Original Article

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Histopathological Features Predicting Neuroendocrine Morphology in Primary Breast Tumors: A Retrospective Analysis

Mine Ozsen[1], Kazim Senol[2], Sahsine Tolunay[1], Mustafa Sehsuvar Gokgoz[2], Turkkan Evrensel[3]

[1]Department of Pathology, Uludag University Faculty of Medicine, Bursa, Turkey
[2]Department of General Surgery, Uludag University Faculty of Medicine, Bursa, Turkey
[3]Department of Medical Oncology, Uludag University Faculty of Medicine, Bursa, Turkey

ABSTRACT

Objective: Neuroendocrine neoplasms of primary breast tumors are rare compared to locations, such as the respiratory system and gastrointestinal system, where they are frequently observed. The diagnostic criteria for primary neuroendocrine tumors of the breast have been changed since first description. Morphological and immunohistochemical features helpful in their diagnosis, which vary due to the heterogeneous nature of these tumors, are highlighted in this retrospective study. The purpose was to determine specific histopathological features that can identify neuroendocrine morphology in primary breast tumors.

Materials and Methods: Cases diagnosed with invasive breast carcinoma from resection materials in a single center between 2011 and 2022 and in which neuroendocrine markers were investigated were included. Demographic information, initial histopathological diagnosis, presence of tumor in another organ, tumor location, size and surgical details of the cases were obtained from the hospital database and pathology reports. The slides were re-evaluated in terms of tumor growth pattern, cribriformity, tubule formation, nuclear features, prominence of nucleoli, palisading and basal location of nuclei, presence of grooves, cytoplasmic features and evidence of cytoplasmic border.

Results: The presence of basally located nuclei, absence of tubule formation, inconspicuous nucleoli, fine nuclear chromatin, granular cytoplasm and inconspicuous cytoplasmic borders were frequent findings in tumors with neuroendocrine features ($p<0.05$). These features may help differentiate primary breast tumors with neuroendocrine features from other breast carcinomas.

Conclusion: The histopathological features that are different from the specific features seen in classical neuroendocrine tumors, the absence of specific clinical and radiological findings, the inability to study neuroendocrine markers in every laboratory and the need to prove that the breast tumor is not a metastasis all create diagnostic difficulties for primary breast neuroendocrine neoplasms. We believe that the results of this study may help diagnose and identify more specific histomorphological features that help determine neuroendocrine morphology in primary breast tumors.

Keywords: Breast; neuroendocrine carcinoma; neuroendocrine neoplasia; neuroendocrine tumor; primary

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Key Point

- The histopathological features that are different from the specific features seen in classical neuroendocrine tumors, the absence of specific clinical and radiological findings, the inability to study neuroendocrine markers in every laboratory and the need to prove that the breast tumor is not a metastasis are all conditions that create diagnostic difficulties for primary breast neuroendocrine neoplasms. This study might help to understand and define the clinicopathological features of these rare tumors.

Introduction

Neuroendocrine neoplasms, which can occur in various locations, and are particularly common in the respiratory and gastrointestinal system, constitute less than 1% of all breast tumors (1).

Primary breast neuroendocrine tumors, which were first defined as "breast carcinoma with a carcinoid growth pattern" by Feyrter and Hartmann in 1963, were first included in the World Health Organization (WHO) classification in 2003 (2). Various changes have been made in the diagnostic criteria since the 2003 WHO classification (3rd edition, 2003) which are now present in the current classification (5th edition, 2019). In the latest classification, the diagnosis should be made by evaluating the expression rate of cells with neuroendocrine features and neuroendocrine markers. Thus, tumors showing neuroendocrine features and neuroendocrine

Corresponding Author:
Mine Ozsen; m.isikoglu@hotmail.com

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marker expression of more than 90% are defined as neuroendocrine neoplasms. Based on further evaluation of histological features, such as whether they show histology of a small or large cell neuroendocrine carcinoma (NEC), they may either be defined as a neuroendocrine tumor (NET) or NEC. Tumors with equivocal histological features and neuroendocrine marker expression are classified as invasive breast carcinoma of no special type (IBC-NST) with neuroendocrine differentiation. Although expressing neuroendocrine markers, solid papillary carcinoma and the hypercellular variant of mucinous carcinoma are tumors that are not classified as neuroendocrine neoplasms of the breast (3).

