

Original Article

Ovarian microcystic stromal tumors: clinical, radiological, and pathological studies of two cases

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Abstract: We observed two unusual cases of ovarian microcystic stromal tumors (MST). These two patients had no obvious clinical symptoms, and the imaging findings were separately diagnosed as cystic teratoma and ovarian malignant tumors. Significantly, during the operation, none of the pathologists considered the possibility of MST. The two cases showed similar morphological and immunophenotypic characteristics: some nests were made up of microcysts with round or oval shapes, and the cavity was bright and empty. In some areas, the cell nests of microcysts were not obvious and were identified as solid cell nests. The tumor cells contained eosinophilic cytoplasm and neutral nuclei. Mitotic figures were rare. Immunohistochemistry indicated that the tumor cells were all positive for CD10, vimentin, WT1, and β -catenin, but negative for Cytokeratin, α -inhibin, CD99, ER, PR, S-100, EMA, CD56, CgA, Syn, Pax-8, Desmin, SMA, and calretinin. The Ki67 index was less than 5%. Based on the above characteristics, a diagnosis of ovarian MST was made after the operation. The final repeated CT scan revealed no recurrence during the post-surgical course. Here the clinical, radiological and pathological characteristics of these two cases diagnosed as ovarian MST are presented in order to help avoid future misdiagnosis and over-treatment.

Keywords: Microcystic stromal tumor, ovary, differential diagnosis

Introduction

Microcystic stromal tumors (MST) are a kind of rare, sex cord stromal tumor which were long described as an “unclassified ovarian tumor” [1, 2], but now they are recognized as a new entity according to the revised World Health Organization sex cord-stromal tumor classification [3]. MST was first pointed out by Irving and Young in 2009 and was considered to be a benign tumor, but the origin of this kind of neoplasm is still unclear [4, 5]. In this study, we report two cases of MST and present a related literature review, and we describe the cases' clinic-pathological characteristics in order to improve the understanding of this unusual tumor among radiologists, pathologists, and gynecologists.

Materials and methods

Clinical data collected

In this study, information and tissue samples from two cases diagnosed with MST were ob-

tained from the Department of Pathology, Yantai Yuhuangding Hospital. The clinical data, including the follow-up information, was collected.

Sample process and morphological observation

The samples were soaked in 10% buffered formalin for complete fixation after surgery. Subsequently, tissue dehydration and paraffin embedding were done. 4 μ m sections were cut from tissue blocks for hematoxylin and eosin (H&E) staining. The tissue morphology was observed under a microscope.

Immunohistochemical staining

The EnVision two-step method was used by the automatic immunostainer (VENTANA) for immunohistochemical staining and the DAB color. Each slice was stained with known positive tissues as a positive control, and the negative control replaced the antibody with PBS. All the antibodies, including cytokeratin, vimentin, a-

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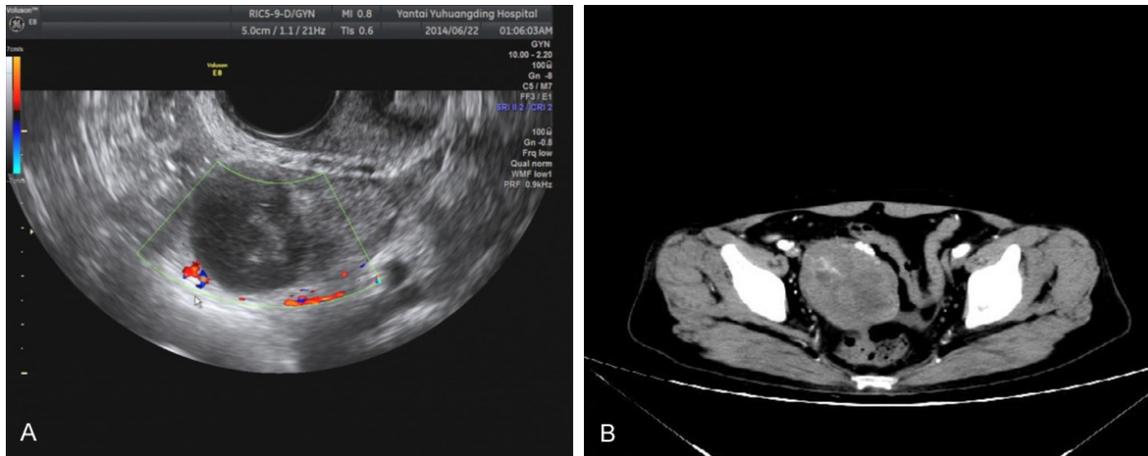


