Primary pure large cell neuroendocrine carcinoma of the ovary
A rare case report and review of literature
Xue Peng, MM1, Hongjing Wang, MD, PhD2

Abstract
Introduction: Ovarian large cell neuroendocrine carcinoma (LCNEC), or ovarian non-small cell neuroendocrine carcinoma, which is a newly described tumor in the classification of primary ovarian neoplasms by the World Health Organization, is a rare entity that is frequently associated with a surface epithelial and germ cell neoplasm component. Few cases have been reported in the literature, and only 18 primary pure ovarian LCNEC cases have been reported so far, including our 1 case. Ovarian LCNEC is a highly aggressive tumor with a poor prognosis even at an early stage.

Patient concerns: We report a case of a 55-year-old postmenopausal woman who complained of abdominal pain. CT examination revealed a mass in the right adnexial region and CA125 level was elevated.

Diagnosis: She underwent an exploratory laparotomy, and diagnosed as LCNEC histopathologically.

Interventions: Cytoreductive surgery was administered to the patient, and had accepted 5 cycles of chemotherapy consisting of paclitaxel and cisplatin.

Outcomes: Follow-up for 12 months showed no clinical or radiological evidence of disease recurrence.

Conclusion: This case is 1 of the ovarian LCNEC which is a rare and extremely malignant tumor. Diagnosis requires histopathology and immunohistochemistry. The treatment includes primary cytoreductive surgery followed by chemotherapy.

Abbreviations: APUD = amine precursor uptake and decarboxylation, CKs = cytokeratins, IHC = immunohistochemistry, LCNEC = large cell neuroendocrine carcinoma, NSE = neuron-specific enolase.

Keywords: clinical characteristics, large cell neuroendocrine carcinoma, ovary, pathology, prognosis

1. Introduction

Neuroendocrine tumors are a group of tumors that originate from amine precursor uptake and decarboxylation (APUD) cells, which generally occurs in the digestive system and lung. Primary and secondary gynecologic neuroendocrine tumors are both uncommon, accounting for only 2% of gynecologic tumors.[1]

Ovarian large cell neuroendocrine carcinoma (LCNEC) is synonymous with ovarian NSCNE,[2] which is a newly described tumor in the classification of primary ovarian neoplasms according to the World Health Organization (2003).[3] It can be divided into 2 types, one is pure which only contains LCNEC, another is mixed which compose with surface epithelial or germ cell neoplasm. Since Collins[4] reported the first case of ovarian LCNEC in 1991, only a total of 60 cases have been reported in the literature so far, including our 1 case, and all were case reports. Moreover literature reports is mixed more, pure only 17 cases, ours for 18 cases.

Ovarian LCNEC is a highly aggressive tumor with a poor prognosis even at an early stage. Due to the rarity of the disease and the lack of systematic population-based studies or registration data, there is hitherto no consensus on the optimal treatment.

We report a case of recent encounter of pure ovarian LCNEC, and summarize the clinicopathological features with a literature, so as to deepen the recognition of this disease.

2. Case presentation

A 55 year old, gravida 2, parity 1, postmenopausal woman complained of abdominal pain, and used of antibiotics but not effective self-intermittent a month ago, she had no chest tightness, cough, hemoptysis, hematochezia and other symptoms. A CT examination revealed that a irregular, poorly circumscribed, cystic and solid mass was felt occupying the right adnexial region measuring 7 × 6 × 6 cm with ovarian vascular pedicle sign. In
addition, multiple pelvic lymph node enlargement was shown. Her CA125 level was elevated to 443.6U/ml, and Pap cervical cancer screening was normal. Gastroscopy and chest X-ray were within normal limits. A exploratory laparotomy was carried out and 200 ml of bloody ascitic fluid was drained. Laparotomy demonstrated an irregular and solid mass of the right ovary measuring 8 x 7 x 5 cm, which was dense adhesion with sigmoid colon, rectum, appendix and parietal pelvic wall. Scattered milliary nodules are seen in the abdominal cavity measuring 0.1–0.2 cm in diameter. Multiple right pelvic lymph nodes and para-aortic lymph nodes were enlarged about 2 cm in diameter, and prostrate beside the abdominal aorta and vena cava. A right salpingo-oophorectomy was performed, and intraoperative frozen section showed poorly differentiated carcinoma of the right ovary. Consequently, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, omentectomy, and appendectomy were performed.

