

## Carcinosarcoma-like endometrioid carcinoma of the uterus: case report of rare non-high-grade tumor

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A rare case of endometrioid carcinoma of the uterine corpus with sex cord like formation and hyalinization in a 54-ys-old woman is described. It was low stage (pT1a) tumor composed predominantly of common endometrioid carcinoma grade 2, with exophytic area of biphasic carcinosarcoma-like component. This area contained glands of endometrioid carcinoma with shadow and squamous cells and with transitions to mesenchymal appearing stromal component. The stromal component was of low-grade appearance, and it was composed of spindle to ovoid cells which formed compact fascicles or which lay in abundant myxoid and hyalinized matrix. The tumor expressed estrogen and progesterone receptors, beta-catenin and cyclin D1, and it was negative for p53, myogenic markers (actin, desmin) and stromal marker CD10. Morphological and immunohistochemical features were different from those of malignant mixed mullerian tumor, and they were suggestive of beta-catenin mutated carcinoma. However, distinction of this tumor from high-grade carcinosarcoma is difficult, especially by examination of intraoperative frozen section. Knowledge of this tumor entity and immunohistochemical technique are important for correct diagnosis.

**Keywords:** endometrioid carcinoma with sex cord like formation and hyalinization, carcinosarcoma, shadow cell differentiation, adenoacanthoma, uterus, beta-catenin

### Karcinosarkómu podobný endometrioidnému karcinóm: popis prípadu non-high-grade tumoru

Opísaný je prípad endometrioidného karcinómu tela maternice, so „sex-cord like“ štruktúrami a hyalinizáciou. Šlo o tumor u 54-ročnej ženy s nízkym štádiom nádorového postihnutia. Histologicky mal štruktúru grade 2 endometrioidného karcinómu so „shadow cell“ a skvamocelulárnu diferenciáciu. V tumore bolo navyše exofytické ložisko s bifázickou morfológiou. Stromálny komponent v tejto časti tumoru bol nízkomalígného výzoru, obsahoval vretenovité a ovoidné bunky uložené buď kompaktne, alebo v hojnom myxohyalínnom matrinx. Imunohistochimicky exprimoval tumor estrogénové a progesterónové receptory, beta-katenín a cyklín D1. Negatívne boli p53, myogénne markery (dezmin, aktín) a marker stromálnej diferenciácie CD10. Morfológia a imunohistochémia tumoru sa líšili od klasického vysokostupňového malígného mulleriánskeho tumoru (karcinosarkómu) a silne suponovala beta katenín-mutovaný karcinóm. Diferenciálna diagnóza tumoru môže byť ťažká, najmä v peroperáčnej rýchlej biopsii. Pre diagnózu je dôležité poznanie tejto novej jednotky a imunohistochémia.

**Kľúčové slová:** endometrioidný karcinóm so „sex-cord like“ štruktúrami a s hyalinizáciou, karcinosarkóm, „shadow cell“ diferenciácia, adenoakantóm, maternica, beta-katenín

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### Introduction

In 2005, Murray et al. described a rare variant of endometrioid carcinoma (EC), which strongly resembled malignant mixed mullerian tumor (MMMT) histologically, but which behaved like common non-high-grade endometrioid carcinoma (EC)<sup>(1)</sup>. This tumor termed „EC with sex cord like formation and hyalinization“ (ESCFH) contains, in addition to endometrioid glands, areas with morphology that resembles sar-

coma. After Murray et al's paper, several additional reports were added to the literature<sup>(2-3)</sup>. All of these studies emphasized that the tumor strongly mimics MMMT, although its behavior is similar to that of common non-high-grade EC. As both epithelial and stromal component appear non-high-grade, a term „low-grade carcinosarcoma“ was proposed<sup>(4)</sup>. In this report, we would like to present our recent case of this rare lesion.

