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Original Article

Small cell carcinoma of the endometrium: a clinicopathological and immunohistochemical study

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Abstract: Objective: To investigate both clinicopathological and immunohistochemical characteristics of small cell carcinoma (SCC) of the endometrium, and to explore the diagnosis, treatment and prognosis of the disease. Methods: A retrospective analysis was performed on clinicopathological data of a patient with SCC of the endometrium in our hospital, who underwent comprehensive surgery of radical hysterectomy, bilateral adnexectomy, pelvic lymphadenectomy, omentectomy, appendectomy, and bilateral ovarian vein ligation. Paraffin blocks of formaldehyde-fixed tumor tissue were cut and stained for histological and immunohistochemical studies. Results: microscopic examination showed clusters of small-sized cells with scant cytoplasm, hyperchromatic nuclei and high mitotic activity. The patient was classified as endometrial SCC stage Ib according to the clinical staging of the International Federation of Gynecology and Obstetrics (FIGO). Immunohistochemical tests revealed positive staining for synaptophysin (Syn) and CD56, and the proliferation rate measured with the proliferative marker (Ki67) was approximately 70 percent of tumour cells. The patient was given 4 sessions of postoperative chemotherapy. Tumor markers were within normal range during follow-up examinations, and the patient had survived tumor free for two years. Conclusion: Primary SCC of the endometrium is extremely rare, and is reported to have a strong invasiveness and a poor prognosis. Immunohistochemistry technique is an important tool for clinical diagnosis of the disease. Comprehensive treatments composed of surgery, radiotherapy and chemotherapy may improve the prognosis.

Keywords: Small cell carcinoma of the endometrium, pathological characteristics, immunohistochemistry

Introduction

Small cell carcinoma (SCC) is a type of highly malignant neuroendocrine cancer, which arises most commonly in the lungs, accounting for 15% to 20% of all lung tumors [1]. In the female reproductive system, SCC frequently occurs in the cervix and constitutes only 2% of all cervical cancer [2]. Primary SCC of the endometrium is an extremely rare histological type of endometrial cancer [3]. This paper reported a case of SCC of the endometrium, explored its clinicopathological and immunohistochemical characteristics, and discussed its treatment and prognosis.

Material and methods

General information

A 50-year-old female suffering from postmenopausal bleeding (lasting over 10 days) presented for physical examination. Ultrasonic examination showed a 4.4 cm x 3.3 cm sized mass in the uterine cavity. Diagnostic curettage revealed (intrauterine matter) the tumor was a small cell tumor, mostly likely poorly differentiated carcinoma. The uterus was removed by radical hysterectomy and subject to pathology examinations.

Materials

The following antibodies were purchased from Fuzhou Maixin Biotech. Co., Ltd. including ready-to-use mouse anti-human CD56 monoclonal antibody, ready-to-use mouse anti-human KI-67 monoclonal antibody, SP immunohistochemistry staining kit and DAB color development kit were also purchased from Fuzhou Maixin Biotech. Co., Ltd.

Methods

Specimens were fixed by formaldehyde (40 g/L), dehydrated, embedded in paraffin. The

