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# Dedifferentiated Mixed Stromal-Smooth Muscle Tumor of the Uterus. Report of a Case

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## Summary

So-called dedifferentiation in mesenchymal neoplasms of the uterus is very rare. Among conventional low-grade stromal tumors only three cases of dedifferentiation were reported, whereas in mixed stromal-smooth muscle tumors the dedifferentiation was yet not described. Here we present such a case of low-grade mixed stromal-smooth muscle tumor with dedifferentiation. The tumor occurred in 52-years-old postmenopausal patient. The high-grade component representing a dedifferentiation showed morphology of undifferentiated sarcoma with myxoid change. The low-grade component with morphology of mixed stromal-smooth muscle tumor was limited to a few peripheral areas of the lesion. Immunohistochemically, the low-grade component showed typical positivity for CD10, estrogen receptor, progesterone receptor, and focal reactivity for myoid markers, whereas the dedifferentiated component expressed only vimentin, CD10 and estrogen receptor. This case demonstrates that low-grade mixed stromal-smooth muscle tumor of the uterus can dedifferentiate like a pure stromal tumor. It shows that extensive sampling/histological search may be needed for recognition of a minor component in a dedifferentiated tumor.

**Key words:** uterus – mixed stromal-smooth muscle tumor – dedifferentiation – fibrous endometrial stromal tumor

## Súhrn

### Dediferencovaný zmiešaný stromálny-hladkosvalový tumor maternice. Popis prípadu

Zatiaľčo fenomén dediferenciácie je dobre známy v low-grade nádoroch mäkkých tkanív a kostí, u low-grade stromálneho tumoru maternice bol popísaný len v troch prípadoch a vždy šlo o dediferenciáciu v konvenčnom stromálnom tumore. V kazuistike prezentujeme prípad dediferenciácie v low-grade zmiešanom stromálnom-hladkosvalovom tumore maternice. Low-grade komponent bol nájdený fokálne v periférnej zóne high-grade stromálneho sarkómu. Prevládajúca high-grade zložka mala morfológiu nízko diferencovaného myxoidného sarkómu. Imunohistochemicky bol low-grade komponent pozitívny na CD10, vimentín, estrogénové a progesterónové receptory a miestami na myoidné markery. High-grade komponent exprimoval len vimentín, CD10 a progesterónové receptory. Prípad demonštruje, že zmiešaný low-grade stromálny-hladkosvalový tumor maternice môže dediferencovať podobne ako konvenčný stromálny tumor. Pre rozpoznanie dediferenciácie môže byť potrebný extenzívny sampling tumoru (kvôli zachyteniu minoritnej zložky), podobne ako tomu bolo v prezentovanom prípade.

**Kľúčové slová:** maternica – zmiešaný stromálny-hladkosvalový tumor – dediferenciácia – fibrózny endometriálny stromálny tumor

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## Introduction

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The coexisting of low-grade and high-grade tumor of the same origin in one tumor mass is well recognized especially in soft tissue and bone tumors, and it was termed dedifferentiation (7).

In uterine stromal tumor the dedifferentiation was described only very rarely (2, 13, 14), and it was not reported in mixed stromal-smooth muscle tumor to our knowledge. Here we present a case of high-grade stromal sarcoma that apparently has arisen inside the low-grade mixed stromal-smooth muscle tumor (9) through the process of dedifferentiation.

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## Materials and Methods

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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, alcian blue at pH2.5, and Gomori's stain for reticulin fibers. For immunohistochemistry, the sections were stained with antibody against vimentin (V9), epithelial membrane antigen (EMA, E29), S100 protein (polyclonal),  $\alpha$ -smooth muscle actin (1A4), desmin (D33), h-caldesmon (h-CD), CD34 (Qbend 10), CD99 (MIC2 gene product, 12E7), Ki 67 (MIB1), S100 protein (polyclonal), HMB45 (HMB45), melan-A (A103) (all from DAKO), CD10 (56C6, Novocastra), cytokeratin AE1/AE3 (Boehringer),  $\alpha$ -inhibin (R1, Serotec), KI-67 (MIB1, Immunotech), estrogen receptor (ER1D, Immunotech) and progesterone receptor (1A6, Immunotech) using the avidin-biotin peroxidase complex technique. Appropriate controls were used. The clinical information was obtained from physician of the patient.

