

# Small biopsy pathology of mass lesions of the endometrial cavity: differential diagnostic considerations

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**Keywords:** endometrium, tumour, differential diagnosis, carcinoma, carcinosarcoma, adenosarcoma, PEComa

## Abstract

Sampling for histological examination is usually part of the work-up for further planning with regard to the management of patients presenting with uterine bleeding. This review, utilising the classification of the World Health Organization, aims to discuss some commonly recurring differential diagnostic problems on small biopsy specimens. Diagnostic difficulties generally relate to representativeness of the sample, determining the site of the lesion, and fragmentation and trauma artefact. Reference is made to clinical relevance, and attention drawn to some lesser known diagnostic entities. Morphological features and immunohistochemical markers that are useful in certain differential diagnostic scenarios are highlighted. The level of diagnostic certainty should be indicated in the report, and when the limitations do not permit a definite diagnosis in a small sample, the pathologist should provide the clinician with a differential diagnosis on which further management decisions can be based.

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South Afr J Gynaecol Oncol 2014;6(1):7-14

## Introduction

Mass lesions arising in the uterine cavity are a common problem. The presenting symptom is usually bleeding. Sampling for histological examination by endometrial biopsy, curettage or polypectomy is usually part of the work-up for further planning with regard to management for those aged 35 years and older, and/or at high risk of uterine malignancy (hyperoestrogenism, clinically), unless the endometrium is less than 4 mm thick at the first bleeding episode. Persistent bleeding, regardless of endometrial thickness, necessitates hysteroscopy and endometrial sampling.

Pathologically, the lesion may turn out to be anything from banal (a simple endometrial polyp) to highly malignant (carcinosarcoma), with radically different therapeutic and prognostic implications. A study of 1 011 women with endometrial polyps identified postmenopausal status as the only clinical or demographic factor significantly associated with atypical hyperplasia and cancer.<sup>1</sup>

This review, written by consultant general histopathologists, is intended for the gynaecologist and oncologist, as well as the pathologist. The article aims to discuss some commonly recurring differential diagnostic problems, and to highlight some lesser known diagnostic entities. While most of the entities discussed in this paper are relatively easily diagnosed on resection specimens, recognition of many of them is significantly more challenging with small biopsies. The problems relate to representativeness of the sample with regard to histological type, e.g. biphasic lesions, and tumour grading; determining the site of lesion, e.g. endometrial versus cervical, and primary versus metastatic tumours; and fragmentation and trauma artefact.

The various differential diagnostic problems discussed in this paper have a varying degree of bearing on immediate subsequent management. Most high-grade malignancies are treated with a combination of surgery and chemotherapy (and radiation therapy). Hysterectomy is usually part of the staging process that would determine oncological management in the postmenopausal patient.

This provides an opportunity to further specify or modify the initial pathological diagnosis. However, in some cases, the surgical procedure differs, e.g. whether or not pelvic lymphadenectomy is performed, or in rare cases, the primary treatment is with chemotherapy, as with choriocarcinoma.

A practical classification of mass lesions of the uterine corpus, adapted from the World Health Organization (WHO) definitions, is given in Table 1.<sup>2</sup> Carcinosarcoma, although generally regarded and treated today as a variant of high-grade endometrial carcinoma, will be considered under biphasic tumours.

**Table 1:** Morphological classification of mass lesions of the endometrial cavity

#### Tumours with an epithelioid morphology

- Carcinoma
- *Trophoblastic lesions:* Placental site trophoblastic tumour, epithelial trophoblastic tumour and choriocarcinoma
- *Certain mesenchymal tumours:* Epithelioid smooth muscle tumours
- Sex cord-like tumours of the uterus
- Perivascular epithelioid cell tumour

#### Biphasic lesions composed of epithelium and mesenchyma

- Endometrial polyp
- *So-called Müllerian tumours:* Adenosarcoma and carcinosarcoma\*

#### Purely mesenchymal lesions

- *Smooth muscle tumours:* Leiomyoma and leiomyosarcoma
- Rhabdomyosarcoma
- *Endometrial stromal tumours:* Endometrial stromal nodule, low-grade endometrial stromal sarcoma and high-grade undifferentiated uterine sarcoma

\*: Carcinosarcoma, previously known as malignant mixed Müllerian tumour, is regarded as a type of high-grade endometrial carcinoma, according to the 2009 International Federation of Gynecology and Obstetrics classification

## Epithelioid tumours

### Carcinoma

Endometrial carcinoma is the most common type of female genital tract malignancy in the developed world. There are over nine different histological types according to the WHO.<sup>2</sup> A detailed discussion of different subtypes and their respective differential diagnoses is beyond the scope of this article. Endometrioid carcinoma is by far the most common form, followed by serous carcinoma and clear cell carcinoma.

