Glandular Neoplasia of the Uterine Cervix and Its Related Lesions

13

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Abstract

This chapter describes the pathology of glandular neoplasia of the uterine cervix. The spectrum of endocervical glandular malignancy is wide and sometimes diagnostically challenging. While most cervical adenocarcinomas are secondary to Human Papillomavirus infection, some tumors are unrelated to it; these lesions are now recognized for their aggressive clinical behavior and still obscure pathogenesis. The description of each adenocarcinoma type in this chapter follows an etiology (HPV-related versus unrelated) and traditional morphology-based approach. Important diagnostic situations such as diagnosis of stromal invasion, pattern-based assessment, and staging are also discussed. The chapter also presents the pathology of mixed lesions with a glandular component and benign glandular proliferations that need to be distinguished from preinvasive and invasive endocervical malignancy.

Keywords

Adenocarcinoma · Cervix · Endocervical · HPV · Early invasive adenocarcinoma · Pattern-based classification · International Endocervical Adenocarcinoma Classification and Criteria · Adenocarcinoma in situ · Lobular endocervical glandular hyperplasia · Usual-type adenocarcinoma · Signet-ring cell · Intestinal · Stratified mucin producing carcinoma · Adenoma malignum · Minimal deviation adenocarcinoma · Gastric type adenocarcinoma · Endometrioid carcinoma · Clear cell carcinoma · Mesonephric carcinoma · Serous carcinoma · Mixed adenocarcinoma · Adenosquamous carcinoma · Glassy cell carcinoma · Metastatic adenocarcinoma · Endocervical polyp · Nabothian cyst · Tunnel cluster · Diffuse laminar endocervical hyperplasia · Endometriosis · Endocervicosis · Tubo-endometrioid metaplasia · Microglandular hyperplasia · Arias-Stella reaction · Mesonephric hyperplasia

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13.1 Introduction

13.1.1 The Normal Endocervix

Our current understanding of the development, anatomy, and histology of the normal endocervix is based on the initial models by *C. F. Fluhmann*, who described the endocervical mucosa as a complex system of mucosal infoldings [1, 2]. Unlike other mucosal linings such as the endometrium, the basic structural unit of the endocervix is not a vertical tube but a series of mucosal infoldings coursing in various directions (Fig. 13.1). Folding occurs due to epithelial proliferation driven by hormonal stimulation, and leads to the formation of clefts and grooves [1, 2]. The haphazard distribution and orientation of the endocervical mucosal clefts and grooves is reflected in the heterogeneous architecture seen in routine bidimensional tissue preparations of the cervix. This complexity contributes to our difficulty in distinguishing between abnormal proliferations confined to the epithelial compartment (in situ) and those invading cervical stroma, as discussed further in this chapter.

13.1.2 Endocervical Adenocarcinoma: Epidemiologic and Classification Trends

Compared to invasive squamous cell carcinoma, screening strategies have been less effective at detecting endocervical glandular malignancies around the globe. Indeed, the relative incidence of adenocarcinoma has increased from ~5% to ~20% between the 1960s and the 2000s [3, 4]. Cumulative incidence rates have increased internationally, particularly in women 30 years of age and older [5]. In the United States,

W. Zheng et al. (eds.), *Gynecologic and Obstetric Pathology, Volume 1*, https://doi.org/10.1007/978-981-13-3016-2_13

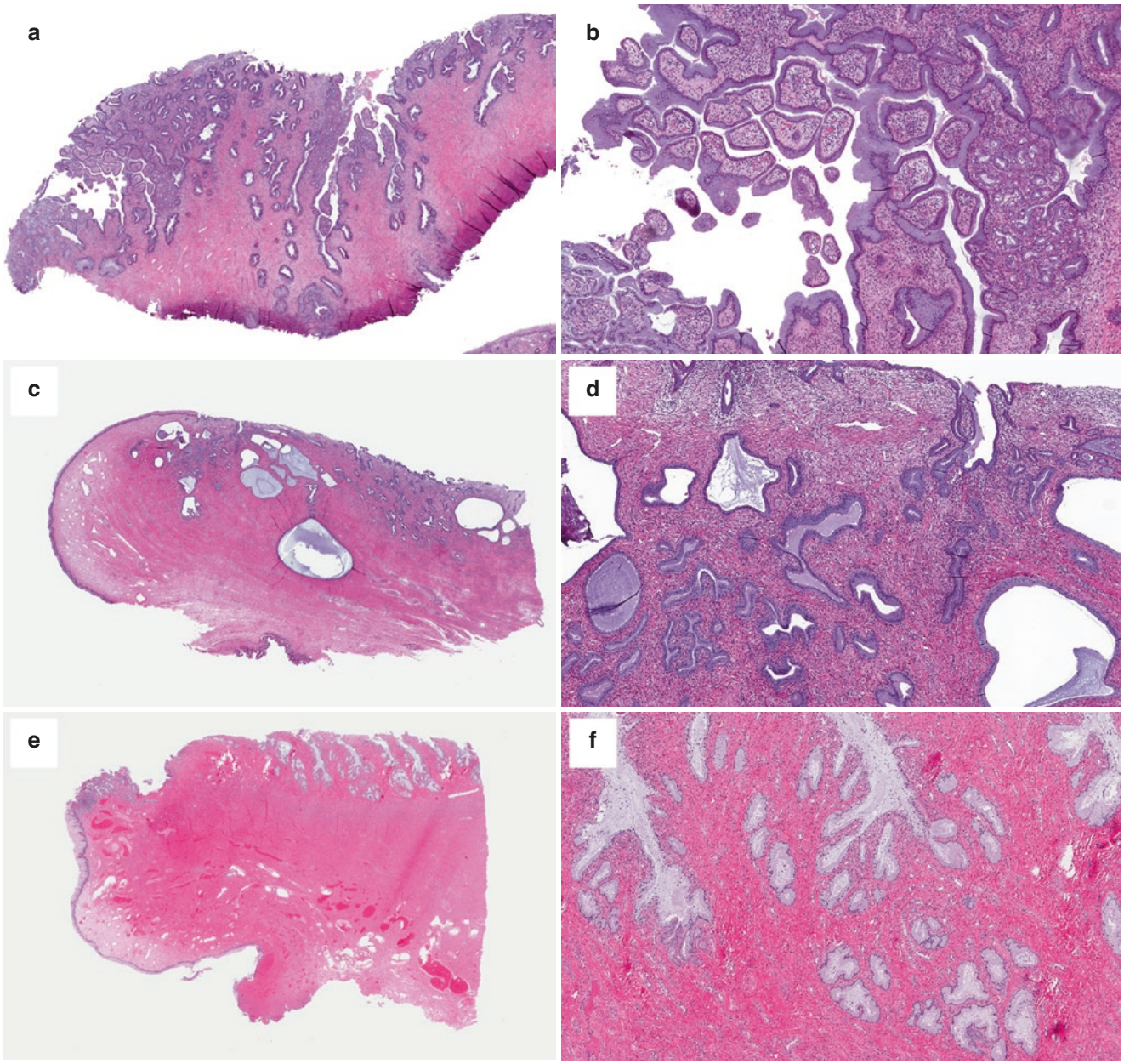

Fig. 13.1 Normal endocervix. The Endocervical mucosa is comprised of numerous surface infoldings, which gradually leads to the formation of clefts and grooves (seen as "glandular" structures in routine preparations) (**a**). The distribution of these structures is rather haphazard (**b**). Communication with the canal can eventually become obliterated, leading to the formation of cystically dilated glands (**c**, **d**). A more lobulated pattern can also be seen, with a centrally dilated cleft and peripheral grooves organized in a uniform "lobular" distribution (**e**, **f**)

incidence rates of endocervical adenocarcinoma have shown an increment of 32.2%, from 1.09/100,000 women in 1975 to 1.44/100,000 women in 2007 [6]. Similar increases have been documented in more recent literature from Denmark and the Netherlands, despite well-established screening programs [7, 8]. These surge in incidence can be attributed to differences in the diagnostic performance of the Pap test for glandular (versus squamous) lesions or may be caused by increased detection in some populations. However, the growing case numbers suggest that screening methods may not be adequate to detect adenocarcinoma in situ (AIS), as supported by the significant number of women with negative or low-risk Pap results before the glandular neoplasm is identified [9]. From an epidemiologic perspective, endocervical neoplasia is associated with higher socioeconomic and educational levels than squamous neoplasia. In addition, risk factors for squamous malignancy such as early and frequent sexual activity and smoking are less frequently associated with glandular lesions [10].

Virtually all squamous cell carcinomas and high-grade squamous intraepithelial lesions of the uterine cervix are related to high-risk Human Papilloma Virus (HPV) infections [11]. While the same was previously presumed for endocervical glandular neoplasms [12], recent evidence reveals a more heterogeneous landscape:

- The majority (85–90%) of adenocarcinoma in situ and invasive adenocarcinoma cases are indeed related to high-risk HPV, mainly HPV18 and HPV16, the rest being positive for HPV45 and other more rare HPV subtypes [13–15]. Coexistence of HPV-related glandular and squamous neoplasia is a common occurrence [16].
- A minor proportion of endocervical adenocarcinomas (10–15%) is negative for HPV [13, 17, 18]. Most of these cases belong to certain adenocarcinoma subtypes, including gastric, clear cell, and mesonephric categories. This subset of HPV-negative carcinomas has distinct morphology and clinical behavior compared to HPV-related lesions.

This chapter presents the relevant pathologic and clinical features of the diverse forms of endocervical glandular neoplasia. While the terminology employed mirrors the current World Health Organization (WHO) classification, cervical glandular proliferations covered here are categorized based on: (a) their pathogenesis (HPV-dependent versus independent) and (b) recent biology-based criteria and classification proposals. The chapter also covers the most common benign endocervical proliferations as they pertain to the differential diagnosis of preinvasive and invasive glandular malignancy.

13.2 Preinvasive Glandular Neoplasia

13.2.1 Nomenclature

In the last two decades, the terminology used for the categorization of endocervical adenocarcinoma precursors has shifted towards simplification. Formerly proposed terms such as cervical intraepithelial glandular neoplasia (CIGN), glandular atypia, and glandular hyperplasia have been largely abandoned given the lack of data proving an association with AIS and with invasive adenocarcinoma [19]. Unlike squamous lesions, there is currently no evidence that the cervical in situ glandular neoplasia spectrum includes a definable low-grade category.

The term "*Endocervical Glandular Dysplasia*" (EGD), proposed for noninvasive lesions with features bordering on but not diagnostic of AIS [20], suffers from significant interobserver variation especially in its distinction from benign cervix [21]. Moreover, its biologic and clinical significance has not been firmly established. Its occurrence in patients with concurrent AIS or invasive adenocarcinoma is rare; in this scenario, most EGD harbor an HPV infection, implying that they are subtle forms of AIS [22]. In contrast, isolated EGD is usually negative for HPV and p16, contradicting its alleged role as a precursor [22, 23]. Currently available ancillary tools such as p16 and Ki67 immunohistochemistry and HPV testing have improved the stratification of lesions with equivocal features into benign or AIS categories, further obviating the need for an intermediate category like EGD [24]. Given the lack of evidence-based support for alternative / supplementary terminology, the 2014 WHO of Tumours of Female Reproductive Organs eliminated EGD and other categories and recommends the use of AIS as the only established precursor of invasive endocervical glandular malignancy [11].

13.2.2 Adenocarcinoma In Situ, Conventional (HPV-Related) Type

Initially described in 1953 [25], AIS of the cervix is now regarded as a precursor of invasive endocervical adenocarcinoma. This precursor role has been attributed based on the following evidence: (1) women with AIS have a mean age of 35 years at presentation, 10–20 years younger than those with invasive adenocarcinoma; (2) AIS is frequently found adjacent to invasive adenocarcinoma [26]; (3) the spectrum of HPV types in AIS and invasive adenocarcinoma is similar; and (4) invasive endocervical adenocarcinoma has been documented in patients with previous AIS either missed in biopsy or curettage, or diagnosed and left untreated [26, 27].

Clinical Features

AIS is not symptomatic and its diagnosis is made in the context of cytologic screening abnormalities. AIS does not produce a macroscopic abnormality in most cases as the presence of a lesion on colposcopy and/or pathologic gross examination is usually related to a coexistent squamous lesion, an exophytic papillary component (either squamous or glandular) or invasive carcinoma.

Pathologic Features

AIS is defined by the following histologic features [11, 27, 28] (Fig. 13.2):

(a) Columnar epithelium with pseudostratified, enlarged, elongated, hyperchromatic nuclei and variable loss of intracytoplasmic mucin.
(b) Easily identifiable apical mitotic figures and apoptotic bodies (at least one in each gland).
(c) Preservation of the normal glandular architecture, since the neoplastic proliferation is, by definition, restricted to the preexisting endocervical epithelial compartment; architectural complexity is allowed (papillary, micro-

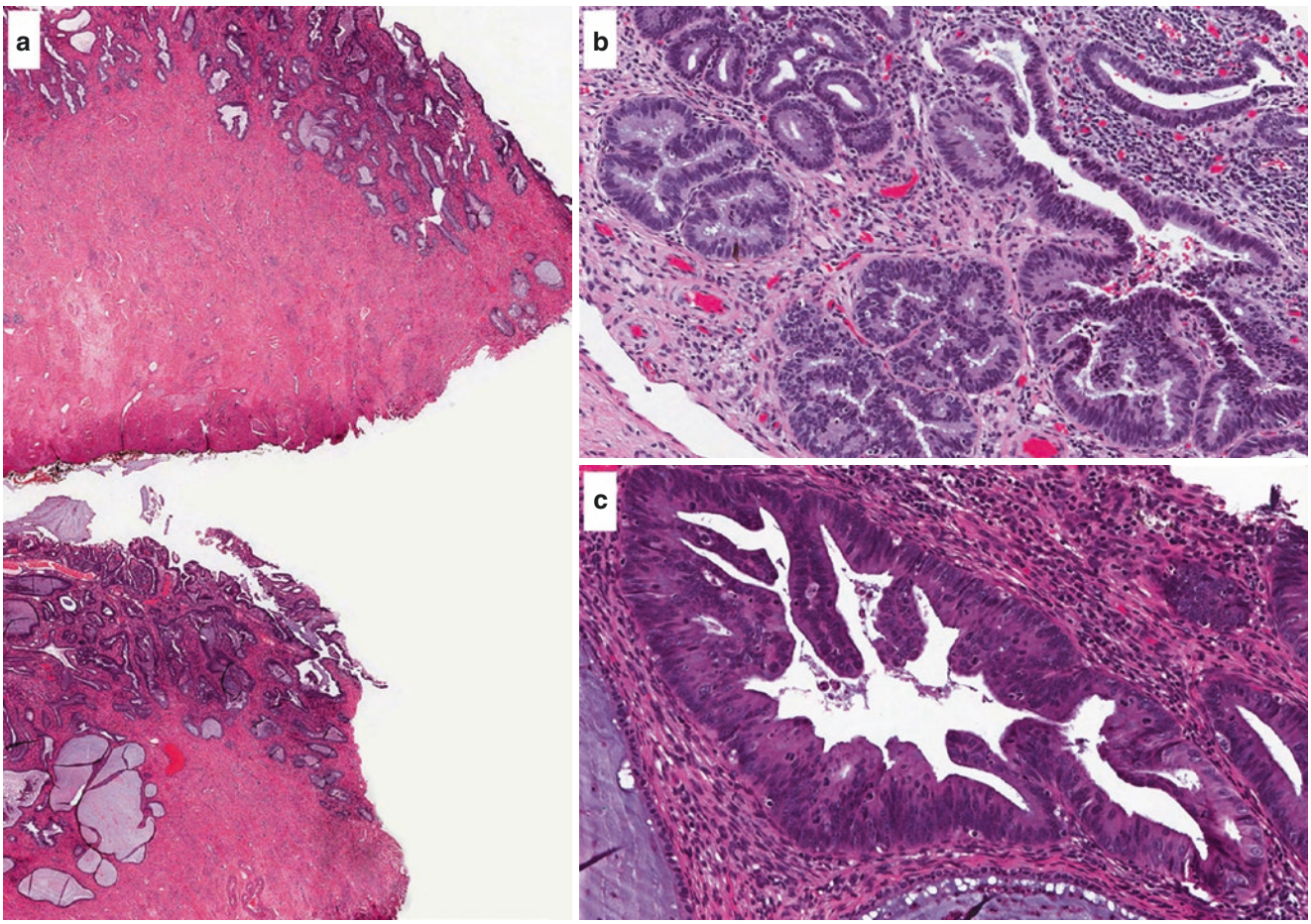

Fig. 13.2 Adenocarcinoma in situ, HPV-related (AIS). The neoplastic glandular proliferation in (**a**) (lower half) has the same density and architecture of the normal endocervix (upper half), in keeping with an in situ process. AIS is characterized by columnar cells with hyperchromatic nuclei, conspicuous apical mitoses and apoptosis, and mucin depletion (**b**, **c**)

papillary, or cribriform growth) as long as it is either confined to the surface or intraglandular (similar size and shape of other AIS glands and normal endocervix).

The lesion is usually centered in the squamous–columnar junction; it can, however, occur in the proximal endocervical canal, as far as 3 cm from the junction in one series [16]. Multifocality is seen in two-thirds of AIS cases.

Similar to its invasive counterparts, the most frequent histologic types of AIS are usual (intracytoplasmic mucin in <50% of the cells) and mucinous endocervical (intracytoplasmic mucin in >50% of cells). Since its original characterization, several other variants of AIS have been described including endometrioid (smaller, rounder nuclei with little to no mucin production), intestinal (goblet cell differentiation, Paneth cells), and tubal. All these variants are related to HPV infection and constitute part of the morphologic spectrum of AIS, commonly seen within the same lesion / patient in varying proportions [29–31].

A less frequent but challenging type of AIS is seen in the form of simple frond-like projections confined to the surface of the cervix. This growth pattern is termed exophytic or villoglandular, and can be seen in usual, mucinous or endometrioid AIS. The exophytic component is comprised of papillary structures lined by abnormal AIS-type epithelium.

Ancillary Studie

P16/*CDKN2A* is a tumor suppressor protein/gene that inhibits cyclin-dependent kinase 4A (*CDK4A*). p16 protein expression with cell cycle progression is mediated by the transcriptional activator E2F and promotes production of the retinoblastoma protein (Rb), which binds to E2F, thus stopping cell cycle progression. In the presence of transcriptionally active HPV, the viral oncoprotein E7 binds competitively to Rb, inactivating it. Rb inactivation causes an increase in free E2F leading to activation of cell cycle progression pathways; this also disrupts the negative feedback loop for p16, which consequently accumulates within the cell. Thus, overexpression of p16 by immunohistochemistry has become an excellent surrogate marker of high-risk HPV infection. Indeed, p16 is identified at high levels in most AIS lesions [23, 32–34]. P16 overexpression is strictly defined as strong,

cytoplasmic *and* nuclear staining in the majority of abnormal cells, which results in a "block" pattern of positivity.

The majority of AIS cells exhibit increased expression of proliferation markers. Ki67 is elevated with a labeling index usually greater than 30%. ProEx C labels nuclear proteins (mini-chromosome maintenance protein 2, MCM2 and topoisomerase II-alpha, TOP2A) that are overexpressed during the aberrant S-phase induction of HPV infected and neoplastic cells; this marker is consistently positive in AIS [34, 35]. Loss of estrogen and progesterone receptor expression is also a common event in AIS, thus ER/PR negativity by immunohistochemistry is helpful in excluding benign mimics and endometrial endometrioid neoplasia which are ER/PR positive [36].

High-risk HPV can be detected in conventional AIS by in situ hybridization or sequencing methods [18, 37]. The most common types are HPV16, HPV18, HPV45, and HPV35 [15, 17, 38]. HPV testing is increasingly available, and should be considered if the differential includes AIS versus benign proliferations or HPV-independent neoplasia.

Differential Diagnosis

The most critical differential diagnoses of AIS are invasive adenocarcinoma, HPV-negative endocervical neoplasia, and certain benign cervical lesions. The latter two scenarios will be discussed here; the distinction between in situ and invasive carcinoma will be explored in the next section.

Rare and under-recognized (until recently), HPV-independent AIS is an important form of cervical glandular neoplasia, given its association with aggressive types of invasive adenocarcinoma, most importantly gastric-type adenocarcinoma [39, 40]. Mucin depletion, or presence of endocervical-type mucin, is more in keeping with conventional-type AIS. In addition, nuclei in HPV-related AIS tends to be elongated and hyperchromatic, compared to the more round nuclei with vesicular chromatin of gastric-type AIS. HPV testing is helpful in this distinction.

A range of benign cervical proliferations can mimic AIS, both architecturally and cytologically. In all these, p16 staining is normal (negative or patchy), which constitutes a valuable tool in the differential exercise. The most relevant entities are listed here, with useful features in their distinction from AIS in parenthesis: (a) tubo-endometrioid metaplasia (absence or paucity of mitoses; lack of hyperchromasia; nuclear expression of estrogen receptor and Bcl-2), (b) endometriosis (overall absence of mucinous differentiation; absence of nuclear atypia and hyperchromasia; presence of endometrial-type stroma and hemosiderin deposition; expression of hormone receptors), (c) immature squamous metaplasia (stratification and orderly, albeit incomplete, squamous differentiation; absence of nuclear atypia; expression of squamous cell markers), and (d) mesonephric remnants (flat to cuboidal cells, less frequently columnar; round, bland nuclei with absence of mitoses; eosinophilic luminal secretions).

Management and Prognosis

In the past, hysterectomy was recommended as the standard treatment for AIS; it is still recommended in patients with other comorbidities benefiting from removal of the uterus (e.g., menorrhagia), those without the need to preserve fertility and those with factors complicating follow-up (e.g., cervical stenosis). Given its safety and superior fertility-related outcomes, conservative management with conization and loop electrosurgical excisional procedure (LEEP) has been increasingly performed. However, the possibility of incomplete excision and recurrence in these treatment modalities warrants close surveillance with cytology and colposcopy [41]. The type of procedure and the margin status are the most important predictive factors of residual disease and recurrence. LEEP is more frequently associated with residual disease (51%) compared to conization (30%) [42]. The prevalence of residual AIS after cold knife conization or LEEP is 16% for excisions with negative margins versus 49% for those with positive margins [42]. Similarly, the prevalence of invasive carcinoma after cold knife conization / LEEP for AIS is 0.1–0.6% for excisions with negative margins versus 5–6% for those with positive margins [42, 43]. AIS recurrence in patients on surveillance after conization is 3% when margins are negative and 17–19% when margins are positive [42, 43].

