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Case Report

Radio-pathological characteristics of primary neuroendocrine breast carcinoma: Series of 4 cases ☆,☆☆

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ABSTRACT

Neuroendocrine breast cancers (NEBCs) are a rare and distinct subtype of breast tumors, characterized by their neuroendocrine differentiation. Despite accounting for less than 1% of all breast cancers, NEBCs present unique diagnostic and therapeutic challenges due to their heterogeneous nature and variable prognosis. Accurate imaging plays a crucial role in the diagnosis, treatment planning, and follow-up of NEBCs, yet remains a complex area due to the rarity of these tumors and overlapping features with more common breast cancers. We present a series of 4 cases of primary NEBC, emphasizing the imaging features and their histopathological correlations. All patients presented with breast lump. Diagnostic Mammography followed by Ultrasound was performed in each case. All 4 cases were categorized as Breast Imaging- Reporting and Data System (BI-RADS)-4. Trucut biopsy was performed and histopathological analysis revealed the diagnosis of NEBC. Patients underwent Surgery followed by Chemotherapy, Hormonal Therapy or Radiation therapy alone or in combination with each other depending upon the histopathological characteristics.

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Abbreviations: NEBCs, Neuroendocrine breast cancers; NET, Neuroendocrine tumors; BI-RADS, Breast Imaging- Reporting and Data System; WHO, World Health Organization; USG, Ultrasonography; ER, Estrogen receptor; PR, Progesterone receptor; HER2/neu, Human epidermal growth factor receptor; UIQ, Upper Inner Quadrant; CT, Computed Tomography; GA, General anaesthesia; DAB, 3,3′-diaminobenzidine; H & E, Hematoxylin and Eosin.

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Introduction

Neuroendocrine tumors (NET) are neoplasms originating from specialized neuroendocrine tissues found throughout the body, primarily in the gastrointestinal tract, pancreas, and lungs. Primary neuroendocrine carcinoma of the breast is a distinct and rare type of breast carcinoma, with an incidence rate of 0.3%-0.5% [1]. It was first recognized and reported by Feyrter and Hartmann in 1963 [2]. To confirm the diagnosis, immunohistochemistry markers for neuroendocrine differentiation, mainly Chromogranin and Synaptophysin, are used, as clinical features and morphology offer little help in distinguishing NEBCs from other breast cancer subtypes [3]. In 2003, the World Health Organization (WHO) classification of tumors of the breast and female genital organs defined NEBC as a specific histological type of invasive breast carcinoma, where more than 50% of the tumor cells express at least 1 neuroendocrine marker [4]. Microscopically, a metastatic NET may be mistaken for primary mammary carcinoma; therefore, the possibility of metastasis to the breast should be ruled out through clinical and radiological examination. Compared to other breast carcinoma subtypes, it tends to follow a more aggressive course with a higher likelihood of local and distant recurrence [5]. We conducted a retrospective analysis of all histopathologically confirmed cases of primary NEBCs imaged in our department between 2019 and 2023, using departmental records and the institutional picture archiving and communication system (PACS). We identified 4 such cases. This series presents their imaging features, correlated with histopathological findings.

Case description, diagnosis and management

Case 1

A 42 years old female presented with painless lump in her left breast for a period of 1 month. It was not associated with overlying skin changes, nipple discharge or any other swelling in right breast or bilateral axilla. On clinical examination, a well-defined, hard, nontender lump was felt in her left breast. Patient was subjected to a diagnostic mammogram (Table 1).

On mammography, an irregular, high density lesion with obscured margins of size ~3.18 × 3.4 × 2.8 cm was noted in middle and posterior 1/3rd of Upper Inner Quadrant (UIQ) of left breast. On Ultrasonography (USG) correlation, an irregular hypoechoic lesion with microlobulated margins, and posterior enhancement without significant vascularity was noted at 10 o'clock position of left breast, categorised as BIRADS 4b lesion. Contrast enhanced mammogram was done which demonstrated Intense homogenous enhancement in early phase (image acquisition done in cranio-caudal view after 2 minutes of contrast administration) with washout on delayed scan (image acquisition done in medial- lateral oblique view after 6 minutes of contrast administration) so BI-RADS was upgraded to 4c (Fig. 1).

Thereafter, patient underwent trucut biopsy of the left breast lesion. Histopathological examination revealed tumor disposed in sheets, nests, cords, and trabeculae. The tumor cells were pleomorphic, round nuclei with stippled to coarse chromatin, occasional nucleolar and scant amounts of pale cytoplasm. Intervening stroma showed myxoid to chondroid

Table 1 – Summary of the clinical presentation, Imaging features, IHC findings and the treatment approaches in all 4 cases.

Case	Clinical presentation	Radiological features		IHC	Treatment approaches
		Mammography	USG		
1	Painless lump	Irregular, high density lesion with obscured margins. CESM- early Intense enhancement with washout on delayed scan.	Irregular hypoechoic lesion with micro lobulated margins, and posterior enhancement.	**Triple negative** Synaptophysin + CD-56 + INSM 1 –Chromogranin A - Ki-67—80%-90%	Left MRM with axillary dissection followed by chemotherapy.
2	Painless lump	Oval, high density, circumscribed lesion.	Irregular, isoechoic lesion with microlobulated margins.	**Luminal B-like** ER+, PR + Her 2-neu - Synaptophysin + Chromogranin + Ki-67—5%	Left MRM with axillary clearance with adjuvant chemotherapy and hormonal therapy.
3	Painless lump	Irregular, high density, lesion with indistinct margins.	Irregular, hypoechoic lesion with micro-lobulated margins. Few enlarged hypoechoic axillary lymph nodes with loss of fatty hilum.	**Luminal B-like** ER+, PR + Her 2-neu - Synaptophysin + INSM-1 + Chromogranin - Ki-67 - 90%.	Right MRM with axillary clearance followed by Chemotherapy, radiotherapy and hormonal therapy.
4	painless lump	Irregular, high density spiculated lesion	Irregular, hypoechoic spiculated lesion.	ER+, PR + Her 2-neu - Synaptophysin + chromogranin + Ki-67—4%	Right MRM with axillary clearance followed by chemotherapy and hormonal therapy.