In this retrospective study, morphological and immunohistochemical features helpful and essential in the diagnosis, which vary due to the heterogeneous nature of these tumors, are highlighted. The main purpose of the study was to investigate specific histological features that can help identify neuroendocrine morphology in primary breast tumors.

Materials and Methods

Cases diagnosed with IBC from resection materials (lumpectomy, segmental mastectomy, modified radical mastectomy or breast-conserving mastectomy) in a single center between January 2011 and October 2022 and in which neuroendocrine markers (Synaptophysin and Chromogranin-A) were studied were included. Cases in which the slides were not suitable for re-evaluation or not accessible, all cases diagnosed with another classification than IBC-NST (including solid papillary carcinoma with synaptophysin and/or chromogranin immunoreactivity and hypercellular mucinous carcinoma) and metastatic NETs were excluded.

Demographic information, initial pathological diagnosis, presence of tumor in an organ other than breast, tumor location, tumor size and surgical information of the cases were obtained from the hospital database and pathology reports.

Hematoxylin and eosin (H&E) stained slides with a thickness of 4–5 micrometers and slides stained with Synaptophysin (Cell Margue, clone MRQ–40, Roche) and Chromogranin -A (Ventana, clone LK2H10, Roche) were re-evaluated by two independent pathologists based on the 2019 WHO Breast Tumors Classification. Tumors showing focal (<10%) neuroendocrine marker expression were defined as IBC-NST with neuroendocrine differentiation, while those with diffuse staining (>90%) were accepted as NET/NEC (Figure 1). The distinction between NET and NEC was made based on the histological features required for the diagnosis of small cell neuroendocrine carcinoma (SCNEC) and large cell neuroe ndocrine carcinoma (LCNEC) (3).

Initial microscopic examination of the tumors from H&E stained slides, included evaluation of the growth pattern, cribriformity, tubule formation, nuclear features, prominence of nucleoli, palisading and basal location of nuclei, presence of grooves, cytoplasmic features, evidence of cytoplasmic borders, tumor grade, presence of venous invasion, lymphatic invasion, perineural invasion, peritumoral desmoplastic reaction, percentage of tumor infiltrating lymphocytes (TIL), presence of tumor necrosis, and microcalcification. Evaluation of the immunohistochemistry slides was the second step of the microscopic examination.

Ethics approval for the study, dated November 10, 2022 and numbered 2022-17/29 was obtained from the Uludag University Faculty of Medicine Clinical Research Ethics Committee.

Statistical Analysis

If continuous variables were normally distributed, they were described as mean ± standard deviation (SD) if the $p>0.05$ in Kolmogorov-Smirnov test or Shapiro-Wilk test ($n<30$), and if the continuous variables were not normal, they were described as median (range). To calculate prevalence, data commands were used. Comparisons between groups were made using Kruskall-Wallis tests for non-normally distributed data. Categorical variables were compared between the groups using the chi-square test or Fisher's exact test.

The level for statistical significance was predetermined at $p<0.05$.