13.2.2.1 Stratified Mucin-Producing Intraepithelial Lesion (HPV-Related AIS, Stratified Variant)

The stratified variant of AIS was initially described by *Park et al.* as stratified mucin producing intraepithelial lesion (SMILE) [44]. As the name implies, SMILE is characterized by its stratified appearance. From low-power magnification, the stratified epithelial architecture is reminiscent of a squamous intraepithelial lesion. However, examination under high-power magnification reveals intracytoplasmic mucin throughout the entire epithelial thickness (Fig. 13.3). SMILE frequently coexists with HSIL and/or conventional AIS. When present, an invasive carcinoma component has glandular, adenosquamous or stratified mucin-producing appearance [44].

Like conventional AIS, SMILE is characterized by p16 overexpression and high Ki67 proliferation index; conversely p63 is negative in columnar cells, and only positive in the basal layer (likely residual reserve cells) [44, 45]. HPV is consistently detected, mostly types 16 and 18. The ultrastructure of SMILE has revealed presence of microvilli, vacuolar structures, and mitochondria in the absence of tonofilaments, supporting the hypothesis that this lesion belongs to the spectrum of endocervical glandular neoplasia [45].

The differential diagnosis of SMILE includes a high-grade squamous intraepithelial lesion (HSIL) undermining normal endocervix, in which the mucinous cells are dispersed and displaced towards the lumen. This contrasts with the diffuse and full-thickness distribution of mucin-producing

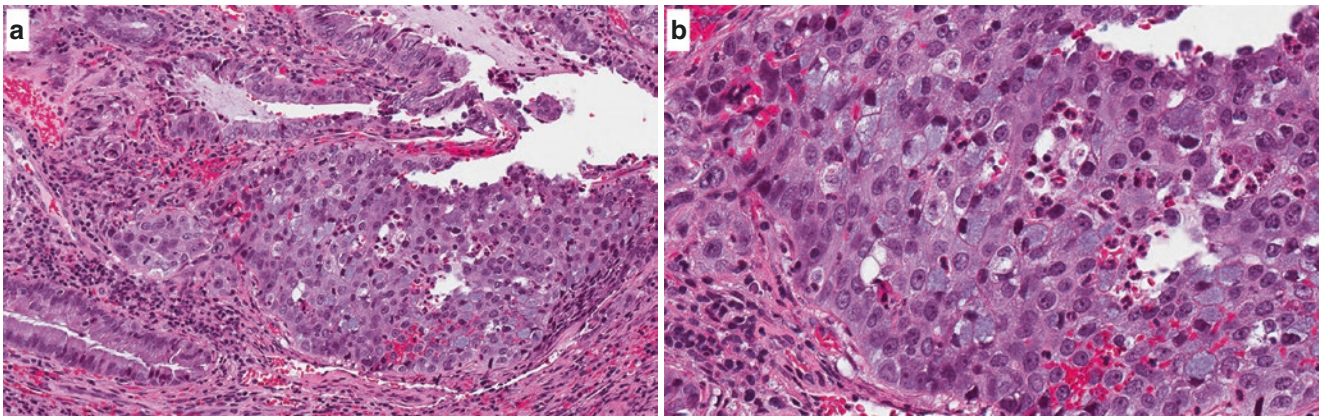

Fig. 13.3 Stratified mucin-producing intraepithelial lesion. This in situ proliferation is stratified, resembling a squamous intraepithelial lesion (A). However, intracytoplasmic mucin can be observed throughout the lesion on high-power view

cells in SMILE. The nuclei of the endocervical mucinous cells surrounded by HSIL have a bland appearance. In contrast, dysplastic nuclear morphology of the mucin-producing population should raise the possibility of SMILE. Conventional AIS can harbor areas of intraglandular complexity that may appear stratified, and both stratified and conventional morphologies can coexist. Finally, immature squamous metaplasia should also be considered; the retained polarization and lack of nuclear dysplasia indicate a benign diagnosis. P16 and Ki67 stains can be performed in equivocal instances.

13.2.3 Adenocarcinoma In Situ, Gastric Type and Lobular Endocervical Glandular Hyperplasia

Compared to HPV-related adenocarcinoma, the pathogenesis of cervical malignancies not related to high-risk HPV infection is less characterized. Nonetheless, the spectrum of gastric differentiation in the endocervix is well recognized; within it, certain lesions are now understood as likely precursors of gastric-type endocervical neoplasia.

Benign gastric (pyloric) metaplasia has been described in the endocervix in two forms:

- Simple gastric metaplasia: Simple gastric-type mucinous epithelium lining otherwise unremarkable endocervical glands [46].
- Tunnel clusters type A [47].

An architecturally more complex gastric-type proliferation, lobular endocervical glandular hyperplasia (LEGH, namely complex gastric metaplasia), was initially described by *Nucci et al.* [48]. Although by itself a benign process, LEGH is included in this section because of its association with gastric-type adenocarcinomas including adenoma malignum: LEGH has been identified in up to 20% of gastric type adenocarcinomas and 50% minimal deviation adenocarcinomas [49–51]. Moreover, gains of chromosome 3q and a loss of 1p (which are common in minimal deviation adenocarcinoma) have been detected in a subset of LEGH (21%) [52]. This evidence suggests that LEGH is a nonobligatory precursor of endocervical gastric-type malignancy.

LEGH is usually an incidental finding; however, it may present as a mass or cyst detected on imaging or examination. Histologically, LEGH is a well-demarcated lesion with lobular/acinar architecture. It is composed of a central gland, sometimes with cystic dilation, surrounded by smaller glands and cysts arranged in a floret-like pattern (Fig. 13.4). Central and peripheral glands are lined by low columnar cells with pale eosinophilic cytoplasm [48, 49]. Cells are mucinous with a similar appearance than the normal endocervix. Nonetheless, the mucin profile, characterized by pale or eosinophilic staining, is different from the slightly basophilic (blue-purple) appearance of the normal mucinous endocervical cell.

Atypical LEGH is a related lesion, also strongly associated with minimal deviation adenocarcinoma (seen in ~30% of cases). Atypical LEGH is characterized by an elevated Ki67 index and abnormal p53 immunohistochemical expression [53]. Furthermore, it shares similar molecular alterations with minimal deviation adenocarcinoma (MDA), in particular 3q gain and 1p loss [51]. From this perspective, atypical LEGH may be considered an immediate precursor of MDA (e.g., pre-cancerous). Atypical LEGH is architecturally consistent with LEGH, but with four or more of the following features:

- Nuclear enlargement.
- Irregular nuclear contours.
- Distinct nucleoli and coarse chromatin.
- Loss of polarity.
- Mitotic figures (occasional).

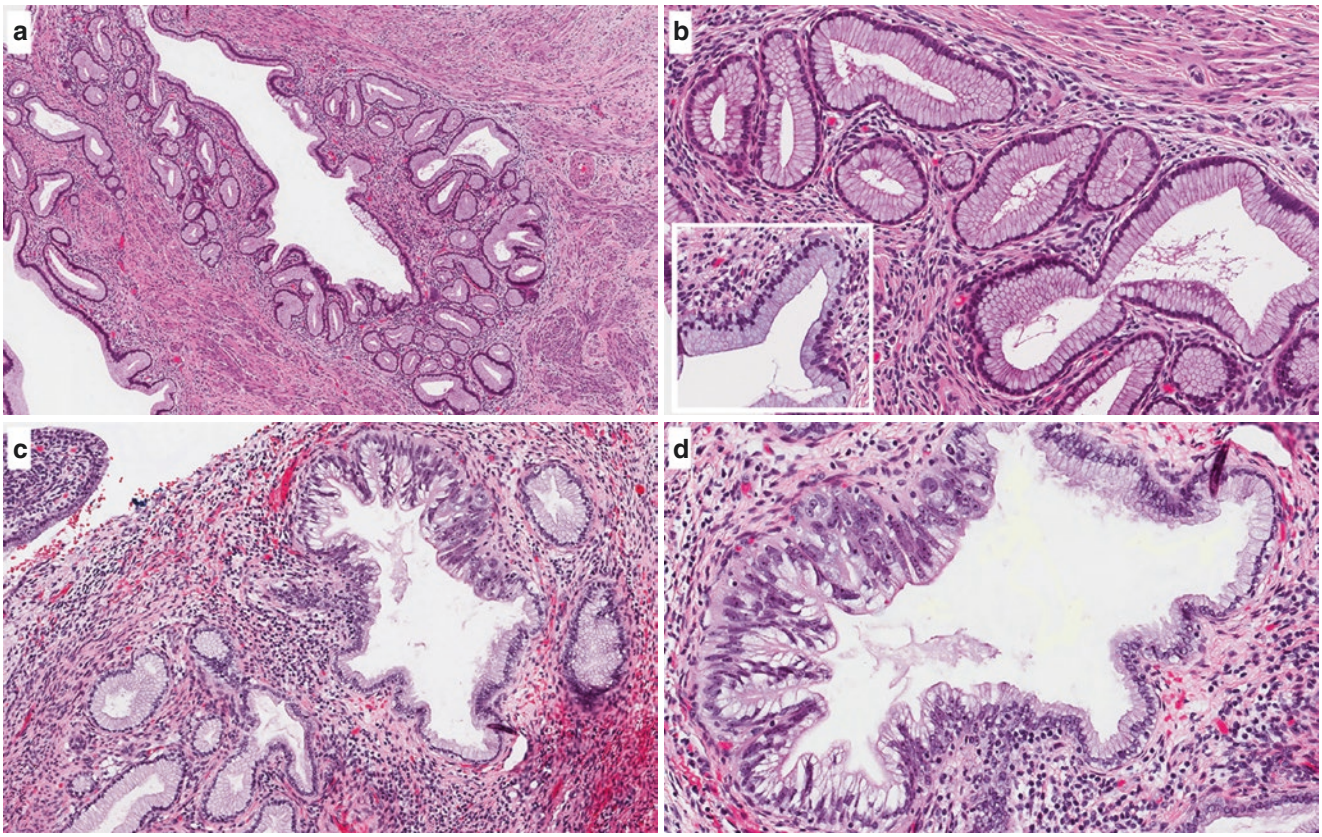

Fig. 13.4 Lobular endocervical glandular hyperplasia (LEGH). A central dilated cleft is surrounded by small, round to tubular glands in a floret pattern (**a**). Lining epithelium is mucinous columnar and highly resembles the normal endocervix (**b**); however, cytoplasm is less basophilic and cell borders are more accentuated (compare to normal endocervix from the same patient, insert). Atypical LEGH; this example is characterized by severe nuclear atypia partially involving a dilated duct in an area of otherwise typical LEGH (**c**, **d**)

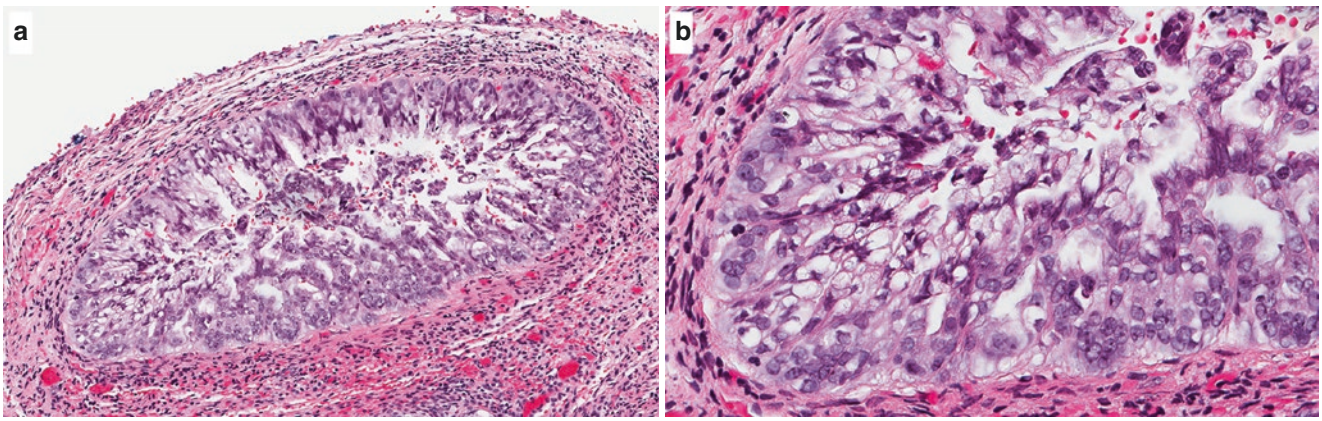

Fig. 13.5 Adenocarcinoma in situ, gastric type. Intraglandular proliferation with micropapillary architecture (**a**), comprised of cells with round, enlarged nuclei and abundant clear cytoplasm (different from the elongated, hyperchromatic nuclei and mucin-depleted cytoplasm of HPV-related AIS) (**b**). This lesion was negative for p16 and HPV testing

– Apoptotic bodies or luminal nuclear debris.
– Intraluminal papillary projections.

Gastric-type adenocarcinoma in situ is also comprised of atypical cells as outlined above, but without the classic lobular architecture of atypical LEGH [46]. The neoplastic cells display evident pleomorphism and cytological features of gastric differentiation; namely abundant, vacuolated, clear to eosinophilic and/or mucinous cytoplasm and distinct cell borders (Fig. 13.5).

The differential diagnosis of atypical LEGH and gastric-type AIS includes: (a) invasive gastric-type adenocarcinoma, in which destructive stromal invasion is evident (marked desmoplasia, solid growth, architectural complexity); (b) HPV-related AIS, which is typically mucin-depleted and contains elongated hyperchromatic nuclei; mitotic activity is conspicuous in HPV-related AIS, and less prominent in gastric-type AIS [39]; HPV-related AIS can be confirmed by demonstrating both p16 IHC overexpression *and* detection of high-risk HPV by molecular testing.

The management of LEGH, atypical LEGH and gastric-type AIS found in biopsy involves excision (conization) with negative margins in order to exclude concomitant invasive malignancy. LEGH can be safely monitored. In reproductive age women, follow-up after conservative excision of atypical LEGH and even gastric-type AIS may be prudent. However, given their association with aggressive types of invasive adenocarcinoma, hysterectomy should be considered as it may have a better therapeutic role.

13.3 Invasive Endocervical Adenocarcinoma

13.3.1 General Considerations

13.3.1.1 Diagnosis of Invasion by Endocervical Adenocarcinoma

Stromal invasion by endocervical adenocarcinoma acquires a variety of histologic patterns, some easily identified as invasive and some with significant overlap with the architecture of the normal cervix, and therefore difficult to assess. HPV-negative invasive endocervical adenocarcinoma tends to be widely infiltrative, and diagnosis of invasion in these lesions is usually straightforward. HPV-positive adenocarcinoma is more heterogeneous, and not infrequently displays more subtle patterns of glandular proliferation referred to by some authors as "AIS-like." Table 13.1 summarizes the morphologic spectrum of stromal invasion by endocervical glandular neoplasia [27, 54].

Table 13.1 Morphologic spectrum of stromal invasion by endocervical adenocarcinoma

Pattern of invasion	Type	Morphologic spectrum
Destructive	Infiltrative growth	Glands with irregular and angulated contours
		Periglandular stromal desmoplastic reaction
		Non-gland forming elements (individual cells; cell clusters, buds or nests)
	Complex/ confluent architecture	Anastomosed, fused or interconnected glandular elements (scant to no stroma in between)
		Seen as cribriform, labyrinth-like or solid patterns
		Endophytic papillary/ micropapillary (within cervical wall)
AIS-like	Increased glandular density	Gland crowding that exceeds the density of the adjacent normal cervix (or in its absence, the expected glandular density in a normal cervix)
		Tight clustering of small glands, sometimes with small and focal gland fusion
	Deep glandular proliferation	Gland extension into deep cervical stroma
		Haphazard distribution (lack of lobulation)
		Close proximity to thick-walled vessels
	Exophytic complex growth	Exophytic papillary or villoglandular growth with epithelial complexity (cribriforming, anastomosing within papillae spaces and/or stroma)

Common circumstances in which distinction between AIS and invasive adenocarcinoma is particularly challenging (and useful hints on how to approach them) include (Fig. 13.6):

- Extensive AIS with lobulated proliferation, increased glandular density and/or areas of complexity are suggestive but not diagnostic of invasion. In these situations, neoplastic glands are superficially located or organized in well-formed lobules, mirroring to an extent the normal cervix architecture. These types of neoplastic growth appear to be relatively indolent with nil risk of nodal metastases (see pattern-based classification section). However, ovarian spread has been documented in these otherwise "borderline" or "in situ like" tumors, indicating that they can potentially behave in a malignant fashion, and therefore are best categorized as invasive carcinoma [55].
- Presence of distorting elements such as inflammation, mucosal erosion / ulceration, previous biopsy site reaction and edema, when prominent, can obscure the presence of invasive elements. Conversely, they can also distort the contours of AIS glands making assessment of invasion difficult. When possible, evaluation should be made in areas away from these changes (which are usually superficial).
- Papillary/villoglandular growth. As mentioned previously, endocervical adenocarcinoma can grow predominantly or exclusively in the surface and acquire an exophytic appearance. When simple (small, non-branching or confluent papillae, stroma devoid of complex glands), such proliferations are most in keeping with AIS. More complex

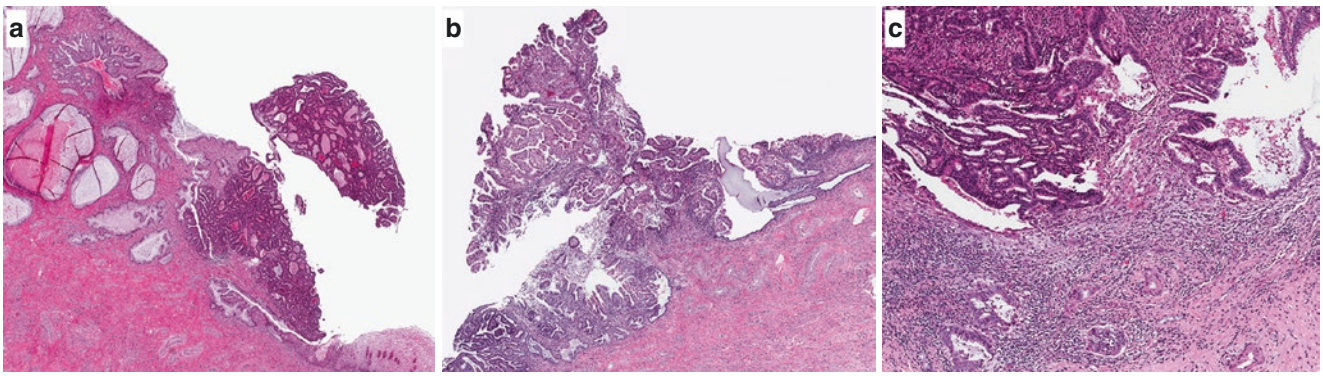

Fig. 13.6 Assessment of stromal invasion by endocervical adenocarcinoma can be challenging when proliferation is well differentiated (purely glandular). Diagnosis of invasion is warranted when the glandular density obviously exceeds that of the adjacent normal cervix (**a**) and when papillary growth is not only in the surface but also involves stroma within papillae or in the cervix per se) (**b**). It is recommended that horizontal extent and depth measurements encompass the entire lesion in these instances. Chronic inflammation can be unrelated to the tumor, and does not necessarily constitute a sign of invasion (**c**). If possible, assessment of invasion should be made in areas devoid of obscuring inflammation; however, densely inflamed areas should be carefully examined for the presence of unequivocal invasive foci (single cells, clusters, LVI, etc.)

degrees of epithelial proliferation encountered include branching and confluent papillae/micropapillae as well as cribriform or confluent glandular elements within the papillary stroma; most pathologists will accept such complexity as a form of invasive adenocarcinoma. Categorization of papillary lesions as in situ or invasive is difficult, particularly in biopsy material. A final diagnosis of AIS should only be made after assessing the underlying stroma and excluding endophytic papillary growth or any other sign of unequivocal stromal invasion [54].

The above situations illustrate the challenge of diagnosing invasion by endocervical adenocarcinoma, which has been stated as difficult or impossible to determine in about 20% of cases [56]. This is likely explained by the architectural overlap between the normal cervix, AIS, and certain forms of nondestructive neoplasia traditionally deemed as invasive, which cannot be reliably distinguished by pathologists [57]. In this exercise, consensus review with colleagues may help reach a defensible diagnosis. If uncertainty persists, a less definitive diagnosis indicating concern for early stromal invasion in the setting of florid AIS may be the best approach.

When diagnosing invasion by endocervical adenocarcinoma, the terms "microinvasive" and "superficially invasive" should be avoided; the former is no longer recommended in cervical neoplasia, while the latter is reserved for squamous tumors and is not suitable for endocervical adenocarcinoma. The main reasons for this include the difficulty of estimating the invasive component in cases with "AIS-like" invasion and in the diagnostic situations outlined above. When the in situ and invasive components cannot be reliably separated, the dimensions of the entire lesion should be provided. This includes the thickness measured from the surface, which replaces the depth parameter, and the horizontal dimensions (measured from the slides and / or estimated from the number of blocks involved). Other estimations of size such as percentage of the cervical circumference involved or the quadrant extension are helpful (but frequently imprecise) additions to the standard tumor size measurements.

13.3.1.2 Staging

Staging definitions as per the latest recommendations from the American Joint Committee on Cancer (AJCC) and the International Collaboration on Cancer Reporting (ICCR). are listed in Table 13.2. Of note, the International Federation of Obstetrics and Gyneaocology (FIGO) recently changed the staging system for cervical cancer; a critical change is that in stage I lesions the horizontal extent criterion was abolished and stage was redefined as Ia1 (depth of invasion <3 mm), Ia2 (depth 3-5 mm), Ib1 (depth > 5 mm or grossly visible lesions <2 cm in size), Ib2 (size 2-4 cm) and Ib3 (size >4 cm). Both staging systems equally apply to squamous, glandular, mixed, and miscellaneous cervical malignancies. Special mention will be given to stage T1a/IA adenocarcinoma, since it is, by definition, based on assessment of microscopic size.

