Small Cell Neuroendocrine Carcinoma of the Endometrium with Difficulty Identifying the Original Site in the Uterus

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Diagnosis of malignant uterine tumor with continuous lesions from the uterine body to the cervix, i.e., endometrial or cervical cancer, depends on the main site of the lesions. However, it may be difficult to differentiate advanced cancer that is widespread in the uterus. We experienced a patient who was diagnosed with small cell neuroendocrine carcinoma (SCNEC) based on histopathological characteristics of SCNEC in the endometrium. This tumor frequently coexists with endometrioid carcinoma, but we had difficulty finding the original site of SCNEC in the endometrium. The patient was a 59-year-old, two-parous woman who underwent hysterectomy after diagnosis of malignant uterine tumor. Preoperative cervical and endometrial histology permitted diagnosis of SCNEC. Imaging showed that most of the anterior uterine wall from the uterine body to cervix was replaced by tumors. Histopathologic findings for the resected uterus showed that most of these tumors were SCNEC, but components of endometrioid carcinoma had developed from the endometrium just beneath the fundus to the lower uterine body. The growth pattern of endometrioid carcinoma was endophytic. Based on this finding, the patient was diagnosed with endometrial SCNEC associated with endometrioid carcinoma. The patient initially responded well after postoperative chemotherapy, but early recurrence led to death at three months after the first treatment. This case shows that SCNEC in the uterine body is likely to coexist with endometrioid carcinoma. These findings are useful to determine the original site in postoperative pathological diagnosis of highly advanced tumors. SCNEC is a rapidly progressive and aggressive tumor in clinical practice, but some cases have a relatively good initial response to chemotherapy and it is important to start treatment early.

Key words: Endometrium, Small cell neuroendocrine carcinoma, Case report

INTRODUCTION

Small cell neuroendocrine carcinoma (SCNEC) in the endometrium is a rapidly progressive tumor, but may have a good response to chemotherapy [1, 2]. SCNEC has a unique tissue type and accounts for 0.8% of endometrial carcinomas, and colocalizes with endometrioid carcinoma and atypical endometrial hyperplasia [3–6]. The tumor is frequently found at an advanced stage because it is highly invasive. We experienced a patient with SCNEC in whom the original site was difficult to detect because tumors ranged from the uterine body to the cervix. A histopathologic examination of the resected uterus showed that most of the tumors were SCNEC, but components of endometrioid carcinoma had developed from the endometrium. The growth pattern of endometrioid carcinoma was endophytic. The patient was diagnosed with a uterine body-derived tumor, and initially responded well to postoperative chemotherapy, but subsequent rapid recurrence resulted in death.

CASE REPORT

The patient was a 59-year-old two-parous female with a body weight of 70 kg, height of 158 cm, and menopause at age 55. She had been diagnosed with hypertension and hyperlipidemia at about 53 years old and was treated with drugs. She had no particular surgical history or family history. She visited a local physician due to aggravated pedal edema and bloating. Computed tomography (CT) detected a uterine tumor with a diameter of 10 cm. Pedal edema was probably caused by exclusion of lymph flow due to the giant uterine tumor. The patient was referred to our hospital for examination and treatment.

Vaginal examination demonstrated that the uterus had a double-fist size and the uterine fundus was at the umbilical height. No gross pathology was found in the uterine cervix, but colposcopy showed a slightly protruded lesion inside the cervix. Bimanual palpation revealed that the right parametrium was soft, but the left one was slightly indurative and the lower uterine

