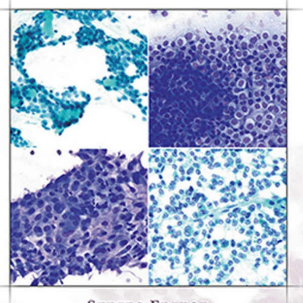
Differential Diagnoses in Surgical Pathology

Cytopathology

Christopher J. VandenBussche
Syed Z. Ali



Series Editor
Jonathan I. Epstein

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Preface

The practice of cytopathology revolves around the creation of a differential diagnosis. Often, without the benefit of the level of architecture seen in histologic sections, the cytopathologist must use the smallest cytomorphologic clues—and even look beyond cells and into the surrounding background—to narrow the differential diagnosis or even arrive at a singular diagnosis.

This book compares similar entities that are often in the differential diagnosis together and focuses on those small details that can help favor one entity over another. In addition to high yield, bulleted cytomorphologic descriptions and representative images, the book also includes important clinical differences between lesions, as well as the latest molecular alterations associated with each entity, when known.

Some of the presented entities are common, while others are rare. This book may be used to learn about a given entity in more detail, to broaden a differential diagnosis, or eliminate less likely diagnoses from a differential. Whether used in a pinch or read from cover-to-cover, we hope this book will become a trusted reference for the reader when cytopathology specimens are encountered.

Christopher J. VandenBussche and Syed Z. Ali

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Gynecologic Cytopathology

1.1 Low-Grade Squamous Intraepithelial Lesion (LSIL) Versus High-Grade Squamous Intraepithelial Lesion (HSIL)

	Low-Grade Squamous Intraepithelial Lesion (LSIL)	High-Grade Squamous Intraepithelial Lesion (HSIL)
Age	Any age but more likely to be transient infection in younger women	Any age
Location	Cervix (also vagina, anus, and vulva)	Cervix (also vagina, anus, and vulva)
Signs and symptoms	None; detected on routine screening or on colposcopy	None; detected on routine screening or on colposcopy
Etiology	Premalignant lesion associated with both low- and high-risk HPV	Premalignant lesion more commonly associated with high-risk HPV types
Cytomorphology	• Squamous cells with enlarged nuclei (Figures 1.1.1 and 1.1.2) • Irregular nuclear borders and/or "raisinoid" nucleus (Figures 1.1.3 and 1.1.4) • Occasional binucleation (Figure 1.1.5) • Koilocytes have, in addition to the above features, a well-defined polygonal perinuclear halo with sharp edges and central clearing (Figures 1.1.3 and 1.1.4)	• Cellular fragments and dispersed single cells (Figures 1.1.6 and 1.1.7) • High N/C ratio due to increased nuclear size and decreased amounts of cytoplasm (Figure 1.1.8) • Hyperchromatic nuclei without prominent nucleoli (Figure 1.1.8) • Markedly irregular nuclear borders (Figure 1.1.9) • Anisonucleosis may be present (Figure 1.1.2) • Dense, opaque cytoplasm in individual cells (Figure 1.1.9)
Special studies	HPV studies	HPV studies
Molecular alterations	Under investigation; mostly driven by HPV oncogenes	Under investigation; mostly driven by HPV oncogenes
Treatment	Colposcopy to exclude the presence of HSIL	Complete excision
Clinical implications	Often regresses, especially in young women	May progress to squamous cell carcinoma if incompletely excised

