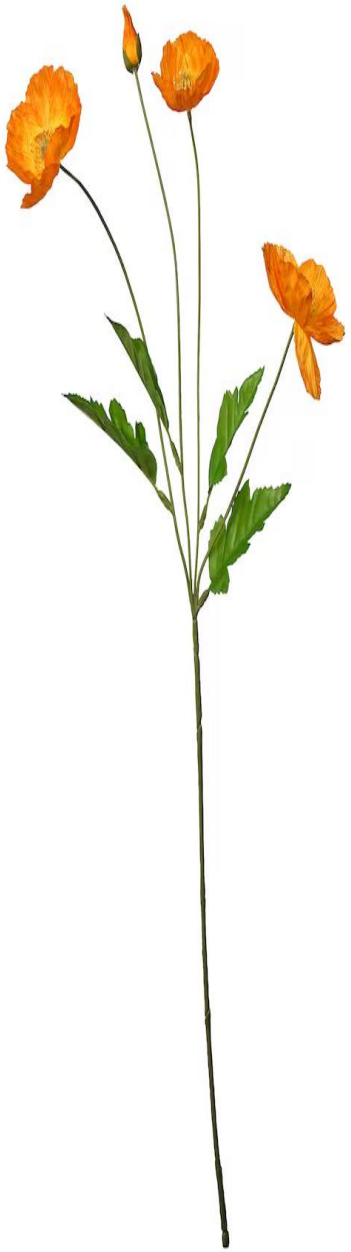


تشخیص CIN در بیوبسی های سرویکس

Dr.Aliakbar shekarchi
AP.CP

Histology of SIL

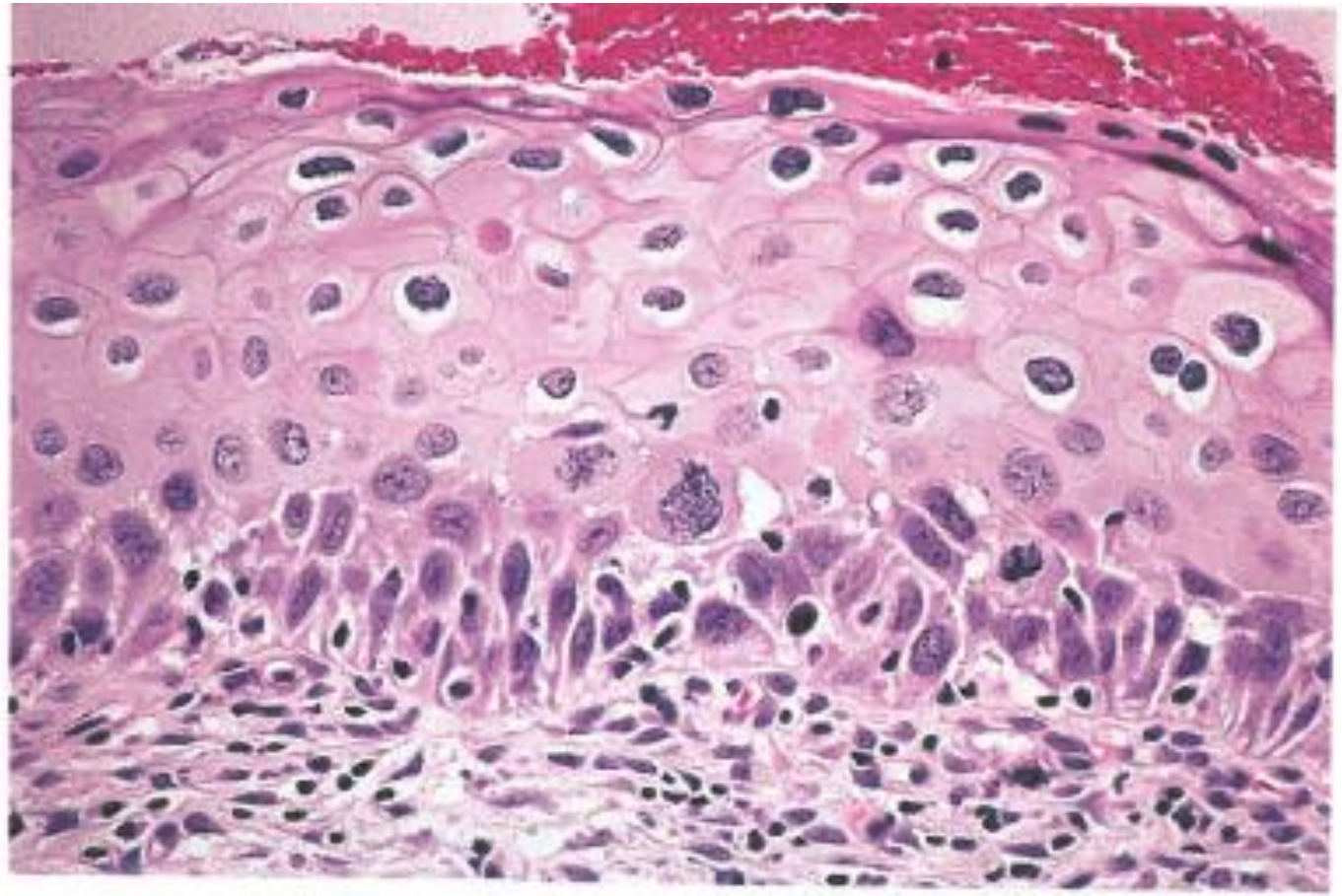


Fig. 19.77 CIN I accompanied by koilocytotic atypia.

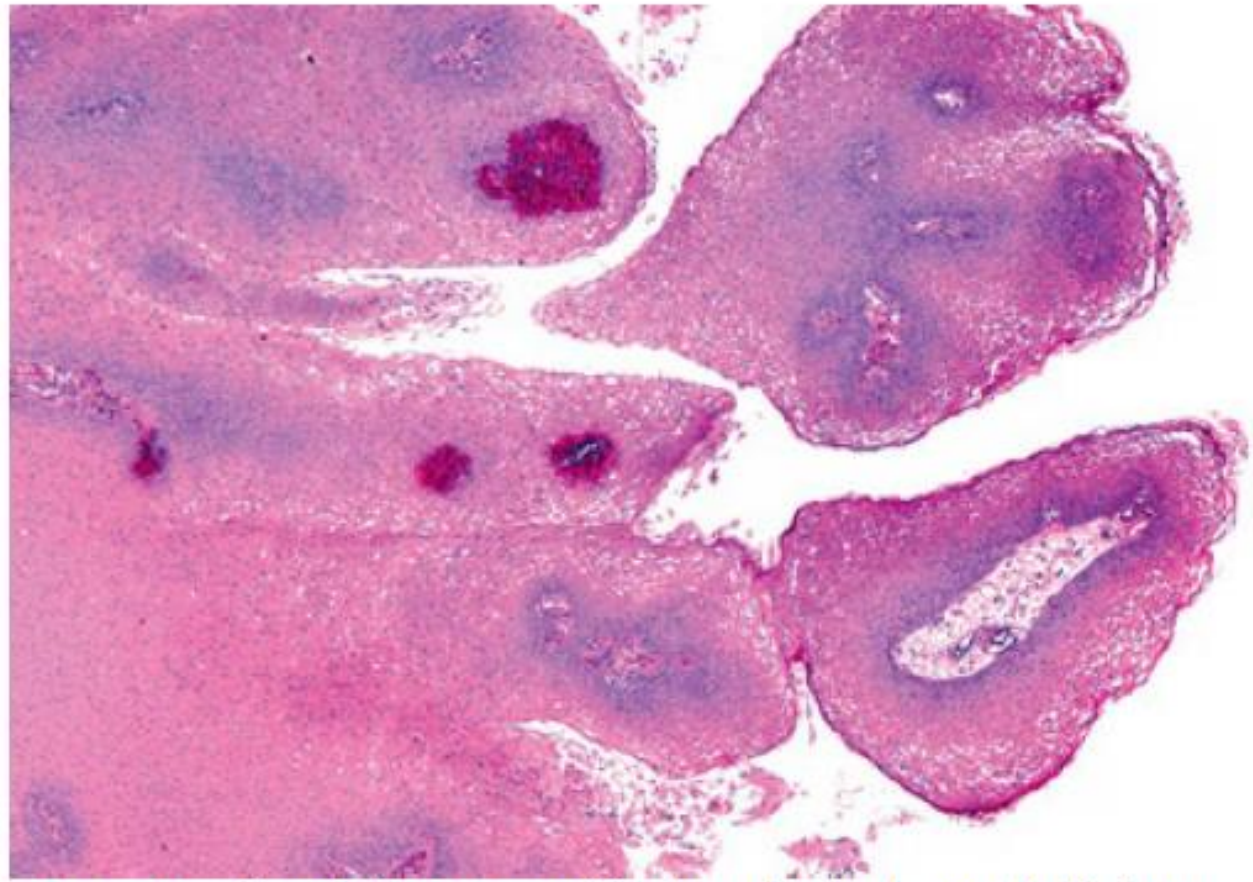


FIG. 5.2 Condyloma acuminatum, typical exophytic type.

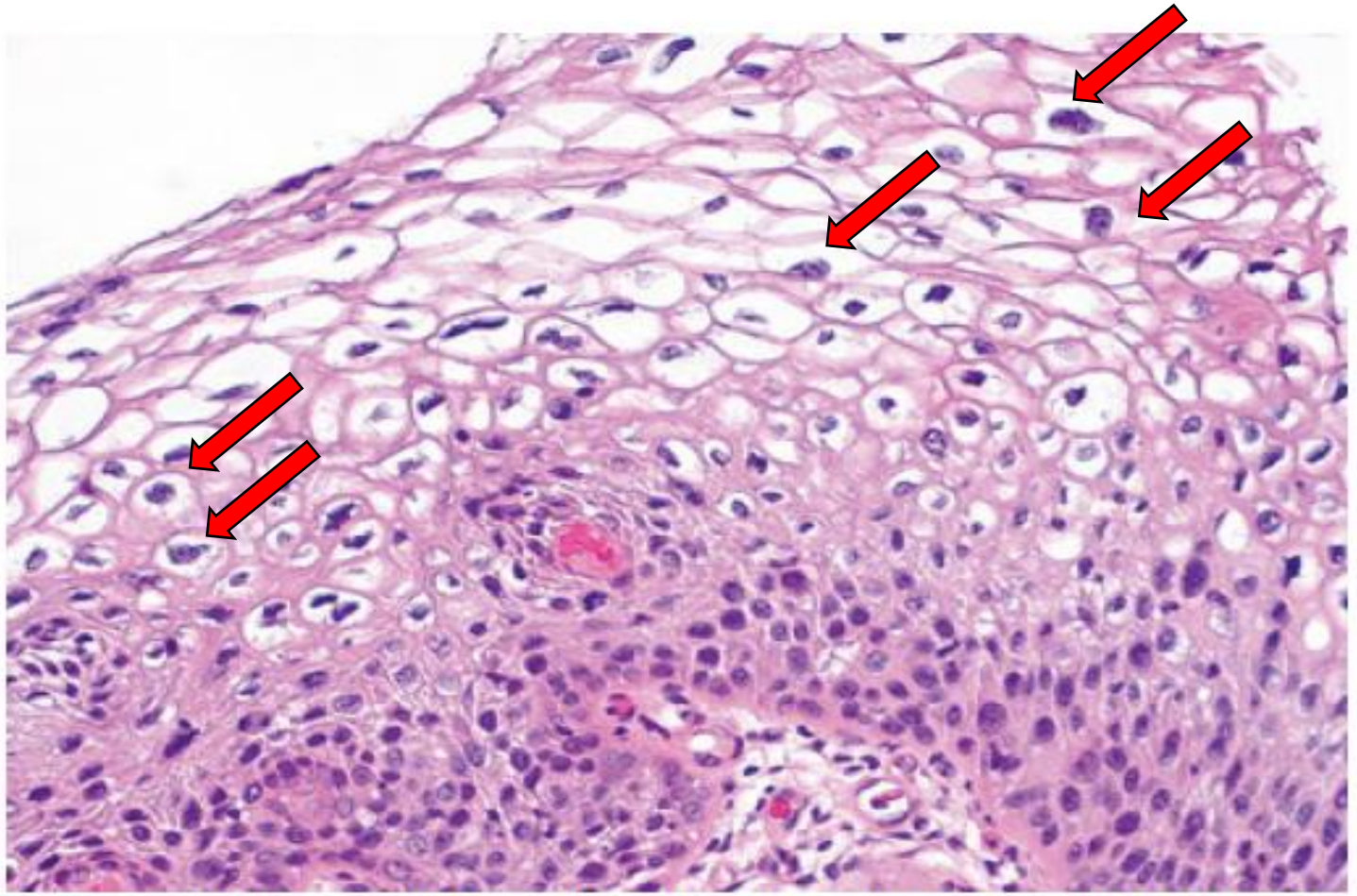


FIG. 5.6 Low-grade squamous intraepithelial lesion (CIN 1). Typical koilocytic atypia with hyperchromatic irregular nuclei and occasional binucleate cells are seen.

