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Small-cell carcinoma-associated ovarian mucinous carcinoma: A case report and literature review

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ABSTRACT

Neuroendocrine neoplasm-associated ovarian mucinous carcinoma occurs extremely rarely. Here, we report an ovarian composite tumor consisting of small-cell carcinoma and mucinous carcinoma in a 51-year-old woman presented with abdominal distention. Ultrasonography revealed the presence of a complex irregular cystic solid mass. Microscopic findings showed pulmonary-type small-cell carcinoma-associated, intestinal-type ovarian mucinous carcinoma-with positive results for several neuroendocrine markers (chromogranin, CD56) and the thyroid transcription factor-1. The patient underwent total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and six cycles of adjuvant chemotherapy but died eight months after the surgery due to disease progression. Few reports are available in China on this clinicopathological feature in this composite tumor type. The timely identification of ovarian small-cell carcinoma among other ovarian tumors is critically important to the accurate and prompt determination of the therapy due to its high invasiveness and metastatic potential.

1. Background

Ovarian carcinoma is one of the most frequent gynecological malignancies worldwide. Ovarian tumors with neuroendocrine differentiation are classified into carcinoids, large-cell neuroendocrine carcinomas (LCNEC), and small-cell neuroendocrine carcinomas [1]. Small-cell carcinoma of the ovary (SCCO) is an extremely rare and aggressive ovarian cancer with a poor prognosis even in cases with early diagnosis. Most often it is present as a unilateral and independent tumor, but SCCO associated with other tumors, such as serous carcinoma and teratoma, has also been previously reported [2,3]. For example, Young et al. [4] found that 12% of the hypercalcemic type of SCCO was characterized by the presence of glands or cysts lined by mucinous epithelial cells. However, SCCO has been identified in only few cases of mucinous carcinoma [3,5–7]. Here, we describe a lesion of small-cell carcinoma-associated mucinous carcinoma in a premenopausal woman.

2. Case presentation

A 51-year-old premenopausal woman presented with progressive abdominal distention for two months. A physical examination revealed a hard, palpable mass in her left lower abdomen. Ultrasonography showed a complex irregular cystic and solid mass (13 cm × 12 cm × 10 cm) and ascites. The following laboratory test results were obtained: serum cancer antigen 125 (CA 125), 311.9 IU/mL; carcinoembryonic antigen (CEA), 5.5 ng/mL; and CA 199, 250.7 IU/mL (normal ranges, < 30 IU/mL, < 5 ng/mL, and < 37 IU/mL, respectively). The patient had no history of smoking, and no mass was detected in the patient's lungs. Total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy were performed to remove all enlargement lymph nodes of the pelvic wall and the lower abdomen. Intraoperative peritoneal lavage chemotherapy with 120 mg cisplatin was conducted during the operation. The patient received six cycles of postoperative chemotherapy with docetaxel (120 mg/m^2) and cisplatin (120 mg/m2). However, she refused to accept secondary surgical treatment and died eight months after the operation. Ultrasound confirmed extensive abdominal metastases

Abbreviations: LCNEC, Large-cell neuroendocrine carcinoma; SCCO, Small-cell carcinoma of the ovary; CA 125, Cancer antigen 125; CEA, Carcinoembryonic antigen; TTF-1, Thyroid transcription factor-1

