Case Report

Uterine tumor resembling ovarian sex-cord tumor: a case report of recurrence after conservative management and review of the literature

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Abstract: Uterine tumor resembling ovarian sex-cord tumor is an extremely rare uterine mesenchymal neoplasm. Less than 100 cases have been described in literature and only eleven cases were treated with a fertility sparing approach. Three patients treated with preservation of reproductive function presented a local relapse; among these, two patients were treated conservatively and one had a second relapse with peritoneal carcinomatosis. We report the case of a 24-year-old nulliparous woman presenting with abnormal uterine bleeding and secondary anemia. She had no comorbidities or familiar history of gynaecological cancer. Trans-vaginal ultrasound and diagnostic hysteroscopy found a submucosal leiomyoma. Resectoscopic myomectomy was performed but final pathological exam revealed a type II uterine tumor resembling ovarian sex-cord. According to the young age and desire to preserve reproductive function, the patient was submitted to fertility-sparing management and follow up was planned (trans-vaginal ultrasound every three months and CT scan every 6 months). A uterine relapse occurred after 20 months, and the patient underwent laparoscopic hysterectomy with salpingectomy and peritoneal biopsies. After ten months from the radical surgery the patient is alive without disease. This is the twelfth case of a uterine tumor resembling ovarian sex-cord treated with preservation of the uterus and the fourth case of recurrence after a fertility sparing treatment. This report is unique for the completeness of the data provided and for the decision of performing radical surgery after disease recurrence because of the tumor more aggressive behaviour, despite the patient did not achieved a pregnancy yet. The optimal diagnostic path and treatment of this rare disease is still uncertain due to the small number of cases reported in literature but apparently a fertility sparing approach can be offered safely to young patients of reproductive age. In cases of recurrent disease the risk and benefit of an organ preserving surgery should be discussed with the patient based on the data extrapolated from the few cases reported until this moment.

Keywords: Uterine tumor resembling ovarian sex-cord tumor (UTROSCT); case report; fertility sparing surgery; conservative management, recurrence

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Introduction

Uterine tumor resembling ovarian sex-cord tumor (UTROSCT) is a rare uterine mesenchymal neoplasm included in the World Health Organization (WHO) 2014 classification in the group of "Endometrial stromal and Related Tumors". UTROSCTS are defined as neoplasm that resembles ovarian sex cord tumors, without a component of recognizable endometrial stroma (1). They were first described in 1976 by Clement and Scully, who identified two subgroups with different biological behaviour and prognosis: type I endometrial stromal tumor with sex cord like elements (ESTSCLE), with a more aggressive behaviour; and type II classic UTROSCTS, with a low malignant potential (2).

Less than 100 cases have been described in literature (3) and, although generally considered to be tumors with benign biological behaviour, uterine and extra-uterine recurrences have been reported (4,5). In rare cases UTROSCT can even lead to patient death, particularly type I tumors (6). The presence of necrosis and mitosis 2/10 HPF, a tumor size ≥10 cm and extra uterine or cervical spread can predict a more aggressive behaviour (7,8). The pathological diagnosis is based on morphologic features and confirmed with immunohistochemistry (IHC). The hallmark for histologic diagnosis is the presence of bland spindle cell proliferation with extensive sex cord-like differentiation and no endometrial stromal component (7). At immunohistochemical analysis at least two sex-cord markers must be expressed: calretinin and another marker such as inhibin, cluster of differentiation 99 (CD 99) or Melan-A (9).

The mean age at diagnosis is 52.2 years; 30% of patients are under the age of 40 (8). The standard surgical treatment is hysterectomy with bilateral salpingo-oophorectomy (BSO). However, since a significant number of patients are women of reproductive age, a conservative surgical treatment is required. UTROSCT is an extremely rare neoplasm and, in the absence of guidelines or recommendation, therapeutic decisions are based on the experience of case reports. Fertility sparing treatment is limited to eleven clinical cases (4,10-17) and, even if the number of patients is too small to draw conclusions, probably this approach is safe if extra uterine spread of the disease is absent.