## Materials and methods

The tissue was fixed in 10% formalin and processed routinely. The sections were stained with hematoxylin and eosin. For immunohistochemistry, the following primary antibodies were used: alpha smooth muscle actin (prediluted, 1A4), h-caldesmon (1:200, h-CD), desmin (prediluted, D33), S100 protein (prediluted, polyclonal), HMB45 (prediluted, HMB45), estrogen receptor (ER) (1:100, EP1), progesterone receptor (PR) (1:25, PgR636), pancytokeratin (1:200, AE1/AE3), epithelial membrane antigen (EMA) (prediluted, E29), vimentin (1:100, Vim 3B4), Ki-67 (prediluted, MIB1), p63 (1:50, DAK-p63), p53 (prediluted, DO-7), MLH1 (prediluted, ES05), MSH2 (prediluted, FE11), MSH6 (prediluted, EP49), PMS2 (prediluted, EP51), alpha-inhibin (prediluted, R1), calretinin (1:100, DAK-Calret 1), CD31 (1:50, JC70A), podoplanin (1:100, D2-40) (all from DAKO, Glostrup, Denmark), myo-D1 (prediluted, EP212, Cell Marque, Rocklin, USA), SOX10 (1:50, EP268, Cell Marque, Rocklin, USA), CD10 (prediluted, SP67, Ventana, Tuscon, USA), CD34 (prediluted, QBend/10, Ventana, Tuscon, USA), beta-catenin (prediluted, 14, Cell Marque, Rocklin, USA), cyclin D1 (prediluted, SP4-R, Ventana, Tuscon, USA). Immunostaining was performed according to standard protocols using an avidin-biotin complex labeled with peroxidase or alkaline phosphatase. Microwave antigen pretreatment was used for immunoreactions with h-caldesmon, CD10, CD34, estrogen receptor, and progesterone receptor. Appropriate positive and negative controls were applied.

## Case report

A 54-ys-old, para 0, gravida 0, woman underwent dilatation and curettage for one year lasting irregular postmenopausal bleeding. The curettage specimen contained non-high grade EC, and therefore a hysterectomy with bilateral salpingo-oophorectomy was performed. Previous medical history of the patient (according to her information) included laparoscopic removal of a benign ovarian cyst 30 years ago. Additional medical history was unremarkable.

## Pathological findings

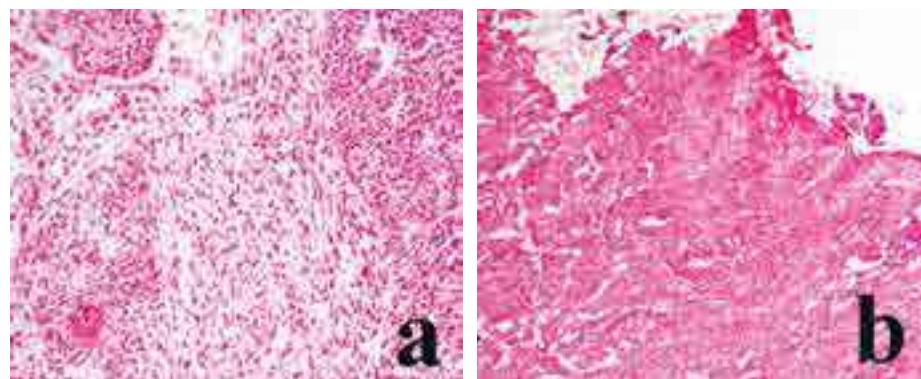
Curettage specimen exhibited non-high-grade EC (grade 2 FIGO) with squamous and shadow cell differentiation<sup>(5-8)</sup> and with beta-catenin nuclear accumulation in squamous cells (**Figure 1**). Beta-catenin stained, in addition, the cytoplasm and cell membranes of all neoplastic cells. ER and PR were positive in 80% and 50% of the cells, respectively.

Routine intraoperative consultation was performed with an aim to determine the depth of myometrial invasion of the tumor. Surprisingly, one of frozen sections showed biphasic neoplasm suggesting MMT with homologous stromal component (**Figure 2a**). However, another frozen section showed „pure” non-high grade EC (**Figure 2a**). Invasive margin in the myometrium contained only EC without sarcoma-like pattern. Considering previous non-high-grade histologic finding in the curettage specimen along with apparently focal nature of the biphasic morphology seen in the frozen

**Figure 1.** Curettage specimen. (a) Endometrioid carcinoma with cluster of shadow cells. (b) Beta-catenin in the nuclei of squamous cells. (c) Estrogen receptor is positive in the glandular cells (upper half of the photomicrograph) and negative in the squamous cells (lower half).