Common types of endometrial carcinoma have been divided into type I, oestrogen-dependent endometrioid adenocarcinoma (corresponding with grade 1 and 2 endometrioid adenocarcinoma) with good prognosis, and type II, traditionally believed to be a non-oestrogen-dependent carcinoma, with serous or clear cell histology and poor prognosis. Grade 3 endometrioid adenocarcinomas do not fall neatly into either category as

they share features of type I and type II cancer, and have not been classified as either, although recent data indicate that they share similar clinical features, immunoprofile and poor survival with the type II group.<sup>3</sup>

Although grading of endometrioid endometrial carcinomas has lost much of its previous significance, pelvic lymphadenectomy is not performed for low grades (grades 1 and 2) endometrioid carcinomas in some centres. The under-grading of tumours is a common problem with small samples, when a high grade constituent of mixed tumours is not represented, or when solid areas and cytologically low-grade areas only are present in endometrioid adenocarcinomas. Gynaecologists are aware of this, and South African practice is to perform lymphadenectomy in all cases, with the possible exception of small (less than 20 mm on sonar) grade 1 endometrioid tumours that are limited to the uterus, with no evidence of myometrial invasion or lower isthmus or cervical involvement on imaging. Apart from potential undergrading on biopsy, the reasons for this include improved staging and pressure on radiation services in South Africa, as radiotherapy may be omitted in many node-negative patients, as well as the high prevalence of advanced tumour at presentation in South Africa. A recent large review advocates lymphadenectomy in all cases as no evidence was found that lymphadenectomy was associated with a significant increase in morbidity.<sup>4</sup> Immunostaining for oestrogen and progesterone receptors (highly expressed in low-grade tumours), and the proliferation marker Ki-67 and p53 (highly expressed in high-grade tumours), may aid the pathologist in differentiating between low-grade (1 or 2) and high-grade (3) tumours.<sup>5</sup>

A small sample size, coupled with trauma artefact, may make it difficult to distinguish between papillary variants of endometrioid carcinoma, including the usual and the villoglandular types, and serous carcinoma (the latter may also have glandular areas). Careful evaluation of cytological and architectural features may assist in making the differential diagnosis as there is a significant overlap between the immunohistochemical phenotypes. (Typically, endometrioid carcinoma is oestrogen receptor-positive, p53-negative and p16-negative or focally positive, and serous carcinoma is oestrogen receptor-negative, p53-positive and p16-positive).<sup>6,7</sup> The importance of this distinction was highlighted by a recent study that demonstrated that uterine serous carcinoma with only endometrial involvement, even when confined to a polyp, was generally associated with a poorer prognosis.<sup>8</sup>

The need to differentiate between endometrial and cervical adenocarcinomas commonly arises when a polypoid mass protruding through the cervical os has been biopsied. The diagnosis carries important consequences

as primary surgery and neoadjuvant therapy may differ. Although a typical mucinous adenocarcinoma, usually of endocervical origin, is easily distinguished from an endometrioid carcinoma, more commonly arising in the corpus uteri, a degree of caution is advised. Rarely, endometrioid tumours may arise as primary lesions in the cervix, and the endometrium can give rise to mucinous tumours. Some tumours also show an overlap in morphological appearance. Immunohistochemistry can be helpful (oestrogen receptor and vimentin positivity in endometrial tumours versus monoclonal carcinoembryonic antigen and p16 staining in cervical carcinomas),<sup>6,9,10</sup> but correlation with appropriate imaging and the clinical impression should be recommended in the pathology report. Final diagnosis in these cases should be made in conjunction with radiological imaging, taking into consideration where the bulk of the tumour lies and the pattern of spread is shown. Operable patients should be managed with radical hysterectomy, adnexectomy and node dissection in uncertain cases.

