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Case Reports

A case of ovarian small cell carcinoma of the pulmonary type that was observed as it developed

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Summary

Introduction: In the case reported here, the authors observed ovarian small cell carcinoma of the pulmonary type as it developed. *Case:* The patient was a 48-year-old woman who underwent a hysterectomy for CIN3 in 2007. A year later, the woman underwent screening for ovarian cancer. A gradually growing ovarian mass was noted. This mass was found to be a mixed tumor. This mixed tumor grew to 36 mm in size, and six months later it had enlarged to 119 mm. After surgery, the tumor was pathologically diagnosed as an ovarian small cell carcinoma of the pulmonary type with a neuroendocrine nature that was positive for CD56 and synaptophysin. Postoperatively, the patient received six courses of combined therapy with irinotecan and cisplatin (CPT-P therapy), and the patient has survived disease-free for over two years. *Conclusion:* Findings suggested that ovarian small cell carcinoma of the pulmonary type is a type 1 ovarian malignancy that develops through an adenoma-carcinoma sequence.

Key Words: Ovarian small cell carcinoma; Pulmonary type; Type 1 ovarian malignancy; CD56; Synaptophysin; Irinotecan and cisplatin.

Introduction

Ovarian small cell carcinoma is a rare tumor that is not categorized as a surface epithelial-stromal tumor, sex cord-stromal tumor, or germ cell tumor. Ovarian small cell carcinomas are divided into two types, a hypercalcemic type involving hypercalcemia and a pulmonary type with a neuroendocrine nature [1]. The origins and clinical features of both types are reported to differ considerably. In addition, there are scant reports of ovarian small cell carcinoma of the pulmonary type. In the case reported here, the authors observed ovarian small cell carcinoma of the pulmonary type as it developed.

Case Report

The patient was a 48-year-old woman (gravida 5, para 3) who underwent a hysterectomy for CIN3 in 2007. A year later, the woman underwent screening for ovarian cancer. The patient's family history was unremarkable. Prior to 2012, there were no abnormal findings in the ovaries (Figure 1A), but screening in June 2012 revealed a mass 36×33 mm in size in the left ovary (Figure 1B). The ovarian mass was followed on monthly transvaginal ultrasound, where it tended to gradually grow (Figure 1C). In October 2012, a cyst with a somewhat solid component had enlarged to a size of 119×74 mm (Figure 1D). At the time, tumor markers within normal ranges, i.e. CA19-9 was 4.6 U/ml and CA125 was 11.2 U/ml, but CEA was elevated at 24.7 ng/ml (normal range: 1-5 ng/ml). Since CEA levels were high, an upper gastrointestinal series and a lower gastrointestinal series were performed, but there was no evidence of lesions. A pelvic MRI scan revealed a cystic mass 130×110 mm in size occupying the cavity of the lesser pelvis. An irregularly shaped and non-uniform intramural nodule six cm in size was noted in the left cystic wall. A contrast-enhanced CT scan revealed contrast enhancement in the left wall of the cystic mass, but obvious evidence of metastasis was not noted. Thus, the mass was diagnosed as a possible malignant ovarian tumor, and a surgical approach was taken.

Macroscopic findings: The ovarian tumor was firmly adherent to the inside of the pelvis. Perioperatively, ascitic cytology was negative for malignancy. The tumor capsule was partially ruptured during surgery, but the tumor was completely removed. Perioperatively, results of a rapid pathologic diagnosis indicated a malignant tumor, so a bilateral salpingo-oophorectomy, pelvic lymph node dissection, para-aortic lymph node dissection, and an omentectomy were performed. The mass had originated from the left ovary. A solid mass was noted (Figure 2) in the thin cyst wall. Sections of the solid component were grayish white, and sites of bleeding that suggested the presence of necrosis in some areas were noted (Figure 2).