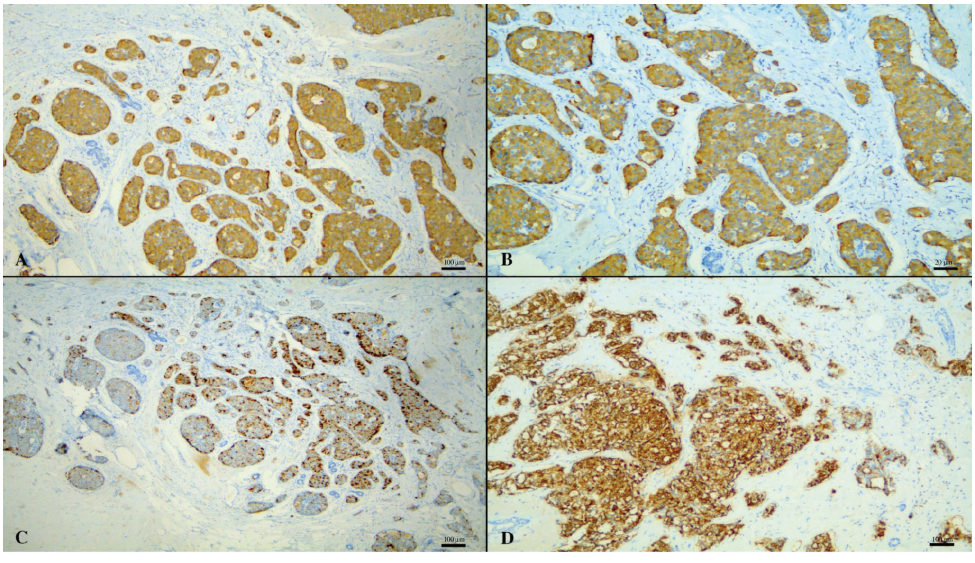

Figure 1. A-B) Diffuse, strong staining with synaptophysin in NET (x40 and x200). **C)** Focal staining with chromogranin in NET (x40). **D)** Synaptophysin staining observed in another NET (x40)

NET: Neuroendocrine tumor

Results

The retrospective study group consisted of 186 cases with available H&E and immunohistochemistry slides. Of the 186 cases, 185 (99.4%) were female and 1 (0.6%) was male. The mean ± SD age was 56.6±11.9 years, ranging from 30 to 85 years. The median age of patients diagnosed with IBC-NST was 55 (30–85) years and of patients with tumors showing neuroendocrine features, median age was 59 (31–83) years. There was no significant difference between the groups in terms of age (p = 0.113).

When histological and immunohistochemical features were re-evaluated, based on 2019 WHO Breast Tumors Classification, 54.8% of the cases were diagnosed as IBC-NST, while neuroendocrine features were found in 45.2%. Of the 84 tumors showing neuroendocrine features, 37 (19.9%) were IBC-NST with neuroendocrine differentiation, 44 (23.7%) were NET and 3 were LCNEC.

Median tumor size was 2.2 (0.5–9.0) cm. Median tumor size was 2.5 (0.6–9.0) cm in tumors with neuroendocrine features and 2.1 (0.5–8.5) cm in tumors without neuroendocrine features. Tumor diameter was significantly larger in tumors with neuroendocrine features (p = 0.029).

Of the tumors with neuroendocrine features, 48 (57.1%) were located in the left breast, 34 (40.5%) were located in the right and 2 (2.4%) were bilateral. According to the Modified Bloom and Richardson System, tumor grade was 1 in 6 (7.1%) cases, grade 2 in 42 (50%) and grade 3 in 36 (42.9%). Venous invasion was observed in 1 (1.2%), lymphatic invasion in 27 (32.1%) and perineural invasion in 19 (22.6%) tumors. Necrosis was present in 41 (48.8%) and microcalcification was present in 44 (52.4%) cases. There was no significant difference between tumor groups in terms of location, tumor grade, venous invasion, lymphovascular invasion, perineural invasion, necrosis and microcalcification (p>0.05).

Peritumoral desmoplastic reaction was mild in 24 (28.6%) of 84 tumors with neuroendocrine features, moderate in 35 (41.7%) and prominent in 25 (29.8%) cases. TIL was not observed in 31 (36.9%) tumors, while it was mild in 40 (47.6%), moderate in 7 (8.3%), and prominent in 6 (7.1%) cases. Peritumoral desmoplastic reaction and magnitude of TIL were significantly lower in tumors with neuroendocrine features (p = 0.0001 and p = 0.0001).

