14 Cervical Neuroendocrine Tumours, Mixed Epithelial/Mesenchymal and Mesenchymal Tumours and Other Miscellaneous Lesions

Anthony T. Williams and Raji Ganesan

Abstract

Cervical cancers are the third most common cancers of the female genital tract. Most of these neoplasms are human papillomavirus (HPV)-related squamous cell carcinomas and adenocarcinomas, but in addition a wide range of uncommon and rare tumours may occur. These may present particular diagnostic challenges resulting from their rarity and the differential diagnoses which may arise at this site.

Neuroendocrine carcinomas (NEC) are not uncommonly encountered in routine practice. They are aetiologically related to HPV and may be associated with squamous and adenocarcinoma or their precursors. Diagnosis of NEC is important as it has a poorer outcome and is treated aggressively with non-surgical modalities. Mixed tumours include the common cervical polyps and the rarer adenosarcomas. The latter has a potential for recurrence and sarcomatous overgrowth. Of the cervical sarcomas, embryonal rhabdomyosarcoma is the commonest at this site and has distinctive appearance and clinical profile.

In general, accurate diagnosis of these entities is important in determining optimal patient management since some tumours may be associated with tumour syndromes and extracervical disease.

Keywords

Neuroendocrine carcinoma · Sarcoma · Mixed tumour Adenosarcoma · Rhabdomyosarcoma · Immunohisto chemistry · Classification

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14.1 Neuroendocrine Tumours

Neuroendocrine cancers of the cervix (NEC) account for less than 5% of all cervical carcinomas [1]. The diagnosis is based on accurate histopathological recognition of neuroendocrine features. The nomenclature of these tumours has changed several times over the years. The present (2014) WHO classification of cervical carcinomas [2] is similar to that used for gastro-entero-pancreatic neuroendocrine carcinomas (Table 14.1). Low-grade neuroendocrine tumours are extremely rare in the cervix and are primarily defined by the same architectural and cytological features used in diagnosis of these neoplasms at other sites. High-grade neuroendocrine carcinomas are more commonly encountered. Up to 25% of neuroendocrine carcinomas are associated with intraepithelial or invasive squamous cell carcinomas or adenocarcinomas [3].

14.1.1 Low-Grade Neuroendocrine Tumours

These are very rare tumours in the cervix [4]. Most reported cases have been in 1970s and 1980s and diagnostic parameters have altered with the widespread use of immunohistochemistry and recognition of high-grade neuroendocrine carcinomas [5]. The diagnosis is made using the same parameters as for carcinoids and atypical carcinoids of the gut. Care should be taken to sample widely to ensure no

Table 14.1 Classification of neuroendocrine carcinomas of the cervix (based on present WHO classification)

Type	Morphology
Low-grade neuroendocrine tumour	Carcinoid
	Atypical carcinoid
High-grade neuroendocrine carcinoma	Small cell neuroendocrine carcinoma
	Large cell neuroendocrine carcinoma

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high-grade features such as mitotic activity, apoptosis or necrosis are overlooked. There is no prescribed treatment for these rare tumours.

14.1.2 High-Grade Neuroendocrine Carcinoma (Small Cell Type, SCNEC)

14.1.2.1 Clinical Features

These are the most common type of neuroendocrine tumour in the cervix. SCNEC mostly occurs in young women. They usually present with irregular vaginal bleeding and may or may not have a cervical mass. They are rarely detected by cervical screening and often present at an advanced stage.

14.1.2.2 Gross Findings

These carcinomas are usually visible at the time of diagnosis. They present as friable cervical masses that tend to ulcerate easily.

14.1.2.3 Microscopic Findings

Fairly monotonous cells that show round to oval nuclei, nuclear hyperchromasia, high nucleocytoplasmic ratio and scant cytoplasm characterize SCNEC. The chromatin pattern appears stippled. Nuclear moulding is seen (Fig. 14.1). There may be streaming artefact, which is a basophilic streak of nuclear material that has been sheared due to crushing of the neoplastic tissue. The carcinomas, typically, show brisk mitotic and apoptotic activity and often exhibit areas of necrosis (Fig. 14.2). Lymphovascular and perineural invasion are often present [6].

14.1.2.4 Immunohistochemical Features

Immunohistochemical staining for neuroendocrine markers aids the diagnosis of SCNEC. The commonly used markers are chromogranin (granular, cytoplasmic), synaptophysin (cytoplasmic), CD56 (membranous with weaker cytoplasmic expression) (Fig. 14.3), and PGP 9.5 (cytoplasmic). In most cases, the staining is diffuse. Chromogranin staining may be focal and appreciated only on high-power examination as punctate, cytoplasmic staining. CD56 and synaptophysin are more sensitive but CD56 lacks contextual specificity, as it can be positive in squamous and adenocarcinomas. Broad-spectrum cytokeratins such as AE1/AE3 (cytoplasmic) are usually positive. Dot-like para-nuclear cytoplasmic staining (Fig. 14.4) may be seen with antibodies to low molecular weight cytokeratins such as CAM 5.2

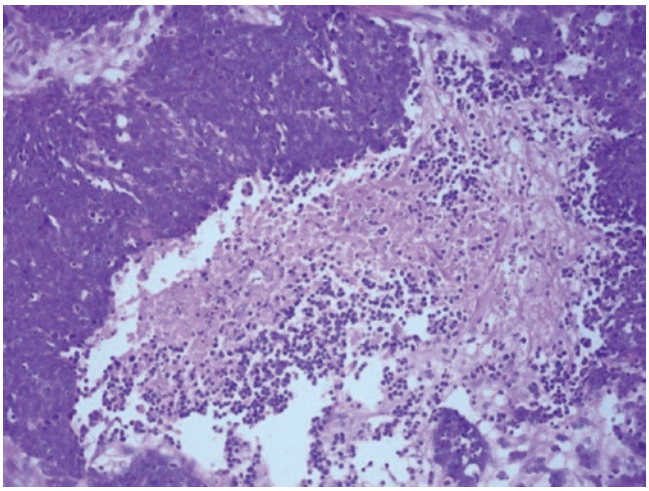

Fig. 14.2 SCNEC showing areas of necrosis

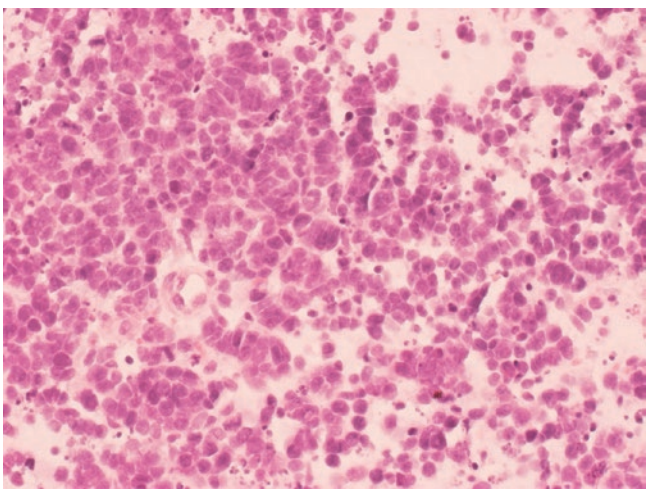

Fig. 14.1 SCNEC showing small ovoid cells with nuclear hyperchromasia, nuclear moulding, apoptosis and mitotic figures

