İSTANBUL ÜNİVERSİTESİ YAYINEVİ

RESEARCH - ARAŞTIRMA
DOI: 10.26650/IUITFD.2021.830495
İst Tıp Fak Derg 2021 / J Ist Faculty Med 2021

NEUROENDOCRINE CARCINOMA OF THE BREAST: 18 CASES WITH LONG-TERM FOLLOW-UP

MEMENİN NÖROENDOKRİN KARSİNOMU: 18 HASTA VE UZUN DÖNEM SONUÇLARI

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Cite this article as: Ozkurt E, Ilhan M, Cucuk OC, Tukenmez M, Cabioglu N, Muslumanoglu M. Neuroendocrine carcinoma of the breast: 18 cases with long-term follow-up. J Ist Faculty Med 2021;84(4):521-5. doi: 10.26650/IUITFD.2021.830495

ABSTRACT

Objective: Primary neuroendocrine carcinoma of the breast (NECB) is a rare distinct type of breast carcinoma. There is limited data about the optimal management, treatment, and prognosis. Therefore, we analyzed the clinicopathological features, management and the clinical outcome of this rare breast carcinoma.

Material and Methods: Patients diagnosed as NECB between July 2008 and January 2018 were included in the study. Medical records were retrospectively reviewed.

Results: A total of 4,896 breast cancer patients were reviewed and 18 NECB (0.4% of all cases) were extracted. The median age was 61.5 (30-82). Thirteen cases (72.2%) underwent breast conserving surgery. Eight patients had axillary lymph dissection. All of the cases were pathological T1 and T2. Only one patient was pathological stage 3. Median tumor size was 20.5mm (10-45). Only two cases presented with small cell subtype, the rest were well-differentiated. Hormone receptor was positive and HER2/neu was negative for all cases. Of the 15 patients with known Ki-67, three had high expressions (≥20%). No local or distant disease recurrences and death related with NECB were detected at a median follow-up period of 101 months (33-148).

Conclusion: NECB is more likely to be hormone receptor positive and HER2/neu negative as luminal A or B subtype. An excellent clinical outcome is remarkable despite a substantial number of patients with axillary lymph node positivity specifically for well-differentiated subtype. Less invasive treatment options should be kept in mind.

Keywords: Neuroendocrine carcinoma, breast neoplasm, prognosis

ÖZET

Amaç: Nöroendokrin meme karsinomu (NMK) nadir görülen ve özellikli bir meme tümörüdür. Bu alt tipin tedavisi ve prognozu ile ilgili bilgiler sınırlıdır. Çalışmamızda, bu nadir görülen tümörün klinikopatolojik özelliklerini, tedavisini ve klinik sonuçlarını inceledik.

Gereç ve Yöntemler: Temmuz 2008 ve Ocak 2018 tarihleri arasında NMK tanısı alan hastaların verileri retrospektif olarak incelendi.

Bulgular: Toplam kayıtlı 4896 meme kanseri hastasının 18'i NMK idi (toplam vakaların %0,4'ü). Ortanca yaş 61,5 (30-82) olarak bulundu. On üç hastaya (%72,2) meme koruyucu cerrahi uygulandı. Sekiz hastaya ise aksiller lenf nodu diseksiyonu yapıldı. Sadece bir hasta patolojik evre 3 iken tüm hastalar patolojik olarak T1 ve T2 idi. Ortanca tümör boyutu 20,5 mm (10-45) olarak bulundu. Sadece iki hasta küçük hücreli alt tipi iken 16 hasta iyi-diferansiye alt tipindeydi. Tüm hastalar hormon reseptör pozitif ve HER2/neu negatifti. Ki-67 değeri bilinen 15 hastadan 3 tanesinde yüksek Ki-67 değeri (>%20) mevcuttu. Ortanca 101 (33-148) aylık takip süresinde lokal-bölgesel veya uzak rekürrens görülmedi. On sekiz hastada hastalığa bağlı ölüm görülmedi.