Pathologic findings: resected specimens of the solid mass featured densely packed short spindle-shaped or oval nuclei with

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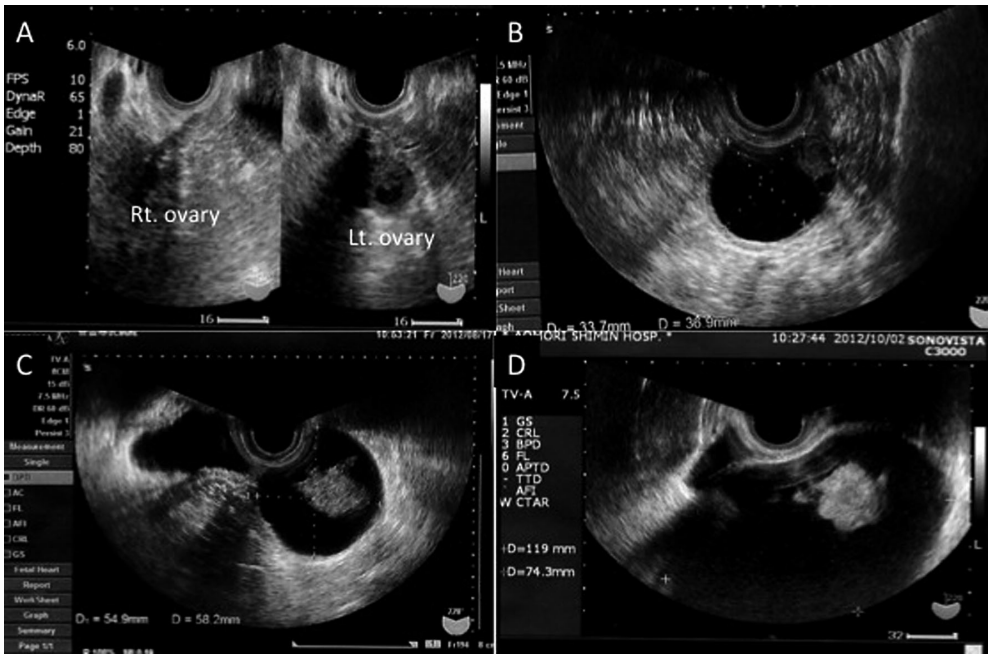

Figure 1. — Changes in ovarian tumor morphology over time. A) Normal left ovary (May 2011). There is a shadow resembling an ovarian follicle inside the ovary, which is normal size. The area within the follicle is hyperechoic. B) Ovarian mass with a long axis of 36 mm (June 2012). The mass is a mixed tumor with a solid component inside. C) Ovarian mass with a long axis of 58 mm (Aug. 2012). A solid component is clearly evident inside the mass. D) Ovarian mass with a long axis of 119 mm (Oct. 2012). This enlarged cystic mass has a solid component and is a mixed tumor. Findings suggested that the tumor was malignant.

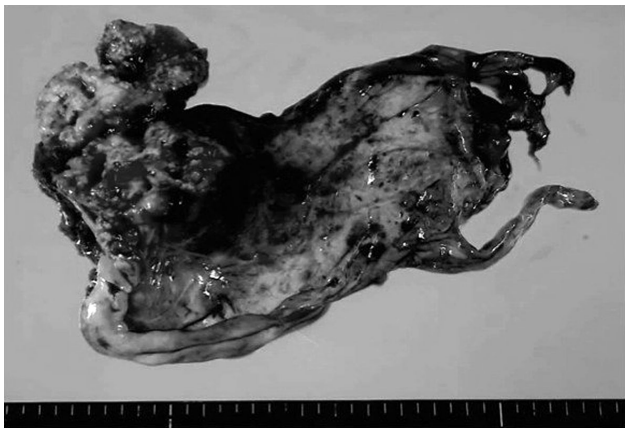

Figure 2. — Macroscopic findings: Sections of the solid component are grayish white, and sites of bleeding that suggested the presence of necrosis in some areas are noted.

abundant chromatin (Figure 3A) resembling small cell carcinoma of the lung, and mitotic figures were also noted. In addition, tubular and cribriform patterns were noted (Figure 3B). The cystic component represented the bulk of the solid tumor nodule. Metastasis was not noted in the left fallopian tube, the right adnexum, the omentum, or pelvic lymph nodes. Thus, the tumor was believed to be a primary ovarian small cell carcinoma. Immunostaining was positive for CD56 (Figure 3C) and synaptophysin, revealing that the tumor had features of a neuroendocrine carcinoma. The tumor was negative for thyroid transcription factor-1 (TTF-1), α-inhibin, PLAP, EMA, and cytokeratin. In addition, serum calcium levels were all normal prior to surgery. Mucous cells resembling a mucous gland adenoma were noted in parts of the cyst wall (Figure 3D). Thus, the cancer was diagnosed as primary ovarian small cell carcinoma of the pulmonary type (FIGO Stage Ic (b), pT1cN0M0).