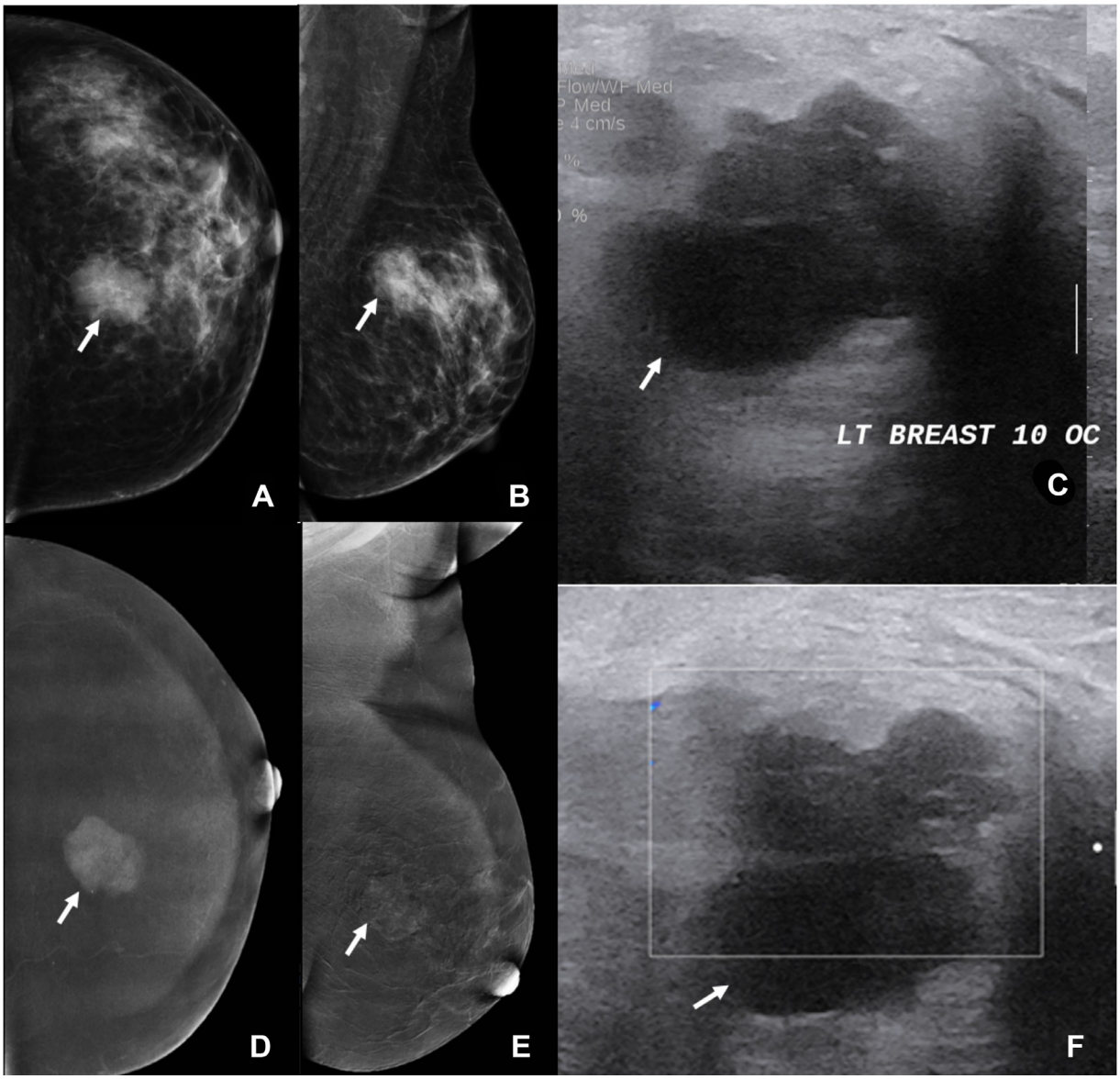

Fig. 1 – Case 1: Mammogram in (A) MLO and (B) CC views showing irregular, high-density lesion with microlobulated margins in UIQ of left breast. Ultrasound shows irregular hypoechoic lesion with microlobulated margins and no vascularity (C,F). Contrast enhanced mammogram- high energy images in CC view show intense homogenous enhancement in early scan (D) and washout in delayed scan in MLO view (E) [arrow].

matrix with focal mucin. Mitotic figures were evident with mitotic rate of 25-26 mitosis per 10 high power fields. On immunohistochemistry, the tumor was negative for Estrogen receptor (ER), Progesterone receptor (PR) and Human epidermal growth factor receptor (HER2/neu) classifying it as "Triple negative" molecular subtype. Ki-67 proliferation index was high (80%-90%). Synaptophysin and CD-56 were positive whereas INSM-1 and Chromogranin- A were negative suggesting the diagnosis of neuroendocrine breast carcinoma (Fig. 2). Patient underwent Modified radical mastectomy with ipsilateral axillary nodal dissection.

Contrast enhanced computed tomography (CT) scan of thorax and abdomen was performed for metastatic workup. There was no evidence of bony, pulmonary, or hepatic metastasis.

Thereafter, the patient underwent left modified radical mastectomy with axillary dissection under General anesthesia (GA). Histopathological evaluation of postoperative specimen confirmed the diagnosis of poorly differentiated neuroendocrine breast carcinoma with Nottingham Histological grade- 3 (score 8). No evidence of lympho-vascular or perineural invasion was present. Surgical margins were clear. No

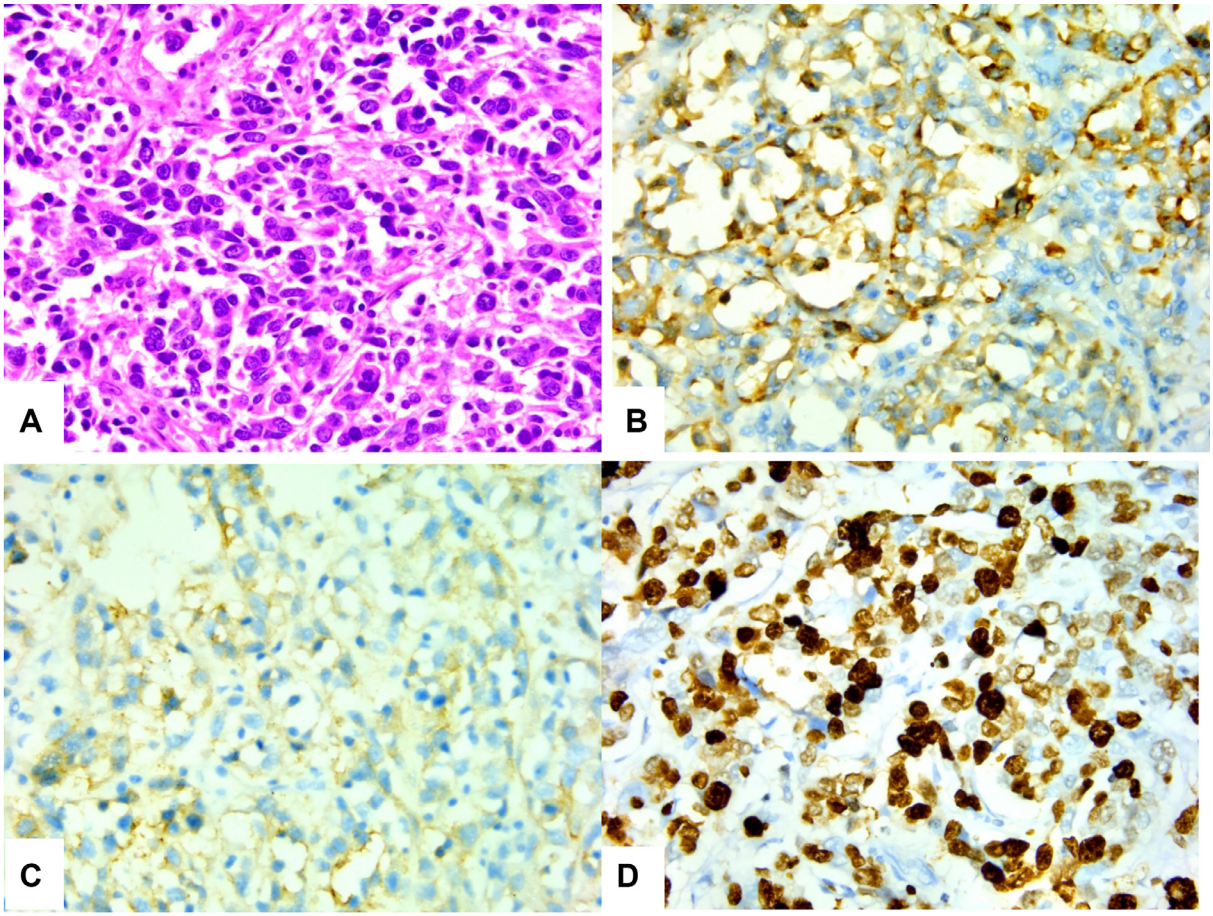

Fig. 2 – Case 1: Histology image through a section from a poorly differentiated neuroendocrine carcinoma: cells in sheets and nests with round to oval nuclei and fragile stippled chromatin showing moderate nuclear pleomorphism (H&EX400) (A). Sections show positivity for synaptophysin (B), CD-56 (C) with very high ki-67 index (B-D DABX400).

evidence of metastasis in the axillary lymph nodes was noted. The patient received 6 cycles of chemotherapy (Etoposide and Carboplatin) and currently is on remission.

