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Case Report

Pathology Section

A Case of Breast Cancer with Neuroendocrine Differentiation

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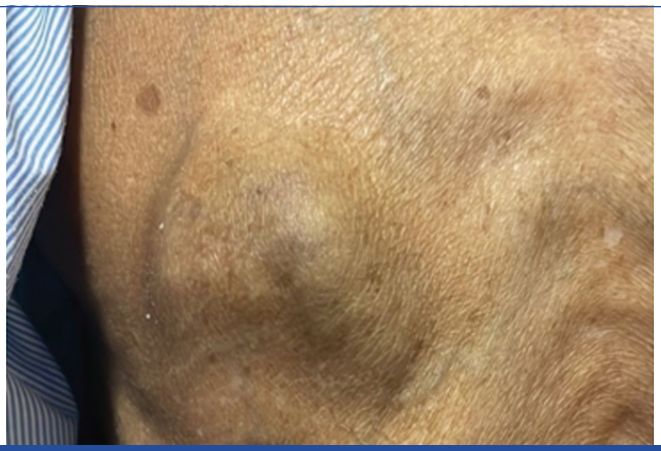
ABSTRACT

A very uncommon and different subtype of breast cancer with particular morphological and molecular characteristics is Neuroendocrine Carcinoma of the Breast (NECB). A 59-year-old female patient presented to the Department of Surgery with a chief complaint of a lump in the right breast, reported to the Department of Surgery whose breast neuroendocrine cancer was diagnosed. After undergoing imaging tests and presenting with a palpable breast lump, the patient's lesion turned out to be worrisome. Neuroendocrine cancer was identified by Fine Needle Aspiration Cytology (FNAC) and subsequent histological analysis. The diagnosis was confirmed by immunohistochemical investigation, which revealed positive staining for neuroendocrine markers. As part of a multimodal treatment regimen, the patient underwent surgery, chemotherapy, and hormonal therapy. Follow-up imaging and clinical examination demonstrated a favourable response to medication, with no indication of a return of the illness. The present case study highlights the importance of NECB as a distinct entity requiring specific care and diagnostic methods. More investigation was required to better understand the best management approaches for this uncommon kind of breast cancer. Reviewing the current state of knowledge about the incidence, demographics, diagnosis, histopathology, staining characteristics of NECB, prognostic factors, differential diagnosis, and available treatments is crucial. During the 12-month follow-up, the patient showed improvement in her clinical condition after receiving adjuvant chemotherapy and hormone treatment. The present instance highlights the need for tailored treatment strategies in circumstances like this and highlights the significance of being vigilant in detecting neuroendocrine differentiation within breast cancer.

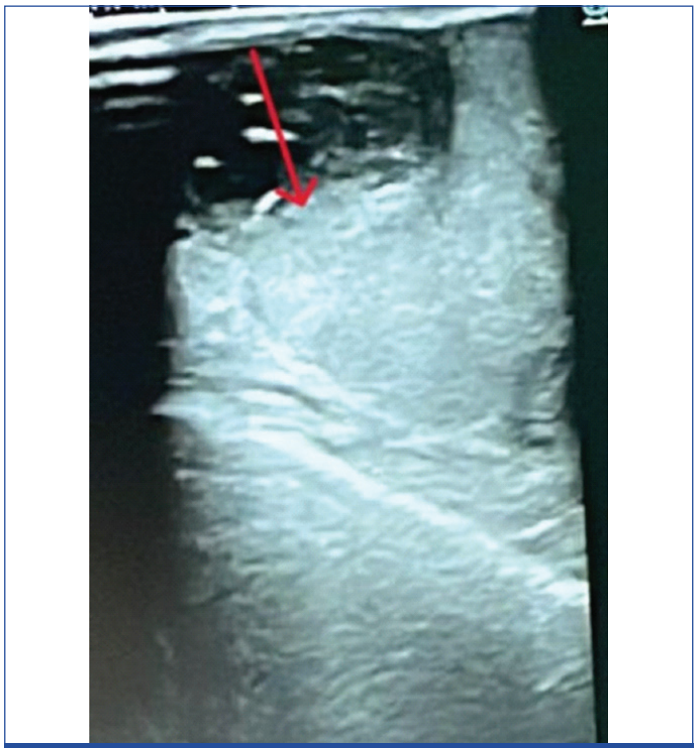
Keywords: Fine needle aspiration cytology, Immunohistochemistry, Neuroendocrine tumour, Solid lesion

