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REVIEW

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Rare Breast Tumors with Neuroendocrine Features and Comprehensive Review of the Literature

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ABSTRACT This study aimed to examine the histopathological characteristics, treatment modalities, survival features, and factors influencing these traits in patients with neuroendocrine neoplasms (NEN) of the breast. We retrospectively reviewed the case records of breast NEN patients who were followed up in Ankara Numune Training and Research Hospital and Ankara City Hospital Medical Oncology clinics from December 2005 to June 2022. After noting their clinical and pathological features in survival files, the obtained data were analyzed and compared. Our single-center study included nine patients with breast NENs. Histologically, four (55.5%) and two (22.2%) patients exhibited well-differentiated neuroendocrine tumor (NET) and poorly differentiated neuroendocrine carcinoma (NEC), respectively. The last two (22.2%) patients showed an invasive breast carcinoma with neuroendocrine differentiation (IBC-NED). All patients underwent surgery after diagnosis. Of them, six (66.7%) and five (55.6%) patients received adjuvant chemotherapy and radiotherapy, respectively. The patients with diagnoses of IBC-NED and breast NEC as well as two patients diagnosed with well-differentiated breast NET received adjuvant chemotherapy. Moreover, all patients received hormonal therapy. The median overall and the median disease-free survival were 10.6 (7.3-13.8) years and 6.2 (1.1-11.3) years, respectively. It is essential to understand the biology of breast NENs to enhance the diagnosis, treatment, and patient outcomes. Hence, further research is warranted to elucidate the underlying mechanisms, validate potential therapeutic targets, and establish optimal management strategies for such patients.

Keywords: Breast neuroendocrine carcinoma; breast neuroendocrine neoplasia; invasive breast carcinoma with neuroendocrine differentiation; well-differentiated neuroendocrine tumor

Breast neuroendocrine neoplasms (NEN) represent an uncommon subgroup of malignancies within the spectrum of breast cancers. These tumors are a heterogeneous group comprising invasive breast cancer of no special type (IBC-NST) with neuroendocrine features in breast cancer [neuroendocrine tumor (NET)], and neuroendocrine carcinoma (NEC).[1] Subsequently, Cubilla and Woodruff introduced the term "primary carcinoid of the breast" in 1977.[2] In 2001, Sapino et al. proposed the initial diagnostic criteria for breast NETs and suggested that tumors expressing >50% of neuroendocrine markers, specifically synaptophysin (SNP) and chromogranin, should be classified as breast NECs.[3,4]

The classification and nomenclature of NENs have historically been complex because older classifications emphasized tumors in specific organ systems. The categorization of neuroendocrine breast tumors has evolved since then. The World Health Organization (WHO) classified NECs into solid, small-cell, and large-cell NECs in 2003.[5,6] Subsequent 2012

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revisions eliminated the stipulation for a certain proportion of cells to exhibit positive immunostaining for diagnosis.[5] Currently, NENs are classified into three categories: well-differentiated NET, poorly differentiated NEC/small-cell carcinoma, and IBC-NED.[7] In the "breast carcinomas with neuroendocrine features" section of the WHO 2012 classification, the "well-differentiated neuroendocrine tumor" subgroup is similar to the carcinoid tumor group, while the "poorly differentiated/small cell NEC" subgroup resembles classical small cell carcinomas in morphology. Thus, this distinction recognizes the neuroendocrine features in these two subgroups when compared to the third group, IBC-NED, which may not necessarily exhibit the characteristic NET features.[5] Invasive breast carcinoma with NED accounts for 2-5% of all IBCs.[6]

Given the rarity of breast NEN, there is a lack of consensus regarding their prognosis and management strategies. Previous studies have yielded conflicting results on their clinical behavior and patient outcomes, thereby highlighting the need for a deeper understanding of this distinct subtype. Hence, this retrospective study aimed to examine the histopathological characteristics, treatment modalities, survival features, and factors influencing these aspects in breast NEN patients. By retrospectively analyzing our follow-up patients, we sought to contribute to the existing knowledge by providing crucial insights into the clinical behavior and management of breast NEN cases.

MATERIAL AND METHODS

We included patients diagnosed with IBC-NED, well-differentiated NETs, and NECs between December 2005 and June 2022. These individuals were receiving follow-up care at Ankara Numune Training and Research Hospital and Ankara City Hospital Medical Oncology clinics. Clinical characteristics and prognostic outcomes were retrospectively extracted from patients' data. Overall survival (OS) was defined as the period from the onset of disease to either death from any cause or the last follow-up. The duration from the onset of disease to either disease recurrence or death from any cause characterized the disease-free survival (DFS).

