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A Rare Breast Cancer: Triple Negative Neuroendocrine Cancer

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1. Abstract

Neuroendocrine breast cancer is a rare type of breast tumour with the incidence of less than 0.1%. In most cases, neuroendocrine breast cancers are hormone receptors positive and HER2 negative. We present a rare case of a 69-year-old female patient with left breast T3 N1 triple negative neuroendocrine cancer with axillary lymph node metastasis. The patient underwent neoadjuvant chemotherapy with subsequent left mastectomy and sentinel lymph node biopsy 2 months later. The histopathological result showed a complete pathological response to neoadjuvant therapy. Patient made uneventful recovery and underwent treatment with adjuvant radiotherapy. As yet, there are only 7 triple negative neuroendocrine breast cancer to our knowledge in the literature search [1].

2. Introduction

Breast cancer is the most common cancer in women and is the fifth most common cause of cancer death in Australia [2]. The multidisciplinary approach including surgery, neoadjuvant therapy, adjuvant therapy has led to five-year survival of 92 % [2].

Neuroendocrine neoplasm arises from neuroectodermal stem cells [3, 4]. Neuroendocrine Breast Cancer (NEBC) comprises only 0.1% of neuroendocrine tumors, however the true incidence is unknown due to different pathological definitions in the past [5]. Due to its rare incidence, the optimal method to diagnose and treat NEBC is also unclear. Most cases of neuroendocrine breast cancer are positive for hormone receptors and almost always negative for HER2 [6].

The 2019 WHO classification defines neuroendocrine breast cancer as a tumour in which >90% of cells show histological evidence of neuroendocrine differentiation. This may be well differentiated neuroendocrine tumour, poorly differentiated neuroendocrine carcinoma and invasive breast cancers of no special type with neuroendocrine differentiation [7]. NEBC are generally staged like breast ductal carcinoma [8]. Neuroendocrine breast cancer is an invasive breast tumour with neuroendocrine markers such as Chromogranin A and Synaptophysin [9]. Histopathology shows nests or trabeculae of cells within fibrovascular stroma [6].

Usual clinical presentation is breast lump with or without nipple retraction and very rarely with paraneoplastic syndrome due to ectopic production of hormone [10]. NEBC are diagnosed with core needle biopsy. When NEBC is found on biopsy, it is essential to exclude metastatic neuroendocrine tumours to the breast from other primary neuroendocrine tumours of organs such as lungs and gastrointestinal tract.

In this case report, we present a patient with triple negative neuroendocrine breast cancer.

3. Case Report

The patient is a 69-year-old female who identified rapidly growing left breast lump with nipple retraction over 2 months. Her background history includes previous biopsy proven benign breast lesions, menarche at 14 with menopause at 50, and family history of breast cancer (maternal grandmother).

On examination, 8 cm mass was identified in the left upper outer quadrant of the breast with nipple retraction. The mass was not tethered to chest wall or overlying skin. There was no palpable axillary lymphadenopathy.

Bilateral mammogram showed suspicious microcalcification in the upper outer quadrant of the left breast with the ultrasound

showing irregular 45x23x27mm lesion (Figure 2). There were also enlarged left axillary lymph nodes measuring 8mm in size. Initial core biopsy of the left breast lesion was reported as invasive carcinoma with triple negative hormone receptor status. Additional core biopsy of the left axillary lymph nodes was positive for metastatic carcinoma with immunohistochemistry confirming poorly differentiated large cell neuroendocrine carcinoma with TTF1 expression, positive chromogranin and synaptophysin (Figure 1). Review of initial core biopsy of left breast lesion showed similar morphology to the nodal metastasis. Positron Emission Tomography/Computed tomography (PET/CT) scan conducted to exclude other primary sources of neuroendocrine tumours and metastasis disease demonstrated suspicious nodes in infraclavicular and subpectoral intramammary chain.

Her case was discussed in the breast Multidisciplinary Team (MDT) meeting and decision was to proceed with neoadjuvant chemotherapy for locally advanced breast cancer and assess the response. The patient received four cycle of dose dense AC (adriamycin and cyclophosphamide) followed by 12 cycles of weekly paclitaxel. By the start of third cycle, there was a significantly reduction of tumor size clinically which was confirmed on CT staging scan. She subsequently completed her neoadjuvant treatment and a near complete radiological response was seen and confirmed by bilateral ultrasound of breast and axilla. The staging CT and bone scan showed no evidence of distant metastasis. Initial surgical plan to proceed with left mastectomy and axillary lymph node dissection was revised to left mastectomy with sentinel lymph node biopsy with a view to proceed with axillary dissection if nodes were still found to be positive.

Both left breast and axillary lymph node were clipped during biopsy prior to commencing neoadjuvant chemotherapy for localization. She underwent left mastectomy and sentinel lymph node biopsy 2 months after neoadjuvant chemotherapy. The histology confirmed the complete pathological response with only fibrosis in tumor bed without involvement of lymph node on sentinel node where both pre-operatively clips were found in the specimens. Further adjuvant radiotherapy was recommended according to our MDT for previous positive chest wall nodes. She has recovered well from her surgery and is currently receiving adjuvant radiotherapy without issues. She will have ongoing follow up for surveillance in the surgical and oncological outpatient clinics.

