case report

Borderline mucinous cystic ovarian tumor with mural nodules (carcinosarcoma)

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Carcinosarcoma mural nodules arising form a mucinous ovarian neoplasm is very rare and only two published cases have been reported. We report a case of a 29-year-old female patient who suffered from severe lower abdominal pain unrelated to menstruation for 1 year. She came to our (Shin-Kong Hospital) gynecology outpatient department in February 2010. The CT scan revealed a large cystic tumor, measuring approximately 36 cm in greatest dimension and at least 2 solid foci were noted. The patient underwent left salpingo-oophorectomy. A carcinosarcoma mural nodule arising within a mucinous ovarian neoplasm was diagnosed. The patient was treated by further chemotherapy and was free of the disease at time of publication. We reviewed the published studies, and in particular looked at the histology and immunohistochemistry of tumors, in which sarcomatoid carcinoma and carcinosarcoma-like nodules were diagnosed. We also discussed the differential diagnosis of the mural nodule in a mucinous cystic neoplasm.

Mucinous cystic tumor with mural nodules is a rare neoplasm; only about 80 cases have been published in the past 30 years.[1] Only two of them had carcinosarcoma in the mural nodules. In these two cases, one was a mucinous cyst adenoma[2] and the other was a mucinous carcinoma.[3] We report a case of a 29-year-old female with a borderline mucinous cystic tumor with mural nodules (carcinosarcoma) (FIGO stage Ia).

CASE

The patient was a 29-year-old nulliparous female and a hepatitis B carrier. She had no operative history and had a normal menstrual cycle. She was unmarried and had no family history of gynecology disease. She did not take any medication in previous years. She suffered had from dysmenorrhea and constipation for years and tolerated it. Lower abdomen swelling was noted for the previous year prior to presentation. She presented with severe lower abdominal pain unrelated to menstruation. She first presented to Shuang-He Hospital and the diagnosis of ovarian tumor was made. The patient came to our (Shin-Kong Hospital) gynecology outpatient department (OPD) for a second opinion in February 2010. At that time, the physical examination was generally normal except for mild tenderness over the lower abdomen with a palpable mass. There was no rebounding pain. The laboratory investigation performed showed an abnormal cancer antigen 125 (CA125) elevated to 55.04 U/mL, CA19-9 elevated to 70.62 U/mL and CA153 elevated to 28.87 U/mL. The carcinoembryonic antigen value and other laboratory data were within normal limits.

The CT scan revealed a large cystic tumor, measuring approximately 36 cm in greatest dimension, with a few thin septa in homogeneous internal attenuation. At least two solid foci were noted and measured approximately 4.5 cm in greatest dimension, attached to the left lateral wall of the tumor (**Figure 1**).

The patient underwent left salpingo-oophorectomy and adhesiolysis. At the time of surgery, a large left ovarian cyst was noted with changes consistent with torsion. The cyst was found to contain a 5400 mL of reddish brown fluid on aspiration. This cystic tumor focally adhered to the peritoneum. The right adnexa were normal on gross examination. The multilocular cystic tumor was received opened in the surgical pathology laboratory. The tumor measured 28×15×3 cm in size and weighed 600 g (**Figure**

