Uterine tumors resembling ovarian sex cord tumors (UTROSCT). Report of a case with lymph node metastasis

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SUMMARY

Uterine tumors resembling ovarian sex cord tumors (UTROSCT) have an uncertain histogenesis. Although generally considered to be benign, they metastasize in some cases. We report the case of a 53-year-old woman who presented with vaginal bleeding. Clinical examination revealed a tumor sized 1.5 cm in diameter localized in the subendometrial region of the uterine wall. Histologically, the tumor consisted of epithelioid oval cells arranged in solid nests, trabeculae and ribbons. Immunohistochemically, approximately 1% of tumor cells expressed strong desmin positivity, calponin in 10% of cells, WT1 in 80% cells, and Ki-67 was positive in about 5 % of tumor cells. All the other immunohistochemical reactions applied including anti-cytokeratin antibodies were negative. The RT-PCR method for identification of the JAZF1-JJAZ1 fusion transcript was negative. In one lymph node in the right iliac artery region, a metastasis of UTROSCT was found. This finding adds to the previously reported UTROSCT cases with metastatic spread.

Keywords: uterine tumors resembling ovarian sex cord tumors – UTROSCT – metastasis – lymph node

Uterine tumors resembling ovarian sex cord tumors (UTROSCT) - popis případu s metastázou do lymfatické uzliny

SOUHRN

Popisujeme vzácný nádor dělohy odpovídající ovariálnímu sex cord nádoru (UTROSCT), který má nejistou histogenezi. Ačkoliv je obecně považovaný za benigní, v některých případech metastazuje. V našem případě šlo o 53letou ženu, která přišla do nemocnice s vaginálním krvácením. Klinické vyšetření ukázalo nádor velikosti v průměru 1,5cm, který byl lokalizovaný subendometriálně ve stěně dělohy. Histologicky byl nádor tvořený epiteloidními oválnými buňkami, které tvořily solidní hnízda, trabekuly a pruhy. V imunohistologickém vyšetření bylo přibližně 1 % nádorových buněk výrazně pozitivní s protilátkou proti desminu, kalponinu u 10 % buněk, WT1 u 80 % buněk a Ki-67 bylo pozitivní asi u 5 % nádorových buněk. Ostatní protilátky včetně protilátek proti cytokeratinům byly negativní. Metoda RT-PCR identifikující fúzní transkript JAZF1-JJAZ1 byla negativní. V jedné lymfatické uzlině v oblasti pravé ilické arterie byla zjištěna metastáza UTROSCT. Tento nález můžeme přiřadit k některým dříve popsaným UTROSCT, u kterých se objevily metastázy.

Klíčová slova: nádor dělohy odpovídající ovariálnímu sex cord tumoru ovaria – UTROSCT – metastáza – lymfatická uzlina

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Uterine tumors resembling ovarian sex cord tumors (UTROSCT) were first reported by Morehead and Bowman in 1945 (1). Later, Clement and Scully (2) classified the tumors into two subgroups. The first was comprised of tumors similar to endometrial stromal tumors with focal epithelioid formations resembling sex cord-like elements of an ovarian tumor making up 10 – 40 % of the overall tumor mass. These group I tumors, referred to as endometrial stromal tumors with sex cord-like elements (ESTSCLE), are considered to be endometrial stromal tumors. They are associated with an increased risk of recurrence and metastases. The other group contains more than 50 % of sex cord-like cells (3). Unlike group I, these tumors are clearly separated from the surrounding tissues, have distinct clinicopathologic features and are benign. Yet, cases were published with tumor recurrence or metastases (4-7). In this report, we present another case of UTROSCT with a metastasis in the pelvic lymph node.

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MATERIAL AND METHODS

In the last year, one case of UTROSCT was noted at the Department of Pathology, University Hospital in Ostrava. The tissues were fixed in 10% buffered formalin and processed using the paraffin technique. The sections were stained by the standard hematoxylin-eosin technique.

