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Case report

Mixed stromal and smooth muscle tumours of the uterus: a report of two cases

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Key words

Mixed • Stromal • Smooth muscle • Tumour • Uterus

Summary

Mixed stromal and smooth muscle uterine tumours, defined as those containing at least 30% of each component as seen by routine light microscopy, are rare. This report describes the morphological features of two such tumours diagnosed in 44-year-old and 50-year-old females complaining from recurrent uterine bleeding that was unresponsive to medical treatment. Morphological and immunohistochemical evaluations were performed, and a final diagnosis of mixed endometrial stromal nodule and smooth muscle tumour of the uterus was rendered in both cases.

Introduction

Small areas of smooth muscle differentiation are commonly seen in otherwise typical endometrial stromal neoplasms, and vice versa, while tumours exhibiting both prominent endometrial stromal and smooth muscle differentiation are relatively rare [1 2]. In the most recent WHO publication, such tumours are called "mixed or combined stromal and smooth muscle tumours" and defined as tumours containing more than 30% of each component [3]. Two cases of mixed stromal and smooth muscle tumours of the uterus with a review of the available literature are presented herein (Tab. I).

Case 1

A 44-year-old woman was evaluated for dysmenorrhoea. Examination revealed a uniformly enlarged uterus of 16 weeks' size. Transvaginal ultrasound revealed a well-defined hyperechoic heterogeneous nodule located in the left lateral aspect of the uterus and measuring 9×8×7 cm with increased vascularity on colour Doppler. A myomectomy was performed. Grossly, the tumour was well circumscribed, but non-encapsulated; the cut surface was myxoid and showed an admixture of soft tan nodules and firm white whorled nodules (Fig. 1). Histologically, it consisted of aggregates of typical smooth muscle cells with bland nuclei and scant to moderate eosinophilic cytoplasm with indistinct cytoplasmic borders, intermixed with 'small darkly staining cells' whorled around small arterioles. Both components were cytologically bland, they were present in the tumour in similar proportions and surrounded by a hyalinised abundant stroma. The smooth muscle areas strongly immunostained with smooth muscle actin (SMA), desmin, calponin and h-caldesmon and lacked CD10. The stromal component was positive for CD10 and negative for all ì smooth muscle markers (Fi2). A diagnosis of mixed stromal and smooth muscle tumour was made even though characterisation of the stromal tumour by histology (endometrial stromal nodule or endometrial stromal sarcoma) was not possible because the interface tumour/surrounding myometrium was not available. A subsequent hysterectomy with bilateral salpingo-oophorectomy was performed, and extensive sampling revealed no microscopic residual tumour. The postoperative course was uneventful with no recurrence or symptoms after 1-year follow-up.

Case 2

A 50-year-old woman presented with a 5-month history of left flank pain and metrorrhagia that was unresponsive to medical treatment. Physical examination revealed a non-tender palpable suprapubic mass. Pelvic ultrasonography showed an enlarged uterus with 14×10 cm isoechoic mass increased vascularity on colour Dop-

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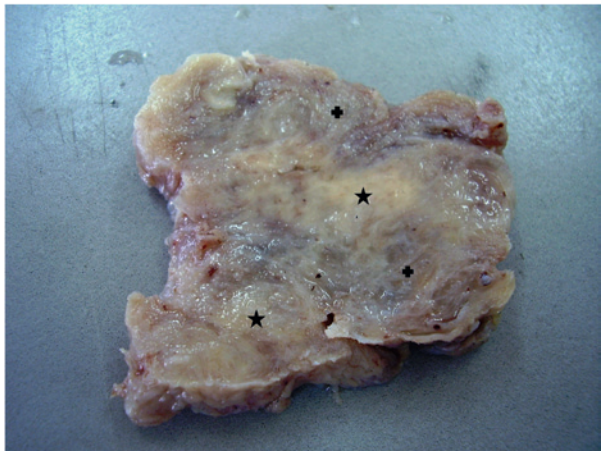
Tab. I. Summary of clinical and pathological features of previously reported cases of mixed stromal and smooth muscle tumors of the uterus.