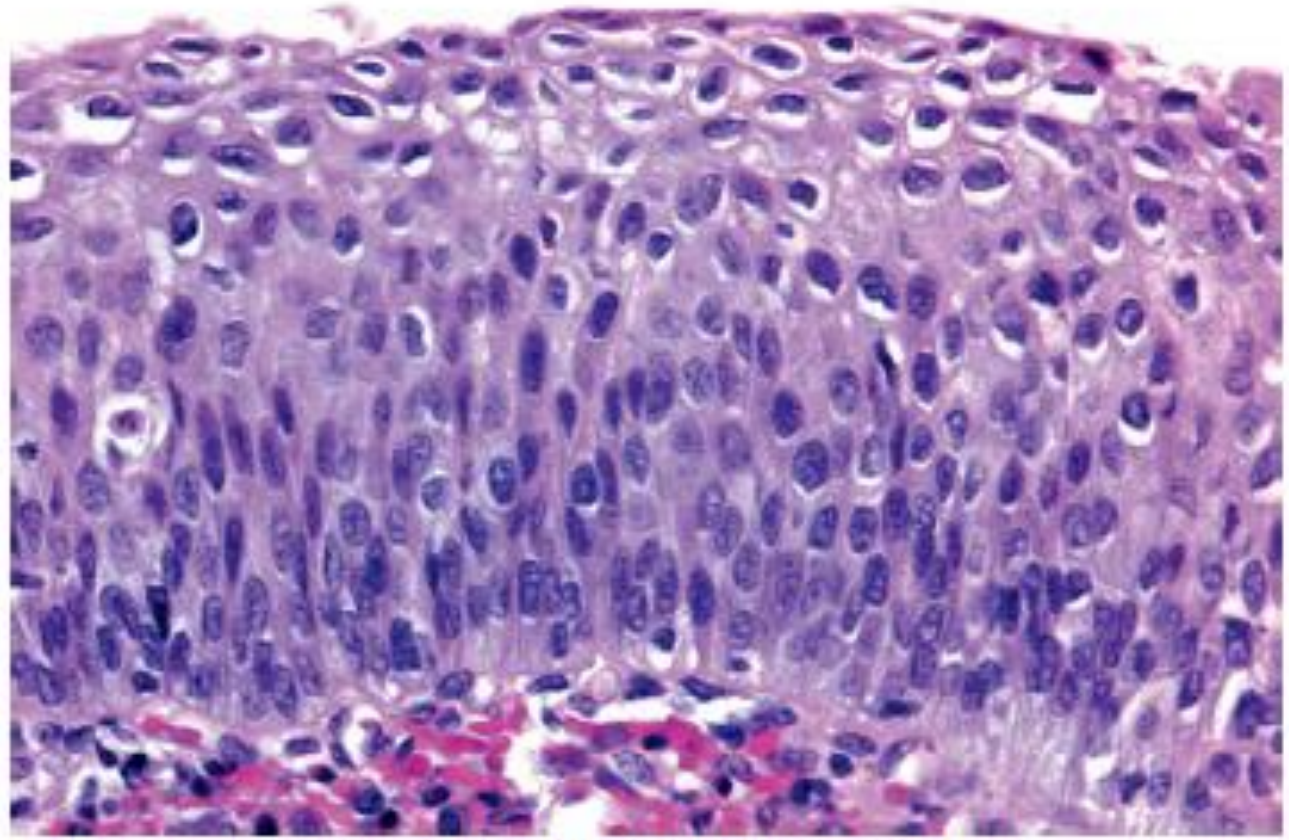


FIG. 5.9 HSIL (CIN 3) with koilocytosis.

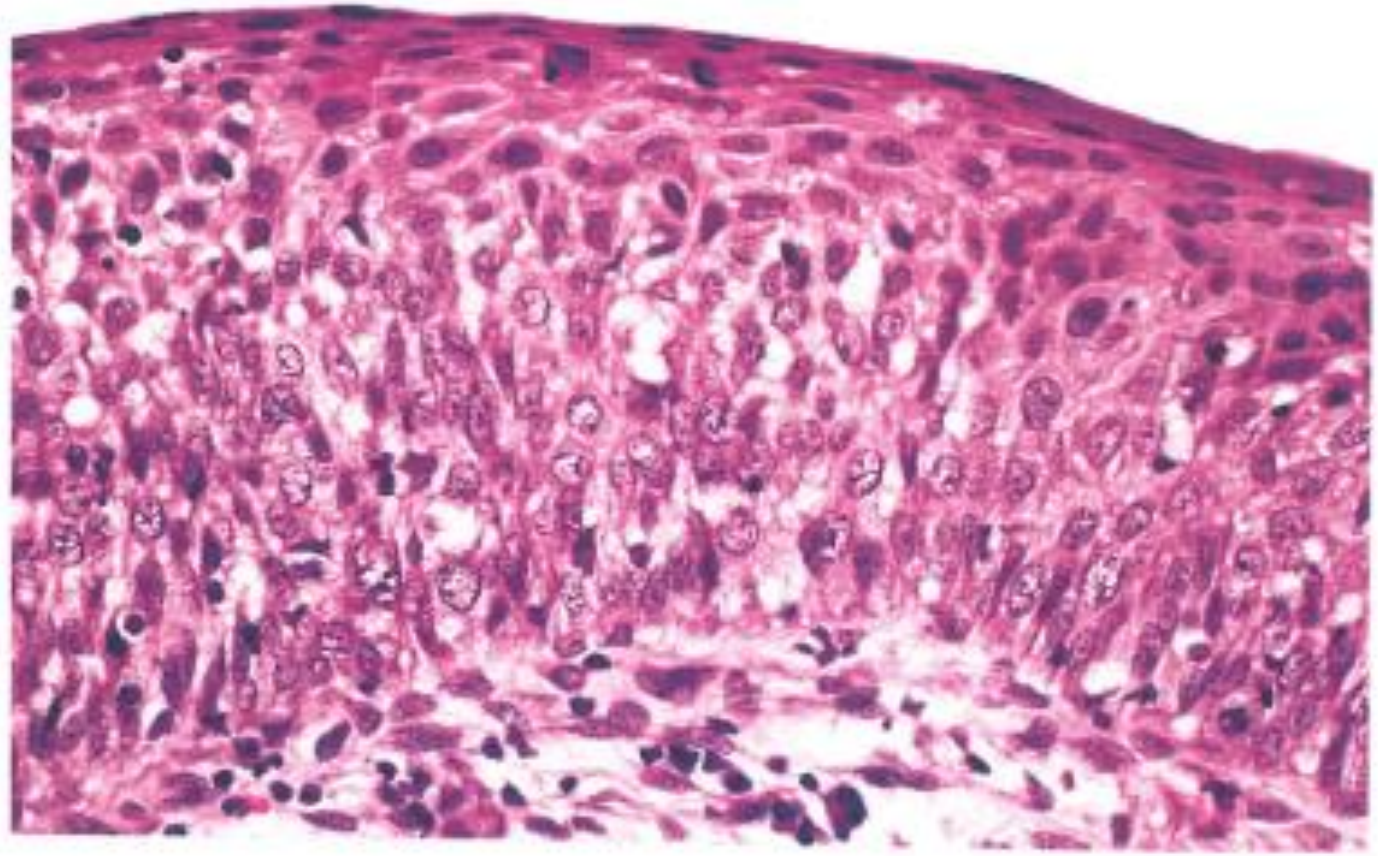


Fig. 19.78 CIN II (moderate dysplasia). There is proliferation and atypia in the lower two-thirds, but some surface maturation is still apparent.

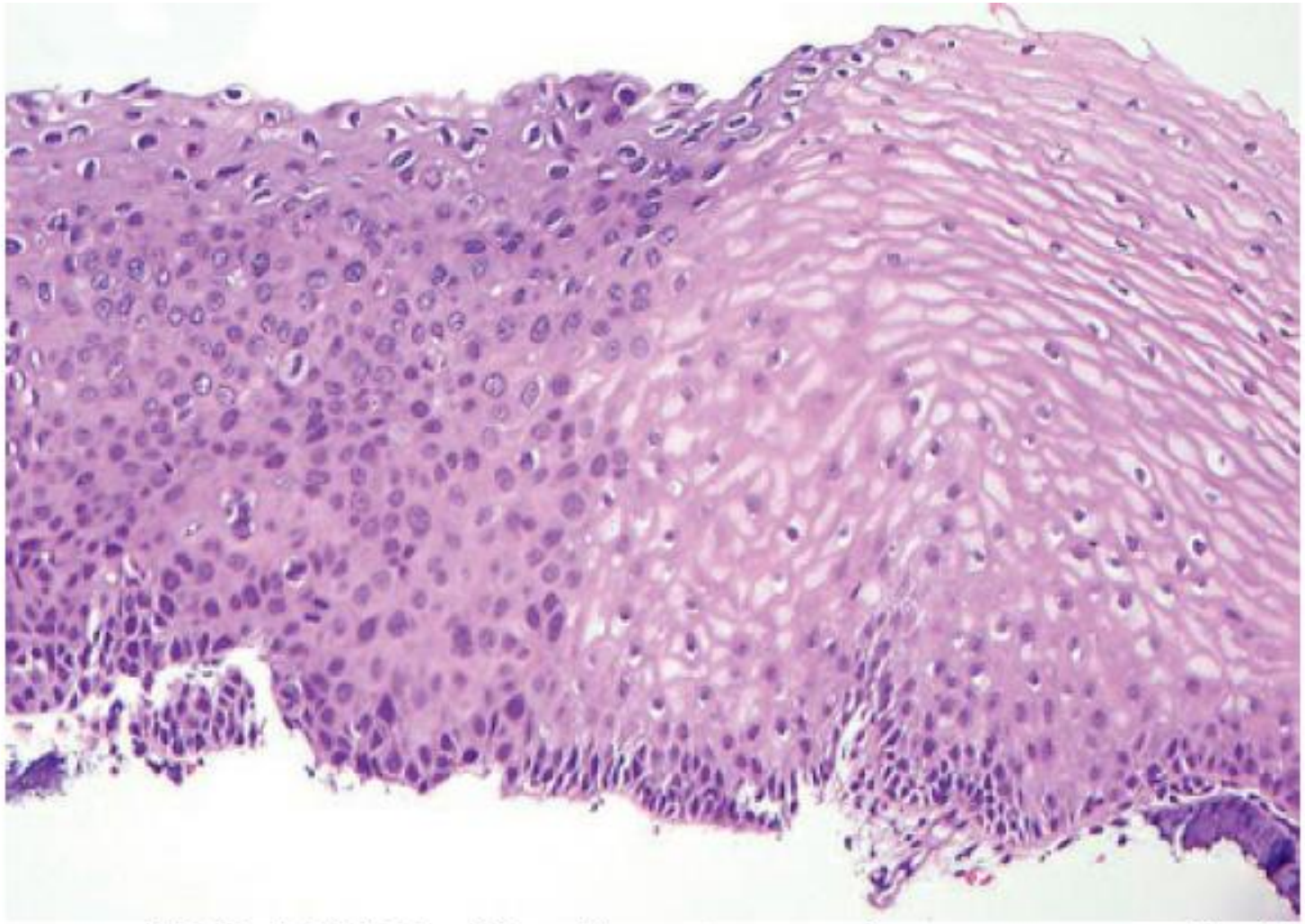


FIG. 5.11 HSIL (CIN 3) with adjacent normal squamous epithelium.

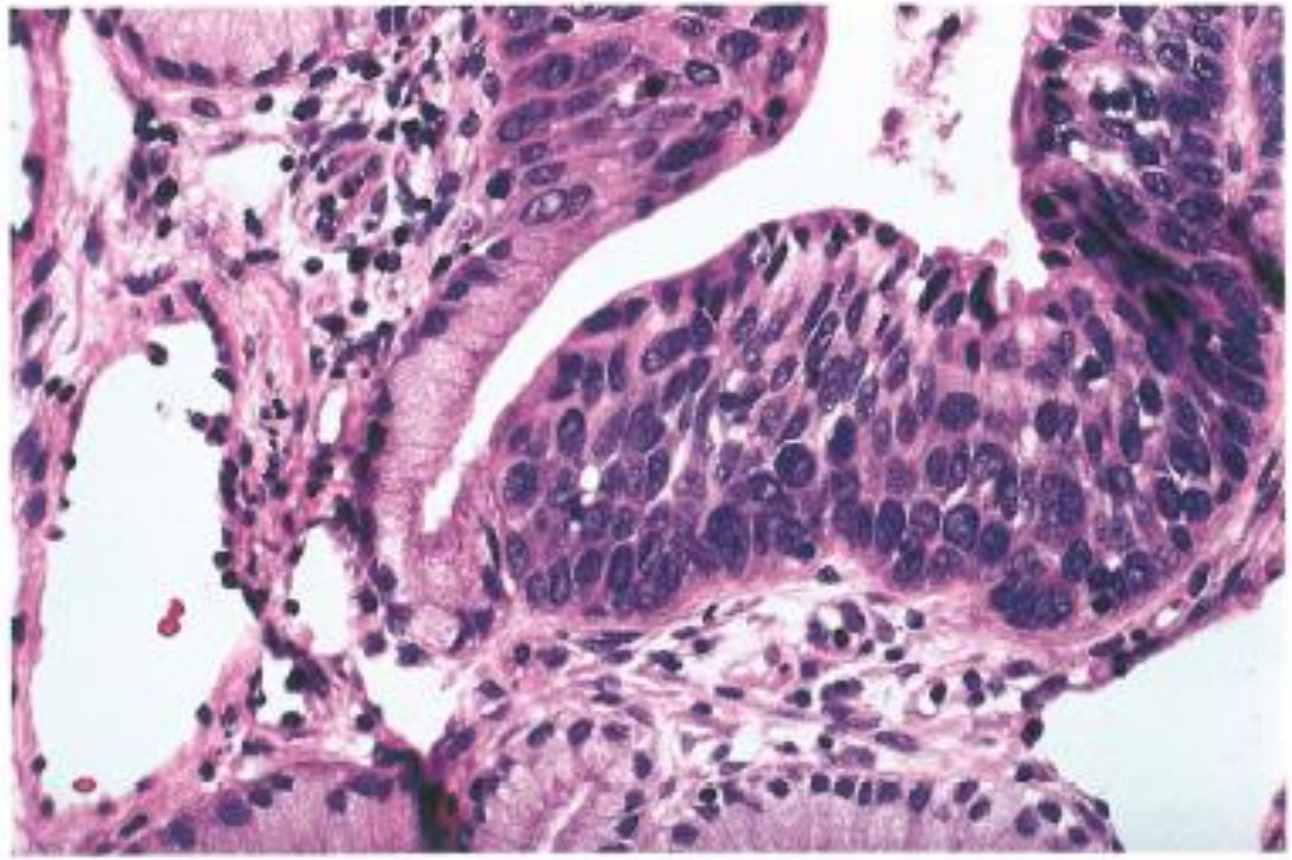


Fig. 19.80 Partial replacement of endocervical glandular epithelium by CIN III.