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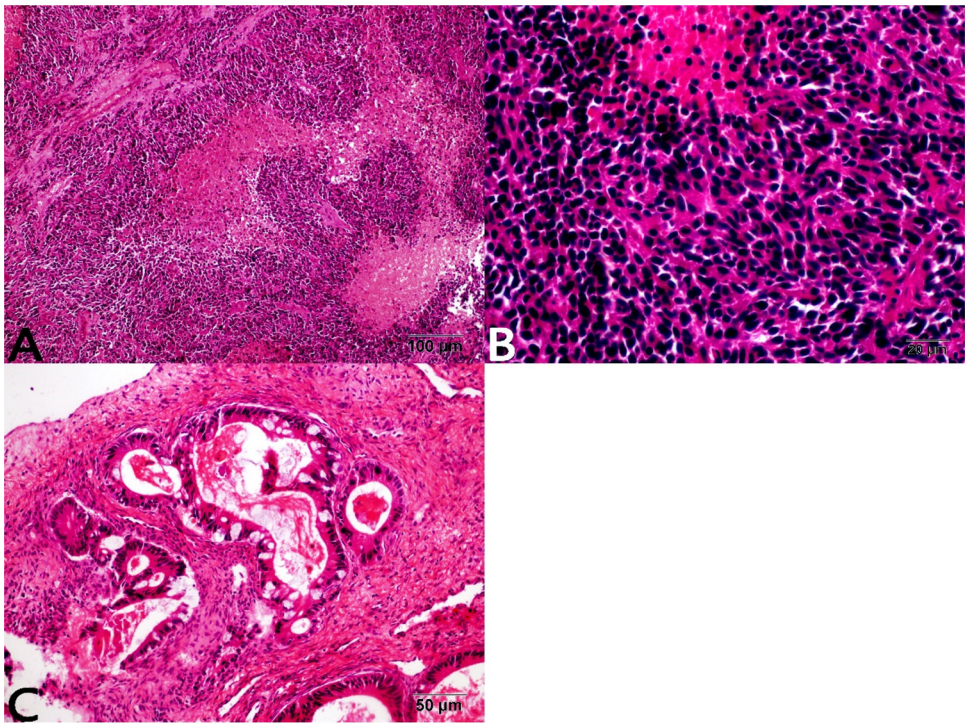

Fig. 1. Microscopic findings of the composite tumor consisting of small-cell carcinoma and mucinous carcinoma. (A)Small-cell carcinoma consisted of nests and sheets of cells with a uniform size, and extensive or focal necrosis was common (HE staining, ×100); (B)A large hyperchromatic nuclei, inconspicuous nucleoli, and either poorly or moderately abundant cytoplasm was found by hematoxylin-eosin (HE staining, ×400); (C) Mucinous adenocarcinoma of the intestinal type (HE staining, ×100).

Using macroscopic examination, we found a smooth mass (13 cm × 12 cm × 10 cm) in the left ovary. The cut surface showed extensive areas of soft yellow-tan tissue separated by zones of mucin-filled small cysts.

Two components consisting of numerous small cysts with a solid tumor nodule adjacent to the cysts were detected by microscopic examination. The tumor of the solid region was composed of nests and sheets of cells with a uniform size, large hyperchromatic nuclei, inconspicuous nucleoli, and either poorly or moderately abundant cytoplasm. The number of the mitotic figures was approximately eight per high-power field, with extensive or focal necrosis (Fig. 1A & 1B). The cystic area consisted of glands, tubules, and small cysts, lined by mucinous epithelium (Fig. 1C). Immunohistochemical positive results were obtained for chromogranin, CD56, pan-keratin, and thyroid transcription factor-1 (TTF-1). However, they were negative for synaptophysin in the solid area, which supported the diagnosis of small-cell carcinoma. Inactivation of the SMARCA4 gene (encoding the BRG1 protein) is a useful marker for the diagnosis of ovarian small-cell carcinoma of the hypercalcemic type [8]. Thus, the positive expression of BRG1 in this case suggested a non-high calcium subtype. Both components exhibited p53, with a strong staining in more than 80% of the tumor cells (Fig. 2), indicating that these tumors might have been p53-mutant.

The immunohistochemical features of the neuroendocrine and mucinous components are listed in Table 1. No tumor cells were found in the ascites. The final diagnosis was pulmonary-type small-cell carcinoma-associated intestinal-type ovarian mucinous carcinoma.

3. Discussion and conclusions

Although ovarian mucinous carcinoma is not uncommon, neuroendocrine neoplasm-associated ovarian mucinous carcinoma occurs rarely. Herein, we report a composite ovarian tumor of mucinous carcinoma and small-cell carcinoma, which, to the best of our knowledge, is be the fifth reported so far (Table 2) [3,5–7]. In previous studies, these lesions were often detected in adult women aged 22–65 years; the patients usually had no characteristic symptoms, except for abdominal distension. Abnormal blood indicators frequently showed increased serous CA125 [9,10], and the maximum diameters of tumors were usually more than 10 cm. The tumor in the present investigation was detected in a premenopausal woman with a history of two-month abdominal distension. Laboratory examination showed increased CA125 and CEA.