**Figure 2.** Frozen sections. (a) Biphasic pattern that simulates malignant mixed mullerian tumor. (b) An area with “pure” endometrioid carcinoma of non-high-grade morphology, with adenoacanthomatous features (upper).



section, the diagnosis of MMMT was not rendered, and the final classification of the tumor was deferred. The tumor infiltrated inner half of the myometrium and therefore a staging lymphadenectomy was not performed.

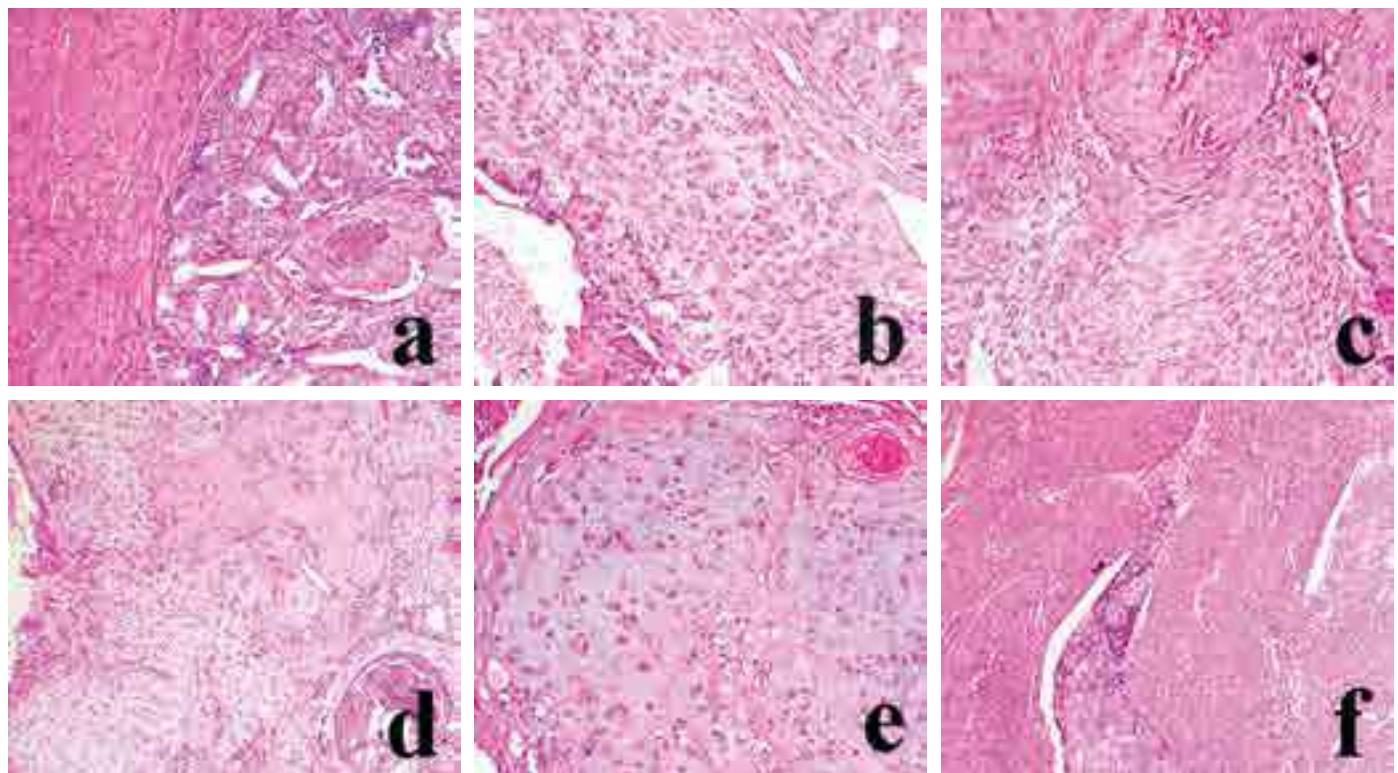
Grossly, the resection specimen of hysterectomy with bilateral salpingo-oophorectomy included uterus measuring 11 cm x 9 cm x 6 cm. A 55 mm tumor was found in the mucosa and myometrium of the posterior wall of the uterine corpus. The tumor was flat, with central irregular polypoid prominence. It had gross appearance of common endometrial EC, with fragile tissue on its surface. Both adnexa were unremarkable.

