16 Cervix and Vagina

Cervical biopsies are common and nearly always performed for the purpose of evaluating squamous or glandular dysplasia. Usually the patient will have a history of an abnormal Pap test or a prior abnormal biopsy finding. Correlation with cytology is nice, but lesions can be focal and/or transient, so perfect agreement is not required.

There are several types of specimens. The smallest is usually the endocervical curettage. This is meant to be a sampling of the endocervix, and so should contain endocervical (columnar) mucosa. These tissue scrapings may have tiny and maloriented fragments, and the tissue can be spread out over a wide area.

If a lesion is seen by the clinician on colposcopy, there may be a cervical biopsy performed, which is a crescent-shaped chunk taken out of the cervix. This tiny specimen is uninked and unoriented. A high-grade lesion requires a cone biopsy, where the transition zone is taken out in a conical fragment with the goal of completely excising the lesion. The cone biopsy may be done with cautery (loop electrosurgical excision procedure) or blade (cold-knife cone). The endocervical margin should be identified and inked to make sure the lesion is not extending up into the canal where it cannot be seen or sampled. The ectocervical margin is also inked, but a positive ectocervical margin is unusual.

Normal Histology

The cervix is covered by a nonkeratinized squamous epithelium that merges into the surrounding vaginal wall. The squamous cells may be full of glycogen and have a plump cleared-out cytoplasm (see Figure 4.8B). In postmenopausal women, the epithelium may become thin and atrophic, with an immature look.

The transition zone represents an abrupt transition to mucous-secreting columnar and glandular epithelium and may be located at the os or within the endocervical canal. Irritation or inflammation at the transition zone may lead to acute and/or chronic inflammation and squamous metaplasia overlying the glandular mucosa. This state is so universal that "chronic cervicitis and squamous metaplasia" is synonymous with normal. Squamous metaplasia, by definition, can only occur at or above the transition zone (Figure 16.1), and so mentioning it confirms that the transition zone was sampled. If you see no endocervical component at all, the specimen is simply "benign squamous mucosa."

Endocervical glands are branching and complex glands that are pale with a dark outline due to the large cytoplasmic mucin vacuole pushing aside a small crescent-shaped nucleus (Figure 16.2). Fragments of glands on endocervical curettage may have a papillary or inside-out look, which is not significant. Squamous metaplasia may fill up and replace glands and must be distinguished from invasive cancer. Crowding of otherwise benign-looking glands is not a feature of concern, as it is in the endometrium.

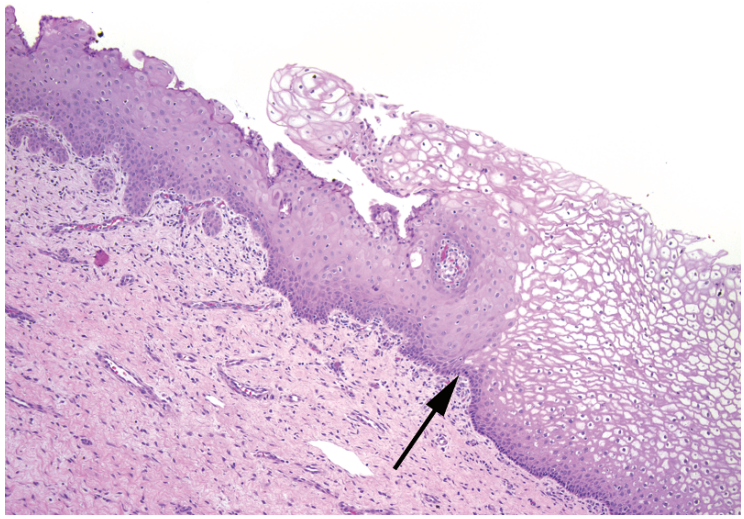

Figure 16.1. Squamous metaplasia at the transition zone. Mature squamous epithelium is seen to the right of the arrow, and squamous metaplasia is seen to the left. In squamous metaplasia, the nuclei may be larger and more immature appearing and the cytoplasm more dense.