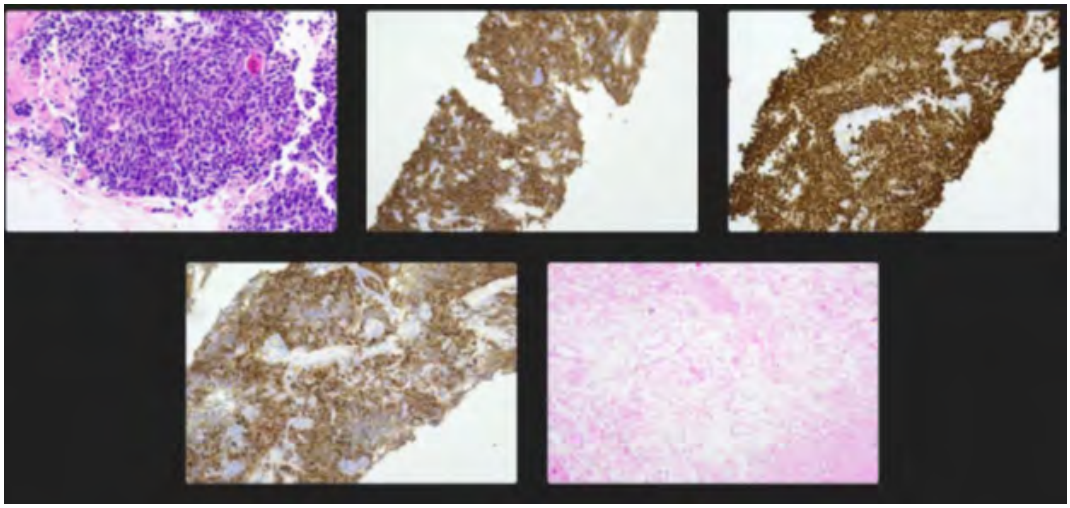

Figure 1: Figure left to right from above down: Transverse section of neuroendocrine tumor, Synaptophysin stain in IHC, TTF1 stain in IHC, Chromogranin in IHC, Post treatment mastectomy

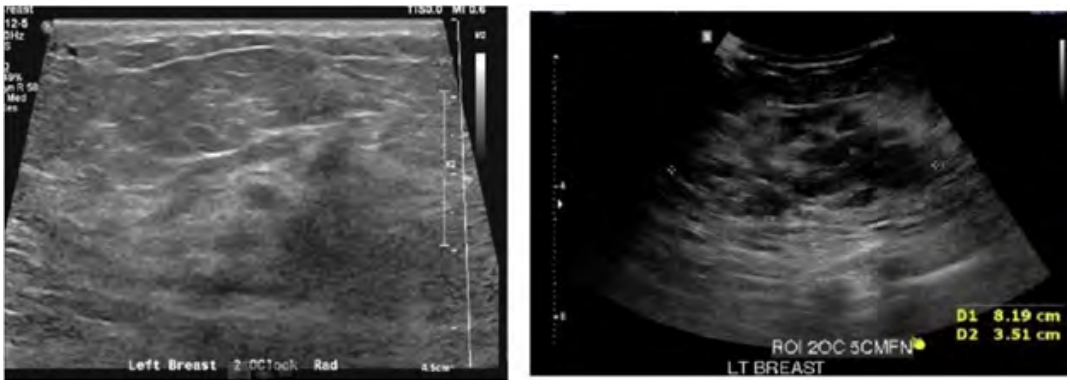

Figure 2: Showing left breast lesion while first referred by GP and repeat ultrasound after review in clinic for progress.

4. Discussion

Tripe negative neuroendocrine breast cancer is an extremely rare type of breast cancer as most of NEBC are positive for hormonal receptor and almost always negative for HER2 mutation. The diagnosis of NEBC is also underreported as staining of neuroendocrine marker is not performed routinely. In one study, less than one third of actual cases were recognized [11]. The treatment of NEBC is not well established as it is poorly defined and there is not enough clinical data of its diagnosis, staging and management [12]. Most literature and studies were based on single case reports and small case series with personalized treatment plan. In Trevisi et al., 2020, of the 45 case reports, only 7 reported cases of triple negative neuroendocrine breast carcinoma over last 10 years [1]. From review for the publications, It is found that most clinicians followed the same therapeutic approach applied in invasive breast cancer [13, 14].

On retrospective review of case reports, the most common treatment for triple negative breast cancer being breast conserving surgery/mastectomy with sentinel lymph node biopsy or axillary dissection depending on the staging of the tumor followed by adjuvant chemoradiotherapy (taxane-based and/or anthracycline-chemotherapy) and endocrine therapy for receptor status and nodal involvement [15].

Further research is needed for diagnosis, staging and prognosis. Promising new identification of neuroendocrine tumor marker and tumor profiling for specifically targeted treatment with chemotherapy are emerging. Mastectomy is currently the preferred treatment of choice due to its aggressive clinical course [6]. Given the excellent pathological response to neoadjuvant systemic therapy in this case, mastectomy with sentinel lymph node biopsy was a safe choice with reduced morbidity. Further evaluation of this approach is required for NEBC and the criteria for selecting NEBC patients for a less aggressive option such as was used in our case. Other modalities of treatment were reported in case reports such as somatostatin analogs for NEBC expressing somatostatin receptor as it plays major roles in gastroenteropancreatic neuroendocrine tumor and further use of antiangiogenic agents for cases expressing VEGFR [6].

5. Conclusion

Our case report demonstrates a successful treatment of very rare entity of triple negative primary neuroendocrine breast cancer despite diagnostic and therapeutic challenges due to limited available data and literature evidence for therapeutic recommendation. It is noted that further research and studies to better understand the pathogenesis, mutation and prognosis of neuroendocrine breast cancer are required to better evaluate and guide the best treatment strategies for patients with NEBC which may demonstrate a degree of variability in the aggressiveness and response to different treatment modalities.

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