

## Case Report

# Primary Small Cell Neuroendocrine Tumour (Carcinoid Tumour) of the Breast: 2 Case Reports and Review of Literature

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**Abstract:** Primary small cell neuroendocrine tumour of the breast is very rare with less than 30 cases have been reported in the literature so far. The morphological and immunohistochemical patterns of this tumour are similar to small cell neuroendocrine cancer of the lung. For this reason, it is often difficult to distinguish a primary small cell neuroendocrine cancer of the breast from a metastatic lesion from other sites. Herewith we present 2 cases of primary small cell neuroendocrine tumour of the breast treated with surgery. Different management plans are discussed. Since there are no satisfactory case series to support a certain therapeutic decision, the treatment of primary neuroendocrine tumour of the breast is the same one offered in patients diagnosed with primary infiltrating breast cancer.

**Keywords:** Breast cancer, carcinoid tumour, neuroendocrine tumour,

## INTRODUCTION

Primary neuroendocrine tumours (carcinoid tumours) of the breast are rare. They were first described by Cubilla and Woodruff in 1977[1]. Since then very few cases have been reported in the literature. Primary neuroendocrine tumours of the breast account for less than 1% the primary breast cancers. Majority of the breast carcinoids are metastatic from sites well known to have neuroendocrine tissue, mainly lung, small bowel and appendix [2-3]. Even the histology of carcinoid tumour can mimic the appearance of breast adenocarcinoma. Radiologically and clinically, carcinoid breast tumour can easily be mistaken for conventional breast cancer. Therefore, probably the most important aspect of carcinoid tumour of the breast is to determine whether it is primary or secondary tumour since the management totally differs from definitive curative surgery to palliative one. However, a thorough patient investigation is needed in order to exclude an occult primary elsewhere. Evidence regarding primary breast carcinoid management is short, since this subtype of neuroendocrine breast neoplasm is consider rather rare. Since there is no large series regarding the presentation and subsequent management of this rare disease, there is difficult to drawn a proper protocol for the management [4]. Herewith we present 2 cases of primary small cell neuroendocrine tumour of the breast treated with surgery and discussed other management options described in the literature.

## METHODS

Information on the management of two patients with breast lump in Shimoga Institute of Medical Sciences and Mc Gann hospital, Shimoga in August 2009 and May 2011 was extracted for publication. Ethical committee clearance was taken before this procedure.

## CASE REPORT 1

A 50 year old postmenopausal woman presented with lump in the upper and outer quadrant of the right breast since 3 months. Mammography revealed highly suspicious mass in the right breast with BIRADS 5 grading. On clinical examination, mobile hard lump of size about 3 cms. was found in the upper and outer quadrant of the right breast with no axillary lymphadenopathy. Fine needle aspiration cytology of the lump was suggestive of duct carcinoma. Routine chest x-ray, ultrasound abdomen and bone scan were normal. With the backup of these investigations we decided to undergo modified radical mastectomy and procedure had been explained to the patient. Breast conserving surgery was avoided since patient was not willing for radiotherapy. On serial sectioning of resected specimen well delineated grey white mass measuring 3x4 cms. was found in the outer and upper quadrant with areas of necrosis. 14 lymph nodes were isolated from axilla. Microscopically multiple sections showed well delineated tumour tissue with surrounding breast tissue. Tumour tissue comprised of groups and sheets of uniform, small cells with meager number of mitotic figures. They are arranged in organoid pattern

with mild fibrosis. These cells showed moderate to abundant granular cytoplasm with round vesicular nuclei and stippled chromatin. Some of the cells showed vacuolated cytoplasm. There was mild lymphocytic infiltration around the tumour cells. There was no evidence of vascular and lymphatic invasion. Base and resected margins appeared to be free from tumour. Sections studied from the resected lymph nodes revealed only follicular hyperplasia with so evidence of metastasis. With these background and special argyrophilic stain the diagnosis of small cell neuroendocrine tumour (carcinoid tumour) right breast was made. This diagnosis was later confirmed by immunohistochemistry. Immunohistochemistry was positive for neuron specific enolase (NSE), chromogranin and synaptophysin. Estrogen and progesterone receptors were strongly positive. To exclude a nonmammary primary site patient was further subjected to chest and abdomen CT scan and In<sup>111</sup> DTPA octreotide scan. Since the CT scan was normal and there was no evidence of increased somatostatin receptor uptake in the patients body the diagnosis of primary neuroendocrine tumour of the breast was established.

Having ensured the diagnosis of primary small cell neuroendocrine (carcinoid tumour) of the breast, the findings were discussed in the breast cancer tumour board meeting. Since the tumour was small, lymph nodes were negative for metastasis, no vascular and lymphatic invasion and it was strongly positive for estrogen and progesterone receptor, the decision to put the patient only on tomosifine 20mg. per day for 5 years and regular follow up was made. Five years post-operatively patient was in good condition with no evidence of recurrence.

