

Neuroendocrine Neoplasms of the Breast

Memenin Nöroendokrin Neoplazmları

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ABSTRACT

Primary neuroendocrine carcinoma of the breast is rare and consists of 0.1% of all breast cancers. In 2019, the World Health Organization newly defined this entity as neuroendocrine neoplasm of the breast and divided in two subgroups according to differentiation pattern. Whether a breast lesion is primary or metastatic has crucial importance for its management and prognosis. Our aim was to briefly summarize the knowledge as to neuroendocrine neoplasm of the breast based on the current literature.

Keywords: Neuroendocrine, breast, neoplasm, carcinoma

ÖZ

Memenin primer nöroendokrin karsinomu nadirdir ve tüm meme kanserlerinin %0,1'ini oluşturur. 2019 yılında Dünya Sağlık Örgütü bu antiteyi yeni memenin nöroendokrin neoplazmı olarak tanımlamış ve farklılaşma paternine göre iki alt gruba ayırmıştır. Meme lezyonunun birincil mi yoksa metastatik mi olduğu, yönetimi ve prognozu için çok önemlidir. Amacımız memenin nöroendokrin neoplazmı ile ilgili bilgileri güncel literatüre dayanarak kısaca özetlemektir.

Anahtar Kelimeler: Nöroendokrin, meme, neoplazm, karsinom

Introduction

Primary neuroendocrine carcinoma of the breast (NECB) is rare and consists of 0.1% of all breast cancers (1). Within all neuroendocrine cancers, the breast represents 1% of the origin (2). Various diagnostic criteria have been used and many classification systems have been proposed since the first introduction of neuroendocrine tumor (NET) in the breast was described.

In the previous World Health Organization (WHO) classification in 2012, these tumors were subclassified into 3 groups: Well-differentiated NET, poorly differentiated neuroendocrine carcinoma (NEC) (or small cell carcinoma) and, invasive breast carcinoma with neuroendocrine differentiation (3). Large cell NECs were not included in this system. Recently in 2019 WHO acknowledged the term of "neuroendocrine neoplasm" (NEN) as a comprehensive definition, which includes tumors at any specific anatomical site whose morphological features and markers are in

accordance with the neuroendocrine differentiation (1). In this classification, there are two subgroups: First is well-differentiated NET which is an invasive tumor characterized by low or intermediate grade and second is poorly differentiated NEC which is characterized by high grade tumor with either small or large cell neuroendocrine. The prerequisite feature of these tumors is harbouring more than 90% of neuroendocrine differentiation pattern. Whereas, conventional type mammary carcinomas which are of a neuroendocrine component of 10-90% in the tumor area are called as mixed invasive and NEC.

Clinical and Radiological Characteristics

These tumors usually occur in postmenopausal women in the sixth decade of life. Similar to other breast carcinoma, breast lump is the major finding in clinical presentation. Few cases present with hormonal hypersecretion syndromes due to hormonal production (3). Interestingly, Kawasaki et al. (4) inquired 89 patients whose complaint was bloody



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nipple discharge on the admission and detected that NEC had been the ethiological cause in nearly a quarter of these patients. As for radiological evaluation, NEN is of no specific imaging characteristics compared with other types of breast cancer.

Some studies have pointed that these tumors tend to recognised larger tumor size and higher probability of axillary metastasis at the time of diagnosis (5,6,7). A population-based study from the surveillance, epidemiology and end results database of Wang et al. (6) compared 142 patients with NEC of breast to invasive breast carcinoma, NOS. Higher histological grade and advanced clinical stage were found in NEC group and neuroendocrine differentiation was detected as an independent adverse prognostic factor. Wei et al. (7) detected lymph node metastasis in 31 of 74 patients with these tumors (42%). In a trial of 36 cases by Keten Talu et al. (8), most of the tumors were T2 and grade 2.

