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Research Letter

Primary pure large cell neuroendocrine carcinoma of the ovary

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Neuroendocrine tumors are more common in the female genital tract than in the male genital tract, and most are uterine small cell carcinomas or ovarian carcinoid tumors. Most ovarian tumors are associated with surface epithelial tumors, Sertoli–Leydig cell tumors, teratoma, small cell carcinoma, pulmonary-type and undifferentiated carcinoma, and nonsmall cell lung cancer [1]. Large cell neuroendocrine carcinoma (LCNEC) of the ovary is unusual and defined as an extremely malignant tumor with an aggressive lethal outcome. For this original and updated review, we searched the databases of PubMed Clinical Queries, MEDLINE, Cochrane Library and UpToDate. We also hand-searched relevant journals and reference lists of identified articles. The keywords used were "ovary", "pure LCNEC", and "immunohistochemistry". We found that only 37 cases of ovarian tumor involving LCNEC associated with surface epithelial stromal tumors and/or teratoma have been reported to date [2–5]. In addition, seven cases of primary LCNEC of the ovary without any associated component have been described [2,3,6–8]. Herein, we present the case of a patient with stage IV primary pure LCNEC of the ovary with liver metastasis and carcinomatosis.

A 50-year-old married, Taiwanese female, G3P3, was referred by a clinical oncologist for the evaluation of a pelvic mass. She denied specific systemic disease, a gynecological history, and undergoing major operations previously. She also denied any significant symptoms, such as compression sensation, lower abdominal pain, or abnormal vaginal bleeding. Because of an increased abdominal circumference and a palpable 20-cm mass in the abdomen that had been present for 2 weeks, she was referred by a clinical oncologist and underwent a suboptimal debulking operation with total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, and appendectomy. Lymph node dissection was omitted to avoid excessive bleeding, and liver palpation found multiple metastases compatible with the previous computed tomographic (CT) finding of liver metastases. The final diagnosis was LCNEC (Fig. 1) of the ovary (International Federation of Gynecology and Obstetrics stage IV; American Joint Committee on Cancer staging T3cN1M1). Brain CT and a bone scan for tumor evaluation were negative. Postoperative adjuvant chemotherapy with paclitaxel + carboplatin was planned; however, she was morbid with nausea, vomiting, anorexia, and general weakness after the chemotherapy and refused further treatment. Although the serum CA125 level dropped from 685.8 to 68.73 U/mL after three cycles of chemotherapy, a newly developed nodular opacity measuring approximately 2.3 cm in the right middle lung was noted. Therefore, disease progression with pulmonary metastases was suspected. Unfortunately, the patient died 3 months post-surgery after sustaining intracranial hemorrhage following an accidental fall-down injury.

The gross pathology examination revealed that the uterus was $13 \times 13 \times 6$ cm in size with multiple myomas and adenomyosis. The left ovary showed a very large fragile mass measuring approximately 25 cm in diameter with pelvic wall and intestinal invasion. The left fallopian tube, parametrium, omentum, and surface of the appendix also showed tumor invasion.

Histologically, the predominant pattern was pleomorphic with hyperchromatic tumor cells arranged in trabecular (Fig. 2A), solid (Fig. 2B), and rosette-like growth patterns (Fig. 2C) with high mitotic activity (Fig. 2D; >20 figures/10 high-power fields) and foci of spotty tumor necrosis.

The tumor cells were positive for chromogranin A (Fig. 3A), vimentin (Fig. 3B), CD56 (Fig. 3C), and neuron specific enolase (NSE) (Fig. 3D) but negative for CK7 and CK20. Diagnosis of LCNEC of the ovary was made based on clinical data, histopathological features, and immunoprofiles.

Primary LCNEC of the ovary is a rare tumor and is now included in the World Health Organization (WHO) tumor classification. According to the WHO, this tumor is synonymous with "undifferentiated carcinoma of nonsmall cell neuroendocrine type" and is defined as "a malignant tumor composed of large cells that show neuroendocrine differentiation" [9]. Although four cases of primary pure LCNEC of the ovary have been described, 30 published cases have been associated with ovarian epithelial tumors or germ cell

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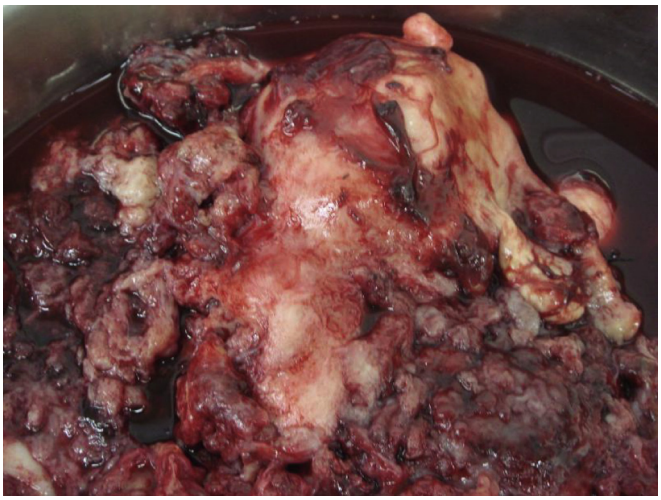

Fig. 1. The main tumor arising from the left ovary showed a very large fragile mass that measured approximately 25 cm in diameter with a bizarre appearance.

tumors [2]. These findings support the hypothesis that ovarian LCNEC most likely arises from the neuroendocrine cells present on surface epithelial stromal tumors or teratoma [10]. One theory on the origin of primary pure neuroendocrine tumors suggests the existence of a primitive endodermal cell that is capable of differentiating into other cell types or the activation of genes promoting neuroendocrine differentiation from non-neuroendocrine cells [11].