Author (year) [reference cited in the text]	Number of cases	Clinical data	Particular pathological findins	Follow-up
Olivia et al. (1998) [1]	15	Patients age: 29-68 (mean 46 years)	- SC: ESS in 6 cases and ESN in 9 cases; the SC predominated in 5 cases and was desmin (-) in all cases - SMC: predominated in 7 cases; showed moderate cytological atypia, mitotic figures (4/10 HPF) and focal tumor cell necrosis in only one case; - Areas of sex-cord differentiation in one case	- One tumour with infiltrative margins recurred 4 years later as pure ESS - 6 patients were alive and free of disease - Data not available for 8 patients
Reena et al. (2005) [6]	2 tumors in the same patient	40-year-old, Uterine bleeding	- SC: ESN - SMC: benign appearance	NA
Zamecnik et al. (2006) [9]	1	52-year-old Uterine bleeding	- SC: high grade stromal endometrial sarcoma CD10(+) and MIB1=35%, with minor foci of low grade ESS that are CD10(+) and MIB1=1% - SMC: benign appearance	No recurrence 8 month after the surgery
Zamecnik el al. (2006) [10]	1	44-year-old	- SC: low grade ESS, HMB45 (+), S100 protein and melan A (-) - SMC: benign appearance	NA
McCluggage et al. (2001) [13]	1	45-year-old Uterine bleeding	- SC: Myxoid ESS with benign endometrial glandular differentiation - SMC (70% of the tumor volume): benign appearance - zoning phenomenon, with glands surrounded by endometrial stroma, which is in turn surrounded by smooth muscle - Intravascular component (intramural and paratubal blood vessels)	NA
Pandey et al. (2010) [17]	2	42-year-old, Abdominal mass and uterine bleeding 45-year-old Abdominal pain and uterine bleeding	- SC: ESN - SMC: benign appearance	NA
Shintaku et al. (2013) [16]	1	74-year-old Uterine bleeding	- SC: low grade ESS with foci of anaplasia CD10(+) - SMC: benign appearance	Metastasis in the lung 9 months later; histological examination showed an anaplastic spindle cell sarcoma CD10+ and Desmin-)
Dunder P et al. (2012) [18]	1	73-year-old, Uterine bleeding	- SC: low grade ESS with myxoïd changes - SMC: benign appearance, epithelioïd cells	NA
Geetha et al. (2008) [19]	1	49-year-old Uterine bleeding	- SC: ESN - No smooth muscle component identified on light microscopy - Desmin immunoreactivity in 50% of the tumor cells	NA

SC: stromal component/ SMC: smooth muscle component/ ESN: endometrial stromal nodule/ EES: endometrial stromal sarcoma/ NA: not available/ +: positive/ -:negative

Fig. 1. Gross appearance of the tumour showing an admixture of soft tan nodules (✚) and firm white whorled nodules (★).



pler suggesting fibroid. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Grossly, the uterus was bulky measuring 18x16x11 cm. Cut sections of the uterus showed a well-circumscribed, non-encapsulated, whitish homogenous mass measuring 15x11x10 cm present within the myometrium, distorting the endometrial cavity, but distinct from it. Histologically, the tumour consisted of two cell types. In some areas, the tumour showed smooth muscle features and consisted of spindle cells with moderate amounts of eosinophilic cytoplasm and cigar-shaped regular nuclei. In other areas (40% of the tumour), however, tumour cells showed typical features of endometrial stromal tumours and resembled stromal cells of proliferative endometrium. Mitoses were rare (< 1/10HPF). The tumour had well circumscribed margins with no infiltration of the surrounding myometrium. The smooth muscle component was strongly positive for smooth muscle actin

(SMA) and h-caldesmon, and focally and weakly CD10-positive, contrasting with the endometrial component which was stained only with CD10 (fig. 3). The final diagnosis was mixed stromal and smooth muscle tumour. The postoperative course was uneventful with no recurrence or symptoms after 3-years follow-up.

Fig. 2. A) A biphasic tumour composed of areas of spindle cells (★) intermixed with more cellular areas of rounded cells (⟵) within a myxoid stroma (HE×100). B) High power view of the stromal component showing small uniform round cells with scant basophilic cytoplasm concentrating around small arterioles (HE×400). C) Reactivity of the smooth muscle component with SMA. D) Reactivity of the stromal component with CD10.