Early (Minimally) Invasive Adenocarcinoma (Stage T1A/IA)

Stage IA lesions are less than 5 mm in depth and 7 mm in horizontal spread. These have a negligible risk of nodal spread compared to tumors of stage IB or larger. Studies addressing the biological behavior of early stage adenocarcinoma have different definitions for what constitutes early invasion. Perhaps the most comprehensive analysis of the literature was performed by *Östör* [56], who studied 436 lesions with an invasive depth of <5 mm. Of these, 126 were

Table 13.2 Staging of carcinoma of the uterine cervix as per American Joint Committee on Cancer (IAJCC), 8th ed and the International Collaboration on Cancer Reporting (ICCR)

TNM	Definition
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (preinvasive carcinoma)
T1	Tumor confined to the cervix (extension to corpus should be disregarded)
T1a	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[a]
T1a1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm in depth, with a horizontal spread of 7.0 mm or less
T1b	Clinically visible lesion confined to the cervix or microscopic disease greater than T1a/IA2
T1b1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	Tumor invades beyond uterus but not to pelvic wall or lower third of vagina
T2a	Tumor without parametrial invasion
T2a1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	Tum or with parametrial invasion
T3	Tumor extends to pelvic wall, involves lower one-third of vagina, causes hydronephrosis or nonfunctioning kidney
T3a	Tumor involves lower one-third of vagina
T3b	Tumor extends to pelvic wall, causes hydronephrosis or nonfunctioning kidney
T4	Tumor invades mucosa of the bladder or rectum, or extends beyond true pelvis
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases (includes inguinal lymph nodes and intraperitoneal disease except metastases to pelvic serosa). It excludes metastases to vagina, pelvic serosa and adnexa

[a]All macroscopically visible lesions, even with superficial invasion, are T1b/IB
[b]Vascular space involvement, venous or lymphatic, does not affect classification
[c]Bullous edema is not sufficient to classify a tumor as T4
[d]Invasion of bladder or rectal mucosa should be biopsy proven

treated by radical hysterectomy, and none had parametrial involvement. Moreover, 155 patients underwent bilateral oophorectomy and none had ovarian metastases. Of the 219 cases in this cohort with pelvic lymph node dissection, five (2%) had metastasis. Overall, there were 15 recurrences and six tumor-related deaths in the cohort. Only 21 cases had conization as the only treatment, and none suffered a recurrence. More recent studies have shown similar results, providing further evidence to recommend conservative management, consisting of conization with negative margins, for patients with stage IA invasive adenocarcinoma [58–60]. Of note, some authors recommend consideration for pelvic lymphadenectomy and conventional surgery (trachelectomy, radical hysterectomy) for patients with stage IA2 tumors *and* lymphovascular space invasion [60, 61].

13.3.1.3 Management

Primary surgery is the treatment of choice for patients with endocervical adenocarcinoma confined to the uterus; in this subset, surgery is superior to primary radiation [62]. Adjuvant systemic treatment is reserved for patients with upstage after pathologic examination of the resected specimen (parametrial involvement, lymph node metastases); in these patients, combination of chemotherapy and radiation is superior to radiation alone [63]. High-risk factors in the excised tumor such as high grade, deep cervical stromal infiltration, uterine corpus involvement, and extensive lymphovascular space invasion should also prompt consideration for systemic adjuvant treatment. Patients with disease beyond the uterus on clinical and radiologic examination undergo primary radiation and chemotherapy [64]. The latter includes Platinum derivatives (Cisplatin, Carboplatin) usually combined with Paclitaxel or other agents.

13.3.1.4 Genetic Profile

Infection by oncogenic HPV is the main causative event in most endocervical adenocarcinomas. Infection occurs in the squamous–columnar junction which harbors a recently characterized reserve cell precursor [65]. As outlined previously for AIS, active HPV infection leads to p16 overexpression. Other than the integration of HPV DNA into the host cell genome, prevalent genetic alterations in endocervical adenocarcinoma include mutations in *PIK3CA*, *KRAS,* and *PTEN*, all members of the *PI3K/Akt/mTOR* signaling cascade [66–69]. Remarkably, these mutations have predictive and prognostic value as they are amenable to targeted therapies [70] and are associated with tumors with destructive invasion [71]. Moreover, *KRAS* mutations are associated with advanced stage and tumor recurrence [71, 72]. Little is known of the molecular landscape of HPV-unrelated endocervical adenocarcinoma types.

13.3.1.5 Pattern-Based Classification

Risk stratification of early (FIGO stage I) invasive endocervical adenocarcinoma is currently based on measurement of tumor width and depth of invasion, as outlined above [73]. A novel classification system based on the pattern, rather than

Table 13.3 Pattern-based classification of HPV-related endocervical adenocarcinoma

Pattern A	Well-demarcated glands with rounded contours, frequently forming groups.
	No destructive stromal invasion.
	No single cells or cell detachment.
	No Lymphovascular invasion.
	Complex intraglandular growth acceptable (i.e., cribriform, papillae).
	Lack of solid growth (i.e., architecture well-moderately differentiated).
	Depth of tumor or relationship to large cervical vessels not relevant.
Pattern B	*Localized* (limited, early) *destructive stromal invasion* arising from pattern A glands (well-demarcated glands).
	Individual or small groups of tumor cells, separated from the rounded gland, often in a focally desmoplastic or inflamed stroma.
	Foci may be single, multiple or linear at base of tumor.
	Lymphovascular invasion +/−.
	Lack of solid growth (i.e., architecturally well-moderately differentiated).
Pattern C	*Diffuse destructive invasion*, characterized by:
	Diffusely infiltrative glands with associated extensive desmoplastic response.
	Glands often angulated or with canalicular pattern, with interspersed open glands.
	Confluent growth filling a 4× field (5 mm): glands, papillae (stroma only within papillae), or mucin lakes.
	Solid, poorly differentiated component (architecturally high grade); nuclear grade is disregarded.
	Lymphovascular invasion +/−.

the size of the invasive component, has been proposed as an alternative for risk stratification that obviates the well-known challenges of size measurement and invasion assessment [74–76]. The classification applies only to HPV-related endocervical adenocarcinoma (see *Nomenclature* section below). It divides invasive tumors into three groups according to the histologic pattern of stromal invasion (Table 13.3, Fig. 13.7).

Initial studies demonstrated that tumors with a nondestructive pattern of invasion (pattern A) were not associated with lymph node metastases, whereas tumors with focally (B) and diffusely (C) destructive patterns had 4% and 23% rates of nodal involvement, respectively [74, 75]. Tumor recurrence was seen in 0%, 1.2 and 22.1% of patients with patterns A, B, and C, respectively, and death of disease was exclusively seen in patients with pattern C tumors (8.8%) [74]. Other studies have found similar findings [77–79]. Pattern of stromal invasion also correlates with tumor size (horizontal spread and depth of invasion): in one study, 90% of pattern A tumors were stage IA, whereas 76% of pattern B and 80% of pattern C tumors were stage IB [78]. Differences in clinical presentation and outcome may have a genetic correlation: mutations in *KRAS*, *PIK3CA,* and other oncogenes commonly altered in endocervical adenocarcinoma are significantly more frequent in destructively invasive (B and C) tumors [71].

Application of the pattern-based classification requires evaluation of the entire tumor. However, pattern evaluation in cone and LEEP specimens has utility, since it is predictive of the final pattern in hysterectomy. Pattern evaluation in biopsy material, however, is less optimal with significant rates of upgrade (from A to C) on excision [78].

The overall interobserver reproducibility of the pattern-based classification is good [79, 80]. The highest level of concordance lies in the distinction between destructive (patterns B and C) and nondestructive patterns (pattern A, adenocarcinoma in situ) [79, 81]. Contrarily, the reproducibility of in situ versus invasive adenocarcinoma (particularly pattern A) diagnosis is poor [79]. Certain circumstances make pattern assessment difficult: tumors with an exophytic papillary component, tumors with brisk inflammation obscuring glandular contours, and tumors with a cellular periglandular stroma suggestive but not definitive for desmoplasia.

13.3.1.6 Nomenclature

The current WHO classification of tumors of the female reproductive system categorizes endocervical adenocarcinoma based on architectural and cytological morphologic features [11]. Histologic subtypes of endocervical adenocarcinoma (usual, mucinous, villoglandular, endometrioid) have been treated over the decades as distinct variants based on their peculiar histologic features. However, their biological and clinical significance has been questioned as multivariate analyses have shown no significant impact of major histologic types of HPV-related adenocarcinoma on patient survival [82].

Our growing knowledge of the etiology and clinical behavior of this disease now serves as a tool to refine classification. From an etiologic point of view, the majority (85–90%) of adenocarcinomas of the cervix are caused by high-risk HPV infection and originate from conventional AIS as their precursor. These tumors are detected at early stages with screening cytology and HPV-testing initiatives [9, 83]. The remaining (10–15%) comprise a heterogeneous group of lesions with a more aggressive clinical behavior, obscure pathogenesis, and need of better early detection tools.

The International Endocervical Adenocarcinoma Classification and Criteria (IECC) has been recently introduced as a more biologically and clinically congruent system to stratify invasive endocervical glandular malignancy, compared to the morphology-based WHO classification [84]. This system divides adenocarcinomas into HPV-related and HPV-unrelated. Subdivision of HPV-unrelated tumors into pertinent subtypes (gastric, clear cell, mesonephric) is important because of their distinct clinico-pathologic features. HPV-related adenocarcinoma subtypes, on the other hand, are similar from a demo-

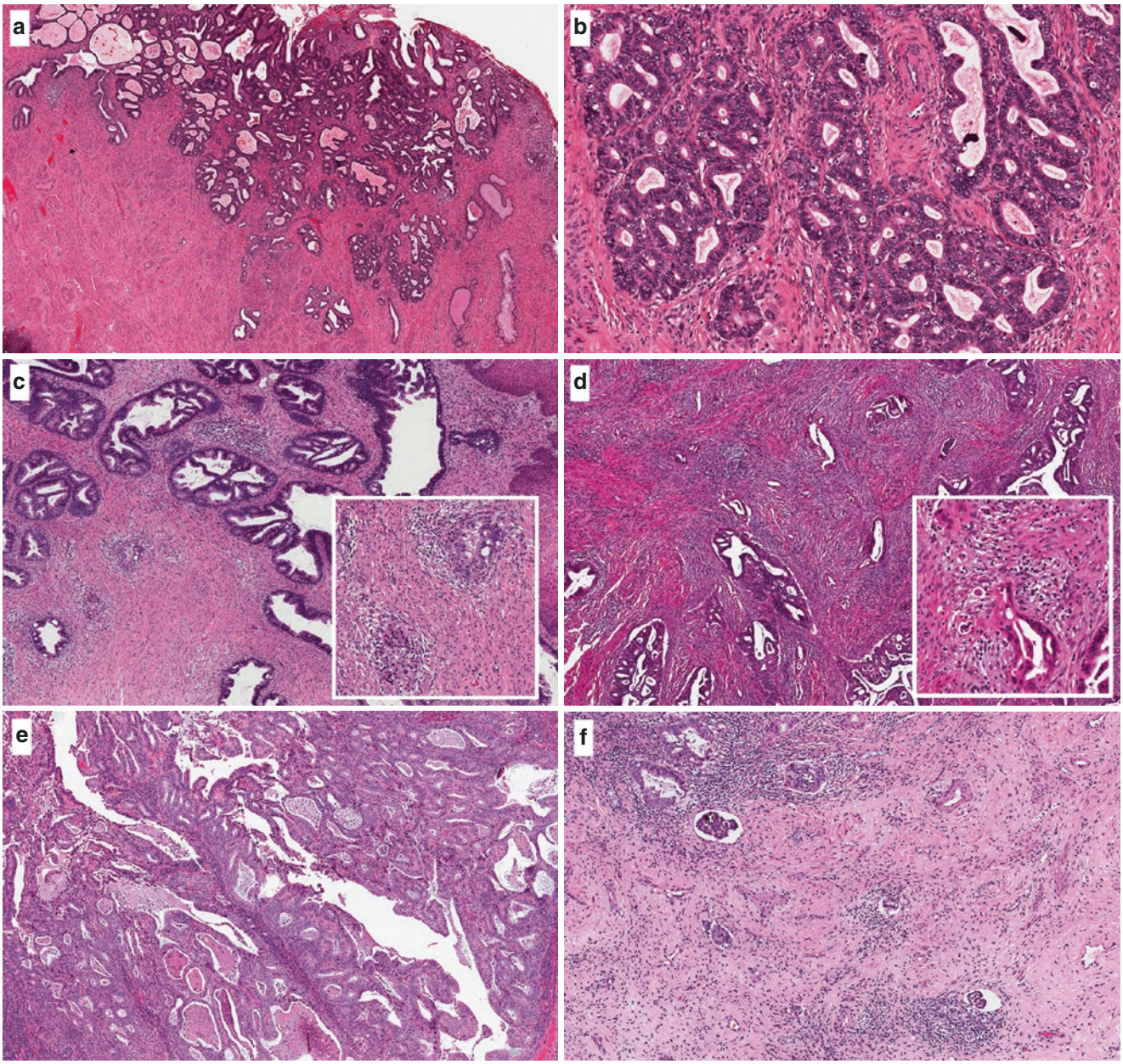

Fig. 13.7 Pattern-based classification. Pattern A (nondestructive) adenocarcinoma is well differentiated and diagnosed purely on the basis of glandular density and distribution (**a**, **b**). Focal destructive invasion, categorized as pattern B, arises from nondestructive glands (**c**); it is seen under high-power magnification as irregular glands and epithelial clusters (insert in C). Diffuse destructive invasion defines pattern C tumors; it can be seen as stromal desmoplasia (**d**), angulated and fragmented glands (insert in D), confluent solid, cribriform of papillary growth (**e**) and lymphovascular space invasion (**f**)

graphic and immunophenotypic perspective. A third group corresponds to rare tumors with unclear relationship to HPV infection (serous carcinoma), as well as unclassifiable and mixed lesions. Each subtype has an expected expression profile of immunohistochemical markers (mainly p16, progesterone receptor, vimentin and p53, see Table 13.4) [84].

It has been recently shown that compared to the WHO system, the IECC approach has superior interobserver agreement among gynecologic pathologists [85]. Importantly, agreement is substantial when distinguishing HPV-related from HPV-unrelated tumors, and in the diagnosis of important HPV-unrelated categories, which carry a more aggressive behavior (gastric). Conversely, the diagnosis of HPV-positive morphologic variants shows inferior reproducibility [85, 86]. Classification by pathologists as per the IECC also showed high correlation with HPV molecular

Table 13.4 Immunohistochemical profile of major types of endocervical adenocarcinoma

	HPV	p16	ER/PR	p53	Vimentin	mCEA
HPV-related	Positive	Overexpressed	Negative	Wild type	Negative	Positive
Gastric-type	Negative	Negative/patchy[a]	Negative	Abnormal[b]	Negative	Positive
Clear cell	Negative	Negative/patchy[a]	Negative	Wild type	Negative	Negative
Mesonephric	Negative	Negative/patchy[a]	Negative	Wild type	Negative	Positive
Endometrioid	Negative	Negative/patchy[a]	Positive	Wild type	Positive	Positive
Serous	Negative	Overexpressed	Pos/Neg	Abnormal	Pos/Neg	Positive

[a]p16 overexpression, independent from HPV infection, can be seen in these categories, particularly in poorly differentiated tumors
[b]Abnormal p53 staining (overexpression or complete absence) is seen in approximately 50% of gastric type tumors

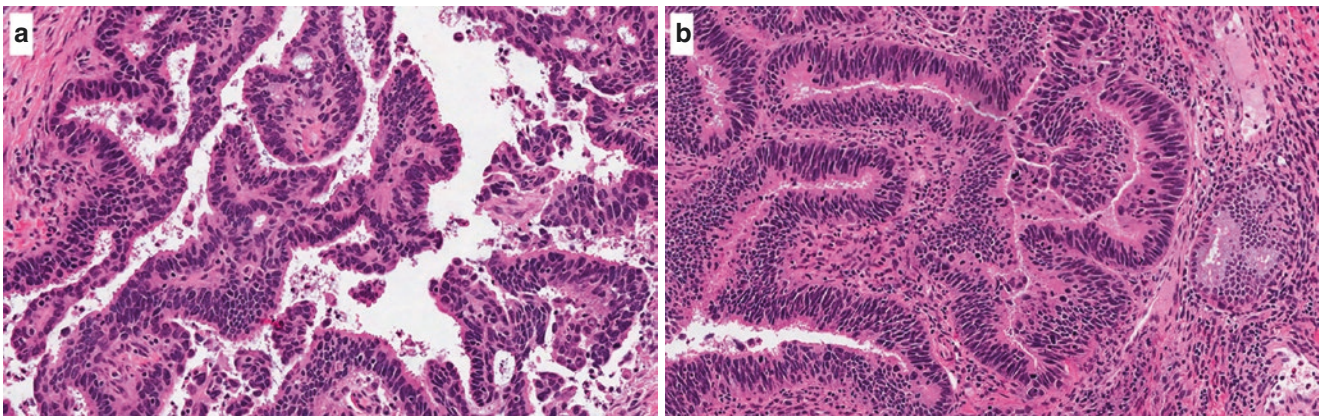

Fig. 13.8 Endocervical adenocarcinoma, usual type. Cytologically, this tumor type displays mucin depletion, nuclear hyperchromasia, and elongation similar to conventional AIS (**a**, **b**)

results. This suggests that the IECC is a more biologically congruent and clinically valuable system in the pathologic approach to endocervical adenocarcinoma.

The following paragraphs describe the pathology of invasive endocervical adenocarcinoma classified as per the IECC scheme (HPV-related and unrelated) and elaborates on the traditional WHO categories when appropriate. Miscellaneous lesions, including those with mixed or unusual patterns of glandular differentiation, are also covered here.

13.3.2 HPV-Related Endocervical Adenocarcinoma

By IECC definition, HPV-related adenocarcinoma contains *apical mitotic figures* and *apoptotic bodies*, easily identifiable at scanning magnification [84]. Well- to moderately differentiated forms of this adenocarcinoma type are characterized by columnar epithelium forming glandular structures of varying sizes and shapes; the luminal borders tend to be smooth. Solid nests, solid conglomerates, and individual cells are seen in poorly differentiated tumors. Morphologic variants are defined by the amount of intracytoplasmic mucin (usual versus mucinous) or by the architecture (villoglandular).

13.3.2.1 Usual Adenocarcinoma

Clinical Features

This subtype is, by far, the most common histologic type of adenocarcinoma of the cervix, accounting for 74–80% of cases [84, 87]. In fact, our cumulative knowledge of HPV-related adenocarcinoma is largely representative of usual-type lesions, by virtue of their frequency. While some patients present with symptoms (abnormal bleeding or pain), nowadays most cases are detected by screening cervicovaginal cytology.

Pathologic Features

Usual-type endocervical adenocarcinoma is comprised of columnar glandular epithelium with pseudostratified, elongated, and hyperchromatic nuclei and cytoplasmic mucin "depletion" (appreciable mucinous cytoplasm in 0–50% of cells only, Fig. 13.8).

Differential Diagnosis

Since usual-type adenocarcinoma has mucin depletion and consequently a pseudo-endometrioid phenotype, the most important differential diagnosis is with endometrioid carcinoma, either of cervical or endometrial origin. True endometrioid neoplastic proliferations display round, low-grade

nuclei and generally lack the hyperchromasia and conspicuous mitotic activity seen in HPV-related endocervical lesions. In addition, the presence of "confirmatory endometrioid" features is in keeping with an endometrioid carcinoma (low-grade glands, squamous differentiation, and adjacent endometriosis) [84, 88]. The value of immunohistochemistry in distinguishing between endometrial and HPV-related usual endocervical adenocarcinoma is discussed later (see "Metastatic adenocarcinoma to the cervix").

13.3.2.2 Mucinous Adenocarcinoma

Counterintuitive to the mucinous nature of the normal endocervix, predominantly or purely mucinous tumors represent only a minority of all cervical adenocarcinomas [87]. They are divided based on the appearance of the intracytoplasmic mucin. It is now recognized that gastric mucinous carcinoma is a biologically separate entity; thus, it will be discussed later.

Mucinous Adenocarcinoma, Not Otherwise Specified

The mucinous variant, not otherwise specified, displays intracytoplasmic mucin in ≥50% of neoplastic cells, usually with a minor component of usual-type (mucin depleted) adenocarcinoma (Fig. 13.9). Mucin is of *endocervical type* (acid-type mucin with pale blue color in H&E preparations and dark purple staining in Alcian blue-PAS stain, akin to the normal endocervix).

Intestinal Type

Pathologic Features

A minority of HPV-related glandular malignancies of the uterine cervix display intestinal differentiation in the form of goblet cells, Paneth cells, and other entero-endocrine cells [89, 90] (Fig. 13.10). These tumors are relatively infrequent, described mostly in case reports and small series. While the biologic behavior of this subtype does not seem to differ from other HPV-related types, one study found that intestinal-type adenocarcinoma in situ was more likely to be associated with early invasive adenocarcinoma than usual-type adenocarcinoma in situ (31% vs. 17%) [30]. By immunohistochemistry, intestinal-type adenocarcinoma is positive for CK7 and negative/patchy for CK20. CDX2 is frequently positive, in keeping with an enteric phenotype [30].

Differential Diagnosis

When diffuse, intestinal differentiation and HPV-related adenocarcinoma may be confused with clear cell or gastric-type adenocarcinoma. It is important to note that gastric-type adenocarcinoma can contain goblet or neuroendocrine cells; thus, attention to the distinct cytologic features of this neoplasm is key (see description later). In addition, gastric-type tumors produce neutral-type mucin, which stains red in PAS-Alcian blue preparations; conversely, acid-type mucins characteristic of intestinal-type epithelium stain dark blue [47]. Another important consideration is secondary (metastatic) involvement of the cervix by an intestinal carcinoma. Primary endocervical tumors will show diffuse and strong p16 staining and are positive for high-risk HPV detection; in addition, patchy CK20 may help exclude colorectal metastases. CDX2 has been negative in intestinal-type endocervical adenocarcinoma in some series [91]; however, it's been shown to be frequently positive in others, limiting its diagnostic value [30, 92].

Signet-Ring Cell Type

Pathologic Features

This variant is exceedingly rare with less than 20 cases reported according to recent English literature reviews [93]. It is characterized by the presence of loose (non-cohesive) round cells with a mucinous vacuole that displaces the

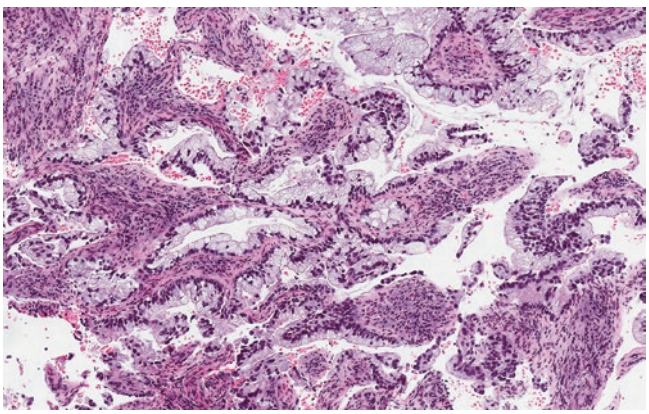

Fig. 13.9 Endocervical adenocarcinoma, mucinous endocervical type. This subtype is diagnosed when more than 50% of tumor cells contain endocervical-type mucin

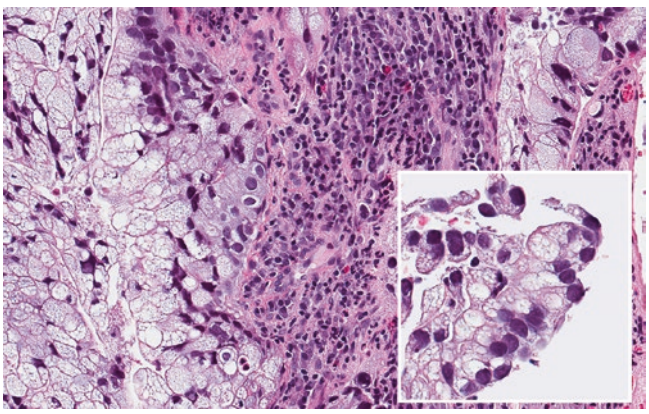

Fig. 13.10 Endocervical adenocarcinoma, mucinous intestinal type. This type is characterized by signs of intestinal differentiation including goblet cells (insert). This lesion was positive for p16 overexpression and high-risk HPV

nucleus to the side (imparting the classic appearance of a signet ring). These cells can grow in confluent sheets or be scattered throughout the stroma, which may appear normal if careful observation at high magnification is not performed. In adjacent areas usual or mucinous NOS morphology can be found. Interestingly, almost all cases subjected to HPV testing in the literature have revealed HPV type 18 DNA [93].

