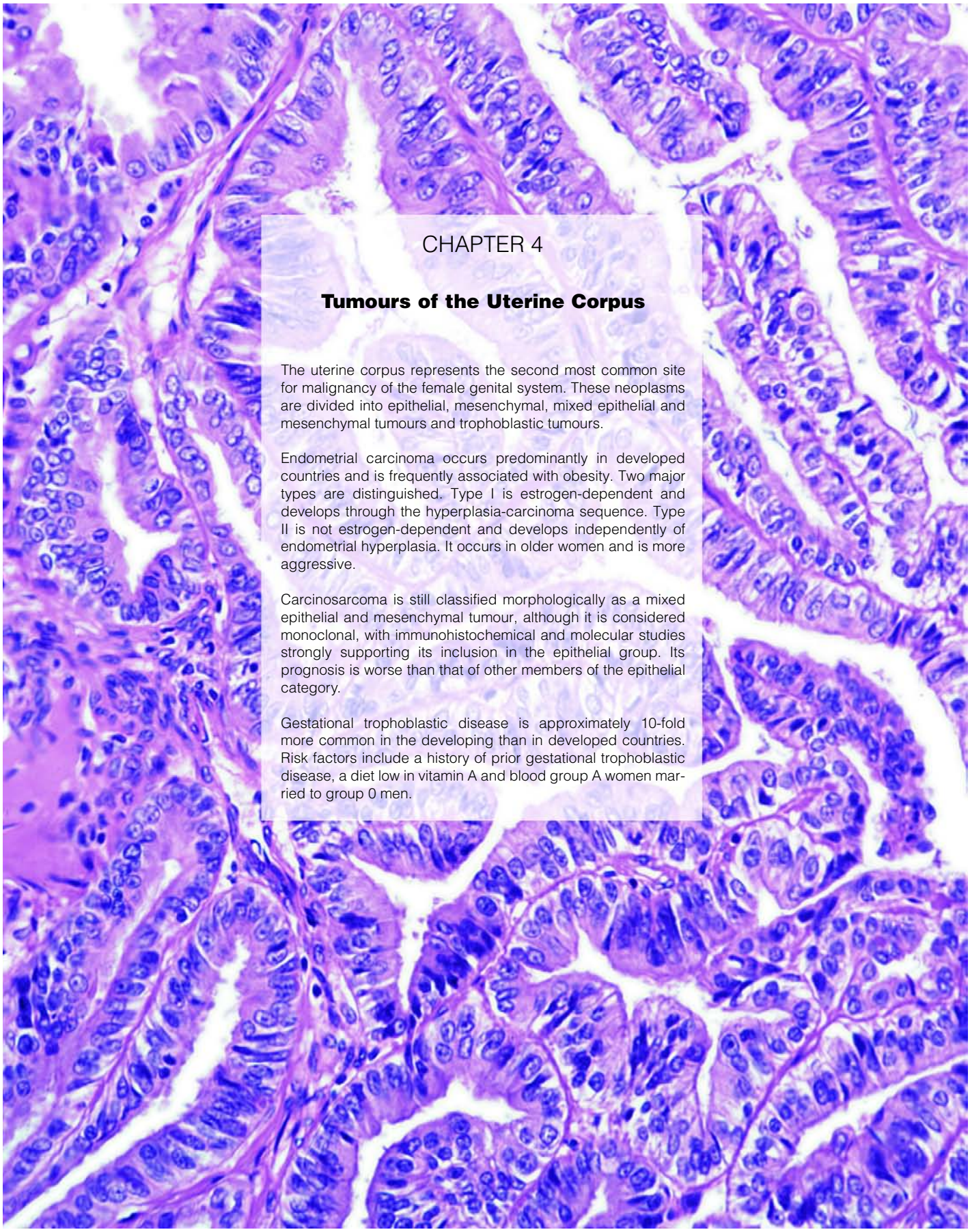

CHAPTER 4

Tumours of the Uterine Corpus

The uterine corpus represents the second most common site for malignancy of the female genital system. These neoplasms are divided into epithelial, mesenchymal, mixed epithelial and mesenchymal tumours and trophoblastic tumours.

Endometrial carcinoma occurs predominantly in developed countries and is frequently associated with obesity. Two major types are distinguished. Type I is estrogen-dependent and develops through the hyperplasia-carcinoma sequence. Type II is not estrogen-dependent and develops independently of endometrial hyperplasia. It occurs in older women and is more aggressive.

Carcinosarcoma is still classified morphologically as a mixed epithelial and mesenchymal tumour, although it is considered monoclonal, with immunohistochemical and molecular studies strongly supporting its inclusion in the epithelial group. Its prognosis is worse than that of other members of the epithelial category.

Gestational trophoblastic disease is approximately 10-fold more common in the developing than in developed countries. Risk factors include a history of prior gestational trophoblastic disease, a diet low in vitamin A and blood group A women married to group 0 men.

WHO histological classification of tumours of the uterine corpus

Epithelial tumours and related lesions
Endometrial carcinoma
- Endometrioid adenocarcinoma 8380/3
  - Variant with squamous differentiation 8570/3
  - Villoglandular variant 8262/3
  - Secretory variant 8382/3
  - Ciliated cell variant 8383/3
- Mucinous adenocarcinoma 8480/3
- Serous adenocarcinoma 8441/3
- Clear cell adenocarcinoma 8310/3
- Mixed cell adenocarcinoma 8323/3
- Squamous cell carcinoma 8070/3
- Transitional cell carcinoma 8120/3
- Small cell carcinoma 8041/3
- Undifferentiated carcinoma 8020/3
- Others

Endometrial hyperplasia
- Nonatypical hyperplasia
  - Simple
  - Complex (adenomatous)
- Atypical hyperplasia
  - Simple
  - Complex

Endometrial polyp
Tamoxifen-related lesions

Mesenchymal tumours
Endometrial stromal and related tumours
- Endometrial stromal sarcoma, low grade 8931/3
- Endometrial stromal nodule 8930/0
- Undifferentiated endometrial sarcoma 8930/3

Smooth muscle tumours
- Leiomyosarcoma 8890/3
  - Epithelioid variant 8891/3
  - Myxoid variant 8896/3
- Smooth muscle tumour of uncertain malignant potential 8897/1
- Leiomyoma, not otherwise specified 8890/0
  - Histological variants
    - Mitotically active variant
    - Cellular variant 8892/0
    - Haemorrhagic cellular variant
    - Epithelioid variant 8891/0
    - Myxoid 8896/0
    - Atypical variant 8893/0
    - Lipoleiomyoma variant 8890/0
  - Growth pattern variants
    - Diffuse leiomyomatosis 8890/1
    - Dissectiing leiomyoma
    - Intravenous leiomyomatosis 8890/1
    - Metastasizing leiomyoma 8898/1

Miscellaneous mesenchymal tumours
- Mixed endometrial stromal and smooth muscle tumour
- Perivascular epithelioid cell tumour
- Adenomatoid tumour 9054/0
- Other malignant mesenchymal tumours
- Other benign mesenchymal tumours

Mixed epithelial and mesenchymal tumours
- Carcinosarcoma (malignant müllerian mixed tumour; metaplastic carcinoma) 8980/3
- Adenosarcoma 8933/3
- Carcinofibroma 8934/3
- Adenofibroma 9013/0
- Adenomyoma 8932/0
  - Atypical polypoid variant 8932/0

Gestational trophoblastic disease
Trophoblastic neoplasms
- Choriocarcinoma 9100/3
- Placental site trophoblastic tumour 9104/1
- Epithelioid trophoblastic tumour 9105/3

Molar pregnancies
- Hydatidiform mole 9100/0
  - Complete 9100/0
  - Partial 9103/0
  - Invasive 9100/1
  - Metastatic 9100/1

Non-neoplastic, non-molar trophoblastic lesions
- Placental site nodule and plaque
- Exaggerated placental site

Miscellaneous tumours
- Sex cord-like tumours
- Neuroectodermal tumours
- Melanotic paraganglioma
- Tumours of germ cell type
- Others

Lymphoid and haematopoetic tumours
- Malignant lymphoma (specify type)
- Leukaemia (specify type)

Secondary tumours

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {921} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM and FIGO classification of non-trophoblastic tumours of the uterine corpus

TNM and FIGO classification [1,2,3]

T – Primary Tumour

TNM Categories	FIGO Stages	
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis	0	Carcinoma in situ (preinvasive carcinoma)
T1	I*	Tumour confined to corpus uteri
T1a	IA	Tumour limited to endometrium
T1b	IB	Tumour invades less than one half of myometrium
T1c	IC	Tumour invades one half or more of myometrium
T2	II	Tumour invades cervix but does not extend beyond uterus
T2a	IIA	Endocervical glandular involvement only
T2b	IIB	Cervical stromal invasion
T3 and/or N1	III	Local and/or regional spread as specified in T3a, b, N1, and FIGO IIIA, B, C below
T3a	IIIA	Tumour involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
T3b	IIIB	Vaginal involvement (direct extension or metastasis)
N1	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
T4	IVA	Tumour invades bladder mucosa and/or bowel mucosa

Note: The presence of bullous edema is not sufficient evidence to classify a tumour as T4.

M1	IVB	Distant metastasis (*excluding* metastasis to vagina, pelvic serosa, or adnexa)

Note: * FIGO recommends that Stage I patients given primary radiation therapy can be clinically classified as follows:
Stage I: Tumour confined to corpus uteri
Stage IA: Length of uterine cavity 8cm or less
Stage IB: Length of uterine cavity more than 8cm

N – Regional Lymph Nodes [4]

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M – Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1, T2, T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

[1] {51,2976}.
[2] A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
[3] The classification applies to carcinomas and malignant mixed mesodermal tumours.
[4] The regional lymph nodes are the pelvic (hypogastric [obturator, internal iliac], common and external iliac, parametrial, and sacral) and the para-aortic nodes.

TNM and FIGO classification of gestational trophoblastic tumours

TNM and FIGO classification[1,2,3]

T–Primary Tumour

TM Categories	FIGO Stages*	
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1	I	Tumour confined to uterus
T2	II	Tumour extends to other genital structures: vagina, ovary, broad ligament, fallopian tube by metastasis or direct extension
M1a	III	Metastasis to lung(s)
M1b	IV	Other distant metastasis

Note: *Stages I to IV are subdivided into A and B according to the prognostic score

M – Distant Metastasis

MX	Metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis to lung(s)
M1b	Other distant metastasis

Note: Genital metastasis (vagina, ovary, broad ligament, fallopian tube) is classified T2. Any involvement of non-genital structures, whether by direct invasion or metastasis is described using the M classification.

Stage grouping

Stage	T	M	Risk Category
I	T1	M0	Unknown
IA	T1	M0	Low
IB	T1	M0	High
II	T2	M0	Unknown
IIA	T2	M0	Low
IIB	T2	M0	High
III	Any T	M1a	Unknown
IIIA	Any T	M1a	Low
IIIB	Any T	M1a	High
IV	Any T	M1b	Unknown
IVA	Any T	M1b	Low
IVB	Any T	M1b	High

	Prognostic score			
Prognostic Factor	**0**	**1**	**2**	**4**
Age	<40	≥ 40		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	
Months from index pregnancy	<4	4-<7	7-12	>12
Pretreatment serum β-hCG (IU/ml)	$< 10^3$	10^3-$<10^4$	10^4-$<10^5$	$\geq 10^5$
Largest tumour size, including uterus	<3 cm	3-<5 cm	≥5 cm	
Site of metastasis	Lung	Spleen, kidney	Gastrointestinal tract	Liver, brain
Number of metastases		1-4	5-8	>8
Previous failed chemotherapy			Single drug	2 or more drugs

Risk Categories: Total prognostic score 7 or less = low risk; Total score 8 or more = high risk

[1] {51,2976}
[2] A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org
[3] The classification applies to choriocarcinoma (9100/3), invasive hydatidiform mole (9100/1), and placental site trophoblastic tumour (9104/1).

Epithelial tumours and related lesions

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Endometrial carcinoma

Definition

A primary malignant epithelial tumour, usually with glandular differentiation, arising in the endometrium that has the potential to invade into the myometrium and to spread to distant sites.

ICD-O codes

Endometrioid adenocarcinoma	8380/3
Variant with squamous differentiation	8570/3
Villoglandular variant	8262/3
Secretory variant	8382/3
Ciliated cell variant	8383/3
Mucinous adenocarcinoma	8480/3
Serous adenocarcinoma	8441/3
Clear cell adenocarcinoma	8310/3
Mixed adenocarcinoma	8323/3
Squamous cell carcinoma	8070/3
Transitional cell carcinoma	8120/3
Small cell carcinoma	8041/3
Undifferentiated carcinoma	8020/3

Epidemology

Endometrial carcinoma is the most common malignant tumour of the female genital system in developed countries, where estrogen-dependent neoplasms account for 80-85% of cases and the non-estrogen dependent tumours make up the remaining 10-15% of cases. The estrogen-dependent tumours are low grade, i.e. well or moderately differentiated and predominantly of endometrioid type. Patients with this form of endometrial cancer frequently are obese, diabetic, nulliparous, hypertensive or have a late menopause. Obesity is an independent risk factor {388}, and in Western Europe, is associated with up to 40% of endometrial cancer {241a}. On the other hand, patients with a large number of births, old age at first birth, a long birth period and a short premenopausal delivery-free period have a reduced risk of postmenopausal endometrial cancer, emphasizing the protective role of progesterone in the hormonal background of this disease {1212}.
In contrast, the non-estrogen dependent type occurs in older postmenopausal women; the tumours are high grade and consist predominantly of histological subtypes such as serous or clear cell as well as other carcinomas that have high grade nuclear features. They lack an association with exogenous or endogenous hyperoestrinism or with endometrial hyperplasia and have an aggressive behaviour {497,2005,2646}.

Pathogenesis

Endometrial cancer is made up of a biologically and histologically diverse group of neoplasms that are characterized by a different pathogenesis. Estrogen-dependent tumours (type I) are low grade and frequently associated with endometrial hyperplasias, in particular atypical hyperplasia. Unopposed estrogenic stimulation is the driving force behind this group of tumours. It may be the result of anovulatory cycles that occur in young women with the polycystic ovary syndrome or due to normally occurring anovulatory cycles at the time of menopause. The iatrogenic use of unopposed estrogens as hormone replacement therapy in older women also is a predisposing factor for the development of endometrial cancer. The second type (type II) of endometrial cancer appears less related to sustained estrogen stimulation.

Clinical features

Signs and symptoms

Although endometrial carcinoma and related lesions can be incidental findings in specimens submitted to the pathologist for other reasons (for example, endometrial biopsy for infertility or hysterectomy for uterine prolapse), in the great majority of cases they present clinically with abnormal uterine bleeding. Since most of these lesions are seen in postmenopausal women, the most common presentation is postmenopausal bleeding, but earlier in life the usual clinical finding is menometrorrhagia {1104}. The most common type of endometrial carcinoma, endometrioid adenocarcinoma, may be manifested by such clinical findings as obesity, infertility and late menopause, since it is often related either to exogenous estrogen

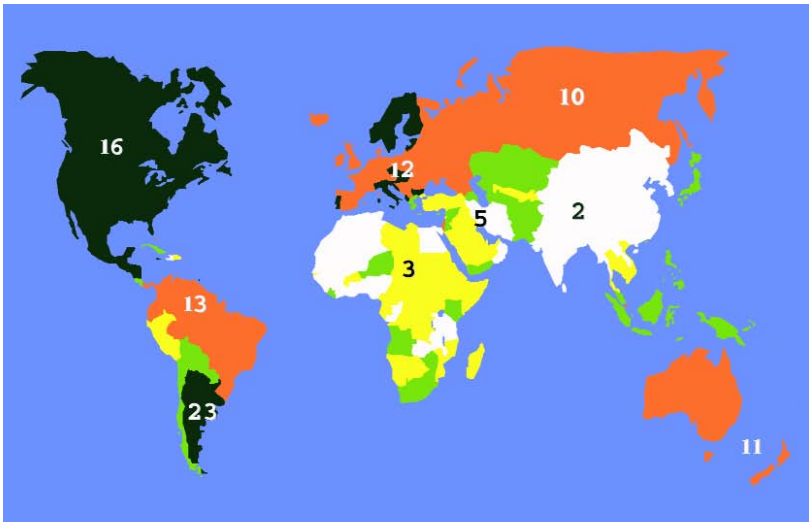

Fig. 4.01 Global incidence rates of cancer of the uterine corpus which occurs predominantly in countries with advanced economies and a Western lifestyle. Age-standardized rates (ASR) per 100,000 population and year. From Globocan 2000 {846}.

administration or to endogenous hyperoestrinism {2276,2648,2805}. Endometrial hyperplasia and atypical hyperplasia have similar clinical associations.

Imaging

Transvaginal ultrasound (US) is the imaging technique of choice for the assessment of the endometrium in symptomatic patients, e.g. in cases of postmenopausal bleeding {133}. In postmenopausal women without hormonal replacement an endometrial thickness of 5 mm is regarded as the upper normal limit {133,2650}. The presence of endometrial thickening on ultrasound or cross sectional imaging is, however, a nonspecific finding. It may be due to endometrial hyperplasia, polyps or carcinoma. The final diagnosis usually needs to be determined by endometrial sampling {133}.

Whereas currently magnetic resonance imaging (MRI) has no established role in screening for endometrial pathology, it is regarded as the best imaging technique for preoperative staging of endometrial carcinoma proven by endometrial sampling. MRI was shown to be superior to computed tomography (CT) in this regard {1135}. It is especially useful for patients with suspected advanced disease, for those with associated uterine pathology, such as leiomyomas, and for those with histological subtypes that signify a worse prognosis {916,1136}.

Macroscopy

Endometrial carcinoma usually arises in the uterine corpus, but some cases originate in the lower uterine segment, and recent studies suggest that the latter may have different clinical and histological features {1323,3067}. Regardless of the histological type, the macroscopic appearance of endometrial carcinoma is generally that of a single dominant mass, usually occurring in an enlarged uterus, although occasionally the uterus is small or the tumour presents as a diffuse thickening of most of the endometrial surface, particularly in the serous type. Endometrial carcinoma is seen more frequently on the posterior than on the anterior wall {2691}.

The typical carcinoma is exophytic and has a shaggy, frequently ulcerated surface beneath which a soft or firm white tumour may extend shallowly or deeply into the underlying myometrium. In advanced cases the tumour may penetrate the serosa or extend into the cervix. An estimate of the extent of tumour may be requested preoperatively or operatively in order to determine the extent of the surgical procedure to be performed {594}. In occasional cases no tumour may be visible macroscopically, with carcinoma identified only at histological examination.

Tumour spread and staging

The staging of uterine tumours is by the TNM/FIGO classification {51,2976}.

Endometrioid adenocarcinoma

Definition

A primary endometrial adenocarcinoma containing glands resembling those of the normal endometrium.

Histopathology

All but a few rare endometrial carcinomas are adenocarcinomas, and the most common of these is the endometrioid type {2691}. Endometrioid adenocarcinoma represents a spectrum of histological differentiation from a very well differentiated carcinoma difficult to distinguish from atypical complex hyperplasia to minimally differentiated tumours that can be confused not only with undifferentiated carcinoma but with various sarcomas as well. A highly characteristic feature of endometrioid adenocarcinoma is the presence of at least some glandular or villoglandular structures lined by simple to pseudostratified columnar cells that have their long axes arranged perpendicular to the basement membrane with at least somewhat elongated nuclei that are also polarized in the same direction. As the glandular differentiation decreases and is replaced by solid nests and sheets of cells, the tumour is classified as less well differentiated (higher grade). Deep myometrial invasion and lymph node metastases are both more frequent in higher grade carcinomas, and survival rates are correspondingly lower {574, 1359}. It should be noted that:

(1). Only those cells which are considered to be of glandular type are considered in the grading schema, so that solid nests of cells showing squamous or morular differentiation do not increase the tumour grade.

(2). Bizarre nuclear atypia should raise the grade by one, e.g. from 1 to 2 or 2 to 3.

(3). It should be emphasized that the presence of bizarre nuclei occurring in even a predominantly glandular tumour may indicate serous or clear cell rather than endometrioid differentiation {2691}.

The distinction of very well differentiated

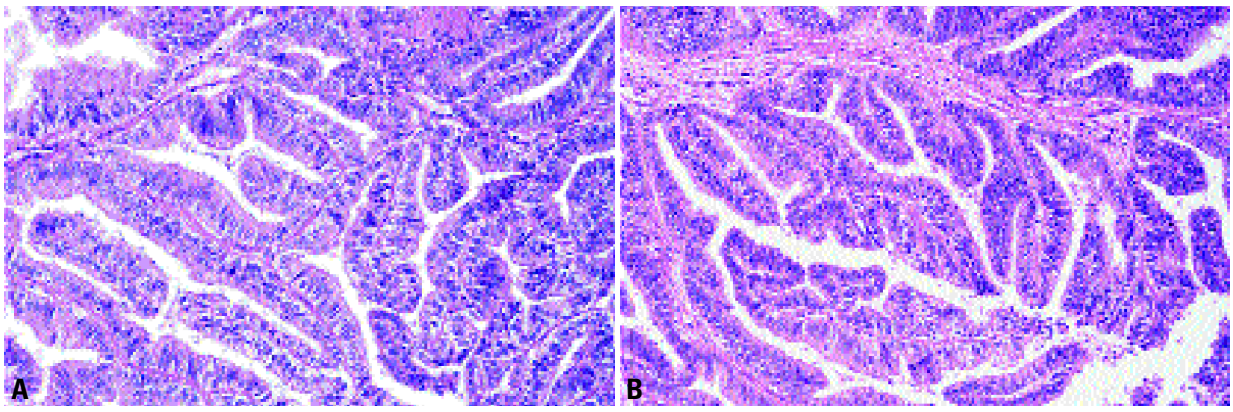

Fig. 4.02 Well differentiated endometrioid adenocarcinoma. **A** Invasion is indicated by back to back glands, complex folds and stromal disappearance. **B** The neoplastic glands are lined by columnar cells with relatively uniform nuclei; note the altered stroma in the top of the field.

endometrioid adenocarcinoma from atypical complex hyperplasia is best provided by stromal disappearance between adjacent glands, i.e. confluent, cribriform or villoglandular patterns {1433,1689,2688,2691}. Other features that may be helpful include a stromal desmoplastic response and/or tumour necrosis. Stromal foam cells may be associated with adenocarcinoma or its precursors.

Variants of endometrioid adenocarcinoma

Endometrial proliferations may exhibit a variety of differentiated epithelial types including squamous/morules, mucinous, ciliated, cleared or eosinophilic cells, and architectural variations including papillary formations. These cell types are often called metaplasias and may be encountered in benign, premalignant and malignant epithelia. When prominent in a carcinoma the neoplasm is termed a "special variant" carcinoma.

Variant with squamous differentiation

From 20-50% or more of endometrioid adenocarcinomas contain varying amounts of neoplastic epithelium showing squamous differentiation. Although the distinction between endometrioid adenocarcinoma with and without squamous differentiation is not clinically important, the recognition of squamous differentiation is nevertheless essential because the squamous or morular elements should not be considered a part of the solid component that increases the grade of an endometrioid carcinoma.

The criteria for squamous differentiation {2691} are as follows:

(1) Keratinization demonstrated with standard staining techniques.

(2) Intercellular bridges and/or

(3) Three or more of the following four criteria:

(a) Sheet-like growth without gland formation or palisading.

(b) Sharp cell margins.

(c) Eosinophilic and thick or glassy cytoplasm.

(d) A decreased nuclear to cytoplasmic ratio as compared with foci elsewhere in the same tumour.

Villoglandular variant

This type is the next most commonly encountered endometrioid adenocarcinoma variant and is usually seen involving part of a low grade endometrioid carcinoma but not the entire tumour. In this pattern numerous villous fronds are seen, but their central cores are delicate, and cells with the usual cytological features (including stratification perpendicular to the basement membrane) line the villi. These features are in contrast to the more complex papillary architecture and high grade nuclear features that are typical of serous and clear cell adenocarcinomas growing in a papillary pattern.

