A case of uterine corpus large cell neuroendocrine carcinoma showing prominent myometrial invasion without any macroscopically clear tumor formation

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Abstract Large cell neuroendocrine carcinoma (LCNEC) arising in the uterine corpus is a very rare. Here, we report our experience with a primary LCNEC in the uterine corpus that showed prominent myometrial invasion without exhibiting any macroscopically distinct tumor formation in the uterine cavity. The patient was a 54-year-old woman. She had a past medical history of right breast cancer and was referred to our department with irregular genital bleeding, elevated serum carcinoembryonic antigen in periodic medical examinations and computed tomography (CT) findings of uterine cavity dilation. Endometrial biopsy suggested a poorly differentiated tumor. Although magnetic resonance imaging (MRI) showed hematometra-like findings in the uterine cavity, it did not indicate any clear endometrial lesion. The myometrium was unequally thickened, and the entire muscle layer showed a high signal intensity on diffusion-weighted images. Fluorine-18-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) showed strong FDG accumulation in the whole uterus, and on the bottom of the uterus,

there was a ring-shaped accumulation mainly in the muscle layer. The postoperative resected specimen did not show any tumor formation in the uterine cavity, whereas the myometrium was hard and thickened, and colored white overall. Histopathological examination revealed prominent myometrial invasion in most layers, cervical stromal invasion and pelvic lymph node metastasis. The diagnosis was a LCNEC of the uterine corpus, at FIGO stage IIIC1 and pT2N1M0. With these patients, we found that functional metabolic images, such as MRI diffusion-weighted images and FDG-PET/CT, were useful in identifying the lesion. Preoperatively, when a poorly differentiated tumor is estimated and characteristic myometrial invasion is suspected, the possibility of LCNEC should be considered.

Keywords Endometrial carcinoma · Neuroendocrine tumor · Large cell neuroendocrine carcinoma · FDG-PET/CT · MRI

Introduction

Large cell neuroendocrine carcinoma (LCNEC) of the uterine corpus is a rare and aggressive tumor. Only 13 cases of LCNEC of the uterine corpus have been reported in the English literature; the features of this carcinoma remain unclear and the prognosis appears to be poor. The cytological and biopsy findings have mainly been reported; however, the specific features of magnetic resonance imaging (MRI) and fluorine-18-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) have seldom been reported. Here, we present a rare case of LCNEC of the uterine corpus which exhibited significant myometrial invasion without clear tumors in the endometrium; we also demonstrate the MRI and FDG-PET/CT features.

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Fig. 1 Cytological findings of LCNEC. **a** There is strong intussusception with the margin showing indistinct clumping of atypical cells (Pap staining; $\times 20$). **b** Scattered small clumps of atypical cells can be

seen showing weak bonding and rosette-like arrangements (Pap staining; $\times 40$). **c** Isolated cells are evident that appear as large bare nuclei containing prominent nucleoli (Pap staining; $\times 40$)

Case report

A 54-year-old woman (gravida 2, para 2) presented with genital bleeding. Her past medical history was significant for bronchial asthma and breast cancer (noninvasive ductal carcinoma), and her mother had breast cancer. The patient had a rising serum carcinoembryonic antigen (CEA) level and hematometra as observed using computed tomography (CT) imaging during follow-up in the Department of Breast Surgery. She was subsequently referred to the Department of Gynecology. Gynecologic examination revealed a very hard corpus of the uterus that was the size of a chicken egg; the cervix and adnexa were normal.

Laboratory tests were unremarkable except for the elevation of the patients' CEA and cancer antigen (CA)19-9 (CEA, 24.6 ng/mL; reference level: <5 ng/mL; CA19-9, 110 U/ml; reference level, <37 ng/mL) levels. The CA125

and neuron-specific enolase (NSE) results were within reference levels.

