Precursor Lesions of the Cervix: Glandular Precursor Lesions

6

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6.1 Intraepithelial Glandular Neoplasm

6.1.1 Synonyms

Endocervical adenocarcinoma in situ (AIS, ACIS); high-grade cervical glandular intraepithelial neoplasia (CGIN).

6.1.2 Etiology

There are two broad types of AIS: HPV-associated AIS, which is common, and HPV-independent AIS, which is very, very rare. At least 90% of HPV-associated AIS cases harbor high-risk HPV, particularly HPV 18 and, less commonly, HPV 16. HPV-independent AIS usually demonstrates gastric pyloric-like differentiation and may be found within or alongside lobular endocervical glandular hyperplasia. Lobular endocervical glandular hyperplasia has been reported to harbor mutations in *STK11*, *GNAS*, and *KRAS*, similar to gastric-type adenocarcinoma.

6.1.3 General Features

Although AIS is not uncommonly encountered in general practice settings, high-grade squamous intraepithelial lesion (HSIL) is far more common. Historical data suggest that only 1–2% of high-grade cervical intraepithelial lesions are HPV-associated AIS. The median age of affected patients is 35 years, possibly younger than patients with HSIL. Most affected patients are identified

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by cytologic screening and, increasingly, by HPV testing. Pap tests are not thought to be as reliable in detecting AIS as for HSIL, and a final diagnosis of AIS is significantly less frequent than invasive adenocarcinoma. There is thought to be a lag time of about 10 years between the development of AIS and invasive adenocarcinoma. Patients only very uncommonly present with symptoms such as vaginal bleeding.

HPV-independent AIS is a very rare entity about which little is known. The median age is 71 years (range, 25–73 years). Neither Pap nor HPV testing was designed to detect this lesion, so these are significantly lacking in sensitivity.

6.1.4 Macroscopy

AIS is most commonly seen in the transformation zone, but it may also be present higher in the endocervical canal. Instead of frequently exhibiting aceto-white lesions and a mosaic pattern at colposcopy, AIS may appear as thickened epithelium and irregular crypts.

6.1.5 General Comments

Adenocarcinoma in situ (AIS) is present in an intraepithelial distribution, usually within glands that aggregate adjacent to endocervical crypts, lining the crypt surfaces or the endocervical canal. There should be no evidence of invasion, such as irregular contours with a stromal reaction or expansion into stroma in a distribution that is incompatible with normal endocervical architecture. Although it has been reported that AIS is frequently multifocal, there is also evidence that most of the apparently multifocal lesions connect to each other. Most lesions are well demarcated from adjacent, non-neoplastic endocervical epithelium. HSIL is frequently found in association with AIS. Rarely, AIS colonizes the lower uterine segment and even less commonly involves endometrium, fallopian tubes, and ovaries, usually by direct extension or exfoliation with implantation in adnexal tissues.

6.1.6 Cytology

In Pap smears, HPV-associated AIS exhibits highly cellular sheets and clusters with microacini/rosettes, nuclear feathering, and palisading. The frequently pseudostratified and sometimes pleomorphic nuclei are hyperchromatic and coarsely granular, usually without nucleoli. In liquid-based preparations, the crowded cellular aggregates have a three-dimensional quality and nuclei that have more open chromatin when compared with smears, and more easily appreciable nucleoli.

6.2 HPV-Associated AIS

At low-power magnification, HPV-associated AIS usually appears to be a blue and densely cellular lesion lacking stromal invasion, as noted above. The typical lesion contains cells with pseudostratified, oval, or cigar-shaped, hyperchromatic and enlarged nuclei with evident mitotic activity (luminal) and apoptosis (basal).

AIS containing columnar cells whose cytoplasm resembles that of non-neoplastic endocervix has been designated "endocervical-type," whereas those lacking easily discernible cytoplasmic mucin used to be termed "endometrioid-type." The distinction between these two types is now considered unnecessary and possibly misleading, because the "endometrioid-type" cases have no virologic, immunophenotypic, or genomic similarity to endometrioid carcinomas of endometrium. Together, these AIS patterns can be referred to as "usual-type" or "usual."

Other variants, probably better described as "patterns," are intestinal, early/superficial, stratified mucin-producing intraepithelial lesion (SMILE), and papillary. These patterns have some features that differ from usual AIS:

- *Intestinal-pattern AIS* differs from usual AIS by virtue of goblet cells and, sometimes, argyrophilic granules. Such cases may not display significant nuclear enlargement or pseudostratification.
- *Early/superficial AIS* is AIS confined to the endocervical canal or superficial crypts, with variable attenuation of pseudostratification, nuclear enlargement, and mitotic activity.
- *SMILE* frequently gives the appearance of HSIL involving endocervical glands at low-power magnification. At higher power, the lesion features stratified (as opposed to pseudostratified) mucin-containing cells, usually with the full range of cytologic abnormalities seen in usual AIS. Some pathologists use the term "adenosquamous carcinoma in situ" instead of SMILE.
- The *papillary pattern* exhibits short exophytic papillae in a limited distribution with cells resembling usual AIS. Its distinction from villoglandular-pattern HPV-associated adenocarcinoma is discussed later in this chapter.

Despite these differences, apical mitoses and apoptosis should still be apparent, at least focally, to confidently diagnosis variant-pattern AIS without ancillary studies. Combinations of usual and variant-pattern AIS are frequently encountered, and all patterns may be subsumed under the term "HPV-associated adenocarcinoma in situ." Detailing the pattern is optional, but it is not recommended to use the term "endometrioid."

6.2.1 Immunohistochemistry and In Situ Hybridization

Almost every case shows a block-like (every cell) staining pattern with p16 and a positive reaction for HR-HPV RNA with in situ hybridization (ISH). ER/PR and PAX2 are usually negative or focal, and Ki-67 labeling is increased. These findings all contrast with those encountered in non-neoplastic endocervix. AIS is PAX8-positive.

Diagnostic Highlights

- Non-invasive endocervical glandular neoplasm with easily identified mitotic figures and apoptosis.
- Several histologic variants exist: intestinal-type (can be CK20-positive); early/superficial type; SMILE (stratified mucin-producing intraepithelial lesion); papillary.
- CK7, PAX8 and HR-HPV ISH positive. Block-like (aberrant) p16 labeling.