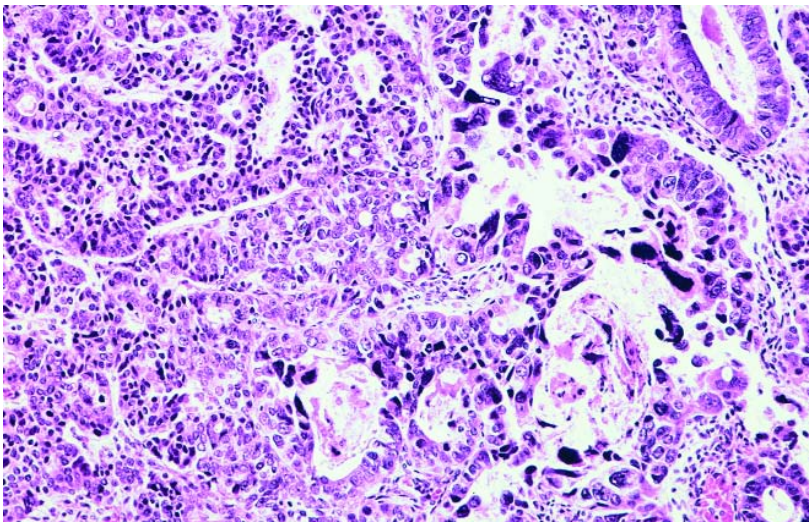

Fig. 4.03 Endometrioid adenocarcinoma. The bizarre nuclear atypia raises the tumour grade but should also prompt consideration of a serous adenocarcinoma.

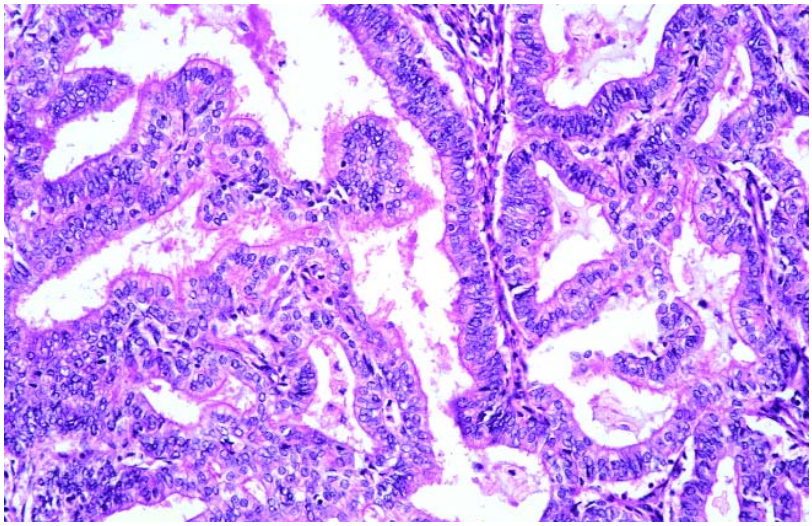

Fig. 4.04 Well differentiated endometrioid adenocarcinoma, ciliated cell variant. Cilia lining the neoplastic glands are prominent.

Secretory variant

Occasional endometrioid adenocarcinomas are composed of glands lined by epithelium with voluminous, usually subnuclear, glycogen vacuoles reminiscent of early secretory endometrium. These tumours have minimal nuclear atypia and are diagnosable as carcinoma only by virtue of a confluent, cribriform or villoglandular pattern. As with the other variants, this pattern may be seen as the only one in an endometrioid adenocarci-

Table 4.01
Grading of type I (endometrioid and mucinous) endometrial adenocarcinoma.

– Grade 1: ≤ 5% non-squamous, non-morular growth pattern – Grade 2: 6-50% non-squamous, non-morular growth pattern – Grade 3: > 50% non-squamous, non-morular growth pattern Note: Squamous/morular components are excluded from grading. Bizarre nuclear atypia should raise the grade by one (i.e. from 1 to 2 or 2 to 3) but may also signify type II differentiation.

noma or may coexist with the usual endometrioid pattern within a single tumour.

Ciliated cell variant
Although occasional ciliated cells may be seen in many endometrioid adenocarcinomas, the diagnosis of the ciliated cell variant is made only when ciliated cells line the majority of the malignant glands. Defined in this manner, this is a rare variant, and the glands often have a strong resemblance to tubal epithelium.

Mucinous adenocarcinoma

Definition
A primary adenocarcinoma of the endometrium in which most of the tumour cells contain prominent intracytoplasmic mucin.

Epidemiology
Mucinous adenocarcinoma comprises up to 9% of all cases of surgical stage I endometrial carcinoma {2454}. However, in most published series it is a relatively rare type of endometrial carcinoma {1842}.

Histopathology
Both endometrioid and clear cell adenocarcinomas may have large amounts of intraluminal mucin, but only mucinous adenocarcinoma contains the mucin within the cytoplasm. The mucin is usually easily visible with hematoxylin and eosin staining but may also be demonstrated with a mucicarmine or other mucin stain.

Variants
Some mucinous adenocarcinomas have a microglandular pattern and may be difficult to distinguish from microglandular hyperplasia of the endocervix in a biopsy specimen {2066}. These neoplasms have been reported as microglandular carcinomas {3224,3241}. Rare mucinous adenocarcinomas of the endometrium may show intestinal differentiation, containing numerous goblet cells.

Differential diagnosis
The main differential diagnosis of the usual endometrial mucinous adenocarcinoma is with a primary mucinous adenocarcinoma of the endocervix. The distinction may be particularly difficult in a biopsy or curettage specimen but is crucial for therapy and may have to be resolved by clinical and imaging studies. Some studies have claimed that immunohistochemistry is useful in determining the site of origin of an adenocarcinoma in such a specimen, with endometrial carcinomas being vimentin and estrogen receptor-positive and carcinoembryonic antigen-negative and the opposite findings for endocervical adenocarcinomas {3180}. Others have found, however, that this distinction is based more on differentiation (endometrioid vs. mucinous) than on site of origin {1393}.

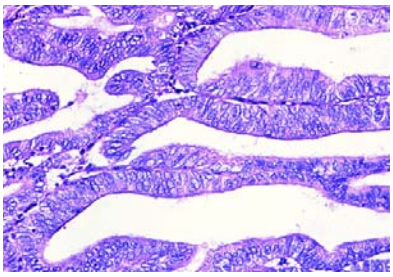

Fig. 4.05 Well differentiated endometrioid adenocarcinoma, villoglandular variant. Villous fronds have delicate central cores and are lined by cells with stratified nuclei.

Grading
Mucinous adenocarcinomas are theoretically graded in the same way as endometrioid adenocarcinomas, but in practice almost all of them are grade 1.

Prognosis and predictive factors
The prognosis appears to be similar to that of other low grade endometrial adenocarcinomas and thus is generally favourable.

Serous adenocarcinoma

Definition and historical annotation
A primary adenocarcinoma of the endometrium characterized by a complex pattern of papillae with cellular budding and not infrequently containing psammoma bodies.
Although long recognized as a common type of adenocarcinoma of the ovary, serous adenocarcinoma was first characterized as a common endometrial tumour in the early 1980s {1186,1590}.

Clinical features
Serous carcinoma typifies the so-called type II endometrial carcinoma, which dif-

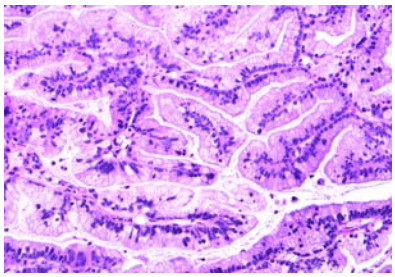

Fig. 4.06 Mucinous adenocarcinoma of the endometrium. All of the tumour cells in this field contain voluminous intracytoplasmic mucin.

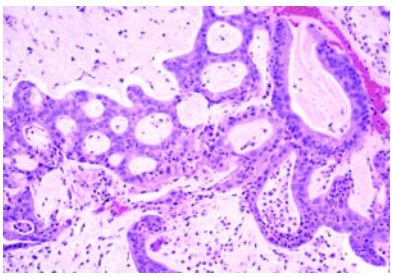

Fig. 4.07 Microglandular carcinoma. Atypia, mitoses and the endometrial location distinguish this tumour from endocervical microglandular hyperplasia.

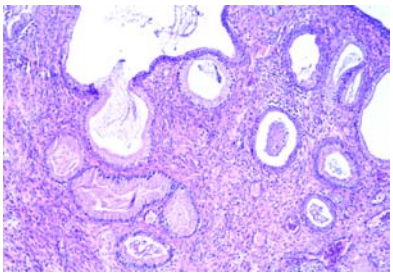

Fig. 4.08 Mucinous metaplasia. Mucinous glands are prominent, however, glandular crowding or atypia is not present.

fers from the prototypical type I endometrioid adenocarcinoma by its lack of association with exogenous or endogenous hyperoestrinism, its lack of association with endometrial hyperplasia and its aggressive behaviour {497, 2005,2646}.

Histopathology

Serous adenocarcinoma is usually, but not always, characterized by a papillary architecture with the papillae having broad fibrovascular cores, secondary and even tertiary papillary processes and prominent sloughing of the cells. The cells and nuclei are generally rounded rather than columnar and lack a perpendicular orientation to the basement membrane. The nuclei are typically poorly differentiated, are often apically rather than basally situated and usually have large, brightly eosinophilic macronucleoli. Mitoses, often atypical and bizarre, and multinucleated cells are commonly present, as are solid cell nests and foci of necrosis. Psammoma bodies are found in about 30% of cases and may be numerous. When the tumour grows in a glandular pattern, the glands are generally complex and "labyrinthine." Serous carcinoma is considered a high grade carcinoma by definition and is not graded.

Precursor lesions

A putative precursor of serous adenocarcinoma is serous endometrial intraepithelial carcinoma, which has also been called endometrial carcinoma in situ and surface serous carcinoma {79,975,2764, 3256}. This lesion is characterized by a noninvasive replacement of benign (most commonly atrophic) endometrial surface and glandular epithelium by highly malignant cells that resemble those of invasive serous carcinoma. Serous endometrial intraepithelial carcinoma has been proposed as the precursor or in situ phase of serous carcinoma, and in most reported studies it has co-existed with invasive serous and, occasionally, clear cell, adenocarcinoma. Clinically, serous endometrial intraepithelial carcinoma has a significance very similar to that of invasive serous adenocarcinoma since it can also be associated with disseminated disease outside the uterus (usually in the peritoneal cavity) even in the absence of invasive carcinoma in the endometrium {79,160,975,2764,3105,3256}.

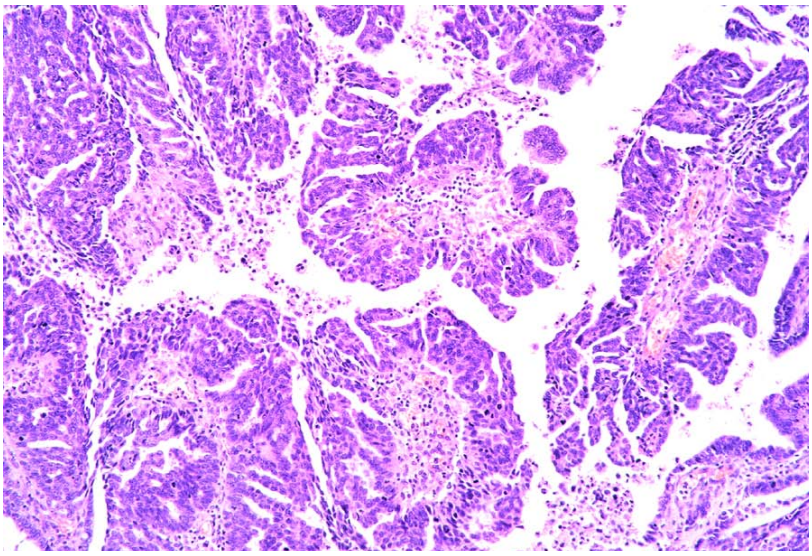

Fig. 4.09 Serous adenocarcinoma of the endometrium. Broad papillary stalks are covered by secondary micropapillae with considerable exfoliation of tumour cells.

Prognosis and predictive factors

This tumour has a tendency to develop deep myometrial invasion and extensive lymphatic invasion, and patients commonly present with extrauterine spread at the time of diagnosis. However, even in the absence of a large or deeply invasive tumour extrauterine spread is common, as are recurrence and a fatal outcome {160,1370,3105}.

Clear cell adenocarcinoma

Definition

An adenocarcinoma composed mainly of clear or hobnail cells arranged in solid, tubulocystic or papillary patterns or a combination of these patterns.

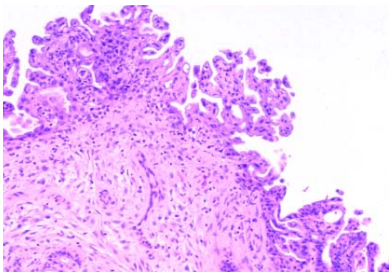

Fig. 4.10 Surface syncytial change. This benign papillary syncytial proliferation is distinguished from serous adenocarcinoma by the lack of atypia.

Epidemiology

The other major type II carcinoma of the endometrium is clear cell adenocarcinoma. It is less common than serous carcinoma (1-5%, as opposed to 5-10% of all endometrial carcinomas) but occurs in the same, predominantly older, patient population.

Tumour spread and staging

Similar to serous adenocarcinoma, patients with clear cell adenocarcinoma are frequently diagnosed in advanced clinical stages.

Histopathology

Histologically, clear, glycogen-filled cells and hobnail cells that project individually into lumens and papillary spaces characterize the typical clear cell adenocarcinoma. Unlike similarly glycogen-rich secretory endometrioid adenocarcinomas, clear cell adenocarcinoma contains large, highly pleomorphic nuclei, often with bizarre and multinucleated forms. The architectural growth pattern may be tubular, papillary, tubulocystic or solid and most frequently consists of a mixture of two or more of these patterns. Although psammoma bodies are present in approximately one-third of serous adenocarcinomas, they are rarely seen in clear cell adenocarcinomas. Occasionally, the tumour cells have granular

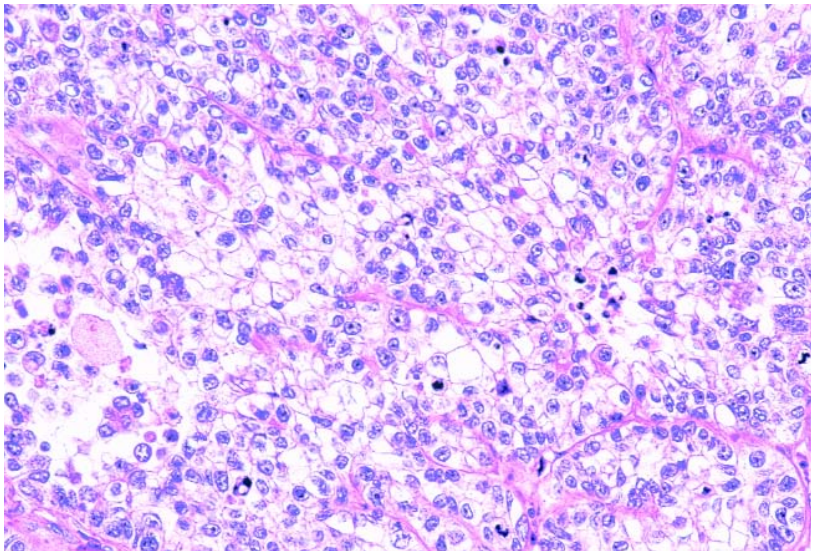

Fig. 4.11 Clear cell adenocarcinoma of the endometrium. The tumour has a predominantly solid pattern with occasional poorly formed tubules. The cytoplasm is clear, and cell walls are distinct.

eosinophilic (oncocytic) cytoplasm rather than the more characteristic clear cytoplasm {2258,2678}. This cell type may comprise the entire tumour and make it difficult to recognize as a clear cell adenocarcinoma. Endometrial clear cell adenocarcinomas are not graded.
Serous endometrial intraepithelial carcinoma may also be seen in association with clear cell adenocarcinoma, and the associated benign endometrium is generally atrophic rather than hyperplastic.

Prognosis and predictive factors
Patients with clear cell adenocarcinoma are frequently diagnosed in advanced clinical stages, and, thus, have a poor prognosis {24,400,1595,3003}. On the other hand, clear cell adenocarcinoma limited to the uterine corpus has a considerably better prognosis than serous adenocarcinoma of the same stage.

Mixed adenocarcinoma

Definition
Mixed adenocarcinoma is a tumour composed of an admixture of a type I (endometrioid carcinoma, including its variants, or mucinous carcinoma) and a type II carcinoma (serous or clear cell) in which the minor type must comprise at least 10% of the total volume of the tumour. The percentage of the minor component should be stated in the pathology report. It is generally accepted that 25% or more of a type II tumour implies a poor prognosis, although the significance of lesser proportions is not well understood {2646,2691}.

Squamous cell carcinoma

Definition
A primary carcinoma of the endometrium composed of squamous cells of varying degrees of differentiation.

Epidemiology
Squamous cell carcinoma of the endometrium is uncommon; only about seventy cases have been reported {2397}.

Clinical features
Squamous cell carcinoma of the endometrium usually occurs in postmenopausal women and is often associated with cervical stenosis and pyometra.

Histopathology
Its histological appearance is essentially identical to that of squamous cell carcinoma of the cervix and similarly includes a rare verrucous variant {2654}.

Differential diagnosis
The much more common situation of a cervical squamous cell carcinoma extending into the endometrium must be excluded. Predominantly squamous differentiation of an endometrioid adenocarcinoma must also be excluded before making the diagnosis of primary pure squamous cell carcinoma of the endometrium.

Prognosis and predictive factors
The prognosis of most squamous cell carcinomas of the endometrium is rather poor, although the verrucous variant may be more favourable.

Transitional cell carcinoma

Definition
A carcinoma in which 90% or more is composed of cells resembling urothelial transitional cells. Lesser quantities of transitional cell differentiation would qualify the tumour as a mixed carcinoma with transitional cell differentiation.

Epidemiology
Transitional cell differentiation in endometrial carcinomas is extremely uncommon with fewer than 15 cases reported {1554,1669}. Among patients with known racial origin, 50% are non-White (African, Hispanic, or Asian). The median age is 61.6 years (range 41-83 years).

Clinical features
The main complaint at presentation is uterine bleeding.

Macroscopy
The tumours are often polypoid or papillary with a mean size of 3.5 cm. Infiltration of the myometrium is apparent in some cases.

Histopathology
The transitional cell component is often grade 2 or 3 and assumes a papillary configuration. It is always admixed with another type of carcinoma, most often endometrioid, but it may be clear cell or serous. HPV-associated koilocytotic changes occur rarely. Only the transitional cell component invades the myometrum deeply {1669}. All endometrial transitional cell carcinomas are negative for cytokeratin 20 (CK20), but half are positive for cytokeratin 7 (CK7) {1554,1669}.

Differential diagnosis
The differential diagnosis includes metastatic transitional cell carcinoma from

the ovary and bladder. Unlike primary endometrial tumours, those metastatic to the endometrium are pure transitional cell tumours. The CK7 positive, CK20 negative immunoprofile also supports müllerian rather than urothelial differentiation.

Somatic genetics
Human papillomavirus (HPV) type 16 has been detected in 22% of cases studied; however, the results were negative for types 6, 11, 18, 31 and 33 in all cases assessed {1554,1672}. These findings suggest that HPV may play an aetiologic role in at least some cases.

Prognostic and predictive factors
Although information on prognostic factors is limited on these rare tumours, several women who have survived have had low stage (stage I) disease. At least two cases with extrauterine extension of the disease to either the adnexa or ovarian hilus have survived over 5 years following radiation therapy suggesting that these tumours may have a more favourable response to radiation therapy than other stage II endometrial carcinomas.

Small cell carcinoma

Definition
An endometrial carcinoma resembling small cell carcinoma of the lung.

Epidemiology
Small cell carcinoma of neuroendocrine type is an uncommon tumour of the endometrium that comprises less than 1% of all carcinomas.

Histopathology
The histological appearance is similar to that of small cell carcinoma in other organs. Small cell carcinomas are positive for cytokeratin and mostly positive for neuroendocrine markers, whereas one-half are positive for vimentin.

Prognosis and predictive factors
In contrast to small cell carcinoma elsewhere in the female genital tract, the prognosis is far better in stage I disease with a 5-year survival of about 60% {23, 1271}.

Undifferentiated carcinoma

Undifferentiated carcinomas are those lacking any evidence of differentiation.

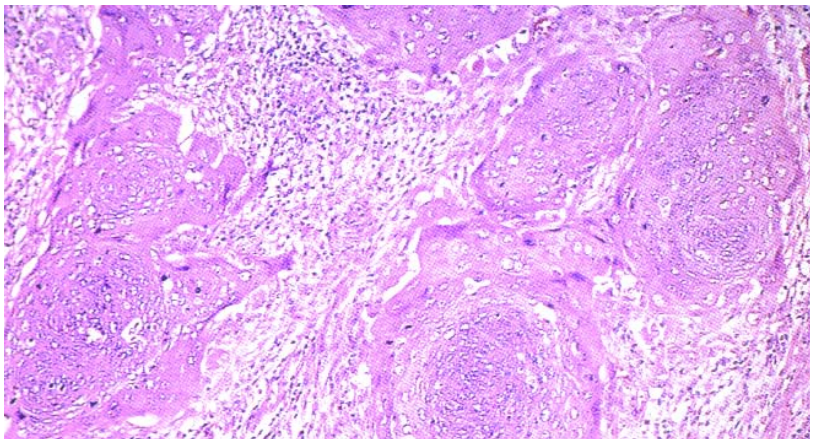

Fig. 4.12 Squamous cell carcinoma of the endometrium. This invasive tumour forms well differentiated squamous pearls. Note the reactive stroma with inflammatory cells.

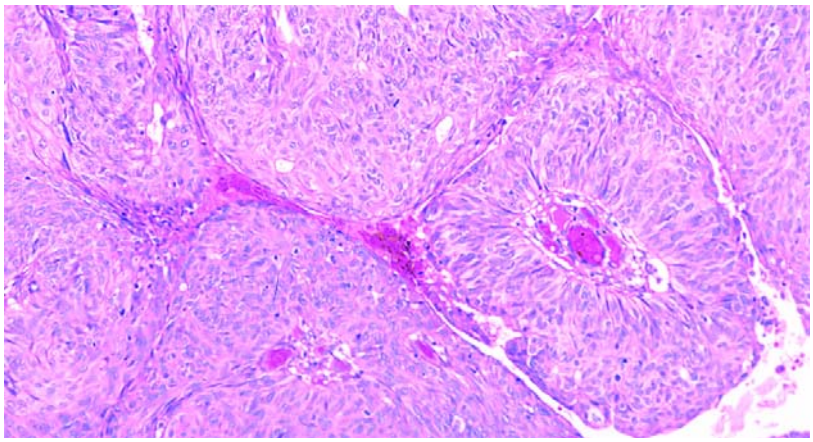

Fig. 4.13 Transitional cell carcinoma. The neoplasm forms papillae lined by low grade stratified transitional type epithelium.

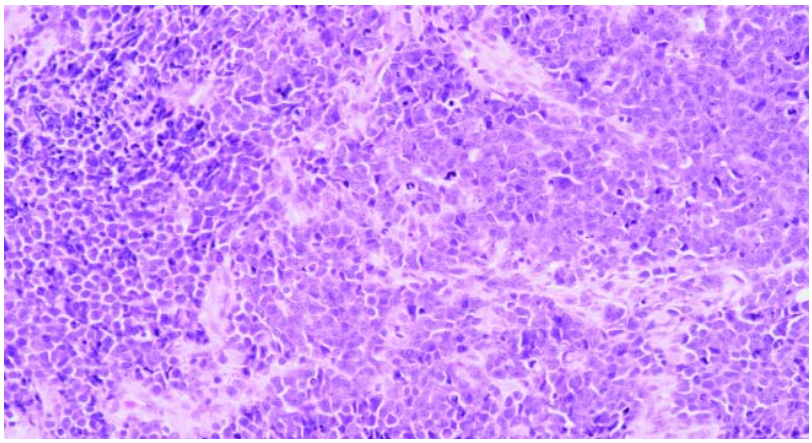

Fig. 4.14 Small cell carcinoma. The tumour is composed of small cells with high nuclear to cytoplasmic ratios.

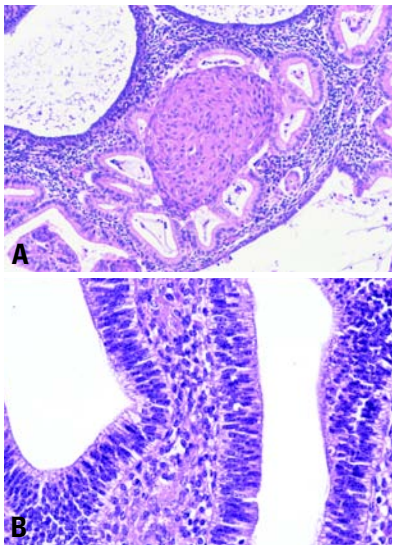

Fig. 4.15 Simple hyperplasia. A The endometrial glands vary from dilated to compact and are bridged by a large squamous morule. **B** Note the pseudostratified columnar epithelium with elongated nuclei lacking atypia.