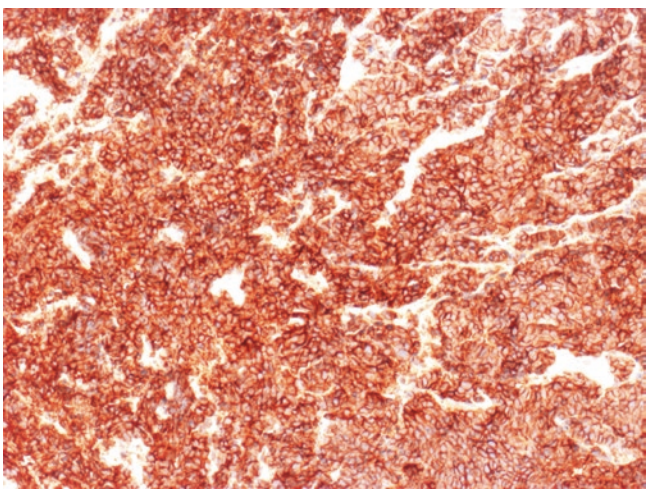

Fig. 14.3 CD56 staining of SCNEC showing strong, diffuse, membranous positivity

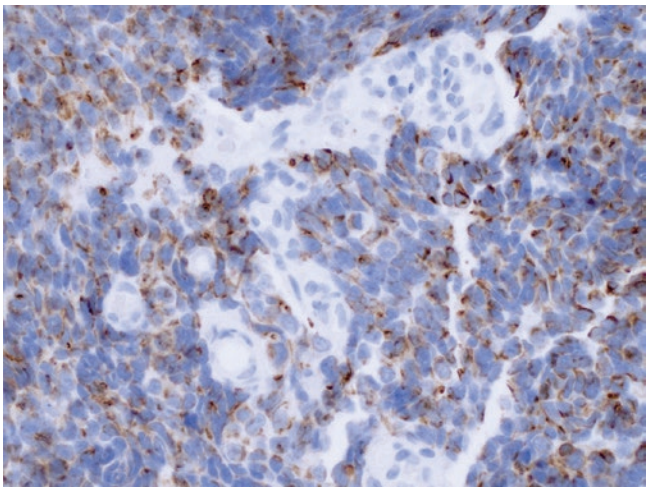

Fig. 14.4 Typical dot-like, paranuclear staining of SCNEC with CAM 5.2

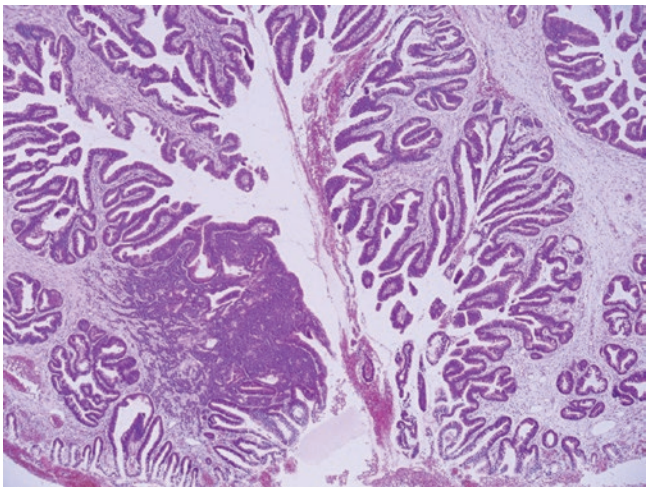

Fig. 14.5 SCNEC associated with high-grade CGIN/AIS (adenocarcinoma in situ)

(cytoplasmic). Unlike neuroendocrine carcinomas from other sites, there are no established criteria of Ki67 labelling index and mitotic count in neuroendocrine neoplasms of the cervix [7].

Once the diagnosis of SCNEC is made on a cervical biopsy, it is appropriate to confirm a cervical origin. Use of TTF-1 (nuclear) to exclude a lung primary is not reliable as non-pulmonary SCNECs can be positive with the marker. SCNECs are generally CK7 positive (cytoplasmic); however, they can also be CK20 (cytoplasmic) positive making differential cytokeratin staining unhelpful [8]. PAX8 (nuclear) expression, which is usually used to confirm an origin from the female genital tract, can also be positive in pancreatic neuroendocrine tumours and is, therefore, of limited use in this scenario [9]. SCNEC, like other types of cervical cancer, is associated with high-risk HPV infection, most often with HPV type 18. Overexpression of p16 (cytoplasmic and nuclear) is regarded as a surrogate marker for the presence of high-risk HPV and demonstrated by block staining with p16. This can be useful in confirming a cervical origin [10] as SCNEC of the lung are not aetiologically associated with HPV [11].

SCNEC can coexist with squamous and adenocarcinomas of the cervix and their precursors (Fig. 14.5). In this context, the morphology and immunohistochemistry of the SCNEC remains the same as pure SCNECs; whilst the expression of neuroendocrine markers in the epithelial component is restricted to chromogranin staining of few cells in the neoplastic glands. In the presence of the two distinct components, it is recommended that the diagnostic bottom line states adenocarcinoma or squamous cell carcinoma admixed with neuroendocrine carcinoma [2].

14.1.2.5 Molecular Features

Comprehensive molecular characterization of SCNEC is not available. Due to the rarity of the tumour, the integrated genomic and molecular characterization of cervical cancers does not have a separate subset of neuroendocrine neoplasms. To date, loss of heterozygosity (LOH) at specific gene or chromosomal regions in SCNEC using polymorphic microsatellite markers has been investigated in small studies. The commonest finding was LOH in any region of the short arm of chromosome 3 (3p) [12]. Small studies have shown that the neuroendocrine carcinomas show similar genetic alterations to the squamous and/or glandular component, implying common origin for both [13].

14.1.2.6 Differential Diagnoses

A diagnosis of SCNEC can be made on morphology alone when typical features of hyperchromasia, scant cytoplasm, nuclear moulding, mitosis and apoptosis are present. Marker expression may be focal and difficult to interpret in small biopsies. The main differential diagnoses are other neoplasms composed of small cells including non-keratinizing small cell squamous cell carcinoma, undifferentiated carcinoma, lymphoma, melanoma and rhabdomyosarcoma.

It is perhaps most important to differentiate SCNEC from small cell squamous carcinomas as the latter has a significantly better prognosis [14]. Squamous cell carcinomas can be composed of small cells and, especially when non-keratinizing, can be difficult to differentiate from SCNEC. Cells constituting squamous cell carcinomas are cohesive and intercellular bridges can be seen. Even when the cytoplasm is scanty it tends to surround the nucleus unlike SCNEC where the cytoplasm is eccentrically located.

Squamous cell carcinomas lack the nuclear moulding and apoptosis seen in SCNEC. On immunohistochemistry, squamous cell carcinomas are consistently negative for neuroendocrine markers (CD56, chromogranin, synaptophysin, PGP9.5). Many squamous cell carcinomas will stain for p63 (nuclear). NECs can co-exist with other epithelial malignancies including adenocarcinomas and squamous cell carcinoma. When there are two distinct morphological and immunohistochemical components, it is recommended that the diagnostic bottom line states adenocarcinoma or squamous cell carcinoma admixed with neuroendocrine carcinoma [2] rather than adenocarcinoma or squamous cell carcinoma with neuroendocrine differentiation. The former terminology allows the clinician to manage the patient as a high-grade NEC.

