Breast carcinoma with neuroendocrine features: a brief review

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Abstract
Breast carcinoma with neuroendocrine features (BCNF) is a rare entity that is defined by a neuroendocrine (NE) architecture and cytomorphology combined with an immunohistochemical expression of chromogranin A or B and/or synaptophysin. According to the 2012 World Health Organization (WHO) classification, they are classified into three subtypes: invasive breast carcinoma with NE differentiation, well-differentiated NE tumor, and poorly differentiated small cell carcinoma. BCNF are typically positive for the estrogen and progesterone receptor and negative for Her-2/neu protein. The clinical features are not sufficiently specific to distinguish BCNF from other breast carcinomas. BCNF can mimic benign lesions on mammography, so the additional use of ultrasound or MRI can improve detection. Other imaging tests are useful to detect or rule out metastatic disease. Although standardized treatment guidelines have not yet been established, the mainstay of treatment for early BCNFs is surgery. Adjuvant treatment decisions should be individualized and should take into consideration the prognostic and predictive factors, clinical evidence and the patient’s overall health treatment preferences. Therapeutic options in the metastatic setting include surgery, chemotherapy, peptide receptor radionuclide therapy and molecular-targeted agents. These options are not mutually exclusive and are interchangeable.

Key words: Breast cancer; special types; neuroendocrine carcinoma; outcome
1. Introduction

Neuroendocrine tumors (NETs) are rare neoplasms that arise from the cells throughout the diffuse endocrine system. The most frequent primary localizations occur in the bronchopulmonary tract, stomach, small intestine, appendix, rectum, thymus, and pancreas [1]. Nevertheless, they can be found in most of the human body organs. Disease management poses a significant challenge because of the heterogeneous clinical presentations and varying degree of aggressiveness.

Feyrter et al. (1963) described two cases of invasive breast cancer with a carcinoid growth pattern [2]. Cubilla and Woodruff (1977) reported eight cases of breast carcinoma with the same features [3]. Azzopardi et al. found that only 5% of conventional infiltrating carcinomas were argyrophilic by the Grimelius staining procedure [4]. Papotti et al. (1989) identified another 51 cases of breast carcinoma with neuroendocrine (NE) differentiation using structural, immunologic, and electron microscopic analysis [5]. Shin et al. (2000) comprehensively described nine cases of small cell NE carcinoma of the breast [6]. In the next year, Sapino et al. first suggested a specific definition of NE breast carcinoma in a review article [7]. The World Health Organization (WHO) histologic classification of tumors of the breast and female genital organs first recognized NE carcinoma of the breast as a distinct type with NE architecture and cytology combined with an immunohistochemical (IHC) expression of the NE vesicle markers chromogranin A or B and/or synaptophysin in more than 50% of the neoplastic cells. NE carcinomas of the breast were classified into three subtypes, as follows: solid, small cell, and large cell carcinomas [8]. In 2012, the WHO revised the category, renaming them as breast carcinoma with NE features (BCNF) (Table 1). The same category was included in the class of rare epithelial tumors and subdivided into invasive breast carcinoma with NE differentiation, well-differentiated NE tumor, and poorly differentiated small cell carcinoma [9]. The explicit criterion of NE immunoreactivity in more than 50% of neoplastic cells was excluded. The morphologic subtype of invasive breast carcinoma with NE differentiation could include invasive ductal carcinoma not otherwise specified, lobular or medullary carcinomas. Although a cut-off value of Ki-67 was established for other NE tumors, it has not yet been established for BCNFs [10].

2. Epidemiology

BCNF is a rare entity. Epidemiological cohort studies with sample sizes greater than 1000 patients have shown an incidence of 0.27%, 0.5%, and 1.43% [11-13]. In the Surveillance Epidemiology and End Results (SEER) database, only 142 cases of BCNF were identified for the period from 2003 to 2009, which corresponded to the incidence of < 0.1% [14]. Results of the study by Makretsov et al. on the tissue microarray (TMA) blocks of 334 patients with breast carcinoma, with the criteria of NE immunoreactivity in more than 50% of neoplastic cells would be included in the BCNF category [15].