Instead the treatment of the disease recurrence is still uncertain due to the small number of cases reported in literature. In fact only three recurrences have been described in patients treated conservatively (4,12): two underwent tumor resection and one radical surgery after completion of childbearing. One of the recurrences managed with preservation of the reproductive function had a second relapse with peritoneal carcinomatosis.

Here we report a rare case of UTROSCT, in a young woman who was first treated conservatively and, after the relapse, with radical surgery. This is the fourth case of disease recurrence after fertility sparing treatment of UTROSCT and the first managed with radical surgery before completion of childbearing. We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/gpm-21-5).

Case presentation

In January 2018, a 24-year-old woman, never pregnant, presented abnormal uterine bleeding (metrorrhagia) and secondary anemia (haemoglobin 8 g/dL). She had no comorbidities and a history of previous regular menses. Trans-vaginal ultrasound (TV-US) and hysteroscopy reported a submucosal uterine leiomyoma of 3 cm in diameter and a resectoscopic myomectomy was planned.

In March 2018, she underwent myomectomy, but final pathology was type II UTROSCT. The tumor had low mitotic activity (1/10 HPF), absence of necrosis and the neoplastic cells expressed calretinin, desmin, WT1, CD10, cytokeratin, ER and PgR. Rare neoplastic cells were positive for cyclin D1. CD117 and caldesmon were not expressed.

In April 2018, the patient was referred to our Institution (Division of Oncologic Gynecology, Azienda Ospedaliero Universitaria di Bologna, Italy) to plan the subsequent treatment. She desired fertility preservation. Staging pelvic magnetic resonance imaging (MRI) and a thoraco-abdominal computerized tomography (CT) scan were negative for uterine disease persistence or distant metastasis.

A conservative management was proposed according to the patient's age, desire of childbearing and tumor characteristics (low mitotic index tumor, dimension of tumor and negative imaging). Therefore, periodic clinical checks were scheduled: physical examination and ultrasound every three months and CT scan every 6 months. Because the patient preferred to delay the pregnancy, she was referred to a reproductive specialist for discussing the possibility of cryopreservation of oocytes, but she declined this option.

Twenty months after the diagnosis, a follow up

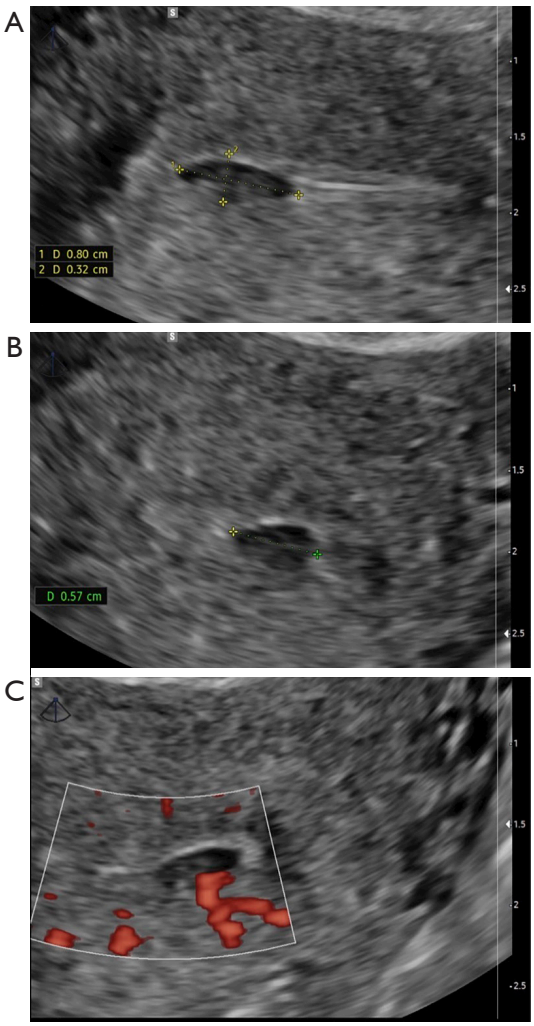

Figure 1 Sonographic images of UTROSCT recurrence. (A,B) Shows an hypoechoic, heterogeneous mass in the endometrium with well-defined margins; (C) shows the feeding vessel. UTROSCT, uterine tumor resembling ovarian sex-cord tumor.

ultrasound showed a hypoechoic, heterogeneous 8×3×6 mm mass in the endometrium. The mass had well-defined margins and a feeding vessel and raised the suspicion of disease relapse (*Figure 1*).