SCCO is usually classified into two types based on the specific clinical features and pathological findings: hypercalcemic and pulmonary, but age, serum calcium levels, histology, ultrastructure, and DNA ploidy may diversify its features [11]. The hypercalcemic type is more frequent in young women, whereas the pulmonary type usually occurs in elderly with an average age of 59 years (range 28–85 years). A follicle-like structure, large cells with abundant cytoplasm, and prominent nucleoli are often observed in the hypercalcemic type. Our ultrastructural examination showed more poorly developed rough endoplasmic reticulum in cells of the pulmonary type than in cells of the hypercalcemic type. The pulmonary type is typically large and predominantly solid, with frequent necrotic areas. The tumor cells have round, ovoid, or slightly spindled hyperchromatic nuclei, often with a “salt-and-pepper” chromatin and moulding. The cytoplasm is scant, and abundant mitotic activity and frequent apoptosis are usually detected, with conspicuous necrosis. The immunohistochemistry results of the hypercalcemic type SCCO revealed tumor cells that were positive for EMA, pan-keratin, WT1, calretinin, CD10, and p53. The neuroendocrine markers chromogranin, CD56, synaptophysin and PGP9.5 are variably positive in tumors of the pulmonary type. Chromogranin positivity may be predominantly focal with punctuate cytoplasmic immunoreactivity [3.9]. We could not judge the classification of SCCO based on the blood calcium levels because they were not determined preoperatively in this patient. Recently, the inactivation of the SMARCA4 gene was reported to be highly specific for the hypercalcemic type SCCO [12]. Therefore, we evaluated BRG1 expression, encoded by SMARCA4. Since the neuroendocrine component was positive for BRG1, we concluded that the small-cell carcinoma component in this case was not of the hypercalcemia type. Two of the five reported so far cases with SCCO and mucinous carcinoma (Table 2) were SCCO of the pulmonary type, whereas the diagnosis was unclear in the other three cases. In our case, primary SCCO of the pulmonary type consisted of small cells with a scanty cytoplasm and indistinct cellular borders. The nuclei were hyperchromatic with evenly dispersed chromatin and indistinct nuclear