Differential Diagnosis

When encountering a cervical adenocarcinoma with signet-ring cell differentiation, a metastatic carcinoma from gastrointestinal or breast origin should be considered. Actually, this scenario may be even more frequent than a primary endocervical signet-ring cell carcinoma. It is important to know that not all metastatic cases have a previous or concurrent history of gastric or mammary cancer, and the cervical lesion may be the presenting sign / symptom [94, 95]. Features suggestive of metastases include extensive cervical involvement with prominent lymphatic vascular invasion and absence of an intraepithelial precursor (AIS or HSIL). Conversely, detection of HPV DNA can confirm a primary cervical origin. Immunohistochemistry has a value in excluding a breast primary; signet-ring mammary carcinomas are almost always of lobular type, and will express hormone receptors and GATA3. Unfortunately, the immunophenotype of cervical and gastrointestinal signet-ring cell carcinomas overlaps, since both are positive for CK7 and show variable expression of CK20, CDX2, and mucins [96]. In HPV-negative and equivocal cases, the pathologist should raise the possibility of metastases and prompt clinical and radiologic investigations to exclude it.

Prognosis and Management

Prognosis is very poor in patients with advanced stage at presentation. Early stage tumors, on the other hand, tend to be associated with good prognosis after surgical +/− adjuvant systemic treatment [97, 98].

Stratified Mucin-Producing Carcinoma

Pathologic Features

Recently, an invasive carcinoma with morphology reminiscent of SMILE has been described under the name "invasive stratified mucin-producing carcinoma" (ISMC) [99]. Most of these carcinomas are associated with adjacent SMILE. The invasive lesion is comprised of stratified, immature nuclei with variable intracytoplasmic mucin, usually with solid and/or nested tumor architecture (Fig. 13.11). Most of these lesions are architecturally moderately or poorly differentiated; however, cytologic features tend to be low grade (nuclei similar to other HPV-related variants, intracytoplasmic mucin), which is a helpful diagnostic clue. Like SMILE, electron microscopy studies of ISMC showed ultrastructural evidence of glandular differentiation with microvilli, vacuolar structures, and mitochondria, supporting the hypothesis that these lesions represent stratified variants of endocervical glandular malignancy [45].

Differential Diagnosis

The differential diagnosis of ISMC includes adenosquamous carcinoma, since both lesions display a stratified neoplastic population. Adenosquamous carcinoma is comprised of distinct glandular and squamous populations. The presence of a definitive squamous cell component (keratinization, intercellular junctions) will favor this entity. Absence of squamous differentiation, diffuse scattered presence of mucin-producing cells, and adjacent SMILE are features more consistent with ISMC.

13.3.2.3 Villoglandular Carcinoma

Pathologic Features

This adenocarcinoma type is characterized by its prominent exophytic papillary growth. Villoglandular adenocarcinoma

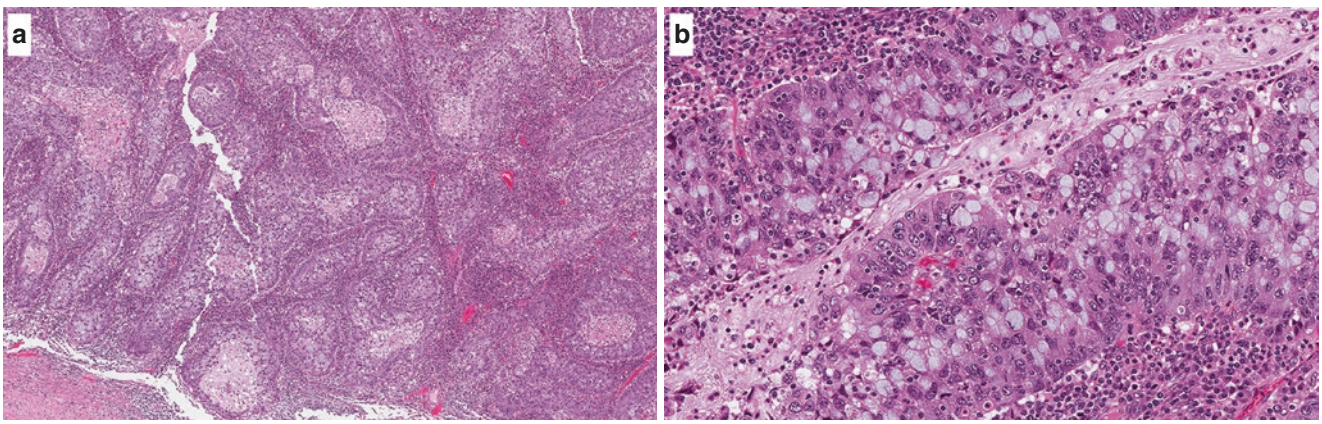

Fig. 13.11 Invasive stratified mucin-producing carcinoma. Gland formation is retained in this invasive tumor; however, lining epithelium is stratified (**a**) and comprised of mucin-producing atypical cells (**b**)

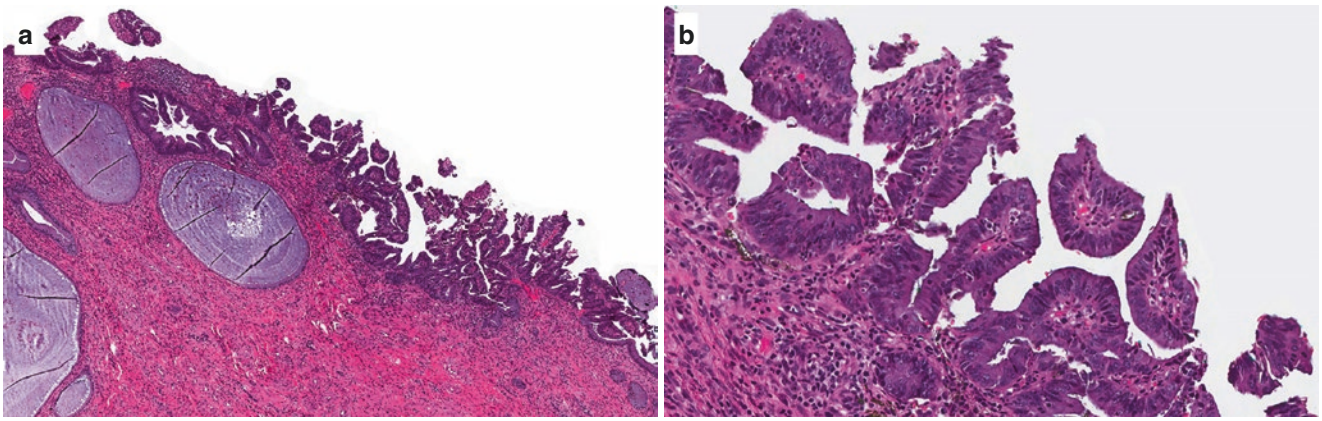

Fig. 13.12 Endocervical adenocarcinoma, villoglandular type. The lesion is usually superficial and exophytic (**a**); papillary-like projections are lined by columnar epithelium akin to usual-type adenocarcinoma (**b**)

is described as predominantly superficial and composed of papillae of varying thickness and length, containing central fibrous cores with numerous inflammatory cells [100, 101] (Fig. 13.12). Papillae are lined by columnar pseudostratified epithelial cells similar to adenocarcinoma of the usual- or mucinous-types. The deep aspect of the tumor consists of branching tubular glands, well demarcated from the adjacent cervical stroma.

Differential Diagnosis

Similar to other types of HPV-related adenocarcinoma, the differential diagnosis includes endometrial endometrioid carcinoma involving the cervix, since some endometrial endometrioid carcinomas display villoglandular growth. The presence of HPV-related features (apical mitoses, apoptosis, and hyperchromatic elongated nuclei) should suggest an endocervical process. Immunohistochemistry can be helpful to differentiate cervical primary from endometrial metastasis (see "metastatic carcinoma to cervix"). Other primary cervical lesions can display prominent exophytic papillary growth, importantly serous and clear cell carcinoma. Unlike high-grade forms of adenocarcinoma, nuclear atypia in villoglandular carcinoma is at most moderate and the nuclear-to-cytoplasmic ratio is low. An abnormal p53 stain argues against villoglandular carcinoma, and suggests a serous neoplasm (less likely clear cell). Napsin-A expression should raise concern for clear cell carcinoma.

Prognosis and Management

The prognosis of villoglandular adenocarcinoma was traditionally considered excellent, and conservative management with simple excision was advocated [100, 101]. More recently, however, tumor recurrence and death from disease have been documented in a significant proportion of cases [102–104], and survival analyses have shown similar trends between villoglandular and other subtypes [82, 105]. In a relatively large recent cohort, the overall and disease-free 5-year survival was 82% and 75%, respectively [106]. Importantly, several pathologic features are associated with poor prognosis, including involvement of the deep cervical stroma, lymphovascular space invasion, lymph node metastases, and advanced stage at presentation [102, 107]. Consequently, conservative surgical treatment should only be considered after cone / LEEP evaluation demonstrates negative margins and tumor restricted to the surface / superficial stroma [106, 108]. Standard treatment, akin to other adenocarcinoma types, is the norm for patients with clinical or pathologic adverse factors.

13.3.3 HPV-Unrelated Endocervical Adenocarcinoma

13.3.3.1 Gastric Mucinous Adenocarcinoma (Including Minimal Deviation Adenocarcinoma)

Awareness of the existence of HPV-unrelated neoplasms has markedly increased over the last decade, greatly due to the advances in our understanding of gastric-type differentiation in the endocervix. Indeed, according to recent classifications, gastric type adenocarcinoma is the most frequent type of HPV-independent endocervical adenocarcinoma.

Clinical Features

The median age of patients with gastric type adenocarcinoma is 49 years (range 37–84) [109]. Presenting symptoms include bleeding, watery vaginal discharge, and cytologic abnormalities (atypical cells with yellowish-orange intracytoplasmic mucin) [46]. A latex agglutination test using HIK1083 (a marker of pyloric gland mucin) is available as a screening tool for patients with watery discharge; initial studies on this tool demonstrated high sensitivity and specificity for gastric-type proliferations (LEGH, atypical LEGH and MDA) [110].

Pathologic Features

Macroscopically, the lesion can be polypoid or ulcerated; in typical cases the cervical wall is indurated and expanded in a circumferential fashion (so-called "barrel" shaped cervix) [111].

Gastric differentiation in the cervix is defined as conversion towards a gastric, "pyloric" type mucinous phenotype. Gastric mucins are neutral, whereas endocervical mucins are acidic. Neutral mucins stain pale red in Alcian blue/PAS special stain, whereas acid mucins stain dark purple/blue [47]. On H&E preparations, gastric-type epithelium is characterized by cells with *clear or pale eosinophilic cytoplasm* and *distinct cell borders* [109]. The reproducibility of the diagnosis of gastric-type adenocarcinoma as defined is substantial [112]. On the other hand, interobserver agreement of the distinction between minimal deviation adenocarcinoma and benign endocervical proliferations is poor, likely due to its deceptively bland morphology [113].

Gastric-type adenocarcinoma is classified into two groups: MDA (also known as Adenoma Malignum) and gastric adenocarcinoma not otherwise specified (GA-NOS). MDA is characterized by (Fig. 13.13):

- *Low-grade morphology:* minimal to absent cytologic atypia, abundant apical mucin, well-defined glands with a claw-like pattern.
- *D*eep haphazard gland distribution with minimal to no desmoplastic reaction.

This low-grade morphology must be present in 90% or more of the tumor. If less, the tumor is classified as GA-NOS [114, 115] (Fig. 13.14). GA-NOS tumors are usually moderately to poorly differentiated with destructive and florid stromal invasion. Lymphovascular space invasion is frequent (48% of cases).

Ancillary Studies

By immunohistochemistry, tumor cells are frequently positive for markers of gastric epithelial differentiation MUC6 and HIK1083, although expression can be focal [109, 116]. Other frequently positive markers include PAX8, carbonic anhydrase IX, CA19-9, CK7, CK20 (focal), and CDX2 (focal) [117]. PAX2 expression is lost in most cases [117, 118]. Unlike HPV-related tumors, GAS and MDA usually lack p16 overexpression (stain is either negative or patchy); however, high-grade GAS and occasional MDA cases can demonstrate p16 overexpression, unrelated to HPV [84, 119]. In such instance, HPV detection studies should be considered. p53 expression is abnormal in approximately 45% of gastric-type tumors, whereas most (~100%) HPV-related carcinomas show normal (wild type) expression [120]. Loss of PAX2 expression has been documented in MDA but not in benign lesions [118]. Estrogen and progesterone receptors are typically negative.

Gastric mucinous adenocarcinoma has been found to be negative for HPV infection in numerous studies [114, 121, 122]. Besides this, the molecular mechanisms underlying the pathogenesis of gastric-type adenocarcinoma are still largely unknown. MDA has been described in patients with Peutz-Jeghers syndrome, which is related to alterations in the *LKB1/STK11* gene [111]. Interestingly, *LKB1/STK11* mutations have also been identified in sporadic MDA [123].

Differential Diagnosis

The differential diagnosis of gastric mucinous endocervical adenocarcinoma is wide. MDA can be mistaken as benign endocervical tissue, even in resection specimens. A haphazard arrangement of the glands, extension into deep stroma, and circumferential cervical involvement are all abnormal features that should raise suspicion for a malignant process. While subtle, the clear to eosinophilic mucinous profile of MDA and GAS glands can be appreciated by an attentive eye and contrasted with the mucin of the normal endocervix.

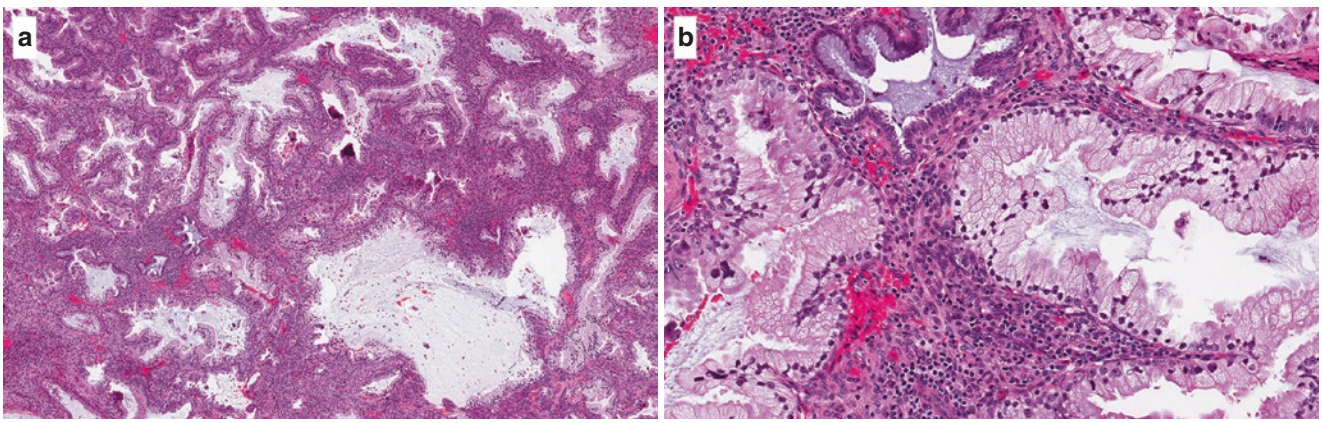

Fig. 13.13 Gastric-type endocervical adenocarcinoma, minimal deviation type. Well-formed glands haphazardly distributed throughout the cervical wall (**a**); neoplastic glands display "gastric" features including abundant pale vacuolated cytoplasm and distinct cell borders (**b**); epithelium is extremely bland (compare to normal cervical gland on top center)

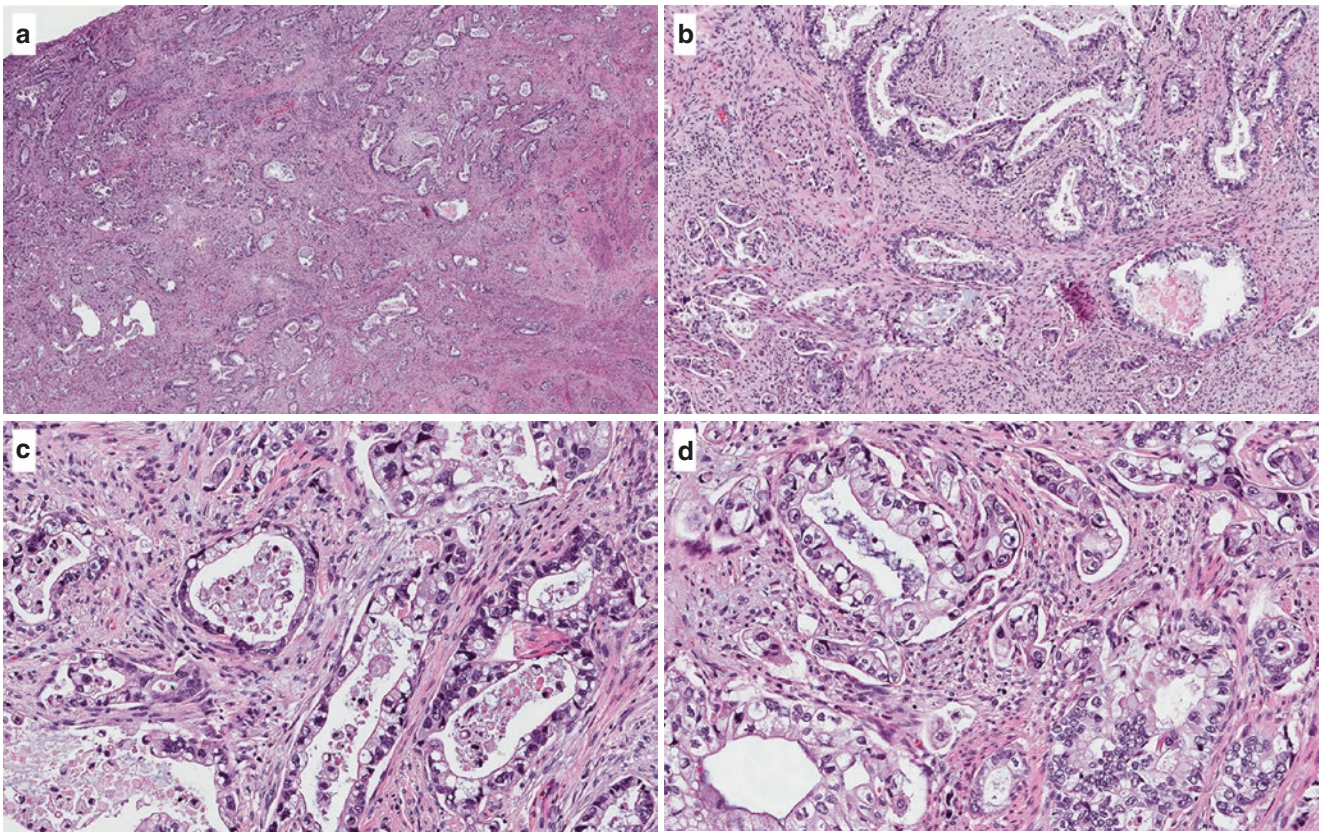

Fig. 13.14 Gastric-type endocervical adenocarcinoma, not otherwise specified. These tumors tend to be widely infiltrative (**a**) and less differentiated, at least focally (**b**, lower left). Gland forming epithelium displays marked nuclear pleomorphism and abundant vacuolated mucinous cytoplasm (**c** and **d**)

Unlike LEGH, MDA lacks a lobulated architecture and often extends beyond the superficial stroma.

Tumors in the GAS spectrum can be easily recognized as malignant; however, distinction from a HPV-related lesion can be difficult. In fact, adenocarcinomas with mixed morphology have been described; these cases display areas with usual-type morphology (mucin-depleted cells with apical mitoses and apoptosis) admixed with areas of gastric-type morphology (abundant, pale to eosinophilic cytoplasm) [124]. These cases demonstrate either a gastric (most commonly) or a usual phenotype by ancillary studies (HIK1083, p53, p16, and HPV molecular studies) indicating that they are tumors with variant morphology instead of truly "mixed" lesions. This highlights the importance of ancillary testing in the pathologic diagnosis of endocervical adenocarcinoma, as depicted by the IECC. Another important, although infrequent, differential is a metastatic gastric carcinoma to the cervix. These lesions usually have signet-ring cells, which are not typical of GAS. However, morphologic and immunophenotypic similarity exists, and exclusion of a gastrointestinal tract primary should be recommended to the treating physician if one cannot be convinced that a gastric-type malignancy is primary cervical or metastatic in origin.

Prognosis and Management

Gastric-type endocervical mucinous adenocarcinoma is a biologically aggressive neoplasm. Compared to usual-type adenocarcinoma, it has significantly higher rates of ovarian, pelvic, and abdominal metastases as well as regional and distal lymph node involvement [114]. Up to 60% of cases present at stage II or higher. 5-year disease-free survival is 30%, and overall survival is 42% (compared to 77 and 91% for usual-type tumors, respectively) [109, 114]. Importantly, this tumor has a poor prognosis regardless of the degree of differentiation. In fact, similarly to poorly differentiated tumors, extremely well differentiated forms (MDA) have high rates of extra-uterine spread with up to 50% mortality rate [114].