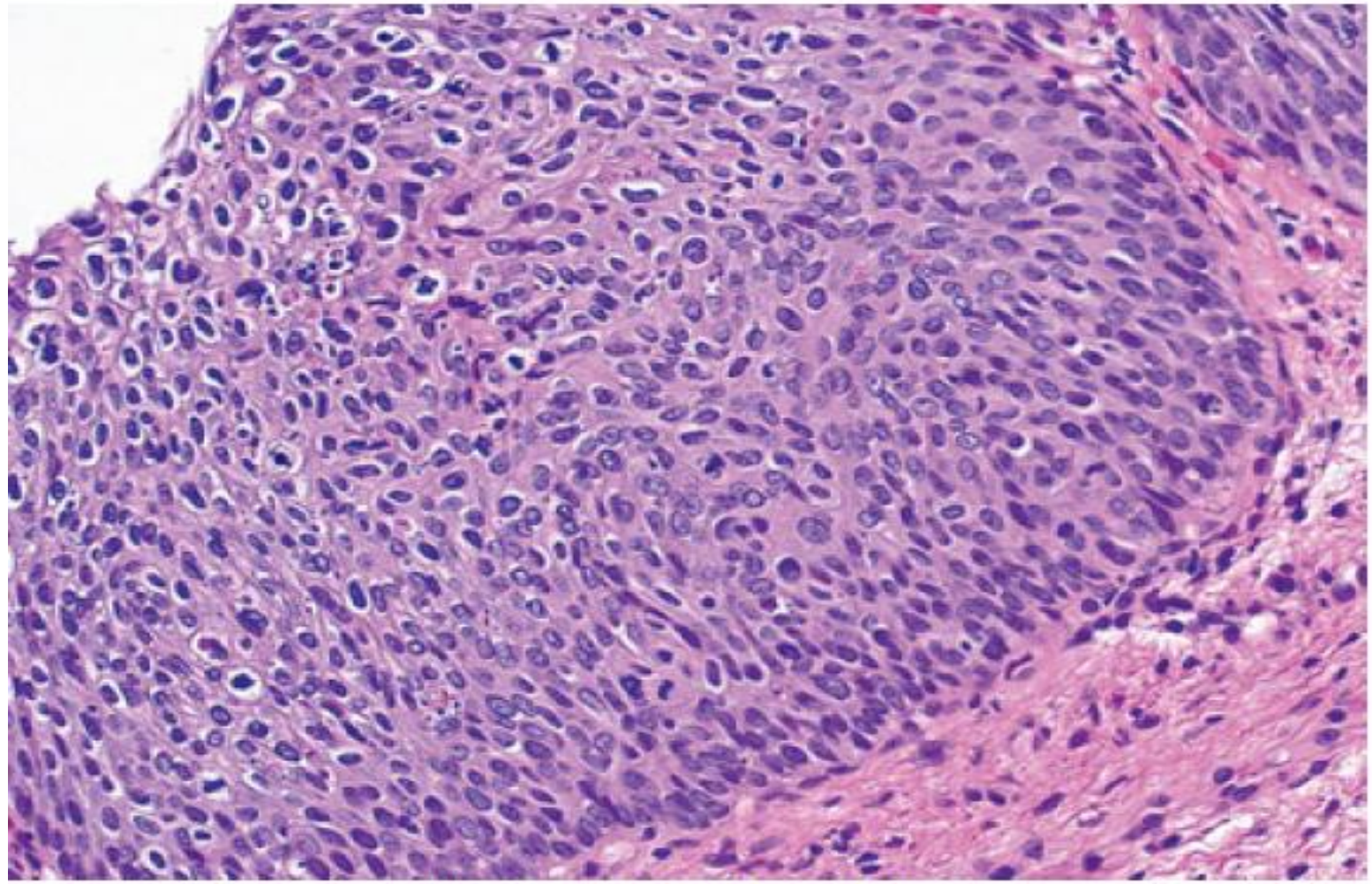


FIG. 5.12 HSIL (CIN 3).

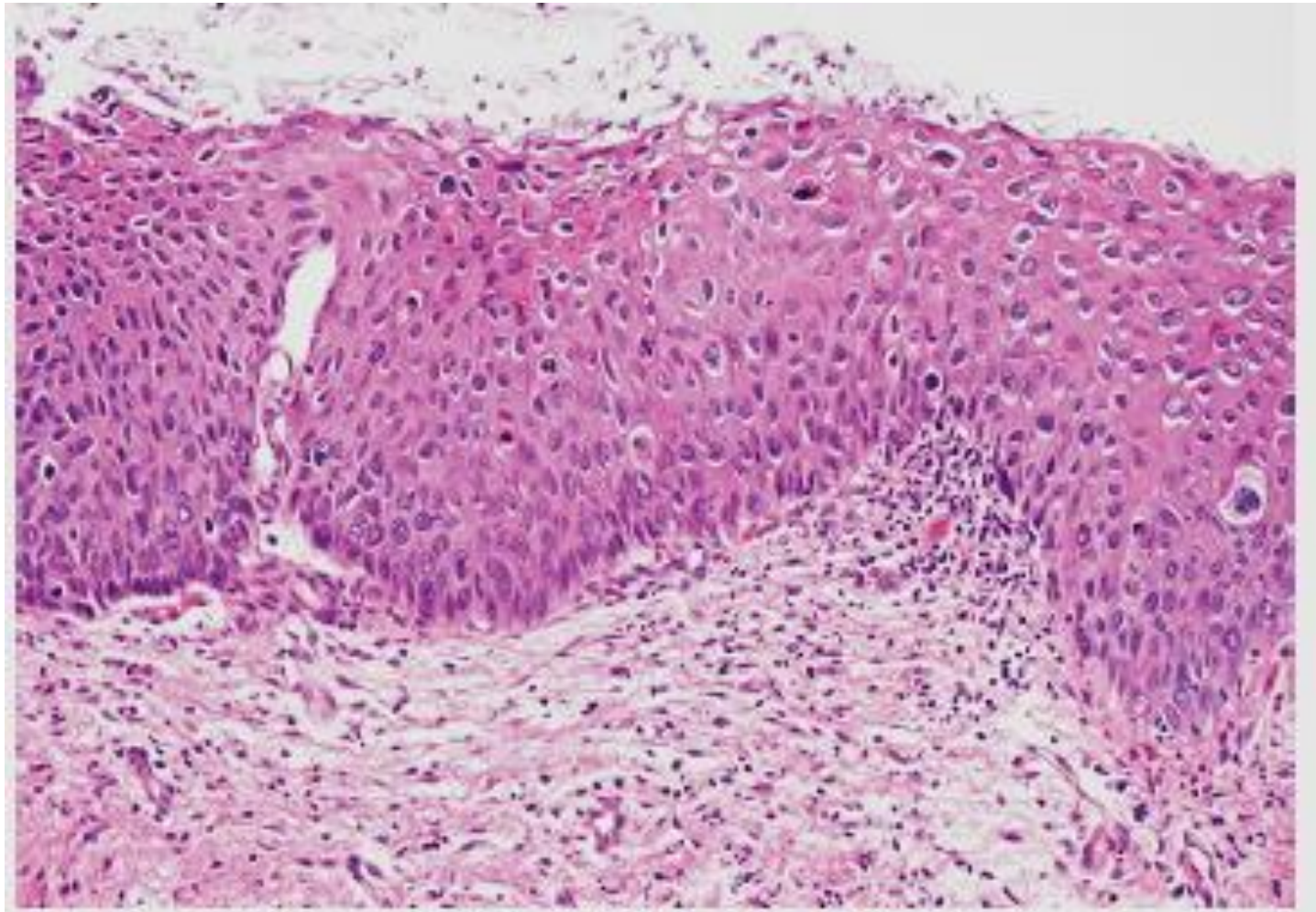


FIG. 5.8 HSIL (CIN 2) with koilocytosis.

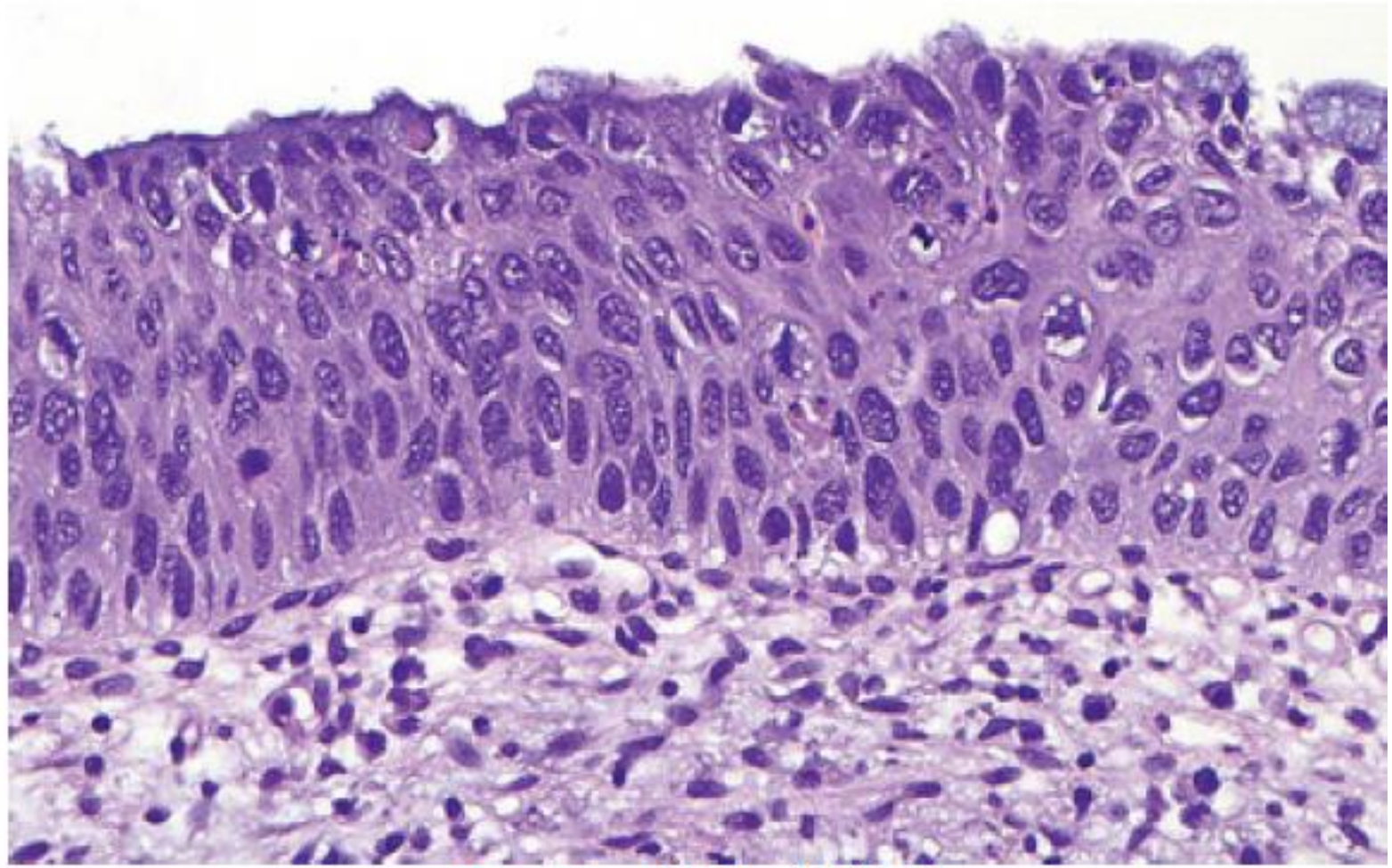


FIG. 5.13 HSIL (CIN 3).

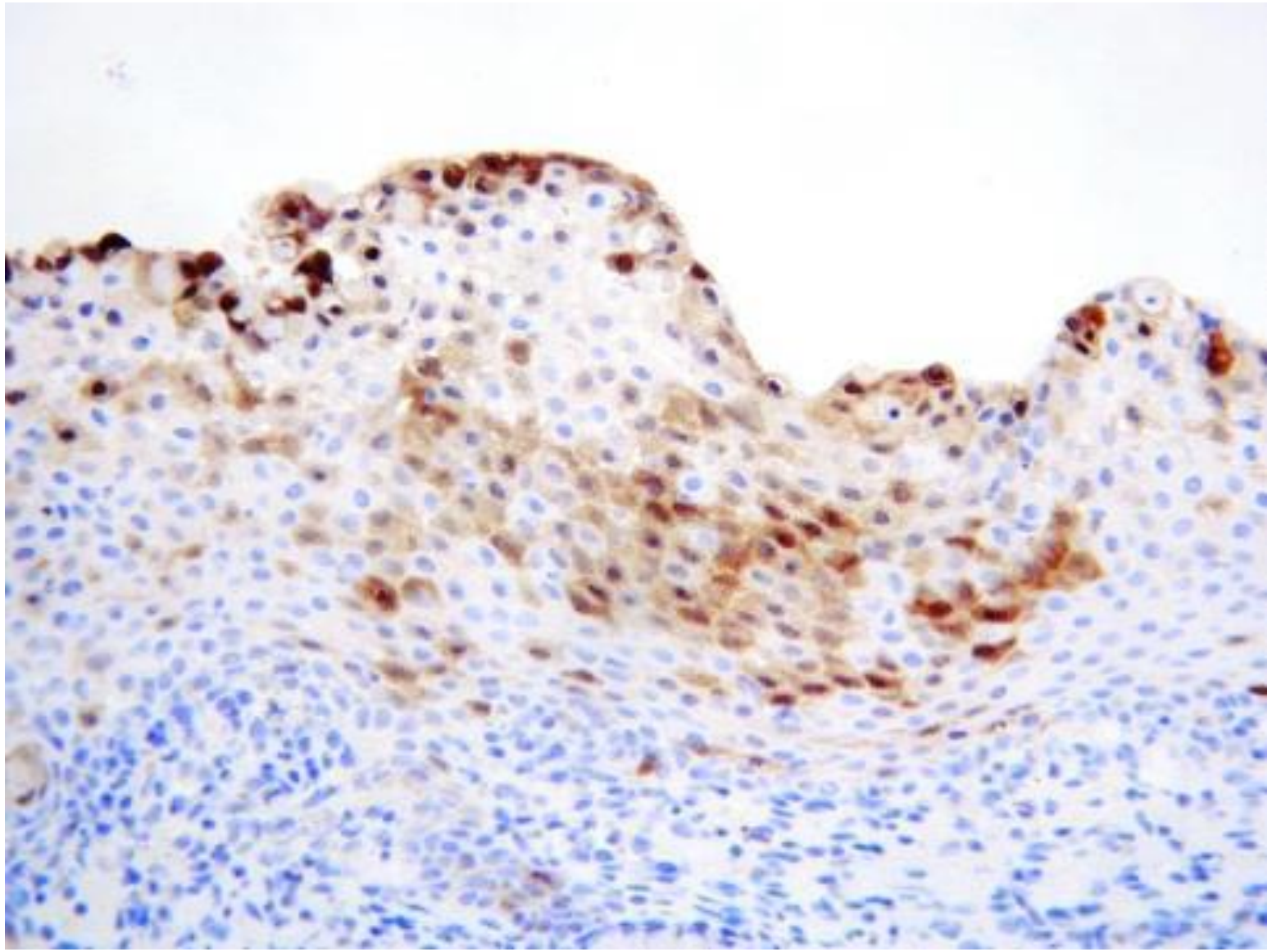
P16

- P16 is a 16 kDa protein encoded by CDKN2A, within the INK4/ARF tumour suppressor locus on Chromosome 9 (9p21.3).
- Immunostaining for p16 has emerged as a surrogate for detection of potentially transforming hrHPV infection.