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## Case Report

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A 52-year-old non-obese patient (para 0, gravida 0, menopause 2 years ago) with mild hypertension was admitted for several days history of uterine bleeding. The ultrasound revealed tumor of the uterine wall and clinical diagnosis uterus myomatosis was rendered. A hysterectomy with bilateral adnexotomy and omentectomy was performed. Intraoperatively, the adnexa and omentum were found to be normal. Subsequently, the patient received pelvic irradiation, and she is without recurrent disease eight months after the surgery.

**Grossly**, the uterus was enlarged by 9x10x12cm tumor (figure 1). The tumor appeared to be limited to the myometrium and endometrium, obliterating the cavum uteri and almost full thickness of the myometrium. Invasion through the uterine serosa and adventitia was not seen. The tumor was grossly well circumscribed and unencapsulated. The cut surface was vaguely lobular, pale gray, and mostly of gelatinous and lesser of fibrous appearance. The consistence was mostly soft, but in some peripheral zones it was firm and resembled that of leiomyoma.

**Histologically**, approximately 90% of the tumor volume was composed of high-grade sarcoma (figures 2 and 3A) that had invaded in some areas into the adjacent myometrium and into adipose tissue of the parametrium. The cells

in this component were of ovoid to spindle/stellate shape. There was high nuclear atypia and numerous mitoses (13/10HPF). The prominent feature of this component was myxoid change with occasional stromal mucin pools resembling superficially the non-lipogenic pattern of myxoid liposarcoma (4) or myxofibrosarcoma (1, 4, 6). However, the vessels (although they were quite numerous) lacked any plexiform or curvilinear arrangement. The high-grade component merged imperceptibly with areas of low-grade mixed stromal-smooth muscle tumor (figures 2 and 3B). The first sections from the tumor contained only a single focus with low-grade pattern, but additional extensive sampling [50 tissue blocks] revealed additional foci. This minor low-grade component was found in some peripheral areas of the tumor. It contained cells of two types. One type was small ovoid cell resembling normal endometrial stromal cell (figures 3B and 3C) and the second type was a spindle cell of myoid appearance, with elongated nucleus and eosinophilic cytoplasm (figure 3D). The spindle cells were often arranged in the fascicles. The intercellular stroma of this component showed pronounced hyalinization and very rare myxoid change. The nuclear atypia was low and mitoses were rare. The histologic features were consistent with low-grade mixed stromal-smooth muscle tumor with hyalinization (9, 10). Additional findings in the resectate were as follows: normal finding in both ovaries and oviducts; atrophy in remaining endometrium; chronic inflammation and squamous metaplasia in the cervix.

**Immunohistochemically**, the low-grade component was positive diffusely for CD10 (figure 4A), vimentin, ER (figure 4B), and progesterone receptor (PR) (figure 4C). In addition, numerous of low-grade spindle cells expressed actin and desmin (figure 4D). H-caldesmon was positive in very rare spindle cells. MIB1 index was 1% (figure 4C). All other antibodies gave negative results. The high-grade component was positive diffusely for vimentin and CD10 (figure 4A). Estrogen receptor (ER) was positive in 40% of its cells (figure 4B), and MIB1 index was 35% (figure 4D). All other markers were negative.

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## Discussion

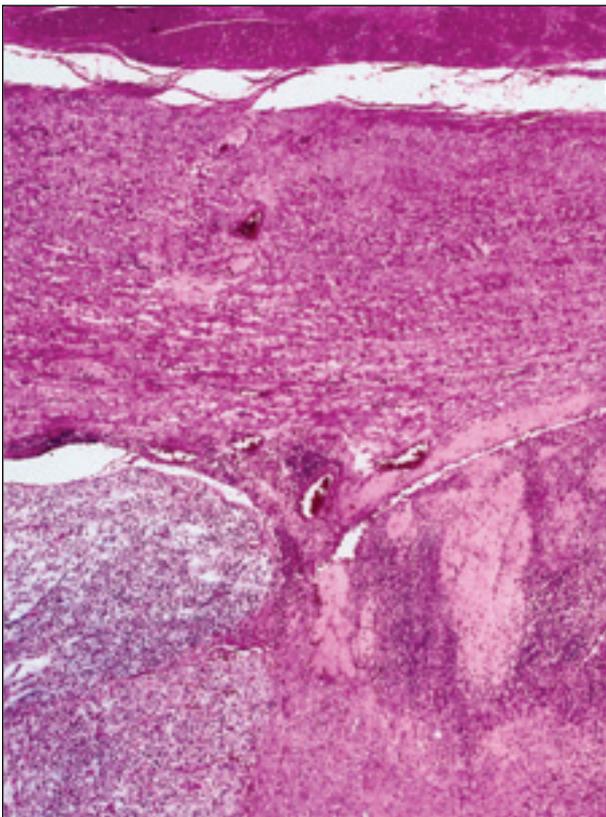
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The phenomenon of dedifferentiation is well recognized in mesenchymal tumors of soft tissue and bone (5, 7). It represents a morphological indicator of tumor progression when a low-grade lesion transforms into high-grade tumor. From the genetic point of view, this progression is

