x2cm hypoechoic mass/lesion with increased vascularity in upper and outer quadrant of left breast. Opposite side of breast was unremarkable. USG suggested possibility of malignant mass/lesion in left breast. Complete preoperative work up was done and Left sided modified Radical Mastectomy was performed.

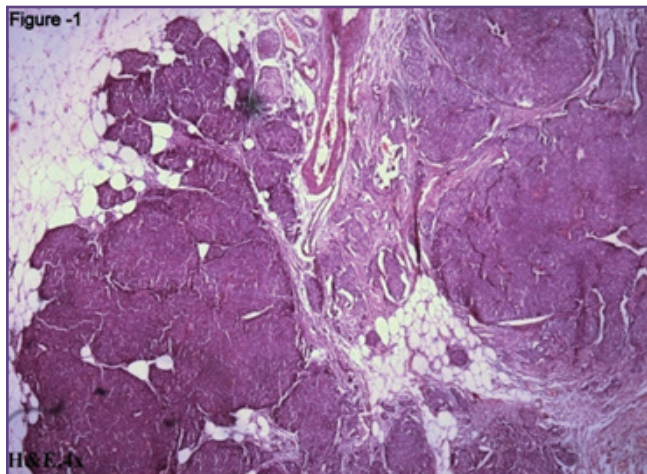


Fig. 1: solid islands and nests associated with foci of intraductal carcinoma (H&E stain, 4X)

Gross examination: Specimen consisted of left sided modified radical mastectomy. Total specimen measured 17x15x3cm. Skin flap measured 16x12cm. Axillary tail measured 8x6x2cm. Single whitish infiltrative mass was present in upper outer quadrant measuring 2.5x2x2 cm. Distance of tumor from base was 5mm. rest of the breast was unremarkable. Total 16 lymphnodes were identified and dissected.

Microscopic examination: Sections from tumor showed invasive carcinoma with solid islands and nests associated with foci of intraductal carcinoma [Fig 1]. Solid islands of tumor cells are separated by fibrovascular stroma [Fig 2]. Tumor cells are round to oval, polygonal with finely granular (stippled) nuclear chromatin with eosinophilic cytoplasm [Fig 3]. Some tumor cells show plasmacytoid and spindle appearance along with pseudorosette formation.[Fig 4]. Intracellular and extracellular mucin is present. Focal necrosis & mitoses (<2/10 HPF) are also present. Vascular invasion is present. Perineural invasion is absent. Out of 16 dissected lymphnodes one lymphnode shows evidence of metastatic carcinoma.

IHC studies were performed on 4- μ m thick, formalin-fixed, paraffin-embedded tissue sections by standard avidin –biotin technique with synaptophysin. Appropriate positive and negative control samples were used. IHC studies showed strong and diffuse cytoplasmic positivity in >50% of cell population [Fig 5], which confirmed the diagnosis of primary neuroendocrine carcinoma.

The full radiological (CT scan & MRI) workup was done to rule out primary tumour elsewhere but they were unremarkable. So, final diagnosis of primary neuroendocrine carcinoma of breast was made. As radiological findings were unremarkable further IHC workup was not done.

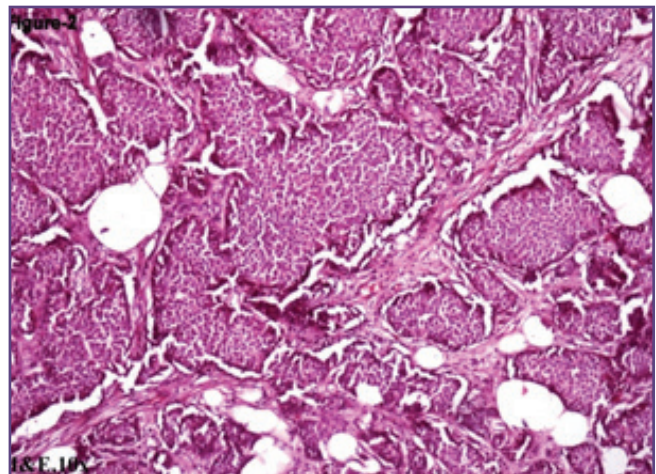


Fig. 2: Solid islands of tumor cells are separated by fibrovascular stroma (H&E stain, 10X)

