Int J Clin Exp Med 2018;11(4):4232-4236
www.ijcem.com /ISSN:1940-5901/IJCEM0061745

Case Report

Primary pure large cell neuroendocrine tumor of the whole uterus: a rare case report

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Received May 19, 2017; Accepted February 6, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: In recent years, the incidence of uterus large cell neuroendocrine carcinoma (LCNEC) is rare. Some cases have been reported about LCNEC of cervix, endometrial, mesometrium or ovary. Here we reported a 74-year-old female patient who suffered from large cell neuroendocrine tumors invaded the greatest dimensions of nearly the whole genital tract just except vagina and fallopian tubes and infiltrated the full thickness wall of the uterus. The patient sought medical advice just because of recurrent swelling abdominal pain and we were surprised to find the huge tumor in her uterus. On pathologic staging, Stage IIIC LCNEC with pelvic and para-aortic lymph nodes disseminated was diagnosed and systemic treatment for example chemotherapy might be taken to improve her survival according to the Guide. But her family refused chemotherapy because of her old age. AS LCNEC is a kind of widespread malignancy and it usually presents rapid progression and high mortality, the patient finally died of multiple pulmonary metastases less than 2 months after the operation, confirming highly aggressive behavior of LCNEC.

Keywords: Large cell neuroendocrine tumor, uterus, case report

Introduction

LCNEC is a kind of invasive malignancy showing early metastasis, rapid progression and high relapse rate. The WHO defines this kind of carcinoma as an undifferentiated one with cellular and nuclear features, which consists of large-sized cells, hyperchromatic, fine granular and molded nuclei [1]. More simply, LCNEC is defined as malignant tumor composed of large cells that show neuroendocrine differentiation [2]. Although the cytological abnormality can aid, the pathologic examination depended on immunohistochemical theory is the main method for the diagnosis [1, 3, 4] and the prognosis now still need to be improved in the early stage for systemic treatment. There is no unified therapy at present, but operation using radiotherapy and chemotherapy can improve the performance of survival [5].

LCNEC often attacks woman who is perimenopausal or postmenopausal, and the major clinical performances include irregular vaginal bleeding, pelvic masses and lower abdomen pains, easy shifts to the bone, lung, brain, liver etc [4, 6].

Materials and methods

The tissue specimens were routinely fixed in 10% buffered formalin, embedded in paraffin, and serially sectioned into 5-μm-thick sections. Sections were stained with hematoxylin and eosin for routine histological examination. Additional immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue sections. The primary antibodies used in this study were shown in the **Table 1**.

Clinical history

A 74-year-old female was admitted to our department on July 25th 2016 with recurrent swelling abdominal pain without irregular vaginal bleeding for nearly one month. The patient's past medical history was remarkable only for hypertension which can be controlled by nifedipine release tablets. Her family history was negative for malignancy and any other diseases. Menstrual period was regular from age 12.

Table 1. Immunohistochemisty on large cell neuroendocrine tumor

Antigens	Antibodies (clone)	Source	Result
Chromogranin	DAK-A3	DAKO	+++
Synaptophysin	Polyconal	DAKO	+++
CD56	UJ13A	DAKO	+++

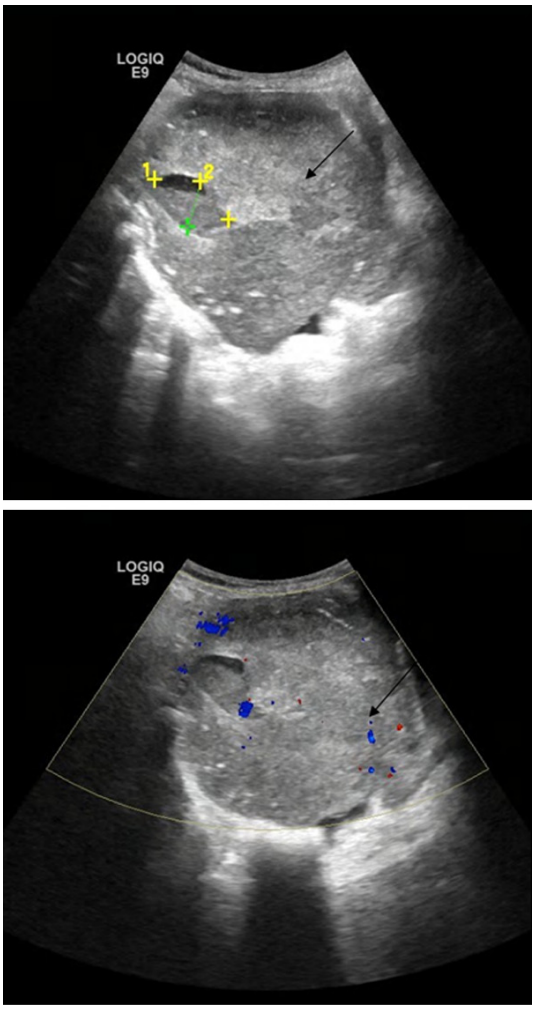

Figure 1. Gynecological ultrasound revealed a solitary pelvic mass without normal uterus and adnexa.

