Taiwanese Journal of Obstetrics & Gynecology 57 (2018) 144–149

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Large cell neuroendocrine carcinoma of the endometrium: A case report and literature review

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ARTICLE INFO

Article history:
Accepted 25 May 2017

Keywords:
Neuroendocrine carcinoma
Endometrium
Chemotherapy
Radiotherapy

ABSTRACT

Objective: To report a case and review published cases of large cell neuroendocrine carcinoma (LCNEC) of the endometrium.

Case report: A 51-year-old female presented with postmenopausal bleeding and a palpable pelvic mass. An endometrial biopsy showed a malignant mixed Mullerian tumor (MMMT). Suboptimal debulking surgery was performed. The final pathology revealed stage IVB endometrial LCNEC. Post-operative adjuvant chemotherapy with cisplatin and etoposide was administered. Two months after discontinuing adjuvant chemotherapy, salvage chemotherapy with cisplatin and ifosfamide was administered due to tumor progression; however, obstructive ileus was noted 2 months later. A segmental small bowel resection and palliative colostomy were performed. She died secondary to a post-operative infection 8 days after the operation.

Conclusion: Endometrial LCNEC is a rare but aggressive disease. If diagnosed, combined therapies, including staging surgery, following by adjuvant radiotherapy and chemotherapy, should be performed.

Introduction

The two main types of cancer of the uterus are uterine sarcoma and endometrial carcinoma [1]. Endometrial carcinoma, which arises in the cells of the endometrium, is the most common malignancy of the female genital tract [2]. In 2015, an estimated 54,870 new cases of uterine cancer and 10,170 cancer-related deaths occurred in the United States [3]. In Taiwan, there were 1500 new cases of endometrial cancer, and the incidence continues to increase [4]. The major histologic type of endometrial carcinoma is endometrioid adenocarcinoma. Non-endometrioid histology includes mucinous, serous, clear cell, mucinous, squamous, neuroendocrine, and undifferentiated types [1].

Neuroendocrine neoplasms occur predominantly in the lung, but can be occasionally found in the gastrointestinal and genitourinary tracts. These tumors consist of a spectrum of malignancies, which are recognized by generic neuroendocrine marker expression (i.e. synaptophysin and chromogranin detected by immunohistochemistry). Neuroendocrine tumors are classified as poorly-differentiated neuroendocrine carcinoma (NEC) and well-differentiated neuroendocrine tumor (NET) based on the differentiation grade. The former is further categorized into small and large cell neuroendocrine carcinomas (SCNECs and LCNECs, respectively). In short, a LCNEC is defined as a malignant tumor composed of large cells that show neuroendocrine differentiation [5]. LCNECs usually develop in the lungs. Within the female reproductive tract, LCNECs are always diagnosed in the uterine cervix [6] and ovary [7], and rarely in the uterine endometrium.

LCNECs of the female genital tract usually involve the uterine cervix and ovary, and rarely occur in the endometrium [8]. Only 15 cases of endometrial LCNECs have been reported in the English literature (Table 1) [9–18]. Herein we present a 51-year-old woman with the diagnosis of LCNEC of the endometrium. We also reviewed the literature pertaining to endometrial LCNECs.

Case report

A 51-year-old Taiwanese woman sought evaluation at a local hospital because of postmenopausal vaginal bleeding and a

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https://doi.org/10.1016/j.tjog.2017.12.025

Table 1
Reported cases of large cell neuroendocrine carcinoma of the endometrium.