Immunohistochemistry

Immunohistological examination was carried out using the avidin-biotin complex (ABC) method with antibodies against estrogen receptors (ER; NOVOCASTRA, dilution 1:50, clone GF11),

progesterone receptors (PR; NOVOCASTRA, dilution 1:200, clone 16), CD10 (DB BIOTECH, dilution 1:100), desmin (BIOGENEX, prediluted, clone 33); antibodies produced by DIAGNOSTIC BIOSYSTEMS: HMB45 (dilution 1:50, clone HMB45), pancytokeratin AE1-AE3 (dilution 1:50, clone AE1+AE3), CK20 (prediluted, clone KS20.8); and antibodies produced by DAKO, Glostrup, Denmark: CD99 (prediluted, clone 12E7), calponin (dilution 1:50, clone CALP), WT1 (prediluted, clone 6F-H2), S-100 protein (dilution 1:600, polyclonal), CD117 (1:400, polyclonal), CK7 (dilution 1:100, clone OV-TL 12/30), calretinin (dilution 1:50, clone DAK-Calret1), Ki-67 (dilution 1:50, clone MIB-1), inhibin (dilution 1:10, clone R1), and smooth muscle actin (dilution 1:100, clone 1A4).

RT-PCR method for detecting the JAZF1-JJAZ1 fusion transcript

The presence of the JAZF1-JJAZ1 fusion transcript was analyzed using the RT-PCR method. RNA was extracted from paraffin-embedded tissue using the RecoverAll Total Nucleic Acid Isolation Kit (Ambion, Austin, USA). An amplification of a 247-bp product of the PGK gene and of 133-bp and 105-bp products of the beta2-microglobulin gene was used to test the quality of the extracted RNA as previously described (8-10). A 93-bp part of the JAZF1-JJAZ1 fusion transcript was amplified with primers JAZF1-369-FW with sequence 5´CCACCCATCACCCCCTCCT´3 (complementary to JAZF1) and JJAZ1-400-RV with sequence 5´TGCTATGAGATTCCGAGTTC´3 (complementary to JJAZ1) (11). The sample was run in duplicate. No fusion transcript was detected using the RT-PCR method with fusion-specific primers in the analyzed sample.

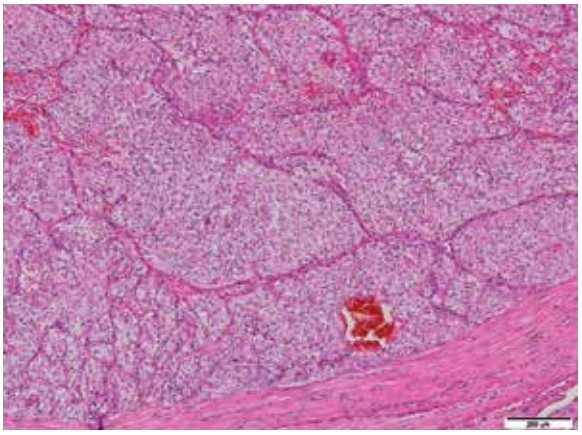

Fig. 1. Primary tumor in the uterus. Foci of tumor cells surrounded by fine septa. Hematoxylin - eosin stain. Bar scale = 200 µm.

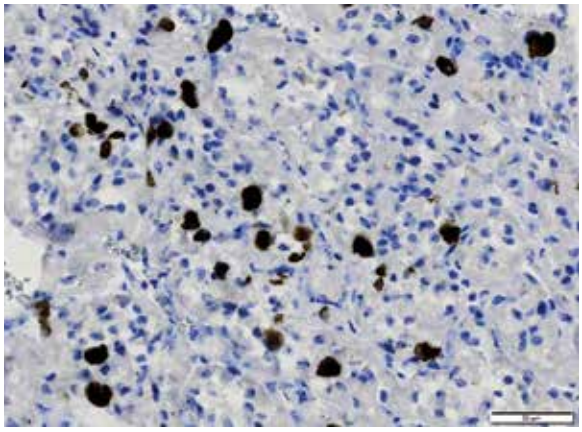

Fig. 2. Some cells of UTROSCT expressing desmin. Immunohistochemistry. Bar scale = 50 µm.

