Original Article

Neuroendocrine carcinoma of the breast with hyperprolactinemia: report of two cases and a minireview

Qinqin Zhang1*, Li He2*, Wei Lv3, Ningxia Wang4

Departments of 1Thyroid and Breast Surgery, 2Emergency, Nanxishan Hospital of Guangxi Zhuang Autonomous Region, Guilin 541002, Guangxi Zhuang Autonomous Region, China; 3Department of General Surgery Panyu Central Hospital, Guangzhou 511400, China; 4Department of Breast Surgery, The First Affiliated Hospital of Jinan University, Guangzhou 510630, China. *Equal contributors.

Received March 11, 2020; Accepted April 27, 2020; Epub June 1, 2020; Published June 15, 2020

Abstract: Neuroendocrine carcinoma of the breast (NECB) is a rare type of breast cancer. The clinical features and morphology between NECB and other subtypes of breast cancer are indistinguishable. Currently, the diagnosis of NECB mainly relies on immunohistochemical markers including chromogranin and synaptophysin. It is urgent to find new diagnostic markers for NECB. Some evidence suggests a link between high prolactin level and breast cancer development, however, it is unclear whether NECB may be associated with hyperprolactinemia. Here we report two cases of primary NECB with hyperprolactinemia. One patient had a history of mental disorder, while the other experienced pregnancy. Metastatic and associated tumors were not found in both cases, and postoperative studies showed one case was hormone-receptor-dependent, but the other was hormone-receptor-independent. The cases presented here suggest hyperprolactinemia may contribute to NECB development.

Keywords: NECB, hyperprolactinemia

Introduction

Prolactin is secreted by lactotroph cells of the anterior pituitary gland, mammary gland, lymphocytes, uterus, prostate, and placental decidua. The hormone stimulates DNA synthesis, epithelial cell proliferation, and milk production in the breast by prolactin receptors [1]. While the physiological functions of PRL in the mammary gland are well known, its role in breast cancer is unclear. A few studies investigated the correlation between hyperprolactinemia and breast cancer, but the results are inconclusive [2-5]. It is possible that hyperprolactinemia is associated with specific types but not all types of breast cancer. NECB is a very rare type of breast cancer. It comprises approximately 1% of all breast cancers [6], and currently there are no specific treatment guidelines for NECB. Although various characteristics of this disease have been described, its pathogenesis is completely unknown. In the present study, two cases of NECB presented with hyperprolactinemia are reported, and the diagnosis of NECB and its possible relationship to hyperprolactinemia are discussed.

Case report 1

The patient was a 46-year-old female and admitted to our hospital in the year of 2013 with a lump in the left breast found three months earlier. Before admission to our hospital, a biopsy was performed in other hospital. The lump greatly increased after biopsy.

The patient has a history of more than 20 years of mental disorder and once treated with clozapine and risperidone. She has no family history of breast cancer. Six years ago, she delivered a female infant through vaginal birth without postpartum breastfeeding. Tubal ligation was performed for contraception, and there were no further pregnancies. The patient had been in menopause for one year.

Admission examination revealed normal development, moderate nutrition, normal body tem-
Neuroendocrine carcinoma of breast with hyperprolactinemia

Table 1. Related clinical indicators

<table>
<thead>
<tr>
<th>Related clinical indicators</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pg/mL)</td>
<td>&lt;11.8</td>
<td>&lt;10</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>3.10</td>
<td>4.17</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>0.84</td>
<td>1.24</td>
</tr>
<tr>
<td>Prolactin (mIU/mL)</td>
<td>4200</td>
<td>6524</td>
</tr>
<tr>
<td>Progest (ng/mL)</td>
<td>0.48</td>
<td>0.1</td>
</tr>
<tr>
<td>Testost (ng/mL)</td>
<td>0.53</td>
<td>0.18</td>
</tr>
<tr>
<td>SCC (ng/mL)</td>
<td>3.6</td>
<td>6.6</td>
</tr>
<tr>
<td>CA19_9 (U/mL)</td>
<td>35.55</td>
<td>15.0</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td>3.04</td>
<td>0.52</td>
</tr>
</tbody>
</table>