Case 2

A 62-year-old female with postmenopausal status presented with a painless lump in left breast for 2 months. On clinical examination, there was well-defined hard lump in lower inner quadrant of left breast. She underwent bilateral breast mammography which revealed an oval, high density, circumscribed lesion in lower inner quadrant of left breast. A solitary group of punctate calcification was also present in UOQ. On USG, there was presence of irregular, isoechoic lesion measuring ~1.7 × 1.5 × 1 cm with micro lobulated margins in left breast with mild peripheral and central vascularity on color Doppler (Fig. 3). The left breast lesion was characterized as BI-RADS 4b.

Trucut biopsy of the left breast lesion was performed followed by histopathological examination which revealed tumor arranged in form of nests and lobules which were floating in pools of mucin with round nuclei, stippled chromatin, inconspicuous nucleoli and moderate cytoplasm. Immunostaining depicted strong cytoplasmic positivity of Synaptophysin and chromogranin with Ki-67 proliferation index of 5%. Tumor was positive for ER and PR and negative for HER2/neu with molecular classification of "Luminal B-like". Therefore, diagnosis of Mucinous breast carcinoma with neuroendocrine differentiation was made (Fig. 4).

Patient underwent left modified radical mastectomy with axillary clearance under GA. Postoperative specimen was sent for histopathological examination which confirmed the preoperative diagnosis of mucinous carcinoma with neuroendocrine differentiation with no evidence of lymph-nodal metastasis. Patient received adjuvant chemotherapy with 4 cycles of Adriamycin and cyclophosphamide followed by 4 cycles of Paclitaxel and planned on hormonal therapy of Letrozole for 10 years.

Case 3

A sixty-three years old woman with postmenopausal status presented with lump in right breast for a period of 3 months. It was not associated with overlying skin changes, nipple discharge or any other swelling in left breast. On clinical examination, there was well-defined lump at 5 o′ clock position of right breast. Mammography reveals an irregular, high density,

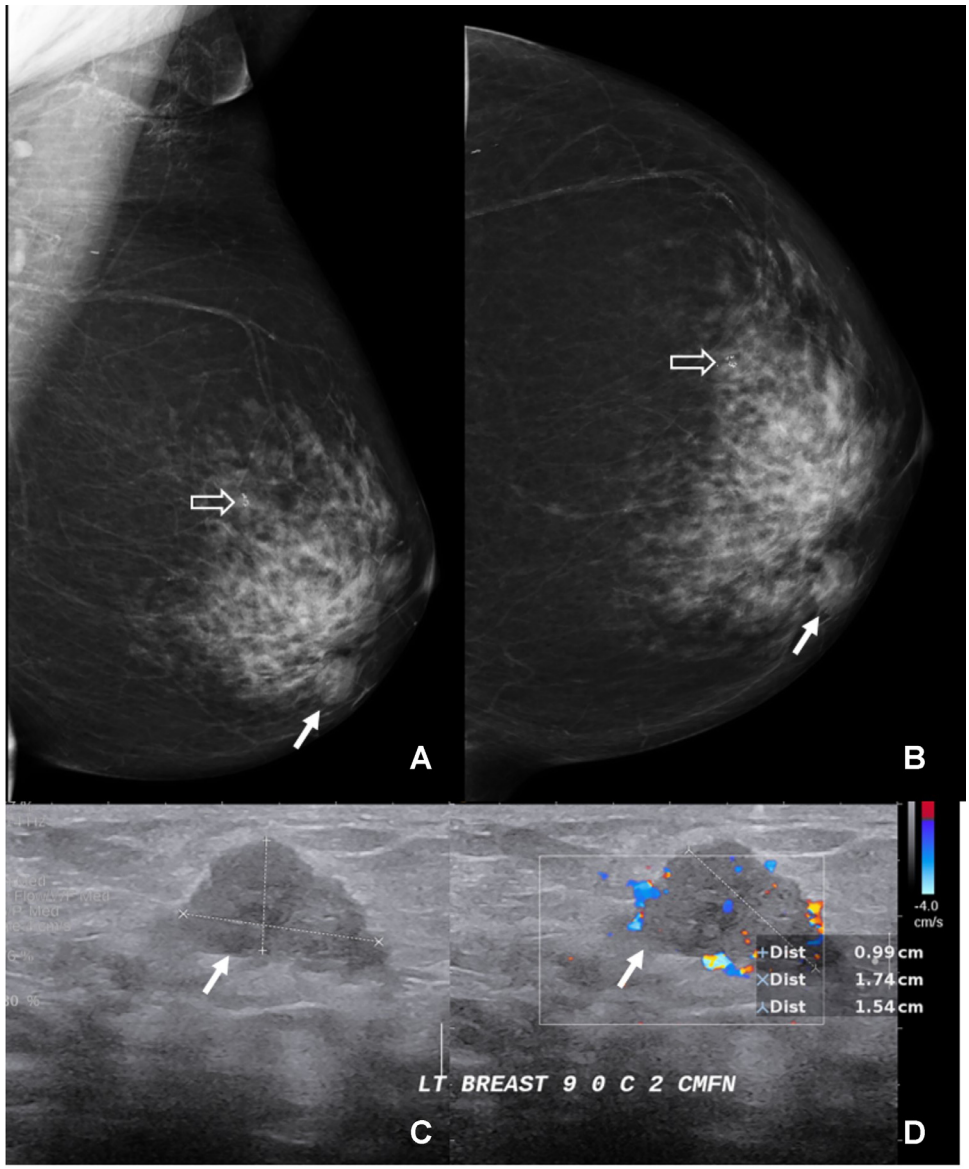

Fig. 3 – Case 2: Mammogram in (A) MLO and (B) CC views show irregular equal-density lesion with circumscribed margins in upper inner quadrant of left breast. Ultrasound shows irregular hypoechoic lesion with micro lobulated margins (C) and vascularity on color Doppler (D) [soild arrow]. A solitary group of punctate calcification is also visible in UOQ on Mammogram (blank arrow).

lesion with indistinct margins and adjacent trabecular thickening in LIQ of right breast. Sonography reveals an irregular, hypoechoic lesion with microlobulated margins measuring ~2.6 × 2.8 × 3 cm at 5-6 O'clock position showing mild central and peripheral vascularity. Few enlarged hypoechoeic lymph nodes with loss of fatty hilum were present in right axilla suggesting infiltration (Fig. 5).

