Large cell neuroendocrine carcinoma originating from the uterine endometrium: a report on magnetic resonance features of 2 cases with very rare and aggressive tumor

Natsuko Makihara,1 Tetsuo Maeda,2 Meiko Nishimura,3 Masashi Deguchi,1 Ayako Sonoyama,1 Koji Nakabayashi,1 Fumi Kawakami,3 Tomoo Itoh,3 Hitoyo Yamada1
1Department of Obstetrics and Gynecology, 2Department of Radiology, and 3Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Japan

Abstract

Neuroendocrine carcinomas (NEC) of the female genital tract are aggressive and uncommon tumors, which usually involve the uterine cervix and ovary, and are seen very rarely in the endometrium. Only less than 10 cases of large cell NEC (LCNEC) of the endometrium have been reported in the literature and their radiological findings are not well described. We report here two cases of pathologically proven LCNEC of the uterine endometrium. In both cases, the uterine body was enlarged and the tumor occupied part of the uterine cavity. Endometrial mass exhibited heterogeneous high intensity on T2-weighted magnetic resonance (MR) images, and diffusion-weighted MR images revealed high intensity throughout the tumor, consistent with malignancy. The histopathological examination of the biopsy specimen from the endometrium suggested a diagnosis of LCNEC, and the one from the cervix had no malignant finding. Physical examination revealed that she had enlarged uterus and right supraclavicular lymphadenopathy. The laboratory tests were unremarkable, except for the elevation of serum neuron-specific enolase (NSE; 630 ng/mL; reference level, <12 ng/mL), cancer antigen 125 (202 U/mL; reference level, <35 U/mL), lactate dehydrogenase (279 IU/L; reference level, 115–217 IU/L), and interleukin receptor-2 (767 U/mL; reference level, 122–466 U/mL). MR images of lower abdomen, but not urinary bladder revealed hypointensity including high intensity expanding in the endometrium, suggestive of intratumoral hemorrhage, on T2-weighted images (Figure 3A), and apparent primary tumor in the other organs, except for the uterus (Figure 2A). FDG-PET/CT imaging. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation.

Case Report #1

A 73-year-old woman (gravid 2, para 2), having no history of gynecologic disorders, visited a local hospital with lumbar and abdominal distention and was referred to the Kobe University Hospital as soon as the presence of large uterine tumor was detected by computed tomography (CT) imaging. The histopathological examination of the biopsy specimen from the endometrium suggested a diagnosis of LCNEC, and the one from the cervix had no malignant finding. Physical examination revealed that she had enlarged uterus and right supraclavicular lymphadenopathy. The laboratory tests were unremarkable, except for the elevation of serum neuron-specific enolase (NSE; 630 ng/mL; reference level, <12 ng/mL), cancer antigen 125 (202 U/mL; reference level, <35 U/mL), lactate dehydrogenase (279 IU/L; reference level, 115–217 IU/L), and interleukin receptor-2 (767 U/mL; reference level, 122–466 U/mL). MR images of lower abdomen, but not urinary bladder revealed hypointensity including high intensity expanding in the endometrium, suggestive of intratumoral hemorrhage, on T2-weighted images (Figure 3A), and apparent primary tumor in the other organs, except for the uterus (Figure 2A). FDG-PET/CT imaging. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation.

Case Report #2

A 73-year-old woman (gravid 6, para 3), having no history of gynecologic disorders, visited a local hospital with heavy discharge and genital bleeding, and was then referred to our hospital. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation. The histopathological diagnosis of endometrial biopsy was adenocarcinoma with solid poorly differentiated component, which showed focal positivity of CD56 suggesting neuroendocrine differentiation.
weighted MR images showed heterogeneously enhanced tumor (Figure 3B), and diffusion-weighted MR images revealed high intensity throughout the tumor (Figure 3C), consistent with a malignant uterine tumor. Paraortic lymphadenopathies were identified on the abdominal CT. She underwent abdominal total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and pelvic-paraortic lymphadenectomy. Grossly, the uterine cavity was dilated and showed a white tumor involving the fundic region, and the tumor infiltrated to the myometrium deeply. The isthmic and cervical areas were uninvolved, and the bilateral adnexa and omentum were free of metastasis. Microscopically, the carcinoma displays a neuroendocrine morphology, including organoid nesting with large zones of necrosis, trabecular growth, rosettes and peripheral palisading patterns (Figure 4A). Immunohistochemistry revealed diffuse positivity for synaptophysin, chromogranin, CD56 and p53 (Figure 4B). The pathologic diagnosis was appropriate for large cell neuroendocrine carcinoma of the endometrium, and because of the metastasis to right internal iliac lymph nodes and left external iliac lymph node, the final stage was 3c. She was thereafter treated by chemotherapy (intravenous cisplatin; 60 mg/m² and irinotecan; 60 mg/m²). After 6 cycles of chemotherapy, this patient was disease-free during 6 months. However, FDG-PET/CT, which was performed 13 months after the operation, revealed increased FDG uptake in paraaortic lymph nodes, being suspected of the recurrence.

