Benign Tumors and Tumor-like Lesions of the Cervix

4

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Contents

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R. A. Soslow et al. (eds.), *Atlas of Diagnostic Pathology of the Cervix*, https://doi.org/10.1007/978-3-030-49954-9_4

4.1 Giant Condyloma

4.1.1 Definition

The most common forms of cervical squamous intraepithelial lesions caused by human papillomavirus (HPV) are discussed in Chap. 5. They are typically flat or slightly raised. Very rarely, infection with low-risk HPV types leads to an exophytic proliferation, large enough to manifest as a mass and simulate malignancy of the cervix. These proliferations, which are significantly more common in the vulva, have been termed "giant condyloma" [1].

Giant condyloma is typically seen in women of reproductive age or postmenopausal, who often present with abnormal bleeding. Growth during pregnancy has been reported [1, 2]. Diagnostic imaging and colposcopy show an exophytic mass involving the distal cervix and occupying the upper vagina. The lesion can cover the ectocervix completely and extend into the endocervical canal.

4.1.2 Synonyms

In the past, the term *condyloma acuminatum* was used for all low-grade squamous lesions of the cervix displaying HPV cytopathic effect [3]. Because most such lesions are in fact flat, the terms *condyloma acuminatum* and *giant condyloma* are now reserved for grossly visible exophytic lesions caused by low-risk HPV.

4.1.3 Etiology

HPV types 6 or 11 have been detected in these lesions by in situ hybridization and polymerase chain reaction [1].

4.1.4 Macroscopy

Excisional specimens show a cauliflower-like lesion with exophytic projections, ranging from finger-like to broad-based, showing a tan, rugged surface. Tumor size ranges from 2 to 7 cm (median 4 cm) [1, 2].

4.1.5 Microscopy

Giant condyloma is characterized by the following features (Figs. 4.1, 4.2, 4.3, 4.4):

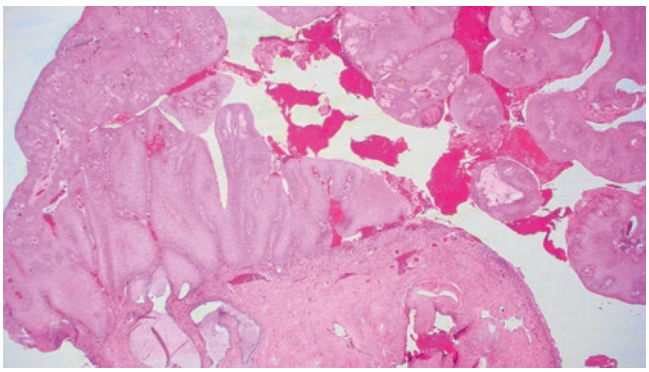

Fig. 4.1 Giant condyloma. This large lesion is composed of bulbous epithelial papillary projections. The proliferation is exophytic, with minimal to no involvement of the underlying cervical stroma (notice the smooth interface)

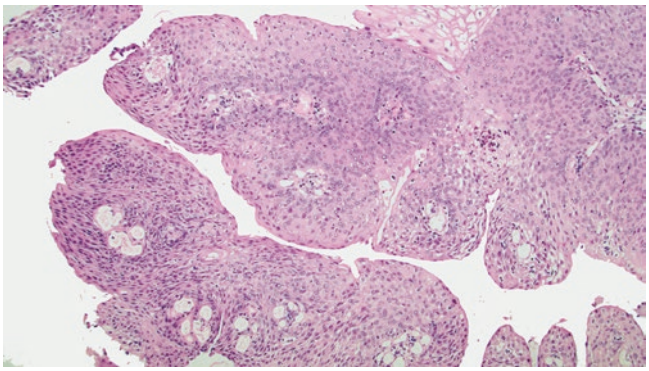

Fig. 4.2 Giant condyloma. Maturing squamous epithelium displays papillary architecture

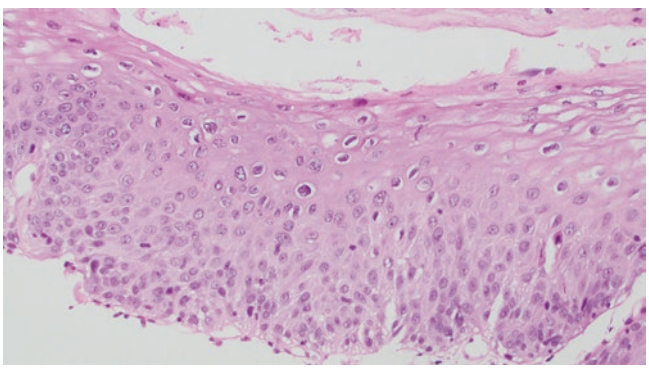

Fig. 4.3 Giant condyloma. Human papillomavirus (HPV) cytopathic changes are evident in mid and superficial epithelial layers, including perinuclear halos, nuclear hyperchromasia, and nuclear contour irregularity

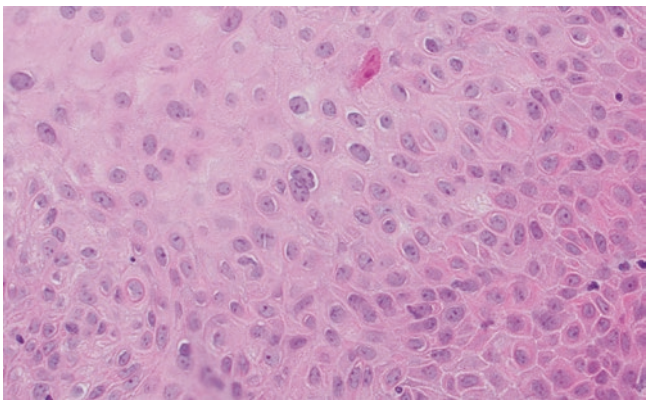

Fig. 4.4 Giant condyloma. Binucleation can be seen, usually attributed to HPV infection

- Exuberant squamous proliferation with verruciform and papillary architecture.
- Epithelial HPV cytopathic changes in mid and superficial layers, including nuclear enlargement, nuclear membrane irregularity ("raisinoid" nuclei), clumped hyperchromasia, binucleation, and perinuclear halos. The population is otherwise bland (particularly at the base) and retains maturation.
- The fibrovascular cores are indistinct and are often compressed or thinned by the epithelial growth.
- The base of the lesion shows a smooth front with absence of infiltration into the cervical stroma.

By immunohistochemistry, p16 is negative or shows only patchy cytoplasmic staining. Ki67 labelling is limited to the basal and parabasal epithelial layers.

4.1.6 Differential Diagnosis

- *Squamous papilloma* is a term used in the past for non-condylomatous exophytic squamous proliferations. Thus, they lack HPV cytopathic changes and are cytologically bland. In the cervix, this diagnosis is one of exclusion, as most squamous lesions in this anatomic location are related to HPV infection. *Fibroepithelial stromal polyp*, a related and overlapping entity, also lacks HPV-cytopathic effect and has a more prominent stromal component.
- Some *low-grade squamous intraepithelial lesions (LSILs)* can show papillary growth. Some are immature and have been described as "papillary immature metaplasia" [4–6]. Like giant condyloma, papillary immature metaplasia is also associated with HPV types 6 and 11. Unlike giant condyloma, mature and immature exophytic LSILs are small, and their exophytic nature is better seen on microscopic examination. Conversely, giant condyloma presents as an evident cervical mass.
- *Inverted transitional papilloma of the cervix* is a rare lesion with characteristic endophytic growth, also associated with low-risk HPV; in particular, HPV type 42 has been detected [7, 8]. The lesion tends to be small (<2 cm). Microscopically, it is composed of anastomosing trabeculae of transitional-type epithelium. Unlike condyloma, this tumor has endophytic growth into the cervical stroma, and often shows glandular differentiation.
- *Warty (condylomatous)* and *papillary (squamotransitional) variants of high-grade squamous intraepithelial lesion and squamous cell carcinoma* can be encountered. In contrast to the bland morphology of giant condyloma, these proliferations show loss of maturation, proliferation in upper epithelial layers, loss of organization of the basal layer, and cytologic atypia.
- *Verrucous carcinoma of the cervix* is exceedingly rare [9], and like its counterpart in the vulva, is regarded as unrelated to HPV infection. Unlike condyloma, verrucous carcinoma shows growth into the cervical stroma, typically in the form of well-shaped nests with smooth borders, retained maturation, and minimal to absent atypia. In addition, HPV-cytopathic changes are absent.

4.1.7 Prognosis

Giant condyloma is benign. Although persistent growth can be observed (especially under immunosuppression or pregnancy), malignant transformation, destructive local growth, or metastases have not been reported.

Conservative excision is recommended, particularly in young patients in whom fertility preservation is desired. Because excluding malignancy is important, initial sampling should ideally aim for complete excision or at least include the base of the tumor.

Diagnostic Highlights

- Giant condyloma is a very rare squamous proliferation related to low-risk HPV infection.
- This diagnosis should be considered in any clinically visible cervical mass with retained maturation, presence of koilocytes and absence of squamous atypia.
- Giant condylomas have exophytic growth and lack invasion into the underlying stroma.

4.2 Endocervical Polyp

4.2.1 Definition

Exophytic lesion of the endocervix composed of an admixture of benign epithelial (glandular and squamous) and mesenchymal elements. Endocervical polyps are common and can occur at any age, although most are diagnosed during reproductive years. The lesion may be asymptomatic or may manifest with abnormal bleeding or pain.

4.2.2 Synonyms

Not applicable.

4.2.3 Etiology

Most endocervical polyps appear to be a reactive process: inflammation is seen in about 75% of polyps, and metaplastic changes are common [10]. Moreover, upregulation of pro- and anti-inflammatory genes has been demonstrated in endocervical polyps [10]. Some polyps, particularly when large, may be neoplastic in nature.

4.2.4 Macroscopy

The lesion is typically located in the endocervical canal. Less often, it involves the cervical os. It is exophytic, with a pedunculated or sessile base. Most polyps are <2 cm in size. So-called giant endocervical polyps have been reported, with sizes often exceeding 10 cm [11, 12]. Surface congestion, ulceration, and granulation tissue can be seen.

4.2.5 Microscopy

The epithelial compartment of an endocervical polyp is of endocervical mucinous type (simple, cuboidal to columnar, with pale, basophilic cytoplasmic staining and small, uniform basal nuclei). Squamous metaplasia, microglandular hyperplasia, and tubo-endometrioid metaplasia are common changes, particularly on the surface and in the setting of inflammation. A prominent reserve cell layer is usually recognized at the basal aspect of the epithelium. Squamous cysts and epidermal adnexal structures are rarely encountered [13, 14]. The stroma is typically normocellular or hypocellular when compared with the normal cervical stroma. It contains variably sized vessels, which tend to be thick-walled towards the polyp base. Acute and/or chronic inflammation, erosion, and granulation tissue formation are common occurrences. Cartilaginous and osseous metaplasia has been described [15]. Epithelial and stromal elements are bland and lack architectural complexity or cytologic atypia (Figs. 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, 4.11, 4.12).