Case	Age	Initial stage	Symptoms/Signs	Immuno-profile positivity	Surgery	Further treatment (RT)	Further treatment (CT)	Follow up (Time after diagnosis)	Recurrence/ Persistence	Metastatic site
1 [9]	52	IC[a]	PMB	NSE, SNP	TAH, BSO	RT (unspecified)	EPcis	Died of tumor (10 mo)	Yes	Brain, lung
2 [10]	50	IIIC[a]	PMB	NSE SNP	TAH, BSO, OMY, PPALND	RT (WP)	EPcar	Alive (12 mo)	No	None
3 [10]	80	IC[a]	PMB	NSE CGA	TAH, BSO, PLND	None	None	Died of tumor (5 mo)	Yes	Unspecified but disseminated
4 [10]	77	IIB[a]	PMB	NSE SNP CGA CD56	TAH, BSO	RT (WP)	None	Died of tumor (23 mo)	N/A	N/A
5 [10]	79	IIIA[a]	PMB	NSE CGA CD56	TAH, BSO, biopsies of omentum and peritoneum	RT (WP)	None	Alive (2 mo)	No	None
6 [10]	88	IIIC[a]	PMB	NSE CGA CD56	TAH, BSO, PLND	RT (WP)	None	Alive (1 mo)	No	None
7 [11]	42	IC[a]	AUB	SNP CGA CD56	RH	None	Platinum-based combination therapy	Alive (9 mo)	No	None
8 [12]	59	IIIB	AGC	NSE SNP CD56	RH, BSO, OMY, PPALND	RT (WP + B)	Unspecified	Alive (5 mo)	No	None
9 [13]	40	IB	AUB	SNP CD56	TAH, BSO, PLND, OMY	None	None	Alive (16 mo)	No	None
10 [14]	70	IB	PMB, mild abdominal pain	SNP CGA CD56	TAH, BSO, OMY	None	EPcis	Alive (6 mo)	Yes	Liver
11 [15]	59	IIIC2	PMB	NSE SNP CGA CD56	TAH, BSO, OMY, PPALND, APPY	RT (WP + B)	TC, PLD, EP + Oct	Died of tumor (12 mo)	Yes	None
12 [16]	73	IVB[b]	Lumbago, abdominal distention	NSE SNP CGA#2	None	None	None	Died of tumor (1 mo)	N/A	Bone, right supraclavicular lymphadenopathy
13 [16]	73	IIIC1	PMB	SNP CGA CD56	TAH, BSO, OMY, PPALND	None	IP, EPcar	Died of tumor (19 mo)	Yes	Kidney, lung
14 [17]	71	IVB	PMB	SNP CGA CD56	RH, BSO, OMY, PPALND	None	None	Died of tumor (1 mo)	N/A	N/A
15 [18]	51	IIIA	Uterine tumor at transvaginal sonography	SNP CGA CD56	RH, BSO, OMY, PPALND	None	IP	Alive (20 mo)	No	None
16 [Present case]	51	IVB	PMB, pelvic tumor, AGC	SNP CGA CD56	TAH, BSO, OMY	None	EPcis, ifosfamide + cisplatin	Died of tumor (9 mo)	Yes	Intraabdominal dissemination

AUB, abnormal uterine bleeding; AGC, atypical glandular cells; CGA, Chromogranin A; CT, chemotherapy; B, vaginal brachytherapy, EPcar, etoposide/carboplatin; EPcis, etoposide/cisplatin; IP, irinotecan/cisplatin; N/A, not available or not applicable; NSE, neuron-specific enolase; Oct, octreotide; OMY, omentectomy; RH, radical hysterectomy; PLD, pegylated doxorubicin; PLND, pelvic lymph node dissection; PMB, postmenopausal bleeding; PPALND, pelvic and paraaortic lymph node dissection; RT, radiotherapy; SNP, synaptophysin; TC, paclitaxel/carboplatin; WP, whole pelvic radiotherapy; mo, month.

[a] 1998 FIGO staging; otherwise, 2009 FIGO staging.

[b] Tissue diagnosis from autopsy.

palpable pelvic tumor of 3 months duration. The pelvic examination and sonography revealed an enlarged uterus with a disrupted endometrial-myometrial border. The Papanicolaou smear showed atypical glandular cells, which was confirmed by endometrial biopsy. The findings consisted predominantly of carcinomatous features with well-differentiated (Fig. 1A) and poorly-differentiated carcinoma, characterized by a nested pattern of highly atypical cells (Fig. 1B). In addition, small foci of an admixture of malignant epithelial and mesenchymal components were discernible (Fig. 1C). The carcinomatous component of the tumor was cytokeratin- and vimentin-positive on immunohistochemical staining (Fig. 1D–F). Therefore, the tentative diagnosis was endometrial malignant mixed Mullerian tumor (MMMT). She was referred to our hospital for further treatment.

