

## CHAPTER 6

### **Tumours of the Vagina**

Although the incidence rate of vaginal intraepithelial neoplasia is increasing, that of squamous cell carcinoma is decreasing, reflecting earlier detection and more successful treatment. Human papillomavirus infection is a risk factor for both vaginal intraepithelial neoplasia and squamous cell carcinoma.

In past decades, clear cell adenocarcinoma occurred in young women, about two-thirds of whom had been exposed transplacentally to diethylstilbestrol. At that time, it was the most important glandular lesion of the vagina and the second most common epithelial malignancy. The precursor lesion appears to be atypical adenosis.

The most important non-epithelial tumours are malignant melanoma and sarcoma botryoides.

## WHO histological classification of tumours of the vagina

Epithelial tumours			
Squamous tumours and precursors			
Squamous cell carcinoma, not otherwise specified	8070/3	Leiomyosarcoma	8890/3
Keratinizing	8071/3	Endometrioid stromal sarcoma, low grade	8931/3
Non-keratinizing	8072/3	Undifferentiated vaginal sarcoma	8805/3
Basaloid	8083/3	Leiomyoma	8890/0
Verrucous	8051/3	Genital rhabdomyoma	8905/0
Warty	8051/3	Deep angiomyxoma	8841/1
Postoperative spindle cell nodule			
Squamous intraepithelial neoplasia			
Vaginal intraepithelial neoplasia 3 / squamous cell carcinoma in situ	8077/2	<b>Mixed epithelial and mesenchymal tumours</b>	
Benign squamous lesions	8070/2	Carcinosarcoma (malignant müllerian mixed tumour; metaplastic carcinoma)	8980/3
Condyloma acuminatum		Adenosarcoma	8933/3
Squamous papilloma (vaginal micropapillomatosis)	8052/0	Malignant mixed tumour resembling synovial sarcoma	8940/3
Fibroepithelial polyp		Benign mixed tumour	8940/0
Glandular tumours			
Clear cell adenocarcinoma	8310/3	<b>Melanocytic tumours</b>	
Endometrioid adenocarcinoma	8380/3	Malignant melanoma	8720/3
Mucinous adenocarcinoma	8480/3	Blue naevus	8780/0
Mesonephric adenocarcinoma	9110/3	Melanocytic naevus	8720/0
Müllerian papilloma		<b>Miscellaneous tumours</b>	
Adenoma, not otherwise specified	8140/0	Tumours of germ cell type	
Tubular	8211/0	Yolk sac tumour	9071/3
Tubulovillous	8263/0	Dermoid cyst	9084/0
Villous	8261/0	Others	
Other epithelial tumours			
Adenosquamous carcinoma	8560/3	Peripheral primitive neuroectodermal tumour /	9364/3
Adenoid cystic carcinoma	8200/3	Ewing tumour	9260/3
Adenoid basal carcinoma	8098/3	Adenomatoid tumour	9054/0
Carcinoid	8240/3	<b>Lymphoid and haematopoietic tumours</b>	
Small cell carcinoma	8041/3	Malignant lymphoma (specify type)	
Undifferentiated carcinoma	8020/3	Leukaemia (specify type)	
<b>Mesenchymal tumours and tumour-like conditions</b>			
Sarcoma botryoides	8910/3	<b>Secondary tumours</b>	

<sup>1</sup> 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, /2 for in situ carcinomas and grade 3 intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

<sup>2</sup> Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are only available for lesions categorized as squamous intraepithelial neoplasia grade 3 (e.g. vaginal intraepithelial neoplasia/VAIN grade 3) = 8077/2; squamous cell carcinoma in situ = 8070/2.

## TNM and FIGO classification of carcinomas of the vagina

TNM and FIGO classification <sup>1,2</sup>			N – Regional Lymph Nodes <sup>3</sup>			
T – Primary Tumour			NX Regional lymph nodes cannot be assessed			
TNM Categories	FIGO Stages		N0 No regional lymph node metastasis			
TX		Primary tumour cannot be assessed	N1 Regional lymph node metastasis			
T0		No evidence of primary tumour	M – Distant Metastasis			
Tis	0	Carcinoma in situ (preinvasive carcinoma)	MX Distant metastasis cannot be assessed			
T1	I	Tumour confined to vagina	M0 No distant metastasis			
T2	II	Tumour invades paravaginal tissues but does not extend to pelvic wall	M1 Distant metastasis			
T3	III	Tumour extends to pelvic wall	<b>Stage Grouping</b>			
T4	IVA	Tumour invades <i>mucosa</i> of bladder or rectum, and/or extends beyond the true pelvis	Stage 0	Tis	N0	M0
			Stage I	T1	N0	M0
			Stage II	T2	N0	M0
			Stage III	T3	N0	M0
				T1, T2, T3	N1	M0
			Stage IVA	T4	N0	M0
			Stage IVB	Any T	Any N	M1

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

<sup>1</sup> (51,2976).

<sup>2</sup> A help desk for specific questions about the TNM classification is available at <http://tnm.uicc.org>.

<sup>3</sup> The regional lymph nodes are: Upper two-thirds of vagina: the pelvic nodes including obturator, internal iliac (hypogastric), external iliac, and pelvic nodes, NOS. Lower third of vagina: the inguinal and femoral nodes.

# Epithelial tumours

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## Squamous tumours

### Definition

Primary squamous epithelial tumours of the vagina are the most frequent neoplasms at this site. They occur in all age groups but preferentially in the elderly. Vaginal intraepithelial neoplasia (VAIN) is considered a typical, though not obligatory, precursor lesion of squamous cell carcinoma.

### ICD-O codes

Squamous cell carcinoma	8070/3
Vaginal intraepithelial neoplasia (VAIN), grade 3	8077/2
Squamous cell carcinoma in situ	8070/2
Squamous papilloma	8052/0

### Squamous cell carcinoma

#### Definition

An invasive carcinoma composed of squamous cells of varying degrees of differentiation. According to the International Federation of Gynaecology and Obstetrics (FIGO), a tumour of the vagina involving the uterine cervix or the vulva should be classified as a primary cervical or vulvar cancer, respectively. Additionally, before the diagnosis of a primary vaginal carcinoma can be established, a 5-10 year disease free

interval is required to rule out recurrent disease in those patients with a prior preinvasive or invasive cervical or vulvar neoplasm.

#### Epidemiology

Squamous cell carcinoma comprises up to 85% of vaginal carcinomas and accounts for 1-2% of all malignant tumours of the female genital tract [634, 1193]. The mean age of patients is about 60 years.

#### Aetiology

In squamous cell carcinoma persistent infection with high-risk human papillomavirus (HPV) is probably a major aetiological factor. The same risk factors are observed as for vaginal intraepithelial neoplasia (VAIN), i.e. previous preinvasive or invasive disease of the lower genital tract, immunosuppression and prior pelvic irradiation [303]. The development of VAIN and eventual progression to invasive disease is most likely, though the progression rate is unknown [347].

Prior pelvic irradiation is a predisposing factor for vaginal squamous carcinoma [303,748,3075]. Simultaneous or prior preinvasive or invasive disease elsewhere in the lower genital tract is observed in up to 30% of cases [220,2227,2480].

#### Clinical features

##### Signs and symptoms

The commonest symptom is a bloody vaginal discharge. Nearly 75% of patients present with painless bleeding, urinary tract symptoms or postcoital bleeding; however, the patient may be completely asymptomatic. Pelvic pain and dysuria usually signify advanced disease [2499]. Most cases occur in the upper third of the vagina and are located on the posterior wall [2265].

##### Imaging

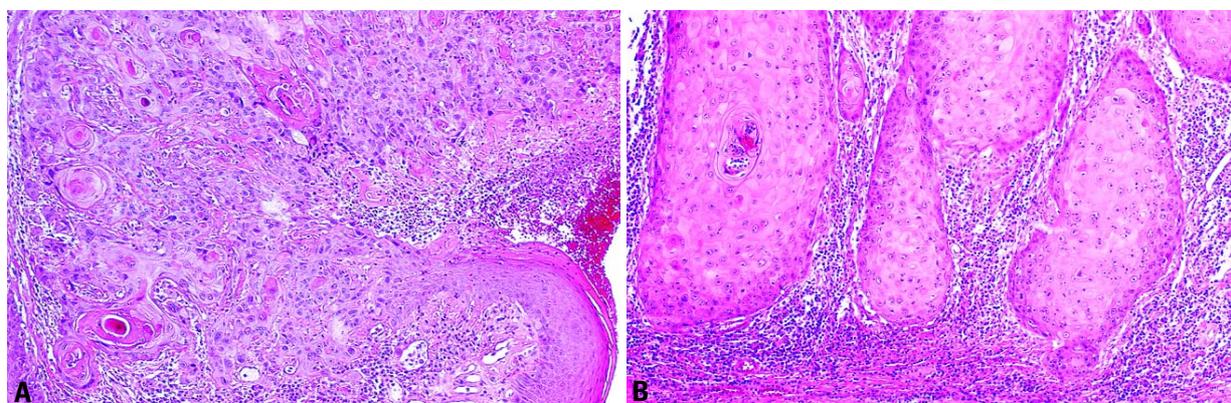
Magnetic resonance imaging (MRI) of the pelvis can be used to image vaginal tumours as well as to assess whether pelvic or inguinal lymphadenopathy is present. The MRI appearance, however, is not specific, and inflammatory changes and congestion of the vagina may mimic vaginal carcinoma [439].

##### Exfoliative cytology

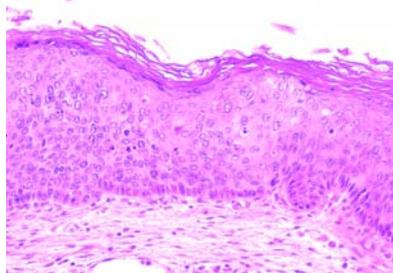
Occasionally, cancer cells of vaginal origin may be observed in cervical smears.

##### Macroscopy

Tumours may be exophytic, ulcerative or annular and constricting. The lesions vary in size from being undetectable to greater than 10 cm. They may be polypoid, sessile, indurated, ulcerated or fun-



**Fig. 6.01** Squamous cell carcinoma. **A** Keratinizing type. Carcinoma arises from the surface epithelium and forms several keratin pearls. **B** Non-keratinizing type. The neoplasm forms prominent squamous pearls with little keratinization.

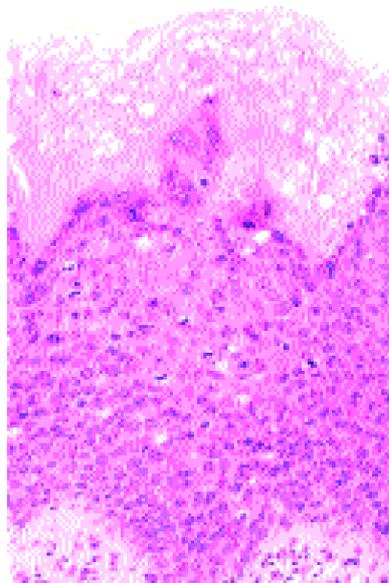


**Fig. 6.02** Vaginal intraepithelial neoplasia, grade 2. Nuclear features of intraepithelial neoplasia are evident in the lower two-thirds of the squamous epithelium with overlying parakeratosis.

gating and may be found anywhere within the vagina. Squamous cell carcinoma, the commonest vaginal carcinoma, is ulcerative in half of cases, exophytic in a third and annular and constricting in the remainder.

