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Original Article

Uterine tumors resembling ovarian sex cord tumor (UTROSCT): 4 cases report and literature review

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Abstract: Uterine tumors resembling ovarian sex cord tumor (UTROSCT) is an extremely rare type. It is currently distinguished from endometrial stromal tumors with sex cord-like element (ESTSCLE). We reported four cases recently with UTROSCT to describe the histological morphology, immunophenotype, and clinical behavior. During July, 2014 and Dec, 2015, two patients underwent surgical treatment respectively at Tianjin Medical University Cancer Institute & Hospital and Tianjin Central Hospital of Gynecology Obstetrics, the other two were consultant cases. Hematoxylin & Eosin and Immunohistochemical staining were performed. The sections were reviewed by three independent pathologists to confirm the diagnosis. Four patients with an age range of 35 to 80 years underwent the surgical treatment for UTROSCT. And the biopsy specimen was sent for histopathology and immunohistochemistry. Besides, genes were examined in the two cases, gene fusions of JAZF1-SUZ12 was not detected and FOXL2 gene mutation was also not found. UTROSCTs are polymorphic neoplasms with true sex cord differentiation. Generally, the primary management strategy remains surgical.

Keywords: Uterus, uterine tumors resembling ovarin sex cord tumor, gene, JAZF1-SUZ12, FOXL2

Introduction

Uterine tumors resembling ovarian sex cord tumor (UTROSCT) is an unusual type of endometrial stromal tumor, which were classified as sex cord-like tumor in the 2014 World Health Organization Classification. UTROSCTs were first described by Clement and Scully in 1976 [1]. They separated uterine tumors with sex cord-like elements into two types. Type I tumors represented endometrial stromal nodules or sarcomas, in which there are significant areas (>10% of the tumors) of epithelial-like structures that have an appearance reminiscent of an ovarian sex cord-stromal tumor. Some of these cases have been revealed a recurrent translocation resulting in a JAZF1-JJAZ1 gene fusion by Staats et al, but not in any of 24 cases if UTROSCT [2]. Tumors of this type are commonly referred to as endometrial stromal tumors with sex cord-like element (ESTSCLE). Inversely, type II tumors consisting predominantly or exclusively of sex cord-like elements, are usually known as uterine tumors resembling ovarian sex cord tumor (UTROSCT) [3]. It typically presents with low recurrence rate and is closer in histogenesis to ovarian sex cord stromal tumors.

UTROSCTs are intramural or submucosal tumors growing into the endometrial cavity. Some cases were reported to develop recurrence, whereas most of UTROSCTs behave in a benign way. We investigated 4 cases of UTROSCT, immunohistochemical study and molecular pathology analysis were performed in the study. Different markers were expressed on these tumors that suggest their polyphenotypic origins, and the gene fusion was not found in these tumors which is general expressed in low grade endometrial stromal sarcoma.