**Discussion**

LCNEC usually develops in the lungs. In the gynecological organs, LCNEC generally affects in the uterine cervix and ovary, and much less rarely in the uterine endometrium.² According to the World Health Organization classification, neuroendocrine tumors in the uterine cervix are categorized into the 4 categories of typical carcinoid, atypical carcinoid, small cell carcinoma (SmCC) and LCNEC. LCNEC in the uterine endometrium is extremely rare and represents less than 1% of all primary endometrial carcinomas.² Mulvany and Allen reported that patients with LCNEC of the uterus endometrium had a mean age of 75 years (50-88 years), and they were older than patients with LCNEC of the uterine cervix.²

As we measured serum NSE values in these two cases, it was found that the value of the Case #1 was raised and that of the Case #2 was within normal limit. Therefore, it is hard to say that these values are useful markers in diagnosis of LCNEC.

Kiyokawa et al. cited 6 cytological features of LCNEC of the uterine cervix as the following:² i) presence of cell necrosis, ii) dispersion of tumor cells, some of which forming loosely arranged clusters with irregular stratification or in file-like fashion, iii) occasional nuclear protrusion at the periphery of clusters, iv) high N/C ratio with round to oval nuclei, 3 to 6 times in size of lymphocytes, v) increased coarse granular chromatin and 1 to 3 prominent nucleoli, and vi) which cytoplasm faintly stained light green and ill-defined cell border. These features are similar to those of LCNEC in other organs such as the lungs and closely resemble poorly differentiated adenocarcinoma, making the two types of tumors extremely hard to differentiate especially by small biopsy specimens.² In fact, Case #2 was diagnosed as poorly differentiated carcinoma according to preoperative endometrial sampling. In such cases, immunohistochemical staining for chromogranin A, CD56, or synaptophysin may help to confirm neuroendocrine differentiation.

To the best of our knowledge, specific image findings of LCNEC of the uterus have never been reported. In both of the present cases, the uterine body was enlarged and the tumor occupied part of the uterine cavity. On T2-weighted MR images, the tumor involved both the myometrium and endometrium, and ill-defined endometrial-myometrial border was revealed. Endometrial mass exhibited heterogeneous high intensity on T2-weighted MR images, and this heterogeneity may represent necrosis and diffuse hemorrhage in the tumors.³ Moreover, diffusion-weighted MR images revealed high intensity throughout the tumor, consistent with malignancy. These MRI findings of the 2 cases were somewhat similar to the MR image findings for SmCC, having many similarities to LCNEC.²,³ These MRI findings of neuroendocrine carcinoma have been found to mimic those of type cancer including poorly differentiated endometrial adenocarcinoma, which is another malignant tumor of the uterine corpus that invades the endometrium, or malignant lymphoma, uterine sarcoma, and metastatic
In actuality, the image findings in Case #1 led to a diagnosis of malignant lymphoma, while the image findings in Case #2 led to a diagnosis of endometrial cancer with myometrial invasion, respectively. PET/CT is a functional imaging method of metabolic processes and is being used extensively in gynecologic oncology, which offers important information for the pre-, intra-, and postoperative management. In the current Case #1, actually, FDG-PET/CT revealed increased FDG uptake in the systemic metastases as well as in the primary uterine tumor, and in Case #2, it detected the recurrent lesion of the para-aortic lymph node. In patients with known malignant gynecologic lesions, therefore, PET may contribute to confirm the presence or absence of distant metastases at other sites and may assist in the selection of an appropriate treatment. NEC including LCNEC of the uterine body is known to have rare incidence, poor prognosis and no established treatment. In the treatment, patients should be given multimodality therapy including surgery, chemotherapy, and radiotherapy. As for the chemotherapy, patients are generally received six cycles of cisplatin (60 mg/m², day 1) and etoposide (60 mg/m², day 1, 8, and 15). In Case #1, because the patient had numerous metastases throughout her body, it was impossible for her to undergo surgery. Administration of chemotherapy was considered, but due to worsening of the patient’s performance status, any active treatment was impossible. So, only pain control was provided, and the patient died 5 weeks after her initial examination. The patient in Case #2 underwent surgery and postoperative adjuvant chemotherapy, but 6 months later PET scans revealed recurrence.

**Conclusions**

We encountered 2 cases of LCNEC originating from the endometrium, which is extremely rare and has an extremely poor prognosis. Adequate consensus has not been reached on the treatment of the NEC, and more accumulation of the reports is needed to establish treatment methods. LCNEC is a highly malignant neoplasm with no characteristic findings in terms of diagnostic imaging and pathology; so definitive diagnosis of LCNEC preoperatively is difficult. However, when laboratory test, pathologic diagnosis of endometrial tissue, and CT/MRI imaging suggest a poorly differentiated uterine malignancy, PET/CT scans should be performed as a general assessment to help with diagnosis.

**References**

3. Terada T. Large cell neuroendocrine carcinoma with sarcomatous changes of the endometrium: a case report with immunohistochemical studies and molecular genetic study of KIT and PDGFR. Pathol Res Pract...


