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Unraveling The Mystery.

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ABSTRACT

Background: Neuroendocrine breast carcinomas (NEBCs) are a unique and, as yet, poorly understood subtype of breast cancer affecting two to five percent of all breast cancers. Because NEBC is histologically similar to invasive ductal carcinoma, it is difficult to diagnose, and immunohistochemistry analysis is also required. Because it is rare, there is no consensus on the best management approaches, and treatment is frequently selected from standard breast cancer regimens. Case Presentation: A case is described of a 77-year-old woman presenting with a right breast tumor that was growing. On clinical examination, the mass in the upper outer quadrant was a 3 × 3 cm oval mass, a firm and movable mass, with no evidence of axillary lymphadenopathy. The two questionable lesions were seen on ultrasound and PET-CT imaging tests. The second lesion was neuroendocrine differentiated invasive carcinoma of no special type, and the first lesion's histopathological analysis was invasive mammary carcinoma with localized neuroendocrine differentiation (30%). Immunohistochemistry was positive for chromogranin expression localized and for synaptophysin positivity high. The tumor was hormone receptor positive; therefore, the patient was started on medication afterwards following a modified radical mastectomy (MRM). Discussion: A localized neuroendocrine differentiation in a primary breast carcinoma demands a careful histopathological and immunohistochemical analysis. There is an early-stage disease due to the lack of distant metastases and locoregional lymphadenopathy. Long-term monitoring is essential, however, because NEBC is unexpected and said to be still the primary course of therapy; however, molecular profiling may help identify new therapeutic targets in the future. Conclusion: It demonstrates the complexity of diagnosis and treatment of NEBC, and put a challenge to improve the reporting of the cases, form the treatment guideline, as well as molecular research of this rare disease. Since such a rare cancer may be treated in such a novel way, there is hope other developments in precision medicine and tailored medicines may improve outcomes for the patient**.**

Keywords: *Neuroendocrine Breast Carcinoma, Histopathological Analysis, Immunohistochemistry, Hormone Receptor Positive, Molecular Profiling, Precision Medicine..*

INTRODUCTION

Neuroendocrine tumors of the breast (NECB), an uncommon but diverse category of breast cancers, account for approximately 2–5% of all breast cancers identified [1]. These tumors are identified and categorized histologically and molecularly, as their subjects are far less obvious than other neuroendocrine tumours (NETs) of lung and gastrointestinal tract [2]. In 2003, the World Health Organization (WHO) established NECB as a separate pathological entity because more than 50% of tumor cells are positive for neuroendocrine markers [3]. Over time, the newer versions in 2012 and 2019 that further classified NECB to well-differentiated NETs, poorly differentiated NECs, and invasive breast carcinomas with neuroendocrine features took into account the possibility of neuroendocrine differentiation even in proportion to lower neuroendocrine marker expression [2]. However, NECB is still underdiagnosed and underrecognized, as it has yet to achieve standard classification in patients with breast cancer [4], since its recent categorization breakthroughs. Clinical oncology is not able to make an exact diagnosis of NECB because the disease has a low prevalence, and it has a histological overlap with

other breast cancers.

As with the clinical presentation of NECB, its radiologic and histologic presentation can be confused with that of invasive ductal carcinoma of no special type (IDC-NST) [5]. A breast lump in most cases is painless; other patients have more severe symptoms such as axillary lymphadenopathy, nipple retraction, or skin ulceration, which may be signs of more advanced illness [6]. Because NECB is rare and there are few large-scale clinical investigations, it is difficult to create conclusive clinical and prognostic indicators. Data available comes in the vast majority of the cases from case reports and small retrospective studies [7]. Some studies suggest that the patients with NECB are more likely to have the systemic metastases at the diagnosis than IDC-NST, the most common metastatic organs being the liver, lungs, and bones [8]. However, the fact that NECB does not always have the hormonal hypersecretion symptoms that typically characterize gastroenteropancreatic NETs is evidence for the fact that histological and immunohistochemical confirmation is essential for diagnosis. Diagnosis and categorization of NECB is in need of a multidisciplinary strategy using radiologic, histologic, and molecular profiling approaches in light of these diagnostic complications.