Postoperative course: a standard form of chemotherapy to treat ovarian small cell carcinoma of the pulmonary type has yet to be established, and there are few case reports of effective treatments. The tumor's histopathology resembled that of small cell carcinoma of the lung, so in accordance with the standard regimen for treatment of small cell carcinoma of the lung, the patient was administered CPT-P therapy consisting of irinotecan 60 mg/m^2 and cisplatin 60 mg/m^2 every four weeks in a total of six courses. CEA was 24.7 ng/ml prior to surgery but decreased to 2.0 ng/ml after surgery. Since the tumor was a small cell carcinoma, NSE was elevated at 14.7 ng/ml (normal range: less than 12.0 ng/ml) when it was measured using specimens collected prior to surgery. After surgery, however, it returned to a normal level of 7.3 ng/ml. Six courses of chemotherapy were completed, and currently the patient is being followed and there is no evidence of recurrence.

Discussion

In the current case, the patient was monitored after initial tumor formation via screening for ovarian cancer. This allowed surgery to be performed earlier when the tumor's features suggested a malignant tumor, i.e. a change to a mixed tumor and tumor enlargement. Ovarian malignancies are categorized into two types, type 1 that develops through an adenoma-carcinoma sequence, and type 2 that develops through mutations [2]. Tracing the natural history of the current case suggests that ovarian pulmonary-type small cell carcinoma followed a type 1 pattern of development with an adenoma-carcinoma sequence.

First reported by Dickersin *et al.* in 1982 [3], ovarian small cell carcinoma is categorized as a tumor of un-

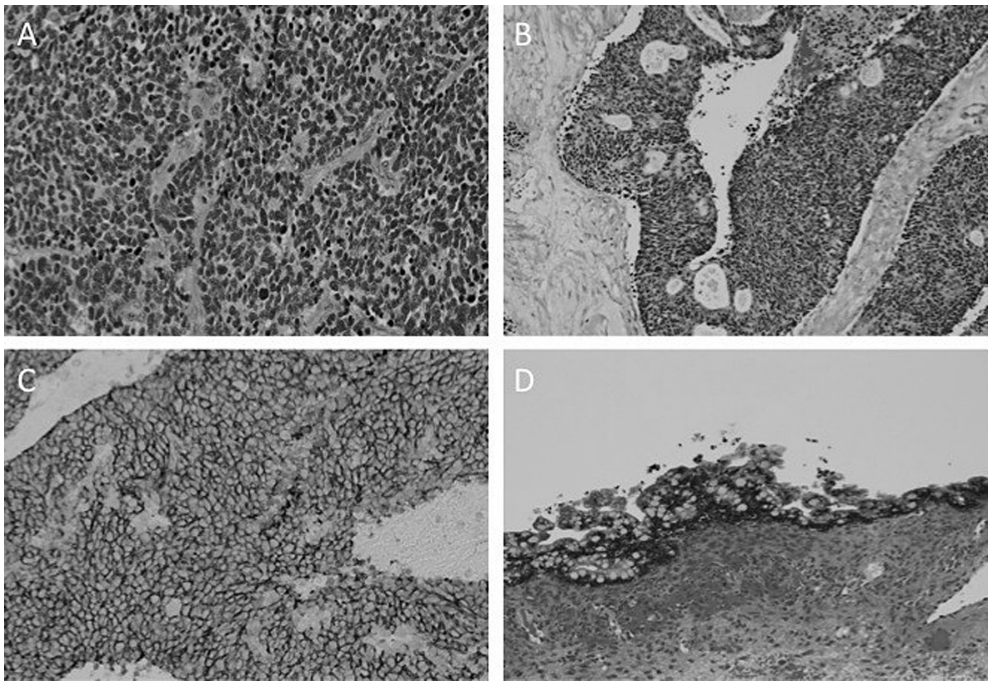

Figure 3. — Microscopic findings: A) HE staining. Densely packed short spindle-shaped or oval nuclei with abundant chromatin are observed and mitotic figures are also noted (magnification ×200). B) HE staining. Tubular and cribriform patterns are noted (magnification ×100). C) Immunohistochemistry. Immunostaining is positive for CD56 (magnification ×100). D) HE staining. Mucous cells resembling a mucous gland adenoma are noted in parts of the cyst wall (magnification ×100).

