An Ovarian Large-Cell Neuroendocrine Carcinoma Accompanied by Clear Cell Carcinoma with Specific High Level of AFP: Case Report and Review of the Literature

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Case Report

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Abstract

Background

Large cell neuroendocrine carcinoma (LCNEC) is a rare histological subtype of ovarian cancer. A few cases have been reported in literature with high invasiveness and poor prognosis. However, there still have not accepted criteria for diagnosis and treatment of LCNEC.

Case presentation:

We report an unmarried 37 year-old woman who was diagnosed with LCNEC associated with clear cell carcinoma and the tumor index was manifested with a specific increase of AFP. The case received six courses of Etoposide and carboplatin chemotherapy as an adjuvant therapy after primary curative surgery. However, she relapsed within 6 months after surgery and metastasized rapidly to distant organs despite combination chemotherapy of paclitaxel, cisplatin and bevacizumab and died 18 months after primary surgery.

Conclusions

This is the first reported case of LCNEC manifested with a specific increase of AFP and characteristically metastasized to the spine as recurrence. Since LCNEC present with aggressive malignancies and can easily metastasize to distant place through hematogenous approach, we recommend that adding Bevacizumab in primary chemotherapy may be beneficial to extend disease-free survival. Further research are needed to find the best treatment of LCNEC so as to improve the prognosis of patients.

Background

Large cell neuroendocrine carcinoma (LCNEC) of the ovary is a rare histological subtype of ovarian cancer which characterized by the presence of large cells with ample cytoplasm, highly malignant nuclei, abundant mitotic activity, necrosis and have a tendency to neuroendocrine differentiation^[1]. However, uptill now, there exist no generally accepted criteria for neuroendocrine tumor differentiation, which usually depends on histochemical and immunohistochemical analysis. Trabecular architecture, insular architecture with or without central necrosis, and cytoplasmic granularity usually suggest the neuroendocrine differentiation^[2]. Additionally, immunohistochemical makers such as chromogranin A, synaptophysin and CD56 are required to confirm the diagnosis of LCNEC^[3, 4]. LCNEC is usually accompanied by other epithelial and germ tumor, pure LCNEC is extremely rare^[5-8]. Despite extensive surgery and adjuvant chemotherapy performed for this type of tumor, the prognosis is common poor in the published literatures, even when diagnosis is made at an early stage^[3, 9, 10]. Here, we present a case of a 37 year old woman who was diagnosed with stage IIIA1 LCNEC of the ovary. She was characterized by presence of combined clear cell carcinoma and elevated AFP level, which were different from other

reported LCNEC cases. We present the clinical details and imaging findings, followed by discussions of treatment and prognostic factors.

Case Presentation

A 37-year-old unmarried woman without sexual life who complained of abdominal distension with frequent urination for a month attended to our hospital. Physical examination revealed that the abdomen was obviously swollen and a mass was detected in abdomen. Ultrasonographic tomography and magnetic resonance imaging(MRI) demonstrated a monocular cyst measuring 25 cm in diameter in the abdominal cavity(Fig. 1, 2). Preoperative serum level of Alpha-fetoprotein (AFP) was 962.23ng/mL, carbohydrate antigen (CA)125 was 40.30U/mL and CA19-9 was 421.46U/mL, while other tumor index like squamous cell carcinoma associated antigen(SCC), carcinoembryonic antigen(CEA) and lactate dehydrogenase were within normal ranges. Chest computed tomography (CT), gastroscope and colonoscopy also showed no abnormalities. After discussion about the possible risk factors of each treatments, she chose radical surgery. A huge cystic mass with part of solid component in pelvic and abdominal cavity was found at laparotomy. We suctioned the sac fluid to shrink the mass under the protection of the incision and explore that the tumor originated from right ovary. The uterus, tubes, left ovary and omentum were normal and no other tumor was evident in the abdominal cavity. Pelvic and para-aortic lymph nodes were not swollen upon palpation. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic lymphadenectomy, abdominal aortic lymph node resection and multiple peritoneal biopsy were performed. Peritoneal washing cytology was negative. On pathological examination, the right attachment composed ovarian clear cell carcinoma (approximately 10%) and poorly differentiated carcinoma (consistent with large cell neuroendocrine carcinoma, accounting for approximately 90%, Fig. 3a, b, c). Most of the tumor had a characteristic nest formation with central and peripheral coagulative necrosis. A metastasis lesion was observed in one of the right internal iliac lymph nodes under the microscope. Immunohistochemistry was performed to assess the features of the large cells. The neuroendocrine component proved positive for CD56, chromogranin, and synaptophysin(Fig. 3d, e, f). Besides, the tumor cells were also intensely positive for CK and CK7(Fig. 3g,h), while immunostaining for ER and PR were negative.