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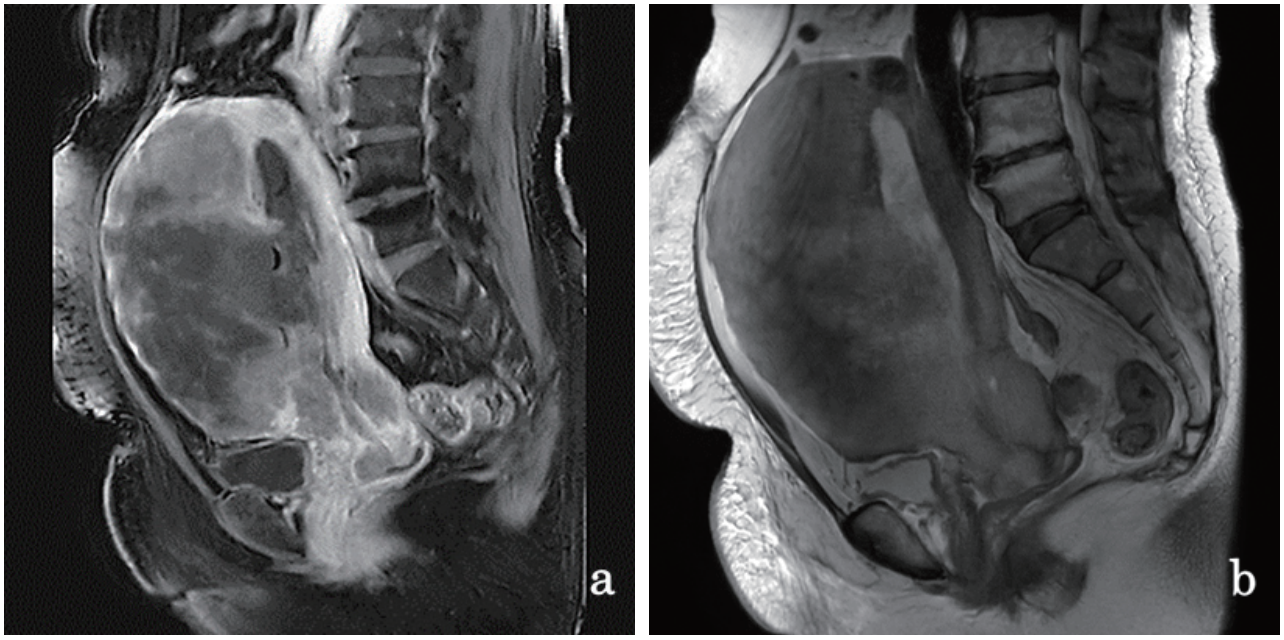

Fig. 1 (a) Contrast-enhanced T1-weighted image. (b) Contrast-enhanced T2-weighted image. Preoperative MRI showed that almost all of the anterior uterine wall from the uterine body to the cervix was replaced by tumors.

body felt hard. Cervical and e ↄ fndometrial cytology showed poorly differentiated carcinoma, and cervical and endometrial biopsy indicated SCNEC.

Magnetic resonance imaging (MRI) detected a giant uterine tumor in the anterior wall of the uterine body, including lesions that had replaced the muscle layer from the uterine body to the cervix (Fig. 1). Furthermore, the cervical stroma was circumferentially unclear due to the lesions. CT showed multiple lymphadenopathy from the pelvis to the paraaortic regions. Positron emission tomography-computed tomography (PET/CT) showed abnormal FDG accumulation corresponding to the uterine tumor. Similar accumulation was also detected in the bilateral internal iliac, left external iliac and paraaortic arteries, and the left subclavian lymph nodes.

Tumor marker levels of CA125 and CA19−9 were high (122.5 and 66.8 U/mL), whereas SCC and CEA were below reference values (1.1 ng/mL and 3.4 mg/dL). Neuron-specific enolase (NSE), a marker for neuroendocrine tumors, was extremely high (1300 ng/mL; reference value < 16.3 ng/mL), but pro-gastrin releasing peptide (pro-GRP) was less than the reference value (71.0 pg/mL; reference value < 81.0 pg/mL).

A surgical plan was designed after the patient was diagnosed with a giant uterine-body-derived tumor reaching the cervix based on clinical manifestation. However, imaging revealed extensive generalized lymph node metastasis; therefore, complete resection was difficult. To extract the uterine tumors and perform debulking surgery, the patient underwent simple hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. The total hemorrhage volume was 1950 mL and the weight of resected tumors was 2380 g. Almost all of the resected uterine muscle layers were replaced by tumors, and hemorrhagic and necrotic lesions had reached the serosa (Fig. 2). Peritoneal cytology was positive and many cells with SCNEC findings were detected. Metastasis was found in the greater omentum and right external iliac lymph nodes. Retroperitoneal lymphadenopathy that was palpable at a size of > 2 cm extended from the pelvic to paraaortic lymph node regions, resulting in suboptimal surgery. The postoperative advanced stage was pT3aN1M1 and the FIGO stage was IV B due to omental and lymph node metastasis.

