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Neuroendocrine Carcinoma of the Breast: Epidemic, Clinicopathological Features and Treatment

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Abstract

Purpose: To evaluate the clinical and pathologic features and treatment of neuroendocrine carcinoma of the breast.

Patients and Method: This is a case series study on 10 patients diagnosed with neuroendocrine breast cancer carcinoma and treated from 1/1/2015 to 30/06/2016 at HCMC Oncology Hospital.

Results: The median age is 50 (range 24 to 59). The median duration of disease awareness before hospitalization was 14 weeks (range 2 to 52 weeks). One patient has her history of breast cancer, 1 patient has family history of breast cancer (her aunt). 90 percent of cases presented with a palpable mass of the breast, 10% of cases presented with nipple hemorrhage. Two cases had breast cancer in both sides, 2 cases had 2 lesions in the breast. Median tumor size at hospitalization was 3 cm, 2 cm (range 1 cm to 10 cm). 100% of cases were neuroendocrine carcinoma of the breast and 75% of cases were grad 2. On biological subgroup analysis, we found that 10% of cases were triple negative, 5% of cases were HER2 positive and 65% of patients had high Ki67 levels (>10%). 90% of patients received surgery initially. Taxane-based adjuvant or neoadjuvant chemotherapy was indicated for 50% of patients, but none of them received trastuzumab. We couldn't evaluate overall survival of the whole group because of the limitation of time.

Conclusion: The incidence of neuroendocrine carcinoma of the breast is very rare. The biological nature of invasive breast cancer of this group is usually nonaggressive. Diagnostic delay >3 months is considered an adverse prognostic factor in our series. In general, the treatment for this group of patients is not different from other subtypes. Patients of this group need to be indicated targeted therapy if possible.

Keywords: Breast cancer; Neuroendocrine carcinoma; Prognosis; NECB

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Background

Neuroendocrine Carcinoma (NEC) of the breast is a rare type of cancer. It is first documented in 1963, and occasionally appears in the medical literature [1].

WHO estimates this type of breast cancer, which is uncommon and under-researched, to comprise about 2% to 5% of breast carcinoma [2]. The biological characteristics of NEC of the breast and its management are not well researched. Our research aims to review the pathology and management of 11 patients with NEC of the breast from 2015 to 2016.

Materials and Methods

Case series report

Every patient with NEC of the breast who was admitted and treated at HCMC Oncology Hospital from January 1st, 2015 to June 30th, 2016 with the pathology report of NEC of the breast. SPSS 17.0 was used to process data. Survival estimation using Kaplan-Meier method. Correlation analytics using Log-rank test. Multivariate analytics using Cox Regression.

Results

Patients characteristics

During our research time, 11 patients with NEC of the breast were treated in the Surgical Oncology Department 4 and the Medical Oncology Department 4 of HCMC Oncology Hospital. We recorded their clinical settings, radiologic results, pathology reports.

Average age is 50 years old, median: 57 years old (range 24 to 59 years old). Menstrual status:

3 menstrual, 8 menopause. Median time to symptomatic: 14 weeks (range 2 to 52 weeks). One patient had a history of breast cancer. One patient had an aunt with breast cancer. No patient had a history of using contraceptives. Ninety percents of patients came for a checkup because of breast tumors, the other 10% because of bloody nipple discharge. There were two cases of bilateral breast cancer, two cases of one sided breast cancer with two lesions. Median of the tumor's size is 3.2 cm (1 cm to 10 cm). There were 18.2% cases with a size >5 cm at diagnosis. Eighty two percents did a Fine Needle Aspiration (FNA) at diagnosis and the results were: 01 case of fibrocystic change, 02 cases of atypical ductal hyperplasia, 02 cases of papilloma, and 04 cases of adenocarcinoma. About seventy two percents did a biopsy: 01 case of ductal papillary carcinoma (5%), 01 case of suspected ductal papillary carcinoma (5%), 02 cases of solid papillary carcinoma in situ (10%), 03 cases of neuroendocrine tumor (15%), 01 case of adenocarcinoma grade 2 with unknown origin (5%). Immunohistology was done: CHROMO, NSE, CD56, E CADHERIN, and S10. Grade 1, 2, 3 were of the following: 6 cases (45%), 1 (9.1%), 4 (27.3%). Subtypes of Luminal A, Luminal B/Her2 -, Luminal B/Her2 +, Her2 +, triple negative were: 6 (54.5%), 2 (18.2%), 0 (0%), 1 (9.1%), 2 cases (18.2%) respectively.