4.2.6 Differential Diagnosis

- There is morphologic overlap between endocervical polyp and *cervical adenofibroma*, which is reportedly exophytic in most cases. Both lesions are likely part of a continuum, though the term *adenofibroma* is better suited for lesions with a more prominent fibromatous

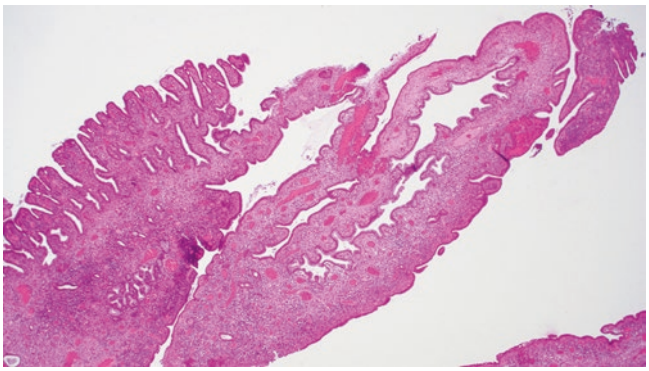

Fig. 4.5 Endocervical polyp. This exophytic lesion is composed of benign endocervical glands and supporting stroma with dense chronic inflammation

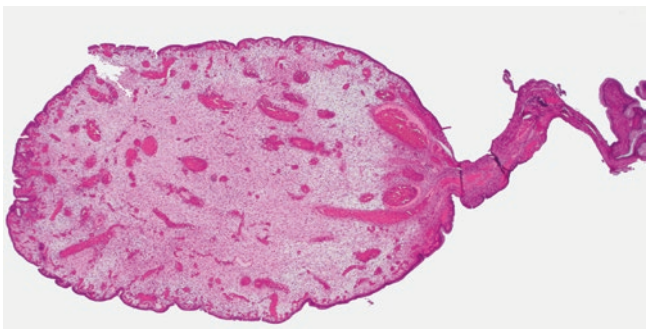

Fig. 4.6 Endocervical polyp. This example is entirely composed of bland granulation tissue-like stroma and is lined by benign endocervical epithelium

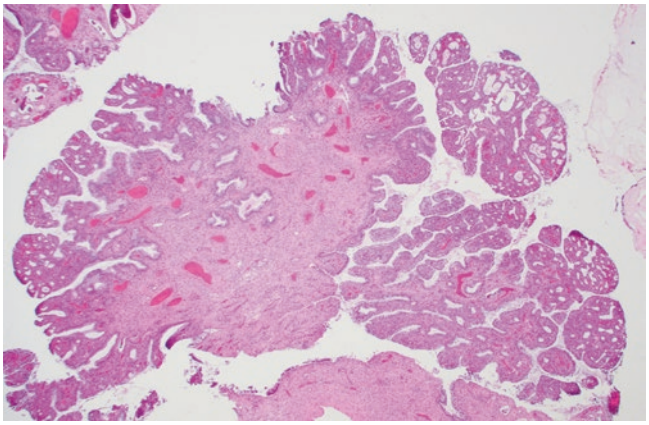

Fig. 4.7 Endocervical polyp. The epithelial component can be florid towards the surface

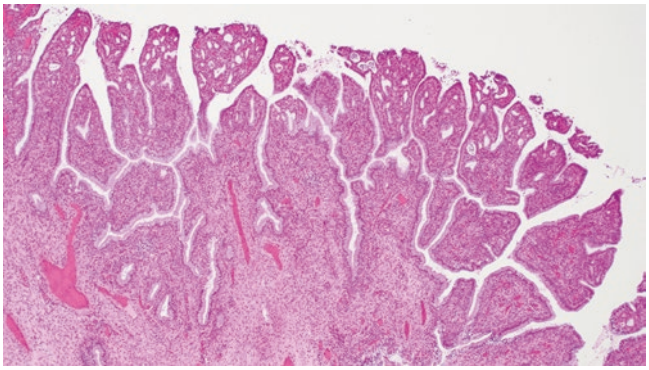

Fig. 4.10 Endocervical polyp. The spectrum of reactive epithelial changes commonly seen in the surface epithelium includes papillary change. Notice the significant inflammatory component, resembling chronic papillary cervicitis

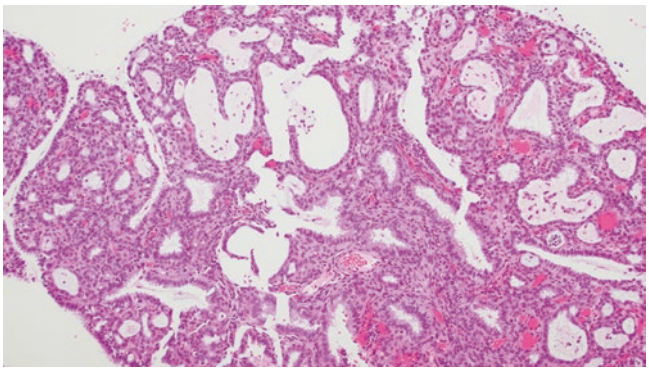

Fig. 4.8 Endocervical polyp. At higher magnification, areas of microglandular hyperplasia are observed

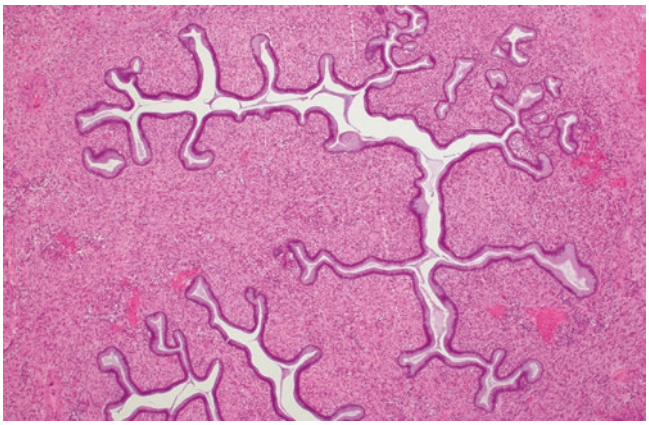

Fig. 4.11 Endocervical polyp with unusual features. Protrusions of stroma towards the luminal aspect of the glands may raise concern for adenosarcoma. Notice that the intraluminal mesenchymal projection is not well-developed and does not have a leaf-like pattern

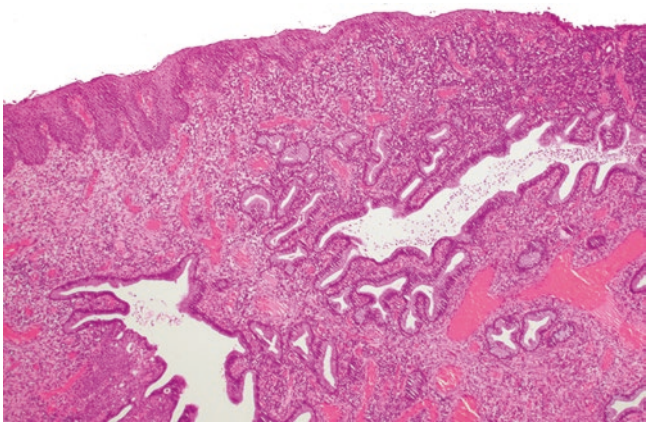

Fig. 4.9 Endocervical polyp. The spectrum of reactive epithelial changes commonly seen in the surface epithelium includes squamous metaplasia

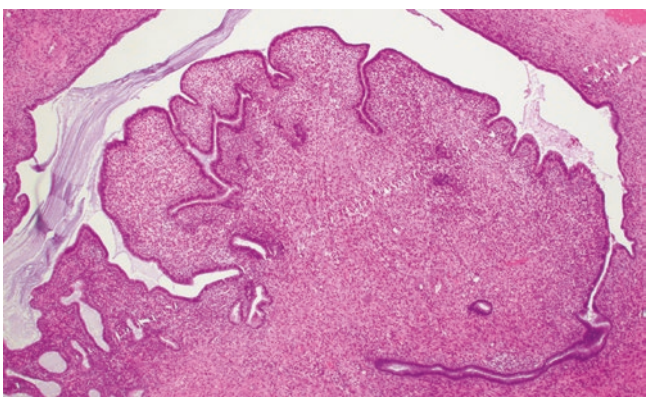

Fig. 4.12 Endocervical polyp with unusual features. Protrusions of stroma towards the luminal aspect of the glands may raise concern for adenosarcoma. Similar to Fig. 4.11, leaf-like (phyllodes-like) growth is not well-developed, and the stroma is not condensed around glands

component or those predominantly or purely intramural.

- *Müllerian adenosarcoma* can arise in the endocervix and can be deceptively bland at scanning magnification. However, it tends to be larger than most endocervical polyps (size >5 cm) and has a distinctive configuration of the stromal component, which includes periglandular stromal condensation ("cuffing"), prominent intraglandular growth in the form of leaf-like projections that collapse the gland lumen, stromal cytologic atypia, and at least two mitoses per 10 high power fields (HPFs). Importantly, focal mitoses and poorly developed leaf-like architecture and/or cuffing can be seen in endocervical polyps [16]. When diffuse and well-developed, these characteristics should raise concern for adenosarcoma.
- *Endometrial polyp* is a consideration in lesions located proximally in the canal, bordering the lower uterine segment. In fact, some polyps have mixed endometrial and endocervical glandular and stromal components.
- *Cervical endometriosis* can be polypoid. Unlike endocervical polyp, it contains a cellular stroma reminiscent of proliferative-phase endometrial stroma. Hemosiderin-laden macrophages are helpful, if they cannot be attributed to surface hemorrhage or granulation.
- In the pediatric population, large and rapidly growing lesions may raise concern for *botryoid rhabdomyosarcoma*. Pathologic examination should carefully look for the presence of a subepithelial band-like condensation of round cells with high nuclear-to-cytoplasmic ratio and rhabdoid features.

4.2.7 Prognosis

Endocervical polyps are indolent lesions. Simple excision is curative in most cases, although recurrence is possible. Endocervical polyps can harbor an intraepithelial lesion or carcinoma [17, 18], which is more often observed in reproductive-age women [19, 20]. For this reason, and to exclude adenosarcoma, thorough sampling is recommended.

Diagnostic Highlights

- Endocervical polyp is a benign lesion, likely reactive in nature in most cases.
- Glandular compartment often exhibits reactive changes including metaplasia and microglandular change.
- Stromal compartment is bland, normocellular or hypercellular; it is not expansile and lacks atypia and periglandular condensation.

4.3 Adenofibroma

4.3.1 Definition

Benign tumor composed of benign glandular and fibromatous mesenchymal elements. Adenofibroma is more common in perimenopausal and postmenopausal women presenting with abnormal bleeding [21].

4.3.2 Synonyms

Not applicable.

4.3.3 Etiology

Very rare. Most lesions described are likely adenomyomas or adenosarcomas. Coexistence with cervical endometriosis has been reported [21].

4.3.4 Macroscopy

The lesion can be predominantly solid or can present as a multiloculated cystic mass [22]. Polypoid growth is described in most cases [23, 24].

4.3.5 Microscopy

The tumor is well-circumscribed from the surrounding wall. Most tumors are exophytic. The glands have significant variation of shape and size, with frequent dilated forms. Glands tend to be spaced throughout the tumor, but clustering with honeycomb appearance can be seen [25]. Mitoses and atypia are absent. The stromal component is normocellular and is composed of bland, fibroblastic spindle cells, evenly spaced in between collagen fibers, which can appear hyalinized. The stroma does not collapse or obscure the glandular elements. No periglandular condensation of stroma (glandular cuffing) is present. Mitoses and atypia are absent (Figs. 4.13, 4.14, 4.15).

4.3.6 Differential Diagnosis

- *Low-grade adenosarcoma* can at first glance appear bland, thus mimicking adenofibroma. Indeed, a few tumors formerly classified as adenofibromas have metastasized and were reclassified as low-grade adenosarcoma [26]. Thus, the diagnosis of adenofibroma is one that first requires exclusion of adenosarcoma. Additional sampling

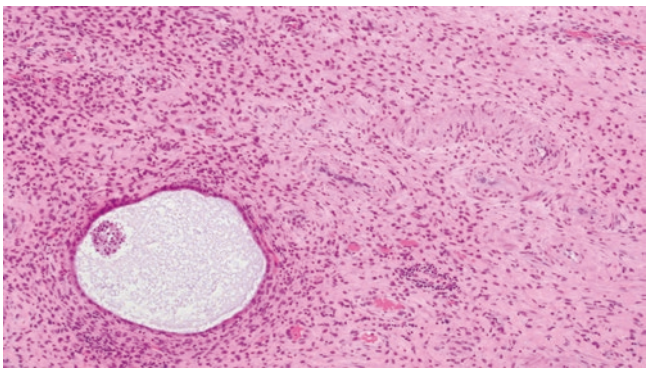

Fig. 4.13 Cervical adenofibroma. The tumor is composed of abundant but otherwise indistinct fibrous stroma admixed with benign glandular elements

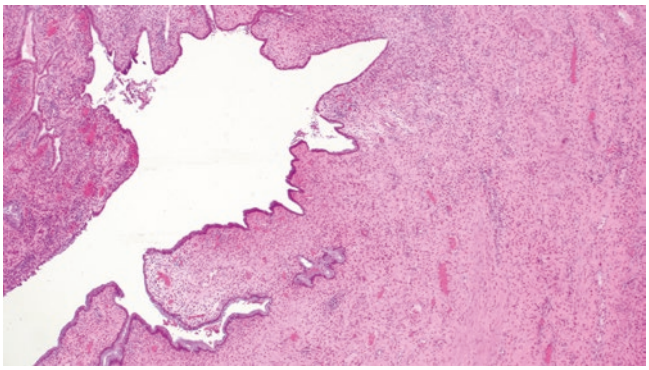

Fig. 4.14 Cervical adenofibroma. The epithelial component can show contour irregularity and cystic dilatation

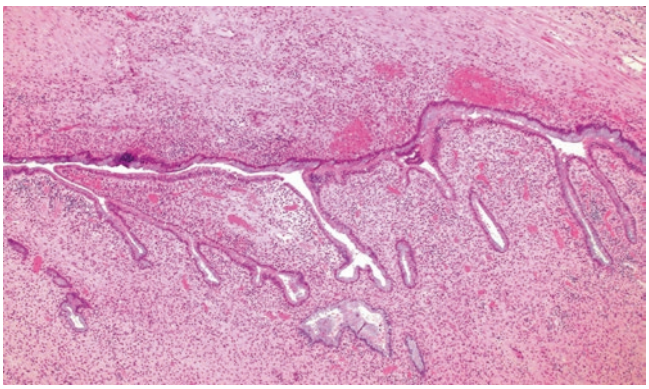

Fig. 4.15 Cervical adenofibroma. Stromal inflammation can be prominent, imparting a cellular appearance at low-power magnification. The fibroblastic stromal population is, nonetheless, bland and evenly distributed

may be required. The presence of stromal cytologic atypia, mitotic activity, periglandular stromal condensation, well-developed and diffuse intraluminal growth with leaf-like architecture, cervical wall invasion, and/or heterologous elements warrant consideration for the diagnosis of adenosarcoma [27].