Figure 1. An image scan of MST. A. First case: The mass with a low echo was found in the right attachment area by ultrasound. There was abundant liquid components and a lack of ingredients. The blood flow in the cyst was not rich and this disease was considered to be ovarian cystic teratoma. B. Second case: A solid mass was found in the right ovary accompanied by an uneven enhanced signal. A malignant tumor in the right ovary was diagnosed with a CT scan.

inhibin, CD99, CD10, ER, PR, WT1, S-100, EMA, CD56, CgA, Syn, Pax-8, desmin, SMA, β -catenin, calretinin, and Ki67, used in this study were bought from Beijing Zhongshang Jinqiao Biotechnology Co., Ltd.

Results

Clinical data

Case 1: The patient was a 46-year-old female. The cyst was found in the right attachment area, and the patient did not experience any abdominal pain, distension, or vaginal discharge during the previous year. There was no significant change in the mass according to the regular review. The patient had no other medical history and was sent to the Department of Gynecology with the clinical diagnosis of a pelvic mass. Using a preoperative ultrasound examination, a circular liquid dark mass with a size of 2.8 cm \times 2.5 cm area was detected in the right ovary. This dark area had a clear boundary, a thick wall, but no blood flow signal (**Figure 1A**). There was no abnormal echo in the left ovary. The ultrasound diagnosis was a chocolate cyst in the right ovary. The patient underwent a right accessory resection under laparoscopy. During the operation, the uterus was found to be normal, but two small leiomyoma were seen at the end of the uterus with diameters of 0.4 cm and 0.6 cm respectively. An ovarian cyst about 3 cm in diameter on the

right ovary was found with a smooth surface and no adhesion to the surrounding tissues. The right side of the fallopian tube and the left accessory showed a normal appearance. No abnormalities were found in the pelvic region or in the other organs in the abdomen. Subsequently, the right ovarian cortex was open and the cyst was exposed. The contents of this cyst included old bleeding, and the capsule wall was tough. The cyst was resected completely and then sent for a pathological examination. Macro pathology showed a piece of cystic tissue, the volume of which was 4.5 cm \times 3 cm. The wall of the cyst was soft and had an uneven thickness. The inner wall was grayish red and rough. The pathological diagnosis done during the operation indicated that the sex cord stromal tumor on the right ovary should be taken into account, but its nature was not easy to clear. The patient was followed up for fifty four months after surgery and repeated imaging showed no tumor recurrence.

Case 2: The patient was a 56-year-old female found with a pelvic mass in a physical examination who was then she was sent to our Department of Gynecology. The patient had occasional pain in the left lower abdomen with no fever, diarrhea, or vaginal discharge. She had a history of hypertension for ten years, gout for four years, cerebral infarction for two years, and diabetes for two months. A solid mass on the right ovary with a size of 7.7 cm \times 5.6 cm \times