Getting married on age 25, she was fertile with one odinopoeia and one abactio. On abdominal examination, a firm and irregular mass was felt occupying the suprapubic region with restricted mobility thus gently touch might lead to hypogastralgia. Gynecologic examination as below: vulva presented senile atrophy; vagina was unobstructed with little discharge and without ensanguine; cervix was atrophy and smooth, with mild pendulum pain.

Other physical examinations were essentially normal. Hematologic work-up revealed red blood count 4.80 × 10^{12}/L; leukocyte count, 6.0 × 10^{9}/L; platelet count, 293 × 10^{9}/L. Normal urine routine test and stool routine test. Normal even the levels of the majority of the tumor markers: Carcinoembryonic antigen (CEA), cancer antigen (CA)125 and CA199. Electrocardiogram and cardiac ultrasound were unremarkable. Chest X-ray, superficial lymph node, urologic and digestive system ultrasound were taken pre-operation and denied distant metastasis. A gynecological ultrasound revealed a solitary pelvic mass without normal uterus and adnexa (**Figure 1**). Pelvis magnetic resonance imaging (MRI) confirmed a 12 cm × 11 cm × 10 cm mass with obscure boundary in pelvic cavity (**Figure 2**). Preoperative diagnosis was double with gynecologist sarcoma and designed as stage IIIA according to the international Federation of Gynecology and Obstetrics (FIGO) staging.

A debulking operation was optimally performed, which included total abdominal hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymph nodes dissection on July 29th, 2016. During the operation, we saw the increscent uterus without pelvic sanguis; synechia of intestines and posterior uterine but that can be bluntly dissected; irregular and tuberculous surface and earthworm change of the blood vessel; brittle fallopian tubes; atrophic and off-white ovaries; pelvic and para-aortic enlarge lymph node with diameter 0.5-1.0 cm. Abnormal nodules were undiscovered on the surface of peritoneum, intestinal tube, omentum majus, liver, gall bladder, pancreas, spleen and kidney during the operation. Surgical margins were free of tumor.

The frozen section showed a uterine mass about 15 × 11 × 9 cm and the tissue was polypoid (**Figure 3**). On pathologic staging, Stage IIIC LCNEC with pelvic and para-aortic lymph node disseminated was diagnosed. Microscopic examination showed abundant cytoplasm, some of which contained eosinophilic granules. Cells were arranged in an insular and trabecular pattern. Nuclear fission was salient. Pelvic and para-aortic lymph nodes were violated. The uterine mass showed a malignant tumor composed of large round to oval cells and features of neuroendocrine differentiation (nesting, tra-

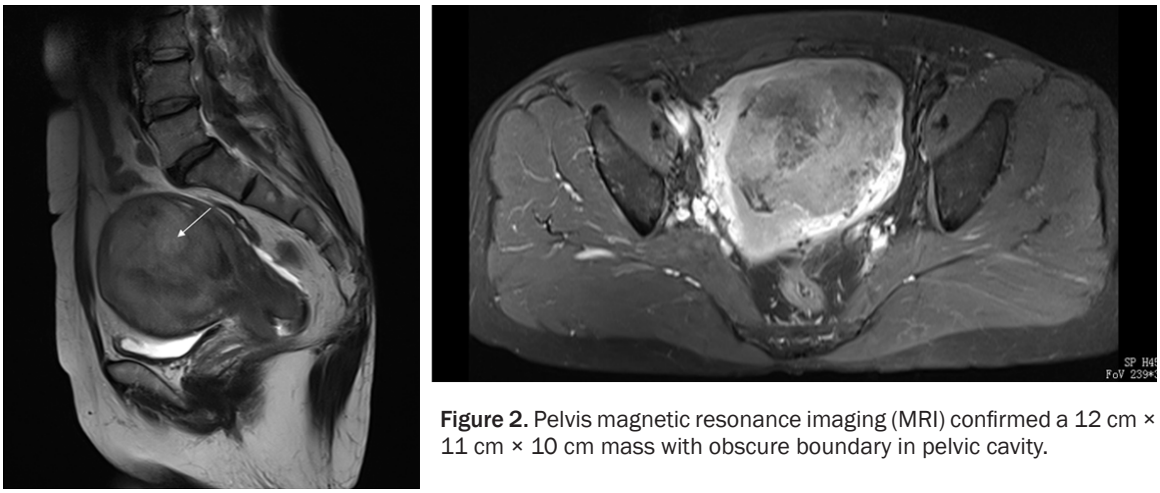

Figure 2. Pelvis magnetic resonance imaging (MRI) confirmed a 12 cm × 11 cm × 10 cm mass with obscure boundary in pelvic cavity.