#### CASE REPORT 2

A 90 year old female presented with lump in the left breast since 1 month with no other complaints. On clinical examination, small nodule of size 2 cms. was palpated in outer and upper quadrant of left breast with no axillary lymphadenopathy. She was subjected to wide local excision biopsy of the nodule under local anesthesia. Hematoxylin-Eosin morphology assisted immunohistochemistry (positive for NSE, chromogranin, synaptophysin and ER, PR) confirmed the diagnosis of small cell neuroendocrine tumour. To exclude a nonmammary primary site, the head and neck, chest abdomen and pelvis examination found no other abnormality. The diagnosis was primary solid

small cell neuroendocrine tumour of the left breast. Considering her age, the patient was further subjected to hormonal therapy only. There was no recurrence in 1 year follow up.

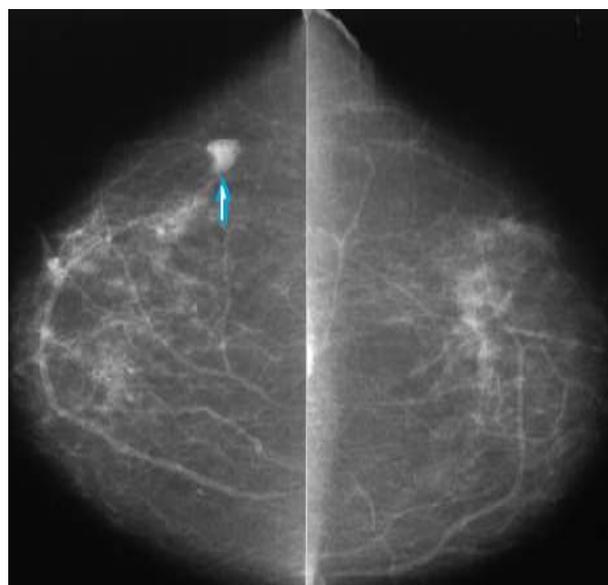


Fig. 1: Right Breast Mass

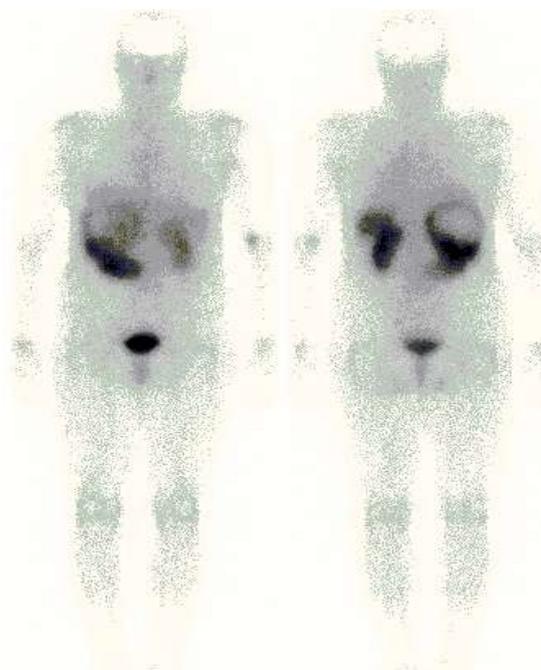
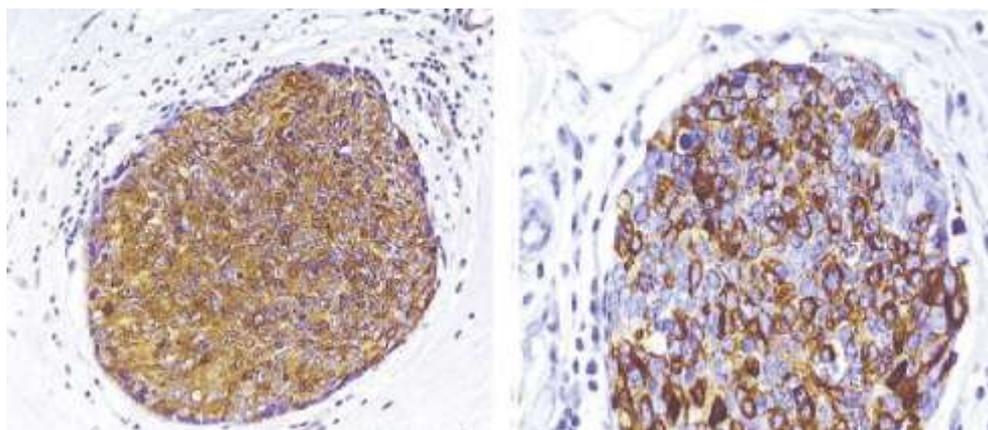


Fig. 2: In<sup>111</sup> Octreotide Scan



**Fig. 3: Magnified Synaptophysin and Chromogranin Stain**

### DISCUSSION

Rather rare, primary neuroendocrine carcinomas of the breast were recently recognized as a separate entity from other tumours. The World Health Organization defines them as tumours that exhibit morphological features similar to those of neuroendocrine tumours of both the gastrointestinal tract and lung, and express neuroendocrine markers like synaptophysin and chromogranin in more than 50% of the cell population. These tumours are usually seen in the fifth or sixth decade and have no definitive clinical or imaging features [5]. The origin of the neuroendocrine breast tumour is unclear, but they are thought to arise from endocrine differentiation of a breast carcinoma rather than from preexisting endocrine cells in the breast [6].