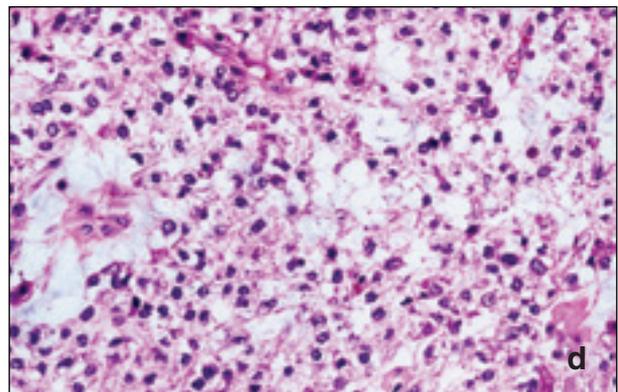
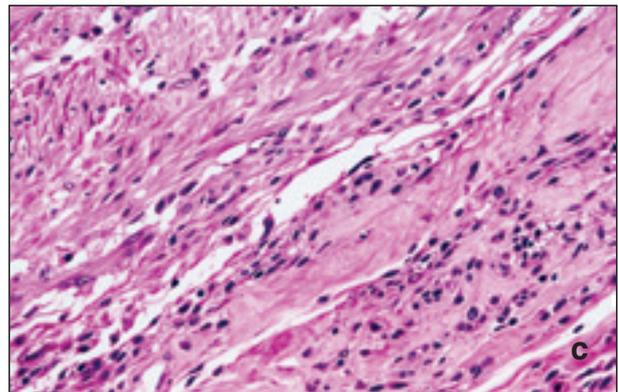
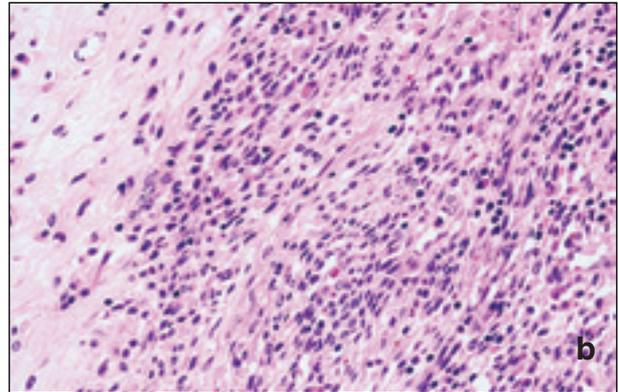
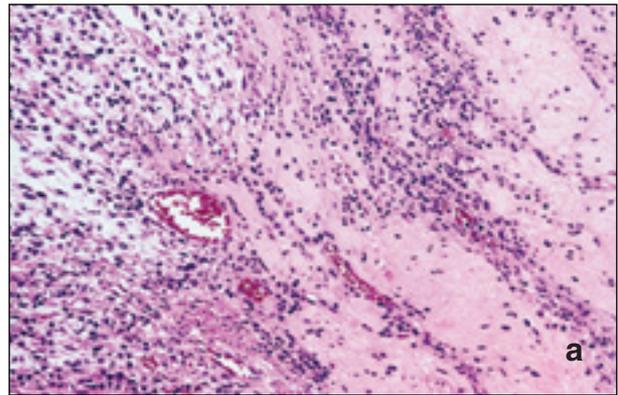
caused by accumulation of additional genetic and epigenetic changes in originally low-grade lesion that poses lower number of such changes. Histologically the dedifferentiated tumors contain both low- and high-grade patterns, which are always and to various extend spatially