Magnetic resonance imaging (MRI) demonstrated an enlarged uterus with diffuse infiltration of the uterine myometrium and left adnexa (Fig. 2A). Extensive pelvic and para-aortic lymphadenopathy, and bilateral hydroureters were identified (Fig. 2B). A chest X-ray revealed no apparent abnormalities. Laboratory testing was unremarkable, with the exception of an elevated CA-125 (242.5 U/ml [reference level, <35 U/ml]). There were no symptoms or other clinical bases for metastatic disease at that time. We performed a laparotomy for a presumptive advanced endometrial cancer. Grossly, the tumor arose from the endometrium with involvement of the full thickness of the myometrium to the uterine serosa, and extending to the cervical stroma. In addition, we noticed tumor masses on the omentum and peritoneum. The aim of surgery was to remove the intra-abdominal tumor to alleviate her abdominal discomfort caused by the tumor mass effects and to acquire a final pathology. She underwent suboptimal debulking surgery, including abdominal total hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and cytoreduction. Her recovery was uneventful.

Microscopically, poorly-differentiated carcinoma was characterized by solid sheets of large cells (Fig. 3A) with a moderate amount of cytoplasm and large nuclei. The mitotic count of tumor cells (Fig. 3B) was >10 per 10 high power field (10/10 HPF) with marked necrosis and hemorrhage (Fig. 3C). The tumor cells were diffusely positive for cytokeratin, p53, synaptophysin, and CD56, and focally positive for chromogranin, but negative for estrogen receptor (Fig. 4). The clinical stage was cT3bN2M1 based on AJCC 7 and FIGO staging, and the pathologic stage was pT3bNxM1, FIGO IVB.

She received six cycles of adjuvant chemotherapy with cisplatin (80 mg/m^2 on day 1) and etoposide (80 mg/m^2 on days 1–3) over a 3-week interval. The follow-up CA-125 level was 7.7 U/ml. Abdomino-pelvic MRI revealed the decreased sizes of the pelvic and para-aortic lymph nodes. Two months after completion of adjuvant chemotherapy, she had progressive back pain, anorexia, and constipation. The serum CA-125 level was elevated (63.6 U/ml) and a 2-cm lesion above the vaginal stump, enlarged retroperitoneal lymph nodes, and hepatic metastases were noted on the follow-up CT scans. Hence, she began salvage chemotherapy with cisplatin (75 mg/m^2) and ifosfamide (5g/m^2) with mesna over a 3-week interval. Obstructive ileus due to tumor progression occurred after 2 cycles of salvage chemotherapy. CT revealed decreased sizes of the retroperitoneal lymph nodes and hepatic metastases, but severe pelvic adhesions and disseminated peritoneal carcinomatosis. She underwent a palliative segmental small bowel resection and colostomy. Although flatus was noted through the colostomy, she had progressive abdominal distention with no passage of intestinal content. The heavy tumor burden of peritoneal and mesenteric diseases was acknowledged with a poor functioning colostomy. Ertapenem was prescribed after surgery at the recommendation of the infectious disease specialist. The antibiotic was switched to meropenem to cover *Pseudomonas* because of a febrile