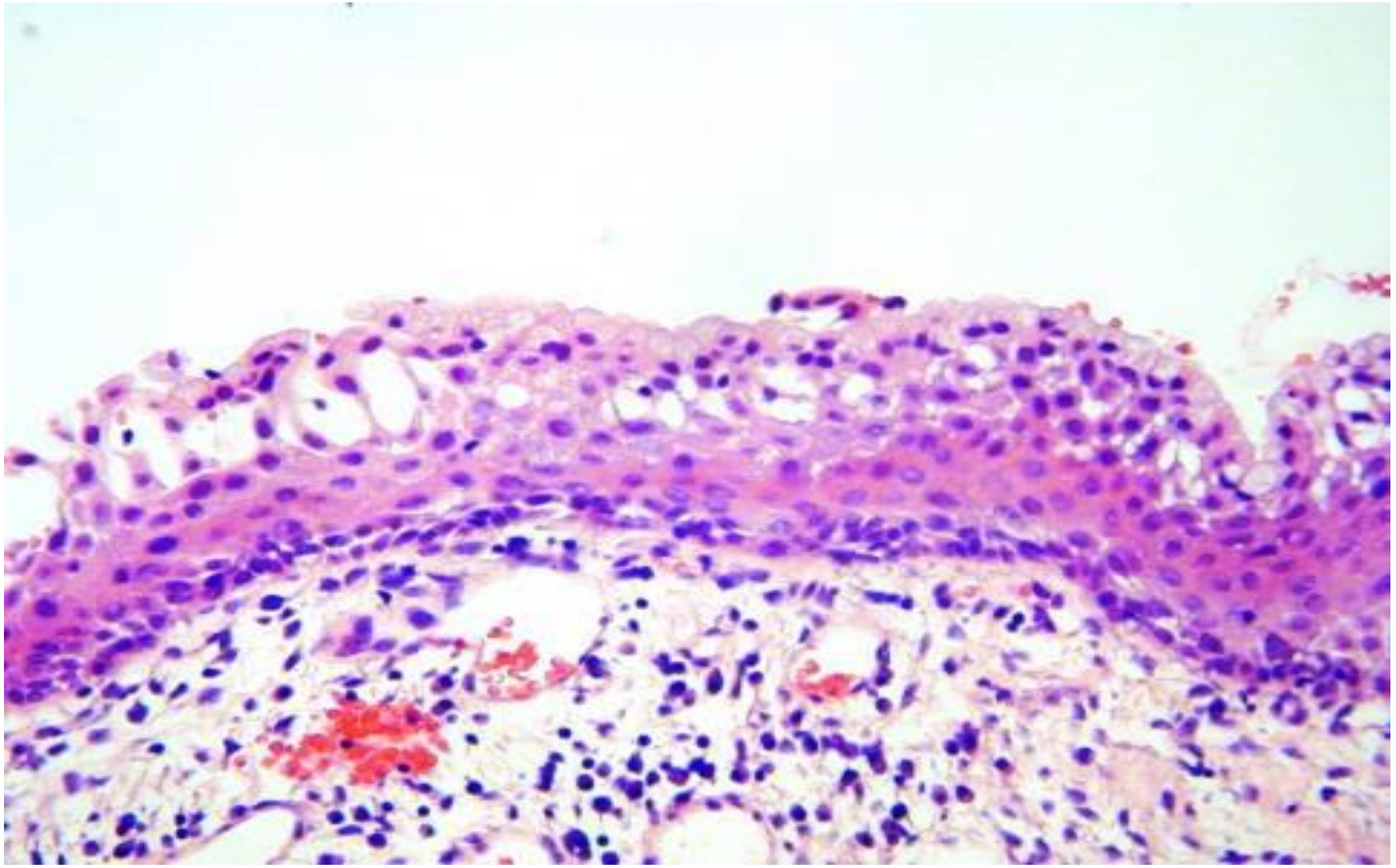
P16 immunohistochemistry interpretation

P16 figures in HSIL

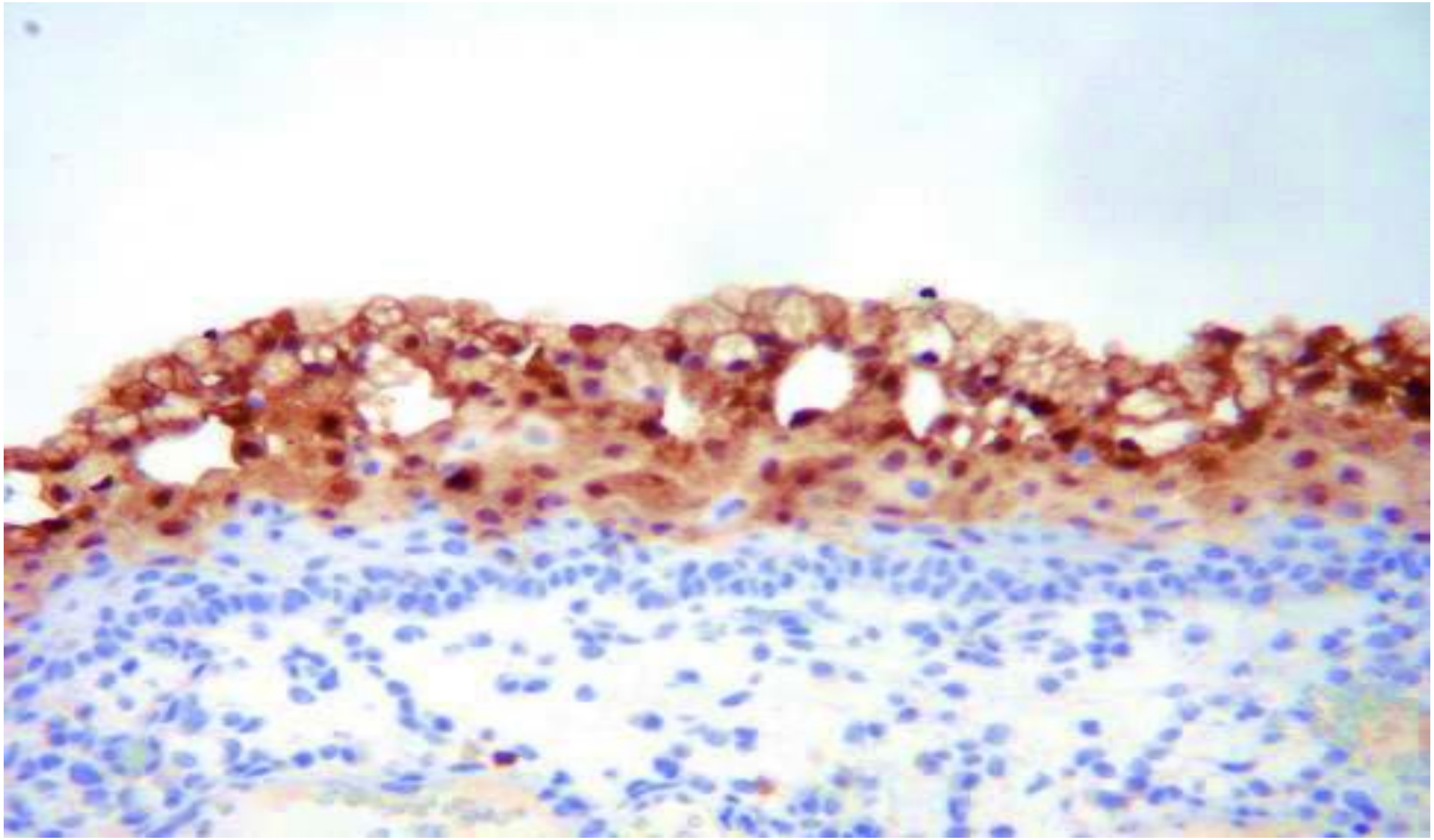
- Intense cytoplasmic and nuclear p16 positivity is typically present within the full thickness of the lesion or at least within its lower third (‘block positive’ staining) consistent with the presence of a HRHPV, most commonly HPV 16 (especially in younger women), less commonly types 18, 31, and others.
- Weak focal p16 staining is considered negative.
- Block positive p16 staining helps confirm a diagnosis of HSIL vs LSIL and HSIL vs its benign mimics and improves interobserver agreement in SIL grading.



Patchy p16 staining in normal cervical squamous epithelium.

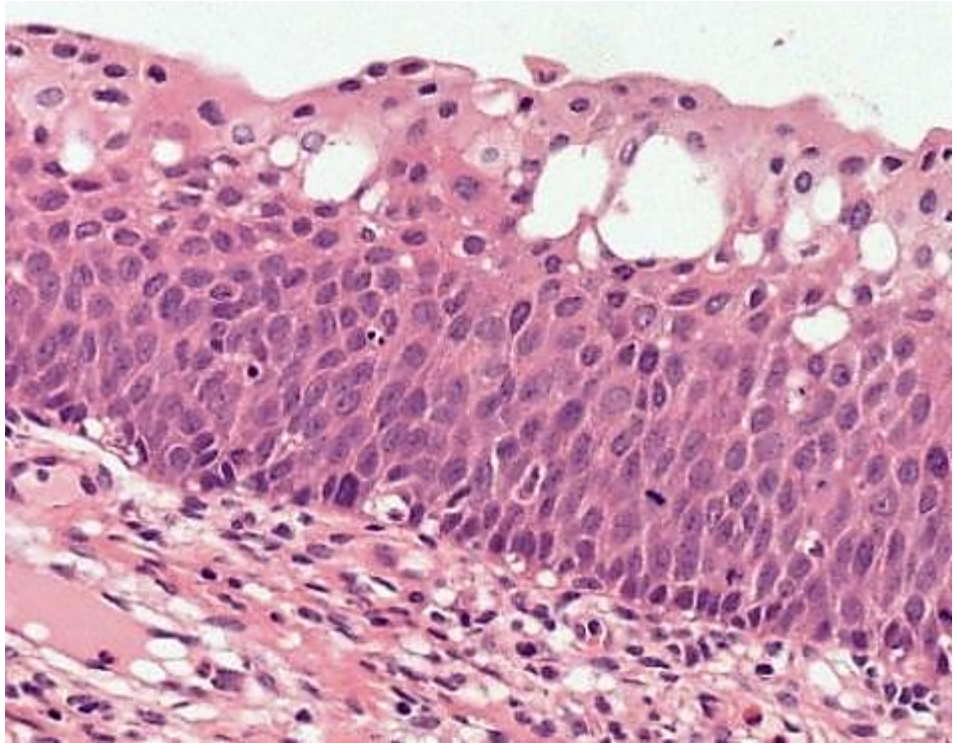


Immature squamous metaplasia of the cervix.

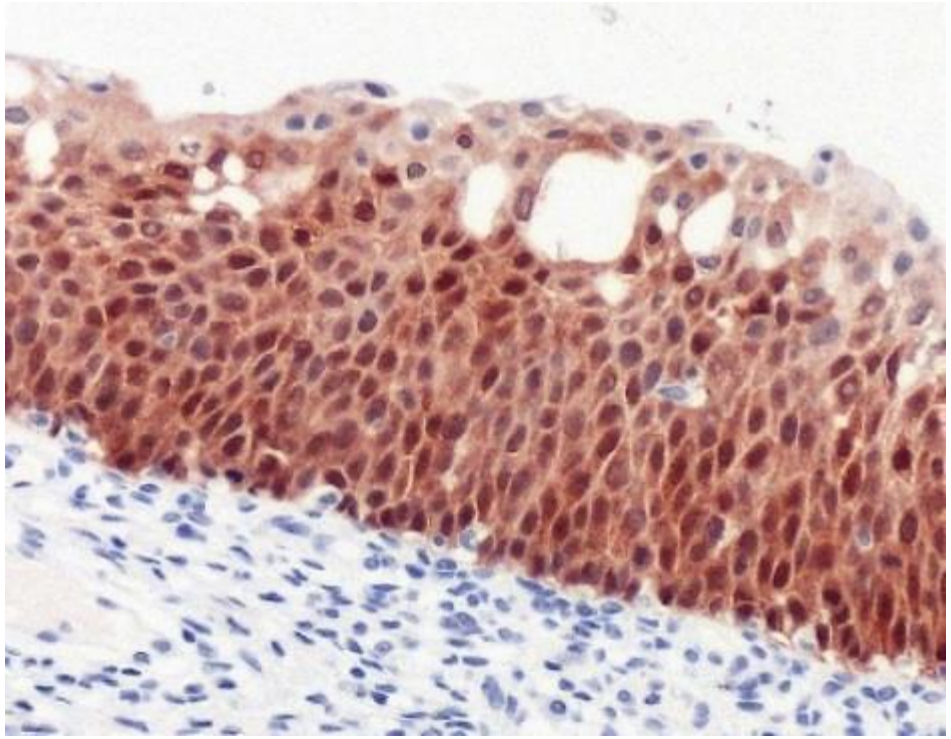


p16 staining in the immature metaplastic squamous epithelium is typically patchy with sparing of the basal layer.