#### Tumour spread and staging

Squamous cell carcinoma spreads predominantly laterally to the paravaginal and parametrial tissues when located in the lower and upper vagina, respectively. Tumours also invade lymphatics, metastasizing to regional lymph nodes and eventually distant sites including the



**Fig. 6.03** Vaginal intraepithelial neoplasia, grade 3. The upper portion of the epithelium is covered by hyperkeratosis. The remaining cells are characterized by nuclear enlargement and pleomorphism.

**Table 6.01**

Terminology of premalignant vaginal squamous epithelial lesions.

Classification	Synonyms	
Vaginal intraepithelial neoplasia, grade 1	Mild dysplasia	Low grade VAIN
Vaginal intraepithelial neoplasia, grade 2	Moderate dysplasia	High grade VAIN
Vaginal intraepithelial neoplasia, grade 3	Severe dysplasia and carcinoma in situ	High grade VAIN
VAIN = vaginal intraepithelial neoplasia		

lungs, liver and brain. The staging of vaginal tumours is by the TNM/FIGO classification {51,2976}. Approximately 25% of patients present with stage I disease, one-third with stage II disease and 40% with stage III or IV disease {220,748,1245,1524,2301,2480}.

#### Histopathology

Vaginal squamous cell carcinoma has the same histological characteristics as such tumours in other sites. Most cases are moderately differentiated and non-keratinizing {2301}. Rarely, the tumours have spindle-cell features {2778}. Warty carcinoma is another variant of vaginal squamous cell carcinoma {2339}. The tumour is papillary with hyperkeratotic epithelium. Nuclear enlargement and koilocytosis with hyperchromasia, wrinkling of the nuclear membrane and multinucleation are typical changes {1541,2936}. Verrucous carcinoma has a papillary growth pattern with pushing borders and bulbous pegs of acanthotic epithelium with little or no atypia and surface maturation in the form of parakeratosis and hyperkeratosis. For a more detailed discussion of the subtypes of squamous cell carcinoma see chapter 5 or 7.

#### Prognosis and predictive factors

Radiation is the preferred treatment for most cases of vaginal carcinoma {1524,2217,2981}. In Stage I disease located in the upper part of the vagina, a radical hysterectomy, pelvic lymphadenectomy and partial vaginectomy may be considered {55,171}. Otherwise, radiation therapy given as intracavitary therapy, interstitial implants and/or external pelvic/inguinal radiation, often in combination, is the most frequently adopted modality {1524,2217}. In tumours of the

middle or lower third of the vagina the external radiation field should include the inguinal and femoral lymph nodes.

The clinical stage is the most significant prognostic factor {220,748,1245,1524,2301,2480}. Recurrences are typically local and usually happen within 2 years of treatment. The five-year survival rates are 70% for stage I, 45% for stage II, 30% for stage III and 15% for stage IV. The overall 5-year survival is about 42% {220,748,1245,1524,2301,2480}.

Tumour localization, grade or keratinization or patient age has not been demonstrated to have prognostic significance.

#### Vaginal intraepithelial neoplasia

##### Definition

A premalignant lesion of the vaginal squamous epithelium that can develop primarily in the vagina or as an extension from the cervix. VAIN is often a manifestation of the so-called lower genital tract neoplastic syndrome. Histologically, VAIN is defined in the same way as cervical intraepithelial neoplasia (CIN).

##### Synonyms

Dysplasia/carcinoma in situ, squamous intraepithelial lesion.

##### Epidemiology

VAIN is much less common than CIN, though its true incidence is unknown. There is some evidence that the incidence of VAIN has increased in recent decades, particularly among young and immunosuppressed women. The mean age for patients with VAIN is approximately 50 years. The majority of VAIN cases occur in women who have had a prior hysterectomy or who have a history of cervical or vulvar neoplasia {1626,2403}.

### Aetiology

The fact that both VAIN and vaginal carcinoma are much less common than cervical neoplasia has been explained by the absence of a vulnerable transformation zone in the vagina. VAIN is associated with HPV infection in most cases. At least 15 different HPV types have been identified in VAIN. As in the cervix, VAIN 2 and VAIN 3 are associated with high-risk HPV types, of which type 16 is the most frequent. Mixed HPV types have also been identified in multifocal VAIN lesions and also in a single lesion [239, 2565]. In VAIN 1 a mixture of low and high-risk HPV types can be detected.

### Clinical features

#### Signs and symptoms

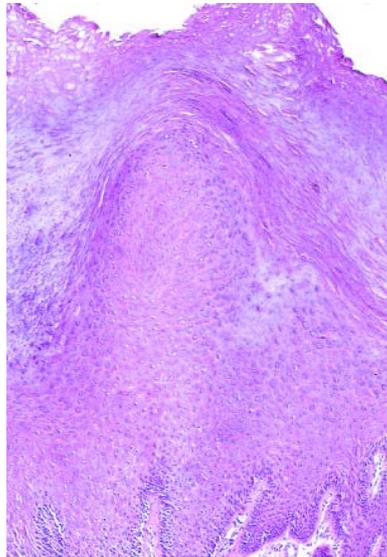
VAIN may be isolated but is more commonly multifocal [710,1626]. Isolated lesions are mainly detected in the upper one-third of the vagina and in the vaginal vault after hysterectomy. VAIN is asymptomatic and cannot be diagnosed by the naked eye.

#### Colposcopy

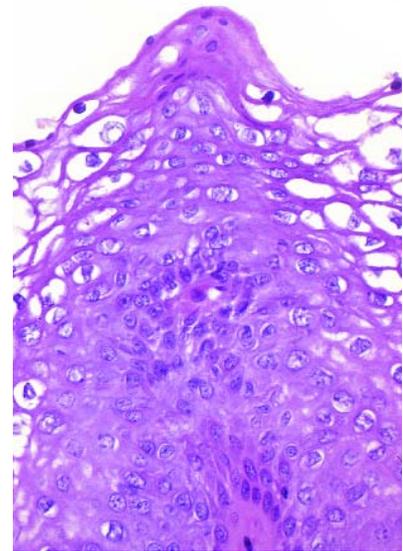
VAIN may be suspected by a cervico-vaginal cytology preparation, but the diagnosis can only be made by a colposcopically directed biopsy. If the colposcopy of the cervix is normal after an abnormal cytological smear, a careful colposcopic examination of all the vaginal epithelium should be performed. VAIN lesions are always iodine-negative. The presence of punctation on a sharply demarcated aceto-white area is the single most reliable colposcopic feature suggestive of VAIN [2565].

### Histopathology

The histopathology of VAIN is similar to that of CIN. Many VAIN 3 lesions also



**Fig. 6.04** Condyloma acuminatum. Papillomatosis, acanthosis and hyperkeratosis are associated with a few koilocytes in the superficial layers.



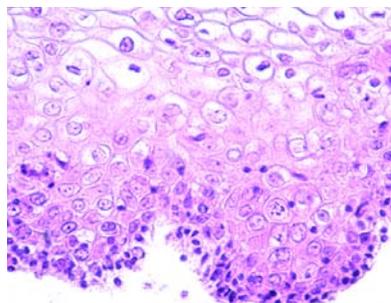
**Fig. 6.05** Spiked condyloma. Papillomatosis is associated with HPV-infected cells with a clear cytoplasm (koilocytes).

show hyperkeratosis. The so-called "flat condyloma" shows koilocytosis in the superficial layers of the epithelium with normal or only hyperplastic basal layers without nuclear atypia. However, the distinction between flat condyloma and VAIN 1 with koilocytosis is not always possible. Other differential diagnoses of VAIN include atrophy, squamous atypia and transitional cell metaplasia [3085] as well as immature squamous metaplasia in women with adenosis. A distinction is made based on the nuclear features of the epithelium.

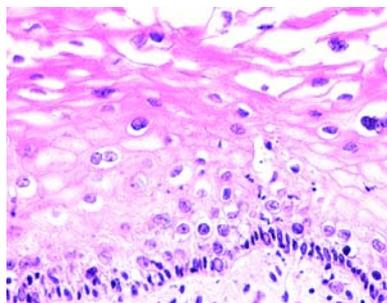
The relationship of the VAIN terminology to that of dysplasia and carcinoma in situ of the vagina is shown in Table 6.01.

### Prognosis and predictive factors

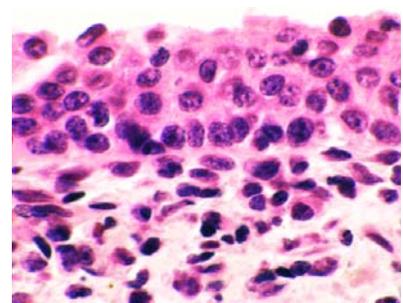
The natural history of VAIN has been less extensively studied than that of CIN. In one study 23 patients with a mean age of 41 years were followed for at least 3 years with no treatment [49]. One-half of the VAIN lesions were multifocal. Progression to invasive vaginal carcinoma occurred in only 2 cases, and VAIN persisted in 3 additional cases. Thus, VAIN spontaneously regressed in 78% of cases. A retrospective review of 121 women with VAIN showed that the recurrence rate was 33% [710]. Progression to invasive vaginal cancer occurred in 2%. In another study of 94 patients with VAIN, the progression rate to cancer was 5% [2674].



**Fig. 6.06** Vaginal intraepithelial neoplasia, grade 1. Note the koilocytosis and the slightly thickened and disorganized basal layers.



**Fig. 6.07** Flat condyloma. Note the cytopathic effects of human papillomavirus (koilocytosis) with a normal basal layer of the squamous epithelium.



**Fig. 6.08** Atrophy. The cells are small, accounting for the nuclear crowding. Nuclei are uniform with discernible nucleoli. Mitoses are not detectable.

High grade VAIN appears to be an important precursor of invasive cancer; progression occurred in 8% of cases of high grade VAIN despite the fact that most of the patients were treated, whereas low grade VAIN regressed in 88% of women without treatment {2403}.

### **Condyloma acuminatum**

#### **Definition**

A benign neoplasm characterized by papillary fronds containing fibrovascular cores and lined by stratified squamous epithelium with evidence of HPV infection, usually in the form of koilocytosis.

#### **Epidemiology**

Condylomas are sexually transmitted. There is strong evidence that their incidence has increased since the 1960s. The incidence is much higher in women than in men. They often occur on the mucosal epithelium of the vagina. However, because condylomas are often subclinical and not reported, their true incidence remains unknown.

#### **Aetiology**

Non-oncogenic HPV types 6 and 11 are found in the majority of condylomas {1837}. Patients with visible condylomas can be simultaneously infected by other HPV types (mixed HPV infection).

#### **Clinical features**

##### **Signs and symptoms**

Vaginal lesions are easily overlooked during a speculum examination. Vaginal condylomas present in the same way as those on the vulva and the cervix {1070, 2144}. They can be single or multiple. Condylomas can cover most of the vaginal mucosa and extend to the cervix and may be small or large. Most commonly, they occur adjacent to the introitus and in the vaginal fornices. Condylomas can be papular or macular. The latter has been also called "flat condyloma", noncondylomatous wart virus infection or subclinical papillomavirus infection.

