Myxoid mixed low-grade endometrial stromal sarcoma and smooth muscle tumor of the uterus. Case report

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SUMMARY
We report the case of a 73-year-old female with myxoid mixed low-grade endometrial stromal sarcoma and smooth muscle tumor of the uterus. Grossly, the tumor sized 130 x 130 x 100 mm involved the uterine corpus almost in its entirety. Histologically, the tumor consisted of two cell types. In some areas, the tumor cells showed typical features of endometrial stromal tumors and resembled stromal cells of proliferative endometrium. In other areas, however, the tumor showed smooth muscle features and consisted of larger mostly epitheloid cells with a moderate amount of cytoplasm. In all areas, myxoid changes and multiple hyalinizing giant rosettes were present. The tumor infiltrated the myometrium in a pattern typical of low-grade endometrial stromal sarcoma. Immunohistochemically, the tumor cells showed expression of vimentin, estrogen and progesterone receptors and variable expression of CD10, α-smooth muscle actin, desmin, h-caldesmon, and cytokeratin AE1/AE3. Other markers examined including CD99, α-inhibin, cytokeratin CAM5.2, S-100 protein, and HMB45 were negative. To the best of our knowledge, mixed low-grade endometrial stromal and smooth muscle tumor with myxoid changes has not been described to date.

Keywords: endometrial stromal sarcoma – mixed stromal-smooth muscle tumor – myxoid – uterine tumors

Smíšený myxoidní low grade endometriální stromální sarkom a hladkosvalový nádor dělohy. Popis případu

SOUHRN
Popisujeme neobvyklý smíšený myxoidní low grade endometriální stromální sarkom a hladkosvalový nádor dělohy vzniklý u 73leté ženy. Makroskopicky se jednalo o nádor velikosti 130 x 130 x 100 mm postihující tělo dělohy téměř v celém rozsahu. Histologicky byl nádor tvořen dvěma typy buněk. V některých oblastech se jednalo o buňky s rysy typickými pro endometriální stromální nádory, které připomínaly stromální buňky proliferačního korporálního endometria. Jinde byly patrny buňky s hladkosvalovými rysy převážně epiteloidního vzhledu s objemnější cytoplazmou. Ve všech oblastech byly místy přítomny myxoidní změny a mnohočetné obrovské hyalinizující rozety. Nádor infiltroval myometrium způsobem typickým pro low grade endometriální stromální sarkom. Imunohistochemickým vyšetřením jsme v nádorových buňkách prokázali expresi vimentinu, estrogenových a progesteronových receptorů a variabilní expresi CD10, α-hladkosvalového aktinu, desminu, h-caldesmonu a cytokeratinu AE1/AE3. Ostatní vyšetřované markery včetně CD99, α-inhibinu, cytokeratinu CAM5.2, S-100 proteinu a HMB45 byly negativní. Smíšené low grade endometriální stromální sarkomy a hladkosvalové nádory dělohy jsou vzácné a jejich myxoidní varianta doposud nebyla popsána.

Klíčová slova: endometriální stromální sarkom – smíšený stromální-hladkosvalový nádor – myxoidní – nádory dělohy

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Endometrial stromal tumors represent a group of rare benign and malignant tumors. These tumors are classified according to their growth and cell type into endometrial stromal nodule, low-grade sarcomas called endometrial stromal sarcoma (ESS), and high-grade sarcomas called undifferentiated endometrial sarcoma (UES). The UES category includes the monomorphic type (formerly high grade ESS) and pleomorphic type (1). From these tumors, low grade ESS is the most common and represents approximately 0.2 % of all malignant uterine tumors and 10–20 % of malignant mesenchymal uterine tumors (2). In typical cases, the ESS consists of cells resembling stromal cells of proliferative endometrium. However, some tumors may show unusual features and the diagnosis in such cases can be difficult. We described an unusual case of mixed low-grade ESS and a smooth muscle tumor of the uterus with myxoid changes.