CASE REPORT

A 59-year-old female came to Surgery Department for an outpatient appointment and presented with a lump in the right breast located in the upper outer quadrant that had been present for one year. She also had a history of hypertension. On physical examination, a palpable lump measuring 5×3 cm was noted. The lump was initially small and gradually progressive, exhibiting painless swelling, hard consistency, non tenderness, free mobility, and attached to the pectoralis major [Table/Fig-1]. There was no history of local temperature increases or discharge. The patient had a history of hypertension for four months. The provisional diagnosis was a lump in the left breast under evaluation. The patient underwent an ultrasound examination and a fine-needle aspiration cytology procedure. Breast ultrasonography breast showed evidence of a well-defined hyperechoic solid cystic (predominantly solid) lobulated lesion measuring 5×3 cm at the 12 o'clock position, showing increased vascularity on colour Doppler in the right breast [Table/Fig-2].



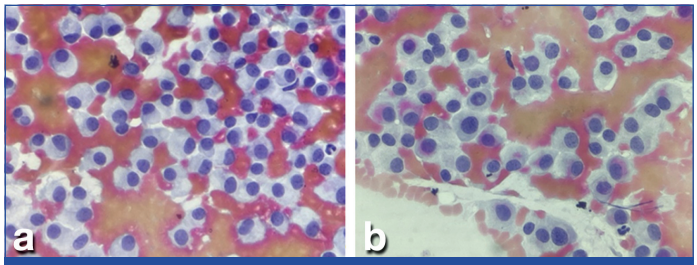
[Table/Fig-1]: Clinical photomicrograph of the right breast.



[Table/Fig-2]: Ultrasonography breast showed, well-defined hyperechoic solid cystic lesion (predominantly solid) lobulated lesion at the 12 o'clock position in the right breast.

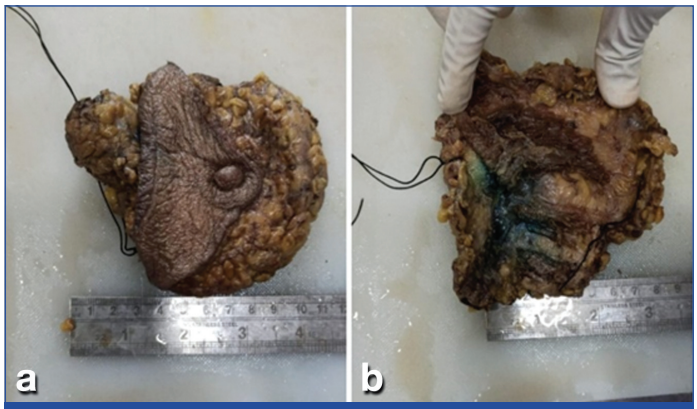
There was normal breast parenchyma with no focal lesion in the left breast. A few lymph nodes were noted in the right and left axillae. The largest lymph node, measuring 16×9 mm, was noted in the right axilla with a maintained fatty hilum. The ultrasound of the breasts suggests a Phyllodes tumour in the right breast with cystic changes {Breast Imaging-Reporting and Data System-(BI-RADS)

4B/4C category} [1] as suspicious. Laboratory investigations, like complete blood count, coagulation profile, liver and kidney function tests, and random blood glucose, were within normal limits. Aseptic procedures were followed during the FNAC. The FNAC smears stained with May Grunwald Giemsa (MGG) and Papanicolaou (PAP) stains showed cellular smears. The smears mostly show dissociated cell populations, with cells placed in cords as well as small nodules in an organised pattern. The cells were intermediate in size, cuboidal to polygonal, containing central or eccentric hyperchromatic nuclei arranged moderately. The nuclei also show mild pleomorphism, micronuclei, and microvesicular chromatin. The cytoplasm was modest and showed an apical and paranuclear aggregate of fine magenta granules. Also, seen in smears are a few scattered nuclei and hyaline-shaped flakes were seen in proximity to cell sheets [Table/Fig-3a,b].