Detailed clinical information regarding each patient was documented, including age, tumor location, tumor size, histological grade, nodal metastasis status, hormone receptor expression, tumor subtype, follow-up duration, and treatment modalities. This study adhered to Helsinki Declaration principles and followed good clinical practice recommendations. We obtained ethical approval from the Ankara City Hospital Medicine and Health Sciences Research Board (date: April 26, 2023, no: E.Kurul-E1-23-3494).

STATISTICAL ANALYSIS

The statistical analyses were performed utilizing SPSS 25.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were reported as frequencies and percentages, while means±standard deviations and medians (interquartile ranges) were used for continuous variables. The Kaplan-Meier method was used for survival analysis. A p value <0.05 was deemed statistically significant.

RESULTS

Our single-center study included nine patients with breast NENs. Histological examination revealed well-differentiated NETs (55.5%) in four patients, poorly differentiated NEC (22.2%) in two patients, and IBC-NED (22.2%) in two patients. The median age at diagnosis was 64 (58-69) years, 65 (50-81) years, and 52 (48-55) years for IBC-NED, well-differentiated NETs, and NECs, respectively (Table 1).

Upon evaluating the tumor's location, three (60%) patients displayed a well-differentiated NET pattern localized in the right breast, while two (40%) patients exhibited its location in the left breast. The tumors in all patients with poorly differentiated breast NEC and IBC-NED were localized in the right breast. The mean tumor sizes were 17 mm (13-40 mm), 35.5 mm (35-36 mm), and 41.5 mm (30-53 mm) in patients diagnosed with well-differentiated breast NET, poorly differentiated breast NET, and IBC-NED, respectively (Table 1).

Immunohistochemical staining for SNP was positive in all specimens, indicating typical NED. Moreover, chromogranin staining was positive in seven (77.8%) patients, negative in one (11.1%) patient, and uncertain in one

TABLE 1: Clinicopathological characteristics of all patients.

	Well-differentiated neuroendocrine tumor n (%)	Neuroendocrine carcinoma n (%)	Invasive breast carcinoma with neuroendocrine differentiation n (%)
Age (Years) Median (Minimum-Maximum)	65 (50-81)	52 (48-55)	64 (58-69)
ECOG PS			
0	1 (20%)	2 (100%)	0
1	2 (40%)	0	2 (100%)
2	1 (20%)	0	0
3	1 (20%)	0	0
Localization			
Right	3 (60%)	2 (100%)	2 (100%)
Left	2 (40%)	0	0
Operation			
Modified radical mastectomy	3 (60%)	2 (100%)	1 (50%)
Breast-conserving surgery	2 (40%)	0	1 (50%)
Tumor diameter (cm)	17 (13-40)	35.5 (35-36)	41.50 (30-53)
ER			
Negative	0	0	0
Positive	5 (100%)	2 (100%)	2 (100%)
PR			
Negative	0	0	0
Positive	5 (100%)	2 (100%)	2 (100%)
HER2			
Negative	5 (100%)	0	2 (100%)
Positive	0	2 (100%)	0
Chromogranin			
Negative	1 (20%)	0	0
Positive	4 (80%)	1 (50%)	2 (100%)
Unknown	0	1 (50%)	0
Synaptophysin			
Negative	0	0	0
Positive	5	2	2
Stage			
pT2N0M0	1 (20%)	1 (50%)	1 (50%)
pT3N1M0	1 (20%)	0	0
pT1N0M0	2 (40%)	0	0
pT1N1M0	1 (20%)	0	0
pT2N1M0	0	1 (50%)	1 (50%)

ECOG PS: Eastern Cooperative Oncology Group performance score; PR: Progesterone receptor; ER: Estrogen receptor.

(11.1%) patient. All patients exhibited positive staining for hormone receptors like estrogen receptor (ER) and progesterone receptor (PR). All NEC patients showed HER2-positive staining (Table 1).

All patients underwent surgery after diagnosis. Three well-differentiated NET patients were suitable for modified radical mastectomy, while breast-conserving surgery was performed in two patients. All NEC patients underwent modified radical mastec-

TABLE 2: Adjuvant treatment modalities of the group.

	All groups n (%)
Adjuvant chemotherapy	
No	3 (33.3)
Yes	6 (66.7)
Radiotherapy	
No	4 (44.4)
Yes	5 (55.6)
Hormonotherapy	
Tamoxifen	1 (11.1)
Aromatase inhibitors	8 (88.9)

tomy. Additionally, one IBC-NED patient underwent a modified radical mastectomy while the other received breast-conserving surgery.

Six (66.7%) and five (55.6%) patients received adjuvant chemotherapy and radiotherapy, respectively. All IBC-NED and breast NEC patients, as well as two diagnosed with well-differentiated breast NET, received adjuvant chemotherapy. Furthermore, all patients received hormonal therapy, with eight (88.9%) and one (11.1%) receiving aromatase inhibitors and tamoxifen, respectively (Table 2).