2.1. Pathology
The samples displayed a right ovarian tumor measuring 8 x 7 x 5 cm, capsule intact, external surface was irregular and nodular, and its cut section shows a solid, a yellow-white focus and partial old hemorrhage and a massive necrotic area.

2.2. Microscopy
Poorly differentiated malignant tumor-carcinoma were shown in the right ovary. Right fallopian tube, uterine wall and right pelvic lymph nodes showed tumour deposits. When the hematoxylin and eosin stained slides were examined under the microscope, the tumour comprised mostly of solid sheets, islands, or bands formations, less tumor stroma, accompanied by wide areas of necrosis. It had large round to ovoid nuclei, occasionally with prominent nucleoli, coarse chromatin, and frequently showed a high mitotic rate.

2.3. Immunohistochemistry (IHC)
IHC was performed in order to confirm the ultimate histological diagnosis. The tumor cells were positive for P53, P16, CD56, neuron-specific enolase (NSE), with focal staining for cytokeratins (CK)-P. While immunostaining for synaptophysin, WT-1, CK7, CK20, ER, PR, and chromogranin A were negative. Ki67 positive rate is about 85%.

According to the clinical manifestation, histopathological features, and IHC profiles, suggested a final diagnosis of ovarian LCNEC as International Federation of Gynecology and Obstetrics clinical stage III.

The patient recovered well postoperatively, and blood examination of NSE and CA125 gradually decreased (Table 1). Five cycles of postoperative paclitaxel and carboplatin chemotherapy were completed 8 months ago.

Simultaneously, it is recommended the patient with radiation consulting, but did not receive radiotherapy yet. Eleven months after the operation, right inguinal lymph node enlargement was found, with a maximum of 2.8 x 1.1 cm, however, biopsy indicated that it was only lymphatic tissue and adipose fibrous tissue, and tumor markers were also within the normal range. Follow-up for 12 months showed no clinical or radiological evidence of disease recurrence now.

3. Discussion
Neuroendocrine tumors originate from APUD cells, which generally occurs in the digestive system and lung, and also present in normal epithelium of the female genital tract. Several theories have been proposed as to the origin of ovarian LCNEC, including just overgrown from the APUD cells present in epithelial tumors or teratomas, the potential of primitive endodermal cells to differentiate into other cell types. The other possibility is that ovarian LCNEC may develop from non-neuroendocrine cells through activation of genes promoting neuroendocrine differentiation. Ovarian LCNEC is a very rare tumour. To the best of our knowledge, only a total of 60 cases have been reported in the literature, including our 1 case. 42 cases were mixed while 18 cases were pure (Table 2). The present case is the eighteenth case of pure ovarian LCNEC.

It has been reported in the literature that ovarian LCNEC can be developed in premenopausal and postmenopausal women, ranging from 18 to 80 years, while 6–8 years younger than other common types of epithelial ovarian cancers. The age of pure type was ranging between 27 to 77 years and a median age of 41 years. Clinical manifestation is often similar to the presentation of epithelial ovarian cancer at initial presentation. The most common clinical manifestation was abdominal pain and distension in 66.7% (12/18) of cases, similarly to our case. Followed by pelvic mass (3/18), other clinical symptoms were amenorrhea and vaginal bleeding (1/18), dysphonia and difficulties because of the metastasis to the CNS (1/18) and urinary frequency (1/18). One side was more common and no significant difference between left and right, only 2 cases were reported in bilateral ovaries, and 1 case was microscopically involved in contralateral ovaries. Most of the LCNEC are partially solid or cystic, with size ranging from 6 and 35 cm (mean size, 14.53 ± 6.36 cm). In present case was a solid mass with size of 8 cm. The CA125 levels range from 63.4 to 6595 U/ml. Eventhough the level of CA125 usually increase in epithelial ovarian cancers and correlate with cancer stages or responses to treatment, Ki EY et al.