Undifferentiated carcinomas show, at least focal, staining with AE1/AE3 and EMA and lack staining for neuroendocrine markers.

Lymphomas are morphologically more dyshesive than SCNEC. Their nuclei tend to be rounded and do not show the moulding seen with SCNEC. Staining for CD45 (membranous) will be positive with lymphomas.

Melanomas can be composed of small cells. Primary mucosal melanomas of the cervix are rare tumours. They tend to have a junctional component that may not be visible on small biopsies. When amelanotic they pose a difficult differential from SCNEC, as both tumours can be mitotically and apoptotically prodigious. Melanomas are positive for S100 (nuclear), Melan A (membranous) and SOX10 (nuclear).

14.1.2.7 Prognosis and Management

Neuroendocrine tumours of the gynaecologic tract are rare and pose a significant clinical challenge. Management is guided by accurate pathological diagnosis. For early-stage cervical neuroendocrine carcinoma patients, tumour recurrence is significantly associated with the presence of lymph node metastases, depth of invasion, and the presence of lymphovascular space invasion.

Consensus guidelines published by the Society of Gynecologic Oncology (SGO) recommend multimodality treatment for early stage tumours [15]. In the past, 5-year survival rates of 14% to 29% were typical, but more recently 5-year survival of 45% has been reported and this may be likely to the result of aggressive multimodal therapy [16]. Targeted therapies that are being studied include angiogenesis inhibitors, mTOR inhibitors, VEGF inhibitors and tyrosine kinase inhibitors. Irrespective of the stage, the outcome is poorer for neuroendocrine carcinomas compared to squamous cell carcinomas. In pooled studies, the hazard ratio for death in early stages has been noted as 2.96 and in late stages as 1.70 for neuroendocrine carcinoma in comparison with squamous cell carcinoma [17].

14.1.3 High-Grade Neuroendocrine Carcinoma of the Large Cell Type (LCNEC)

14.1.3.1 Clinical Features

LCNEC are rarer than SCNEC, with less than 100 cases reported in literature. They present with clinical symptoms and signs similar to those of SCNEC.

14.1.3.2 Microscopic Findings

LCNEC typically display an organoid pattern, with cells organized in solid, nesting and trabecular patterns. Nuclear moulding is not seen. The neoplastic cells are large polygonal to round cells with eosinophilic cytoplasm (Fig. 14.6). Geographic tumour necrosis is seen in some tumours (Fig. 14.7). Mitotic activity is brisk and numerous mitotic figures are seen. Vascular invasion is common (Fig. 14.8).

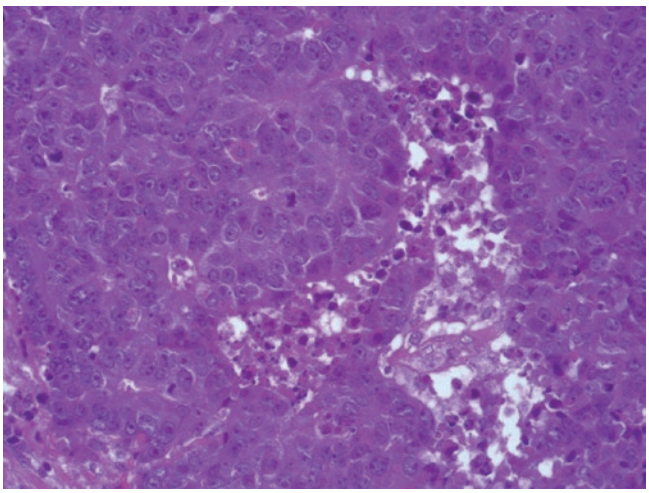

Fig. 14.6 High-power view of LCNEC showing round and polygonal cells with abundant eosinophilic cytoplasm. Mitotic activity, apoptosis and necrosis are also seen