It is historically easy to diagnosis NECB as histologically, but can diagnosis NECB for that NECB has distinctive expression of neuropeptide markers, chromogranin A (CgA) and synaptophysin (Syn) which are entirely not found in other Breast Cancers [9]. However, for some of these NECB, the differential expression of histological and neuroendocrine markers have yet to be properly studied enough to allow some of the NECB to be misclassified as a conventional breast carcinoma. As second-generation neuroendocrine biomarkers, including insulinoma-associated protein 1 (INSM1), ISL1, and the application of IHC and molecular profiles, have made it possible for NECB classification improvement. However, no information about the histogenesis of NECB exists. Other researchers state that the tumors originate from either existing breast neuroendocrine cells or normal breast carcinoma cells that are undergoing neuroendocrine trans differentiation [11]. To establish an NECB correct diagnosis and therefore implement appropriate treatment measures, it is necessary to develop an appropriate and consistent histopathological and molecular diagnostic framework.

Specifically, a molecular makeup of NECB is still under study, and the tumors have shown initial genetic changes that are different from the ones seen in traditional breast carcinomas. In comparison with invasive ductal carcinoma of no special type (IDC-NST) [7], NECB has lower rates of PIK3CA and TP53 mutations, which have been related to the biology of breast cancer. In addition, these tumors share with NECB the fact that they are typically mutated in genes such as GATA3, FOXA1, and ARID1A [12]. Amplifications in FGFR1 and CCND1 have been found in some NECB patients and thus may act as therapeutic targets for individualized therapy [13]. Curiously, despite these new discoveries, the development of NECB is limited by a lack of comprehensive research into the real potent carcinogens causing NECB. So next generation sequencing (NGS) might contribute in improving NECB sub classification since NECB sub classifications become more and more important for molecular profiling of breast cancer.

Because no established recommendations exist for treating NECB, dilemmas ensue in how to treat this disease, and many of the treatments used for the treatment of extrapulmonary neuroendocrine carcinomas and IDC-NST are used. As of now, surgery is still a sentinel therapy for localized NECB, while mastectomy or breast-conserving surgery is performed as per the size of the tumor and node involvement [14]. Adjuvant systemic treatment still has an unknown function because NECB does not always respond predictably to classic breast cancer regimens. Among all patients, most have hormone receptor positive status, which is known to be frequently treated with endocrine treatment with aromatase inhibitors or selective estrogen receptor modulators (SERMs), and this should be recognized [6]. Favorable outcomes from poorly differentiated NECB chemotherapy regimens similar to those employed for small cell lung carcinoma could be considered [15]. As a result, CDK4/6 inhibitors and somatostatin analogs have been promising in a small number of NECB patients, and more research is needed to further validate their efficacy. NECB is this type of rare, and in this tumor group, treatment should be individualized by receptor status, type of tumor, and metastatic burden; the more the better (or none) in the presence of a multidisciplinary tumor board.

NECB casts doubt on traditional prognostic models in breast cancer, therefore, we are aware of NECB, but unsure of its prognosis. The studies have found a more aggressive disease course with higher rates of distant metastasis and recurrence, and other studies have indicated that NECB, in particular, can have a good prognosis like IDC-NST [6]. Prognostic variables determining the results of NECB are tumor grade, receptor status, high Ki-67 proliferation index, and nodal or distant metastases [16]. Less treatment options and poorer survival are offered to patients with NECB and poor or high-grade tumors [17]; however, NECB that is hormone receptor positive may be eligible for endocrine therapy. Consequently, NECb still remains more extensively researched, and due to the lack of large cohort studies and prospective trials, such survival statistics for NECb are quite limited. Personalized oncology may further develop itself to combine the precision medicine technique with molecular profiling that enhances prognostic forests and treatment plans for NECB patients. There is no standard treatment for the NECB breast cancer subtype. A little was known about it, despite certain variations in the degree of development of immunohistochemistry and molecular profiling. Variations of other breast cancer' treatments are the basis for the choice of treatment. So, the studies that should be continued in the future are the clinical trials, the genetic studies, and biomarker-driven treatments.