Sonuç: NMK genellikle hormon reseptör pozitif ve HER2/neu negatif olacak şekilde luminal A veya B olarak tespit edilmektedir. Aksilla pozitif hastalar olsa da özellikle iyi-diferansiye alt grupta sağ kalımlar çok iyidir. Bu hastalarda daha az girişimsel tedavi seçenekleri göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Nöroendokrinkarsinom, meme neoplazmı, prognoz

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Submitted/Başvuru: 24.11.2020 • **Revision Requested/Revizyon Talebi:** 30.03.2021 •
Last Revision Received/Son Revizyon: 06.04.2021 • **Accepted/Kabul:** 06.08.2021 • **Published Online/Online Yayın:** 17.09.2021

INTRODUCTION

Primary neuroendocrine carcinomas of the breast (NECB) are rare neoplasms of the breast with similar morphological features to neuroendocrine tumors of the gastrointestinal tract and lung (1). The World Health Organization (WHO) described neuroendocrine marker expression in at least 50% of the total cell population of NECB. Expression of neuroendocrine markers, specifically synaptophysin and chromogranin A are generally present (2). According to the WHO classification, NECB has three subtypes based on the morphology as well-differentiated neuroendocrine tumors, small cell neuroendocrine carcinomas, and invasive carcinomas of the breast with neuroendocrine differentiation (3).

NECB is the disease of the sixth and seventh decade of females who are generally postmenopausal (4). Although the prevalence was reported between 2 and 5% in the WHO 2003 classification, recent studies demonstrated that it is between 0.1 and 0.5% (4-6).

NECB is associated with a more aggressive behavior, higher propensity for local recurrence, and poorer prognosis than ductal carcinoma (7). The optimal treatment for primary NECB is poorly known because of limited reports. These tumors can be misdiagnosed due to the lack of distinguishing features on presentation and imaging. It is important to recognize these tumors and distinguish them from other poorly differentiated tumors of the breast and metastatic small cell carcinomas from the lung in order to avoid diagnostic errors that could have therapeutic and prognostic implications for these patients. In this study, we demonstrated the clinicopathological characteristics, management and clinical outcomes of this rare breast carcinoma.

MATERIALS AND METHODS

Patients with a diagnosis of NECB between July 2008 and January 2018 were retrospectively evaluated. Demographic features, clinicopathological factors, treatment modalities, and outcomes of patients were recorded. Each patient was carefully managed in order to rule out breast metastasis of neuroendocrine carcinomas from other organs such as the gastrointestinal tract or lung. All patients were managed as breast carcinoma not otherwise specified (NOS) in concordance with international guidelines.

Up-to-date WHO criteria for NECB definitions were used. Tumors were stained by immunohistochemistry for neuroendocrine markers, synaptophysin and/or chromogranin-A along with estrogen receptor (ER) and progesterone receptor (PR), HER2/neu expression, and Ki-67 levels. Adjuvant treatment (chemotherapy, radiotherapy and endocrine therapy) was decided as in invasive ductal carcinoma of the breast.

Categorical and continuous variables were summarized using descriptive statistics (e.g. median, range, frequency, and percentage). Kaplan-Meier method was used for survival analysis. All statistical analyses were performed using the SPSS program (Version 22.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Between July 2008 and January 2018, 4,896 breast cancer patients were treated in our clinic and 18 cases were identified that fulfilled the 2003 WHO criteria for NECB. The incidence of NECB was 0.4% and all cases were female. The median age was 61.5 (30-82). All cases underwent radiologic evaluation by mammogram, ultrasound, and magnetic resonance imaging (MRI) if needed. If axillary lymph nodes were clinically positive, positron emission tomography and computed tomography (PET/CT) were also performed.

Most of the cases (75%) underwent breast conserving surgery. Axillary lymph node dissection (ALND) was performed for eight patients. All patients had sentinel lymph node biopsy, except one patient that had clinically stage II nodal disease. She underwent direct ALND. The median tumor size was 20.5 mm (10-45). Pathological stage II nodal disease was also present in one patient who was mentioned before. Of the 18 cases, 16 were classified as well-differentiated and two were small cell neuroendocrine carcinoma according to the WHO criteria. All cases were hormone receptor positive and HER2/neu negative. Only two patients that demonstrated with small cell neuroendocrine carcinoma had higher levels of Ki-67 (60% and 80%). Synaptophysin and chromogranin-A expression were present in all cases. Details of clinical and pathologic features are presented in Table 1.

The median follow-up time was 101 months (33-148). Adjuvant treatment was administered as for the same principles for invasive ductal carcinoma of the breast. Seventeen patients had endocrine therapy with tamoxifen in premenopausal and anastrazole in postmenopausal patients. The only patient who did not received endocrine therapy was an 82-year old patient with co-morbidities. There was no mortality associated with NECB. One patient died of cardiac events. No local recurrences or distant metastases were detected (Table 2).