- *Gastric-type adenocarcinoma, minimal deviation type* features well-formed but haphazardly distributed glands. Unlike adenofibroma, the tumor lacks circumscription. In addition, the glandular component shows gastric-type differentiation (claw-shaped glands; hypermucinous, tall, columnar epithelium; clear, foamy or granular eosinophilic cytoplasm; distinct cell borders). In contrast, the glands of adenofibroma resemble the normal endocervix.
- There is morphologic overlap between cervical adenofibroma and *endocervical polyp*, as adenofibroma is often polypoid and polyps can have prominent fibromatous stroma.
- *Adenomyoma* can be distinguished from adenofibroma by the presence of a myomatous component in between glandular elements. The mesenchymal component of many cervical adenofibromas reported in the literature has a smooth-muscle appearance, suggesting they may in fact be adenomyomas [21, 28].

4.3.7 Prognosis

Adenofibroma is a benign tumor, although it can recur if incompletely excised [29]. Thus, complete removal is recommended.

Diagnostic Highlights

- Adenofibroma of the cervix is well-circumscribed and often exophytic.
- Adenofibroma of the cervix is exceedingly rare; consider the possibility of adenomyoma and adenosarcoma first.

4.4 Adenomyoma

4.4.1 Definition

Benign tumor composed of benign glandular and myomatous mesenchymal elements. This tumor is more common in the uterine corpus. It usually affects adult women, with a mean age at presentation of 40 years (range 21–55) [30, 31]. The lesion may cause abnormal bleeding or mucoid discharge, or it may be asymptomatic. Diagnosis of multiple lesions during early pregnancy has been reported [32].

4.4.2 Synonyms

Not applicable.

4.4.3 Etiology

Unknown.

4.4.4 Macroscopy

The tumor can be polypoid (more often) or intramural (occasionally). Most have a tumor size <8 cm. Large size (up to 23 cm) is infrequent [30, 33]. The lesion is well-circumscribed, with a firm or rubbery cut surface and multiple cystic areas containing mucoid material [34].

4.4.5 Microscopy

The tumor features an admixture of benign glands and myomatous stroma. The glandular component is evenly distributed, but it can be irregular, with variation of glandular size and shape. Glands are of endocervical type (akin to the normal endocervix). Thus, they are positive for Alcian-blue (given their acid mucin composition). It is important to note that PAS positivity (denoting neutral mucin) has been reported [35]. On occasion, an adenomyoma located in the cervix features endometrial-type glands and surrounding stroma [36]. Epithelial metaplasia is common. Lobular configuration and papillary infoldings can be seen [37]. The stroma is composed of smooth-muscle fascicles. "Symplastic-like" features, adipose tissue, mucin extravasation with secondary inflammation, and adenofibroma-like surface areas can be seen [37]. The tumor border is usually well defined, although intratumoral smooth muscle may merge with the surrounding stroma imperceptibly [30]. There is no cytologic atypia or proliferation. Both glandular and myomatous components are diffusely positive for estrogen receptor (ER) (Figs. 4.16, 4.17, 4.18, 4.19) [37].

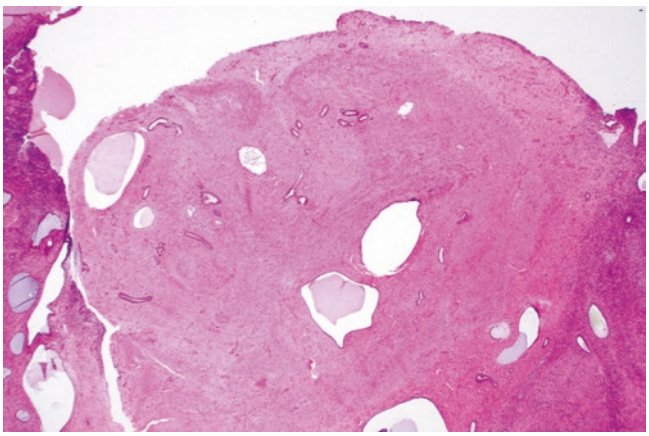

Fig. 4.16 Cervical adenomyoma. This sessile, polypoid lesion is well-circumscribed and shows an admixture of glandular and myomatous elements

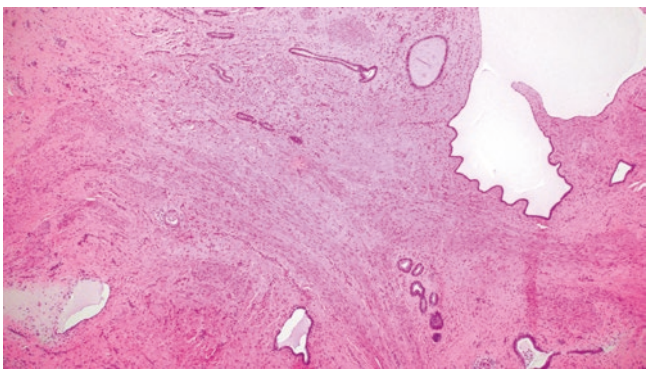

Fig. 4.17 Cervical adenomyoma. The epithelial and mesenchymal components are evenly distributed, with no significant gland crowding or stromal expansion

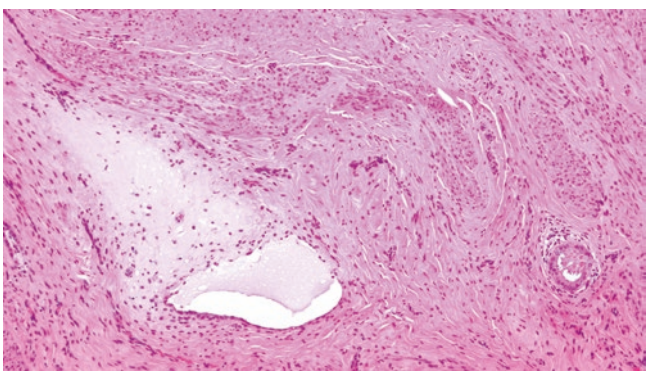

Fig. 4.18 Cervical adenomyoma. The mesenchymal component demonstrates a smooth-muscle phenotype with bland, fusiform cells arranged in fascicles. The glandular component is represented by simple epithelium, which often shows metaplastic change

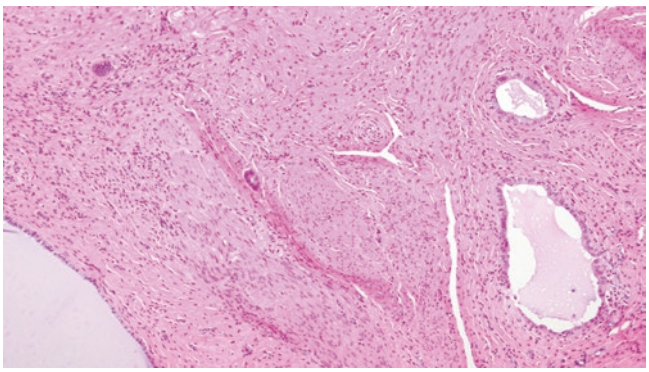

Fig. 4.19 Cervical adenomyoma. The mesenchymal component demonstrates a smooth-muscle phenotype with bland, fusiform cells arranged in fascicles. The glandular component is represented by simple epithelium, which often shows metaplastic change

4.4.6 Differential Diagnosis

- *Atypical polypoid adenomyoma* is typically seen in the uterine corpus and lower uterine segment, and occasionally involves the upper endocervix. Its appearance can overlap with adenomyoma, especially in partial and fragmented samples. Unlike cervical adenomyoma, atypical polypoid adenomyoma contains florid endometrioid glands featuring crowding and irregularity.
- Adenomyoma differs from minimal deviation *gastric-type adenocarcinoma,* because of its well-demarcated and non-infiltrative interface, lobular glandular configuration, myomatous stroma, and absence of desmoplasia and wall infiltration. Moreover, the glandular component is predominantly of the endocervical type, lacks diffuse gastric-type differentiation, and is ER positive.
- *Adenosarcoma* only very rarely exhibits smooth-muscle differentiation; instead, it typically features stromal atypia, mitoses, stromal condensation, and well-developed intraglandular leaf-like growth.
- *Cervical adenofibroma* is a rare entity and a diagnosis of exclusion; adenosarcoma is more common. In contrast to adenomyoma, adenofibroma lacks significant smooth-muscle differentiation in the stroma.

4.4.7 Prognosis

Cervical adenomyomas are benign, and surgical excision is usually curative [37]. Polypectomy, however, can lead to incomplete excision, and recurrence in this setting has been reported [31].

Diagnostic Highlights

- Adenomyoma features benign endocervical-type glands in a myomatous stroma.
- The differential diagnosis includes atypical polypoid adenomyoma and gastric-type adenocarcinoma, particularly in fragmented or partial samples. Attention to the circumscription of the lesion, as well as the simple architecture and bland cytomorphology of the glands, is important.

4.5 Leiomyoma

4.5.1 Definition

Leiomyoma is a benign neoplastic proliferation of smooth-muscle cells. Primary cervical leiomyomas are very uncommon, accounting for less than 1% of all uterine leiomyomas [38]. Like their counterparts of the uterine corpus, cervical leiomyomas often present with abnormal bleeding, abdominal pain or discomfort, urinary retention, constipation, or a prolapsed mass or uterus [39, 40]. Growth during pregnancy can occur [41]. Age at presentation has a wide range, but most cases occur between the third and sixth decades of life [42].

4.5.2 Synonyms

Fibroid; variants include lipoleiomyoma, leiomyoma with bizarre nuclei, cellular leiomyoma, cotyledonoid leiomyoma, epithelioid leiomyoma, and myxoid leiomyoma.

4.5.3 Etiology

Unknown. Hormonal stimulation may play a role, as most patients are premenopausal or perimenopausal at the time of presentation.

4.5.4 Macroscopy

Tumor size in reported cases averages 7 to 10 cm [42]. Asymptomatic lesions are more often small (<3 cm). At the other end of the spectrum, the lesion can be as large as 30 cm and can extend to the retroperitoneum [43]. Anatomically, leiomyomas can be subdivided into interstitial (intramural), supravaginal, and polypoidal [44].

Macroscopically, the tumor is well demarcated and easily separates ("shells out") from the adjacent wall. The cut surface has a whorled appearance, pale tan color, and rubbery to soft consistency. Necrosis and hemorrhage are typically absent. Hydropic change with cavitation (degenerative in nature) can be observed [45].

