# Primary Neuroendocrine Neoplasms of Breast

Subjects: Oncology

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Primary neuroendocrine carcinoma of the breast (NECB) as defined by the World Health Organization (WHO) in 2012 is a rare, but possibly under-diagnosed entity. It is heterogeneous as it entails a wide spectrum of diseases comprising both well-differentiated neuroendocrine tumors of the breast as well as highly aggressive small cell carcinomas.

neuroendocrine carcinoma of the breast | small cell carcinoma of the breast | case series | review | diagnostics | histology | management

## 1. Introduction

Neuroendocrine neoplasia (NEN) are a rare, heterogeneous group of tumors that originate from the diffuse endocrine system with variable clinical behavior depending on the differentiation of the tumor. According to the WHO classification, NEN can be stratified based on their histological differentiation into low- (grade 1; G1), intermediate- (grade 2; G2), and high-grade (grade 3; G3) neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinoma (NEC), featuring a highly elevated Ki67 proliferative index and/or mitotic rate [1]. Well-differentiated NET (G1, G2) typically have a low proliferative index and retain high expression of somatostatin receptors (SSTR). Advanced well-differentiated NET that are ineligible for resection are managed in most cases with somatostatin analogs (SSAs), such as octreotide and lantreotide, peptide receptor radionuclide therapy and targeted agents, such as everolimus and sunitinib [2][3][4][5]. In contrast, poorly differentiated carcinomas are associated with rapid progression and a poor long-term prognosis. In most cases, these patients are treated with systemic cytotoxic chemotherapy. Neuroendocrine neoplasia may occur in almost all organ systems. In most cases NEN occur within the gastroenteropancreatic system (70% of all cases) and the bronchopulmonary system (25%) [6]. Examples of rare primaries are thyroid gland (8.6%) [7], skin (5%) [7], bladder (0.35–1%) [8] and larynx (0.23%) [9]. Mammary origin accounts for less than 1% among neuroendocrine tumors [10][11][12][13][14]. Their incidence among breast cancer has been reported to range from 0.1% to 5% [13][15][16][17]. These tumors are thought to arise from endocrine differentiation of breast carcinoma rather than from pre-existing endocrine cells with malignant transformation [18].

## 2. Review of the Literature and Discussion

### 2.1. Summary of the Case Reports

We report a series of five patients with histologically confirmed diagnosis of NECB who have been followed at our institution. According to the 2012 WHO classification, three patients (cases 1–3) suffered from a well/moderately differentiated NECB and two patients (cases 4 and 5) suffered from a small cell carcinoma of the breast.

Two out of three patients with well/moderately differentiated NECB (cases 1–3) presented with clinical symptoms (pain, erythema, skin and nipple retraction). Clinical work-up included mammography, ultrasound, CT-imaging, and punch biopsy in all patients. Interestingly, all were in a localized disease stage without distant metastases at the time of diagnosis. Immunohistochemical analysis showed expression of synaptophysin, chromogranin, GATA3, and nuclear hormone receptors (estrogen receptor (ER), progesterone receptor (PR)). Ki-67 was below 10% in all cases. All patients underwent partial mastectomy including lymphadenectomy. Two patients received radiation therapy, one of them received additional hormone therapy, while none of them were treated with chemotherapy. All remained free from recurrence during follow-up.

Our patients with small cell carcinoma (cases 4 and 5) displayed clinical symptoms and underwent more extensive diagnostics including bone scintigraphy, bronchoscopy, colonoscopy, and upper endoscopy. Moreover, those patients were in a more advanced disease stage with distant metastases already at the time of diagnosis. Histological analysis showed poor differentiation, featuring a Ki-67 proliferation index of at least 40%. Immunohistochemical staining revealed positive expression of synaptophysin in both cases and additionally weak expression of chromogranin in one case. There was no expression of the estrogen receptor (ER) in both cases, while case 4 at least showed weak expression of the progesterone receptor (PR). HER2neu was negative in both cases. In case 5 the transcription factor GATA3 was indicative of a primary tumor of the breast, while in case 4 E-cadherin was found. Unfortunately, additional staining for transcription factors (e.g., GATA3) in case 4 was not possible, since there was not enough material left and the patient is deceased. Both patients with small cell carcinoma of the breast initially received chemotherapy with Carboplatin and Etoposide but died after a rather short period of tumor response.