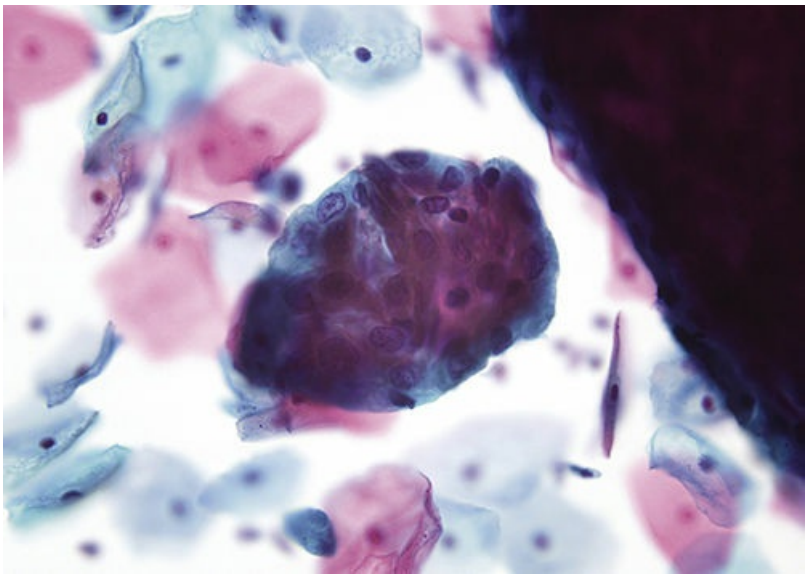

FIGURE 1.1.1 Low-grade squamous intraepithelial lesion (LSIL). A fragment of atypical squamous cells. The amount of cytoplasm is maintained, but the nuclei are significantly larger than those seen in adjacent intermediate cells.

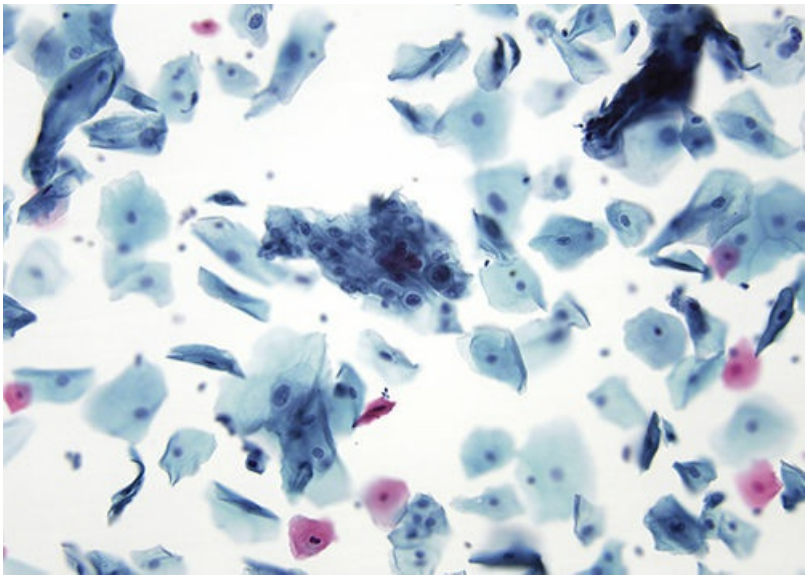

FIGURE 1.1.2 Low-grade squamous intraepithelial lesion (LSIL). The cells in this central fragment have polygonal cytoplasm and their nuclei are enlarged compared with adjacent intermediate cells. Examination at higher magnification is required to determine whether perinuclear halos are present, but greatly increased nuclear size alone is sufficient for a diagnosis of LSIL.

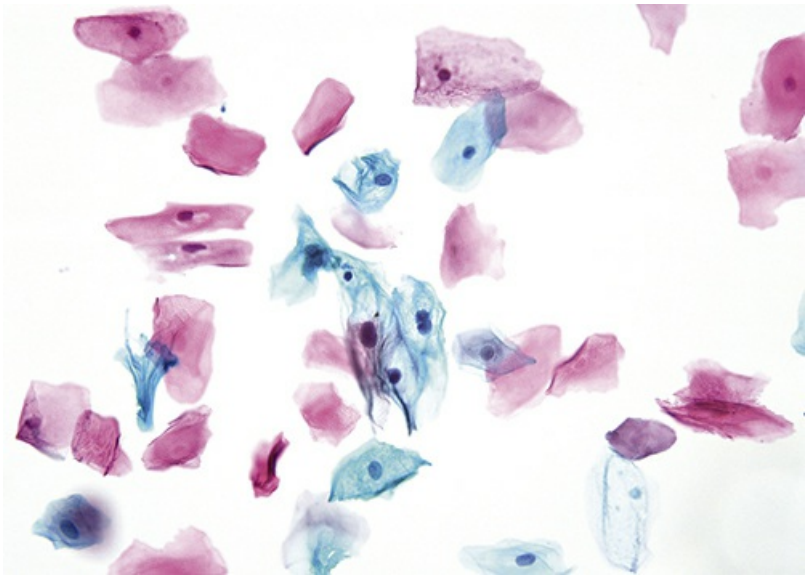

FIGURE 1.1.3 Low-grade squamous intraepithelial lesion (LSIL). These cells are koilocytes because they have nuclear atypia (hyperchromasia, enlargement, and binucleation) and perinuclear clearing (halo) with sharp edges.