When the two groups were compared in terms of molecular subtyping, the distribution was significantly different (p = 0.003). Tumors with neuroendocrine features were predominantly in the luminal subgroup. Tumors without neuroendocrine features were predominantly in the Luminal B subgroup (48%), but showed a diffuse distribution. 25.5% of IBC-NSTs were Luminal A, 48% were Luminal B, 3.9% were HER2 positive and 22.5% were triple negative, while in the other group, these rates were 31%, 63.1%, 1.2% and 4.8%, respectively. Of the tumors with neuroendocrine features 54.8% showed a growth pattern of large solid islands (islands containing more than about 100 cells) and 57.8% of tumors diagnosed as IBC-NST showed a pattern of small solid islands. When growth patterns were compared, large solid islands were significantly more common in tumors with neuroendocrine features (p = 0.0001). There was no significant difference between tumor groups in terms of cribriformity, palisading or grooves (p<0.05). The presence of basally located nuclei, absence of tubule formation, inconspicuous nucleoli, fine chromatin, granular cytoplasm and indefinite cytoplasmic borders were detected more frequently and significantly more common in tumors with neuroendocrine features (p<0.05) (Figure 2). It was thought that these features may help differentiate primary breast tumors with neuroendocrine features from other breast carcinomas (Table 1).

The results were also evaluated by univariate and multivariate analysis in logistic regression tests. There was no significant difference between the groups in terms of gender, tumor lateralization, grade, lymphovascular invasion, perineural invasion, necrosis or microcalcification. A significant difference was detected between the groups in terms of peritumoral desmoplastic reaction, peritumoral lymphocytic reaction, molecular subtypes and growth patterns. The difference between groups in terms of peritumoral desmoplastic reaction was solely due to IBC-

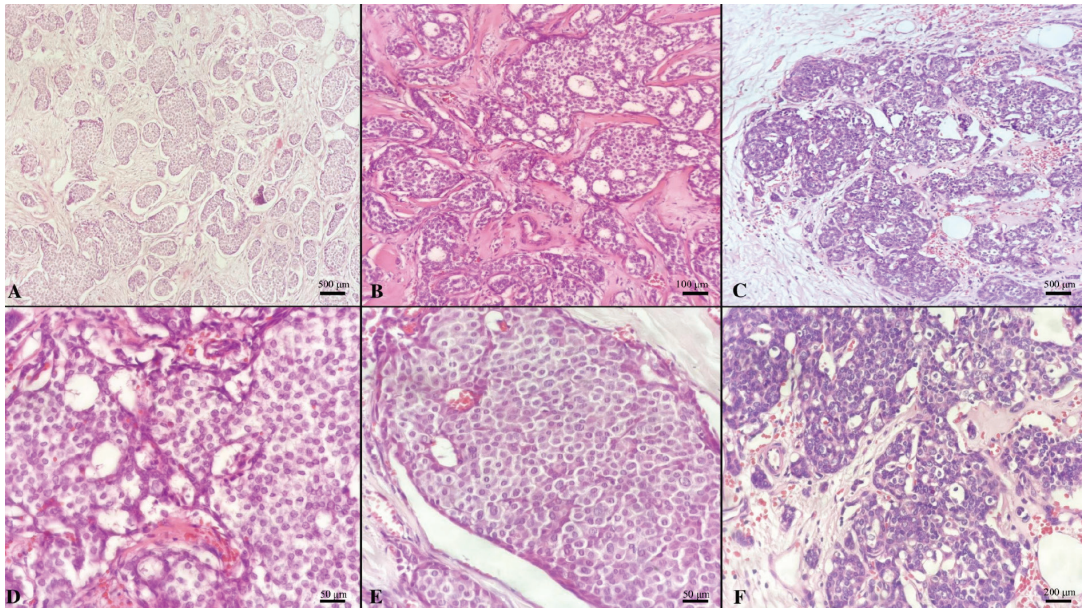

Figure 2. A-B) NET showed a growth pattern of solid islands (H&E x40 and H&E x100). **C)** Absence of tubule formation in NET (H&E x40). **D-E)** Nucleoli are not prominent in tumor cells and fine chromatin is observed (H&E x400). **F)** Indefinite cytoplasm borders in NET (H&E x200)