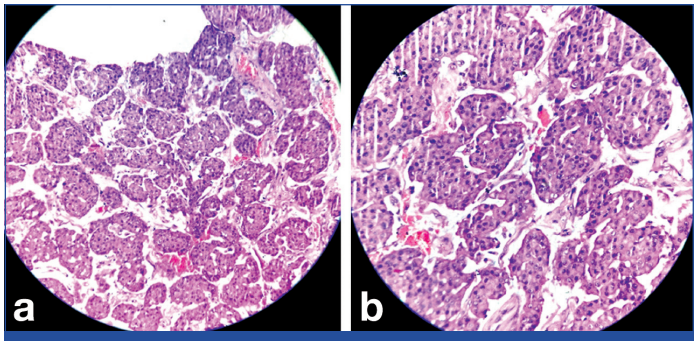
[Table/Fig-3]: a) The cells placed in cords as well as small nodules. The cells are intermediate in size and are cuboidal to polygonal containing central or eccentric hyperchromatic nuclei with moderate arrangement (40x, PAP); b) The nuclei also show mild pleomorphism, micronuclei, and microvesicular chromatin. The cytoplasm was modest and showed an apical and paranuclear aggregate of fine magenta granules (40x, PAP).

The cytomorphological characteristics pointed to a right breast neuroendocrine carcinoma. Following a right Modified Radical Mastectomy (MRM), the patient underwent axillary clearance, and the tissue was submitted for histopathological analysis. The specimen of MRM with the axillary pad of fat measured 12×11×2 cm. On the cut section of the right breast, diffuse grey-white areas measuring 4×3×2.8 cm with irregular borders and haemorrhagic areas were observed [Table/Fig-4a,b]. Fibrous, rubbery, grey-white patches were seen in the adjacent breast tissue. An axillary dissection revealed the presence of 12 lymph nodes. On microscopy, tumour cells were distributed in diffuse sheets and occasionally trabecular patterns, with thin fibrous septa separating them. Each tumour cell was round and tiny, with a polygonal nucleus that produced mucin and finely granular chromatin, as well as pale, eosinophilic cytoplasm [Table/Fig-5a,b].

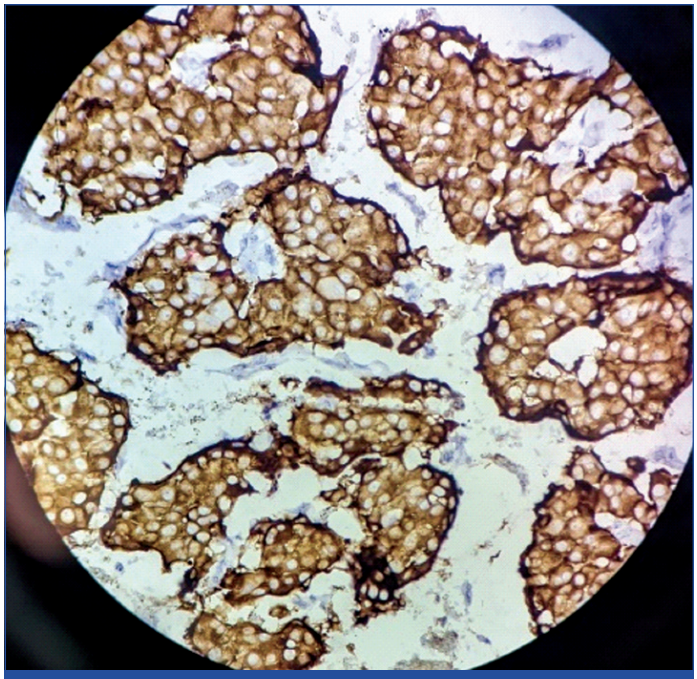


[Table/Fig-4]: a,b) Gross specimen of right MRM breast.