## 2.2. Terminology, Frequency, Epidemiology

Primary neuroendocrine carcinomas of the breast are rare and were first described by Feyrter and Hartmann in 1963 [19]. In 2002, Sapino et al. first proposed a more specific definition for NECB [20], which was subsequently adopted by the World Health Organization (WHO) as a unique type of breast cancer the following year [17]. The incidence of NECB is only poorly understood [13][15][16][17]. Lopez et al. [16] and Günhan et al. [15] analyzed 1368 and 1845 cases of breast cancer, respectively, and found that, by using WHO diagnostic criteria of 2003, NECB only account for 0.3% and 0.5% of breast cancer, which is much less than the 2–5% rate reported by the WHO [17]. In this context, it is important to note that NECB might be under-reported since NET specific markers are not routinely applied in breast cancer patients and many NECB might been overseen in clinical practice. According to the WHO Classification of Tumors of the Breast of 2012, NECB are stratified into three subgroups based on morphology: (1) well-differentiated neuroendocrine tumors, (2) invasive carcinomas of the breast with neuroendocrine differentiation, and (3) small cell carcinomas of the breast [17]. As opposed to the previous guidelines of 2003, diagnosis can be set up regardless of the percentage (50% threshold) of tumor cells expressing neuroendocrine

markers [17]. Well-differentiated NECB (G1, G2) are characterized by a low proliferation index, retained expression of somatostatin receptors (SSTR), and are associated with an extraordinary favorable prognosis when compared to other malignancies. In contrast, small cell carcinomas of the breast are histologically poorly differentiated, feature a high Ki-67 proliferation index of >20%, and are associated with a dismal prognosis. Most patients with NECB are postmenopausal women and the incidence in males and younger women is low [21]. The median age of 64 years (49–78) in our case series is consistent with results from a Chinese case series including 126 cases with NECB [21] and previous reports [17][20]: only one patient (case 3) was diagnosed at age of 49 and was in perimenopause at that time.

## 2.3. Clinical Presentation and Diagnostic Work-Up

Diagnosis of NECB can only be made by the pathologist, since the clinical presentation and imaging findings are not distinct from other types of breast cancer. In many cases, NECB present as painless, palpable retro-areolar mass with secondary symptoms such as nipple retraction, fixation to deep tissues, skin ulceration, lymphadenopathy, or bloody nipple discharge [21][22]. In our case series, no patient suffered from bloody nipple discharge, carcinoid syndrome or hormonal hypersecretion and only four patients suffered from clinical symptoms such as pain, erythema, palpable mass, and skin retraction before initial diagnosis. NECB represent rather small tumors. In our case series, median tumor size was 18 mm (10–53 mm). In line, Lopez et al. reported sizes from 7 to 53 mm [16].

Radiological features of NECB are unspecific in most cases. However, some studies suggested that NECB might appear as a round, sharply circumscribed, hyperdense mass in mammography and as an irregular or microlobulated hypoechoic solid mass with increased vascularity on ultrasound [15][23][24]. Additionally, somatostatin receptor scintigraphy (SRS) or positron-emission tomography/computed tomography (PET/CT) with 68-Gallium-labeled somatostatin analogs (e.g., DOTATOC) may be used to detect well-differentiated NET, while 18-fluorodeoxyglucose (FDG)PET-CT can be used in poorly differentiated NEC with a high proliferation rate [25][26][27].

All patients in this study with well/moderately differentiated NECB received a punch biopsy after mammography and ultrasound of the breast. Further clinical work-up included CT-imaging and one case of Ga68-PET showing an SSR-positive primarius (case 1) before surgery. Patients with small cell carcinoma underwent more comprehensive diagnostics including CT-imaging, bone scintigraphy, bronchoscopy, colonoscopy, and upper endoscopy.

## 2.4. Histology

A reliable pathological diagnosis can only be made by analyzing specimens obtained by core needle biopsy or surgery, whereas fine-needle aspiration cytology is not recommended due to the similarity of NECB's cytological features to those of invasive ductal carcinoma and intra-ductal papilloma [25][27][28]. Primary NECB comprise several histologic subtypes that differ from one another in cell type, level of invasiveness, and growth pattern [29]. Until 2003 WHO defined NECB as tumors of epithelial origin, with morphology similar to gastrointestinal and pulmonary neuroendocrine tumors and positive staining for neuroendocrine markers in at least 50% of the total cell population [17]. The following WHO classification guidelines 2012 do not include a percentage of tumor cells

expressing neuroendocrine markers as the WHO acknowledged that the 50% threshold of cells with neuroendocrine marker expression was arbitrary [17][30]. In our experience, it is sometimes difficult to differentiate neuroendocrine morphology from a ductal morphology. This is exemplified in our patient no 3, who was initially diagnosed with DCIS. A threshold value of positive staining for neuroendocrine markers in at least 50% of the total cell population may be helpful in order to have objective criteria allowing different pathologists to come to the same conclusion in cases that are not entirely clear.

The utilization of detailed immunohistochemical staining and various imaging modalities are essential in establishing an accurate diagnosis. Neuroendocrine markers such as chromogranin and synaptophysin have the best sensitivity and specificity for immunohistochemical evaluation [31]. Other less specific markers showing positive expression are neuron-specific enolase (NSE), CK7, and CK56 [16][32]. TTF-1 and CDX2 stains are typically negative [33]. While NECB is often positive for hormone receptors (ER, PR), HER2neu is usually negative, although there are also reports of HER2neu-positive NECB [16][34]. In our case series, only one patient showed slight positivity of HER2neu expression. Expression of estrogen and progesterone receptors was demonstrated in all our cases with well and moderately differentiated NECB, while in one case of small cell carcinoma of the breast hormone receptor status was negative and in the other case PR was only expressed in 15% of tumor cells. In this context, Shin et al. report that hormone receptors in small cell neuroendocrine tumors are expressed in fewer cases (<70%) than in well/moderately differentiated NECB [35]. There are indications that these receptors are also expressed in neuroendocrine tumors of other origin. According to several expert groups PR expression in NET metastases indicates in many cases a pancreatic primary and can also be associated with duodenal origin [36][37][38]. Further, Curioni-Fontecedro et al. demonstrated that ER expression is frequent in all NEN of the lungs [39]. Hence, a prospective single-arm, unicentric clinical trial (HORMONET, NCT03870399) testing tamoxifen in well differentiated gastroenteropancreatic and pulmonal NET has been started [40].