Biopsies should be carefully examined for the presence of a malignant stromal component which would indicate a carcinosarcoma. The interglandular desmoplastic stroma of a carcinoma may exhibit increased cellularity and enlarged fibroblasts, but significant cytological atypia and mitotic activity are absent. This is further discussed under *Carcinosarcoma*.

Secondary malignancies of the uterine corpus are rare. Only a third will affect the endometrium and can be detected in biopsy specimens.<sup>2</sup> Tumours can invade the uterine corpus directly from neighbouring organs and via haematogenous dissemination. Lobular carcinoma of the breast, diffuse-type adenocarcinoma of the stomach, and colorectal adenocarcinoma and malignant melanoma, are more frequently encountered in the latter group.<sup>2</sup> A metastatic tumour should be suspected if there is an unusual histological pattern, partial replacement of the endometrium with occasional entrapped benign endometrial glands, and lack of premalignant changes in the background endometrium. While a high index of suspicion on the pathologist's part, coupled with the judicious use of immunohistochemistry, contributes to recognising secondary malignancy, the importance of clinical history cannot be overemphasised. Neglecting to mention a known prior malignancy on the request form is a serious omission, which may lead to a delay in making the correct diagnosis, wasteful expenditure in terms of unnecessary immunostains, or at worst, misdiagnosis.

Distinguishing undifferentiated carcinomas from epithelioid mesenchymal tumours [usually leiomyosarcomas or perivascular epithelioid cell tumour (PEComa)] is usually relatively straightforward with immunohistochem-

istry. A panel of markers should be used as epithelial markers, which are not infrequently expressed by sarcomas with an epithelioid morphology.

### Trophoblastic tumours

Mainly diseases of childbearing age, gestational choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelial trophoblastic tumour (ETT) can present as polypoid masses.

Choriocarcinoma comprises a mixture of malignant cytotrophoblastic and syncytiotrophoblastic cells, and widely expresses beta human chorionic gonadotropin (BHCG) on immunohistochemistry, as well as producing high serum levels of BHCG. PSTT is a tumour of intermediate trophoblast and produces human placental lactogen, but no significant expression of BHCG. Distinguishing between the two is important as choriocarcinoma is treated with systemic chemotherapy, while PSTT requires surgical treatment, although neoadjuvant and adjuvant chemotherapy now also have a role in treatment.<sup>11,12</sup>

Differentiating PSTT from benign exaggerated implantation site reaction (EISR) may be very difficult on biopsy specimens, both being characterised by intermediate trophoblasts that infiltrate smooth muscle and vessel walls.

A proliferation index of intermediate trophoblast cells exceeding five per cent, as determined by Ki-67 immunohistochemistry, is a helpful feature to aid recognition of PSTT in small biopsies.<sup>13</sup> PSTT usually presents several months after pregnancy, in contrast to EISR, where the pregnancy is usually more recent.

ETT can be a challenging histological diagnosis, as it should be differentiated from PSTT (histological pattern and p63-positivity), squamous cell carcinoma (clinical history and histology), epithelioid smooth muscle tumours (immunohistochemistry) and PEComa (immunohistochemistry).<sup>13-15</sup>

BHCG production helps to distinguish choriocarcinoma from undifferentiated endometrial carcinomas, both histologically and clinically. The clinical setting is usually different.

### Sex cord-like tumours of the uterus

Placed under the miscellaneous category in the WHO classification,<sup>2</sup> uterine tumours that resemble ovarian sex cord tumours, are rare benign neoplasms of putative endometrial stromal origin, and composed solely of sex cord elements. Rare in the uterine corpus, typically they present as an endometrium-based polyp. They show a diverse morphology and immunoprofile, and can be mistaken for endometrial carcinoma or other

mesenchymal tumours. They differ from endometrial stromal tumours with extensive sex cord-like differentiation in that they lack neoplastic endometrial stroma, and differ from endometrial carcinoma with a sex cord arrangement in that they lack frank carcinomatous areas, if adequately sampled, and demonstrate smooth muscle (smooth muscle actin and desmin) and sex cord markers (inhibin and calretinin) on immunohistochemistry. Distinguishing them from epithelioid smooth muscle tumours (ESMTs), an important differential, is more challenging as malignant ESMTs may recur or metastasise. Although there is a significant overlap in morphology and immunoprofile, smooth muscle tumours are typically negative for inhibin and calretinin.<sup>13,16</sup>