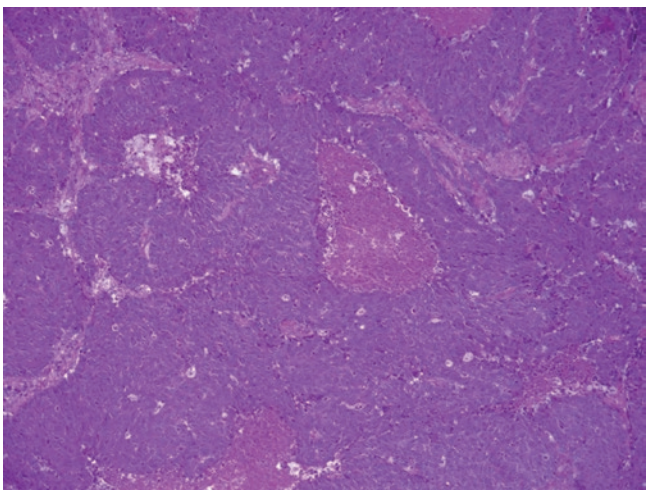

Fig. 14.7 Low-power view of LCNEC showing solid pattern of growth and necrosis

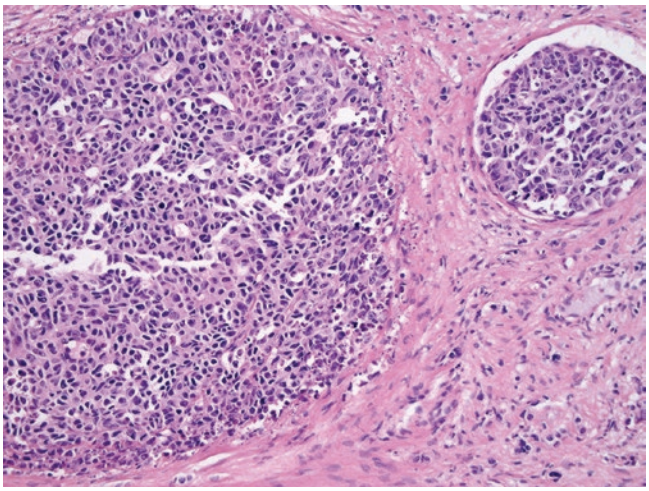

Fig. 14.8 Vascular invasion in LCNEC

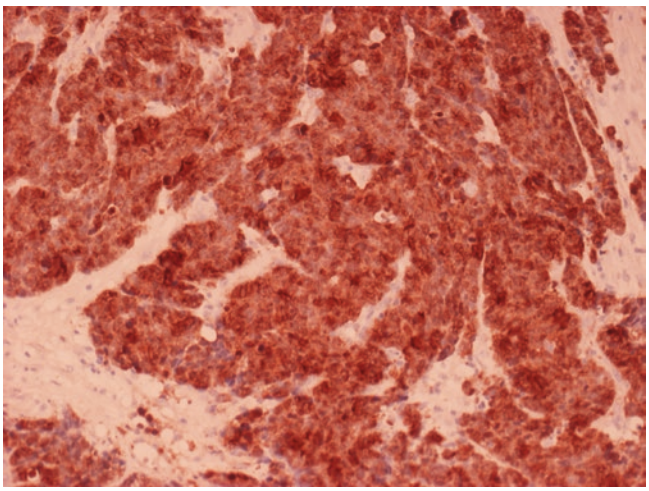

Fig. 14.10 P16 shows nuclear and cytoplasmic staining in LCNEC

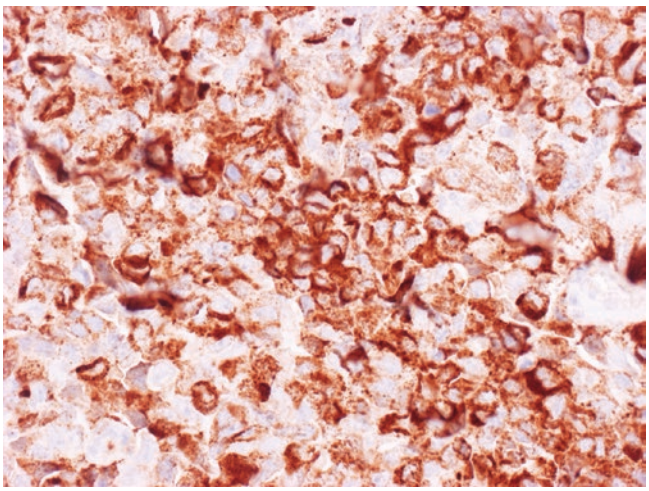

Fig. 14.9 Chromogranin shows granular, cytoplasmic staining in LCNEC

14.1.3.3 Immunohistochemical Features

Immunohistochemical expression of neuroendocrine markers, such as chromogranin (Fig. 14.9), is a requirement for this diagnosis [2]. These carcinomas are also aetiologically associated with high-risk HPV infection [11]. This can be confirmed by block positive staining with p16 (Fig. 14.10). The key features of neuroendocrine carcinomas are summarized in Table 14.2.

14.1.3.4 Differential Diagnoses

The presence of high-grade nuclear atypia in large cells with eosinophilic cytoplasm, brisk mitosis and necrosis should raise the suspicion of LCNEC. The main differential diagnosis is poorly differentiated squamous or adenocarcinomas. Expression of neuroendocrine markers, even focally, should prompt a diagnosis of LCNEC. Presence of glandular or squamous areas indicates a co-existent squamous or adenocarcinomas and does not detract from the diagnosis of LCNEC.

Table 14.2 Summary of key features of SCNEC and LCNEC

Features	SCNEC	LCNEC
Clinical presentation	Abnormal vaginal bleeding Cervical mass	Abnormal vaginal bleeding Cervical mass
Morphology	Small cells Scanty cytoplasm Solid and trabecular patterns common Nuclear moulding Basophilic streaks Brisk mitotic activity Necrosis Can be associated with squamous carcinoma and adenocarcinoma	Large cells Abundant eosinophilic cytoplasm Solid and trabecular patterns common Nuclear moulding Brisk mitotic activity Necrosis Can be associated with squamous carcinoma and adenocarcinoma
IHC	Not mandatory for diagnosis *Positive:* Chromogranin Synaptophysin CD56 PGP 9.5 P16 TTF1 Cytokeratins CAM5.2—paranuclear dot-like *Negative* p63	Mandatory for diagnosis *Positive:* Chromogranin Synaptophysin CD56 PGP 9.5 P16 TTF1 Cytokeratins *Generally negative* p63
Differential diagnosis	Other small, round, blue cell tumours—lymphoma, melanoma, rhabdomyosarcoma, small cell squamous carcinoma	Poorly differentiated squamous carcinoma and adenocarcinoma

14.1.3.5 Prognosis and Management

Management and prognosis of these tumours is similar to that of SCNEC, not least because clinical guidelines and trials do not separate these rare neoplasms from SCNEC.

14.2 Mixed Epithelial—Mesenchymal Tumours

14.2.1 Endocervical Polyp

14.2.1.1 Clinical Features

Endocervical polyps are common lesions that occur mostly in peri- and postmenopausal women. Most polyps are not symptomatic [18]; however, some patients present with intermenstrual, post-coital or postmenopausal bleeding.

14.2.1.2 Microscopic Findings

Endocervical polyps are fibroepithelial lesions whose surfaces are covered by endocervical mucinous epithelium that commonly shows squamous metaplasia or microglandular hyperplasia. Surface ulceration, papillation and inflammation are commonly seen (Fig. 14.11 inset). The core often contains dilated cystic glands. The stroma can show foci of decidualization during pregnancy or with exogenous progesterone use. Scattered "atypical" stromal cells are usually present in variable numbers.

14.2.1.3 Differential Diagnoses

The main differential diagnoses are cervical adenomyomas and cervical adenosarcomas. The former are distinguished by the presence of smooth muscle in their stroma. Cervical adenosarcomas (discussed later) show increased cellularity of stroma immediately underlying the epithelium—a feature that is not seen in cervical polyps. Endocervical polyps may recur and in such cases careful examination is required to rule out an adenosarcoma.

14.2.2 Other Polypoid Lesions

Mullerian papillomas are benign polypoid lesions that occur in the cervix and vagina of children—the average age of presentation being 5 years. They present with vaginal bleeding and are no more than 2 cm in greatest dimension [19]. They are composed of fine, branching, fibrous papillae lined by non-atypical, cuboidal or hobnail epithelium. The mucinous epithelium that is seen in endocervical polyps is not a feature of this entity (Fig. 14.12 inset).

Giant cervical polyps are distinguished by their size—greater than 4 cm. They are rare and have a benign outcome after removal [20]. Rarely, metastatic malignancies may present as endocervical polyps [21].

Endocervical polyps are managed by removal, often in an outpatient setting. Although the vast majority are benign, histopathological examination is required to rule out the possibility of a more sinister lesion [22].

14.2.3 Endocervical Adenomyoma

14.2.3.1 Clinical Features

These are uncommon tumours that present as polypoid lesions. They may present with abnormal vaginal bleeding but are often asymptomatic. In reported cases, the age range is between 21 and 55 years of age [23].

14.2.3.2 Microscopic Findings

Endocervical adenomyomas are relatively well-circumscribed lesions that blend, at the periphery, with the surrounding cervical stroma. The lesional glands are widely

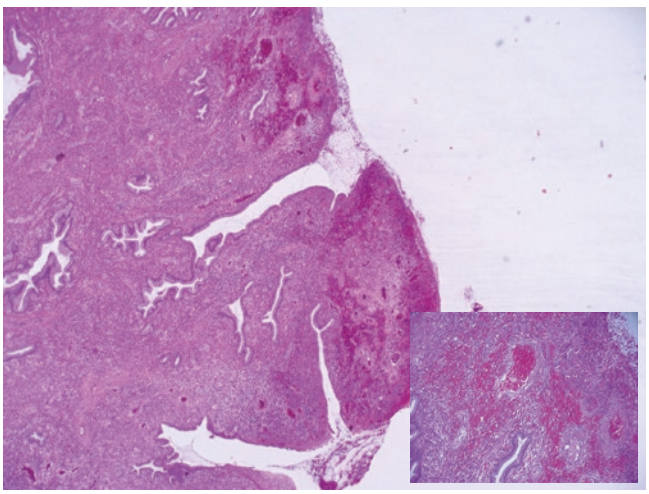

Fig. 14.11 Low-power view of a benign endocervical polyp showing inflammation and ulceration. The stromal cells in the area of ulceration show reactive atypia (inset)

