Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT). Report of Case Suggesting Neoplastic Origin of Intratumoral Myoid Cells

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Summary

We report a case of double uterine tumor resembling ovarian sex cord tumor (UTROSCT). The tumor was composed of sex cord-like cords, nests and tubules, and bundles of myoid cells. The lesion was interesting especially in regard to histogenesis of intratumoral myoid cells. It is not known whether these cells are neoplastic or whether they represent preexisting myometrial smooth muscle cells entrapped into the tumor. In the present case, the sex cord-like epithelioid cells showed immunohistochemically myoid features in addition to features of epithelial, sex cord and endometrial stromal differentiation. The spindle cells expressed myoid, epithelial and endometrial stromal markers, but some of them were positive for sex cord marker calretinin. This immunophenotypic overlap between sex cord-like and myoid spindle elements indicates that the spindle cells of UTROSCT represent divergent line of differentiation of neoplastic cell rather than entrapped myometrial cells. It further expands the spectrum of possible differentiations in this polyphenotypic neoplasm.
Key words: uterine tumor resembling ovarian sex cord tumor – UTROSCT - immunohistochemical examination – smooth muscle differentiation - CD10

Súhrn

Tzv. „uterine tumor resembling ovarian sex cord tumor" (UTROSCT). Popis prípadu s nálezom podporujúcim neoplastický pôvod intratumorálnych myoidných buniek

Popisujeme prípad UTROSCT-u, ktorý bol zaujímavý z hľadiska histogenézy myoidných buniek (tieto bunky sú často v týchto tumoroch prítomné medzi typickými „sex cord-like" štruktúrami). Doposiaľ je diskutované, či ide o bunky neoplastické alebo len o nenádorové bunky preexistujúceho myometria. V prezentovanom prípade bola imunohistochemicky zreteľná v sex cord bunkách aj myoidná diferenciácia (okrem epitelovej a sex-cord diferenciácie). Na druhej strane, ojedinelé myoidné bunky exprimovali sex cord marker calretinín. Toto fenotypické prekrývanie favorizuje nádorový pôvod myoidných buniek a rozširuje spektrum možných diferenciácií v UTROSCT-e. Ďalším imunohistochemickým nálezom bola pozitivita cytokeratínu a stromálneho markeru CD10 v sex-cord aj myoidných bunkách. Pozorovanie komplexného fenotypu ďalej podporuje nedávne výsledky Irvinga a spol., ktorý označili UTROSCT za polyfenotypický nádor s „pravou" sex cord diferenciáciou.

Kľúčové slová: maternica - UTROSCT – myoidná diferenciácia - CD10 – inhibín

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So-called uterine tumor resembling ovarian sex cord tumor (UTROSCT) is composed typically of sex cord-like elements (2, 20). In addition to the sex cord-like structures, many UTROSCTs contain also a second component of spindle cells with smooth muscle features (2, 18, 19). Whereas the sex cord component is neoplastic without any doubt, the origin of myoid spindle cells is still controversial (8, 18, 19). They are either neoplastic or they represent preexisting myometrial smooth muscle cells entrapped into the tumor (8, 18, 19). Recently, we have seen a case that adds information to this question. The tumor showed, in addition to the positivity for sex cord markers, an unquestionable immunoreactivity for smooth muscle markers in the sex cord-like structures. Moreover, rare spindle myoid cells expressed sex cord marker calretinin (14). This immunophenotypic overlap bet-

ween sex cord-like and myoid spindle elements indicates that the spindle cells represent divergent line of differentiation of the neoplastic cell rather than the entrapped myometrial cells. Our additional findings confirm a recently described polyphenotypic nature of UTROSCT (8).

Materials and Methods

The formalin fixed tissue of the surgically removed specimen was routinely processed and the sections were stained with hematoxylin and eosin, PAS with and without diastase stains, and alcian blue at pH2.5. For immunohistochemistry, the sections were stained with antibody against epithelial membrane antigen (EMA, E29), α-smooth muscle actin (1A4), desmin (D33), h-caldesmon (h-CD), calponin (CALP), CD34 (Qbend 10), S100 protein (polyclonal), HMB45 (HMB45), melan-A (A103) (all from DakoCytomation), CD99 (HO36-1.1, Neomarkers), CD10 (56C6, Novocastra), α-inhibin (R1, Serotec), calretinin (5A5, Novocastra), cytokeratin AE1/AE3 (Boehringer) using the avidin-biotin peroxidase complex technique. Appropriate controls were used. The clinical information was obtained from the patient`s physician.