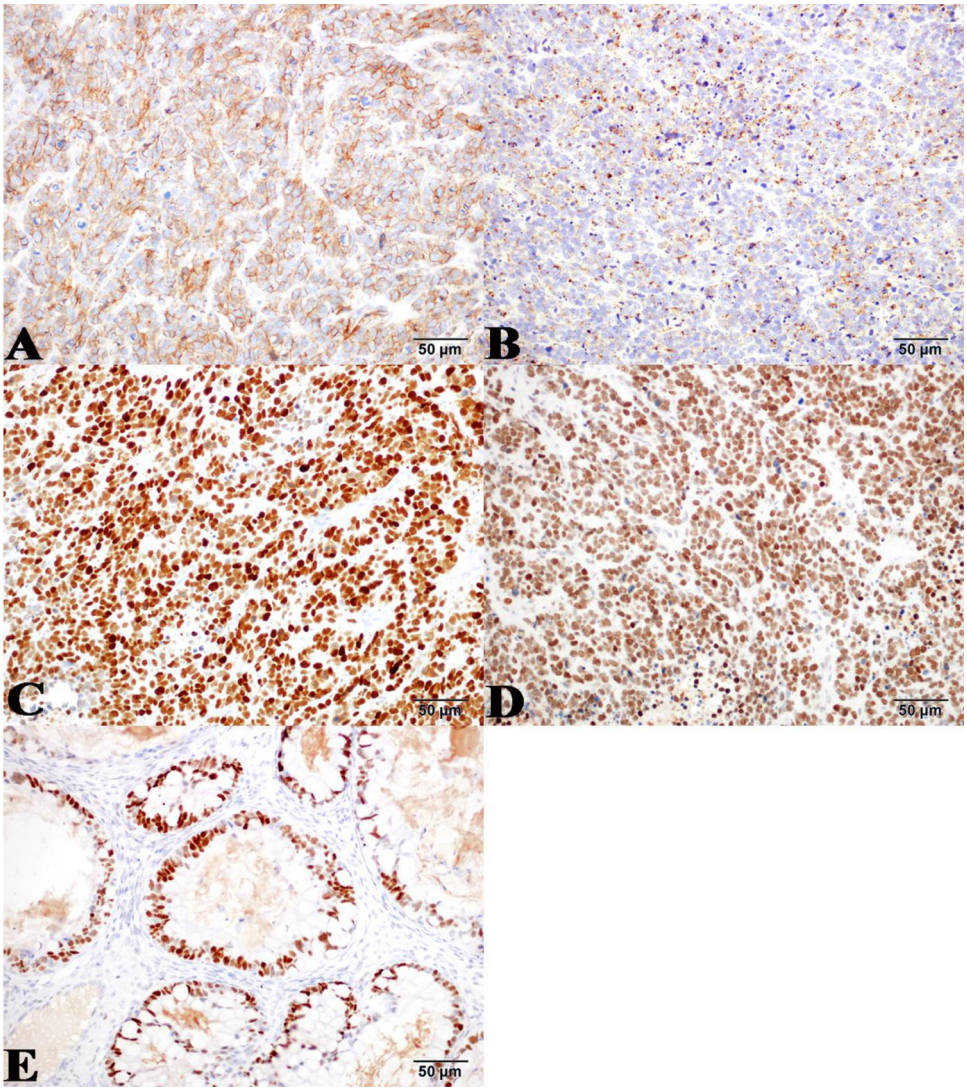

Fig. 2. Immunohistochemical features of the composite tumor (×200). Small-cell carcinoma was positive for CD56 (A), CgA (B), P53 (C), and BRG1 (D). Mucinous carcinoma was positive for P53 (E).

envelopes and nucleoli. Extensive necrosis, obvious atypia, and numerous mitotic figures suggested high malignance of SCCO. The tumor cells of SCCO were positive for CD56, NSE, and chromogranin but negative for synaptophysin. Both small-cell carcinoma and mucinous carcinoma cells were P53- and P16-positive.

The combination of metastatic adenocarcinoma and gastrointestinal tract small-cell carcinoma can be considered the most important differential diagnosis of the case described in this paper. Generally, gastrointestinal neuroendocrine tumors are relatively rare. In our study, the patient had no past history of gastrointestinal tumors, and no symptoms of gastrointestinal tumors were present. We found that the tumor cells in the present investigation were CK7-positive but CK20-negative. Primary hypercalcemic type SCCO are considerably difficult to distinguish from metastatic small-cell carcinoma of the lungs. Neuroendocrine carcinoma is similar morphologically and immunohistochemically despite the site of its origin. Therefore, sufficient clinical data are critical to its precise identification. In the chest computerized tomography examination performed postoperatively, we found no positive results. According to the World Health Organization (WHO), primary ovarian LCNEC possesses the characteristics of solid nests or trabecular patterns; presence of large tumor cell with a high mitotic rate, with positive reactivity for chromogranin, synaptophysin, pan-keratin, and CD56. Pulmonary type SCCO is morphologically characterized by the availability of small cells with obvious necrosis and lower immunohistochemical reactivity for pan-keratin and chromogranin [13]. In addition, primary SCCO should also be distinguished from the primitive neuroectodermal tumor, granular cell tumor, malignant lymphoma, intraabdominal desmoplastic small round-cell tumor, and anaplastic carcinoma.

The prognosis of mucinous carcinoma associated with SCCO is very poor. Although the five cases reported were all regarded as early-stage, without extraovarian invasion and metastasis after tumor detection, four patients died within 10 months after the surgery, and the follow-up period of the remaining patient was only nine months. Liver metastasis occurred in most patients despite the several cycles of adjuvant chemotherapy performed [3,5–7]. Generally, small-cell carcinoma has a significantly worse prognosis than mucinous carcinoma. Hence, in cases where both components coexist, the small-cell carcinoma may determine the prognosis. Patients diagnosed with hypercalcemic type SCCO usually have a very poor survival, generally dying within only two years. Eichhorn et al. reported that after long-term follow-up, five of seven patients died at an average of eight months (1–13 months), one patient died after an unknown time interval, and one was still alive at 7.5 years. In addition, two other patients had recurrent or residual disease at six and eight months, respectively [11]. The patient in our case also died eight months after the operation.

Table 1
Immunohistochemical properties of the different components of the ovarian tumor.

