CASE REPORT

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Small Cell Neuroendocrine Carcinoma of the Endometrium: Literature Review

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ABSTRACT Neuroendocrine carcinoma (NEC) of the endometrium is an uncommon tumor. Among the 80 cases of small cell neuroendocrine carcinoma of endometrium (SCNCE), that have been reported up to now. The tumors were either pure NEC or mixed with other histotypes , most commonly endometrioid carcinoma. We report a case of primary small cell neuroendocrine carcinoma of endometrium. The clinical symptoms related to SCNCE are similar to those of endometrial cancer. Immunohistochemical studies with neuroendocrine markers are necessary to make a definitive diagnosis and differentiate it from other small cell carcinomas. The only known prognostic factor is the stage of the disease. Although SCNCE is a rare tumor, it is a tumor that must be kept in mind as it is high grade and has a poor prognosis in this context. Multicentre studies are needed to identify specific prognostic factors and develop different treatment options.

Keywords: Small cell carcinoma; neuroendocrine carcinoma; endometrium

Small cell carcinoma (SCC) is a very poor tumor originating from the neuroendocrine system.[1] Although it may occur from any organ, extrapulmonary origin is rare for small cell neuroendocrine carcinoma (SCNEC). It is most commonly originating from gastrointestinal tract (33%) followed by genitourinary tract (20%), head and neck (11%), and breast (10%) respectively.[2]

SCNEC of the gynecological system is extremely rare. The frequency of incidence is as follows: SCNEC of the cervix, ovary, endometrium (SCNCE), vagina, and vulva.[3]

CASE REPORT

The article was prepared with the consent of the patient. We obtained the informed consent form from the patient. A 48-year-old perimenopausal woman presented to our gynecology outpatient clinic with vaginal bleeding and abdominal pain. In the routine biochemical study, fasting blood glucose was found to be 169.8 mg/dL, WBC 21.77 10^3/uL, CRP <2.00 mg/L, and HCT 40.3%. Since no clear pathology was detected in abdominal ultrasonography, endometrial curettage was performed for diagnostic purposes, which revealed a malignant epithelial tumor as pathological diagnosis. Afterwards, surgical treatment was planned and radical hysterectomy-bilateral salpingo-oopherectomy-pelvic and paraaortic lymphadenectomy was performed. Macroscopically, a malignant mass of 6.7x2 cm in size was found in the lower uterine segment. The microscopic study revealed a tumor with poorly differentiated small round cells located in the lower uterine segment-endometrium and associated with the cervical intraepithelial carcinoma. Tumor cells were present in the endometrium, endometrial polyp, and cervical stroma. However, they were not observed in cervical glands, fallopian tubes, and ovaries.

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In the pathological examination, the tumor cells were small size forming sheets, cords and nests, as well as single cells with scanty cytoplasm, hyperchromatic nuclei and high mitotic rate (Figure 1, Figure 2). In immunohistochemical study, tumor cells showed positive staining with P16, CD56, synaptophysin and neuron specific enolase (Figure 3). There was no staining with desmine, vimentin, CA125, LCA, CEA, CK7, HMB45, S100, P63, and CD99. Ki67 proliferative activity was greater than 90%.

Based on the present morphological appearance and immunohistochemical staining, the tumor was diagnosed as SCNCE. Tumor staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) staging. According to the FIGO staging system, the tumor was surgically classified as pT1bN0 and IB.

Postoperative contrast-enhanced upper abdominal-pelvic MR-diffusion MRI revealed several metastatic lymph nodes, with the largest being 35x24 mm in size, around the left iliac artery and the celiac artery.

The patient was given three weeks of intravenous chemotherapy consisting of 170 mg/day (D), D1-D3 and cisplatin 135 mg/D, D1. This treatment was repeated in 6 cycles.

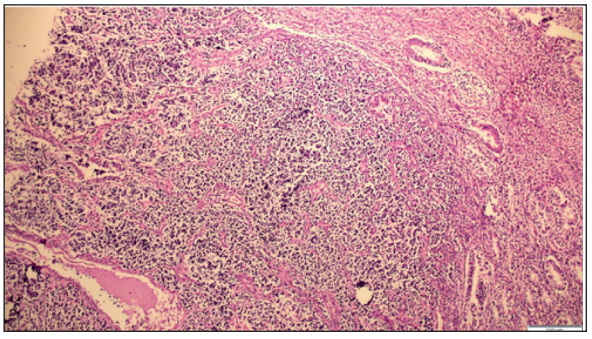

FIGURE 1: Small size neoplastic cells between endometrial glands on the right side (Hematoxylin-eosin, original magnification 40×).

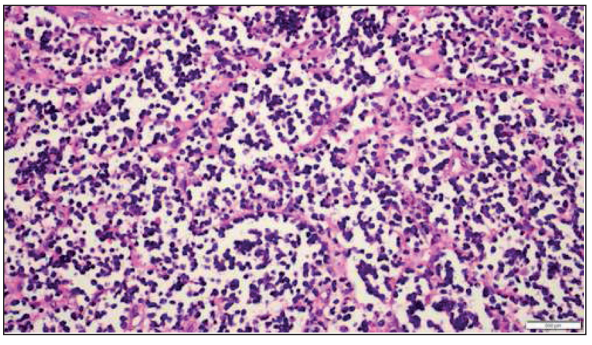

FIGURE 2: Endometrial small cell neuroendocrine carcinoma at high power magnification demonstrating trabecular and solid growth patterns, with neoplastic cells of small size, a high nucleus to cytoplasm ratio, and nuclear molding (Hematoxylin-eosin, original magnification 200×).