#### **Colposcopy**

Typical exophytic condylomas show digitate projections with vascularized cores producing loop-like patterns or punctuation {1070,2144}. The application of acetic acid augments the diagnosis of vaginal condylomas. Micro-papillary vaginal condylomas may be diffuse and may completely cover the vagina. This manifestation is known as condylomatous vaginitis. Reverse punctuation can be seen by colposcopy after acetic acid application. Spiked condylomas appear as small and elongated white spikes focally or diffusely distributed on the vaginal wall {1070, 2144}.

#### **Histopathology**

Condyloma acuminatum has a complex, arborizing architecture with hyperkeratosis, parakeratosis, acanthosis and papillomatosis as well as the typical cytopathic effects of HPV. It can be distinguished by clinical examination alone from vaginal micropapillomatosis, which has no significant relationship with HPV infection and is believed by some to be a normal anatomical variant of the lower genital tract {967}. The latter also lacks the histological features of condyloma.

### **Squamous papilloma**

#### **Definition**

A benign papillary tumour in which squamous epithelium without atypia or koilocytosis lines a fibrovascular stalk.

#### **Synonyms**

Vaginal micropapillomatosis, squamous papillomatosis.

These terms are applicable when numerous lesions are present.

#### **Epidemiology**

Squamous papillomas do not appear to be sexually transmitted.

#### **Aetiology**

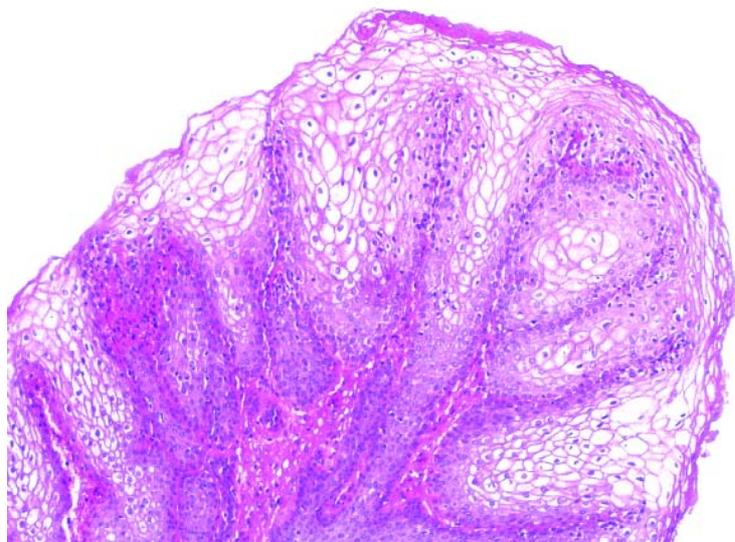
Based on in situ hybridization studies using the polymerase chain reaction, vaginal micropapillary lesions appear unrelated to human papillomavirus {967}, and their aetiology is unknown.

#### **Clinical features**

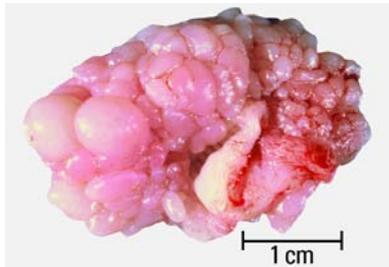
Squamous papillomas may be single or multiple. When numerous, they occur near the hymenal ring and are referred to as vaginal micropapillomatosis. The lesions are usually asymptomatic but may be associated with vulvar burning or dyspareunia. They may be difficult to distinguish from condyloma by inspection. However, on colposcopic and histological examination papilloma is composed of a single papillary frond with a central fibrovascular core.

#### **Histopathology**

In squamous papilloma the squamous epithelium covers a central fibrovascular core and shows acanthosis but lacks koilocytosis. It has a smooth surface and lacks significant vascular structures. It lacks the complex arborizing architecture and koilocytes of condylomas.



**Fig. 6.09** Squamous papilloma. The fibrovascular core is covered by squamous epithelium with a smooth surface that lacks koilocytosis but shows acanthosis and papillomatosis.



**Fig. 6.10** Fibroepithelial polyp. A multilobulated polypoid lesion arises from the vaginal wall.

However, it is important to note that there may be a time during the evolution of condylomas when koilocytes are not easily identifiable.

### Fibroepithelial polyp

#### Definition

A polyp lined by squamous epithelium that contains a central core of fibrous tissue in which stellate cells with tapering cytoplasmic processes and irregularly shaped thin-walled vessels are prominent features.

#### Synonym

Stromal polyp.

#### Clinical features

This lesion can occur at any age but has a predilection for pregnant women.

#### Macroscopy

These are polypoid lesions, usually solitary.

#### Histopathology

These polypoid lesions are characterized by a prominent fibrovascular stroma covered by squamous epithelium [380]. They lack epithelial acanthosis and papillary architecture. Bizarre stromal cells, marked hypercellularity and elevated mitotic counts including atypical forms have been described that can lead to an erroneous diagnosis of sarcoma botryoides, but a cambium layer and rhabdomyoblasts are absent, and mitotic activity is typically low [2067].

### Glandular tumours and their precursors

#### ICD-O codes

Adenocarcinoma, NOS	8140/3
Clear cell adenocarcinoma	8310/3
Endometrioid adenocarcinoma	8380/3

Mucinous adenocarcinoma	8480/3
Mesonephric adenocarcinoma	9110/3
Adenoma, NOS	8140/0
Tubular	8211/0
Tubulovillous	8263/0
Villous	8261/0

### Clear cell adenocarcinoma

#### Definition

An invasive neoplasm with an epithelial component that contains one or more cell types, most commonly clear cells and hobnail cells, but flat and/or eosinophilic cells may, on occasion, predominate.

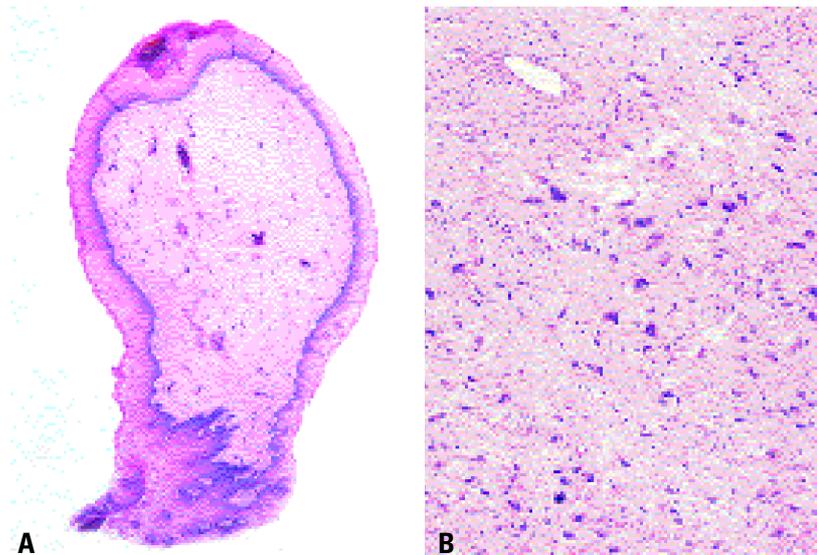
#### Epidemiology

The occurrence of cases of vaginal clear cell adenocarcinoma associated with in utero exposure to diethylstilbestrol (DES) was responsible for an increase in incidence of adenocarcinoma in young women from the 1970s [1194]. In the early 1970s the peak incidence of clear cell adenocarcinoma was around 19 years, the youngest patient being 8 years. With the ageing of the DES-exposed cohort, the peak incidence has been shifting towards an older age group.

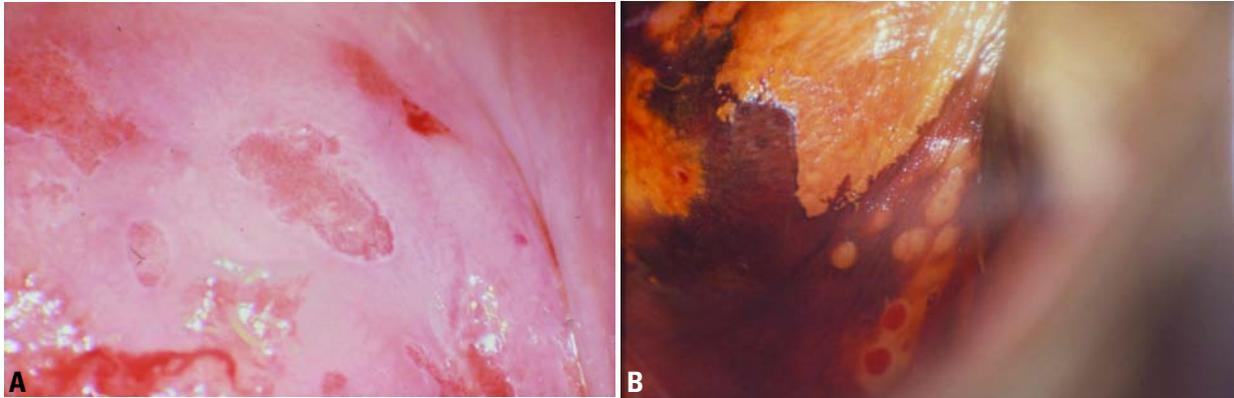
#### Aetiology

DES was prescribed for threatened or repeated abortions from the 1940s to the early 1970s. Millions of women were exposed in utero to this and related drugs

in several countries, including the United States, France and the Netherlands [2946]. DES is a teratogen and causes a variety of congenital abnormalities of the lower genital tract in about 30% of the female offspring [1883]. The absolute risk of clear cell adenocarcinoma of the vagina or cervix is estimated at 1:1000 [1843]. About two-thirds of the cases of clear cell adenocarcinoma occurring in individuals under the age of 40 are linked to transplacental DES exposure. DES inhibits the development of urogenital sinus-derived squamous epithelium that is destined to become vaginal epithelium and normally grows up to the junction of the ectocervix and endocervix, replacing the pre-existing müllerian-derived columnar epithelium. The embryonic müllerian epithelium that is not replaced persists and develops into adenosis. Adenosis is found immediately adjacent to the tumour in over 90% of cases and is thought to be the precursor of clear cell adenocarcinoma. The rarity of clear cell adenocarcinoma in the exposed population suggests that DES is an incomplete carcinogen or that susceptibility factors are necessary for it to produce neoplastic transformation. Genetic factors and hormonal disruption by environmental toxins are implicated. A maternal history of prior spontaneous abortion increases the risk of clear cell adenocarcinoma [2161]. Endogenous estrogens probably also play a role,



**Fig. 6.11** Fibroepithelial polyp. **A** This polypoid lesion is composed of stroma and covered by squamous epithelium. **B** The stroma contains scattered bizarre multinucleated giant cells.



**Fig. 6.12** Adenosis of the vagina. **A** By colposcopy red granular areas of adenosis are apparent. **B** Colposcopy after iodine application. The areas of adenosis do not stain.

since most cases of clear cell adenocarcinoma are first detected around the time of puberty.

#### Localization

Whilst any part of the vagina may be involved, clear cell adenocarcinoma most often arises from its upper part. A primary vaginal clear cell adenocarcinoma may also involve the cervix. According to FIGO criteria about two-thirds of clear cell adenocarcinomas after DES exposure are classified as tumours of the vagina and one-third of the cervix [1131]. In non-DES exposed young women and post-menopausal women this ratio is reversed.