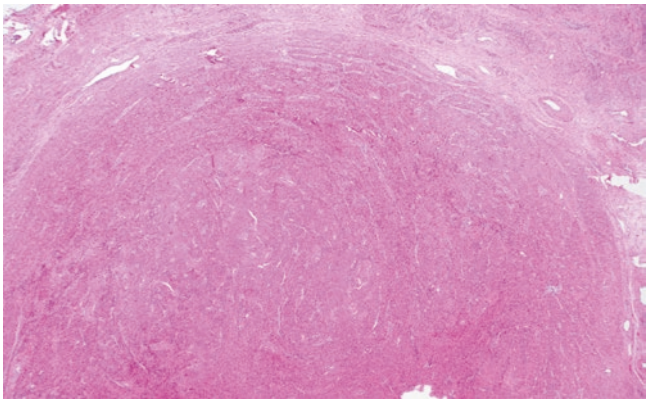

Fig. 4.21 Leiomyoma. The tumor shows uniform cellularity and a smooth interface with the surrounding cervical wall

4.5.5 Microscopy

Most uterine leiomyomas are of conventional (spindle cell) type. These are comprised of spindle cells arranged in intersecting fascicles (Figs. 4.20, 4.21, 4.22, 4.23, 4.24, 4.25). The cells have elongated nuclei with blunted ends (cigar shape) and uniform chromatin distribution. Cytoplasm is discernible and has an eosinophilic appearance. Schwannoma-like cellular distribution can be observed. The cell population is uniform and lacks significant cytologic atypia. Mitotic activity can be encountered but is fewer than 10 mitoses in

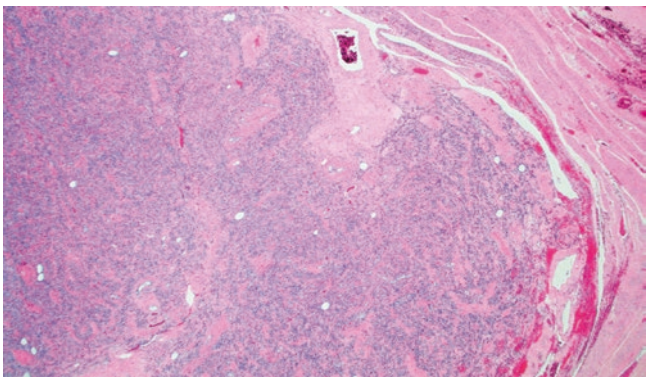

Fig. 4.22 Leiomyoma. Some tumors are hypercellular, compared with the surrounding uterine wall. Notice the smooth, non-infiltrative interface

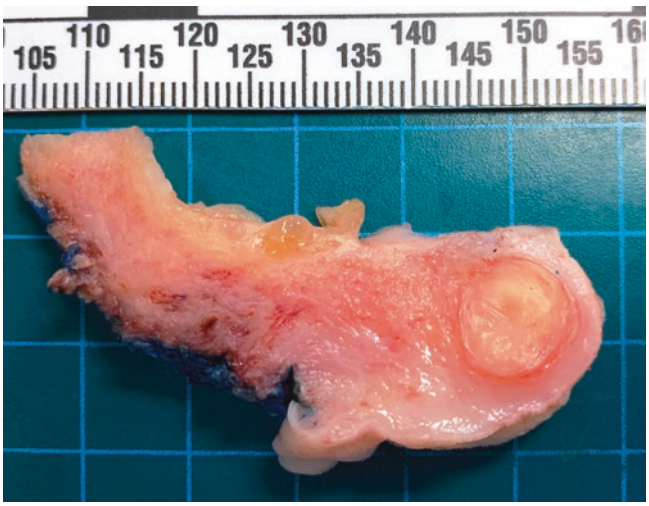

Fig. 4.20 Leiomyoma. Macroscopically, the tumor is located in the distal aspect of the cervix, and has a smooth, well-defined contour. The cut surface in this case is solid and homogeneous. (*Courtesy of* Anna-Marie Moskaluk, Sunnybrook Health Sciences Centre, Toronto, Canada)

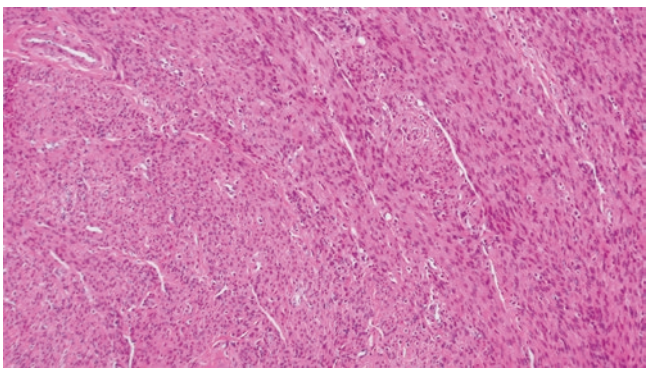

Fig. 4.23 Leiomyoma. The tumor is comprised of bland, monotonous cells arranged in fascicles. When the fascicles are cut longitudinally (*right*), the nuclei are elongated with round ends. When the fascicles are cut transversely (*left*), the nuclei are round to ovoid

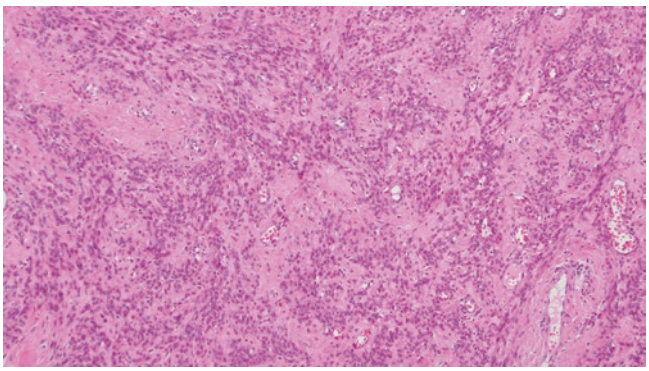

Fig. 4.24 Leiomyoma. Cellular fascicles are separated by varying amounts of collagenous stroma

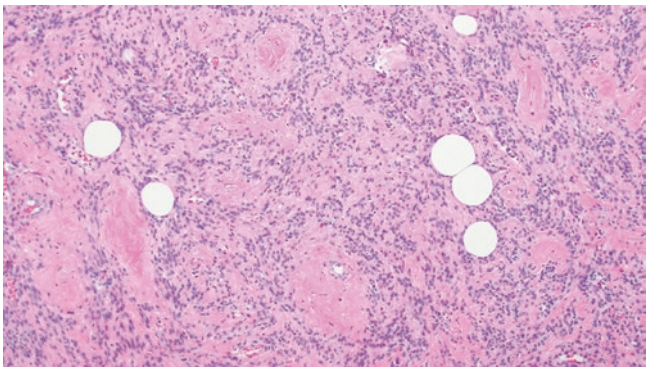

Fig. 4.25 Leiomyoma. Mature adipose tissue can be observed in different proportions. The term *lipoleiomyoma* is used in these instances

10 high-power fields (HPFs). Tumor cell necrosis is absent. Degenerative changes including edema, pseudocystic degeneration, ischemic-type necrosis, dense collagenous hyalinization, and myxoid change can be seen [45]. The latter is usually minor, although a predominant myxoid leiomyoma in the cervix has been described [44].

Lipoleiomyomas are characterized by the presence of mature adipose tissue elements throughout the tumor [46]. The diagnosis of leiomyoma variants (cellular, with bizarre nuclei, cotyledonoid) follows definitions established for uterine leiomyomas.

4.5.6 Differential Diagnosis

- *Submucosal leiomyoma arising in the uterine corpus* and protruding through the canal is a slightly more common occurrence than cervical leiomyoma [38]. Correlation with radiologic and clinical findings, as well as careful gross examination, are required to make this distinction.
- *Other rare benign entities* in the differential include schwannoma, neurofibroma, and lesions with a smooth-muscle component such as myofibroblastoma, angiomyofibroblastoma, and adenomyoma.
- The distinction between conventional leiomyoma and *leiomyosarcoma* of the cervix follows the same criteria outlined for smooth-muscle tumors of the uterine corpus. The tumor is classified as malignant if it has two or more of the following: necrosis, moderate to severe atypia, and more than 10 mitoses in 10 HPFs (see Sect. 11.5) [47].
- *Myxoid and epithelioid variants* (see Sect. 11.5) are rare, and their occurrence in the cervix is not fully described. For now, it is advised to use uterine criteria for these variants as well. Thus, diagnosis of myxoid or epithelioid leiomyoma requires absence of necrosis, atypia, proliferation, vascular invasion, and infiltrative borders.
- *Poorly differentiated squamous cell carcinoma* of the cervix can feature a spindle cell component, which can be mistaken for a leiomyoma. These lesions also have a conventional squamous component and feature significant atypia and proliferation in both epithelioid and spindle cell areas. Immunohistochemistry with p16 and HPV studies can be helpful. Thorough sampling is always required if there is any suspicion of malignancy and should include the tumor interface with the surrounding wall, as well as any grossly abnormal tumor areas.

4.5.7 Prognosis

Leiomyomas are benign. Conservative, complete excision or definitive surgical treatment with hysterectomy can be considered. Local control with medication or embolization can be considered. If untreated, the lesion can cause complications like cervical inversion [48].

Diagnostic Highlights

- Leiomyomas of the cervix are rare, but feature the same morphologic features of their counterparts in the uterine corpus.
- Submucosal lesions tend to be symptomatic, presenting with abnormal vaginal bleeding.
- The morphologic approach for the distinction from leiomyosarcoma is the same as in lesions from the uterine corpus (see Sect. 11.4).

4.6 Fibroepithelial Stromal Polyp

4.6.1 Definition

Exophytic mucosal lesion composed predominantly of bland mesenchyme (including lower genital stromal cells) and lined by benign cervical epithelium. This lesion is more common in the vagina and the vulva. The lesion can be asymptomatic and discovered incidentally on examination, or it can produce abnormal bleeding or pain. Most women are of reproductive age, and some lesions are diagnosed during pregnancy [49].

4.6.2 Synonyms

Not applicable.

4.6.3 Etiology

Unknown. Unlike endocervical polyps, fibroepithelial stromal polyps do not appear to be reactive in nature, as they are not associated with prominent inflammation [49]. Hormonal stimulation may play a role.

4.6.4 Macroscopy

Most polyps are small (<1 cm). "Giant" polyps, measuring >4 cm in size, are infrequent [50]. Grossly, the lesion typically has a frond-like appearance. The overlying mucosa is indistinct. The cut surface is uniform and soft to rubbery.

4.6.5 Microscopy

Fibroepithelial stromal polyp is characterized by an evenly distributed and relatively hypocellular proliferation of bland stromal cells admixed with collagen and vessels of varying thickness. Thick-walled vessels are more often seen at the polyp base. The tumor often contains distinctive stromal cells with multinucleated and stellate nuclei, which are typical of the vaginal and vulvar superficial stroma but have also been described in the cervix [51]. They tend to be located towards the surface. The stromal cells are otherwise bland and uniform, with spindled, wavy nuclei. The lesion is lined by mature and/or metaplastic squamous epithelium. Endocervical glands are absent, except for occasional glands trapped in the periphery (Figs. 4.26, 4.27, 4.28, 4.29, 4.30) [52].

A subset of fibroepithelial stromal polyps features hypercellularity, bizarre stromal nuclei, and atypical mitoses, but subepithelial and periglandular stromal condensation is not

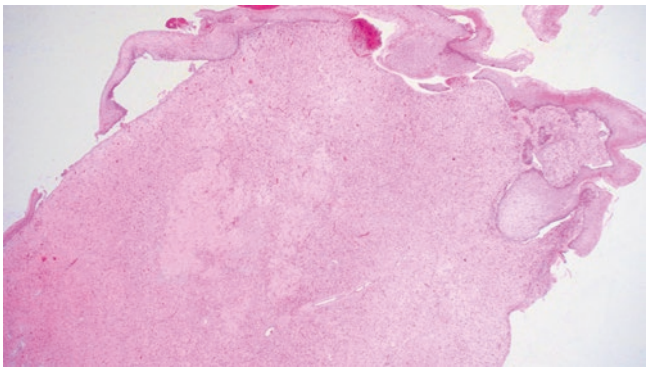

Fig. 4.26 Fibroepithelial stromal polyp. The lesion is polypoid and lined by benign squamous mucosa. Notice the absence of a clear tumor demarcation from the subepithelial stroma, and the lack of epithelial elements within the tumor

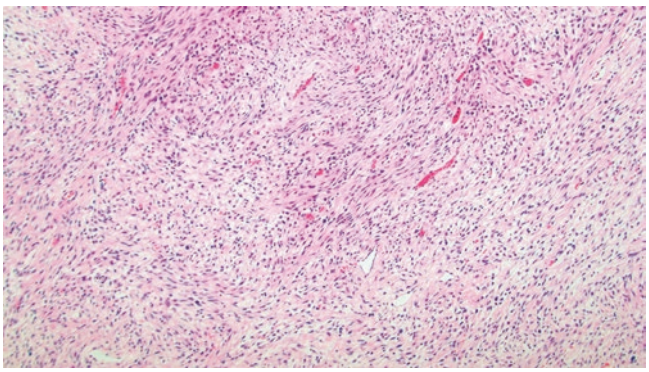

Fig. 4.27 Fibroepithelial stromal polyp. The spindle cell population is bland and uniformly distributed

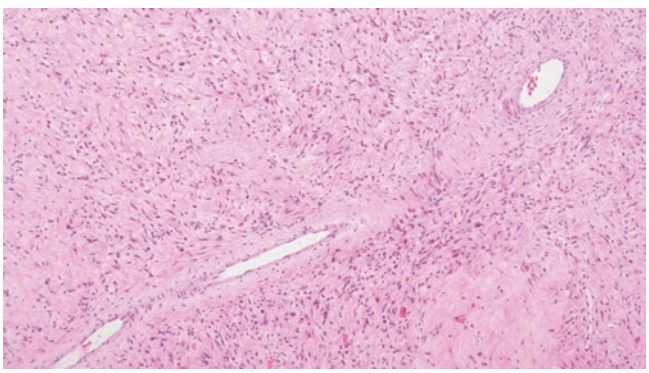

Fig. 4.28 Fibroepithelial stromal polyp. The vasculature of the polyp varies in thickness and distribution. Thick-walled vessels are usually present, often in the polyp base or stalk