Results

In the uterus removed from a 39-year-old patient, two well-circumscribed leiomyoma-like nodules were found. Their diameter was 20mm and 4 mm, respectively. Grossly, the larger tumor appeared to be mucosal/intramural whereas the small lesion was mucosal. **Histologically**, both tumors had features of UTROSCT (2, 8), with typical bland appearing sex cord-like trabeculae and tubules, and with population of spindle cells of focal smooth muscle appearance (Fig. 1). The sex cord-like cells were of epithelioid shape, and contained slightly eosinophilic cytoplasm. Isolated sex cord-like cells or rare small groups of them had foamy cytoplasm. The nuclei of sex cord-like cells were bland, ovoid, and contained small nucleoli. Among the spindle elements, some cells resembled undefined fibroblast-like cell but many of them showed myoid features, such as eosinophilic cytoplasm, cigar-shaped nuclei and tendency for fascicular arrangement. Spindle cells were often closely associated with sex cord-like structures, sometimes creating strong impression that myoid cells and epithelioid sex cord-like cells share common origin. Leydig cells were not found. Both tumors were well circumscribed, lacking significant atypia and mitotic activity, and therefore we considered them two synchronous benign lesions. The larger tumor showed a predominance of the spindle cells whereas the small lesion consisted of mostly sex cord-like cell population. Typical conventional pattern of endometrial stromal tumor (small ovoid cells and abundant vessels) was not present in either lesion.

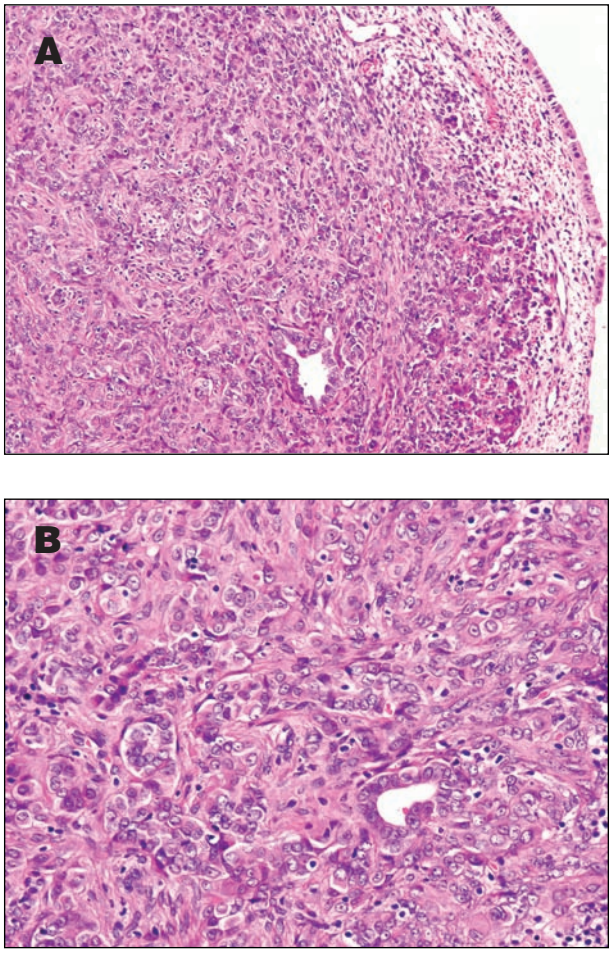

Fig. 1. Morphologic features of UTROSCT. **A and B,** intramucosal tumor with sex cord-like trabeculae and tubules, **C**, intramural tumor containing myoid fascicles and sex cord-like structures with rare foamy cells

Immunohistochemically (Fig. 2), myoid markers desmin, h-caldesmon, calponin and alpha-smooth muscle actin (19) highlighted the spindle cells, but focally they were unquestionably positive also in the sex cord-like epithelioid cells. Except for h-caldesmon, this reactivity included even some cells of the tubules. Among sex cord markers, calretinin (14) and CD99 (11) were positive in numerous epithelioid cells and in rare spindle cells. Melan A (21) was positive in foamy cells and in some epithelioid cells. Inhibin (11) reactivity was restricted to some epithelioid cells. CD10 (stromal cell marker) (1) was expressed by both spindle and sex cord-like cells. Pancytokeratin was often positive in both epithelioid and spindle cells. EMA, S100 protein and HMB45 were negative.