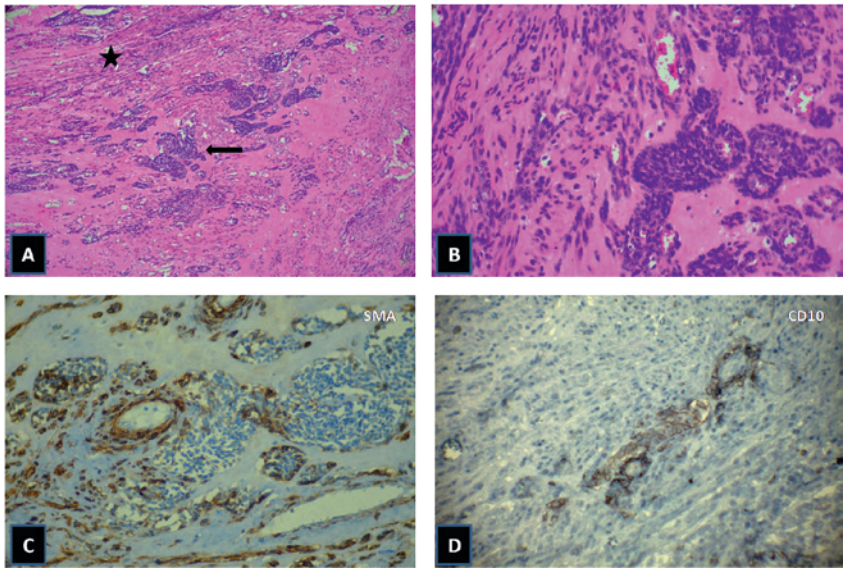
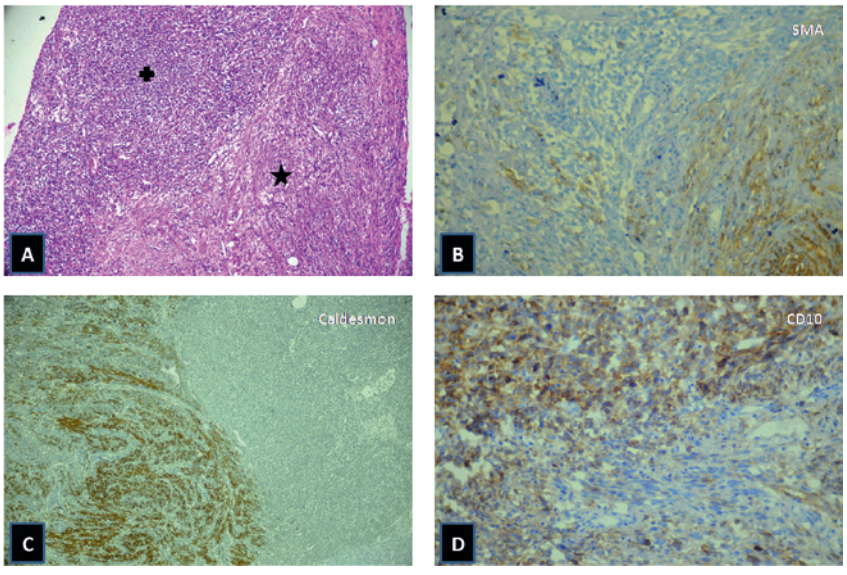


Fig. 3. A) Photomicrograph showing mixed endometrial stromal smooth muscle tumour with both components. Note the transition between the stromal component (✚) and the smooth muscle component (★) (HE×100). B and C) The smooth muscle component was immunostained with SMA and caldesmon. (D) Strong immunostaining of stromal tumour cells and weak immunostaining of smooth muscle cells with CD10.



Discussion

Mixed endometrial stromal and smooth muscle tumours of the uterus have been the focus of limited number of studies, partly because of under-recognition of these tumours and their uncommon occurrence [1 2]. The histogenesis of these tumours is uncertain. It has been suggested that multipotential cells are present in the uterus that can differentiate into both endometrial stroma and smooth muscle [4]. In their original report, Oliva et al. [5] found a high frequency of t(7;17)(p15;q21) translocation, resulting in the fusion of the JAZF1 and JJAZ1 genes, in endometrial stromal tumours with smooth muscle differentiation. As this translocation represents the most common cytogenetic alteration observed in low-grade endometrial stromal tumours, the authors suggested that the endometrial stromal and smooth muscle components of these tumours have the same origin, either from a common precursor cell with pluripotential differentiation or from endometrial stromal cells that have undergone smooth muscle metaplasia. They also proposed use of the detection of this chromosomal abnormality in the diagnostic of stromal tumours with smooth muscle differentiation when the smooth muscle component is predominant [5].

The clinical presentation does not differ from that of uterine tumours of pure endometrial stromal or smooth muscle origin, with uterine bleeding representing the most common symptom as seen in Table 1. On radioimaging, the softer areas of endometrial stroma may be misinterpreted as either cystic degeneration or uterine leiomyosarcoma. Specific diagnosis therefore requires evaluation of the entire tumour [6].

In almost all reviewed cases, mixed stromal and smooth muscle tumours of the uterus present as a solitary intramural nodule, but polypoid appearance and multiple tumours have been reported as well (Tab. I). On gross examination, these tumours often show an admixture of soft tan to yellow nodules and firm white whorled nod-

ules, or alternatively the areas of firm tissue may be seen at the periphery of softer nodules, which is not characteristic of smooth muscle tumours in general [7].