#### Clinical features

Vaginal bleeding, discharge and dyspareunia are the most common symptoms, but women may be asymptomatic. Abnormal cytologic findings may lead to

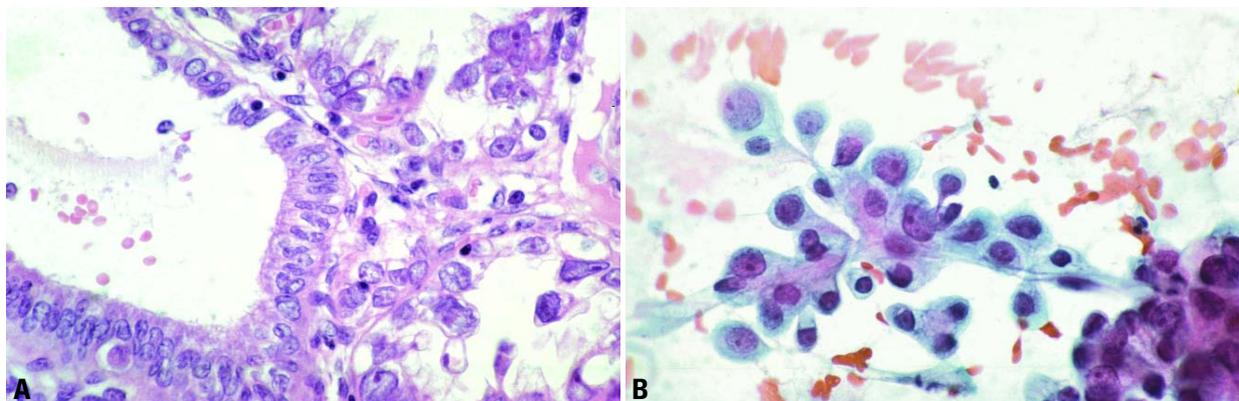
detection, but care must be taken to sample the vagina as well as the cervix since cervical smears are relatively insensitive for the detection of clear cell adenocarcinoma [1132].

Clear cell adenocarcinomas typically are polypoid, nodular, or papillary but may also be flat or ulcerated. Some clear cell adenocarcinomas are confined to the superficial stroma and may remain undetected for a long time [1131,2386]. Such small tumours may be invisible on macroscopic or even colposcopic examination and are only detected by palpation or when tumour cells are shed through the mucosa and detected by exfoliative cytology. Large tumours may be up to 10 cm in diameter.

#### Histopathology

Clear cell adenocarcinoma of the vagina has an appearance similar to those aris-

ing in the cervix, endometrium and ovary. Clear cell adenocarcinomas may show several growth patterns; the most common pattern is tubulocystic, but it also may be solid or mixed. A papillary growth pattern is seldom predominant. The main cell types are clear cells and hobnail cells. The appearance of the clear cells is due to the presence of abundant intracytoplasmic glycogen. Hobnail cells are characterized by inconspicuous cytoplasm and a bulbous nucleus that protrudes into glandular lumens. The tumour cells may also be flat with bland nuclei and scant cytoplasm in cystic areas or have granular eosinophilic cytoplasm without glycogen. The nuclei vary considerably in appearance. They may be significantly enlarged with multiple irregular nucleoli in clear and hobnail cells, or they may have fine chromatin and inconspicuous nucleoli in flat cells. The num-



**Fig. 6.13** Clear cell adenocarcinoma. **A** Note the neoplastic tubules lined by hobnail cells on the right and adenosis of the tuboendometrial type on the left. **B** Cytological preparation shows hobnail cells with anisonucleosis, unevenly distributed chromatin, nucleoli and vacuolated cytoplasm.

ber of mitoses varies but is usually less than 10 per 10 high power fields. Psammoma and intracellular hyaline bodies may occasionally be encountered.

### Cytopathology

In cytological preparations the malignant cells may occur singly or in clusters and resemble large endocervical or endometrial cells. Typically, the nuclei are large with one or more prominent nucleoli. Nuclei may be bizarre. The bland cytological features of tumours that show only mild nuclear atypia may, however, hamper cytological detection.

### Prognosis and predictive factors

Clear cell adenocarcinoma may be treated by radical hysterectomy, vaginectomy and lymphadenectomy or by external beam or local radiotherapy. The tumour spreads primarily by local invasion and lymphatic metastases and has a recurrence rate of 25%. The incidence of lymph node disease increases dramatically with tumour invasion beyond 3 mm in depth. Lymph node metastases occur in 16% of patients with stage I disease and 50% of those with stage II disease. Haematogenous metastasis to distant organs occurs mainly to the lungs. The 5-year survival of patients with tumours of all stages is approximately 80% and is close to 100% for patients with stage I tumours. Most recurrences occur within 3 years. Long disease-free intervals of more than 20 years have been observed. Factors associated with a favourable prognosis are: low stage, small tumour size, a tubulocystic pattern, low mitotic activity and mild nuclear atypia.

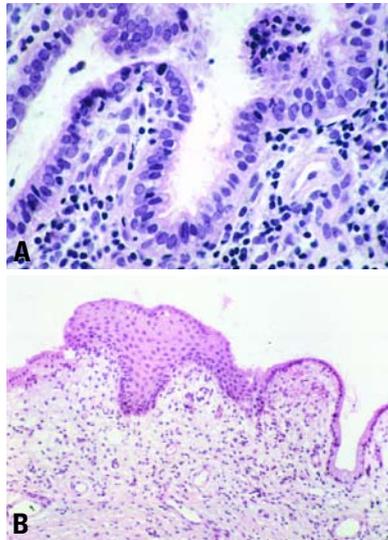
### Adenosis

#### Definition

Adenosis is the presence of glandular epithelium in the vagina and is thought to be the result of the persistence of embryonic müllerian epithelium.

#### Epidemiology

Adenosis has been reported to occur in approximately 30% of women after in utero exposure to DES. Congenital adenosis may be present in up to 8% of unexposed women. Adenosis has been described after laser vaporization or intravaginal application of 5-fluorouracil [730].



**Fig. 6.14** Adenosis of the vagina. **A** Note the tuboendometrioid type glands. **B** On the surface within adenosis is a focus of squamous metaplasia.

#### Localization

The most frequent site of involvement is the anterior upper third of the vagina.

#### Clinical features

##### Signs and symptoms

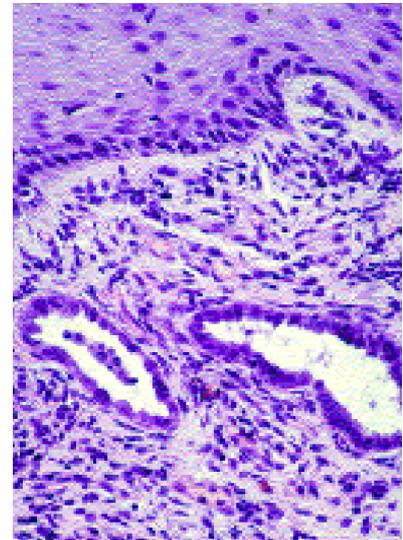
Adenosis is usually asymptomatic. Some women present with a mucous discharge, bleeding or dyspareunia. Adenosis may spontaneously regress at the surface and be replaced by metaplastic squamous epithelium, particularly with increasing age. Because of the risk of development of clear cell adenocarcinoma within the vaginal wall, palpation, colposcopic examination and cytological smears are necessary to monitor patients with adenosis.

#### Colposcopy

Areas of adenosis and associated squamous metaplasia may be visible colposcopically and by iodine staining [2046]. Adenosis may be occult or may present as cysts or as a diffusely red granular area.

#### Cytology

Cytology can be helpful in the diagnostic evaluation of DES-exposed women (see below). It may serve a dual purpose, as a means for detection of adenocarcinoma or as a follow-up procedure after treatment of the lesion.



**Fig. 6.15** Submucosal atypical adenosis of the vagina. Note the nuclear enlargement and atypia in the glands.

Adenosis can be detected on cytological examination by the finding of columnar or metaplastic squamous cells in scrapes of the middle and upper third of the vagina. However, similar findings may occur in non-DES-exposed women as a result of contamination of the vaginal specimen by columnar or metaplastic squamous cells from the cervix.

#### Histopathology

Adenosis is characterized by the presence in the vagina of columnar epithelium resembling mucinous epithelium of the endocervix (mucinous type) and/or the endometrium or the fallopian tube (tuboendometrial type). Adenosis may be found on the surface or deeper in the stroma. Mixtures of the various types of adenosis may be encountered. Squamous metaplasia may occur as a result of healing.

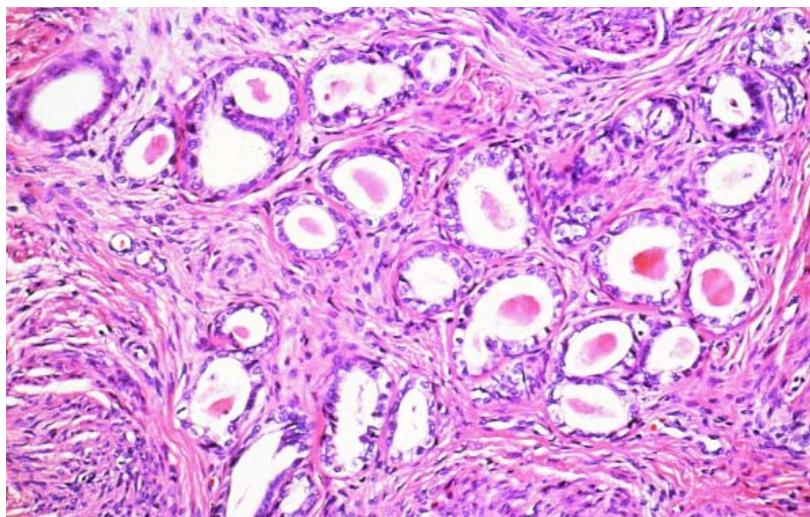
#### Atypical adenosis

##### Definition

Atypical adenosis is the presence of atypical glandular epithelium in the vagina. It is reported to be a precursor lesion of clear cell adenocarcinoma.

#### Histopathology

Atypical adenosis occurs in the tuboendometrial type of adenosis and is a fre-



**Fig. 6.16** Mesonephric remnants. The wall of the vagina contains clusters of uniform dilated tubules with luminal hyaline material.

quent finding immediately adjacent to clear cell adenocarcinoma. The atypical glands tend to be more complex than those of mucinous adenosis and are lined by cells with enlarged, atypical, pleomorphic, hyperchromatic nuclei that contain prominent nucleoli. Mitotic figures are infrequent, and hobnail cells may be present.

#### **Differential diagnosis**

A distinction from clear cell adenocarcinoma may be difficult if the atypical adenosis shows a pseudoinfiltrative pattern of small glands. Conversely, clear cell adenocarcinoma displaying a tubulocystic pattern may be erroneously interpreted as adenosis. However, unlike tubulocystic clear cell adenocarcinoma with bland flattened cells, atypical adenosis is composed of cuboidal or columnar epithelium.

#### **Prognosis and predictive factors**

Management may be local excision or follow-up {2609}.

#### **Endometrioid adenocarcinoma**

Only a few primary endometrioid adenocarcinomas of the vagina have been reported. The histological appearance resembles that of the much more common endometrioid adenocarcinoma of the endometrium. A few cases have

been described in association with adenosis as well as cases arising in vaginal endometriosis {1155,3251}.

