Clinical Case Report

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Mixed large and small cell neuroendocrine carcinoma of the endometrium with serous carcinoma

A case report and literature review

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Abstract

Rationale: Endometrial neuroendocrine carcinoma is a rare histological subtype of endometrial cancer, divided into low-grade neuroendocrine carcinoma (carcinoid) and high-grade neuroendocrine carcinoma (small cell and large cell neuroendocrine carcinoma). It is characterized by high invasiveness and poor prognosis. L/SCNEC is an extremely rare pathological type of endometrial carcinoma, and the number of reports on this condition is few globally.

Patient concerns: A 54-year-old Chinese female presented with vaginal bleeding.

Diagnoses: Outpatient hysteroscopy and endometrial biopsy were performed, and the pathological examination revealed that cervix was invaded by endometrial malignancy. The patient underwent a laparoscopic radical hysterectomy was diagnosed with the mixed large and small cell neuroendocrine carcinoma (L/SCNEC) of the endometrium combined with serous carcinoma III C2 (FIGO2009).

Interventions: Chemotherapy-radiotherapy-chemotherapy "sandwich" treatment was performed as postoperative therapy.

Outcomes: After three chemotherapy circles, the patient showed no evidence of further disease progression.

Lessons: L/SCNEC is a rare and invasive disease. Once diagnosed, comprehensive treatments including surgery, radiotherapy, and chemotherapy can prolong the survival of patients and improve the prognosis.

Abbreviations: FIGO = International Federation of Obstetrics and Gynecology, L/SCNEC = the mixed large and small cell neuroendocrine carcinoma, NECE = endometrial neuroendocrine carcinoma.

Keywords: clinical pathology, endometrial cancer, neuroendocrine carcinoma, treatment

1. Introduction

Endometrial neuroendocrine carcinoma (NECE) is a rare histological type of endometrial cancer, presenting with high invasiveness and poor prognosis. At diagnosis, most of the cases are at advanced disease state without specific clinical manifestations. Although majority of patients visit the doctor for vaginal bleeding, a small number of patients seek medical help for paraneoplastic syndrome (such as retinopathy, Cushing's syndrome). However, postoperative pathological examination confirms that the patients have neuroendocrine carcinoma of the endometrium.[1]

According to the WHO 2014 classification criteria, NECE is classified into low-grade neuroendocrine carcinoma (carcinoid) and high-grade neuroendocrine carcinoma (small cell and large cell neuroendocrine carcinoma), which is similar to the neuroendocrine carcinoma of the gastrointestinal tract.[2] The mixed large and small cell neuroendocrine carcinoma (L/SCNEC) of the endometrium is extremely rare. Herein we present a 54-year-old patient diagnosed with L/SCNEC with serous carcinoma showing extensive tumor metastasis which has spread to the cervical stroma, and retrospect 7 cases of L/SCNEC reported in literature (Table 1).

This report is the first retrospective report on L/SCNEC, which is likely to serve as a reference for the relevant clinical treatments and diagnosis of this condition.

2. Case report

A 54-year-old female visited our hospital on July 21st, 2018 for "irregular vaginal bleeding for more than 4 months." Color ultrasonic examination showed an endometrial mass of 33*38*31 mm in dimension (Fig. 1A). The cervix was 28 mm long, and a low echo group showed 15*14*12 mm in dimension. The patient underwent hysteroscopy at the outpatient service on

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Table 1

Reported cases of the mixed large and small cell neuroendocrine carcinoma of the endometrium.

Case	Years	Author	Age	Symptoms	Surgery	Stage	Pathology	Further treatment	Follow-up
1	2008	Mulvany[15]	88	Bleeding	HystBSO + LN	IIIC	L/SCNEC + EC	RT	AWD
2	2016	Pocrnich[5]	65	Bleeding	HystBSO + LN	IA	L/SCNEC + EC	RT	DOD, 9 mo
3	2016	Pocrnich[5]	68	Bleeding	HystBSO	IIIA	L/SCNEC + EC	CCRT	NED, 24 mo
4	2016	Pocrnich[5]	68	Bleeding	HystBSO + LN + App	IIIB	L/SCNEC + EC + CCC	CCRT	DOD, 13 mo
5	2016	Pocrnich[5]	87	Bleeding	HystBSO + Obx	IVB	L/SCNEC + EC	CT	DOD, 21 mo
6	2016	Pocrnich[5]	55	Bleeding abdominal pain	HystBSO + App + STbx	IVB	L/SCNEC	NA	DOD, 3 mo
7	2016	Pocrnich[5]	37	Bleeding	HystBSO + Obx + pbx	IVB	L/SCNEC	CT	DOD, 2 mo
Current 2018			54	Bleeding	LRH + BSO + LN	IIIC2	L/SCNEC + SCA	CCRT	AWD