Diagnosis

NEN is of characteristic morphological features. Neuroendocrin tumor cells form nests, islands, alveolar-like structures surrounding by fibrovascular stroma with trabecular architecture, minimal tubular differentiation, which are characterized by uniform round or spindle-shaped cells with nuclear palisading, abundant finely granular eosinophilic cytoplasm and nuclei with “salt and pepper” chromatin distribution (1,5). These tumors express neuroendocrin markers such as chromogranin, synaptophysin, and neuron-specific enolase. In case of detection of neuroendocrin appearance on light microscopy, applying detailed immunohistochemical staining is the key point in achieving an accurate diagnosis (9). Luminal A and B phenotypes account for the vast majority of NEN (10). Most of them are HER2 negative.

After the diagnosis of NEN, metastasis to the breast should be ruled out by clinical imaging. Positron emission tomography-computed tomography is an important tool in this circumstance. Previous clinical history is also helpful. The presence of ductal carcinoma *in situ* supports the diagnosis of primary breast NEN (5). Differentiating primary NEN from metastatic one is crucial part of the management due to the diversity of treatment approaches (11). Unnecessary surgical interventions can be avoided in a metastatic setting. Neither neuroendocrin markers nor the presence of hormon receptors are useful in distinguishing these two entities. A panel of immunohistochemical site-specific lineage markers which point out its origin may be helpful in this setting. For example: TTF-1 is specific for pulmonary, CDX2 for gastrointestinal tract, mammaglobin, GATA3 and GCDFP15 for breast (2). However, the probability

of an overlapping in the immunohistochemical expression analysis among NENs arising from different sites should be born in mind.

Treatment

There is no standard treatment protocol for NEN. Surgery is the first-line therapy as similar as the treatment of invasive ductal carcinoma of breast. Li et al. (12) investigated 126 cases with NECB from the Chinese population during a period between 1990 and 2015. Despite that 70% of their diseases were stage 1 or 2, mastectomy has been carried out in 79% of the patients. However, recent trials demonstrate that breast conservation surgery as well as sentinel node biopsy supplanted mastectomy in many cases.

There is no consensus on the optimal adjuvant chemotherapy protocol. Usually, NEC is treated with chemotherapeutics for small cell lung carcinoma such as platin based therapy. On the other hand, patients with NET and invasive breast carcinoma with neuroendocrin differentiation receive cytotoxic therapy similar to conventional breast cancer such as anthracycline and taxane based regimens. Some studies revealed survival advantages of radiotherapy and endocrine therapy according to hormone receptor status in patients with NET of breast (7,13). In contrast, Wang et al. (6) found that radiation therapy did not prolong survival. Along with a limited number of cases, there are conflicting results in the literature.

Prognosis

Whether NEN is of prognostic significance is remained unclear yet (14). Despite its luminal phenotype, most studies have reported an aggressive clinical course and poor outcome for patients with NECB (7,15,16). Small cell NEC is associated with a worse prognosis than other types (12). In contrast to majority of invasive ductal carcinoma with luminal type, NEN usually harbors a significantly lower frequency of PIK3CA mutation which is associated with favorable clinicopathological characteristics including low grade and small tumor size (16). This molecular feature may be related to their aggressive clinical behavior and worse prognosis. On the other hand, lower grade and mucin production are related to better prognosis (14). In the light of all these data and studies, it is possible to say that NETs behave similarly to other invasive breast cancers and should be managed in a clinically equivalent manner (17).

Conclusion

Neuroendocrine breast cancer types are more rare than other types of breast cancer (18). These tumors should be born in mind and appearance of neuroendocrin features should prompt the pathologist to evaluate these tumors by

special immunohistochemical markers. Treatment approach of NEN of the breast is similar to that of breast ductal carcinoma. However, prognosis has not been particularly elucidated yet except NEC which is associated with the poor prognosis.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ş., G.O.K., Concept: E.Ş., Ş.O., G.O.K., A.A.G., S.A., Design: E.Ş., Ş.O., G.O.K., A.A.G., S.A., Analysis or Interpretation: E.Ş., Ş.O., G.O.K., A.A.G., S.A., Literature Search: E.Ş., Ş.O., S.A., Writing: E.Ş.

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