#### **Mucinous adenocarcinoma**

Primary mucinous adenocarcinoma of the vagina is rare. Only a few cases have been reported {745}. Like the other non-clear cell adenocarcinomas of the vagina, this type of tumour is predominantly reported in peri-menopausal women. Histologically, the tumour may resemble typical endocervical or intestinal adenocarcinomas of the cervix {909}. Due to its rarity, little is known about its aetiology and behaviour. A relationship to vaginal adenosis has been described {3168}, suggesting a müllerian origin. An unusual variant of mucinous adenocarcinoma has been described in neovaginas {1218,1941}.

#### **Mesonephric adenocarcinoma**

Mesonephric (Gartner) duct remnants are mostly situated deep in the lateral walls of the vagina. Only a few cases of carcinoma arising from mesonephric remnants in the vagina have been reported, and none since 1973. These tumours are composed of well-formed tubules lined by atypical, mitotically-active, cuboidal to columnar epithelium that resemble mesonephric duct remnants. Unlike clear

cell adenocarcinoma, mesonephric carcinoma does not contain clear or hobnail cells, intracellular mucin or glycogen, and the tubules are often surrounded by a basement membrane.

#### **Müllerian papilloma**

Müllerian papilloma may arise in the vagina of infants and young women {2977} (see also chapter on the cervix). A few examples have arisen in the wall of the vagina {1817}. Occasional local recurrences have been reported {1719}, and in one instance repeated removal of recurrent müllerian papillomas was necessary {708}. The origin of the tumour is not clear, although reports support a müllerian origin {1719}.

#### **Tubular, tubulovillous and villous adenoma**

##### **Definition**

Benign glandular tumours with enteric differentiation {494}.

##### **Clinical features**

Patients may be premenopausal or postmenopausal. Clinical examination may reveal a polypoid mass.

##### **Histopathology**

The adenomas are histologically similar to colonic types and have been subclassified as tubular, tubulovillous or villous. The epithelium is stratified and contains columnar cells with mucin. The nuclei are oval to elongated and dysplastic. Adenocarcinoma arising from a vaginal adenoma has been reported {1935}.

##### **Differential diagnosis**

Aside from endometriosis and prolapsed fallopian tube, the most important lesions in the differential diagnosis are metastatic carcinoma and extension or recurrence of endometrial or endocervical adenocarcinoma. An adenoma is generally polypoid and lacks invasive borders, marked architectural complexity or high grade cytological features.

#### **Uncommon epithelial tumours**

##### **Definition**

Primary epithelial tumours of the vagina other than those of squamous or glandular type. These tumours are described in more detail in the chapter on the cervix.

**ICD-O codes**

Adenosquamous carcinoma	8560/3
Adenoid cystic carcinoma	8200/3
Adenoid basal carcinoma	8098/3
Carcinoid	8240/3
Small cell carcinoma	8041/3
Undifferentiated carcinoma	8020/3

**Adenosquamous carcinoma**

A carcinoma composed of a mixture of malignant glandular and squamous epithelial elements {2360}.

**Adenoid cystic carcinoma**

An adenocarcinoma which resembles adenoid cystic carcinoma of salivary gland origin but usually lacks the myoepithelial cell component of the latter {2781}.

**Adenoid basal carcinoma**

A carcinoma with rounded, generally well differentiated nests of basaloid cells showing focal gland formation; central squamous differentiation may be present as well {1906,1986}.

**Carcinoid**

A tumour resembling carcinoids of the gastrointestinal tract and lung {936}.

**Small cell carcinoma**

A carcinoma of neuroendocrine type that resembles small cell carcinomas of the lung {1371,1869,1877,2281}.

**Undifferentiated carcinoma**

A carcinoma that is not of the small cell type and lacks evidence of glandular, squamous, neuroendocrine or other types of differentiation.

# Mesenchymal tumours

A.G. Östör

## Vaginal sarcomas

### Definition

Malignant mesenchymal tumours that arise in the vagina.

### ICD-O codes

Sarcoma botryoides	8910/3
Leiomyosarcoma	8890/3
Endometrioid stromal sarcoma, low grade	8931/3
Undifferentiated vaginal sarcoma	8805/3

### Epidemiology

Sarcomas are rare and comprise <2% of all malignant vaginal neoplasms {633}.

### Aetiology

There are virtually no clues to the pathogenesis of this group of tumours.

### Clinical features

#### Signs and symptoms

Malignant tumours usually present with bleeding and/or discharge and a mass and are usually readily detected by clinical examination. Occasional cases are detected by an abnormal cytological examination. Some sarcomas, however, are asymptomatic, and the diagnosis is, therefore, delayed.

#### Imaging

The extent of tumour spread may be determined by transvaginal ultrasound.

### Tumour spread and staging

Vaginal sarcomas spread by direct extension and by metastasis; the latter occurs both by lymphatic and haematogenous routes. The tumour initially grows into the vaginal wall and soft tissue of the pelvis, bladder or rectum. The staging of vaginal sarcomas in adults utilizes the TNM/FIGO classification {51,2976}.

### Sarcoma botryoides

#### Definition

A malignant mesenchymal tumour composed of small, round or oval to spindle-

shaped cells, some of which show evidence of striated muscle differentiation.

#### Synonym

Embryonal rhabdomyosarcoma.

### Epidemiology

Sarcoma botryoides (Greek bothryos: grapes) is the most common vaginal sarcoma and occurs almost exclusively in children and infants <5 years of age (mean 1.8 years) {633}, although occasional cases are encountered in young adults or even postmenopausal women. At least two cases of sarcoma botryoides have been described in pregnancy {2709}.

### Clinical features

These tumours present typically as a vaginal mass that on clinical and macroscopic examination appears soft, oedematous and nodular, papillary, polypoid or grape-like, often protruding through the introitus.

### Macroscopy

The tumours vary from 0.2-12 cm in maximum dimension and may be covered by an intact mucosa or be ulcerated and bleeding. The sectioned surface displays grey to red areas of myxomatous change and haemorrhage.

### Tumour spread and staging

In children the Intergroup Rhabdomyosarcoma Study group clinical classi-

fication is used, which is based on the combined features of extent of disease, resectability and histological evaluation of margins of excision {99}.

### Histopathology

The neoplasm is composed of cells with round to oval or spindle-shaped nuclei and eosinophilic cytoplasm that may show differentiation towards striated muscle cells. Typically, there is a dense cambium layer composed of closely packed cells with small hyperchromatic nuclei immediately subjacent to the squamous epithelium that may be invaded. The nuclei have an open chromatin pattern and inconspicuous nucleoli. The central portion of the polypoid mass is typically hypocellular, oedematous or myxomatous. The mitotic rate is high. Rhabdo-myoblasts (strap cells), which may be sparse, may be found in any of the patterns. Their recognition may be facilitated by immunohistochemical staining with antibodies directed against actin, desmin or myoglobin. Although the first two antibodies are more sensitive than myoglobin, they are not specific for skeletal muscle differentiation. Ultrastructural examination may reveal characteristic features of rhabdomyoblastic differentiation, such as thick and thin filaments with Z-band material.

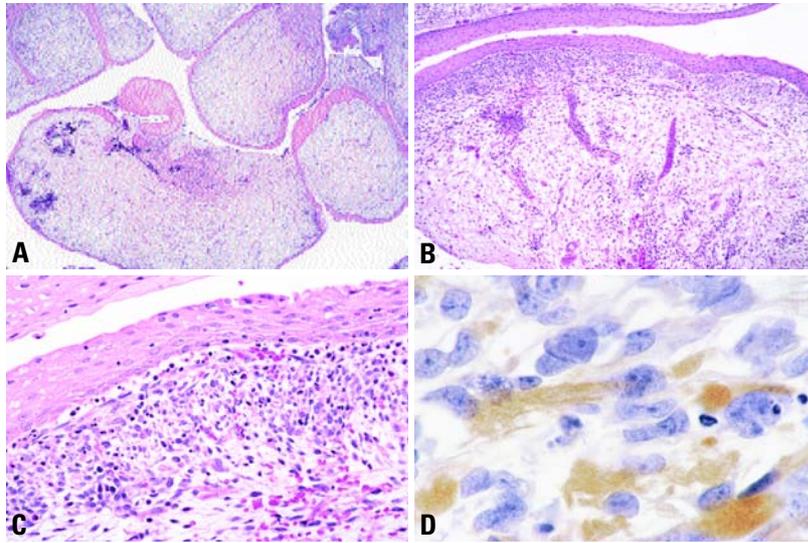
### Differential diagnosis

The distinction from a benign fibroepithelial polyp with bizarre nuclei is important.

**Table 6.02**

Clinical classification of vaginal sarcoma botryoides / rhabdomyosarcoma {99}.

I	Complete surgical resection
IIa	Excision, margin positive
IIb	Excision, lymph nodes positive
IIIa	Biopsy only
IIIb	Partial surgical excision (gross disease present)
IV	Metastatic disease



**Fig. 6.17** Sarcoma botryoides. **A** Polypoid masses of tumour are covered by squamous epithelium. **B** A subepithelial cambium layer overlies oedematous tissue. **C** Higher magnification of the cellular subepithelial cambium layer. **D** The positive immunostain for desmin confirms the myoblastic differentiation. Note the nuclear pleomorphism.

The clinical setting, the characteristic low power appearance, the absence of a cambium layer and striated cells and a typically low mitotic index establish the correct diagnosis of a fibroepithelial polyp [2055,2067,2141].

#### Genetic susceptibility

One instance of sarcoma botryoides has been reported in a child with multiple congenital abnormalities and bilateral nephroblastomas suggesting a possible genetic defect [1965].

#### Prognosis and predictive factors

The prognosis of sarcoma botryoides in the past was poor, but an 85% 3-year survival rate has recently been achieved with wide local excision and combination chemotherapy. Second malignancies in long-term survivors of vaginal embryonal rhabdomyosarcoma have not been reported to date.

#### Leiomyosarcoma

##### Definition

A malignant tumour composed of smooth muscle cells.

##### Epidemiology

Although leiomyosarcoma is the most common vaginal sarcoma in the adult and the second most common vaginal

sarcoma, only approximately 50 cases have been reported [599]. They accounted for only 5 of 60 cases in the only large series of vaginal smooth muscle tumours [2879].

##### Macroscopy

Macroscopically, they are sometimes multilobulated and form masses from 3-5 cm. The sectioned surface has a pink-grey, "fish-flesh" appearance with scattered foci of haemorrhage, myxoid change or necrosis. The overlying mucosa may be ulcerated.

##### Histopathology

Histologically, they are identical to their counterparts elsewhere. It may be difficult to predict the behaviour of some smooth muscle tumours. Currently, it is recommended that vaginal smooth muscle tumours that are larger than 3 cm in diameter and have 5 or more mitoses per 10 high-power fields, moderate or marked cytological atypia and infiltrating margins be regarded as leiomyosarcoma [2879]. An epithelioid variant with a myxoid stroma has also been described [456]. As in the uterus, occasional sarcomas arise from leiomyomas [1682].

##### Differential diagnosis

Leiomyosarcomas should be differentiated from the benign condition of post-

operative spindle cell nodule [2861]. The latter is a localized non-neoplastic lesion composed of closely packed spindle-shaped cells and capillaries occurring several weeks to several months postoperatively in the region of an excision. It may closely resemble a leiomyosarcoma, but the history of a recent operation at the same site facilitates its diagnosis.