Ethics statement

This case report was prepared in accord with the ethical principles of the Declaration of Helsinki and the institutional ethics committee rules. For the publication of clinical information, histological results, and imaging data, the patient's informed written consent was obtained prior. This report has no personally identifiable information. Recording the occurrences of primary neuroendocrine carcinoma due to breast is useful to increase the clinical understanding and improve patient treatment since it is a rare entity. The research was carried out without undergoing any experimental procedures beyond regular clinical treatment, and as it is, it was not in violation of any relevant ethical guidelines. As the case is retrospective without any experimental interventions, ethical clearance was not needed.

Case presentation

A case of 77 years old unmarried nulliparous female homemaker with an enlarging mass in right breast which is slowly developed over the past 12 months. The lump as it grew over time was a small mass at first. At this time, she also had on-and-off pain above the bump. However, there was not a history of appetite reduction, weight loss, or nipple discharge. Other parts of the body had no complaints of edema. Management of her systemic hypertension and type 2 diabetes mellitus mediated was done with regular medication for over 20 years. She had also already been treated for pulmonary TB 29 years back. There was neither previously known family history of breast cancer nor history of previous procedures.

On clinical examination hard movable, 3 X 3 cm oval lump in upper outer quadrant on right breast 5 cm away from nipple areolar complex (NAC) was palpable. No tethering or ulceration on the skin surface over the tumor was observed. Both there was no nipple discharge nor retraction. Palpable lymphadenopathy was not seen when the right axilla was examined. The left breast and axilla had nothing unusual about them. Clinical symptoms were tentatively staged as T2 N0 Mx.

Investigations

On further investigation, 2 lesions were found in the right breast at 11 and 9 o'clock. A BIRADS 5 lesion was identified at 11 o'clock, and a trucut biopsy was guided by USG there to clarify what might be the nature of the lesion. It was found that invasive mammary cancer was present, Nottingham score 7.

A PET CT scan was performed to rule out distant as well as locoregional metastasis. The lesion shown extended on the skin surface in the upper inner quadrant of the right breast. The outer quadrant of the right breast was found to have another small but concerning lesion. Yet there were no distant metastases and no locoregional lymphadenopathy. Blood tests were within the regular limits. In Table 1, the compilation of the imaging and histological data is presented for a systematic description of the diagnostic findings.

Table 1: Summary of Investigations

Investigation	Findings
Ultrasound	Two lesions at 11 o'clock and 9 o'clock positions
USG-guided Trucut Biopsy	Invasive Mammary Carcinoma with Nottingham score 7
PET-CT	Malignant lesion in upper inner quadrant and another suspicious lesion in outer quadrant of right breast, no lymphadenopathy or distant metastasis
Blood Investigations	Normal

Surgical Procedure

A right MRM was performed on the patient under general anesthesia. On operating on her, a tumor in the upper outer quadrant was found to be 3 × 4 cm. She underwent axillary lymph node and right breast tissue removal, and these specimens were submitted for histology. Two separate lesions were evidenced by histopathological analysis. The first lesion was situated in the upper outer quadrant and had features of invasive mammary cancer with localized neuroendocrine differentiation (30%). The second lesion was diagnosed as an invasive mammary cancer of no special type (NST) in the lower outer quadrant. Immunohistochemistry (IHC) analysis confirmed and added localized positivity for chromogranin and high positivity for synaptophysin in the first lesion. Both tumors were also positive for E-Cadherin which was compatible with their epithelial origin. The final diagnosis was right breast invasive cancer of the type T2N0M0 with localized neuroendocrine differentiation. Because of the tumor's hormone receptor status, the patient has been put on aromatase inhibitors and still follows up along with routine. A summary of results from the immunohistochemistry and histopathology is depicted in Table 2.