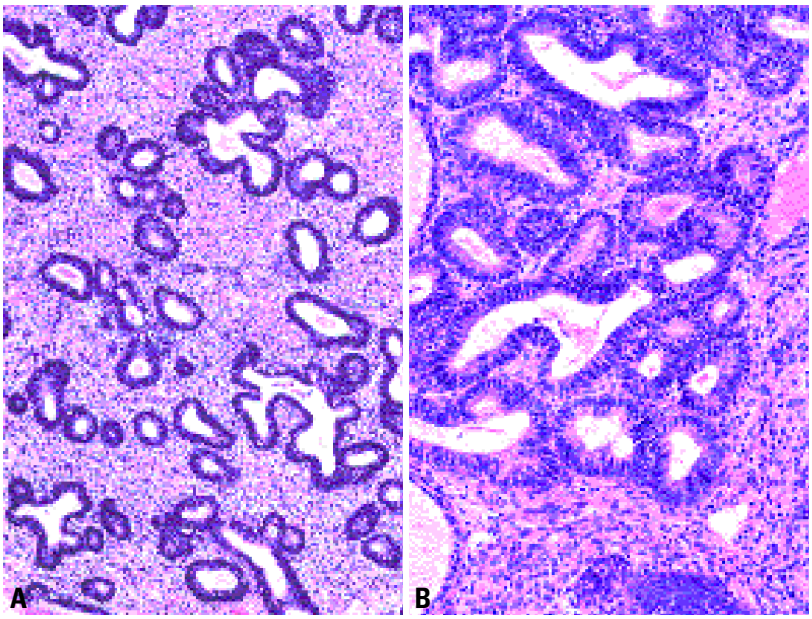

Fig. 4.16 Complex hyperplasia. **A** The endometrial glands show branching and budding. **B** There is glandular crowding; however, cytological atypia is absent.

Rare types of endometrial carcinoma

Almost every type of carcinoma reported elsewhere has been described in at least a single case report as primary in the endometrium.

Histopathology

These tumours are histologically (and usually clinically, if enough cases are available for analysis) identical to their more common counterparts in other organs. They include adenoid cystic carcinoma {985}, glassy cell carcinoma {1103} and mesonephric carcinoma {2110}. Oncocytic/oxyphilic carcinoma is thought by some to be a variant of clear cell carcinoma, whereas others consider it to be a separate tumour.

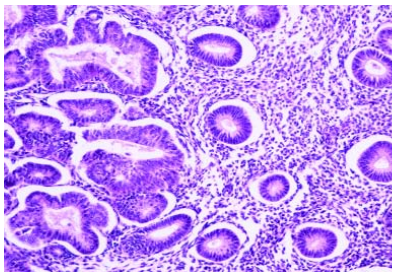

Fig. 4.17 Focal atypical hyperplasia. Atypical hyperplasia is seen on the left and a cyclic endometrium on the right.

Endometrial hyperplasia

Definition

A spectrum of morphologic alterations ranging from benign changes, caused by an abnormal hormonal environment, to premalignant disease.

Criteria for histological typing

The endometrial hyperplasias are classified by their degree of architectural complexity as simple or complex (adenomatous) and by their cytological (nuclear) features as hyperplasia or atypical hyperplasia.

The endometrium is uniquely endowed throughout the female reproductive lifespan with a complex regular cycle of periodic proliferation, differentiation, breakdown and regeneration. This high cellular turnover, conditioned by ovarian hormones and growth factors, has many opportunities for losing its regulatory controls. Endometrial hyperplasia encompasses conditions that range from benign estrogen-dependent proliferations of glands and stroma to monoclonal outgrowths of genetically altered glands.

The high degree of morphological variability of endometrial proliferations even within the same sample is responsible for the difficulty in defining consistent and clinically meaningful diagnostic criteria {240,3135}. A further complication is fragmentation and scantiness of many aspiration biopsies. Nevertheless, histological interpretation remains the most accessible, albeit somewhat subjective, method of evaluating endometrial hyperplasias.

WHO classification

Many classifications had been proposed prior to 1994 when the World Health Organization (WHO) adopted its current

Table 4.02
World Health Organization classification of endometrial hyperplasia {2602}.

Hyperplasias (typical)
Simple hyperplasia without atypia
Complex hyperplasia without atypia (adenomatous without atypia)
Atypical hyperplasias
Simple atypical hyperplasia
Complex atypical hyperplasia (adenomatous with atypia)

schema {1535,2602}. Although this classification has been widely applied, its reproducibility is somewhat disappointing {240,1433}, and molecular data with direct implications for histological diagnosis were unavailable at the time of the 1994 classification {1956}. Nevertheless, it remains the best available classification and has been adopted in this new edition.

Endometrial hyperplasias are assumed to evolve as a progressive spectrum of endometrial glandular alterations divided into four separate categories by architecture and cytology. The vast majority of endometrial hyperplasias mimic proliferative endometria, but rare examples demonstrate secretory features. The entire spectrum of metaplastic changes may be observed in hyperplastic endometria.

Hyperplasias without atypia

Hyperplasias without atypia represent the exaggerated proliferative response to an unopposed estrogenic stimulus; the endometrium responds in a diffuse manner with a balanced increase of both glands and stroma. In simple hyperplasia the glands are tubular although frequently cystic or angular, and some even show minor epithelial budding. The lining is pseudostratified with cells displaying regular, elongated nuclei lacking atypia. In complex (adenomatous) hyperplasia the glands display extensive complicated architectural changes represented by irregular epithelial budding into both lumina and stroma and a typical cytology with pseudostratified but uniform, elongated and polarized glandular nuclei; squamous epithelial morules can be present. There is most often a shift in the gland to stroma ratio in favour of the glands.

Atypical hyperplasias

The main feature which differentiates this category from the previous one is the atypical cytology of the glandular lining as represented by loss of axial polarity, unusual nuclear shapes that are often rounded, irregularity in the nuclear membranes, prominent nucleoli and cleared or dense chromatin. Atypia occurs nearly always focally.

Simple atypical hyperplasia features atypical glandular cytology superimposed on the architecture of simple hyperplasia. This pattern is extremely unusual. The frequently found complex atypical (adenomatous with atypia) hyperplasia is a lesion characterized by an increased glandular complexity with irregular outgrowths and cytological atypia. There may be associated foci of non-endometrioid differentiation such as squamous morules. Due to the expansion and crowding of glands, the interglandular stroma is diminished but remains present. Characteristic features of adenocarcinoma are absent.

The assessment of cytological atypia is the key problem in assigning individual cases to one of the four different WHO categories. Definitions of cytological atypia are difficult to apply in the endometrium because nuclear cytological changes occur frequently in hormonal imbalance, benign regeneration and metaplasia {1619,2033}. Paradoxically, atypical hyperplasia may exhibit more atypical features than adenocarcinoma {2688}, and some grade 1 invasive endometrioid carcinomas have an extremely bland cytology. Perhaps, it would be more appropriate to consider cytological changes in the context of overall glandular architecture. Indeed, architectural focality of the lesion is so closely linked with atypia that possibly they are inseparable. In this way, atypia is best observed by comparison with adjoining normal glands.

Caveat: sampling problems

The focal nature of atypical endometrial hyperplasias may allow young women to maintain fertility, but has the disadvantage of possible underdiagnosis due to incomplete sampling. The problem is greatest in scanty fragmented specimens, something commonly encountered in routine office biopsies. Clearly, this situation is responsible for the false negative biopsies during follow up.

Hysteroscopic direction may assist in targeting a macroscopically apparent localized lesion but is not a common practice in most settings.

Contemporary approach to endometrial hyperplasia

Poor reproducibility of the 1994 WHO hyperplasia schema {240,1433} has led to a proposal to reduce the number of diagnostic classes {240}. New concepts of pathogenesis have been incorporated into an integrated genetic, histomorphometric and clinical outcome model of

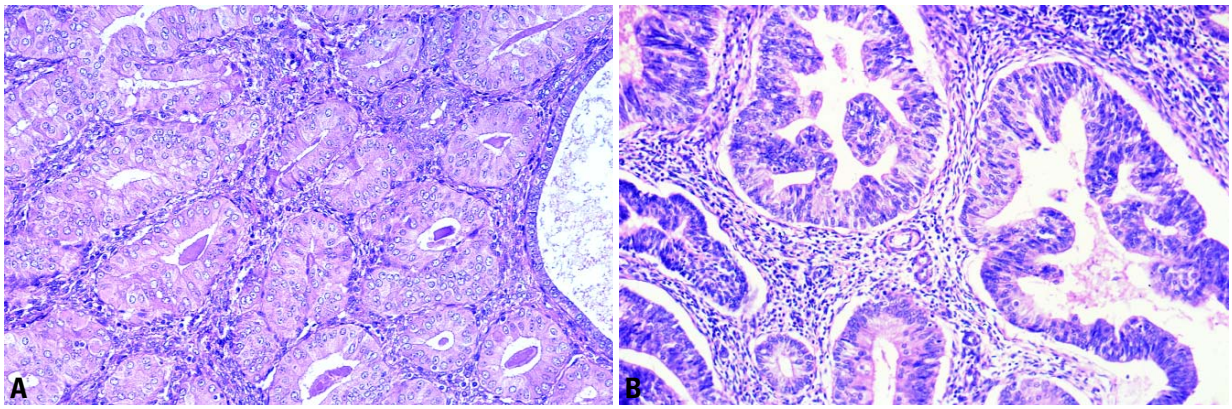

Fig. 4.18 Complex atypical hyperplasia. **A** There is glandular crowding with eosinophilic cytoplasm and nuclear enlargement, loss of polarity and prominent nucleoli. On the right is a residual, non-atypical cystic gland. **B** The glands are tortuous with epithelial tufts (reflecting abnormal polarity) protruding into the lumens and show cytological atypia.

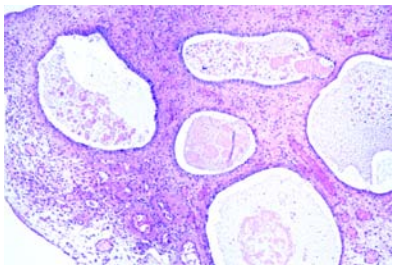

Fig. 4.19 Endometrial polyp. The glands are cystic and contain mucoid material, the stroma is fibrous, and the vessels are prominent.

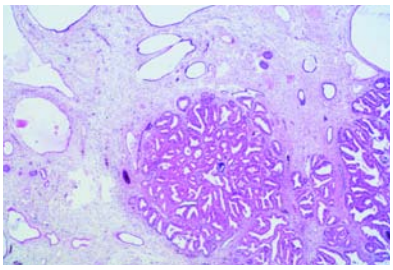

Fig. 4.20 Endometrial polyp with complex hyperplasia. Note the foci of crowded, convoluted glands in an atrophic endometrial polyp.

premalignant disease {1956,1958} (see section on genetics of endometrial carcinoma and precursor lesions).The clinical relevance of the model, however, has yet to be established.

Endometrial polyp

Definition

A benign nodular protrusion above the endometrial surface consisting of endometrial glands and stroma that is typically at least focally fibrous and contains thick-walled blood vessels.

Histopathology

Histologically, they are pedunculated or sessile lesions with a fibrous stroma in which characteristic thick-walled, tortuous, dilated blood vessels are found. The glandular component is patchily distributed and shows dilated, occasionally crowded glands lined with an atrophic epithelium, although rarely cyclic activity may be observed. Rare cases of atypical stromal cells have been documented in endometrial polyps {2834}, similar to those seen in polyps of the lower female genital system. Polyps can be differentiated from polypoid hyperplasias due to the distinctive stromal and vascular features of the former. Atypical hyperplasias and malignant tumours including adenocarcinomas of endometrioid and other types such as serous, as well as sarcomas and mixed tumours {2675} can be found arising in polyps.

Somatic genetics

Endometrial polyps constitute benign monoclonal proliferations of mesenchyme {891} and frequently show karyotypic abnormalities of chromosomal regions 6p21 and 12q15 {2854}, sites in which the *HMGIC* and *HMGIY* genes are located.

Prognosis and predictive factors

Polyp resection or polypectomy are the treatments of choice with few recurrences reported {2928}.

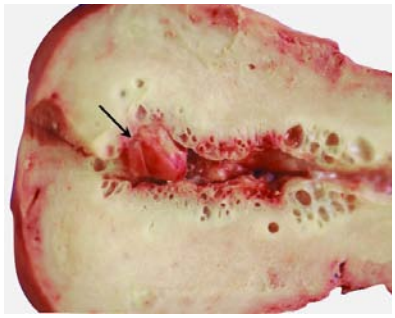

Fig. 4.21 Uterine tamoxifen-related lesion.Thickened myometrium in a 69 year old patient with subendometrial cysts and a polyp (arrow).

Tamoxifen-related lesions

Definition

Lesions that develop in the endometrium in patients undergoing long term tamoxifen therapy.

Epidemiology

Patients undergoing long term tamoxifen treatment often have enlarged uteri and frequently show endometrial cysts; up to 25% have endometrial polyps {531}.

Macroscopy

Tamoxifen-related polyps differ from non-iatrogenic endometrial polyps in that they are larger, sessile with a wide implantation base in the fundus and frequently show a honeycomb appearance.

Histopathology

Histologically, the differential features with normal endometrial polyps include the bizarre stellate shape of glands and the frequent epithelial (mucinous, ciliated, eosinophilic, microglandular) and stromal (smooth muscle) metaplasias {665,1437,2558}. There is often a periglandular stromal condensation (cambium layer). Malignant transformation occurs in up to 3% of cases, and endometrioid adenocarcinoma is the most frequent type. However, other types of malignant neoplasm such as serous carcinoma and carcinosarcoma may develop in this setting.

Somatic genetics

Despite these histological differences, the cytogenetic profile of tamoxifen-related polyps is identical to non-iatrogenic polyps {609}.

Genetics of endometrial carcinoma and precancer

Genotype and histotype

Endometrial adenocarcinoma is characterized by the abrogation of *PTEN* or *TP53* tumour suppressor pathways, respectively, for the endometrioid (type I) and non-endometrioid (type II, including serous and clear cell types) clinicopathological subgroups {2647}. Deletion and/or mutation of the *PTEN* and *TP53* genes themselves are early events with widespread distribution in advanced tumours and a presence in the earliest

Fig. 4.22 *TP53* mutations in endometrial carcinoma. Left: Wild type sequence in an endometrioid carcinoma: Exon 8 mutations in two serous carcinomas (arrows). Middle: GTT > TTT; Val > Phe (codon 274). Right: CGT > CAT; Arg > His (codon 273).

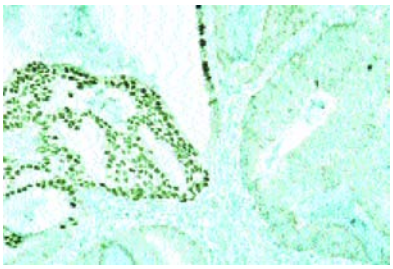

Fig. 4.23 Endometrioid adenocarcinoma (type I). Note the focal accumulation of mutant TP53 protein within a *TP53* wild-type carcinoma.

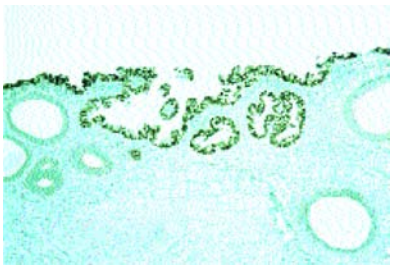

Fig. 4.24 Serous intraepithelial carcinoma (type II) expresses TP53 mutant protein.

Table 4.03
Altered gene function in sporadic endometrioid (type I) and non-endometrioid (type II) endometrial adenocarcinoma.

Gene	Alteration	Type I	Type II	References
TP53	Immunoreactivity (mutant)	5-10%	80-90%	{228,2647}
PTEN	No immunoreactivity	55%	11%	{1957}
KRAS	Activation by mutation	13-26	0-10%	{228,1512,1594,1787}
Beta-catenin	Immunoreactivity (mutant)	25-38%	rare	{1787}
MLH1	Microsatellite instability / epigenetic silencing	17%	5%	{799,826,1594}
P27	Low immunoreactivity	68-81%	76%	{2562}
Cyclin D1	High immunoreactivity	41-56%	19%	{2562}
P16	Low immunoreactivity	20-34%	10%	{2562}
Rb	Low immunoreactivity	3-4%	10%	{2562}
Bcl-2	Low immunoreactivity	65%	67%	{1512}
Bax	Low immunoreactivity	48%	43%	{1512}
Receptors				
ER and PR	Positive immunoreactivity	70-73%	19-24%	{1512}

ER = Estrogen receptor
PR = Progesterone receptor

detectable premalignant (type I) {1959} or non-invasive malignant (type II) phases of tumourigenesis {2647,2863}. A comprehensive model of sequential genetic damage has not been formulated for endometrial cancer despite a growing number of candidate genes.

PTEN checks cell division and enables apoptosis through an Akt-dependent mechanism. Functional consequences of *PTEN* mutation may be modulated in part by the hormonal environment, as *PTEN* is expressed only during the estrogen-driven proliferative phase of the endometrium {1957}. The use of PTEN immunohistochemistry as a tool for diagnosis of clinically relevant neoplastic endometrial disease is limited by the fact that one-third to one-half of type I cancers continue to express PTEN protein, and loss of *PTEN* function occurs as an early event that may precede cytological and architectural changes {1959}.

TP53 is the prototypical tumour suppressor gene capable of inducing a stable growth arrest or programmed cell death. Mutant protein accumulates in nuclei, where it can be readily demonstrated by immunohistochemistry in most serous (type II) adenocarcinomas {228}. Staining for TP53 is not routinely indicated, but the association of positive staining with a poor clinical outcome may be informative in suboptimal, scanty or fragmented specimens.

Molecular delineation of premalignant disease

Type I cancers begin as monoclonal outgrowths of genetically altered premalignant cells, and many bear genetic stigmata of microsatellite instability, *KRAS* mutation and loss of *PTEN* function that are conserved in subsequent cancer {1642,1956}. The earliest molecular changes, including *PTEN*, are detectable at a stage before glands have undergone any change in morphology {1959}. The accumulation of genetic damage is thought to cause emergence of histologically evident monoclonal lesions. Further elaboration of the histopathology of endometrial precancers has been accomplished through correlative histomorphometric analysis of genetically ascertained premalignant lesions {1958}. Because these lesions were initially defined by molecular methods, their diagnostic criteria differ from those of atypical endometrial hyperplasia. They have been designated endometrial intraepithelial neoplasia ("EIN") {1955},

Table 4.04
Essential diagnostic criteria of endometrial intraepithelial neoplasia (EIN).

EIN Criterion	Comments
1. Architecture	Gland area exceeds that of stroma, usually in a localized region.
2. Cytological alterations	Cytology differs between architecturally crowded focus and background.
3. Size >1 mm	Maximum linear dimension should exceed 1 mm. Smaller lesions have unknown natural history.
4. Exclude benign mimics and cancer	

and many examples with correlative genotypes and morphometry can be seen online at www.endometrium.org.

Endometrial intraepithelial neoplasia (EIN)
This lesion is defined as the histopathological presentation of premalignant endometrial disease as identified by integrated molecular genetic, histomorphometric and clinical outcome data. Tissue morphometry (D-Score {153} predictive of cancer outcome) and genetic studies are cross validating in that these methodologically independent techniques provide concordant identification of EIN lesions when applied to a common pool of study material {1958}. The EIN scheme partitions endometrial proliferations into different therapeutic groups. Distinctive diagnostic categories include:
(1) Benign architectural changes of unopposed estrogens (endometrial hyperplasia).
(2) EIN.
(3) Well differentiated adenocarcinoma.

The histological changes produced by unopposed estrogens (non-atypical hyperplasias) are quite unlike localizing EIN lesions. The latter originate focally through monoclonal outgrowth of a mutant epithelial clone with altered cytology and architecture. Computerized morphometric analysis, which quantifies specific architectural patterns associated with increased clinical cancer risk {154}, objectively defined the morphology of monoclonal EIN lesions. Because of differing diagnostic criteria, only 79% of atypical endometrial hyperplasias translate to EIN, and approximately a third of all EIN diagnoses are garnered from non-atypical hyperplasia categories.

Genetic susceptibility
The overwhelming majority of endometrial cancers are sporadic, but they may rarely present as a manifestation of multicancer familial syndromes. Examples include hereditary nonpolyposis colon cancer (HNPCC), caused by mutation of DNA mismatch repair genes that produce constitutive microsatellite instability {799} and Cowden syndrome in patients with germline *PTEN* inactivation {1957}.

Prognosis and predictive factors
In addition to tumour type and, for type I adenocarcinomas, tumour grade, other histological and non-histological determinations influence the prognosis of endometrial carcinoma. The most important of these is the surgical stage, which in 1988 replaced the clinical staging system that had been in use for many years {2642}. The extent of surgical staging performed is based in part on the medical condition of the patient and in part on the preoperative or intraoperative assessment of tumour risk factors such as type and grade, depth of myometrial invasion and extension to involve the cervix {2692,2714}.
Myometrial invasion is thus an important issue, both as a prognostic factor in its own right and as a determinant of the extent of staging and of subsequent therapy in cases treated by hysterectomy. FIGO divides stage I tumours into IA (limited to the endometrium), IB (invasion of less than half of the myometrium), and IC (invasion of more than half of the myometrium), {51,2976}. Some oncologists, however, make treatment decisions based on thirds (inner, mid, outer) of myometrial invasion or distance in millimetres (mm) from the serosal surface. Thus, the pathologist can best satisfy the desires for all of this information by reporting the maximal depth of tumour invasion from the endomyometrial junction and the thickness of the myometrium at that point (e.g. 7 mm tumour invasion into a 15 mm thick myometrium) {2686}. True myometrial invasion must be distinguished from carcinomatous extension (not invasion) into pre-existing "tongues" of endometrium penetrating the myometrium or into foci (sometimes deep-seated) of adenomyosis {2652, 2688}. It should also be noted that tumour extension to the uterine serosa raises the stage to IIIA. Vascular or lymphatic space invasion is an unfavourable prognostic factor that should be reported {78}. Perivascular lymphocytic infiltrates may be the first clue to vascular invasion and, thus, should prompt deeper levels within the suspect block and/or the submission of more tissue sections for histological examination.
It is also important to evaluate cervical involvement in the hysterectomy specimen since extension to the cervix raises the stage to II. The distinction between stage IIA and IIB is based on whether the extension involves the endocervical surface and/or underlying glands only or invades the cervical stroma. One should be aware that an adenocarcinoma involving glands only might be an entirely separate adenocarcinoma in situ primary in the endocervix.
Non-histological factors may also play a role in determining the prognosis of endometrial carcinoma. It is unclear at the present time, however, what the cost/benefit ratio of performing additional studies might be since the prognosis and treatment are currently based on the combination of tumour type, grade, where appropriate, and extent, as discussed above. Nevertheless, patients with carcinomas of intermediate prognosis, such as stage I well differentiated endometrioid adenocarcinoma with focal deep myometrial invasion might benefit from additional information including such factors as tumour ploidy {1349,1441}, hormone receptor status {575,1441}, tumour suppressor genes {1309,1449}, oncogenes {1205,1449}, proliferation markers {966,1449,2012} and morphometry {2751}. Which, if any, of these or other studies will prove to be most useful is problematic at this time.

Mesenchymal tumours and related lesions

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F.A. Tavassoli
R.L. Kempson
W.G. McCluggage
U. Haller
R.A. Kubik-Huch

Definition
Uterine mesenchymal tumours are derived from the mesenchyme of the corpus consisting of endometrial stroma, smooth muscle and blood vessels or admixtures of these. Rarely, these tumours may show mesenchymal differentiation that is foreign to the uterus.

Epidemiology
The most common malignant mesenchymal tumours of the uterine corpus are leiomyosarcoma and endometrial stromal tumours, and both are more frequent in Black than in White women {1139, 1729}.

Clinical features
Signs and symptoms
The most common presentation for mesenchymal tumours is uterine enlargement, abnormal uterine bleeding or pelvic pain.

Imaging
Non-invasive imaging, usually by ultrasound, but occasionally by magnetic resonance imaging (MRI), can be utilized in selected cases to distinguish between a solid ovarian tumour and a pedunculated leiomyoma or to distinguish leiomyomas from adenomyosis. On MRI leiomyomas present as well delineated lesions of low signal intensity on T1 and T2-weighted images. They may, however, undergo degenerative changes resulting in various, non-specific MRI appearances {1947,2971}. On MRI the presence of a large, heterogeneous mass with irregular contours should raise concern for sarcoma.