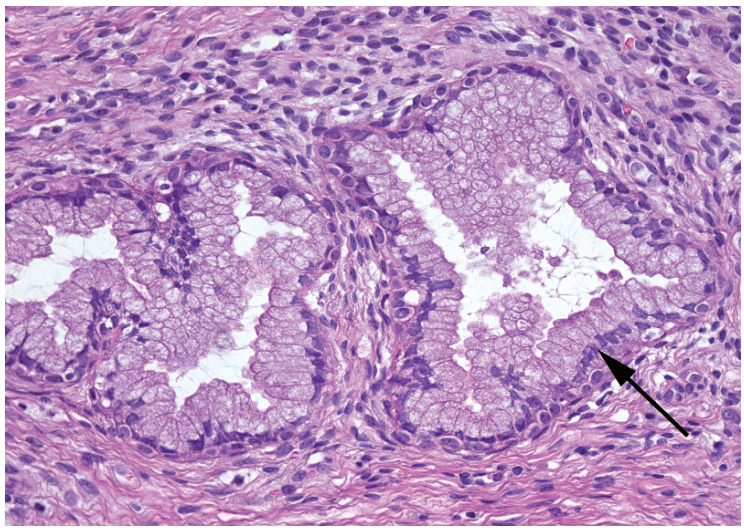

Figure 16.2. Endocervical glands. Normal endocervical glands are composed of tall columnar cells with apical mucin and small basal nuclei (arrow).

The cervical stroma is very fibrotic (as you will find when cutting through one), so it looks pink and spindly. There are a variety of normal cysts and glandular proliferations that may occur within the stroma.

The Approach to the Endocervical Curettage

First look at the slide on the tray, and circle a single level of the tissue—it may be spread out over a wide area, but may be duplicated several times on the same slide. At low power, look for fragments of squamous epithelium and endocervical glands. The presence or absence of each is noted in the diagnosis. There may be a fair amount of background mucus (stringy pale

pink amorphous substance) and inflammation. Concentrate on the actual epithelial fragments, if there are any. A smear of scattered endocervical cells (columnar cells with apical mucin) may be all you get, but ideally there are fragments of squamous epithelium to evaluate. These are evaluated by the same criteria as the biopsy, described next.

The Approach to the Biopsy

On low power, first survey the squamous epithelium and the endocervical glands to look for areas that stand out as being more disorganized, darker, denser, or more inflamed than other areas. This applies to the squamous epithelium as well as to individual endocervical glands. Any suspicious area should be studied at higher magnification to look for the following:

- Low-grade squamous intraepithelial lesion (LSIL; cervical intraepithelial neoplasia grade 1 [CIN1])
  - Low-grade squamous intraepithelial lesion is a viral cytopathic effect that affects primarily the upper cell layers of the epithelium.
  - The cells have pleomorphic, wrinkled, hyperchromatic nuclei with a perinuclear cleared halo; these are called *koilocytes*. Binucleation is common (Figure 16.3).
  - It can look haphazard at low power, but the basal layer should be maintained, and mitoses should not be higher than the lower one third.
- High-grade squamous intraepithelial lesion (HSIL; CIN2–3)
  - High-grade squamous intraepithelial lesion is a persistence of immaturity along with dysplastic changes. Essentially, the basal cells are becoming "immortalized," like a cancerous cell, and are not maturing and differentiating as they should.
  - The overall impression is of a denser and darker epithelium due to the high nuclear/cytoplasmic (N/C) ratios.

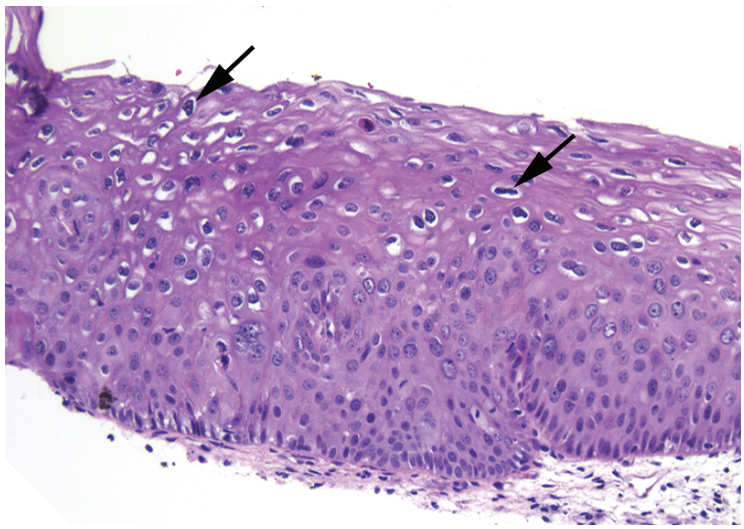

Figure 16.3. Low-grade squamous intraepithelial lesion. The hallmark of low-grade squamous intraepithelial lesion is the koilocyte, which is a squamous cell with HPV viral cytopathic effect. The nuclei are hyperchromatic (dark) and raisinoid (crinkly; see arrows), with a surrounding clear halo in the cytoplasm. Other good features include superficial nuclei that are larger than the nuclei below them and binucleated cells.