| Table 1 |
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| Tumor marks shown in our case of ovary LCNEC. |

| Stage               | CA125 U/ml (normal: <35) | CA199 U/ml (normal: <30.9) | HE4 pmol/l (normal premenopausal: <70, postmenopausal: <140) | NSE ng/mL (normal: <15) |
|---------------------|--------------------------|-----------------------------|-------------------------------------------------|------------------------|
| preoperative        | 443.6                    | —                           | —                                               | —                      |
| before 1st cc;po    | 175.1/75.9               | 3.7/5.3                     | 29.8                                            | 44.85                  |
| before 2nd cc;po    | 13.2                     | 9.7                         | 30.7                                            | 17.34                  |
| before 3rd cc;po    | —                        | —                           | —                                               | 12.21                  |
| Latest results (8 mo) | 4.2                     | 7.5                         | —                                               | 14.32                  |

*cc* = cycles of chemotherapy, “po” = postoperative. “*” this check is not performed, 1. LCNEC = large cell neuroendocrine carcinoma.
Table 2
Clinicopathologic, treatment modality, tumor markers, and follow-up of reported cases with pure ovarian LCNEC.

| Case (N) | Authors          | Age | Size Dimension, Laterality, gross findings | Stage (FIGO) | clinical manifestation | Tumor markers | Primary operation | Metastases at primary operation | Post-operative therapy (cycles) | Follow-up (time after operation) | complications |
|----------|------------------|-----|--------------------------------------------|--------------|------------------------|---------------|------------------|-----------------------------|-------------------------------|---------------------------------|---------------|
| 1        | Behnam et al. 2004 | 27  | 17 cm, Left, solid and cysts               | Ia           | pelvic mass            | normal        | Resection of ovarian tumor (OBM+PL; right GEPAR) | None | TC(6) | NRM(10 m)                      | None                           |
| 2        | Yasuda et al. 2006 | 44  | 9 cm, Right, solid                        | IIc          | abdominal distension   | CA125 1300 U/ml | TAH; BSO/OMT | unknown | chemotherapy details unknown | DOD(10 m)                     | None                           |
| 3        | Lindroos, 2007    | 64  | 14 cm, Right, solid                       | IIIb         | abdominal discomfort and nausea | CA125 3.0 U/ml; CEA 30 mg/L; (normal < 5) | TAH; BSO/OMT | None | BEP | NRM(9 m)                      | Breast carcinoma               |
| 4        | Veras et al., 2007 | 42  | Laterality and size, unknown, cysts       | IV            | Pelvic pain            | unknown       | TAH; BSO        | unknown | cisplatin-based chemotherapy (at least 6) | DOD(20 m)                     | None                           |
| 5        | Dondi et al. 2009 | 73  | 9 cm, Left, solid                         | IIIc         | metastatic CNS disease, dysuria and difficulties in verbal expression | CA125 2.3 mg/L; CEA 1.1 mg/L | TAH; BSO/OMT | left-sided nephrectomy; mesenterial metastasis resection | TC | CNS recurrence; y kno(2 m); NRM(2 m) | endometrial carcinoma, breast carcinoma |
| 6        | Tsuji et al. 2011 | 46  | 15 cm, Right, solid                       | III           | abdominal distension   | CA125 914 U/ml; LDH 1790 IU/L; (normal < 40); NSE 210 U/mL; (normal < 10) | TAH; BSO/OMT | right-sided pelvic cysts | TC | DOD(4 m) | None                           |
| 7        | Aslam et al. 2009 | 76  | 35 cm, Left, solid and cysts              | II           | abdominal pain         | normal        | TAH; BSO/OMT; APP, PL; PAL; cervical mass | unknown | No | septic shock and died soon before chemotherapy | None                           |