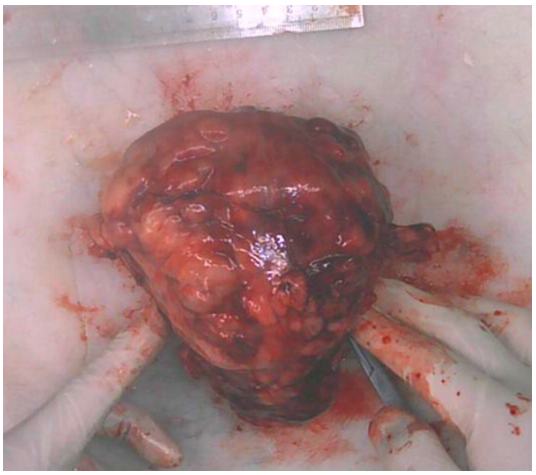

Figure 3. The uterine mass of 15 × 11 × 9 cm and the tissue was polypoid.

beculae, rosettes, pseudorosette and palisading). The cytoplasm was eosinophilic to pale. The Nuclei was hyperchromatic and pleomorphism with brisk mitotic activity that abundant with the average count of 36 mitoses/10 HPFs (**Figure 4A**, **4B**). In addition, the pathomorphology showed large cell neuroendocrine carcinoma invading cervix, endometrium, perimetrium, myometrium and bilateral ovaries. Fortunately the fallopian tubes escaped. Immunohistochemistry showed diffusely positive for markers CD56 (**Figure 4C**, **4D**), chromogranin A (CgA) (**Figure 4E**, **4F**) and synaptophysin (Syn) (**Figure 4G**, **4H**) and negative for CD3, CD20, CD21, Bcl-6, MUM-1, CD10, Bcl-2, HMB45, CD79a, CD38, CD138, CK-P, SMA, CD163, desmin and Vimentin. Ki-67 proliferative index was 80%.

Discussion

Large cell neuroendocrine carcinoma (LCNEC) was originally defined in the lung and subsequently adopted into the WHO classification of lung tumors [7]. In the near decades, reports have revealed that LCNEC also arises in extrapulmonary sites like female genital tract. To our knowledge, the current case is first reported with the most widely scope of the malignant infringement in the database.

LCNEC of female genital tract is a kind of aggressive and rare tumor, which has gradually increased morbidity in recent years. Its prognosis is generally very poor even when the diagnosis is made at an early stage. Some cases have been reported about LCNEC of the cervix [3, 5, 8-13], ovary [6, 14] and endometrium [15, 16]. This extremely rare clinical presents a huge mass arising from the uterus of a 74-year-old female. It involved nearly the whole genital tract just except vagina and fallopian tube. Grossly, the uterine was dilated and showed a 15 cm huge tumor in the greatest dimensions infiltrating the full thickness wall of the uterus and involving the cervix and bilateral ovaries. Fallopian tubes and omentum were free of metastasis. The mass owned the neuroendocrine features of positive immunohistochemical markers, such as chromogranin, synaptophysin and CD56 and high Ki-67 labeling. Maybe initially germ cell somewhere in the uterus made tumor mulifocality and the pessimistic stage. It is possible that the tumor started on the cervix or the endometrium, the ovary