13.3.3.2 Endometrioid Adenocarcinoma

In this textbook, this tumor type is defined following the IECC recommendations which differ from the WHO classification. The latter defines endometrioid carcinoma as "morphologically similar to endometrioid adenocarcinomas of the uterine corpus" and divides it etiologically into HPV-related and endometriosis-related (HPV-negative) categories [11]. Unfortunately, this WHO definition, as with prior literature,

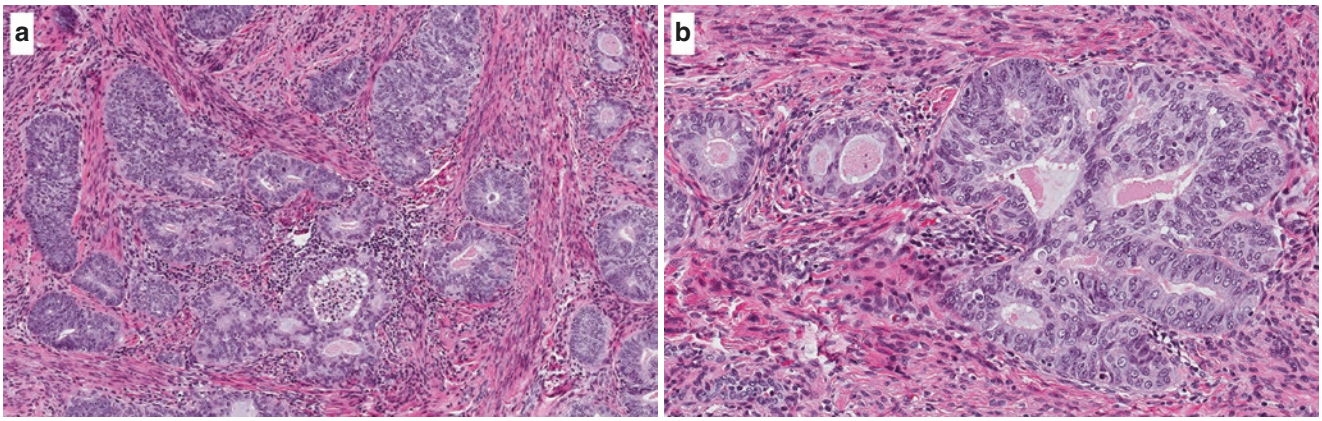

Fig. 13.15 Endometrioid endocervical adenocarcinoma. The morphology is identical to that seen in endometrial endometrioid carcinoma (see Fig. 13.19a,b). Cells are columnar and mucin-depleted, but lack the hyperchromasia, elongation, and mitotic activity of HPV-related adenocarcinoma (**a**, **b**)

is vague, greatly overlapping with the description of usual-type and endometrioid-type carcinomas. Not surprisingly, the diagnosis of endometrioid endocervical adenocarcinoma is one that often causes confusion among pathologists and treating clinicians. The IECC approach is preferred because it separates true "endometrioid" morphology from the spectrum of HPV-related cervical glandular neoplasia.

Pathologic Features

The term endometrioid carcinoma, as per IECC, is reserved for tumors with low-grade endometrioid glands *and* confirmatory endometrioid features (squamous metaplasia, endometriosis, Fig. 13.15). Under this definition, endometrioid carcinoma is rare, representing ~1% of cervical adenocarcinomas [84]. It is suggested to originate from endometriosis or other type of endometrioid-type precursor in the cervix, and is unrelated to HPV infection [125].

A similar entity is the so-called "minimal deviation endometrioid adenocarcinoma" [126, 127]. This term refers to neoplasms with bland glandular endometrioid cytomorphology and deceptively well-differentiated architecture; usually located in the upper endocervix/lower uterine segment [128, 129].

Differential Diagnosis

The chief differential diagnosis is a primary endometrial endometrioid carcinoma with a "minimal deviation" pattern of spreading into cervical stroma [130, 131]. The immunophenotype of these lesions mirrors that of an endometrial endometrioid carcinoma (ER positive, vimentin positive, CEA negative) [128]. Given the considerable histologic and immunophenotypic overlap, determination of origin (endocervical or endometrial) in this context can be quite difficult in biopsy material, thus deferral to assessment on hysterectomy is recommended. One last consideration is the occurrence of synchronous primary endometrial and endocervical endometrioid carcinomas, which has been suggested in a few patients based on DNA clonality and loss of heterozygosity [132].

13.3.3.3 Clear Cell Adenocarcinoma

Clinical Features

Clear cell carcinoma of the uterine cervix accounts for 4% of all cervical adenocarcinomas [133]. An association with in utero exposure to diethylstilbestrol (DES) has been described; in patients with such exposure, incidence peaks at young age (median age 26 years) and again later in life (median age 71 years) [134, 135]. Use of DES during pregnancy has been long discontinued. Nowadays, only a minority of clear cell carcinomas are related to DES exposure (6% in one study) [136]. Median age of patients with clear cell carcinoma is 53 years. Most patients present with vaginal bleeding. Cervicovaginal cytology is abnormal only in a small proportion of cases (18%), limiting its screening value for this entity [136].

Pathologic Features

Histologically, clear cell carcinoma is arranged in tubulocystic, papillary and solid patterns, similar to its ovarian and endometrial counterparts [137]. Papillae usually have hyalinized fibrovascular cores. The cytomorphology of clear cell carcinoma is distinctive: tumor cells are cuboidal, have clear (translucent) cytoplasm and enlarged nuclei that protrude towards the luminal aspect, giving a "hobnail" appearance (Fig. 13.16). Cells with clear cytoplasm can be only focal or absent (their presence is not required for this diagnosis). "Non-clear" cells have a vaguely eosinophilic and granular cytoplasm.

Ancillary Studies

Unlike usual-type adenocarcinoma, cervical clear cell carcinoma is unrelated to HPV infection [138]. Microsatellite instability and somatic mutations of microsatellite repeats

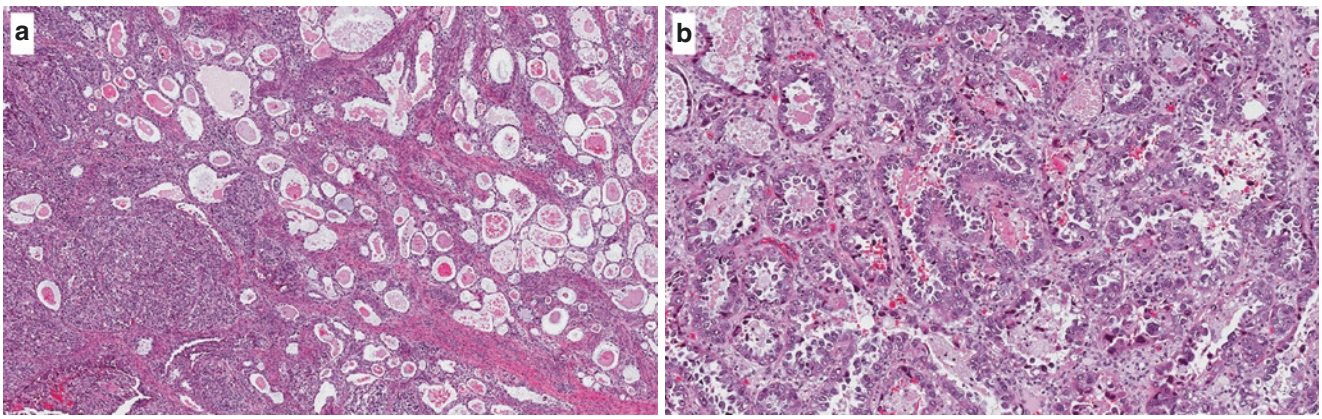

Fig. 13.16 Clear cell endocervical adenocarcinoma. The lesion usually has varying architecture with tubulocystic (**a**, right) and solid (**a**, left) patterns. Tumor cells have scant cytoplasm and highly atypical nuclei protruding towards the lumen (hobnail pattern) (**b**). Notice the absence of clear cytoplasm in this area of the tumor (clear cytoplasm is not a requirement for this diagnosis)

has been documented in clear cell carcinoma, predominantly in cases associated with DES exposure [139]. EGFR and HER2 overexpression has been observed in 75% and 25% of cases, respectively, as well as activation of *AKT* and *mTOR* in 58% and 50% of cases, respectively [138].

While unrelated to HPV infection, p16 is frequently strongly and diffusely positive in clear cell carcinoma [120]. Also, like most other types of endocervical adenocarcinoma, estrogen and progesterone receptors are negative in this tumor. On the other hand, monoclonal carcinoembryonic antigen (CEA) appears to be consistently negative in clear cell carcinoma, and may be of value in distinguishing clear cell from other subtypes [120]. Napsin-A is frequently positive in endocervical clear cell carcinoma [140]; however, Arias-Stella reaction can also express this marker [141].

Differential Diagnosis

The differential diagnosis includes not only other types of cervical glandular malignancy but also benign lesions, most importantly microglandular hyperplasia and Arias-Stella reaction. Microglandular hyperplasia can have a complex architectural appearance with back-to-back glands mimicking a tubulocystic clear cell carcinoma. However, cells in microglandular hyperplasia contain mucinous cytoplasm and lack nuclear atypia. Arias-Stella reaction is an important differential. Although it is usually seen in the context of pregnancy or high-dose progestin exposure, such history may not be apparent in all cases. Arias-Stella reaction is characterized by cells with abundant cytoplasm and markedly enlarged nuclei. However, unlike clear cell carcinoma, the nuclear-to-cytoplasmic ratio remains low (since cytoplasm is abundant) and there is no mitotic activity. Rare malignant lesions in the differential, particularly in the pediatric population, include yolk sac tumor (reticular pattern, Schiller-Duval bodies, α-fetoprotein expression) and alveolar soft part sarcoma (PAS-positive intracytoplasmic crystals).

Prognosis and Management

The majority of patients with cervical clear cell carcinoma are diagnosed at early stage (FIGO stage I or II) and have an overall good prognosis. Pelvic lymph node involvement is seen in 25% of patients and is associated with lymphovascular space invasion. Chemotherapy and radiation has been reported to be useful in advanced-stage tumors or with high-risk factors (lymphatic vascular invasion, parametrial involvement, tumor size >4 cm, >2/3 cervical stromal invasion, positive margins) [133, 136].

13.3.3.4 Mesonephric Adenocarcinoma

Clinical Features

Mesonephric carcinoma of the cervix represents less than 1% of all cervical carcinomas [142]. The morphologic and immunohistochemical similarities with mesonephric remnants support a mesonephric derivation [143, 144]. Patient age at presentation ranges from 24 to 72 years (median age 43–52 years) [144–146]. Most patients present with abnormal bleeding, abnormal Pap smear, or with a mass detected on examination.

Pathologic Features

Macroscopically, the tumor presents in the lateral aspect of the cervix or with circumferential cervical involvement. Microscopically, mesonephric carcinoma characteristically shows a spectrum of architectural patterns including tubuloglandular, ductal, retiform, solid, spindle cell, and sex cord-like (Fig. 13.17). Better differentiated areas have small, round, glandular, and tubular structures containing eosinophilic luminal secretions, resembling benign mesonephric structures. A retiform pattern is characterized by slit-like spaces outlined by branching papillae. Solid and spindle cell components are usually present in variable proportions. When present, the spindle cell component usually has malig-

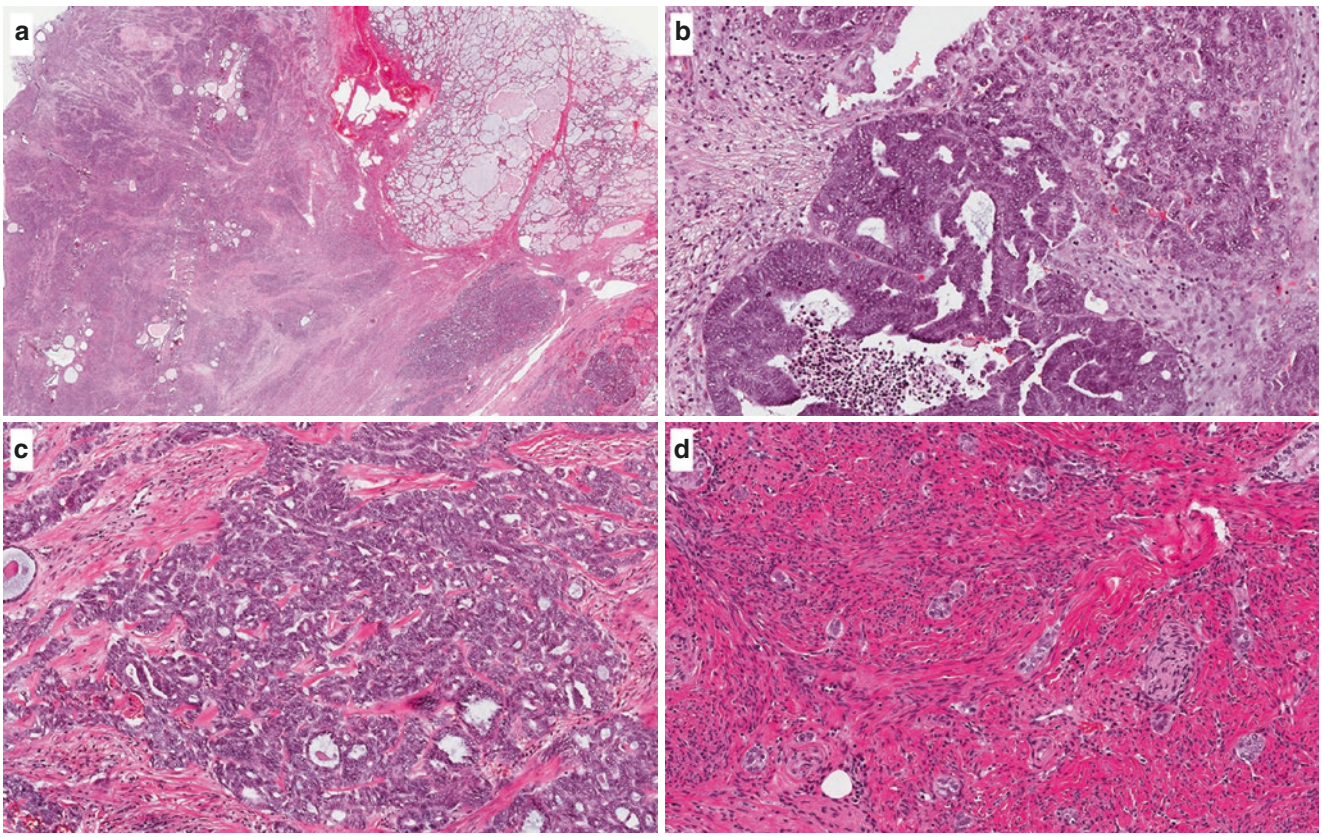

Fig. 13.17 Mesonephric adenocarcinoma. This tumor was located in the deep cervical and uterine wall. Carcinoma typically has a range of architectural patterns including tubulo-glandular (**a**), ductal (**b**), and retiform (**c**). Deceptively bland infiltration, mimicking mesonephric hyperplasia, can be observed (**d**)

nant features resembling an endometrial stromal sarcoma. In these cases, the term "malignant mixed mesonephric tumor" has been used [145, 146].

Ancillary Studies

By immunohistochemistry, mesonephric carcinoma cells are positive for keratins, calretinin, vimentin, CD10 (apical staining), and GATA3; conversely, they lack estrogen and progesterone receptor expression [144, 147]. Of importance, this tumor is also positive for PAX8 and can express p16, although focally in most cases [148]. At the molecular level, mesonephric carcinoma is characterized by recurrent *KRAS* mutations, detected in 81% of cases [142]. HPV has not been detected in this tumor [148].

Differential Diagnosis

The differential diagnosis mainly includes Müllerian (endocervical or endometrial) adenocarcinoma and mesonephric remnants. A deep cervical or uterine wall location and a variety of architectural patterns will be more in keeping with a mesonephric neoplasm. Conversely, definitive mucinous, tubal, or endometrioid morphology indicates a Müllerian tumor. In challenging cases, immunohistochemistry can help; the most useful markers, as described above, are GATA3, CD10, calretinin, p16, and ER/PR.

Prognosis and Management

The biologic behavior of mesonephric carcinoma appears to be better than Müllerian cervical adenocarcinomas when adjusted for stage. Nonetheless, recurrences have been reported in early stage cases and adverse outcome is usually seen in cases with advanced stage [144]. Malignant mixed mesonephric tumors tend to present at advanced stage suggesting a more aggressive course [146].

13.3.4 Other Adenocarcinoma Types

13.3.4.1 Serous Carcinoma

Primary cervical serous carcinoma is rare; in fact, some authors believe that its occurrence is debatable and that cases reported actually represent either lower uterine segment endometrial tumors or cervical metastases of endometrial, tubal, ovarian or peritoneal origin [149, 150]. This derives from the observation that, by using strict current morphologic and immunohistochemical criteria, such diagnosis is hardly

ever encountered nowadays [84]. As a counterargument, misdiagnosis may explain some but not all cases of endocervical serous carcinoma reported in the literature [151–153]. For instance, 3 out of 10 endocervical serous carcinomas studied by *Nofech-Mozes et al.* underwent hysterectomy or pelvic exenteration, and no endometrial or tubo-ovarian malignancy was identified; these tumors were included following strict criteria (high-grade, pleomorphic nuclei and focal papillary tufting in at least 50% of its mass) [154]. Therefore, endocervical serous carcinoma as an entity remains in the current IECC and WHO classification systems.

Clinical Features

In its initial descriptions, the age at presentation of cervical serous carcinoma was wide, with a peak in young patients (<40 years old) followed by a second peak after 65 years of age [152]. Most patients present with abnormal vaginal bleeding and abnormal cytologic findings.

Pathologic Features

Microscopically, serous carcinoma of the cervix displays the characteristic papillary and micropapillary tufting seen in other sites. Severe nuclear atypia is a requirement for this diagnosis; it is usually evident at low-power magnification as pleomorphic cells with loss of polarity, high nuclear-to-cytoplasmic ratio, and prominent eosinophilic nucleoli (Fig. 13.18). Mitotic activity is usually high, >10 mitoses per 10 HPFs [152]. Psammoma bodies are observed in a minority of cases.

Ancillary Studies

Mutation of the *TP53* gene is an early carcinogenic event in serous carcinoma of the female genital tract, and abnormal expression of p53 has been reported in endocervical serous carcinoma [154, 155]. WT1 expression has been observed in only a few patients; in fact, when encountered, this finding should raise suspicion for a tubo-ovarian primary. Only 6 out of 17 (35%) cases in the pooled literature were positive for high-risk HPV DNA [155–158].

Differential Diagnosis

Given its rarity, the diagnosis of endocervical serous carcinoma is one of exclusion. Clear cell and gastric type endocervical adenocarcinomas usually display marked nuclear pleomorphism. The architecture of clear cell carcinoma is usually distinct, characterized by the presence of tubulocystic areas or simple papillae with hyalinized cores. Gastric type adenocarcinoma has a more columnar glandular architecture and cells contain abundant, vacuolated mucinous cytoplasm. Ancillary studies have limited value: abnormal p53 expression and p16 overexpression can be seen in serous, gastric, and clear cell types. Other markers such as Napsin-A (for clear cell) and HIK1083 (for gastric type) can be considered. HPV-related endocervical adenocarcinoma of the usual

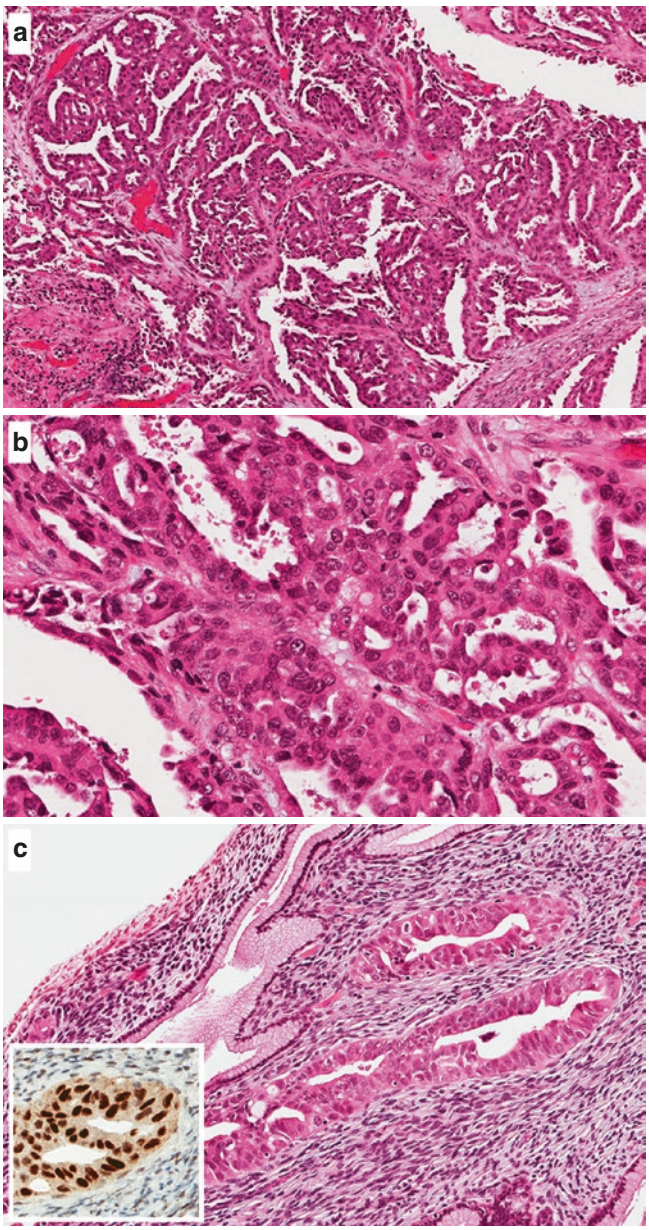

Fig. 13.18 Serous endocervical carcinoma. Tumor in this case was confined to the cervix; endometrium, ovaries and tubes were unremarkable. It is possible, however, the the tumor originated in the lower uterine segment. Tumor shows complex micropapillary growth with slit-like spaces (**a**); tumor cells have high-grade features including prominent nucleoli and high nuclear-to-cytoplasmic ratio (**b**). An intraglandular component with similar morphology and p53 overexpression was also identified (**c**, insert). This lesion was negative for p16 and HPV molecular studies

(endocervical) type can also mimic serous carcinoma, especially if having solid or papillary architecture; these lesions tend to have a lower nuclear-to-cytoplasmic ratio and lesser degrees of atypia. Importantly, p53 will help in this differential as staining is normal in usual-type endocervical adenocarcinoma. Lastly, in the presence of an unequivocal serous carcinoma based on morphology and immunophenotype, endocervical origin should only be entertained after an endo-

metrial or upper genital serous carcinoma has been thoroughly excluded.

Prognosis and management

Prognosis largely depends on tumor stage with tumors showing extra-uterine spread at presentation (FIGO stage II or greater) having dismal 5-year survival [153, 159]. Radical surgery followed by radiation and/or chemotherapy is the standard of treatment. Upfront chemoradiation, usually recommended in patients with advanced disease, can have a significant response [160, 161].