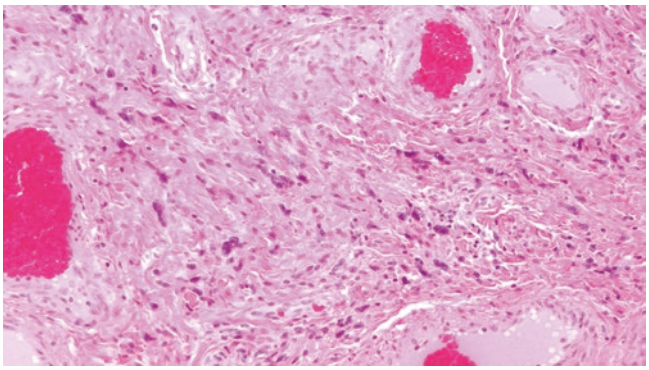

Fig. 4.29 Fibroepithelial stromal polyp. When found, the presence of multinucleated hyperchromatic stromal cells is helpful in the diagnosis. These are usually located in the superficial aspect of the tumor

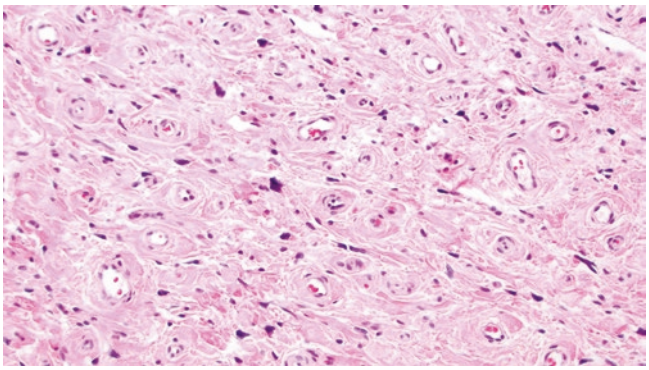

Fig. 4.30 Fibroepithelial stromal polyp. When found, the presence of stellate, mildly enlarged, and hyperchromatic stromal cells is helpful in the diagnosis. These are usually located in the superficial aspect of the tumor

present. These "pseudosarcomatous" polyps have been described in the vulva, vagina, and cervix [53].

By immunohistochemistry, the stromal cells are positive for desmin, vimentin, and estrogen and progesterone receptors [53–55].

4.6.6 Differential Diagnosis

- There is overlap in the descriptions of *squamous papilloma*, fibroepithelioma, and fibroepithelial polyp found in the literature. Indeed, many authors have considered these the same entity. In the lower genital tract, fibroepithelial stromal polyp is regarded as a mesenchymal proliferation as the stroma is often the predominant component. Squamous papilloma, on the other hand, is small and composed mostly of branching, benign squamous epithelium within scant underlying stroma.
- Similarly, there is overlap with descriptions of *adenofibroma*. At least one lesion reported as fibroepithelial polyp shows cystically dilated endocervical glands, and it is likely to represent a polypoid adenofibroma [50]. The diagnosis of fibroepithelial stromal polyp should be reserved for polypoid lesions in which the mesenchymal component is predominant and contains lower genital stellate or multinucleated stromal cells.
- Unlike fibroepithelial polyp, *exophytic squamous intraepithelial lesions* display HPV-cytopathic changes. Likewise, *warty squamous cell carcinoma* shows significant nuclear atypia, loss of maturation, and brisk mitotic activity, which are all absent in fibroepithelial polyp.
- Pseudosarcomatous fibroepithelial stromal polyp needs to be distinguished from cervical sarcomas. The differential includes *rhabdomyosarcoma* (pediatric population, subepithelial condensation of highly atypical cells with rhabdoid features), *leiomyosarcoma* (large size, necrosis, and destructive growth into the uterine wall) and *NTRK-altered sarcoma* (infiltrative growth, frequent positivity for S100, and absence of desmin expression).

4.6.7 Prognosis

Fibroepithelial stromal polyps are benign. Surgical excision is the treatment of choice. Local, non-destructive recurrence of pseudosarcomatous polyps has been reported [53].

Diagnostic Highlights

- Fibroepithelial stromal polyp is more common in vulva and vagina.
- Consider the diagnosis of fibroepithelial polyp if the lesion is exophytic, lined by benign squamous epithelium, and has a prominent stromal component with submucosal stellate or multinucleated cells.
- First exclude other possibilities such as condyloma and rhabdomyosarcoma.

4.7 Other Lower Genital Mesenchymal Lesions

4.7.1 Definition

This section encompasses a group of benign mesenchymal neoplasms with predilection for the lower genital tract (vulva, vagina, and less commonly, cervix). Only lesions reported in the uterine cervix are included here.

Mammary-type myofibroblastoma is a benign neoplasm with myofibroblastic phenotype. Initially described in the breast, it is now known to have a wide anatomic distribution [56]. Median age is 45 years [57]. Three cases of angiomyofibroblastoma in adult women (fifth decade) have been reported [58–60]. One case of superficial angiomyxoma in a 40-year-old woman has been documented [61].

4.7.2 Synonyms

Not applicable.

4.7.3 Etiology

Unknown. As most of these lesions are positive for estrogen and progesterone receptors, hormonal stimulation has been implicated in their origin.

4.7.4 Macroscopy

Myofibroblastoma can be polypoid or intramural (usually superficial); the cut surface is rubbery and nodular. Median size is 4.5 cm (range 3.8–6.5 cm) [57]. Angiomyofibroblastoma is well-defined and small (typically <2 cm). Superficial angiomyxoma presents as a pedunculated or sessile mucosal mass.

4.7.5 Microscopy

These neoplasms are non-encapsulated, well-circumscribed, and show a clear separation from the superficial stroma (Figs. 4.31, 4.32, 4.33, 4.34, 4.35, 4.36, 4.37, 4.38, 4.39).

Myofibroblastoma is composed of bland spindle and stellate cells separated by collagen bundles and varying amounts of adipose tissue [62]. Mitoses are rare. By

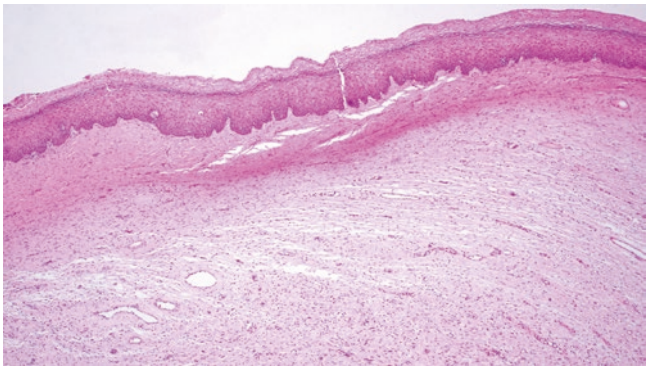

Fig. 4.31 Myofibroblastoma. In contrast to fibroepithelial stromal polyp, this lesion has a visible demarcation from the subepithelial connective tissue

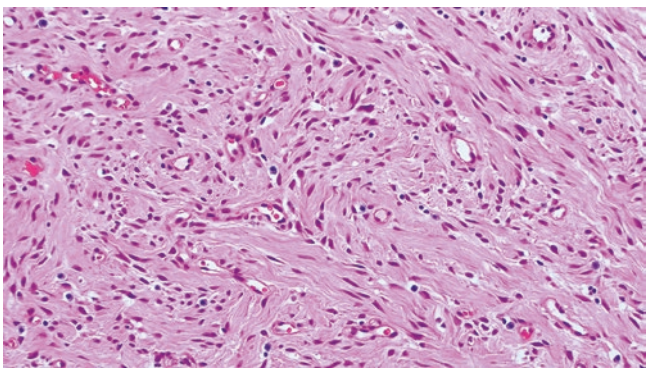

Fig. 4.32 Myofibroblastoma. The lesion is composed of bland fusiform cells dispersed in a collagenous matrix

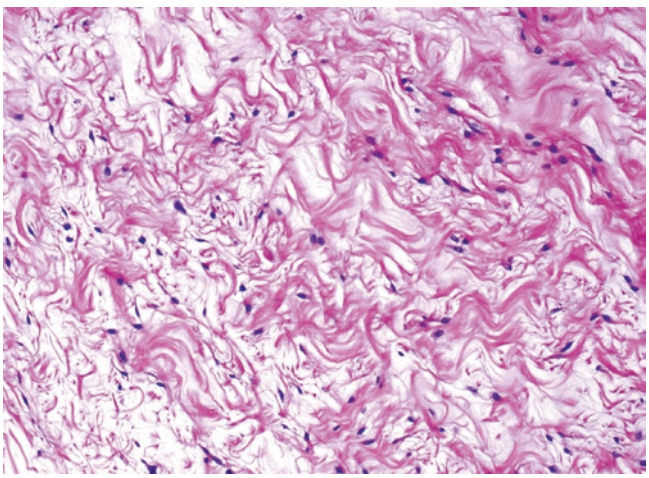

Fig. 4.33 Myofibroblastoma. Eosinophilic collagen bundles are admixed with the spindle cell component

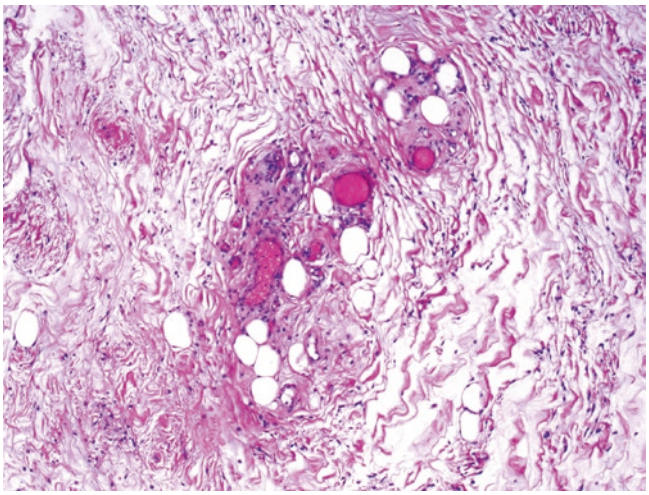

Fig. 4.34 Myofibroblastoma. The tumor may have a mature adipocytic component

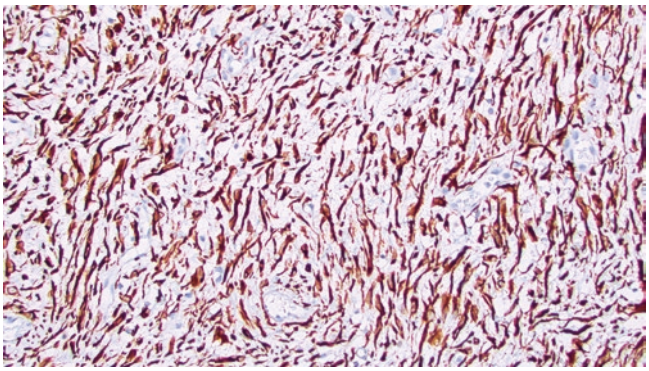

Fig. 4.35 Myofibroblastoma. Tumor cells are usually positive for desmin

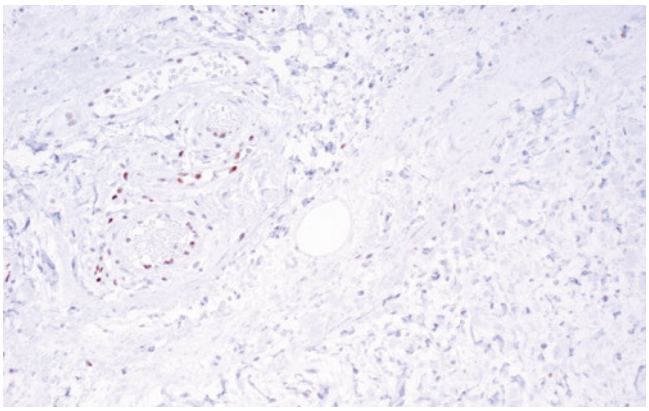

Fig. 4.36 Myofibroblastoma. Loss of *RB1* nuclear expression is helpful in distinguishing myofibroblastoma from its mimics. Notice the positive internal control in the endothelium

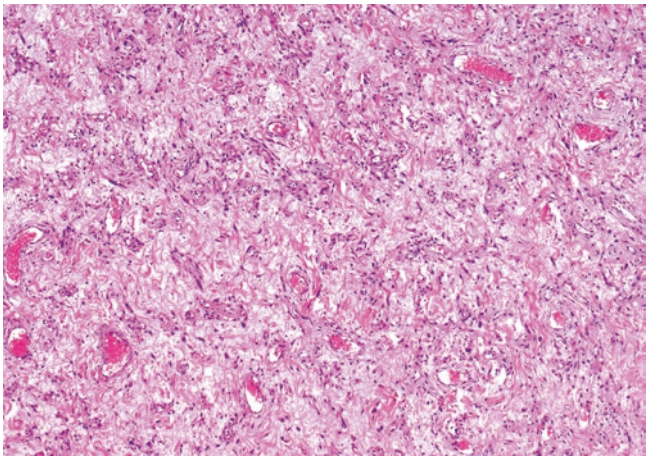

Fig. 4.37 Angiomyofibroblastoma. This tumor shows clusters of bland stromal cells separated by relatively hypocellular areas, imparting an appearance of alternating cellularity