Endometrial stromal and related tumours

Definition and historical annotation
Endometrial mesenchymal tumours in their better-differentiated forms are composed of cells resembling those of proliferative phase endometrial stroma. Numerous thin-walled small arteriolar type (plexiform) vessels are characteristically present.
Endometrial stromal sarcomas (ESS) have been traditionally divided into low and high grade types based on mitotic count. However, since high grade endometrial sarcomas lack specific differentiation and bear no histological resemblance to endometrial stroma, it has been proposed that they be designated undifferentiated endometrial or uterine sarcoma {811}. In this classification the distinction between low grade ESS and undifferentiated endometrial sarcoma is not made on the basis of mitotic count but on features such as nuclear pleomorphism and necrosis.

ICD-O codes

Endometrial stromal sarcoma, low grade	8931/3
Endometrial stromal nodule	8930/0
Undifferentiated endometrial sarcoma	8930/3

Histopathology
Endometrial stromal tumours are composed of cells resembling those of proliferative endometrial stroma and are far less frequent than smooth muscle tumours. Endometrial stromal tumours are subdivided into benign and malignant groups based on the type of tumour margin {1432,2054,2097,2883}.
Those with pushing margins are benign stromal nodules, whereas those with infiltrating margins qualify as stromal sarcomas. There is general agreement on the morphologic definition of typical cases of both low grade ESS and undifferentiated endometrial sarcoma. Characteristically, low grade ESS, a clinically indolent neoplasm, features a plexiform vasculature, minimal cytological atypia and infrequent mitotic figures. The usual undifferentiated sarcoma, a highly aggressive neoplasm, lacks a plexiform vasculature, features substantial cytological atypia and has frequent and often atypical mitotic figures. However, there is no valid evidence that the isolated finding of a mitotic index of 10 or more per 10 high power fields is an adverse prognostic finding in a neoplasm that is otherwise a typical low grade ESS. A small minority of cases share features of low grade ESS and undifferentiated sarcoma, and their classification is controversial.

Immunoprofile
The neoplastic cells of both the stromal nodule and low grade ESS are immunoreactive for vimentin, CD10

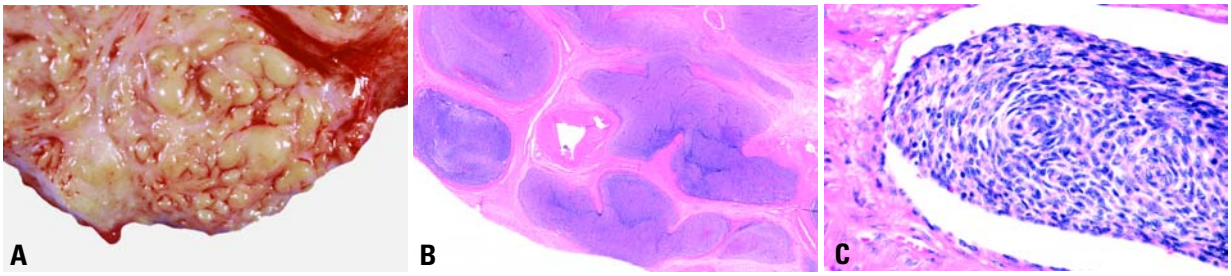

Fig. 4.25 Low grade endometrial stromal sarcoma (ESS). **A** Worm-like, soft, yellow masses focally replace the myometrium. **B** The myometrium is extensively infiltrated by basophilic islands of low grade ESS. **C** A tongue of low grade ESS protrudes into a vascular space.

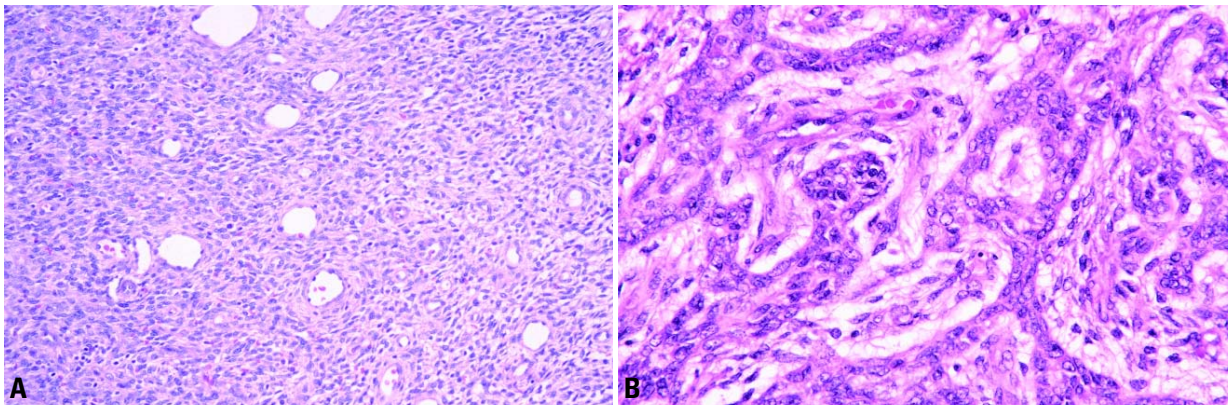

Fig. 4.26 Low grade endometrial stromal sarcoma (ESS). **A** There is a proliferation of endometrial stromal cells lacking atypia around spiral arteriole-like blood vessels. **B** Note a sex cord-like pattern in a low grade ESS.

{486,1821} and at least focally for actin {914}. They are usually, but not always {914}, negative for desmin and h-caldesmon {2065,2101,2488}. Low grade ESS is almost always positive for both estrogen and progesterone receptors. {1411,2350,2502}. Rarely, low grade endometrial stromal tumours, particularly those with areas displaying a sex cord pattern, may be positive for alpha-inhibin {1521}, CD99 {167} and cytokeratin {29}. The sex cord areas may also be immunoreactive for desmin, whereas the surrounding endometrial stromal cells are not {678,1661}.

Somatic genetics

Fusion of two zinc finger genes (*JAZF1* and *JJAZ1*) by translocation t(7;17) is present in most low grade endometrial stromal tumours {1189,1252,1503}. Endometrial stromal nodules and low grade ESSs are typically diploid with a low S-phase fraction {292,1220}.

Prognosis and predictive factors

The histological distinction between undifferentiated endometrial sarcoma and low grade ESS has important implications regarding prognosis {2601} Low grade ESSs are indolent tumours with a propensity for local recurrence, usually many years after hysterectomy. Distant metastases are less common. In contrast, undifferentiated endometrial sarcomas are highly aggressive tumours with the majority of patients presenting with extrauterine disease at the time of diagnosis and dying within two years of diagnosis {232,811}.

Endometrial stromal sarcoma, low grade

Definition

This tumour fits the definition of endometrial stromal tumour presented above and is distinguished from the stromal nodule on the basis of myometrial infiltration and/or vascular space invasion.

Epidemiology

Low grade ESS is a rare tumour of the uterus accounting for only 0.2% of all genital tract malignant neoplasms {645, 1509,1745}. In general low grade ESSs affect younger women than other uterine malignancies; studies have demonstrated that the mean age ranges from 42-58 years, and 10-25% of patients are premenopausal {437,645}.

Clinical features

The clinical features have been discussed above.

Macroscopy

Low grade ESS may present as a solitary, well delineated and predominantly intramural mass, but extensive permeation of the myometrium is more common, with extension to the serosa in approximately half of the cases. The sectioned surface appears yellow to tan, and the tumour has a softer consistency than the usual leiomyoma. Cystic and myxoid degeneration as well as necrosis and haemorrhage are seen occasionally.

Localization

Metastases are rarely detected prior to the diagnosis of the primary lesion {29,684,3222}. Extrauterine extension is present in up to a third of the women with low grade ESS at the time of hysterectomy. The extension may appear as worm-like plugs of tumour within the vessels of the broad ligament and adnexa.

Histopathology

Low grade ESS is usually a densely cellular tumour composed of uniform, oval to spindle-shaped cells of endometrial stromal-type; by definition significant atypia and pleomorphism are absent. Although most tumours are paucimitotic, mitotic rates of 10 or more per 10 high power fields can be encountered, and a high mitotic index does not in itself alter the diagnosis. A rich network of delicate small arterioles resembling the spiral arterioles of the late secretory endometrium supports the proliferating cells. Cells with foamy cytoplasm (tumour cells, foamy histiocytes, or both) are prominent in some cases. Endometrial type glands occur in 11-40% of endometrial stromal tumours {516,1343,2054}. Sex cord-like structures may also be found {511}. Myxoid and fibrous change may occur focally or diffusely {2054,2102}. Perivascular hyalinization and a stellate pattern of hyalinization occur in some cases. Reticulin stains usually reveal a dense network of fibrils surrounding individual cells or small groups of cells. Necrosis is typically absent or inconspicuous.

Focal smooth muscle differentiation (spindle or epithelioid) or cells with differentiation that is ambiguous between stromal and smooth muscle cells may develop in endometrial stromal tumours; these

areas are limited to less than 30% of the tumour. When the smooth muscle component comprises 30% or more of the tumour, the lesion is designated as a mixed endometrial stromal and smooth muscle tumour. Focal rhabdoid differentiation has been described in one case {1813}.
The differential diagnosis includes stromal nodule, intravenous leiomyomatosis, adenomyosis with sparse glands and adenosarcoma. In a biopsy or curettage specimen it is often impossible to distinguish low grade ESS from a stromal nodule, a non-neoplastic stromal proliferation or a highly cellular leiomyoma.

Histogenesis

Extrauterine primary endometrioid stromal sarcomas occur and often arise from endometriosis {280}.

Prognosis and predictive factors

Low grade ESS is characterized by indolent growth and late recurrences; up to one-half of patients develop one or more pelvic or abdominal recurrences. The median interval to recurrence is 3-5 years but may exceed 20 years. Pulmonary metastases occur in 10% of stage I tumours {1311}.
The 5-year survival rate for low grade ESS ranges from 67% {2048} to nearly 100% with late metastases and a relatively long-term survival despite tumour dissemination {437,811,2263}. The surgical stage is the best predictor of recurrence and survival for ESSs {300,437}.
Both recurrent and metastatic ESSs may remain localized for long periods and are amenable to successful treatment by resection, radiation therapy, progestin therapy or a combination thereof {300,1750,3089}.
Conservative management has been advocated for some patients with low grade ESS {1677}. In some studies that have utilized progestin therapy, 100% survival rates have been achieved even for patients with stage III tumours {2263}.

Endometrial stromal nodule

Definition

A benign endometrial stromal tumour characterized by a well delineated, expansive margin and composed of neoplastic cells that resemble proliferative phase endometrial stromal cells supported by a large number of small, thin-walled arteriolar-type vessels.

Clinical features

Women with a stromal nodule range in age from 23-75 years with a median of 47 years {292,437,2098,2101,2102,2883}. About one-third of the women are postmenopausal. Two-thirds of the women present with abnormal uterine bleeding and menorrhagia. Pelvic and abdominal pain occur less frequently.

Macroscopy

The tumour is characteristically a solitary, well delineated, round or oval, fleshy nodule with a yellow to tan sectioned surface. The median tumour diameter is 4.0 cm (range 0.8-15 cm) {2883}. About two-thirds are purely intramural without any apparent connections to the endometrium, 18% of the lesions are polypoid, and others involve both the endometrium and myometrium.

Histopathology

The histological appearance is identical to that described above for low grade ESS except for the absence of infiltrative margins {292,437,2097,2098,2101,2102,2883}. Rare, focal marginal irregularity in the form of finger-like projections that do not exceed 3 mm is acceptable. Smooth and skeletal muscle along with sex cord differentiation may be present focally {1685}.
The differential diagnosis includes low grade ESS and highly cellular leiomyoma. The presence of at least focal typical neoplastic smooth muscle bundles, large, thick walled vessels and strong immunoreactivity with desmin and h-caldesmon and the absence of reactivity with CD10 help distinguish a highly cellular leiomyoma from a stromal nodule.

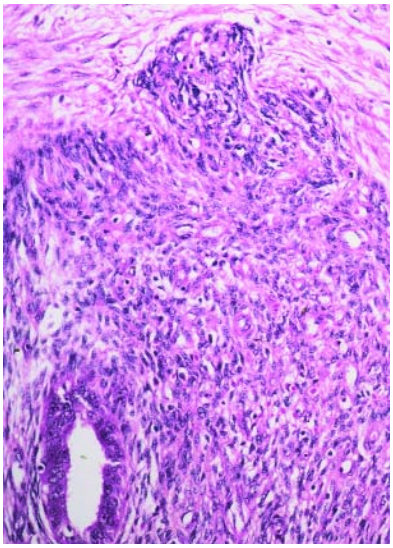

Fig. 4.27 Low grade endometrial stromal sarcoma (ESS). Myoinvasive low grade ESS that shows endometrial glandular differentiation. The myometrium is seen above.

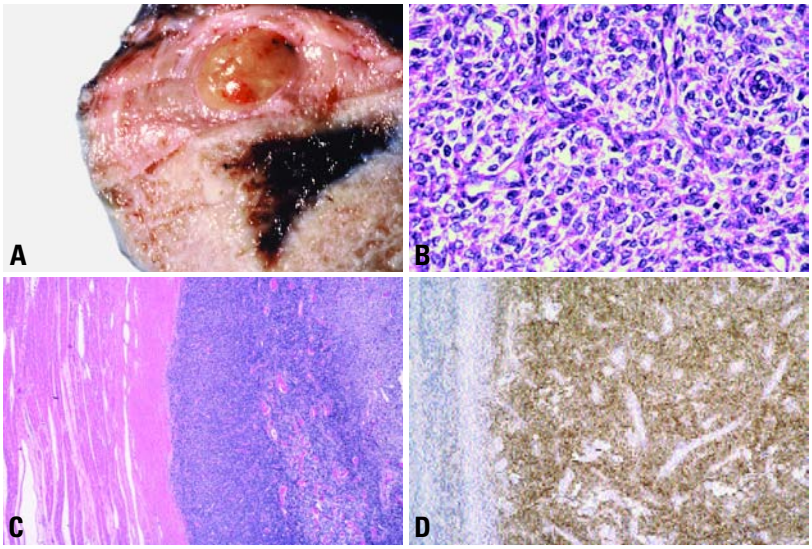

Fig. 4.28 Endometrial stromal nodule. A Note the circumscribed, bulging, yellow nodule in the myometrium. B Cytologically bland ovoid cells without discernible cytoplasm proliferate in a plexiform pattern and are supported by small arterioles. **C** The circumscribed myometrial nodule is composed of closely packed cells. D The tumour cells are strongly immunoreactive for CD10.

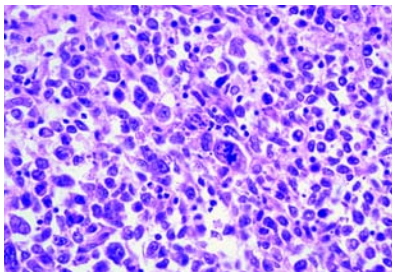

Fig. 4.29 Undifferentiated endometrial sarcoma. Atypical tumour cells show no resemblance to normal endometrial stromal cells. Note the presence of an abnormal mitotic figure.

Prognosis and predictive factors
Endometrial stromal nodules are benign {437,2101,2883}. A hysterectomy may be required if the lesion has not been completely excised.

Undifferentiated endometrial sarcoma

Definition
A high grade endometrial sarcoma that lacks specific differentiation and bears no histological resemblance to endometrial stroma.

Synonym
Undifferentiated uterine sarcoma.

Macroscopy
Macroscopically, undifferentiated uterine sarcomas are characterized by one or more polypoid, fleshy, grey to yellow endometrial masses and often show prominent haemorrhage and necrosis.

Histopathology
Histologically, undifferentiated endometrial sarcomas show marked cellular atypia and abundant mitotic activity, often including atypical forms. They lack the typical growth pattern and vascularity of low grade ESS {651,811} and displace the myometrium in contrast to the infiltrative pattern of low grade ESS. They resemble the sarcomatous component of a carcinosarcoma, and the possibility of carcinosarcoma and other specific sarcomas should be excluded with adequate sampling.
These sarcomas are most often aneuploid with an S-phase fraction greater than 10% {292} and negative for estrogen and progesterone receptors.

Prognosis and predictives factors
These tumours are aggressive, and death occurs from tumour dissemination within three years after hysterectomy in most cases.

Smooth muscle tumours

Definition
Benign or malignant neoplasms composed of cells demonstrating smooth muscle differentiation.

ICD-O codes

Leiomyosarcoma, NOS	8890/3
Epithelioid variant	8891/3
Myxoid variant	8896/3
Smooth muscle tumour of uncertain malignant potential	8897/1
Leiomyoma, NOS	8890/0
Leiomyoma, histological variants	
Cellular leiomyoma	8892/0
Epithelioid leiomyoma	8891/0
Myxoid leiomyoma	8896/0
Atypical leiomyoma	8893/0

Table 4.05
Diagnostic criteria for leiomyosarcoma.

	Standard smooth muscle differentiation	Epithelioid differentiation	Myxoid differentiation
Histology	Fascicles of cigar-shaped spindled cells with scanty to abundant eosinophilic cytoplasm	Rounded cells with central nuclei and clear to eosinophilic cytoplasm	Spindle-shaped cells set within an abundant myxoid matrix
Criteria for leiomyosarcoma	Any coagulative tumour cell necrosis In the absence of tumour cell necrosis the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ≥ 10mf/10hpf. When the mitotic index is less than 10mf/10hpf, the chance of recurrence is low (less than a 2-3%) and the tempo of recurrence is slow. This group is labelled "atypical leiomyoma with low risk of recurrence".	Any coagulative tumour cell necrosis In the absence of tumour cell necrosis the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ≥ 5mf/10hpf	Any coagulative tumour cell necrosis In the absence of tumour cell necrosis, the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ≥ 5mf/10hpf
Comments	In the absence of coagulative tumour cell necrosis and significant atypia a high mitotic index is compatible with a benign clinical course. When the mitotic index exceeds 15 mf/10hpf the term "mitotically active leiomyoma with limited experience" can be used The category "leiomyoma with limited experience" is also used for smooth muscle neoplasms that have focal moderate to severe atypia	Focal epithelioid differentiation may be mimicked by cross-sectioned fascicles of standard smooth muscle	The very common perinodular hydropic degeneration should not be included in this group

mf/10hpf = mitotic figure(s) per 10 high power fields. See ref. {211} for discussion of mitosis counting techniques.

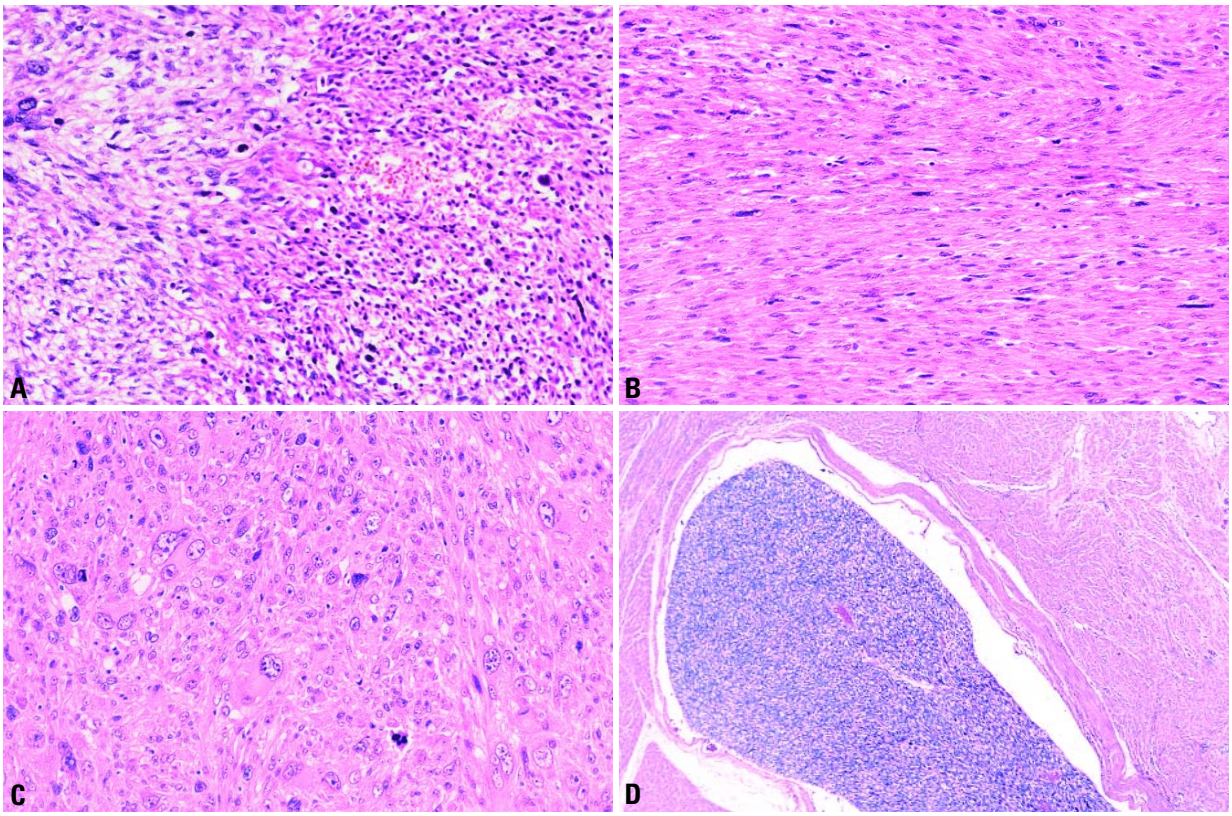

Fig. 4.30 Leiomyosarcoma. **A** This tumour exhibits typical coagulative tumour cell necrosis on the right. This pattern of necrosis features an abrupt transition from viable tumour cells to necrotic tumour cells without intervening collagen or granulation tissue. **B** This tumour has a low level of atypia. This degree of atypia should prompt careful search for more diagnostic features. **C** A high level of atypia and apotosis is apparent in this tumour. **D** Leiomyosarcoma with intravascular tumour growth. The differential diagnosis includes intravenous leiomyomatosis, low grade endometrial stroma sarcoma (ESS) and leiomyosarcoma with vascular invasion. High power showed a poorly differentiated neoplasm with marked cytologic atypia and a high mitotic index. These are not features of low grade ESS or intravenous leiomyomatosis.

Lipoleiomyoma	8890/0
Leiomyoma, growth pattern variants	
Diffuse leiomyomatosis	8890/1
Intravenous leiomyomatosis	8890/1
Benign metastasizing leiomyoma	8898/1

Leiomyosarcoma

Definition

A malignant neoplasm composed of cells demonstrating smooth muscle differentiation.

Epidemiology

Leiomyosarcoma represents the most common pure uterine sarcoma and comprises slightly over 1% of all uterine malignancies {1139}. The incidence of leiomyosarcoma is reported to be 0.3-0.4/100,000 women per year {1139}. Leiomyosarcoma arises nearly exclusively in adults. The median age of patients with leiomyosarcoma was 50-55 years in larger studies {947,1745}, and 15% of the patients were younger than 40 years. The risk factors for endometrial carcinomas such as nulliparity, obesity, diabetes mellitus and hypertension are not known to relate to leiomyosarcoma.

Clinical features

Leiomyosarcomas localized to the uterus and leiomyomas produce similar symptoms. Although a rapid increase in the size of the uterus after menopause may raise the possibility of leiomyosarcoma, in fact sarcoma is not more prevalent (less than 0.5%) in women with "rapidly growing" leiomyomas {1622,2187}.

Leiomyosarcoma may spread locally, regionally or by haematogenous dissemination. This fact of natural history has implications for both diagnosis and management. Local and regional extension may produce an abdominal or pelvic mass and gastrointestinal or urinary tract symptoms. Haematogenous dissemination is most often to the lungs. Leiomyosarcoma is only infrequently diagnosed on endometrial samplings {1622}.

Macroscopy

Leiomyosarcomas are characteristically solitary intramural masses and are usually not associated with leiomyomas. Leiomyosarcomas average 8.0 cm in diameter and are fleshy with poorly defined margins. Zones of haemorrhage and necrosis characteristically interrupt their grey-yellow or pink sectioned surface.