DISCUSSION

Primary NECB is a rare tumor. On specimens, if more than 50% of the cells express any of neuroendocrine markers (chromogranin-A, chromogranin-B, neuron specific enolase, and synaptophysin), it can be described as primary NECB (1). This criteria distinguishes NECB from other breast carcinomas that show only neuroendocrine morphological features or focal (i.e.,<50%) neuroendocrine

Table 1: Demographic and pathologic features of cases (n=18)

Factors	Category	n	%
Median age		61.5 (30-82)	
	<60	8	44.4
	≥60	10	55.6
AJCC cT stage	I	7	38.9
	II	10	55.6
	III	1	5.6
AJCC cN stage	0	13	72.2
	I	4	22.2
	II	1	5.6
Operation type	BCS	13	72.2
	Mastectomy	5	27.8
Axillary surgery	SLNB	10	55.6
	ALND	1	5.6
	SLNB + ALND	7	38.9
Median tumor diameter (mm)		20.5 (10-45)	
AJCC pT stage	I	9	50
	II	9	50
AJCC pN stage	0	11	61.1
	I	6	33.3
	II	1	5.6
AJCC p stage	I-A	6	33.3
	II-A	8	44.4
	II-B	3	16.7
	III-A	1	5.6
ER status	Positive	18	100
	Negative	0	0
PR status	Positive	17	94.4
	Negative	1	5.6
HER2/neu status	Positive	0	0
	Negative	18	100
Ki-67 (n=15)	Positive (≥20%)	3	20
	Negative (<20%)	12	80
Factors	**Category**	**n**	**%**
MBR grade	I	0	0
	II	15	83.3
	III	3	16.7
WHO classification	Well-differentiated	16	88.9
	Small cell	2	11.1
Adjuvant treatment	**Chemotherapy**		
	Yes	9	50
	No	9	50
	Radiotherapy		
	Yes	11	61.1
	No	7	38.9
	Endocrine therapy		
	Yes	17	94.4
	No	1	5.6

AJCC: American Joint Committee on Cancer, BCS: Breast conserving surgery, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection, ER: Estrogen receptor, PR: Progesterone receptor, HER2/neu: Human epidermal growth factor receptor-2, MBR: Modified Bloom-Richardson, WHO: World Health Organization

Table 2: 5-year and 10-year survival features of the patients

Median follow-up (month)	101 (33-148)
5-year disease free survival	100%
5-year overall survival	94.1%
10-year disease free survival	100%
10-year overall survival	94.1%

differentiation. The rate of NECB was 0.4% in our series, that is similar to previously published series (0.1-0.5%) (4-6).

NECB is detected as especially round spiculated masses on mammogram (5). They generally present homogeneous echogenicity with some posterior acoustic enhancement on sonography. It morphologically seems like triple negative breast tumors. However, these findings are not specific for NECB. As diagnosis and differential diagnosis is made by pathologic evaluation with neuroendocrine markers, metastasis from a primary neuroendocrine tumor other than breast should be excluded, and a core biopsy is recommended (8). Almost two thirds of NECB are associated with ductal carcinoma *in-situ* that distinguishes these masses from metastases (9). We performed core needle biopsy for all cases. On advanced stages, PET/CT can be used for systemic evaluation. We performed PET/CT for five clinical axilla positive patients and there were no distant metastasis. The surgical treatment strategy is generally similar with the management of ductal carcinoma. As many

patients are early stage, specifically T1 and T2 cases, we performed breast conserving surgery for 13 (72%) patients. Although only seven patients had pathological axillary lymph node positivity, we performed ALND on eight patients. One patient whose final pathologic nodal evaluation was negative reported as positive in intraoperative pathologic evaluation of the sentinel lymph node. So that ALND was decided upon.

The WHO has classified NECB into three groups as well-differentiated neuroendocrine tumors, small cell neuroendocrine carcinomas, and invasive carcinomas of the breast with neuroendocrine differentiation (3). Sixteen patients in our cohort were well-differentiated and two were small cell. Most of the primary NECB express ER up to 90-100% and PR up to 80-90% (7). This level of hormone receptor positivity is significant for survival. HER2/neu overexpression in NECB is very rare so that most studies in literature classified NECB as luminal A or sometimes luminal B type (10-12). In large series by Bogine et al. and Lavigne et al. they reported that almost 50% of cases are luminal A and 50% are luminal B (11, 12). In our series, only three cases of the 15 with a known Ki-67 status were luminal B (high Ki-67 ≥20%). All the cases were hormone receptor positive and there were no HER2/neu positivity.