Table 2: Histopathological and Immunohistochemistry Findings

Lesion	Histopathology	Immunohistochemistry
Lesion 1 (Upper Outer Quadrant)	Invasive Mammary Carcinoma with focal neuroendocrine differentiation (30%)	Synaptophysin: Strongly Positive, Chromogranin: Focal Positivity, E-Cadherin: Positive
Lesion 2 (Lower Outer Quadrant)	Invasive Mammary Carcinoma, No Special Type (NST)	E-Cadherin: Positive

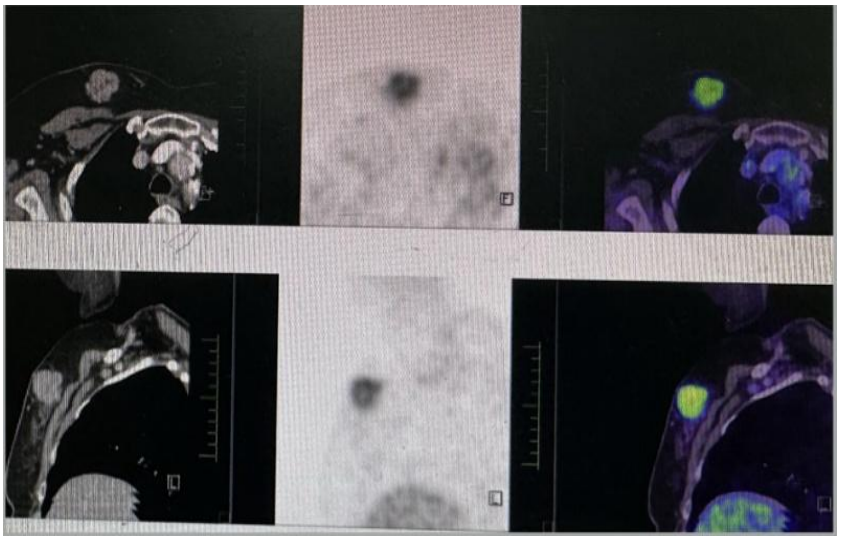

Figure 1: PET-CT Scan Imaging

Fig 1 reveals a suspicious, suspected lesion in the outer right breast and a malignant tumor in the upper inner right breast. As no bulky disease is shown, its shortening is suggested, representing a confined disease stage (T2N0M0). The PET CT data agree with the histological findings and prove that this is a case of surgery.

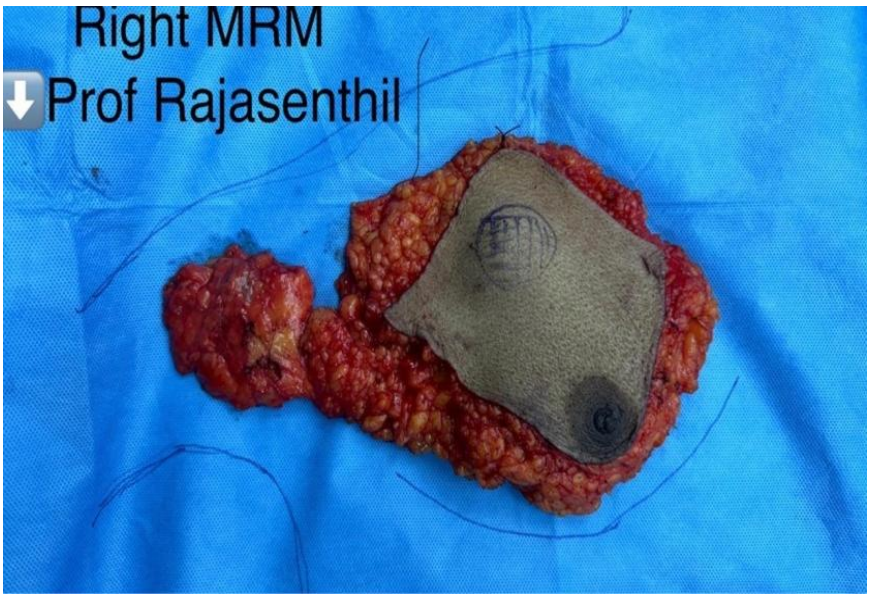

Figure 2: Gross Specimen (Post-Mastectomy)

Two different areas of the right breast specimen involve tumors in the upper outer quadrant and the lower outer quadrant. A solid, hard, white appearance is a characteristic of invasive carcinoma. The gross pathology enhances the correlation of imaging findings with tissue-based confirmation of malignancy.