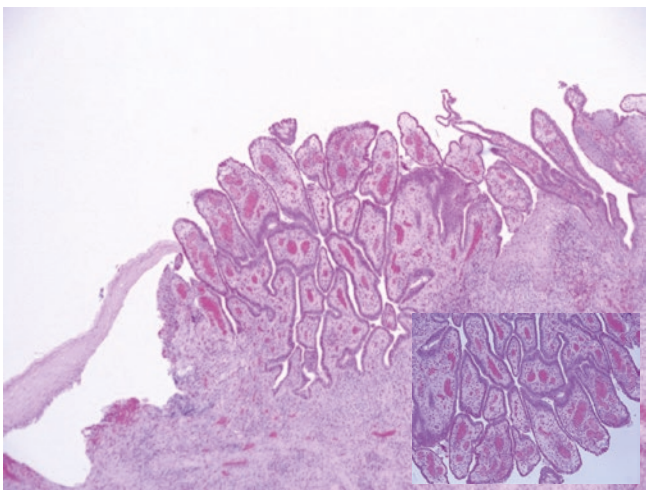

Fig. 14.12 Low-power view of a Mullerian papilloma with blunt papillae lined by non-atypical cuboidal cells. The cuboidal cells do not contain mucin (inset)

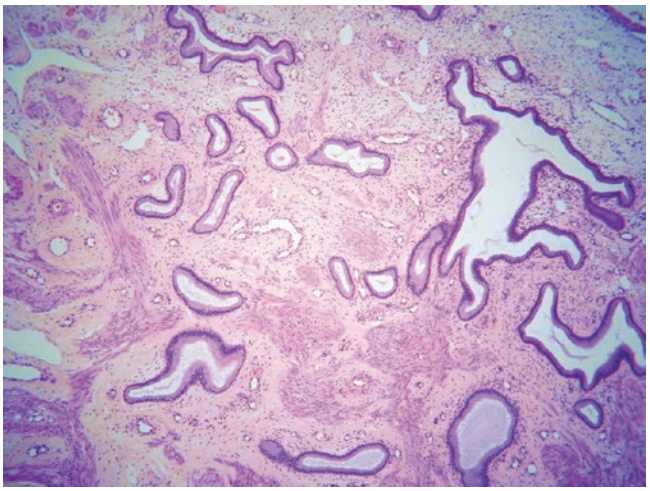

Fig. 14.13 A cervical adenomyoma showing glands widely separated by stroma that contains smooth muscle. (Courtesy Professor WG McCluggage, Belfast, UK)

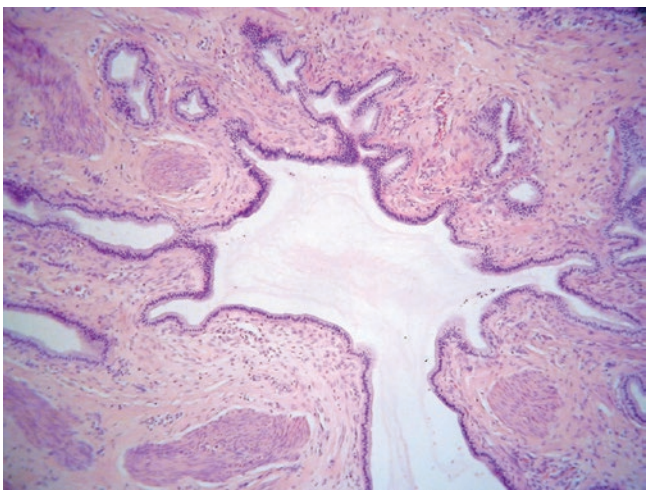

Fig. 14.14 The glands have a lobular architecture with a centrally dilated gland. (Courtesy Professor WG McCluggage, Belfast, UK)

spaced and separated by smooth muscle (Fig. 14.13). The latter may show foci with bizarre nuclei. The glands often have a lobular architecture with a centrally dilated gland surrounded by smaller glands (Fig. 14.14).

14.2.3.3 Differential Diagnoses

The most important differential diagnosis is adenoma malignum or minimal deviation adenocarcinoma. Both adenomyomas and minimal deviation adenocarcinoma are characterized by the presence of bland mucinous glands in smooth muscle. In the carcinoma, this is a manifestation of deep invasion of the cervical stroma [24]. In differentiation between these entities it is helpful to note that adenomyomas commonly present as polyps whilst adenoma malignum is a deeply invasive mural lesion. Features favouring the diagnosis of an adenomyoma are the lobularity of glandular architecture, absence of nuclear atypia, desmoplastic response lymphovascular or perineural invasion, although these features may be absent, or not focally seen in minimal deviation adenocarcinoma. Use of PAX2 (nuclear) staining may be helpful. PAX2 stains benign Mullerian epithelial proliferations but staining is lost in minimum deviation adenocarcinomas [25].

Some benign endocervical polyps may contain small amounts of smooth muscle in their stroma. The smooth muscle component in these situations is wispy and is not organized enough to consider a diagnosis of adenomyoma.

14.2.3.4 Prognosis and Management

Initial management of adenomyomas is by polypectomy. Recurrences are not uncommon and hysterectomy may be done. Examination of the hysterectomy specimens generally show that residual polyp, if any, is confined to the cervix.

14.2.4 Atypical Polypoid Adenomyoma

14.2.4.1 Clinical Features

These tumours are rare in the cervix and occur more commonly in the corpus. They present as polyps.

14.2.4.2 Microscopic Features

These are polypoid tumours in which the glands are lined by endometrioid-type epithelium exhibiting extensive squamous metaplasia and foci of luminal necrosis. The glands are often closely packed and the stromal component is often more cellular and shows a low degree of mitotic activity.

14.2.4.3 Differential Diagnosis

Adenomyomas of usual type are considered in the differential, as they contain endometrioid-type glands and smooth muscle. In atypical polypoid adenomyomas, the glands are closely packed with very scanty intervening stroma.

The other diagnostic consideration is adenosarcoma. On low-power examination, adenosarcomas show a club-like/leaf-like (phyllodes-like) growth pattern. The stroma, especially subepithelially, shows some atypia and mitotic activity and they lack a significant smooth muscle stromal component.

14.2.4.4 Prognosis and Management

Most cases are treated by polypectomy. Very few case reports are found in the literature [26] and therefore their behaviour, assumed to be benign, cannot be robustly evidenced.

14.2.5 Adenosarcoma

14.2.5.1 Clinical Features

These are biphasic tumours that occur most often in the uterine corpus and less commonly in the cervix. With cervical tumours, the patients present in the reproductive age. Presenting symptoms include vaginal bleeding, polyp detected on routine examination and abdominal pain. A history of recurrent polyps may be obtained in some cases [27].

14.2.5.2 Microscopic Features

Cervical adenosarcomas are polypoid lesions. They have a characteristic appearance on low-power examination with glands of varying shapes and variably conspicuous leaf-like, intraglandular projections secondary to stromal excess (Fig. 14.15). The lining epithelium is often mucinous, endocervical in type, but any form of Mullerian differentiation can be seen. On higher magnification, the stromal cells show mild atypia and mitotic activity and these features are most appreciable in the immediately subepithelial stroma—the so-celled cambium layer. According to the World Health Organisation definition, mitotic activity of 2 or more per 10 high-power fields, in the stroma, is required for a diagnosis of adenosarcoma. In practice the diagnosis is less dependent on the mitotic count and most pathologists will make the diagnosis when the characteristic architecture and cambium layer is present [27]. Cervical adenosarcomas may contain heterologous elements such as cartilage and rhabdomyoblasts. Sarcomatous overgrowth (Fig. 14.16) is defined as the presence of pure sarcoma, often high-grade, in at least 25% of the lesion [28].