### Perivascular epithelioid cell tumour

These are rare tumours of uncertain malignant potential, showing an epithelioid or spindle cell morphology. They can arise in the uterus, as well as in the retroperitoneum, and are related to epithelioid angiolipoma and sugar tumour. Approximately 9% arise in the context of tuberous sclerosis. The main differential diagnosis is with epithelioid smooth muscle tumours, endometrial stromal sarcoma and metastatic melanoma in view of the morphology and the fact that they express HMB-45 (and often Melan-A), apart from frequent positivity with smooth muscle actin, desmin, oestrogen receptor and CD10. A wide immunohistochemical panel is recommended to establish the diagnosis, as well as clinicopathological correlation.<sup>17,18</sup>

## Lesions with epithelioid and spindle cell components

### Endometrial polyp

Endometrial polyps are common in postmenopausal women, although they will not always cause symptoms.

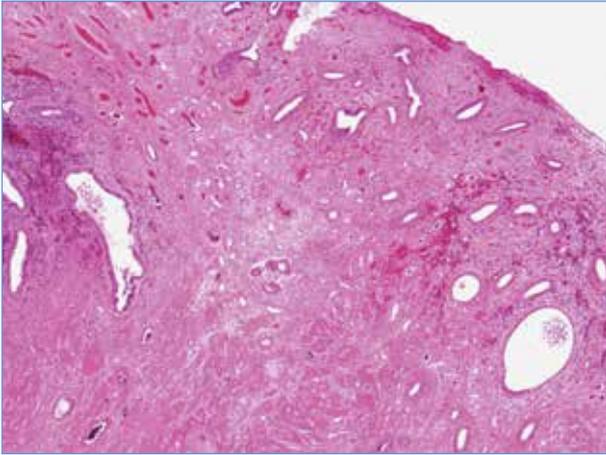
Recognising the presence of a polyp in a scanty, dissociated endometrial sample may be challenging. A polyp may be suspected if there are fragments that differ from the background endometrium by virtue of exhibiting glandular dilatation and proliferative activity, stromal fibrosis and thick-walled blood vessels. Polypoid endometrial hyperplasia without atypia may be distinguished from polyps as they lack these features. The presence of some background normal endometrium may also indicate a polyp, although hyperplasia will also start as a focal lesion. This distinction may have therapeutic implications. Endometrial hyperplasia should be treated with progestins, whereas a polyp requires no additional treatment after fractional dilatation and curettage. Atypical hyperplasia and carcinoma can arise in polyps, and their presence will determine further management. A recent study found that a polyp size larger than 15 mm is predictive of the presence of hyperplasia.<sup>19</sup> Differentiating simple polyps from biphasic Müllerian tumours will now be covered.

### Biphasic Müllerian tumours

Biphasic Müllerian tumours are a diverse group characterised by the simultaneous presence of Müllerian epithelial and mesenchymal components, the latter homologous (uterine type, e.g. endometrioid stroma or smooth muscle) or heterologous (non-uterine, e.g. skeletal muscle, adipocytic or cartilaginous). The WHO classification includes two vanishingly rare entities.<sup>2</sup> Adenofibroma is a benign lesion in which the epithelial component is usually endometrioid, and the stroma has a fibroblastic quality. The features may overlap with a simple endometrial polyp. Fortunately, there are no therapeutic implications. Carcinofibroma is a malignant neoplasm composed of carcinomatous epithelial and benign mesenchymal components, the stroma usually being fibrous, but it can be heterologous. Benign Müllerian polyps with a smooth muscle component, Müllerian adenomyoma and atypical polypoid adenomyoma (APA) have three constituents: endocervical or endometrial glands, endometrial stroma, and benign smooth muscle, usually occurring in a lobulated arrangement with bands of muscle separating lobules of glands and stroma. There is a wide overlap in clinical presentation and size, although APA tends to present at a younger age and smaller size. Both Müllerian adenomyoma and APA are considered to be benign. However, APA tends to recur if incompletely resected, and there have been case reports of APA progressing to endometrial carcinoma.<sup>20</sup>