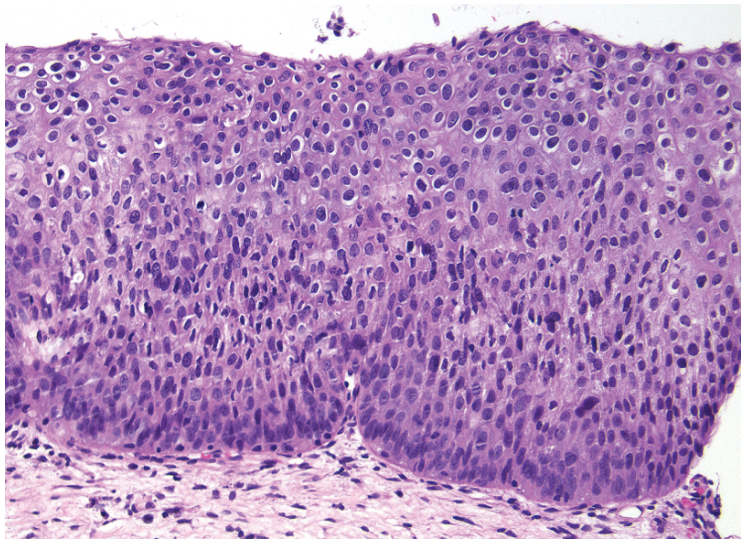

Figure 16.4. High-grade squamous intraepithelial lesion. In a high-grade lesion, paradoxically, the nuclei may not look as abnormal as in low-grade squamous intraepithelial lesion. The hallmark of high-grade squamous intraepithelial lesion is a persistence of immature-appearing cells throughout the epithelium. The nuclei are hyperchromatic and may have slightly irregular nuclear outlines, but the most striking feature at low power is the high nuclear/cytoplasmic ratios present from top to bottom.

- Atypia is seen in all cell layers, from the bottom up. The nuclei may not be as large or as bizarre as LSIL but are uniformly crowded, enlarged, and hyperchromatic with clumped chromatin and irregular membranes (boulder nuclei), and mitoses are present in the upper two thirds (Figure 16.4).
- CIN2 may show maturation at the surface or overlying LSIL.
- CIN3 shows full-thickness immaturity and atypia.
- HSIL can grow into endocervical glands, which should be mentioned in the diagnosis.

Do not confuse HSIL with *immature squamous metaplasia*, which has the following characteristics:

- Well-defined cell borders and low N/C ratios
- The "boiling mud" look (Figure 16.5)
- Usually pinker than HSIL
- Birds-egg nuclei (smooth, round, with even chromatin)
- Surface mucin or columnar layer

In very tough cases, the two can be differentiated by Ki67 and p16. Ki67 should be positive only in the basal layer in metaplasia, and p16, a marker for human papillomavirus infection, should be negative (or at most, focal).

Reactive Changes

Be wary of calling an SIL in the context of extensive acute inflammation (neutrophils). Reactive changes include the following:

- Regularly spaced nuclei with prominent nucleoli, homogeneous size, and smooth contours (Figure 16.6)
- Maturing upper layers without atypia
- Spongiotic edema

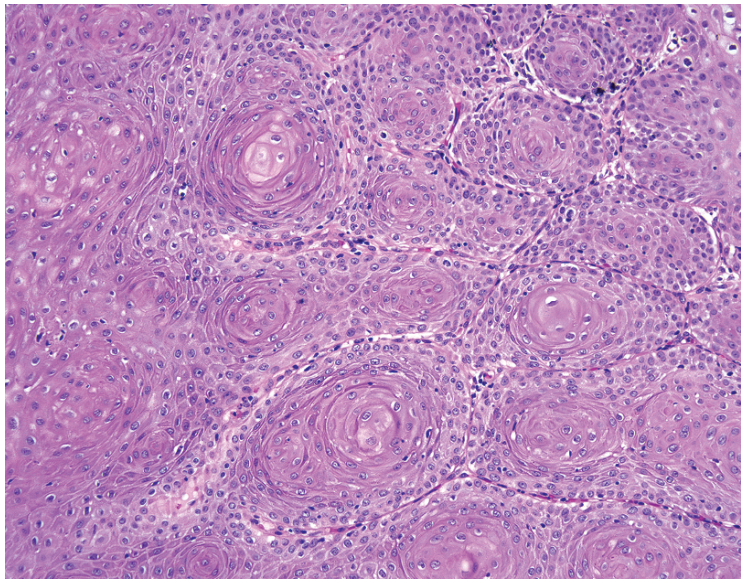

Figure 16.5. Immature squamous metaplasia. A tangential cut of squamous metaplasia can look like a lesion. However, this pattern of concentric whorls of cells with central pools of pink cytoplasm (resembling the boiling mud puddles of Yosemite) is typical of benign squamous metaplasia.