App = appendectomy, AWD = alive with disease, CCRT = concurrent chemoradiotherapy, CCC = clear cell carcinoma, CT = chemotherapy, DOD = died of disease, EC = endometrial carcinoma, HystBSO = hysterectomy with bilateral salpingo-oophorectom, LN = lymph node dissection, LRT = laparoscopic radical hysterectomy, L/SCNEC = the mixed large and small cell neuroendocrine carcinoma, NA = not available, NED = no evidence of disease, Obx = omental biopsy, pbx = peritoneal biopsy, RT = radiation therapy, SCA = serous carcinoma, STbx soft tissue biopsy.

August 6th, 2018. The posterior wall of uterus endometrium was significantly thickened and the surface had atypical blood vessels (Fig. 1B). After a week the endometrial curettage pathological reports presented that there were cervical and endometrial malignant tumors. Therefore, the patient was admitted to our hospital with a malignant tumor of endometrium. Tumor markers carbohydrate antigens 125 and human epididymis protein 4 were in normal ranges and cervical exfoliative cytology examination showed that there were no intraepithelial lesions or malignant lesions.

Gynecological examination displayed a barrel-shaped enlargement of the cervix in the smooth and hard nature, and the uterus was in the posterior position. The anterior wall of the uterus can touch the hard nodules, with poor activity and no tenderness. According to the hysteroscopy and the pathological results, the patient was diagnosed with endometrial carcinoma which had invaded the cervix.

Therefore, the laparoscopic surgical staging of endometrial cancer was performed under general anesthesia on 21st August, 2018. The intraoperative exploration revealed that the uterus was in the middle of the pelvic cavity and enlarged as the size of 50 days of pregnancy with a smooth surface. The appearance of the bilateral oviduct and ovary, and the main ligament were normal, no tumor was seen on the peritoneum, and omentum intestinal surface. There were no abnormalities in the pelvic and abdominal aortic lymph nodes. Abdominal lavage cytology, laparoscopic radical hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy were performed.

The sectional specimen illustrated that intrauterine solid tumor of posterior uterine wall protruding from the muscle wall to uterine cavity was 3 cm in diameter, and slightly brittle in texture and pale in color. Cervical isthmus intermural tumor was detected with a diameter of 2 cm and no brittle texture but appeared grayish white, involving the cervical stroma. There was no lesion in the vaginal fornix. The appearance of the bilateral attachments was normal, and the lymph nodes were not significantly enlarged.