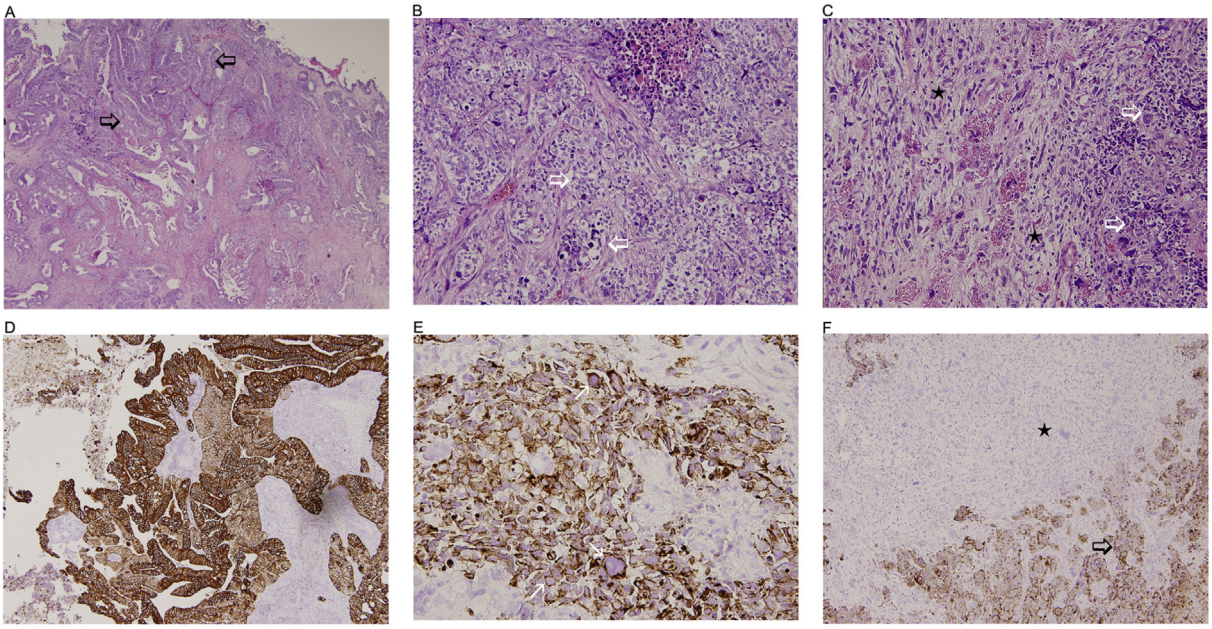

Fig. 1. Histology of the specimens of endometrial biopsy. **(A)** Well-differentiated endometrial adenocarcinoma with atypical cells, reduced stroma, and "back to back" aspect of the tumor glands (arrows) (hematoxylin and eosin, original magnification x40). **(B)** Poorly-differentiated carcinoma characterized by nested pattern (arrows) (hematoxylin and eosin, original magnification x200). **(C)** The tumor was composed of biphasic admixture with malignant epithelial (arrows, epithelioid) and malignant mesenchymal components (stars, spindle) (hematoxylin and eosin, original magnification x200). **(D)** Cytokeratin (CK) was diffusely positive in the well-differentiated endometrial adenocarcinoma (cytokeratin, original magnification x40). **(E)** CK showed dot-like perinuclear pattern (arrows) in the poorly-differentiated area (cytokeratin, original magnification x200). **(F)** CK staining showed a transitional zone between the carcinomatous component (arrow, positive for CK) and sarcomatous component (star, negative for CK) (cytokeratin, original magnification x400).

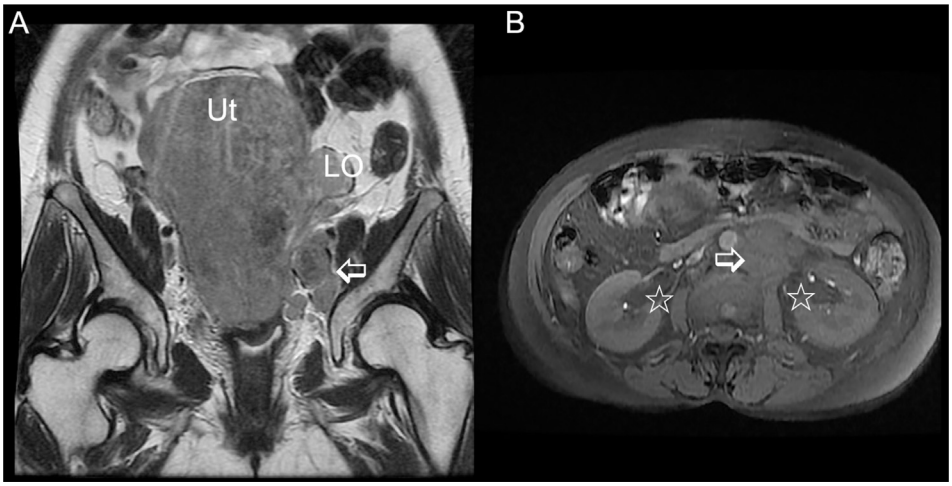

Fig. 2. **(A)** Coronal view of T2-weighted MRI showed enlarged uterus (Ut) with diffuse infiltration of the uterine myometrium, left adnexal invasion (LO), and enlarged left pelvic lymph nodes (arrow). **(B)** Axial view of T1-weighted MRI with contrast showed enlarged para-aortic lymph nodes (arrow) and bilateral hydroureters (stars).

episode 3 days postoperatively. An intra-abdominal infection was suspected by the infectious disease specialist. The patient's condition deteriorated due to multi-organ failure, and she died 8 days postoperatively.

