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CASE REPORT/OLGU SUNUMU

SMALL CELL NEUROENDOCRINE CARCINOMA OF THE BREAST: CASE REPORT AND REVIEW OF THE LITERATURE

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MEMENİN KÜÇÜK HÜCRELİ NÖROENDOKRİN TÜMÖRÜ: OLGU SUNUMU VE LİTERATÜRÜN GÖZDEN GEÇİRİLMESİ

ÖZET

Küçük hücreli karsinom esas olarak akciğerin kanseridir ancak çok nadiren memede de görülebilir. Bu yazıda ellibir yaşında bayan hastada, tümörün klinik, patolojik özellikleri ve tedavi modaliteleri güncel literatür eşliğinde tartışılacaktır. Ellibir yaşında bayan hasta polikliniğimize sol memede ele gelen kitle şikayeti ile müracaat etti. Fizik muayenede sert, yarı mobil kitle palpe edildi. Tru-cut biyopsi sonucunda, fibröz stromada invaziv solid adalar tarzında gelişim paterni gösteren, bazıları iğsi şekilli atipik epitelyal hücrelerden oluşan tümöral doku görüldü. Tümör hücreleri, pleomorfik, hiperkromatik nükleuslu ve dar sitoplazmalı idi. İmmunhistokimyasal olarak NSE, synaptophysin, TTF-1 ve CK7 ile diffüz kuvvetli boyanma oldu. Myoepitelyal belirteçler (p63, kalponin), GCDFP 15, CK20, mammoglobin ile boyanma olmadı. Ki67 proliferatif indeksi %90 idi. Östrojen reseptörü negatif, progesteron reseptörü pozitif ve cerbB2 negatif idi. Bu bulgularla tümöre 'nöroendokrin özellik gösteren küçük hücreli karsinom' tanısı verildi ve T2N0M0 meme kanseri tanısı ile opere edildi. Adjuvan tedavide 4 kür siklofosfamid, adriamisin kemoterapisi verildi. Bu tedaviye 3 kür karboplatin, etoposide kemoterapisi eklendi. Küçük hücreli meme kanserleri, yüksek grade' li, lenfovasküler invazyon olasılığı yüksek, hormon reseptörleri çoğunlukla negatif olan dolayısıyla sağkalımın kötü olduğu tümörler olarak biliniyordu. Akciğerin küçük hücreli kanserinde kullanılan cisplatin, etaposide ve irinotekan gibi ajanların tedavide kullanılmasıyla daha uzun sağkalım süreleri bildirilmeye başlamıştır.

Anahtar sözcükler: meme kanseri, küçük hücreli kanser, nöroendokrin tümör

ABSTRACT

Small cell carcinoma is the cancer of the lung but, rarely can be seen in the breast. In this paper, the clinical and pathological features and treatment of small cell breast carcinoma diagnosed in a fiftyone year old female patient is outlined with the context of current literature. The patient presented with a lump in her left breast. On physical examination, a hard, semi-mobile mass was palpated. At tru-cut biopsy, the tumoral tissue was composed of atypical epithelial cells, some with fusiform structure and invasive, solid growth pattern in fibrous stroma. Immunohistochemically, the cells were stained diffusely and homogenously with NSE, synaptophysin, TTF-1 and CK7. There was no staining with myoepithelial markers (p63, calponin), GCDFP 15, CK20, and mammoglobulin. Ki67 proliferative index was 90%. Estrogen receptor was negative, progesteron receptor was 30% positive and cerbB2 score was 0. With these findings, the tumor was diagnosed as "small cell breast carcinoma with neuroendocrine features". After surgery, cyclophosphamide and adriamycine chemotherapy was given for four cycles. Additional carboplatin and etoposide combination chemotheraphy was given for three cycles. It is known that small cell breast cancers are high grade tumors with increased lymphovascular invasion and mostly negative hormone receptors and therefore they have low survival rates. But with the introduction of agents like platins, etoposide and irinotecan into the systemic treatment of small cell carcinoma of the lung, longer survival periods have been started to be reported.

Key Words: breast carcinoma, small cell carcinoma, neuroendocrine tumor

The tumors of the breast other than ductal, lobular and ducto-lobular types are called "rare breast cancers" and comprise 8-9% of all breast cancers (1). Small cell breast cancer (SCBC) is probably the least frequent one among rare breast cancers. Small cell carcinoma is a cancer of the lung for the most part. But, 2.5-5% of the cases have been reported in areas other than the lungs. Gastrointestinal tractus, urinary bladder ,uterus and prostate are the other organs that these tumors can also be seen (2).

Tumors represent similar histomorphological features with the organ they settled in and are known as poorly differentiated and agressive tumors (3). Breast is the rarest area for these tumors. To date, around 30 cases of SCBC have been reported in the literature. The recognition and differentiation of these tumors from other poorly differentiated breast tumors and metastatic small cell carcinomas is important for accurate treatment. In this paper, the clinical and pathological features and treatment of small cell breast carcinoma will be outlined with the light of current literature.