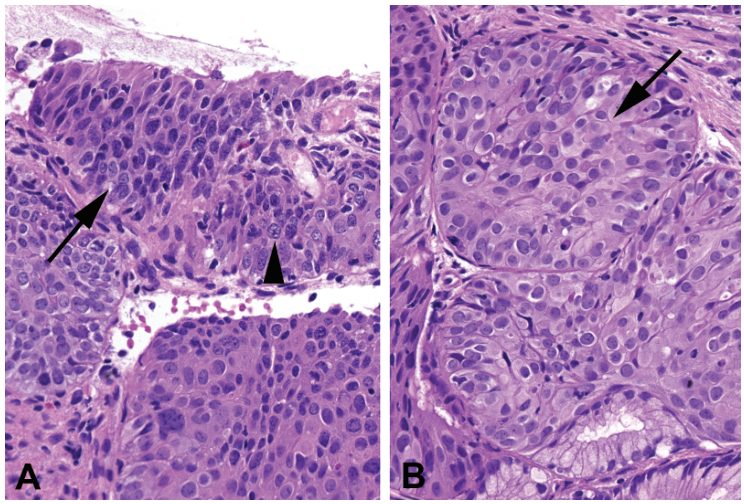

Figure 16.6. Dysplasia versus reactive changes. **(A)** In this example of high-grade squamous intraepithelial lesion, the dysplastic nuclei are irregularly shaped and appear to interlock together like stones in a wall (arrow). The quality of the chromatin is characteristic as well; it is dark and granular. Occasional nucleoli are visible (arrowhead), but they are surrounded by clumpy chromatin within the nucleus. **(B)** In reactive changes, the nuclei may be enlarged, but each nucleus remains smooth and oval in shape. The chromatin has a fine, even texture and is pale in color compared to the dysplastic cells in A. Small dense nucleoli are visible in many of the cells (arrow).

Invasive Squamous Cell Carcinoma

In the case of extensive HSIL (which is functionally carcinoma in situ), you should carefully search for evidence of invasion. As with squamous carcinoma in the skin or oropharynx, identifying invasion can be difficult and depends on multiple features. Features of invasion are similar to those in other sites:

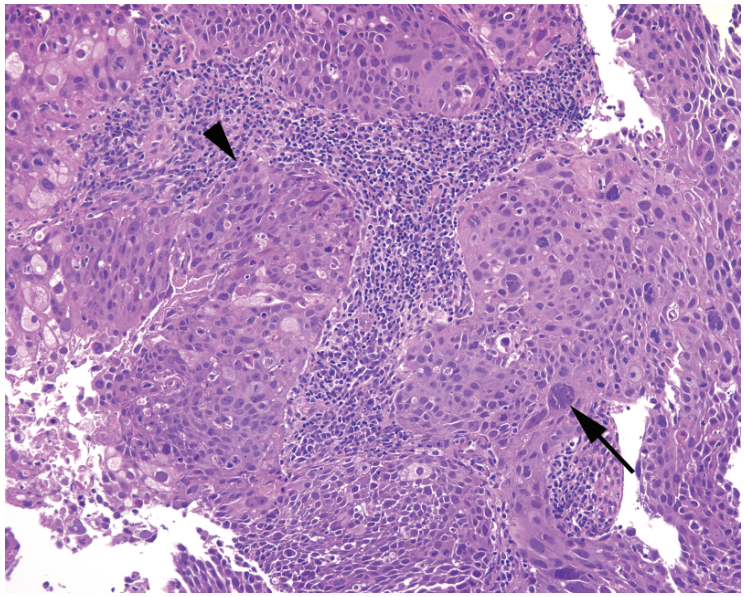

FIGURE 16.7. Invasive squamous cell carcinoma. Broad fronts of cells push into the stroma of the cervix, and at the leading edge there is a ragged border with individual infiltrating cells (arrowhead). Occasional huge and pleomorphic cells are visible (arrow).

- Deep keratinization
- Large nucleoli
- Blurred or sawtooth interface between epithelium and stroma (Figure 16.7)
- Loss of palisading basal layer
- Desmoplastic response within stroma

Invasion to a depth of less than 3 mm is considered microinvasion and has a better prognosis.

The differential diagnosis for invasion includes pseudoepitheliomatous hyperplasia, glandular involvement by HSIL, and placental site nodules. HSIL has a tendency to crawl down into endocervical glands, much like squamous metaplasia does. Although this is important and should be mentioned, it must be differentiated from invasion. Clues include remnants of columnar epithelium, a smooth rounded contour to the gland, and the lack of individual cells in the stroma.