Table 1. Differences between the 3rd and 4th edition of the Word Health Organization (WHO) classification of breast tumors.

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<tr>
<td>neuroendocrine carcinoma of the breast</td>
<td>carcinoma with neuroendocrine features</td>
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<tr>
<td>solid neuroendocrine carcinoma</td>
<td>neuroendocrine tumor, well-differentiated</td>
</tr>
<tr>
<td>large cell neuroendocrine carcinoma</td>
<td>invasive breast carcinoma with neuroendocrine differentiation</td>
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<tr>
<td>small cell / oat cell carcinoma</td>
<td>poorly differentiated neuroendocrine / small cell carcinoma</td>
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cells showed an incidence of 2.7% [15]. Another study on the TMA blocks of 240 patients with breast carcinoma performed in Denmark based on the same criteria showed an incidence of 5.4% [16]. A recent retrospective analysis at the Oncologic Center of the University Hospital in Düsseldorf showed an incidence of 4.5% [17]. The marked differences in the reported incidence of BCNF in the two types of studies are due to the completely different data collection procedures. There was no systematic analysis and reevaluation. In the second group of studies, which showed much higher incidence, the immunoreactivity was reevaluated with stricter diagnostic criteria. In the authors’ own experience the frequency of BCNF is approximately 0.5% of all invasive mammary carcinomas (S.V., unpublished data).

3. Histopathology and molecular pathology of BCNF

The histogenesis of BCNF has not been fully clarified. An initial theory suggested that the BCNF cancer cells were derived from argyrophilic cells of neural crest origin that migrated to the mammary duct [3]. Another theory supports in situ development from NE cells found in the breast [18-19]. A novel hypothesis suggests that BCNF results from an early divergent differentiation event in breast carcinogenesis in which neoplastic stem cells differentiate into epithelial and endocrine lines, respectively [20-21]. NE carcinomas are graded into well-differentiated neuroendocrine carcinomas, which are usually of low- to intermediate-grade (Figure

![Figure 1A-D. A: Hematoxylin and Eosin (H&E, 10x) of a case of invasive breast carcinoma with neuroendocrine differentiation (histologic grade 2); (B): Diffuse and strong positivity for estrogen receptor (ER); the tumor cells were also strongly positive for neuroendocrine markers including Chromogranin-A (C) and Synaptophysin (D).](image-url)
A high-grade or small-cell variant of BCNF belongs to the poor prognostic group [22]. Chromogranin A or B and synaptophysin are generally utilized as the NE vesicle markers and are typically positive in BCNF [9] (Figure 1C-D). Other less specific markers such as neuron-specific enolase ([NSE], typically positive in high-grade variants/small cell NE carcinomas), neural cell adhesion molecule CD-56, neurofilament protein triplet, bombesin receptors and Leu7 should be avoided. Of note, NE differentiation (by histochemical and immunohistochemical markers) may be seen in up to 30% of other breast carcinoma subtypes including ductal carcinoma of no-special-type, mucinous carcinomas (hypercellular variant) and solid papillary carcinomas [9]. A cytogenetic study by Xiang et al. showed that BCNF share some cytogenetic abnormalities such as trisomy of chromosomes 7 and 12 with pulmonary and gastrointestinal NE neoplasms, suggesting that trisomy 7 and 12 may be common molecular aberrations in all NE tumors [23]. Molecular profiling data on BCNF are sparse. A recent study on the mutational profile of BCNF revealed frequent PIK3CA and FGFR gene mutations [24]. BCNFs are clustered together with mucinous A and B tumors on the molecular level, which supports the results of the immunohistochemical analysis. Consequently, positivity to estrogen (ER) and progesterone receptors (PR) is a practically constant characteristic including 50% of high-grade variants (Figure 1B), whereas the expression of c-erbB2/Her-2/neu is negative, as in luminal breast carcinomas. BCNFs are typically stained negative for basal markers (CK5/6, CK14, p63) as well as the EGFR protein. [25-26].

