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A challenging breast cancer type; Differentiation to neuroendocrine tumors

Zorlu bir meme kanseri türü; Nöroendokrin tümörlere farklılaşma

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Abstract

Aim: Neuroendocrine type breast carcinomas are rarely observed. Most of these tumors are seen as cell-differentiated neuroendocrine breast carcinoma but with all this infrequency, there is also a rarer type which is called as pure neuroendocrine breast carcinoma. The common locations for neuroendocrine tumors are lung and gastrointestinal system (stomach and pancreas). Although estimations vary, the annual incidence of clinically significant neuroendocrine tumors is approximately 5-6.5 per 500,000; two thirds are carcinoid tumors and one third is other neuroendocrine tumors. The estimated prevalence is 35 per 100,000. In this article, we analyze the patients admitted with breast problems and had the diagnosis of breast cancer with neuroendocrine differentiation or purely neuroendocrine tumor.

Methods: Retrospective cohort study is designed to review neuroendocrine breast cancer patients. Female patients with pathological examination which have neuroendocrine components in neoplasm were reviewed. Demographics, preoperative imaging, diagnostic evaluations, operation and pathological examination records of patients were recorded.

Results: Neuroendocrine breast cancer was observed in 11 patients in study period. All patients received standard therapy like non-specific breast cancer. Only two of 11 patients (18%) were diagnosed with neuroendocrine differentiation in preoperative period by biopsy. One patient received neoadjuvant treatment. Modified radical mastectomy was performed in eight patients (72.8%). Breast conserving surgery was performed in remaining three patients.

Conclusion: Neuroendocrine breast cancer is rare entity, and diagnose at preoperative period may be challenging. In most cases the correct diagnosis is made after proper examination of the postsurgical specimen. Future studies for specific treatments would be of interest.

Keywords: Breast cancer, Neuroendocrine tumor

Öz

Amaç: Nöroendokrin tip meme karsinomlarına nadiren rastlanmaktadır. Bu tümörlerin çoğu hücreye göre farklılaşmış nöroendokrin göğüs karsinoması olarak görülmekle birlikte, bu nadiren de olsa, saf nöroendokrin göğüs karsinoması olarak adlandırılan daha seyrek bir türü vardır. Nöroendokrin tümörlerin ortak yerleri akciğer ve gastrointestinal sistemdir (mide ve pankreas). Tahminler değişse de, klinik olarak önemli nöroendokrin tümörlerin yıllık insidansı 500.000'de yaklaşık 5-6.5; üçte ikisi karsinoid tümörler, üçte biri diğer nöroendokrin tümörlerdir. Tahmini yaygınlık her 100.000 için 35'tir. Bu yazıda meme problemi ile başvuran ve nöroendokrin diferansiyasyon gösteren meme kanseri veya tamamen nöroendokrin tümör tanısı alan hastalar incelenmiştir.

Yöntemler: Retrospektif kohort çalışması, nöroendokrin meme kanseri hastalarını incelemek üzere tasarlanmıştır. Neoplazmda nöroendokrin bileşenlere sahip patolojik inceleme yapılmış kadın hastalar gözden geçirildi. Hastaların demografik özellikleri, preoperatif görüntüleme, tanı değerlendirmeleri, ameliyat ve patolojik inceleme kayıtları kaydedildi.

Bulgular: Çalışma döneminde 11 hastada nöroendokrin meme kanseri tespit edildi. Tüm hastalara, spesifik olmayan meme kanseri gibi standart terapi uygulanmıştır. Ameliyat öncesi dönemde 11 hastanın sadece ikisinde (%18) biyopsi ile nöroendokrin farklılaşma saptanmıştır. Bir hasta neoadjuvan tedavi aldı. Sekiz hastada (%72,8) modifiye radikal mastektomi uygulandı. Geri kalan üç hastada meme koruyucu cerrahi uygulandı.

Sonuç: Nöroendokrin meme kanseri nadir görülen bir hastalıktır ve preoperatif dönemde teşhis zor olabilir. Çoğu durumda, doğru teşhis, cerrahi sonrası numunenin uygun şekilde incelenmesinden sonra yapılır. Spesifik tedaviler için gelecek çalışmalar ilgi çekici olacaktır.