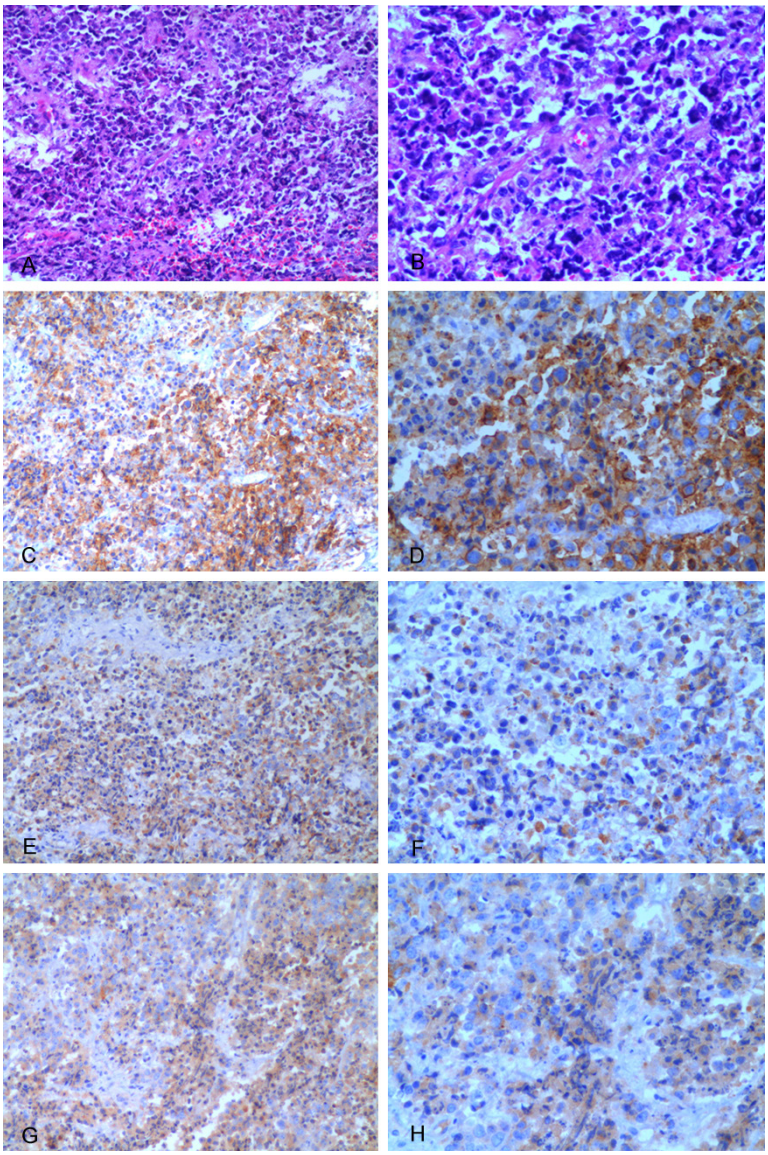

Figure 4. (A, B) Hematoxylin and eosin (H and E) stained section shows diffused tumor cells displaying characteristics of LCNEC: large round to oval cells, abundant cytoplasm, arranged in an insular and trabecular pattern and nuclear fission. (A: × 10; B: × 20); (C, D) Large cell neuroendocrine carcinoma cells were strongly positive for CD56 (Immunohistochemical stain) (C: × 10; D: × 20); (E, F) Large cell neuroendocrine carcinoma cells were strongly positive for chromogranin A (Immunohistochemical stain) (E: × 10; F: × 20); (G, H) Large cell neuroendocrine carcinoma cells were strongly positive for synaptophysin (Immunohistochemical st ain) (G: × 10; H: × 20).

and quickly spread to the near tissues. Nevertheless, it's out of our ability to reach the dinkum oil.

The incidence of pure large cell neuroendocrine carcinoma (LCNEC) of uterus is very rare. It often attacks perimenopausal or postmenopausal women with a mean age of 60 years. Abnormal uterine bleeding is the most frequent initial complaint [17], but in this report is exceptional. Histologically, they can be admixed with endometrioid adenocarcinoma, or a component of a malignant mixed mullerian tumor [3, 18]. The invasive component is generally the neuroendocrine carcinoma. Deep myometrial invasion, metastasis to distant organs, and decreased survival appear to be the features of neuroendocrine while necrosis, vesicular nuclei, frequent mitotic figures and apoptotic bodies are microscopic characteristic. The diagnosis is confirmed by immunohistochemical staining of diffuse positivity for neuroendocrine markers synaptophysin, chromogranin, CD56 [1, 3, 4, 19].

Though there is no unified therapy for uterus LCNEC at present, even for early stage disease, the conventionally treatment in a multimodal fashion including pelvic lymphadenectomy, radical hysterectomy and adjuvant chemotherapy is highly recommended, due to the aggressive nature of neuroendocrine tumour. Of the various factors, stage can be observed to be the most significant predictive one, followed by tumor volume, the invasive scope and muscular layer depth, old age, gender. The presence of lymph node metastasis is the most important negative prognostic factor with advanced stage [16]. In this case, pelvic and para-aortic lymph node as well as bilateral accessories disseminated made the diagnosis of stage IIIC. What's more, it's a huge tumor in the greatest dimensions infiltrating the full thickness wall of the uterus attacked a 74 year-old patient who refused postoperative treatment, thereby, multiple pulmonary metastasis has took place in a short time and threatened her life in further treatment stage.

In summary, the author reported an extremely rare case of pure uterus large cell neuroendocrine tumor of stage IIIC (FIGO stage) with pelvic and para-aortic lymph node as well as bilateral accessories disseminated.

Acknowledgements

We acknowledge the work of our team and the cooperation of the patient.

Disclosure of conflict of interest

None.

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