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Case

The 51 years old female patient presented with a mass in her left breast. The mass has been noticed by the patient for two weeks. The patient was in menopause and had given birth to two children. There was no family history of breast and ovarian carcinoma, no history of oral contraceptive use and at physical examination hard, semi-mobile mass 2x1 cm in size was palpated in the outer upper quadrant of the left breast. The physical examination of the contralateral breast and both axilla was normal. There was not any pathological finding in other systemic examination. At breast ultrasonography, the mass was measured as 21x19 mm in size, irregular, heterogenous, hypoechoic and solid in character.

The tissues around the lesion was swollen with no lymphadenopathy in axilla.

At mammography, reticular pattern around the lesion was recorded and the lesion was reported as BIRADS-5. Liver function tests, CEA, CA15-3 and other laboratory tests were all within normal range and tru-cut biopsy was performed.

At pathological examination, the tumoral tissue was composed of atypical epithelial cells some with fusiform structure and invasive, solid growth pattern in fibrous stroma.

Tumor cells were pleomorphic with hyperchromatic nucleus and narrow cytoplasm. (Figure- 1). Immunohistochemically, the cells were stained diffusely and homogenously with NSE, synaptophysin, TTF-1 and CK7 (Figure-2). There was no staining with myoepithelial markers (p63, calponin), GCDFP 15, CK20, and mammoglobulin. Ki67 proliferative index was 90%. (Figure-3). With these findings, the tumor was diagnosed as "carcinoma with neuroendocrine features".

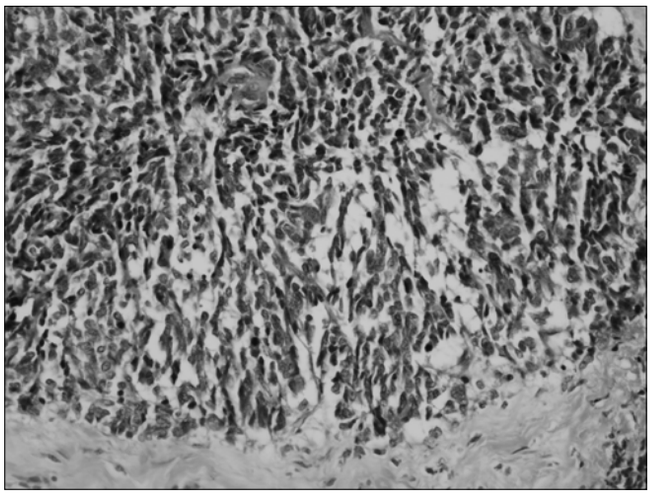

Figure 1. Small cell carcinoma in the breast (Hematoxilen & Eosin, x400)

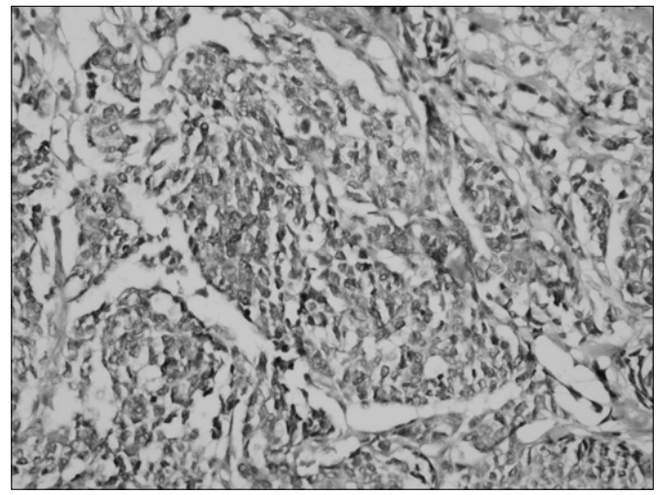

Figure 2.TTF-1 positivity proven with immunohistochemistry

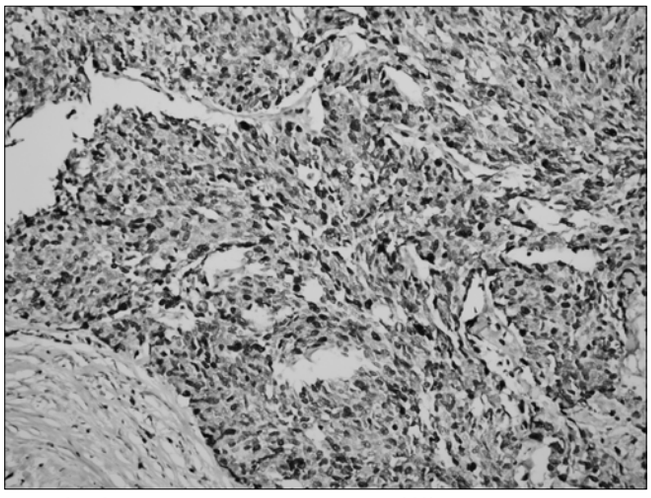

Figure 3. Ki67 proliferative index is calculated as 90% by immunohistochemistry. (x400)

At this point, we decided to search for extramammarian sites. There was no other lesion in abdominal ultrasonography, whole body bone scintigraphy and PET CT. The patient was operated with the diagnosis of T2N0M0 breast cancer and breast conserving surgery with sentinel lymph node biopsy was performed. Axillary dissection was not performed as the SLNB was negative.