USG guided linear core biopsy of the right breast lesion was performed followed by histopathological examination which revealed tumor disposed in sheets, nests, cords, and organoid pattern. Tumor cells were moderately pleomorphic, round nuclei with stippled to coarse chromatin and scant amounts of pale eosinophilic cytoplasm. Immunohistochemistry reveals ER/PR positive and Her-2 neu negative tumor with molecular classification of "Luminal B-like". Synaptophysin and INSM-1 were positive and chromogranin was negative with Ki-67 proliferation index of 90%. Therefore, diagnosis of NEBC was made (Fig. 6).

Patient underwent right modified radical mastectomy with axillary clearance under GA. Postoperative specimen was sent for histopathological examination which confirmed the preoperative diagnosis of NEBC with 5 lymph nodal metastasis. Patient thereafter received 6 cycles of chemotherapy (Etoposide and Carboplatin) followed by 15 cycles of radiotherapy and planned on hormonal therapy of aromatase inhibitor Letrozole for 10 years.

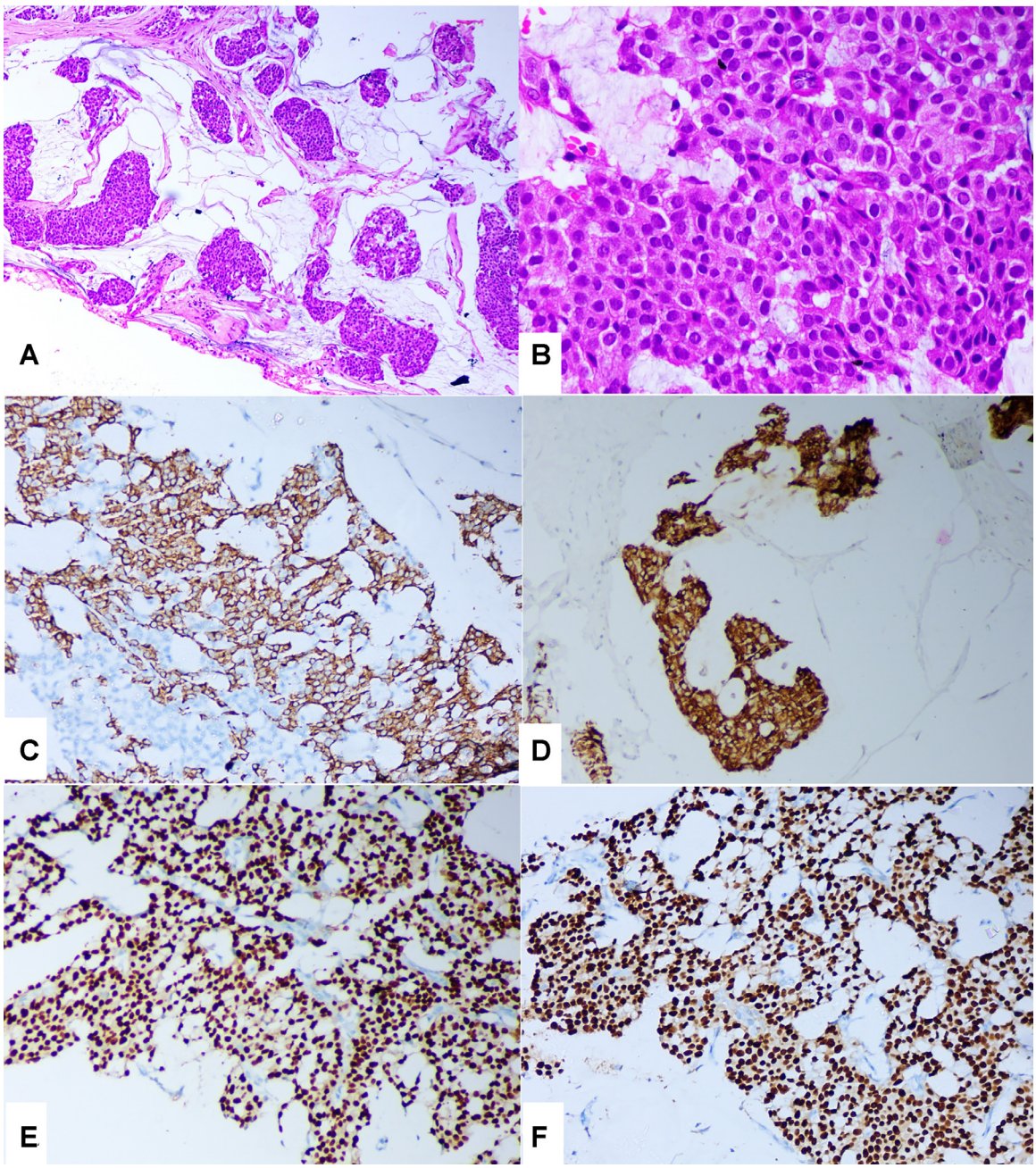

Fig. 4 – Case 2: Haematoxylin and Eosin stained section showing tumor cells arranged in form of nests and lobules. Cells are floating in pools of mucin, 100x (A), Hematoxylin and Eosin stained section shows tumor cells with round nuclei. Stippled chromatin, inconspicuous nucleoli and moderate cytoplasm is also visible, 400x (B), Immunostain, Synaptophysin showing strong cytoplasmic positivity in tumor cells, 200x (C), Immunostain chromogranin showing strong cytoplasmic positivity in tumor cells, 200x (D), Immunostain estrogen receptor (ER) showing strong (3+) nuclear positivity in approx. 100% tumor cells, 200x (E), Immunostain progesterone receptor (PR) showing strong (3+) nuclear positivity in approx. 100% tumor cells, 200x (F).

Case 4

A sixty-eight Year old female presented with painless lump in her right breast for 2 months. On clinical examination, lump was hard and nontender. Diagnostic mammography revealed an irregular, high density lesion with spiculated margins and adjacent trabecular thickening in upper outer quadrant of right breast. Two other oval lesions with equal density and circumscribed margins were also noted, with one showing coarse calcifications. On sonography, an irregular, hypoechoic lesion with spiculated margins was seen at 9 o' clock position with no significant vascularity on color Doppler in