A subsequent diagnostic hysteroscopy showed a sessile, yellowish-white, bilobed endometrial mass similar to a polyp of 15×20×5 mm in size on the posterior uterine wall, with abnormal vascularization.

In December 2019 a resectoscopic biopsy of the lesion for pathological analysis confirmed the relapse of UTROSCT. The relapse had a greater mitotic activity

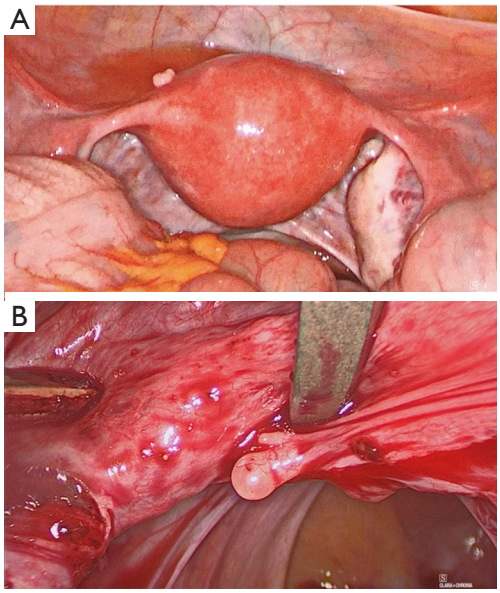

Figure 2 Intraoperative findings. (A) Shows the uterine serosa with sporadic millimetric nodules; (B) shows the fallopian tubal surface with irregularities

(5/10 HPF) compared to the first diagnosis, myometrial infiltration and positive surgical margins. Because of these characteristics the local multidisciplinary tumor board recommended radical surgery.

In February 2020, after discussion with the patient, laparoscopic hysterectomy with bilateral salpingectomy and peritoneal biopsies was performed. The postoperative course was regular, without adverse or unanticipated events, and the patient was discharged after three days (*Figure 2*).

Pathological analysis on the uterus confirmed the presence of UTROSCT with myometrial infiltration of 3 mm of the posterior uterine wall. IHC was positive for calretinin, CD99 and cytokeratin. Endosalpingiosis was reported in the peritoneal biopsy of the prevescical peritoneum and fallopian tubes. The patient did not undergo adjuvant therapies. She was followed with TV-US every 6 months and thoraco-abdominal CT scan every 12 months. Ten months after radical surgery, the patient was alive without disease.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Table 1 UTROSCT treated with fertility sparing surgery

N	Author, year	Age at diagnosis	Symptoms	Tumor size (mm)	Treatment	Conception	Recurrence
1	Garuti *et al.*, 2009	29	Metrorrhagia	50	Hysteroscopic tumor resection	No	No
2	Hillard *et al.*, 2004	32	Spotting, infertility	n/a	Laparoscopic tumor resection	Yes	No
3	Anastasakis *et al.*, 2008	28	Intermestrual bleeding	n/a	Hysteroscopic tumor resection	Yes	No
4	Schraag *et al.*, 2017	24	Metrorrhagia	n/a	Hysteroscopic tumor resection	No	Yes
5	Schraag *et al.*, 2017	28	Pelvic heaviness	100	Laparotomic tumor resection	Yes	Yes
6	Jeong *et al.*, 2015	32	Infertility, prolonged menstruation	30	Hysteroscopic tumor resection	Yes	Yes
7	Berretta *et al.*, 2009	26	Intermestrual bleeding	22	Hysteroscopic tumor resection	No	No
8	Giordano *et al.*, 2010	26	Intermestrual bleeding	22	Hysteroscopic tumor resection	No	No
9	Bakula-Zalewska *et al.*, 2014	25	n/a	40	Hysteroscopic tumor resection	No	No
10	Bakula-Zalewska *et al.*, 2014	24	n/a	30	Hysteroscopic tumor resection	No	No
11	De Franciscis *et al.*, 2016	38	Metrorrhagia, infertility	10	Hysteroscopic tumor resection	Yes	No
12	Present case	24	Metrorrhagia, anemia	30	Hysteroscopic tumor resection	No	Yes