The histopathological characteristics indicated a breast Neuroendocrine Tumour (NET) with mucin production. All 12 lymph nodes showed reactive lymphadenitis. Immunohistochemistry for Chromogranin protein immunohistochemistry revealed a generalised positive staining [Table/Fig-6], while synaptophysin exhibited negative staining. The ultimate diagnosis was confirmed as breast neuroendocrine cancer. The patient received adjuvant chemotherapy



[Table/Fig-5]: a) Tumour cells are distributed into diffuse sheets and occasionally trabecular patterns, with thin fibrous septa separating them (40x, H&E); b) Each tumour cell is round and tiny, with a polygonal nucleus that produces mucin and finely granular chromatin, as well as pale, eosinophilic cytoplasm (40x, H&E).



[Table/Fig-6]: Chromogranin protein immunohistochemistry revealed a generalised positive immunological staining (40x, H&E).

(cyclophosphamide, adriamycin, and 5-fluorouracil) and hormonal treatment (Tamoxifen) were administered to the patient. There were no metastases or local recurrences seen throughout the 12-month follow-up period.

DISCUSSION

A small group of tumours that originate from neuroendocrine cells found throughout the body are known as Neuroendocrine Neoplasms (NEN) [1]. Primary NETs of the breast are extremely uncommon; more typically, NENs are linked to the respiratory and gastrointestinal systems. NECBs are exceedingly rare and seldom diagnosed tumours, accounting for less than 0.1% of all breast cancers and less than 1% of all NETs [2]. Feyrter and Hartmann identified primary NECB, an uncommon form of breast cancer, in 1963 [3]. The patient in this investigation was 59 years old. According to published research, these tumours often affect older women in their sixth or seventh decade of life [4]. The World Health Organisation (WHO) Classification of Tumours series' third edition of 2003 recognised NECB as a separate entity. NENs of the breast are classified as either NECs (high-grade tumours) or NETs (low-grade tumours) according to the most recent WHO classification in 2019. Breast NETs are characterised as epithelial-originated tumours in which atleast half of all invasive tumour cell types express neuroendocrine immunohistochemistry markers, chromogranin, and synaptophysin. Their morphology is comparable to that of pulmonary and gastrointestinal NETs [5]. The histological features and degrees of differentiation in these patients vary widely. Since they don't have a distinctive natural clinical history,

Author	Age of the patient	Histopathological features
Kumar M et al., 2022 [3]	46 years	Tumour cells are arranged in small sheets and solid nests and separated by fibrous stroma
Gîvan I et al., 2021 [4]	44 years	Tumour cells are disposed of in nests and islands
El Arab KF et al., 2022 [5]	50 years	Neuroendocrine Tumours (NET)
Aryal V et al., 2022 [8]	52 years	Solid sheets and rosettes of tumour cells having round to oval nuclei with powdery chromatin

[Table/Fig-7]: Comparison of the present case with published literature of the last 3-4 years reported features of primary Neuroendocrine Carcinoma of the Breast (NECB) [3,4,5,8].

it might be challenging to suspect them when they first arrive. Regarding the histogenesis of primary NETs in the breast, there are two major ideas. The first, and more contentious, idea states that the malignant transformation of normal neuroendocrine cells is the source of these tumours. The second explanation, which is more frequently recognised, claims that during the early stages of carcinogenesis, the process of neuroendocrine differentiation happens when neoplastic stem cells develop into distinct cell lines, namely epithelial and endocrine [6].