6.2.2 Differential Diagnosis

- *Non-neoplastic atypia*. This atypia can be attributed to repair/reactive changes, radiation, tuboendometrioid metaplasia, endometriosis and Arias-Stella reaction, each of which is discussed in separate chapters. With the exception of repair/reactive changes, the remaining entities are either mitotically inactive or contain only occasional mitotic figures, a contrast with AIS. Furthermore, none of these lesions shows block-like (every cell) staining with p16 or positive signals for HR-HPV RNA using ISH. See Chap. 3 for further details.
- *Atypia of uncertain etiology*. There may still be uncertainty about the nature of an endocervical glandular lesion once entities showing non-neoplastic atypia are excluded. It is recommended to use extensive sampling (including deeper sections) and p16 and/or HR-HPV ISH with Ki-67 as ancillary tests. Block-like (every cell) staining with p16, a positive reaction using ISH, and increased proliferation with Ki-67 confirm AIS given glandular morphology with atypical features. It may still be impossible to confidently distinguish between neoplastic and non-neoplastic endocervix, particularly when the lesion is tiny. This diagnostic uncertainty should be conveyed in the surgical pathology report. In the past, the term "endocervical glandular dysplasia" was used for this "grey-zone" category. This terminology has now been abandoned, as HPV and proliferation can only be recognized in a subset of so-called "dysplastic" lesions. Furthermore, a biologically distinctive lesion that is an intermediary between normal and AIS has not been described. In extremely rare situations, the lesion in question may be AIS that is HPV-independent (see Sect. 6.3 below). See Chap. 3 for further details.
- *HSIL within endocervical glands*. This differential diagnosis really pertains only to SMILE. As both SMILE and HSIL are HPV-associated lesions, p16, HR-HPV ISH, and Ki-67 are not discriminatory. Rather, the constituent cells of SMILE contain cytoplasmic mucin with minimal p63/p40 labeling, in contrast to HSIL.
- *HPV-independent AIS*. This neoplasm usually lacks block-like, every-cell p16 labeling and, by definition, should lack HR-HPV RNA. The proliferative rate is only moderately elevated, compared with the background, and mutation-type p53 staining may be present, helping to exclude HPV-associated AIS.
- *Invasive adenocarcinoma*. Examples showing irregular contours with a stromal reaction at the periphery should be considered invasive. Note that some examples of AIS have an associated brisk lymphoplasmacytic infiltrate, which is not necessarily a sign of invasion. Expansion into stroma in a distribution that is incompatible with normal endocervical architecture can be found in examples of endocervical adenocarcinoma with a non-destructive invasion pattern, also known as Silva pattern A (discussed in Chap. 8). When there is uncertainty regarding the presence of non-destructive invasion, it is acceptable to report "superficial invasion cannot be excluded," provided that the lesion is no more than 3 mm thick and no lymphovascular invasion is present.
- *"Villoglandular" adenocarcinoma*. This differential diagnosis refers only to AIS lesions with an exophytic papillary pattern. A diagnosis of "villoglandular" adenocarcinoma, usually made only in a resection (cold knife cone biopsy, trachelectomy or hysterectomy), rests on the presence of exophytic, slender, finger-like papillae lined by cells that are identical to those found in AIS. Therefore, the distinction between AIS with papillary architecture and "villoglandular" adenocarcinoma is subjective. A reasonable guideline that is more objective is to only diagnose papillary AIS when the lesion is not clinically apparent or mass-forming and the papillae are short and limited in distribution.
- *Secondary adenocarcinoma with an intraepithelial distribution* is uncommon and most or all cases arise in the uterine corpus or adnexa. A lesion resembling intraepithelial high-grade serous carcinoma in the cervix should be evaluated for mutation-type p53 labeling, as this would be unexpected in HPV-associated AIS; caution is advised with the use of p16 in this context because both high-grade serous carcinoma and AIS would show block-like, every-cell staining. Confirmation of serous carcinoma in the cervix indicates that it is a secondary lesion since primary cervical serous carcinomas are either extraordinarily rare or nonexistent. Another example of a secondary intraepithelial neoplastic glandular lesion is atypical endometrial hyperplasia (AH), present in the lower uterine segment where it interdigitates with the upper endocervix. AH does not feature cells with highly atypical nuclei, a high mitotic index, or abundant apoptosis. This lesion should be contiguous with the corpus, ER/PR-positive, and negative for block-like p16 staining and HR-HPV RNA by ISH.

6.2.3 Cases

1. A 35-year-old woman presented to her gynecologist for Pap testing (Figs. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6).
2. A 45-year-old woman presented with vaginal bleeding. She underwent endometrial curettage (Figs. 6.7, 6.8, 6.9, 6.10, 6.11, 6.12, 6.13, 6.14, 6.15, 6.16).
3. A 28-year-old patient with a Pap interpreted as atypical glandular cells (Figs. 6.17 and 6.18).
4. A 40-year-old woman underwent a cervical biopsy at colposcopy after atypical glandular cells were reported on a Pap smear (Figs. 6.19 and 6.20).
5. A 41-year-old woman undergoes a routine Pap test and then endocervical curettage and cone biopsy (Figs. 6.21, 6.22, 6.23, 6.24, 6.25).
6. A 38-year-old woman with a cervical biopsy interpreted as HSIL involving endocervical glands (Figs. 6.26, 6.27, 6.28).

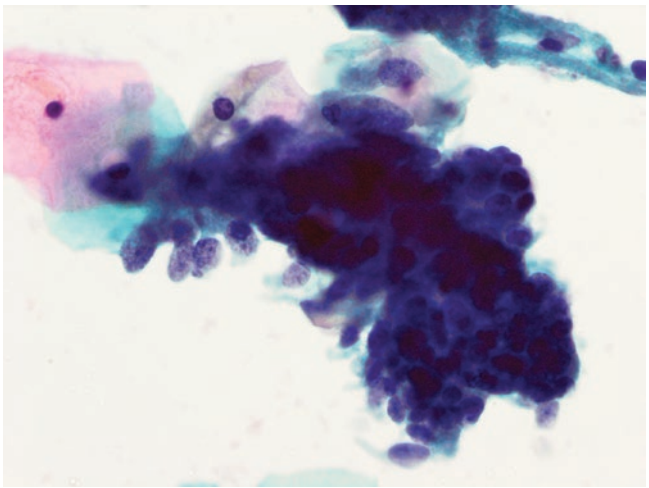

Fig. 6.1 HPV-associated adenocarcinoma in situ (AIS) in a Pap smear: Three-dimensional cluster with peripheral nuclear feathering

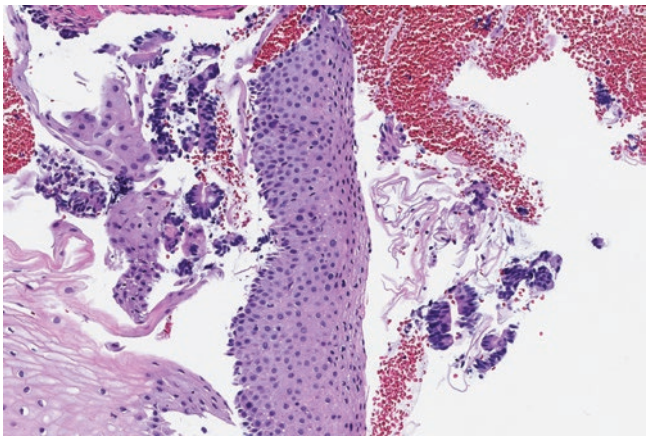

Fig. 6.3 AIS and high-grade squamous intraepithelial lesion (HSIL) in endocervical curettage: A strip of HSIL (center) with tiny clusters of darkly stained cells consistent with AIS

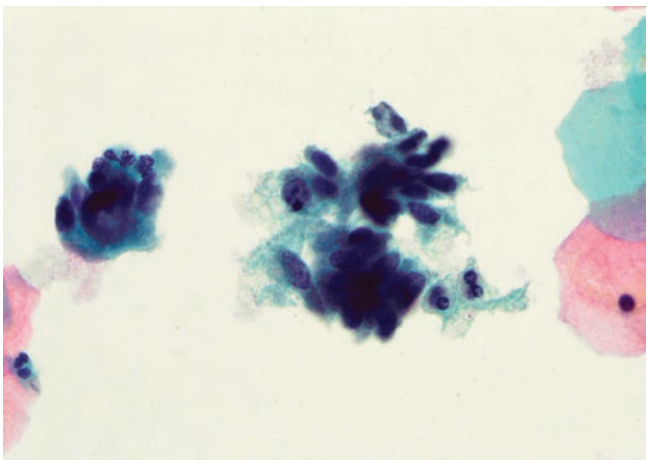

Fig. 6.2 AIS in Pap smear: Small clusters of darkly stained nuclei. The patient underwent colposcopy and endocervical curettage