**Histologically (Figure 3),** permanent sections exhibited typical glandular and cribriform EC, FIGO grade 2. This pattern was seen in 90% of the neoplasm. In addition, exophytic part of the tumor, comprising 10% of the tumor volume, contained glands of EC admixed with a non-high-grade mesenchymal appearing component of spindle to epithelioid cells. The glands in this area showed conspicuous squamous differentiation with formation of shadow cells and with keratin material. The mixture of the glands with the stromal component resulted in striking biphasic appearance. The fusiform and epithelioid cells of the stroma formed clusters, cords and ill-defined fascicles. They were often embedded in the hyalinized or myxoid matrix. In addition, the stroma contained isolated clusters of shadow cells in the reactive appearing fibrosis and numerous dystrophic calcifications. An osteoid formation was not found. In the invasive margin in

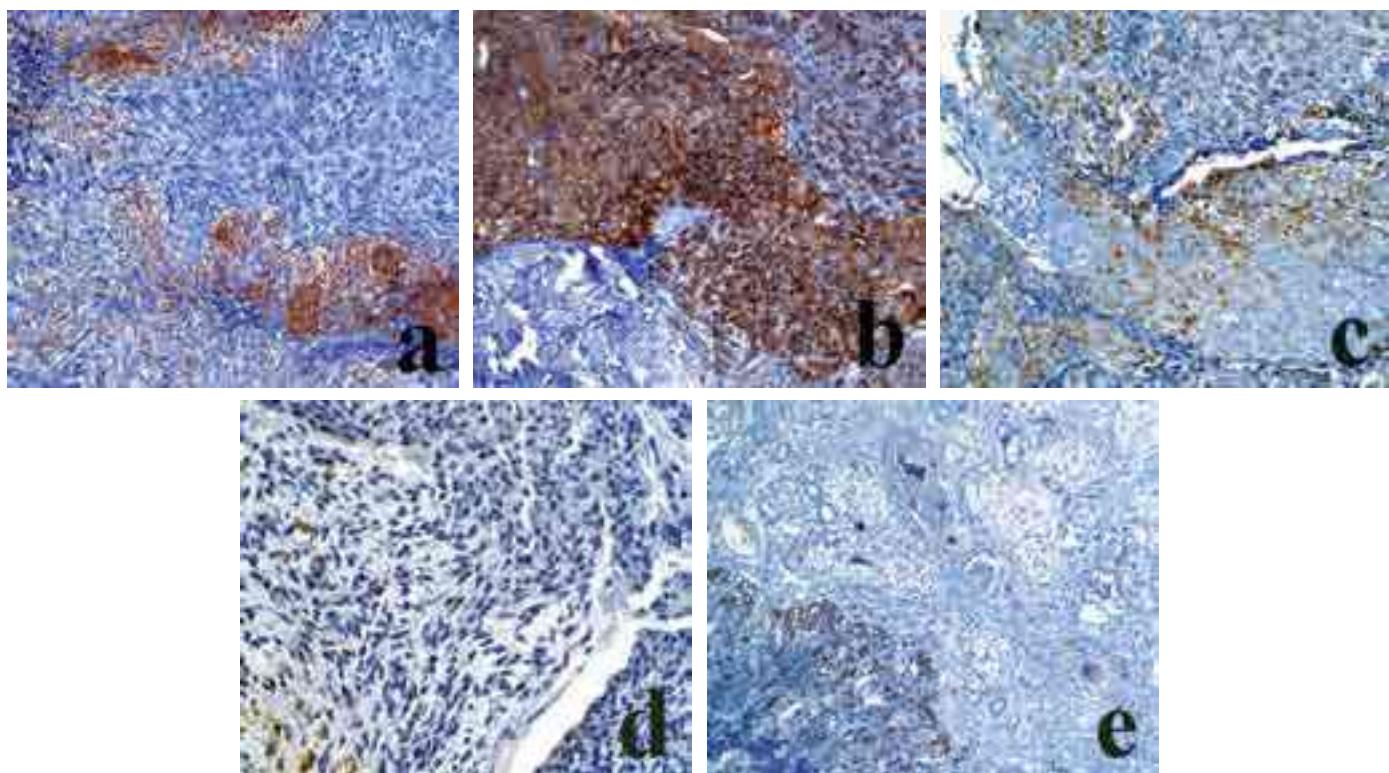
the myometrium, rare clusters of carcinoma cells were seen in the podoplanin-negative vascular spaces, which was interpreted by us as a hemovascular invasion<sup>(9-11)</sup>. Lymphatic podoplanin-positive spaces did not contain any tumor cells.