SCC, Squamous cell carcinoma associated antigen; CA19_9, carbohydrate antigen19_9; AFP, alpha fetoprotein; CEA, Carcinoembryonic protein.

perature, and no lymphadenectomy in any part of the body. An old scar of about 5 cm long was observed in the upper outer quadrant of the left breast. Her breast exhibited local skin flushing and no ulceration, while her skin temperature was slightly high. A lump of approximately 5.5 × 6.5 cm in size was located near the scar. It exhibited clear borders, lobulated surface, no adhesion to the pectoralis major, and mild tenderness. Substantial amounts of milky discharge were released when the bilateral nipples were pressed.

Auxiliary examination found no metastases with abdominal B ultrasound, gynecology B ultrasound, chest radiography, chest CT, PET-CT, or other tests. As shown in Table 1, tumor marker carcinoembryonic antigen (CEA) and cancer antigen including (CA153, CA125 and CA199) levels were normal. The values of estradiol, follicle-stimulating hormone, luteinizing hormone, progesterone and testosterone were normal and these levels of sex hormones did not reach a menopausal level, but PRL level was notably high (>4200 mIU/L; as a reference, PRL level of non-pregnant females 109-562 mIU/L). Brain magnetic resonance imaging (MRI) suggested potential pituitary microadenoma.

Biopsy was conducted in the previous hospital and found the tumor was stage III invasive carcinoma and showed the following: estrogen receptor (ER) 2% (+), progesterone receptor (PR) < 1% (+), and human epidermal growth factor receptor (Her-2) (+).

After admission to our hospital, modified radical mastectomy was performed. Early pathologic examination revealed a gray-white mass with a diameter of 6.5 cm below the upper outer quadrant of the breast and scar marks. The cut surface was off-white with clear boundaries (Figure 1A). When the nipple was incised, milky exudates were observed. Under a light microscope, tumor cells appear to be arranged in plagues, nests and cords. They had scant cytoplasm, round/oval nuclei, thin chromatin, and visible nucleoli (Figure 1B and 1C). Immunohistochemical examination showed the following: ER <1% (+), PR <1% (+), Her-2 (-), E-cadherin (+), cytokeratin 5/6 (CK5/6) (+), synaptophysin (Syn) (+), chromogranin A (CgA) (-), neuron-specific enolase (NSE) partially (+), s-100 partially (+), Ki-67 about 50% (+), CD56 (-) (Figure 1D and 1E). The results were consistent with NEC of the left breast (solid type). The nipple and fascia were not involved. None of the 35 axillary lymph nodes showed metastasis.

Two months after tumor resection, PRL level was measured again and found to be 6524 mIU/L. CA125, CA199, and other tumor markers were normal. When the right nipple was squeezed, there was still a lot of milky discharge. As of this publication, the patient’s wound has healed, and postoperative chemotherapy has begun.

Case report 2

The other case was a 34-year-old female with a lump in the right breast that was identified in late pregnancy. The patient has no family history of breast disease and no other diseases. She gave birth to a baby by cesarean without breastfeeding after childbirth and was admitted to our hospital. Examination revealed two very close lumps on the right breast, measuring 3 × 2 cm and 2 × 1 cm. No liquid was discharged when the bilateral nipples were pressed. B-ultrasound and chest radiography showed no metastases. As shown in Table 1, the tumor markers CEA, CA125 and CA153 were present at normal levels. PRL level was notably higher (4147 mIU/L).