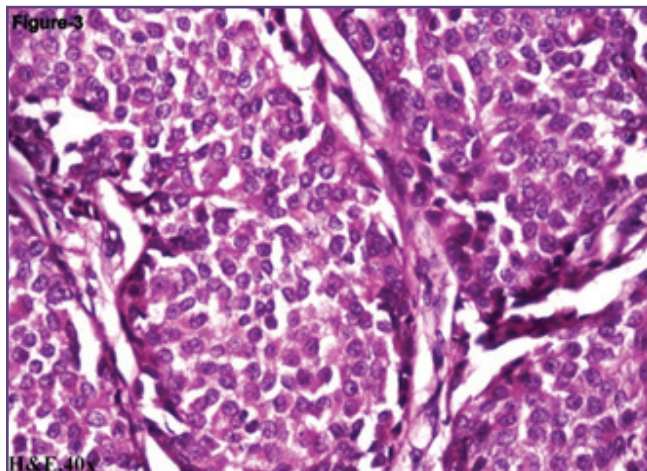


Fig. 3: Tumor cells are round to oval, polygonal with finely granular (stippled) nuclear chromatin with eosinophilic cytoplasm (H&E stain, 40X)

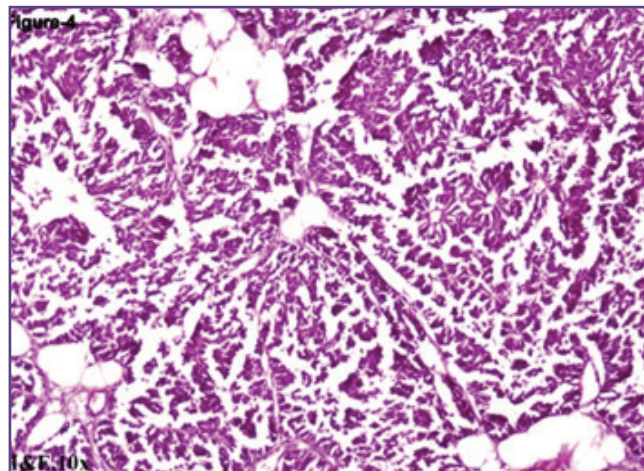


Fig. 4: tumor cells show plasmacytoid and spindle appearance along with pseudorosette formation. (H&E stain, 10X)

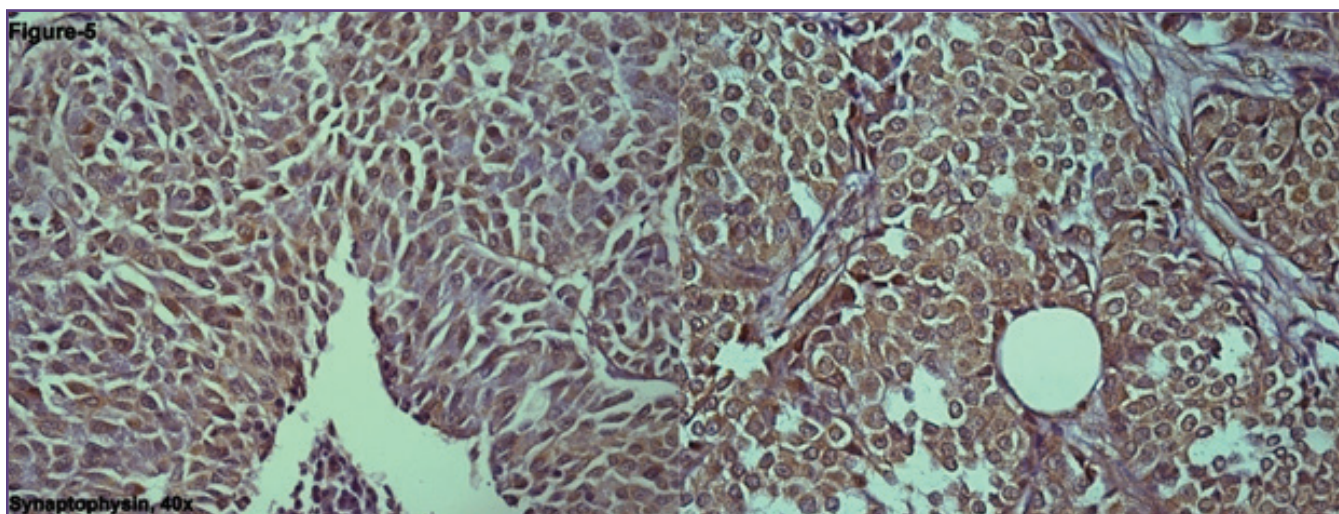


Fig. 5: Tumor cells show strong and diffuse cytoplasmic positivity in >50% of cell population (Immunostain, 40X)

