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BREAST CANCER WITH NEUROENDOCRINE DIFFERENTIATION - THE CURRENT STATE OF KNOWLEDGE AND CLINICAL IMPLICATIONS

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ABSTRACT

Background. Breast neuroendocrine neoplasms (BNETs) represent a rare and heterogeneous subgroup of breast cancers, comprising 2-5% of all breast carcinomas. Their classification has undergone significant changes following the WHO 2019 and 2022 revisions, which redefined diagnostic criteria and introduced new subtypes.
Aim. This review aims to summarise the current state of knowledge on BNETs and discuss clinical implications for practicing oncologists, with emphasis on pathomorphological features, diagnosis, treatment, and prognosis.
Material and methods. A comprehensive review of the literature was conducted using PubMed. Studies published between 2010 and 2024 were included. Search terms included 'neuroendocrine breast neoplasm', 'BNET', 'neuroendocrine carcinoma breast', and 'breast NET'.
Results. BNETs are classified into well-differentiated neuroendocrine tumours (NETs, G1/G2) and poorly differentiated neuroendocrine carcinomas (NECs, G3). Diagnosis requires immunohistochemical confirmation with synaptophysin and chromogranin A. Treatment follows IBC-NST guidelines, with emerging options including SSAs, PRRT, and targeted agents for PIK3CA-mutated tumours. Prognosis varies significantly between subtypes, with NECs showing 5- year survival rates of 32.2-50.5% compared to 62.4-74% for NETs.
Conclusions. BNETs require multidisciplinary management. Future studies should focus on developing subtype-specific treatment protocols and validating novel diagnostic markers and therapeutic targets.

KEYWORDS

Breast Cancer, Neuroendocrine Neoplasm, Neuroendocrine Tumour, Neuroendocrine Carcinoma, Immunohistochemistry, WHO Classification

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1. Introduction

Neuroendocrine differentiation (NE) is diagnosed on the basis of the presence of neurosecretory granules in neoplastic cells in tumor specimens. These cells with a characteristic phenotype also express NE markers such as chromogranin (CG) , synaptophysin (SYN), CD56, PGP9.5 and NSE. In the latest WHO classification from 2019, tumors with NE differentiation > 10% become neuroendocrine tumors. NE differentiating breast cancers are a group of heterogeneous tumors. They are morphologically similar to NE (NET) tumors of the lung or gastrointestinal tract (GI), but also invasive breast cancers without a special type (IBC-NST), including other special subtypes, like solid papillary (SPC) and mucous carcinomas type B cancer (type B MC) [1]). All of them exhibit variable NE morphological features and / or NE markers expression. In the most recent nomenclature, the differentiation of NE in the range of 10-90% consists of invasive breast cancers with NE differentiation (IBC-NST-NE). On the other hand, neuroendocrine tumors constitute the subgroup with the highest differentiation of NE above 90% (NED – neuroendocrine predominant tumors), divided into low-grade (NET – neuroendocrine tumor) and high-grade (NEC – neuroendocrine carcinoma) tumors. Special sub-types of invasive breast cancer such as solid papillary carcinoma and mucinous carcinoma type B are now classified separately, compared to the classification from 2012. The clinical value of NE differentiation in breast cancers is not well investigated and still has no influence on treatment decision-making.

2. Epidemiology

Breast cancer (BC) is the most common cause of death among the women population. According to the Polish Cancer Registry they are responsible for almost 15 % of death among all cancers in the Polish population. However survival rate has significantly increased, which presents promising signs for future therapy improvement. Primary neuroendocrine breast neoplasms are quite rare, they compose only 2-5% of all BCs. Epidemiology data can be illusive due to change in BNET classification published by WHO in 2019 [23]

3. Pathomorfological features

BNETs are characterised by neuroendocrine architectural and cytological features, which must be confirmed by immunohistochemical positivity for neuroendocrine markers. Histologically, BNETs are characterized by finely granular ("salt-and-pepper") nuclear chromatin, inconspicuous nucleoli, and moderate to abundant granular cytoplasm. The tumors typically exhibit nesting or trabecular growth patterns, composed of densely cellular aggregates of spindle-shaped, plasmacytoid, or polygonal cells embedded within a delicate fibrovascular stroma. NETs typically present as low or intermediate grade tumours (G1 or G2) by the Nottingham grading system, while NECs are invariably classified as grade 3, characterised by brisk mitotic activity. Moreover, BNETs are not stratified using mitotic count, Ki-67 proliferation index, or the presence of necrosis. The diagnosis of BNETs is further complicated by a high rate of misclassification; neuroendocrine differentiation has been reported to be overlooked in the majority of cases in some series, highlighting the need for careful morphological assessment and routine application of neuroendocrine markers in morphologically suspicious cases [1,5,7,11,18]