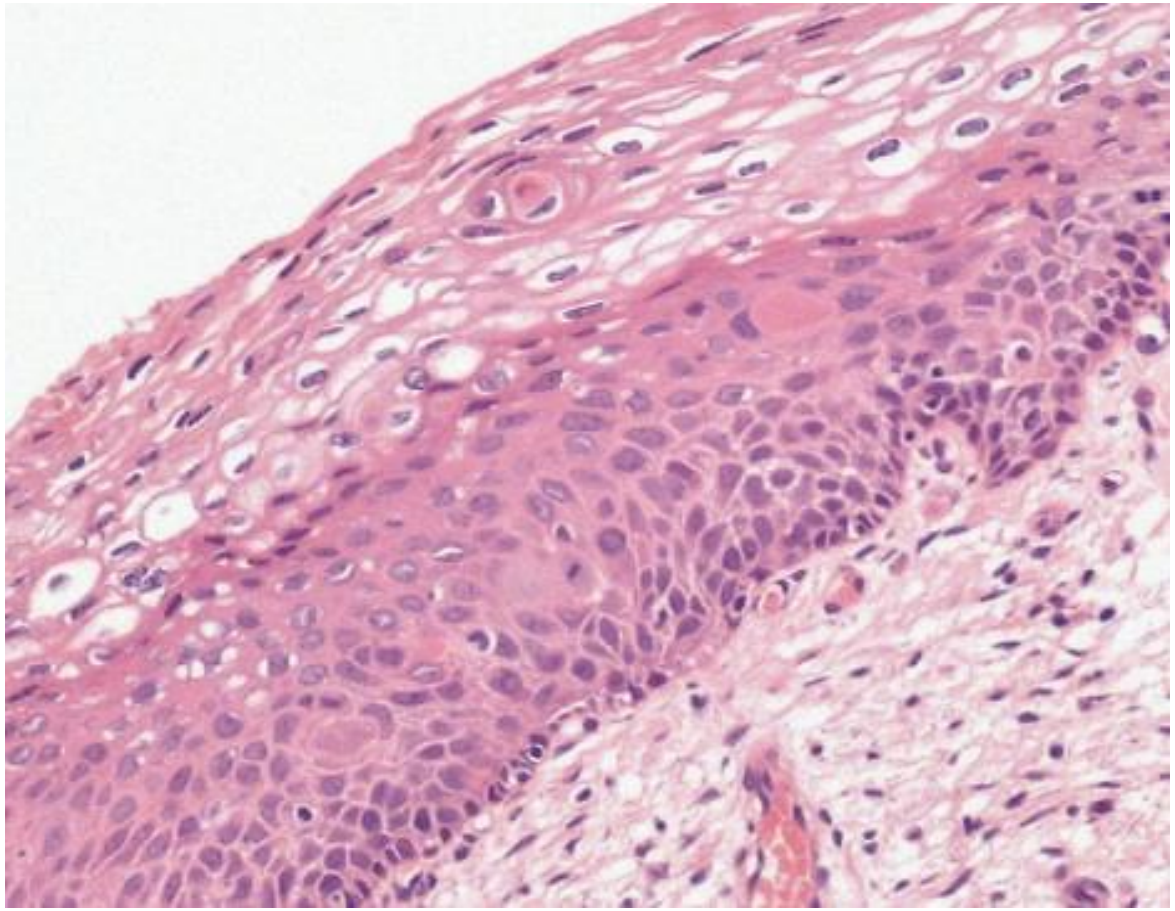
- ***Abnormal expression in squamous epithelial lesions fulfils ALL of the following (this pattern has been described as BLOCK POSITIVE staining):***
  - Strong and continuous nuclear OR more typically nuclear and cytoplasmic expression in all epithelial cells in the basal and parabasal layers with upward extension
  - Upward extension must involve at least the lower one-third of the epithelial thickness
  - Abnormal expression must extend for at least 6 cells across

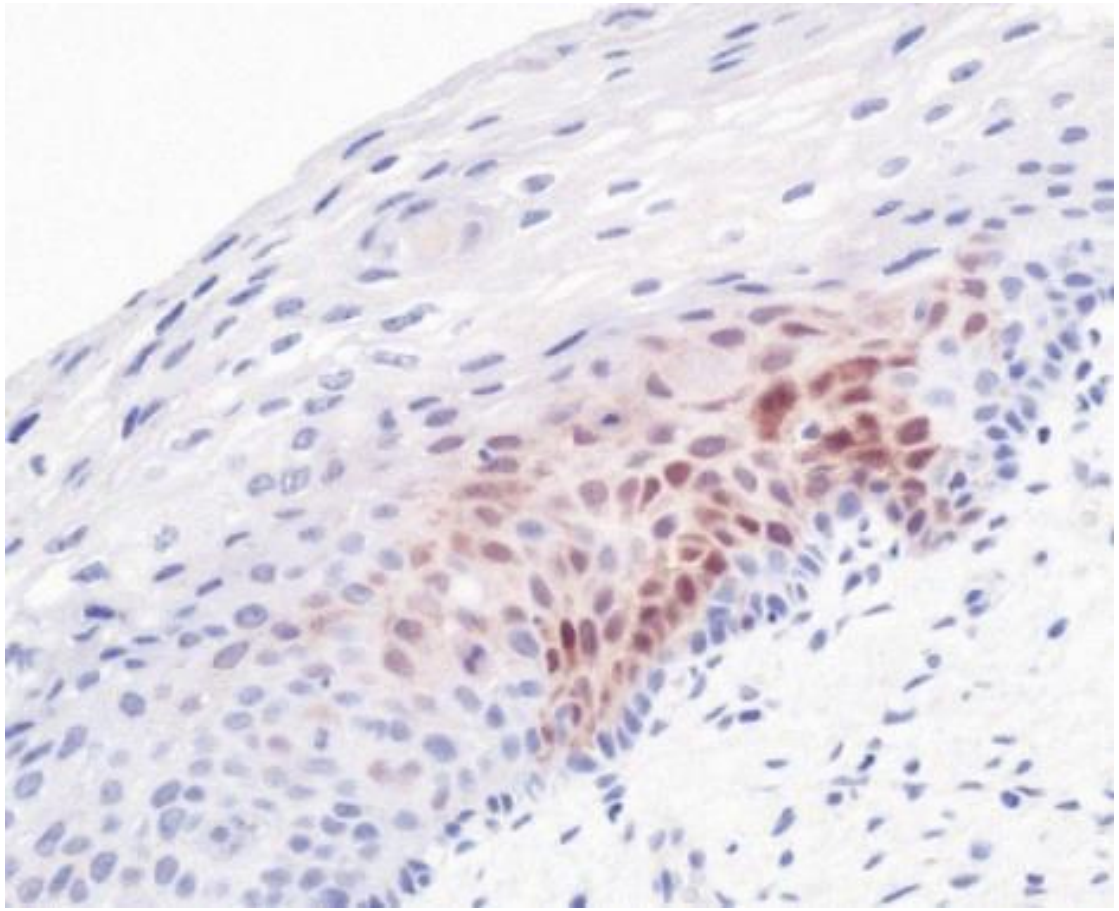


HSIL (CIN2) of the cervix

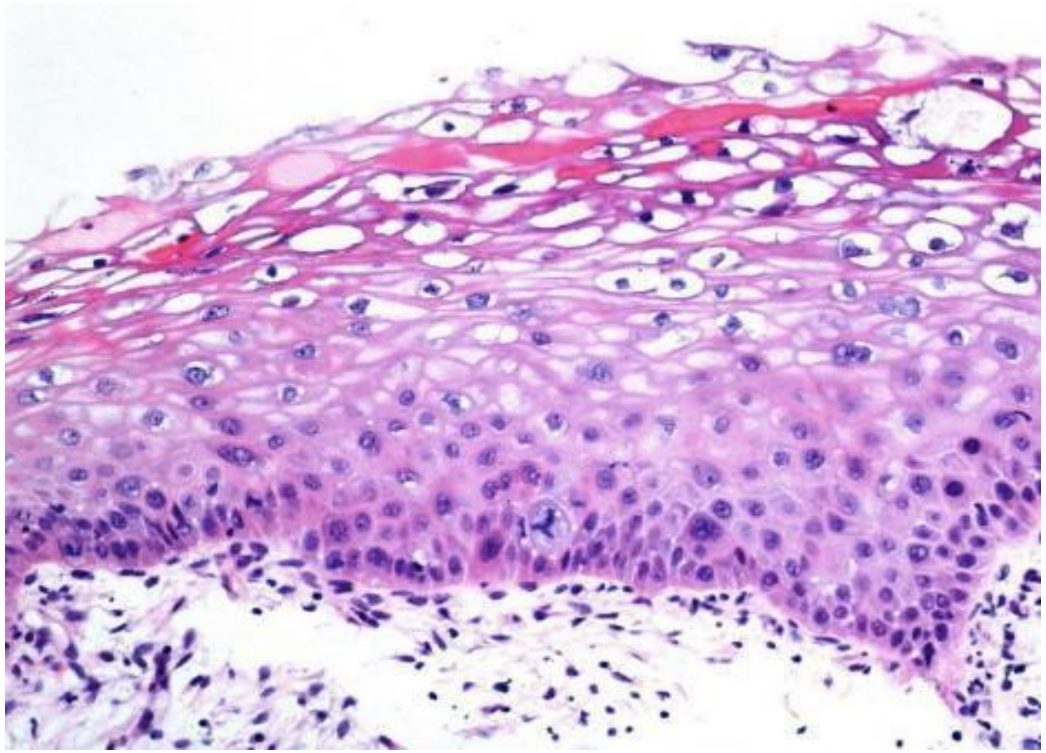


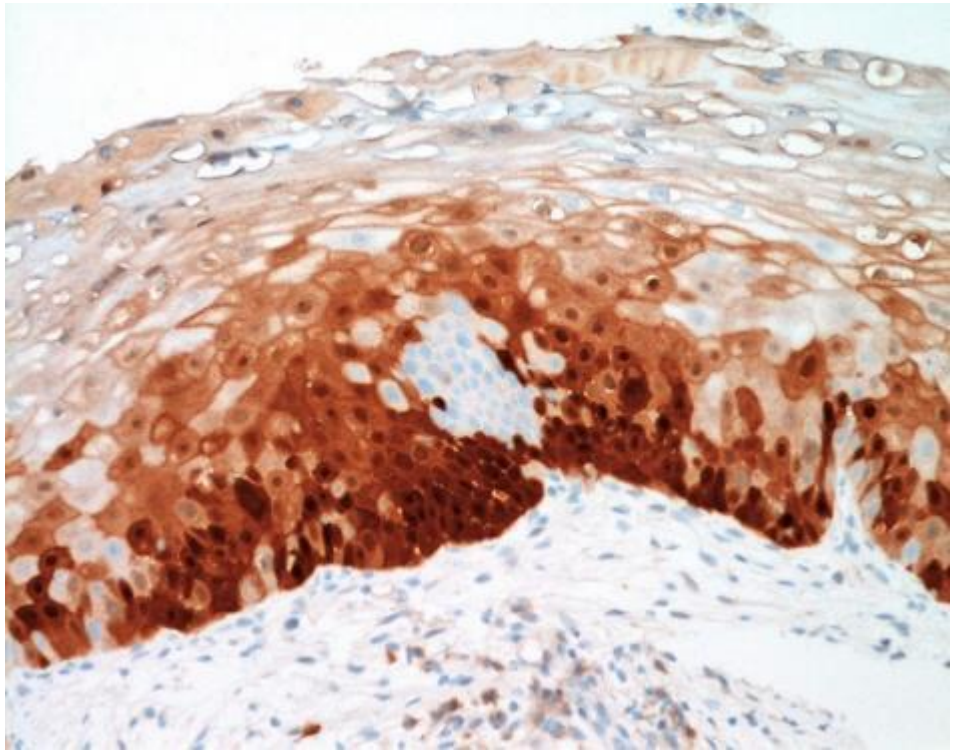
Diffuse/block positive expression of p16 in HSIL





Cervical squamous epithelium with morphological features indeterminate between HSIL and LSIL.
Patchy non-block staining for p16 supports the diagnosis of a non-hrHPV-associated LSIL in this context.





-Cervical squamous epithelium with maturation pattern resembling LSIL but atypical mitotic figure concerning for HSIL.

- The p16 staining meets the criteria of continuous basal positivity with upward extension to the lower one-third of the epithelial thickness, qualifying as diffuse/block positive. Note that this does not determine lesion grade, which should be assessed morphologically.