To establish a diagnosis of mixed stromal and smooth muscle tumour, both components should occupy at least 30% of the neoplasm by haematoxylin and eosin staining [3 8]. The components tend to be sharply demarcated, although they occasionally merge onto each other. The stromal elements are typical of endometrial stromal neoplasms, either a stromal nodule or a low-grade stromal sarcoma, and consist of uniform small cells with round nuclei and scanty cytoplasm with small thin walled blood vessels scattered uniformly throughout the stromal component. Zámecník et al. [9] reported areas of dedifferentiation of the stromal component that appeared mainly as a high grade sarcoma with few reminiscent areas of low grade endometrial stromal sarcoma. In fact, the stromal component of the tumour described in that case represents 90% of the tumour's surface; thus, from a quantitative point of view, the tumour would not meet the requirements for 30% smooth muscle component as defined by the WHO, and should not be considered as a mixed stromal and muscle tumour.

The immunophenotype of stromal cells is identical to that observed in other endometrial stromal tumours. In most tumours, these cells do not stain for desmin or only scattered cells stain. Zamecnik el al. described a case of mixed stromal and smooth muscle tumour of the uterus where the stromal component showed surprising immunoreactivity with HMB45 and negativity of other melanocytic markers such as melan A, tyrosinase and microphthalmia transcription factor; they thus suggested that mixed stromal and smooth muscle tumours of the uterus could represent partial differentiation towards perivascular epithelioid cell tumours (PEComa) [10].

Histological features of smooth muscle differentiation includes typical smooth muscle morphology reminiscent of that seen in leiomyomata or nodules with prominent central hyalinisation (the so-called starburst pattern) that merge with characteristic areas of stromal differentiation [11]. Smooth muscle cells vary in appearance from typical spindle-shaped cells with abundant eosinophilic cytoplasm in the fascicles and aggregates to rounded epithelioid cells with clear or amphophilic cytoplasm in nodules. Despite their variable appearance, smooth muscle cells have a typical immunophenotype and show uniform strong positive staining for smooth muscle actin and desmin. Large thick-walled blood vessels are typically present in these areas. The smooth muscle component is usually benign; Olivia et al., however, reported a case with moderate cytologic atypia, focal tumour cell necrosis and 4 mitotic figures/10 high-power fields [1]. Areas of sex cord-like differentiation and glandular elements have been described in mixed endometrial stromal-smooth muscle neoplasms; endometrial stromal nodule with both smooth and skeletal muscle components has also been described [1 12 13]. Intravascular extension is a rare event in mixed stromal and smooth muscle tumours of the uterus; McCluggage et al. [13] described an intravascular component located within the dilated vessels of the myometrium and the fallopian tube, consisting of a mixture of endometrial glands, endometrial stroma and smooth muscle, and exhibiting a zoning phenomenon. Mikami et al. [14] reported a case of endometrial stromal sarcoma with extensive smooth muscle differentiation resembling intravenous leiomyomatosis with extension to the inferior vena cava and cardiac chambers; for that reason, the authors considered the neoplasm as a mixed stromal and smooth muscle tumour, although the smooth muscle component represented only 5% of the entire primary uterine tumour [14].

Immunohistochemical staining should be interpreted with caution in these tumours; in fact, the smooth-muscle component is often positive for CD10 and smooth-muscle markers, as observed in our first case, and this profile may lead to diagnosis of pure smooth muscle neoplasia [15]. Hence, immunohistochemical staining should be correlated with the different morphological components of the tumour. Conventional areas of endometrial stromal neoplasia should be positive for CD10, but not positive for more than one smooth muscle marker, being more positive for actin and desmin [7].

The main differential diagnosis of combined stromal and smooth muscle tumours is with highly cellular leiomyomas, in which the densely cellular areas may resemble the endometrial stromal component. Cellular leiomyomas, however, show the presence of large blood vessels with thick muscular walls throughout the tumour and lack a starburst pattern [6].

These tumours should also be distinguished from infiltration of the surrounding myometrium by a typical low-grade stromal sarcoma, and delineation requires close correlation between the gross and microscopic features with knowledge as to where the tissue blocks have been taken from.

Notably, it is the endometrial stromal pattern that dictates the biological behaviour of the tumour. Those dominated by endometrial stroma with an infiltrating margin may recur or metastasise [1 16]; therefore, similar to a conventional endometrial stromal nodule, thorough assessment of tumour borders is essential.

In summary, we report two cases of mixed stromal and smooth muscle tumour of the uterus. Through this report, we emphasise that the immunohistochemical results in these tumours should be interpreted in correlation with the appearance of the different areas identified on histological examination, and that distinction from cellular leiomyoma is of primary importance because of different clinical behaviour and management.

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