The preoperative endometrial cytology was positive. There was strong intussusception, with the margin showing indistinct clumping of atypical cells. The lesion was a suspected endometrioid adenocarcinoma (Fig. 1a). There were scattered small clumps of atypical cells showing weak bonding and rosette-like arrangements (Fig. 1b). There were isolated cells appearing as a large bare nucleus containing distinct nucleoli (Fig. 1c). Endometrial biopsy suggested poorly differentiated endometrial carcinoma, such as endometrial adenocarcinoma grade 3, and undifferentiated carcinoma because of the poor glandular structure (Fig. 2).

MRI of the lower abdomen demonstrated uterine hematometra and myometrial invasion without the presence of clear tumors in the endometrium (Fig. 3a, b). The

Fig. 2 Histological findings of endometrial biopsy. Histologically processed endometrium biopsy showing a malignant tumor composed of large round to oval cells arranged in the poorly glandular structure.

The nuclei are vesicular, at places hyperchromatic, and show moderate pleomorphism with frequent mitotic activity (HE staining; $\times 20$, $\times 40$)

uterine corpus was unequally thickened, and the junctional zone was unclear. On diffusion-weighted imaging, the uterine corpus showed remarkable hyperintensity and the apparent diffusion coefficient (ADC) value was very low ($0.42 \times 10^{-3} \text{mm}^2/\text{s}$; Fig. 3c, d). FDG-PET/CT revealed strong FDG uptake (standard uptake value [SUV] max: 9.67) in the uterus (Fig. 4). Lymph node metastasis and distant metastatic focus were not identified.

Modified radical hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and omentectomy were performed. Grossly, the uterine endometrium was atrophic, and there was no evidence of a tumor in the cavity. The myometrium was white and very hard and hypertrophic (Fig. 5). Microscopically, the tumor had deeply infiltrated the myometrium, and the sequence between the endometrium and the carcinoma was partly recognized. It was composed of malignant medium-sized or relatively large-sized cells with hyperchromatic nuclei and well-demarcated nests with peripheral palisading and a rosette-like growth pattern (Fig. 6a, b, c). There was a high mitotic activity (40–50/10HPF). Nucleoli were seen in a few cells. On immunohistochemical evaluation, the tumor cells were diffusely positive for CD56, chromogranin A and synaptophysin, which are neuroendocrine markers (Fig. 7). These findings were similar to large cell neuroendocrine tumors of the lung, that is, LCNEC is characterized by the neuroendocrine morphology (nesting, palisading and rosettes), a high mitotic rate, necrosis, cytologic features similar to non-small cell lung cancer and positive immunohistochemical staining for neuroendocrine markers [1]. The pathologic diagnosis was appropriate for LCNEC of the endometrium. Because of cervical invasion and metastasis to the

pelvic lymph nodes, the final tumor classification was confirmed as International Federation of Gynecology and Obstetrics (FIGO) stage IIIC1, pT2N1M0.

The patient was treated with adjuvant chemotherapy for six cycles (intravenous irinotecan [CPT-11] and cisplatin [CDDP]), which was well tolerated. Three months after completing the last dose of chemotherapy, recurrence was diagnosed in the form of liver metastasis. Although second-line chemotherapy (intravenous paclitaxel and carboplatin) was administered, brain and lung metastases were discovered during the second-line chemotherapy. The patient died at 22 months after the first operation.

Discussion

Neuroendocrine tumors arising in the uterine corpus are rare. In the World Health Organization Classification of Tumours 4th Edition, revised in 2014, the uterine corpus section has been modified to include neuroendocrine tumors. There are now two classifications: Carcinoid tumors are classified as low-grade neuroendocrine tumors, while small cell neuroendocrine carcinomas (SCNECs) and LCNECs are classified as high-grade neuroendocrine tumors. It is hoped that in the future, there will be a further accumulation of cases of this disease and elucidation of its pathology.