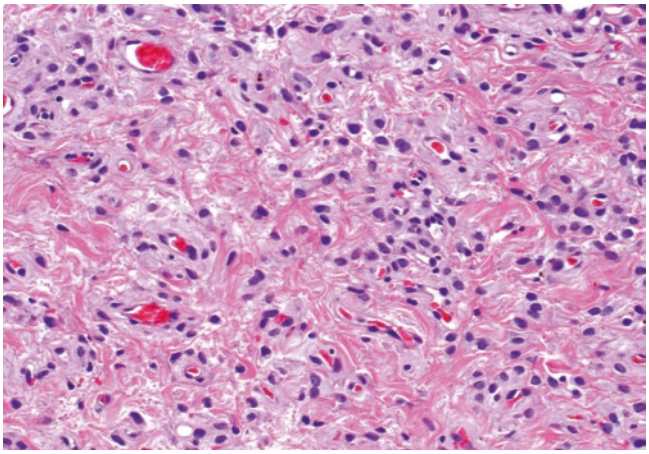

Fig. 4.38 Angiomyofibroblastoma. The tumor cells have an epithelioid appearance; they vaguely aggregate around small vessels

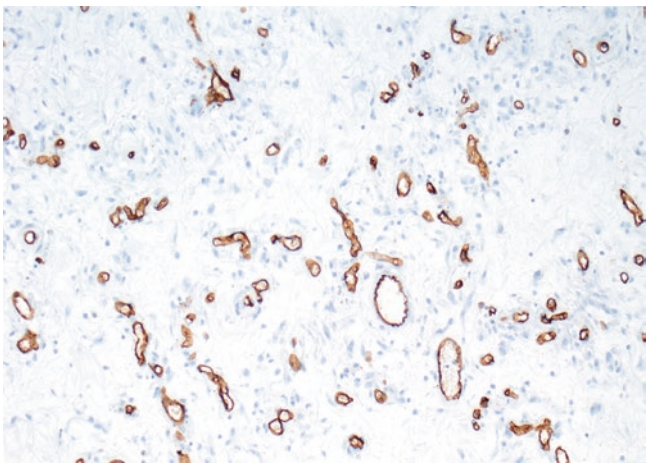

Fig. 4.39 Angiomyofibroblastoma. Tumor cells are usually negative for CD34. Notice the positive internal control in the endothelium

immunohistochemistry, cells are positive for hormone receptors, desmin, and CD34, and are negative for S100 [63]. Pseudosarcomatous change with plump vesicular pleomorphic nuclei has been described in one case [64]. Loss of *FOXO1* on 13q14, associated with *RB1* loss of expression, has been documented in lower genital myofibroblastoma [65].

Angiomyofibroblastoma is composed of spindle and epithelioid stromal cells aggregated around thin-walled vessels. The cellular perivascular areas alternate with areas of hypocellularity, imparting a zonal appearance on low-power magnification [58]. Adipose tissue is often present. Tumor is positive for hormone receptors. Smooth muscle marker expression is variable, and CD34 is negative in most cases [66].

Superficial angiomyxoma is hypocellular and features bland spindle and stellate-shaped cells in a prominent myxoid matrix. Thin-walled vessels predominate. Stromal cells are positive for CD34 and negative for desmin and hormone receptors.

4.7.6 Differential Diagnosis

- In the cervix, *leiomyoma* is a more common occurrence than myofibroblastoma and angiomyofibroblastoma. Although there is significant overlap between these lesions, a well-developed fascicular architecture with tapered-end, fusiform nuclei and eosinophilic cytoplasm should prompt the diagnosis of leiomyoma.
- *Fibroepithelial stromal polyp* can enter in the differential. Unlike the entities discussed here, fibroepithelial stromal polyp lacks circumscription and clear demarcation from the epithelium and submucosal stroma.
- *Sarcomas* of the uterine cervix are rare, but when encountered, they can be misdiagnosed as a benign entity. Most sarcomas will feature infiltrative borders, cytologic atypia, and/or brisk proliferation, features that should not be seen in the benign tumors described here (see Sect. 11.1).

4.7.7 Prognosis

Myofibroblastoma, angiomyofibroblastoma, and superficial angiomyxoma are benign tumors, and no recurrences or metastases after complete excision have yet been documented.

Diagnostic Highlights

- Vulvovaginal mesenchymal lesions have been rarely reported in the cervix.
- Myofibroblastoma is composed of bland spindle and stellate cells separated by collagen bundles and varying amounts of fat.
- Angiomyofibroblastoma is composed of spindle and epithelioid stromal cells which form hypercellular areas around thin-walled vessels, separated by hypocellular areas.
- Superficial angiomyxoma features bland spindle and stellate-shaped cells in a prominent myxoid matrix.

4.8 Lesions with Neuroectodermal and Nerve Sheath Differentiation

4.8.1 Definition

Lesions in this category are infrequent in the cervix. Schwannoma is a benign peripheral nerve sheath tumor of Schwann cell derivation. It is often seen in superficial soft tissues and extremities in middle-aged patients [67]. Multiple schwannomas ("schwannomatosis") occur in the setting of germline *SMARCB1* mutations and neurofibromatosis type 2 [67, 68].

Neurofibroma can be sporadic or related to neurofibromatosis type 1 [69]. Plexiform neurofibroma, a subtype characterized by multiple nodularities affecting the peripheral nerve, is associated with neurofibromatosis type 1 [70]. Cases involving the cervix present with abnormal bleeding, irritative urinary symptoms, or cervical stenosis [69]. In most cases, other sites are involved, including skin, other gynecologic sites, and viscera [70, 71].

Glial heterotopia is a rare but documented phenomenon in the female genital tract, predominantly involving the cervix [72]. It typically presents in reproductive-age, multiparous women, some with history of abortion and curettage procedures [73, 74].

4.8.2 Synonyms

Schwannoma: Neurilemmoma; schwannomatosis.

Neurofibroma: Plexiform neurofibroma.

Glial heterotopia: Glial polyp.

4.8.3 Etiology

Schwannoma and neurofibroma likely arise from intramural nerves. Derivation from stromal fibroblastic cells of the cervix has also been postulated [75].

Glial heterotopia is believed to occur after implantation of fetal brain tissue in the cervix, which has been supported by DNA genotype testing [74]. There is no reported association with ovarian mature or immature teratomas [73].

4.8.4 Macroscopy

Schwannoma is usually small (<2 cm) and appears as a nodular swelling or protrusion on the cervical mucosa. Most neurofibromas are solitary, small, and superficial. Plexiform neurofibromas are large and involve significant portions of the peripheral nerve, giving a typical "bag of worms" appearance [69]. Glial heterotopia is grossly seen as small (<2 cm), polypoid lesions involving the endocervical canal.

4.8.5 Microscopy

Schwannomas are encapsulated and feature spindle cells arranged in characteristic alternating areas of cellularity. Antoni type-A areas have tightly packed sheaths of spindle cells with a palisading and swirling appearance. Antoni type-B areas are loosely packed. Cystic degeneration and Verocay body-like structures can be encountered. In some tumors, Antoni A areas predominate (Figs. 4.40, 4.41, 4.42). Tumor cells are positive for S100 and GFAP, and are negative for HMB45, neurofilament, desmin, and smooth muscle actin [76].

Neurofibroma can be localized (single lesion with preservation of the nerve), diffuse (large mass obliterating the nerve), or plexiform (multiple nodularities deforming the nerve). The tumor is well-circumscribed but not encapsulated. The spindle cell population shows wavy nuclei with pointed ends, dispersed in a myxoid-to-collagenous matrix. Cells are usually positive for neurofilament and S100, usually with a focal or patchy distribution.

Glial heterotopia is seen as lobulated mature glial tissue covered by normal cervical epithelium. A lymphoplasmacytic inflammatory component can be observed. The lesion is positive for S100 and GFAP [72].

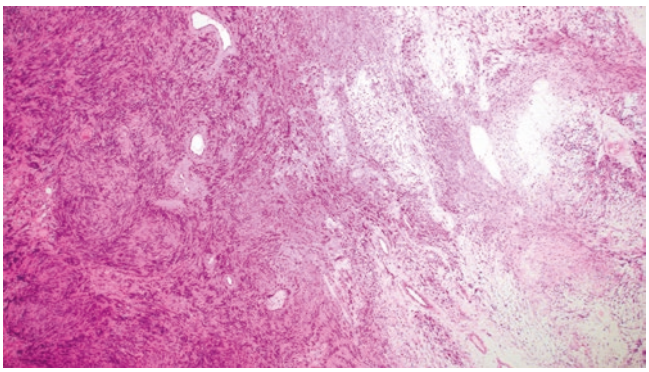

Fig. 4.40 Schwannoma. This neoplasm characteristically has hypercellular (Antoni-A, *left*) and hypocellular (Antoni-B) areas

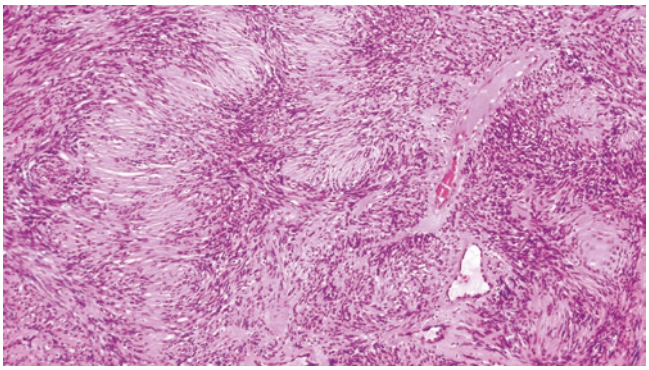

Fig. 4.41 Schwannoma. Antoni-A areas are hypercellular, comprised of sheets of spindle cells with nuclear palisading

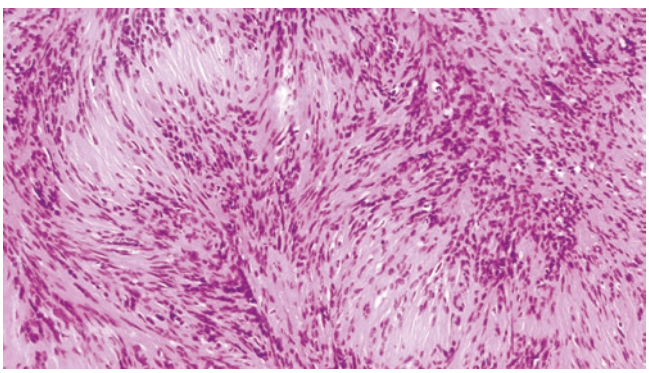

Fig. 4.42 Schwannoma. Spindle cells have a swirling appearance

4.8.6 Differential Diagnosis

- *Schwannoma* and *neurofibroma* are clinically and morphologically similar. Schwannoma is favored in the presence of a true capsule, biphasic appearance, and diffuse positivity for S100.
- *Malignant peripheral nerve sheath tumor (MPNST)* can rarely occur in the cervix [67, 76]. Importantly, neurofibromas can undergo malignant transformation towards MPNST, particularly in the setting of neurofibromatosis. The presence of prominent cellular atypia, hyperchromasia, necrosis, and any proliferation (>1 mitosis in 10 HPFs) should raise this possibility.
- *Leiomyoma* can resemble tumors of neural derivation grossly and microscopically. Indeed, neurilemmoma-like areas are not uncommon in leiomyoma. However, the typical smooth-muscle morphology is always appreciated. Expression of smooth-muscle markers is supportive.
- Given its frequently polypoid appearance, glial heterotopia can be misdiagnosed as *endocervical poly*p and *adenofibroma*. Recognition of the astrocytic morphology in the stromal component is key in this differential and can be confirmed with GFAP stain.

4.8.7 Prognosis

The treatment of choice for these benign lesions is complete excision, after which the prognosis is excellent.

Diagnostic Highlights

- Schwannoma is an encapsulated lesion featuring spindle cells arranged in characteristic alternating areas of cellularity.
- Neurofibroma can be localized, diffuse or plexiform. It is non-encapsulated and features a uniform population of bland spindle cells.
- Glial heterotopia is composed of lobulated mature glial tissue covered by normal cervical epithelium. It is believed to represent implantation of fetal neural tissue from previous pregnancies.

4.9 Lipoma

4.9.1 Definition

Adipocytic neoplasms are exceedingly rare in the cervix, presumably because of the scant amount of adipose tissue in this anatomic location. Lipoma is defined as a benign lesion composed of mature adipose tissue. Lipomas of the uterus are usually found incidentally in postmenopausal patients [77].