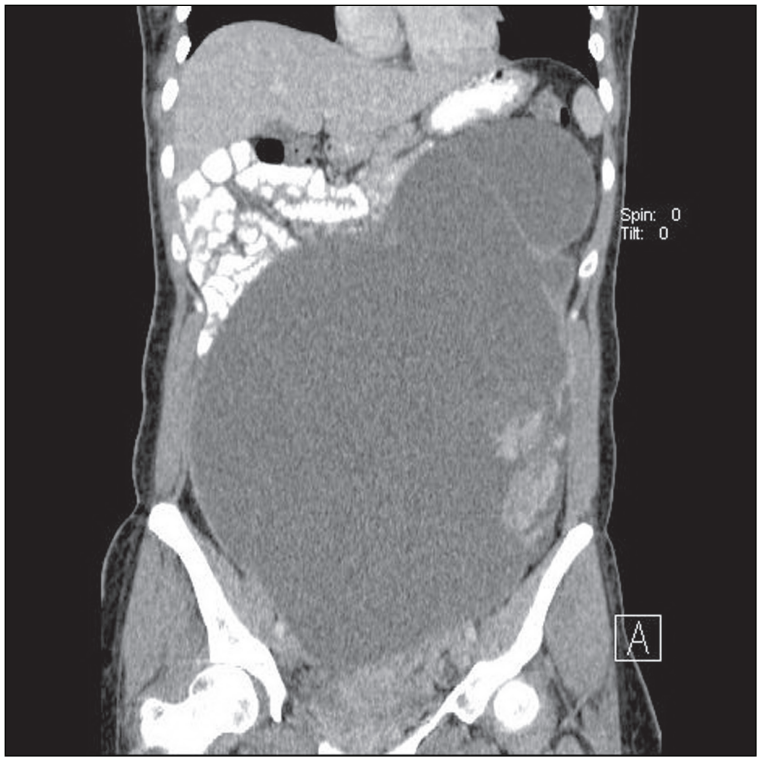

Figure 1. The abdominal CT scan. One huge cystic tumor in homogeneous internal attenuation, at least two foci of solid parts, around 4.5 cm attach to left lateral wall of the tumor.

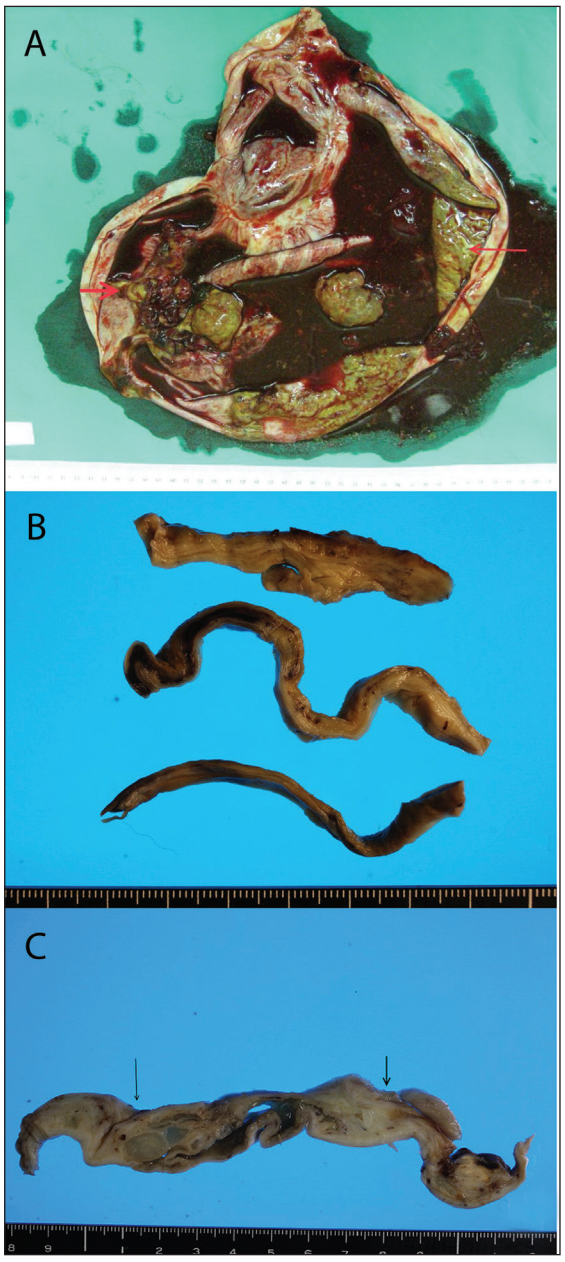

Figure 2. The cystic tumor was opened when received. Two pieces of elastic clot-like masses inside detach partially from cystic wall. A) Several yellow, solid nodules adhesive on the ovary cyst internal surface (thick arrow) and one diffuse yellow, solid patch also adhesion on internal surface (thin arrow), B) The diffuse patch measured only 0.3 cm thick. C) The septa was partially thickened with a multicystic pattern and mucous material inside (thin arrow). The mural nodule was present at the right side (thick arrow).