Our search of the English literature revealed only 13 reported cases of LCNEC of the uterine corpus (Table 1) [2–9]. The patients were mostly elderly, with a median age of 71 (range 40–88 years) years, and eight patients had advanced disease at stage III or higher. In studies that reported follow-up data, five of nine patients died within

1 year, indicating that the prognosis of this disease is very poor regardless of the stage. Moreover, it has been reported that many cases have additional histological types. Thus, the 13 patients included three who were complicated with endometrioid adenocarcinoma, one who was complicated with endometrioid adenocarcinoma together with small cell carcinoma and one who was complicated with uterine sarcoma. The case that we have reported on here involved pure LCNEC.

As previously reported, treatment for most of the patients has consisted of such strategies as postoperative radiotherapy and cisplatin-based chemotherapy; however, an evidence-based therapeutic approach has not yet been established. On the basis of preoperative endometrial biopsy, we suspected that our patient had a poorly differentiated tumor. Consequently, we performed surgery that

included para-aortic lymph node dissection. As postoperative adjuvant chemotherapy, we selected the CPT-11 + CDDP regimen used to treat small cell lung cancer. The CPT-11 + CDDP regimen has also been reported as a treatment for LCNEC of the uterine cervix [10].

Neuroendocrine tumors generally have two histological features, namely neuroendocrine morphology and neuroendocrine differentiation. The neuroendocrine morphology has a histological architecture of palisade-like arrangements and a rosette-like structure. Neuroendocrine differentiation is characterized by the presence of neuroendocrine substances in the cytoplasm or cell membrane; immunostaining using neuroendocrine markers such as CD56, chromogranin A and synaptophysin is useful for the identification of neuroendocrine tumors. However, neuroendocrine tumors are poorly differentiated; for that

Fig. 3 **a** Sagittal T2-weighted image showing a hematometra-like area in the uterine cavity but no clear endometrial lesion. **b** Axial T2-weighted image. The muscle layer of the uterine corpus is unequally thickened, and the junctional zone is unclear. **c** Diffusion-weighted

image ($b = 1000 \text{ s/mm}^2$). The entire muscle layer of the uterine corpus shows a high signal intensity. **d** ADC map. The ADC is markedly decreased ($0.42 \times 10^{-3} \text{ mm}^2/\text{s}$)

Fig. 4 FDG-PET/CT. Strong fluorodeoxyglucose accumulation can be seen in the whole uterus (maximum specific uptake value = 9.67), while on the bottom of the uterus, there is ring-shaped accumulation, mainly in the muscle layer

Fig. 5 Macroscopic findings. The uterine cavity appears smooth with no tumor formation. The myometrium (hard and thickened) is white in color overall

reason, they can often be difficult to differentiate preoperatively from grade 3 endometrioid adenocarcinomas, undifferentiated carcinomas and mesenchymal tumors.

Very few reports have dealt with the imaging diagnosis of LCNEC of the uterine corpus. Makihara et al. [8] reported that, as in the case of poorly differentiated tumors and sarcomas, T2-weighted images showed heterogeneous high intensity, while diffusion-weighted images showed high signal intensity. Makihara et al. also found that FDG-

Fig. 6 Histological findings of LCNEC. **a** Well-circumscribed solid cell nests can be seen forming. Tumor cells in endometrial stroma infiltrate the myometrium (HE staining; $\times 10$). **b, c** Many mitotic figures, a peripheral palisading and rosette structure can be seen (HE staining; $\times 20$, $\times 40$)

Fig. 7 Immunohistochemical findings. The tumor cells are positive for CD56, chromogranin A and synaptophysin

PET/CT was useful for the diagnosis of not only the primary lesion but also metastatic lesions and recurrent disease, because FDG showed good accumulation in the lesions. In our present patient, functional metabolic imaging, such as MR diffusion-weighted images, FDG-PET/CT and other imaging modalities were useful in depicting the morphological characteristic of our patient's myometrial invasion.