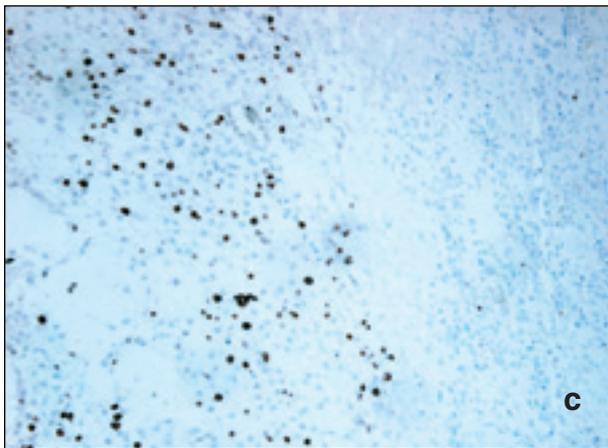
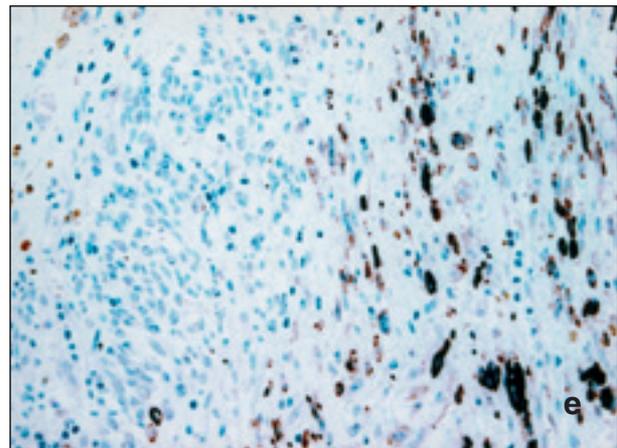
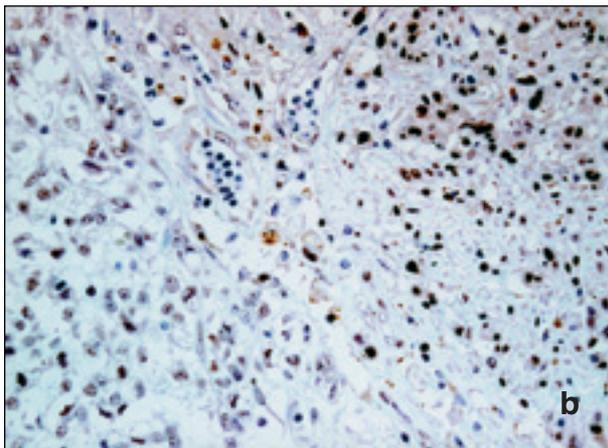
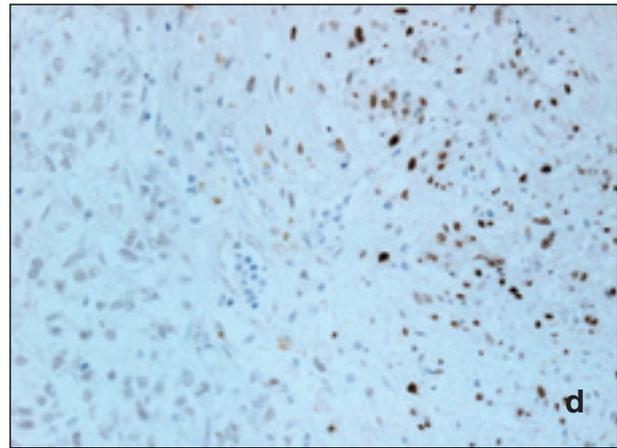
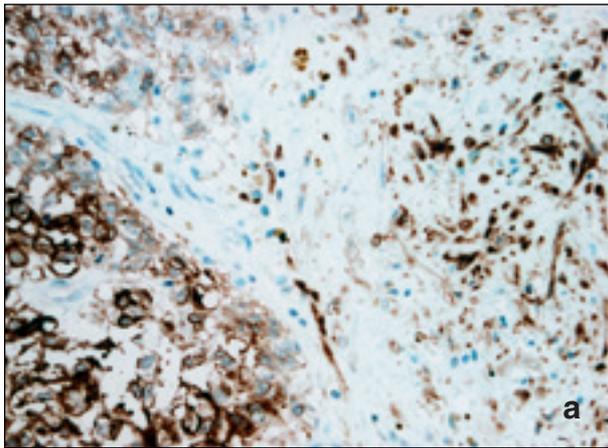
**Fig. 1.** Gross appearance of the resectate. The tumor is well circumscribed and its cut surface is myxoid and fibrous