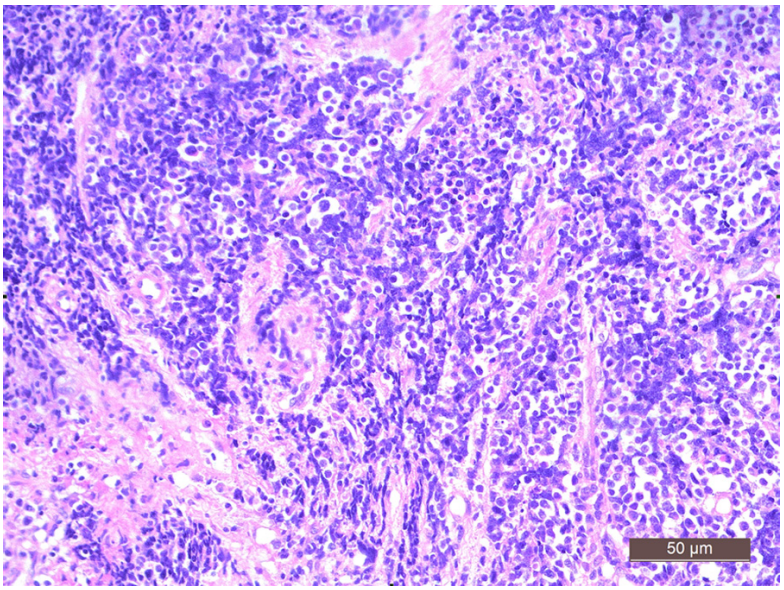

Figure 1. Microscopic observation of small cell carcinoma (×200): oval to round small cells with scant cytoplasm and unnoticeable nucleolus; some have evenly distributed chromatin.

sections were subjected to hematoxylin-eosin (HE) staining and immunohistochemical staining, and were examined under a light microscopy. The 3-step SP method was used for immunohistochemical staining. Briefly, the sections were dewaxed and incubated with 3% H_2O_2 solution at room temperature (RT) for 10 min to block endogenous peroxidase activity. Sections were rinsed with water and incubated with solution containing 0.1% trypsin at 37°C for 15 min. Sections were washed 3 times in TBS for 5 min each. TBS was removed and each sections was incubated with 50 ul of Mouse anti-human antibodies at RT for 10 min. Serum was discarded and 50 ul of primary antibody was added to each section for overnight incubation at 4°C. Control section was incubated with TBS. Sections were washed 3 times in TBS for 5 min each and TBS was removed. Each section was added 50 μl of biotinylated second antibody and incubated at 37°C for 30 min. Sections were washed 3 times in TBS for 5 min each and TBS was removed. Each section was added 50 μl of streptomycin-horseradish peroxidase-labeled third antibody at 37°C for 30 min. Each section was pre-incubated with 100 μl of freshly prepared DAB solution and observed under microscope for 3-10 min. Sections were then washed with water to terminate color development, stained with hematoxylin, dehydrated and mounted with neutral gum.

Results

Gross examination

The uterus measuring 11.0 cm × 4.0 cm × 4.0 cm was removed by radical hysterectomy. The front wall of the uterus was cut for pathological examination. The endometrium was smooth, and a slightly raised small focal area in the size of 2.0 cm × 1.5 cm was observed. Muscle wall of the uterus was 2.5 cm thick without any obvious lump. The 6.0 cm × 6.0 cm × 4.5 cm sized cervix had smooth external orifice, which was attached to a 3.0 cm-long vaginal wall. Two cysts in diameter of 1.5-1.0 cm containing clear liquid were identified in left ovary measuring 3.3 cm × 2.5 cm × 1.5 cm, which was attached to a 8.0 cm × 0.4 cm sized oviduct. No significant pathological change was identified in the 2.5 cm × 1.5 cm × 0.5 cm sized right ovary with attached oviduct (7.5 cm × 0.4 cm) and appendices vesiculosa.

Microscopic observation

Microscopic observation of tumor mass showed that uniform, oval to round, small-sized cells with scant cytoplasm formed nest-like clusters. Round, oval or irregularly shaped nuclei with small nucleoli exhibited finely granular, hyperchromatic, and evenly distributed chromatin (**Figure 1**).

Immunohistochemical examination

As shown in **Figure 2A** and **2B**, immunohistochemical staining demonstrated that the tumor cells were positive for synaptophysin (Syn) and CD56, and the proliferation rate measured with the proliferative marker (Ki67) was approximately 70 percent of tumour cells (**Figure 2C**). Tumor cells showed positive staining with low molecular weight antikeratin AE1, but a negative reaction with AE3. Staining with anti-epithelial membrane antigen (EMA), chromogranin A (CgA), CD10, vimentin, estrogen receptor (ER), or progesterone receptor (PR) was negative.