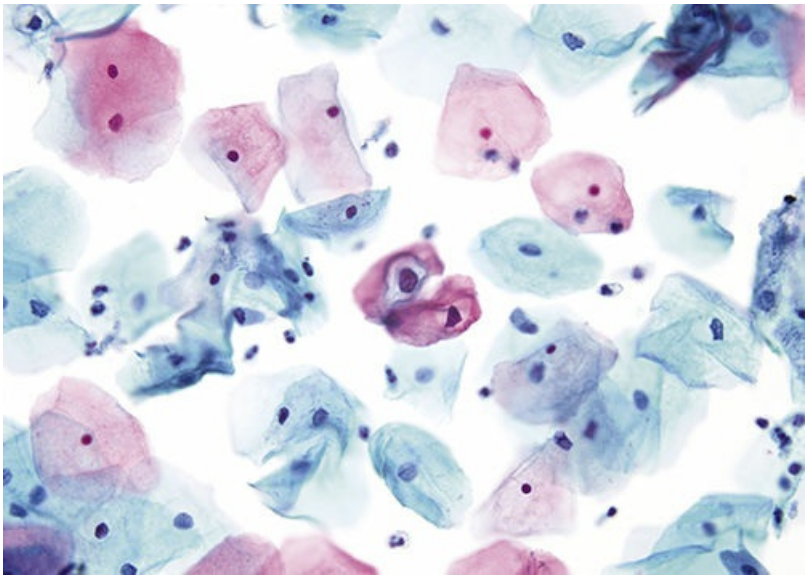

FIGURE 1.1.4 Low-grade squamous intraepithelial lesion (LSIL). These koilocytes have enlarged nuclei with irregular borders ("raisinoid nuclei"), hyperchromasia, and polygonal shaped, well-defined perinuclear halos.

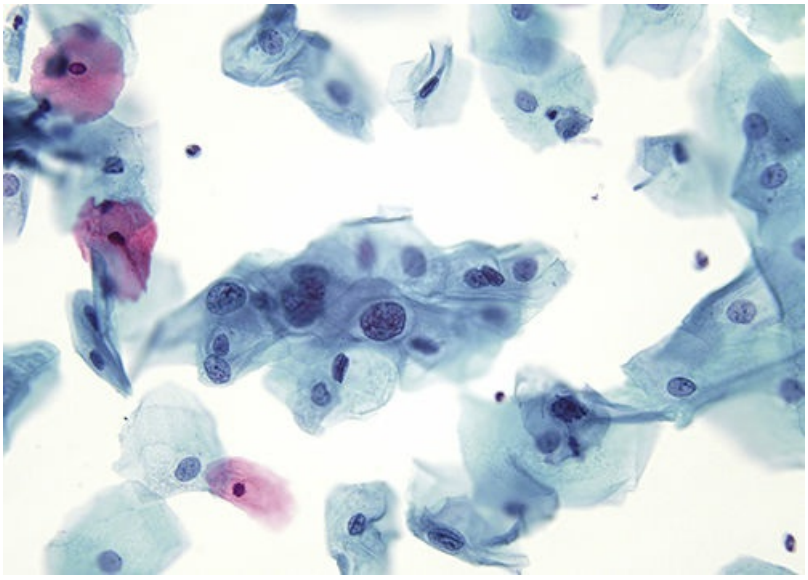

FIGURE 1.1.5 Low-grade squamous intraepithelial lesion (LSIL). Agroup of LSIL cells that demonstrate nuclear enlargement, binucleation, hyperchromasia, anisonucleosis, and irregular nuclear borders. Well-defined perinuclear halos are absent but are not needed to diagnose LSIL in this case, given the presence of other atypical features.