Pathologic diagnosis was right breast NEC (small cell type), mucinous differentiation (Figure 2A and 2B). Immunohistochemical examination found the following: cancer ER 90% (+), PR 20% (+), Her-2 (+), E-cadherin (+), cytokeratin 7 (CK7) (+), Syn >50% (+), CgA partially (+), NSE >50% (+), Ki-67 about 80% (+) (Figure 2C-E). The nipple and fascia were not involved. None

Table 1. Related clinical indicators

<table>
<thead>
<tr>
<th>Related clinical indicators</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pg/mL)</td>
<td>&lt;11.8</td>
<td>&lt;10</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>3.10</td>
<td>4.17</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>0.84</td>
<td>1.24</td>
</tr>
<tr>
<td>Prolactin (mIU/mL)</td>
<td>4200</td>
<td>6524</td>
</tr>
<tr>
<td>Progest (ng/mL)</td>
<td>0.48</td>
<td>0.1</td>
</tr>
<tr>
<td>Testost (ng/mL)</td>
<td>0.53</td>
<td>0.18</td>
</tr>
<tr>
<td>SCC (ng/mL)</td>
<td>3.6</td>
<td>6.6</td>
</tr>
<tr>
<td>CA19_9 (U/mL)</td>
<td>35.55</td>
<td>15.0</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td>3.04</td>
<td>0.52</td>
</tr>
</tbody>
</table>

SCC, Squamous cell carcinoma associated antigen; CA19_9, carbohydrate antigen19_9; AFP, alpha fetoprotein; CEA, Carcinoembryonic protein.
of the four sentinel lymph nodes showed metastasis.

Discussion

Although there is evidence that prolactin is involved in the development of breast cancer [7], the role of prolactin in NECB is unclear. We reported here two cases of breast cancer with an unusual combination of hyperprolactinemia and neuroendocrine carcinoma.

Neonatal NECB’s cell morphology is similar to lung and gastrointestinal tract, and it can be divided into four subtypes: solid-type NEC, atypical carcinoid, small-cell or oat-cell carcinoma, and large-cell NEC. NEC can be diagnosed using immune markers and electron microscopy. Further subdivision requires morphologic characterization. The pathologic characteristics of primary NECB overlap substantially with other types of breast cancers, and the typical histologic manifestation is invasive ductal carcinoma. The patient of the first case was diagnosed with invasive cancer using biopsy performed in an outside hospital. After admission to our hospital, further immunohistochemical examination revealed multiple neuroendocrine indicators suggesting NEC. Neuron-specific enolase (NSE) is the most common neuroendocrine indicator of NECB, and its expression in all
Neuroendocrine carcinoma of breast with hyperprolactinemia

Types of breast carcinoma range from 16% to 50% [8]. Since NSE is also expressed in breast cancer cells without argentophilic grains, NSE cannot be used as the sole indicator for diagnosing NECB. Syn and CgA were also considered to be reliable indicators for the diagnosis of NECB. Their positive expression rates were 91% and 41%, respectively [8, 9]. The patient in the first case was positive for NSE and Syn, but negative for CgA. This type of breast cancer is typically estrogen- and progesterone-receptor-dependent. Kawasaki et al. reported that neuroendocrine intraductal carcinoma of the breast showed higher ER and PR positive expression rates than non-neuroendocrine intraductal carcinoma of the breast, but it had a lower rate of Her-2 expression [10]. Wei et al. showed that NECB had higher ER and PR positive expression rates than general invasive ductal carcinoma but lower Her-2 expression [11]. Zhang et al. reported that in 32 cases of NECB, the positive expression rates of ER and PR were 84.38% and 68.75%, respectively [12]. In the present cases, one of the patients was negative for ER, PR, and Her-2 expression.

Since no neuroendocrine cells have ever been found in normal breast tissues, the cellular origin and pathogenesis of NECB remains unknown. Cubilla and Woodruff did not find argentophilic particles in normal breast epithelial cells and proposed that NECB might originate from neural crest argentophilic cells. Another hypothesis is that during the process of malignant transformation, mammary epithelial cells may acquire the ability to differentiate and gradually transform into neuroendocrine cells, eventually leading to NECB. These two hypotheses attempt to explain the cellular origin of NECB from two different perspectives. Further studies are needed to elucidate the exact mechanisms by which these processes occur.