Etoposide and cisplatin treatment were started as a postoperative therapy. However, the patient developed renal dysfunction due to nephrotoxicity of cisplatin, which was then replaced with carboplatin. The combination of etoposide and carboplatin was given for 6 cycles. CT after the completion of treatment showed no remaining measurable lesion, and lymphadenopathy in the left subclavian, pelvic to paraaortic lymph nodes had almost disappeared. A PET/CT scan showed no clear accumulation of FDG, and tumor markers had decreased to within the reference range (CA125: 5.6 U/mL, NSE: 12.5 ng/mL). Thus, the patient was judged to have achieved complete remission and the first treatment was completed.

Two months after the first treatment, marked generalized pain developed. CT revealed multiple lymph node metastases, increased peritoneal metastasis, and aggravated bilateral hydronephrosis, leading to diagnosis of recurrent carcinoma. CA125 was 31.9 U/mL, still within the reference range, but NSE had markedly increased to 354.0 ng/mL.

The recurrence early after treatment and the high-grade SCNEC malignancy suggested that the disease was treatment-resistant and that the prognosis was poor. Palliative care mainly with pain relief was planned and opioids were administered orally. One week after diagnosis of recurrence, the patient was hospitalized as an emergency due to aggravated bilateral hydronephrosis associated with pyelonephritis and rapidly increased serum creatinine (17 mg/dL). The oral opioid was replaced with continuous intravenous infusion and bilateral nephrostomy was performed, after