2A). The fallopian tube was normal on gross examination. The external surface of the cyst wall was smooth. Further examination showed two pieces of clot-like materials within the cyst wall, measuring approximately 5.5 cm in greatest dimension. The internal surface of the ovarian cyst showed multiple yellow, solid nodules measuring up to 5×4×2 cm in greatest dimension. In addition, there was also a diffuse yellow, solid area measuring approximate 25×10 cm in dimension and 0.3 cm in thickness present on the internal aspect of the cyst (**Figure 2B**). The septa were thickened up to 2.5 cm in diameter. A cross section of the septa showed multiple small cysts with a mucoid material (**Figure 2B**). Multiple sections of tumor were taken and fixed in neutral-buffered formalin and embedded in paraffin. The sections were stained with hematoxylin and eosin. Immunochemistry using cytokeratin (DAKO, AE1/AE3, 1:100) and vimentin (DAKO, 1:100) was done on some sections. Immunoreactivity was interpreted as positive or negative.

Microscopic features

The cyst was lined by mucinous epithelium showing a benign and borderline change focally with intestinal differentiation (**Figure 3A**). The multicystic cavity contained mucus materials inside. The external aspect of the cyst showed no reactive response and no evidence of rupture. The mural nodules were composed of spindle-shaped to ovoid-shaped cells with marked nuclear pleo-

morphism (**Figure 3B**). They had large clear nuclei with prominent nucleoli. These cells were located just below the mucinous epithelium that appeared circumscribed but devoid of a capsule. The mitotic activity was increased, and approximately 8 mitoses per 10 high-power field were recorded. Focally, there was osteoid metaplasia (**Figure 3C**). There was no evidence of vascular invasion. These spindle-shaped cells were seen to invade into the stroma of the cyst. The diffuse yellow patch seen on gross examination also contained pleomorphic spindle-shaped cells that were similar in appearance to those seen in the mural nodules (**Figure 3D**). Some large mural nodules extended toward the lumen of the cyst and showed hemorrhage, acute and chronic inflammation, and necrosis (**Figure 3E**). Immunochemistry performed showed the atypical spindle-shaped cells to exhibit strong vimentin positivity. Cytokeratin was negative. This reaction pattern was consistent with a nonepithelial component (sarcoma). Some areas were reported with several large cells that contained eosinophilic cytoplasm, and enlarged hyperchromatic and pleomorphic nuclei with large eosinophlic nucleoli. A higher magnification view of these components is shown in **Figure 3F**. Some of these cells were dispersed within the sarcoma stroma (**Figure 4A**) and some formed glandular structures (**Figure 4B**). The immunostaining performed using cytokeratin demonstrated a strong positive reaction and a negative reaction to vimentin (**Figure 4C**), confirming that they were epithelial in nature. These cells were not similar in appearance to the mucinous epithelium lining the main cyst. No transitional area was seen. The sarcoma cells were clearly distinguished from the carcinoma cells by vimentin positivity (**Figure 4D**).

The microscopic examination of the left tube showed no evidence of tumor. The abdominal washing cytology performed was negative. Based on the above findings, a borderline mucinous cystic tumor with mural nodules (carcinosarcoma), pathologic FIGO stage Ia, was diagnosed. No further biopsy or operation done after the left salpingo-oophorectomy.

After the operation, CA125 decreased to 21 U/mL in April. The patient had adjuvant chemotherapy taxotere (75 mg/m^2) and carboplatin (5AUC) every 3 weeks for 6 cycles after the operation, but had to stop because of hepatitis B exacerbation after 4 cycles of chemotherapy. After chemotherapy, CA125 decreased to 13 U/mL in December. She was followed at National Taiwan University Hospital OPD for 10 months and is free of the disease.