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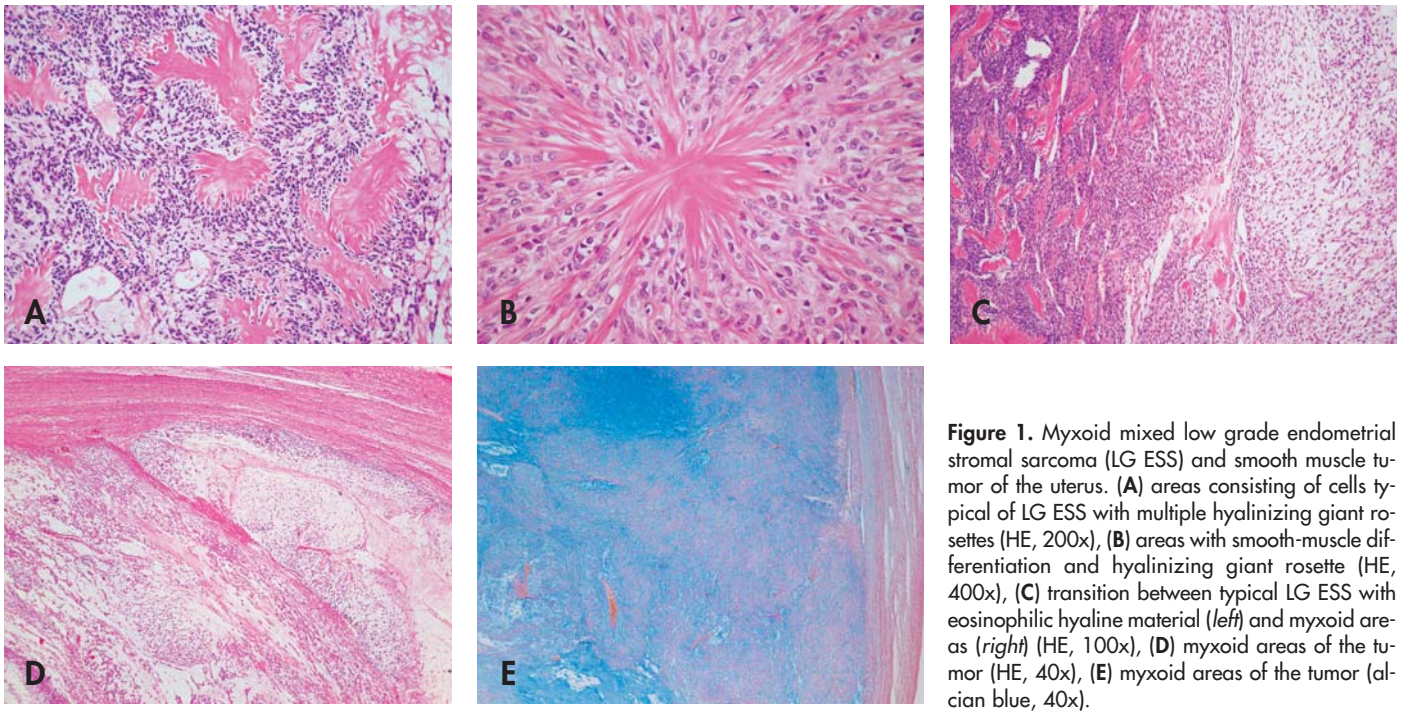

Figure 1. Myxoid mixed low grade endometrial stromal sarcoma (LG ESS) and smooth muscle tumor of the uterus. (**A**) areas consisting of cells typical of LG ESS with multiple hyalinizing giant rosettes (HE, 200x), (**B**) areas with smooth-muscle differentiation and hyalinizing giant rosette (HE, 400x), (**C**) transition between typical LG ESS with eosinophilic hyaline material (*left*) and myxoid areas (*right*) (HE, 100x), (**D**) myxoid areas of the tumor (HE, 40x), (**E**) myxoid areas of the tumor (alcian blue, 40x).

CLINICAL HISTORY

A 73-year-old female with a history of recurrent postmenopausal bleeding was referred to the Oncogynecological Centre of our hospital. She already underwent 7 curretage biopsies at the regional hospital, however, no diagnostic material was obtained. An ultrasound examination revealed an uterine tumor growing into the cavity and infiltrating the myometrium. The uterine contour was deformed due to multiple intramural and submucous nodules. One of these nodules located in the isthmus did not allow for an adequate biopsy using an endocavital approach. So the tru-cut biopsy of the uterine tumor was performed and three samples 10–15 mm in length were obtained. Nevertheless, the histologic diagnosis was equivocal. For that reason, the patient underwent a hysterectomy with bilateral salpingoophorectomy. Based on the final histology and negative signs of advanced disease revealed during a consequent CT scan of the lung, abdomen and pelvis, the patient was not indicated for the adjuvant treatment. She remains under regular follow-up every 3 months. At present, the patient shows no signs of tumor relapse 12 months after the diagnosis.