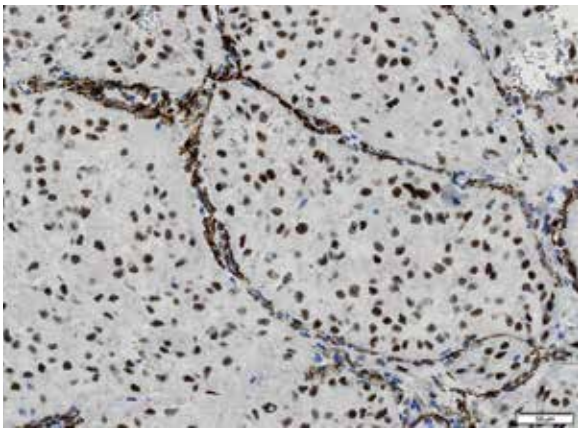

Fig. 3. Tumor cells expressing WT1. Immunohistochemistry. Bar scale = 50 µm.

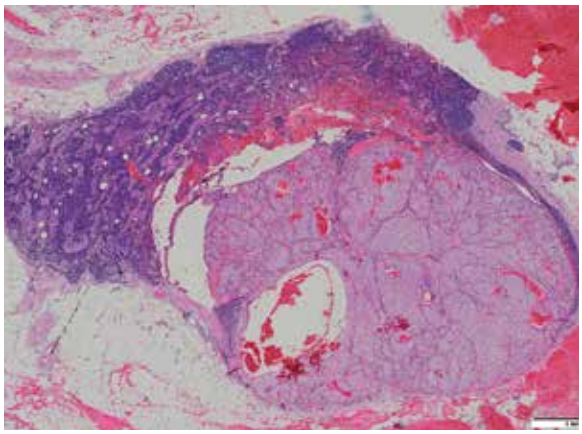

Fig. 4. Metastasis of UTROSCT to the lymph node. Hematoxylin - eosin stain. Bar scale = 1 mm.

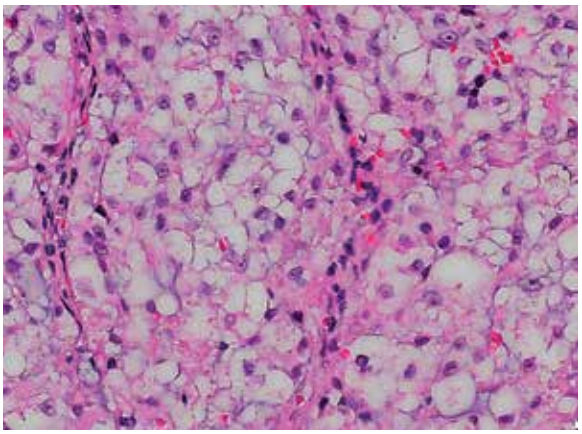

Fig. 5. Higher magnification of the lymph node metastasis. Hematoxylin - eosin stain. Bar scale = 20 µm.

CASE REPORT

A 53-year-old woman presented at the hospital with metrorrhagia. The patient had regular gynecological check-ups, always with negative results. During her previous visit, a hyper-

Table 1. Antibodies used and immunohistological results

	Uterine tumor	Metastasis to the lymph node
ER	Neg.	Neg.
PR	Neg.	Neg.
AE1-AE3	Neg.	Neg.
CK7	Neg.	Neg.
CK20	Neg.	Neg.
desmin	1 % ++	1 % ++
SMA	Neg.	Neg.
calponin	10 % +	10 % +
calretinin	Neg.	Neg.
WT1	80 % +	80 % +
Inhibin	Neg.	Neg.
CD10	Neg.	Neg.
S100	Neg.	Neg.
HMB45	Neg.	Neg.
CD99	Neg.	Neg.
CD117	Neg.	Neg.
Ki-67	< 5 % +	< 5 % +

echoic structure sized approximately 29 mm had been found in the uterine wall. The right ovary was small and the left ovary could not be visualized. Hysteroscopy revealed a polypoid mass with an uneven surface on the endometrium. UTROSCT was histologically diagnosed. Given the findings and persistent metrorrhagia, the patient gave consent for a hysterectomy.