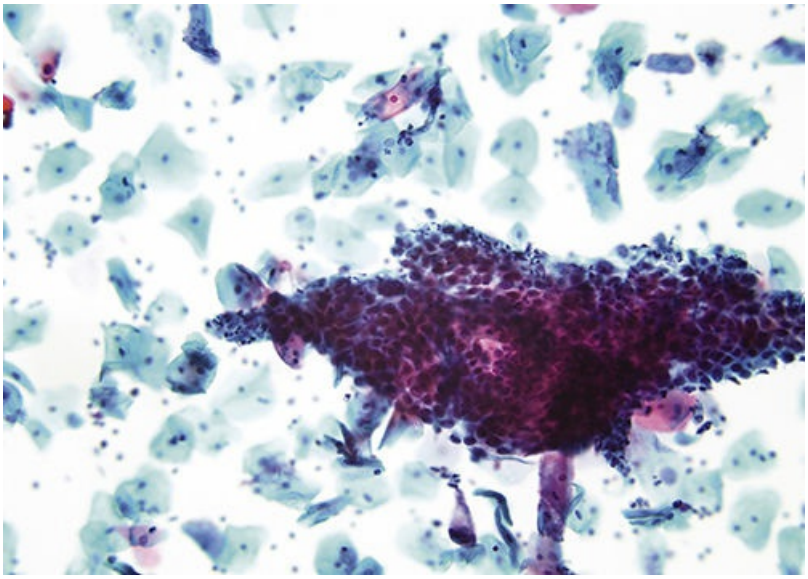

FIGURE 1.1.6 High-grade squamous intraepithelial lesion (HSIL). A fragment of small, hyperchromatic cells. The cells have very little cytoplasm and appear to have irregular shapes, causing concern for HSIL. Examination at higher magnification is required to confirm these cells as HSIL versus other entities that can cause hyperchromatic crowded groups.

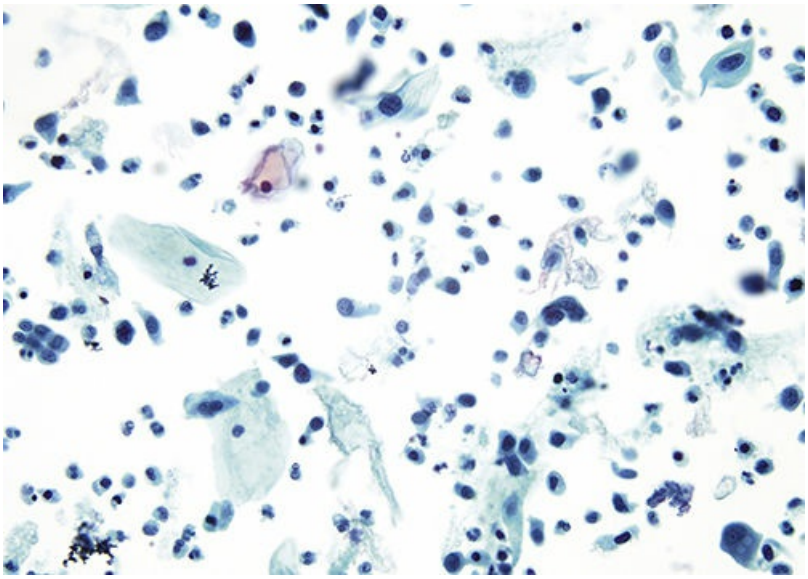

FIGURE 1.1.7 High-grade squamous intraepithelial lesion (HSIL). The cells in this field are predominantly dispersed. Several cells have high N/C ratios and enlarged dark nuclei with irregular nuclear borders. If such cells are seen in sufficient numbers, a diagnosis of HSIL can be made.