Discussion

UTROSCTs are neoplasms composed of sex cord-like epithelioid cells that are arranged in cords, trabeculae, small nests and tubules resembling granulosa or Sertoli cell tumors of the ovary (2). A subset of tumors contains myoid spindle cells. In their initial description by Clement and Scully (2), UTROSCT were designated as Group II tumors, characterized by benign behavior, to distinguish them from endometrial stromal sarcomas with sex cord-like elements (Group I tumors, ESTSCLE). In contrast with UTROSCT, ESTSCLE contain always (in addition to the sex cord-like structures and spindle cells) the areas of "conventional" stromal tumor composed of small cells and abundant vessels. In the recent WHO classification of tumors of the uterine corpus, UTROSCTs (i.e., former Group II tumors) are placed in the miscellaneous category (20). However, the overlap between UTROSCT and ESTSCLE causes that many investigators consider UTROSCT to be variant of endometrial stromal tumor (18).

Differential diagnosis of UTROSCT (former Group II tumors) includes, in addition to the above mentioned ESTSCLE, endometrioid carcinoma with sertoliform sex cord-like areas (3, 6) and other carcinomas, leiomyoma with plexiform (epithelioid) features (4) and metastasis of ova-

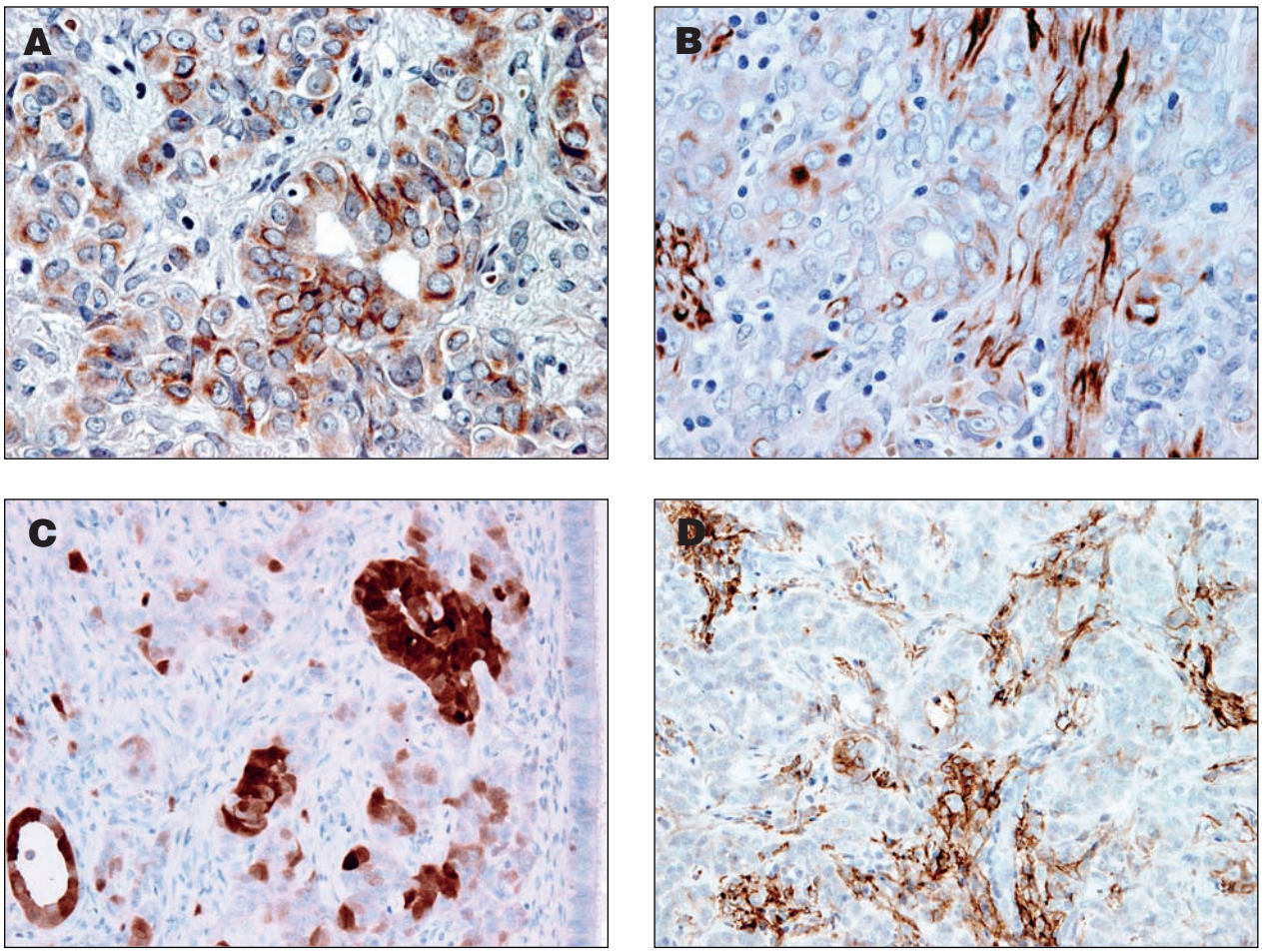

Fig. 2. Immunohistochemical findings. **A,** desmin positivity seen in sex cord elements, **B**, calponin in both sex cord and spindle cells, **C**, calretinin in sex cord cells and in rare spindle cells, **D**, CD10 in both spindle and sex cord cells

rian Sertoli-Leydig cell tumor (23). Endometrioid carcinoma with sex cord-like areas shows, at least focally, features of clearly epithelial phenotype, i.e. glandular pattern and strong immunohistochemical positivity for EMA that is lacking in UTROSCT. This applies generally also for metastatic breast carcinoma and other epithelial tumors. Moreover, epithelial tumors are usually negative for sex cord markers. Leiomyoma may contain sex cord-like cords and trabeculae, but it lacks positivity for sex cord markers. Metastatic ovarian Sertoli-Leydig cell is distinguished by knowledge of existing primary lesion in the ovary.