Macroscopically, the right uterine horn was found to contain a spherical tumor, 1.5 cm in diameter, surrounded by uterine muscles.

A biopsy examination of the polypoid structure (sized 1.0 cm x 1.5 cm x 1.0 cm) removed during hysteroscopy was performed. The histological examination showed epithelioid structures forming trabeculae, ribbons or solid nests. Epithelioid cells predominated, making up more than 50 % of the tumor. The tumor cells contained light cytoplasm. The tumor met the criteria for ovarian sex cord tumors. A similar histological appearance was observed in the tumor detected by hysterectomy in the uterine wall. The tumor cells were surrounded by spindle cells with positivity to desmin and smooth muscle actin. Also approximately 1% of epithelioid sex cord-like cells expressed strong cytoplasmic positivity to desmin, calponin was positive in 10 % and WT1 in 80 % of cells (Fig. 1-3).

There were no atypical cells, tumor invasion into the blood or lymph capillaries or necroses. The mitotic activity was very low (<1 mitosis/10 HPF).

Ki-67 was positive in about 5 % of tumor cells. The other antibodies did not react with the tumor (Tab. 1). Hysterectomy and a bilateral adnexectomy were performed. During the procedure, pelvic and paraaortic lymph nodes were also removed. One lymph node in the region around the right internal iliac artery was found to contain a metastasis of the same appearance as the tumor in the uterine wall (Fig. 4,5). Immunohistological examination showed the same positivity as the primary tumor in the uterus - i.e. the primary tumor lesion in the uterus and the lymph node metastasis had an identical phenotype.

In the paraffin block, the JAZF1-JJAZ1 chimeric transcript was examined. The sample was run in duplicate. No fusion transcript was detected using the RT-PCR method with fusion-specific primers in the analyzed sample.

Since the hysterectomy procedure, the patient has been without signs of tumor progression for 10 months of follow-up.

DISCUSSION

UTROSCT is a rare tumor with an uncertain histogenetic origin. Whereas some authors suggest that these tumors belong to ESTSCLE, just with a higher presence of sex cord-like elements, others (3,5) consider them an individual category of tumors. According to the 2003 World Health Organization classification, these tumors belong to a group of miscellaneous neoplasms and the category of sex cord-like tumors, with a predominant pattern of sex cord-like elements (12). The tumor is made up of epithelioid cells with the appearance of ovarian sex cord-like elements. In the histological pattern, there are ribbons, trabeculae, small nests or tubules resembling granulosa or Sertoli cell tumors of the ovary. UTROSCT with retiform sex cord-like differentiation was also reported (13). Rarely, Call-Exner bodies may be present (14). This component is considered to be tumorous.

Histogenetically, the tumors are likely to arise from multipotent mesenchymal cells of the uterus. These cells may differentiate in various directions. This corresponds with expression of individual markers as seen in these tumors (14). Hillard et al. (15) suggests that uterine tissue at the endomyometrial junction exhibits a pluripotent capacity to differentiate into a range of cells composing epithelial, stromal, or myometrial tissue.

UTROSCT are made up of sex cord-like trabeculae and tubules as well as elongated cells. The relationship of these elongated cells to the tumor itself has not been clearly elucidated. Apart from the opinion that these are myoid cells are randomly incorporated into the tumor, it is hypothesized that these may be tumor cells (16-18). Zamecnik et al. (19,20) detected immunohistologically myoid differentiation not only in elongated cells but also in epithelioid sex cord-like elements. On the other hand, the sex cord-like marker calretinin was expressed by not only epithelioid sex cord-like elements but also by the myoid elongated cells.