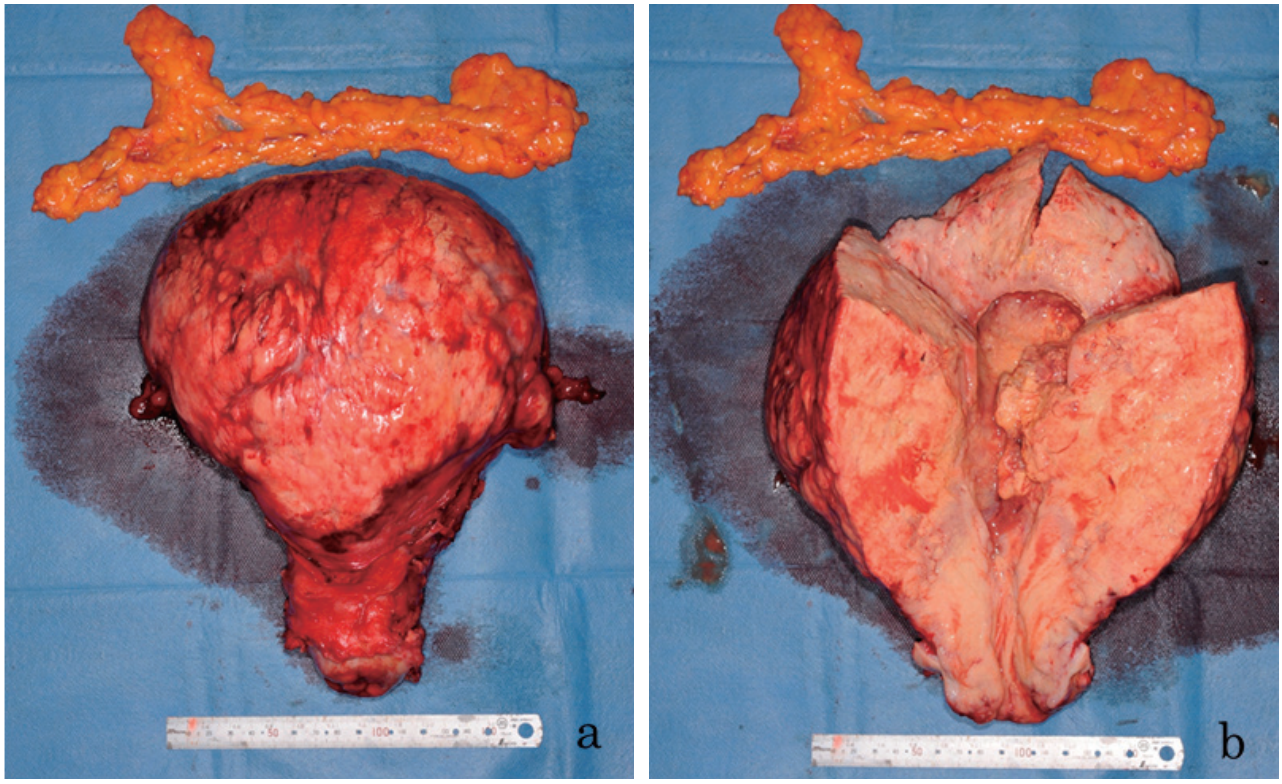

Fig. 2 (a, b) In the extracted uterus, tumors had replaced almost all of the uterine muscle layer and lesions had reached the uterine serosa.

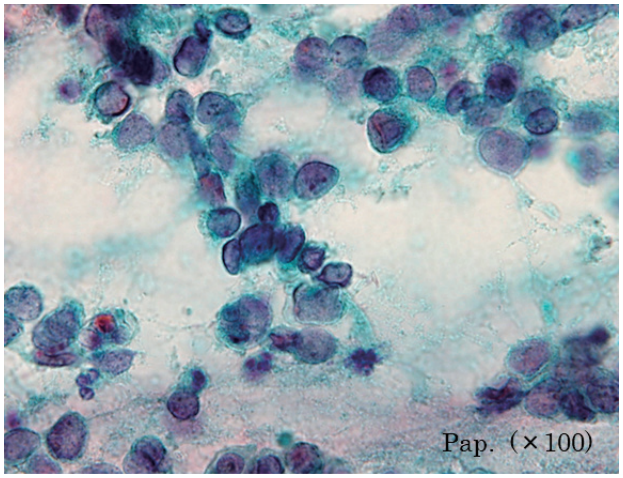

Fig. 3 Endometrial cytology showed scattered small-sized atypical cells (diagnosis: poorly differentiated carcinoma).

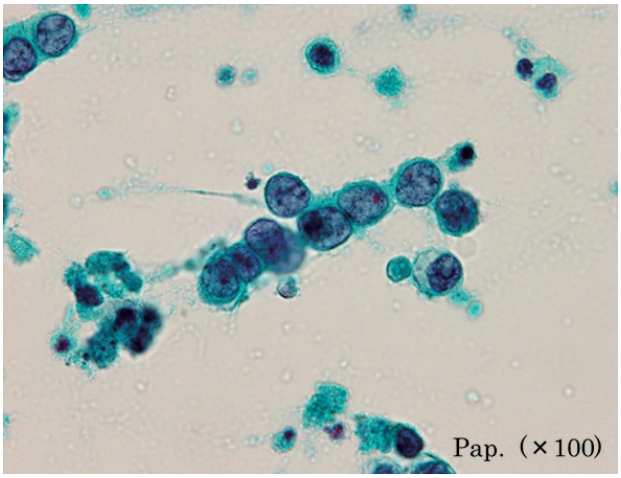

Fig. 4 Ascitic cytology showed atypical cells with a small round shape, bare nuclei and a molding sequence (diagnosis: small cell neuroendocrine carcinoma; SCNEC).

which the patient was discharged to home. However, she died due to disease progression three months after completion of the first treatment, and one month after the diagnosis of recurrence.

CYTOLOGICAL FINDINGS

Cervical and endometrial cytology showed small atypical cells associated with slightly less connectivity that formed a conglomeration in a necrotic background (Fig. 3). Ascitic cytology showed many atypical cells with a small round shape and scanty cytoplasm. A small conglomeration with a molding sequence was interspersed, which corresponded to SCNEC (Fig. 4).

HISTOPATHOLOGICAL FINDINGS

Preoperative cervical histology revealed suborbicular or irregular cells with eosinophilic cytoplasm and swollen nuclei that had invaded and proliferated diffusely. Some cells had a small alveolar or ribbon-like structure. The tumor cells contained scanty cytoplasm and hyperchromatic nuclei. Mitosis and necrosis were apparent and the patient was diagnosed with SCNEC. Endometrial histology showed similar findings to cervical histology, although many tissue fragments were found and most were degenerative and necrotic.