13.3.4.2 Metastatic Adenocarcinoma to the Cervix

Secondary involvement of the uterine cervix by carcinoma is, in most instances, caused by an endometrial malignancy. Metastases from other genital organs and from extra-genital sites are, in comparison, quite uncommon [162]. The relatively small size of the cervix and its limited vasculature relative to the volume of stroma are possible explanations for the rarity of this scenario [163, 164]. Not surprisingly, misdiagnosis of a metastatic cervical lesion as primary endocervical adenocarcinoma occurs commonly (up to 42% of cases) [162].

Endometrial Adenocarcinoma

Involvement of cervical stroma by endometrial carcinoma is an important diagnosis, since it influences staging and subsequent patient management. Well-differentiated endometrioid carcinoma can mimic an HPV-related usual-type endocervical carcinoma; both are mucin-depleted and display glands with tall columnar to cuboidal cells (Fig. 13.19). Features that should raise the possibility of an endometrial primary are: round nuclei with less conspicuous pseudostratification and relative hypochromasia, squamous differentiation that appears bland morphologically, secretory differentiation and foamy histiocytes within the periglandular stroma. The presence of a precursor lesion is also a helpful clue in determining origin (AIS versus endometrioid intraepithelial neoplasia, especially in biopsy material). Microglandular hyperplasia can be cribriform, mimicking endometrioid carcinoma involving the cervix. Nonetheless, microglandular hyperplasia has a characteristic stratification pattern (with a layer of basal reserve cells underneath a layer of columnar mucinous to clear cells) and bland nuclear morphology. As discussed previously, a primary cervical endometrioid carcinoma is a rare but documented event, and should be considered if definitive endometrioid features are present in a background of cervical endometriosis.

Immunohistochemistry for ER, p16, vimentin, and mCEA is widely used to assist in the distinction between endometrioid endometrial carcinoma and HPV-related endocervical adenocarcinoma (either usual or mucinous type). The expected profile of HPV-related endocervical adenocarcinoma is p16 overexpressed (diffuse and strong, nuclear and cytoplasmic), ER negative, vimentin negative, and mCEA positive (membranous); the opposite profile is expected in endometrioid tumors: p16 negative or patchy, ER positive (any nuclear staining, typically diffuse—50% or more), vimentin positive (membranous), and mCEA negative [36, 165–167]. Nonetheless, as many as 50% of endocervical and 30% of endometrial carcinomas deviate from the expected profile at least in one marker [168]. It is important to note that high-grade endometrial carcinomas can have p16 over-

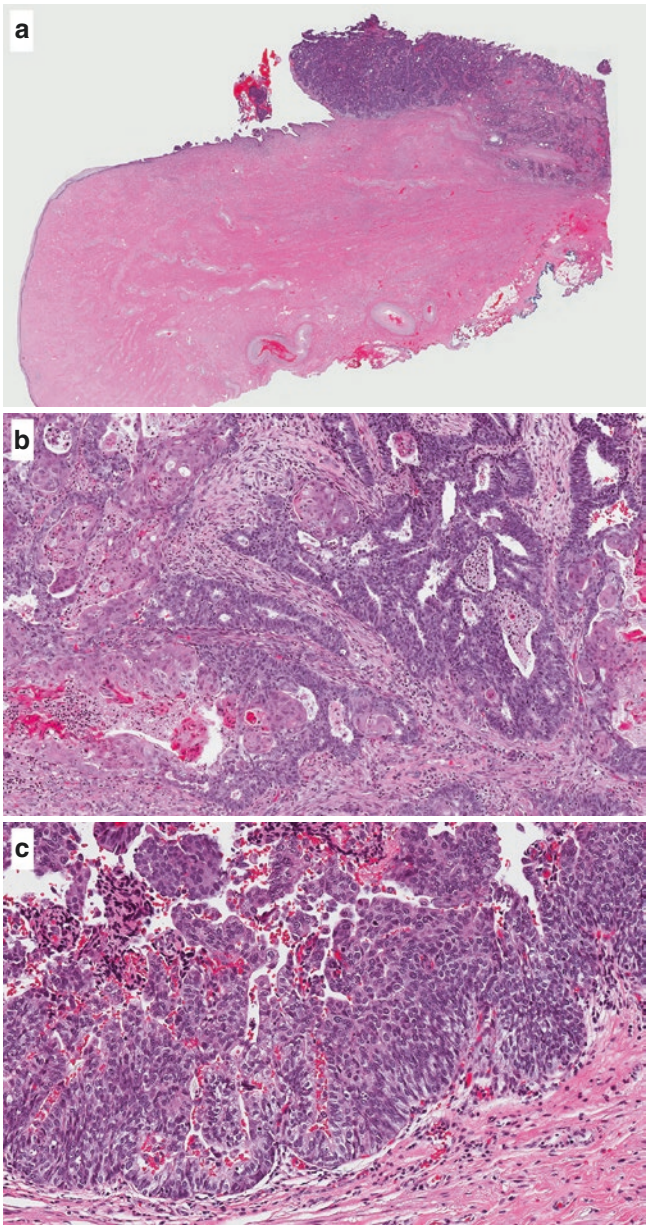

Fig. 13.19 Metastatic adenocarcinoma to the cervix. The most common carcinoma secondarily involving the cervix is endometrial, usually by direct extension from the corpus (**a**); classic endometrioid morphology is observed, including squamous differentiation (**b**). Urothelial carcinoma can spread to the cervix in a pagetoid fashion mimicking a primary cervical malignancy (**c**)

expression; HPV molecular studies can be used in this scenario.

Gastric Adenocarcinoma

Although gastric carcinoma metastatic to the cervix is rare, awareness of its occurrence is important since almost half of patients present without previous history of gastric cancer [94, 95] and the primary is discovered synchronously with the cervical lesion or after the possibility of metastases is raised by the pathologist [163]. Most metastatic tumors are poorly differentiated and have a signet-ring cell component. The following features should raise concern for secondary origin: poor differentiation, extensive lymphovascular space invasion, multifocality, and extension to other pelvic organs. When a tumor with signet-ring morphology is encountered, the possibility of a primary cervical signet-ring cell mucinous carcinoma should be considered and investigated with p16 staining and HPV molecular testing. Primary endocervical gastric-type adenocarcinoma can also mimic metastases, both histologically and immunophenotypically; sometimes, distinction cannot be made with certainty, and correlation with clinical and radiologic findings is required. Prognosis of patients with metastatic gastric carcinoma to the cervix is poor with rapid (<1 year) progression and death of disease.

Colorectal Adenocarcinoma

Patients are usually postmenopausal and present with abnormal bleeding; the cervical lesion can be the presenting sign [163, 169]. The clinical course is aggressive, with a median survival of 11 months (range 1–60) [169, 170]. As a diagnostic pitfall, the tumor frequently displays features mimicking a cervical or endometrial endometrioid carcinoma in surgical material. The tumor appearance ranges from well to poorly differentiated (some with signet-ring cell component); cells form pseudo-endometrioid glands with striking atypia and luminal necrosis. Wide infiltration into the cervical wall, prominent lymphatic vascular invasion and signet-ring morphology should raise concern for metastases. Markers of colorectal origin can be of value, particularly CK20 and SATB2 which are negative or patchy in primary cervical while diffusely positive in colorectal tumors. In addition, p16 and HPV testing can provide further evidence of cervical origin.

Urothelial Carcinoma

Spread of urothelial carcinoma to female reproductive organs is a very rare event [171–173]. The malignant process usually arises in the urinary bladder, and reaches the cervix in a pagetoid fashion either by direct intraepithelial spread or seeding; indeed, most lesions involving the cervix are in situ or only superficially invasive [171, 174]. Cervical involvement tends to manifest with bleeding or cytologic abnormalities, months to years after the diagnosis of urothelial carcinoma. However, cervical manifestations can be the presenting sign of malignancy. The prognosis is dictated by the stage and histologic grade of the primary urothelial malignancy [171].

The microscopic appearance is that of an intraepithelial proliferation with stratified transitional cytomorphology and papillary or flat architecture. Metastatic urothelial carcinoma to the cervix can closely resemble a primary cervical neoplasm, either in situ (AIS, squamous intraepithelial lesion) or invasive. This potential pitfall is particularly important in urothelial carcinomas with squamous or glandular differentiation [175, 176] (Fig. 13.19). By immunohistochemistry, urothelial carcinoma co-expresses CK7 and CK20 [177], which helps in its distinction from primary cervical lesions (CK20 negative). P16 may be of value, although it can also be overexpressed in high-grade urothelial carcinoma, and HPV testing should be considered since high-grade urothelial lesions are unrelated to HPV infection [178]. GATA3 is usually diffusely positive in urothelial lesions, and only focally positive in cervical squamous malignancies [179]. Nonetheless, it is important to note that urothelial carcinomas with squamous and / or glandular differentiation have lower rates of GATA3 expression [180, 181]. S-100 appears to have superior sensitivity in this group of urothelial carcinomas with variant morphology [181].

13.4 Mixed and Miscellaneous Cervical Neoplasms

13.4.1 Adenosquamous Carcinoma

13.4.1.1 Clinical Features

This type of mixed carcinoma represents ~4% of all cervical malignancies [182]. Age at presentation is similar to patients with squamous cell carcinoma, with a median of 46 years [182]. Most patients present with bleeding and/or cytologic abnormalities, and an exophytic or ulcerated lesion macroscopically.

13.4.1.2 Pathologic Features

By definition, adenosquamous carcinoma has areas of both *squamous* and *glandular* differentiation; the former tends to be poorly differentiated, but can be recognized by the presence of intercellular tight junctions and keratinization; the latter is seen as recognizable glands with lumen formation (Fig. 13.20). A clear cell variant has been described; the clear cell change involves the squamous component and is secondary to glycogenization [183].

13.4.1.3 Ancillary Studies

Adenosquamous carcinoma is related to high-risk HPV infection; HPV18 is the most common type identified, followed by HPV16 [184]. It is believed that adenosquamous cell carcinoma may represent a variant of cervical adenocar-

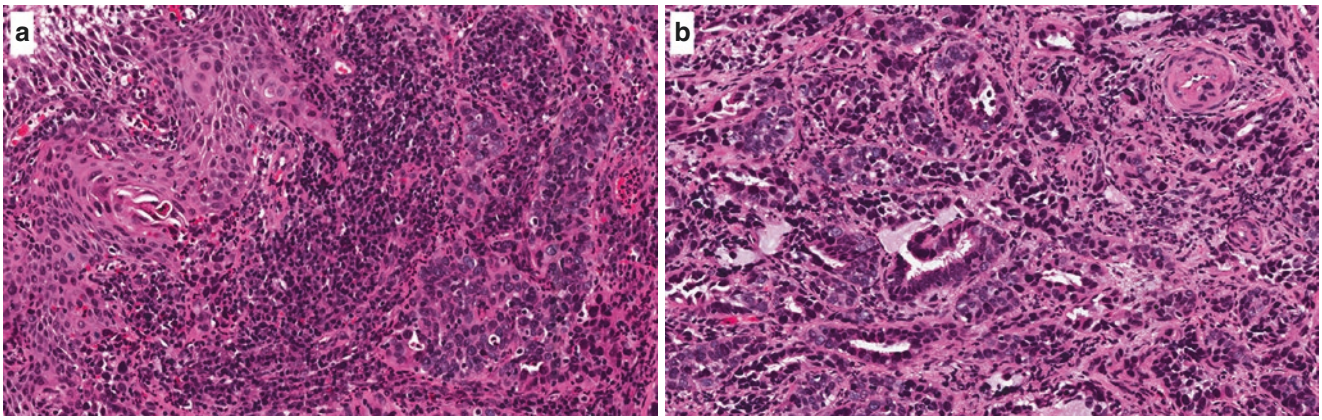

Fig. 13.20 Adenosquamous carcinoma. Unequivocal squamous (**a**) and glandular (**b**) differentiation is required for this diagnosis, the former tends to be poorly differentiated

cinoma. Interestingly, HPV and DNA clonality are identical in both squamous and glandular elements, suggesting biphasic differentiation of an HPV-infected common epithelial precursor [185]. This also correlates with the diffuse and strong p16 expression seen in both tumor components. Expression of squamous (p63, p40, CK5) and glandular (mucins) markers may vary, particularly in poorly differentiated lesions; moreover, they can highlight benign elements admixed with the tumor (areas of entrapped benign glands or squamous metaplasia) and caution in their interpretation is advised. Compared to squamous cell carcinoma, adenosquamous carcinoma shows absent to low ARID1A expression more frequently [186]. Expression of EGFR and PDGFRA is common; however, it does not correlate with *EGFR* and *PDGFRA* activating mutations [187].

13.4.1.4 Differential Diagnosis

The differential diagnosis of adenosquamous carcinoma includes: endometrioid adenocarcinoma with squamous differentiation (glandular component is low grade, squamous component lacks cytologic atypia and retains organization), invasive stratified mucin-producing carcinoma (absence of squamous differentiation), poorly differentiated squamous cell carcinoma (absence of glandular differentiation), adenoid basal carcinoma (basaloid component, squamous and glandular differentiation restricted to the center of the basaloid clusters, lack of desmoplasia or single-cell infiltration), and clear cell carcinoma (cytoplasmic clearing in glandular cells, absence of malignant squamous elements).

Prognosis and Management

Treatment usually involves chemoradiation. Patient outcome, in terms of overall and disease-free survival, is significantly worse in cases of adenosquamous carcinoma compared to squamous cell carcinoma regardless of stage [188–190]. When matched to those with pure endocervical adenocarcinoma, patients with advanced-stage disease adenosquamous carcinoma also have a worse prognosis [191, 192]. Early stage adenosquamous carcinoma, treated with radical surgery, is comparable to adenocarcinoma in terms of outcome [193].

13.4.1.5 13.4.1.1.Glassy Cell Carcinoma

Clinical Features

Glassy cell carcinoma, representing 0.2–9.3% of cervical cancers, is considered by some as a poorly differentiated variant of adenosquamous carcinoma [194]. It is seen in patients on average 10 years younger than those with cervical cancer [195].

Pathologic Features

Microscopically, tumor cells have sharp borders that stain with periodic acid-Schiff (PAS), large round nuclei with visible nucleoli, and eosinophilic cytoplasm with a "ground glass" appearance (hence the glassy cell denomination) (Fig. 13.21). There is no apparent squamous or glandular differentiation [196]. A brisk inflammatory eosinophilic infiltrate is characteristic. This morphology is usually diffuse; nonetheless, the presence of minor "glassy cell" features in otherwise conventional adenosquamous carcinomas and in poorly differentiated non-keratinizing carcinomas has been noted [197].

Ancillary Studies

By immunohistochemistry, glassy cell carcinoma expresses both squamous and glandular markers [198]. Estrogen and progesterone receptors are negative [199]. HPV types 18 and 16 have been demonstrated in both glassy cell carcinomas and adenosquamous carcinomas with focal glassy cell morphology [198, 200].

Differential Diagnosis

Glassy cell carcinoma is in essence a morphologic diagnosis. It can be distinguished from conventional squamous cell car-

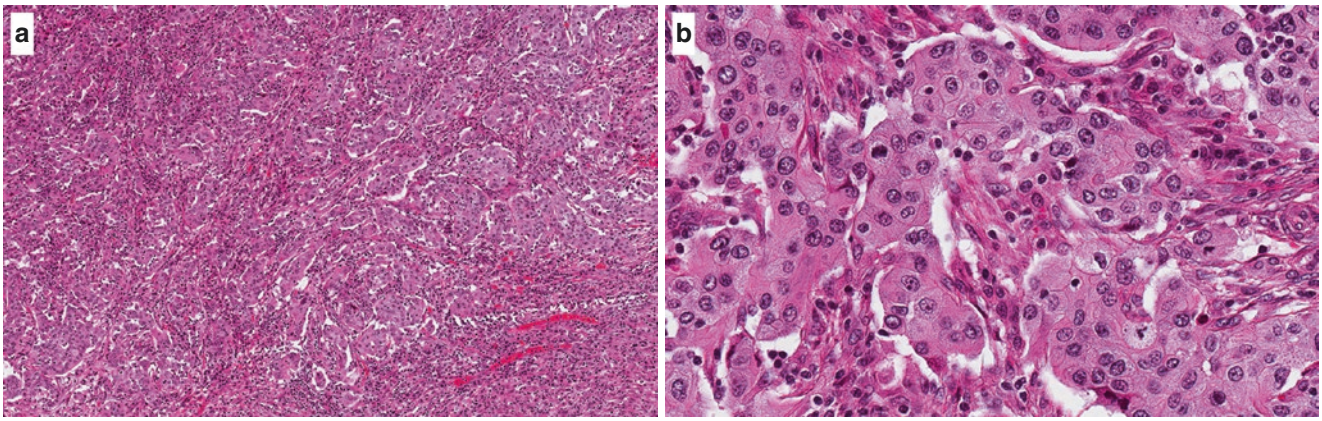

Fig. 13.21 Glassy cell carcinoma. This poorly differentiated tumor has a solid appearance (**a**) and contains pleomorphic cells with abundant polygonal "ground glass" cytoplasm (**b**)

cinoma and poorly differentiated adenocarcinoma by following strict morphologic criteria. An important differential is with epithelioid trophoblastic tumor, since both neoplasms have solid growth and contain cells with eosinophilic cytoplasm and round nuclei. The presence of a syncytial arrangement, abundant necrosis, lack of distinct cell borders, and strong GATA3 and cyclin E expression are features more in keeping with epithelioid trophoblastic tumor.

Prognosis and Management

Glassy cell carcinoma often has an aggressive clinical course with rapid progression and extrapelvic metastases [201]. Overall, 5-year survival is lower for glassy cell carcinoma compared to other cervical cancers (55% vs. 75%, respectively); survival is also poorer when adjusted for stage [194]. Systemic treatment is usually indicated.

13.4.1.6 Mucoepidermoid Carcinoma

This neoplasm is morphologically identical to its counterpart in the salivary glands and is defined by the presence of three cell types (epidermoid, intermediate, and mucin producing) [202]. These cells appear in varying proportions, organized in nests or solid sheets, rudimentary duct-like structures and cysts. Epidermoid cells display eosinophilic cytoplasm but lack keratinization and overt intercellular junctions, unlike adenosquamous carcinoma. Furthermore, mucinous cells are intermixed with other cell types with no definitive gland formation. Intermediate cells are usually the most prominent population; they have basaloid appearance and aggregate in clusters [202].

The main differential diagnosis is with conventional adenosquamous carcinoma. The diagnosis of cervical mucoepidermoid carcinoma should be contemplated only in cases with the classic microscopic appearance. Overt squamous or glandular differentiation and absence of an intermediate cell population are more in keeping with adenosquamous carcinoma. Since the morphologic appearance of mucoepidermoid carcinoma can be bland, it can be confused with a benign proliferation (squamous metaplasia, microglandular hyperplasia); mass forming or infiltrative growth, and haphazard organization of the diverse cell types should raise concern for malignancy rather than a benign process.

Although mucoepidermoid carcinoma falls into the spectrum of adenosquamous differentiation, there is evidence that it is a distinct biologic entity since it harbors recurrent abnormalities in the *CRTC1* and *MAML2* genes (fusion or rearrangements) similar to salivary gland mucoepidermoid carcinomas [202].

13.4.2 Adenoid Basal Cell Carcinoma (Epithelioma)

13.4.2.1 Clinical Features

This rare tumor, representing less than 1% of cervical cancers, is composed of nests of bland basaloid cells with variable glandular and squamous differentiation. Like tumors with adenoid cystic differentiation, adenoid basal lesions can be divided into two groups: pure adenoid basal tumors and mixed tumors, the latter having a second component, such as squamous cell carcinoma, adenoid cystic carcinoma small cell carcinoma or, rarely, carcinosarcoma [203, 204].

Adenoid basal carcinomas usually occur in postmenopausal women (median age 66 years, range 19–91) [203]. They are frequently associated with a high-grade squamous intraepithelial lesion (HSIL); in fact, most cases are discovered incidentally on LEEP or cone after a biopsy diagnosis of HSIL [205].

13.4.2.2 Pathologic Features

Histologically, adenoid basal carcinoma is composed of small round nests of basaloid cells with peripheral palisading. Although growth and distribution are haphazard, there is no stromal desmoplastic reaction. Towards the central/lumi-

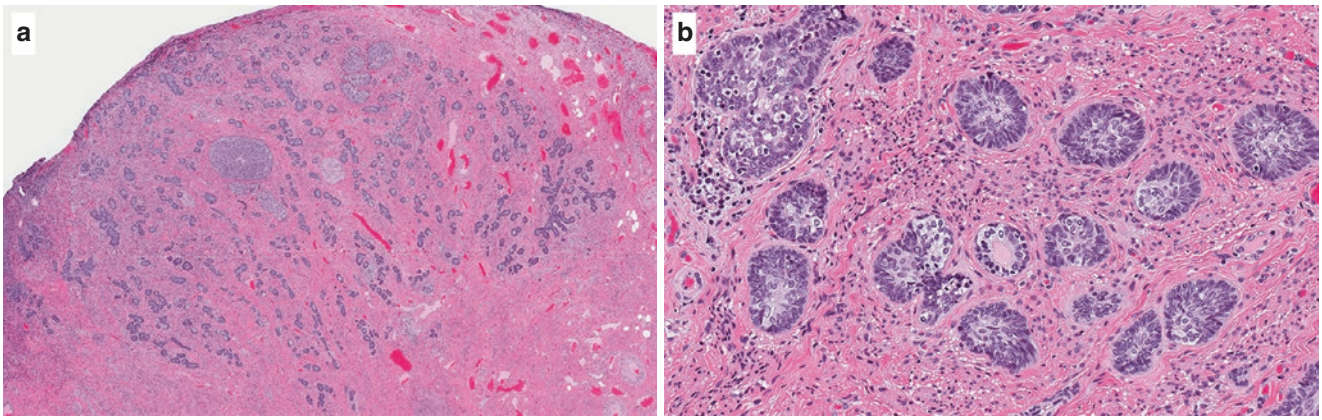

Fig. 13.22 Adenoid basal carcinoma. This basaloid proliferation is haphazardly distributed throughout the cervical stroma; however, there is no desmoplasia (**a**). Nests have smooth outer contours; they may have central squamous or glandular differentiation, however the periphery retains a basaloid appearance (**b**)

nal portion of the nests, squamous and glandular differentiation can be appreciated (Fig. 13.22). The tumor lacks lymphovascular and perineural invasion [206]. High-risk HPV is detected in the vast majority of lesions [203, 205].

13.4.2.3 Differential Diagnosis

The differential diagnosis includes adenoid cystic carcinoma, squamous cell carcinoma, and adenosquamous carcinoma, although it is important to bear in mind that these lesions can coexist. These malignancies tend to present clinically as a mass. In addition, identification of the distinct nested architecture and basaloid pattern with palisading in adenoid basal carcinoma suffices in most instances. Immunohistochemistry for CAM5.2 highlights the basaloid cell population in the periphery of the nests, and can be of value in distinguishing squamous cell carcinoma from adenoid basal carcinoma with extensive squamous metaplasia [207].