During the follow-up period, every participant experienced disease recurrence. The median DFS was 6.2 (1.1-11.3) years in the patient group (Figure 1). The median OS after diagnosis for the study patients was 10.6 (7.3-13.8) years (Figure 2). However, subgroup analyses could not be conducted due to insufficient sample size.

DISCUSSION

The etiology of breast NENs remains unclear. It is suggested that these tumors emerge from the differentiation of the breasts's pre-existing endocrine cells. Another alternative theory suggests that they originate after the neoplastic stem cells differentiate into epithelial and endocrine cells during the early breast cancer development stage.[2,6,8]

SNP and chromogranin-A are a few sensitive and tumor-specific immunohistochemical markers for NETs.[6] The sensitivity levels of neuron-specific enolase and CD56 positivity are comparatively lower.[6] In this study, immunohistochemical staining for SNP was positive in all analyzed pathological specimens, thereby corroborating NED. Seven patients had positive chromogranin staining, one showed a negative result and one patient displayed uncertain findings.

Our study revealed median DFS and OS of 6.2 (1.1-11.3) years and 10.6 (7.3-13.8) years for patients with breast NENs, respectively. Many studies have suggested a 5-year survival rate ranging from 70% to 80% for breast NENs.[9,10] Cloyd et al. demonstrated comparable 5-year OS and disease-specific survival (DSS) rates for patients with well-differentiated NETs and IBC-NED. In contrast, breast NEC patients exhibited markedly lower 5-year OS and DSS rates.[3] Wang et al. and Yang et al. reported that breast NEC had poorer OS and DSS rates in comparison to non-

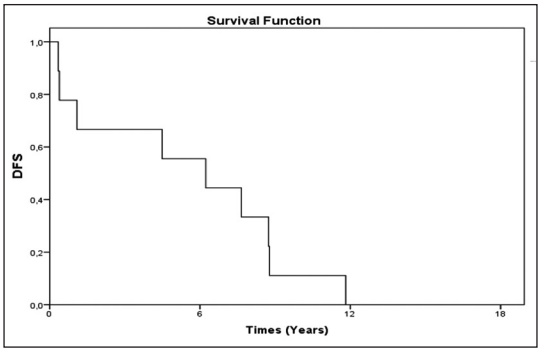

FIGURE 1: Kaplan-Meier analysis for the group's DFS.
DFS: Disease-free survival.

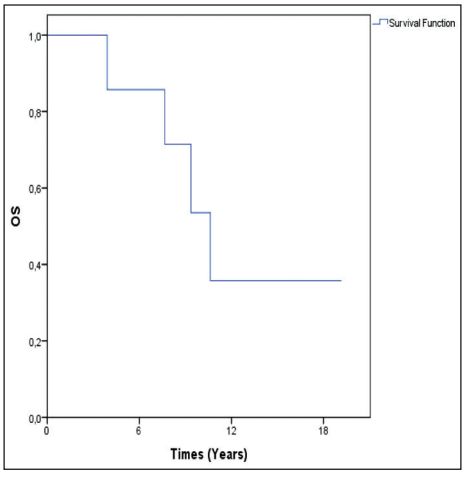

FIGURE 2: Kaplan-Meier analysis for the group's OS.
OS: Overall survival.

specific invasive ductal carcinoma.[11,12] Lavigne et al. found that the DFS of breast NEC patients was shorter than the invasive ductal carcinoma-NST patients but without any significant difference in OS rates.[13] Conversely, Rovera et al. observed that breast NEC patients displayed better survival in comparison to infiltrating ductal and lobular carcinoma patients.[14]

Our findings revealed several important insights into breast tumors with NED. Firstly, we observed that these tumors were predominant in postmenopausal women, which is similar to previous studies.[3,15]

Hormone markers show positive staining in the majority of NECs. Wei et al. observed that 92% (68 out of 72) and 69% (51 out of 72) of NETs were ER- and PR-positive, respectively.[16] Our results were similar, with all patients exhibiting positive staining for ER and PR hormone receptors. Moreover, the expression of ER and PR hormone receptors was frequently observed, indicating the possibility of using hormonal therapies to treat these tumors. Additionally, all well-differentiated breast NET and IBC-NED patients showed negative HER2 levels.