Discussion

The diagnostic criteria for endometrial LCNECs have not been proposed. According to the WHO classification of lung tumors [19], LCNECs are diagnosed based on large cell carcinoma (large cell size with low nuclear to cytoplasmic ratio and >10 mitotic counts in 2 mm^2 of viable tumor [10HPF]) and the presence of both neuroendocrine histology (or ganoid nesting, palisading, rosettes, and trabeculae) as well as one or more immunohistochemical positive neuroendocrine markers (chromogranin, synaptophysin, or CD56). All 16 cases showed at least 2 positive-stained neuroendocrine markers in the immunohistochemical assays (Table 1); however, the pathologic features of endometrial LCNECs closely resemble poorly-differentiated adenocarcinoma, undifferentiated sarcoma, and MMMT. Therefore, it is relatively difficult to differentiate these tumors pre-operatively based on small biopsy specimens [10].

The differential diagnosis of neuroendocrine carcinoma from MMMT requires larger specimens. The differential diagnosis of this

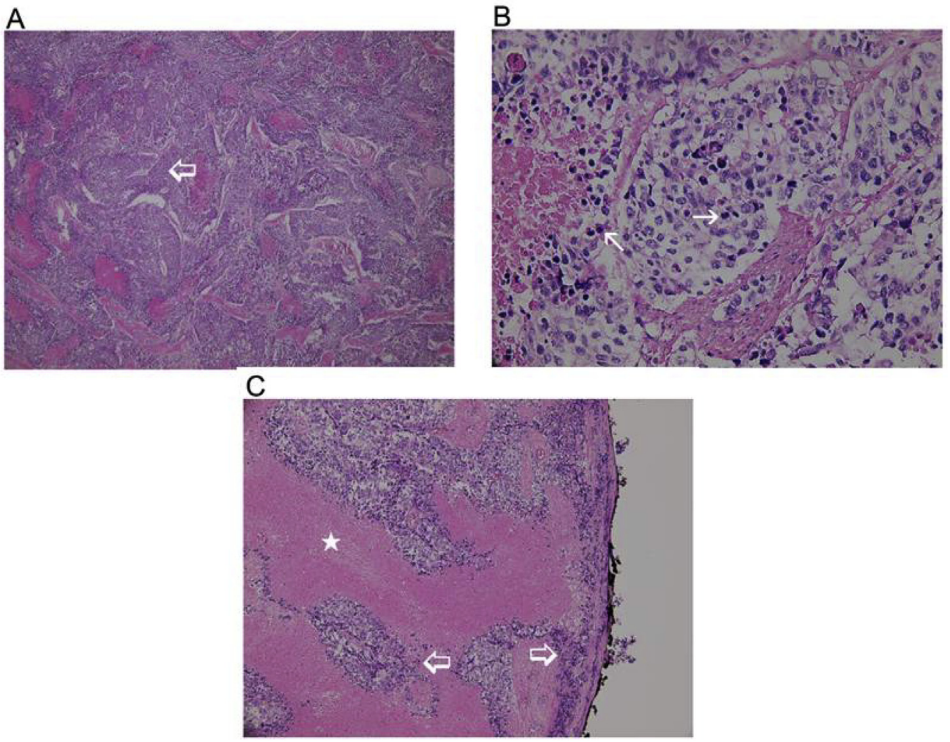

Fig. 3. Histology of the uterine specimen from debulking surgery. The tumor showed **(A)** solid islands (arrow) of large cells with atypia (hematoxylin and eosin, original magnification x40). **(B)** Active mitosis (arrow) (hematoxylin and eosin, original magnification x200). **(C)** marked geographic necrosis (arrows) and hemorrhage (star) (hematoxylin and eosin, original magnification x40).