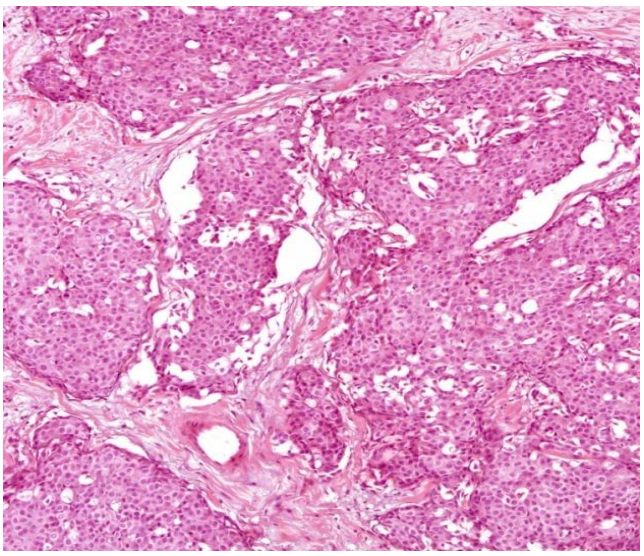

Figure 3: Histopathology Analysis with Neuroendocrine Differentiation

It supports a diagnosis of invasive breast cancer with localized neuroendocrine differentiation confirmed by the histopathology analysis, and it is positive for synaptophysin strongly and focally for chromogranin. These indicators provided a unique distinction of this instance from ordinary invasive ductal carcinoma since they confirmed the presence of neuroendocrine-like tumor cells. The histopathological correlation is necessary for the purpose of improving the treatment plans, especially in a setting where there is mixed differentiation. This is an uncommon finding of invasive breast cancer with localized neuroendocrine differentiation and exemplifies the importance of histological and immunohistochemical investigation to confirm it. The treatment strategy was incorporated with endocrine therapy based on receptor status (per standard procedure for IDC-NST).

Neuroendocrine Differentiation's Clinical and Histopathological Importance in Breast Carcinoma

Breast neuroendocrine tumors (NETs) occur infrequently and, in some cases, can present diagnostic dilemmas because the NETs can be sporadic with otherwise 'normal' breast tissue, leaving a question as to whether there is also invasive cancer in the breast. This 77-year-old female with enlarging breast lump for 1 year with unrelenting but episodic pain, but with no systemic signs such as weight loss, nipple discharge, or distant metastases. She didn't have any family history of hereditary breast cancers or previous breast-related disease, and so her appearance was more in accordance with sporadic instances.. Histologically, this instance is significant by demonstrating a localized neuroendocrine differentiation. Even though invasive mammary carcinoma without a particular type (NST) is still the most common subtypes, there is a presence of neuroendocrine markers (localized chromogranin expression and synaptophysin positivity) showing an area of mixed histological component consisting of an impact on treatment options. According to the standard treatment approach for hormone receptor-positive malignancies, the treatment strategy is based on aromatase inhibitor therapy type modified radical mastectomy (MRM). Nevertheless, long-term follow-up is necessary to rule out recurrence or distant spread because NEBC has a high metastatic potential.

DISCUSSION

This case shows how challenging it may be to diagnose and successfully treat neuroendocrine breast cancer (NEBC) in the elderly. A 77-year-old female was examined; an enlarging tumor in the right breast was observed, invasive mammary cancer, localized neuroendocrine differentiation (30%). Thus, the presence of two different lesions with either localized neuroendocrine differentiation or invasive carcinoma of no special type (NST) of the breast may hint at the existence of mixed histologic subtypes of the breast cancer. This is in line with previous results relating the diversity of histologic patterns found in NEBC to render the diagnosis as well as the treatment plan more difficult [7]. This was also supported by immunohistochemistry (IHC) data, which revealed that chromogranin was basically only positive around the lesion of neuroendocrine differentiation, while synaptophysin showed good positivity. However, due to histological examination not being the optimal way to identify neuroendocrine differentiation, the significance of IHC markers should be emphasized to distinguish the NEBC from conventional breast carcinomas [9].

This radiology perspective highlights the importance of thorough imaging of NEBC patients because they have two separate lesions (at the 11 o'clock and 9 o'clock positions). No malignant mass lesion was found in the right breast area involving the chest wall dermis, although there was a malignant mass lesion seen as a mass lesion near the skin in the right breast's upper inner quadrant demonstrated on PET-CT scans. Earlier research has linked NEBC to a high incidence of systemic metastasis and to an advanced stage of disease [12]. This discovery is noteworthy. The lack of detected metastases could have been due to the pediatric patient with early clinical manifestation and early surgical intervention.