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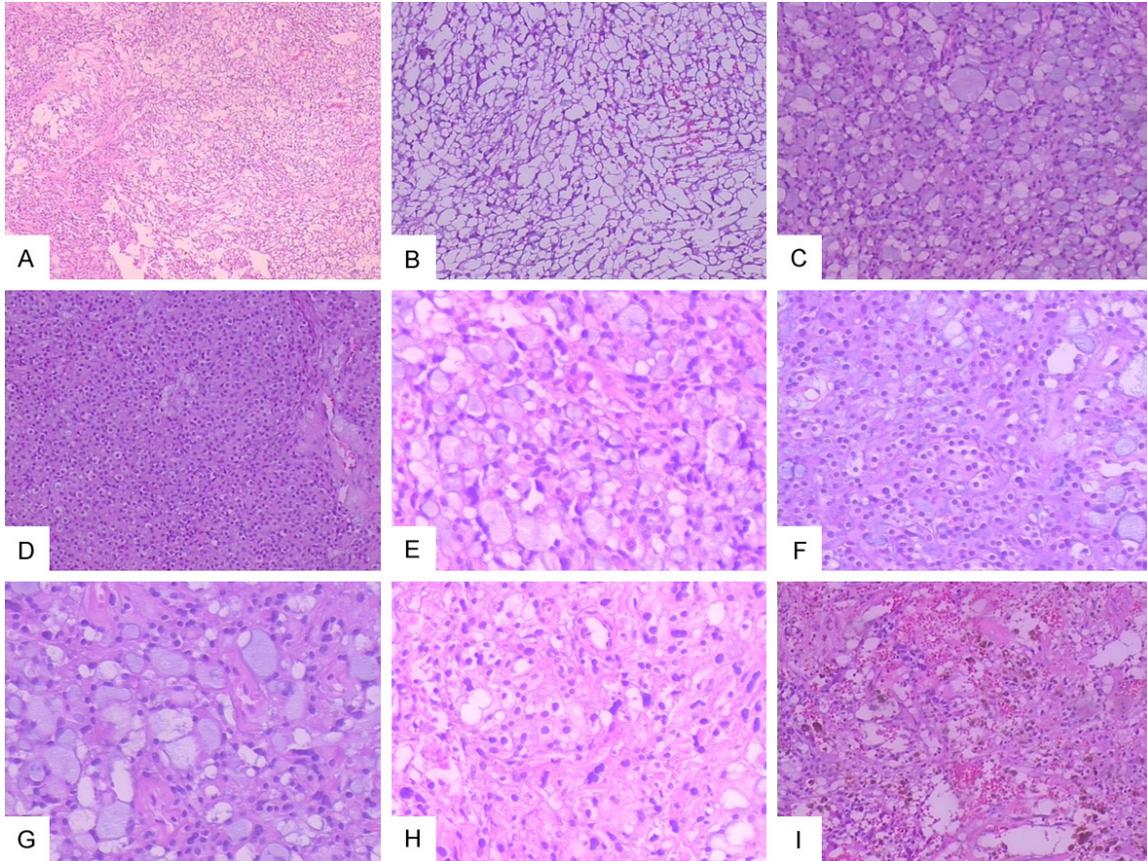


Figure 2. Histological characteristics of MST. (A) Under low magnification, the tumor tissue was divided into nests with different sizes by the hyaline interstitium. There were many microcysts in the nest. (B) The content in these cystic cavities was bright. (C) Pink or light blue secretions could also be observed in some microcysts. (D) There were no microcapsules formed in some areas and the cells were arranged as flaky structures. (E) The tumor cells around the cystic cavity were oval or spindle-shaped with red staining cytoplasm and uniform size nuclei. (F) The tumor cells were uniform in size with clear boundaries showing a “plant cell-like” or “grid-like” appearance in the flaky region. (G) There were abundant and slender capillaries existing between the tumor cell nests. (H) Ugly cells were seen in some areas, and the nucleus was large in volume and irregular in shape. (I) The hemorrhage was found focally. (H&E staining: A-D, I, low magnification; E-H, high magnification).

5.4 cm, including a cystic part with a size of 2.4 cm × 1.8 cm, was found by ultrasound. An enhanced CT Scan showed a solid-cystic mass which was sized 7.4 cm × 6.2 cm × 5.5 cm and considered a malignant tumor (**Figure 1B**). The surgery was performed under general anesthesia. During the operation, the solid tumor was found on the right ovary about 8 cm × 7 cm × 5 cm in size. There was no sputum on the surface, no adhesion to the surrounding tissue, and the left attachment and the right fallopian tube showed no abnormal appearance. Then the patient underwent a laparoscopic hysterectomy and a bilateral accessory resection. The tumor was oval and with a volume of 7 cm × 6 cm × 4 cm, in which the cut surface was gray and had a hard appearing, solid-cystic appear-

ance. Because the pathological examination could not confirm the nature of the tumor, no enlarged resection was performed during the operation. The time of follow-up was forty six months and there was no tumor recurrence.