H&E: Hematoxylin and eosin; NET: Neuroendocrine tumor

Table 1. Intergroup comparisons

	Histopathological diagnosis			
	IBC-NST	**Neuroendocrine differentiation**	**Neuroendocrine tumor**	***p***
Peritumoral desmoplastic reaction				
Mild	8 (7.4)	7 (18.9)	15 (34.1)	
Moderate	36 (33.3)	16 (43.2)	19 (43.2)	**0.0001**
Prominent	64 (59.3)	14 (37.8)	10 (22.7)	
Peritumoral lymphocytic reaction				
Absent	1 (0.9)	7 (18.9)	21 (47.7)	
Mild	44 (40.7)	20 (54.1)	20 (45.5)	**0.0001**
Moderate	44 (40.7)	6 (16.2)	1 (2.3)	
Prominent	19 (17.6)	4 (10.8)	2 (4.5)	
Molecular subtype				
Luminal A	27 (25.0)	8 (21.6)	18 (40.9)	
Luminal B	53 (49.1)	27 (73.0)	23 (52.3)	**0.008**
HER-2	4 (3.7)	0 (0)	1 (2.3)	
Triple negative	24 (22.2)	2 (5.4)	2 (4.5)	
Growth pattern				
Infiltrative	13 (12.0)	1 (2.7)	4 (9.1)	
Large solid islands	11 (10.2)	12 (32.4)	32 (72.7)	
Small solid islands	66 (61.1)	15 (40.5)	4 (9.1)	**0.0001**
Solid	18 (16.7)	7 (18.9)	3 (6.8)	
Trabecular	0 (0)	2 (5.4)	1 (2.3)	
Palisading	14 (13.0)	2 (5.4)	13 (29.5)	0.006
Basally located nuclei	11 (10.2)	5 (13.5)	12 (27.3)	0.026
Groove	11 (10.2)	0 (0)	4 (9.1)	0.134
Presence of tubules	25 (23.1)	6 (16.2)	4 (9.1)	0.119
Presence of nucleoli	64 (59.3)	22 (59.5)	9 (20.5)	**0.0001**
Pleomorphism				
Mild	1 (0.9)	0 (0)	1 (2.3)	
Moderate	28 (25.9)	7 (18.9)	15 (34.1)	0.454
Prominent	79 (73.1)	30 (81.1)	28 (63.6)	
Mitosis				
1	55 (50.9)	17 (45.9)	28 (63.6)	
2	20 (18.5)	7 (18.9)	12 (27.3)	0.053
3	33 (30.6)	13 (35.1)	4 (9.1)	
Nuclear details				
Fine	33 (30.6)	14 (37.8)	19 (43.2)	
Coarse	36 (33.3)	13 (35.1)	5 (11.4)	
Hyperchromatic	11 (10.2)	3 (8.1)	9 (20.5)	**0.041**
Fine peripheral	11 (10.2)	5 (13.5)	8 (18.2)	
Coarse peripheral	17 (15.7)	2 (5.4)	3 (6.8)	

Table 1. Continued

	Histopathological diagnosis			
	IBC-NST	**Neuroendocrine differentiation**	**Neuroendocrine tumor**	***p***
Cytoplasmic details				
Eosinophilic	65 (60.2)	25 (67.6)	14 (31.8)	
Granular	19 (17.6)	10 (27.0)	25 (56.8)	**0.0001**
Clear	24 (22.2)	2 (5.4)	5 (11.4)	
Cell borders				
Conspicous	66 (61.1)	17 (45.9)	14 (31.8)	**0.004**
Inconspicous	42 (38.9)	20 (54.1)	30 (68.2)	

IBC-NST: Invasive Breast Carcinoma of No Special Type; HER-2: Human epidermal growth factor receptor-2