#### Prognosis and predictive factors

Leiomyosarcomas are treated primarily by radical surgical excision (vaginectomy, hysterectomy and pelvic lymphadenectomy). In the only large series of 60 smooth muscle tumours, both benign and malignant, only 5 neoplasms recurred, and in one of these, a tumour with an infiltrative margin, the patient died of lung metastases [2879].

#### Endometrioid stromal sarcoma, low grade

##### Definition

A sarcoma with an infiltrating pattern that in its well differentiated form resembles normal endometrial stromal cells.

##### Histopathology

Low grade endometrioid stromal sarcomas have been rarely encountered in the vagina and resemble their counterparts in the endometrium. In two cases the tumours appear to have arisen from endometriosis [245]. Before concluding that such a neoplasm is primary in the vagina, an origin within the uterus should be excluded [633,1051,2226]. The term undifferentiated vaginal sarcoma is preferred for the high grade lesions.

#### Undifferentiated vaginal sarcoma

##### Definition

A sarcoma with an infiltrating pattern composed of small spindle-shaped cells lacking specific features.

##### Histopathology

Undifferentiated vaginal sarcomas are rare, polypoid or diffusely infiltrating lesions. Spindle to stellate cells with scanty cytoplasm are arranged in sheet-like, fascicular or storiform patterns. The cells exhibit various degrees of nuclear pleomorphism and hyperchromasia. The mitotic index is 10 per 10 high power fields.

### Prognosis and predictive factors

Death from recurrent or metastatic tumour has occurred within 2 years of treatment in about 50% of patients [20, 3236].

### Rare malignant mesenchymal tumours

Rare examples of malignant schwannoma [633], fibrosarcoma [2160], malignant fibrous histiocytoma [3078], angiosarcoma [1804,2298,2931], alveolar soft part sarcoma [402], synovial sarcoma [2095], malignant peripheral nerve sheath tumour [2226] and unclassifiable sarcoma [633] have all been described in the vagina, but they do not exhibit unique clinical or morphological features.

### Benign mesenchymal neoplasms

Of the benign tumours only leiomyomas are relatively common.

#### ICD-O codes

Leiomyoma	8890/0
Genital rhabdomyoma	8905/0
Deep angiofibroma	8841/1

#### Clinical features

Most benign tumours are asymptomatic, but depending on their size and position they may cause pain, bleeding, dyspareunia and urinary or rectal symptoms.

### Leiomyoma

#### Definition

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

#### Epidemiology

Approximately 300 cases of vaginal leiomyoma have been reported. Although the age at presentation ranges from 19-72 years, they typically occur during reproductive life (mean age 44 years) [2879]. Leiomyomas of the vagina are not related to those of the uterus, either in frequency or in racial distribution, the White to Black ratio for uterine and vaginal leiomyomas being 1:3 and 4:1 respectively [222].

### Aetiology

There are virtually no clues to the pathogenesis of this group of tumours. Rare leiomyomas may recur in one or more pregnancies suggesting hormone dependency [2501].

### Histopathology

Vaginal leiomyomas resemble their uterine counterparts. A case of bizarre (symplastic) leiomyoma has been described [264].

### Histogenesis

The histogenesis of smooth muscle tumours is not clear, but myoepithelial cells such as are found in smooth muscle cells of venules or of the vaginal muscularis and myofibroblasts have all been implicated.

### Prognosis and predictive factors

Nearly all are treated by local excision [1682,2486,2523]. An occasional tumour, especially if large, may recur [685,1682].

### Genital rhabdomyoma

#### Definition

An uncommon benign tumour of the lower female genital tract showing skeletal muscle differentiation.

#### Epidemiology

About 20 cases have been reported [1313,2812].

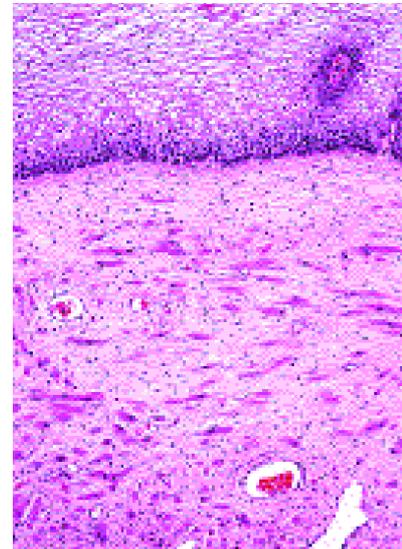


Fig. 6.18 Genital rhabdomyoma. The tumour is composed of individual mature rhabdomyoblasts separated by abundant connective tissue stroma.

#### Clinical features

These tumours occur in middle age women (range 30-48 years) and present as a well defined, solitary mass with the clinical appearance of a benign vaginal polyp [1397].

#### Macroscopy

Genital rhabdomyomas are solitary, nodular or polypoid, ranging in size from

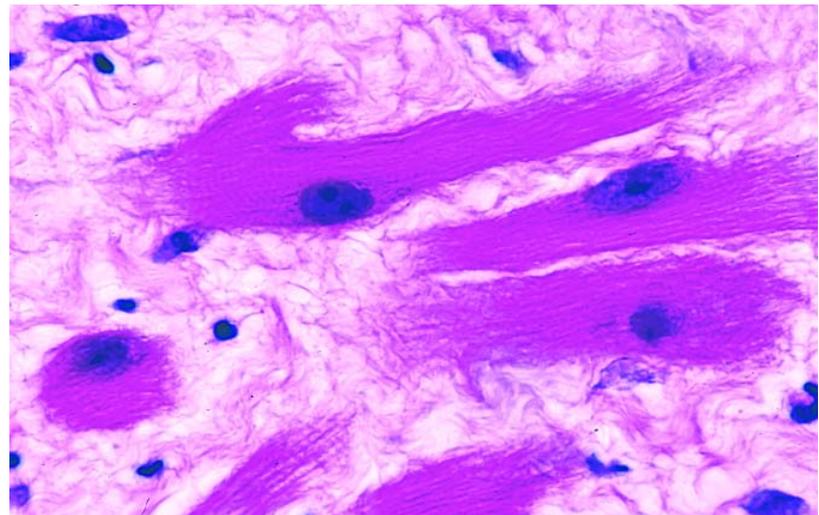


Fig. 6.19 Genital rhabdomyoma. The tumour is composed of individual mature rhabdomyoblasts with cross striations in the cytoplasm and bland nuclei without mitotic activity.

1-11 cm. They may arise anywhere in the vagina, and some protrude into the lumen. The overlying mucosa is usually intact since the tumour arises in the wall. The texture is rubbery and the sectioned surface is grey and glassy.

#### **Histopathology**

They are composed of mature, bland rhabdomyoblasts that are oval or strap-shaped with obvious cross striations in the cytoplasm. Mitotic activity and nuclear pleomorphism are absent. Abundant connective tissue stroma surrounds individual muscle cells. Rhabdo-myoma should not be confused with sarcoma botryoides.

#### **Prognosis and predictive factors**

No recurrences have been reported after complete local excision.

#### **Deep angiomyxoma**

##### **Definition**

A locally infiltrative tumour with a predilection for the pelvic and perineal regions and a tendency for local recurrence composed of fibroblasts, myofibroblasts and numerous, characteristically thick-walled, blood vessels embedded in an abundant myxoid matrix.

##### **Synonym**

Aggressive angiomyxoma.

##### **Clinical features**

Most patients present with a large, slowly growing, painless mass in the pelviperineal region that may give rise to pressure effects on the adjacent urogenital or

anorectal tracts. Imaging studies often show the mass to be substantially larger than clinically suspected.

##### **Macroscopy**

Macroscopically, the tumour is lobulated but poorly circumscribed due to finger-like extensions into the surrounding tissue. The neoplasm is grey-pink or red-tan and rubbery or gelatinous.

##### **Tumour spread and staging**

Deep angiomyxoma is a locally infiltrative but non-metastasizing neoplasm that occurs for the most part during the reproductive years. At least two cases have been reported within the vagina, an uncommon site for this neoplasm [81, 496].

##### **Histopathology**

The tumour is of low to moderate cellularity and is composed of small, uniform, spindle-shaped to stellate cells with poorly defined, pale eosinophilic cytoplasm and bland, often vesicular nuclei. An abundant myxoid matrix contains a variable number of rounded, medium-sized to large vessels that possess thickened focally hyalinized walls. A characteristic feature is the presence of loosely organized islands of myoid cells around the larger nerve segments and vessels [3086]. The neoplasm is positive for desmin in almost all cases, whereas stains for S-100 protein are consistently negative [1431,2082].

##### **Prognosis and predictive factors**

The treatment for this locally aggressive but non-metastasizing neoplasm is pri-

marily surgical with close attention to margins. Approximately 30% of tumours recur locally.

#### **Postoperative spindle cell nodule**

##### **Definition**

A non-neoplastic localized lesion composed of closely packed proliferating spindle cells and capillaries simulating a leiomyosarcoma.

##### **Clinical features**

The lesion develops at the site of a recent operation several weeks to several months postoperatively [2861].

##### **Histopathology**

The lesion is composed of closely packed, mitotically active, spindle-shaped mesenchymal cells and capillaries often with an accompaniment of inflammatory cells.

##### **Differential diagnosis**

The history of a recent operation at the same site serves to distinguish this lesion from leiomyosarcoma. Postoperative spindle cell nodule may closely resemble a leiomyosarcoma or other spindle cell sarcoma, but the history of a recent operation at the same site facilitates its diagnosis.

# Mixed epithelial and mesenchymal tumours

S.G. Silverberg

## Definition

Tumours in which both an epithelial and a mesenchymal component can be histologically identified as integral neoplastic components.

## ICD-O codes

Carcinosarcoma	8980/3
Adenosarcoma	8933/3
Malignant mixed tumour	8940/3
Benign mixed tumour	8940/0

## Epidemiology

These mixed tumours are among the rarest of vaginal primary tumours, which are themselves uncommon primary tumours of the female genital tract. No mixed tumours were found among 753 primary vaginal tumours compiled from ten reports in the literature [2714]. The U.S. National Cancer Data Base Report on Cancer of the Vagina [577] includes only 25 "complex mixed or stromal tumours" among 4,885 submitted cases of vaginal cancer. As expected, there are no epidemiological data available on mixed tumours [2226].

## Aetiology

The aetiology of the tumours in this group that are more often primary in the endometrium, i.e. carcinosarcoma and adenosarcoma is discussed in the chapter on the uterine corpus of this publication. The aetiology of vaginal malignant mixed tumour is essentially unknown.

## Carcinosarcoma

### Definition

A tumour with malignant epithelial and mesenchymal components. Before the diagnosis of a primary vaginal tumour is made, extension from elsewhere in the female genital tract must be excluded.

### Synonyms

Malignant müllerian mixed tumour, malignant mesodermal mixed tumour, metastatic carcinoma.

### Clinical features

These tumours present clinically as a palpable vaginal mass. Carcinosarcomas usually bleed and may occur years after therapeutic irradiation for some

other lesion [2226,2714]. Imaging studies have not been reported for any of these lesions.

## Macroscopy

Carcinosarcomas in their rare primary vaginal manifestations are identical in macroscopic appearance to their far more common endometrial counterparts. Although primary vaginal tumours of this sort are exophytic lesions, carcinosarcomas are more likely to be metastases from the endometrium or elsewhere in the female genital tract and may be deeper in the wall.