Morphological findings

A similar histological morphology was shared in these two cases. Under low magnification, the tumor cells appeared distributed in a flaky or nested arrangement. Among most of the nests, cystic cavities were formed with round or irregular shapes by fusion (**Figure 2A**). The content in these cystic cavities was bright (**Figure 2B**) and had pink or light blue secretions (**Figure 2C**). In some areas, there were no microcapsules for-

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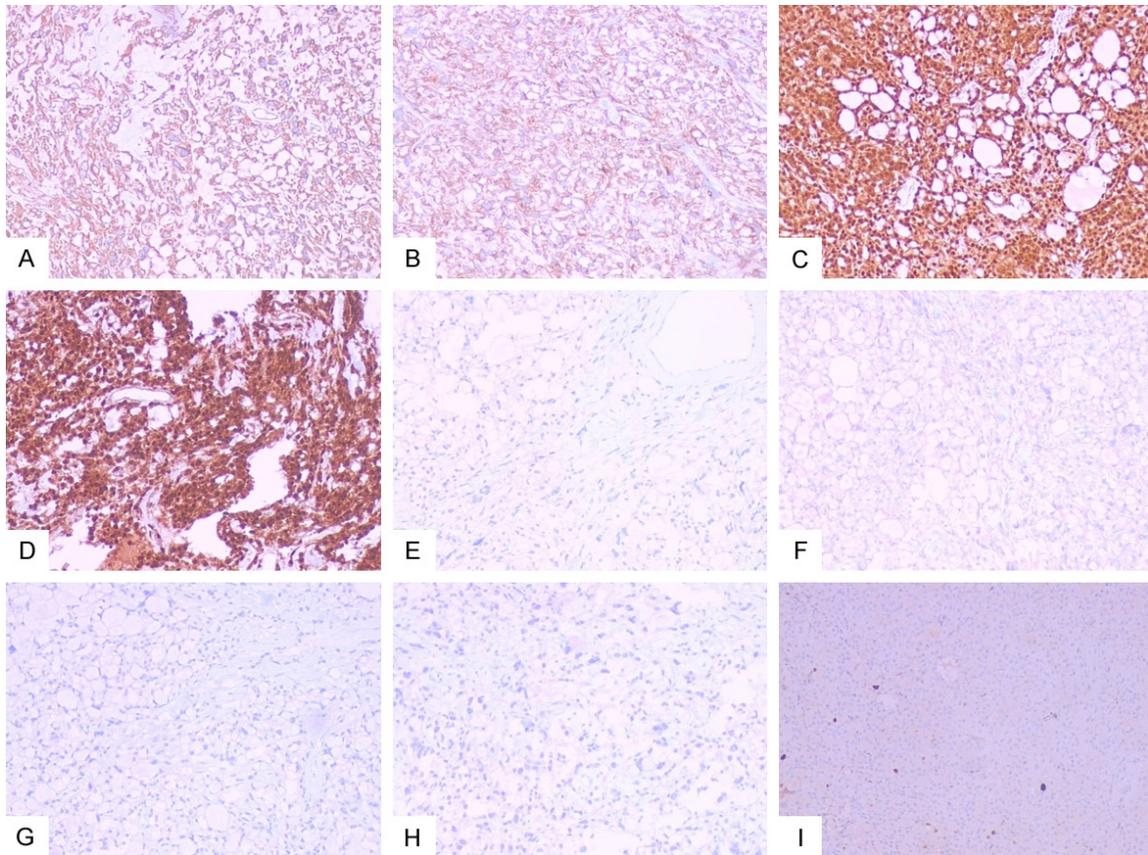


Figure 3. Immunohistochemical features of MST. The tumor cells were positive for (A) vimentin, (B) CD10, (C) β -catenin and (D) WT1 but they were negative for (E) cytokeratin, (F) α -inhibin, (G) syn and (H) pax-8. (I) The Ki67 index was less than 5%. (Envision, Low magnification).

med, and the cells were arranged as a flaky structure (**Figure 2D**). Hyaline degeneration or mucoid degeneration were observed in the interstitium. Under high magnification, the neoplastic cells around the cystic cavity appeared round, oval or spindle-shaped and short, with red staining cytoplasm and a nuclear uniform size (**Figure 2E**). In the flaky region, the tumor cells were uniform in size with a round or oval morphology and a clear boundary showing a “plant cell-like” or “grid-like” appearance. The cytoplasm was basophilic or translucent. The nuclei were round and centered without any obvious atypia, and the nucleoli and mitosis were not easy to see (**Figure 2F**). There were abundant and slender capillaries between the tumor cell nests (**Figure 2G**). In the first case, large and ugly cells were seen in some areas. The nucleus was large in volume and irregular in shape (**Figure 2H**). In the second case, focal hemorrhaging was found (**Figure 2I**).