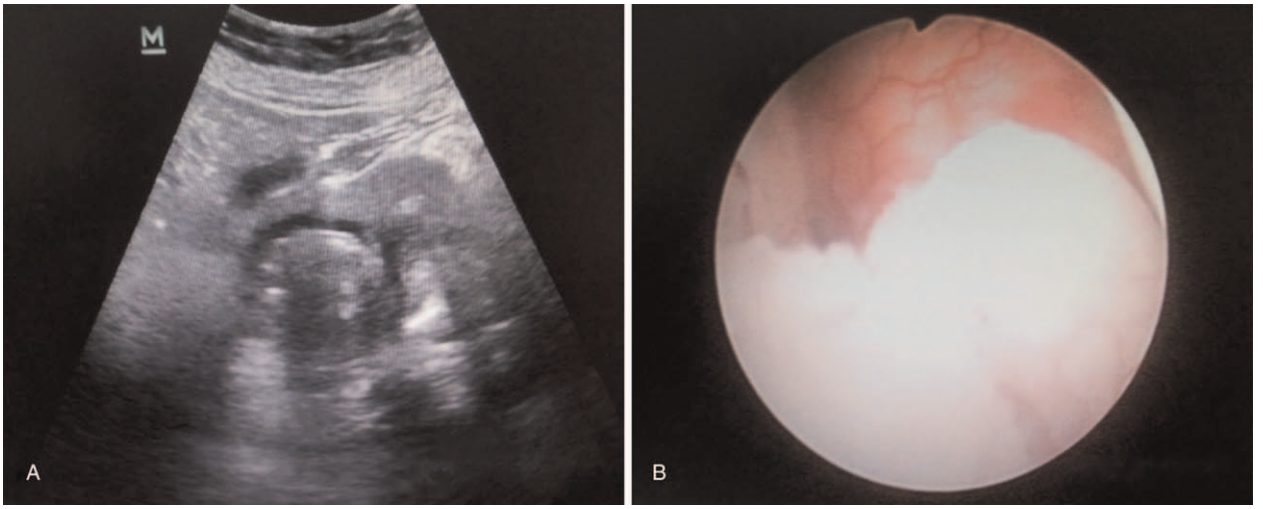

Figure 1. Color ultrasonic examination (A) shows an endometrial mass of 33*38*31 mm in dimension. Hysteroscopy (B) shows the posterior wall of uterus endometrium was significantly thickened and the surface had atypical blood vessels.

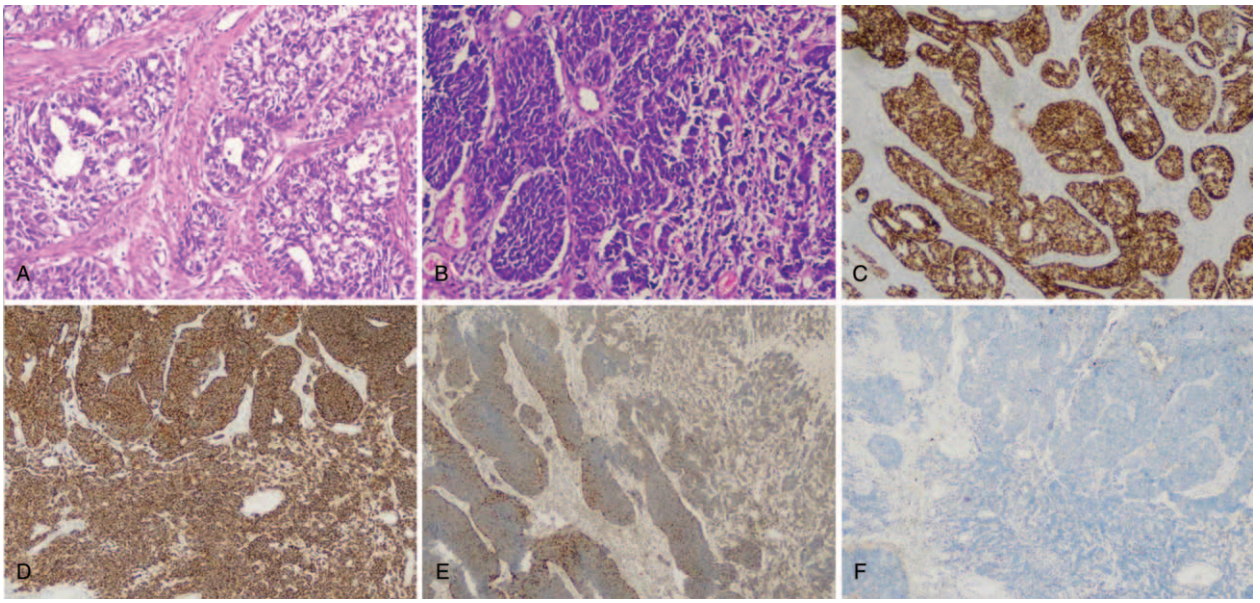

Figure 2. Histological findings of endometrium. (A) High-grade serous carcinoma has an infiltrated growth pattern in myometrial muscle. The neoplastic cells are arranged in nesting, glandular, and ethmoid, with abundant cytoplasm, partial eosinophilic, large nucleus, obvious heterogeneity, and prominent nucleolus. H&E ×100 (B) Neuroendocrine carcinoma is arranged in trabeculae and islands. The tumor cells are large with rich cytoplasm, and the nucleus is pleomorphic, arranged in a mosaic, and the nucleolus is obvious. H&E ×100 (C) The adenocarcinoma manifested positive for PAX-8. (D) Synaptophysin immunolabeling of neuroendocrine carcinoma. (E) Chromogranin A immunolabeling of neuroendocrine carcinoma. (F) Negative immunohistochemical stains for PAX-8 in neuroendocrine carcinoma.