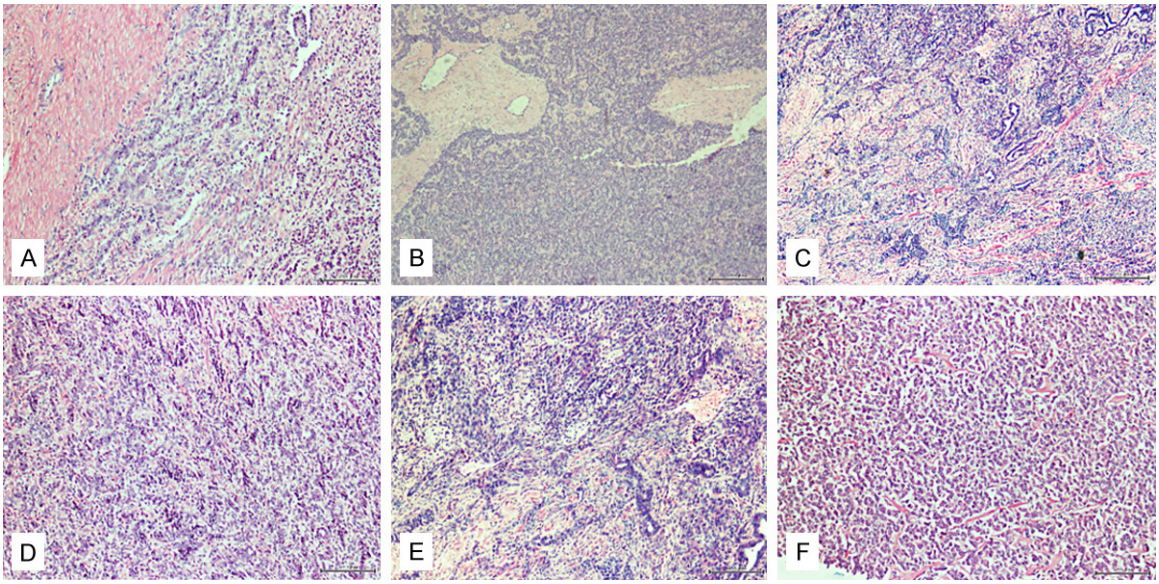

Figure 1. On microscopic examination the UTROSCT exhibits various patterns of sex-cord-like differentiation including cords (A, B) and tubules (C, D). Foamy cells in an UTROSCT case (E). UTROSCT presents a solid structure (F) (original magnification 100×).

Clinical summary

Case 1

A 80-year-old woman presented to our department with postmenopausal vaginal bleeding. Vaginal ultrasound examination revealed an enlarged uterus with a 7 cm diameter solid mass, considering from the submucosal. And subsequent a standard total abdominal hysterectomy with bilateral salpingo oophorectomy were performed.

Case 2

This case was consulted to our hospital. A 36-year-old woman who underwent hysterectomy and bilateral salpingo-oophorectomy, partial resection of the greater omentum and removal of the pelvic lymph nodes due to the possibility of a malignant uterine.

Case 3

A 35-year-old woman presented to Tianjin Central Hospital of Gynecology Obstetrics, in July 2014 with abnormal vaginal bleeding 3 months. Physical examination revealed a large uterus mass. Normal levels of estradiol plus CA125 were measured. The young patients has been treated by local excision of the uterine tumor.

Case 4

A 47-year-old woman, she presented with continued complaints of abnormal menstruation. An enlarged uterus was palpated. The preoperative diagnosis was leiomyoma.

Pathology fingding

Case 1

A 80-year-old woman presented to our department with postmenopausal vaginal bleeding. Vaginal ultrasound examination revealed an enlarged uterus with a 7 cm diameter solid mass, considering from the submucosal. And subsequent a standard total abdominal hysterectomy with bilateral salpingo oophorectomy were performed.

In gross examination, the uterus was 11×9×8 cm. In the uterine cavity, there was a sallow-colored and slightly soft mass arising from the myometrium and extended into endometrium. The tumor measuring 8×7×5.5 cm was well-circumscribed.

On microscopic examination, the tumor border was pushing into the adjacent muscle. The tumor showed predominantly several patterns of sex-cord-like elements and epithelial-like structures, which arranged in cords, trabecu-

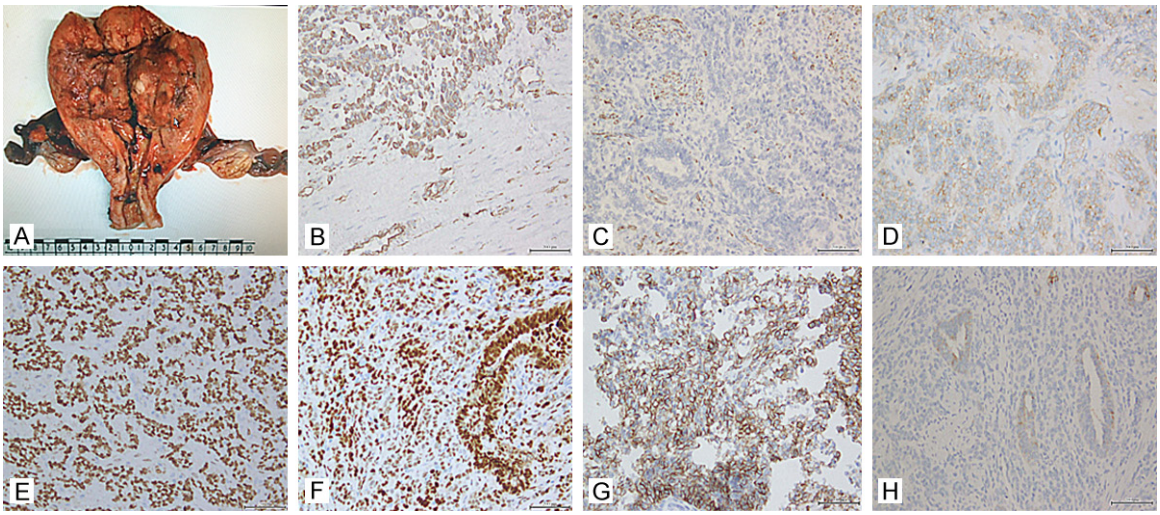

Figure 2. IHC positive staining on UTROSCT cases. A. Gross figure, B. Vimentin, C. Calretinin, D. CD99, E. ER, F. PR, G. CD56, H. CK-pan (original magnification 100×).

lae, nets and tubules (**Figure 1A**). Cytological atypia is minimal and mitoses are rare in this tumor.