MATERIALS AND METHODS

Sections from formalin-fixed, paraffin-embedded tissue blocks were stained with hematoxylin-eosin. Selected sections were analysed immunohistochemically using the avidin-biotin complex method with antibodies directed against the following antigens: vimentin (1:300, Bio-Genex, San Ramon, CA, USA), cytokeratin CAM 5.2 (1:10, Becton–Dickinson, Mountain View, CA, USA), cytokeratin AE1/AE3 (1:50, Dako, Glostrup, Denmark), desmin (1:200, Dako), S-100 protein (1:1600, Dako), CD10 (1:100, NeoMarkers, Fremont), estrogen receptor (1:40, Novocastra, Newcastle, UK), progesterone receptor (1:100, Novocastra), CD99 (1:100, Dako), α-smooth muscle actin (1:100, Dako), α-inhibin (1:10, Dako), h-caldesmon (1:50, Dako), and HMB-45 (1:50, Dako).

RESULTS

Grossly, the uterine corpus measured 140 x 140 x 110 mm. The myometrium was infiltrated by a tumor sized 130 x 130 x 100 mm almost in its entirety. The tumor was multinodular with an apparent focal connection with the endometrium. In some areas the tumor was well circumscribed, in others the tumor border was ill defined. In some areas, the tumor consistency was hard, in others, however, the tumor was gelatinous. The uterine cervix, left fallopian tube, left ovary, and right fallopian tube showed no apparent changes. The right ovary consisted of a multicystic tumor sized 50 x 35 x 35 mm.

Histologically, the uterine tumor showed a heterogeneous pattern and two different tumor cell types were found. In some places, the tumor consisted of cells typical of endometrial stromal tumors resembling

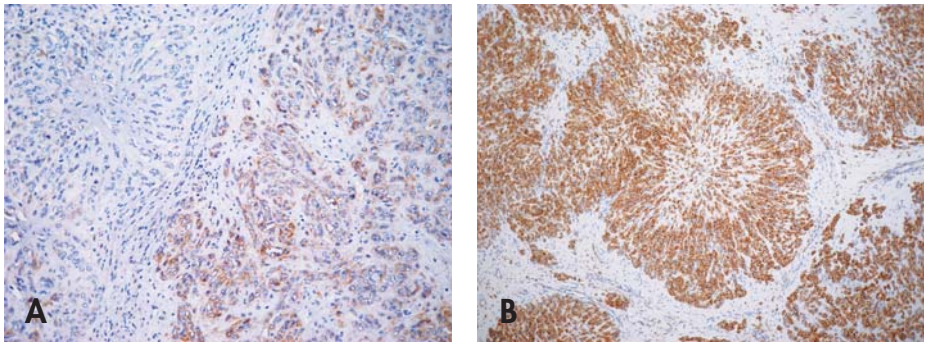

Figure 2. Immunohistochemical findings: (**A**) expression of CD10 in areas of low grade endometrial stromal sarcoma (*right*). Note negative staining of tumor cells in areas with smooth-muscle differentiation (*left*) (200x), (**B**) strong h-caldesmon expression in tumor cells (200x).

stromal cells of proliferative endometrium (Fig. 1A). These cells have a small amount of amphophilic cytoplasm, poorly defined cell borders, and round-to-oval nuclei with finely granular chromatin, small, non-prominent nucleoli and rare mitoses (up to 3/10 HPF). These cells were arranged in diffuse sheets or were separated by intercellular edema. In other areas, the tumor showed smooth muscle features and consisted of larger spindle and mostly epitheloid cells with vesicular nuclei with prominent nucleoli, moderate amount of eosinophilic cytoplasm, and ill-defined cell borders (Fig. 1B). Rare mitoses were found in this tumor cell type (up to 1/10 HPF). These cells were arranged in diffuse sheets. The areas of smooth muscle differentiation comprised more than 30 % of the tumor. Moreover, there were large areas with prominent myxoid features (Fig. 1C, 1D). In the myxoid areas, both tumor cell types could be found arranged in irregular groups or dissociated and separated by ample alcian-blue positive extracellular substances (Fig. 1E). In all areas, multiple hyalinizations and hyalinizing giant rosettes were present. These rosettes were irregular in shape and size and consisted of central hyalinization and bundles of collagen fibers radiating towards the peripheral rim of neoplastic cells. The tumor was in some areas well circumscribed and in other it infiltrated the myometrium in a pattern typical of low-grade endometrial stromal sarcoma. Neither necroses nor angioinvasion were found. The tumor of the right ovary was benign serous cystadenoma.