Gross findings of the resected uterus revealed diffuse hyperplasia in the wall. The tumor in the anterior

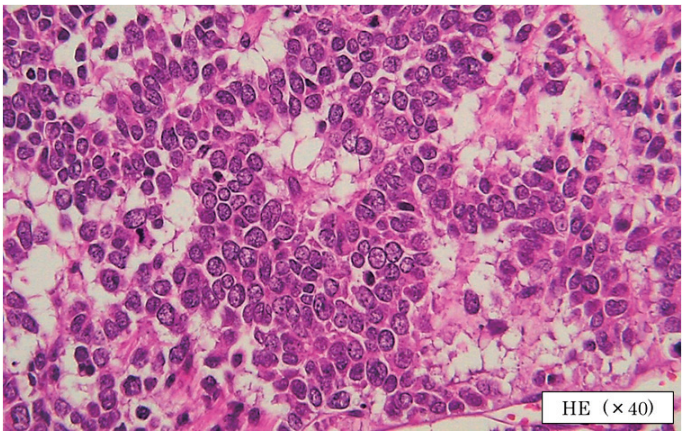

Fig. 5 Histological findings showed cells with eosinophilic cytoplasm and enlarged nuclei that had proliferated diffusely, corresponding to SCNEC.

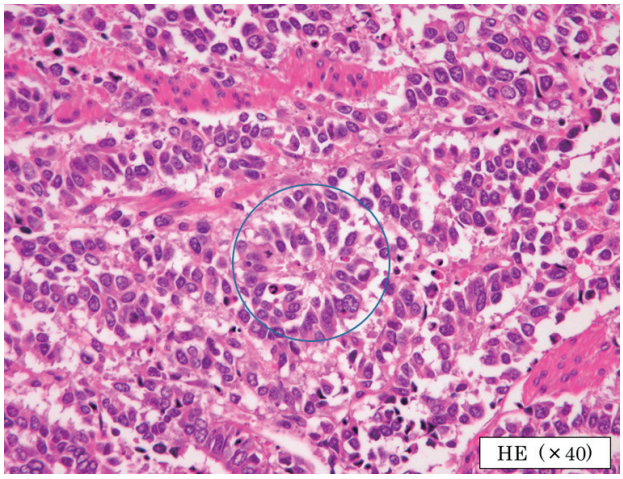

Fig. 6 Histological findings showed a Homer-Wright rosette-like structure specific to neuroendocrine tumor.

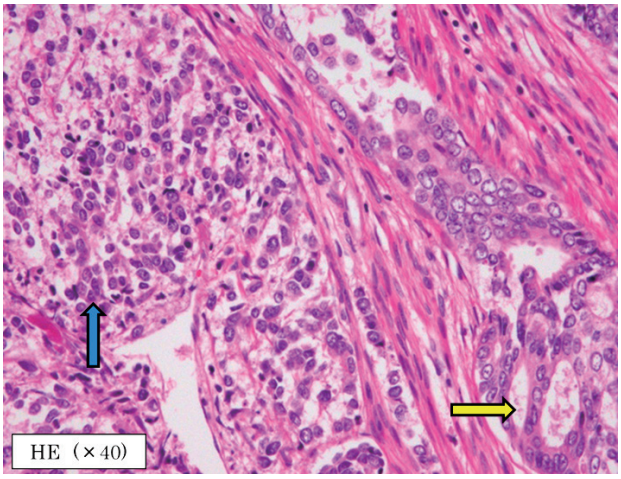

Fig. 7 Histological findings showed components of endometrioid carcinoma with a complicated divergent luminal structure that coexisted with SCNEC (blue arrow: SCNEC component, yellow arrow: endometrioid component).

wall had replaced almost all of the muscle layer and partially broke the serosa. Histopathology revealed diffuse proliferation of small-sized suborbicular or irregular cells with eosinophilic cytoplasm and swollen nuclei (Fig. 5). Some tumor cells had a ribbon-like structure, a Homer Wright rosette-like structure, and small-sized nodulation (Fig. 6). These findings corresponded to SCNEC. Vascular invasion was also found in tumors.