UTROSCT, uterine tumor resembling ovarian sex-cord tumor; n/a, not available.

Discussion

In this clinical case, we report our experience of UTROSCT in a young woman in whom conservative treatment has failed. The reason is due to an increased aggressiveness of the tumor in the relapse. The increase of mitotic activity could lead to a higher risk of disease spread.

A fertility sparing treatment can be an option for young women diagnosed with UTROSCT, however the safety of this approach is uncertain. Literature reported in total eleven cases of UTROSCT treated with preservation of the reproductive function (*Table 1*) and three cases of recurrence after a fertility sparing treatment (*Table 2*). All women were nulliparous with a mean age of 28 years. In total five pregnancies were achieved, including one after the conservative management of a uterine recurrence (4,11-13,17). Four patients conceived spontaneously and one with *in vitro* fertilization (IVF).

Our patient did not attempt to conceive but in literature infertility is common in these women. Possible factors such as distortion of the uterine cavity, alteration of myometrial contractility and chronic inflammatory reaction of the myometrium, could be responsible for the infertility linked to this tumor (18). Indeed, literature data reported that three patients conceived after tumor resection, suggesting a possible direct role (12,13,17).

Assisted reproductive technology (ART) may be an option after tumor resection. However, there are no available data on the effect of infertility treatments on the risk of recurrence of UTROSCT. Our patient did not request cryopreservation of oocytes after the diagnosis of UTROSCT but ovarian stimulation was not contraindicated. In our Institution cryopreservation of

Table 2 Recurrent UTROSCT after fertility sparing surgery

N	Author, year	PFS (months)	Site of recurrence	Recurrence size (mm)	Treatment	Conception after recurrence	Second recurrence
1	Schraag *et al.*, 2017	6	Uterus	15	Laparotomic tumor resection	No	No
2	Schraag *et al.*, 2017	2	Uterus	30	Laparotomic tumor resection	Yes	Yes
3	Jeong *et al.*, 2015	17	Uterus	n/a	Laparoscopic hyesterectomy + bilateral salpingectomy	No	No
4	Present case	20	Uterus	20	Laparoscopic hyesterectomy + bilateral salpingectomy	No	No

UTROSCT, uterine tumor resembling ovarian sex-cord tumor; n/a, not available.

oocytes is offered in all young oncological patients who wish to preserve fertility.

The woman of the present case complained abnormal uterine bleeding as the main symptom according to the literature data. In reported cases, symptoms at diagnosis were abnormal uterine bleeding with or without infertility, pelvic discomfort such as pelvic pain and swelling, especially in postmenopausal women (8). Pelvic discomfort appears to be associated with tumor size, so much so that it is absent in conservatively managed patients in whom the reported tumor size is less than 40 mm, and appears in a patient with a tumor of 10 cm. Moreover tumor size is associated with an increased risk of cervical or extra-uterine spread as reported by Blake *et al.* (8).

In our case, the first diagnosis was a submucosal uterine leiomyoma, this is consistent with literature data that report an incorrect diagnosis on ultrasound and diagnostic hysteroscopy. Presumptive diagnosis of submucosal leiomyoma is reported in 67% of patients followed by endometrial polyp in 33% of cases. Probably the rarity of the disease and the diagnostic approach, often performed by a generalist gynaecologist, can explain the high percentage of misdiagnosis in the first instance. However some common features can be identified if a retrospective analysis is performed.