DISCUSSION

Cystic ovarian epithelial tumors with mural nodules

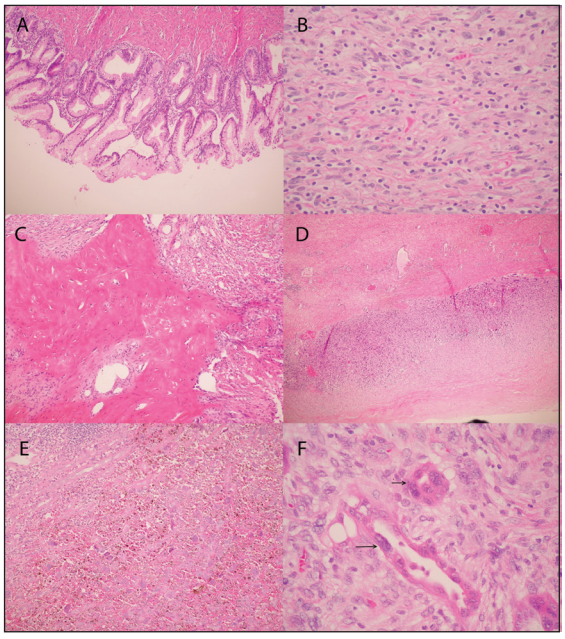

Figure 3. The epithelium cells inside mural nodules. A) Several large cells contain eosinophilic cytoplasm, enlarged hyperchromatic and pleomorphic nuclei with large eosinophlic nucleoli that are dispersed within the sarcoma stroma. B) Similar cells arranged to glandular structures (100×, HE stain). C) Immunostaining showed strong positive reaction of cytokeratin and negative reaction to vimentin. (400×). D) The stroma cells of sarcoma were clearly distinguished from the epithelium cells.

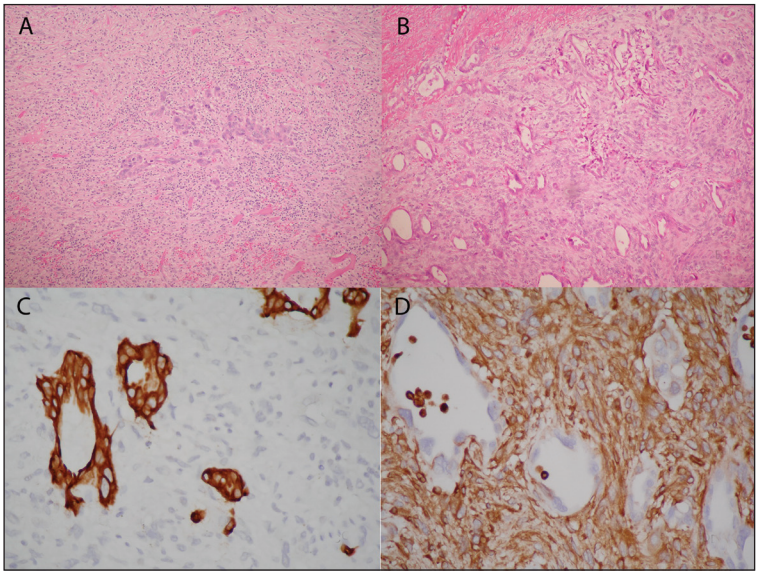

Figure 4. The components of the ovarian tumor with mural nodules. A) The cyst is lined by mucinous epithelium with focally borderline intestinal differentiation. B)The mural nodules are composed of spindle shaped cells with marked nuclear pleomorphism. C) Focal osteoid metaplasia inside mural nodules. D) The pleomorphic spindle shaped cells similar to the components inside mural nodules. E) Some large mural nodules extended toward the lumen of the cyst and showed hemorrhage, acute and chronic inflammation and necrosis (40×). F) There was a higher magnification view of the carcinosarcoma. The arrow points out the epithelial component (400×, H&E stain).

Table 1. The summary of previous classification and analysis of different variants of mural nodules.

Feature	Sarcoma	SLMN	Anaplastic carcinoma	Carcinosarcoma-like	Carcinosarcoma
Patient age	Older	Younger	Older	Younger	Young
FIGO stage	I-IV	Ia	I-IV	I	I-?
Prognosis	Poor	Not effective	Poor	?	?
No. of nodules	-	One to several	Usually single	One	Several
Size (cm)	Large	Small (0.6-6)	Large (1-10)	Small (1.2-5)	1.5-5.5
Circumscription	Good (grossly) Poor (micro)	Good, sharp	Poor	Poor	Variable
Vascular or stromal invasion	Present	Absent	Present	Present	Present
Cell composition	Monotonous	Heterogeneous	Homogenous	Heterogeneous	Homogenous
Inflammatory cells	Sparse	Numerous	Few, variable	Numerous	Few, variable
Giant cells	Common	Common	Uncommon	Common	Few
Spindle cells	Common	Common	Occasional	Common	Common
Large eosinophilic cells	-	Occasional	Common	Common	Common
Cytokeratin	-	Scattered, negative	Diffuse positive	Positive of carcinoma cells	Positive of carcinoma cells
Vimentin	Positive	Positive	Sometimes positive	Carcinoma: ± Stroma: +	Carcinoma: ± Stroma: +
Necrosis	Common	Often		Sometimes	