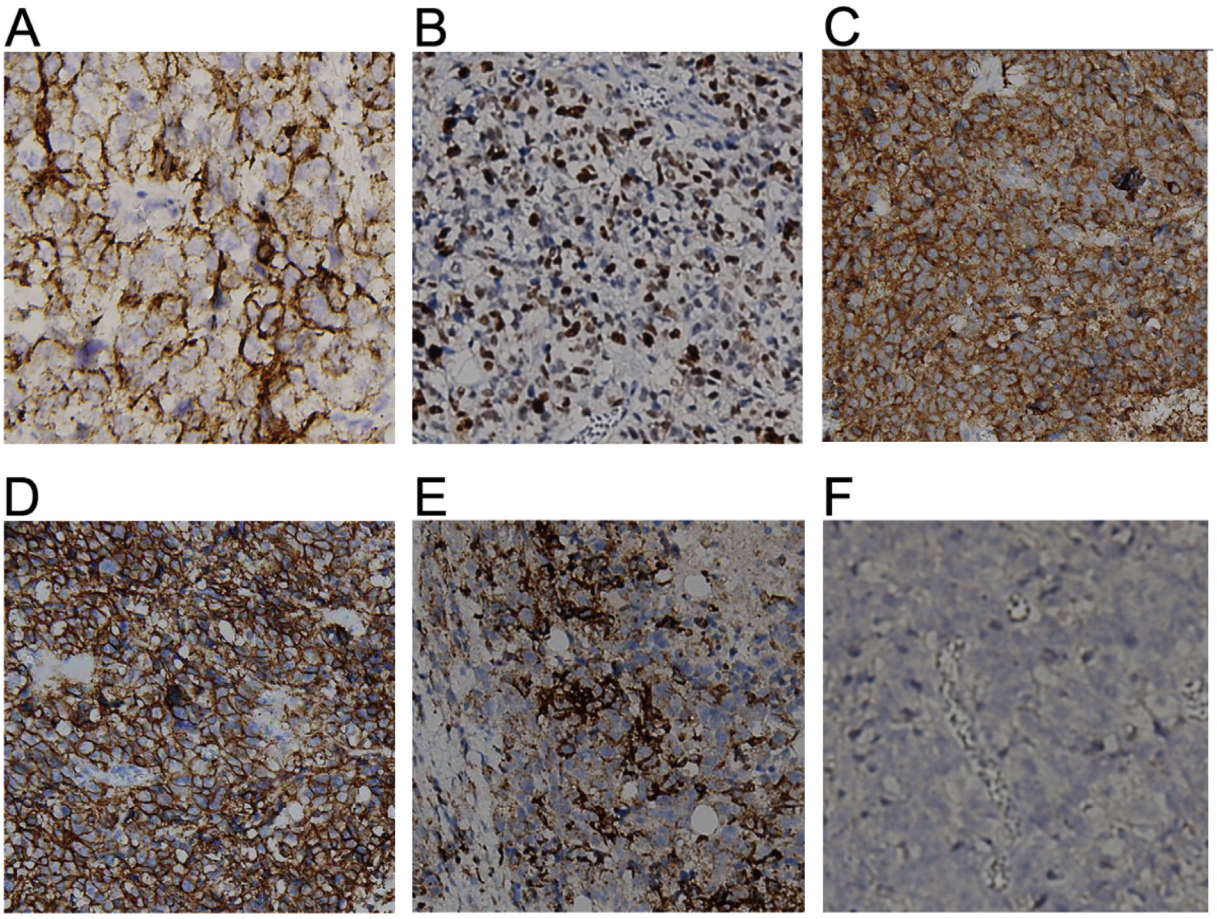

Fig. 4. Immunohistochemical stainings of the whole uterine specimen (original magnification x400). **(A)** Dot-like perinuclear cytokeratin pattern. **(B)** Diffusely positive for p53. **(C)** Diffusely positive for synaptophysin. **(D)** Diffusely positive for CD56. **(E)** Focally positive for chromogranin. **(F)** Negative for estrogen receptor.