NST cases as the proportion of cases showing prominent peritumoral desmoplastic reaction was significantly higher in this group (p = 0.0001). The difference between the groups in terms of peritumoral lymphocytic reaction was also due to cases of IBC-NST. Peritumoral lymphocytic infiltration was significantly less common in the cases showing neuroendocrine features (p = 0.0001). In terms of molecular subtypes, those diagnosed with IBC-NST were most commonly triple negative tumors. The most common cases in the IBC-NST group showing neuroendocrine differentiation were luminal B, and the cases in the NET group were Luminal A and Luminal B. However, the significant difference was again due to the IBC-NST group (p = 0.008). When the distribution of the growth pattern was evaluated, the significance was due to the NET group and the growth pattern of large solid islands was significantly more common in this group (p = 0.0001). The presence of nucleoli was significantly less common in the NET group (p = 0.0001). Additionally, there was a statistically significant difference between the NET group and other groups in terms of fine chromatin, granular cytoplasm and inconspicuous cell borders (p = 0.041, p = 0.0001 and p = 0.004, respectively).

Discussion and Conclusion

Primary neuroendocrine neoplasms of the breast, which are divided into two groups, NET and NEC (SCNEC and LCNEC) in the 2019 WHO Classification of Breast Tumors, are a heterogeneous group of tumors with different clinical behaviors and prognosis. One of the most important stages of making a correct diagnosis is to keep this diagnosis in mind and to be aware of the histomorphological findings. Considering this, histomorphological features that distinguish these tumors were evaluated in the present study.

Primary NETs of the breast are most commonly seen in women in the 6th and 7th decades, but have also been reported at earlier ages and in male patients (3, 4). Through their analysis of the National Cancer Database including 1389 cases of primary breast NETs, Martinez et al. (5) found that 82.9% of the cases were over 50 years of age and 97.9% were female. When compared to IBC-NST, primary breast NET was significantly more common over the age of 70 and the incidence was twice as high in males (5). In the present study, all patients with tumors showing neuroendocrine features were female and the mean age was 59 years, which was not different from the other tumors considered in the study.

The usual clinical presentation is palpable painless mass and no distinguishing features from other breast cancers has been reported. In addition to features similar to other breast cancers on radiological studies, findings that may suggest neuroendocrine neoplasms, such as well-defined, hyperdense, rounded contours on mammography and hypervascular, homogeneous, irregular or microlobular hypoechoic solid masses, may be detected on ultrasonography (6, 7). Kayadibi et al. (8) found that, in the mammographic evaluation, architectural distortion, axillary lymphadenopathy and calcification were more common findings with breast tumors that did not show neuroendocrine features. On magnetic resonance and ultrasonographic evaluation, tumors in this group had irregular shape with more spiculated contours.

The correct diagnosis of a primary NET of the breast is based on a detailed clinical, radiological and histological evaluation. Around 0.2–1.1% of breast malignant tumors are metastatic tumors originating from non-mammary solid organs and only 1–2% of these metastatic neoplasms originate from NECs (3, 4). Metastatic neuroendocrine neoplasms may also show histological features similar to primary breast carcinomas. Treatment protocols and patient management are completely different in these tumors and therefore it is important to examine clinical history of the patient in detail and make a detailed radiological evaluation for an *in situ* component and the primary tumor focus (3, 4, 9). During the archive search we conducted within the scope of case selection, we identified three NEC cases that metastasized to the breast. Of these three, there was no history of malignancy in two, but the absence of *in situ* carcinoma component, a suspicious mass lesion in the lung found in the detailed clinic-radiological evaluation, and the immunohistochemical studies aided the diagnosis.

Cytomorphological features have been described in detail in tumors that develop in locations, such as the respiratory and gastrointestinal systems, where NETs are frequently seen. That the features observed in primary neuroendocrine neoplasms of the breast are not always typical and some features overlap with tumors that do not show neuroendocrine features may give rise to diagnostic difficulties. This is also one of the main reasons that the true prevalence of primary NETs of the breast cannot be determined.