A *placental site nodule* is a remote remnant of pregnancy—aggregates of intermediate trophoblastic cells that have large single nuclei that can look atypical, found in hyaline nodules. Their pink cytoplasm and atypical cells may remind you of deep invasive keratinizing cells (Figure 16.8). However, the cell borders should be less well defined than squamous nests, and the nuclei show bizarre degenerative atypia—large, dark, and smudgy (meaning, little chromatin detail) nuclei without nucleoli.

Miscellaneous Benign Entities

Endocervical polyps have fibrotic (spindly) stroma with a polypoid shape and normal endocervical glands or epithelium. The may have cysts, inflammation, or tubal metaplasia (luminal cilia).

Nabothian cysts are large dilated mucous-filled glands, lined with columnar epithelium. *Tunnel clusters* are lobular groups of complex branching glands (cystic or tubular), with benign columnar epithelium.

Microglandular hyperplasia is associated with oral contraceptive pills. It looks like a proliferation of small back-to-back glands lined with cuboidal or columnar cells with mucin

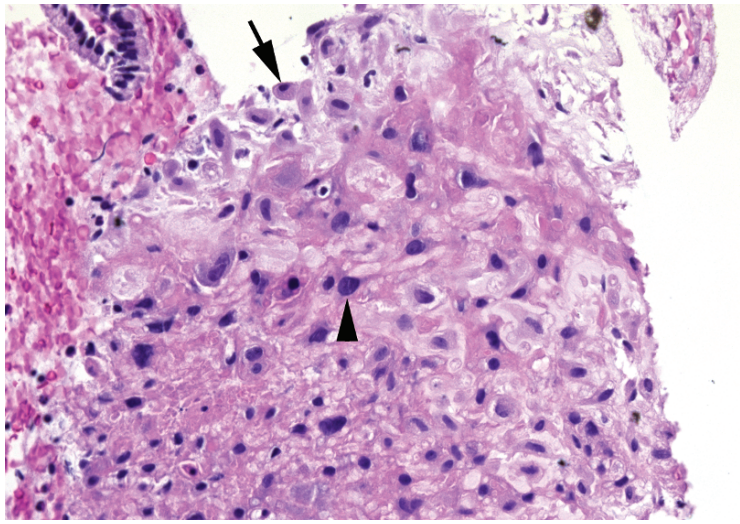

Figure 16.8. Placental site nodule, cervix. Although the dark nuclei and pink cytoplasm are concerning for squamous cell carcinoma, the nuclei are predominantly small and oval, with a few large nuclei visible (arrowhead). These large cells have dark but smudgy (blurred or indistinct) chromatin, without the chunky texture seen in HSIL (see Figure 16.6) and do not have the nuclear membrane irregularity of invasive squamous cell carcinoma (see Figure 16.7). The final clue is what appears to be a decidualized cell at the periphery (arrow).

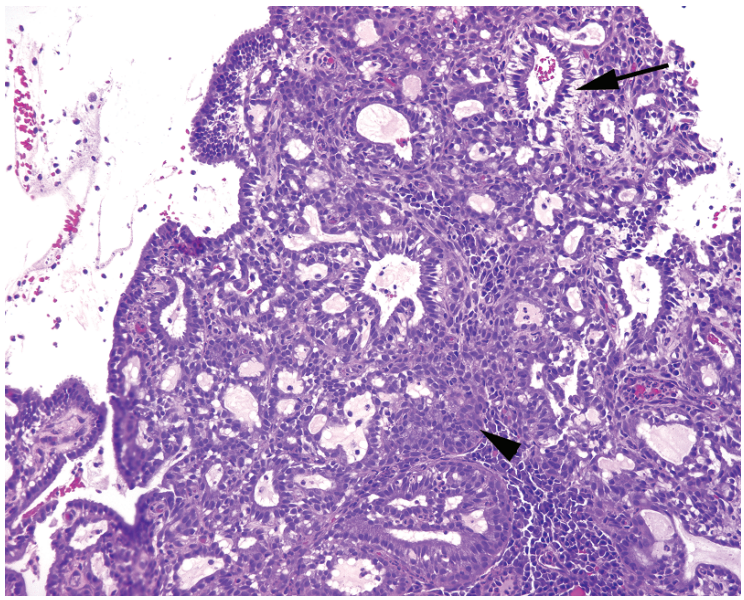

Figure 16.9. Microglandular hyperplasia. These endocervical glands show a very cellular proliferation composed of mucinous cells (arrow) and squamous metaplasia (arrowhead) and a cribriform pattern of lumens. This is benign.

vacuoles (Figure 16.9). The low-power impression is that of a cribriform architecture, but the glands should still appear overall pale and pink, in contrast to the dark blue adenocarcinoma in situ (AIS) (discussed later).