**Immunohistochemically (Figure 4),** pancytokeratin and EMA were positive in the carcinomatous component and in some stromal cells (Figure 4a). Beta-catenin was seen in cells of the basal and parabasal layer of the epithelium and in almost all cells of the stromal component (Figure 4 b). Cyclin D1 stained both epithelial and stromal cells (Figure 4 c). P63 was positive in squamous cells and in rare cells of the glandular epithelium. S100 protein stained focally the cells of myxoid and chondroid areas (Figure 4 d). MIB1 highlighted low proliferation in both stromal and squamous cells. Only 3 percent of these cells were positive, whereas glandular cells displayed MIB1 expression in 40 percent of the nuclei (Figure 4 e). Vimentin stained both components, except of squamous cell differentiation. CD10 was slightly positive in squamous cells and it stained luminal surface of the glandular epithelium. Inhibin and calretinin were negative, ruling out sex cord differentiation in complex neoplasm such as stromal sarcoma with glands and sex cord like structures<sup>(12)</sup>. CD31 and D2-40 highlighted non-neoplastic endothelium, confirming hemovascular invasion of the tumor. The tumor was negative for p53, alpha-smooth muscle actin, desmin, h-caldesmon, myo D1, CD34, SOX10, HMB45, inhibin and calretinin. MMR proteins (MLH1, MSH2, MSH6 and PMS2) did not show any loss of positivity.

**Figure 3.** Histological findings in the resection specimen. (a) Endometrioid carcinoma pattern was predominant. (b) Biphasic pattern with hyalinized low-grade appearing stromal component. (c) Spindle cell transformation of adenoacanthomatous carcinoma. (d) An area of myxoid and hyalinized stromal component. In lower right corner, a small nodule of squamous cells is seen. (e) Focal chondroid appearance of the stromal component resembled chondroid pattern of salivary pleomorphic adenoma. (f) Hemovascular invasion of the tumor.



**Figure 4.** Immunohistochemical findings. (a) Pancytokeratin AE1/AE3 in the epithelium and in rare stromal cells. (b) Nuclear beta-catenin positivity in both epithelial and stromal components. Shadow cells and keratin material are negative (left and bellow). (c) Cyclin D1 was seen in both epithelial and stromal component. (d) Scattered S100 protein positive cells in the stromal component. (e) MIB1 shows high proliferation of adenocarcinoma component (left and bellow) contrasting with low proliferation in myxoid and hyalinized stromal component.



Our final diagnosis was ESCFH, with 5 mm invasion into 20 mm thick myometrium (stage 1 A) and with beta-catenin positive squamous and shadow cell differentiation, suggesting CTNNB1 mutated carcinoma<sup>(13)</sup>. Because the tumor showed hemovascular invasion, one published carcinosarcoma with low-grade appearance had dismal prognosis<sup>(14)</sup> and CTNNB1 mutated EC represents an aggressive subgroup of non-high grade EC<sup>(12-13)</sup>, we proposed that an adjuvant therapy should be considered for the patient. Patient was staged as pT1aNxMx, her Ca125 and HE4 serum markers were negative. After discussion at multidisciplinary meeting and with the patient, adjuvant chemotherapy with carboplatin and paclitaxel was proposed. Two months after the surgery, clinical examinations found no sign of metastasis and recurrence.