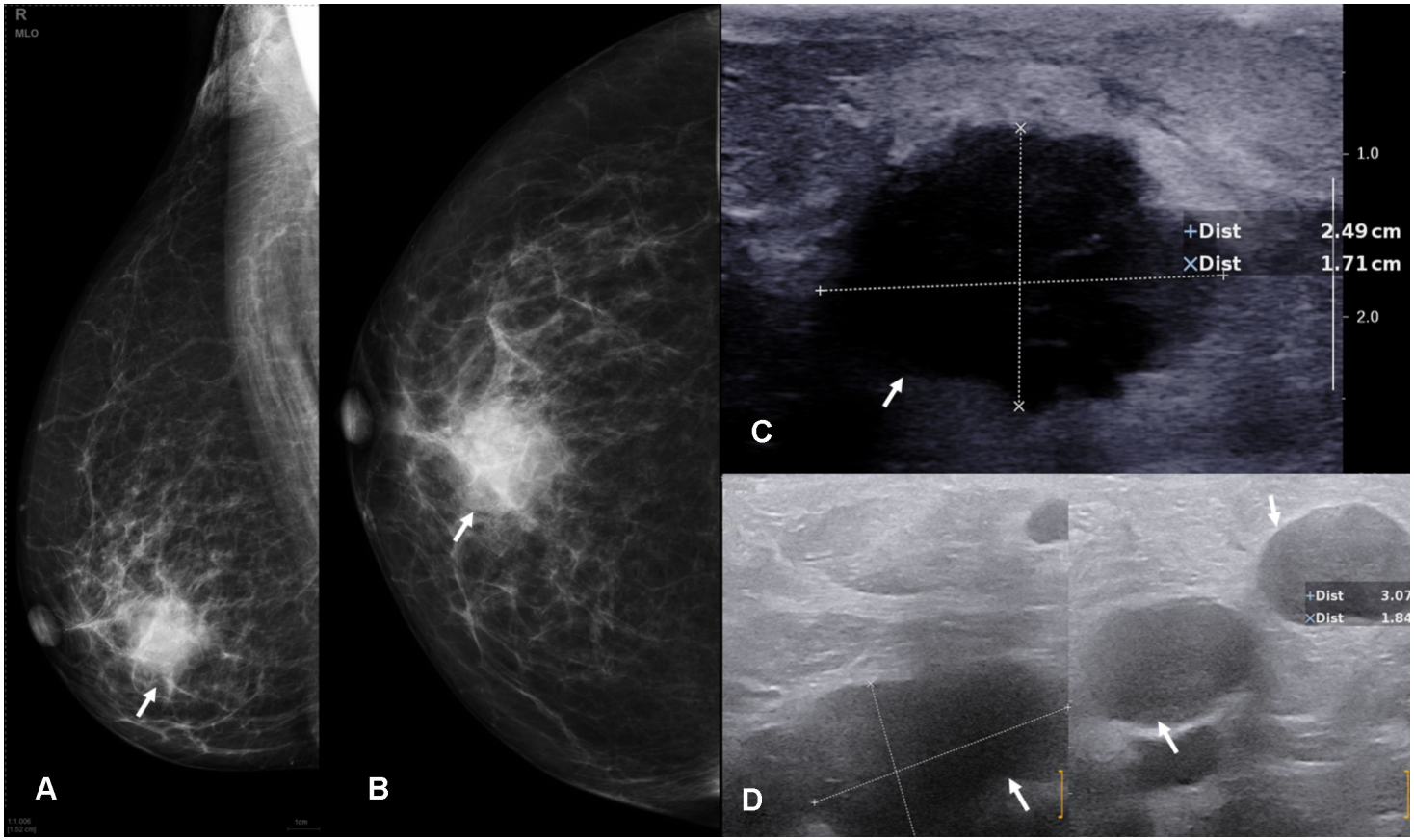

Fig. 5 – Case 3: Right breast mammogram in MLO (A) and CC views (B) shows irregular high-density lesion with indistinct margins in lower inner quadrant. Ultrasound shows irregular hypoechoic lesion with micro lobulated margins (C). Few enlarged hypoechoeic lymph nodes with loss of fatty hilum were present in right axilla suggesting infiltration (D) [arrow].

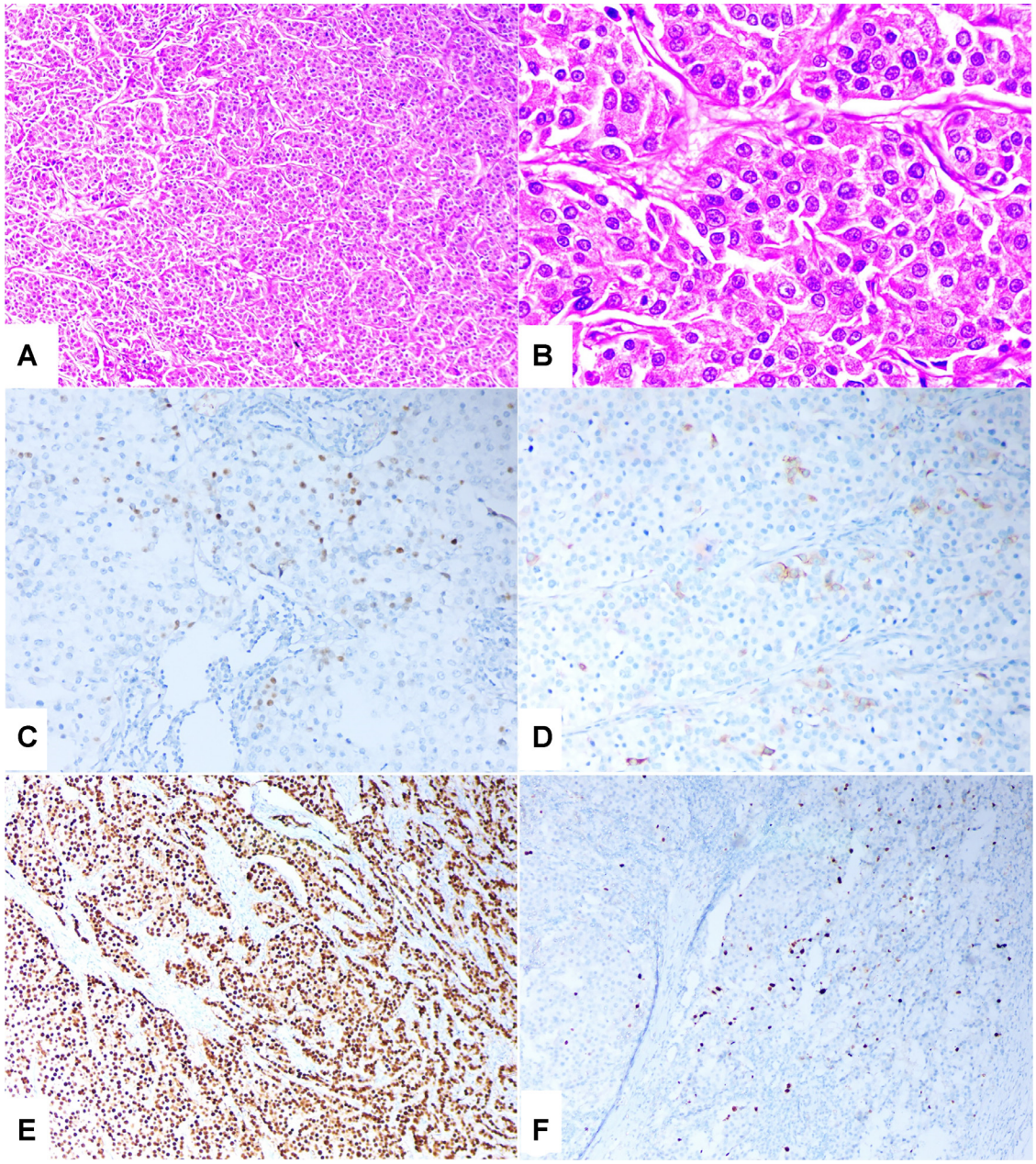

Fig. 6 – Case 3: Hematoxylin and Eosin stained section showing tumor arranged in form of nests, lobules and organoid pattern, 100x (A), H & E stained section showing tumor cells in nests. The cells show round nuclei, salt pepper chromatin, conspicuous nucleoli and moderate cytoplasm, 400x (B), Immunostain INSM-1 showing focal nuclear positivity in tumor cells, 200x (C), Immunostain, Synaptophysin showing focal cytoplasmic positivity in tumor cells, 200x (D), Immunostain Estrogen receptor (ER) showing strong (3+) nuclear positivity in approx. 100% tumor cells, 100x (E), Immunostain progesterone receptor (PR) showing strong (3+) nuclear positivity in 2%-4% tumor cells, 100x (f).

right breast and categorized as BI-RADS 4C. Rest 2 lesions were oval, well circumscribed, homogenously hypoechoic, parallel lesions suggesting the diagnosis of Fibroadenoma, and were categorized as BI-RADS 3 (Fig. 7).