Gene fusions of JAZF1-SUZ12 and FOXL2 gene mutation were not found in the case (data not shown).

No metastasis was identified. No further therapy was instituted.

Case 2

This case was consulted to our hospital. A 36-year-old woman who underwent hysterectomy and bilateral salpingo-oophorectomy, partial resection of the greater omentum and removal of the pelvic lymph nodes due to the possibility of a malignant uterine.

Microscopic examination, the lesion was an irregular interface between the tumor and the adjacent myometrium and presented as polypoid mass projecting into the uterine cavity. This tumor showed several patterns of sex cord-like elements, consisted of pseudotubules, plexiform cords (**Figure 1B**) and nests of polygonal cells with abundant foamy cytoplasm (**Figure 1C**). This tumor has a pseudo-in-filtrative appearance because of incorporated smooth-muscle bundles.

No further therapy was instituted and the patient had no evidence of disease 32 months after the operation.

Case 3

A 35-year-old woman presented to Tianjin Central Hospital of Gynecology Obstetrics, in July 2014 with abnormal vaginal bleeding 3 months. Physical examination revealed a large uterus mass. Normal levels of estradiol plus CA125 were measured. The young patients have been treated by local excision of the uterine tumor.

In gross examination, a solid mass measuring 10×10×10 cm was excised at the fundus of uterus, the sections were dark red, without the whorled pattern of leiomymas (**Figure 2A**). The tumor border was irregular. The intraoperative diagnosis was an enlarging leiomyoma, possibly degenerating.

Microscopic examination, the tumor tissue grew predominantly in solid pattern (**Figure 1D**). The tumor cells were epithelioid with abundant cytoplasm. Besides, some areas displayed a tubule or cord arrangement (**Figure 1E**, **1F**). The patient was re-explored for staging, and total abdominal hysterectomy, pelvic lymph node sampling were performed after four weeks. Most tumour cells display abundant eosinophilic. There was no residual tumor within the myometrium or endometrium.

No gene fusions of JAZF1-SUZ12 and FOXL2 gene mutation were detected also in this case (data not shown).

Table 1. Immunohistochemical profile of uterine tumors resembling ovarian sex cord tumors

Case	Mesenchymal markers			Hormonal markers		Sex cord markers				Neuroendocrine markers			Epithelial markers			Others		
	SMA	Desmin	Vim	ER	PR	Calretinin	WT-1	CD99	Inhibin	Syn	CD56	CgA	CK-pan	CK7	EMA	CD10	HMB-45	Ki67
1	+	–	+	–	+	+	–	+	–	–	+	–	+	+	–	–	–	<1%
2	–	–	+	+	+	+	–	+	–	–	+	–	+	–	–	–	–	<3%
3	–	–	+	+	+	+	–	+	+	–	+	–	+	ND	ND	–	–	5%
4	–	–	+	+	+	+	ND	+	–	ND	ND	ND	+	ND	ND	–	–	8%

ND: not detect.

The patient had been followed at 20 months without evidence of recurrence.

Case 4

A 47-year-old woman, she presented with continued complaints of abnormal menstruation. An enlarged uterus was palpated. The preoperative diagnosis was leiomyoma.

In gross examination, the uterus was 13×10×5 cm. The tumor was measured total 4×3×1 cm. It was poorly circumscribed. The cut surface was fleshy and pale.

The light microscopic features seen in the tumor section, included a tubule and cord-like architecture, and distinct lumen formation was identified. Vascular invasion, heterologous elements and necrosis can be seen.

The patient had no evidence of recurrence after the operation.

Discussion

Diagnosis of UTROSCT is primarily based upon morphologic features and immunohistochemical staining. Positive staining for at least two sex-cord markers is supportive, including Calretinin and at least one other marker [7-9]. Other commonly expressed markers are α-inhibin, CD99, and Melan-A [9]. Besides, these tumors are variably immunoreactive for mesenchymal and epithelial elements as well, frequently positive stains include Vimentin, Desmin, Cytokeratin, epithelial membrane antigen (EMA), CD10, and ER/PR [7].

In our cases, all the tumors showed Calretinin expression, while α-inhibin was present in 1 tumor. Furthermore, all 4 patients showed a presence of CK-pan, Vimentin, CD99 as well as PR. In 3 cases, tumors were also positive for CD56 and ER (shown in **Table 1**; **Figure 2**).