As there is a lack of information due to the low incidence of NECB cases, chemotherapy regimens are not standardized. Nevertheless, general recommendation is treating it similarly to the treatment standards for ductal neoplasms (13). If chemotherapy is administered, the first line treatment choice is anthracycline and taxane based regimens (8). Almost all of the cases reported in the literature are luminal type so the adjuvant endocrine therapy is also a standard of care for most of the cases (13). All patients, except an 82-year old female with co-morbidities, received endocrine therapy in our series. Radiotherapy also must be taken into consideration for patients with breast conserving surgery and for advanced stage patients in the light of international guidelines. We administered adjuvant radiotherapy to 11 of our patients.

There are different survival reports for the outcome and prognosis of NECB patients. Some of them demonstrate worse survival and few of them demonstrate better survival. Most of the studies provide worse survival rates when compared to invasive ductal carcinomas of the same stage. Wang J et al. reviewed the surveillance, epidemiology, and end results (SEER) database for NECB. They indicated that the overall survival and disease specific survival were significantly worse in NECB (n=142) compared with invasive mammary carcinoma, not otherwise specified at the same stage (4). Another study by Zhang et al. also presented that NECB have a higher rate of local recurrence and lower rate of overall survival (14). On the other hand, recent studies express that poorer local control and survival outcomes are associated with small cell subtype of the NECB, not for the well-differentiated subtype (12, 15). These results are more reasonable as we know that morphology is the key for survival of the patients. In our series, we reported excellent survival outcomes with a median follow-up time of 101 months. There was only one death and it was associated with a cardiovascular event. The 5-year and 10-year overall survival rates were both 94.1%. There was no locoregional or distant recurrence during the follow-up time (Disease free survival and disease specific survival were 100%). This is probably because 16 of the 18 patients in our cohort were well-differentiated subtype. Even so, two patients with small cell subtype had 99 (AJCC stage 2A) and 62 (AJCC stage 3A) months of follow-up time with no locoregional or distant recurrences. In the light of the results of these recent studies and our study, the need for chemotherapy for well-differentiated NECB should be questioned. Additionally, we can even consider omitting surgical axillary lymph node staging for patients with early stage and favorable tumor biology as demonstrated by Özkurt et al. for tubular breast cancers (16).

However, we should always keep in mind that small cell subtype is aggressive and can metastasize even after several years from initial diagnosis so that long-term close follow-up is recommended.

In conclusion, NECB is a different subtype and rare variant of breast carcinoma. Our results suggest that NECB is more likely to be ER/PR positive and HER2/neu negative as luminal A or B subtype. An excellent clinical outcome is remarkable despite a substantial number of patients with axillary lymph node positivity specifically for well-differentiated subtype. This favorable prognosis might be due to good tumor biology profile associated with hormone receptor positivity with a substantial benefit from hormone therapy and other adjuvant therapies. Finally, we must be aware of the small cell subtype of NECB and follow-up closely for a long time as it can present with advanced stage disease and distant metastasis.

Acknowledgements: This manuscript was checked for compliance with English grammar by Dr. Sami Pinarbasi, who is a native English speaker from the United Kingdom and working as Associate Lecturer in the Department of History, Politics and Philosophy, Manchester Metropolitan University.

Ethics Committee Approval: Ethics committee approval was not received due to the retrospective nature of the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.Ö., M.T., N.C., M.M.; Data Acquisition- E.Ö., M.İ., Ö.C.C.; Data Analysis/Interpretation- E.Ö.; Drafting Manuscript- E.Ö., M.İ., Ö.C.C.;

Critical Revision of Manuscript- M.M., M.T., N.C.; Final Approval and Accountability- E.Ö., M.İ., Ö.C.C., M.T., N.C., M.M.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Teşekkür: Yazının İngilizce gramer denetimi anadili İngilizce olan, Manchester Metropolitan Üniversitesi Tarih, Siyaset ve Felsefe Bölümü Öğretim Üyesi Dr. Enver Sami Pınarbaşı tarafından yapılmıştır.

Etik Komite Onayı: Retrospektif çalışma olduğundan etik komite onayı alınmamıştır

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- E.Ö., M.T., N.C., M.M.; Veri Toplama- E.Ö., M.İ., Ö.C.C.; Veri Analizi/Yorumlama- E.Ö.; Yazı Taslağı- E.Ö., M.İ., Ö.C.C.; İçeriğin Eleştirel İncelemesi- M.M., M.T., N.C.; Son Onay ve Sorumluluk- E.Ö., M.İ., Ö.C.C., M.T., N.C., M.M.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

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