CASE REPORT

Primary Neuroendocrine Carcinoma of the Breast

Abdul Rehman

ABSTRACT

Primary neuroendocrine carcinoma of the breast (NECB) is an extremely rare variant of breast cancer having aggressive clinicopathological behaviour and poor prognosis. A 62 years old woman presented with a painless lump in the left breast. Microscopic and immunohistochemical evaluation of the core-tissue biopsy and of the mastectomy specimen revealed moderately-differentiated neuroendocrine carcinoma of the breast. She was labeled as a case of primary neuroendocrine carcinoma of the breast after an infallible exclusion of any concomitant lesion elsewhere in the body. Modified radical mastectomy with level II axillary clearance, chemoradiotherapy and Famoxifen have led to an uneventful 5-year survival till the last follow-up.

Key words: *Primary neuroendocrine carcinoma of the breast. Neuroendocrine carcinoma of the breast. Immunohistochemistry. Chromogranin. Synaptophysin. Neurone-specific enolase. Cytokeratins.*

INTRODUCTION

Primary neuroendocrine carcinoma of the breast (NECB) is an exceedingly rare but reportedly a highly aggressive breast malignancy due to its immense propensity for early locoregional recurrences, distal metastasis and dismal prognosis. Its extreme rarity can be judged from the fact that up till now only fewer than 50 cases of primary NECB have been reported in the medical literature.[1] It can pose diagnostic and therapeutic challenges even to shrewd clinicians because of its rarity, non-specific symptomatology, architectural similarities to conventional variants of breast cancer, categorization as primary or secondary neuroendocrine carcinoma, and non-existing consensus regarding therapeutic strategies.[2]

The aim of reporting this case is to acquaint the health professionals with clinicopathological features, diagnostic work-up, therapeutic approaches and prognostic factors of this unique breast malignancy.

CASE REPORT

A 62 years old postmenopausal nulliparous woman presented with a gradually enlarging painless lump in her left breast of 6 months duration. She gave no history of nipple discharge, eczema, or distortion. There was no lump in the axilla or presence of constitutional symptoms. She strongly denied history of breast, endometrial, ovarian or cervical cancer in her first or second degree-relatives. She was non-alcoholic and non-addict and did not receive any hormonal replacement therapy. Her general physical and systemic examinations were unremarkable. Examination of the left breast revealed a solitary, non-tender, firm to hard, well-circumscribed lump, measuring 1 x 2 x 2 cm in dimensions, located in the upper inner quadrant (UIQ) at 11 O'clock position, about 2.0 cm away from the nipple-areolar complex. The lump was neither adherent to the skin nor to the underlying pectoral muscles. The overlying skin exhibited no edema, erythema, dimpling, puckering or peau d'orange appearance. The left nipple-areolar complex showed no structural or positional abnormality. Compression of the lump failed to exude any serous or blood-stained nipple discharge. Clinically, there was no appreciable ipsilateral axillary lymphadenopathy. Examination of the right breast and axilla showed no abnormality.

Laboratory work-up revealed a normal hemogram and biochemical and metabolic profiles. Chest X-ray (PA view) showed no osseous, cardiopulmonary, pleural or pericardial pathology. Sonography depicted a well-delineated oval-shaped, solid hypo-echoic breast lump exhibiting hypervascularity on Doppler ultrasound. Mammography confirmed the presence of a high-density lesion with faintly infiltrative margins in the Upper Inner Quadrant (UIQ) of the left breast (BIRADS 5). FNAC showed a suspicious cytology (C-4 cytology). However, histological examination of core-tissue biopsy of the lump unveiled a moderately-differentiated carcinoma forming cribriform patterns of nests of small polygonal cells separated by fibrovascular stroma. Immunohistochemical staining of the tissue of core-biopsy was strongly positive for chromogranin-A and synaptophysin (more than 80% of the cell population) and negative for smooth muscle antigen (SMA, Figures 1 and 2). Nuclear receptor analysis showed striking positivity for estrogen (> 80%) and progesterone (> 60%) receptors and

Department of General Surgery, PAEC General Hospital, Islamabad.

Correspondence: Dr. Abdul Rehman, House No. 537, Street No. 18, Chaklala Scheme-3, Rawalpindi-46000.
E-mail: surgeonarehman@yahoo.com

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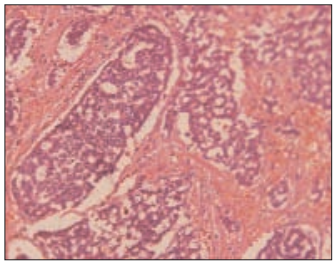

Figure 1: Cribriform patterns of nests of small cell showing positivity for chromogranin-A

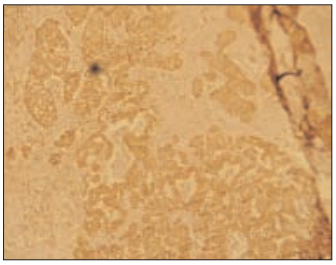

Figure 2: Cribriform patterns of nests of small cell with positivity for synaptophysin.

absolute negativity for HER2/neu (c-erbB2) oncogene. Metastatic work-up with abdominal and transvaginal ultrasonography, CT scan of the chest, abdomen and pelvis as well as bone scintigraphy failed to display any concomitant lesion elsewhere in the body. Based on the criteria of more than 50% neuroendocrine differentiation of the cell population, strong positivity for neuroendocrine markers, expression of estrogen and progesterone receptors, and comprehensive exclusion of any concurrent lesion elsewhere in the body, it was labeled as a case of primary NECB.