Markers	Source	Clone	Neuroendocrine component	Mucinous component
Pan-keratin	MXB	AE1/AE3	+ membrane	+
EMA	MXB	E29	–	+
CK7	MXB	OV-TL12/30	+	+ scattered
CgA	MXB	LK2H10 + PHE5	+	+
Syn	MXB	SP11	–	–
PR	DAKO	PgR 636	–	+ 8%
S-100	MXB	4C4.9	–	–
ER	ZSGB	EP1	–	–
SMA	MXB	14A	–	–
Inhibin	DAKO	R1	–	–
CD56	MXB	56C04	+	–
Ki-67	DAKO	MIB-1	+ 70%	+ 40%
Calretinin	DAKO	DAK-Calret-1	+ scattered	–
Vimentin	MXB	V9	–	–
Cam5.2	ZSGB	CAM5.2	–	+
CA125	MXB	TA347	–	–
CK20	MXB	Ks20.8	–	–
D2-40	DAKO	D2-40	–	–
WT-1	MXB	WT49	–	–
NSE	MXB	E27	+	–
TTF-1	MXB	SPT24	+	–
P53	DAKO	DO-7	+	+
P16	MXB	6H12	+	+
BRG1	XTBT	EPNCIR111A	–	+

The occurrence of a collision tumor comprising a primary neuroendocrine tumor of ovary and mucinous carcinoma is extremely rare. Here, we report such a case in a premenopausal female. After comprehensive literature search, we found that, so far, only a few cases have been reported on this type of collision tumor [3,5–7]. HE and immunohistochemical staining for several neuroendocrine markers (chromogranin, CD56), CK20, CK7, and TTF-1 were performed to confirm the diagnosis of collision tumor. The histogenesis of neuroendocrine tumors is currently unclear. Mature neuroendocrine cell components are considered to have the potential for neoplastic transformation into ovarian neuroendocrine tumors [7,11]. Another viewpoint is that ovarian neuroendocrine tumors may be obtained as a result of the neoplastic neuroendocrine transformation of non-neuroendocrine cells, which is accompanied by gene sequence activation, similar to that of neuroendocrine cells [7,14,15]. Another hypothesis is that neuroendocrine tumors originate from teratoma cells [16]. The last hypothesis supports the existence of pure SCCO, which directly developed from normal ovarian tissue and was further confirmed by the detection and isolation of neuroendocrine cells in normal ovaries [16,17].

In summary, Small-cell carcinoma-associated ovarian mucinous carcinoma is an extremely rare tumor with high-grade malignancy that often occurs in adult women with complaints of abdominal distension. The timely identification of small-cell carcinomas among other ovarian tumors is vital to the prompt and accurate determination of the therapy and the accurate prognosis prediction because of their highly invasive and metastatic potential.

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Authors' contributions

Zhe Wang conceived and designed the experiment. Jie Wei

Table 2
Summary of the cases of small-cell carcinoma-associated ovarian mucinous carcinoma.

Cases	Ages (years)	Location	diagnosis	Tumor size (cm)	FIGO stage	Therapy	Follow-up
Grandjean et al [3].	32	Left ovary	SCCPT + microinvasive mucinous cystadenocarcinoma	20 × 13 × 11	IA	BSO + Omen + ChT	NED, 9 months
Jones et al [6].	65	Left ovary	SCC + mucinous cystadenocarcinoma	16.5 × 13.6 × 9	IA	TAH + BSO + Omen + Appen	Died of hepatic metastases and peritoneal implants, 10 months
Khurana et al [5].	22	right ovary	SCC + mucinous adenocarcinoma	Not mentioned	IA	USO + Appen + ChT	Died of multiple liver metastases, 3 months
Collins et a l [7].	34	Left ovary	SCC + mucinous adenocarcinoma	16 × 11 × 8	IC	TAH + BSO + Omen + ChT	Died of multiple metastases, 6 months
Present case	51	Left ovary	SCCPT + mucinous adenocarcinoma	9.9 × 7.2 × 6.8	IA	TAH + BSO + Omen + ChT	Died, 8 months

Note: SCCPT = small-cell carcinoma of pulmonary type; SCC = small-cell carcinoma; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; Omen = omentectomy; Appen = appendectomy; ChT = chemotherapy; USO = unilateral salpingo-oophorectomy; NED = no evidence of disease.

performed the experiments. Jie Wei and Yingmei Wang contributed the acquisition of data. Jie Wei and Peifeng Li analyzed and interpreted the data. Jie Wei and Yingmei Wang wrote the manuscript. Jie Wei, Linni Fan and Mingyang Li revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of the Air Force Military Medical University. The consent to participate is not applicable.

Consent for publication

Written informed consent was obtained from the patient's daughter for the publication of this case report and any accompanying images.

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Declaration of Competing Interest

The Authors declare that there is no conflict of interest.

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