SLMN: Sarcoma-like mural nodules ?: unknown.

are rare neoplasms and were first described by Prat in 1979.[4] The epithelium of the cyst may be lined by benign, borderline, or malignant cells. Several kinds of mural nodules have been reported. They are further classified into sarcoma-like, sarcoma, and anaplastic carcinoma. Baergen et al classified mural nodules into reactive (sarcoma-like), benign, carcinoma (with a variant of combined carcinoma and reactive elements), sarcoma, and combined carcinoma and sarcoma (carcinosarcoma) in 1995.[5] The WHO Classification divided the mural nodules of ovarian mucinous cystic tumors into malignant (anaplastic carcinoma, sarcoma, or carcinosarcoma) and benign (sarcoma-like) in 2003. On review of the published studies of the serous borderline ovarian tumor with mural nodules, Gungor et al found that they were extremely rare and only five cases have been published.[1,6]

The prognosis of these cystic ovarian epithelial tumors with mural nodules is uncertain. Sarcoma-like nodules are considered to be reactive and do not affect the prognosis.[4,7] Sarcoma and anaplastic carcinoma are considered to have a poor prognosis except in cases staged as FIGO stage Ia with no tumor rupture.[5,8-10] The outcome of cystic ovarian epithelial tumors with mural nodules depends on the histology of nodules (carcinoma or sarcoma) and the stage of the disease. Thus, it is very important to determine the exact components of the mural nodules since the prognosis of these tumors is related to the histology.

As the number of these cases increased, it became easier to determine the different components within the mural nodules. The main difficulty with mural nodules arises when there is more than one component within nodules, especially sarcoma and sarcoma-like components. It is not easy to distinguish between sarcoma and sarcoma-like components within nodules since both of them contain pleomorphic cells with bizarre nuclei and many mitotic figures. The sarcoma nodules typically are seen in older patients and are large in size. They contain a monotonous cell population, showing poor circumscription, with vascular or stromal invasion and lack of inflammatory cells. On the other hand, sarcoma-like nodules show a polymorphous population of cells composed of inflammatory cells and giant cells, with no evidence of vascular or stromal invasion.[11]

Immunohistochemistry is useful to separate the

Table 2. Summary of the cases of ovarian mural nodule tumors, with new terminology and carcinosarcoma.

Reference (year)	Case	Epithelial ovarian tumor	Mural nodule	Age	FIGO stage	Therapy	Follow-up
Mural nodule tumors with new terminology, carcinoma							
Andrews et al (2008)	1	Serous, borderline	Sarcomatoid carcinoma	49	I	TAH + BSO + Omen + appen	DOD, 32 months (liver metastasis)
Chang et al (2005)	1	Mucinous borderline	Carcinosarcoma-like	35	I	TAH + BSO + Omen + appen	NED, 14 months
Bagué et al (2002)	2	Mucinous borderline	Sarcoma-like + anaplastic carcinoma	75	Ia	Surgery + ChT	NED, 15 years
		Mucinous borderline	Sarcoma-like + anaplastic carcinoma	75	Ia	Surgery + ChT	NED, 15 years
Suurmeijer (1991)	1	Mucinous carcinoma	Carcinosarcoma-like	30	I, Rupture	TAH + BSO + Omen + ChT	NED, 5 years
Søndergaard and Kaspersen (1991)	1 (Case 2)	Mucinous cystadenocarcinoma	Sarcoma-like + anaplastic carcinoma	37	I	RH + BSO + Omen + appen	NED, 18 months
Rosa et al (1991)	1	Serous, borderline	Sarcomatoid carcinoma	?	II	?	DOD, 6 months (pulmonary, bone metastasis)
McCullough et al (1988)	1	Serous, cystadenocarcinoma	Sarcomatoid carcinoma	44	III	TAH + BSO + ChT	DOD, 6 months (liver metastasis)
Fujii et al (1985)	1	Mucinous borderline	Sarcoma-like + anaplastic carcinoma	29	I	TAH + BSO	NED, 22 months
Mural nodule tumors with carcinosarcoma components							
Present case (2010)	1	Mucious borderline	Carcinosarcoma	29	Ia	USO + ChT	NED, 10 months
Søndergaard and Kaspersen (1991)	1 (Case 3)	Mucinous cystadenoma	Carcinosarcoma	29	I	RH	NED, 24 months
Bruijn et al (1987)	1	Mucinous carcinoma	Carcinosarcoma	27	Ia	USO + Omen	?