In many of the reported cases [2, 4–6], the developmental morphology of the LCNEC tumor in the uterine corpus was accompanied by tumor formation in the uterine cavity, but in our patient, there was no clear tumor formation in the uterine cavity. Nevertheless, the uterine body of our case was very hard and thickened, being histopathologically characterized by tumor cell invasion of nearly all of the myometrium. In the MRI examination, even though there was no clear evidence of endometrial lesions, the muscle layer was unequally thickened;

diffusion-weighted images showed a high signal intensity in the entire muscle layer, while the ADC value was markedly reduced. FDG-PET/CT revealed strong FDG accumulation in the whole uterus; on the bottom of the uterus, there was a ring-shaped accumulation that occurred mainly in the muscle layer. FDG has been known to undergo physiological accumulation in the brain, but Miyasaka et al. [11, 12] found it to also be intensely taken up by central nervous tissue components of an ovarian mature cystic teratoma. It could be speculated that FDG is similarly taken up by neuroendocrine tumors, causing an increase in the maximum SUV to increase.

LCNEC of the uterine corpus is a rare tumor having a poor prognosis. Preoperative diagnosis is difficult, and an optimal treatment approach remains to be established. Preoperatively, when a poorly differentiated tumor is evaluated on the basis of cytology and biopsy, and characteristic myometrial invasion is suspected based on

Table 1 Clinical features of large cell neuroendocrine tumors of the endometrium reported in the literature and in the present case

Case	Authors	Age	Gross appearance	Surgery	Stage	Histology	Outcome (months)
1	Erhan et al. [2]	52	50 mm polypoid	TAH, BSO	Ic	Pure LCNEC	DOD3
2	Mulvany et al. [3]	50	22 mm polyp	TAH, BSO, PPALND, OM	IIIc	Pure LCNEC	AWD12
3	Mulvany et al. [3]	80	45 mm polypoid	TAH, BSO, PLND	Ic	LCNEC + endometrioid grade 3	DOD5
4	Mulvany et al. [3]	77	75 mm polyp	TAH, BSO	I Ib	LCNEC + endometrioid grade 1	DOD23
5	Mulvany et al. [3]	79	Thickening of myometrium	TAH, BSO, biopsies of omentum and peritoneum	IIIa	LCNEC + endometrioid grade 3	AWD2
6	Mulvany et al. [3]	88	50 mm polypoid	TAH, BSO, PLND	IIIc	LCNEC + SCNEC + endometrioid grade 3	AWD1
7	Albores-Saavedra et al. [4]	42	45 mm polypoid	RH	Ic	Pure LCNEC	AWD9
8	Terada et al. [5]	40	30 mm polypoid	TAH, BSO, PLND, OM	Ib	LCNEC + sarcomatoid	AWD16
9	Deodhar et al. [6]	70	35 mm polypoid	TAH, BSO, OM	Ib	Pure LCNEC	AWD6
10	Shahabi et al. [7]	59	Polypoid	TAH, BSO, PPALND, OM, APPY	IIIc2	Pure LCNEC	DOD12
11	Makihara et al. [8]	73	Submucosal type leiomyoma	None	IVb	Pure LCNEC	DOD12
12	Makihara et al. [8]	73	White tumor	TAH, BSO, PPALND, OM	IIIc1	Pure LCNEC	AWD13
13	Nguyen et al. [9]	71	Polypoid	RH, BSO, PPALND, OM	IVb	Pure LCNEC	DOD1
14	Present case	54	Hard and hypertrophic myometrium	TAH, BSO, PPALND, OM	IIIc1	Pure LCNEC	DOD22

TAH total abdominal hysterectomy, BSO bilateral salpingo-oophorectomy, OM omentectomy, RH radical hysterectomy, PLND pelvic lymph node dissection, PPALND pelvic and para-aortic lymph node dissection, APPY appendectomy, DOD dead of disease, AWD alive with disease

functional metabolism images, such as MRI diffusion-weighted images or FDG-PET/CT, the possibility of LCNEC should be considered.

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Conflict of interest The authors declare that they have no conflict of interest.

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