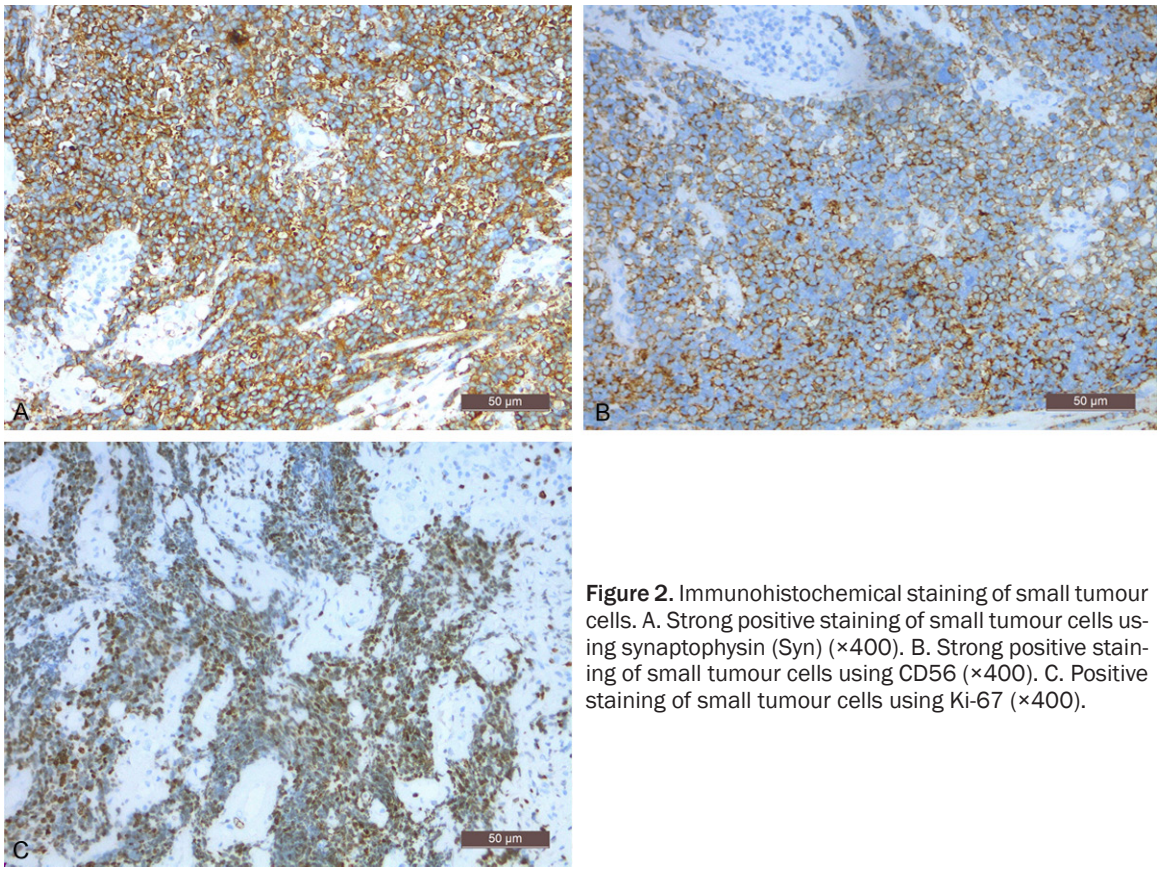

Figure 2. Immunohistochemical staining of small tumour cells. A. Strong positive staining of small tumour cells using synaptophysin (Syn) (×400). B. Strong positive staining of small tumour cells using CD56 (×400). C. Positive staining of small tumour cells using Ki-67 (×400).

Diagnosis

Immunohistochemical studies provided strong evidence for the neuroendocrine differentiation of the tumor cells. Pathological report specified that the 1.0 cm × 0.5 cm sized small cell neuroendocrine carcinoma of the endometrium had invaded about 1/4 of the full thickness of muscle wall of the uterus. No tumor cells were identified at the junction of uterus and cervix, or in ascitic fluid. No tumor lesion was observed in appendix or omentum. Reactive lymph node hyperplasia was negative (left pelvic 0/6, right pelvic 0/6, left common iliac 0/1, and right common iliac 0/2).

Postoperative treatment

The patient was given 4 sessions of intravenous postoperative chemotherapy, which was composed of intravenous paclitaxel (175 mg/m^2, D1) and carboplatin (0.65 g, D1). Tumor markers were within normal range during follow-up examinations, and the patient had survived tumor free for two years.