A further detailed examination of the tumor indicated that endometrioid carcinoma had proliferated and formed a luminal structure with complicated branching in the area just beneath the fundus to the lower uterine body. The growth pattern of endometrioid carcinoma was endophytic and these components were also mixed with SCNEC, the major component of the tumor (Fig. 7). In the resected uterus, SCNEC was clearly dominant compared to endometrioid carcinoma. The lesion of endometrioid carcinoma was localized to the area just beneath the fundus to the lower uterine body. Immunostaining performed in the area with both components showed that the SCNEC region was positive for CD56, chromogranin A and synaptophysin (Fig. 8), whereas endometrioid carcinoma with an irregular luminal structure that was negative for these markers. The SCNEC component was also strongly positive in p16 immunostaining, whereas the endometrioid carcinoma was less positive for p16. The Ki-67 index of the SCNEC component was 80%, whereas those of the endometrioid carcinoma components were 10–20%.

DISCUSSION

SCNEC is a high-grade and aggressive neuroendocrine carcinoma that occurs in the uterus. The original site of SCNEC is more commonly the uterine cervix compared to the uterine body. The incidence of SCNEC in the uterine body accounts for 0.8–1.0% of endometrial carcinomas [6–10], and about half of SCNECs in the uterine body coexist with endometrioid carcinoma [6]. Therefore, these cases may be diagnosed as endometrioid carcinoma by preoperative cytology and histology, and as poorly differentiated carcinoma because of strong cellular and structural atypia and poor differentiation. Consequently, such cases are frequently differentiated as Grade 3 endometrioid carcinoma. Cytological findings reveal a relatively low connective level and a scattered status. Therefore, typical findings of SCNEC, including a nuclear molding sequence, are not commonly observed.

SCNEC is seldom diagnosed by preoperative cytology [11, 12], and our case was diagnosed as poorly differentiated carcinoma, but not SCNEC, by cervical and endometrial cytology. Therefore, comprehensive diagnosis using histology is necessary. Since peritoneal