Besides, genes were examined in two of the cases. JAZF1-SUZ12 fusion gene and FOXL2 gene mutation were not detected.

UTROSCTs had been recognized as endometrial stromal tumors with focal sex cord-stromal component or as granulosa cell tumors of the uterus because of their similarity to granulosa cell tumors of the ovary [10, 11]. Nomenclature of the tumors is indefinitely until the 2014 World Health Organization classification published. In this classification, UTROSCT was regarded as a separate group to identify endometrial stromal sarcomas. Due to some authors considering, these tumors have a better prognosis than endometrial stromal sarcomas. According to the amount of sex cord-like element present, ESTSCLE was given to type I tumors and UTROSCT was defined type II. In our four presented cases, sex cord-like epithelial component predominated (>50%) the mesenchymal elements, so the final diagnosis of UTROSCT was given for each case.

In our study, it is better to define and provide certain evidence for clinical correct diagnosis of UTROSCT. In summary, particular attention should be paid to diagnosis and treatment of these tumors. Women who have well-circumscribed tumors without invasion with these tumors can choose conservative management or be treated by hysteroscopic removal of the tumor with close follow-up [12].

Uterine tumors with sex cord-like elements occur in middle-aged women, the average age is around 50 on clinic. The main symptom is abnormal bleeding or pelvic pain. Most patients have an enlarged uterus or a perceived uterine mass. UTROSCTs are commonly myometrial tumors, and they also can be submucosal and grow into the endometrial cavity or even though the cervical orifice [13]. Some cases of cervical UTROSCT has been reported recently.

In gross, UTROSCTs' cut surface are yellow to tan, or dark red and has a circumscribed or slightly irregular periphery, the average diameter is 6-7 cm. Recently, these tumors have been proposed to origin from endometrial stromal or uncommitted cells in the uterus and do not harbor the JAZFI-JJAZI gene fusion that characterizes endometrial stromal tumors, indicating that they are unlikely to be endometrial stromal neoplasms.

Immunohistochemistry is useful to demonstrate the presence of sex cord-like element, because of the sex cord-like areas of uterine tumors resembling ovarian sex-cord tumors revealed positive for one or more epithelial, smooth muscle, and sex cord markers. CK7, EMA, SMA, α-inhibin, Calretinin, Melan-A, CD99, WT-1, CD56, ER, PR as well as Vimentin are the most useful markers for UTROSCT. Some of these markers stain presented focally and some broadly.

In addition, UTROSCTs have features that may cause them to be confused with more other common tumors, especially in limited biopsy samples [14], and should be included in the differential diagnosis when a gland-forming neoplasm with an unusual appearance identified in a cervical or endometrial biopsy specimen.

Morphologically, tumor cells are small and round with scanty cytoplasm, the nuclei are generally small and regular with indistinct nucleoli, arranged in nets patter simulating a low-grade endometrial stromal sarcoma. Some time, the tumor cells are separated by numerous foamy histocytes. Strong staining for CD10 and Vimentin were features that led to an initial consideration of a low-grade endometrial stromal sarcoma. Uterine tumors resembling ovarian sex-cord tumor is composed of cellular trabeculae arranged in a plexiform patter simulating a granulosa cell tumor. Strong staining for α-inhibin and Calretinin were features that led to an initial consideration of a granulosa cell tumor.

JAZF1-SUZ12/JJAZ1 gene fusion product was amplified by RT-PCR, and the exon 1 region of FOXL2 was amplified by PCR. Because it has been shown that these tumors do not harbor the JAZF1-SUZ12/JJAZ1 gene fusion that characterizes endometrial stromal tumors, indicating that they are unlikely to be endometrial stromal neoplasms. Because it has been shown that these tumors do not harbor the FOXL2 gene fusion that characterizes granulosa cell tumor, indicating that they are unlikely to be a granulosa cell tumor.

Positive staining for estrogen and progesterone receptors is present. Positive staining for more markers of sex-cord differentiation is seen in those UTROSCT. But the tumor demonstrate decreased levels of nuclear staining for the proliferation marker Ki-67 (MIB-1), together with the absence of heterologous mesenchymal elements and clear-cut carcinoma, help to differentiate these rare tumors from a MMMT and an endometrioid adenocarinoma with a sertoliform pattern. Neoplasms with neuroendocrine differentiation enter into the differential diagnose of UTROSCT because they may have cords of cells reminiscent of sex-cord elements. The absence of EMA, Chromogranin, Synaptophysin, or other neuroendocrine markers should help exclude this possibility.

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Disclosure of conflict of interest

None.

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