Endometriosis appears as dense blue palisaded columnar glands without mucus, surrounded by edematous endometrial-type stroma. The dark glands can be very eye catching

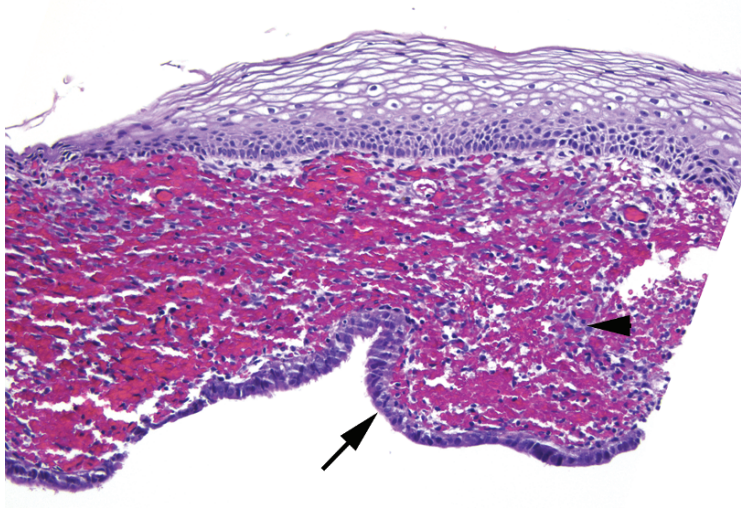

Figure 16.10. Endometriosis. This cervical biopsy specimen shows a squamous epithelium overlying stroma with hemorrhage. At the bottom of the fragment there is a dark cuboidal lining (arrow) resembling endometrial epithelium. The telltale endometrial stroma (arrowhead) is mostly obscured by blood.

and can even show mitoses, so recognizing the stroma is the key to making the diagnosis (Figure 16.10). The presence of extravasated red blood cells or hemosiderin is very helpful.

Glandular Lesions

Most pathologists do not use endocervical dysplasia as a diagnosis and only use the two ends of the spectrum, reactive atypia and AIS, for atypical noninvasive glandular lesions. Glands with AIS should stand out as being distinctly different from their benign neighbors (they look much darker). Recognizing these glands requires a conscious effort to look for them, however, because the eye tends to focus on the squamous epithelium, and AIS can be subtle at scanning magnification.

Features of AIS include the following:

- Close clusters of dark glands may resemble intestinal crypts or a tubular adenoma (Figure 16.11).
- Nuclei are tall and pseudostratified, enlarged, and hyperchromatic.
- Nucleoli may be present.
- Luminal mitoses and apoptosis are common.
- Papillary or cribriform architecture may be present and, if confluent, should raise the possibility of stromal invasion.
- Mucin may be present as scattered vacuoles or as discrete goblet cells (intestinal type).
- Ki67 staining is markedly elevated, and p16 staining should be diffusely positive (AIS is an HPV-associated lesion).

Invasive Adenocarcinoma

The most common variant of invasive adenocarcinoma is the endocervical type (“usual type”), which is an invasive form with the morphology seen in AIS. Features of invasion include the following:

- Cell clusters diving off into the stroma, as with squamous cell carcinoma
- Desmoplastic response

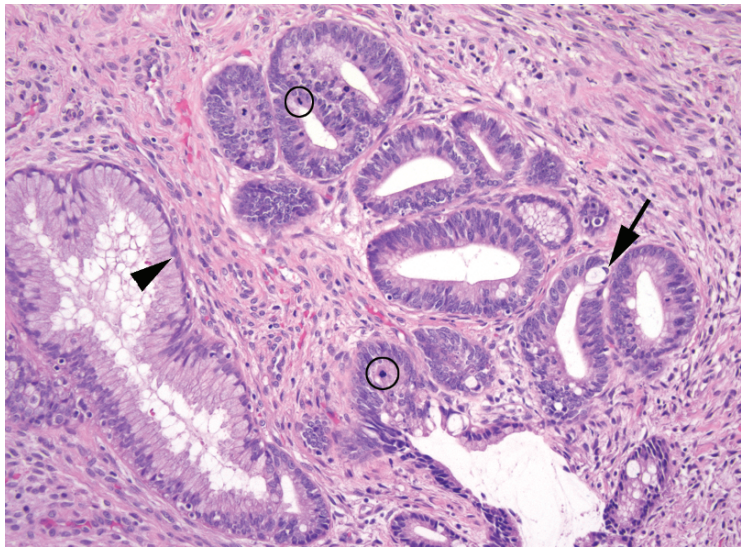

Figure 16.11. Adenocarcinoma in situ. This field shows some residual normal endocervical glands (arrowhead) adjacent to a very abnormal population with dark, elongated, crowded, and stratified nuclei representing adenocarcinoma in situ. Occasional intestinal-type goblet cells (arrow) and mitoses (circles) are present.