4.9.2 Synonyms

Not applicable.

4.9.3 Etiology

Unknown. Proposed theories include metaplasia of smooth muscle or other mesenchymal cells in the uterus, development from a misplaced mesenchymal precursor, or fat implantation after trauma or surgery [78].

4.9.4 Macroscopy

Cervical lipoma appears grossly as a well-demarcated, soft and yellow mass. Uterine lipomas range in size from a few millimeters to 10 cm [77].

4.9.5 Microscopy

Lipomas are non-encapsulated, well-demarcated lesions composed of mature adipose tissue. Collagenous septa of varying amounts separate adipocytes. A spindle cell lipoma variant containing floret-like multinucleated cells has also been described (Figs. 4.43, 4.44) [79].

4.9.6 Differential Diagnosis

- *Lipoleiomyoma*, though also rare, is a more likely occurrence in the cervix than pure lipoma. The presence of

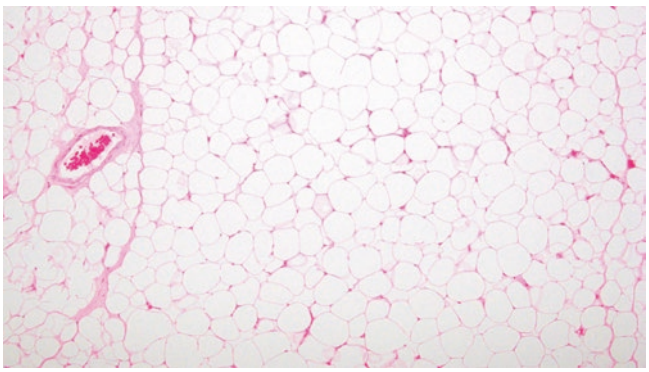

Fig. 4.43 Lipoma. Mature adipose tissue with univacuolated cells, most with indistinct nuclei

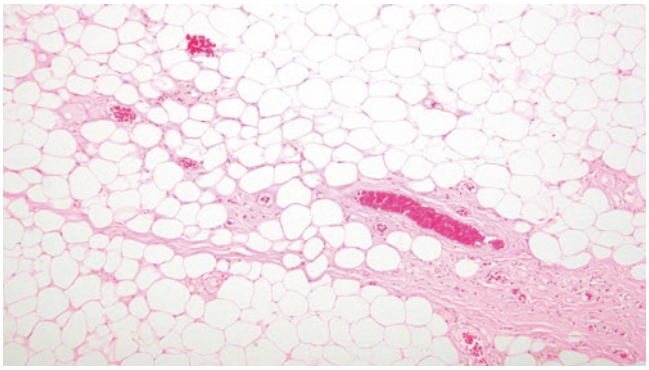

Fig. 4.44 Lipoma. Collagenous septa containing vascular structures can be seen. Notice the absence of atypical cells within the collagenous septa

smooth muscle throughout the lesion should prompt this diagnosis.

- Other benign mesenchymal tumors that may harbor an adipocytic component include *angiomyofibroblastoma* and *mammary-type myofibroblastoma*.
- *Atypical lipomatous tumor* contains atypical cells within fibrous septa and variation in the size of adipocytes. Lipoblasts, when found, are also supportive of this diagnosis. MDM2 immunohistochemistry and testing for 12q13–15 amplification can be considered.

4.9.7 Prognosis

Lipomas are benign. Excision is curative.

Diagnostic Highlights

- Pure lipomas are very rare in the uterine cervix.
- When encountering a lesion with adipose tissue differentiation, consider leiomyoma, angiofibroblastoma and mammary-type myofibroblastoma first.

4.10 Hemangioma

4.10.1 Definition

Hemangioma is a benign localized proliferation of vascular channels. Hemangiomas of the uterine cervix are exceedingly rare [80–82]. Most patients are of reproductive age, with a median age at presentation of 33 years [83]. Lesions usually are asymptomatic and incidentally found on excisional material. Less often, they may manifest with abnormal bleeding or be found as a mass on pelvic examination.

4.10.2 Synonyms

Cavernous hemangioma; capillary hemangioma.

4.10.3 Etiology

The pathogenesis of cervical hemangiomas remains unclear, but the reproductive-age predominance, occurrence during pregnancy [84, 85], and their frequent estrogen and progesterone receptor positivity [83, 86] have led to the hypothesis that hemangiomas are secondary to hormonal stimulation.

4.10.4 Macroscopy

Median lesion size is 2 cm, although it can be as large as 10 cm [83]. The lesion is usually ill-defined, soft and spongy, with a blue or port-wine color (Fig. 4.45).

4.10.5 Microscopy

The lesion is a non-encapsulated, irregular but usually well-demarcated proliferation of tightly packed, dilated, and congested blood vessels lined by flat, bland endothelium. About 75% of cervical hemangiomas are cavernous; the rest have been described as capillary hemangiomas [83]. Most lesions are intramural. Involvement usually exceeds 50% of the wall thickness and approaches the outer cervical margin. Polypoid growth and extension to the vagina can rarely occur (Figs. 4.45, 4.46, 4.47, 4.48).

Elastic stain shows absence of elastic fibers in the vessel walls. By immunohistochemistry, lining endothelium is positive for estrogen and progesterone receptors, ERG, CD31, and CD34.

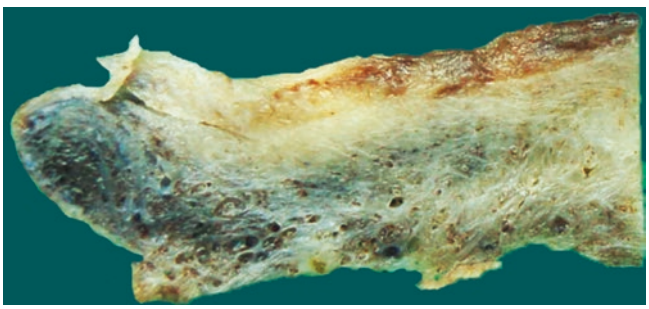

Fig. 4.45 Cervical hemangioma. Macroscopically, the lesion is seen as an ill-defined area of dilated, congested, and tightly packed spaces extending to the outer wall and the distal aspect of the cervix

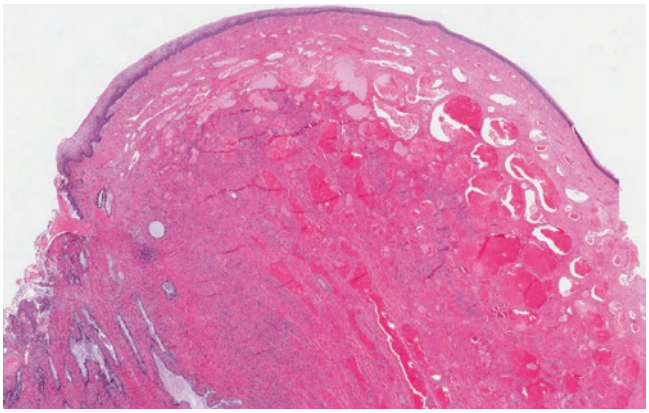

Fig. 4.46 Cervical hemangioma. The vascular proliferation usually involves a significant portion of the wall. In this example, the distal cervix (lip) is involved

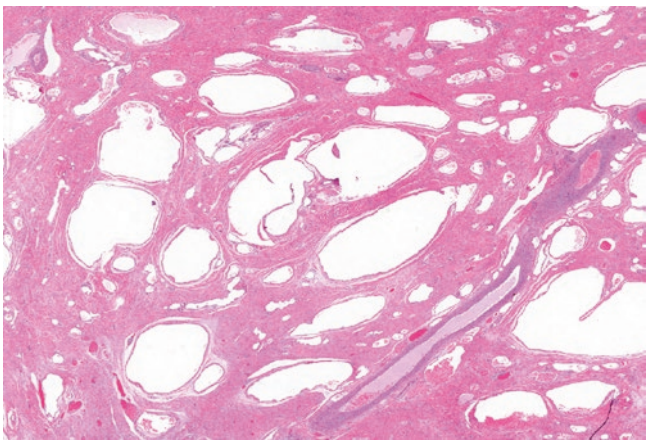

Fig. 4.47 Cervical hemangioma. The dilated venous vascular structures are haphazardly distributed in the cervical wall

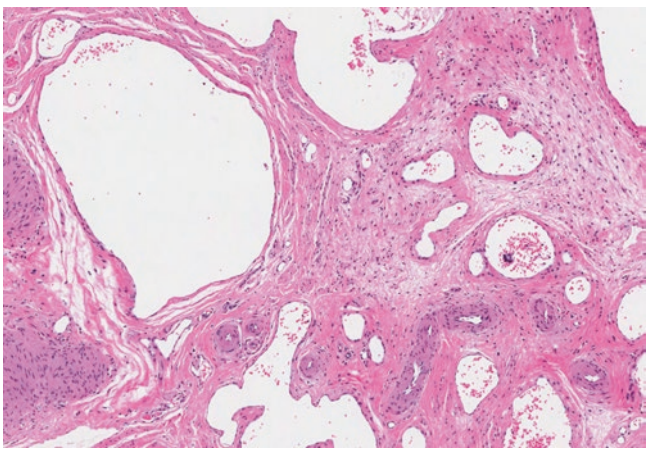

Fig. 4.48 Cervical hemangioma. The lesion has a predominance of dilated venous vessels

4.10.6 Differential Diagnosis

- *Hemangioendothelioma* and *angiosarcoma* also can occur in the cervix (see Sect. 11.15) [80, 87–90]. These tumors are more likely to grow rapidly and cause morbidity. The presence of atypical or overtly malignant cytologic features should raise concern for these diagnoses.
- *Arteriovenous malformation of the cervix* has been reported [91]. Unlike hemangioma, this lesion contains not only venous but also thick arterial vessels, arranged haphazardly.
- *Epithelial proliferations* such as tunnel clusters or squamous cell carcinoma may mimic a vascular lesion at low-power magnification [92]. Evaluation of the cytologic detail and immunohistochemistry for epithelial and vascular markers will aid in this differential.

4.10.7 Prognosis

Hemangiomas involving the cervix are indolent lesions. Recurrences or distant spread have not been reported. Local excision and hysterectomy are valid management options if the lesion is symptomatic. Spontaneous regression has been documented in two patients who declined excision and were managed with observation [84, 93].

Diagnostic Highlights

- Cervical hemangiomas are rare; they often express hormone receptors and tend to affect reproductive-age women, suggesting a role of hormonal stimulation in their pathogenesis.
- Most lesions are cavernous hemangiomas (75%).

4.11 Cervical Diverticulum

4.11.1 Definition

Exceedingly rare anomaly defined as a sac or pouch of the uterine wall connected to the Müllerian tract and lined by Müllerian epithelium. Patients are of reproductive age and present with abdominal pain, abnormal bleeding, or ectopic pregnancy within the diverticulum [94–96]. They may have history of previous Cesarean section or curettage. Occurrence in nulliparous patients has also been reported [94]. The lesion often mimics a leiomyoma on clinical examination and imaging. Hysterosalpingography or hysteroscopy can be useful in demonstrating the anomaly [97].

4.11.2 Synonyms

Not applicable.

4.11.3 Etiology

It has been suggested that diverticula arise from a site of weakness in the lateral uterine wall, either congenitally [94] or after surgery (e.g., Cesarean section) or trauma [98].

4.11.4 Macroscopy

The lesion ranges in size from 2.5 to 16 cm [94]. Most cases are located in the anterior or lateral aspect of the endocervix. The lesion is well defined. Sectioning shows a cavity connected to the endocervical canal, usually with a discernible mucosal lining. The wall can be distended or can be similar to the uterine wall in thickness and appearance (Figs. 4.49, 4.50).

4.11.5 Microscopy

The lumen of the diverticulum is lined by normal endocervical epithelium. The wall is composed of unremarkable cervical-type or myometrium-like tissue (Figs. 4.51, 4.52).