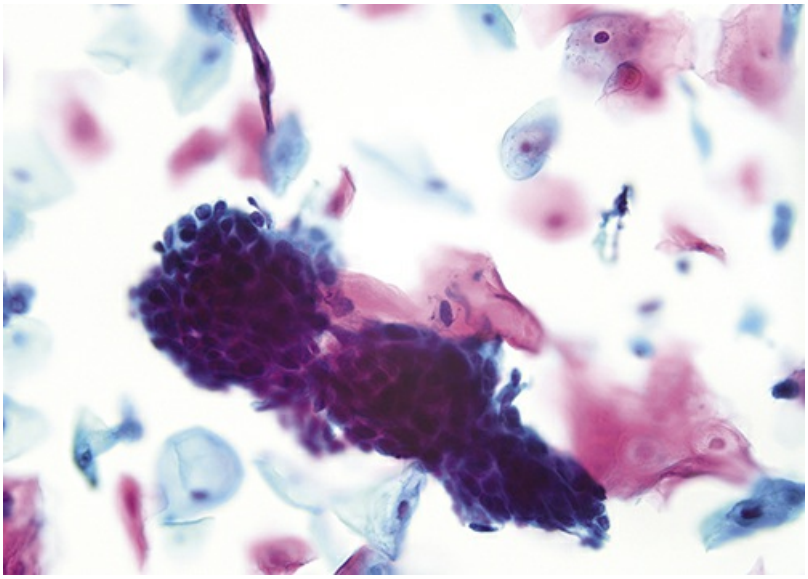

FIGURE 1.1.8 High-grade squamous intraepithelial lesion (HSIL). This fragment contains cells with hyperchromasia and very little cytoplasm. HSIL cells are often much smaller than LSIL cells, since LSIL cells usually maintain their cytoplasm.

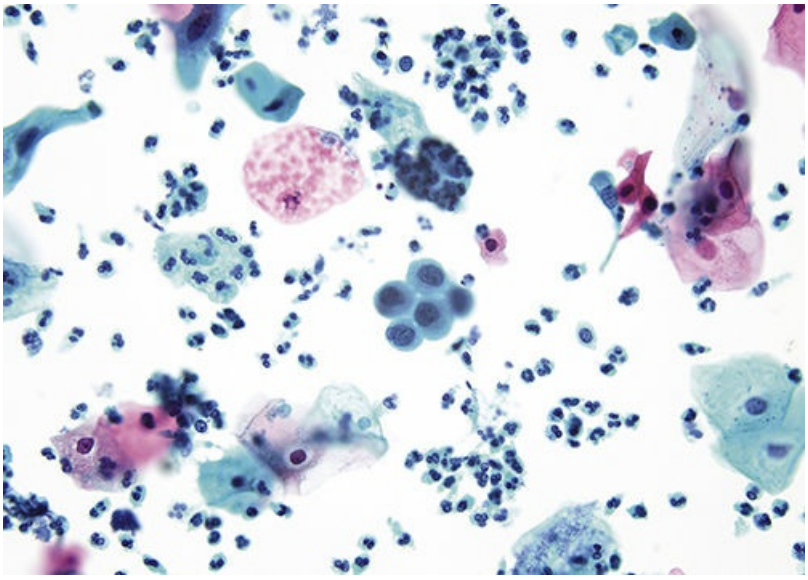

FIGURE 1.1.9 High-grade squamous intraepithelial lesion (HSIL). The five cells seen centrally are concerning for HSIL, as they have enlarged dark nuclei with irregular nuclear borders. The cytoplasm has a dense opaque look, suggesting these cells have arisen from an area of squamous metaplasia and at very least represent atypical immature squamous metaplasia.

1.2 High-Grade Squamous Intraepithelial Lesion (HSIL) Versus Squamous Cell Carcinoma

	High-Grade Squamous Intraepithelial Lesion (HSIL)	Squamous Cell Carcinoma
Age	Any age	Any age
Location	Cervix (also vagina, anus, and vulva)	Cervix (also vagina, anus, and vulva)
Signs and symptoms	None; detected on routine screening or on colposcopy	Dyspareunia; bleeding; vaginal discharge; mass on colposcopy; may be asymptomatic
Etiology	Premalignant lesion more commonly associated with high-risk HPV types	Progression of HSIL secondary to HPV infection (usually high-risk subtype)
Cytomorphology	• Cellular fragments and/or dispersed single cells (Figures 1.2.1 and 1.2.2) • High N/C ratio due to increased nuclear size and decreased amounts of cytoplasm (Figures 1.2.3 and 1.2.4) • Hyperchromatic nuclei without prominent nucleoli (Figures 1.2.3 and 1.2.4) • Markedly irregular nuclear borders may be present • Anisonucleosis may be present (Figure 1.2.5) • Dense, opaque cytoplasm in individual cells	• Malignant cells in fragments and/or present singly (Figures 1.2.6 and 1.2.7) • Enlarged cells with large nuclei and high N/C ratios (Figure 1.2.8) • Nuclear contour irregularities (Figure 1.2.7) • Anisonucleosis (Figure 1.2.9) • Cells may be keratinizing, with pink cytoplasm and irregular cytoplasmic extensions and pyknotic nuclei (Figure 1.2.10) • Necrosis may be present (Figure 1.2.9)
Special studies	HPV studies	None; a cytomorphologic diagnosis