Anahtar kelimeler: Meme kanseri, Nöroendokrin tümör

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Introduction

Neuroendocrine tumors (NETs) are epithelial neoplasms with predominant neuroendocrine differentiation. NETs arise in most organs of the body [1]. The general locations are lung or gastrointestinal organs such as stomach and pancreas. Annual incidence of clinically significant neuroendocrine tumors is approximately 5-6.5 per 500,000 cases; and two third of cases are carcinoid tumors. The prevalence has been estimated as 35 per 100,000. However, NETs is very rarely seen in breast. Generally, neuroendocrine breast cancers (NBC) are neuroendocrine differentiated types. The first recognition occurred in 1963 [1-4]. There was no formal criteria until World Health Organization (WHO) defines neuroendocrine breast carcinomas as "NETs of the breast as having >50% neoplastic cells expressing neuroendocrine markers" [1, 5]. The estimations of WHO is that the neuroendocrine breast cancer is uncommon and unclear because of the patients with NBC do not have a significant family story and specific characteristics.

Due to inadequate researches and low number of cases about NBC, the treatment and prognosis of these cancer types are not well-known. According to present surgical literature, prognosis of NBC is dependent to metastatic activity of cancer and the therapy which applied to the patient. Though, the prognosis is poor [6-9]. Nowadays, there are new treatments such as peptide receptor radionuclide therapy which aims to identify the specific receptor and destroy the tumor cells. The main types of these cancer types are identified according to positive markers and the majority of cell differentiation as solid, large cell or small cell [10-12].

The management of NBC can be classified by a grading system which allows the use of mitotic rate or Ki-67 index to define grade as high–grade, intermediate–grade and low–grade. Prognosis of atypically located neuroendocrine tumors is poor, irrespective of the primary origin. However, small cell carcinoma involvement within NETs ends with poorer prognosis [12-14].

Types of reports about NBC in surgical literature are case reports and case series. In this study, we aimed to perform the analysis of case series of NBC patients.

Material and methods

Female patients that operated for breast cancer in four years period were reviewed. Patients with pathological examination which had neuroendocrine components in neoplasm included into study.

Patients' demographic data were recorded. All patients underwent ultrasonography (USG) examination and mammography, selectively. Magnetic resonance imaging was performed as needed. Preoperative biopsy reports were evaluated.

Surgical modalities for breast and axilla were recorded. Pathological examinations of specimen were evaluated delicately. Patients were followed-up at six months. Additional diagnostic and treatment modalities were evaluated.

Pathological examination

For positive confirmation of neuroendocrine differentiation, specific immunohistochemical markers (chromogranin A and synaptophysin) were used. The types of tumors are evaluated as solid, large cells, small cells and pure NBC, or cell differentiation NBC.

Ki-67, estrogen and progesterone, HER-2 levels were identified for neuroendocrine differentiation in the purpose of management of treatment choice. The other possible primary organs were also investigated.

Results

A total 156 patients were operated for breast cancer between 2009 and 2012. NBC was observed in 11 (7%) patients according to pathological examination of operative specimen. These patients constituted study group.

Median age of patients was 65.2 (range: 36 – 86). Preoperative diagnostic modalities were examined in study group. All patients have had an examination of breast ultrasonography and mammography according to requirement of diagnostic support. Three patients (27.2%) were underwent magnetic resonance imaging for breast.

All study Patients were diagnosed as breast cancer by the way of needle core biopsy. Details of preoperative pathological reports were listed in table 1. Only two of 11 patients (18%) were diagnosed as NBC in preoperative period by biopsy.

Table 1: Preoperative pathologic report of biopsy.