UTROSCTS at ultrasound imaging are solid and heterogeneous, hypo or isoechoic if compared to the adjacent myometrium, with well-defined margins, vascularized with a feeding vessel and at hysteroscopy are yellowish-gray submucosal masses with abnormal vascularization. Those features, already indicated in other reports, were described as well in our patient when the disease recurrence was detected.

Even if the standard surgical treatment of UTROSCTS consists of hysterectomy with BSO, tumor resection with free margins is a possible option if a fertility sparing approach is attempted. In premenopausal women it is possible to perform hysterectomy with ovarian preservation. Our patient received a hysteroscopic tumor resection, as most of the women treated conservatively (82%). In some cases, the necessity of a second operative hysteroscopy was described in order to obtain free margins (10,12). Laparotomic or laparoscopic tumor resection was performed in a minority of cases (16%). Intraoperative complications (heavy bleeding and unintended morcellement of the uterine mass) occurred during laparotomic tumor resection probably because the tumor was large and without a clear cleavage plane with the adjacent myometrium (4).

Minimally invasive surgery (MIS) with tumor morcellation has a potential risk of peritoneal dissemination and disruption of pathologic specimen and should be avoided according to principles of correct management of uterine sarcomas (7,19). However, the low malignant potential of UTROSCT and the absence of positive cytology, peritoneal disease or cancer progression in patients treated with MIS (hysteroscopic or laparoscopic tumor resection) suggest a low risk of adverse oncological outcomes in this group of patients.

Including our case report, a relapse after fertility sparing treatment occurred in four patients (33%).

Recurrences are infrequent in patients treated with hysterectomy and BSO and death is an extremely rare event. Blake *et al.* described 4 recurrences (11%) and one death (2.7%) on 36 cases with reported survival

outcomes (8). Generally, recurrences were treated with radical surgery as in our case, and conservative treatment is reported in two cases with a poor outcome.

The conservative treatment consisted in laparotomic tumor resection in both patients. One of them had a second relapse with infiltration of ovaries, pelvic peritoneum and vaginal wall twelve months after the delivery of a healthy baby and radical surgery was then performed.

The third patient, five months after completing childbearing, had a hysterectomy with bilateral salpingectomy and a recurrence was highlighted at pathologic analysis (13).

The number of patients with a UTROSCT's relapse after fertility sparing surgery is too small to draw conclusions about the optimal treatment of the recurrent disease but some considerations can be done. With only one exception, which exhibited a larger size, the recurrent cases did not show different characteristics at the time of diagnosis and first treatment.

Probably it is reasonable and safe to offer a fertility sparing surgery in all women of reproductive age with a diagnosis of UTROSCT if extra uterine spread of the disease is absent.

The UTROSCT described in this report relapsed twenty months after the primary treatment.

All the recurrences occurred in the first 2 years (2–20 months) after the diagnosis. According to these data, women who wish to achieve a pregnancy must be encouraged and, if a spontaneous conception does not happen in a relatively brief period of time, ART must be considered. If pregnancy is obtained, after the delivery the choice of hysterectomy must be discussed with the patient for the possibility of occult persistent disease. In case of recurrence the safety of a conservative management is unknown and the patient must be informed of the possible risk and benefit based on the small number of information available in literature.

In conclusion the relevance of this report is related to the rarity of the disease and the absence of clear indication on the management of recurrent disease after fertility sparing treatment. Furthermore this case report provides an accurate and complete description of UTROSCT recurrence after conservative treatment and allows a comparison between pathologic characteristics of the first diagnosis and the recurrence. A limitation is the lack of surgical and ultrasound images before the diagnosis of UTROSCT because the patient received the first treatment in another hospital.

UTROSCT must be referred to centres with expertise in rare gynaecological tumors especially in young women candidates for fertility sparing treatment. The creation of a national or international register of this neoplasm can be beneficial for the development of guidelines for the diagnosis and treatment of UTROSCT.

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Footnote

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