known origin. Ovarian small cell carcinomas are categorized into two types, a pulmonary type and a hypercalcemic type [1]. Both types are rare, highly malignant, and have a poor prognosis. However, the clinical features of the two differ. Tumors of the pulmonary type are reported in patients from 28-85 years of age. These tumors are found in relatively older women with a mean age of 59 years. Half of these tumors of the pulmonary type affect both ovaries and have a histology resembling small cell carcinoma of the lung. These tumors of the pulmonary type are also reported to be accompanied by a surface epithelial tumor, and these tumors are thought to have the features of a neuroendocrine carcinoma [1]. In contrast, tumors of the hypercalcemic type are reported to occur from nine to 43 years of age. These tumors are found in younger women with a mean age of 24 years. These tumors also affect one ovary, and these tumors are accompanied by hypercalcemia in about two-thirds of cases [4].

Ovarian small cell carcinoma of the pulmonary type has a histology like that of small cell carcinoma of the lung. Tumor cells are small and round, oval, or spindle-shaped, and these cells are arranged in nests or bands. A carcinoma of this type is characterized by a substantial increase in nuclear chromatin, indistinct nucleoli, and nuclear grooves. Such a tumor also has features of a neuroendocrine carcinoma. According to Eichhorn *et al.*, immunostaining of nine neuroendocrine carcinomas revealed that seven were positive for NSE and two were positive for chromogranin [5]. In the current case, there was a surface epithelial component in part of the cyst wall, suggesting that the tumor might have been a mucinous adenoma. In addition, the tumor was negative for NSE and chromogranin, but it was positive for neuroendocrine markers such as CD56 and synaptophysin. These findings suggested that the tumor was a pulmonary-type small cell carcinoma.

Most small cell carcinomas are primary small cell carcinomas of the lung, and 2.5% of all small cell carcinomas are believed to originate at sites besides the lung [6]. In addition to the lung, small cell carcinoma is reported to also originate from the cervix, the small intestine, the thymus, and the skin [7]. To diagnose a tumor arising in the ovary, diagnostic imaging must be used to rule out the presence of primary foci at other sites. In addition, immunostaining of primary small cell carcinoma of the lung is frequently positive for TTF-1 [8]. In the current case, the tumor was negative for TTF-1. Serum levels of NSE are often reported to be elevated in ovarian small cell carcinoma. In the current case, NSE levels were slightly elevated and returned to normal after surgery. High levels of CEA were also noted in the current case, and these levels similarly returned to normal after surgery. No previous studies of ovarian small cell carcinoma have reported noting high CEA levels, and CEA might serve as an indicator in addition to tumor markers like NSE.

Ovarian small cell carcinoma is often highly malignant and it often has a poor prognosis. Several studies have reported treating ovarian small cell carcinoma in accordance with the standard treatment for epithelial ovarian cancer [4, 7]. If the patient is younger, only one side is affected, and there is no macroscopic spread beyond the ovary, an

adnexectomy is performed on the affected side to preserve fertility according to reports [4, 7]. Many studies, however, have reported performing surgery similar to that for ovarian cancer since ovarian small cell carcinoma is highly malignant [4, 7]. Ovarian small cell carcinoma is also rare, so a standard chemotherapy regimen has yet to be determined, and there are few case reports of effective treatment. In most cases, chemotherapy is given as additional treatment [7]. The standard chemotherapy regimen that is often chosen to treat primary small cell carcinoma of the lung is CPT-P therapy or etoposide+cisplatin therapy. However, several studies have reported that chemotherapy in the form of paclitaxel+carboplatin therapy or docetaxel+carboplatin therapy (DC therapy) is effective in treating ovarian small cell carcinoma [9-11]. In some cases of ovarian small cell carcinoma, an epithelial ovarian tumor is also noted, and ovarian small cell carcinoma may develop from a surface epithelial tumor as a precursor. These are probable reasons why chemotherapy is effective [12].

Ovarian pulmonary-type small cell carcinoma is probably a type 1 ovarian cancer. Thus, screening for ovarian cancer effectively identified this carcinoma in the current case. After surgery, the patient was given six courses of irinotecan+cisplatin therapy. Evidence of recurrence was not noted over two years after treatment concluded. At the current point in time, chemotherapy is likely to have been effective. Ovarian small cell carcinoma is seldom encountered in routine practice, and there are few case reports of ovarian small cell carcinoma of the pulmonary type. In addition, a treatment for ovarian small cell carcinoma has yet to be established, and there are few cases reported of effective treatments. In the future, additional cases must be compiled and a treatment needs to be established.

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