Molecular alterations	Under investigation; mostly driven by HPV oncogenes	Most commonly mutations in PIK3CA, KRAS, and EGFR
Treatment	Complete excision	Depends on stage; conization, hysterectomy, pelvic lymph node dissection, and/or chemoradiation
Clinical implications	May progress to squamous cell carcinoma if incompletely excised	Depends on stage; best if complete surgical removal

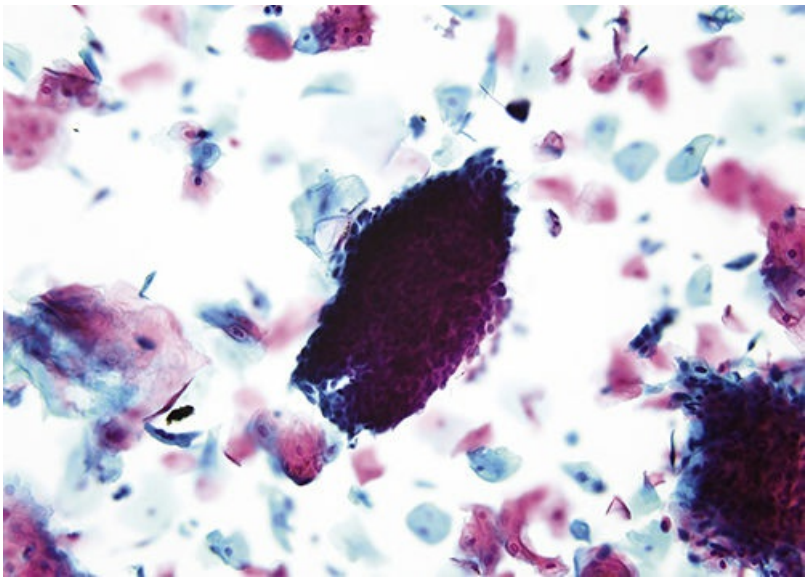

FIGURE 1.2.1 High-grade squamous intraepithelial lesion (HSIL). These tissue fragments contain numerous crowded, hyperchromatic nuclei. At this magnification, these cells could represent either HSIL or squamous cell carcinoma, but no features of squamous cell carcinoma are seen to allow such a diagnosis. In many instances, it can be difficult to distinguish HSIL from squamous cell carcinoma on a Pap test, but both diagnoses require rapid clinical follow-up.