Due to the architectural similarity to neuroendocrine tumors from other origin, NECB can be easily mistaken for neuroendocrine tumors metastatic to the breast. Finding a DCIS component indicates the breast as a primary tumor location [41]. The expression of transcription factors such as GATA3, which is a more sensitive and specific marker than mammoglobin, hints towards a mammary origin. Despite GATA3 also being expressed in urothelial, renal, germ cell tumors, and paragangliomas [42][43][44], a positive expression in extramammary NEN has not been described [41][45]. Additionally, positive expression of hormone receptors (PR, ER) in well/moderately differentiated NECB also play an important role in differentiating primary and secondary lesions [41][45][46]. In our case series, GATA3 was positive in all three cases, in which it was performed, while a DCIS component was described only in one patient (case 3). Transcription factors such as TTF-1 and CDX2, which show positivity in metastases of the lung (TTF1) and of gastrointestinal origin (CDX2), were negative [27][45]. All our patients with well and moderately differentiated NECB showed positive hormone receptor expression. As hormone receptors are expressed in fewer cases in small cell carcinomas of the breast in contrast to NECB [35], the presence of PR in case 4 is indicative of a primary of the breast. Additionally, in a series of 18 metastatic NETs in the breast by Perry et al. no expression of PR was found, differentiating these metastatic lesions from primary breast tumors [47].

### 2.5. Management

As there is a lack of large clinical studies, there are almost no standardized recommendations for treatment of NECB. Most treatments of NECB reported in the literature and in the present study (only in regard to well/moderately differentiated NECB) are similar to the treatment of ductal-type, while Anlauf et al. highlight the importance of treatment according to NET guidelines [48]. According to both guidelines, surgery is the mainstay of treatment for early NECB. The surgical procedure (breast conserving partial mastectomy, total mastectomy) depends on the location of the tumor and the clinical stage [49][50]. In this context, patients in cases 1–3 underwent partial mastectomy, while patients with small cell neuroendocrine carcinoma were not administered to surgery due to widespread metastases. In well/moderately differentiated NECB surgery is usually followed by radiotherapy depending on the size of the tumor and lymph node status [25][27]. In line, two out of three patients were subjected to radiotherapy. Chemotherapy is used as adjuvant therapy in patients with high risk of relapse or as neoadjuvant therapy in cases of locally advanced or inoperable NECB [27]. Combinations of platinum agents and etoposide, as it is recommended for small cell neuroendocrine tumors, and taxane-based chemotherapy, routinely used for other types of breast cancer, are commonly administered [28][51]. Both of our patients with small cell carcinoma of the breast initially received chemotherapy with Carboplatin and Etoposide, which is first-line therapy according to NET treatment guidelines [52]. Nevertheless, Inno et al. recommend treatment according to guidelines on ductal carcinoma due to lack of data for Cisplatin/Etoposide in breast tumors.

Antihormonal therapy has proven efficacy in patients with hormone receptor-positive breast carcinomas. According to Richter-Ehrenstein et al. adjuvant antihormonal therapy is the standard adjuvant therapy in hormone receptor positive NECB [46], which is why all patients with NECB ($n$ = 7) in Lopez et al.'s study received antihormone therapy [16]. In contrast, only one of our patients with NECB and positive hormone receptor expression received antihormonal therapy as the other two patients rejected treatment due to lack of established guidelines. The prognostic role of HER2neu in NECB is not clear, but it can be assumed that it is analog to other invasive breast carcinomas, therefore anti-HER2neu therapy can also be considered for HER2neu-positive NECB. In the case of SSR-positive tumors, peptide receptor radionuclide therapy (PRRT), which is a tumor-targeted systemic radiotherapy that enables the specific delivery of radionuclides directly to tumor cells inducing tumor cell death [53][54][55], has been recommended after failure of conventional chemotherapy or also as first or second line therapy [48][56].

Thus, optimal treatment of NECB requires simultaneous consideration of both neuroendocrine and non-neuroendocrine breast tumor features. Nevertheless, a majority of expert groups recommend mainly treatment according to ductal carcinoma guidelines as a consequence of scarcity of available data. This clearly indicates the need for further studies to investigate sustainability. In our opinion, it is particularly useful to consider NET guidelines with regard to positive SSR status and possible diagnostic and therapeutic modalities.

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