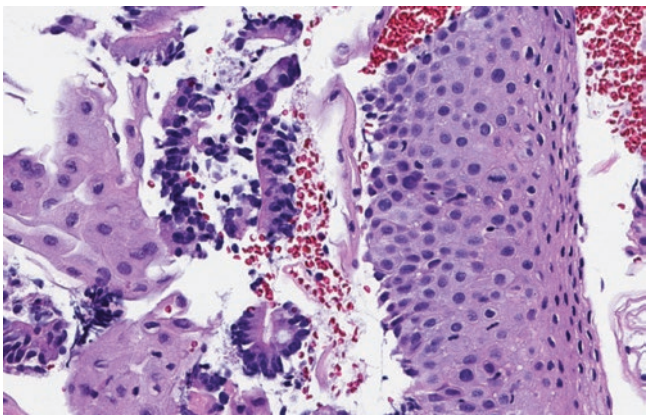

Fig. 6.4 AIS and HSIL in endocervical curettage: Largely mucin-depleted fragments of endocervical glandular tissue with high nuclear:cytoplasmic (N:C) ratios, darkly stained nuclei, and a goblet cell. The patient then underwent cold knife cone biopsy

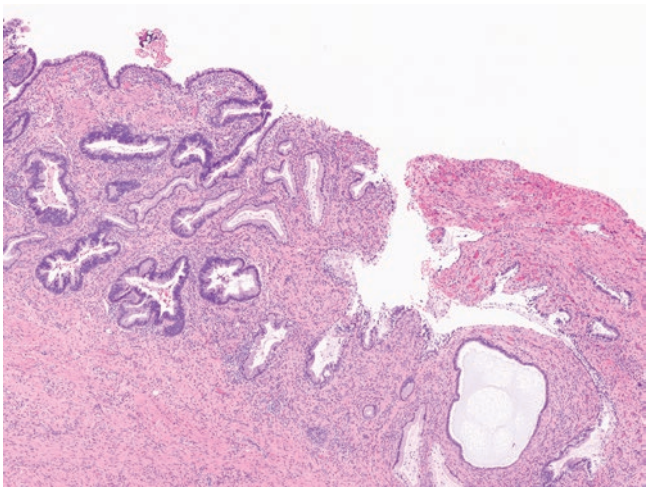

Fig. 6.5 AIS in cone biopsy: AIS (upper left) has a low-power profile demonstrating that the distribution of AIS largely conforms to that of normal endocervical glands. No invasion is identified

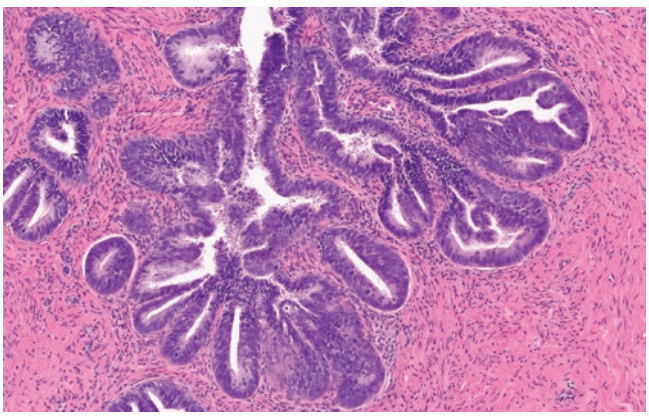

Fig. 6.6 AIS, high-power magnification: AIS is composed of aggregated, non-invasive glands showing mucin depletion, pseudostratified and darkly stained nuclei, with conspicuous apical ("floating") mitoses and subtle karyorrhectic debris/apoptosis. Mucin-depleted AIS is no longer considered "endometrioid."

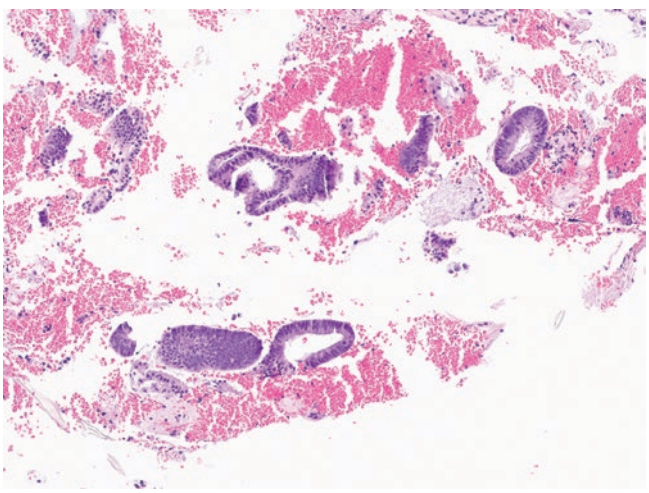

Fig. 6.7 AIS in endometrial curetting: The differential diagnosis included proliferative endometrium and AIS

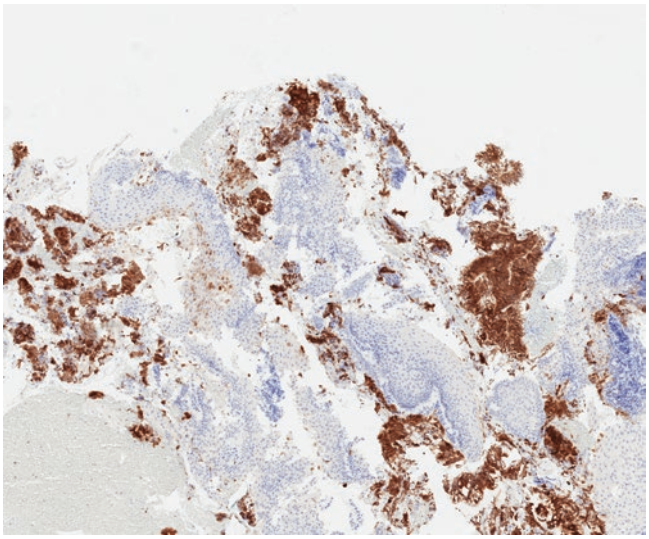

Fig. 6.8 Use of p16 immunohistochemistry on the endometrial curetting in the same patient as Fig. 6.7 showed diffuse staining of dispersed tissue fragments, supporting a diagnosis of AIS instead of proliferative endometrium. The patient underwent cold knife cone biopsy

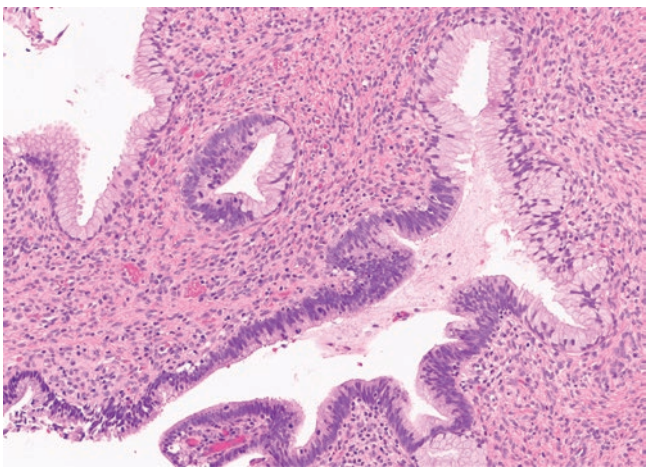

Fig. 6.9 High-power magnification shows AIS partly involving an endocervical gland. AIS is mucin-depleted, with pseudostratified, darkly stained nuclei with apical mitoses and basal karyorrhectic debris/apoptosis