Histopathology

The usual leiomyosarcoma is a cellular tumour composed of fascicles of spindle-shaped cells that possess abundant eosinophilic cytoplasm. Typically, the nuclei are fusiform, usually have rounded ends and are hyperchromatic with coarse chromatin and prominent nucleoli. Tumour cell necrosis is typically prominent but need not be present. The mitotic index usually exceeds 15 figures per 10 high power fields. Vascular invasion is identified in up to 25% of leiomyosarcomas. Giant cells resembling osteoclasts occasionally are present in otherwise typical leiomyosarcomas, and, rarely, xanthoma cells may be prominent {1058,1776}.

A diagnosis of leiomyosarcoma should be made with great caution in women less than 30 years of age and only after exclusion of exposure to Leuprolide, which sometimes induces a pattern of necrosis identical to coagulative tumour cell necrosis {664}.

Epithelioid variant

Epithelioid leiomyosarcomas combine an "epithelioid" phenotype with the usual features of malignancy, i.e. high cellularity, cytological atypia, tumour cell necrosis and a high mitotic rate {130,1538, 2292}. Specifically, epithelioid differentiation denotes tumour cells that have a rounded configuration with eosinophilic to clear cytoplasm. When the cytoplasm is totally clear the label "clear cell" is used. Most malignant epithelioid smooth muscle tumours are of the leiomyoblastoma type, although clear cell leiomyosarcoma has been reported.

Myxoid variant

Myxoid leiomyosarcoma is a large, gelatinous neoplasm that often appears to be circumscribed on macroscopic examination {131,1465}. The smooth muscle cells are widely separated by myxoid material. The characteristic low cellularity largely accounts for the presence of only a few mitotic figures per 10 high power fields in most myxoid leiomyosarcomas. In almost all instances myxoid leiomyosarcomas show cellular pleomorphism and nuclear enlargement. They commonly show myometrial and, sometimes, vascular invasion.

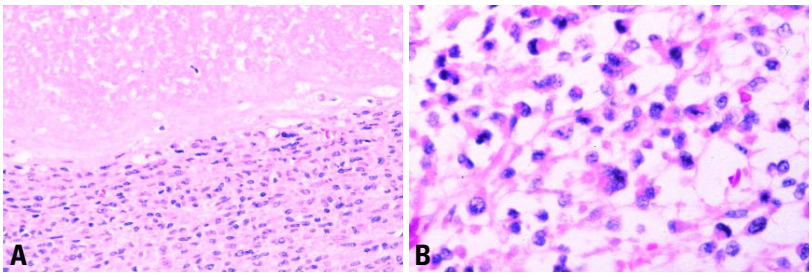

Fig. 4.31 Epithelioid leiomyosarcoma. **A** Tumour cell necrosis is present in the upper half of the field adjacent to highly pleomorphic cells. **B** The tumour cells exhibit nuclear pleomorphism, and mitotic figures are easily found.

Prognosis and predictive factors

Leiomyosarcoma is a highly malignant neoplasm {1745,2096}. The variation in survival rates reported historically is largely the result of the use of different criteria for its diagnosis. Overall 5-year survival rates range from 15-25% {185,231,377,812,1585,3005,3109}. The 5-year survival rate is 40-70% in stage I and II tumours {291,947,1381,1585, 1765,1797,2045,2049,2200,3139}. Premenopausal women have a more favourable outcome in some series {947, 1381,1585,1797,3005,3139} but not in others {185,1148}. Most recurrences are detected within 2 years {231,377,1148, 1381}.

The prognosis of leiomyosarcoma depends chiefly upon the extent of spread. For tumours confined to the uterine corpus, some investigators have found that the size of the neoplasm is an important prognostic factor {812,1364, 2049} with the best demarcation occurring at 5 cm. Several recent series, including the large Gynecologic Oncology Group study of early stage leiomyosarcoma, have found the mitotic index to be of prognostic significance {811,947,1585,1745}, whereas others have not {812}. The utility of grading leiomyosarcomas is controversial, and no universally accepted grading system exists. Pathologists should comment on the presence or absence of extrauterine extension and/or vascular space involvement, the maximum tumour diameter and the mitotic index.

Smooth muscle tumour of uncertain malignant potential

Definition

A smooth muscle tumour that cannot be diagnosed reliably as benign or malignant on the basis of generally applied criteria.

Histopathology

This category of smooth muscle tumour of uncertain malignant potential should

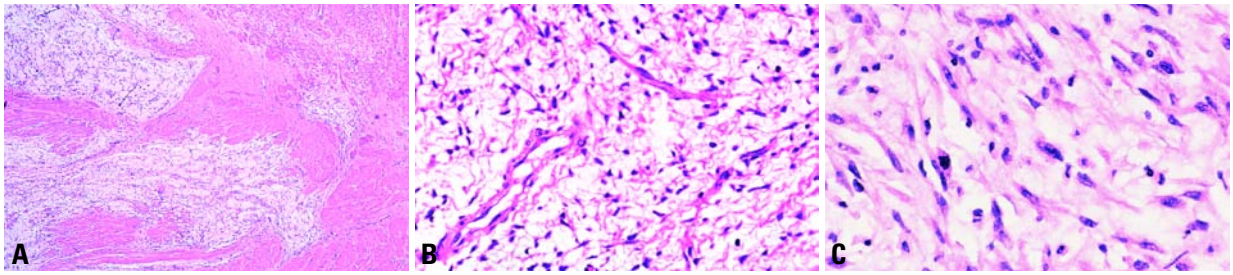

Fig. 4.32 Myxoid leiomyosarcoma. **A** A paucicellular myxoid neoplasm infiltrates the myometrium. **B** Relatively bland spindle-shaped tumour cells are widely spaced in a myxoid matrix containing a delicate vasculature. **C** Nuclear pleomorphism and mitotic figures, although few in number, can be found.

be used sparingly and is reserved for smooth muscle neoplasms whose appearance is ambiguous for some reason, and the relevant diagnostic possibilities differ in their clinical implications {211}. Examples include cases in which the subtype of smooth muscle differentiation is in doubt, i.e. standard smooth muscle, epithelioid or myxoid, and application of the competing classification rules would lead to different clinical predictions. On other occasions the assessment of a diagnostic feature, e.g. the type of necrosis or the interpretation of mitotic figures, is ambiguous, and the competing alternative interpretations would lead to different clinical predictions.

Table 4.06
Definition of terms used in the diagnosis of uterine smooth muscle neoplasms.

Term	Definition or comment
Necrosis	Death of a portion of tissue
Coagulative tumour cell necrosis	Abrupt transition from viable tumour to necrotic tumour, ghost outlines of cells usual, haemorrhage and inflammation uncommon.
Hyaline necrosis	Intervening zone of collagen or granulation tissue between nonviable and viable tumour, haemorrhage common, cellular outlines often not visible.
Atypia	Assessed at scanning power
Diffuse vs. focal	Cells diffusely present in most fields examined vs. scattered widely spaced aggregates of cells
None to mild	
Moderate to severe	Pleomorphic type: Nuclear pleomorphism appreciated at scanning power Uniform type: Cells lack pleomorphism but exhibit uniform but marked nuclear chromatin abnormalities
Mitotic index	Expressed in mitotic figures per 10 high power fields in the mitotically most active areas
	Only unequivocal mitotic figures are counted {211}

Leiomyoma

Definition
A benign neoplasm composed of smooth muscle cells with a variable amount of fibrous stroma.

Macroscopy
Leiomyomas are typically multiple, spherical and firm. The sectioned surface is white to tan and has a whorled trabecular texture. Leiomyomas bulge above the surrounding myometrium from which they are easily shelled out. Submucosal leiomyomas distort the overlying endometrium, and, as they enlarge, they may bulge into the endometrial cavity and produce bleeding. Rare examples become pedunculated and prolapse through the cervix. Intramural leiomyomas are the most common. Subserosal leiomyomas can become pedunculated, and on torsion with necrosis of the pedicle the leiomyoma may lose its connection with the uterus. Very rarely, some become attached to another pelvic structure (parasitic leiomyoma). The appearance of a leiomyoma often is altered by degenerative changes. Submucosal leiomyomas frequently are ulcerated and haemorrhagic. Haemorrhage and necrosis are observed in some leiomyomas, particularly in large ones in women who are pregnant or who are undergoing high-dose progestin therapy. Dark red areas represent haemorrhage and sharply demarcated yellow areas reflect necrosis. The damaged smooth muscle is replaced eventually by firm white or translucent collagenous tissue. Cystic degeneration also occurs, and some leiomyomas become extensively calcified.

Histopathology
Most leiomyomas are composed of easily recognized smooth muscle featuring whorled, anastomosing fascicles of uniform, fusiform cells. Characteristically, the spindle-shaped cells have indistinct borders and abundant, often fibrillar, eosinophilic cytoplasm. Sometimes, particularly in cellular leiomyomas, the cytoplasm is sparse, and the fascicular arrangement of the cells may be muted.

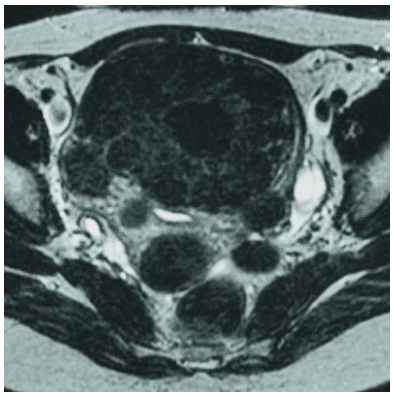

Fig. 4.33 MRI showing an enlarged uterus with multiple leiomyomas.

Nuclei are elongated with blunt or tapered ends and have finely dispersed chromatin and small nucleoli. Mitotic figures usually are infrequent.
Most leiomyomas are more cellular than the surrounding myometrium. Leiomyomas lacking increased cellularity are identified by their nodular circumscription and by the disorderly arrangement of the smooth muscle fascicles within them, out of alignment with the surrounding myometrium.
Degenerative changes are common in leiomyomas. Hyaline fibrosis, oedema and, on occasion, marked hydropic change can be present {525}. Haemorrhage, necrosis, oedema, myxoid change, hypercellular foci and cellular hypertrophy occur in leiomyomas in women who are pregnant or taking progestins. Not infrequently, there is increased mitotic activity near the areas of necrosis.
On the other hand, the coagulative tumour cell necrosis common in leiomyosarcoma is not associated very often with acute inflammation and haemorrhage. Progestational agents are associated with a slight increase in mitotic activity, but not to the level observed in a leiomyosarcoma. In addition, the mitotic figures seen in conjunction with inflammatory necrosis have a normal histologi-

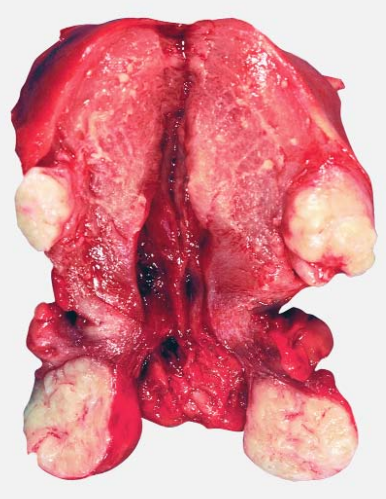

Fig. 4.34 Leiomyomas. The sectioned surface shows typical circumscribed, rubbery, white nodules.

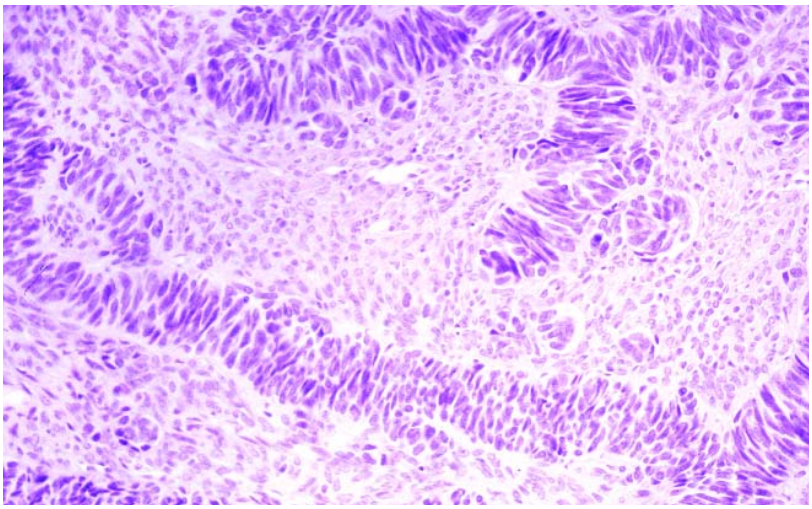

Fig. 4.35 Epithelioid leiomyoma with sex cord-like features. The presence of smooth muscle rules out an endometrial stromal or pure sex cord-like tumour.

cal appearance. The margins of most leiomyomas are histogically circumscribed, but occasional benign tumours demonstrate interdigitation with the surrounding myometrium, which may rarely be extensive.

Immunoprofile

Smooth muscle neoplasms react with antibodies to muscle-specific actin, alpha-smooth muscle actin, desmin and h-caldesmon. Anomalous expression of cytokeratin immunoreactivity is observed frequently both in the myometrium and in smooth muscle tumours, the extent and intensity of reactivity depending on the antibodies used and the fixation of the specimen. Epithelial membrane antigen is negative in smooth muscle tumours. CD10 reactivity may focally be present.

Histological variants

Most subtypes of leiomyoma are chiefly of interest in that they mimic malignancy in one or more aspects.

Mitotically active leiomyoma

Mitotically active leiomyomas occur most often in premenopausal women. They have the typical macroscopic and histological appearances of a leiomyoma with the exception that they usually have 5 or more mitotic figures per 10 high power fields {211,2293}. Occasionally, these smooth muscle tumours contain >15 mitotic figures per 10 high power fields, in which case the term mitotically active leiomyoma with limited experience is used. The clinical evolution is benign, even if the neoplasm is treated by myomectomy. It is imperative that this diagnosis not be used for neoplasms that exhibit moderate to severe nuclear atypia, contain abnormal mitotic figures or demonstrate zones of coagulative tumour cell necrosis.

Cellular leiomyoma

Cellular leiomyoma accounts for less than 5% of leiomyomas, and by definition their cellularity is "significantly" greater than that of the surrounding myometrium {211,2101}. The isolated occurrence of hypercellularity may suggest a diagnosis of leiomyosarcoma, but cellular leiomyomas lack tumour cell necrosis and moderate to severe atypia and have infrequent mitotic figures. A cellular leiomyoma comprised of small cells with scanty cytoplasm can be confused with an endometrial stromal tumour. This problem becomes particularly difficult with what has been termed the highly cellular leiomyoma.

Haemorrhagic cellular leiomyoma and hormone induced changes

A haemorrhagic cellular or "apoplectic" leiomyoma is a form of cellular leiomyoma that is found mainly in women who are taking oral contraceptives or who either are pregnant or are postpartum {1960,2050}. Macroscopic examination reveals multiple stellate haemorrhagic areas. Coagulative tumour cell necrosis is generally absent. Normal mitotic figures are present and are usually confined to a narrow zone of granulation

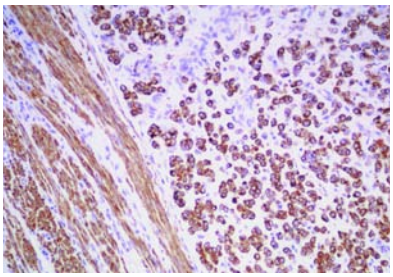

Fig. 4.36 Epithelioid leiomyoma. Both tumour cells on the right and normal myometrium on the left are immunoreactive for desmin.

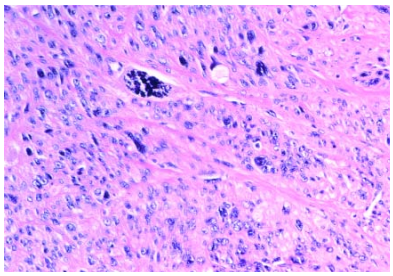

Fig. 4.37 Atypical leiomyoma. This cellular neoplasm exhibits nuclear pleomorphism but no mitotic figures or tumour cell necrosis.

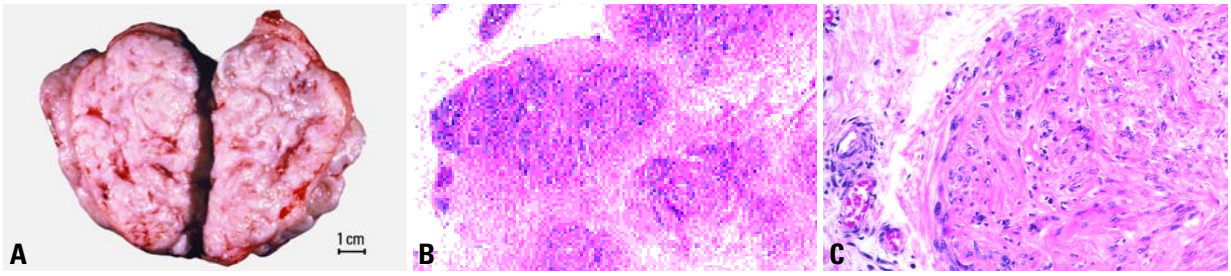

Fig. 4.38 Leiomyoma with perinodular hydropic degeneration. **A** Sectioned surface shows a lobulated neoplasm. **B** Nodules of smooth muscle are delimited by oedematous bands of collagen in which are suspended large calibre vessels. **C** The tumour is composed of uniform spindle-shaped smooth muscle cells.

tissue in relation to areas of haemorrhage.

Epithelioid leiomyoma

Epithelioid leiomyomas are composed of epithelial-like cells {130,1538,2292}. They are yellow or grey and may contain visible areas of haemorrhage and necrosis. They tend to be softer than the usual leiomyoma, and most are solitary. Histologically, the epithelioid cells are round or polygonal, they are arranged in clusters or cords, and their nuclei are round, relatively large and centrally positioned. There are three basic subtypes of epithelioid leiomyoma: leiomyoblastoma, clear cell leiomyoma and plexiform leiomyoma. Mixtures of the various patterns are common, hence the designation "epithelioid" for all of them.

Small tumours without cytological atypia, tumour cell necrosis or an elevated mitotic index can be safely regarded as benign. Plexiform tumourlets invariably are benign. Epithelioid leiomyomas with circumscribed margins, extensive hyalinization and a predominance of clear cells generally are benign. The behaviour of epithelioid leiomyomas with two or more of the following features is not well established:

(1). Large size (greater than 6 cm).

(2). Moderate mitotic activity (2-4 mitotic figures per 10 high power fields),

(3) Moderate to severe cytological atypia

(4) Necrosis

Such tumours should be classified in the uncertain malignant potential category, and careful follow-up is warranted. Neoplasms with 5 or more mitotic figures per 10 high power fields metastasize with sufficient frequency that all should be regarded as epithelioid leiomyosarcoma.

Myxoid leiomyoma

Myxoid leiomyomas are benign smooth muscle tumours in which myxoid material separates the tumour cells {131,1465}. They are soft and translucent. Histologically, abundant amorphous myxoid material is present between the smooth muscle cells. The margins of a myxoid leiomyoma are circumscribed, and neither cytological atypia nor mitotic figures are present.

Atypical leiomyoma (pleomorphic, bizarre or symplastic leiomyoma)

When unassociated with either coagulative tumour cell necrosis or a mitotic index in excess of 10 mitotic figures per 10 high power fields, cytological atypia, even when severe, is an unreliable criterion for identifying clinically malignant uterine smooth muscle tumours. These atypical cells have enlarged hyperchromatic nuclei with prominent chromatin clumping (often smudged). Large cytoplasmic pseudonuclear inclusions often are present. The atypical cells may be distributed throughout the leiomyoma (diffuse) or they may be present focally (possibly, multifocally). When the atypia is at most multifocal and the neoplasm has been completely sampled, such tumours are designated "atypical leiomyoma with minimal, if any, recurrence potential." Such lesions have behaved benignly except for a single reported case.

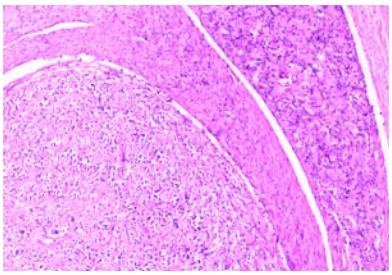

Fig. 4.39 Intravenous leiomyomatosis with atypical (symplastic and epithelioid) features. Note the tumour plugs in myometrial vessels at the lower left and mid-right.

Lipoleiomyoma

Scattered adipocytes in an otherwise typical leiomyoma are a relatively common finding; a leiomyoma that contains a striking number of these cells is called a lipoleiomyoma {2357,2671}.

Growth pattern variants

Growth pattern variants may produce unusual clinical, macroscopic and/or histological features.

Diffuse leiomyomatosis

Diffuse leiomyomatosis is an unusual condition in which numerous small smooth muscle nodules produce symmetrical, sometimes substantial, enlargement of the uterus {518}. The hyperplastic smooth muscle nodules range from histological to 3 cm in size, but most are less than 1 cm in diameter. They are composed of uniform, bland, spindle-shaped smooth muscle cells and are less circumscribed than leiomyomas. The clinical course may be complicated by haemorrhage, but the condition is benign.

Dissecting leiomyoma

Dissecting leiomyoma refers to a benign smooth muscle proliferation with a border marked by the dissection of compressive tongues of smooth muscle into the surrounding myometrium and, occasionally, into the broad ligament and pelvis {2469}. This pattern of infiltration may also be seen in intravenous leiomyomatosis. When oedema and congestion are prominent, a uterine dissecting leiomyoma with extrauterine extension may resemble placental tissue; hence the name cotyledonoid dissecting leiomyoma {2470}.

Intravenous leiomyomatosis

Intravenous leiomyomatosis is a very rare smooth muscle tumour featuring nodular masses and cords of histologically benign smooth muscle growing within venous channels outside the confines of a leiomyoma {1928,2051}. Intravenous leiomyomatosis should be distinguished from the common vascular intrusion within the confines of a leiomyoma. Macroscopically, Intravenous leiomyomatosis consists of a complex, coiled or nodular myometrial growth often with convoluted, worm-like extensions into the uterine veins in the broad ligament or into other pelvic veins. On occasion, the growth extends into the vena cava, and sometimes it extends into the right heart. Histologically, tumour is found within venous channels that are lined by endothelium. The histological appearance is highly variable, even within the same tumour. The cellular composition of some examples of intravenous leiomyomatosis is similar to a leiomyoma, but most contain prominent zones of fibrosis or hyalinization. Smooth muscle cells may be inconspicuous and difficult to identify. Any variant smooth muscle histology, i.e. cellular, atypical, epithelioid or lipoleiomyomatous, may be encountered in intravenous leiomyomatosis.

Benign metastasizing leiomyoma

Benign metastasizing leiomyoma is an ill-defined clinicopathological condition which features "metastatic" histologically benign smooth muscle tumour deposits in the lung, lymph nodes or abdomen that appear to be derived from a benign uterine leiomyoma {798,2923}. Reports of this condition often are difficult to evaluate. Almost all cases of benign metastasizing leiomyoma occur in women who have a history of pelvic surgery. The primary neoplasm, typically removed years before the extrauterine deposits are detected, often has been inadequately studied. Most examples of "benign metastasizing leiomyoma," however, appear to be either a primary benign smooth muscle lesion of the lung in a woman with a history of uterine leiomyoma or pulmonary metastases from a histologically non-informative smooth muscle neoplasm of the uterus. The findings of a recent cytogenetic study were most consistent with a monoclonal origin of both uterine and pulmonary tumours and the interpretation that the pulmonary tumours were metastatic {2923}. The hormone dependence of this proliferation is suggested by the finding of estrogen and progesterone receptors in metastatic deposits and the regression of tumour during pregnancy, after the menopause and after oophorectomy.

Somatic genetics

Uterine leiomyomas often have chromosomal abnormalities detectable by cytogenetic analysis, most frequently involving the *HMGIC* (12q15) and *HMGIY* (6p21) genes {2204a}.

Miscellaneous mesenchymal tumours

Definition

A diverse group of mesenchymal tumours of the uterus that do not show predominantly smooth muscle or stromal differentiation.

Mixed endometrial stromal and smooth muscle tumour

Definition and historical annotation

These neoplasms, previously designated stromomyoma, are composed of an admixture of endometrial stromal and smooth muscle elements {1448,2098, 2550,2860}. Small areas of smooth muscle differentiation are commonly seen in otherwise typical endometrial stromal neoplasms and vice versa, but a minimum of 30% of the minor component is recommended for the designation of mixed endometrial stromal-smooth muscle neoplasm {2098}.

Macroscopy

These neoplasms may have a predominant intramural, submucosal or subserosal location. Some have been described as well circumscribed, whereas others have been multinodular or have had infiltrating margins. Some neoplasms contain areas with a whorled appearance admixed with tan foci that are softer than typical leiomyomas {2098}.