Report Details	Number of Patients
Invasive ductal breast carcinoma	7
Breast carcinoma with mucinous differentiation	1
Micro-invasive ductal breast carcinoma developed on the basis of solid papillary carcinoma	1
Intra-cystic and solid papillary carcinoma with abundant neuroendocrine differentiation	1
Mucinous carcinoma of the breast with neuroendocrine differentiation	1

Patients were prepared for operation with routine laboratory tests. One patient received neoadjuvant treatment. Modified radical mastectomy was performed in eight patients (72.8%). Breast conserving surgery was performed in three patients (27.2%). Multifocal tumor was seen in three patients (27.2%). Maximum tumor diameter of patients was between 0,5 cm and 12 cm. Details of patients' operative data were listed in table 2.

Table 2: Patients' characteristics

No	Operation	Reported Tumor Sizes (cm)
1	MRM	12x10x6, 4x3x1.5
2	MRM	2.2
3	MRM	1.8x1.8x1.5
4	BCS	1.5x2x1
5	MRM	4.5x3.5x2.5
6	MRM	1x1x1.8, 1.5x1x1, 0.2
7	BCS	3.2x1.8x1.2
8	MRM	3x3x2.5
9	MRM	3x3x2, 1x0.8x0.6, 0.6, 0.3
10	BCS	2.5
11	MRM	3.2x3x2.6

MRM: Modified radical mastectomy, BCS: Breast conserving surgery

One of the patients, who had pure neuroendocrine breast cancer, had a specific imagining test which is 68-Galyum-DOTA, TOC-PET/CT for metastatic level and the peptide receptor radionuclide therapy. The test result showed that the treatment is not useful for the patient.

Discussion

Although NBC is a rare, the treatment of these tumors is not very different from other breast cancer types. There are new treatments for neuroendocrine types of tumors such as peptide receptor radionuclide therapy which aims to identify the specific receptor on the tumors. The receptors for this treatment are somatostatin analogs. One of our patients who had pure neuroendocrine breast carcinoma was assessed for this treatment and observed the treatment is useful for pancreatic carcinomas which secretes somatostatin [1-5].

The concept of NBC was first described in 1977 [1, 2, 12]. And in 2000, some other authors defined neuroendocrine differentiation; defined as pure NE tumors if indicators are in more than 50% of tumor cells. World Health Organization categorized those tumors into a different group of breast tumors in 2003 [1]. NBC do not have specific clinical or radiological characteristics to differentiate them from other breast tumors [1, 8]. In our study, most of NBC cases were diagnosed as a different type of breast cancer.

NBC have three sub-types morphologically: solid, small cell/oat cell, and large cell neuroendocrine carcinomas [3, 12, 13]. The grade of histological differentiation in NBC is considered the most important factor for prognosis. Solid NBCs are usually well-differentiated tumors, small cell/oat cell and large cell NBCs are poorly differentiated [14-16].

Genetic alterations of NBC are to be determined as molecular studies are scarce. At present, point mutations studied in a small series of NBC and showed recurrent mutations affecting PIK3CA and the FGFR family (FGFR1 and FGFR4). 17 HRAS and KDR mutations were observed in single cases [17]. A subsequent analysis has recently showed that NBC seem to harbor a repertoire of somatic mutations distinct from that of common lower frequencies of TP53 and PIK3CA mutations [18].

The rare variants of NBC occur predominantly in postmenopausal women, and they are associated with more aggressive tumors and with a poorer progression-free survival than invasive carcinomas of no special type. At the molecular level, the subgroup of NBC is characterized by low levels of PIK3CA mutations. This molecular feature explains the unfavorable prognosis of NBC. Larger molecular studies of NBC are warranted. The clinical decision-making for patients with NBC is based on proper grading and immune-phenotyping of the lesions, similar to any invasive breast carcinomas. An accurate identification of this NBC on molecular level may be useful to better tailor patient adjuvant therapy within luminal carcinomas [17-20].

Main limitation of this study is low patient volume, and retrospective nature of study design. NBC is rare disease, in literature most of the studies have similar problem. This issue limits the conclusion of the study.

In conclusion, NBCs are rare, accounting for up to 7% of all breasts tumors and approximately 1% of all NETs. Preoperative diagnose even with histopathological assessment might be challenging, however in most cases, the tumors are well differentiated. In most cases the correct diagnosis is made after proper examination of the postsurgical specimen. Future studies for specific treatments would be of interest.

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