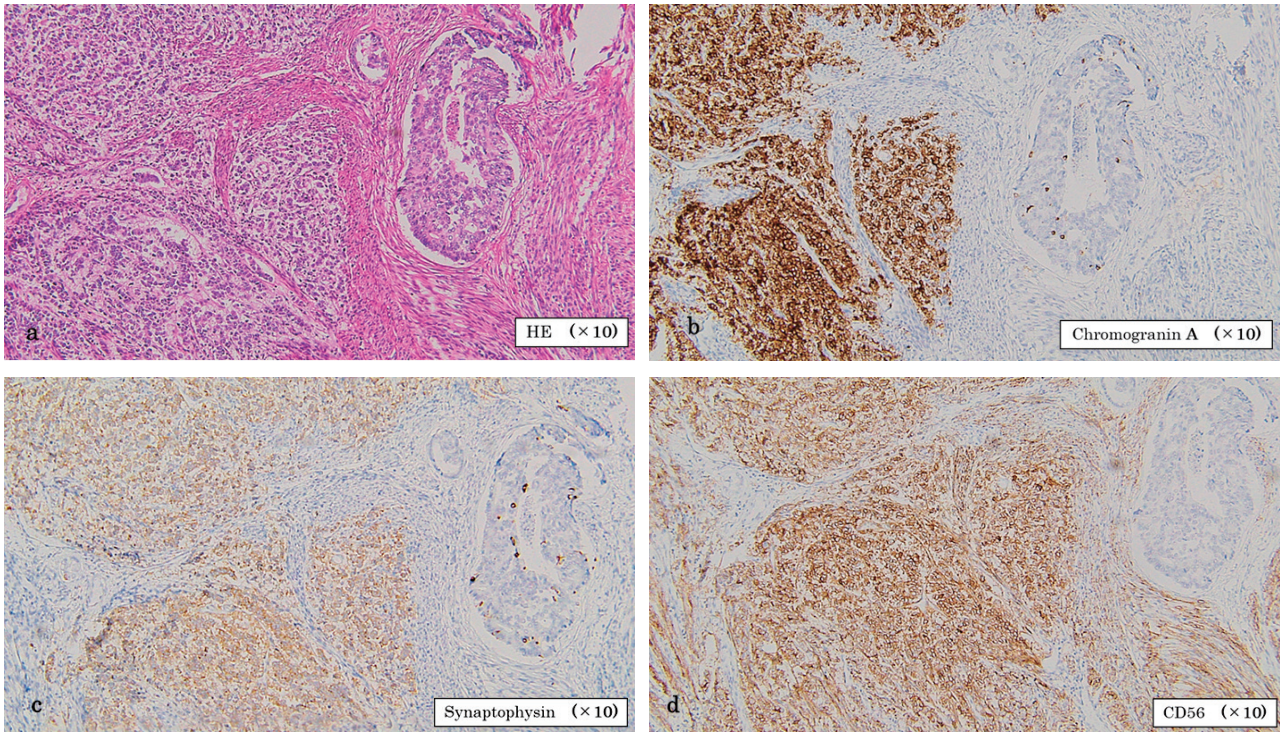

Fig. 8 (a) HE staining and immunostaining with (b) chromogranin, (c) synaptophysin, and (d) CD56 as markers for neuroendocrine tumors were all positive in the SCNEC component.

cytology in this case revealed SCNEC, ascites puncture may be helpful to diagnose high-grade cases with progression outside the uterus, including serosal rupture and omental metastasis, when ascites is easy to sample before surgery.

We had difficulty in determining the original site in this case because the tumors ranged from the uterine body to the cervix. A histopathologic examination showed that most tumors were SCNEC, but components of endometrioid carcinoma had developed with an endophytic growth pattern from the endometrium in a localized area just beneath the fundus and lower uterine body (Fig. 7). Endometrial SCNEC is well known to coexist with endometrioid carcinoma, and in this case, both had developed from the endometrium. However, histological transitional findings between these tumor types were not observed. Both components coexisted histologically around the deep side of the endometrioid carcinoma lesion. Immunostaining of SCNEC components showed strongly positive results for p16. SCNEC that develops in the uterine cervix is thought to have strong a relationship with HPV infection and is well known to have strong expression of p16 [13]. However, as described above, this case had coexistence with endometrioid carcinoma in the endometrium and was diagnosed as primary endometrial carcinoma. There are case reports of HPV-independent SCNEC developing in the endometrium that was p16-positive on immunostaining [14, 15]; however, it is difficult to diagnose patients with SCNEC in the uterine cervix based on p16 expression alone.

In this case, both endometrioid carcinoma and SCNEC had extensively invaded more than half of the muscle layer. However, SCNEC showed deeper invasion than endometrioid carcinoma and some tumors were exposed to the uterine serosa. SCNEC was found on the surface of the extracted greater omentum and many findings consistent with SCNEC were detected by peritoneal cytology. Such findings of progression outside the uterus show that SCNEC is an aggressive tumor with a course of rapid aggravation.

Endometrial SCNEC is a rare tissue type, and a therapeutic strategy remains to be established, despite the aggressiveness of the tumor. Cytoreductive surgery is important for initial treatment and adjuvant therapy after cytoreductive surgery can improve the prognosis [9, 16, 17]. We have experienced patients who responded well to initial chemotherapy. Therefore, immediate surgery and chemotherapy are preferable to prolong disease-free survival and maintain a good performance status. However, there is no standard adjuvant therapy for endometrial SCNEC, and conventional pharmacotherapy for small-cell lung cancer is still used, based on etoposide, irinotecan and amrubicin [18, 19]. The NCCN guidelines specify that the first-line therapy for small-cell lung cancer is a combination of etoposide and a platinum-based agent (cisplatin or carboplatin) [21, 22], and the same regimens are generally used for endometrial SCNEC.

Molecular targeted drugs that are used for many cancers may also be effective, as shown by use of combined cisplatin + etoposide and bevacizumab in patients with small-cell lung cancer and subsequent maintenance therapy with etoposide + bevacizumab [22]. The utility of a combination with bevacizumab has also been shown in treatment of SCNEC in the gynecological field [23]. Recent advances in molecular genetic analysis have permitted pembrolizumab to be used for malignant tumors with high-frequency microsatellite instability (MSI-high) and this may be new therapeutic option for advanced and recurrent cases after standard treatment [24]. These new therapies may also be applicable to endometrial SCNEC and may improve treatment outcomes [15, 25, 26].

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