A study of 26 cases of Müllerian adenomyoma describes proliferative endometrial glands. The glands were surrounded by compact and spindly endometrial stroma, which, in turn, were bordered by leiomyomatous smooth muscle. One to two normal mitotic figures per 10 high-power fields have been observed in the endometrial stroma in a few cases, but no mitotic activity has been noted in the myometrial component (Figure 1). Müllerian adenomyoma was associated with adenomyosis in some cases.<sup>21</sup> Endometrial polyp lacks a significant smooth muscle component and lobularity in the differential diagnosis of Müllerian adenomyoma. The glands are usually seen at the periphery in a leiomyoma with entrapped endometrium, and are not surrounded by endometrial stroma.<sup>13</sup> Recently, a variant of Müllerian adenomyoma was described with prominent epithelioid smooth muscle differentiation.<sup>22</sup>

The glandular component in APA exhibits varying degrees of architectural complexity, cytological and mitotic activity, separating it from Müllerian adenomyoma.<sup>13</sup> Muscle-invasive endometrial adeno-carcinoma should show frankly malignant glands, the absence of periglandular endometrial stroma, and should exhibit some desmoplastic stromal response. Low-grade Müllerian adenosarcoma with smooth muscle differentiation can be difficult to separate in small or fragmented specimens where no



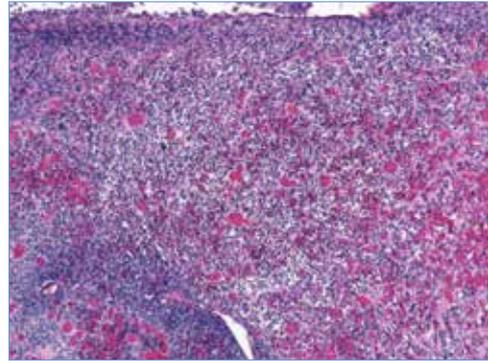
**Figure 1:** Polypoid adenomyoma. Benign endometrial glands are present in a lobular arrangement, surrounded by endometrial-type stroma and smooth muscle bundles (haematoxylin and eosin x 20)

atypical endo-metrioid stroma is present, and where the “phyllodes tumour-type” intraglandular or leaf-like growth pattern cannot be appreciated.<sup>23</sup>

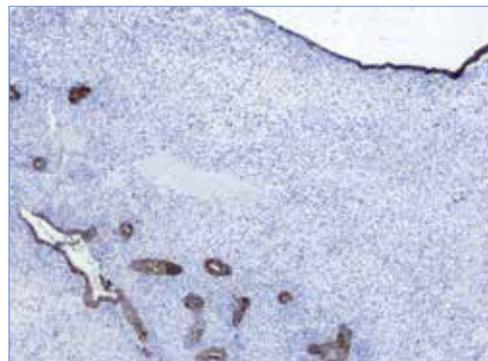
### **Low-grade Müllerian adenosarcoma**

Low-grade Müllerian adenosarcoma is defined as a biphasic growth of benign or atypical epithelium and low-grade malignant stroma, the latter resembling endometrial stromal sarcoma or fibrosarcoma.<sup>2</sup> It presents as a polypoid mass in postmenopausal women. It is differentiated from a cellular endometrial polyp, and adenomyoma and adenofibroma, by the presence of at least two mitoses per 10 high-power fields, marked stromal hypercellularity with periglandular cuffing, and more-than-mild stromal atypia.<sup>13</sup> Recently, Ki-67 immunostain has been shown to be a useful adjunct tool to diagnosis. A distinct increase in Ki-67-positive nuclei has been identified in adenosarcomas in the periglandular zone, compared with the adjacent stroma, regardless of the mitotic count (20% in periglandular zones versus less than 5% in the adjacent stroma). This zonation is not observed in any case of atypical polypoid adenomyomas or endometrial polyps.<sup>24</sup> Myometrial or vascular invasion is not a prerequisite for diagnosis.