As of now, the most recent WHO classification of breast tumours includes primary neuroendocrine carcinomas. One exceptionally uncommon kind of breast tumour is primary invasive neuroendocrine differentiated breast cancer. The digestive tract, endocrine pancreas, and respiratory system are the areas where NETs are most frequently discovered; the breast is an uncommon location [7]. Comparison of the present case with published literature has been presented in [Table/Fig-7] [3,4,5,8]. According to the WHO's 4th updated edition, neuroendocrine breast tumours fall into three groups: i) well-differentiated; ii) poorly-differentiated neuroendocrine/small cell carcinoma; and iii) invasive breast cancer with neuroendocrine differentiation. Atypical carcinoids, small cell carcinomas, large cell carcinomas, and solid neuroendocrine carcinomas are the four categories into which these tumours are divided [8]. Clinically, the lump was palpable, small and gradually progressive, painless, firm to hard in consistency, non tender, and freely mobile. Radiologically, a well-defined hyperechoic solid cystic (predominantly solid) lobulated lesion shows increased vascularity on the colour Doppler. The diagnosis of a NET cannot be made using any particular radiological or clinical marker. Cytologically, the cells are intermediate in size and are cuboidal to polygonal, containing central or eccentric hyperchromatic nuclei with moderate arrangement. The nuclei also show mild pleomorphism, micronuclei, and microvesicular chromatin. The cytoplasm was modest and showed an apical and paranuclear aggregate of fine magenta granules. After that, the patient had axillary clearance following a right MRM, and the tissue was submitted for histopathology analysis. Grossly, diffuse grey-white areas with irregular borders and haemorrhagic areas are seen. Fibrous, rubbery, grey-white patches were seen in the adjacent breast tissue. Histopathologically, tumour cells are distributed into diffuse sheets and occasionally trabecular patterns, with thin fibrous septa separating them. Each tumour cell is round and tiny, with a polygonal nucleus that produces mucin and finely granular chromatin, as well as pale, eosinophilic cytoplasm. Given that the microscopic characteristics are sporadically present, the diagnosis requires the use of immunohistochemistry markers such as chromogranin and synaptophysin. The treatment for invasive breast cancer with neuroendocrine characteristics is the same as that for other types of invasive breast cancer. Depending on the tumour's stage and location, surgery is usually the first line of therapy [9]. For surgical therapy, mastectomy, axillary lymph node dissection, and metastasectomy are typically combined. Breast mammography and ultrasonography showed almost no specific or pathognomonic signs. According to Park YM et al., several radiological characteristics, such as a high-density non calcified round, oval, or lobular mass with non spiculated edges, indicate the possibility of NETs in the breast [10]. Radial scar, stromal fibrosis, abscess, invasive lobular carcinoma, localised adenosis, fibroadenoma/phyllodes tumour, and invasive ductal carcinoma are examples of differential diagnosis. The kind of adjuvant treatment can be determined using immunohistochemistry [2]. The patient's age, the involvement of the axillary lymph nodes, the clinical stage, and the presence of hormone receptors are among the factors that often influence the prognosis of breast cancer with neuroendocrine characteristics [1]. Based on the Surveillance, Epidemiology, and End Results Programme database (SEER database), the multivariate analysis concluded that neuroendocrine differentiation was an independent unfavourable prognostic risk [11]. A positive prognosis might be influenced by the existence of a related mucinous component [12]. For all combined tumour subtypes, primary NETs in the breast have a 5-year survival rate of more than 80%. On the other hand, new research has provided information on the prevalence of metastases and locoregional recurrences, improving the overall prognosis [13]. Reduced disease-free survival and a poor prognosis are linked to higher grades, larger tumours, and localised lymph node metastases [14].

When a cancer that is not suitable for surgery has spread locally, neoadjuvant chemotherapy may be used.

CONCLUSION(S)

The present case report concludes by highlighting the importance of identifying neuroendocrine differentiation within breast cancer, an uncommon and difficult-to-diagnose entity. Although rare, knowledge of this variation is essential for directing care choices and enhancing patient outcomes. The fact that the patients have been successfully managed with a customised treatment strategy highlights the significance of personalised care when managing rare subtypes of breast cancer. To further enhance clinical management methods for this particular population of patients, more study is needed to better understand the molecular features and therapeutic responses of neuroendocrine-differentiated breast cancer.

Authors contributions: Shakti Sagar: Drafting the case report and overview of patient management. Dr. Samarth Shukla: Reporting of the excised specimen sent for histopathological investigation and giving the suitable diagnosis. Informed consent for publication of their clinical details and clinical images was obtained from the patient. All the authors read and approved the final version of this manuscript.

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