## Discussion

The present tumor shows features of ESCFH<sup>(1-3,17-19)</sup>. The non-high grade appearing glands of EC were admixed with cords and fascicles of epithelioid or fusiform cells within hyalinized stroma. The tumor resembles strongly MMMT, and especially in the frozen section the diagnosis is difficult, as we have experienced in our case. The knowledge of this type of EC is crucial to avoid misdiagnosis of MMMT. Examining frozen section, it was helpful for us that the slides from previous curettage specimen were available for a review. In addition, we have seen in frozen sections that biphasic pattern was strictly focal whereas typical MMMT shows diffuse

biphasic pattern in majority of cases<sup>(20-22)</sup>. However, in rare MMTs the sarcomatous component can be limited even to a single focus, but this seems to be exceedingly rare and the known data about this phenomenon are limited to our knowledge. We have experience with one case of MMT which was in fact a large EC that contained a single 15x10x10mm focus of gradual transition to pleomorphic and rhabdomyoblastic sarcoma<sup>(23)</sup>. Some published series of MMT mention very rare cases of MMT which contained only small amount of biphasic pattern<sup>(20-22)</sup>.

Immunohistochemically, our case lacked several typical features of MMT and this also was helpful for differential diagnosis. It was negative for p53, its epithelial component expressed ER and PR, MIB1 index in the stroma was very low, and the stromal component did not express muscle markers and stromal marker CD10. In addition, the stromal cells were positive for beta-catenin. This expression was found by Wani et al in all cases of ESCFH, which contrasted with beta-catenin negativity of sarcomatous component in all cases of MMTs<sup>(2)</sup>. In the low-grade appearing stromal component, we have seen focal S100 protein positivity in myxoid areas. This expression is very difficult to interpret. It can reflect myoepithelial, schwannian and cartilaginous differentiation, all of which can show myxoma-like morphology. We would favor myoepithelial differentiation, because some cells of the stroma expressed cytokeratin and microscopic picture resembled that of myxoid and chondroid areas in pleomorphic

adenoma of the salivary gland. Moreover, the schwannian phenotype includes SOX10 positivity which was absent in the present tumor<sup>(24)</sup>.

Additional interesting finding in our case is squamous and shadow cell differentiation<sup>(5-8)</sup>. This „adenoacanthomatous“ feature was seen in a great majority of ESCFH<sup>(1,2)</sup>. We concur with Murray et al that there exists a histogenetic relationship between the squamous cells and the cells of the stroma. It seems to us that catenin+/p63+ cells in the basal layer of squamous nests give rise to stromal cells which retain catenin expression and which also often retain the epithelial immunophenotype.

The cell differentiation positive for beta-catenin and cyclin D1, as it was observed in our case, is frequently associated with CTNNB1 mutation<sup>(13,15-16)</sup>. According to recent studies, such non-high-grade EC with catenin and cyclin expression behave more aggressively and represent less favorable group in the spectrum of non-high-grade EC<sup>(15,16)</sup>. Interestingly, one new study of adenoacanthomatous EC by Andrade et al. found that these tumors had a 5.6-fold increased risk for recurrence in comparison with EC without squamous cell differentiation<sup>(25)</sup>. However, additional studies of adenoacanthomatous EC are still needed in our opinion,

because the results in previously published series were variable<sup>(26,27)</sup>.

In conclusion, we have described rare case of ESCFH. The tumor strongly simulated high-grade MMMT especially in frozen section, representing a diagnostic pitfall. In permanent sections, the non-high-grade morphology of both components, conspicuous squamous and shadow cell differentiation and immunohistochemical features different from those of MMMT were most important for the correct diagnosis.

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