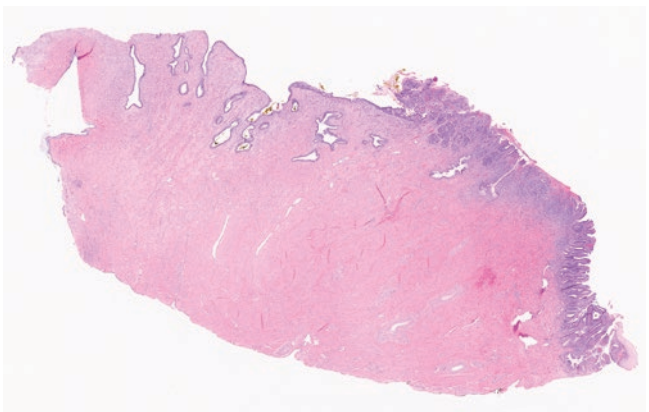

Fig. 6.10 AIS in cone biopsy with a positive margin

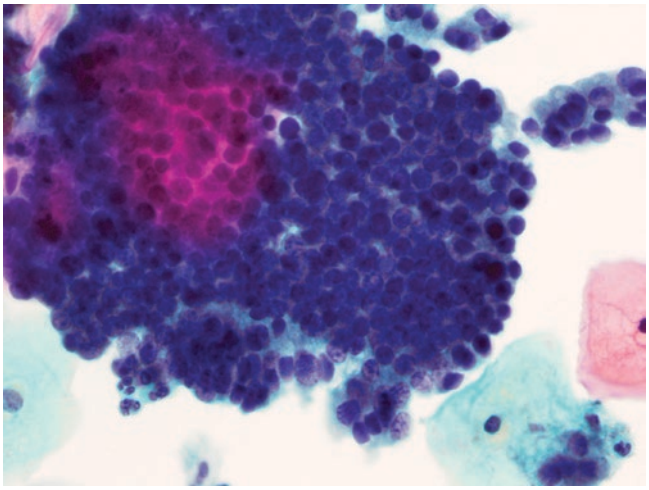

Fig. 6.11 AIS in Pap test following cone biopsy: Three-dimensional cluster with darkly stained nuclei and increased N:C ratios. Mucin-depleted AIS is no longer considered "endometrioid." The patient did not desire further pregnancies and opted for simple hysterectomy rather than repeat cone biopsy

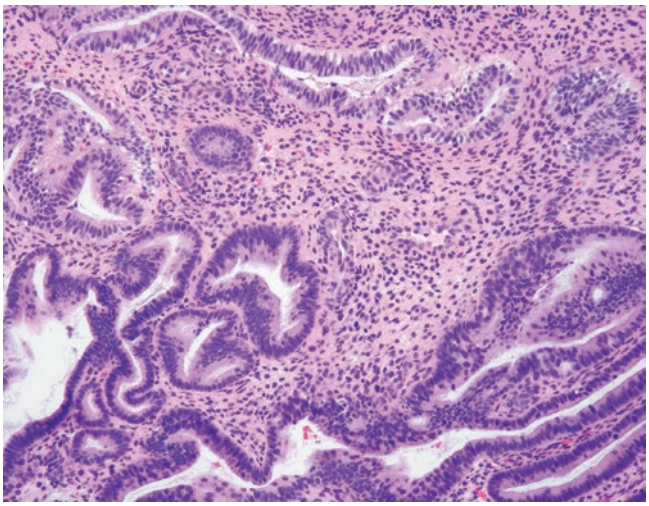

Fig. 6.12 AIS, though uncommon, can grow superficially to invlove the endometrium even there is no obvious destructive invasion in the primary tumor.

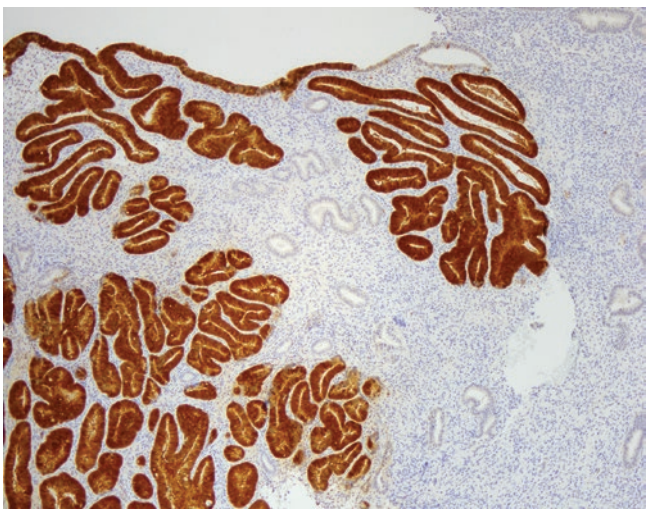

Fig. 6.13 AIS in endometrium: Block-like every-cell staining with p16

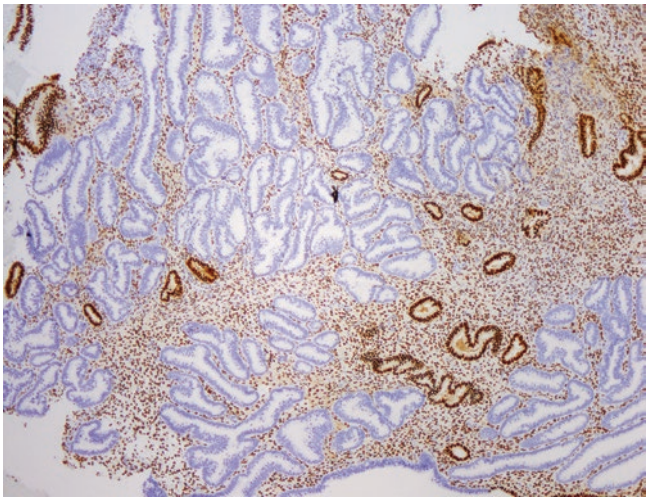

Fig. 6.14 AIS in endometrium: Progesterone receptor (PR) negative

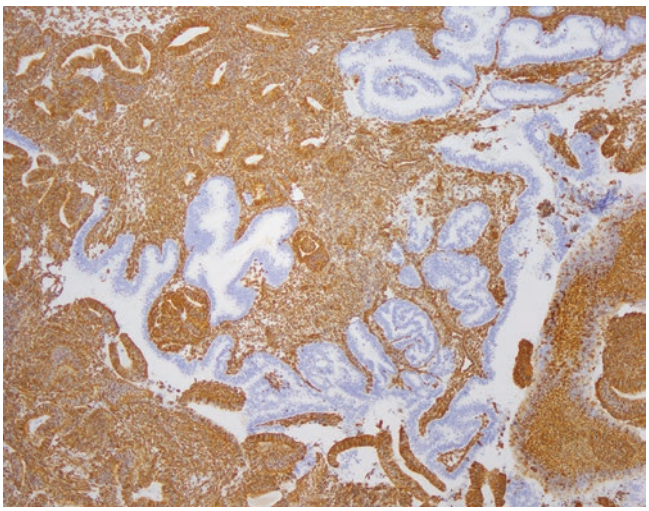

Fig. 6.15 AIS in endometrium: Vimentin negative

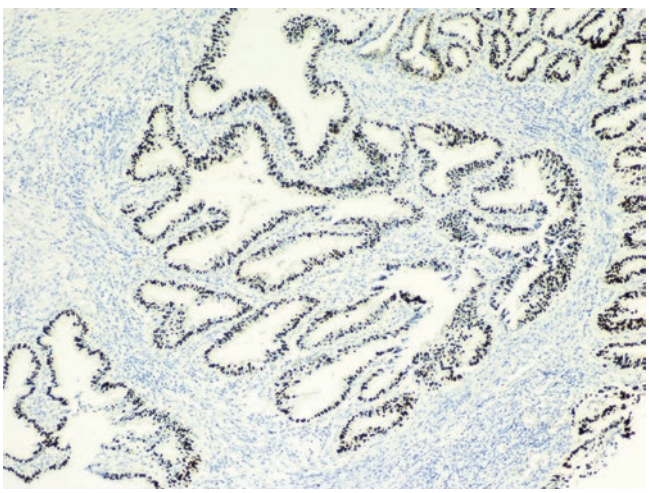

Fig. 6.16 AIS in endometrium: HR-HPV positive by in situ hybridization (ISH)