In addition, as in other research [18], the radiologic findings in this presentation (a potential, suspicious lesion in the outer quadrant) are also consistent with its nonspecific appearance, which makes the lesion often indistinguishable from other breast cancers. Although these diagnostic difficulties still necessitate a combination of radiologic evaluation, histological examination, and IHC profiling for precise NEBC categorization and staging, this information provided in this report will enable better communication between oncologists and pathologists.

The treatment strategy was based on this in that the tumor was based on the status of the tumor hormone receptor and was modified radical mastectomy (MRM) followed by aromatase inhibitors. In earlier work, it is also suggested that NEBC often expresses estrogen receptor (ER) and/or progesterone receptor (PR) positivity, meaning endocrine therapy is a good regime for cases where both receptor positivity occurs [19]. NEBC is still disputed on the best way to treat it, since there are no set standards for treatment of NEBC; therefore, treatment plans are taken from those that are used for the treatment of conventional invasive breast cancers. Even in more severe or metastatic disease, however, surgery is still the mainstay of treatment, and adjuvant chemotherapy or targeted treatment might be needed. Recently, it has been shown that NEBC has particular molecular characteristics, which include amplification of FGFR1 and CCND1 that might be used as potential therapeutic targets in future clinical trials [13]. Because NEBC is rare, long-term survival outcomes and improved treatment recommendations will require evaluation by larger cohort studies.

While NEBC is still being researched for prognosis, reports as to how NEBC does clinically relative to traditional breast carcinomas have been mixed. Nevertheless, poorly differentiated or high-grade NEBC patients often show a high rate of recurrence and distant metastasis and worse survivals as compared to other studies that reported well-differentiated NEBC prognosis comparable to IDC NST [17]. The lack of distant metastases and lymph node involvement at presentation points to a better prognosis for our patient. Recurrence is, however, not always late, and follow-up is long. Meanwhile, the Ki-67 proliferation index has also been investigated recently as a prognostic indicator in NEBC, and the higher Ki-67 levels were shown to be related to more aggressive disease behavior [20]. Ki67 levels were not reported in our patient but could be added to the standard diagnostic workup in the evaluation of risk and individualized treatment planning. Since biomolecular profiling and precision medicine will continue to develop, future studies should aim to identify biomarkers that will allow improvement to the prognosis and future treatment plans of NEBC patients.

CONCLUSION

Nonhomogeneous in its histology, neuroendocrine breast carcinoma (NEBC) is a difficult diagnosis of breast cancer, the incidence of which is low. This is the case of a 77-year-old woman with invasive breast cancer and localized neuroendocrine differentiation, demonstrated to exemplify the need for combining clinical, radiographic, and histological evaluation and immunohistochemical finding to achieve precise diagnosis and treatment planning. While this is discordant for 2 such lesions in 1 such patient, of whom 1 exhibits neuroendocrine differentiation and 1 is an invasive NST carcinoma, we must take the time to thoroughly evaluate the histology. It had a large synaptophysin positivity, and its positivity was proven useful in deciding whether these tumors could be detected in immunohistochemistry. Because the tumor was positive for the hormone receptor, endocrine treatment was begun after MRM, since MRM was completed. It is an early diagnosis as the metastasis is not distant and lymphadenopathy is locoregional. To put it bluntly, NEBC arguing seemed to be in favor of the protocol, but the long-term follow-up should be to continually look out for metastasis or recurrence as the biological activity was still so unpredictable. New molecular research is often seen as similar to invasive ductal carcinoma (IDC), but eventually different genetic changes will yield tailored treatments. NEBC is an instance of the need for NEBC, pathologists, and physicians to be better educated about NEBC. There is not enough research in large-scale investigations and genetic profiling to optimize the treatment approaches and further refine the diagnostic criteria since it is a rare disease with the lack of standard treatment protocols. The advance of precision medicine and targeted medicines now offers fresh hope to NEBC patients, and future strategies of managing NEBC patients that can be more tailored and more effective are now within reach.

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