Different NETs have differing proportions of somatostatin receptor (SSTR) expression. Five SSTR subtypes (SSTR1-5) are G-protein-coupled plasma membrane receptors with seven transmembrane regions [27]. The localization of coding genes is on different chromosomes [28]. Comparisons regarding amino acid homology and pharmacological profiles of the SSTR subtypes have revealed two subgroups; SSTR 1 and 4, and SSTR 2, 3, and 5. SSTR2 has been shown to exist in two forms: SSTR2A and SSTR2B, generated by the alternative splicing of mRNA [29]. SSTR2 is overexpressed in the majority of neuroendocrine tumors [30]. That makes it a good candidate for molecular-targeted therapy with the long-acting somatostatin analogues (SSA).

4. Imaging

The goal of imaging modalities including mammography, breast ultrasound, and breast magnetic resonance imaging (MRI) is to confirm the presence of a mass, its exact location and extent. On mammograms, BCNFs appear as hyperdense oval, round or lobular noncalcified masses with sharply demarcated, nonspiculated margins (Figure 2) [11]. Sonographically, BCNFs typically appear as irregular solid masses with cystic components having poorly defined margins. They are hypoechoic and some of them have posterior acoustic enhancement. Color Doppler mode shows a high vascularity [11]. Breast MRI demonstrates a hypointense, irregular lesion on T1-weighted sequences with early and rapid initial contrast enhancement. The enhancement kinetic curves type 2 (plateau) and type 3 (decline after initial upslope) are considered the most suspicious for malignancy [11, 31-32].

Figure 2. Mammography of the right breast in a 56-year-old female revealed an oval, hyperdense mass with sharply demarcated, nonspiculated margins. Histopathologic examination along with immunohistochemistry confirmed breast carcinoma with neuroendocrine features.
5. Clinical characteristics

As with other types of breast cancer, BCNFs are more common in females. Very few cases have been described in males [14,33-35]. The average age for disease onset is between the sixth and seventh decade of life, 10 years later than the usual types of breast carcinoma [14]. A lump with a diameter of 1-2 centimeters and nipple discharge are the two most common initial clinical presentations in patients with BCNF. Axillary lymph nodes are generally not enlarged or painful. Manes et al. reviewed previous published case reports of metastatic BCNFs and analyzed the metastatic pattern. The most common metastatic sites were bones, liver, and lung, like in luminal subtypes of breast carcinoma. Pancreatic metastases were observed in two patients with BCNFs. A very low incidence of brain metastases is found in patients with BCNFs [36]. Some authors have described metastases from BCNFs to the thyroid, stomach, heart, renal cell carcinoma, and adrenal gland [37-39]. The first recurrence of the disease should be biopsied as a part of the workup. This ensures accurate determination of metastatic disease and tumor histology, and allows for biomarker determination and selection of an appropriate treatment. Making the proper diagnosis of BCNF can be challenging for pathologists and clinicians alike. The pathological differential diagnoses should include Merkel cell carcinoma, lymphoma, melanoma, and metastasis from digestive, bronchopulmonary and pancreatic neuroendocrine tumors (on the basis of immunohistochemical staining of CDX-2, CK7, CK20, GATA3, GCDFP-15, Isl1, TTF-1, and mammaglobin) [40]. In general, these stains should be used as a panel and interpreted in conjunction with clinical findings and imaging studies. According to Upalakalin, 36% of BCNF cases reported in the published literature were metastases [41]. Therefore, the presence of NE differentiation should alert the clinician to search for another primary tumor. Computed tomography scans of the chest, abdomen and pelvis are recommended. Gadoxetic acid-enhanced magnetic resonance imaging (MRI) has demonstrated satisfactory results in the characterization of hepatic lesions. Sonographies are useful to guide percutaneous biopsy and to assess the general state of internal body organs and cardiac function, especially when carcinoid heart disease is suspected (nevertheless, it occurs very rarely). Endoscopy treatments can also help diagnose small NE cancers of other localizations and control carcinoid symptoms, like bronchospasm and diarrhea. SSTR scintigraphy with Indium-111 is very accurate in detecting metastatic disease, although it has some limitations. Usually, the scans cannot detect primary tumors smaller than one centimeter in diameter. Similarly, if the tumor does not have the SSTR, or has a low affinity for the SSA octreotide, it cannot be detected by SSTR scintigraphy [42]. In those cases, two other nuclear scans (the positron emission tomography (PET) scan and metaiodobenzylguanidine (MIBG) scan) are used in conjunction in order to detect metastatic lesions that would have been missed on conventional imaging or are located in clinically hidden or difficult areas. A few years back, novel Gallium-68 labeled SSA were developed as PET tracers for NETs. They have shown excellent results. When suspecting bone metastases, a bone scan will show them earlier than any other imaging procedure. Blood and urine biomarkers can improve diagnostic accuracy.