In the histomorphological evaluation, low or medium grade tumors consisting of spindle-shaped, plasmacytoid or polygonal-shaped cells with eosinophilic, granular or clear cytoplasm showing a growth pattern in the form of trabecular and/or cellular solid islands should be evaluated for neuroendocrine features. Thin fibrovascular stroma, rosette formation and peripheral palisading are other histomorphological features that can be observed in these tumors (3, 10). The presence of intracellular and/or extracellular mucin, no prominent rosette formation, palisading and salt-and-pepper chromatin, absence of monotonous round-oval nucleoli, conspicuous nucleoli, plasmacytoid morphology and organoid growth pattern are observed in primary NETs of the breast but are not frequently expected features in NETs arising in other locations (11, 12). Kelten Talu et al. (13) compared primary breast carcinomas with and without neuroendocrine features and found that higher histological and nuclear grade, lymphovascular invasion, comedo-type ductal carcinoma *in situ*, and the presence of tumor-related microcalcification were significantly less common in tumors with neuroendocrine features. In the present study, a growth pattern in the form of large solid islands, absence of cribriformity, absence of tubule formation, absence of nucleoli, presence of fine chromatin, eosinophilic granular cytoplasm and cells with inconspicuous cytoplasmic borders were found significantly more frequently in tumors with neuroendocrine features. However, no histomorphological feature alone is sufficient to diagnose neuroendocrine neoplasms.

In the study of Bogina et al. (14), neuroendocrine features were considered by histomorphology in only 34% of tumors with neuroendocrine features. Thus immunohistochemical studies are mandatory for the exact diagnosis. Synaptophysin, Chromogranin-A, CD56, neuron specific enolase (NSE) and protein gene product 9.5 (PGP 9.5) are the main immunohistochemical stains used for NETs. Second generation markers, such as insulinoma-associated protein (INSM1) and syntaxin-1 (STX1) have been claimed to have higher sensitivity and specificity (15). The sensitivity and specificity of NSE and CD56 immunohistochemistry are lower than synaptophysin and chromogranin A (16). Razvi et al. (17) investigated the use of INSM1 immunohistochemical stain as a neuroendocrine marker in luminal B breast cancers. When synaptophysin, chromogranin, CD56 and INSM1 were used in double and quadruple combinations, INMS1 showed higher sensitivity compared to Chromogranin A and CD56.

In terms of molecular subtyping, primary neuroendocrine neoplasms of the breast are frequently of the luminal B type. These tumors are usually estrogen and/or progesterone receptor positive and almost always human epidermal growth factor receptor-2 (HER-2) negative. However, recently studies also describe HER-2 positive NETs of the breast (18, 19). In the present study, tumors with neuroendocrine features were commonly in the luminal B subgroup (63.1%), while only one case was HER-2 positive.

Primary neuroendocrine neoplasms of the breast are tumors that can cause diagnostic difficulties, considering their low incidence, and non-specific clinical and radiological features. Although the histological features observed in NETs of other organs are also observed in NETs of the breast, similar features can also be observed in *in situ* or IBCs that do not show neuroendocrine features. The absence of specific clinical and radiological findings, the inability to study neuroendocrine markers in every laboratory, and the need to prove that the breast tumor is not a metastasis are all conditions that create diagnostic difficulties. We believe that the results of this study may help diagnose and identify the more specific histomorphological features that help determine neuroendocrine morphology in primary breast tumors.

Ethics Committee Approval: Ethics approval for the study, dated November 10, 2022 and numbered 2022-17/29 was obtained from the Uludag University Faculty of Medicine Clinical Research Ethics Committee.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: K.S., S.T., M.S.G.; Concept: M.O., S.T.; Design: M.O., S.T., T.E.; Data Collection and/or Processing: M.O., S.T., M.S.G., T.E.; Analysis and/or Interpretation: M.O., S.T.; Literature Search: M.O., S.T.; Writing: M.O., S.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

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