Discussion

The usual location of Primary Neuroendocrine Carcinoma is in lungs and it has high malignant potential with grim prognosis. Recently, similar tumors have been reported to occur in various extra pulmonary sites, such as uterine cervix, pancreas, larynx, trachea, small intestine, stomach, prostate and breast⁴⁻⁶. Primary NECB were recently recognized as a distinct entity. Definition by The WHO is as follows: Tumors that exhibit morphologic features similar to those of neuroendocrine tumors of both gastrointestinal tract and lung, and that express neuroendocrine markers in more than 50% of the cell population³. In 2012³, WHO revised the category and divided neuroendocrine carcinomas into three subtypes: 1) neuroendocrine tumor,

well-differentiated; 2) neuroendocrine carcinoma, poorly differentiated/small cell carcinoma; and 3) invasive breast carcinoma with neuroendocrine differentiation. These tumors are usually seen in elderly women around the sixth or the seventh decade of life³ and they have no specific clinical or imaging features.

There is uncertainty about the histogenesis of neuroendocrine breast tumors. They are thought to be originated from endocrine differentiation of a breast carcinoma rather than from pre-existing endocrine cells in the breast⁷.

Metastatic neuroendocrine tumors to the breast have also been reported⁸. CT scan is a useful imaging screening study in detecting primary locations. Exclusion of primary

lung and gastrointestinal tract tumor can be done by CT scan of thorax and abdomen. Furthermore, usefulness of an octreotide scan has also been reported in identifying other sites of endocrine tumors.

Morphologically⁹, different subtypes of neuroendocrine carcinomas of breast include solid neuroendocrine carcinoma, atypical carcinoid, small or oat cell carcinoma and large cell neuroendocrine carcinoma. Sapino et al¹⁰ have recently described five subtypes of neuroendocrine breast carcinoma. These subtypes are solid cohesive, alveolar, small-cell/Merkel cell-like, solid papillary and cellular mucinous carcinomas.

Histologically^{4,11,13} the most important features are cellular monotony, nuclear palisading and pseudorosette formation with scanty or no mitotic activity and nuclei with stippled (salt and pepper) chromatin. Morphological Resemblance of NECB to NET (Neuroendocrine Tumors) from other cells of origin makes it challenging to distinguish them from metastasis from other sites. Presence of an intraductal component is a useful criterion to confirm the breast as the origin of a neuroendocrine carcinoma.

Immunohistochemical studies for neuroendocrine markers are useful in diagnosis of neuroendocrine tumors. Most commonly used markers are NSE, cytokeratins (AE1/AE3, CAM 5.2 or CK7) and neuroendocrine differentiation indicators such as Grimelius stain, synaptophysin, Leu 7, serotonin, bombesin and chromogranin A or B¹¹⁻¹². Immunostaining for estrogen and progesterone receptor provides an additional evidence for the primary origin of a tumor in breast.

Most important predictor of prognosis is the histologic grade. Solid neuroendocrine carcinoma is considered to be well-differentiated tumor. But, small cell or oat cell carcinoma and large cell neuroendocrine carcinoma are poorly differentiated. Therefore, we can assert that patients with a solid neuroendocrine carcinoma or have a better prognosis than those with small cell or oat cell carcinoma and with large cell neuroendocrine carcinoma. Poor prognostic indicators are regional lymph node metastasis and high nuclear grade both for disease free survival and overall survival as demonstrated in one retrospective study¹³.

There is no standard treatment protocol and large variety of chemotherapy protocols have been employed in treating this entity. Most patients are treated like other carcinomas of breast.

Conclusion

In conclusion, NECB is a subtype of mammary carcinoma with various distinctive features. Although solid type of NECB has slightly better prognosis than other types of NECB, these NECB have more aggressive course than ductal carcinoma, with a propensity for local and distal recurrence and poorer overall survival. Long term follow up of large number of patients would be required to fully understand this entity.

Acknowledgements

We are thankful to our senior histopathology technicians Mrs. Bhamini M McEwan and Mr. Moses McEwan for their dedication in their work by providing good quality of sections, slides and staining, so that we could diagnose this entity.

Funding

None

Competing Interests

None declared

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