6. Treatment options

Surgery is considered to be the primary treatment for breast carcinoma. An accurate preoperative assessment including the size and extent of the tumor is essential for making a choice between a radical mastectomy and breast conserving surgery [15,43-44]. The sentinel lymph node biopsy is the least invasive initial assessment of lymph node status but is not appropriate for everyone. In some cases, more extensive lymph node dissection might be needed. Lymph node dissection can occur at the same time or later, and can be regional or radical. In metastatic breast cancer, the role of surgery is debatable, but it can improve local control of bulk disease. Regarding chemotherapy, the literature is sparse. The choice of chemotherapy agents is usually dictated by the histopathological characteristics of a tumor. Patients with poorly differentiated small cell BCNF have been treated with the chemotherapy regimens cisplatin-etoposide and paclitaxel-carboplatin, which are commonly used in small cell lung cancer, gynecological cancers and melanoma [45]. Anthracycline- or taxane-based chemotherapy regimens were administrated before hormonal therapies in cases that were treated as breast cancers. Postoperative irradiation is less common [33]. Long-acting SSA have an established role in the
8. Conclusions

BCNF is a rare, special type of breast carcinoma with distinct morphology, positivity for neuroendocrine markers and luminal molecular profile. Current evidence suggests that histologic grading and tumor stage are the best prognostic parameters. Further molecular studies should elucidate molecular pathways that drive BCNF carcinogenesis and provide new, targetable biomarkers for patients with advanced/or metastatic disease.

Author contributions

PJ performed literature review, wrote the article and gave the final approval. BK and ZG gave the idea for the article, participated in drafting the article and gave the final approval. SS and SV critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval.

7. Prognosis

Data regarding prognosis are controversial. A multivariate analysis performed on the basis of the SEER database showed that NE differentiation was an independent adverse prognostic factor [14]. The results of a retrospective comparative study by Zhang et al. showed that BCNF has a poorer overall survival (OS), local recurrence-free survival (LRFS) rate, and a higher rate of distant recurrence. Several factors (higher T classification, M classification, TNM stage) are inversely relevant to OS, LRFS, and DRFS [49]. Bogina et al. showed that NE differentiation does not affect the prognosis of BCNF in terms of cancer-specific survival. A shorter OS and disease-specific survival was recorded in patients with BCNF compared with patients that had invasive breast carcinoma not otherwise specified [50]. The conflicting data regarding prognosis of these tumors may be due to the heterogeneity of tumors that are put in this category as one entity. When compared grade-to-grade and stage-to-stage, these tumors have a similar prognosis as other invasive breast carcinomas [51,52].
References