14.2.5.3 Differential Diagnosis

Benign endocervical polyps and cervical adenomyomas—both of which lack the characteristic architecture of adenosarcomas. The category of adenofibromas is not included in the mixed epithelial and mesenchymal tumours of the cervix as the so-called adenofibromas can behave as low-grade malignancies [29].

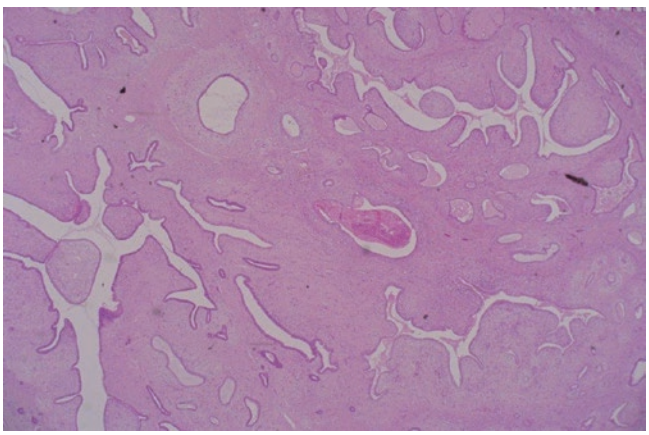

Fig. 14.15 Low-power view of an adenosarcoma showing the stromal excess resulting in a leaf-like pattern of the glands. Periglandular stromal condensation is seen

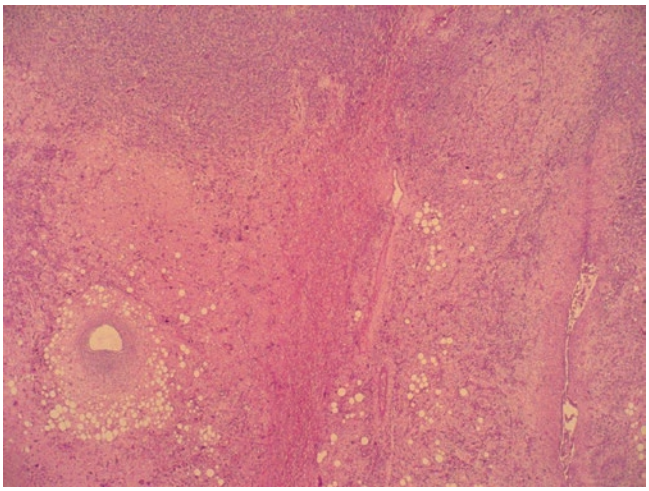

Fig. 14.16 Sarcomatous overgrowth in adenosarcoma. The latter is recognizable by the small benign gland with periglandular stromal condensation. Heterologous fat component is present

Carcinosarcomas are the main differential diagnosis in cases that show the presence of heterologous elements like rhabdomyoblasts or sarcomatous overgrowth. In adenosarcomas, only the mesenchymal component is malignant, whilst in carcinosarcomas both the epithelial and mesenchymal elements show high-grade malignant changes.

Rhabdomyosarcomas are rare tumours. When they entrapped benign glands, they can be mistaken for an adenosarcoma. They typically show high-grade atypia and will not show the subepithelial stromal condensation that is typically seen in adenosarcomas.

14.2.5.4 Prognosis and Management

Adenosarcomas are treated primarily by surgery in the form of hysterectomy. A decision for radiotherapy or chemotherapy is based on the extent of the primary tumour. Adverse prognostic features include sarcomatous overgrowth and recurrence after primary treatment [30].

14.2.6 Carcinosarcoma

14.2.6.1 Clinical Features

Carcinosarcomas of the uterine cervix are extremely rare. Cervical carcinosarcoma may originate in the endocervical/Mullerian epithelium or in mesonephric duct remnants [31, 32]. The patients are generally postmenopausal and present with a polypoid mass and bleeding.

14.2.6.2 Macroscopic Findings

Grossly, the polyps appear fleshy and often necrotic.

14.2.6.3 Microscopic Findings

The carcinomatous component is usually one that resembles a primary cervical carcinoma such as a squamous cell carcinoma or adenoid basal carcinoma [33]. If the carcinosarcoma is of mesonephric derivation, then the epithelium is usually GATA3 positive and negative for PAX8, oestrogen receptors and p16 [34]. The sarcomatous component is usually homologous.

14.2.6.4 Differential Diagnosis

Distinction from adenosarcoma has already been described. It is important to rule out an origin from the endometrium. Imaging may helpful in the distinction.

14.2.6.5 Prognosis and Management

Radical surgery is the mainstay of treatment. Cervical carcinosarcomas are often confined to the cervix, unlike their corpus counterparts which often present with spread beyond the uterus. This may account for the relatively better prognosis of cervical carcinosarcomas.

Table 14.3 provides a summary of the key features of mixed tumours of the cervix.

Table 14.3 Summary of key features of mixed tumours of the cervix

	Morphology	Clinical behaviour
Endocervical polyp	Polyps Covered by glandular and squamous epithelium Microglandular hyperplasia common	Benign
Mullerian papilloma	Polyps occurring in children Fine, branching, fibrous papillae Cuboidal epithelium	Benign
Endocervical adenomyoma	Circumscribed lesions Glands separated by smooth muscle	Benign, may recur
Atypical polypoid adenomyoma	Endometrioid-type epithelium exhibiting extensive squamous metaplasia Stroma usually muscular	Benign, may recur Need to ensure they are not endometrial in origin
Adenosarcoma	Glands with leaf like, intraglandular projections Periglandular stromal condensation May contain heterologous elements Stromal overgrowth—poor prognosis	Low-grade malignancy
Carcinosarcoma	Both epithelial and stromal elements are malignant	Malignant

Summary of key features of sarcomas of the cervix

	Morphology	IHC	Molecular features
Rhabdomyosarcoma	Polypoid Cellular, mitotically active cambium layer underlining normal epithelium	Myogenin and MyoD1 positive	Up to 20% have germline mutations of DICER 1
ESS	Vasopermeative tumour Low-grade ESS similar to endometrial stroma High-grade ESS shows atypia and mitotic activity	Low-grade ESS—CD10 positive High-grade ESS—Cyclin D1 positive	Low-grade ESS—JAZF1-SUZ12 fusion High-grade ESS—YWHAE-NUTM2 gene fusion
ASPS	Large tumour cells with organoid pattern separated by delicate septa	TFE3 positive	ASPSCR1—TFE3 gene fusion
Leiomyosarcoma	Spindle or epithelioid cells with atypia, mitotic activity and tumour cell necrosis	SMA, Desmin, h-caldesmon positive	
MPNST	Fascicular pattern with atypia and mitosis	S100 positive CD34 positive in fibroblastic variant	
PNET	Sheets of small, round, blue cells with scanty cytoplasm and evenly dispersed chromatin. Brisk mitotic activity	CD99, FLI1 positive	Chromosomal translocation t(11;22)(q24;q12)
PEComa	epithelioid and spindled cells arranged in nests with intervening, delicate vascular network	HMB45, Melan A MiTF, SMA positive	Inactivation of TSC1 or TSC2 genes
Angiosarcoma	Vasoformative malignant tumour	CD31, CD34 and FVIII RA positive	
Liposarcoma	Lipoblasts with atypia and mitosis	S100 positive	
Proximal-type epithelioid sarcoma	Multinodular pattern Large, severely atypical epithelioid cells	Keratin, vimentin, BRG1, FLI1 positive INI 1 negative	SMARCB1 deletions

14.3 Sarcomas

Sarcomas presenting in the uterine cervix are rare, representing less than 1% of all malignancies [35] and available data concerning their behaviour is limited to that from case reports and small case series. A wide range of tumour histotypes are described, including tumours more commonly seen in the uterine corpus and those which normally present at other anatomical sites [36–38]. Whilst the morphologic spectrum of these tumours may be broadly the same as in extra-cervical lesions, they may not be initially considered in the differential diagnosis of cervical samples. Precise classification is of increasing importance as specific tumours may be associated with particular targetable mutations to allow the delivery of precision adjuvant treatment.