patient based on endometrial curettage and debulking surgery is an interesting issue. The endometrial biopsy slides at the local hospital were reviewed. The diagnosis of MMMT according to the mixture of both carcinomatous and sarcomatous components was confirmed. When tracing the histologic change in the deep layer of the curettage specimen, nested and organoid structures were identified, thus implying the possibility of other pathology, including neuroendocrine carcinoma. The abundant expression of neuroendocrine immunostains, i.e., synaptophysin and CD56, were identified in the hysterectomy specimen. Neoplastic metaplasia from low-grade endometrioid carcinoma to MMMT and LCNEC was suggested. Dedifferentiated carcinoma was ruled out due to the lack of undifferentiated carcinoma, but not a neuroendocrine carcinoma in the deep myometrium. Considering the pathologic results of the endometrial curettage and hysterectomy, the final diagnosis of this patient was endometrial LCNEC with superficial focal MMMT. In addition, no specific clinical manifestations could be identified for this disease, as shown in Table 1. Like the features in the MRI (Fig. 2A and B), the differential diagnosis should include advanced endometrial cancer, malignant lymphoma, uterine sarcoma, and metastatic cancer [16].

Stage is the key prognostic factor for SCNEC [20]; however, stage does not serve as a significant prognostic factor for endometrial LCNEC because of the limited patient number and lack of long-term follow up. Only 6 patients have been reported to have > a 12-month survival, and 4 of 6 patients were stage III (Table 1). There were three patients, including our patient, with stage IVB disease. One of the patients died 1 month later without any treatment [16] and one died 1 month after radical surgery [17]. Our patient survived for 9 months and tolerated 6 cycles of adjuvant chemotherapy. Partial remission was demonstrated by a normal serum CA-125 level and MRI after completion chemotherapy; however, rapid progression of the residual tumor resulted in her death, even after salvage chemotherapy.

Five patients, including our patient, had documented recurrence/persistence and metastases (Table 1). The metastatic locations included the supraclavicular lymph nodes, brain, lungs, liver, kidneys, bone, and disseminated sites [9,10,14,16]. Three of the patients were in early stages at the time of diagnosis [9,10,14]. Our patient had a persistent tumor with rapid intra-abdominal dissemination after a short period of partial remission. Even in the early stages, endometrial LCNECs appear to have an aggressive course with a strong propensity for rapid recurrence and distant metastasis (Table 1).

Generally, standard surgical procedures for gynecologic malignancies include total hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection. Cytoreductive surgery, including omentectomy, is performed for clinically advanced stage and serous or clear cell histology to reduce the tumor burden. As shown in Table 1, seven patients received adjuvant pelvic radiotherapy and/or chemotherapy [9,10,12,15]. Three of these patients survived for >12 months, and 4 lived without disease relapse. Therefore, radiotherapy might have therapeutic effects on some endometrial LCNEC patients.

A first-line chemotherapy regimen for primary LCNEC of the endometrium has not been established, and data is largely extrapolated from SCNEC of the lung [18]. Therefore, we generally used adjuvant chemotherapy with etoposide and platinum (EP) and/or irradiation. Even if the initial response rate is high in early-stage disease, recurrence, distant metastasis, or progressive chemo-resistant disease frequently develop [17]. Like LCNEC of the cervix, cyclophosphamide/doxorubicin/vincristine (CAV), irinotecan/platinum (IP), or topotecan can be considered as second-line therapies for endometrial LCNEC [16,18,21,22]. Two stage III patients receiving primary adjuvant chemotherapy with irinotecan and cisplatin survived for >15 months, as shown in Table 1 [16,18]. Recently, irinotecan and cisplatin have been suggested as a better regimen for pathologic stage I-IIIA completely resected pulmonary high-grade neuroendocrine carcinoma patients in a randomized phase III trial [23]. Octreotide, a synthetic somatostatin analog, was a therapeutic choice combined with chemotherapy [15,24].

Endometrial LCNEC is a rare, but aggressive disease. Endometrial LCNEC should be differentially diagnosed from other uterine malignancies. Adjuvant radiotherapy and chemotherapy might have a better therapeutic impact on endometrial LCNEC.

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