| 8        | Ochiita et al. 2017 | 66  | 11 cm, Right, solid                       | IV            | multiple lung nodules in a chest X-ray, pelvic mass | CA125 6.95 U/ml | TAH; BSO/OMT; APP(3); BC (with 4 sessions before operation) | unknown | No | Right-sided pelvic lymphadenectomy | None                           |
| 9        | Shukunati et al. 2012 | 40  | 7 cm, Left, 15 cm right, solid and cysts | IIIc         | acute abdominal and pain abdomen, fever, itching | CA125 2.88 U/ml; CEA 7.68 U/ml; | TAH; BSO/OMT | left-sided pelvic metastases | TC | CNS recurrence; y kno(2 m); NRM(2 m) | None                           |
| 10       | Lin et al. 2014   | 50  | 25 cm, Left, solid                        | III           | pelvic mass            | CA125 6.85 U/ml | TAH; BSO/OMT | unknown | chemotherapy details unknown | DOD(3 m) | None                           |
| 11       | Li EY et al. 2014 | 77  | 15 cm, Unknown, solid                     | III           | abdominal distension   | CA125 13.4 U/ml | TAH; BSO/OMT | unknown | neck LN | EP | septic shock and died 1.5 m | coronary artery disease |
| 12       | Unknown, Left, unknown | 58  | abdominal discomfort                      | Ia           | pelvic mass            | unknown       | TAH; BSO/OMT | left-sided PAL | unknown | first TC(3); second TC(2); recurrent, died 7.2 m | None                           |
| 13       | Unknown, Left, unknown | 67  | abdominal discomfort                      | II           | urinary frequency       | CA125 7.81 U/ml | TAH; BSO/OMT; APP(2); PL; bilateral pelvic mass | TC | NRM(5 m) | None                           |
| 14       | Agnani et al. 2016 | 35  | 6 cm, Left, solid and cysts               | III           | Abdominal pain, anorexia, vaginal bleeding | CA125 and CEA were raised | TAH; BSO/OMT | PL; multiple biopsy | TC | NRM(3 m) | None                           |
| 15       | Heral et al. 2016 | 75  | 13 cm, Right, solid                       | IV            | pelvic mass            | CA125 63.4 U/ml | BSO/OMT; APP; PL; cervical mass; TAH | liver | EP(2) + TC(3) | NER(16 m) | breast cancer                 |
| 16       | Dogra et al. 2016 | 73  | 10 cm, Right, solid                       | III          | pelvic pain            | normal        | TAH; BSO/OMT; pelvic masses | unknown | Surface of the omentum; partial peritoneum; pelvic area; right fallopian tube; right LN | TCO(3) | NER(3 m) | None                           |
| 17       | Yang X et al. 2019 | 70  | 20 cm, Right, solid                       | II           | abdominal pain         | CA125 3.467 U/ml; NSE 24.83 ng/ml | TAH; BSO/OMT | pelvic masses | unknown | EP(3) | NRM(4 m) | None                           |
| 18       | Present case      | 55  | 8 cm, Right, solid                        | III           | abdominal pain         | CA125 4.43 U/ml | TAH; BSO/OMT; APP PL | right-sided pelvic mass; right LN | TCO(3) | NER(3 m) | None                           |

**APP** = Appendectomy, **AWD** = alive with disease, **BEP** = bleomycin, **cis-platin** and **etopside**, **BSO** = bilateral salpingo-oophorectomy, **DOD** = dead of disease, **EP** = etopside and cis-platin, **FIGO** = International Federation of Gynecology and Obstetrics, **LN** = lymph nodes, **LSO** = Left salpingo-oophorectomy, **M** = month(s), **NRM** = no recurrence or metastases, **OB** = ovariectomy, **OMT** = Omentectomy, **PAL** = para-aortic lymph node dissection, **PB** = pelvic lymphadenectomy, **R** = partial biopsy, **PL** = Pelvic lymphadenectomy, **SO** = right salpingo-oophorectomy, **TAH** = total hysterectomy, **TC** = paclitaxel and carboplatin.
have reported that the CA125 levels are not specific to clinical courses in ovarian LCNEC. Other tumor markers including CEA, NAE, and so on may rise but not specific. Ovarian LCNEC metastasis in the pelvis and peritoneal cavity is common, while lung, brain and bone are relatively rare.\cite{10,22} Cokmen et al.\cite{23} first reported a case of ovarian LCNEC skin metastasis in the extremities 2 months after operation.