Histopathology

A population of small cells with round to ovoid nuclei and inconspicuous cytoplasm characterizes the endometrial stromal component. Numerous small arterioles are a characteristic feature. The endometrial stromal component usually exhibits minimal cytological atypia, and the mitotic rate is variable. Areas exhibiting sex cord-like differentiation and perivascular hyalinization may be present in the endometrial stromal component {2098}. A case has been described with an associated glandular component consisting of benign endometrial glands surrounded by endometrial stroma {1812}.

The smooth muscle component is usually benign in appearance and is often arranged in nodules with a prominent central area of hyalinization creating a starburst appearance. However, in some cases the smooth muscle component may exhibit any one or a combination of

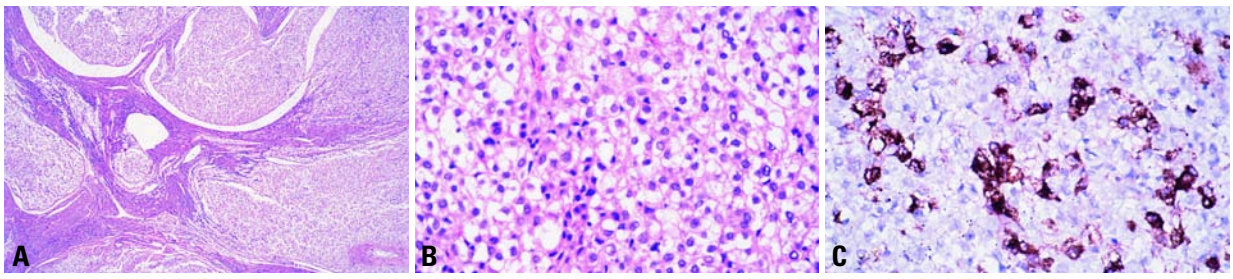

Fig. 4.40 Perivascular epithelioid cell tumour. **A** Low power image shows a "tongue-like" growth pattern, similar to low grade endometrial stromal sarcoma. **B** High power image shows epithelioid cells with clear to pale granular cytoplasm without significant atypia or mitotic figures. **C** HMB-45 stain is positive.

cytological atypia, tumour cell necrosis and conspicuous mitotic activity.
The smooth muscle component is positive for desmin and alpha-smooth muscle actin. However, there may be positivity of the endometrial stromal component with these antibodies, and they cannot be used to reliably distinguish between endometrial stroma and smooth muscle. Studies have shown that markers such as CD10 that stain endometrial stroma but are focally positive in many smooth muscle neoplasms and h-caldesmon and calponin that stain smooth muscle may be of value in distinguishing the two components {44,486,1821,2065}. Sex cord-like areas may exhibit immunohistochemical staining with alpha-inhibin and other sex cord-stromal markers {1521, 1808}.

Prognosis and predictive factors
The limited literature on these rare neoplasms suggests that they should be evaluated and reported in the same way as endometrial stromal neoplasms; i.e. malignant if there is vascular or myometrial invasion, benign otherwise {2098, 2311}.

Perivascular epithelioid cell tumour

Definition
A tumour composed predominantly or exclusively of HMB-45-positive perivascular epithelioid cells with eosinophilic granular cytoplasm. It is a member of a family of lesions thought to be composed, at least in part, of perivascular epithelioid cells. Other members of this group include some forms of angiomyolipoma and lymphangioleiomyomatosis, as well as clear cell 'sugar' tumour.

Synonym
PEComa.

Epidemiology
The age of patients ranged from 40-75 years with a mean of 54 {2998}.

Clinical features
Most patients present with abnormal uterine bleeding.

Macroscopy
A mass is present in the uterine corpus.

Histopathology
The tumours are divided into two groups {2998}. The first demonstrates a tongue-like growth pattern similar to that seen in low grade ESS. These tumours are composed of cells that have abundant clear to eosinophilic pale granular cytoplasm and stain diffusely for HMB-45 and also variably express muscle markers. The second group is composed of epithelioid cells with less prominent clear cell features and a smaller number of cells that are HMB-45 positive. These tumours exhibit more extensive muscle marker expression and a lesser degree of tongue-like growth than the first group.

Genetic susceptibility
One-half of the patients in the second group had pelvic lymph nodes involved by lymphangioleiomyomatosis, and one-fourth had tuberous sclerosis.

Prognosis and predictive factors
Hysterectomy is the usual treatment. Some uterine cases have exhibited aggressive behaviour. Uterine perivascular epithelioid cell tumour should be considered of uncertain malignant potential until long-term outcome data for a larger number of patients become available {2998}.

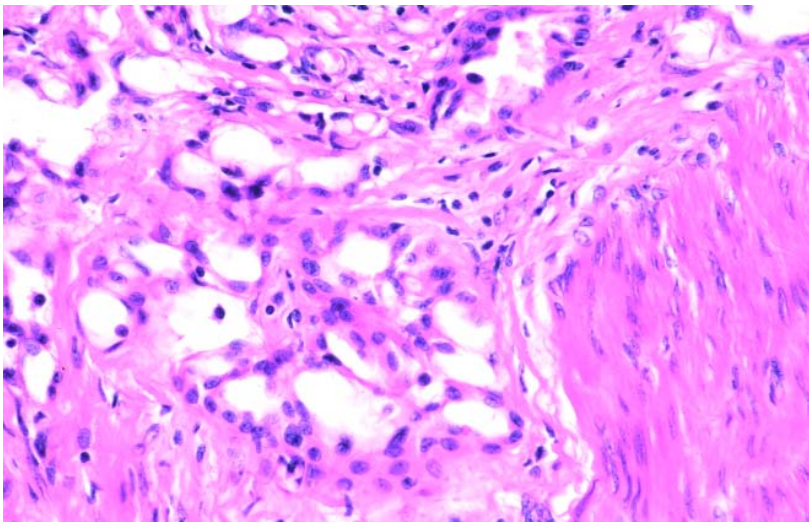

Fig. 4.41 Uterine adenomatoid tumour. The tumour is composed of tubules lined by bland cuboidal cells within the myometrium.

Adenomatoid tumour

Definition
A benign tumour of the uterine serosa and myometrium originating from mesothelium and forming gland-like structures.

ICD-O code 9054/0

Clinical features
They are usually an incidental finding in a hysterectomy specimen. Occasionally, they may be multiple or associated with a similar lesion in the fallopian tube.

Macroscopy
Macroscopically, adenomatoid tumours may resemble leiomyomas, being well circumscribed intramural masses. However, in many cases they are less well defined and of softer consistency. They may occur anywhere within the myometrium but are often located towards the serosal surface.

Histopathology
On low power examination adenomatoid tumour is usually composed of multiple small, often slit-like, interconnecting spaces within the myometrium. On higher power these are composed of tubules lined by a single layer of cells that may be cuboidal or attenuated. The lesion often has an infiltrative appearance. Sometimes the spaces are dilated resulting in a cystic pattern that was confused with lymphangioma in the past, and in other cases a more solid growth pattern is apparent. There is little nuclear atypia or mitotic activity, and there is no stromal desmoplastic response. Occasional tumours may exhibit signet-ring cell histology, focally or diffusely, which may

cause obvious diagnostic problems. Sometimes a papillary pattern may be apparent. Ultrastructural examination shows the long slender microvilli characteristic of mesothelial cells.

Immunoprofile

Immunohistochemical positivity with anti-cytokeratin antibodies and anti-mesothelial antibodies, such as HBME1 and calretinin, is usual. This finding may be useful in the distinction between adenomatoid tumour and lymphangioma. There is no reactivity with Ber-EP4, helping to exclude a carcinoma in those cases that have signet-ring cell morphology {211, 2101,2123}.

Histogenesis

The histogenesis has been debated in the past, but immunohistochemical and ultrastructural studies have shown these neoplasms to be of mesothelial origin. When located within the uterus {654, 2041,2311,2768,2924}, they are probably derived from the serosal mesothelium.

Prognosis and predictive factors

Adenomatoid tumours are invariably benign with no risk of recurrence or metastasis.

Rare mesenchymal tumours

Definition

A variety of mesenchymal tumours, both malignant and benign, occurring within the uterus that are not endometrial stromal, smooth muscle or mesothelial in type. These are rare and are identical histologically to their counterparts arising in more usual sites.

Malignant tumours

In cases of malignancy the neoplasm should be extensively sampled in order to exclude sarcomatous overgrowth in a MMMT or an adenosarcoma. The most common of these neoplasms to arise in the uterus is *rhabdomyosarcoma* {716, 1149,1814,2112}. The latter is usually of embryonal type in young females and of pleomorphic type in the middle aged or elderly. Occasional cases of uterine alveolar rhabdomyosarcoma have also been described {475}. Occasional residual entrapped benign endometrial glands may be present, especially towards the surface of these neoplasms. That finding should not be taken as evidence of an adenosarcoma. Other malignant mesenchymal neoplasms described in the uterus include *malignant fibrous histiocytoma* {1404}, *angiosarcoma* (including the epithelioid variant) {2551,2853}, *liposarcoma* {180}, *osteosarcoma* {784, 1137,1844}, *chondrosarcoma* {1489}, *alveolar soft part sarcoma* {2319}, *Ewing tumour*, *malignant peripheral nerve sheath tumour*, *malignant pigmented neuroectodermal tumour of infancy* {2580} and *peripheral primitive neuroectodermal tumour* {638,1894,2017}. In general, these are all bulky neoplasms, frequently high stage at presentation, and the histology is similar to their counterparts elsewhere. Immunohistochemical studies may assist in establishing a definitive diagnosis.

Haemangiopericytoma has also been described in the uterus, but it is likely that most of the reported cases represent vascular endometrial stromal neoplasms {2693}.

Malignant rhabdoid tumours have also been described {948,1255}. Since a rhabdoid component may rarely be found in an otherwise typical endometrial stromal neoplasm {1813}, it is possible that some rhabdoid tumours represent an unusual histological variant of an endometrial stromal or some other neoplasm. As with other extrarenal rhabdoid tumours, the uterine neoplasm may represent a peculiar histological growth pattern that may be found in a variety of neoplasms; therefore, extensive sampling should be undertaken to exclude a diagnosis of rhabdoid differentiation in another more common neoplasm. Only when other elements are not identified should a diagnosis of uterine malignant rhabdoid tumour be considered.

Benign tumours

Benign tumours include lipoma, haemangioma, lymphangioma and rhabdomyoma {466,686}. Occasional uterine myxomas have been described in Carney syndrome {2654}. Before diagnosing these entities, a lipoleiomyoma should be excluded in the case of lipoma, a vascular leiomyoma in the case of haemangioma, an adenomatoid tumour in the case of lymphangioma and a myxoid smooth muscle neoplasm in the case of myxoma. A single case of postoperative spindle cell nodule of the endometrium that occurred following a uterine curettage has been described {504}.

Mixed epithelial and mesenchymal tumours

W.G. McCluggage
U. Haller
R.J. Kurman
R.A. Kubik-Huch

Definition
Tumours of the uterine corpus composed of an epithelial and a mesenchymal component.

ICD-O codes

Carcinosarcoma	8980/3
Adenosarcoma	8933/3
Carcinofibroma	8934/3
Adenofibroma	9013/0
Adenomyoma	8932/0
Atypical polypoid variant	8932/0

Carcinosarcoma

Definition
A neoplasm composed of an admixture of malignant epithelial and mesenchymal components.

Synonyms
Malignant müllerian mixed tumour, malignant mesodermal mixed tumour, metaplastic carcinoma.
These tumours are still classified as "mixed" by convention, although there is increasing evidence that they are monoclonal and should be considered subsets of endometrial carcinoma.

Epidemiology
Carcinosarcoma is the most common neoplasm of this group {703}. Carcinosarcomas usually occur in elderly postmenopausal women, although occasional cases may occur in younger women and rarely even in young girls. The median age of patients presenting with carcinosarcoma is 65 years, higher than that of patients with leiomyosarcoma {813,1745}. Less than 5% of patients are younger than 50 years.

Aetiology
An occasional case is secondary to prior pelvic irradiation. In recent years an association between long term tamoxifen therapy and the development of uterine carcinosarcoma has been suggested {813,1811,2947}.

Clinical features
Signs and symptoms
Vaginal bleeding is the most frequent presenting symptom of patients with carcinosarcoma, followed by an abdominal mass and pelvic pain {703}. Carcinosarcomas may be polypoid and may prolapse through the cervix to present as an upper vaginal mass. The most important diagnostic method is uterine curettage, but in 25% of cases the diagnosis is made following hysterectomy {2965}.

Imaging
Magnetic resonance imaging (MRI) of women with a typical carcinosarcoma usually shows an enlarged uterus with a widened endometrial cavity and evidence of deep myometrial invasion. Whereas a carcinosarcoma cannot be distinguished from endometrial carcinoma by means of MRI, the presence of a large tumour with extensive myometrial invasion as well as the presence of ovarian or intraperitoneal metastases should raise suspicion {1060,2838}.

Macroscopy
At the time of presentation uterine carcinosarcomas are usually polypoid, bulky, necrotic and haemorrhagic neoplasms that fill the endometrial cavity and deeply invade the myometrium, often extending beyond the uterus. If cartilage or bone forms a significant portion of the neoplasm, the neoplasm may have a hard consistency. Occasionally, these neoplasms may arise within a benign endometrial polyp.

Tumour spread and staging
Intra-abdominal and retroperitoneal nodal metastases are frequent {1745}.

Histopathology
The malignant epithelial element is usually glandular, although rarely it may be non-glandular, most commonly consisting of squamous or undifferentiated carcinoma. The glandular component may be either endometrioid or non-endometrioid, such as serous or clear cell in type.
The sarcomatous elements may be either homologous or heterologous. In homologous neoplasms the mesenchymal component usually consists of undifferentiated sarcoma, leiomyosarcoma or endometrial stromal sarcoma and is usually, although not always, high grade. Heterologous mesenchymal elements most commonly consist of malignant cartilage or malignant skeletal muscle in the

Table 4.07
Nomenclature of mixed epithelial and mesenchymal tumours defined by phenotypes of epithelial and mesenchymal components.

	Benign epithelium	Malignant epithelium
Benign mesenchyme	Adenofibroma Adenomyoma (including atypical)	Carcinofibroma
Malignant mesenchyme	Adenosarcoma	Carcinosarcoma

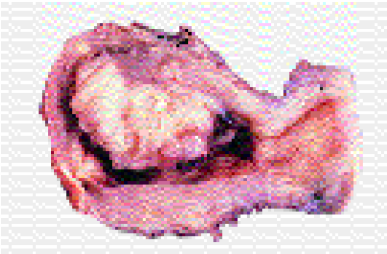

Fig. 4.42 Carcinosarcoma. Sagittal section of the uterus shows a solid, polypoid tumour within the fundus.

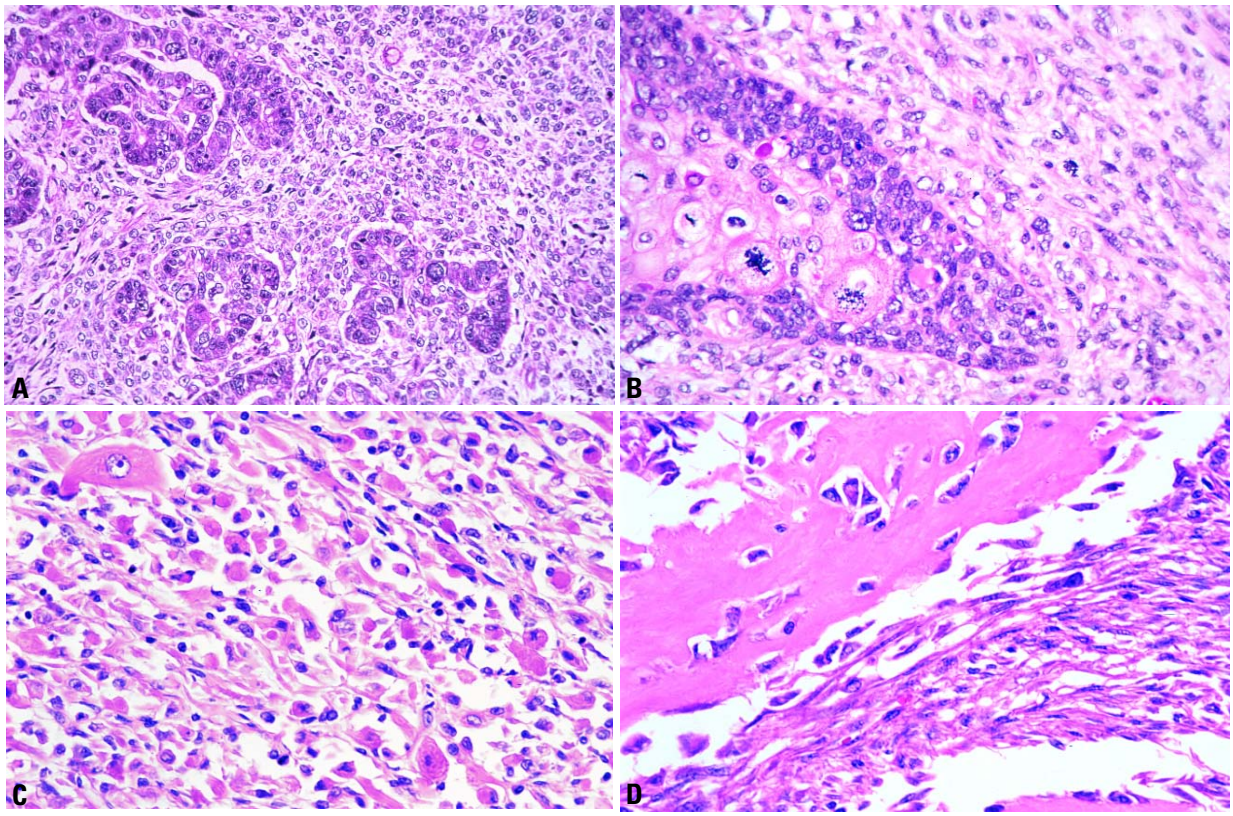

Fig. 4.43 Carcinosarcoma. **A** A biphasic tumour is composed of poorly differentiated malignant glands and sarcomatous elements. **B** A biphasic tumour is composed of a solid aggregate of malignant epithelium with central squamous differentiation and sarcomatous elements. Mitoses are frequent. **C** High power image shows a mesenchymal component resembling rhabdomyosarcoma. **D** High power image shows a mesenchymal component resembling osteosarcoma.

form of rhabdomyoblasts, although other elements such as osteosarcoma and liposarcoma may rarely occur.

In general, both carcinomatous and sarcomatous elements are easily identifiable, although in some cases one or other element may form a minor component that may be only identified following extensive sampling of the neoplasm. Any uterine neoplasm composed of high grade sarcoma, especially when heterologous elements are present, should be extensively sampled in order to rule out a carcinosarcoma or sarcomatous overgrowth in an adenosarcoma. In most instances the two elements are sharply demarcated, but in some they appear to merge with transitional forms between the two elements. Eosinophilic hyaline inclusions are commonly seen, especially in the sarcomatous elements {2359}.

Occasionally, a carcinosarcoma may be identified in an otherwise benign endometrial polyp. A uterine carcinosarcoma with a component of yolk sac tumour has been described in a patient with an elevated serum alpha-fetoprotein level {2665}. Occasional tumours with a rhabdoid phenotype {190} or a malignant neuroectodermal component {931} have also been described. Occasional uterine carcinosarcomas of mesonephric origin have been reported {3171}. Other unusual histological features include melanocytic {77} and neuroendocrine differentiation {537}.

Immunoprofile

In general, the epithelial elements are immunoreactive with anti-cytokeratin antibodies and the mesenchymal elements with vimentin. The mesenchymal elements often show focal staining with anti-cytokeratin antibodies supporting an epithelial origin of this component. The usual concordance of TP53 stains between the epithelial and mesenchymal components supports a common monoclonal origin for both elements {1796, 2827}. Desmin, myoD1, myoglobin and sarcomeric actin staining may highlight a rhabdomyosarcomatous mesenchymal component. Cartilaginous elements usually stain with S-100 protein.

Histogenesis

It should be noted that clinical, immunohistochemical, ultrastructural and molecular studies have all suggested that carcinosarcomas are really metaplastic carcinomas in which the mesenchymal component retains at least some epithelial features in the vast majority of cases {1809}. Though still classified as "mixed" by convention, these tumours are perhaps better considered subsets of endometrial carcinoma and certainly should not be grouped histogenetically or clinically with uterine sarcomas {1810}. On the other hand, the tumours other than carcinosarcoma in this group are considered to be true mixed tumours.

Prognosis and predictive factors

The clinical course of uterine carcinosarcoma is generally aggressive with a poor overall prognosis, considerably worse than that of a poorly differentiated endometrial carcinoma. The pattern of spread is generally similar to that of high grade endometrial carcinoma, and deep myometrial invasion and extrauterine spread are often observed at the time of presentation. The clinical staging is the same as that for endometrial carcinoma. Some studies have found no independent prognostic factors other than tumour stage, whereas others have found that the characteristics of the epithelial component such as high grade carcinoma, including serous or clear cell components, are associated with a worse prognosis {2692}. Previously, it was thought that the presence of heterologous mesenchymal components indicated a worse outcome; however, recent larger studies have suggested that the histological features of the mesenchymal component bear no relationship to the overall prognosis {2692}.

The biological behaviour of uterine carcinosarcomas is more akin to high grade endometrial carcinomas than to uterine sarcomas {282,2692}. Carcinosarcomas primarily spread via lymphatics, whereas pure uterine sarcomas commonly spread haematogenously. Detailed studies of uterine carcinosarcoma have shown that metastatic foci and foci within lymphatic or vascular spaces are commonly carcinomatous with pure sarcomatous elements being rare {282,2692,2767}.

Although the tumour stage is the most important prognostic factor, recurrences may be encountered even in those rare cases lacking myometrial infiltration. However, tumours confined to an otherwise benign polyp appear to have a somewhat better outcome {188,1382}.

Adenosarcoma

Definition

Adenosarcoma is a biphasic neoplasm containing a benign epithelial component and a sarcomatous mesenchymal component.

Epidemiology

Adenosarcoma occurs in women of all ages, ranging from 15-90 years with a median age at diagnosis of 58. Adenosarcomas have been reported in women undergoing tamoxifen therapy for breast cancer {509} and occasionally after prior pelvic radiation {515}. There is no association of adenosarcoma with obesity or hypertension.

Clinical features

Typical symptoms of patients with adenosarcoma are abnormal vaginal bleeding, an enlarged uterus and tissue protruding from the external os. The tumour may not be correctly diagnosed as adenosarcoma until re-excision of a recurrent polypoid lesion {515}.

Macroscopy

Adenosarcomas typically grow as exophytic polypoid masses that extend into the uterine cavity. Rarely, they may arise in the myometrium, presumably from adenomyosis. Although the tumour is usually a single polypoid mass, it sometimes may present as multiple papillary masses. On sectioning, the surface is tan brown with foci of haemorrhage and necrosis. Small cysts are frequently present. Most adenosarcomas do not invade the myometrium.

Histopathology

Under low magnification a leaf-like pattern closely resembling phyllodes tumour of the breast is observed. Isolated glands, often dilated and compressed into thin slits, are dispersed throughout the mesenchymal component. Characte- ristically, there is stromal condensation surrounding the glands and clefts. It is in these areas where the greatest degree of stromal atypia and mitotic activity is present. By definition the epithelium is benign and may show focal metaplastic changes. The mesenchymal component of an adenosarcoma is generally a low grade homologous stromal sarcoma containing varying amounts of fibrous tissue and smooth muscle. Mesenchymal mitotic figures, usually stated to be more than one per 10 high power fields, are required in the hypercellular cuffs. Cytological atypia is typically only mild, but is occasionally moderate. Sex cord-like components resembling those in endometrial stromal sarcomas are found in less than 10% of adenosarcomas. Heterologous components consisting of striated muscle (most commonly), cartilage, fat and other components are present in approximately 10-15% of tumours The diagnosis of sarcomatous overgrowth is made if the pure

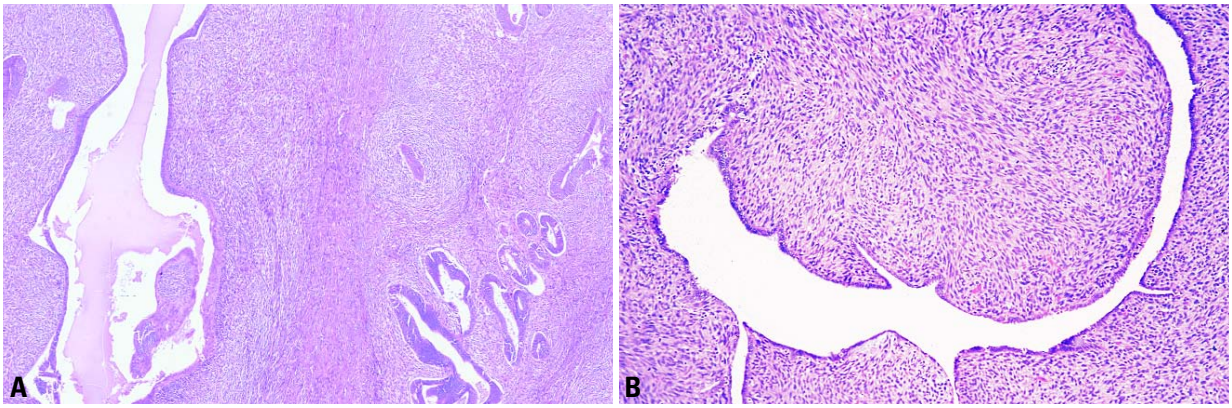

Fig. 4.44 Adenosarcoma. **A** The tumour is composed of tubular and convoluted, cleft-like glands of endometrioid type surrounded by a cuff of cellular mesenchyme. **B** A polypoid structure compresses a glandular lumen producing a leaf-like pattern similar to that of a mammary phyllodes tumour. The epithelial component is cytologically bland, and the mesenchymal component is cellular and fibromatous without significant nuclear atypia but contained abundant mitoses.

sarcomatous component, usually of high grade, occupies 25% or more of the total tumour volume.