Discussion

SCC is a type of malignant neuroendocrine cancer most commonly in the lung. Primary SCC of the endometrium is an extremely rare histological type of small cell cancer, which is highly malignant with extensive distant metastases and poor prognosis for survival, and thus is very difficult to treat.

SCC of the female genital tract accounts for only 2% of all gynecologic malignancies, with the highest proportion occurring in the cervix, followed by ovary [4]. The incidence of endometrial and vulvovaginal cancer is extremely rare, and SCC of the endometrium constitutes only 0.8% of all endometrial cancers [4]. So far, more than 80 cases of SCC of the endometrium have been reported, the majority of which occurs in women who have had more than one delivery. The average age of onset for patients with the disease is 60 years old which is significantly higher than that of patients with adenocarcinoma (aged above 50) [5]. However, the patient in this study was much younger. Cases

of younger patients were also reported previously [6].

The clinical symptoms related to SCC of the endometrium are similar to those of endometrial cancer, including abnormal vaginal bleeding, followed by abdominal mass, abdominal pain, etc [7]. Most often, the symptoms of gynecologic inflammation and cancer conceal each other. Therefore, postmenopausal women with symptoms of pelvic inflammatory disease are suggested to exclude the possibility of malignant tumors through a comprehensive gynecological examination, diagnostic imaging and tumor markers assay [8]. Ju W et al. reported that small cell neuroendocrine carcinoma of the endometrium is often accompanied by paracancerous syndrome such as visual impairment or kidney membranous glomerulonephritis, due to neuroendocrine disorders caused by increased hormones or serum antibody induced by tumor cells [4, 9]. In this study, neither paraneoplastic syndromes nor special clinical symptoms were observed, and irregular vaginal bleeding was the main symptom. SCC of the endometrium is highly aggressive, and paraaortic lymph node metastasis is very likely to occur. Distant metastasis to other parts of the body such as the cervix, vagina, ovaries, fallopian tubes, lungs, bones, brain, spine, and pelvis lymph nodes has been frequently observed during diagnosis, and thus the disease has extremely poor prognosis.

Large intrauterine tumor is generally identified in patients with the disease, which exhibits infiltrative or polypoid growth, and may be associated with bleeding and necrosis. Section of the tumor is pale and crispy, and may look like a fillet. The tumor can infiltrate deep into muscle, and even penetrate the plasma membrane.

Microscopic examination revealed uniform, oval to round, small-sized tumor cells with scant cytoplasm formed flaky, cord-like or nested cell mass. Round, oval or irregularly shaped nuclei with inconspicuous nucleoli exhibited hyperchromatic, and evenly distributed chromatin, and high mitotic activity. In a study of 16 patients performed by Huntsman et al. [10], mitotic activity was observed in 10 successive high power fields (HPF), whereas mitoses was found in 6 to 7 HPF with with flakes of necrotic tissues in this study. Rosette-like structures were observed in cell-rich area. Van Hoeven et al. reported one patient with short shuttle or small oval shaped tumor cells in ascetic fluid. These cells had clear, irregular nuclear membrane, inconspicuous nucleoli, and granular chromatin. Visible necrosis was also observed [11].

The diagnosis of SCC of the endometrium needs evidence of endometrial origin, small tumor cells, and more importantly, positive immunohistochemical staining for at least one neuroendocrine marker [11]. The most common positive neuroendocrine markers for these tumors are Syn, neuron specific enolase (NSE), CgA and cytokeratin (CK) [4, 12, 13]. In a immunohistochemical study performed by Huntsman et al. [10], reactions with neuroendocrine markers demonstrated that 1/9 cases were positive for NSE, 1/8 positive for natural killer factor (Leu-7), 1/9 positive for CgA, and 0/8 positive for Syn, whereas detection of epithelial markers found out that 8/10 cases were positive for CK, 4/8 positive for EMA, and 3/8 weakly positive for carcinoembryonic antigen (CEA). Van Hoeven et al. reported that 7/10 cases were NSE-positive, 6/9 Leu-7-positive, 4/10 CgA-positive, 2/10 Syn-positive, 5/10 AE1-positive, 6/10 EMA-positive, and 2/7 S-100-positive [11]. In this study, the tumor cells were strongly positive for both Syn and CD56, strongly confirming the change in neuroendocrine indicators. The protein Syn is involved in synaptic transmission, and commonly identified in neuroendocrine cells and the central nervous system. Immunohistochemical examination may also be informative in diagnosing and differentiating SCC of the endometrium from benign and malignant diseases of the endometrium [14], which will be further discussed in 3.5.

