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Case Report
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Neuroendocrine Carcinoma of Breast: Case Report and Review of Literature

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Abstract

Primary neuroendocrine tumors of the breast are relatively rare and aggressive tumors that present a great diagnostic and therapeutic challenge. Amongst the Neuro Endocrine Carcinomas of Breast (NECB), small cell neuroendocrine tumors are associated with poorest prognosis. We present our experience with a case of primary small cell NECB, the diagnostic and management strategy along with a review of literature.

Keywords: Neuro Endocrine Carcinoma of Breast (NECB); Small cell neuro endocrine tumors; Case report

Introduction

Neuroendocrine carcinomas arise from neuroendocrine cells and arise commonly in the bronchopulmonary and gastrointestinal system. Primary neuroendocrine tumors of the breast are rare tumors comprising 0.1% to 5% of all breast carcinoma [1,2]. WHO had recognized and defined mammary neuroendocrine carcinomas in 2003 as tumors expressing neuroendocrine markers in more than 50% of tumor cells [3,4]. Later in 2012, WHO subdivided Neuroendocrine Tumors into Three Subtypes:

1. Neruroendocrine Tumors-Well Differentiated
2. Poorly Differentiated/Small Cell Carcinoma
3. Invasive Breast Carcinoma with Endocrine Differentiation

Ideally, NECB should arise from neuroendocrine cells in the breast, but these cells are not present in normal breast tissue. Another theory is that NECB arises as a result of early differentiation of breast cancer stem cells into neuroendocrine and epithelial lines [5]. The presence of an intraductal component is an important factor to certify that the primary origin is in the breast. NECB is often found to be positive for hormone receptors, but Her 2 neu is almost always negative, though in a few cases Her 2 neu positivity is reported [5,6].

We report the case of a young lady diagnosed with a primary small cell neuroendocrine tumor of the breast and subsequent management of the case with a review of literature.

Case Report

A 39-year-old breast feeding lady and mother of four children, presented with a right breast lump, gradually increasing in size and associated with pain, for 10 months. There was no family history of breast or ovarian cancer. The breast examination revealed a firm, mobile, non-tender lobulated lump, with no skin changes, in the right upper quadrant, measuring approximately 4 cm × 5 cm. There were no palpable lymph nodes in both axillae and the left breast was normal. Imaging of the breast showed a large lobulated lesion at 12 o'clock position, measuring 37 mm × 23 mm with vascularity, along with a smaller lesion at 10 o'clock position, 3 cm from nipple, measuring 11.4 mm × 5.1mm. Additionally multiple dilated ducts, giving cystic appearance, at 2-3 o'clock position, 1 cm from nipple and multiple axillary lymph nodes with preserved fatty hilum, were observed.

A trucut biopsy revealed possibility of neuroendocrine tumor with Immune Histo Chemistry (IHC) positive for Chromogranin and PAN CK but negative for NSR, Synaptophysin and Vimentin. Computerized Tomography (CT) staging showed the breast lump along with bilateral axillary nodes with loss of fatty hilum and no evidence of lesions in the chest or abdomen, thus ruling out a primary neuroendocrine tumor, at other site, which could have metastasized to the breast.

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Intraoperatively two additional nodules were found in the same breast. Frozen section was positive for malignancy and hence the patient underwent modified radical mastectomy. Histopathology classified the tumor as primary small cell neuroendocrine tumor with areas of high-grade infiltrating duct carcinoma. The patient was subsequently referred to an oncologist for further management.

Pathological examination of the operated specimen revealed the following:

Gross examination

An irregular firm pale tan brown to grey mass measuring 4.5 cm × 3.5 cm near the superior border. The cut surface showed pale grey white and tan brown areas merging with adjacent nodular yellow areas. The nodular area is seen all along the base merging with the tumor and measuring 7.5 cm × 2 cm.one small nodule in the breast parenchyma .28 lymph nodes were isolated.

Microscopy

Right MRM specimen-two types of tumor tissue were found.

One was highly pleomorphic with large cells showing hyperchromatic nuclei, anisonucleosis, prominent nucleoli and eosinophilic to vacuolated cytoplasm with brisk mitoses (15-18/10 hpe), bizarre cells, tumor giant cells, areas of squamous metaplasia and large areas of necrosis suggestive of infiltrating ductal carcinoma.

Immunohistochemistry for high grade infiltrating duct carcinoma

ER positive (2+5=7) PR positive (2+1=3), Her2 neu negative and Ki 67 high (greater than 90%).

The second tumor was composed of small and medium sized relatively uniform cells arranged in solid sheets, trabeculae and rosettes interspersed with, thin walled, capillaries. Tumor cells showed hyperchromatic nucleus and stippled chromatin, small nucleoli and brisk mitoses. Large, areas of necrosis were noted (suggestive of neuroendocrine tumor of the breast).

Immunohistochemistry for neuroendocrine tumor of the breast

Positive for Synaptophysin, NSE and Chromogranin.

ER positive (1+4=5), PR positive (2+2=4) and Her2 neu negative

Final diagnosis

Primary neuroendocrine carcinoma (small cell type) with areas of high-grade infiltrating duct carcinoma in a lactating breast.