Immunohistochemically, both types of tumor cells showed expression of vimentin, estrogen and progesterone receptors. In addition, most tumor cells with features typical of LG ESS showed expression of CD10 (Fig. 2A), and focal expression of cytokeratin AE1/AE3, α-smooth muscle actin and desmin. On the contrary, larger spindle or epitheloid tumor cells with smooth muscle features showed only the focal expression of CD10, and most of these cells showed the expression of α-smooth muscle actin and desmin. Expression of h-caldesmon was found in about 30 % of these cells (Fig. 2B). However, in the myxoid areas, tumor cells with epitheloid features showed the expression of vimentin but were α-smooth muscle actin, CD10, desmin, and h-caldesmon negative. In some areas, tumor cells expressing CD10, h-caldesmon, and desmin were intermingled with each other. Other markers examined including CD99, α-inhibin, cytokeratin CAM5.2, S-100 protein and HMB45 were negative.

DISCUSSION

Low grade ESS in typical cases consists of cells resembling stromal cells of proliferative endometrium. In such cases, the diagnosis is usually straightforward. However, some tumors may show unusual features and the diagnosis in such cases can be difficult. These unusual features include the presence of sex cord-like structures, glandular elements, a smooth muscle component, skeletal muscle differentiation, and fibrous / myxoid changes (3,4). Moreover, unusual cell types such as fibroblastic cells, rhabdoid cells, atypical pleomorphic bizarre cells, or cells with epitheloid / deciduoid features can be found (5–7).

In our case, the tumor showed a heterogeneous pattern including myxoid changes and the presence of smooth muscle differentiation. Focal smooth muscle differentiation in endometrial stromal tumors is commonly observed. However, mixed low-grade endometrial stromal tumors and smooth muscle tumors are rare. These mixed tumors were defined in the past as those having at least 30 % of each component (8). Currently, mixed tumors are regarded as those having a significant amount of both elements (1). The clinical behaviour of these tumors is determined by the endometrial stromal component, therefore some authors classified them according to the stromal component as endometrial stromal nodule or ESS with smooth muscle differentiation and not as mixed tumors. Sometimes, hyalinizing giant rosettes, also referred to as a "star-burst" pattern, can be found in mixed endometrial stromal and smooth muscle tumors of the uterus (8,9). In our case, these rosettes were present in a large amount. However, they are by no means pathognomonic for mixed endometrial stromal and smooth muscle tumors. Similar structures are typical features of hyalinizing spindle cell tumor with giant rosettes, which is regarded as a variant of low grade fibromyxoid sarcoma (10,11). This tumor typically occurs in deep soft tissues, however, it can be found in many other places including broad ligaments (12). Moreover, hyalinizing giant rosettes can be found rarely in other mesenchymal tumors such as leiomyomas of soft tissues, neurilemmomas and fibrosarcomatous dermatofibrosarcoma protuberans (13). However, in pure ESS, these rosettes were mentioned only in one case (14).