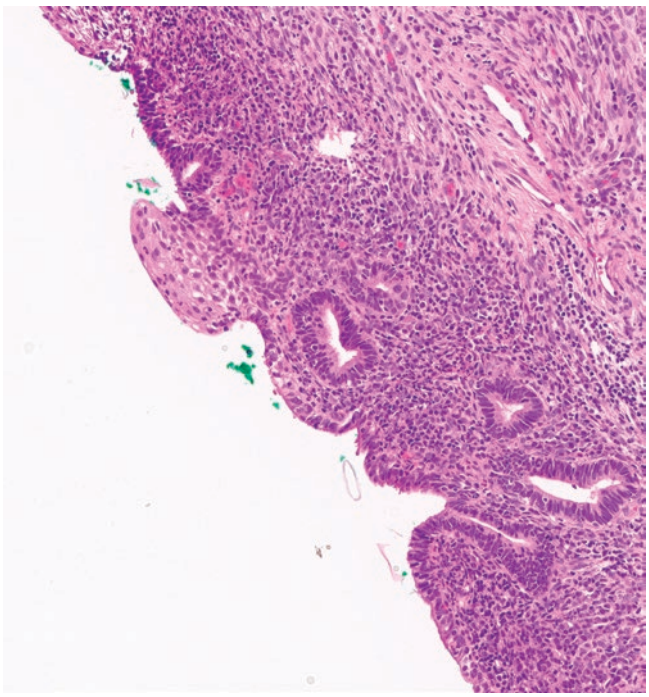

Fig. 6.17 Early/superficial AIS: The lesion is focal and limited to superficial crypts and surface epithelium

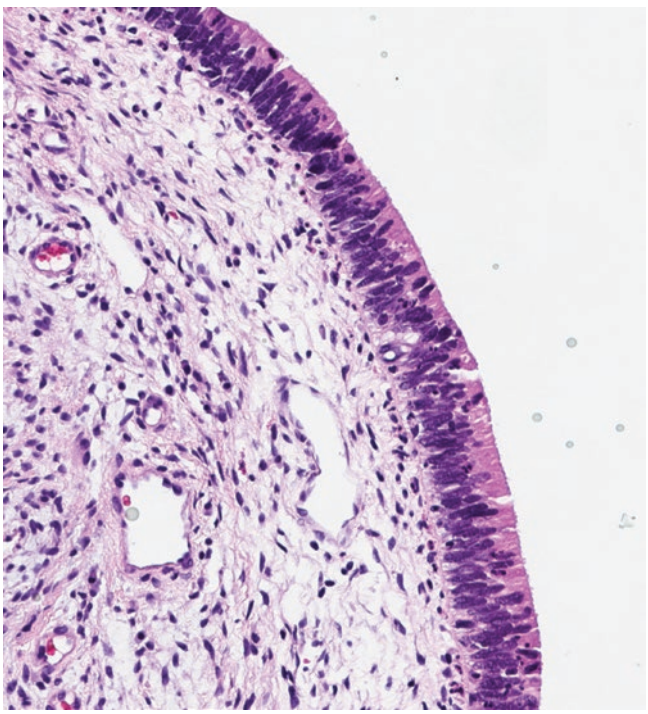

Fig. 6.18 Early/superficial AIS: The lesion is mucin-depleted, with pseudostratified nuclei, apical mitoses, and apoptosis

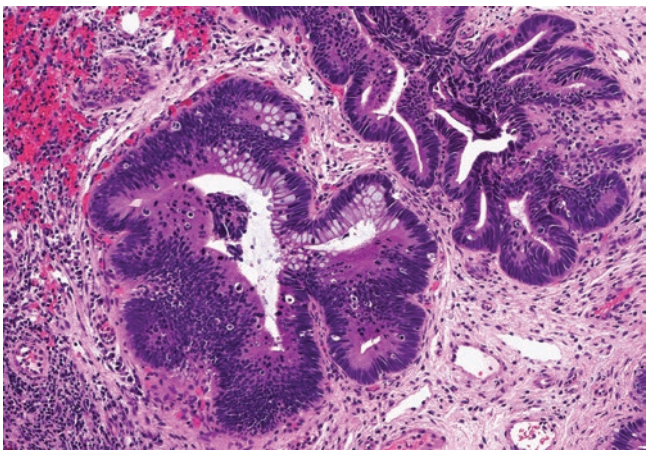

Fig. 6.19 AIS with intestinal mucinous differentiation in cervical biopsy. Goblet cells are found only focally

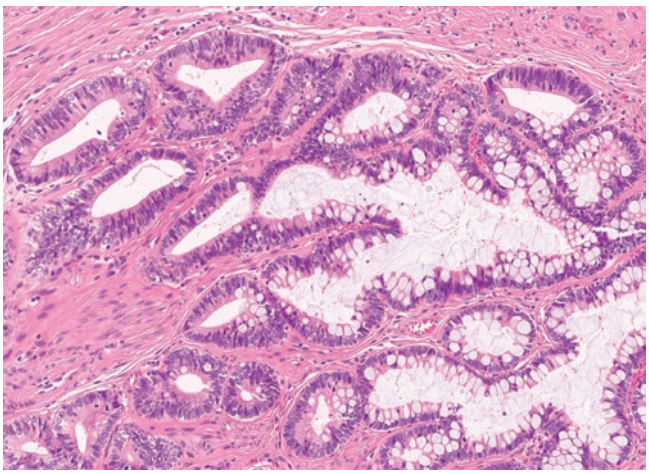

Fig. 6.20 AIS with intestinal mucinous differentiation in cone biopsy: Easily recognized goblet cells