Immunoprofile
As might be expected, the epithelial component reacts with a broad spectrum of antibodies to cytokeratins. The mesenchymal component usually reacts focally with antibodies to CD10. Variable degrees of staining for smooth muscle markers, desmin and caldesmon, can also be observed.

Differential diagnosis
The differential diagnosis includes adenofibroma and in children sarcoma botryoides (embryonal rhabdomyosarcoma).

Prognosis and predictive factors
Adenosarcoma is considered a low grade neoplasm but recurs in approximately 25-40% of cases, typically in the pelvis or vagina, and distant metastasis has been reported in 5% of cases {515}. The metastases almost always are composed of a sarcomatous element only, but rarely epithelium has been reported. Factors in the primary tumour that are predictive of a poor outcome are extrauterine spread, deep myometrial invasion into the outer half of the myometrium and sarcomatous overgrowth. Vascular invasion is usually not identified but, if present, is a poor risk factor. Rhabdomyosarcomatous differentiation was an adverse prognostic factor in one series {1388}. There appears to be no correlation between the prognosis and the level of mitotic activity. Long-term follow-up is necessary because recurrences may manifest after many years. Most tumour deaths occur more than five years after the diagnosis.

Carcinofibroma

Definition
A neoplasm composed of an admixture of a malignant epithelial element and a benign mesenchymal component.

Epidemiology
These are extremely uncommon neoplasms with few cases reported in the literature {1286,2228,2916}.

Histopathology
In one case the epithelial component was clear cell in type {2228}. The mesenchymal component is usually fibrous, although occasional cases with a heterologous mesenchymal component have been described and have been designated as carcinomesenchymoma {459}.

Prognosis and predictive factors
The behaviour is not well established since so few cases have been reported but would be expected to depend on the stage, depth of myometrial invasion and histological subtype of the epithelial component.

Adenofibroma

Definition
A biphasic uterine neoplasm composed of benign epithelial and mesenchymal components.

Epidemiology
Uterine adenofibroma is an uncommon neoplasm, much less frequent than adenosarcoma, which occurs most often in postmenopausal patients but also in younger women. {3245}. Occasional cases have been associated with tamoxifen therapy {1258}.

Macroscopy
Adenofibromas usually present as polypoid lesions, commonly have a fibrous consistency on sectioning, and sometimes contain dilated cystic spaces.

Histopathology
Adenofibromas have a papillary or club-like growth pattern. They are composed of benign epithelial and mesenchymal components, the epithelial component forming a lining on the underlying mesenchymal core. Cleft-like spaces are often present. The epithelial component may be endometrioid or ciliated in type but often is non-descript cuboidal or columnar. Rarely, there are foci of squamous metaplasia. The mesenchyme is usually of a non-specific fibroblastic type, although rarely it may contain endometrial stromal or smooth muscle components. Stromal atypia, mitotic activity and periglandular cuffing are absent or inconspicuous. Rarely, adipose tissue or skeletal muscle components are present, and such lesions have been designated lipoadenofibroma or adenomyofibroma {1239,2711}.

Differential diagnosis
If there is a stromal mitotic count of >1 mitosis per 10 high power fields, marked stromal hypercellularity with periglandular cuffing and/or more than mild stromal atypia, a diagnosis of low grade adenosarcoma should be made.

Prognosis and predictive factors
Adenofibromas are benign lesions, although they may recur following "polypectomy" {2625}. Occasional

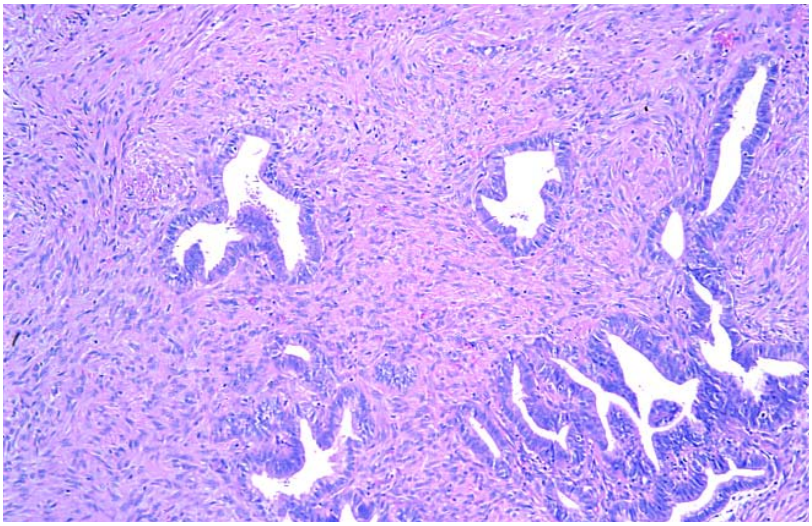

Fig. 4.45 Atypical polypoid adenomyoma. This polypoid lesion shows a biphasic epithelial and stromal proliferation. The glandular component consists of endometrioid glands with a variable degree of complexity, whereas the mesenchymal component is myofibromatous and cytologically bland.

tumours may superficially invade the myometrium, but metastases have not been reported. Invasion of myometrial veins has also been described {514}. Occasional cases have been focally involved by adenocarcinoma, but the association is probably incidental {1873}.

Adenomyoma including atypical polypoid adenomyoma

Definition

A lesion composed of benign epithelial (usually endometrial glands) and mesenchymal components in which the mesenchymal component is fibromyomatous Atypical polypoid adenomyoma is a variant of adenomyoma in which the glandular component exhibits architectural complexity with or without cytological atypia.

Epidemiology

Adenomyoma may occur at any age, whereas atypical polypoid adenomyoma characteristically occurs in premenopausal women {1690,1801,3228}.

Macroscopy

Adenomyomas and atypical polypoid adenomyomas usually are polypoid submucosal lesions but may rarely be intramural or subserosal {1002}. They have a firm sectioned surface. Atypical polypoid adenomyoma usually involves the lower uterine segment or upper endocervix.

Histopathology

Adenomyoma is composed of an admixture of benign endometrial glands (there may be minor foci of tubal, mucinous or squamous epithelium) with minimal cytological atypia and architectural complexity embedded in a benign fibromyomatous mesenchyme. Often endometrial type stroma surrounds the endometrial glandular component, and the former is in turn surrounded by smooth muscle {1002}.

Atypical polypoid adenomyoma

In atypical polypoid adenomyoma the glands characteristically show marked architectural complexity; there is no endometrial type stroma around the distorted glands. There is often also cytological atypia that varies from mild to marked. Foci may be present that architecturally resemble well differentiated adenocarcinoma, and such tumours have been designated "atypical polypoid adenomyoma of low malignant potential" {1690}. Extensive squamous or morular metaplasia of the glandular elements, with or without central necrosis, is a common finding. The mesenchymal component is composed of swirling and interlacing fascicles of benign smooth muscle.

Differential diagnosis

It should be noted that many simple endometrial polyps contain a minor component of smooth muscle within the stroma; however, this finding alone is not sufficient for the diagnosis of adenomyoma. The designation adenomyoma has also been used for a localized adenomyosis that forms a discrete mass, but such usage is confusing and not recommended.

Differentiation from a well differentiated endometrioid adenocarcinoma invading the myometrium may be difficult, especially on a curettage or biopsy specimen. However, the usual lack of pronounced cellular atypia and the absence of a stromal desmoplastic response would be against a diagnosis of adenocarcinoma. Additional features against a diagnosis of carcinoma are the usual youth of the patient and the presence of normal endometrial fragments in the sample.

Genetic susceptibility

Atypical polypoid adenomyomas may occur in women with Turner syndrome {517}.

Prognosis and predictive factors

Adenomyoma is generally cured by simple polypectomy, but if associated with myometrial adenomyosis, symptoms may persist. Atypical polypoid adenomyoma may recur, especially following incomplete removal. In addition, superficial myometrial infiltration is often identified in hysterectomy specimens, a finding that may be more common in those cases with marked glandular architectural complexity {1690}. A small number of cases are associated with an underlying endometrioid adenocarcinoma with a transition zone between the two components {1882, 2813}.

Gestational trophoblastic disease

D.R. Genest
R.S. Berkowitz
R.A. Fisher
E.S. Newlands
M. Fehr

Definition

A heterogeneous group of gestational and neoplastic conditions arising from trophoblast, including molar gestations and trophoblastic tumours.

Epidemiology

Gestational trophoblastic disease (GTD) varies widely among various populations with figures as high as 1 in 120 pregnancies in some areas of Asia and South America compared to 0.6-1.1 per 1000 in the United States {1162}. The incidence of hydatidiform moles is greater in women older than 40 years {161} and is also increased in those younger than 20 years. Patients who have had prior GTD are more at risk of having a second GTD after subsequent pregnancies. Other risk factors include: a diet low in vitamin A, lower socioeconomic status and blood group A women married to group 0 men {161,162,244,363}.

Aetiology

Hydatiform moles arise from abnormal conceptions. Partial moles result from diandric triploidy, whereas complete moles result from diandry (fertilization of an empty ovum). Up to 50% of choriocarcinomas and 15% of placental site trophoblastic tumours follow complete moles.

Table 4.08
The U.S. National Institutes of Health staging classification for gestational trophoblastic disease (GTD).

- I Benign GTD
  - A. Complete hydatidiform mole
  - B. Partial hydatidiform mole
- II Malignant GTD
  - A. Non-metastatic GTD
  - B. Metastatic GTD
    - 1. Good prognosis: absence of any risk factor
    - 2. Poor prognosis: presence of any risk factor
      - a. Duration of GTD >4months
      - b. Pre-therapy serum β-hCG>40,000 mIU/mL
      - c. Brain or liver metastasis
      - d. GTD after term gestation
      - e. Failed prior chemotherapy for GTD

Clinical features

Signs and symptoms

A complete molar pregnancy usually presents with first trimester bleeding, a uterus larger than expected for gestational age and the absence of fetal parts on ultrasound in association with a markedly elevated beta-human chorionic gonadotropin (β-hCG) level {568}. Other signs include hyperemesis, toxaemia during the first or second trimester, theca lutein cysts and hyperthyroidism. Patients with partial molar gestations usually present as spontaneous abortions, sometimes with increased β-hCG levels. GTD should always be considered when a patient has continued vaginal bleeding following delivery or abortion.

Imaging

A characteristic pattern of multiple vesicles (snowstorm pattern) is commonly seen with complete molar pregnancy. The diagnosis of partial molar pregnancy by ultrasonography is more difficult.

Tumour spread and staging

Choriocarcinoma spreads haematogenously and may involve the lung (57-80%), vagina (30%), pelvis (20%), brain (17%), and liver (10%) {168,243}. Since β-hCG titres accurately reflect the clinical disease, histological verification is not required for diagnosis. Staging should be based on history, clinical examination and appropriate laboratory and radiological studies.

Metastatic GTD is also categorized by the WHO scoring system as low, medium, and high risk {51,2976}. The individual scores for each prognostic factor are added together to obtain a total score. A total prognostic score less than or equal to 4 is considered low risk, a total score of 5-7 is considered middle risk, and a total score of 8 or greater is considered high risk. (See TNM and FIGO classification of gestational trophoblastic tumours at the beginning of the chapter).

Somatic genetics

Overexpression of TP53 protein may be associated with more aggressive behaviour in gestational trophoblastic disease since it is more commonly observed in complete moles and choriocarcinoma {937,1616,2307}, but *TP53* mutations are uncommon {471}. Overexpression of the *p21* gene has also been detected in complete moles and choriocarcinoma {469}. No correlation between p21 and TP53 expression has been detected in gestational trophoblastic disease.

Both complete mole and choriocarcinoma exhibit overexpression of several growth factors including c-Myc, epidermal growth factors receptor (EGFR), c-erbB-2, Rb, mdm2, and bcl-2 as compared to normal placenta and partial mole {938,2966}. Expression of c-fms protein does not differ between normal placenta and gestational trophoblastic diseases {938}. In one study strong immunostaining of c-erbB-3 and epidermal growth factor receptor in extravillous trophoblast of complete mole was significantly correlated with the development of persistent gestational trophoblastic tumour {2966}. The molecular pathogenesis of gestational trophoblastic diseases may involve these and potentially other growth-regulatory factors.

Prognosis and predictive factors

Major adverse prognostic variables for GTD are:

(1) Age >39
(2) Prior term pregnancy
(3) Interval from antecedent pregnancy of >12 months
(4) β-hCG >105 IU/litre
(5) Tumour mass >5cm
(6) Disease in liver and brain
(7) Failure of 2 or more prior chemotherapies

The above factors are included in a prognostic score (see the TNM and FIGO classification of gestational trophoblastic tumours at the beginning of the chapter). The patients are separated into low risk and high risk groups for different treatments {1123,3111}.

The prognosis of patients with low risk disease is very close to 100% survival, whilst patients with high risk disease have a survival of 85-95%, depending on the number of patients with ultra high riskdisease in the patient population.

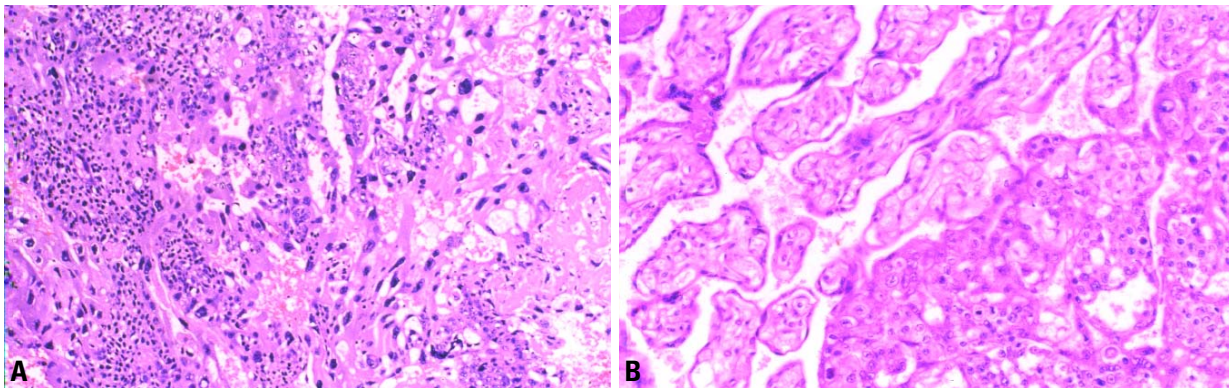

Fig. 4.46 **A** Gestational choriocarcinoma. Note the plexiform pattern with triphasic differentiation into cytotrophoblast, syncytiotrophoblast and intermediate trophoblast and marked cytological atypia. **B** Intraplacental choriocarcinoma. There is a distinct interface between malignant biphasic trophoblast in the maternal intervillous space seen on the lower right and mature chorionic villi on the left.

Trophoblastic tumours

Definition

Neoplasms derived from trophoblast.

ICD-O codes

Choriocarcinoma	9100/3
Placental site trophoblastic tumour	9104/1
Epithelioid trophoblastic tumour	9105/3

Gestational choriocarcinoma

Definition

A malignant neoplasm composed of large sheets of biphasic, markedly atypical trophoblast without chorionic villi.

Clinical features

Gestational choriocarcinoma may occur subsequent to a molar pregnancy (50% of instances), an abortion (25%), a normal gestation (22.5%) or an ectopic pregnancy (2.5%) {1203}.

In rare cases an intraplacental choriocarcinoma is diagnosed immediately following pregnancy from placental pathological examination {343,722,907,1923}.

Histopathology

Choriocarcinoma consists of an admixture of syncytiotrophoblast, cytotrophoblast and intermediate trophoblast as single cells and clusters of cells with prominent haemorrhage, necrosis and vascular invasion {775a,1593,1801a, 1802a,2011,2024a,2077a}. Choriocarcinoma does not possess tumour stroma or vessels; correspondingly, the diagnostic viable tumour is located at the periphery of haemorrhagic foci.

Extraordinarily, choriocarcinomas have developed and been diagnosed as intraplacental tumours {112,343,722,907, 1562,1923,2103}.

Immunoprofile

All trophoblastic cell types are strongly immunoreactive for cytokeratins {640}. In addition, the syncytiotrophoblast is strongly immunoreactive for β-hCG and weakly immunoreactive for human placental lactogen (hPL); intermediate trophoblast shows the opposite immunoprofile {935}.

Differential diagnosis

The differential diagnosis of choriocarcinoma in endometrial curettings includes previllous trophoblast from an early gestation, persistent molar tissue following hydatidiform mole, placental site trophoblastic tumour, epithelioid tro-

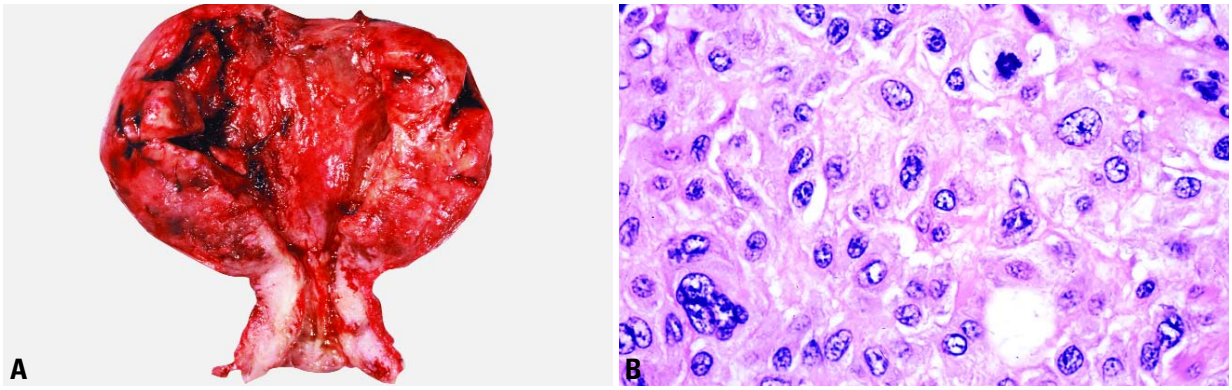

Fig. 4.47 **A** Placental site trophoblastic tumour. Coronal section shows the neoplasm diffusely infiltrating the uterine wall. **B** Tumour cells show marked cytological atypia and numerous mitotic figures.

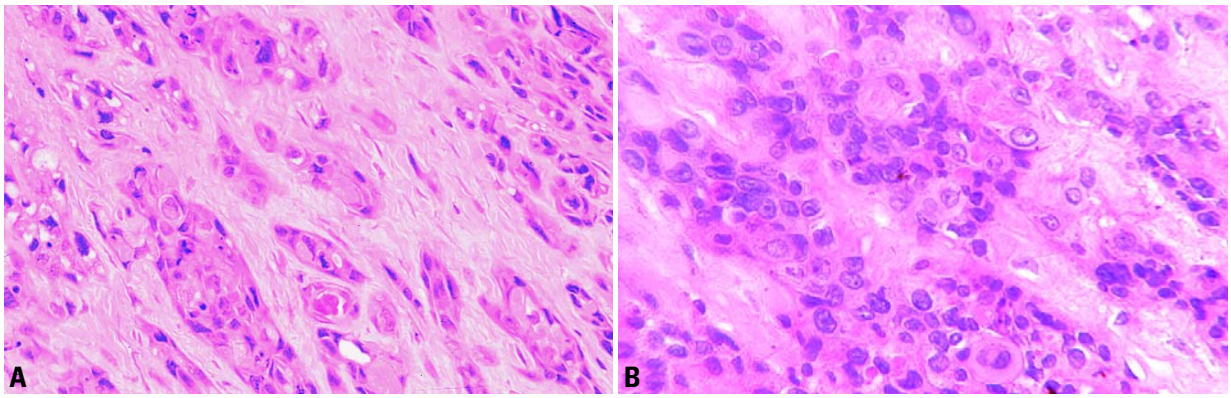

Fig. 4.48 Epithelioid trophoblastic tumour. **A** Neoplastic aggregates are better defined than in placental site trophoblastic tumour and may resemble carcinoma. **B** Groups of tumour cells, occasionally with clear cytoplasm, are separated by a hyaline stroma.

phoblastic tumour and undifferentiated carcinoma.

Somatic genetics
Recent studies using cDNA microarray analysis have demonstrated decreased expression of heat shock protein-27 in choriocarcinoma, a finding which has been associated with chemotherapy responsiveness in other cancers {3014}.

Placental site trophoblastic tumour

Definition
A monophasic neoplasm composed of intermediate trophoblast and cytotrophoblast without a significant component of syncytiotrophoblast.

Histopathology
The tumour cells are medium to large sized and mononuclear or multinucleated with mild to marked nuclear atypia, prominent nucleoli, eosinophilic to clear cytoplasm, scattered mitoses and occasional intranuclear inclusions {746,747, 842,861,933,1018,1019,1177,1237, 1511,1540,1543,1589,2967,3202,3227}. They permeate the myometrium and vessels in a manner reminiscent of the implantation site trophoblast.

Differential diagnosis
The differential diagnosis of placental site trophoblastic tumour includes placental site nodule, exaggerated implantation site, epithelioid leiomyosarcoma, epithelioid trophoblastic tumour and poorly differentiated carcinoma. Extensive sampling and immunohistochemistry for keratin, β-hCG and hPL are helpful in distinguishing among the above lesions {2658,2659}.

Somatic genetics
A Y-chromosomal locus and/or new (paternal) alleles not present in adjacent normal uterine tissue was demonstrated in all cases of placental site trophoblastic tumour studied confirming the placental origin of these neoplasms {2747}.

Prognosis and predictive factors
Placental site trophoblastic tumours are rare, and their biological behaviour is variable. The major prognostic variable is a long interval from the last known antecedent pregnancy. All patient deaths from placental site trophoblastic tumour in the Charing Cross series occurred when the interval from the last known pregnancy was greater than 4 years. An elevated mitotic index predicts a poor outcome {842}.

Epithelioid trophoblastic tumour

Definition
A tumour composed of a monomorphic population of intermediate trophoblastic cells closely resembling those of the chorion laeve (membranous chorion).

Histopathology
The epithelioid trophoblastic tumour is a relatively uncommon, recently described neoplasm that differs from the placental site trophoblastic tumour in that the tumour cells of the epithelioid trophoblastic tumour are smaller and less pleomorphic and grow in a nodular as opposed to a diffusely infiltrative pattern. Because they are frequently found in the cervix, they may be confused with hyalinizing squamous cell carcinomas. Epithelioid trophoblastic tumours are focally immunoreactive for placental-like alkaline phosphatase (PLAP) and hPL but strongly and diffusely immunoreactive for E-cadherin and epidermal growth factor receptor {2658}.

Somatic genetics
A Y-chromosomal locus and/or new (paternal) alleles not present in adjacent normal uterine tissue was demonstrated in all cases of epithelioid trophoblastic tumour studied confirming the placental origin of this neoplasm {2747}.

Prognosis and predictive factors
Based on available data, the behaviour of epithelioid trophoblastic tumour resembles that of placental site trophoblastic tumour.

Hydatidiform mole

Definition
An abnormal placenta with villous hydrops and variable degrees of trophoblastic proliferation.