Anterior and posterior surfaces were positive for tumor. Superior, inferior, lateral and medial margins were free of tumor. None of the lymph nodes of 28 isolated were positive. A small fibroadenoma was also noted.

Discussion

The first reported case of NECB was by Feyrter and Hartmann in 1963, who described it as an invasive breast cancer with morphological features similar to intestinal carcinoids [7,8]. Later in 1977 eight cases of breast cancer with carcinoid like growth pattern was described by Cubilla and Woodruff [8]. After reviewing the literature Wade et all, was the first to describe the term small cell carcinoma of the breast in 1983 [9].

Most of the patients usually present in the sixth to seventh decade of life [10,11]. However, in our case the patient was a relatively young 39 years old lactating women. The youngest age reported of a patient with NECB was 28 years [12]. Ours is the second youngest age group of lactating patients reported for primary small cell NECB.

Not more than 30 cases of small cell NECB were reported in most literature, but we found that the largest study to date used the Surveillance, Epidemiology and End results (SEER) registry between 1973 and 2010, wherein a total of 199 patients with small cell neuroendocrine tumor of the breast were included in the study [13]. Most literature concludes that small cell neuroendocrine tumor of the breast is an extremely aggressive form of tumor with poor prognosis [14,15]. Reports suggest that the course of small cell NECB is as aggressive as a pulmonary small cell carcinoma [16,17].

All possible differential diagnosis like Merkel cell carcinoma, lymphoma, melanoma and neuroendocrine tumors metastatic to the breast should be ruled out before establishing a diagnosis of primary NECB [8].

Our case is a typical example of primary small cell carcinoma of the breast. This patient had a breast lump with blood and radiological investigations failing to demonstrate a primary neuroendocrine tumor, elsewhere in the body. The initial investigation starting with Fine Needle Aspiration Cytology (FNAC), was also suspicious for small cell NECB. It revealed features of malignant small round to oval cells arranged in syncytial and monolayered fragments, acini, linear cords and rosettes with stippled chromatin, anisonucleosis, scanty cytoplasm with cell to cell, molding. The diagnosis of NECB was further reinforced by trucut biopsy after immunohistochemistry. Since a preoperative working diagnosis was available, the presence of a primary neuroendocrine carcinoma elsewhere, metastasizing to the breast was excluded through investigations.

The exact histogenesis of these tumors are still uncertain but the most accepted theory of them being originating as a differentiation of a breast carcinoma rather than neuroendocrine cells is supported even in our case report where NECB was found in association with ductal carcinoma [18].

The diagnosis of primary small cell NECB was primarily based on histological features of scanty cytoplasm, presence of inconspicuous nucleoli, a high mitotic rate and presence of uniform small cells. This was demonstrated in the FNAC, trucut and final histopathology specimen in our case. Several reports suggest that the presence of necrosis was common in NECB, but it can also be present in other breast carcinomas. Immunohistochemistry staining studies conducted in most cases were positive for chromogranin A, synaptophysin, NSE, Leu 7 etc. [19]. In our case, Immunohistochemistry was positive for chromogranin A, synaptophysin and NSE and histopathology of the MRM specimen was suggestive of a primary small cell carcinoma.

There is no generalized consensus on the management of NECB. Most studies suggest that surgery plays a pivotal role in the management. The type of surgery depends on the location of the tumor and the clinical stage [20].

The tumor in our case was multicentric, and hence, after a frozen section of the multicentric sites, a decision was taken to proceed with a modified radical mastectomy. A careful review of the literature revealed only one case of a multicentric low-grade tumor [21], but our case was unique in that it was a multicentric high-grade tumor.

Our patient underwent a modified radical mastectomy of the right breast, followed by chemotherapy on 21/9/15. She is on regular

follow-up and is doing well, with no evidence of recurrence or metastases.

A review of the literature revealed that a dimorphic pattern on histology was described in six cases, specifically a combination of small cell NECB with invasive lobular carcinoma in three cases, invasive ductal carcinoma in two cases, and squamous cell carcinoma in one case [19,22,23]. Our case, too, had a dimorphic pattern of primary small cell NECB with invasive ductal carcinoma.

The choice of systemic therapy should be individualized based on tumor size, nodal metastases, etc. Patients with hormone receptor positivity and high Ki67 may benefit from adjuvant chemotherapy in addition to endocrine therapy. Our patient also had receptor positivity as well as a high Ki67 (>90%) and hence underwent chemotherapy and endocrine therapy [23,24]. The role of adjuvant radiotherapy should be considered as for other types of breast carcinoma, as no specific guidelines are established.

The prognosis of small cell NECB was thought to be grave, but several recent reports suggest that if they are detected early and if there are no lymph node metastases, the prognosis seems to be better [16,23,25]. Hence the overall prognosis mainly depends on the stage of the disease.

Conclusion

NECB represents a rare neoplasm. The overall prognosis depends on the subtypes of NECB and the stage of the disease. Our case is distinctive with regards to the rarity of the small cell subtype, which carries a poor prognosis. If detected early and lymph node metastases are absent, the prognosis is better.

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