The accurate diagnosis of SCC of the endometrium must rely on both routine pathological examination and immunohistochemical results. Van Hoeven et al. [11] have proposed diagnostic criteria described as follows: 1. uniform, small- to medium-sized tumor cells form flaky or nested cell mass, which may or may not be associated with other tumors, such as adenocarcinoma. 2. At least one neuroendocrine marker should be positive in immunohistochemical examination. 3. Clear evidence of primary SCC of the endometrium must be identified to exclude the possibility of invasion or transfer of small cell cancer from other parts of the body.

Endometrial stromal sarcoma occurs in older women, especially postmenopausal patients with lower abdominal pain and other symptoms. Microscopic observation shows that uniform, small-sized tumor cells are arranged in concentric circles around spiral arteries. Interstitial hyaline degeneration and foam cells may also be observed. Tumor cells often grow into the vasculature. Detection of reticular fibers and CD10-positive may be helpful for diagnosis. In contrast, patients with small cell cancer are positive for endocrine markers such as NSE, Syn, CgA, etc. and have rosette-like tumor cell mass.

SCC is more common in the cervix compared to the endometrium. Therefore, primary tumor should be identified in the uterus in order to exclude the possibility of primary SCC of the cervix. In addition, possibility of primary SCC of other parties of the body such as lung and ovary should also be excluded.

Malignant mixed mesodermal tumors often occur in postmenopausal women. Microscopic observation showed that tumor cells were poorly differentiated. Tumor is composed of adenocarcinoma and sarcoma, which form a clear boundary between each other. Sarcomas are further subdivided into homologous and heterologous types. The former are often smooth muscle lesions, whereas the latter may be formed by cells of striated muscle, cartilage or bone, which makes it easy to be differentially diagnosed from SCC.

SCC of the endometrium may be misdiagnosed as non-Hodgkin's lymphoma because evenly distributed, uniform, small-sized cells are observed in both cancers. Immunohistochemical examinations can be employed for differential diagnosis between the two. While the former is positive for neuroendocrine marker, the latter expresses leukocyte common antigen (LCA), CD20 or CD45RO.

While SCC of the endometrium is very rare, endometrial cancer accompanied by other malignant tumors is even rarer. Previous references have reported that the disease is highly malignant with poor prognosis. Postoperative survival is often less than a year [10]. Currently, there is not any optimal treatment plan and comprehensive treatments consisting of surgery, radiotherapy and chemotherapy are always adopted. Details of chemotherapy can refer to treatment for small cell lung cancer, during which combination of daunorubicin-cyclophosphamide or etoposide-cisplatin is used [15]. The current patient with stage Ib small cell cancer underwent both surgery and postoperative TP regimen chemotherapy composed of intravenous paclitaxel (210 mg, D1) and carboplatin (0.65 g, D1), which achieved satisfactory results. Postoperative pathological examination confirmed that the tumor had invaded about 1/4 of the full thickness of muscle wall of the uterus. No tumor cells were identified at the junction of uterus and cervix, or in ascitic fluid. No tumor lesion was observed in appendix or omentum. Reactive lymph node hyperplasia was negative. The patient had been in good physical condition after over a year since the surgery, and no recurrence was identified by both tumor markers assay and imaging examination. Therefore, the prognosis of SCC of the endometrium may be closely related to clinical staging and postoperative tumor tissue residues. The stage of the SCC of the endometrium has been reported to be the only known prognostic factor in a previous study, during which one of the patients had a stage IC tumor and was free of disease for 58 months, whereas another patient had a stage IVB tumor and died of the disease 7 months after surgery [6]. However, more cases are required to identify the prognostic factors and to form a general treatment strategy for SCC of the endometrium.

Disclosure of conflict of interest

None.

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