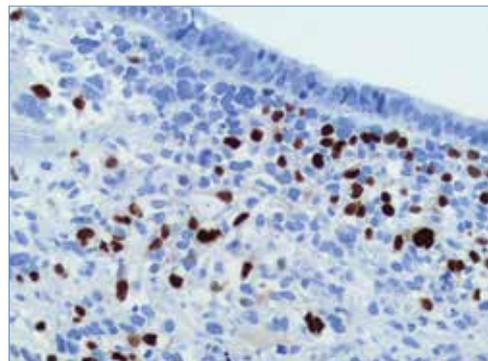
Adenosarcoma is furthermore characterised by a “fibroadenomatoid-type” intraglandular growth pattern, which is reputed to separate it from other lesions with a sarcomatous stromal component, such as low-grade endometrial stromal sarcomas. It is also retained at least in areas when the stroma undergoes high-grade transformation, thus differentiating such lesions from high-grade stromal sarcomas. High-grade transformation [so-called “Müllerian adenosarcoma with sarcomatous overgrowth” (MASO)] occurs in 10% of tumours. The diagnosis requires that pure high-grade sarcoma should amount to at least 25% of the tumour volume, according



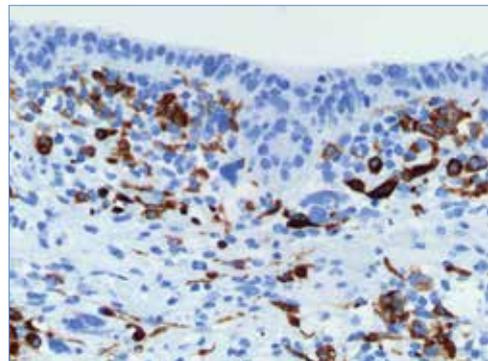
**Figure 2a:** The tumour is composed of benign endometrial glands and malignant stroma, comprising rhabdomyoblasts which show condensation under the surface and around the glands. Haematoxylin and eosin x 40



**Figure 2b:** The epithelial component is highlighted by cytokeratin immunostain. Cytokeratin AE1/3 x 20



**Figure 2c:** The rhabdomyoblasts show nuclear staining with myogenin. Myogenin x 400



**Figure 2d:** Cytoplasmic reaction with desmin antibody. Desmin x 400

**Figures 2 a, b, c and d:** Müllerian adenosarcoma with rhabdomyosarcomatous overgrowth.

to the WHO criteria.<sup>2</sup> Heterologous elements, including cartilage, fat and rhabdomyoblasts, are quite common, and sex cord-like areas can occur (Figure 2 a, b, c and d). Differential diagnostic difficulties are highlighted elsewhere in the manuscript.

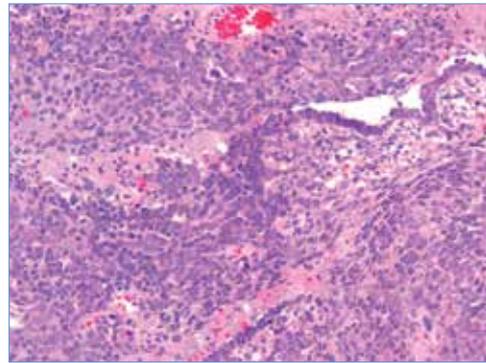
### **Carcinosarcoma**

The coexistence of distinct malignant epithelial and sarcomatous mesenchymal components defines carcinosarcoma. This entity, previously known as malignant mixed Müllerian tumours, is considered to be a type of high-grade endometrial carcinoma ("metaplastic carcinoma") according to the 2009 International Federation of Gynecology and Obstetrics classification,<sup>25</sup> in line with the classification that is applied to other organs.

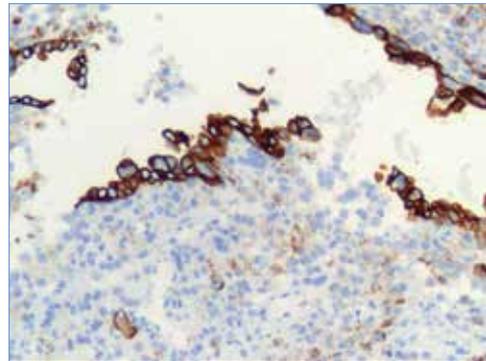
In some cases where the carcinomatous elements dominate, a poorly represented sarcomatoid component may be difficult to recognise on small biopsy specimens. Malignant spindle cell and carcinomatous areas often merge imperceptibly with an indistinct interface, a useful feature for recognising carcinosarcoma.