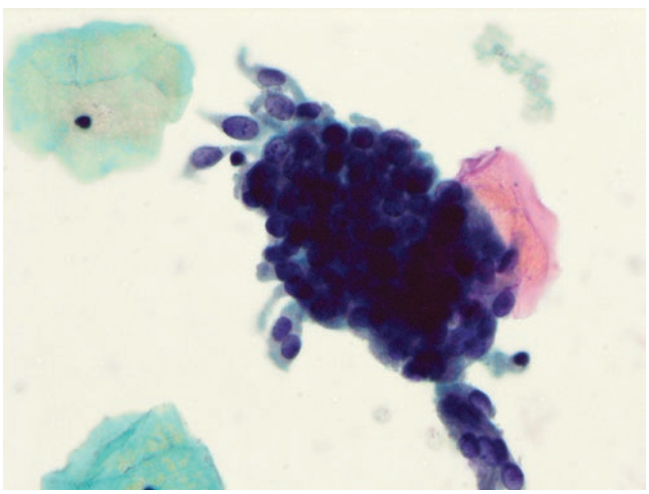

Fig. 6.21 AIS in Pap

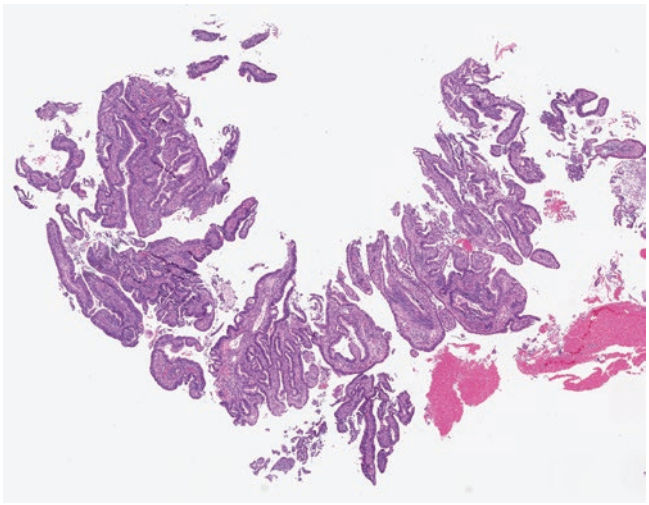

Fig. 6.22 Fragments of adenocarcinoma in endocervical curetting. This degree of glandular complexity is unusual for pure AIS

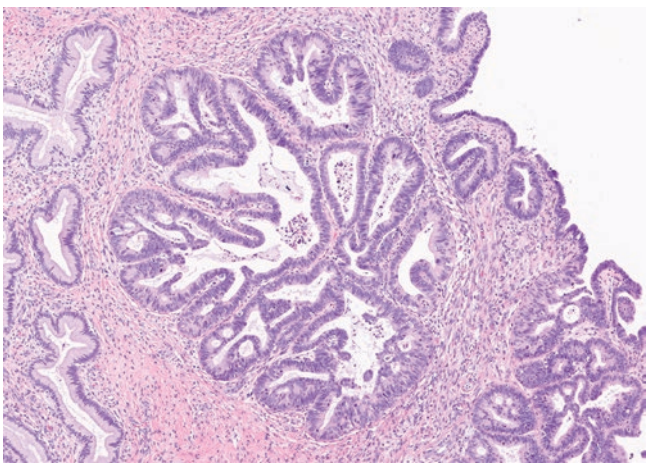

Fig. 6.23 AIS with glandular complexity in cone biopsy: This non-invasive cluster of glands with architectural complexity (cribriform and intraglandular papillae) can still be diagnosed as AIS, as there is no evidence of invasion in this field. The presence of such glandular complexity is sometimes associated with invasive carcinoma

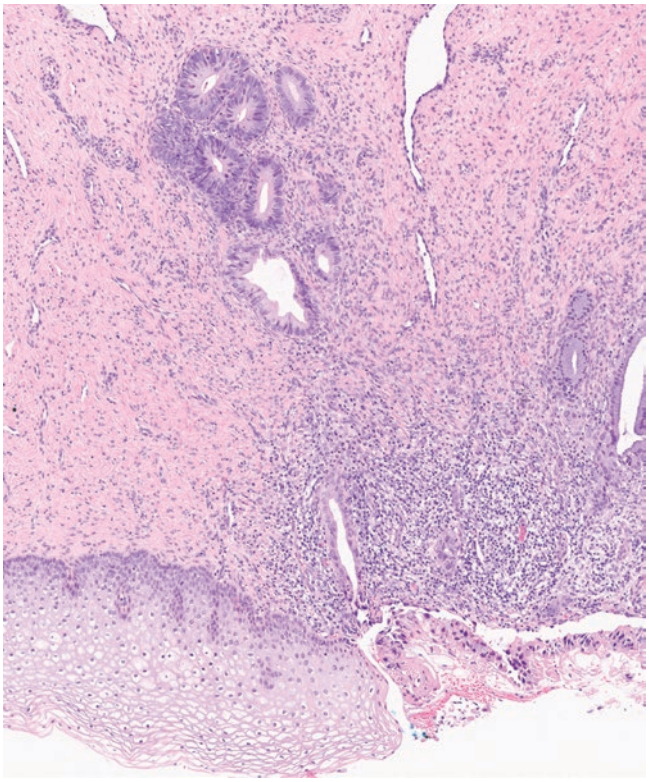

Fig. 6.24 AIS in a biopsy site: The differential diagnosis included invasive adenocarcinoma and AIS in a biopsy site. The presence of a biopsy site with a cluster of glands resembling AIS is sufficient to exclude invasion in this site

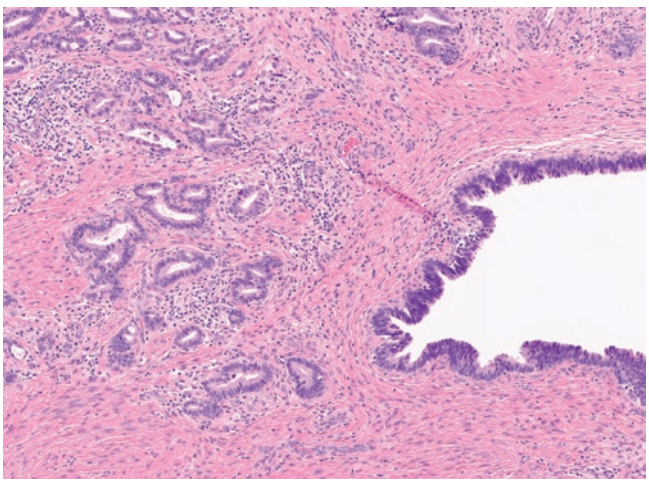

Fig. 6.25 AIS (at right) and invasive HPV-associated invasive endocervical adenocarcinoma (at left): The randomly oriented, pointed glands are no longer lobulated. Poorly formed glands and a subtle stromal reaction to invasion are present

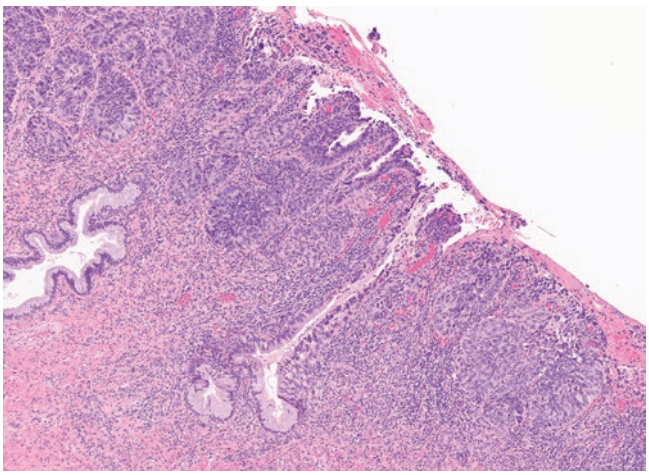

Fig. 6.26 Stratified mucin-producing intraepithelial lesion (SMILE) in cone biopsy. The lesion resembles HSIL at low power