In the first case of NECB, we found the patient’s PRL level was notably high, which may be due to long-term use of the antipsychotic drugs clozapine and risperidone. A history of pregnancy may account for the hyperprolactinemia of the second case. Hyperprolactinemia is common in psychiatric patients since the prolactin-raisin antipsychotic. Hyperprolactinemia is a state of elevated serum PRL [13]. In a recent study, approximately 40%-90% of patients treated with a first-generation antipsychotic had a prolactin level above the upper limit of the normal range [14]. Other studies indicated nearly two-thirds of patients (61.3%) taking first-generation antipsychotic had hyperprolactinemia; 61.6% in female and 60.8% in male patients [15]. But different antipsychotic drugs have different effects on prolactin. Related studies have found that clozapine used for more than six weeks can significantly reduce PRL. Risperidone can also continuously increase PRL levels. However, quetiapine, olanzapine, and ziprasidone were found to have little or no effect on PRL [16].

A possible role of PRL in breast cancer is an intriguing hypothesis, but menstrual status, hormone receptor status, especially that of estrogen receptor, and the involvement of lymph nodes may also contribute to confuse the analysis of this association [2]. A retrospective cohort study found the use of antipsychotic dopamine receptor antagonist was related to a 16% increase in breast cancer (adjusted hazard ratio 1.16; 95% CI 1.07, 1.26), with larger dosages and greater risk. The causal link between raised prolactin and breast cancer is further supported by increased incidence of breast cancer in women who use antiprovoic dopamine receptor antagonists [17]. The conclusion is that the antipsychotic dopamine receptor antagonist may increase the small but significant risk of breast cancer. Overall, given that the first-generation antipsychotic drugs can increase the prolactin level of dopamine receptor antagonist users and increase the incidence of breast cancer, circulating PRL higher than normal levels may play a key role in promoting the occurrence of breast cancer. In breast and prostate tissues, PRL has been shown to regulate breast stem cells and progenitor cells through paracrine mechanisms, which are associated with tumorigenesis and drug resistance [18]. Recent studies have shown that PRL can promote the movement, invasion, and metastasis of various breast cancer cells [19]. Several pathways and molecular effects triggered by PRL activation have been shown to be involved in focal adhesions and remodeling of actin fibers and increase the vitality of breast cancer cells. NECB is a rare and distinct category of breast cancer with different histologic subtypes.

Timely and accurate pathologic diagnosis of NECB is very important. Pathologic examination is a gold standard for qualitative diagnosis.
Neuroendocrine carcinoma of breast with hyperprolactinemia

of tumors, and the detection of neuroendocrine markers contributes to the diagnosis of NECB. There are few reliable reports on the prognosis of NECB. Tian et al. reported that patients with positive ER and PR expression had a good overall prognosis [20]. We reported here, however, a less common, non-hormone-receptor-dependent NECB, whose biologic activity and prognosis are worthy of further study. Nipple discharge has also been reported as one of the clinical manifestations of NECB.

In summary, the current study presented two rare cases of neuroendocrine carcinoma of the breast associated with hyperprolactinemia. In these patients, hyperprolactinemia may make patients more likely to develop breast cancer, but there has been no report on the correlation between hormone levels and NECB incidence. Whether high PRL plays any role in NECB deserves further investigation, and further studies and more case reports are needed to confirm this link.

Acknowledgements

Informed consent was obtained from all individual participants included in the study.

This work is financially supported by research grants from Guangxi Natural Science Foundation project (2019JJJA140700).

Disclosure of conflict of interest

None.

Abbreviations

NECB, Neuroendocrine carcinoma of the breast; PRL, Prolactin; CEA, carcinoembryonic antigen; MRI, magnetic resonance imaging; ER, estrogen receptor; PR, progesterone receptor; Her-2, human epidermal growth factor receptor-2; CK5/6, cytokeratin 5/6; Syn, synaptophysin; CgA, chromogranin A; NSE, neuron-specific enolase;NSE, Neuron-specific enolase.

Address correspondence to: Ningxia Wang, Department of Breast Surgery, The First Affiliated Hospital of Jinan University, Guangzhou 510630, China. E-mail: 939037355@qq.com

References