FIGURE 3: Immunostaining shows diffuse positivity for neuron specific enolase (Original magnification 400×)

DISCUSSION

The incidence of SCNEC in the female reproductive system is quite low. However, recent studies have shown that the incidence of these tumors may increase due to an increase in the accuracy of diagnosis and diagnostic techniques.[3] Primary SCNCE represents less than1% of all endometrial cancers. A total of 80 cases of SCNCE have been reported so far.[4]

At the time of diagnosis, SCNCE is usually of a very large volume and shows a profound myometrial infiltration. Unlike other types of endometrial cancer, approximately 70% of cases have lymphovascular invasion and paraaortic lymph node metastasis is very common.[5]

In a study by Yue et al., SCNCE accounted for 0.1% (2/1903) of all endometrial cancers. Lymphovascular invasion was present in 82.4% of the patients. Lymph node metastasis rate was 35.0%. The mean survival time was 43.6 months (range 16-77 months). This tumors has an aggressive clinical course and may present with metastasis. It most commonly metastasizes to the lung, liver, brain, bone and even skin.[3]

In our case, contrast-enhanced upper abdominal-pelvic MR-diffusion MRI revealed metastatic lymph nodes around the left iliac artery and the celiac artery.

SCNCE is frequently associated with other types of endometrial cancer subtypes, most commonly endometrioid adenocarcinoma, although both accompanying large cell and serous carcinomas have been reported.[6] In our case, SCNCE was accompanied by cervical intraepithelial carcinoma.

Early diagnosis is the only option for long-term survival in patients with SCNCE. The average age at diagnosis is over 60 years (23-87 years). Usually, patients with SCNCE present to the hospital with lower abdominal swelling, abdominal pain, abnormally heavy bleeding at menstruation or postmenopausal uterine bleeding. Our case was admitted to our clinic with uterin bleeding and abdominal pain.

Katahira et al.reported a series of 43 cases of endometrial SCC. In these cases, the mean age was 60 years, and only four cases were 40 years or younger. Three of these four cases were found to be in the FIGO stage IVb tumor. The late detection of the disease in premenopausal women may be due to the absence of a well-known alarm symptom, such as post-menopausal bleeding, or a more aggressive biological tumor behaviour.[7]

Van Hoeven et al. suggested three diagnostic criteria for small cell neuroendocrine endometrial carcinoma: 1) In HE-stained sections, dense sheet-like growth of morphologically small to intermediate-sized tumour cells; 2) Immunohistochemical reactivity for one or more neuroendocrine markers; 3) definitive evidence of endometrial origin.[8] In our case, all these three criteria were observed.

In immunohistochemistry, the identification of neuroendocrine specific markers (Chromogran A, NSE, Synaptophysin, CD56, NCAM, Leu-7) is required for diagnosis and differentiation from other small cell tumors.[8] Our case was histologically compatible with SCC. Immunohistochemical staining profile of tumor cells was evaluated for definitive diagnosis. Synaptophysin, CD56 and NSE were all positive. As a result, our case was diagnosed as SCNCE.

Because it is rare, there is insufficient data to produce the most appropriate treatment approach for SCNCE. Treatment methods are planned by taking the treatment options in traditional endometrial cancers and lung SCC. The high degree of aggression of the tumor and the risk of distant metastasis report that a combination of surgery and multimodal therapy is necessary.[7]

Surgical treatment consisting of radical hysterectomy with regional lymphadenectomy is the first choice in early stage cases. Chemoradiation is an reasonable treatment option for advanced or non-surgical patients. Chemoradiation with EP (etoposide/cisplatin), concurrent with pelvic radiation is an appropriate treatment.[3]

The prognosis of SCNCE is poor. The 5-year survival rate was found to be between 17-64% in different studies. Average survival varies between 12-21 months but shortens to 5 months in advanced stage.[4,9]

In conclusion, SCNCE is a rare but aggressive tumor with poor prognosis. A comprehensive approach is still the main treatment approach. Multicentric prospective controlled studies are necessary to determine the specific factors affecting prognosis and to improve existing treatment methods.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Nilgün Söğütçü;* ***Design:*** *Nilgün Söğütçü;* ***Control/Supervision:*** *Nilgün Söğütçü;* ***Data Collection and/or Processing:*** *Nilgün Söğütçü, Dinçer Yıldırım;* ***Analysis and/or Interpretation:*** *Nilgün Söğütçü, Dinçer Yıldırım;* ***Literature Review:*** *Nilgün Söğütçü;* ***Writing the Article:*** *Nilgün Söğütçü;* ***Critical Review:*** *Nilgün Söğütçü;* ***References and Fundings:*** *Nilgün Söğütçü, Dinçer Yıldırım;* ***Materials:*** *Nilgün Söğütçü, Dinçer Yıldırım.*

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