- Glands that are significantly deeper into the stroma than the benign glands (on perpendicular section)
- Glands with AIS features that are too crowded, or back to back

Endocervical adenocarcinoma may be hard to distinguish from endometrial adenocarcinoma. However, the endocervical variety should be diffusely p16 positive, whereas the endometrial type is usually estrogen and progesterone positive. See images and test yourself on cervical lesions at http://screening.iarc.fr/atlashisto.php.

Vaginal and Vulvar Epithelium

Human papillomavirus can cause similar lesions in the vagina and vulva. As in the cervix, the lesions are grouped into low-grade and high-grade, corresponding to vaginal intraepithelial neoplasia grade 1 (VAIN1)/vulvar intraepithelial neoplasia grade 1 (VIN1) and VAIN2–3/VIN2–3. The clinical term *bowenoid papulosis* refers to VIN3, synonymous with carcinoma in situ (Figure 16.12). As in the cervix, these lesions can progress to invasive squamous cell carcinoma.

Papillary Lesions

An exophytic viral lesion with LSIL-type changes is called a *condyloma acuminatum*. The LSIL features are somewhat subtler in a condyloma, and the nuclei may not be as obviously koilocytic. However, the presence of a verrucous (papillary, hyperkeratotic, and parakeratotic) lesion is virtually diagnostic of a condyloma (Figure 16.13). Non-HPV-related squamous papillomas also occur, usually in the vestibule, but without evidence of viral changes or hyperkeratosis. Finally, if the lesion is composed of more stroma than epithelium, it is most likely a fibroepithelial polyp (skin tag).

Inflammatory Skin Conditions

Lichen sclerosus appears as a flat, white, shiny patch clinically and in developed form looks like a bland pale swath of collagen (homogenous hyalinization) just beneath a thinned and

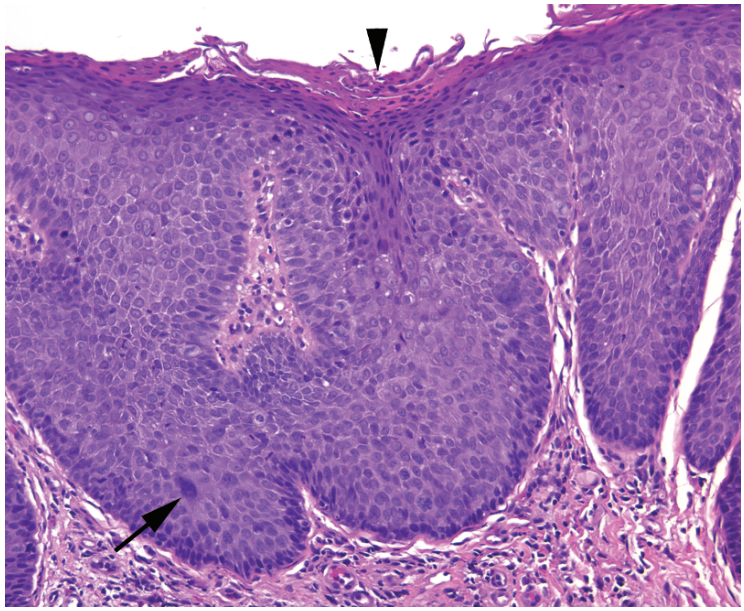

Figure 16.12. Vulvar intraepithelial neoplasia (VIN3). This biopsy specimen shows hyperkeratosis and parakeratosis (arrowhead) overlying a very blue squamous epithelium. Although the nuclear changes are not as obvious as in high-grade cervical lesions, there is loss of polarity and high nuclear/cytoplasmic ratios in the superficial epithelium. Occasional large atypical cells (arrow) are visible.