3. Pathological outcome

Tumor cells were not detected in the peritoneal lavage fluid.

The endometrium had mixed adeno-neuroendocrine carcinoma in which serosal carcinoma (Fig. 2A) accounts for about 20% and high-grade neuroendocrine cancer (Fig. 2B) accounts for about 80%. Metastasis of carcinoma was found in lymph nodes adjacent to abdominal aorta and pelvic lymph nodes. Neuroendocrine carcinoma was observed in the right ovary, and the bilateral oviduct and left ovary displayed negative reaction.

Immunohistochemistry demonstrated positive results as follows: P16, P53 mutation, CK broad-spectrum, Villin, and Ki-67 greater than 80%. CDX-2, CK20, estrogen receptor, progesterone receptor were all negative. The adenocarcinoma manifested tested positive for CK7 and PAX-8 (Fig. 2C). Neuroendocrine carcinoma tested positive for Synaptophysin (Syn) (Fig. 2D), chromogranin A (CgA) (Fig. 2E), CD56, and CK7 was weakly positive, while PAX-8 was negative (Fig. 2F). According to the stage revision of FIGO 2009 endometrial carcinoma, high-grade neuroendocrine carcinoma of the endometrium with serous carcinoma was diagnosed as stage III C2.

This patient was administrated with adjuvant chemotherapy after radical operation with cisplatin and etoposide over a 3-week interval, and she was put on the chemotherapy- radiotherapy-chemotherapy "sandwich" therapy. During the first chemotherapy circle, the patient developed nausea and vomiting with grade 2 and bone marrow suppression with grade 4 according to CTCAE Version 5.0. We reduced the dose of etoposide in the subsequent chemotherapy cycle. After 3 circles of chemotherapy, she received radiotherapy and displayed no evidence of further disease progression. According to the RECIST1.1 criteria, the patient achieved a complete response. We plan to follow up the patient for 5 years. The follow-up schedule includes chest, abdominal, and pelvic computed tomography scanning and pelvic examination every 3 to 6 months in the first 3 years, and every 6 to 12 months from 4 to 5 years. If metastasis is suspected, an imaging examination will be chosen based on the symptoms.

4. Discussion

According to the WHO classification criteria for 2014, neuroendocrine carcinoma of the endometrium is classified into low-grade carcinoid and high-grade small-cell and large-cell neuroendocrine carcinoma.[2] Endometrial high-grade neuroendocrine carcinoma is a rare histological type of endometrial carcinoma, accounting for 1% of all endometrial cancers.[3] In this case, L/SCNEC combined with serous carcinoma (adenocarcinoma component is consistent with serous carcinoma, accounting for about 20%; neuroendocrine cancer shows the existence of high-grade neuroendocrine carcinoma, accounting for about 80%; the microscopic shows large cells accounting for about 70%, and small cells accounting for about 30%) is presented. Clinically, it is extremely rare. So far, 7 reports of such tumors were identified on the PubMed as shown in Table 1.

The average onset age of endometrial cancer is 60 years, of which 75% occurs in women over 50, and about 90% of patients with endometrial cancer have vaginal bleeding, especially after menopause.[4] The onset age of NECE is wide, ranging from 37 to 87, the median age is 57, and the most common onset age is from 60 to 70.[5] The mean age of patients is 60 years and the main complaint is abnormal genital bleeding, similar to other endometrial carcinomas.[6] Notably, NECE is more common in older postmenopausal women. The most common clinical manifestation of NECE is abnormal vaginal bleeding, but there are 2 cases of Cushing's syndrome,[7,8] 4 cases of retinopathy,[9–12] and 1 case of lower abdominal pain, weight loss, and abnormal symptoms of vaginal drainage.[13] For patients presenting with paraneoplastic syndrome, the

possibility of NECE should be tested. The average age of this retrospective case is 65 years old. Eight patients had abnormal vaginal bleeding and 1 patient had symptoms of lower abdominal pain (Case 6). No paraneoplastic syndrome was found.

About 70% cases of endometrial cancer are restricted to the uterus without a clear uterine enlargement and a positive pelvic examination.[4] Stage is a key prognostic factor for endometrial cancer. However, the stage is not an important prognostic factor for NECE because patient data is limited, and NECE is mostly diagnosed at the advanced course of the disease.[14] We found that 7 patients with L/SCNEC were at advanced (stage IIIA-IVB) and only 1 patient was at stage IA (Case 2) (Table 1).