At macroscopic evaluation, the cream colored tumoral mass with relatively definitive margins and 2,5x2,3x2 cm in size was recognized. Twentytwo mitosis in 10 high power field was noticed and there was lymphovasculer emboli around the tumor tissue. At immunohistochemical analysis, estrogen receptor (ER) was negative, progesteron receptor (PR) was 30% positive and cerbB2 score was score 0. Surgical resection margins were negative and the case was accepted as small cell carcinoma of the breast.

Cyclophosphamide (600 mg/m^2) and adriamycine (60 mg/m^2) chemotherapy was given for 4 cycles with 21 days interval. Additional carboplatin (300 mg/m^2) for one day and etoposide (120 mg/m^2) for three days combination chemotheraphy was given for three cycles. Adjuvant radiotherapy was given after completion of chemotherapy. The patient is being followed-up for one year without any sign of reccurrence.

Discussion

Histomorphological features of small cell tumors of both breast and lung are similar. Tumor cells contain hyperchromatic nucleus with increased nucleus/cytoplasm ratio and are spherical or elliptical in shape. Number of mitosis in tumor tissue is high (4,5). Diffuse expression of neuroendocrine markers like chromogranin or synaptophysin in more than 50% of the tumor cells is defined as neuroendocrine differentiation (6,7). Neuroendocrine differentiation rate among whole breast tumors is 5-8% (8). This rate is higher for small cell tumors. Neuroendocrine differentiation is associated with poor prognosis (9-11).

The presence of neuroendocrine cells in normal breast tissue could not be shown, but small cell carcinoma cases showing dimorphic pattern in invasive ductal and lobular carcinomas had been reported.The presence of pluripotent precursor cells that transform to ductal, lobular or small cell carcinoma of the terminal ductal lobular unit is brought to the mind by this occurence (12). The molecular study of Hoang et al makes us to think that small cell neuroendocrine tumors appears as the late phenomenon of organ specific typical carcinomas (13).

In order to give the diagnosis of primary small cell carcinoma of the breast there should be no focus other than the breast or insitu component should be displayed. In situ component has been reported in 2/3 of the patients reported in literature (9). Screening of the other parts of the body is more important for the cases with no insitu component.

SCBC may show a varied reactivity with immunohistochemical markers. The morphological and immunohistochemical patterns of this tumor are similar to that of the lung. However, all cases reported in literature showed immunoreactivity for one or more epithelial markers. At least one of the immunohistochemical markers like cytokeratin CAM5.2, AE1/3 and cytokeratin 7 should be positive for SCBC diagnosis (14). Staininig with neuroendocrine markers is less reliable. Thyroid transcription factor (TTF-1) was previously thought to be a spesific marker for primary lung carcinoma. But, expression of in the in situ component of the tumor has also been reported in literature (15). ER and PR could be positive, but as this positivity could be seen in small cell carcinomas seen in lungs and other parts of the body, it can not be used as a proof for breast origin (16). No Her2 positive SCBC has been reported so far.

It is known that small cell breast cancers are high grade,tumors with increased lymphovascular invasion and mostly with negative hormone receptors and therefore they have low survival rates. Traditional breast cancer agents like cyclophosphamide and adriamycine was used to be used. Median survival of 8-9 months had been reported in literature in the 90's (10). With the increased number of cases reported in the literature, the survival has been shown to be related to the stage of the disease at the time of diagnosis (17).

But with the introduction of agents like platins, etoposide and irinotecan into the systemic treatment of small cell carcinoma of the lungs, the longer survival periods (more than 5 years) have been started to be reported (18,19). Beside the two cases of complete remission with neoadjuvant treatment with cisplatin and etoposide (4,10), a progressed case with neoadjuvant application of adriamycine and docetaxel had also been reported (17). Hormonotherapy should be given to all patients with positive receptors.

In our case, the diagnosis was made with histomorphological features and immunohistochemical findings. In-situ component was not seen in the specimen,and the diagnosis of SCBC was made with the absence of pathology in the organs other than the breast. Histomorphological features of the tumor was displayed with tru-cut biopsy in the preoperative period. The chemotherapeutic agents specific to lung cancer have been continued after the use of breast cancer specific agents. The adjuvant treatment of our patient has been terminated with the use of radiotherapy. The survival of our patient supports the idea that the stage of the disease at the time of diagnosis and current treatment modalities are related to the prognosis.

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