4. Diagnosis

BNETs diagnosis evaluation is not different from any other BCs. Typically starts with physical examination, mammography, ultrasonography or magnetic resonance imaging, followed by core needle biopsy (CNB) which is crucial to definitive diagnosis, as no specific clinical features have been identified [6]. Physical examination starts with breast palpation, in most cases we can palpate a painless lump, typically in upper outer quadrant [2]. Examination must be complemented by lymph node palpation to assess for enlargement or abnormality. Radiological features in the mammography include irregular, high density lesions, while in the ultrasonography we observe irregular hypoechogenic lesions. [3,4]

4.1 Immunohistochemistry

Histopathological examination with immunohistochemistry (IHC) is required to make a final diagnosis. Syn, CgA, neuron-specific enolase (NSE), and neural cell adhesion molecules(CD56) are traditional markers for all NENs. The most reliable markers include Syn and CgA. NSE and CD56 are mostly used in screening than for diagnosing BNETs. The insulinoma-associated protein 1 (INSM1) and SSTRs are novel neuroendocrine markers. INSM1 shows high sensitivity and specificity across various NENs, such as lung, gastrointestinal and other organs, while SSTR2A has a 71% positive rate in neuroendocrine carcinomas. Some specific IHC markers can distinguish primary BNETs from metastatic. TTF-1 and CDX-2 are the perfect example. TTF-1 is positive in lung metastases in 70% of cases and CDX-2 is almost 100% positive in gastrointestinal metastases, but they are both negative in primary BNETs. From the other side there are some IHC markers specific in primary BNETs while they are negative in metastases. GATA-3, mammaglobin and GCDFP15 show such a capability. [5,6,7]

4.2 Differential diagnosis and molecular features

Molecular characteristics also can be helpful. Most of the BNETs cases present a low Ki67, HER-2 negative and hormone receptor positive (ER/PR+). Diagnostic imaging such as CT scans and PET (CT)- FDG-18 or PET (CT) with gallium-labeled somatostatin analogues 68 are used in metastasis detection; they should be performed in all of the cases. Although PET (CT) with gallium-labeled somatostatin analogues 68 should be used in differentiation from a diverse primitive site in the case of well-differentiated neuroendocrine carcinomas, when PET(CT)-FDG-18 may be indicated for in a scarcely differentiated neuroendocrine carcinoma with a high proliferation rate. Gene expression profiles showed that 88% BNETs have luminal phenotype, 42-52% of them were luminal A and 48-58% luminal B. BNETs exhibit a low incidence of PIK3A mutations (7-33%), absence of TP53 mutations, and the presence of FOXA1 mutations. Some cancers present FGFR and RAS mutations also. [5, 6, 7, 9, 14]

5. Treatment

Surgical treatment, radiotherapy, and systemic therapy, based on classical prognostic and predictive factors, constitute the current standard of care [8]. Due to the limited data, genetic factors, therapeutic approaches and randomization trails in BNETs there is no special pathway of treatment or even target therapy. Typical pathway of treatment in localized BNETs is surgery and adjuvant AP chemotherapy or neoadjuvant TC chemotherapy followed by surgery. Hormonal therapy is recommended while ER/PR is positive. In locally advanced BNETs EP based chemoradiation is a standard of treatment. When a metastatic version is observed, the first line of treatment should be etoposide/platinum (EP) or irinotecan/carboplatin (IC) chemotherapy, if we observe refractory for less than 6 months we perform dual immune checkpoint inhibitors (ICIs) or FOLFIRI protocol or cyclin dependent kinase 4/6 inhibitors. If refractory is for more than 6 months than we do retreatment with EP [5]

5.1 Surgery

Generally, surgery is the primary treatment for BNETs, with the approach tailored to tumor location and stage, and cases with lymph node metastasis are managed similarly to invasive breast cancers[7]. There is a potential for breast conserving surgery in early diagnosed BNETs, but some patients prefer traditional mastectomy due to fear of recurrence, genetic testing and advance in reconstructive surgery. [14-15]