USG guided biopsy of the suspicious lesion was performed followed by histopathological examination which revealed tumor disposed in nests separated by fibrovascular septae. Tumor cells were monomorphic with eccentrically placed round nucleus and stippled chromatin showing mitosis and necrosis. Immunohistochemistry revealed ER/PR positive and Her-2 neu negative tumor. Synaptophysin and Chromogranin were positive with Ki-67 index of 4%. Therefore, diagnosis of neuroendocrine tumor was made.

Patient underwent right modified radical mastectomy with axillary clearance under GA. Postoperative specimen was sent for histopathological examination which confirmed the preoperative diagnosis of neuroendocrine breast carcinoma with no lymph nodal metastasis. Patient thereafter received 6 cy-

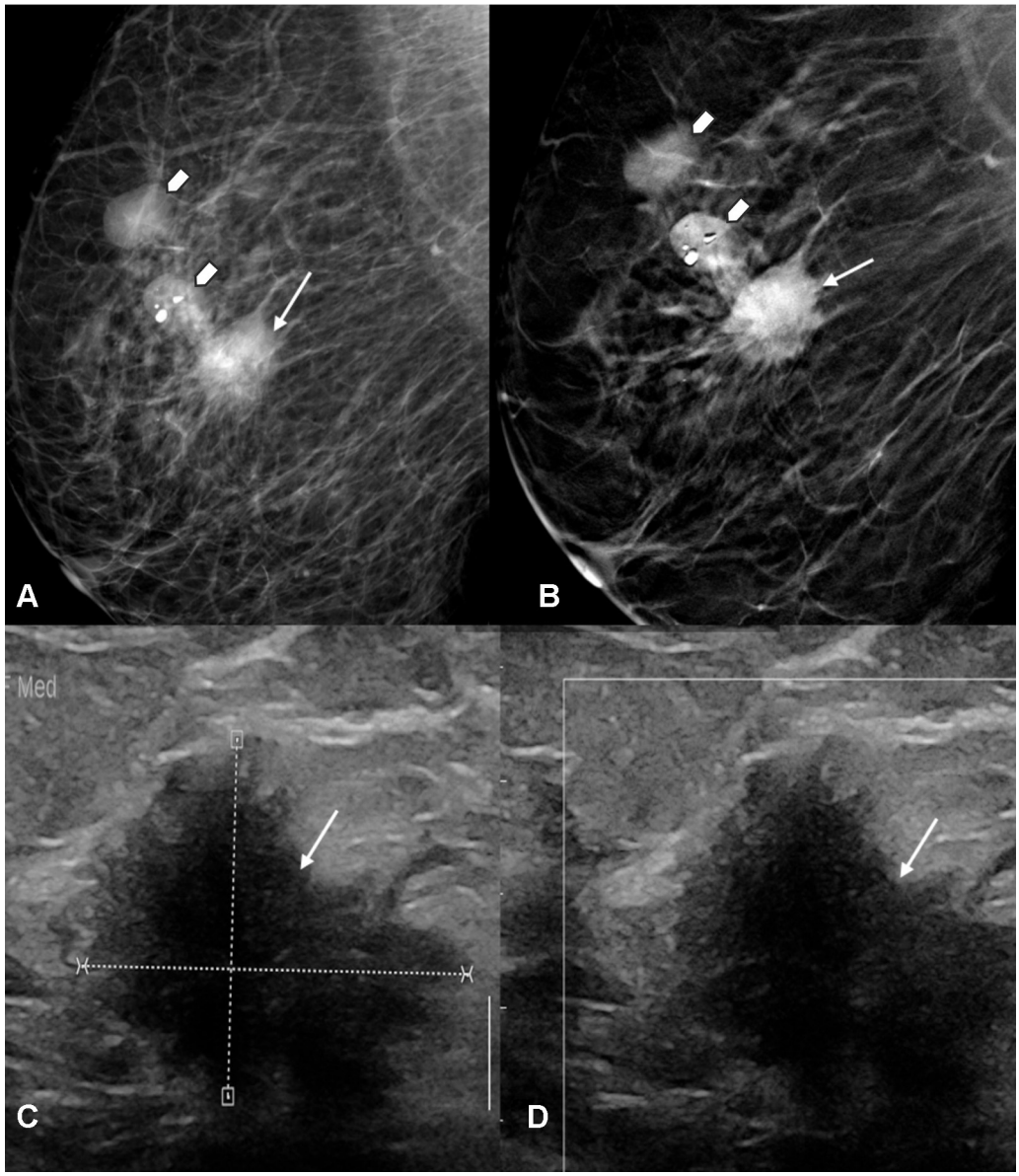

Fig. 7 – Case 4: Mammogram in MLO view shows an irregular high density lesion with spiculated margins in right breast (A), better demonstrated on 2D synthesized mammogram (B). USG correlation reveals an irregular hypoechoic spiculated lesion (C) with no significant vascularity on color Doppler (D) [arrow]. Also note the presence of 2 oval circumscribed equal density lesions in right breast, one showing coarse calcifications categorized as BIRADS 3 (short white arrow).

cles of chemotherapy (Doxorubicin and Cyclophosphamide) and planned on hormonal therapy of aromatase inhibitor Letrozole for 10 years.

Discussion

Breast cancer is the most common cancer in women worldwide with improved survival rates due to better screening methods, early diagnosis and advanced treatment techniques. Primary neuroendocrine tumor of breast is less recognized subtype of breast carcinoma [6]. It was only in 2003, however, that the WHO recognized neuroendocrine tumors of the breast as a separate entity of breast cancer, based on the definition provided by Sapino et al. [7]. In 2012, the WHO acknowledged that the 50% threshold of cells with neuroendocrine markers expression was arbitrary; therefore in the new classification, invasive carcinomas with neuroendocrine differentiation were included in the group of NEBC regardless of the percentage of tumor cells expressing neuroendocrine markers [5]. According to the 2012 WHO classification, based on morphology, breast tumors with neuroendocrine features are divided into 3 groups: (a) neuroendocrine tumor, well-

differentiated (carcinoid-like); (b) neuroendocrine carcinoma, poorly differentiated/small-cell carcinoma; and (c) invasive carcinoma with neuroendocrine differentiation.

In 2019, newly revised WHO classification described the term "Neuroendocrine neoplasm" as a term for all tumors with dominant neuroendocrine differentiation, dividing into (a) neuroendocrine tumor, including G1 and G2, and (b) neuroendocrine carcinoma, including small cell and large cell. Invasive carcinomas without dominant neuroendocrine features (<10% neuroendocrine morphology) are classified as invasive carcinoma, no special type (NST). Tumors with ≥10% neuroendocrine morphology are included in the category of neuroendocrine neoplasm, and further divided into neuroendocrine tumor and carcinoma [8]. The diagnosis of primary breast carcinoma with neuroendocrine feature requires complete clinical, radiological and pathological examination of the patients [7]. These tumors are usually seen in elderly postmenopausal women in sixth–seventh decade of life [9]. In our case series, 3 women were postmenopausal and one was premenopausal. Patients with NET usually present with breast lump, ulceration or nipple discharge [9]. In our study, all 4 cases presented with breast lump.