14.3.1 Rhabdomyosarcoma/Embryonal Rhabdomyosarcoma

Rhabdomyosarcoma is the most frequent sarcoma to arise within the cervix. The tumour arises in a generally younger group of women (from late teens to early 20s, although is described across a wide age range) [39, 40]. An association with ovarian Sertoli-Leydig cell tumours, pleuropulmonary blastoma and thyroid goitre is recognized, as a result of an underlying germline mutation of DICER1. Up to 20% of women with cervical embryonal rhabdomyosarcoma have other DICER1 associated tumours [40].

Tumours usually present with vaginal bleeding and/or a polypoid mass, which may occasionally be removed by polypectomy. The mass is covered by benign Mullerian glandular epithelium and similarly benign glands may be found buried within the stroma. Occasionally, squamous differentiation of the epithelium may also be present. The tumour stroma may be hypocellular and oedematous, but hypercellular foci are usually evident and increased around the glandular epithelium with the formation of a cambium layer (Fig. 14.17). Mitoses and apoptosis are usually identifiable in these more cellular areas. The stromal cells have small, hyperchromatic nuclei, scant cytoplasm (Fig. 14.18) and fine cytoplasmic processes: some cells with more extensive eosinophilic cytoplasm and cytoplasmic cross-striations may be present but these are not always evident and are not essential for diagnosis.

Islands of hyaline or cellular benign cartilage may be present. Some areas may show features resembling alveolar rhabdomyosarcoma. Areas with red blood cell extravasation, frank haemorrhage or necrosis may be seen. Expression of myogenin (nuclear) and myoD1 (nuclear) may be demonstrable in a proportion of nuclei. Smooth muscle actin (cytoplasmic) and h-caldesmon (cytoplasmic) are usually negative [41, 42].

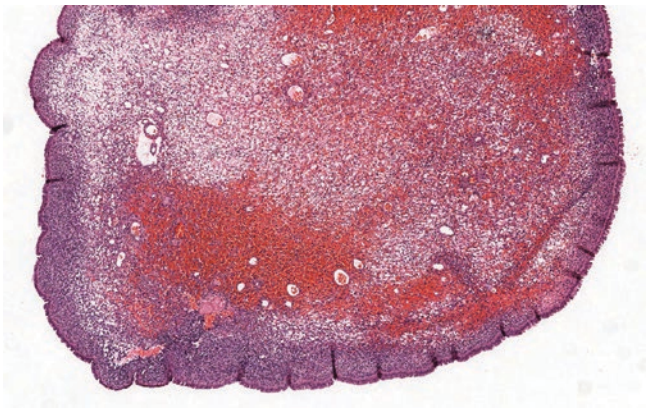

Fig. 14.17 Embryonal rhabdomyosarcoma showing subepithelial hypercellularity—the so-called cambium layer.

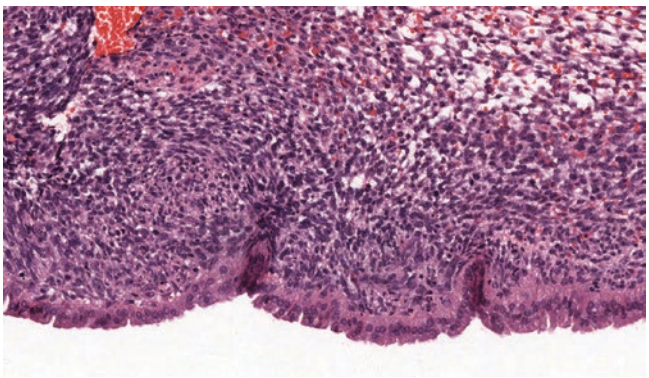

Fig. 14.18 High-power view of cambium layer shows hyperchromatic, small, oval cells with nuclear atypia and mitotic activity

The differential diagnosis includes an endocervical polyp (when paucicellular) and adenosarcoma. Features favouring embryonal rhabdomyosarcoma include the absence of phylloides-like architecture, relative paucity of glands, and high-grade (primitive) appearance of periglandular sarcoma.

14.3.2 Endometrial Stromal Sarcoma

The endometrial stromal sarcomas (ESS) are a diverse group of mesenchymal tumours, which are infrequently reported in the cervix, despite the cervix being a relatively common site of endometriosis, from which these tumours may arise [43].

ESS may be low or high grade. Low-grade ESS are more common, show characteristic morphology and usually present relatively little diagnostic challenge. Tumour cells in low-grade ESS usually show strong, diffuse expression of CD10 (membranous and cytoplasmic), and will often demonstrate expression of smooth muscle actin and, less often, desmin. Diagnostic difficulty may arise when endometrioid-type glands are present within the tumour as this may create morphologic overlap with endometriosis and has been noted to

lead to delayed diagnosis in cervical biopsies [44]. Conversely, pauciglandular endometriosis (stromal endometriosis or "stromatosis") may mimic a neoplastic mesenchymal proliferation. The absence of a mass lesion, superficial location and presence of stromal breakdown may aid recognition.

High-grade endometrial stromal sarcoma has more recently been distinguished as a distinct clinico-pathological entity, with a characteristic YWHAE-NUTM2 gene fusion. Presentation as a cervical mass has been described, in a 26-year-old woman, in association with vaginal bleeding [45].

14.3.3 Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) is a rare neoplasm, with distinctive morphology but of uncertain histogenesis, most commonly found in the deep soft tissue of the thigh or buttock in adults or in the head and neck region in infants and children. Small number of cases have been described in the female reproductive tract, including the cervix [46–48]. The natural history of disease typically involves localized disease at the time of presentation, but late recurrence with metastatic disease may occur.

The tumour cells are large, uniform and epithelioid with clearly defined cell borders, copious eosinophilic granular cytoplasm and central bland nuclei with prominent nucleoli. Tumour cells are characteristically arranged with organoid architecture into solid nests, separated by delicate septa containing sinusoidal vascular channels. Loss of cohesion or necrosis of the cells in the centre of the nests frequently (although not always) results in a pseudo-alveolar appearance (Fig. 14.19). Tumour cells often contain rhomboid- or rod-shaped intracytoplasmic inclusions, or coarse intracytoplasmic granules, highlighted by staining for diastase-PAS.