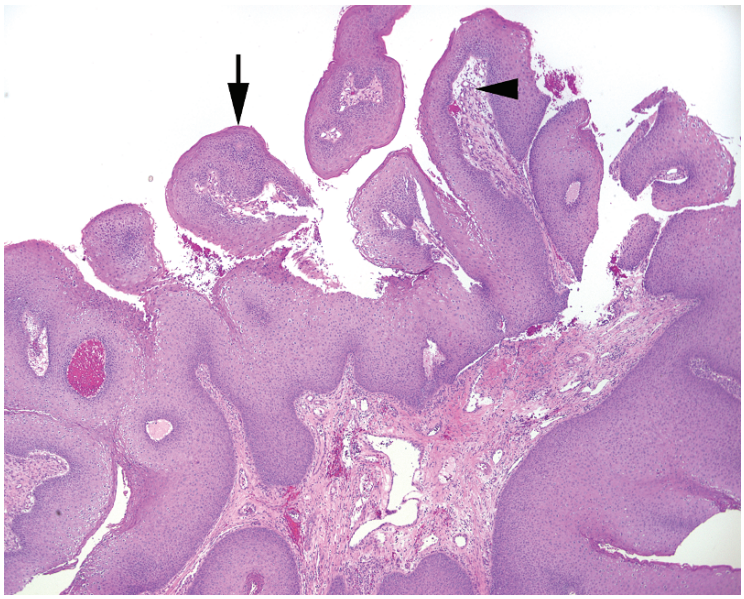

Figure 16.13. Condyloma. This exophytic lesion has prominent fibrovascular cores (arrowhead) underlying a thickened and hyperkeratotic squamous epithelium (arrow). Koilocytic or LSIL-type changes are not always obvious in condylomas.

flattened epidermis (Figure 16.14). *Lichen simplex chronicus*, on the other hand, is related to chronic spongiotic dermatitis and is characterized by epidermal thickening and hyperkeratosis over chronic inflammation in the dermis. It is a diagnosis of exclusion; you should first rule out fungal infection and squamous dysplasia.

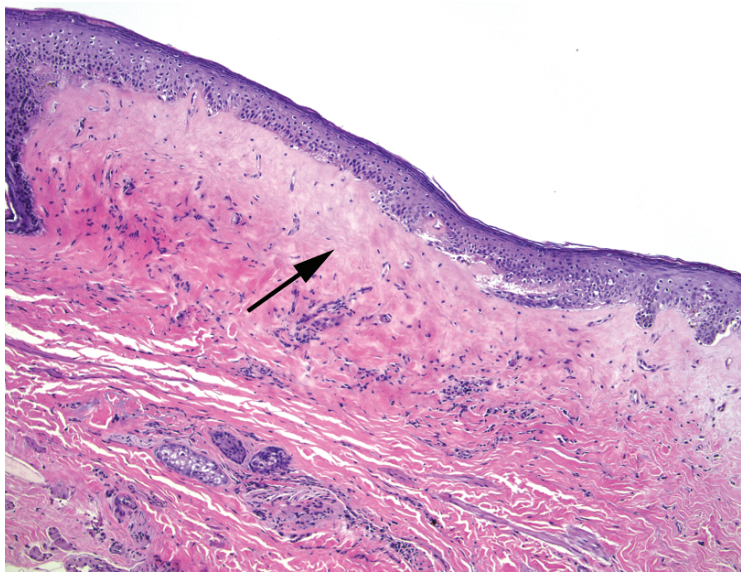

Figure 16.14. Lichen sclerosus. The epithelium is thin and atrophic, and the collagen underneath is pale, dense, and homogenized in texture (arrow). The dermal–epidermal junction is flattened, with an absence of rete.

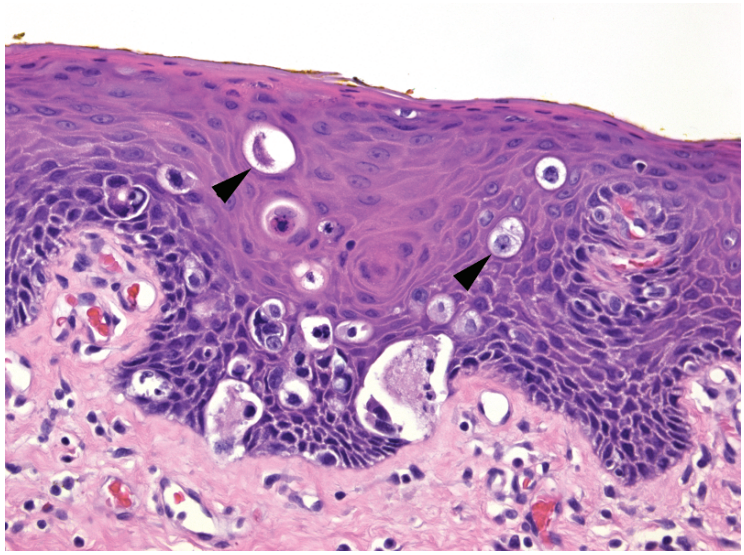

Figure 16.15. Paget's disease. Several nonsquamous cells (arrowheads) are visible within the squamous epithelium.

Paget's disease, extramammary type, is not an inflammatory skin disorder but may be mistaken for one clinically. Unlike in the breast, it does not always indicate an underlying adenocarcinoma. However, in other respects it is analogous to mammary Paget's, with large atypical carcinomatous cells percolating through a benign epidermis (Figure 16.15).

Melanoma, vulvar type, must always be in your differential diagnosis when you see pagetoid-type cells. A simple immunopanel will differentiate the two.