Park et al evaluated the clinical, imaging, and histopathologic characteristics of primary neuroendocrine breast carcinoma. NEBC was visible on 94.3% mammograms and occult on 5.7%. All mammographically occult cancers were visible at Ultrasound. On mammograms, the most common presentation was a mass (82.9%) followed by calcifications (26.4%). Of the masses, 69.7% were round, oval, or lobular and 30.3% were irregular. About 77.9% masses had circumscribed, obscured, indistinct, or microlobulated margins and 22.1% had spiculated margins. Most common Ultrasound features were irregular shape (65.4%), indistinct margin (43.6%), hypoechoic echopattern (78.4%), and had no or enhanced posterior acoustic features (77.9%) [10]. Jeon CH also evaluated imaging features of NET. On mammogram, most common shape was oval followed by irregular. On Sonography, most of the lesions were irregular, hypoechoic without posterior features [11]. Few other studies have also shown same results [12,13]. In our series too, most common Mammographic pattern was irregular shaped, high density lesion with variable margin characteristics. Most common USG pattern was an irregular, hypoechoeic, lesions with microlobulated margins and no posterior features.

Neuroendocrine-type primary breast carcinomas are believed to arise from the varied endocrine and exocrine differentiation of a neoplastic epithelial progenitor cell during carcinogenesis, rather than from pre-existing neuroendocrine stem cells. This theory is supported by 3 main points: (a) the absence of reported hyperplastic or benign neuroendocrine lesions in the breast, unlike other organs such as the gastrointestinal tract and lungs; (b) breast carcinomas with neuroendocrine differentiation resemble typical breast cancers in their histopathological characteristics; and (c) breast cancer cells with undifferentiated features have demonstrated the capability for neuroendocrine expression [14].

In primary neuroendocrine carcinoma of the breast, over 50% of the cell population exhibits neuroendocrine differentiation. In a study by Keltan et al. [15], Synaptophysin was positive in 34 cases and negative in 2 cases, whereas Chromogranin showed positive staining in 23 cases and negative in 13 cases. Both synaptophysin and chromogranin were positive in 16 cases. In the current case series, there is diffuse positivity for synaptophysin and negativity for chromogranin in 2 cases, while both synaptophysin and chromogranin are positive in another 2 cases.

In a case study by Yiqun Li et al. [16], ER and PR receptors were detected in 81.0% and 72.2% of patients, respectively, while the HER-2 protein was overexpressed in 15.1% of patients. However, the presence of the ER alone is insufficient to confirm the mammary origin of a neoplasm, as it does not exhibit universal expression in normal breast tissues and is not exclusive to mammary tumors. Furthermore, the expression of the androgen receptor is lower in neuroendocrine tumors (15%-18%) compared to nonspecial luminal invasive carcinomas [17]. In the current series of cases, 1 case demonstrated negativity for ER, PR and HER-2 neu receptors, and was categorized as triple-negative according to molecular classification. In the other 3 cases, both ER and PR were positive, with HER-2 neu being negative.

Breast carcinomas which show neuroendocrine differentiation are- mucinous carcinoma, ductal carcinoma, infiltrating lobular carcinoma, low-grade insular carcinoma, small cell undifferentiated carcinoma, and ductal carcinoma in situ. Notably, mucinous carcinoma has the strongest association with neuroendocrine differentiation [18,19]. In our study, Patient 2 was diagnosed with mucinous breast carcinoma that exhibited neuroendocrine differentiation. Kashiwagi et al. conducted subtyping in 71 cases of mucinous carcinoma based on hormone receptor (HR) and HER2 expression. Their findings revealed that of these cases, 68 (95.8%) were HR-positive/HER2-negative, 1 (1.4%) was HR-negative/HER2-positive, and 2 (2.8%) were HR-negative/HER2-negative [20]. Our second case tested positive for ER and PR, and negative for HER2/neu. Generally, tumors that are ER+/PR+ have a better prognosis compared to those with high levels of HER2/neu expression [21]. Although mucinous carcinomas with neuroendocrine differentiation generally prognosticate well, an overexpression of HER2/neu is associated with an increased risk of recurrence and metastasis [22].

In the management of neuroendocrine tumors, the treatment strategies often mirror those used for various types of invasive breast cancer [23,24]. However, the lack of data from prospective clinical trials limits our understanding of their optimal management [17]. While breast-conserving surgery (BCS) with or without adjuvant therapy is commonly employed, mastectomy is generally preferred due to the aggressive nature of neuroendocrine tumors at an early stage [25]. It is crucial to distinguish between primary and metastatic neuroendocrine tumors to determine the most appropriate surgical approach, whether BCS or mastectomy, along with axillary node dissection [3]. In the case series presented here, all 4 patients underwent modified radical mastectomy with axillary clearance.

Radiotherapy to the chest wall should be administered if there is evidence of skin, pectoral muscle, or thoracic wall involvement, or if there are 4 or more metastatic axillary lymph nodes [17]. The protocols for adjuvant radiotherapy in NEBC are not specifically studied but are based on the guidelines proposed for various subtypes of inva-

sive breast cancer [26,27]. Our 3 patients were not scheduled to receive radiotherapy due to the lack of involvement of the chest wall, skin, or lymph nodes. However, Patient-3, who had lymph nodal metastasis, underwent 15 cycles of radiotherapy.

Adjuvant systemic therapy is determined on a case-by-case basis, taking into account factors such as the patient's age, comorbidities, stage, biological characteristics of the tumor, and risk of relapse [28]. Patients diagnosed with hormone receptor-positive tumors are typically considered for adjuvant hormonal therapy. Our first patient, who has triple-negative cancer, did not receive endocrine therapy. Meanwhile, patients with postmenopausal status and positive ER/PR status are prescribed the aromatase inhibitor letrozole for duration of 10 years.

In several studies, the Ki-67 index served as the basis for choosing adjuvant chemotherapy. Patients with a Ki-67 index of $\leq$ 15% were administered an anthracycline-based regimen, while those with a Ki-67 index $>$ 15% were treated with cisplatin and etoposide [29,30]. This approach aligns with our case series: patients with a Ki-67 index of 80-90% underwent cycles of etoposide and carboplatin, whereas those with a Ki-67 index of 4%-5% received 6 cycles of cyclophosphamide and doxorubicin.

In conclusion, primary neuroendocrine tumors of the breast are less recognized entities, and their biological behavior, clinical and imaging features, treatment, and prognosis remain poorly understood. Since radiological features are insufficient to distinguish these tumors from invasive breast carcinoma, reporting new cases is crucial for their identification through imaging. In the era of precision medicine, prioritizing targeted molecular strategies is essential. This remains a vital area of research for understanding and developing the most appropriate therapeutic plans to improve clinical outcomes.

Patient consent

Written informed consent for patient information and images to be published was provided by the patients.

REFERENCES

[1] Yuan M, Chen D, Sun H, Wang X, Wan D. Primary neuroendocrine carcinoma of the breast with leptomeninges metastasis: a case report and literature review. J Int Med Res 2022;50(9). doi:10.1177/03000605221118505.