Immunohistochemistry staining results

Immunohistochemistry showed that these two cases had the same immunohistochemical pattern and that the tumor cells were all stained positively with the antibody vimentin (**Figure 3A**), CD10 (**Figure 3B**), β -catenin (**Figure 3C**), and WT1 (**Figure 3D**) but stained negatively with the antibody cytokeratin (**Figure 3E**), CD-99, ER, PR, α -inhibin (**Figure 3F**), S-100, CgA, Syn (**Figure 3G**), EMA, CD56, desmin, Pax-8 (**Figure 3H**), SMA, and calretinin. The indexes of Ki67 in the two cases were less than 5% (**Figure 3I**). The immunohistochemistry staining results are shown in **Table 1**. On the basis of the histological features and the immunohistochemical characteristics, a diagnosis of ovarian MST was made.

Discussion

MST is one kind of rare sex cord stromal tumor which has been seen in recent years. By review-

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Table 1. Results of antibodies employed in the immunohistochemistry study

Antibody	Clone	Dilution	Result
Anti Cytokeratin	AE1/AE3	1:100	-
Anti Vimentin	UMAB159	1:50	+
Anti α -inhibin	AMY82	1:50	-
Anti CD99	PCB1	1:50	-
Anti CD10	UMAB235	1:100	+
Anti ER	EP1	1:100	-
Anti Ki67	UMAB107	1:100	< 5%
Anti PR	6F11	1:50	-
Anti WT1	6F-H12	1:100	+
Anti S-100	Rabbit polyclonal	1:100	-
Anti EMA	UMAB57	1:100	-
Anti Syn	EP158	1:100	-
Anti CgA	LK2H10	1:100	-
Anti CD56	UMAB83	1:100	-
Anti Pax-8	OTI6H8	1:100	-
Anti Desmin	EP15	1:100	-
Anti SMA	UMAB237	1:100	-
Anti β -catenin	UMAB15	1:100	+
Anti calretinin	Rabbit polyclonal	1:100	-

ing the literature, we determined that the clinical characteristics of MST are as follows: (1) All the patients are adults without bias towards young women or older women. (2) The tumors always occur in the unilateral ovary, but there was occasional reports of this tumor occurring in the testes [6]. (3) Lower abdominal pain or pelvic mass is the most common, clinical, first symptom. (4) The tumor has clear boundaries within the ovarian tissue, and a few cases showed a solid-cystic appearance and necrosis [7, 8]. (5) None of the cases reported in the literature had any evidence of disease after surgery [9]. The two cases described here are currently free of disease and without any symptoms.

Until now, no specific imaging characteristics of ovarian MST have been documented. Predominantly cystic masses with solid components which have shown FDG avidity and mild vascularity have been reported [10]. The first case in our group was misdiagnosed as a cystic teratoma due to multiple cystic components, few solid components, and an insufficient blood flow signal in the mass. The second case was diagnosed as an ovarian malignant tumor by radiologists due to the uneven and enhanced signal in the solid part. Therefore the possibility

of MST should be considered in the imaging examination, and radiologists should pay more attention to this disease to avoid a missed diagnosis or a misdiagnosis, although this is rare.

Pathologically, the tumors are cystic or cystic-solid, and it is uncommon that the tumors are completely solid in gross [11-13]. The cyst might contain a remote hemorrhage and the solid region always shows a pale or yellow appearance [14]. The classic histological features include: (1) MST consists of a mixed microcapsule and a solid structure. (2) A thick hyaline or mucinous fibrous mass could be observed in the interstitium. (3) Viscous or bloody fluid is in the capsule. (4) The microcapsules are round or oval and some areas could be integrated into larger, irregular cavities. (5) The tumor cells are single in shape with round nuclei. Vacuoles are common in the cytoplasm, the chromatin is fine, the nucleolus is not obvious, and mitosis is rare. (6) Degenerative tumor cells and calcification in the stroma could be seen in a few cases [15-18]. MST in the ovary generally shows immunohistochemical positive staining for vimentin, CD10, β -catenin, CyclinD1 and WT1 [19-21]. A few cases showed weak cytokeratin positive locally. The α -inhibin, Pax-8, and calretinin are almost all negative. β -catenin expression in the nucleus and most point β -catenin mutations were identified in the majority of cases, which suggests that the Wnt/ β -catenin pathway may play a crucial role in the tumorigenesis of MST [22].