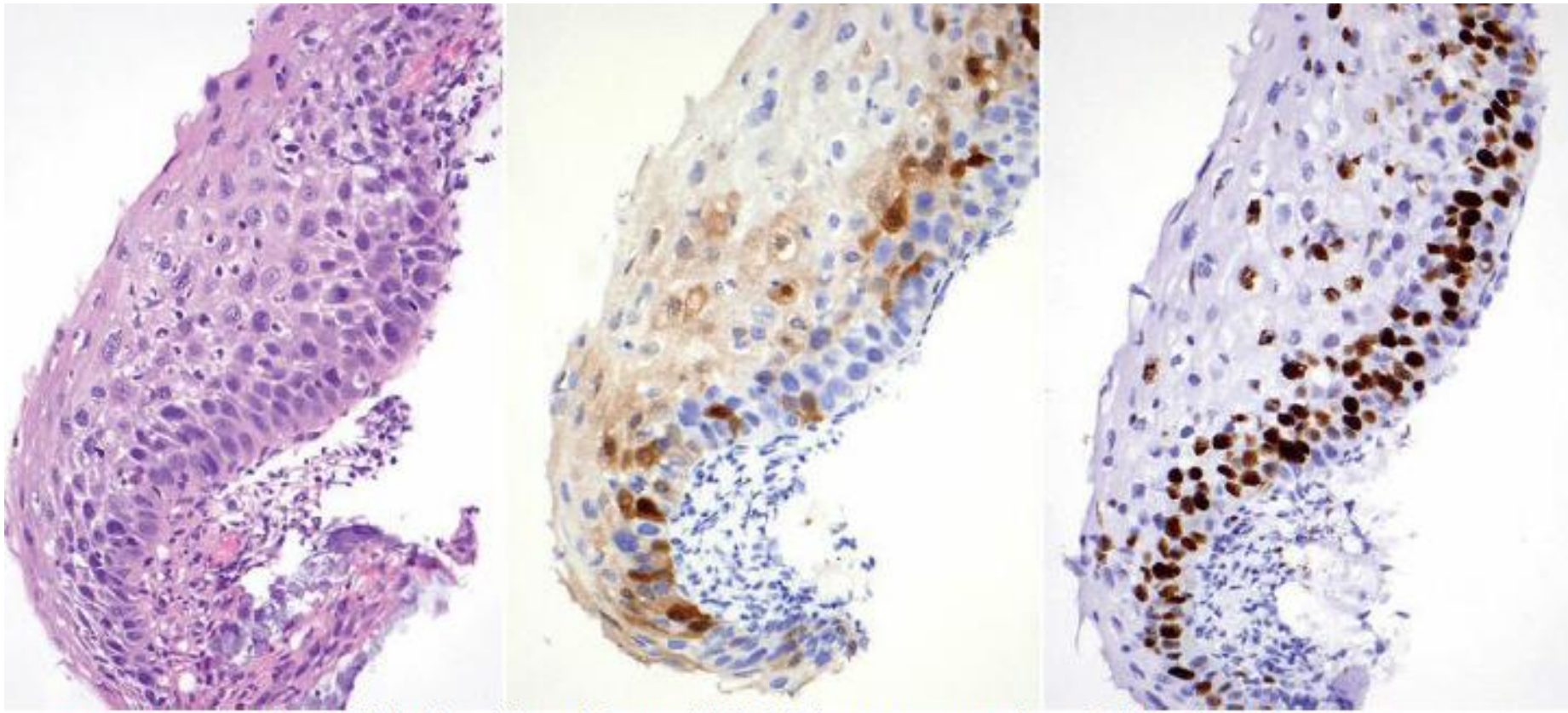
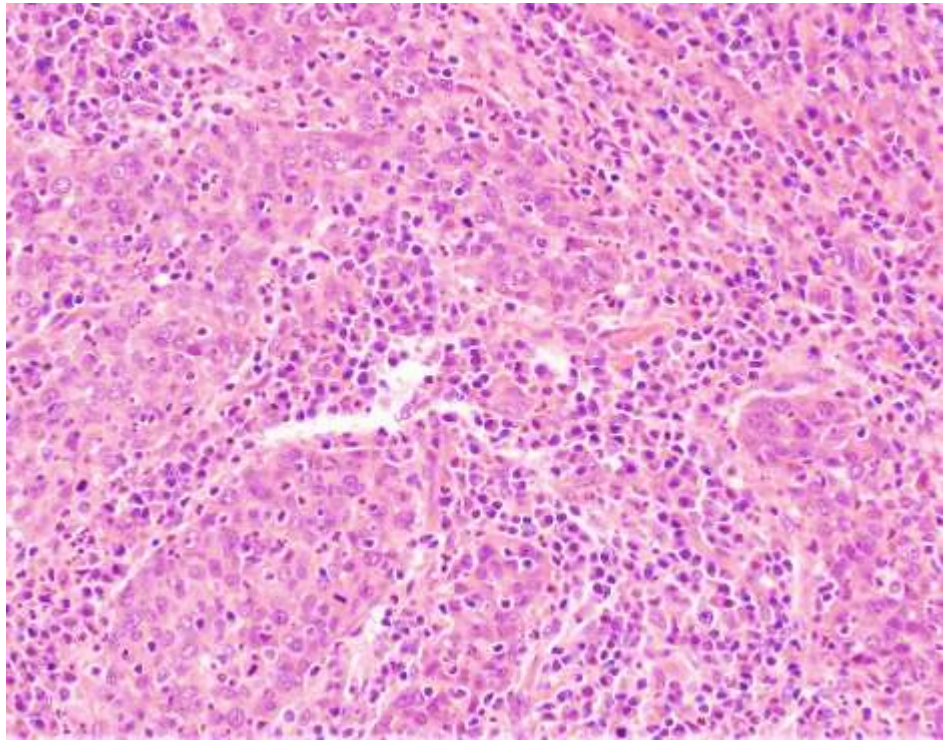
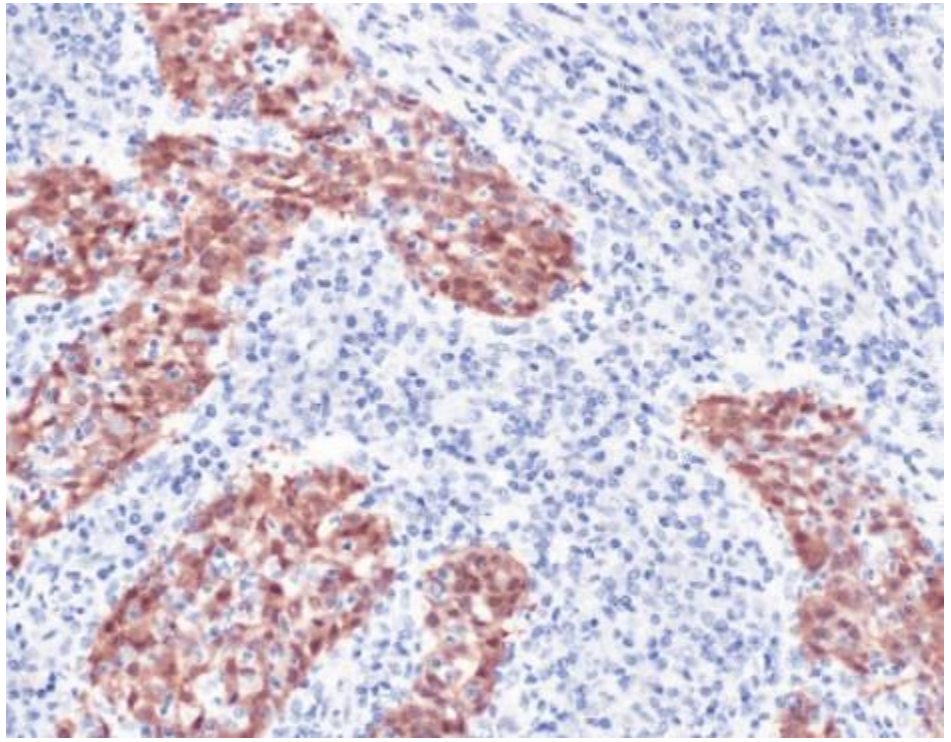


FIG. 5.7 LSIL (CIN 1) with p16 and Ki-67 immunostains. This dysplastic squamous epithelium is potentially morphologically concerning for HSIL (CIN 2) on H&E. The p16 immunostain (middle) demonstrates focal patchy staining, and the Ki-67 (right) is more prominent along the basal layer, making a diagnosis of LSIL (CIN 1) most appropriate.

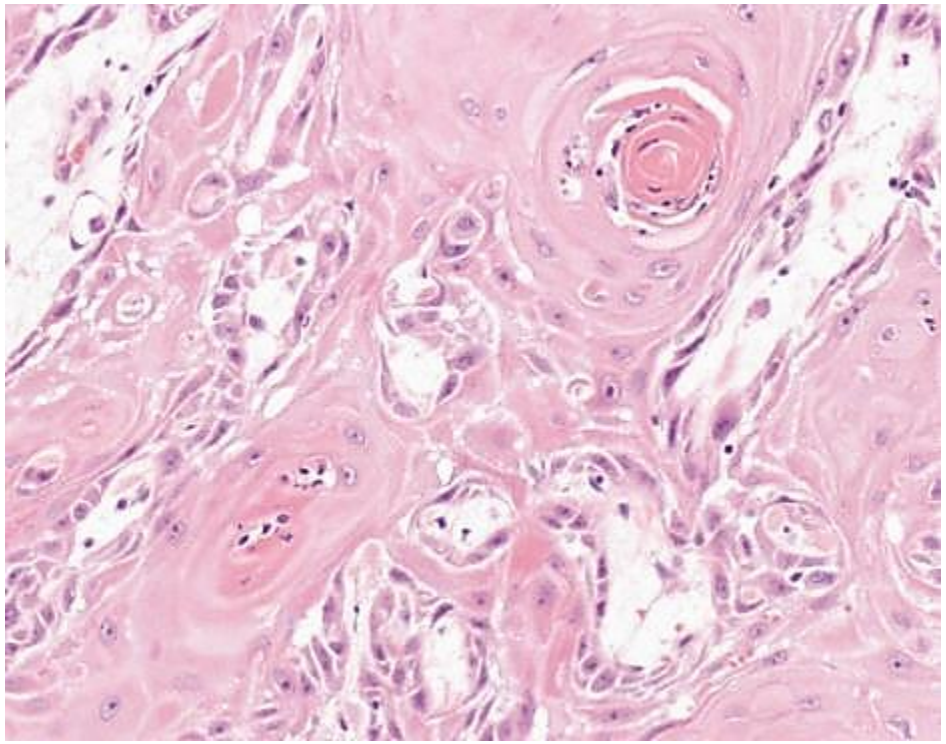
- **Reporting terminology:**
  - Use of the word ‘positive’ is not recommended in pathology reports owing to potential for confusion.
  - Report as
    - PRESENCE vs ABSENCE OF ABNORMAL (DIFFUSE/BLOCK POSITIVE) EXPRESSION

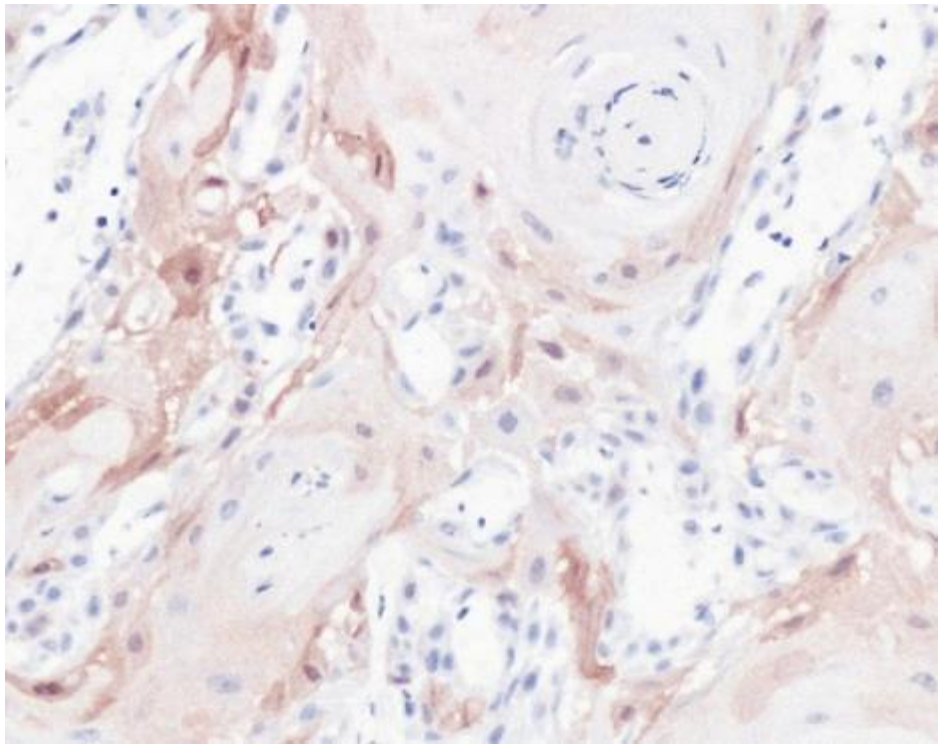
      OR
    - ABNORMAL (DIFFUSE/BLOCK POSITIVE EXPRESSION) vs NEGATIVE/NORMAL expression





Cervical squamous cell carcinoma, non-keratinizing type
Diffuse p16 staining in the carcinoma cells are typical of hrHPV-associated carcinoma..





Vulval squamous cell carcinoma, keratinizing type.
Focal non-block p16 staining in the absence of continuous basal positivity is in keeping with an HPV-independent etiology.

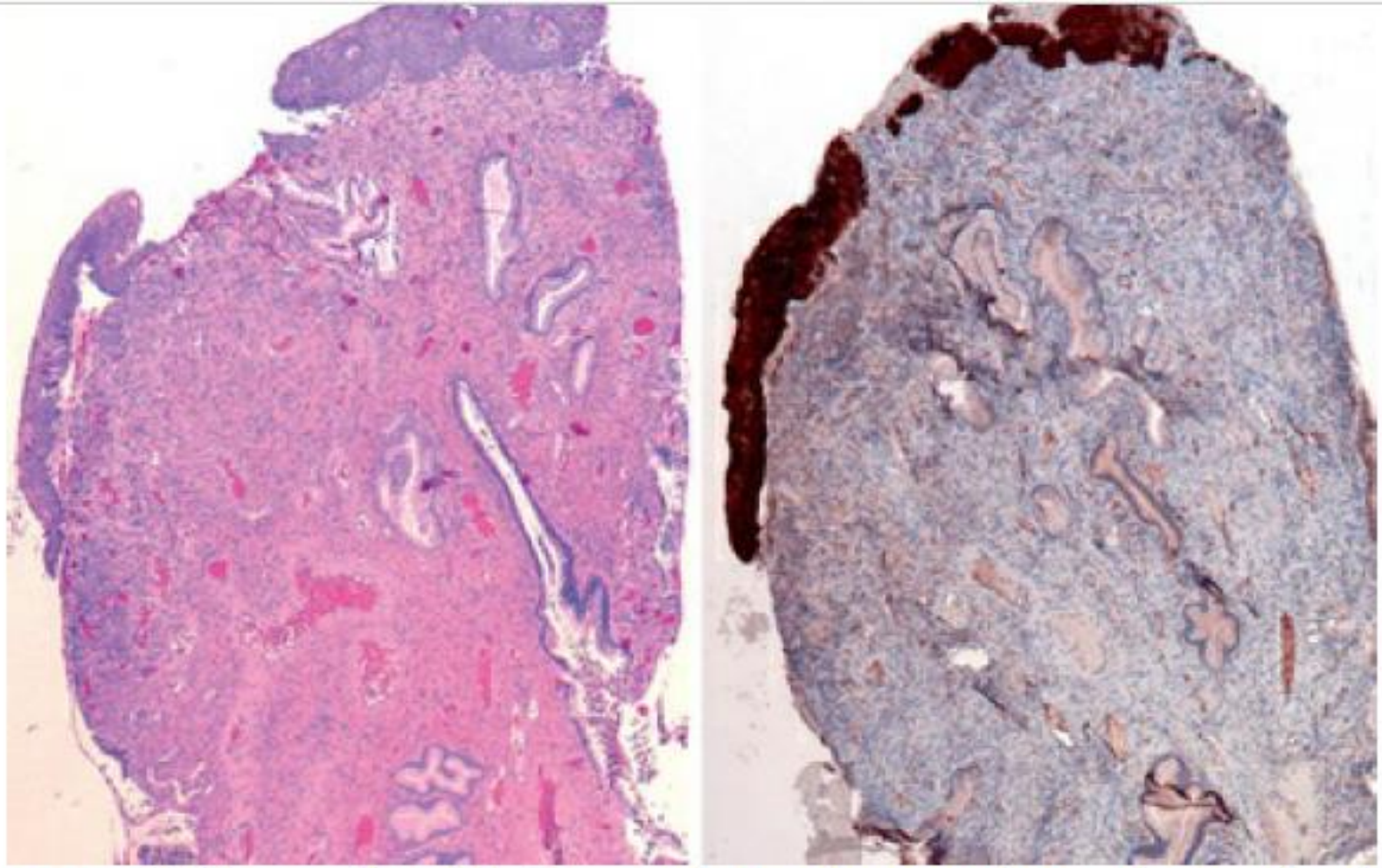


FIG. 5.14 HSIL confined to the surface of an endocervical polyp (left, H&E; right, p16 stain).