Morphologically, neuroendocrine carcinomas of the breast include solid neuroendocrine carcinoma, atypical carcinoid, small cell or oat cell carcinoma (SCNC) and large cell neuroendocrine carcinoma (WHO classification). Even though the histology is specific for neuroendocrine tumour, positive neuroendocrine marker must be present in order to make the diagnosis. The presence of intraductal component is a helpful criterion to confirm the breast as the origin of neuroendocrine carcinoma<sup>5</sup>. Moreover immunostaining for progesterone and estrogen receptor can provide additional evidence for the primary origin of a tumour in the breast. Primary histology result (carcinoid tumour) needs further assessment to clarify whether this tumour is either primary or secondary, since primary breast carcinoids are treated mainly with a radical surgical approach like modified radical mastectomy; if this lesion is a metastatic carcinoid of primary site elsewhere, nothing more than lumpectomy is needed to confirm the disease. Axillary dissection should be avoided and mastectomy is also probably not required [4].

The prognosis of primary neuroendocrine carcinoma of the breast mainly depends upon the stage at which it presents rather than its neuroendocrine differentiation.

Wen-chiu tsai *et al.* [7] reviewed 32 reported cases of primary neuroendocrine tumour of the breast from the literature with its 4 years follow up. Those are classified according to WHO standards in to solid neuroendocrine tumour, large cell and small cell (oat cell) variety. Among these solid and large cell neuroendocrine tumour of the breast have shown good prognosis with surgery and adjuvant chemotherapy and/or radiotherapy. Small cell variety appeared to be more aggressive with poor outcome even with surgery and adjuvant therapy. Even the lymph node metastasis was more with small cell neuroendocrine carcinoma of the breast even though the relation between lymph node metastasis and survival rate was not statistically significant in their study due to small number of cases studied [7]. This small cell (oat cell) variety of neuroendocrine cancer of the breast is a very rare tumour (our 2 case reports) with less than 30 cases were reported in the literature. The morphological and immunohistochemical patterns of this tumour are similar to small cell neuroendocrine carcinoma of the lung [8]. For this reason, it is often difficult to distinguish a primary SCNC of the breast from a metastatic lesion from other sites [9-10]. Common cancers that have been known to metastasize to the breast include those from the prostate, lung, thyroid, the hematopoietic system and malignant melanoma. With immunohistochemical analysis, a distinction between a primary tumour and a metastatic lesion is possible. SCNC of the breast is positive for cytokeratin 7 and negative for cytokeratin 20, whereas the SCNC of the lung is negative for both [11]. In<sup>111</sup> DTPA – octreotide scintigraphy is considered an accepted method to know the existence of carcinoid tumour throughout the body [4]. If a patient has a clinically detectable breast lump thought to be neuroendocrine carcinoma with known carcinoid activity anywhere in the body, then suspicious of metastasis rather than primary should be sought since there are serious ramifications regarding treatment. Sandostatin analogs can be used for patients who have a positive octreotide scan.

'Carcinoid syndrome' like skin flushing and diarrhea produced by the various hormones released from the tumour though rare are usually seen during the late in the disease in about 10% of patients with carcinoid breast tumour. Treatment of primary neuroendocrine tumour of the breast is primarily surgery ranging from breast conserving surgery to modified radical mastectomy. Radiotherapy may be needed if breast conserving surgery is planned. Literature shows very poor prognosis for SCNC of the breast because of extensive vascular, lymphatic invasion and high proliferating index [12-13]. Mucin production is a common feature in neuroendocrine breast tumour and the mucinous differentiation is an important indicator of low biological aggressiveness. Estrogen and progesterone receptor expression is also correlated with a better prognosis. Currently SCNC of the breast is considered an extremely aggressive tumour for which there is no uniform consensus about a standardized treatment. The best choice advised to be modified radical mastectomy as a surgical management. Since in SCNC the lymph node involvement and the recurrence rate is more, it is managed with adjuvant chemotherapy with drugs similar to management of SCNC of lung [11]. Hormonal therapy with estrogen and progesterone receptor modulator like toremifene is also very effective in appropriate individuals. Immunotherapies with interferon and sandostatin have been shown to reduce the size of carcinoid tumour of the breast and slow the growth of metastatic tumours in as much as 17% of patients. On the whole, the prognosis of the carcinoid tumour of the breast is fairly positive. Most carcinoid tumour of the breast is slow growing and 5 year survival rate following the surgical removal which has not metastasized can be as high as 90%.

## CONCLUSION

Primary neuroendocrine (carcinoid tumour) tumour of the breast is very rare. Its diagnosis requires exclusion of this being a metastasis originating from a primary carcinoid located elsewhere in the body. Treatment is mainly surgical. Small cell variant of neuroendocrine tumour of breast is still very rare and may require aggressive management with adjuvant chemotherapy, radiotherapy and hormonal therapy. New studies including larger patient population are needed to standardize a treatment regimen for this very rare tumour.

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