When making the diagnosis, LCNEC should be distinguished from some other tumors such as primary or metastatic carcinoid tumor, small cell carcinoma of the pulmonary or hypercalcemic type, metastatic neuroendocrine carcinoma, anaplastic carcinoma arising in mucinous tumor, or primitive neuroectodermal tumor [12]. Primary and metastatic carcinoid tumors can be distinguished from LCNEC by their low mitotic activity, cytological uniformity, organized architectural patterns, and absence of necrosis [5]. Microscopically, primary LCNEC is characterized by large tumor cells, specifically oval to round in shape, which are usually arranged in solid nests, sheets, or a trabecular pattern. The glandular or cribriform formation is less frequently observed. The differential diagnosis and pathological structures are presented in Table 1 [5,12].

Histologically, the tumor has large vesicular nucleoli or coarse chromatin without predominant nucleoli and sometimes has extensive necrosis and numerous mitoses [7,10]. In our case, the pleomorphic and hyperchromatic tumor cells were arranged in trabecular, solid, and rosette-like growth patterns with high mitotic activity and foci of spotty tumor necrosis.

Neuroendocrine differentiation can be confirmed by immunohistochemical analysis due to the neuroendocrine nature of the cell, as these cells express at least one neuroendocrine marker (e.g., CD56, chromogranin A, synaptophysin, or NSE) [2,10]. In the case presented, the immunohistochemical stains showed that the tumor cells were positive for CD56, chromogranin, and NSE but negative for the epithelial markers CK7 and CK20. Thus, this case fulfills the structure and immunohistochemical criteria for a primary pure LCNEC of the ovary.

Because of the rarity of this condition, only limited data are available to guide the treatment of patients with LCNEC of the ovary. Most patients undergo primary surgery to obtain the definitive tissue diagnosis and staging and a tumor debulking operation. Follow-up study was available in 38 reported cases (including this one), and 30 patients received chemotherapy. Various combinations of chemotherapy had been chosen, including

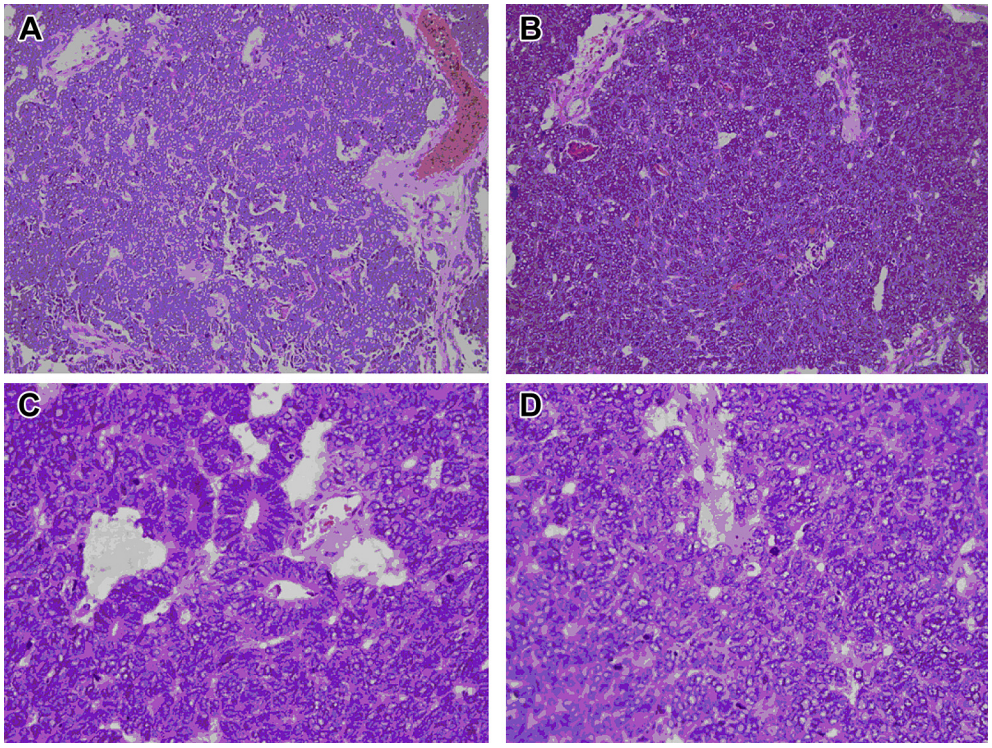

Fig. 2. Histological examination results indicated that the tumor was a large cell neuroendocrine carcinoma. Low-power view of neuroendocrine carcinoma showing (A) trabecular, (B) solid, and (C) rosette-like growth patterns. High-power view of the neuroendocrine carcinoma showing variable tumor cells with oval nuclei. (D) Fine, evenly distributed chromatin and inconspicuous nucleoli were present with numerous mitoses.