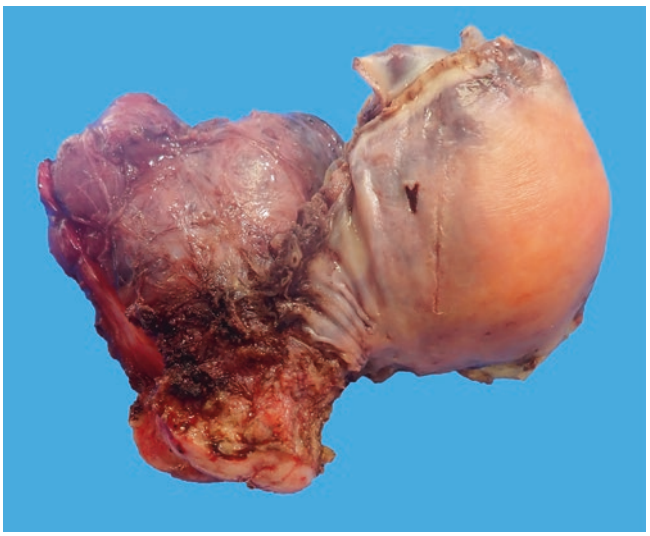

Fig. 4.49 Cervical diverticulum. A large nodular protuberance is noted on the lateral aspect of the cervix. (*Courtesy of* Dr. Mirko Miladinovic and Dr. Alice Pham, North York General Hospital, Toronto, Canada)

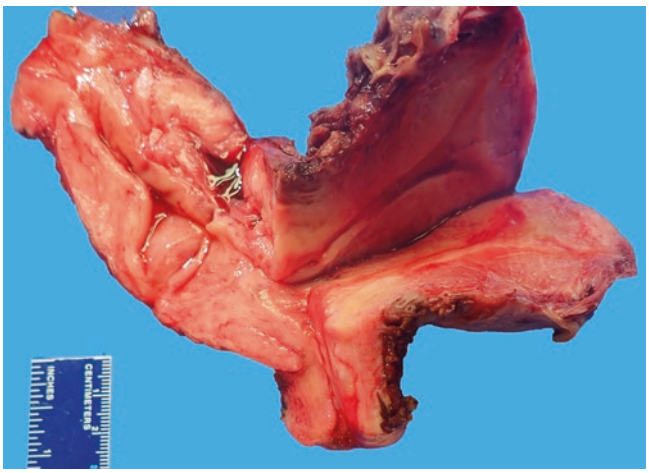

Fig. 4.50 Cervical diverticulum. Upon sectioning, the lesion has a central cavity lined by mucosa and showing patent communication with the endocervical canal. (*Courtesy of* Dr. Mirko Miladinovic and Dr. Alice Pham, North York General Hospital, Toronto, Canada)

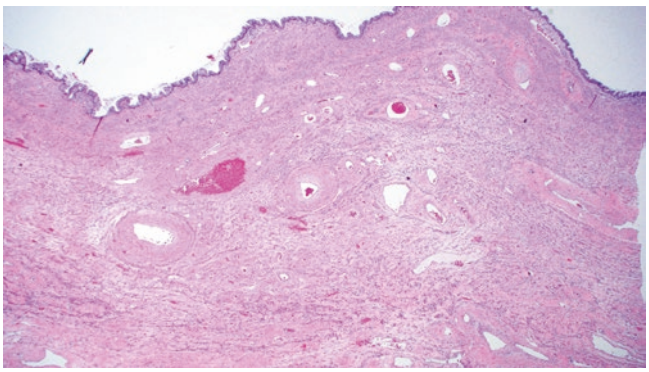

Fig. 4.51 Cervical diverticulum. The wall of the lesion is lined by unremarkable endocervical epithelium and is composed of fibromuscular and vascular connective tissue. In this case, the distribution of the mesenchymal elements of the wall is rather haphazard

Leiomyomas can be found within the diverticulum wall or adjacent to it [94]. Superficial inflammation, reactive and metaplastic epithelial changes, or scar-like tissue can be observed.

4.11.6 Differential Diagnosis

- *Uterine sacculation* is an unusual phenomenon described in pregnancy, in which placental growth takes place in an

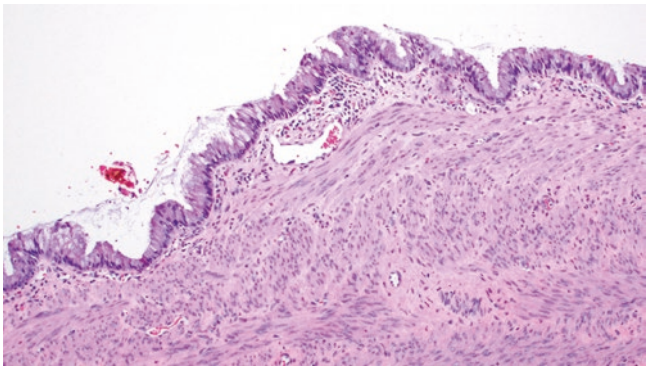

Fig. 4.52 Cervical diverticulum. The lining is of endocervical mucinous type. Notice the myomatous subepithelial stroma in this case

area of thinning of the uterine wall, leading to the formation of a "saccule" containing placenta and/or fetus [99, 100]. The sac can be anterior, posterior, or lateral. It is often associated with a retroverted, often incarcerated, gravid uterus [101]. It can involute spontaneously [100]. Unlike sacculation, diverticula generally do not manifest during pregnancy, feature an intact endocervical mucosa, and do not regress spontaneously.

- Cervical diverticulum can be clinically diagnosed and managed as *leiomyoma*. Routine careful macroscopic examination is important in this differential, as it can demonstrate a lumen with patent communication with the uterine canal. Microscopic identification of a normal endocervical lining and benign wall are confirmatory. It is important to note that cervical leiomyomata and diverticulum can coexist [94].

4.11.7 Prognosis

Uterine diverticula are indolent, but they can be complicated with infertility, infection, blood clot collection, or ectopic pregnancy [102, 103].

Diagnostic Highlights

- Cervical diverticulum is an exceedingly rare phenomenon.
- Consider this diagnosis in the presence of a lateral mass containing a cavity in communication with the endocervical canal.
- The cavity is lined by normal endocervical epithelium, and surrounded by a normal cervical or myomatous wall.

4.12 Placental Site Nodule

4.12.1 Definition

Nodular or plaque-like lesion composed of intermediate extravillous trophoblast in a fibrinoid matrix [104]. This lesion is more commonly seen in the lower uterine segment and upper endocervix [105]. It is usually discovered incidentally months to years after a previous gestation (see Sect. 12.2).

4.12.2 Synonyms

Placental site plaque.

4.12.3 Etiology

Distal migration of extravillous trophoblast in the context of an intrauterine gestation. Alternatively, seeding of trophoblast in the cervix during delivery or evacuation of products of conception, or remnants of a resolved ectopic cervical gestation.

4.12.4 Macroscopy

Most lesions are not grossly visible. Lesion size is usually 1 cm or less.

4.12.5 Microscopy

The lesion is well-demarcated and has a nodular or plaque-like configuration. The periphery often shows a lymphoplasmacytic inflammatory component and decidualized stromal cells. The lesion is composed of clusters of lesional trophoblastic cells. These are round to polygonal and feature eosinophilic or clear cytoplasm [106]. Clusters and individual cells are separated by hyalinized eosinophilic material, which is more prominent towards the center of the lesion. Necrosis and mitoses are absent to minimal (Figs. 4.53, 4.54, 4.55, 4.56) [104].

By immunohistochemistry, trophoblastic cells are positive for human placental lactogen (hPL) p63, Mel-CAM (CD146, usually weak or patchy), inhibin and GATA3 [106]. The Ki67 proliferation index is less than 10%.

4.12.6 Differential Diagnosis

- The eosinophilic and epithelioid appearance of the trophoblastic cells may mimic *invasive squamous cell carci-*

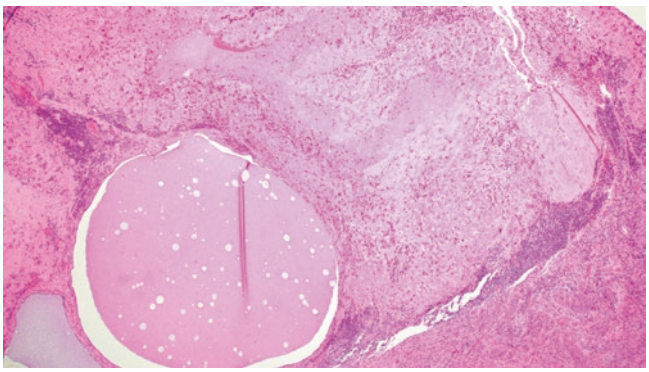

Fig. 4.53 Placental site nodule. The lesion is superficially located (see benign cystic glands on left lower aspect) and has a nodular shape. Notice the well-circumscribed border

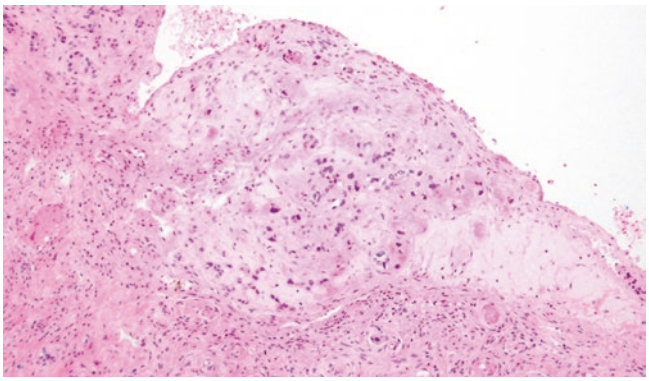

Fig. 4.54 Placental site nodule. The lesion is often located on the mucosal surface and has a smooth, non-infiltrative interface with the underlying wall

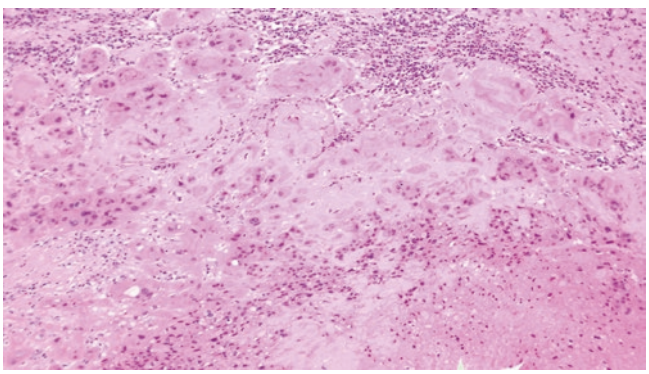

Fig. 4.55 Placental site nodule. The intermediate trophoblastic cells are arranged in clusters, nests, or individually, and are surrounded by amorphous, hyalinized extracellular material. Notice the brisk chronic inflammatory infiltrate towards the periphery of the lesion (*top aspect*)

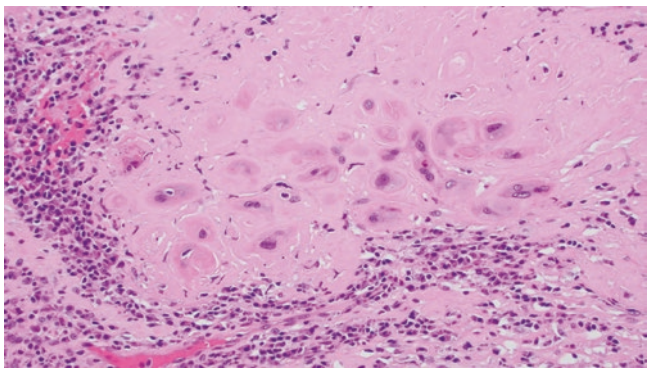

Fig. 4.56 Placental site nodule. The cells are polygonal and contain eosinophilic cytoplasm and round nuclei. They are separated by amorphous eosinophilic matrix. Notice the absence of necrosis and mitoses

noma. The presence of a well-circumscribed border, abundant eosinophilic material encasing lesional cells, and absence of mitoses are more in keeping with placental site nodule. The presence of high-grade squamous intraepithelial lesion can help, although this finding has been reported to coexist with placental site nodule [107]. By immunohistochemistry, both squamous cell carcinoma and placental site nodule are positive for p63, but placental site nodule is positive for inhibin and GATA3 and is negative or patchy for p16 [108].

- *Epithelioid trophoblastic tumor* is also composed of intermediate trophoblasts (see Sect. 12.2). Unlike placental site nodule, this neoplasm usually manifests clinically and tends to be larger. Microscopically, epithelioid trophoblastic tumor is also well-demarcated, but it features sheets and nests separated by extensive necrosis. The term "atypical placental site nodule" has been coined to describe lesions with one or more atypical features, namely moderate to severe nuclear atypia, mitoses (especially when atypical), necrosis, infiltrative borders, and/or a Ki67 index of 8–10% (bordering on the threshold for epithelioid trophoblastic tumor) [109]. The presence of any of these features should prompt careful examination and additional sampling to exclude epithelioid trophoblastic tumor.

4.12.7 Prognosis

Placental site nodule is a benign lesion. No further treatment is required. Follow-up with repeated sampling is prudent after a diagnosis of atypical placental site nodule, as 14% of these lesions are associated with concurrent or subsequent malignant gestational trophoblastic disease [109].

Diagnostic Highlights

- Most placental site nodules in the cervix are incidental and microscopic.
- The diagnosis of atypical placental site nodule should be considered if the lesion has one or more of the following: moderate to severe nuclear atypia, mitoses (especially when atypical), necrosis, infiltrative borders, and/or a Ki67 index of 8–10%.
- Surveillance and subsequent sampling is prudent after a diagnosis of atypical placental site nodule.

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