## Tumour spread and staging

Staging and spread of these malignant tumours are identical to those of primary vaginal carcinomas [2714]

## Histopathology

Primary vaginal carcinosarcoma is histologically identical to its endometrial counterpart. A vaginal metastasis from an endometrial or other primary carcinosarcoma may contain only the carcinomatous or rarely the sarcomatous component [1388,2692].

## Prognosis and predictive factors

Most women with primary vaginal carcinosarcomas have rapidly developed metastases and died.

## Adenosarcoma

### Definition

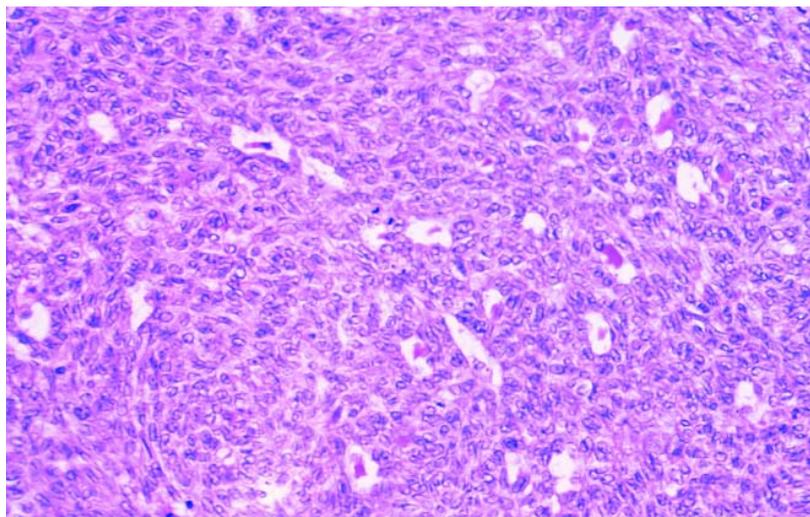
A mixed tumour composed of a benign or atypical epithelial component of müllerian type and a malignant appearing mesenchymal component.

### Clinical features

Adenosarcoma presents clinically as a palpable vaginal mass.

## Macroscopy

Although primary vaginal adenosarcoma is typically an exophytic lesion, adenosarcomas are more likely to be metastases from the endometrium or



**Fig. 6.20** Malignant mixed tumour of the vagina. The cellular tumour is composed of sheets of oval to spindle-shaped cells with occasional gland-like formations and mitotic figures.

elsewhere in the female genital tract and may be deeper in the wall.

### Histopathology

Primary vaginal adenosarcoma is histologically identical to its endometrial counterpart. Metastatic adenosarcoma generally consists of the sarcoma alone {2692}

### Prognosis and predictive factors

Adenosarcomas of the vagina are not reported in enough numbers or detail to establish their prognosis.

### Malignant mixed tumour resembling synovial sarcoma

#### Definition

An extremely rare biphasic malignant tumour resembling synovial sarcoma and containing gland-like structures lined by flattened epithelial-appearing cells and a highly cellular mesenchymal component. There is no evidence of müllerian differentiation.

#### Clinical features

The two reported cases of mixed tumour resembling synovial sarcoma presented as polypoid masses in the lateral fornix in women of ages 24 and 33.

#### Histopathology

The mixed tumour resembling synovial sarcoma, as its name suggests, is composed of gland-like structures lined by round to flattened epithelial-appearing cells embedded in a spindle cell matrix. In one reported case electron microscopic study suggested synovial-like differentiation {2095}, whilst in another, a possible origin from mesonephric rests was proposed {2652}.

### Prognosis and predictive factors

Follow-up was too short to establish the clinical malignancy and survival rates of the two malignant mixed tumours resembling synovial sarcoma reported in the literature.

### Benign mixed tumour

#### Definition

A well circumscribed benign tumour histologically resembling the mixed tumour of salivary glands with a predominant mesenchymal-appearing component and epithelial cells of squamous or glandular type.

#### Synonym

Spindle cell epithelioma.

#### Clinical features

The benign mixed tumour is usually asymptomatic, typically is a well-demarcated submucosal mass and has a predilection for the hymenal region {335, 2714}.

It tends to occur in young to middle-aged women, with a mean age of 40.5 in the largest series reported {335}.

#### Macroscopy

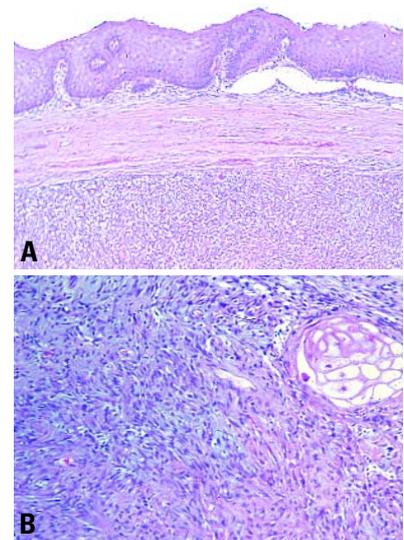
Benign mixed tumours are circumscribed, grey to white, soft to rubbery masses, usually measuring from 1-6 cm {335,2714}

#### Histopathology

The spindle cell component predominates histologically and lacks atypia or significant mitotic activity. Randomly interspersed are nests of benign-appearing squamous cells and, less frequently, glands lined by low cuboidal to columnar epithelium commonly demonstrating squamous metaplasia. Hyaline globular aggregates of stromal matrix are also frequently seen.

#### Immunoprofile

In an immunohistochemical study of a large series of cases, the spindle cells were strongly keratin-immunoreactive in 90% cases {335}. They showed only minimal expression for smooth muscle actin and were uniformly negative for S-100 protein, glial fibrillary acidic protein and factor VIII-related antigen {335,2717}. The tumours coexpressed CD34, CD99 and Bcl-2 {2717}.



**Fig. 6.21** Benign mixed tumour. **A** Low power magnification shows circumscription without involvement of the overlying squamous epithelium. **B** Note the squamous nest within a spindle cell proliferation.

#### Histogenesis

The only benign vaginal tumour classically designated as a mixed tumour because of its histological resemblance to the benign mixed tumour (pleomorphic adenoma) of salivary glands has been renamed spindle cell epithelioma because of immunohistochemical and ultrastructural evidence suggesting purely epithelial differentiation {335}.

Unlike mixed tumours of salivary glands, these vaginal tumours show no immunohistochemical or ultrastructural features of myoepithelial cells {2717}. Origin from a primitive/progenitor cell population has been postulated {2717}.

### Prognosis and predictive factors

The benign mixed tumour has never metastasized in reports of over forty cases; however, local recurrences have been noted.

# Melanotic, neuroectodermal, lymphoid and secondary tumours

R. Vang  
F.A. Tavassoli  
E.S. Andersen

## Melanocytic tumours

### Definition

A tumour composed of melanocytes, either benign or malignant.

### ICD-O codes

Malignant melanoma	8720/3
Blue naevus	8780/0
Melanocytic naevus	8720/0

### Malignant melanoma

#### Definition

A tumour composed of malignant melanocytes.

#### Epidemiology

Malignant melanoma is a rare but very aggressive tumour of the vagina. Patients have an average age of 60 years and most are White {492}.

#### Clinical features

They typically present with vaginal bleeding, and some may have inguinal lymphadenopathy. The more common loca-



**Fig. 6.22** Melanoma of the lower anterior vaginal wall. Note the large, polypoid heavily pigmented tumour.

tions are in the lower third of the vagina and on the anterior vaginal wall.

#### Macroscopy

The lesions are pigmented and usually 2-3 cm in size.

#### Histopathology

The lesions are invasive and may display ulceration. Most have a lentiginous growth pattern, but junctional nests can be seen. In-situ or pagetoid growth is not typical. The cells are epithelioid or spindle-shaped and may contain melanin pigment. There is brisk mitotic activity. Tumour cells express S-100 protein, melan A and HMB-45.

#### Differential diagnosis

As "atypical" or dysplastic melanocytic lesions of the vagina have not been evaluated, histological separation of "borderline" melanocytic lesions from melanoma is not always possible. Nests of epithelioid cells raise the possibility of a poorly differentiated carcinoma. Spindle cell differentiation may create confusion with sarcomas.

#### Prognostic and predictive factors

##### Clinical criteria

Patients have been treated by a combination of surgery, radiation and chemotherapy. The prognosis is poor with a 5-year survival rate of 21% and a mean survival time of 15 months {314}.

##### Histopathological criteria

Assessment of Clark levels, as is done for melanomas of skin, is not possible given the lack of normal cutaneous anatomical landmarks. Most tumours have a significant thickness, but even a thin melanoma does not necessarily portend a favourable prognosis. One study found that mitotic activity correlates better with the clinical outcome than the depth of invasion {314}.

### Blue naevus

#### Definition

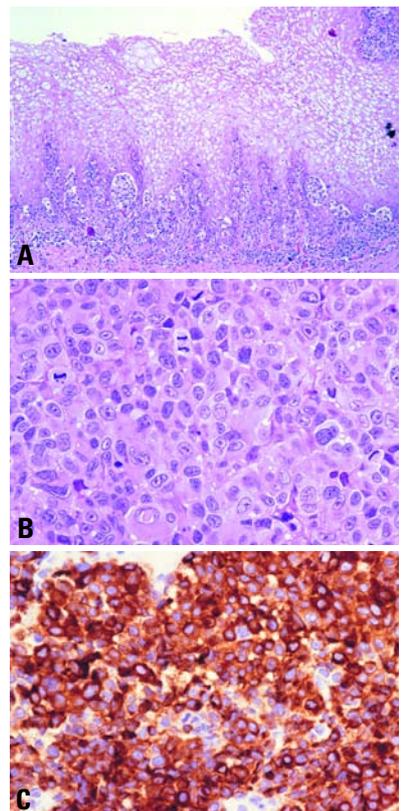
A proliferation of subepithelial dendritic melanocytes.

#### Clinical features

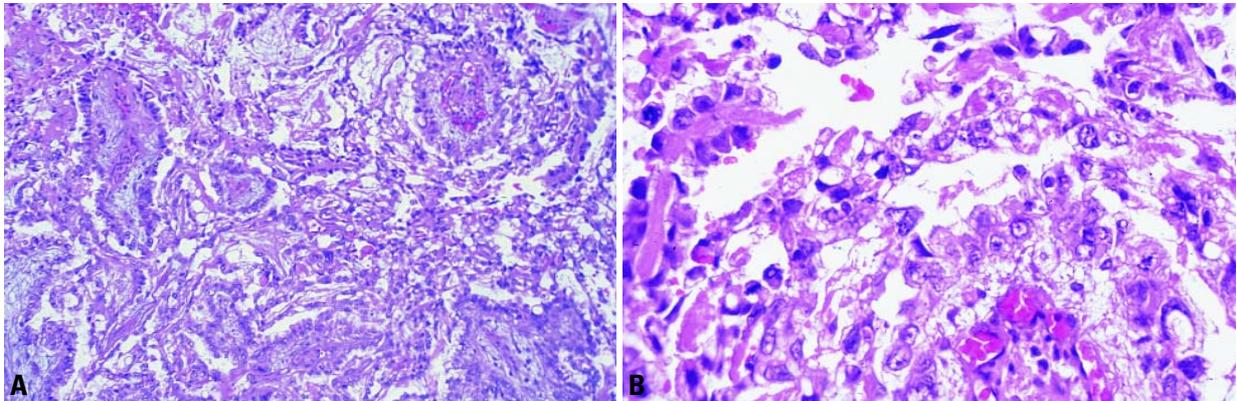
Though rare, both common and cellular variants of blue naevus have been reported in the vagina {2400,2929}. The common variant typically presents as a blue-black macule and the cellular variant as a nodule.