ICD-O codes

Hydatidiform mole, NOS	9100/0
Complete	9100/0
Partial	9103/0
Invasive	9100/1

Complete hydatidiform mole

Definition
A hydatidiform mole involving most of the

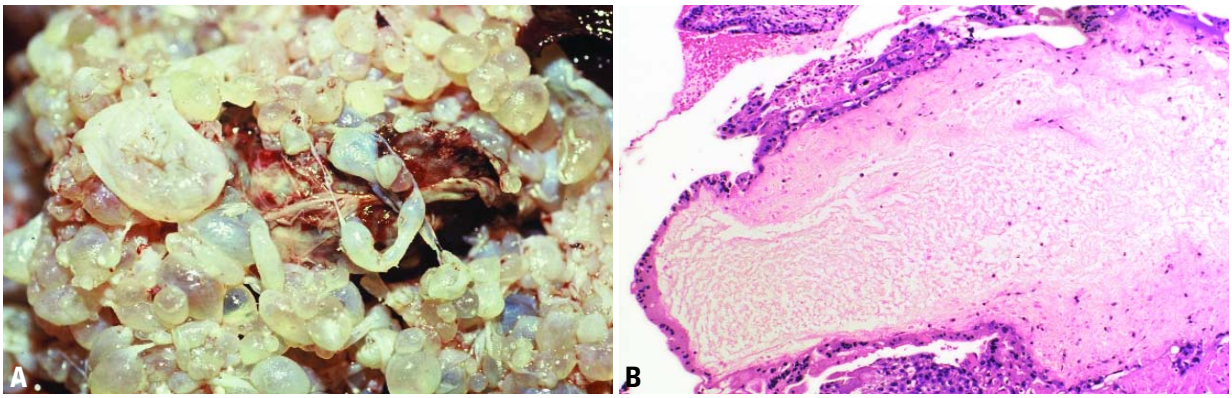

Fig. 4.49 **A** Classic complete hydatidiform mole. Note the dilated chorionic villi with the typical "bunch of grapes" appearance. **B** This molar villus is cavitated with circumferential trophoblastic hyperplasia and atypia.

chorionic villi and typically having a diploid karyotype.

Histopathology

The villous hydrops of a complete mole is characterized by extensive cavitation. The trophoblastic proliferation differs from normal villi by its circumferential distribution, hyperplasia and cytological atypia {978,1203}. Intermediate trophoblast of the molar implantation site characteristically displays marked cytologic atypia {1901}. A gestational sac, amnion, umbilical cord and fetal tissue are not found {481}. It has recently been suggested that villous stromal nuclear negative staining for the paternally imprinted gene product p57 may be diagnostically useful for confirming the diagnosis of a complete mole {425}. The extent of trophoblastic atypia and hyperplasia do not correlate with the behaviour in complete mole {776,978}.

In the past most complete hydatidiform moles were diagnosed early in the second trimester at an average gestational age of 14 weeks {1924}. Currently, with the widespread use of routine ultrasonography in pregnancy, complete moles are diagnosed between 8 and 12 weeks of gestational age {1924}. Moles diagnosed at this "early" stage differ histologically from moles diagnosed in the second trimester {1426,1924}. Although villous cavitation may be minimal in an "early" mole, other characteristic villous stromal features are present, including hypercellularity and a myxoid basophilic stroma (resembling that of a myxoid fibroadenoma). In addition, unusual villous shapes with complex bulbous protrusions ("cauliflower-like" villi) and trophoblastic atypia are present.

Somatic genetics

Complete and partial molar pregnancies have distinctly different cytogenetic origins. Complete moles generally have a 46,XX karyotype, and the molar chromosomes are completely of paternal origin {1385}. Most complete moles appear to arise from an anuclear empty ovum fertilized by a (23X) haploid sperm that then replicates its own chromosomes {3172}. Whereas most complete moles have a 46,XX chromosomal pattern, about 10% of complete moles have a 46,XY karyotype {2197}. The 46,XY complete mole arises from fertilization of an anuclear empty egg by two sperm. While all chromosomes in a complete mole are entirely of paternal

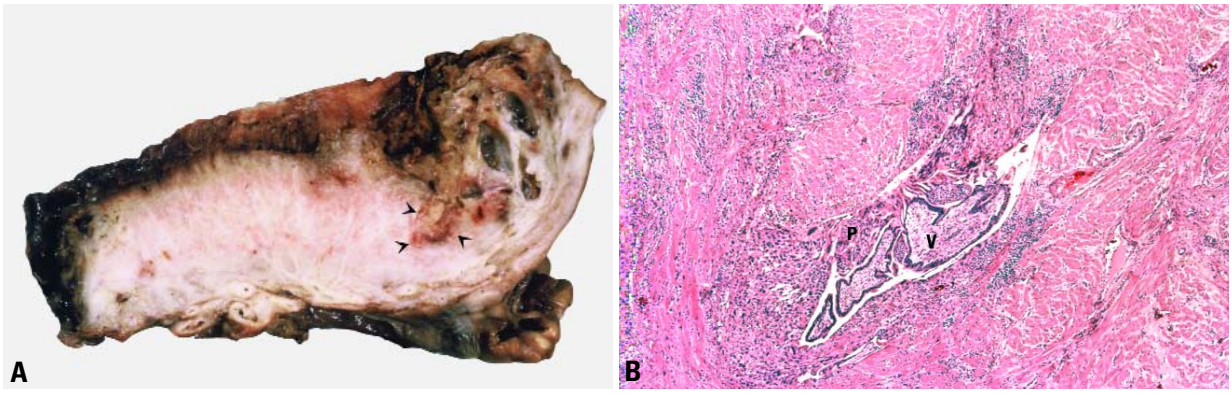

Fig. 4.50 Invasive complete hydatidiform mole. **A** Sectioned surface shows dilated villi and invasion of the myometrium (arrowheads). **B** Note the molar villus (V) within a myometrial vein showing a fibroedematous core surrounded by hyperplastic trophoblastic proliferation (P).

origin, the mitochondrial DNA is of maternal origin {146}.

Partial hydatidiform mole

Definition
A hydatidiform mole having two populations of chorionic villi, one of normal size and the other hydropic, with focal trophoblastic proliferation. The lesion typically has a triploid karyotype.

Histopathology
Histologically, partial moles are characterized by the concurrence of four features {977,1319,1593,2170,2348,2365, 2828,2829}:
(1) Two populations of villi, one hydropic and one "normal";
(2) Minimal trophoblastic hyperplasia involving syncytiotrophoblast.
(3) Enlarged cavitated villi.
(4) Other villi with scalloped borders, often containing trophoblastic inclusions.
Stromal blood vessels often contain nucleated fetal red blood cells; other evidence suggesting fetal development is common, including portions of the chorionic sac wall, amnion, umbilical cord and embryonic/fetal tissue.
The differential diagnosis of partial hydatidiform mole includes:
(1) Complete mole.
(2) Hydropic abortus.
(3) Several rare sporadic genetic syndromes with focal placental hydrops and a fetus, such as the Beckwith-Weidemann syndrome {1558} and placental angiomatous malformation {2522}, which collectively have been termed "placental mesenchymal dysplasia" {1337}.
In instances in which the histological diagnosis is uncertain, cytogenetic analysis or flow cytometry may be of assistance {549,882,933,1485,1557-1563,2170}.

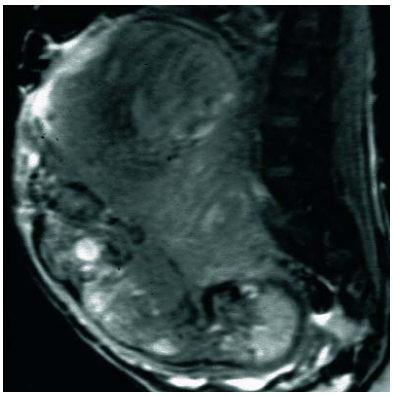

Fig. 4.51 MRI of hydatidiform mole adjacent to a normal fetus in a twin pregnancy.

Somatic genetics
In contrast to complete moles, partial moles generally have a triploid karyotype that results from fertilization of an apparently normal ovum by two sperm {2828}. The reported incidence of triploidy in partial moles varies from 90-93% respectively {1560,1593}. When fetuses are identified with partial moles, they usually have stigmata of triploidy including multiple congenital anomalies and growth retardation.

Invasive hydatidiform mole

Definition
Invasive hydatidiform mole is defined as villi of hydatidiform mole within the myometrium or its vascular spaces.

Histopathology
Most invasive moles follow complete hydatidiform mole and have the characteristic histological appearance of that lesion. Rare examples of invasive partial mole have also been described {33, 942,1065,2841,3131}. A hysterectomy is usually required for the histological diagnosis.

Metastatic hydatidiform mole

Definition
Metastatic hydatidiform mole is defined as extrauterine molar villi within blood vessels or tissues, most commonly the vagina or the lung.

Non-neoplastic, non-molar trophoblastic lesions

Placental site nodule or plaque

The placental site nodule or plaque {1260,3203} is a well circumscribed lesion with abundant hyalinized stroma infiltrated by scattered, degenerated-appearing intermediate trophoblastic cells; these cells show no significant cytological atypia, but rare mitoses may be present.

Exaggerated placental site

The exaggerated implantation site represents a non-neoplastic exaggeration of the normal implantation process, usually found concurrently with immature villi.

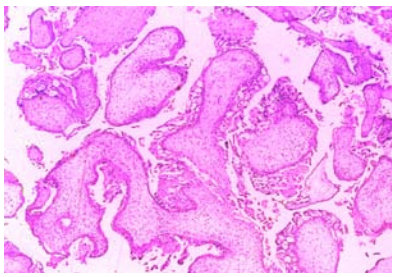

Fig. 4.52 "Early" complete mole. Some villi have toe-like bulbous protrusions. Trophoblastic proliferation and cavitation are minimal. The stroma is hypercellular and myxoid.

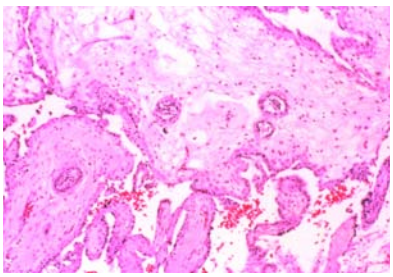

Fig. 4.53 Partial hydatidiform mole. There are two populations of villi; the larger is markedly irregular with scattered cavitation, numerous trophoblastic inclusions and minimal hyperplasia.

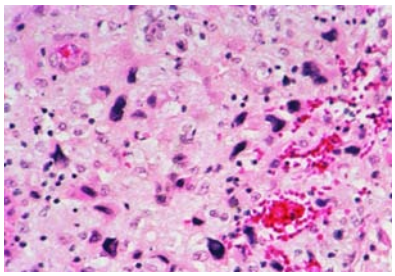

Fig. 4.54 Markedly atypical implantation site trophoblast in a case of early hydatidiform mole.

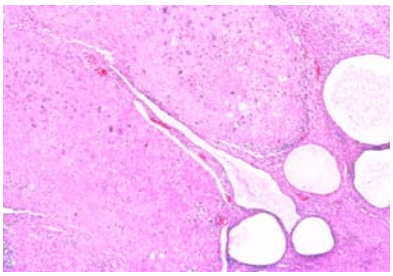

Fig. 4.55 Placental site nodule. Note the well circumscribed eosinophilic endomyometrial nodules.

Sex cord-like, neuroectodermal and neuroendocrine tumours, lymphomas and leukaemias

F. Nogales
F.A. Tavassoli

Sex cord-like tumours

Definition
Tumours of the uterine corpus that closely resemble some true ovarian sex cord tumours.

Epidemiology
Among these rare tumours the most numerous are the sex cord-like tumours {511}, which closely resemble some true ovarian sex cord tumours.

Histopathology
These are diagnosed only when they are not found within otherwise classical endometrial stromal or smooth muscle tumours. Histologically, sex cord elements are represented by trabecular ribbons and nodules or isolated cells with luteinized or foamy cytoplasm that are histologically and immunohistochemically identical to ovarian steroid-producing cells, being strongly positive for alpha-inhibin, calretinin and CD99 {167, 1521,1808}. They may be capable of hormone-secreting activity {2034}. They have a prominent epithelial component that can be tubular, retiform {3247} or glomeruloid. They also show frequent positivity for cytokeratins, vimentin, smooth muscle actin and, occasionally, epithelial membrane antigen (EMA) {930}.

Neuroectodermal tumours

Definition
A variety of tumours of the uterine corpus that show neuroectodermal differentiation.

Epidemiology
Different types of neuroectodermal tumours are found in the uterus. When pure, they usually present in young patients {1188}; however, when mixed with carcinoma or carcinosarcoma they are usually found in older women {638, 931,2710}. Recently, peripheral primitive neuroectodermal tumour/Ewing tumour has been reported in both young {1597} and postmenopausal patients {2710}.

Histopathology
Well differentiated variants with an appearance similar to low grade astrocytoma {3201} should be differentiated from non-neoplastic fetal parts implanted in the endometrium following abortion. Most often, the tumour cells differentiate into neuroblastic, neuroepithelial, glial and neuronal elements {1188}. Peripheral primitive neuroectodermal tumour/Ewing tumour shows a characteristic immunophenotype positive for neuron-specific enolase, vimentin and CD99 as well as the presence of *EWS/FLI-1* fusion transcripts.

Prognosis and predictive factors
All neuroectodermal tumours except the well differentiated astrocytic forms behave in a highly malignant fashion.

Melanotic paraganglioma

Definition
A tumour morphologically identical to paraganglioma, but functionally producing mainly melanin pigment instead of neuroendocrine granules.

Epidemiology
Only two examples of melanotic paraganglioma have been described in the uterus in women 31 and 46 years of age {2866}.

Macroscopy
Both were incidental findings in uteri removed for unrelated benign lesions. The larger lesion was 1.5 cm and appeared as a black pigmented lesion on macroscopic examination; the other was a histological finding.

Histopathology
Both lesions were well circumscribed and composed of large nests of round or angulated polygonal cells with abundant clear or granular pale eosinophilic cytoplasm. Both cases had psammoma bodies, and large amounts of coarse melanin

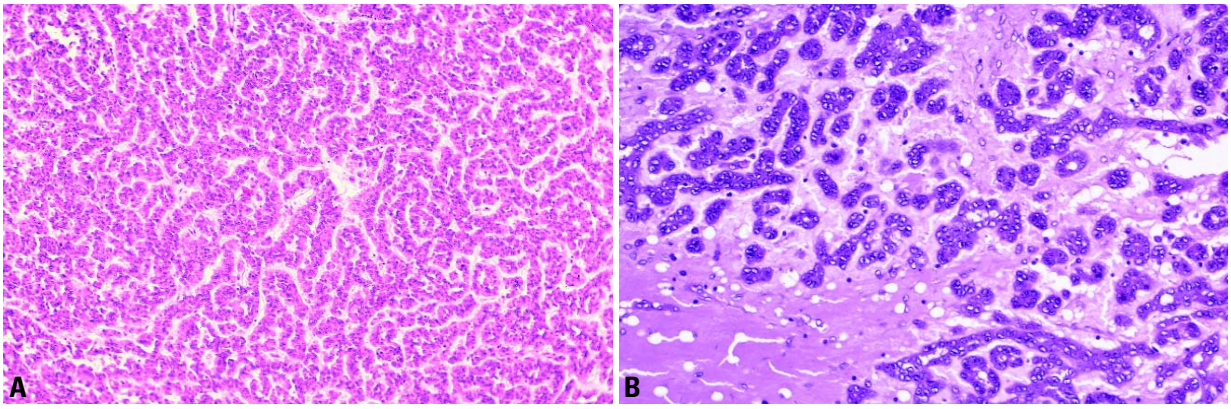

Fig. 4.56 Sex cord-like tumour. **A** Trabecular pattern is prominent. **B** The neoplasm shows a cord-like pattern.

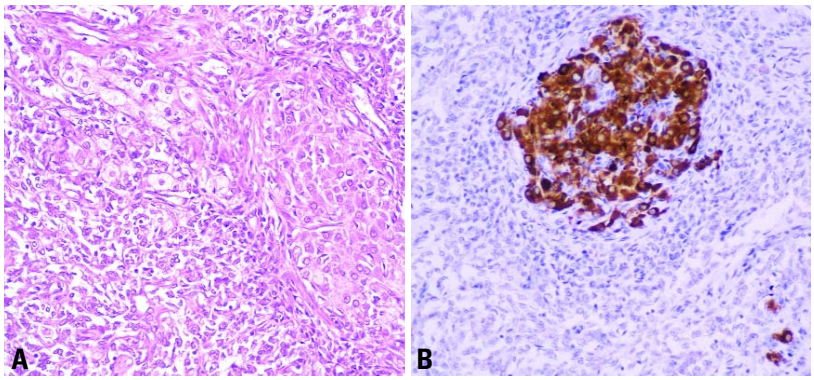

Fig. 4.57 Sex cord-like tumour. **A** Several nodules composed of luteinized cells with ample eosinophilic to vacuolated cytoplasm are present. **B** The nodule of luteinized cells stains positively for alpha-inhibin.

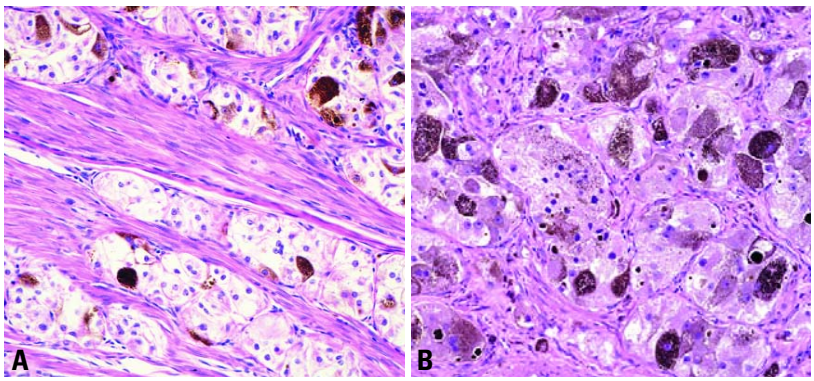

Fig. 4.58 Melanotic paraganglioma. **A** Note the nests of polyhedral cells with abundant clear cytoplasm. **B** Tumour cells have uniform nuclei and contain coarse melanin pigment.

granules were present in many cells. The large cells do not stain with S-100 protein. At the ultrastructural level intracellular melanosomes and premelanosomes abound, and a few neuroendocrine granules are present; the cells lack microvilli or dendritic processes.

Prognosis and predictive factors

Both women were free of any recurrences at 2.2 and 3.2 years after the discovery of the tumour {2866}.

Lymphomas and leukaemias

Definition

A malignant lymphoproliferative or haematopoetic neoplasm that may be primary or secondary.

Clinical findings

The patients typically present with vaginal bleeding {2354}.

Tumour spread and staging

Most lymphomas and leukaemias that involve the uterine corpus are a manifestation of disseminated disease. On rare occasions the corpus is the first known site of a malignant lymphoma.

Histopathology

The majority of cases are of the large B cell type {114}. Lymphomas of the uterine corpus must be distinguished from an atypical lymphoma-like inflammatory lesion of the endometrium. The latter is characterized by a massive infiltrate of lymphoid cells, some of which are immature. The presence of other inflammatory cells including plasma cells and neutrophils within the infiltrate and the typical absence of myometrial invasion or a macroscopic mass are helpful in the differential diagnosis {851}. Cases of uterine leiomyoma massively infiltrated by lymphocytes may also mimic a lymphoma {488}.

Rare tumours

Definition

A variety of benign or malignant tumours of the uterine corpus that are not otherwise categorized.

Histopathology

Germ cell tumours such as teratomas and yolk sac tumours can develop in the endometrium, either in a pure form {398,2196,2763,2836} or associated with endometrioid tumours {103,2665}. Extrarenal Wilms tumours (nephroblastomas) have also been reported in the uterus {1783,1934}. Their histological appearance is similar to that of the tumours occurring in other sites.

Secondary tumours of the uterine corpus

V. Abeler
U. Haller

Definition
Tumours of the uterine corpus that originate from, but are discontinuous with, a primary extrauterine tumour or a tumour in the cervix or elsewhere in the uterus.

Clinical features
Signs and symptoms
The mean age of patients with extragenital tumour metastasis to the uterus is 60 years. Patients have abnormal uterine bleeding since most neoplasms metastatic to the uterus infiltrate the endometrium diffusely.

Imaging
Imaging studies are non-specific {1240, 1282,1576,3184}.

Macroscopy
Metastases may appear as solitary or multiple tumours or be diffusely infiltrating.

Histopathology
The majority of metastases to the uterus are confined to the myometrium. However, approximately one-third involve the endometrium and thus can be detected in biopsy specimens {1529}. Metastatic carcinoma within the endometrium and/or myometrium characteristically infiltrates as single cells, cord or glands. The appearance is particularly striking in lobular carcinoma of the breast, which usually retains its single-file pattern, and with metastatic signet-ring cell carcinoma of the stomach or colon. Metastatic colon carcinoma of the usual type may form large tumour masses and can mimic an endometrial carcinoma of mucinous or endometrioid type.
Metastatic carcinoma in the endometrium should be suspected if one or more of the following features are present {1539}.
(1) A tumour with an unusual macroscopic or histological pattern for primary endometrial carcinoma.
(2) Diffuse replacement by tumour of endometrial stroma with sparing of occasional normal endometrial glands.
(3) Lack of premalignant changes in endometrial glands.
(4) Lack of tumour necrosis
For specific identification of certain primary tumours immunohistochemical studies are frequently required.

Origin and histogenesis
In most instances the primary tumour is well known, or disseminated disease is clinical evident. Occasionally, a tumour diagnosed by curettage or hysterectomy represents the first sign of an extrauterine primary tumour.
Secondary tumours of the uterine corpus can be divided into two major groups: tumours of the genital and extragenital organs. Neoplasms of neighbouring organs such as cervix, fallopian tubes, ovaries, bladder and rectum can metastasize to the uterine corpus via lymphatics or blood vessels but mostly represent local direct extension.
Haematogenous or lymphatic uterine metastases from any extragenital primary tumour may occur but are extremely rare. Reported primary tumours include carcinomas of the breast, stomach, colon, pancreas, gallbladder, lung, urinary bladder and thyroid and melanoma {192,1452,1455,1529,1531, 1620,1720}. Mammary lobular carcinoma, gastric signet-ring cell carcinoma and colonic carcinoma are the most frequently reported extragenital primary tumours {1529,1531}.

Prognosis and predictive factors
When uterine metastases are present, the patient usually has widely disseminated disease. However, in one series the average survival was 20 months after the diagnosis of uterine metastases. The reason for this relatively favourable outcome might be the predominance of cases of metastatic breast carcinoma {1529}.

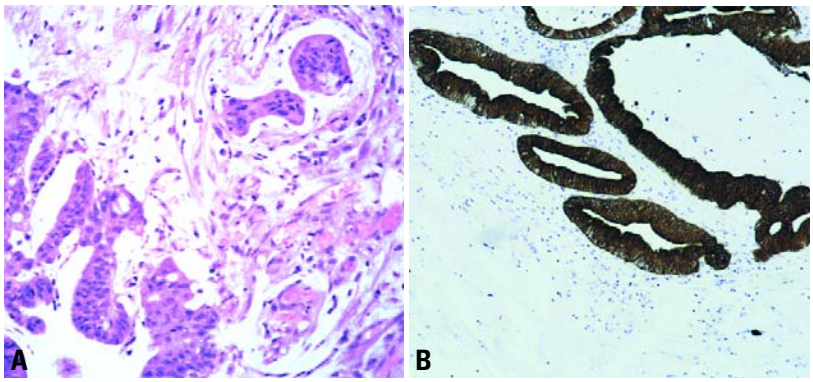

Fig. 4.59 Metastatic colon carcinoma to the myometrium. **A** Note the tumour cells in lymphatic vessels in the right upper portion of the field with a plexiform pattern on the left. **B** The neoplastic glands are positive for cytokeratin 20.

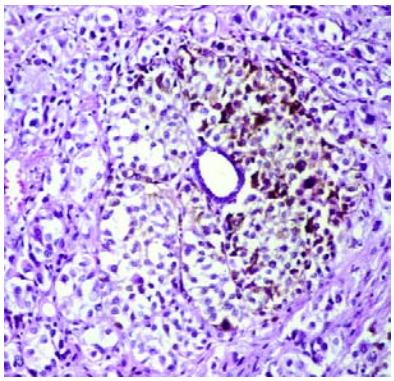

Fig. 4.60 Metastatic melanoma to the endometrium. Tumour cells containing melanin pigment surround an atrophic endometrial gland.