Differential diagnosis of endometrial stromal tumors is largely dependent on its histological structure. In typical cases, the diagnosis is usually straightforward and no ancillary methods are needed. However, some tumors can reveal the above-mentioned unusual features. In such cases, the differential diagnosis is broad and includes uterine tumors resembling ovarian sex-cord tumors, adenomyosis, smooth muscle tumors (including atypical and myxoid ones), perivascular epitheloid cell tumors (PEComas), and rare uterine tumors such as those with skeletal muscle differentiation or rhabdoid cells. Correct diagnosis in these cases requires immunohistochemical analysis using a panel of antibodies including smooth muscle markers (such as desmin and h-caldesmon), markers of skeletal muscle differentiation, markers of sex-cord differentiation (such as α-inhibin, calretinin, and melan A), and antibody against CD10, which is used as a marker of endometrial stromal differentiation. Regarding the expression of the CD10, we should be aware that this marker is neither specific nor absolutely sensitive to endometrial stromal differentiation and some cases of ESS (such as fibroblastic / myxoid variant) can be CD10 negative or only focally positive. Moreover, some tumors of other histogenesis such as smooth muscle tumors or PEComas can express CD10 (15,16). Therefore, immunohistochemical results should always be correlated with histological features of the tumor. In addition, endometrial stromal tumors commonly show translocation t(7;17) involving two zinc finger genes, JAZF1 and JJAZ1 (17). Analysis of this abberation may be diagnostically useful (18,19).

In conclusion, we described an unusual case of myxoid mixed low grade ESS and a smooth muscle tumor of uterus. To the best of our knowledge, mixed endometrial stromal and smooth muscle tumor with myxoid changes has not been described to date. Our case emphasizes the possible morphologic and immunophenotypic heterogenity of mixed endometrial stromal and smooth muscle tumors, which should be borne in mind to avoid misdiagnosis of other tumors with different histogenesis and prognosis.

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MONITOR
aneb **nemělo by vám uniknout, že ...**

■ GYNEKOPATOLOGIE

... přítomnost nepravidelných velkých jader má u světlobuněčného karcinomu ovaria prognostický význam

Světlobuněčný karcinom ovaria je často považován za nádor se špatnou prognózou, pro jehož grading v současné době nejsou definovaná kritéria. Někteří autoři doporučují automaticky hodnotit všechny tyto nádory na podkladě histologického typu jako grade 3. Ukazuje se však, že přinejmenším část (možná většina) světlobuněčných karcinomů ovaria má v časných stádiích prognózu dobrou a jiní autoři proto opět pouze na podkladě histologického typu hodnotí tyto nádory jako grade 2.

Autoři z několika japonských pracovišť analyzovali 87 světlobuněčných karcinomů ovaria ve stádiu pT1 se zaměřením na výskyt buněk s nepravidelnými velkými jádry a jejich význam pro prognózu. Jako velké jádro autoři hodnotili jádro, které mělo alespoň dvojnásobnou velikost (délku) oproti mediánu velikosti (délky) všech nádorových jader. V případě výskytu velkých jader se hodnotila jejich kontura. Jádra s nerovnou jadernou membránou byla klasifikována jako nepravidelná velká jádra. Aby byl případ s ohledem na výskyt těchto jader hodnocen jako pozitivní, muselo alespoň 10 % všech velkých jader spadat do skupiny nepravidelných velkých jader. U 2 případů s nejpočetnějšími velkými jádry autoři provedli podrobnou analýzu ve vztahu k celkovému počtu jader (počítali 20 zorných polí při zvětšení 200x). U případu s největším počtem velkých jader bylo hodnoceno celkem 1253 jader, z toho 31 bylo velkých jader (2,5 %) a 4 nepravidelná velká jádra (0,32 %). Z uvedených výsledků vyplývá, že hodnocení výskytu těchto jader si nežádá složitější morfometrickou ani matematickou analýzu. Minimální počet velkých jader nebyl stanoven a k zařazení do pozitivní skupiny tedy stačí 1 velké jádro, které má současně nepravidelnou jadernou membránu.

Statisticky autoři hodnotili vztah výskytu nepravidelných velkých jader k 5ti letému bezpříznakovému období / 5ti letému přežití. Výsledky byly následující: všechny nádory – 88,9 % / 90,3 % pacientek; nádory bez nepravidelných velkých jader – 98,3 % / 100 % pacientek; nádory s nepravidelnými velkými jádry – 59,7 % / 62% pacientek.

Na podkladě získaných výsledků lze konstatovat, že výskyt nepravidelných velkých jader se zdá být prognosticky významným faktorem, jehož hodnocení je poměrně jednoduché. Pokud se prokáže jeho význam na větším souboru pacientek, mohl by se stát základem pro grading světlobuněčných karcinomů ovaria.

Zdroj:
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