For the reason of understanding the histogenesis of UTROSCT, several studies have attempted to phenotype the sex cord-like cells with variable evidence supporting myoid (7, 10, 15, 17, 22, 24), epithelial (5, 12) and true sex cord differentiation (9, 11, 13, 16). Quite recently, Irving et al. demonstrated that UTROSCT is a polyphenotypic neoplasm (8) expressing epithelial antigens, sex cord markers and markers of endometrial stromal differentiation. Regarding the myoid differentiation, the authors found desmin positivity to be restricted to spindle cell bundles whereas the sex cord-like cells were desmin-negative. This finding of phenotypic difference between myoid spindle cells and non-myoid sex cord cells raised again the question on nature of the myoid cells in UTROSCT (2, 8). They could represent preexisting smooth muscle cells entrapped into the tumor rather than "true" smooth muscle differentiation in the sex cord-like neoplasm. Irving et al. (8) state, like Oliva et al. did previously (18), that this histogenesis remains still unclear. They add that although desmin reactivity in UTROSCT has been reported, this finding warrants strong consideration of smooth muscle neoplasm (8, 18, 19). Our observation of synchronous positivity for epithelial, stromal, and sex cord markers supports the theory of a polyphenotypic nature of UTROSCT. In addition, our finding of reactivity for smooth muscle markers in both spindle and sex cord-like component along with reactivity of rare spindle cells for sex cord marker calretinin demonstrates the phenotypic overlap between sex cord and spindle cells. This overlap suggests that the cells with fully developed smooth muscle phenotype are neoplastic rather than myometrial cells entrapped into the tumor. Moreover, the presence of smooth muscle cells in the intramucosal lesion is better explainable as a result of tumor differentiation because normal endometrium usually contains no smooth muscle cells that could be entrapped. Thus, our observations indicate that myoid differentiation expands the polyphenotypic spectrum of differentiations that occur in UTROSCT.

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ERRATUM

V práci ZÁMEČNÍK M., STANÍK M.: Dedifferentiated mixed stromal – smooth muscle tumor of the uterus. Report of a case (Čes.-slov. Patol., 42, 2006, No. 2, p. 81–85) došlo vinou tiskárny k přehození obrázků A–E ve Fig. 4 na straně 84.

Publikujeme tedy znovu celý obrázek.

Omlouváme se oběma autorům.