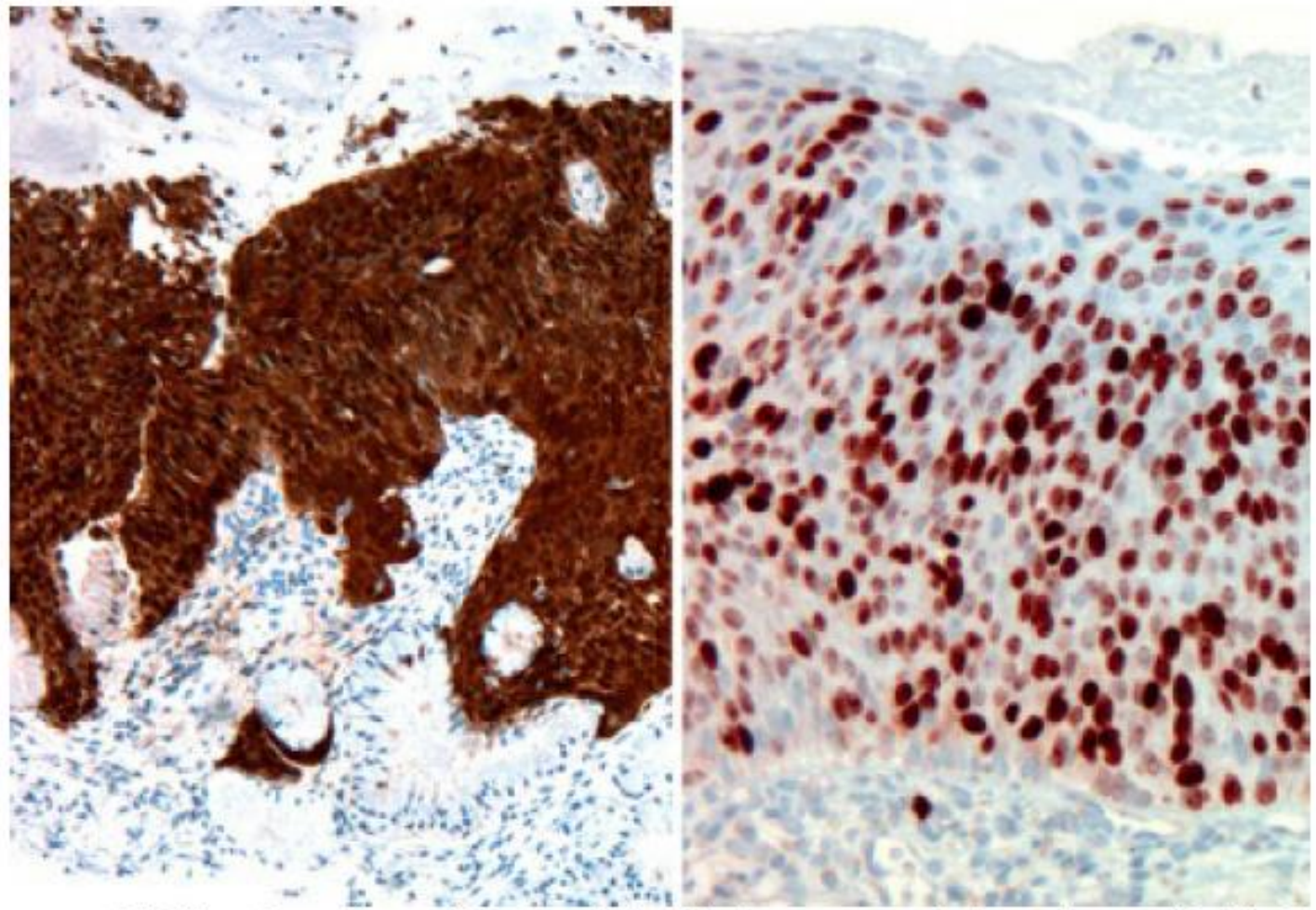


FIG. 5.15 HSIL showing diffuse full-thickness staining for p16 (left) and MIB1 (right).

Significance of p16 in anogenital intraepithelial neoplasia

Can p16 be used to grade squamous intraepithelial neoplasia?

- p16 is not a surrogate for grade; up to 50% of cases of LSIL (HPV/CIN1) are p16 positive.
- Grading of SIL (CIN) should be based on morphological criteria.

Does the thickness of stained epithelium matter?

- Although staining broadly mirrors the extent of epithelial differentiation, the extent of vertical p16 staining within the squamous epithelium does not *necessarily* correlate with CIN grade.

Is p16 expression abnormal in all high risk HPV infections?

- Abnormal p16 IHC is a marker of E7 mediated inactivation of Rb protein and is therefore a *diagnostic* marker of transforming hrHPV infection (*necessary but not sufficient* for progression to cancer).
- p16 expression is not abnormal in ALL hrHPV infections as these form a spectrum from silent, though productive to transforming/abortive infections; abnormal p16 expression is not seen in silent/latent infections and in half of the CIN1 lesions caused by hrHPV.

ProExC

- ProExC is a newer marker that targets the expression of genes overexpressed in cervical cancer. In contrast to nondysplastic lesions, almost all HSILs exhibit strong nuclear staining with ProExC within the full thickness (75–100%) of the lesion.
- Guo et al. found that using ProExC and p16 provided a higher specificity for the detection of HSIL than either marker alone.

Mitotic figures in HSIL

- Mitotic figures, normal and abnormal, are usually present in all layers.
- Mimica et al. found that >33% MIB1+ cells in the upper two-thirds of the epithelium was a highly specific and sensitive discriminator for HSIL vs LSIL. Similar findings were reported by Galgano et al.,

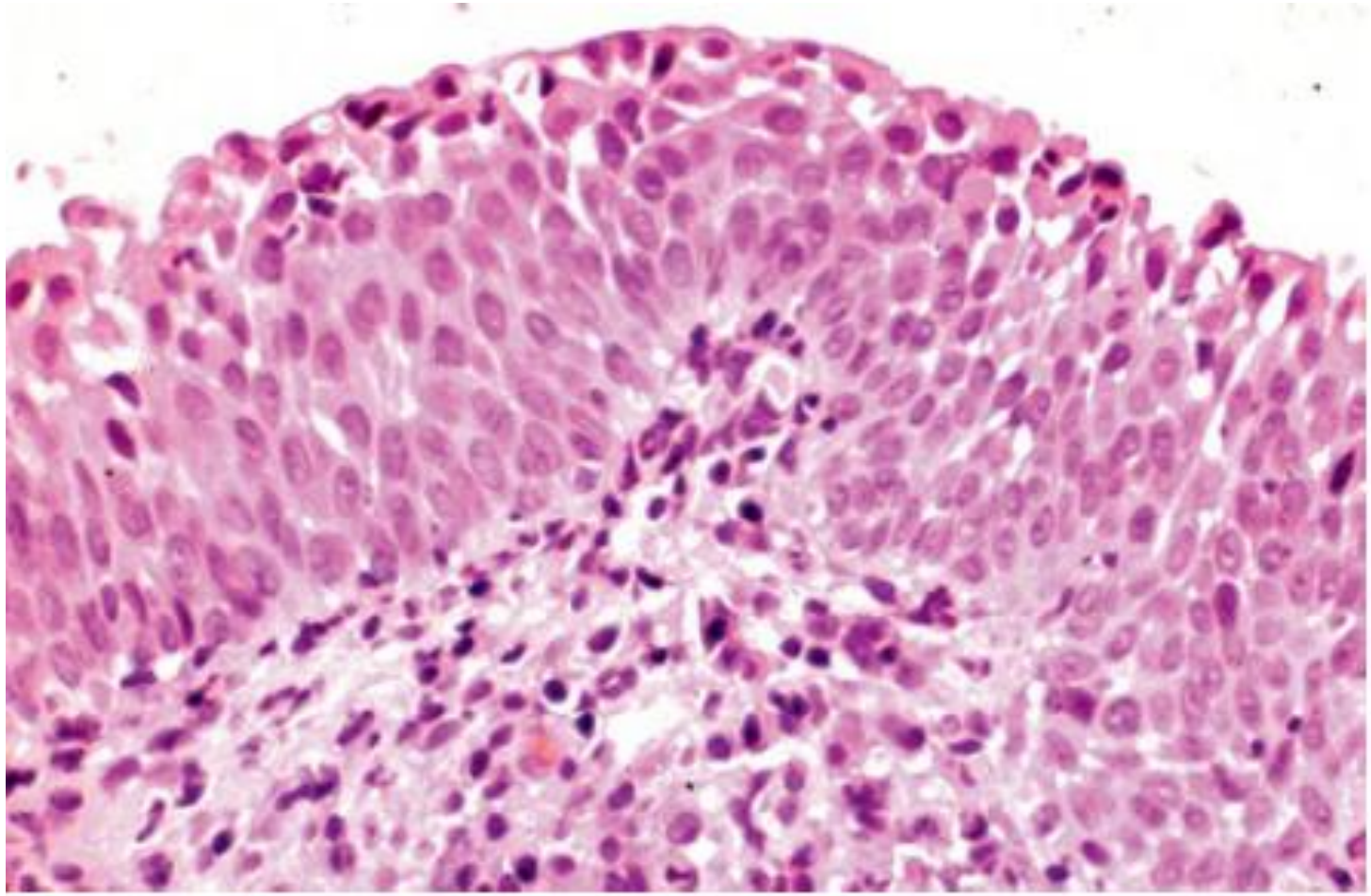
Differential diagnosis of SILs

Condyloma (LSIL) vs squamous papilloma & fibroepithelial polyps.

- Condyloma (LSIL) vs squamous papilloma and fibroepithelial polyps. The presence of koilocytes is usually diagnostic of condyloma, but in its absence, any MIB-1+ cells in the upper two thirds of the epithelium strongly favor condyloma (Pirog et al.).

In its early phases, metaplastic squamous epithelium

- In its early phases, metaplastic squamous epithelium is often composed of a monotonous population of cells with a high N:C ratio that lack the cytoplasmic maturation in the superficial layers present in mature squamous metaplasia.
- In contrast to SILs, immature squamous cells have minimal crowding, absent to mild cytologic atypia, uniformly distributed fine chromatin, and smooth nuclear contours. Mitoses are uncommon and if present are typical and confined to the basal layers. The papillarity, koilocytosis, and p16 staining of papillary immature metaplasia are absent.
- Florid squamous metaplasia that can be mistaken for ISqCC.



.Typical immature squamous metaplasia

Papillary immature metaplasia (PIM)

- PIM, which may extend into the endocervical canal, is characterized by filiform papillae composed of immature parabasal-type squamous cells with bland features. Endocervical columnar cells may persist on the surface of the lesion.
- There is minimal cell crowding, well-defined cell membranes, an increased N:C ratio, smooth nuclear contours, and uniformly distributed, fine chromatin.
- Mitoses are uncommon and typical.
- Superficial koilocytes are usually present focally, consistent with the usual presence of low-risk HPV.However, rare PIMs abut an HSIL, presumably due to a synchronous HRHPV infection.
- PIMs have a low Ki-67 index in the mid and upper layers, in contrast to HSILs and most papillary squamous carcinomas , lesions with which PIM may be confused.

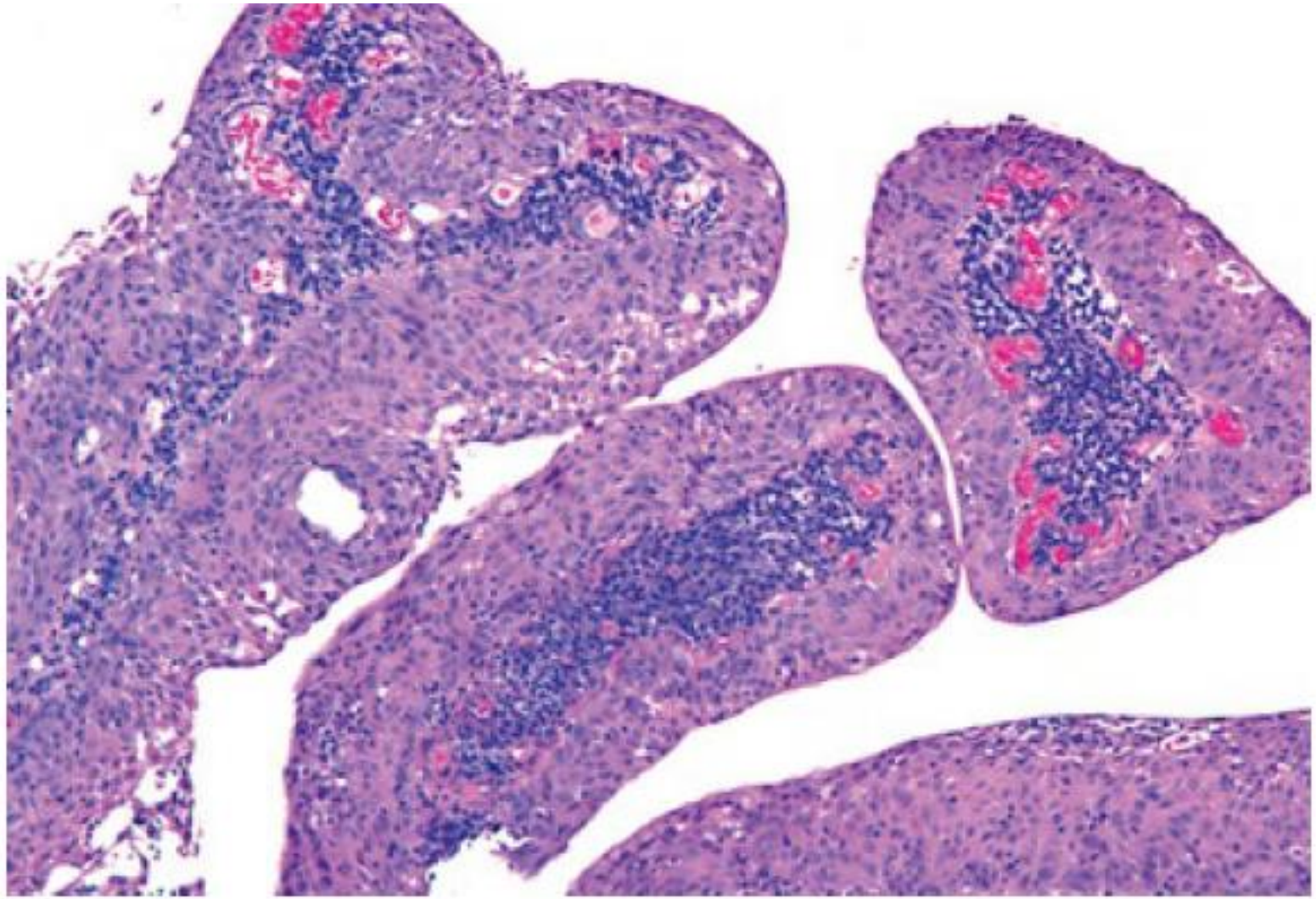


FIG. 5.19 Papillary immature metaplasia.