Management

There were 10 cases receiving surgery first: 10% with breast reconstruction, 90% with mastectomy and axillary lymph node dissection. Chemotherapy regimens with taxane were used in 60% of cases and none used trastuzumab. Two cases (18.2%) received adjuvant radiotherapy. Two cases had relapses and metastasis. These two cases had a large tumor (5 cm to 7 cm), grade 3, 5 metastatic lymph nodes. Side of metastasis was bone, liver, supraclavicular lymph nodes.

Discussion

Clinical manifestation and diagnosis

Clinical characters and pathology:

Age at the time of diagnosis: The average age in our study is 50 years old. Bing Wei et al. [3] showed that the average age is 61 years old (range 29 to 82, median 63). Patients with NEC were older than control with statistical significance, but had no difference compared to breast cancer patients in general according to SEER's database.

Menstrual status: 03 patients were menstrual, the other 08 had menopause. According to Bing Wei et al. [3] the majority of patients with NEC of the breast was menopausal (72%), 15% menstrual, 01% pre-menopausal, and 12% with unknown menstrual status. The number of menopausal patients was greater with statistical significance, which was compatible with older age at diagnosis of patients with NEC.

The clinical stage at diagnosis: T categorization: 18.2% with tumors >5 cm. Bing Wei et al. [3] showed that there was no difference in tumors' size between NEC patients and controls. Primary NECB has no distinct clinical characteristics compared to other breast cancer's types. It can be a solid tumor in the breast with or without axillary lymph nodes. There can be symptoms of endocrine activities of the tumor but it is exceedingly rare. Occasionally there are clinical manifestations of atopic secretion of epinephrine, norepinephrine, or calcitonin. NEC is usually diagnosed in women of 60 to 70 years of age. There are only a few cases of NECB in men.

Radiological characteristics are unspecific. Some authors reported that NECB usually presented on mammography with a clear border, hyperintensity, and on ultrasound as a hypoechoic mass with undefined margin, hypervascularized, with cystic components. Magnetic resonance imaging shows uniformly low signal intensity.

FNA is not sufficient to diagnose NECB because of characteristics similar to that of invasive ductal carcinoma and ductal papilloma. Thus, diagnosis is made with core biopsies or open biopsies. Differential diagnoses are Merkel's carcinoma, lymphoma, melanoma and neuroendocrine tumors metastasized to the breast. The appearance of ductal carcinoma in place with local components is an important evidence of the tumor's primary characteristic. To exclude other types of tumors metastasized to the breast; other radiological tests are used, such as CT-scanner of the chest and abdomen. Somatostatin Receptor Scintigraphy (SRS) and PET-CT with 68 Ga-somatostatin analogues are useful to diagnose the primary tumor in cases of well differentiated NEC. PET-CT with 18-fluorodeoxygluose can be useful in cases of NEC with fast proliferation, especially when the tumor is large without local components nor endocrine receptors, and no metastatic axillary lymph nodes [4].

Prognosis

In a study based on the population from SEER's database, from 2003 to 2009, 142 cases of NECB had 50% cells positive for neuroendocrine markers according to whose 2003 standards. In this study, NECB patients' overall survival and disease specific survival were worse than that of invasive ductal carcinoma NOS of the same stage. Multivariate analysis of other prognostic factors such as age, tumor's size, lymph node status, histological grade, endocrine receptor status, and management showed that neuroendocrine differentiation is a reversed prognostic factor.

In a retrospective analysis of 55 cases of early stage NECB compared to 115 control cases, progression free survival was worse in NECB patients with statistical significance, but not cancer specific survival. In NECB patients, large tumor's size (>20 mm), late stages, negative endocrine receptors, and no surgery are associated with shorter overall survival. Proliferation index and histological subtypes are prognostic factors in NECB. In a large study on Chinese NECB patients, Ki67 over 14% is associated with worse progression free survival and overall survival. According to histological subtypes, small cell carcinoma has significantly worse prognosis compared to other subtypes of NECB.

Management

Surgery is the mainstay management of early NECB and the type of surgery is selected based on the location and clinical stage of the tumor. There is no study on adjuvant radiation based on recommendations of other types of invasive breast cancer.

Systemic therapy should be selected based on individual biological characteristics and relapse risk. Tumor's size and metastasized lymph nodes are still prognostic factors to evaluate relapse risk of NECB. Chemotherapy can be used in the adjuvant setting for patients with high relapse risk, or in neoadjuvant settings for locally advanced or unresectable NECB. Positive endocrine receptor patients should receive endocrine therapy. Many chemotherapy regimens have been reported in the medical literature, including that combination of anthracycline and/or taxane for other types of breast cancer, or of platinum and etoposide commonly used for small cell lung cancer. These regimens are but not limited to Fluorouracil/epirubicin/cyclophosphamide; cyclophosphamide and doxorubicin; cyclophosphamide/methotrexate/fluorouracil;

paclitaxel; carboplatin/paclitaxel; carboplatin or cisplatin and etoposide; cisplatin and irinotecan. Evidence is lacking for the strength of platinum and etoposide in adjuvant therapy for NECB, suggesting the same principles of ductal adenocarcinoma treatment. If chemotherapy is indicated, regimens with anthracycline and/or taxane should be prioritized.