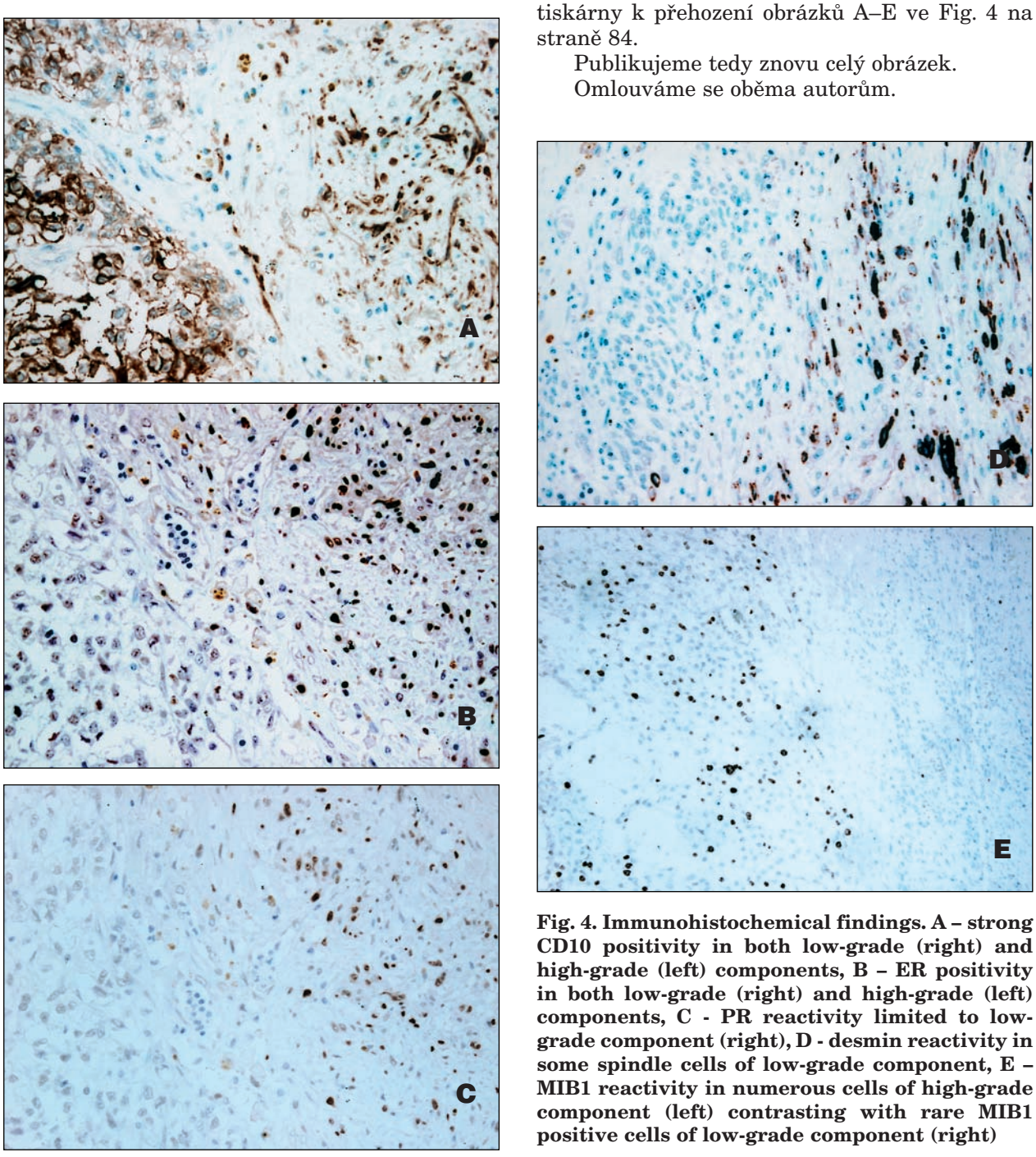

Fig. 4. Immunohistochemical findings. A – strong CD10 positivity in both low-grade (right) and high-grade (left) components, B – ER positivity in both low-grade (right) and high-grade (left) components, C - PR reactivity limited to low-grade component (right), D - desmin reactivity in some spindle cells of low-grade component, E – MIB1 reactivity in numerous cells of high-grade component (left) contrasting with rare MIB1 positive cells of low-grade component (right)