Immunohistochemistry for cytokeratin and epithelial membrane antigen (to highlight epithelial differentiation), CD10 (to identify endometrioid-type stroma), and smooth muscle actin and desmin (to determine leiomyosarcomatous differentiation), as well as myogenin, myoglobin, MyoD1 and desmin (for rhabdomyosarcomatous areas), can assist with the diagnosis (Figure 3 a, b, c and d). However, making the distinction with regard to small biopsies has become less significant since uterine carcinosarcomas are now staged and treated similarly to high-grade epithelial endometrial carcinomas, and are no longer considered to be uterine sarcomas.<sup>26</sup> Nevertheless, the five-year, disease-free survival of carcinosarcoma, stage by stage, was found to be worse than that for serous carcinoma, clear cell carcinoma and grade 3 endometrioid adenocarcinoma (53.4% vs. 59%, 68.8% and 76.2%, respectively).<sup>25</sup>

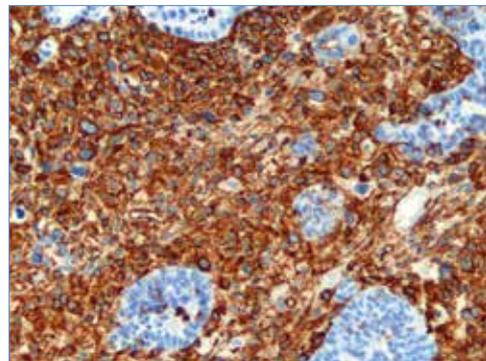
Although typically, both components are high grade, rarely one or the other may be low grade, widening the differential diagnoses to include MASO. Frank malignant features are absent from the epithelial component in the latter. Endometrioid carcinoma with heterologous elements is an otherwise typical endometrial carcinoma that contains minor foci of benign bone, cartilage or fat. Sarcomatoid endometrioid carcinoma, another uncommon type of endometrial carcinoma, is distinguished from carcinosarcoma because it shows the transition from typical carcinomatous areas to spindled areas, but lacks heterologous components. Differentiating between the two is not always possible in a small sample.<sup>13</sup>



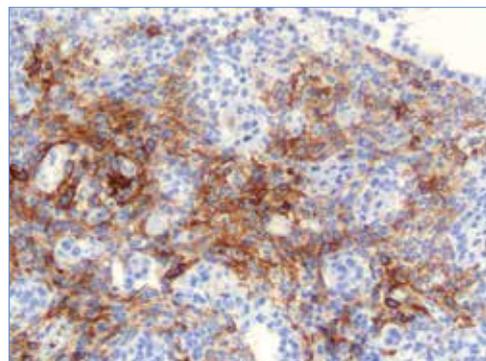
**Figure 3a:** Both the glands and stroma show frankly malignant cytological features. Haematoxylin and eosin x 100



**Figure 3b:** Both the glands and stroma show frankly malignant cytological features. Haematoxylin and eosin x 100



**Figure 3c:** The stroma is diffusely positive with vimentin. The glands were negative in this case. Vimentin x 100



**Figure 3d:** CD10, a marker of endometrial-type stroma, is focally positive. CD10 x 100

**Figure 3 a, b c and d:** Carcinosarcoma.

## Spindle cell mesenchymal tumours

### Smooth muscle tumours

Submucosal leiomyomas or leiomyosarcomas are sometimes sampled in endometrial curettings or during hysteroscopic polypectomies. The differential diagnosis with other spindle cell tumours is wide. Smooth muscle differentiation is fortunately easily proven by immunohistochemistry. This may be necessary in atypical morphological variants, such as epithelioid or myxoid smooth muscle tumours. Separating malignant lesions can be challenging in small samples. The presence of coagulative (as opposed to “infarction-type”) necrosis, a mitotic count of more than 10 per 10 high-power fields, and diffuse cytological atypia, are the criteria used for conventional spindle cell lesions, but these are modified for epithelioid and myxoid variants. Borderline cases continue to pose a challenge. More recently, the term “smooth muscle tumour of unknown malignant potential” has been devised as a diagnostic bracket for such lesions. A detailed discussion of this is beyond the scope of this review, and the reader is referred to standard texts and current literature.<sup>27</sup>