Based on clinical pathology, large cell neuroendocrine carcinoma (LCNEC) is defined as a large cell expressing the neuroendocrine markers, CgA, Syn and neural cell adhesion molecule (CD56).[15] The morphology of LCNEC is similar to that of small cell lung cancer and large cell carcinoma, and about half of the cases present with the endometrioid adenocarcinoma component and carcinosarcoma.[16] Many LCNECs are misdiagnosed as carcinosarcoma, especially in cases with high-grade tumor components of small cells. The diagnosis of SCNEC requires at least 1 positive neuroendocrine marker: CgA, neuron-specific enolase, Syn or CD56.[13,17] Immunohistochemical results of the L/SCNEC of the endometrium are listed in Table 2. This case series show that CgA and Syn are positive in most NECEs. This is consistent with previous studies. The immunohistochemical staining results of the patient in this report show positive tests for CgA, Syn and CD56. Combined with microscopic morphological findings, the patient was diagnosed with L/SCNEC and serous carcinoma. This diagnosis was confirmed by pathologist.

In many reports, the most common mixed histological type of NECE is endometrial adenocarcinoma, with endometrioid carcinoma being the most common, followed by serous carcinoma, and pure NECE is rare.[14–20] In the retrospective cases, 4 cases were mixed with endometrioid carcinoma (Case 1, Case 2, Case 3, Case 5), 1 case had mixed clear cell carcinoma (Case 4), and only 2 cases had pure small cell neuroendocrine carcinoma (Case 6 and Case 7). The patient in this case report had L/SCNEC with serous carcinoma, which further confirms that most NECEs are mixed with other histological types, and the pure type is relatively rare.

Due to the rarity of NECE and the lack of prospective data to guide treatment, there is no standard treatment guideline for such tumors, and its treatment is based on the traditional treatments of endometrial and small cell lung cancer, like surgical resection, radiation therapy, and chemotherapy.[17,19] Unless the patient wishes to preserve her fertility, the main treatment for endometrial cancer is panhysterectomy, bilateral salpingo-oophorectomy with lymph node assessment, and adjuvant treatment is given by considering the risk factors of recurrence after surgical treatment.[4]

All 8 patients were reported to have undergone a panhysterectomy, bilateral salpingo-oophorectomy, with/without lymph node assessment. Three patients had stage IVB, and 1 patient who was the youngest (37 years old) underwent radical surgery and died after 2 months of adjuvant chemotherapy. One patient who was not given adjuvant treatment died after 3 months. One patient with combined endometrioid carcinoma received adjuvant chemotherapy but died after 21 months, and was 1 of 3 patients with a survival time longer than 12 months. One patient with stage IA who underwent radiotherapy lived for 9 months. The patient with the longest survival time received concurrent chemoradiotherapy after radical surgery, up to 24 months.

It should be noted that endometrial-sized mixed-cell neuroendocrine carcinoma has a high degree of malignancy, short survival time, and poor prognosis. Surgery combined with chemoradiotherapy prolongs the survival time of patients.[21] Therefore, the patient in this case report is given the above treatment in which chemotherapy-radiotherapy-chemotherapy "sandwich" treatment was administrated after radical therapy with the expectation that it can achieve the optimal disease control.

In conclusion, L/SCNEC with serous carcinoma of the endometrium is highly malignant and has a poorer prognosis compared to pure carcinoma. Neuroendocrine carcinoma is more aggressive, with most patients dying within 1 to 2 years. Comprehensive treatment including surgery, radiotherapy, and chemotherapy can improve the prognosis of patients and prolong overall survival. However, such tumors are clinically rare and there is limited evidence to support our views. Therefore, more samples are required to confirm the present findings. Designing an effective therapy protocol through investigations and analysis of reported cases is of high necessity.

Table 2

Summary of immunohistochemical staining.

Case no.	Syn	CgA	CD56	P16	Pax-8	CK18
1	−	+	+	−	−	−
2	+	+	+	+	+	+
3	+	+	+	+	−	−
4	+	−	−	+	+	+
5	+	−	−	−	+	+
6	+	+	+	+	−	+
7	+	+	−	−	−	−
Current	+	+	+	+	+	−

CgA = chromogranin A, Syn = synaptophysin.
−, not performed; −, negative; +, positive.

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