Adenoid basal hyperplasia, an allegedly related lesion, has been described as a superficial proliferation extending less than 1 mm from the superficial epithelial basement membrane at the level of the squamous–columnar junction [208]. Unlike adenoid basal carcinoma, HPV testing is negative in adenoid basal hyperplasia.

13.4.2.4 Prognosis and Management

Pure adenoid basal carcinoma has a benign behavior with no metastases, lymph node involvement, recurrences, or deaths reported to date [203]. Hence, the term "epithelioma" is favored by many authors over the term "carcinoma." Mixed lesions also have an excellent prognosis, likely because most are diagnosed and treated at an early stage. Nonetheless, the presence of a second malignant component may have an adverse prognostic impact. Thus, after a biopsy diagnosis of adenoid basal carcinoma, surgical excision with negative margins and evaluation of the entire tumor is warranted in order to exclude a second component.

Table 13.5 Classification of adenoid cystic carcinomas of the female lower genital tract

Taken from Xing et al. [205]	Pure adenoid cystic carcinoma	Mixed carcinoma with adenoid cystic differentiation
Patient age	Median 48 years, range 27–74	Median 76 years, range 50–86
Adenoid cystic component	100%	Usually <25%
High-risk HPV	Not detected	Detected (usually HPV16)
P16 immunohistochemistry	Non-diffuse	Diffuse and strong
Perineural invasion	~50%	Absent

13.4.3 Adenoid Cystic Carcinoma

13.4.3.1 Clinical Features

Tumors of the lower genital tract with adenoid cystic differentiation can be divided in two groups: pure adenoid cystic carcinomas and adenoid cystic carcinomas mixed with a second component, usually squamous cell carcinoma or adenoid basal carcinoma [209]. The main differences between these types are depicted in Table 13.5. Mixed tumors occur in older patients and are usually related to high-risk HPV infection; in these, the adenoid cystic component is usually minor and less than 50% of the tumor volume.

13.4.3.2 Pathologic Features

Adenoid cystic carcinoma of the uterine cervix displays the same morphologic features as its counterparts in the salivary gland, upper respiratory tract, breast, and vulva. The tumor is composed of basaloid cells arranged in cribriform, tubular, and solid growth patterns [210]. Tumors with cribriform architecture have cystic areas containing mucinous or eosinophilic secretions, alternating with pseudo-cystic areas

containing basement membrane-like material, positive for collagen type IV and PAS stain [210] (Fig. 13.23). Tumors with solid growth also have basement membrane-like material around tumor nests and cords [211].

13.4.3.3 Ancillary Studies

By immunohistochemistry, adenoid cystic carcinoma is negative for hormone receptors. In addition, MYB expression has been documented. This finding may be related to translocation of the *MYB* and/or *NFIB* transcription factors, which has been documented in adenoid cystic carcinomas of the salivary gland, breast and vulva [212].

13.4.3.4 Differential Diagnosis

The differential diagnosis of adenoid cystic carcinoma includes adenoid basal carcinoma and squamous cell carcinoma. Importantly, all these lesions can coexist. However, distinction between pure adenoid basal and adenoid cystic carcinoma is important, since the former has an indolent prognosis. Both have a basaloid phenotype including expression of basal and myoepithelial markers like S100 [210]. Nonetheless, the histopathology of adenoid cystic carcinoma is usually distinct, and the diagnosis can be ascertained on morphologic grounds in most cases. CD117 (C-KIT) may be of value; its expression is consistently negative in adenoid basal tumors, and appears to be at least focally positive in cervical adenoid cystic carcinoma [213, 214].

13.4.3.5 Prognosis and Management

After a biopsy diagnosis of adenoid cystic carcinoma, the possibility of a second component should be considered. Therefore, excisional sampling with LEEP or cone may be advisable. Initial series of adenoid cystic carcinoma report an aggressive behavior with recurrence or metastases in nearly half of cases at time of follow-up [215]. It remains unclear if prognosis differs between pure and mixed tumors.

13.4.4 Mixed Carcinoma

Truly "mixed" carcinomas of the uterine cervix are uncommon. The usual scenario is of an HPV-related adenocarcinoma with areas of neuroendocrine differentiation (Fig. 13.24). The latter is more commonly of the small cell type. The lesion tends to be large and efface the cervix at the time of presentation. The neuroendocrine component usually comprises the majority of the tumor volume. The prognosis is poor.

Primary carcinosarcoma of the cervix is exceedingly unusual. These lesions occur in a wide age range. They are related to HPV-infection, and frequently are associated with an in situ squamous component [204]. As in the uterine corpus, diagnosis of carcinosarcoma requires the presence of two distinct components: carcinomatous and sarcomatous. The former can be squamous cell, adenoid basal, adenoid cystic, undifferentiated carcinoma, or combinations thereof [204]; the latter is usually homologous. Stage is the most important prognostic factor. Treatment involves primary surgery followed by radiation and chemotherapy [216].

Other rare carcinoma combinations have been reported in the literature, including mesonephric plus neuroendocrine carcinoma [217], villoglandular adenocarcinoma plus transitional cell carcinoma [218, 219], and signet-ring cell adenocarcinoma plus glassy cell carcinoma [220].

13.5 Benign Endocervical Glandular Lesions

The following lesions are covered in this chapter as they usually pertain to the differential diagnosis of preinvasive and invasive endocervical glandular malignancy. Some of these proliferations are reactive in nature (tubo-endometrioid metaplasia); others likely represent embryologic remnants

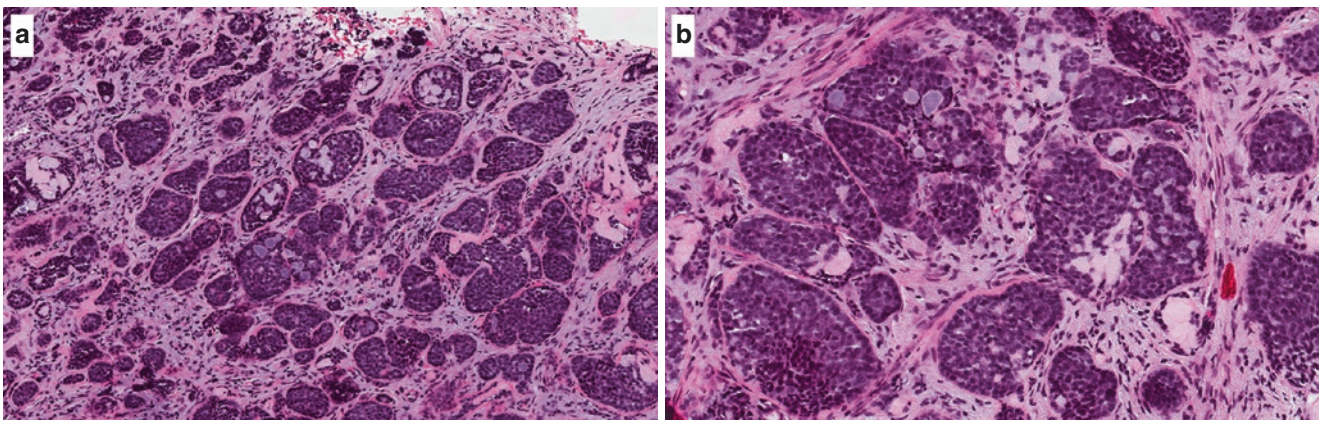

Fig. 13.23 Adenoid cystic carcinoma. Basaloid population with solid and cribriform architecture (**a**). Notice the presence of pseudo-lumens filled with basement membrane material (**b**)

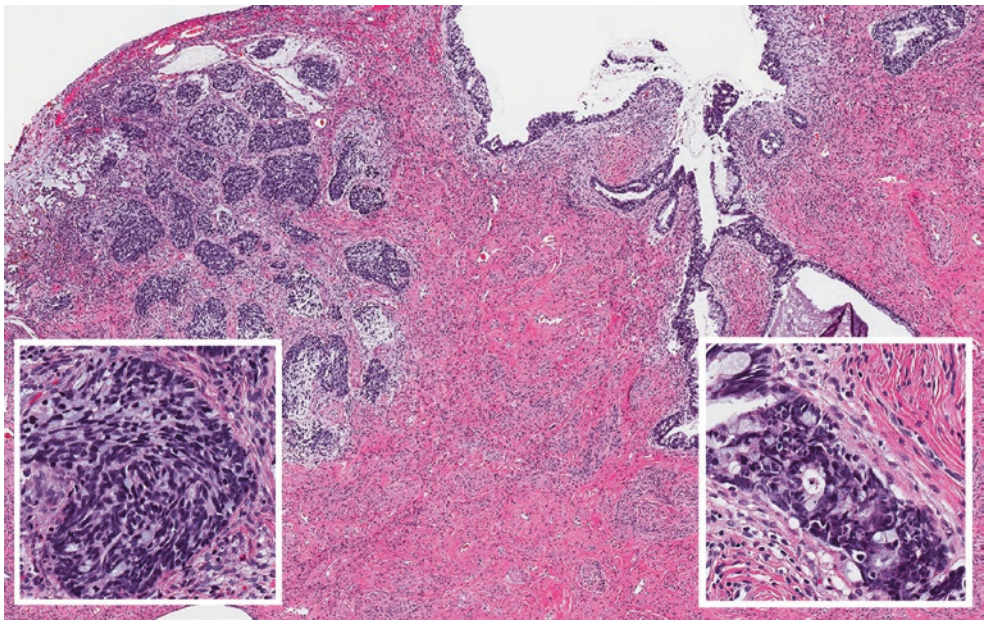

Fig. 13.24 Mixed carcinoma with a glandular (right insert) and neuroendocrine component (left insert); the latter was strongly positive for synaptophysin and chromogranin. The tumor was positive for high-risk HPV

(mesonephric remnants, prostatic tissue) or variations of the normal endocervix (tunnel clusters, nabothian cysts). Some can be secondary to the hormonal background (Arias-Stella reaction). Most are composed of Müllerian epithelium; however, other types of epithelial derivation (mesonephric, epidermal) can be observed.

13.5.1 Endocervical Polyp

13.5.1.1 Clinical Features

Polyps of the uterine cervix are very common, characteristically in adult women. Most cases present with a single polyp, usually are small (1 cm or less), variably located along the endocervical canal.

13.5.1.2 Pathologic Features

Microscopically, the endocervical polyp is defined by an exophytic mucosal lesion containing benign endocervical-type glands and a central / basal fibrovascular core (Fig. 13.25). Variable degrees of inflammation are present in the superficial stroma. Likewise, the overlying epithelium commonly displays reactive changes including squamous metaplasia, tubal metaplasia, or microglandular hyperplasia. Mucosal erosion and granulation tissue is usually a sign of mechanical irritation. Stromal cartilaginous and osseous metaplasia has been described [221]. Epidermoid cysts with keratinization and adnexal structures within an endocervical polyp have also been reported [222, 223].

13.5.1.3 Differential Diagnosis

The main differential of endocervical polyp is from Müllerian adenosarcoma. The glandular component of adenosarcoma usually has a distinct appearance with cystically dilated "rigid" (smooth, concave luminal contours) glands, as well as glands with narrowed lumens due to broad-base protrusions of the stroma, causing a characteristic "leaf-like" pattern. The glands in endocervical polyps show variation in size and shape: their outer contour tends to be festooning and variably convoluted instead of rigid, and glands also tend to retain their lumens. If present, stromal projections do not fully conform to the shape of the space and only fill it partially. The stromal component of the endocervical polyp is non-atypical and lacks the periglandular condensation seen in adenosarcoma; mitoses, if present, are occasional (one per 10 HPFs). Importantly, worrisome indicators for adenosarcoma (rigid glands, leaf-like architecture, periglandular condensation, stromal atypia, 2 or more mitoses/10 HPFs) can be seen *focally* in endocervical polyps. These lesions have been termed "polyps with unusual features", in view of their indolent behavior [224]. If any of these characteristics is present *diffusely* within the tumor, the diagnosis of adenosarcoma must be considered.

Endocervical polyp can also overlap morphologically with other benign conditions, such as endometrial polyp and polypoid endometriosis. In fact, some polyps arise in the upper endocervix/lower uterine segment mucosa, and have mixed endocervical and endometrial features. The term "Müllerian" polyp can be used in this instance. Lastly, the infoldings of the normal endocervical mucosa can appear polypoid in routine preparations from excised material (cone, hysterectomy). The diagnosis of endocervical polyp should be reserved for lesions with truly exophytic architecture and prominent fibro-vasculature stroma within its core.

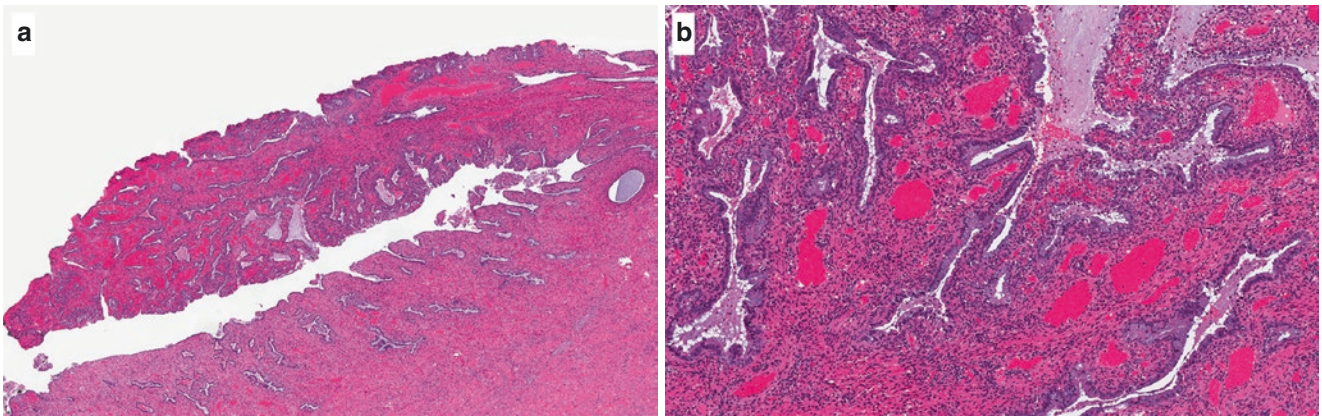

Fig. 13.25 Endocervical polyp. Exophytic proliferation of benign endocervical glands and stroma (**a**), harboring normal mucinous endocervical epithelium and dilated vessels (**b**)

13.5.1.4 Prognosis and Management

Endocervical polyps are indolent lesions; when encountered, simple excisional sampling is sufficient. While benign by definition, endocervical polyps can rarely harbor an intraepithelial lesion or malignancy [225, 226]. Premenopausal women appear to be at higher risk of developing epithelial lesions in a polyp compared to postmenopausal women [227, 228]. It is unclear whether intraepithelial lesions or carcinomas confined to an endocervical polyp carry the same prognosis as early stage cervical carcinoma involving the normal (non-polypoid) cervix. Likewise, sometimes a preexisting endocervical polyp is involved by endometrial carcinoma, which for now should be best interpreted as cervical involvement for staging purposes, even if the rest of the cervix is uninvolved. Whether this situation is clinically different from other forms of cervical involvement is yet to be determined.

13.5.2 Müllerian Papilloma

This very rare lesion typically arises in the posterior vagina or cervix of girls under 10 years of age [229]. Given its exophytic appearance and age distribution, there is commonly clinical concern for botryoid rhabdomyosarcoma. However, the arborizing glandular epithelial morphology of müllerian papilloma makes the distinction straightforward. The lesion is unifocal and small (<2 cm). It is composed of finely branched papillare lined by simple epithelium, typically columnar although a squamous component can be seen [230]. There is no cytologic atypia, stratification, or mitoses. The lesion is benign and local excision is the treatment of choice [231]. Occasional recurrences have been reported [232].

13.5.3 Nabothian Cysts

13.5.3.1 Clinical Features

Nabothian cysts are more prevalent in multiparous women. They are presumably secondary to obstruction of the communication of a cervical crypt with the surface and subsequent cystic enlargement, likely during / after pregnancy. While most are superficial, less than 10 mm in size and asymptomatic, some may acquire significant sizes and involve the deep aspect of the cervical wall. These large cysts may cause a variety of symptoms, ranging from bleeding and discomfort to prolapse, labor passage obstruction, and hematometra [233–235].

13.5.3.2 Pathologic Features

Nabothian cysts are visible grossly as unilocular lesions with thick mucinous to gelatinous material and a smooth lining. Histologically, the cyst is round with concave luminal contours and is lined by a simple layer of columnar to flattened bland mucinous epithelium, cytologically identical to the background normal glands (Fig. 13.26). The surrounding stroma is indistinct from the remaining cervical wall.

13.5.3.3 Differential Diagnosis

Nabothian cysts must be distinguished from minimal deviation adenocarcinoma, particularly when symptomatic, causing cervical enlargement or involving the deep cervix [236, 237]. Minimal deviation adenocarcinoma usually presents as multiple cystic lesions, distorting the cervix but otherwise benign-appearing, both clinically and on pathologic examination. Indicators of minimal deviation adenocarcinoma include: haphazard distribution of cystically dilated glands, usually with accompanying non-cystic glands; different mucin profile compared to the normal cervix, with a paler to vaguely eosinophilic appearance and red staining in PAS-Alcian blue preparations (normal endocervical mucin stains dark blue), nuclear enlargement and atypia, usually very focal and loss of PAX2 expression [118].

13.5.4 Tunnel Clusters

13.5.4.1 Clinical Features

Tunnel clusters are rounded, densely packed aggregates of glands in the endocervical wall. They are vastly more com-

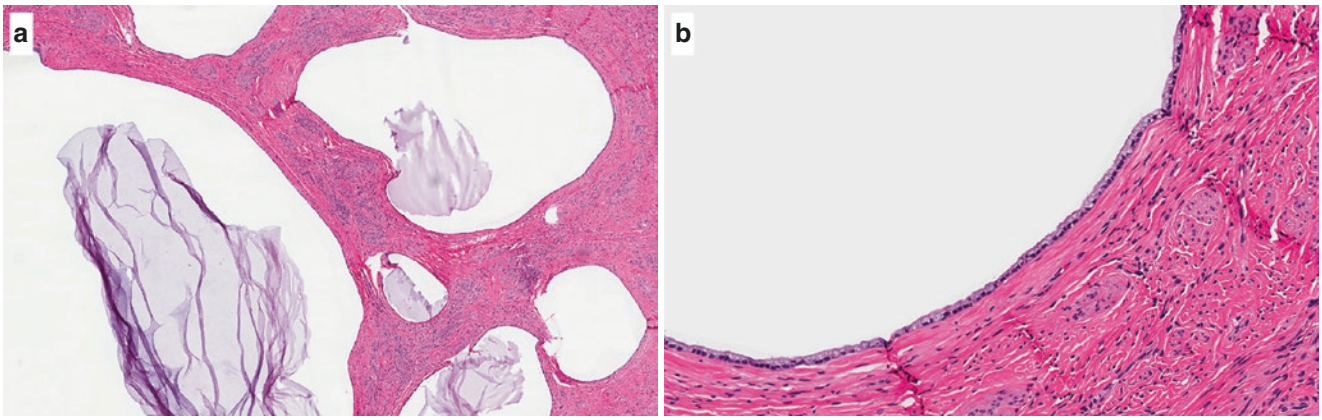

Fig. 13.26 Nabothian cysts. Cystically dilated endocervix, sometimes producing a grossly visible lesion (**a**); cysts are lined by flattened but otherwise unremarkable endocervical epithelium (**b**)

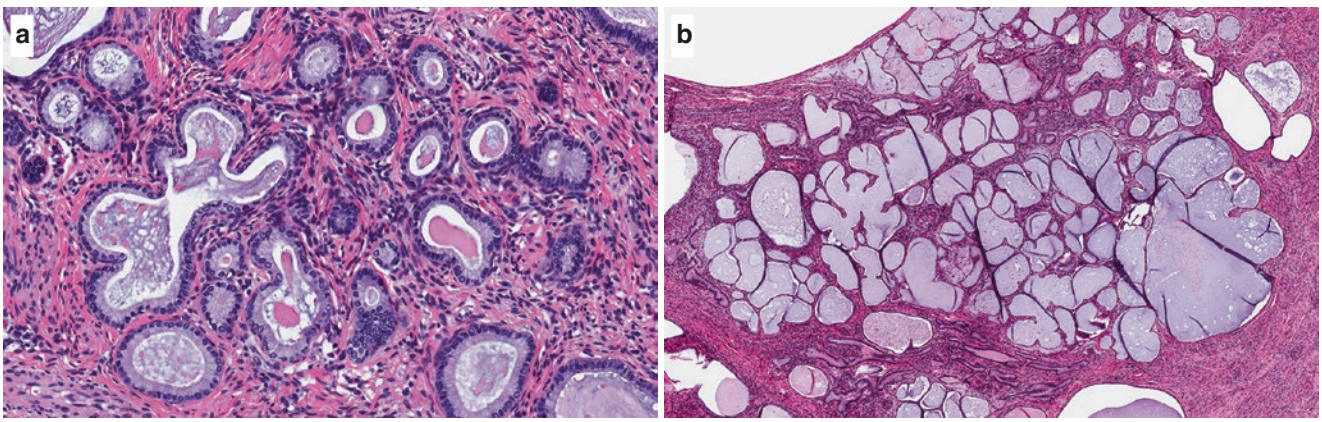

Fig. 13.27 Tunnel clusters. Type-A tunnel clusters appear as well-contoured tight glandular conglomerates (**a**). Type-B tunnel clusters have the same crowded density and smooth contour appearance, but glands have cystic dilation (**b**)

mon in multiparous women. They can present with mucoid discharge, but are usually asymptomatic and only incidentally noted on excision material.

13.5.4.2 Pathologic Features

Tunnel clusters are divided into type-A (non-cystic) and type-B (cystic) [238]. The former are comprised of small glands arranged around a central cleft in a lobulated pattern, all with undulated contours and lined by simple low cuboidal mucinous epithelium [239]. A subset of type-A tunnel clusters has been shown to express gastric (neutral) mucins, and thus thought to belong to the spectrum of endocervical gastric metaplasia [47]. Type-B tunnel clusters tend to be multifocal and, given their larger size, may cause distortion of the mucosa [240]. They are composed of round and dilated glandular structures, also arranged in a tightly packed lobular arrangement which distinguishes them from the normal endocervix (Fig. 13.27).

13.5.4.3 Differential Diagnosis

Similar to nabothian cysts, the differential of tunnel clusters includes endocervical adenocarcinoma, importantly of the gastric (minimal deviation) type. A superficial location, organized lobular architecture and lack of nuclear atypia and proliferation are indicative of tunnel clusters.