Atypical immature squamous metaplasia (AIM).

- AIM has been applied to lesions with absent or minimal maturation of metaplastic squamous epithelium, absent or minimal koilocytosis, and mild nuclear pleomorphism; mitotic figures are rare and confined to the lower third of the epithelium. There is considerable interobserver variation in its recognition.
- *HPV and Ki-67 analyses* :

indicate that AIMs are a heterogenous group that includes HSILs (HRHPV+, high Ki-67 index), possible precursors of HSILs (HRHPV+,absent to low Ki-67 index), and benign reactive lesions (HPV-, absent to low Ki-67 index).

Reactive and reparative changes

- Reactive nuclear atypia, which may include nucleomegaly, hyperchromasia, and bi- or multinucleation, is usually confined to the lower layers (in contrast to SILs), with normal maturation and minimal nuclear enlargement in the upper layers. There may be a sharp demarcation between the atypical cells in the lower layers and the mature cells in the upper layers.
- Unlike typical SILs, reactive cells often show spongiosis,distinct cell borders, regular nuclear spacing, prominent nucleoli or chromocenters, and an absence of marked variation in nuclear size and contour and coarse hyperchromasia. Cytoplasmic halos, if present, are round and uniform with central nuclei.

- Intraepithelial neutrophils may be seen. Numerous neutrophils, ulceration, and necrotic cells should prompt a search for herpetic inclusions . Dense acute and chronic inflammation with lymphoid follicles (follicular cervicitis) suggests chlamydial infection.
- Absence of p16 staining facilitates the distinction from SILs. Also, in contrast to HSILs, Ki-67 staining is usually confined to the lower third of the epithelium.

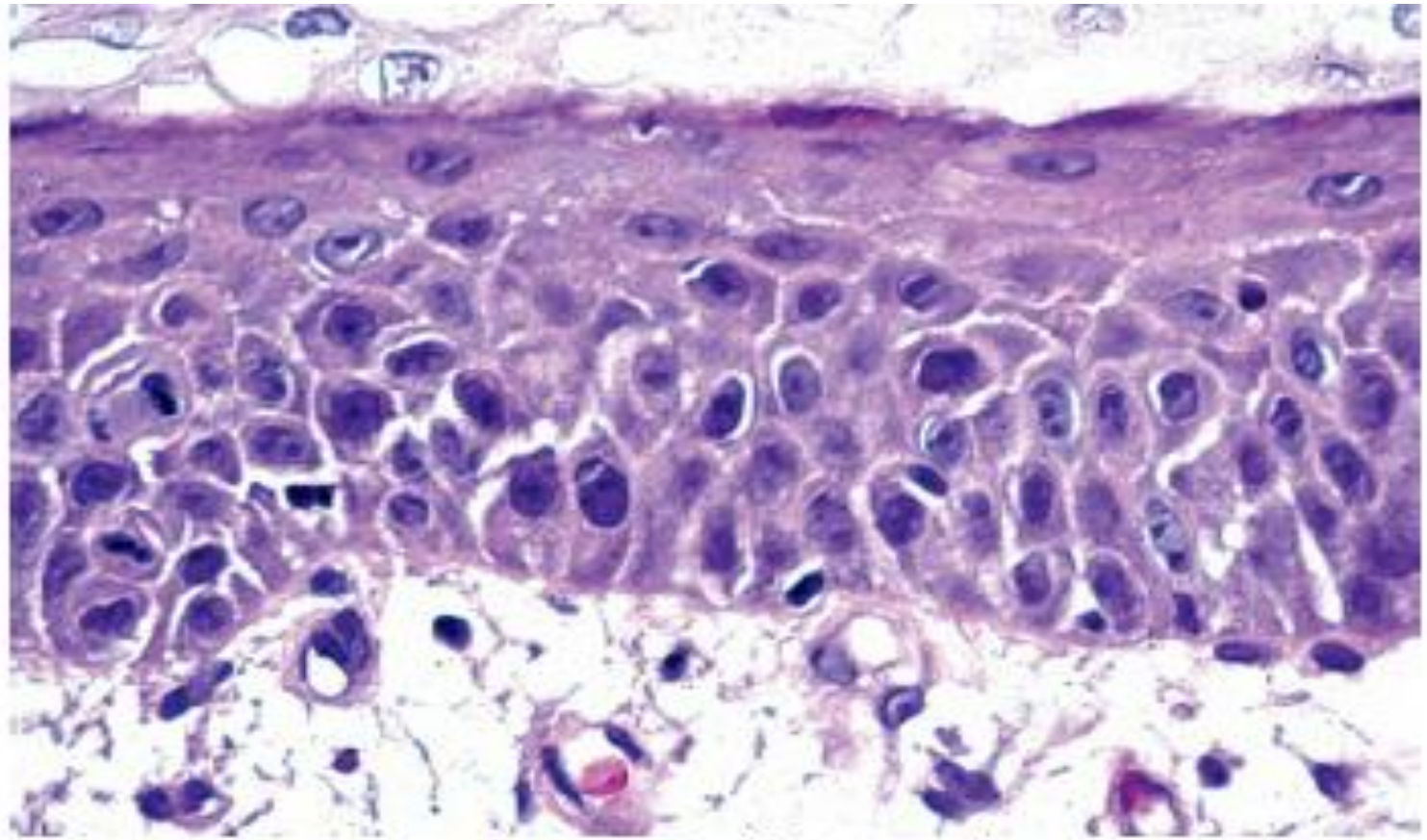


FIG. 5.20 Reactive atypia. Note prominent nucleoli.

Postmenopausal squamous atypia (PSqA) and other forms of pseudokoilocytosis

PSqA, which usually occurs in women >50 years of age,is characterized by prominent perinuclear halos, no more than 2-fold nuclear enlargement, hyperchromasia, and multinucleation. These findings may be misdiagnosed as LSIL, but PSqA is negative for HPV.

There may be associated atrophy and/or transitional cell metaplasia.

Compared to koilocytotic atypia, PSqA has less variation in nuclear size (<2- vs >3-fold) and staining intensity and more finely and evenly distributed nuclear chromatin. The nuclei are uniformly spaced and slightly elongated and lie centrally within a uniformly contoured halo.Occasional nuclear grooves may be present; mitoses are rare or absent.

An absence of bi/multinucleated cells favors PSqA over koilocytotic atypia, whereas the presence of ≥2 binucleated cells in a high-power-field strongly suggests koilocytotic Atypia.

Other forms of pseudokoilocytosis include those in which perinuclear halos occur as an isolated finding with no nuclear atypia (as in normal glycogenated squamous epithelium) or perinuclear halos with mild reactive atypia.

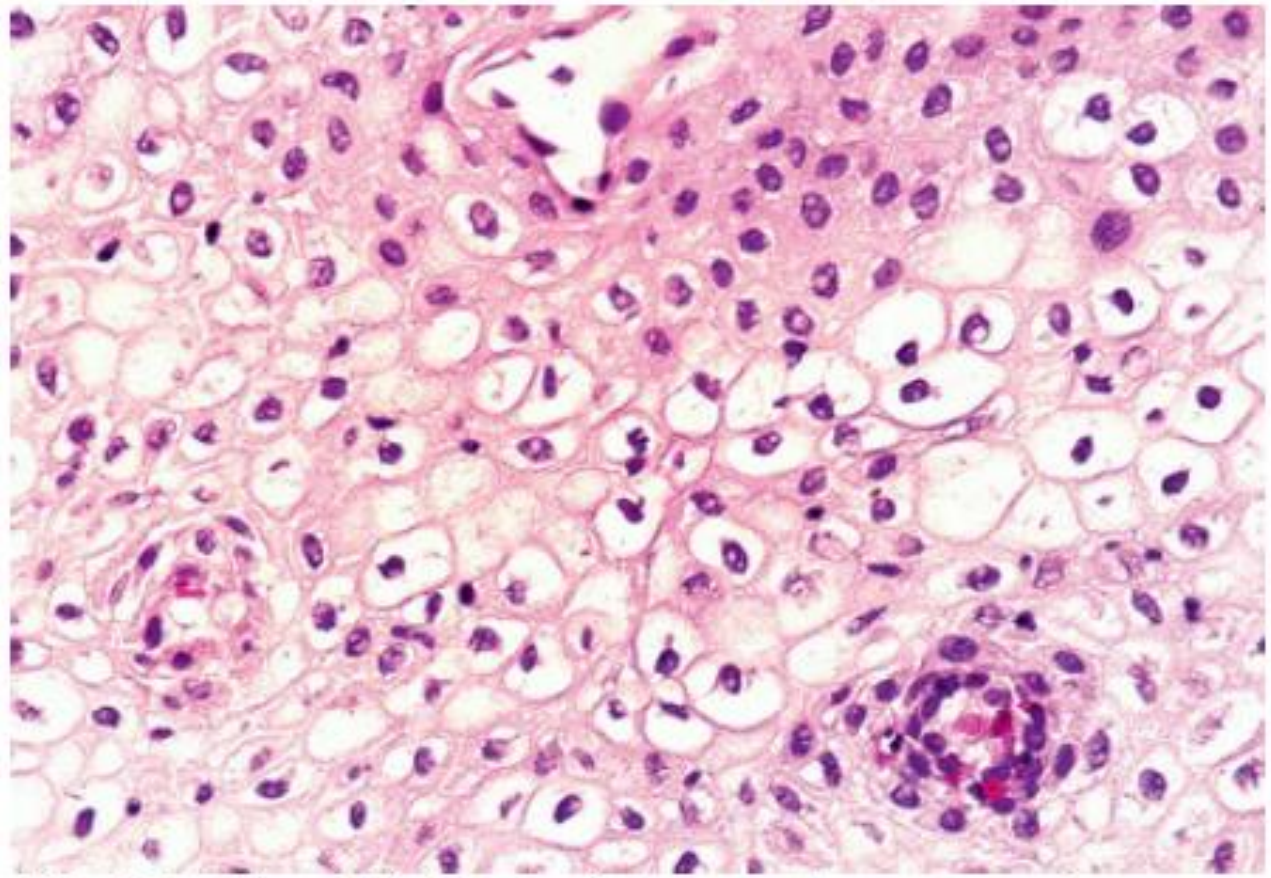


FIG. 5.21 Pseudokoilocytosis in a postmenopausal woman.

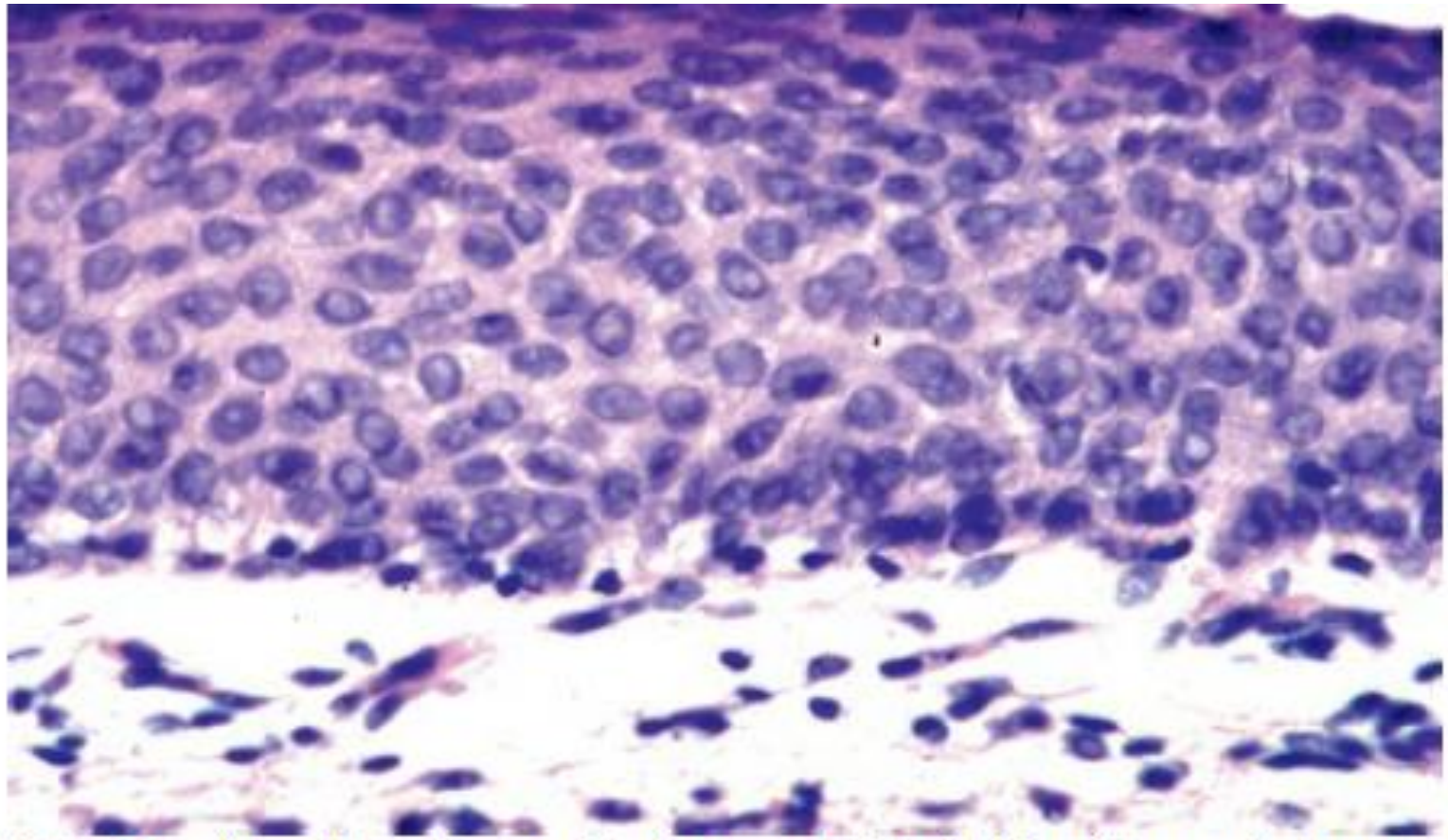


FIG. 5.22 Atrophy. The cells have a high N:C ratio and show no maturation, but the nuclei lack dysplastic features and mitotic figures.

- Transitional cell metaplasia (TCM) and atrophy.
- These processes can suggest a SIL due to loss of the normal maturation and cells with a high N:C ratio, as can enigmatic p16 positivity in some TCMs. The absence of nuclear atypia and mitotic activity points to the correct diagnosis. Additionally, atrophic epithelium is thin and lacks Ki-67 and p16 staining.

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