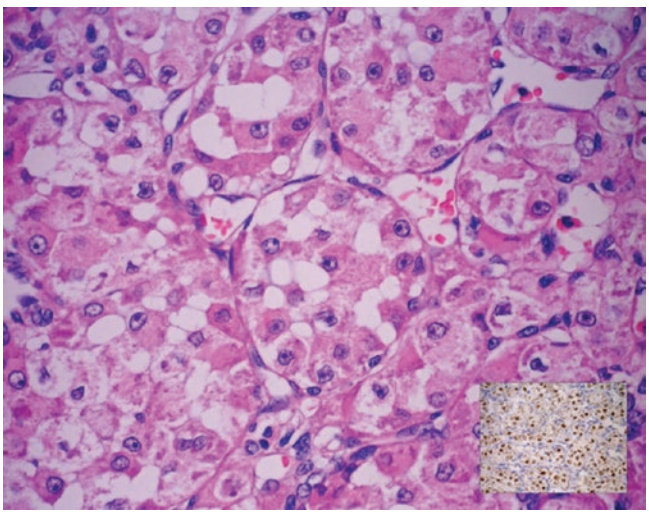

Fig. 14.19 ASPS with uniform and epithelioid cells, clearly defined cell borders, copious eosinophilic granular cytoplasm arranged with organoid architecture into solid nests, separated by delicate septa. The cells are positive for TFE-3 (inset)

Tumour cells show strong nuclear staining with an antibody to the c-terminal portion of TFE3 (nuclear) which is retained in the fusion protein, where most normal cells show only weak or no nuclear reactivity [49]. As a note of caution, TFE staining may also be seen in granular cell tumours that show morphologic overlap with ASPS (and are described in the cervix). Focal staining with immunohistochemistry for desmin (cytoplasmic) and HMB45 (cytoplasmic) is also described.

There is a characteristic gene fusion between ASPSCR1 and TFE3, detection of which by FISH or RT-PCR is confirmatory in diagnostically challenging cases [50]. It is worth noting that this finding may also be present in a subset of renal cell carcinomas. The fusion oncoprotein is a transactivator of the MET (Mesenchymal Epithelial Transition) promoter, suggesting MET inhibitors as potential therapeutic agents in metastatic disease, which is largely resistant to radiotherapy or chemotherapy.

At this site, the main morphologic differential diagnoses are clear cell carcinoma, undifferentiated carcinoma and PEComa, including both conventional and TFE rearranged subtypes, which may show morphologic overlap. A diagnostic immunohistochemistry panel which includes HMB45, MelanA and desmin will aid distinction of these diagnoses [49].

14.3.4 Leiomyosarcoma

Leiomyosarcomas including epithelioid [51–53] and myxoid [54] variants may occasionally occur as primary cervical neoplasms [55] most likely arising from the scattered smooth muscle cells present in the normal cervical stroma. These present as masses which may project into the endocervical canal or vaginal lumen. A case report documents occurrence in the cervical stump following subtotal hysterectomy [56]. The macroscopic appearances resemble those seen in the uterine corpus, with white/grey and fleshy cut surfaces or a gelatinous appearance in myxoid variants. The masses may appear circumscribed or show infiltration into the surrounding stroma. It has been inferred that criteria for malignancy are similar to those seen in the uterine corpus [57].

14.3.5 Malignant Peripheral Nerve Sheath Tumour

A small number of cases of malignant peripheral nerve sheath tumour of the cervix have been described in case reports and one small case series [58, 59]. The tumours

form polypoid or mass lesions and show fascicular architecture with alternating hyper and hypocellular areas, composed of spindle cells among which mitotic figures can be identified. Up to 50% show S100 (nuclear) expression on immunohistochemistry.

A variant endocervical fibroblastic malignant peripheral nerve sheath tumour has been reported in a small series of three cases [60]. These tumours presented as polypoid or mass forming lesions and showed fibroblastic, endoneurial-like differentiation. Morphologic features included compact fascicles of spindled cells in herringbone, fascicular and vaguely storiform patterns. Both diffuse S100 and CD34 (membranous) expression were demonstrated, suggesting possible origin from CD34-expressing endocervical fibrocytes.

14.3.6 Ewings Sarcoma/Peripheral Primitive Neuroectodermal Tumour

Ewings Sarcoma (Peripheral primitive neuroectodermal tumour, PNET) has been rarely described arising in the cervix, in sporadic case reports and small series [61–65].

As at other sites the tumours are composed of well demarcated, lobulated sheets of uniform small cells with round hyperchromatic nuclei containing evenly dispersed chromatin. Cytoplasm is scant and mitotic figures are frequent. Occasional rosettes may be seen. The differential diagnosis includes rhabdomyosarcoma; lymphoma; undifferentiated, small cell squamous and neuroendocrine carcinomas; malignant melanoma and endometrial stromal sarcoma. There is diffuse membranous expression of CD99 with FLI1 (nuclear) and cytokeratin expression occasionally demonstrated. The chromosomal translocation t(11;22)(q24;q12) or the EWS/FLI fusion product may be demonstrable.

14.3.7 Perivascular Epithelioid Cell Tumour

A few case reports describe perivascular epithelioid cell tumour (PEComa) arising in the cervix [66] including with TFE3 gene re-arrangement [67]. The tumours presented with abnormal vaginal bleeding or a mass and in one case was identified on cervical cytology [68]. The tumours are circumscribed with occasional tongue-like protrusions into adjacent stroma and are composed of epithelioid and spindled cells with a delicate vascular network. Tumour cells express HMB45, Melan A (cytoplasmic) and MiTF (nuclear) with frequent positivity for smooth muscle actin. Most tumours demonstrate inactivation of TSC1 or TSC2 genes with activation of the mTOR pathway providing a potential focus of targetable therapy [69].

14.3.8 Angiosarcoma

Angiosarcoma is rarely described arising in the cervix, forming a flat or raised violaceous plaque with an ulcerated haemorrhagic surface [70]. The tumours are composed of infiltrative, anastomosing vascular channels with solid poorly differentiated areas, haemorrhage and necrosis. Tumour cells are flat or cuboidal with atypical nuclei and inconspicuous cytoplasm; the epithelioid variant shows epithelioid endothelial cells with copious eosinophilic cytoplasm and large nuclei with prominent nucleoli. Expression of CD31 (membranous), CD34 and Factor VIII related antigen (FVIII RA—cytoplasmic) may be demonstrated on immunohistochemistry.

14.3.9 Liposarcoma

Cervical liposarcoma is exceedingly rare [35] albeit that adipocytes may be considered a normal constituent of the cervical stroma [71]. A recent report describes a cervical pleomorphic liposarcoma in association with small cell carcinoma of the ovary of hypercalcaemic type in a woman with Li Fraumeni syndrome [72].

14.3.10 Proximal-Type Epithelioid Sarcoma

The proximal variant of epithelioid sarcoma is described to occur at a number of sites in the deep pelvic tissues and vulva, and has occasionally been described as arising in the cervix [73, 74]. The tumour shows a multinodular pattern of growth and is composed of large, epithelioid cells with severe cytological atypia, vesicular nuclei and prominent nucleoli. Rhabdoid features may be observed, or predominate such that the main differential diagnosis is extra-renal rhabdoid tumour. Necrosis may be present but is not generally associated with the granuloma-like pattern seen in the conventional, distal form of epithelioid sarcoma.

14.3.11 Undifferentiated Endocervical Sarcoma

A group of high-grade tumours, termed undifferentiated endocervical sarcoma (encompassing lesions also termed endocervical stromal sarcoma), has been previously described. The diagnosis can be established after excluding other specific diagnoses. In addition to lacking morphologically recognizable patterns of differentiation, these showed expression only of vimentin. Patient outcomes have been described as variable, probably reflecting likely histogenetic variability of lesions within this group [35] some reports of

which preceded the availability of ancillary immunochemical and molecular genetic markers.

In conclusion, the uterine cervix maybe the site of a number of unusual neoplastic proliferations. Knowledge of their occurrence at this site and their distinctive features aids diagnosis of these tumours.

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