Staging for breast NEN is done like other forms of breast cancer while hen planning a treatment regimen.[17] Although there is no specific therapy for breast NEN, breast NEC patients have improved OS with chemotherapy; however, chemotherapy does not help in the OS of well-differentiated NET patients.[12]

Various studies have revealed that breast NEC progresses with a higher incidence of distant metastasis and local recurrence when compared to IBC-NST and NEC has a worse prognosis.[8,18] In another study on 86 patients with primary breast NEC, the 48-month OS rate was 83.5%.[19] Patients with early-stage tumors display a higher survival rate than those with advanced-stage tumors.[20] Patients diagnosed with breast NECs have a 15% and 34% risk of local recurrence and distant metastasis within 5 years, respectively.[21] Surgery is the primary treatment option for early breast NECs. The choice of surgical method is similar for other breast cancers. Tumor size and localization are important considerations for selecting the appropriate surgical method. A few surgical options are modified radical mastectomy, total mastectomy, breast-conserving surgery, and breast reconstruction.[16,18,22] However, our NEC participants underwent a modified radical mastectomy. Depending on the tumor's size and lymph node status, surgery usually follows radiotherapy in well-differentiated NET cases.[17,23]

None of the randomized controlled trials have compared the patients' treatment combinations due to the rarity of breast NEC. Therefore, breast NEC management is based on the retrospective review of the available case reports. Nonetheless, there is no consensus regarding which patient should receive which adjuvant chemotherapy regimen. The most common chemotherapy combinations are cisplatin and etoposide, doxorubicin and cyclophosphamide, or 5-fluorouracil, epirubicin, and cyclophosphamide.[8] Hence, the general approach might include taxane-based and/or anthracycline combination therapy, hormone therapy, and targeted therapy based on receptor expression after surgery.[18]

Tumors expressing hormone receptors can be treated with hormone therapy. It is a crucial component of the hormone receptor-positive breast cancer treatment regimen and is now being used for breast NEC. A study has demonstrated breast NEC patients exhibiting suitable hormone expression may benefit from the survival advantage given by hormone therapy.[22]

Poorly differentiated breast cancers commonly show HER2 positivity. Marijanović et al. reported a HER2-positive primary breast NEC patient who achieved 9-year DFS by adjuvant anti-HER2 therapy.[24]

Wang et al. investigated the effectiveness of radiation therapy in addition to surgery, chemotherapy, and hormone therapy for treating breast NECs and found that radiation therapy did not prolong survival in breast NEC patients.[11]

Although the exact cause is unknown, it may be because NEC is a very aggressive type of cancer that is resistant to radiation therapy. Additional research is necessary to gain a clearer understanding of the role of radiation therapy in treating breast NEC cases.

The current study had a few limitations like a small sample size and retrospective design. The small sample size might have restricted the generalizability of our findings. A larger sample would have fa-

cilitated a more robust statistical analysis and additional associations within the neuroendocrine breast tumor subgroup.

The study's limited sample size of nine patients prevented OS and DFS subgroup analyses. Another constraint was the non-accessibility of certain site-specific lineage markers that might have provided additional insights into the NED of breast tumors. Due to the lack of these specific markers, we were unable to assess their expression and potential impact on the classification and characterization of these tumors. Thus, this limitation may have restricted our exploration of the molecular and genetic aspects of neuroendocrine breast tumors.

CONCLUSION

Our study sheds light on the distinct clinicopathological and molecular features of breast NENs. Investigating the biology of these tumors can improve diagnostic strategies, optimize treatment approaches, and enhance patient outcomes. Additional research is needed to elucidate the underlying pathological mechanisms, validate potential therapeutic targets, and establish treatment strategies for this breast cancer subtype. The lack of established treatment guidelines makes the management of breast tumors with NED challenging. Thus, prospective investigations covering a variety of lineage markers can effectively grasp the diversity and behavior of these tumors. Additional molecular investigations are necessary to identify novel actionable targets for these tumors. However, the efficacy of these targeted agents requires further evaluation in clinical trials specifically designed for such breast NEN cases.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Müge Büyükaksoy, Selin Aktürk Esen, Doğan Uncu;* ***Design:*** *Müge Büyükaksoy, Selin Aktürk Esen, Doğan Uncu;* ***Control/Supervision:*** *Burak Civelek, Öznur Bal, Mehmet Ali Nahit Şendur;* ***Data Collection and/or Processing:*** *Selin Aktürk Esen, Müge Büyükaksoy;* ***Analysis and/or Interpretation:*** *Selin Aktürk Esen; Fahriye Tuğba Köş, Efnan Algın;* ***Literature Review:*** *Müge Büyükaksoy, Selin Aktürk Esen, Doğan Uncu;* ***Writing the Article:*** *Müge Büyükaksoy, Selin Aktürk Esen;* ***Critical Review:*** *Doğan Uncu, Burak Civeler, Efnan Algın, Öznur Bal, Mehmet Ali Nahit Şendur.*

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