In order to get an accurate diagnosis of MST, other ovarian tumors with common microcapsule structures, including sex cord-stromal tumors, epithelial tumors, germ cell tumors and other rare tumor should be excluded and then an MST diagnosis could be made. (1) Sclerosing stromal tumor: a sclerosing stromal tumor also has a unilateral occurrence with cut sections appearing solid and white or pale yellow in color. A sclerosing stromal tumor is often accompanied by edema, cystic formation, and thin walled blood vessels that cannot be observed in MST. Immunohistochemical staining shows that sclerosing stromal tumors are positive to α -inhibin and negative to CD10, WT1 and β -catenin [23]. (2) Juvenile granulosa cell tumor: this tumor also contains cysts with varying sizes in which there are eosinophilic or basophilic substances. Granulosa cells and theca

cells are attached around the cyst cavity wall, and there is no cell inside the wall which is present in MST. Mitosis is common in juvenile granulosa, but it rarely occurs in MST. CD10 staining shows a weak to moderate expression in the granulosa cell tumor which is different from the expression in MST [24]. (3) Thecoma: stromal hyalinization is commonly observed in thecoma which is similar to MST. However the clinical manifestations and pathological characteristics of these two kinds of tumors are significantly different. Thecoma is solid with clear boundaries and yellow cut sections. Cystic degeneration is rare, but MST is mostly a cystic-solid tumor [25]. (4) Sertoli-Leydig cell tumor: moderately differentiated Sertoli-Leydig cell tumors also appear in microcystic structures, which is similar with MST. But the microcapsules are scattered in the tumor and except in the microcapsule regions, the Sertoli and Leydig cell contents are typically observed [26]. (5) Steroid cell tumor: steroid cell tumors, including non-special types of steroid cell tumor, interstitial luteal tumors and Leydig cell tumor, are often associated with increased levels of androgen. In gross examination, a steroid cell tumor is brighter than MST. A diffuse growth pattern in steroidal cell tumors is the most common without the obvious interstitium. The tumor cells are round with rich eosinophilic cytoplasm and a centered nucleus. CD10, α -inhibin, and calretinin are often positive, which is different from MST [27]. (6) Yolk sac tumor: microcapsules or reticular structures are the significant growth pattern for yolk sac tumors which need to be identified with MST. Both of these tumors basically have a unilateral onset with a cystic appearance but the age of the yolk sac tumor is less than 40 years old, and most of them occur between 20 and 30 years old. AFP is increased in almost all patients clinically. Microcapsules and fissures are lined by transparent epithelial cells with atypicality under microscopic observation. Clear corpuscles and basement membrane-like substances are available. Schiller-Duval bodies could be found in some cases and tumor cells are positive for AFP as shown by immunohistochemical staining [28]. (7) Solid pseudopapillary neoplasm: Solid pseudopapillary neoplasm is well known in pancreatic tissue, and the ovary is the most common extrapancreatic site for the occurrence of solid pseudopapillary neoplasms without ectopic pancreatic tissue. Both of these two tumors share many characteristics in histomorphology, im-

munophenotype, and genetic molecular profiles. However, a solid pseudopapillary tumor outside the pancreas is rare and the pseudopapillary structure is absent in MST [29]. (8) Small cell carcinoma accompanied by hypercalcemia: the cysts varying sizes are scattered between nests which is similar to MST. However, the tumors usually occur among young women. The tumor cells are small with fewer cytoplasm and active mitosis. The neoplastic cells also express cytokeratin and are negative for vimentin, WT1, CD10, and β -catenin, which could be helpful to make a differential diagnosis with MST [30]. (9) Clear cell tumor: clear cell tumors may present a microcapsules structure. The tumor contains fibrous collagenous stroma and is covered intraluminally with one or two layers of hobnail cells. The tumor cells are positive for CK7. MST does not have hobnail like cells, and the tumor cells show a negative CK7 expression which can be used to differentiate them from clear cell tumors [31].

Conclusions

In summary, ovarian MST is a unique, benign tumor biologically without specific imaging and histological characteristics. Radiologists, pathologists, and gynecologists should pay much attention to avoid misdiagnosis and over-treatment.

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Written informed consent was obtained from the patients for publication of this paper and any accompanying images.

Disclosure of conflict of interest

None.

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