Patients with positive receptors should receive adjuvant chemotherapy and endocrine therapy. Some centers favor regimens with cisplatin or carboplatin for their efficacy in treating lung NEC [5].

Chieh et al. performed an ad hoc analysis on 86 patients with NECB from 30 reports from 1980 to 2013. Multivariate analysis showed that 48 month OS for all stages was 83.5% (stage IV, III, II, I are respectively 0%, 68.1%, 72.9%, and 95.8%). Unflavored prognostic factors were large tumors (48 month OS are 51.4 *vs.* 97.1% for tumors >5 cm *vs.* ≤ 2 cm) and endocrine receptors (48 month OS are 61.6 *vs.* 97.9% for negative *vs.* positive receptors).

The prognostic role of Her2 in NECB is not clear, but may be similar to other breast adenocarcinoma. Thus, anti-Her2 therapy should be considered for NECB Her2 (+).

In metastatic setting, the treatment should be individually selected based on the overall status and comorbidity, the disease's extension and progression, biologic characteristics of the tumor. Surgery is an acceptable treatment in selective liver metastasis because the survival was reported to improve after liver resection. Liver surgery should be done if R0 is achievable and there is no evidence of advanced disease besides the liver, except bone metastasis which can be controlled with radiation. An alternative treatment to surgery for single lesions is targeted radiotherapy similar to other breast carcinomas.

Patients with multiple metastatic sites should be treated with systemic therapy. In those with positive endocrine receptors, slow progressive diseases with bone or lymph node metastasis, many authors use endocrine therapy with long-term control. With fast progressive diseases, symptomatic and visceral metastasis, chemotherapy should be considered. In the medical literature, the regimens are similar to other metastatic breast cancers and small cell lung cancer's regimens.

In NECB patients with somatostatin receptors, Peptide Receptor Radionuclide Therapy (PPRT) is reported to be effective and well tolerated. In patients with positive SRS or PET-CT Gallium 68, PPRT can be used after failure with conventional chemotherapy or as first and second line in a combined treatment plan.

Prospective

In a recent study, primary or secondary NECB were screened for common gene mutations. These mutations were discovered in 5 out of 15 cases. PIK3CA were identified in 3 cases, 2 of which also had FGFR. This is an interesting discovery because anti-Phosphatidylinositol 3-Kinase (PI3K) and anti-FGFR are in development. In a study by Ang et al. the activation of VEGFR2 was found, and in another study, VEGF-C was reported to have strong exhibition in NECB. These findings can be the basis for research of anti-angiogenic agents.

The PI3K/AKT/mammalian Target of Rapamycin (mTOR) has an important role in development and progression of Pancreatic Neuroendocrine Tumors (pNETs). Everolimus, an mTOR inhibitor, is proved to be effective in well- and averagely-differentiated pNETs and being researched for other types of neuroendocrine tumors. The PI3K/AKT/mTOR pathway seems to be associated with secondary resistance to endocrine therapy in positive endocrine receptor patients. In a phase 3 study, everolimus plused an aromatase inhibitor-exemestane did prolong PFS significantly on metastatic breast cancer patients with ER (+), Her2 (-) who relapsed or advanced with nonsteroidal aromatase inhibitor. The target mTOR is a promising therapy in metastatic NECB [6].

Conclusion

Primary NECB (rare <1%) is diagnosed when there are components of intraductal carcinoma and more than 50% of the cell population proliferating as groups of dense cells with neuroendocrine receptors (diffuse neuroendocrine carcinoma). Also, no NEC tumor outside the breast is noted.

Breast carcinomas with neuroendocrine differentiated components (localized neuroendocrine carcinoma) comprise of 2% to 5% of breast cancer, usually present in women 60 to 70 years of age, though can also be in men. NECB tumors almost have no endocrine activity. The exhibition of ER, PR, and chromogranin synaptophysin is the evidence of breast origin and neuroendocrine differentiation.

Currently there is no consensus on the management and follow-up for breast carcinoma with neuroendocrine components. Most patients receive the same treatment and monitor as invasive ductal carcinoma patients'. Patients should undergo mastectomy rather than reserve surgery and chemotherapy, as well as adjuvant endocrine therapy with positive receptor tumors.

Primary NECB has worse prognosis compared to invasive ductal carcinoma NOS because of higher local and distant relapse, and shorter overall survival and disease free survival.

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