### Rhabdomyosarcoma

Botryoid embryonal rhabdomyosarcoma (BER) is the only type of rhabdomyosarcoma that occurs in the uterus with some frequency. Generally perceived as a disease of prepubertal girls, BER is rare, but well recognised in postmenopausal women, where it can arise in the uterine cervix or corpus, typically presenting as a polypoid mass protruding through the cervical os. Microscopically, the tumour is composed of primitive spindle cells with variable numbers of admixed rhabdomyoblasts that condense to form a cambium layer under the surface mucosa. It can be difficult to separate it from an adenocarcinoma with extensive rhabdomyosarcomatous overgrowth. A benign glandular component and subepithelial stromal condensation are present in both. Adenocarcinoma retains a phyllodes-like intraglandular growth pattern, and tends to show widespread hormone receptor expression, features which are lacking in BER.<sup>28,29</sup> Fortunately, the definitive treatment is the same for both, absolving the pathologist from the need to commit to a definite diagnosis on the preoperative sample.

### Endometrial stromal tumours

Pure endometrial stromal tumours of the uterus are classified into three groups by the WHO:

- Endometrial stromal nodule (ESN).
- Low-grade endometrial stromal sarcoma (LGESS).
- Undifferentiated endometrial sarcoma (UES).<sup>2</sup>

They may present as polypoid masses of varying sizes. Even ESN can grow large. LGESS is often intramural.

ESN and LGESS are both made up of cells that are reminiscent of proliferative-phase endometrial stroma.<sup>30</sup> While ESN is well circumscribed and non-invasive, LGESS exhibits myometrial and vascular invasion. To diagnose ESN histologically, the lesion should have a smooth interface with the adjacent myometrium, and any focal irregularities, such as lobulated or finger-like projections into adjacent myometrium, should not exceed 3 mm in size and three in number.<sup>2</sup> As a consequence, reports on biopsy specimens that contain only part of the lesion, and which show no overt malignant features, should propose a differential diagnosis of ESN versus LGESS, and defer the final diagnosis to the hysterectomy specimen. Differentiating LGESS with glandular differentiation from low-grade adenocarcinomas can be difficult, as discussed previously.

High-grade undifferentiated uterine sarcoma is a diagnosis of exclusion in cases where extensive sampling has failed to demonstrate the presence of smooth or skeletal muscle differentiation, or tiny foci of carcinoma, which would render a diagnosis of carcinosarcoma.<sup>13,30</sup> As a result, the diagnosis cannot be made on small preoperative biopsy specimens. Instead, a descriptive diagnosis of high-grade undifferentiated malignant tumour should be given. The differential diagnosis should include biphasic tumours with a high-grade stromal component and high-grade sarcoma. It has been suggested that a subset of undifferentiated endometrial sarcomas, made up of cells with uniform nuclei, may be a separate entity from those with nuclear anaplasia, and may relate to low-grade endometrial stromal sarcomas.<sup>31</sup>

Recently, cytogenetic abnormalities have been identified that allow differentiation between endometrial stromal sarcomas and high-grade undifferentiated uterine sarcomas, which may be useful in pathologically difficult cases. Endometrial stromal sarcomas usually express hormone receptors, allowing endocrine therapy in most cases. Therefore, hormone receptor stains should always be performed.<sup>32-34</sup>

In conclusion, the WHO classification of uterine tumours provides the reference framework within which communication between the pathologist, surgeon and oncologist takes place. It is important to be aware of the limitations imposed by small diagnostic biopsies. Trauma artefact and fragmentation may further complicate interpretation. The pathologist, rather than trying to offer a single (but not fully substantiated) diagnosis on the basis of a sample, that, however generous, may not be fully representative of the lesion, should provide the clinician with a differential diagnosis on which to base further management decisions. The

clinician can facilitate this process by providing the relevant information on the request form, and by making him- or herself available to discuss a case, should the need arise.

## Declaration

No financial support was received by the authors.

## Conflict of interest

The authors declare no conflict of interest.

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