Some authors (8,17,21) assume that UTROSCT belong among the ESTSCLE tumors, with only an enhanced presence of sex cord-like elements. Others (22,16) admit that it is a special tumor category. Staats et al. (23) found that endometrial stromal tumors including ESTSCLE contain the JAZF1-JJAZ1 chimeric gene that has not been detected in UTROSCT. The authors cannot fully rule out that UTROSCT is an ESTSCLE variant lacking that translocation. On the other hand, this is suggestive of a different genetic mechanism of UTROSCT development. This justifies the classification of these tumors as a special category unrelated to ESTSCLE. In this case, the JAZF1-JJAZ1 chimeric gene was not identified by the RT-PCR method.

Distinguishing UTROSCT from other tumors may be difficult, especially in a small biopsy specimen. The differential diagnosis of UTROSCT includes tumors showing only focal sex cord-like features and tumors which can show overlapping morphological features throughout the whole lesion. Tumors with only focal sex cord-like areas include endometrial stromal tumor with sex cord-like differentiation, endometroid carcinoma, leiomyoma, and malignant mixed müllerian tumor (29,30). However, these tumors show other typical areas different from UTROSCT and, if apparent, recognition of these areas together with immunohistochemical analysis allow us to reach a correct diagnosis. The other tumors entering the differential diagnosis are those showing diffuse features resembling UTROSCT. These tumors include uterine Sertoli-Leydig cell tumor, epithelioid leiomyoma and PEComa (31,32). The correct diagnosis of these lesions can be based on morphological features and immunohistochemistry as well.

UTROSCT are polyphenotypic and polyimmunophenotypic tumors (3,24,25). The immunophenotypic heterogeneity has

led to various opinions on its histogenesis. Some derived the tumor from endometrial stroma (25,26), others from epithelium (27) or smooth muscles (28). The immunohistological profile of UTROSCT is comprised of the following four groups of markers: smooth muscle markers, epithelial markers, sex cord markers and miscellaneous markers. According to Pusiol et al. (29), at least two immunohistological markers should be present. Our case showed positive findings with antibodies against desmin in approximately 1 %, against calponin in 10 % and against WT1 in approximately 80 % of tumor cells. The Ki-67 proliferation marker was positive in less than 5 % of cells. Although the immunophenotype was rather poor, it met the criterion of two positive markers as stated by Pusiol et al. (29). Similarly, some other reported cases showed low antigen expression. In a group of 13 cases, Gupta et al. (25) found one tumor that was positive with antibodies against cytokeratins KL1, calretinin and S100. Retrospectively, Abdullazade et al. (3) reported other authors' cases with very limited immunophenotypes.

In most cases, UTROSCT do not relapse or spread to adjacent tissues and organs. In the past, however, several cases with metastatic spread were noted (4-7). O'Meara (7) reported multiple metastatic lesions in the peritoneal omentum, subcutaneous tissue and lymph nodes in a patient three years after hysterectomy.

Given the fact that UTROSCT are rare tumors, there are no mandatory guidelines as to how radical surgical therapy should be. Generally, a hysterectomy is performed in these cases. Uterus-sparing surgical procedures are not the method of choice. They only preserve the fertility of women who are strongly motivated and with to become pregnant in the future. These patients should be informed that the condition may recur (33). Lymphadenectomy remains a discussed issue. It must be borne in mind that the biological behavior of UTROSCT is uncertain and metastases cannot be ruled out. In the presented case, the patient was indicated for a hysterectomy with bilateral adnexectomy and pelvic and paraaortic lymphadenectomy.

In conclusion, we report another case of metastasizing UTROSCT. The possibility of aggressive behavior of this tumor should be borne in mind when considering the therapeutic approach including the extent of surgery.

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