5.2 Chemotherapy

The choice of treatment for breast NENs should be tailored to factors like tumor characteristics and patient-specific factors, though neoadjuvant chemotherapy may be considered locally advanced. Sensitivity of chemotherapy for neuroendocrine tumors (NETs) is generally lower compared to neuroendocrine carcinomas (NECs), with platinum-based or etoposide-containing regimens. Studies to compare platinum-based treatment with taxane and anthracycline therapies are needed. Hormonotherapy is also a high value treatment option in BNETs, recommended for 5 to 10 years of total usage[11]. Particularly when most of the BNETs are hormone positive. Tamoxifen as a monotherapy is commonly used in premenopausal women, while when metastatic lesions are observed, combination therapy with aromatase inhibitors or fulvestrant and CDK4/6 inhibitors has shown significant improvements in progression-free survival (PFS) and overall survival (OS) compared to endocrine therapy alone [7]. Some other studies acknowledge that in patients with hormone-positive advanced BC who were treated with nonsteroidal aromatase inhibitors compared with everolimus with aromatase inhibitors therapy significantly improved PFS[17]. Somatostatin analogues are key therapeutic options for other organs neuroendocrine neoplasm. Although they did not demonstrate clinical efficacy. However, BNETs are positive for somatostatin receptors 2, 2A, 2B, 3 and 5[17]. More clinical trials should be performed to establish the potential therapeutic role.

5.3 Radiotherapy

Radiotherapy in BNETs should be no different than in INC-NSTs, including chest wall and regional lymph nodes radiation [16]. Patients with BNETs who received whole radiotherapy appeared to have an extended OS time [19]. Adjuvant protocol is not specifically for BNETs but based on the guidelines for INC-NSTs. In some paper authors consider that radiotherapy should be administered if there are more than 4 or more axillary lymph nodes metastasis or skin, thoracic wall or pectoralis muscle are involved [4]. However radiotherapy after BCT is an obligation, due to the protocol. The duration of this therapy is only 6 weeks, excluding weekends[10].

6. New perspectives and novel therapeutic approaches

Personalized endocrine or chemotherapy based on patient-specific factors and tumor characteristics, with tools like Oncotype DX should be considered, helping to assess recurrence risk and guide treatment decisions [6]. In patients with positive somatostatin receptors (SSR), treatment with somatostatin analogues (SSAs) or receptor radionuclide therapy (PRRT) may be considered, though the available data remain limited [11, 14]. Recent studies presented potential therapeutic factors for BNETs including TROP-2, FOLR1, and H3K36Me3 for targeted therapies. Although prospective studies are needed to show their potential [12]. Another research found that alpelisib is a potential target for PIK3A. [13] Immune check-points inhibitors have been proven effective in triple negative breast carcinoma [20]. However there is no clinical data available for BNETs. Recent studies by F. Lutz et al, showed that trefoil factor 1 (TFF1) which plays a role in mucous barrier, had expression up to 73% in breast neoplasm and up to 45% in neuroendocrine neoplasm. There was not a specific distinguishing feature for BNETs. As a potential target for new drugs, we should perform such a study in the future [21].

7. Prognosis

Earlier studies suggested that breast NENs had a comparable or even better prognosis than invasive breast cancer IBC-NST. However, subsequent studies confirmed that BNETs, especially NEC - have a significantly poorer prognosis compared to IBC-NST. The 5 –year survival for NEC was only 32,2% up to 50,5% and for NET 62,4% up to 74%. Prognosis included several factors such as hormone receptor expression, tumor size, grade, stage, Ki67 expression, pathological type and lymph node condition [5, 6, 7]. Chemotherapy including anthracycline/taxane have been shown to improve survival outcomes. However, their effectiveness in early-stage patients remains unclear [22]. Studies in the past did not contain differences between high-grade and low-grade tumors, which lead us to conclude that with inconclusive data. Future studies should focus on newly proposed classification and refine risk stratification and prognostic factors specific to BNETs. [24]

8. Conclusions

Breast Neuroendocrine tumors (BNETs) represent an extremely rare and heterogeneous subgroup of breast carcinomas with neuroendocrine features and positivity for neuroendocrine markers. In the 2022 WHO classification, they were described as a special subgroup: poorly-differentiated neoplasm (NECs) and well-differentiated neuroendocrine neoplasm (NETs). Although most cases are treated with the same methods as INC-NSTs. However, there are some ideas, like SSAs or new drugs for specific factors occurring in BNETs, for instance PIK3A mutations .

Some new diagnostic methods can help us extract neuroendocrine tumors from all breast cancers. IHC with new markers for neuroendocrine tissue is a standard procedure. Future studies should focus on the implementation of new treatments and diagnostic procedures to evaluate their usefulness and effectiveness. Prognosis of BNETs compared to others BC and NEN should also be analyzed to avoid inaccuracies in future studies.

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