According to FIGO stage of ovarian cancer, She was diagnosed as LCNEC for stage $\text{IV}A1$. Since LCNEC occupied 90% of the tumor tissue, based on the experience reported in the literature, six courses of postoperative EP [120 mg/m² VP-16 and carboplatin at AUC 5.0] chemotherapy were carried out after surgery. AFP level decreased to normal after the second course of chemotherapy while other abnormal tumor indexes were decreased to normal after the first course of chemotherapy, indicating that chemotherapy was effective and achieves complete clinical remission. But unfortunately, tumor index of AFP increased again in the six months after surgery and showed a progressive upward trend in the next six months (28.39ng/ml~7346ng/ml). PET-CT scan showed that there were multiple enlarged lymph nodes in the upper and lower left clavicle, left pectoral muscle space, left axillary, left hilum, bilateral diaphragm feet and retroperitoneum. Meanwhile, L3 vertebra showed osteolytic bone destruction, FDG metabolism is abnormally increased, considering metastasis, which further confirmed by Lumbar MRI

(Figure 4). She received TCA (Paclitaxel 200mg d1, Cisplatin 30 mg d1-d3 and Bevacizumab 280m d1 q3w) as an adjuvant chemotherapy. However, clinical responses to this regimen was not observed and her cancer was progressed rapidly. She died of progressive disease 18 months after her primary operation. The timeline of the process of diagnose and treatment for this case was shown in Fig. 5. This study was approved by the ethics committee of Huzhou Central Hospital. Signed informed consent form was obtained from the patient.

Discussion And Conclusions

Ovarian LCNEC is a rare, aggressive poorly-differential neuroendocrine tumor that is often with poor outcome. The histogenesis of neuroendocrine tumors is still unclear. Several hypotheses suggested that LCNEC may derived from ovarian neuroendocrine cells, non-neuroendocrine cells, teratomatous cells or primitive cells^[11], so LCNEC is usually accompanied by other epithelial and germ cell tumors, and pure LCNEC is extremely rare. According to previous cases, associated ovarian cancer is mainly mucinous carcinoma, and endometrioid carcinoma, serous carcinoma or teratoma are less common^[12, 13]. The tumor in our case was lined with a small part of clear cell carcinoma, while most of the tumor consisted of a poorly differentiated component of large tumor cells with large nuclei and prominent nucleoli. Immunohistochemistry revealed that the cells of the poorly differentiated component were diffusely positive for CD56, chromogranin A and synaptophysin, which fulfilled the histopathological criteria for a neuroendocrine carcinoma. To our knowledge, this case presented for the first time that LCNEC can also be associated with clear cell carcinoma.

The initial symptoms presented by ovarian LCNEC with early stage are not typical, and most of them are found accidentally during surgery from rapid pathological examination. The clinical manifestations of ovarian LCNEC with advanced stage are identical to that of epithelial ovarian cancer (EOC), such as presence of an abdominal mass, pain or distention^[9]. In addition, endocrine-related symptoms may occur among some patients with ovarian LCNEC, such as hypercalcemia caused by high secretion of parathyroid hormone, which was reported by Ohira S^[15]. Based on previous reported cases, more than half of patients were diagnosed at an advanced stage(Ⅲ-Ⅳ), indicating that it is difficult to diagnosed ovarian LCNEC at an early stage.

There are no specific tumor index for ovarian LCNEC. Because it is often associated with ovarian epithelial tumors and germ cell tumors, various tumor markers can be elevated^[11], such as carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199), carbohydrate antigen 724 (CA724), carcinoembryonic antigen(CEA) and neuronspecincenolase (NSE). Among them, CA125 elevation occurs most frequently, occupy 83.87%. In our presented case, tumor index was specified by abnormally elevated level of AFP while the level of CA125 was increased slightly. Moreover, it is only manifested as progressive increase in AFP level in the later course of recurrence. To our knowledge, this is the first reported case of LCNEC characterized by specific elevation of AFP level which further to be used as a monitor for disease recurrence and progression in the follow-up.