**Fig. 2.** Low-power view of peripheral tumor part shows low-grade stromal-smooth muscle component (bottom right and top) and myxoid high-grade component (bottom left). The cleft seen in the upper part of the photomicrograph is a border between tumor and myometrium



**Fig. 3.** Histologic features of the tumor. A - transition between low-grade fibrous stromal sarcoma (right) and high-grade myxoid sarcoma (left), B - low-grade stromal component with hyalinization, C - myoid differentiation in low-grade component, D - high-power view of high-grade component



**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 (left), D - desmin reactivity in some spindle cells of low-grade component, E – MIB1 reactivity in numerous cells of high-grade component (right) contrasting with rare MIB1 positive cells of low-grade component (left)**

associated. The difference between grades of differentiation of both components is usually substantial and well apparent histologically [with rare exceptions, such as so-called low-grade dedifferentiation in retroperitoneal atypical lipomatous tumor (5)]. Among tumors of the uterus, the dedifferentiation was well described in müllerian adenosarcomas in which it was termed “sarcomatous overgrowth“ (3). In uterine stromal tumors, the dedifferentiation with coexisting of low grade and high-grade tumor inside one mass was reported to the best of our

knowledge in three cases only (2, 13, 14). The low-grade component of these tumors was “conventional“ stromal tumor with typical small cells and rich vasculature. The dedifferentiation in mixed stromal-smooth muscle tumor, as seen in the present case, was not described before. Rare occurrence of dedifferentiation in both pure stromal tumor and mixed stromal-smooth muscle tumor can reflect close relationship of these two lesions which both according to the current view represent simply variations of a single neoplasm arising from endometrial stroma (9).

In our case the predominant part of the tumor volume contained high-grade stromal sarcoma with extensive myxoid change. This high-grade lesion lacked myoid features that were seen in the minor low-grade component. We believe that such lack of "maturation" of neoplastic stromal cells toward smooth muscle cell phenotype is also related to the malignant progression. The patterns of low-grade tumor were seen only in some peripheral areas of the tumor. This spatial arrangement suggests that the dedifferentiation occurred in the central part of the original low-grade lesion.

In addition to the morphological differences between low grade and high-grade component, we found differences also in immunohistochemical expressions of some markers that are otherwise typical of mixed stromal-smooth muscle tumor. The complete lack of expression of myoid markers in the dedifferentiated areas is in keeping with absence of myoid differentiation seen histologically. The substantial increase of the cell proliferation in the high-grade component [MIB1 index 40% in high-grade component *versus* 1% in low-grade component] corresponds with dedifferentiation as well. ER and PR were positive in low-grade component, as seen commonly in low-grade stromal tumors (8, 11, 12). Dedifferentiated tumor was devoid of PR, which is common in "pure" high-grade stromal sarcomas (8, 12). Interestingly, the high-grade component retained strong ER reactivity. We speculate that this presence of ER stimulated the activity of cell proliferation in this component. Estrogen produced by ovaries could stimulate proliferation of ER+ tumor cells that had been insensitive for opposite effect of progesterone [because of lack of PR].

Regarding an incidence, the dedifferentiation in low-grade stromal tumors of the uterus was described very rarely (2, 13, 14). This may be explained by really rare occurrence of this phenomenon in these tumors, but, alternatively, the rarity of reports can be caused by frequent overlooking of the low-grade component in predominantly high-grade sarcomas due to non-extensive sampling. For resolving of this question the extensive sampling in large series of high-grade uterine sarcomas is needed. We suppose that in such condition more cases of mixed low grade – high-grade tumors could be recognized.

In conclusion, we described a first case of dedifferentiation in low-grade mixed stromal-smooth muscle neoplasm. The case indicates that some high-grade tumors can arise through process of dedifferentiation that is in uterine

mesenchymal tumors still poorly understood. The undifferentiated component loosed some immunohistochemical expressions that are typical of low-grade lesion. On the other hand, some other antigens such as CD10 and ER were retained, thus reflecting the origin of this undifferentiated component from stromal cell. The recognition of similar cases requires adequate or even an extensive sampling to avoid an overlooking of minor component of the tumor.

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