[2] Feyrter F, Hartmann G. Uber die carcinoide wuchsform des carcinoma mammae, insbesondere das carcinoma solidum (gelatinosum) mammae [on the carcinoid growth form of the carcinoma mammae, especially the carcinoma solidum (gelatinosum) mammae]. Frankf Z Pathol 1963;73:24–39 German.

[3] Inno A, Bogina G, Turazza M, Bortesi L, Duranti S, Massocco A, et al. Neuroendocrine carcinoma of the breast: current evidence and future perspectives. Oncologist 2016;21(1):28–32. doi:10.1634/theoncologist.2015-0309.

[4] Hanby, AM., walker, C. Tavassoli FA, Devilee P: Pathology and genetics: tumours of the breast and female genital organs. WHO Classification of Tumours Series - Volume IV. Lyon, France: IARC Press. https://doi.org/10.1186/bcr788.

[5] Yuan M, Chen D, Sun H, Wang X, Wan D. Primary neuroendocrine carcinoma of the breast with leptomeninges metastasis: a case report and literature review. J Int Med Res 2022;50(9):3000605221118505. doi:10.1177/03000605221118505.

[6] Nounou MI, ElAmrawy F, Ahmed N, Abdelraouf K, Goda S, Syed-Sha-Qhattal H. Breast cancer: conventional diagnosis and treatment modalities and recent patents and technologies. Breast Cancer (Auckl) 2015;9(Suppl 2):17–34. doi:10.4137/BCBCR.S29420.

[7] Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, et al. The 2019 World Health Organization classification of tumours of the breast. Histopathology 2020;77(2):181–5. doi:10.1111/his.14091.

[8] Pareja F, D'Alfonso TM. Neuroendocrine neoplasms of the breast: a review focused on the updated World Health Organization (WHO) 5th edition morphologic classification. Breast J 2020;26:1160–7.

[9] Park Sang Eun, Cho Kyu Ran, Song Sung Eun, Woo Ok Hee, Seo Bo Kyoung, Lee Jeonghyun. Mammographic, sonographic, and MRI features of primary neuroendocrine carcinoma of the breast: a case report. J Korean Soc Radiol 2021;82(3):737–42. doi:10.3348/jksr.2020.0105.

[10] Park YM, Wu Y, Wei W, Yang WT. Primary neuroendocrine carcinoma of the breast: clinical, imaging, and histologic features. AJR Am J Roentgenol 2014;203(2):W221–30. doi:10.2214/AJR.13.10749.

[11] Jeon CH, Kim SM, Jang M, Yun BL, Ahn HS, Kim SW, et al. Clinical and radiologic features of neuroendocrine breast carcinomas. J Ultrasound Med Aug 2014;33(8):1511–18. doi:10.7863/ultra.33.8.1511.

[12] Günhan-Bilgen I, Zekioglu O, Ustün EE, Memis A, Erhan Y. Neuroendocrine differentiated breast carcinoma: imaging features correlated with clinical and histopathological findings. Eur Radiol 2003;13:788–93.

[13] Ogawa H, Nishio A, Satake H, Naganawa S, Imai T, Sawaki M, et al. Neuroendocrine tumor in the breast. Radiat Med 2008;26:28–32.

[14] Righi L, Sapino A, Marchiò C, Papotti M, Bussolati G. Neuroendocrine differentiation in breast cancer: established facts and unresolved problems. Semin Diagn Pathol Feb 2010;27(1):69–76. doi:10.1053/j.semdp.2009.12.003.

[15] Talua CK, Leblebicia C. Tulin Kilicaslan Ozturkb, Primary breast carcinomas with neuroendocrine features: clinicopathological features and analysis of tumor growth patterns in 36 cases. Ann Diagn Pathol 2018;34:122 113. doi:10.1016/j.anndiagpath.2018.03.010.

[16] Li Y, Du F, Zhu W, Xu B. Neuroendocrine carcinoma of the breast: a review of 126 cases in China. Chin J Cancer 2017;36:45. doi:10.1186/s40880-017-0211-x.

[17] Irelli A, Sirufo MM, Morelli L, D'Ugo C, Ginaldi L, De Martinis M. Neuroendocrine cancer of the breast: a rare entity. J Clin Med 2020;9(5):1452. doi:10.3390/jcm9051452.

[18] Scopsi L, Andreola S, Pilotti S, Bufalino R, Baldini MT, Testori A, et al. Mucinous carcinoma of the breast: a clinicopathologic, histochemical, and immunocytochemical study with special reference to neuroendocrine differentiation. Am J Surg Pathol 1994;18(7):702–11.

[19] Tse GM, Ma TK, Chu WC, Lam WW, Poon CS, Chan WC. Neuroendocrine differentiation in pure type mammary mucinous carcinoma is associated with favorable histologic and immunohistochemical parameters. Mod Pathol 2004;17(5):568–72. doi:10.1038/modpathol.3800092.

[20] Kashiwagi S, Onoda N, Asano Y, Noda S, Kawajiri H, Takashima T, et al. Clinical significance of the sub-classification of 71 cases mucinous breast carcinoma. Springerplus 2013;2:481. doi:10.1186/2193-1801-2-481.

[21] Adair JD, Harvey KP, Mahmood A, Caralis J, Gordon W, Yanish G. Recurrent pure mucinous carcinoma of the breast with mediastinal great vessel invasion: HER-2/neu confers aggressiveness. Am Surg 2008;74(2):113–16.
[22] Varadharajan E, Priya S, Prakash G, Mugundan A, Easwaramurthi P. Mucinous carcinoma of the breast with neuroendocrine differentiation. Iran J Pathol 2015;10(3):231–6 Summer.
[23] National Comprehensive Cancer Network. Breast Cancer (Version 3). 2020. Available online: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, (accessed on 16 March 2020).
[24] Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 2018;31(12):1770–86. doi:10.1038/s41379-018-0110-y.
[25] Hare F, Giri S, Patel JK, Hahn A, Martin MG. A population-based analysis of outcomes for small cell carcinoma of the breast by tumor stage and the use of radiation therapy. Springerplus 2015;4:138. doi:10.1186/s40064-015-0913-y.
[26] Abou Dalle I, Abbas J, Boulos F, Salem Z, Assi HI. Primary small cell carcinoma of the breast: a case report. J Med Case Rep 2017;11(1):290. doi:10.1186/s13256-017-1467-0.
[27] Adams RW, Dyson P, Barthelmes L. Neuroendocrine breast tumours: breast cancer or neuroendocrine cancer presenting in the breast? Breast 2014;23(2):120–7. doi:10.1016/j.breast.2013.11.005.
[28] Tremelling A, Samuel S, Murray M. Primary small cell neuroendocrine carcinoma of the breast: a case report and review of the literature. Int J Surg Case Rep 2017;38:29–31. doi:10.1016/j.ijscr.2017.07.002.
[29] Yildirim Y, Elagoz S, Koyuncu A, Aydin C, Karadayi K. Management of neuroendocrine carcinomas of the breast: a rare entity. Oncol Lett 2011;2(5):887–90. doi:10.3892/ol.2011.320.
[30] Li Y, Du F, Zhu W, Xu B. Neuroendocrine carcinoma of the breast: a review of 126 cases in China. Chin J Cancer 2017;36(1):45. doi:10.1186/s40880-017-0211-x.