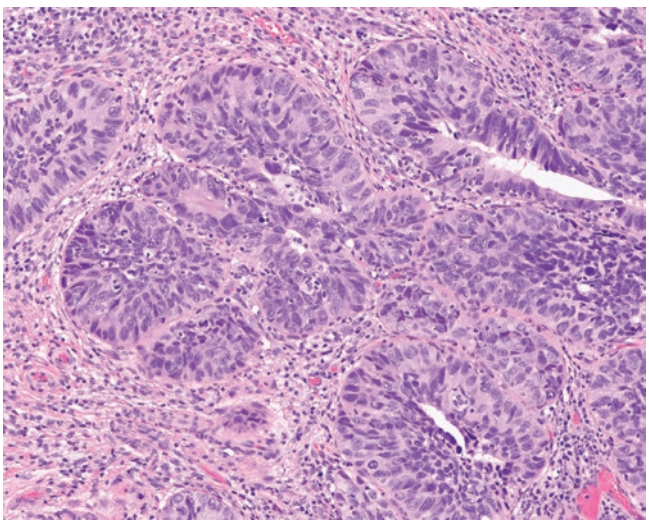

Fig. 6.27 SMILE in cone biopsy: Higher-power magnification demonstrates solid and nearly solid nests of stratified neoplastic cells with delicate, pink cytoplasm (suggesting glandular differentiation) and a peripheral palisade. Like other patterns of AIS, there is a high proliferative rate

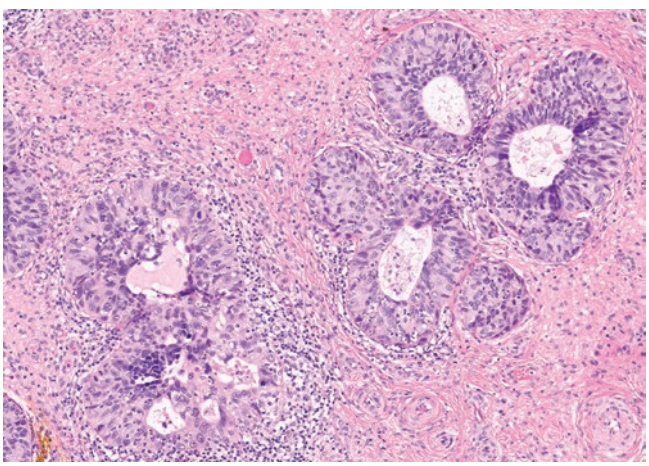

Fig. 6.28 SMILE in cone biopsy: Nuclear stratification of high atypical nuclei with pink cytoplasm that is obviously glandular in nature

6.3 HPV-Independent AIS

Only a few cases lacking an invasive component have been reported. With the exception of the case-reportable "intraepithelial clear cell carcinoma," these are intraepithelial neoplasms with confirmed or suspected gastric pyloric-type differentiation, with or without superimposed intestinal differentiation featuring goblet cells. The most diagnostically straightforward examples are present in association with pyloric metaplasia, including typical or atypical lobular endocervical glandular hyperplasia. There is a cytological spectrum of changes that bridge non-atypical pyloric metaplasia and gastric-type AIS. Although there are no cut-offs that distinguish between lesions on this spectrum, a change from basally placed, tiny nuclei to enlarged nuclei with chromatin abnormalities would signify "atypical" pyloric metaplasia, and the presence of nuclei with obviously malignant features in conjunction with mitotic activity would signify "gastric-type AIS."

6.3.1 Histochemistry and Immunohistochemistry

Gastric-type AIS contains neutral mucin, in contrast to acidic mucin, which can be recognized with a combined PAS and Alcian blue preparation. PAS/Alcian blue staining results in a magenta color that distinguishes between lesions containing pyloric-type neutral mucin and blue staining of acidic mucin in cells with endocervical differentiation. ER and PR are negative or significantly diminished relative to normal endocervix, and HPV ISH is negative. A minority of cases show strong staining with p16. Aberrant p53 staining (usually overexpression) also can be present. Nuclear staining for hepatocyte nuclear factor 1β is usually found (but is not diagnostically helpful), and napsin A and racemase staining are typically negative.

Diagnostic Highlights

- Non-invasive, cytologically atypical glandular neoplasm lacking easily identified mitotic figures and apoptosis.
- Usually gastric-type and variably associated with lobular endocervical glandular hyperplasia and/or invasive gastric-type adenocarcinoma.
- CK7 positive; variable PAX8, napsin A, MUC6, HIK1083, hepatocyte nuclear factor 1-beta, p16 and aberrant p53. Negative HR-HPV-ISH.

6.3.2 Differential Diagnosis

- *Non-neoplastic endocervix*. Gastric-type AIS contains cells that are usually significantly larger and taller than non-neoplastic endocervix and tend to contain clear to

lightly eosinophilic cytoplasm. When present, goblet cells usually indicate a neoplasm, either HPV-associated or HPV-independent. Non-neoplastic endocervix is diffusely positive for ER/PR, contains acidic mucin (unlike gastric-type AIS), and lacks significant nuclear atypia.

- *Pyloric metaplasia*. Pyloric metaplasia, including the cells of lobular endocervical glandular hyperplasia, differs from gastric-type AIS mostly by cytologic appearance; gastric-type AIS contains malignant-appearing nuclei with some mitotic activity.
- *HPV-associated AIS*. In contrast to gastric-type AIS, HPV-associated AIS exhibits easily identified and abundant apical mitotic figures with basal apoptotic bodies, block-like every-cell p16 labeling, and a positive result using HR-HPV RNA ISH.
- *Clear cell carcinoma*. Clear cell carcinoma is usually composed of flat or cuboidal cells, unlike gastric-type AIS; it lacks extensive intracytoplasmic mucin and may be positive for napsin A and racemase.
- *Secondary carcinomas*. Goblet cells can be present in metastatic adenocarcinoma, gastric-type AIS, and HPV-associated AIS, with only the latter typically showing block-like every-cell staining for p16 and the presence of HPV. Secondary adenocarcinomas from the lower gastrointestinal tract are typically CK20 positive and either CK7 negative or weakly positive, in contrast to gastric-type AIS. Distinction between gastric-type AIS and colonization of endocervical mucosa by metastatic adenocarcinoma arising in the upper gastrointestinal or pancreatobiliary tracts may be impossible without clinical correlation, but it should be noted that both scenarios are extremely uncommon. All three neoplasms in the differential diagnosis may be positive for CDX2.

6.4 Case

A 50-year-old woman complained of copious watery vaginal discharge and an endocervical curettage was reported to show pyloric metaplasia. The radiologic impression was Nabothian cysts or minimal deviation adenocarcinoma (a well-differentiated gastric-type carcinoma). The patient underwent cone biopsy (Figs. 6.29, 6.30, 6.31, 6.32, 6.33).