Clinically, LCNEC should be differentiated from primary or metastatic carcinoid tumor, small cell carcinoma of pulmonary type and hypercalcemic type, undifferentiated ovarian carcinoma and metastatic neuroendocrine carcinoma (Table 3). Under light microscopy, the tumour comprised mostly of solid, sheets, islands, or bands patterns, occasionally with focal necrosis. The tumour cells were large and had large round to ovoid nuclei with coarse chromatin and numerous mitoses, typically have abundant eosinophilic cytoplasm that may be granular. It is difficult to diagnose LCNEC in ovary not only because of its clinical symptoms, CA125 level and lack of specific tumor markers, such as NSE, chromogranin A, and synaptophysin, CD56, and various CKs.\cite{3} The presented case also showed positive immunoreactivity to CD56 and NSE but negative for the epithelial markers CK7 and CK20. Based on these, the present case fulfills the structure and immunohistochemical criteria for a primary pure ovarian LCNEC.

Ovarian LCNEC is a highly aggressive tumor with a poor prognosis even at an early stage. Similar to small cell carcinoma, irrespective of its stage, Ovarian LCNEC is very malignant and aggressive and recurrence or metastasis can occur within a short time in most patients.\cite{25} Due to the rarity of the disease and the lack of systematic population-based studies or registration data, there is hitherto no consensus on the optimal treatment. Clinically, surgical excision is mainly adopted and postoperative of platinum-based chemotherapy is supplemented. Radiotherapy may be an option for treatment.\cite{24} Oshita et al.\cite{13} have reported a patient with brain metastasis and she had received wholebrain radiation therapy, and during the 64 months post initial treatment she did not experience tumor recurrence. However, the presented case has not received radiotherapy, and the effect is not clear. There is no consensus on standard treatment yet, but we believe that the combination of aggressive surgery with chemotherapy and adjuvant radiotherapy should be considered as a possible treatment strategy.

In conclusion, ovarian LCNEC is rare and defined as an extremely malignant tumor, with a poor prognosis even at an early stage. Early diagnosis is difficult, diagnosis requires histopathology and IHC. Due to the rarity of the disease and the lack of systematic population-based studies or registration data, there is hitherto no consensus on the optimal treatment.

### Table 3

| Classification | Pathological structures and clinical abnormalities |
|----------------|---------------------------------------------------|
| Primary LCNEC | 1. Solid sheets, islands, or bands patterns, large to intermediate in size, round to ovoid nuclei, coarse chromatin and numerous mitoses 2. Positive reactivity for CgA, Syn, CK and CD56 |
| Primary or metastatic carcinoid tumor | Cytological consistency, with low mitotic activity and absence of necrosis |
| Small cell carcinoma of pulmonary type | 1. Smaller cell with obvious necrosis 2. Less intense immunohistochemical reaction for CK and CgA |
| Small cell carcinoma of hypercalcemic type | 1. Hypercalcemia 2. large cells 3. Follicle-like spaces with pale intracytoplasmic hyaline globules |
| Undifferentiated ovarian carcinoma | 1. Solid with hemorrhage and necrosis 2. Obvious cellular atypia and low differentiation 3. Immunohistochemical epithelial markers were positivity while neuroendocrine markers were negative |
| Metastatic neuroendocrine carcinoma | 1. Bilateral ovarian involvement with multinodular growth pattern 2. Vascular invasion |

CgA = chromogranin A, Syn = synaptophysin.

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