RH=radical hysterectomy; TAH=total abdominal hysterectomy; BSO=bilateral salpingo-oophorectomy; USO=unilateral salpingo-oophorectomy; appen=appendectomy; Omen=omentectomy; ChT=chemotherapy; DOD=died of disease; NED=no evidence of disease; ?=unknown

components within the mural nodules. Before the advent of immunohistochemistry, some carcinoma nodules were misdiagnosed as sarcoma-like (reactive). When using cytokeratin, the positive epithelial cells are identified within the bizarre stromal components of the nodules. On the other hand, immunohistochemistry is not useful to distinguish sarcoma and sarcoma-like nodules since vimentin is positive and cytokeratin is negative in both malignant and reactive components of the nodules.

The age of the patient, prognosis, histologic features, and immunohistochemistry reaction for various mural nodules are summarized in **Table 1**.[5,8,9] The summary here is useful for making the differential diagnosis of the components within the nodules, but exceptions do occur. Within the last 30 years, the terminology used to describe carcinoma and carcinosarcoma components of mural nodules has been somewhat confusing. We reviewed the published studies, and in particular looked at the histology and immunohistochemistry of tumors with mural nodules where the diagnoses of sarcomatoid carcinoma[6,12,13] and carcinosarcoma-like[14,15] were made. After analysis of the histology and immunohistochemistry, sarcomatoid carcinoma and carcinosarcoma-like

tumors were found to be epithelial in nature and represent carcinoma. The cases of sarcomatoid carcinoma have epithelial cells that are often spindle shaped. These epithelial spindle cells and the transition zone between glandular epithelial cells and the stroma cells are cytokeratin positive. The transition zone was not present in our case. Two cases were described in 1991 and 2005[14,15] using the term carcinosarcoma-like, and they described features of carcinoma and sarcoma-like (reactive) elements. In our case, there were malignant stroma cells (sarcoma). Only two real carcinosarcoma cases have been previously published.[2,3] The mural nodule tumors used new terminology that we reclassified as carcinoma and carcinosarcoma. They are summarized in **Table 2**.[2,3,6,12-17]

Mucinous cystic ovarian tumor with mural nodules should be distinguished from malignant mixed mesodermal tumor (MMMT). MMMT is usually a solid neoplasm composed of epithelial and stromal elements. These elements usually do not merge with each other. It is also unusual to find mucinous epithelium in an MMMT. Moreover, MMMT occurs almost exclusively in older patients. In our case, there were several mural nodules. The cyst was lined by mucinous epithelium with subepithelial sarcoma. Some mural nodules had a patch-like appearance. The sarcoma invaded the stroma of the cyst. The sarcoma stroma contained pleomorphic spindle cells with no inflammatory cells. Foci of osteoid metaplasia were present. No evidence of vascular invasion was reported. The eosinophilic large cells dispersed within sarcoma stroma were cytokeratin positive, confirming their epithelial nature (carcinoma).

Reports of carcinosarcoma elements inside mural nodules are rare. A review of the published studies reveals that the mural nodules with anaplastic carcinoma usually had a poor prognosis and were seen in older patients. The two cases shown in **Table 2** reveal that carcinosarcoma occurred in young patients (27 and 29 years old). One was alive well after 24 months of follow-up and the other one was lost to follow-up. Thus, follow-up was only available for two patients including our case. The follow-up periods were also not long enough (24 and 10 months) to ascertain prognosis.

Mural nodules are rarely identified in ovarian cystic tumors, and thus the prognosis is not well defined. It is surprising that even the carcinosarcoma cases also had anaplastic carcinoma components inside. They occur in patients of younger age (below 30 years), and the patients have a relatively better clinical outcome. Because of the above reasons, the existence of sarcoma combined with carcinoma components in mural nodules necessitates careful examination, as the outcome of the tumor depends on the histology.

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