6.5 Clinical Management

A diagnosis of atypical glandular cells or AIS on Pap testing should be followed by colposcopy. If a biopsy or endocervical curetting is positive for AIS, the patient should undergo cold knife cone biopsy, which is preferable to immediate hysterectomy because the results of the cone biopsy may dictate the type of hysterectomy to be performed (possibly a radical hysterectomy if significant invasion is present). LEEP biopsies are not considered optimal for the diagnosis of AIS and its

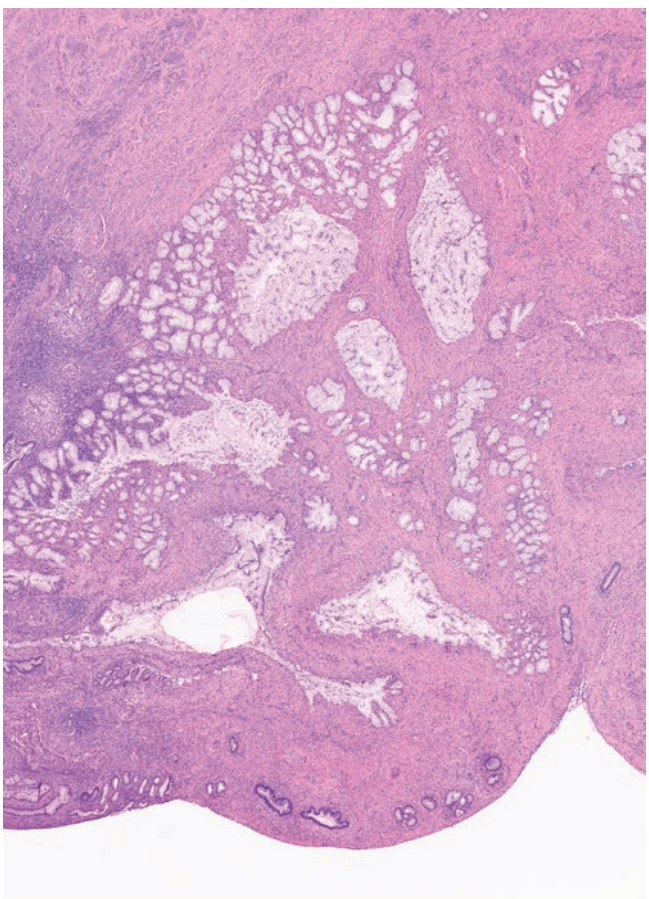

Fig. 6.29 Lobular endocervical glandular hyperplasia (LEGH) in a large cone biopsy: Lobulated aggregates of microacini containing abundant mucin cluster around dilated glands

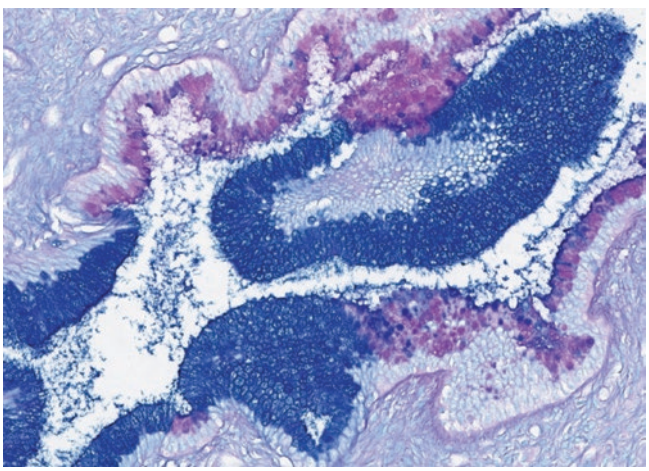

Fig. 6.30 PAS/Alcian blue preparation in LEGH. Magenta color indicates pyloric differentiation (*top center* and *bottom right*), which is present in LEGH and gastric-type AIS

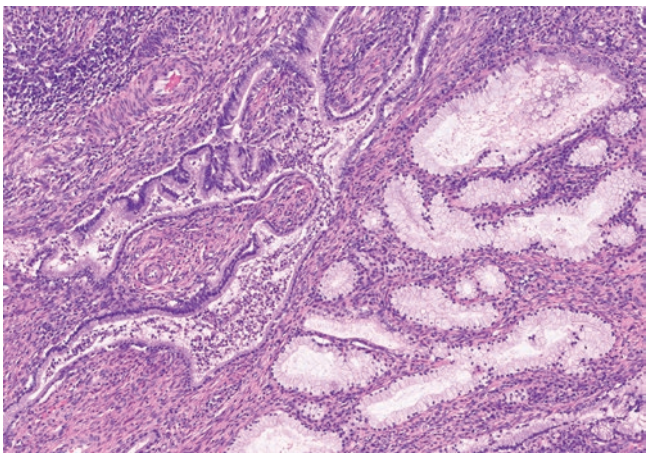

Fig. 6.31 Gastric-type AIS in LEGH: Gastric-type AIS (at left) is found alongside LEGH acini. Note nuclear enlargement and atypia. The degree of pseudostratification, nuclear atypia, and mitotic index are typically less than in HPV-associated AIS

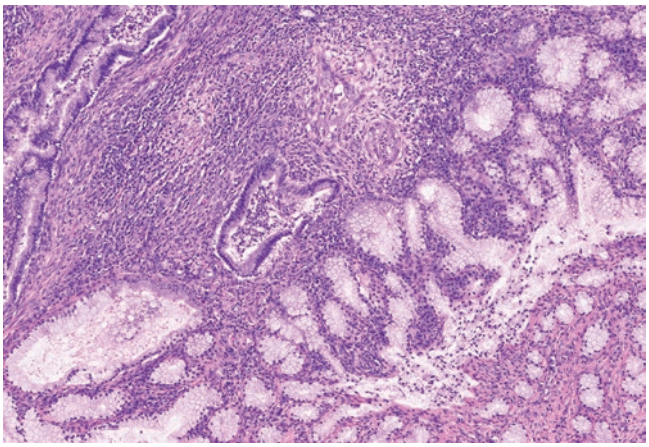

Fig. 6.32 Focally invasive gastric-type adenocarcinoma associated with gastric-type AIS in LEGH. In the field just adjacent to that illustrated in Fig. 6.31, there are two irregularly shaped glands (just above center) containing malignant-appearing nuclei with a stromal reaction

eradication because they may not extend deeply enough into the cervical crypts and often result in positive margins. When AIS is diagnosed in a cold knife cone biopsy, simple hysterectomy is appropriate for women who do not desire further fertility, although many practitioners would not necessarily perform a hysterectomy if AIS were excised in a cold knife cone biopsy with negative margins. Clinical surveillance should be performed if hysterectomy is not planned. When a large portion of the endocervix is replaced by or "carpeted" by AIS, there is a risk of unknown magnitude of concurrent or metachronous endocervical adenocarcinoma in the endometrium and in one or both fallopian tubes and ovaries.

Gastric-type AIS without coincident invasive adenocarcinoma has only recently been described and reported cases are rare, so its natural history is largely unexplored in the literature. Recurrence in the form of invasive gastric-type adenocarcinoma was documented in one patient subsequent to endocervical polypectomy that contained gastric-type AIS.

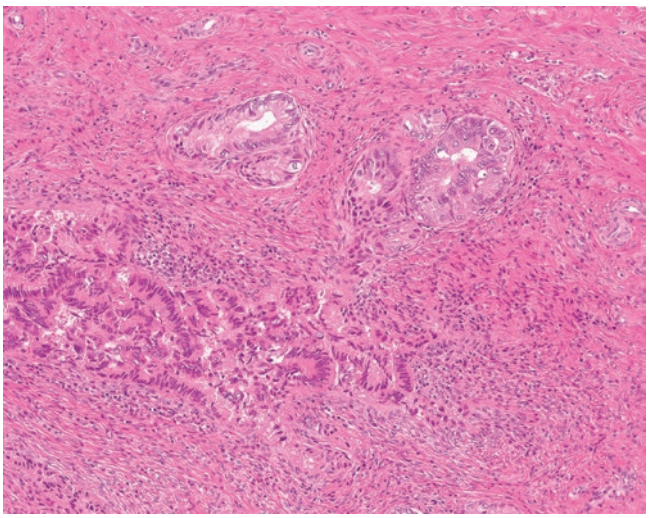

Fig. 6.33 The patient then underwent radical hysterectomy and bilateral salpingo-oophorectomy. Residual gastric-type AIS in hysterectomy

Suggested Reading

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