She underwent left modified radical mastectomy with level-II axillary clearance. Histological and histochemical examinations of the mastectomy specimen re-confirmed the diagnosis of a moderately-differentiated NECB with absence of axillary nodal metastasis. Postoperatively, she was given chemoradiotherapy. Currently, she is on tamoxifen (20 mg/day) and is doing well 5 years after surgery.

DISCUSSION

Primary NECB is an extremely rare tumour accounting for less than 0.1% of all variants of breast cancer and less than 1% of all neuroendocrine tumours of the body. It predominantly affects the middle-aged women in their 6th and 7th decades of lives and only exceptionally involves the male breast. Primary NECB arises from argyrophil cells found sparingly among the epithelial and myoepithelial cells of the breast; first identified by Vogler (1047).[1,2] Historically, argyrophil cells belong to “Diffuse Neuroendocrine System (DNES)”. Anatomically, the components of the DNES are widely scattered throughout the bronchopulmonary, gastrointestinal, genitourinary and endocrine systems including the breast. Physiologically, the DNES is an amalgamation of neural and endocrine regulatory mechanisms responsible for maintaining body homeostasis. Embryologically, the cells of the DNES are derived from the neural crest and are acronymously termed as APUD cells (Amine Precursor Uptake and Decarboxylation) based on their biosynthetic, histochemical and ultrastructural features. Biochemically, the APUD cells contain intracytoplasmic membrane-bound dense neurosecretory granules harbouring regulatory hormones, growth factors, neuroamines, neuropeptides and neurotransmitters and characteristically express neuroendocrine tumour markers like chromogranin, synaptophysin, neuron-specific enolase, and cytokeratins-7.[3]

The exact aetiopathogenesis of primary NECB remains uncertain. It may arise spontaneously in a random fashion (sporadic) like that of our patient or is inherited in an autosomal dominant fashion as a part of well-known familial syndromes (familial) like MEN-1, MEN-II, von Hippel-Lindau's disease, von Recklinghausen's disease and tuberous sclerosis. On the basis of its cellularity, differentiation and histological grade, WHO (2003) proposed a pathological classification of primary NECB as solid, small-cell (oat-cell), and large-cell neuroendocrine carcinoma. Bloom-Scarff-Richardson grading system is equally applicable for further stratification of primary NECB into low-grade (well-differentiated), medium-grade (moderately-differentiated) and high-grade (poorly-differentiated). Primary NECB has profound tendency to invade into the adjacent breast tissue and metastasize to axillary lymph nodes, liver, lungs, bones, brain, and adrenals via lymphovascular invasion.[4,5]

Clinical presentations of primary NECB are notably non-pathognomonic. It may present either as an isolated hard breast lump clinically indistinguishable from other malignant lumps with or without axillary lymphadenopathy or as a breast lump with metastatic and hormonal symptoms. Radiological evaluation of the lump with ultrasonography and mammography often proves inconclusive in reaching the diagnosis. The hallmark criteria for diagnosis of primary NECB include; (1) microscopic evidence of neuroendocrine differentiation in more than 50% of the cell population; (2) presence of *in-situ* component of a common variant of breast cancer in the histological sections; (3) demonstration of intracytoplasmic eosinophilic membrane-bound dense granules of neuroendocrine markers by immunohistochemical techniques; (4) nuclear positivity for expression of estrogen and progesterone receptors with absolute negativity for HER2/neu receptors; and (5) uncontroversial exclusion of any concomitant extra-mammary lesion by highly-sophisticated imaging modalities like transabdominal and transvaginal ultrasonography, CT scans of the chest, abdomen, and pelvis, radionuclide bone scan, octreotide scintigraphy and PET scan.[6,7] More often than not, even after extensive diagnostic efforts the differentiation between primary and secondary NECB remains enigmatic.[2] In order to facilitate this differentiation between primary and secondary NECB, Shetty proposed certain criteria. According to him, a larger tumour (> 4 cm), absence of *in-situ* component, non-expression of estrogen and progesterone receptors, absence of axillary nodal metastasis, and presence of opacity in any other organ of the body are highly suggestive of secondary rather than primary NECB.[8]

Surgery (modified radical mastectomy with axillary clearance) unquestionably is the mainstay of treatment of primary NECB. However, there are lots of controversies regarding adjuvant treatment; possibly due to paucity of the statistical data and scarcity of documented cases in the medical literature. Most treatment guidelines are based on the anecdotal experience gained by the retrospective reviews of the patient's files. Postoperative adjuvant chemotherapy and radiotherapy followed by hormonal therapy are commonly recommended to decrease the incidence of locoregional and systemic recurrences. A wealth of chemotherapeutic regimens has been advocated with conflicting results. The most frequently prescribed chemotherapeutic regimen is VP16-CDDP.[9,10]

In view of extreme rarity and paucity of long-term statistical figures, it is hardly possible to draw firm conclusions regarding prognosis of this rare clinical entity. A large tumour, small cellularity, high-nuclear grade, non-expression of estrogen and progesterone receptors, and presence of lymphovascular invasion, nodal involvement and distant metastases are adverse prognostic factors dismally associated with poor outcome.[9,10]

To put in a nutshell, the diagnosis of primary NECB can only be entertained after an exhaustive microscopic and immunohistochemical evaluation of the tissue biopsy and a thorough exclusion of any associated lesion elsewhere in the body.

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