#### Histopathology

Classic blue naevi contain melanocytes with elongated dendritic processes and heavy cytoplasmic pigmentation. Cellular



**Fig. 6.23** Melanoma of the vagina. **A** Note the prominent junctional component. **B** The tumour cells are epithelioid with abundant eosinophilic cytoplasm, large pleomorphic nuclei, prominent nucleoli, intranuclear inclusions and mitotic figures. **C** Immunostain shows diffuse, strong expression for melan A.



**Fig. 6.24** Yolk sac tumour. **A** The tumour has a labyrinthine pattern with occasional Schiller-Duval bodies. **B** Papillary cores and labyrinthine structures are lined by primitive cuboidal cells with cytoplasmic vacuolization and rare hyaline globules.

variants have a biphasic composition with areas similar to common blue naevus admixed with round nodules. The cells are arranged in nests and short fascicles with a whorled pattern and are plump and spindle-shaped with oval bland nuclei and pale cytoplasm.

#### *Differential diagnosis*

The common variant should not pose a diagnostic problem. The cellular variant may cause confusion with melanoma and smooth muscle tumours. Nuclear atypia and numerous mitotic figures would favour melanoma. Well defined interlacing fascicles, large thick-walled blood vessels, immunohistochemical positivity for muscle markers and negativity for S-100 protein should assist in making the diagnosis of a smooth muscle tumour.

#### **Melanocytic naevus**

##### **Definition**

Melanocytic nevi are defined as proliferation of nests of naevus cells.

##### **Clinical features**

Melanocytic nevi of the vagina are thought to be similar to their counterparts in the skin [1539].

#### **Yolk sac tumour**

##### **Definition**

A primitive malignant germ cell tumour characterized by a variety of distinctive histological patterns, some of which recapitulate phases in the development of the normal yolk sac.

**ICD-O code** 9071/3

##### **Synonym**

Endodermal sinus tumour.

##### **Clinical features**

Patients are usually under 3 years of age. Vaginal bleeding and discharge are the most common symptoms. Serum levels of alpha-fetoprotein may be elevated. A polypoid friable mass is seen on clinical examination with a mean size of 3 cm.

##### **Histopathology**

Vaginal cases resemble their ovarian counterparts.

##### *Differential diagnosis*

Although sarcoma botryoides may be simulated clinically, the histological features resolve any confusion. Clear cell and endometrioid carcinomas may create difficulty in histological separation.

##### **Prognosis and predictive factors**

Combined surgery and chemotherapy may provide a favourable outcome. A disease-free survival of up to 23 years is possible [557].

#### **Peripheral primitive neuroectodermal tumour / Ewing tumour**

##### **Definition**

Tumours of uncertain lineage within the small round blue cell family of tumours.

##### **ICD-O code**

Peripheral primitive neuroectodermal tumour / 9364/3

Ewing tumour

9260/3

##### **Clinical features**

Peripheral primitive neuroectodermal tumour/Ewing tumour (PNET/ET) is rare within the vagina [3002]. A reported case occurred in a 35-year-old woman who presented with a vaginal mass.

##### **Histopathology**

Histological features are similar to PNET/ET in non-vaginal sites. Typically, PNET/ET grows as a diffuse sheet of uniform small cells with scant pale cytoplasm and an intermediate to high nuclear to cytoplasmic ratio. The nuclei are round with evenly dispersed chromatin. Mitotic figures may be numerous, and rosettes may be seen.

##### *Immunoprofile*

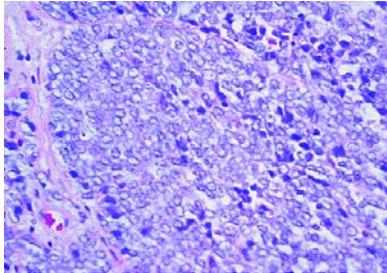
Expression of CD99 would be expected in almost all cases.

##### *Differential diagnosis*

PNET/ET should not be mistaken for rhabdomyosarcoma, non-Hodgkin lymphoma (NHL), melanoma, small cell carcinoma or endometrial stromal sarcoma because of differences in prognosis and treatment. A broad immunohistochemical panel and, if need be, molecular studies, performed on paraffin-embedded tissue should assist in making the correct diagnosis.

##### **Molecular genetics**

Identification of the *EWS/FLI1* fusion transcript derived from the t(11;22)(q24;q12) chromosomal translocation by the



**Fig. 6.25** Peripheral primitive neuroectodermal tumour. Note the sheets of small to medium sized cells with round, pale nuclei, minimal cytoplasm and high nuclear to cytoplasmic ratios.

reverse transcriptase-polymerase chain reaction and Southern blot hybridization would confirm the diagnosis.

#### Prognosis and predictive factors

The experience with PNET/ET of the vagina is limited, but patients with localized tumours in soft tissue sites can potentially be cured with a combination of surgery, chemotherapy and radiation therapy.

### Dermoid cyst

#### Definition

A cystic tumour composed of more than one germ cell layer in which all elements are mature.

#### ICD-O code

Dermoid cyst 9084/0  
Mature cystic teratoma 9080/0

#### Synonym

Mature cystic teratoma.

#### Macroscopy and histopathology

These resemble the same tumour in the ovary.

### Adenomatoid tumour

#### ICD-O code 9054/0

A single case occurring in a 47-year-old woman has been reported [1697].

### Lymphoid and haematopoietic tumours

#### Definition

Tumours of the lymphoid and haematopoietic systems as well as secondary tumours of the vagina.

### Lymphoma

#### Definition

Tumours with lymphoid differentiation arising as either primary (localized) or secondary (disseminated) disease.

#### Clinical features

Lymphomas of the vagina are predominantly of the non-Hodgkin's type [3001]. Patients with primary NHL have a mean age of 42 years, usually present with vaginal bleeding and have a mass on clinical examination. Patients with secondary NHL have a mean age of 65 years, present with vaginal bleeding and usually have a history of NHL.

#### Histopathology

Almost all NHLs primary in the vagina are diffuse large B-cell lymphomas

**Table 6.03** Immunohistochemical and cytogenetic profile of various small cell tumours of the vagina.\*

Immunohistochemical or molecular markers	Peripheral primitive neuroectodermal tumour/Ewing tumour	Rhabdomyosarcoma	B-cell non-Hodgkin lymphoma	Melanoma	Small cell carcinoma	Endometrial stromal sarcoma
Cytokeratin	+/-	+/-	-	-	+	+/-
Muscle specific actin/ desmin	-	+	-	-	-	+/-
Chromogranin/ synaptophysin	+/-	-	-	-	+/-	-
S-100 protein	+/-	-	-	+	-	-
HMB-45	-	-	-	+	-	-
Leukocyte common antigen/ CD20	-	-	+	-	-	-
CD10	-	-	+/-	-	-	+
CD99	+	+/-	+/-	-	-	-
t(11;22)	+	-	-	-	-	-
t(2;13)/ t(1;13)	-	+/-	-	-	-	-
Monoclonal immunoglobulin heavy chain gene rearrangement	-	-	+/-	-	-	-

Key: +/-, variable rate of positivity; \*, Not all markers have been thoroughly tested for each tumour, but expected results are listed.

growing in sheets. Some may have sclerosis. The neoplastic cells are large with round nuclei, vesicular chromatin and nucleoli. Secondary cases are usually diffuse large B-cell lymphomas and are histologically similar to the primary cases.

#### **Immunoprofile**

Almost all NHLs of the vagina (primary or secondary) are of B-cell lineage and typically express CD20.

#### **Differential diagnosis**

The main lesions in the differential diagnosis of NHL include granulocytic sarcoma and other haematological malignancies, carcinoma, melanoma and small round blue cell tumours such as rhabdomyosarcoma. Knowledge of the age, previous history of NHL or leukaemia, and the immunoprofile (keratin, CD20, CD3, CD43, myeloperoxidase, S-100 protein, desmin and other muscle markers) should help establish the correct diagnosis.

#### **Somatic genetics**

Southern blot analysis and polymerase chain reaction (PCR) can demonstrate monoclonal immunoglobulin heavy chain gene rearrangements in vaginal NHL. In-situ hybridization has not confirmed the presence of human papillomavirus DNA or Epstein-Barr virus (EBV) RNA [2999]; however, EBV DNA has been found by PCR [2718].

#### **Prognosis and predictive factors**

Vaginal NHL is usually treated by chemotherapy and radiation. The determination of the Ann Arbor stage is prognostically important for vaginal NHL. Patients with low stage tumours (stages IE and IIE) have a longer disease-free survival than those with high-stage disease have (stages IIIE and IV).

## **Leukaemia**

#### **Definition**

A malignant haematopoietic neoplasm that may be primary or secondary.

#### **Synonym**

Granulocytic sarcoma.

#### **Epidemiology**

Vaginal involvement by leukaemia may either be primary or secondary; however, the latter is much more common [428].

#### **Clinical features**

Leukaemia of the vagina is rare but is usually of the myeloid type (granulocytic sarcoma or "chloroma") [2099]. Patients are elderly, have a mass on clinical examination and may have other evidence of acute myeloid leukaemia.

#### **Histopathology**

A series of primary granulocytic sarcomas of the female genital tract including 3 cases of the vagina was reported [2099]. Granulocytic sarcomas are usually composed of cells with finely dispersed nuclear chromatin and abundant cytoplasm that may be deeply eosinophilic. The identification of eosinophilic myelocytes is helpful in establishing the diagnosis; however, they are not always present. The tumours are positive for chloroacetate esterase.

#### **Immunoprofile**

Granulocytic sarcomas express lysozyme, myeloperoxidase, CD43 and CD68. Staining for CD45 may be seen, but the tumour cells are negative for CD20 and CD3.

#### **Differential diagnosis**

The most important differential diagnosis is malignant lymphoma. Enzyme histochemical stains for chloroacetate esterase

or immunohistochemical stains for myeloperoxidase, CD68 and CD43 will establish the diagnosis in almost all cases [2099].

#### **Prognosis and predictive factors**

Granulocytic sarcoma of the vagina appears to behave in an aggressive fashion. Although experience is limited, the few reported granulocytic sarcomas of the vagina have also been treated with chemotherapy or radiation.

## **Secondary tumours**

#### **Definition**

Tumours of the vagina that originate outside the vagina.

#### **Incidence and origin**

Metastatic tumours are more frequent than primary malignant tumours of the vagina. Tumours may spread by direct extension, most commonly from the cervix or vulva, vascular and lymphatic dissemination or by implantation. Metastatic adenocarcinomas originate from the endometrium, colon, rectum and, more rarely, the breast. Transitional cell carcinoma metastatic from the urethra and the bladder and renal cell carcinomas have been reported. In the past vaginal metastases were reported in up to 50% of cases of uterine choriocarcinoma.

#### **Clinical features**

The primary tumour is often clinically evident or has previously been treated. The most significant symptom is abnormal vaginal bleeding. Vaginal cytology may aid detection. A biopsy is contraindicated in metastatic trophoblastic disease due to the risk of excessive bleeding.