CASE REPORT

Solid Neuroendocrine Carcinoma of the Breast

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ABSTRACT

Primary neuroendocrine carcinoma of the breast is a rare disease that accounts for less than 5% of all cancers arising from the breast. The tumour cells stain positively for chromogranin and synaptophysin. This report describes the occurrence of infiltrating ductal carcinoma of breast with neuroendocrine differentiated tumour in 37 year old female. Early small cell neuroendocrine cancer of the breast that is treated with surgery and adjuvant chemotherapy shows an increased disease-free survival. She is planned for anthracycline/cyclophosphamide based chemotherapy followed by etoposide/platinum based chemotherapy. As her tumour showed ER/PR positivity, she will be given hormonal therapy subsequently, however, more extensive review is required to define a standard treatment protocol for this rare neoplasm.

Key Words: *Neuroendocrine carcinoma. Immunohistochemistry. Breast.*

INTRODUCTION

The breast is a rare site for neuroendocrine tumours. Most neuroendocrine tumours are located in the gastrointestinal tract and the lungs.[1] It accounts for less than 5% of cancers arising from the breast.[2] The first case was described in 1963 by Feyrter *et al*. and sporadically reported in the literature since then.[3-5] While pure neuroendocrine carcinoma of breast is very rare, scattered neuroendocrine cells can be detected in upto 50% of breast tumours. Recently, an additional subset of breast tumours has been described as neuroendocrine differentiated breast tumours.[5] Neuroendocrine differentiation has been reported in both *in situ* and infiltrating breast cancers.

According to World Health Organization (WHO) classification of tumours, neuroendocrine tumour of the breast is a category that includes solid neuroendocrine carcinoma, small cell/oat cell carcinoma and large cell neuroendocrine carcinoma (NEC).[6] The diagnosis of NEC of breast is based on the criteria established in 2003 by the WHO classification system, as per the definition, there is synaptophysin or chromogranin immunohistochemical expression in > 50% of the cells.[2]

Because these tumours are very rare, no controlled trial on their treatment has yet been reported in literature. The descriptions of these cancers are from case reports.

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We report a case of infiltrating ductal carcinoma with neuroendocrine differentiation managed with surgery, chemotherapy and hormonal therapy.

CASE REPORT

A 37 years old pre-menopausal woman, single para, presented with a 6 months history of lump in her left breast. Initially, it was painless but with the passage of time she developed pain, with subsequent development of another lump in her left axilla. She was not having any co-morbidity. She was non-smoker and never used oral contraceptive pills. There is no family history of breast, ovarian or colon cancer.

On examination, she had hard lump palpable in her left breast which was about 7 x 8 cm in size fixed to overlying skin but freely mobile over chest wall. It was associated with *peau d'orange* appearance. Another hard fixed lump about 5 x 5 cm was palpable in left axilla consisting of matted lymph nodes. The right breast examination and other related clinical examination was within normal limits.

She underwent incisional biopsy of mass left breast that was reported by Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, as solid neuroendocrine carcinoma, moderately differentiated. Tumour cells were diffusely positive for chromogranin. Her metastatic workup was done that showed normal haematological and biochemical profile, with no distant metastasis in liver and lungs, however, her bone scan showed tracer uptake in bilateral parietal bones, thoracic vertebra T12 and left acetabulum which were not confirmed histopathologically.

In consultation with surgeon, she was planned for modified radical mastectomy with axillary clearance to remove the bulk of tumour and give symptomatic relief to the patient. Histopathology reported by The Aga Khan University Hospital, Karachi, turned out to be infiltrating

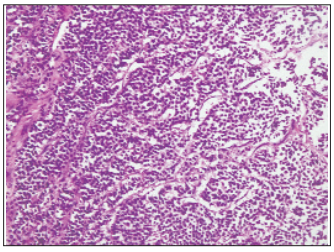

Figure 1: Malignant appearing cells arranged in nests and clusters separated by fibrovascular stroma on H/E stain.