It has been reported that ovarian LCNEC is extremely aggressive and its prognosis seems to be very poor despite extensive surgery and adjuvant chemotherapy. Yang X et al conducted a statistical analysis of previous cases, and found that the median overall survival of LCNEC is only 10.0 months^[11]. The total 5-year survival was 34.9%, and still only 35.3% for stage I cases, even though in over 95% of these cases complete or optimal surgery was performed^[11]. These results may be mainly due to the high recurrence rate of LCNEC, and once recurrence occurs, it is not only limited to the abdominal cavity, but also to specific sites that differed from the usual ovarian cancer distribution. This suggests that LCNEC may have strong lymph-vascular space invasion, which contributes to its poor prognosis^[11]. In our case, although the primary chemotherapy was effective and achieves complete clinical remission, the recurrence rapidly occurred 6 month after primary surgery, no obvious recurrence lesion was found at the beginning, when the patient complained the pain about her lumbar spine, further examination was performed to found the destruction of the vertebra L3, indicating that LCNEC is prone to be hematogenous metastasis. Therefore, for patients with LCNEC, once recurrence occurs, a systemic assessment should be performed to detect metastatic lesions as soon as possible, which may benefiting for early treatment decisions and prognosis.

Until now, there is not an accepted consensus treatment for patients with LCNEC, the clinical management of most reported cases still follow the conventional regimens for epithelial ovarian cancer, which is cytoreductive surgery combined with platinum-based chemotherapy. There were also a few case reports using other chemotherapy options, including cyclophosphamide combined with cisplatin, irinotecan combined with nedaplatin, liposomes doxorubicin monotherapy and BEP programs^[2,8,9,14-16]. But all these reported chemotherapy regimens seem to not be very effective for LCNEC. In our case, the patient was sensitive to initial EP regimen chemotherapy, achieving complete clinical remission, but she relapsed soon after initial treatment, and migrated to spine through hematogenous approach. So we add Bevacizumab for chemotherapy. But the response seems to not be satisfactory as we expected. In retrospective analysis of this case, we are also thinking about whether Bevacizumab could reduce the probability of recurrence and improve its prognosis if it is used in initial treatment since LCNEC easily migrate to distance place through hematogenous approach.

In summary, LCNEC is a very rare historical subtype of ovarian cancer with extremely aggressive behavior. For the first time, We reported a case of LCNEC coexisted with clear cell carcinoma and characterized by elevation of AFP. According to previously reported cases and our case, LENE can easily metastasize to distance place through hematogenous approach, we fiercely recommend that adding Bevacizumab in primary chemotherapy may be beneficial to extend disease-free survival. Due to the low incidence of ovarian LCNEC, it is very difficult to conduct large-scale clinical prospective studies to confirm this proposal. It is urgent to appeal a global medical database of ovarian LCNEC be collected and much more research should be investigated to establish optimal adjuvant chemotherapy.

Declarations

Ethics approval and consent to participate

This report was approved by the Ethics Committee of Huzhou Central Hospital (No.202110016-02).

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

Not applicable. Our manuscript does not contain any numerical data

Authors' contributions

Each author made substantial contributions to the conception and design of this paper. The author(s) read and approved the final manuscript.

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Figures

Figure 1

Abdominal ultrasound scan showed there was a huge mass in pelvic and abdominal cavity.

Figure 2

Pelvic MRI enhancement scan of the huge mass in sagittal plane and axial plane.

A MRI of the mass with increased signal on T2W in the axial plane

B MRI of the mass with decreased signal on T1W in the axial plane

C MRI of the mass with increased signal on T2W in the sagittal plane

Figure 3

Pathological and immunohistochemical findings of this case. (a)

Microscopic finding (hematoxylin-eosin [HE] staining): Junction area of clear cell carcinoma and large cell neuroendocrine carcinoma (original magnification, $\times 10$). (b) Area of clear cell carcinoma (original magnification, $\times 20$). (c) Area of large cell neuroendocrine carcinoma, poorly-differentiated large

cells((original magnification, ×20). (d–f) Immunohistochemical studies of this case for representative neuroendocrine markers: CD56 (d: ×20), chromogranin A (e: ×20) and synaptophysin (f: ×20). Immunohistochemical test also found CK and CK20 were positive(g,h×10).

Figure 4

Lumbar MRI enhancement scan showed destruction of L3 vertebra.

A Destruction of L3 vertebra caused by tumor invasion with decreased signal on T1W in the sagittal plane

B Destruction of L3 vertebra caused by tumor invasion with increased signal on T2W in the sagittal plane

Figure 5

Timeline of the process of diagnose and treatments of this case