13.5.5 Diffuse Laminar Endocervical Hyperplasia

This highly uncommon type of endocervical glandular proliferation is seen as densely packed glands and clefts, concentrated in the superficial mucosal aspect in a band-like fashion and sharply separated from the underlying stroma [241, 242]. Lining epithelium has an endocervical mucinous profile (Fig. 13.28). Due to striking glandular crowding and variable mucosal thickening, diffuse laminar endocervical hyperplasia can be mistaken for malignancy, either endocervical (minimal deviation adenocarcinoma) or endometrial endometrioid. This pitfall applies in particular to biopsy material [243]. Attention to the normal endocervical mucinous profile will aid in identifying this benign process. In excision material, the diagnosis of diffuse laminar endocervical hyperplasia is easier to ascertain based on the superficial location of the glands, its sharp demarcation from the underlying stroma and the absence of significant atypia.

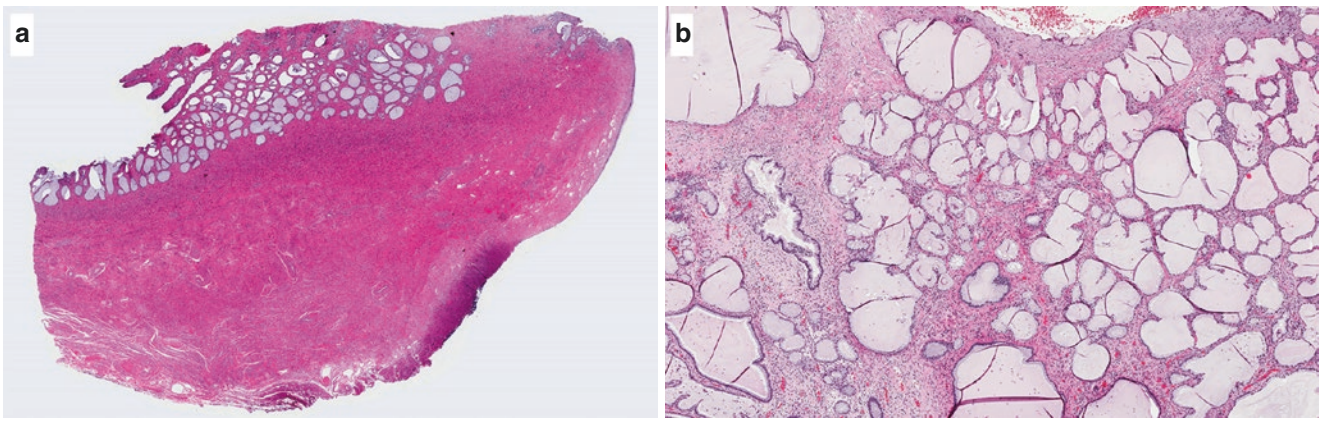

Fig. 13.28 Diffuse laminar endocervical hyperplasia. Increase in glandular density uniformly and diffusely involving the mucosa (**a**), comprised of densely packed glands of varying sizes and shapes (**b**)

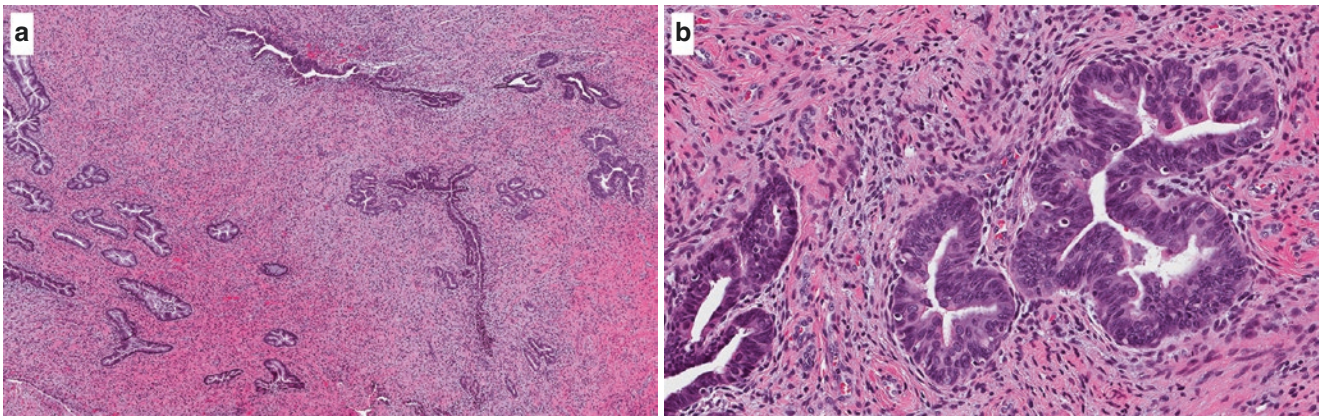

Fig. 13.29 Tubo-endometrioid metaplasia. Glandular proliferation associated with reactive ("pseudo-desmoplastic") stroma in a patient with previous cervical conization (**a**). The proliferation is composed of glands with tubal and endometrioid differentiation and bland morphology (**b**)

13.5.6 Tubo-Endometrioid Metaplasia

13.5.6.1 Clinical Features

Tubo-endometrioid metaplasia (TEM) can pose diagnostic difficulty, since it has some morphologic overlap with endocervical adenocarcinoma of the usual type. TEM is a frequent finding, incidental in most cases: it is seen in 21% cone biopsies and 62% of hysterectomy specimens [244]. An association with previous cone procedure has been reported [245].

13.5.6.2 Pathologic Features

TEM is characterized by columnar glandular epithelium with elongated, cigar-shaped nuclei and uniform cytoplasm with scant to absent cytoplasmic mucin (Fig. 13.29). These features recapitulate the appearance of inactive or proliferative phase endometrium. Tubal differentiation is evident in the form of ciliated cells interspersed with non-ciliated and peg cells. Mitotic activity can be observed, but is usually scant. Involved glands have similar size and distribution to the normal endocervix, usually confined to the superficial layer; however, deep cervical involvement has been reported [246]. The stroma around the glands can be hypercellular, edematous, or myxoid, mimicking desmoplastic reaction [246].

13.5.6.3 Differential Diagnosis

TEM can mimic endocervical adenocarcinoma in situ of the usual (endocervical) type, either in situ or invasive. Both entities depict "mucin-depleted" cells, variable proliferation, and may display reactive stroma. Unlike TEM, endocervical adenocarcinoma has enlarged hyperchromatic nuclei with irregular chromatin distribution, prominent pseudostratification and loss of polarity. Moreover, apical mitoses are usually brisk in adenocarcinoma, and occasional in TEM. In difficult cases, immunohistochemistry is useful. Usual-type endocervical adenocarcinoma is typically positive for p16 overexpression and negative for estrogen receptor and vimentin; BCL-2 is either negative of patchy. The opposite profile is characteristic of TEM (negative or patchy p16,

estrogen receptor and vimentin positive, diffuse BCL-2 expression) [118, 247–249].

13.5.7 Endometriosis

13.5.7.1 Clinical Features

Endometriosis, although a very common affliction, rarely occurs in the cervix, representing only 0.2% of all endometriosis cases in a recent single-institution series [250]. History of previous vaginal pregnancy and/or curettage is seen in most, but not all patients [250, 251]. While many cases are only identified incidentally on pathologic examination, about half present with symptoms (bleeding, pain). Some patients present with atypical glandular cells in screening cytology [252]. Given its rarity, this diagnosis is usually unsuspected clinically.

13.5.7.2 Pathologic Features

The histologic appearance of endometriosis is similar to other sites, harboring endometrial-type glands, stroma, and frequent evidence of hemorrhage (hemosiderin-laden macrophages, Fig. 13.30). Tubal differentiation may also be seen. The lesion is usually located in the mucosal surface [253], but can be present anywhere in the cervical stroma or the paracervical soft tissue.

13.5.7.3 Differential Diagnosis

While there is morphologic overlap between tubo-endometrioid metaplasia and endometriosis, the former lacks the dense endometrial-type stroma of the latter. More importantly, endometriosis can mimic endocervical adenocarcinoma, especially if the endometrial glands display proliferative characteristics (mitoses, elongated and pseudostratified nuclei) and when it infiltrates deeply into the wall [253]. Attention to the presence of endometrial-type stroma and hemosiderin-laden macrophages is very important. Negative / patchy p16 and positive hormone receptors by immunohistochemistry are also in keeping with endometriosis.

13.5.7.4 Prognosis and Management

Instances of microscopic endometrioid and clear cell adenocarcinoma arising in cervical endometriosis have been reported [125, 254]; nonetheless, this appears to be an exceedingly rare phenomenon, as previously discussed (see "endometrioid carcinoma"). Simple excision appears to be sufficient for superficial lesions, with nil recurrence rates reported [250]. On occasion, endometriosis is extensive (deep infiltrating endometriosis) requiring radical excision (trachelectomy, hysterectomy) and close surveillance [255, 256].

13.5.8 Endocervicosis

13.5.8.1 Clinical Features

This rare phenomenon is more frequent in the bladder [257]; however, it can also occur in other pelvic tissues including the anterior outer cervical wall and paracervical soft tissue [258, 259]. It is thought to be a form of Müllerianosis. A role for Cesarean section has been implied in its pathogenesis, which suggests mechanical displacement of endocervical cells and implantation into the outer cervical wall [260].

13.5.8.2 Pathologic Features

The lesion can be grossly visible, measuring up to 3 cm. Endocervicosis is a benign mucinous glandular proliferation, haphazardly oriented within the connective tissue but not infiltrative. Stromal reaction can be seen if there is mucin extravasation [258]. Glandular elements are lined by bland and non-proliferative endocervical-type mucinous epithelium (Fig. 13.31). Expression of estrogen and progesterone receptors has been reported [260].

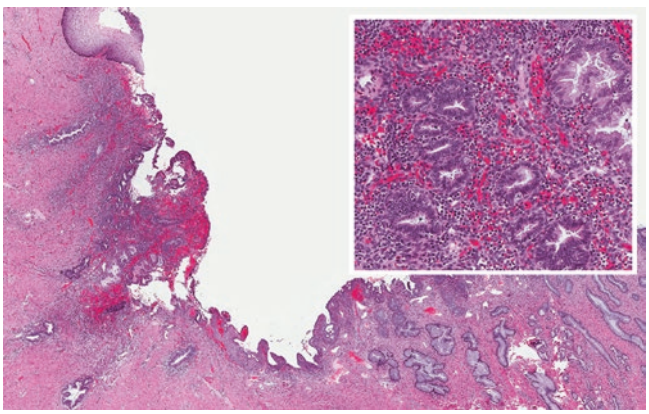

Fig. 13.30 Endometriosis. This lesion is seated in the squamous-columnar junction and depicts endometrial-type glands and stroma (insert)

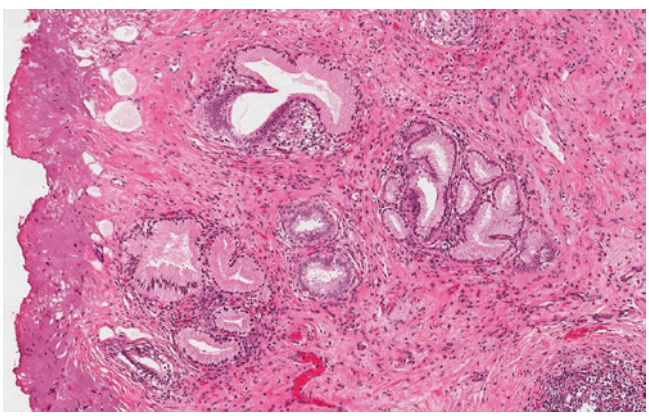

Fig. 13.31 Endocervicosis. This benign proliferation, resembling endocervical epithelium, was identified in the bladder wall

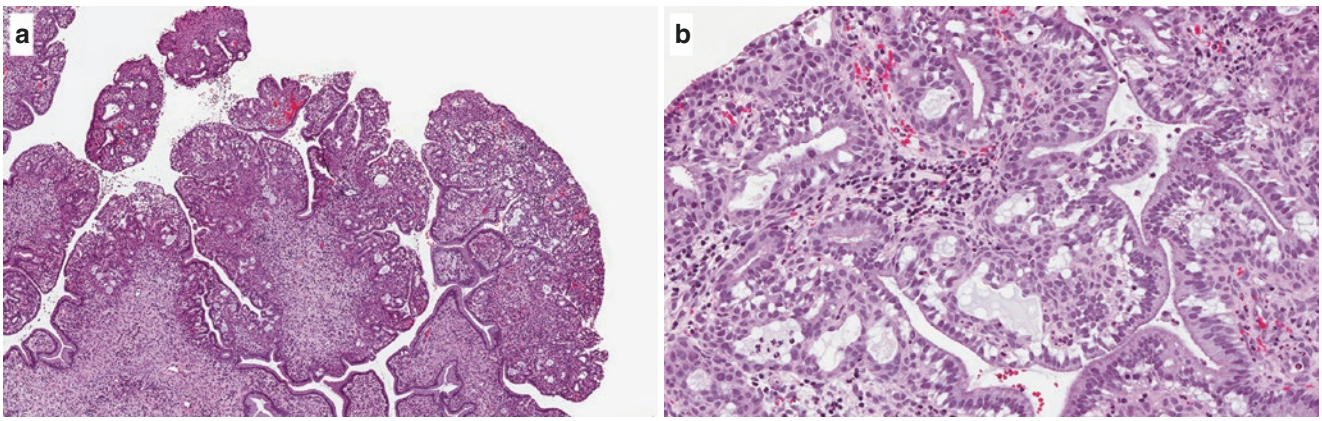

Fig. 13.32 Microglandular hyperplasia (MGH). This change is seen as an area of epithelial crowding, usually in the mucosal surface (**a**). The intraglandular cribriforming and glandular confluence may raise concern for malignancy, particularly endometrioid carcinoma; the presence of a basal (reserve) cell layer is typical of MGH and excludes an endometrial endometrioid neoplasm (**b**)

13.5.8.3 Differential Diagnosis

When encountered, the diagnosis of endocervicosis requires exclusion of adenocarcinoma, especially the minimal deviation type. Endocervicosis is typically confined to the outer cervical wall and paracervical soft tissue, and the stroma between it and the endocervical mucosa is spared. In contrast, a malignant process would feature transmural involvement. The mucin profile of endocervicosis is identical to the native endocervix, which, with a trained eye, can be distinguished from the gastric-type mucinous appearance of minimal deviation adenocarcinoma. Lastly, hormone receptor immunohistochemistry can also be of aid.

13.5.8.4 Prognosis and Management

Endocervicosis is a benign condition with no recurrences reported following surgical excision. Cases of malignant transformation into mucinous adenocarcinoma have been described in extra-cervical locations [261, 262].

13.5.9 Microglandular Hyperplasia

13.5.9.1 Clinical Features

Initial descriptions of this phenomenon attributed it to oral contraceptive use and other hormonal imbalances [263, 264]. However, a subsequent study by *Greeley et al.* showed no association between microglandular hyperplasia (MGH) and exogenous hormonal therapy or pregnancy [265]. Indeed, this lesion is commonly encountered in patients with no history of oral contraceptive use. Inflammation is usually present, suggesting that MGH can be reparative or metaplastic in nature.

13.5.9.2 Pathologic Features

MGH usually does not have a macroscopic correlate; however, it is sometimes identified as areas of erosion or polypoid friable tissue. Microscopically, it is defined as a superficial benign proliferation of endocervical glands with significant crowding and confluent appearance, which imparts a characteristic microacinar and cribriform architecture. The population is bland, composed of uniform columnar or cuboidal glandular cells with vacuolization, usually admixed with a prominent reserve cell layer and immature metaplastic squamous epithelium towards the epithelial base (Fig. 13.32).

13.5.9.3 Differential Diagnosis

The chief differential diagnosis of MGH is adenocarcinoma of endocervical and endometrial origin. The bland cytomorphology of MGH contrasts with the variable but consistent nuclear atypia is seen in most endocervical adenocarcinoma types. Given its striking mixture of complex architecture with bland cytology, MGH can resemble endometrial carcinoma. This is an important differential, especially when endometrial carcinoma displays mucinous differentiation or a microglandular growth pattern, which has been described [266, 267]. Features in keeping with MGH include: uniform subnuclear vacuolization, reserve cell hyperplasia and squamous metaplasia of *basal location* (versus the *superficial / luminal* squamous differentiation in endometrial carcinoma) and absence of foamy macrophages in the stroma [268]. Mitotic activity in MGH is usually less than 3 per 10 HPFs, but it has been recently reported as high as 11 mitoses per 10 HPFs [269]. MGH is diffusely positive for estrogen receptor; conversely, progesterone receptor tends to be negative [268, 270]. Vimentin and p16 are negative in MGH, which aids in its distinction from endometrial and HPV-related endocervical adenocarcinoma, respectively [268, 271].

13.5.10 Arias-Stella Reaction

13.5.10.1 Clinical Features

Arias-Stella reaction is a characteristic change of the endocervical and endometrial glandular epithelium secondary to high circulating progesterone levels. Thus, it is typically seen during/

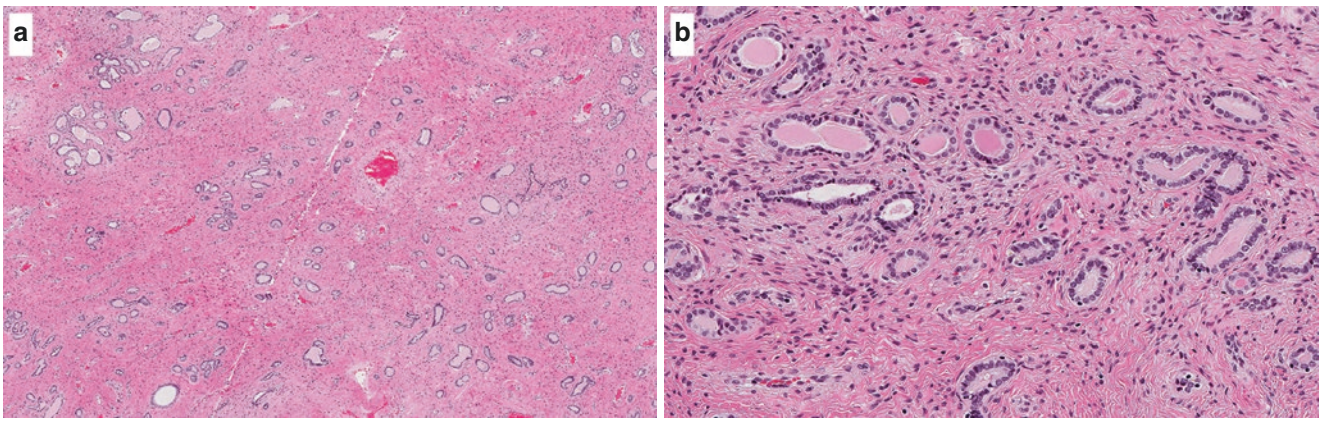

Fig. 13.33 Mesonephric hyperplasia. This lesion can be superficial or deep; glands are haphazardly distributed and display variation of size and shape (**a**). They are lined by flat to cuboidal epithelium without tubal or mucinous differentiation; lumens typically contain eosinophilic material (**b**)

shortly after pregnancy and in patients on exogenous progestin treatment or contraceptive use [272]. Arias-Stella reaction is commonly incidental, but can present as a polyp or a "lesion" detected on gynecologic exam [272]. It usually affects the upper endocervical canal, and it can be multifocal [273].

13.5.10.2 Pathologic Features

On histologic examination, Arias-Stella reaction is characterized by tortuous, "hypersecretory" glands with festooning or ruffled luminal borders, sometimes quite florid with papillary or cribriform patterns. Epithelial cells are large and tall with abundant clear (secretory) cytoplasm and markedly enlarged nuclei. The latter are usually hyperchromatic and irregular in shape, and can protrude towards the lumen ("hobnail" appearance). Mitotic activity is absent to scant.

13.5.10.3 Differential Diagnosis

The striking nuclear features of Arias-Stella commonly raise concern for clear cell carcinoma. This type of malignancy typically has high-grade pleomorphic cells with high nuclear-to-cytoplasmic ratio; conversely, the nuclear-to-cytoplasmic ratio in Arias-Stella reaction remains low (since cytoplasm is abundant) and there is no mitotic activity. P53 can be of aid, since it can be abnormal in clear cell carcinoma [274]. Napsin-A is frequently present in Arias-Stella reaction, limiting the role of this marker in the above differential [141]. Likewise, glands displaying Arias-Stella reaction may have low to absent expression of hormone receptors, limiting their value in separating it from endocervical adenocarcinoma [274, 275].

13.5.11 Mesonephric Remnants and Mesonephric Hyperplasia

13.5.11.1 Clinical Features

Remnants of the mesonephric duct are commonly seen in resection specimens, particularly in the cervical stroma and in the adnexal (paratubal) region. In the cervix, they are most commonly seen in cone and LEEP excisions [143].

13.5.11.2 Pathologic Features

Mesonephric duct remnants appear as groups of round glands and tubules, lined by simple flat to low cuboidal epithelium. The glandular lumen is usually filled with a dense eosinophilic PAS positive, diastase resistant material [143]. Mucinous or ciliated cells are not identified (Fig. 13.33). Hyperplasia of mesonephric ducts is characterized by a glandular population similar to mesonephric remnants, but larger, more irregular and haphazardly distributed [143]. It has been described in a number of architectural patterns, most frequently lobular but also ductal and diffuse. While most cases of mesonephric hyperplasia are incidental, some can be grossly identified as areas of induration or nodularity. They can be as large as 2.5 cm and extend to the deep cervical stroma.

13.5.11.3 Differential Diagnosis

The main differential diagnosis of mesonephric hyperplasia includes mesonephric carcinoma and endocervical adenocarcinoma. Unlike mesonephric hyperplasia, carcinoma produces mass-related symptoms. While the contour of mesonephric hyperplasia can be irregular, a frankly infiltrative border should raise concern for malignancy. Mesonephric carcinoma typically displays marked cytologic atypia, solid and confluent growth, mitotic activity and lymphatic vascular invasion. Endocervical adenocarcinoma typically displays mucinous differentiation at least focally, and lacks the eosinophilic secretions characteristic of mesonephric glands.

Mesonephric hyperplasia can overlap morphologically with tunnel clusters and lobular endocervical glandular hyperplasia. The presence of intra and extracellular mucin in these two entities should be indicative of the correct diagnosis. The distinction between mesonephric remnants and hyperplasia is not only subjective but also inconsequential, since both entities are benign.

13.5.11.4 Prognosis and Management

Mesonephric hyperplasia is regarded as a benign lesion, with no documented progression to malignancy following initial diagnosis [276]. Nonetheless, mesonephric hyperplasia has been found in the vicinity of most mesonephric carcinomas suggesting a potential role as a precursor lesion [144].

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