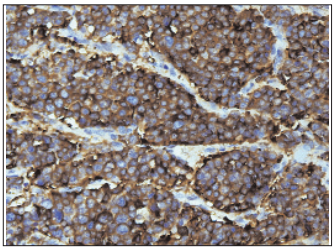

Figure 2: IHC showing diffuse cytoplasmic chromogranin positivity.

ductal carcinoma with neuroendocrine differentiation, grade-II (modified Bloom and Richardson grading system). Tumour cells stained positively for cytokeratin 7 and synaptophysin. Size of tumour was 7.5 x 6 x 5 cm; tumour was 0.2 cm away from deep painted margin. A total of 19 lymph nodes were recovered out of which 9 were involved by tumour. The stage of disease was T3N2M1 (Figure 1 and 2).

Patient was planned for adjuvant chemotherapy at 3 weekly intervals, consisting of 4 cycles of FAC inj. 5-fluorouracil 500 mg/m^2, inj. doxorubicin 50 mg/m^2 and inj. cyclophosphamide 500 mg/m^2 because of their established efficacy in invasive breast carcinomas. It was planned to be followed by 4 cycles of cisplatin 100 mg/m^2 on d1 and inj. etoposide 120 mg/m^2 on d1-3 because of their proven efficacy in breast cancers and small cell lung carcinomas.

At the follow-up of 6 months, the patient received 4 cycles of anthracycline based chemotherapy with poor compliance, however, she did not have any local recurrence or distant metastasis development during this period. Now she is planned for platinum based chemotherapy and will be considered for adjuvant hormonal therapy thereafter.

DISCUSSION

Primary neuroendocrine carcinoma (NEC) of the breast is extremely rare and accounts for less than 5% of all cancers arising from the breast.[2] In 10 – 50% of breast tumours, scattered neuroendocrine cells can be detected depending on the definition and detection methods. A new type of breast tumour has recently been classified as neuroendocrine differentiated breast carcinoma whose features are common with both neuroendocrine and exocrine carcinomas.[5] This indicates the ability of the same tumour cell to produce both exocrine and endocrine substances. Therefore, it should be discriminated from both pure neuroendocrine breast carcinoma and typical breast cancer with focal neuroendocrine differentiation.

These are breast carcinoma expressing predominant neuroendocrine differentiation but lacking specific cyto-architectural features of low grade or high grade neuro-endocrine carcinoma. At least 50% of cells are neuro-endocrine marker positive that require either synapto-physin or chromogranin. These tumours are usually seen in elderly women around the sixth or the seventh decade of life[7] and they have no specific clinical or imaging features. The tumours consist of densely cellular, solid nests and trabeculae of cells separated by delicate fibrovascular stroma (Figure 1).

The prognostic significance of neuroendocrine differen-tiation in mammary carcinoma is unclear. Typically, these tumours present with ER- and PR-positive and HER-2-negative status. Regarding gene expression, profile of endocrine carcinoma overlaps with those of mucinous carcinomas.[8] The outcome of these cancers does not differ from other carcinomas and depends very much on its histological grade. Mucinous differentiation and positivity for estrogen and progesterone receptors are all favourable prognostic factors.[9]

Positive neuroendocrine markers must be found in order to make the diagnosis.[10] The presence of an intraductal component is a helpful criterion to confirm the breast as the origin of a neuroendocrine carcinoma. Moreover, immunostaining for progesterone and estrogen receptor can provide additional evidence for the primary origin of a tumour in the breast.

The prognosis of primary neuroendocrine tumours of the breast could be better in tumours detected at a smaller size, without lymph node involvement and with hormone sensitivity.

In summary, NEC is a subtype of mammary carcinoma with several distinctive features. NEBC are more likely to be ER/PR positive and HER-2 negative. They have a more aggressive course than ductal carcinoma, with a higher propensity for local and distant recurrence and poorer OS. Studies with longer follow-up and greater case numbers will be needed to address this issue.

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