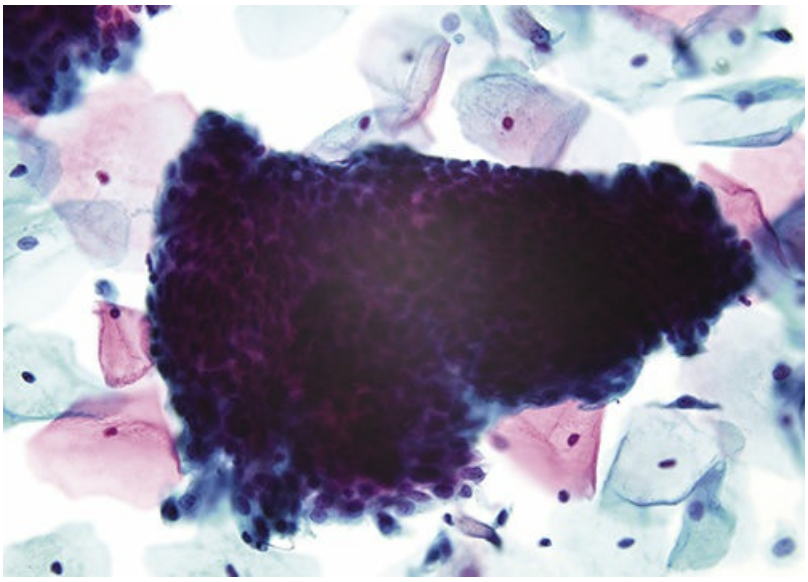

FIGURE 1.2.2 High-grade squamous intraepithelial lesion (HSIL). This fragment contains numerous crowded, hyperchromatic nuclei and forms a three-dimensional structure. The nuclei have high N/C ratios and appear disorganized within the fragment.

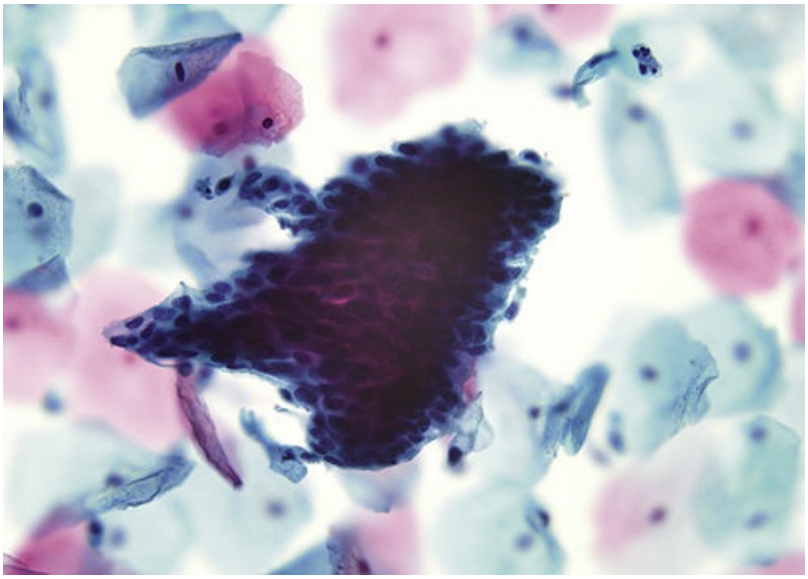

FIGURE 1.2.3 High-grade squamous intraepithelial lesion (HSIL). These hyperchromatic cells have opaque cytoplasm, irregular nuclear borders, and oval-to-elongated nuclei. No additional features suggestive of squamous cell carcinoma can be seen, such as necrosis, keratinization, greatly enlarged nuclei, prominent pleomorphism, or anisonucleosis.

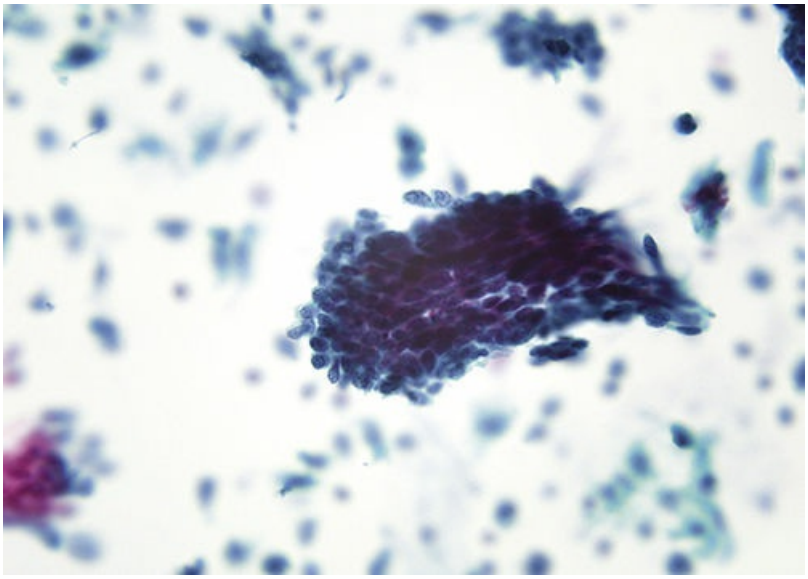

FIGURE 1.2.4 High-grade squamous intraepithelial lesion (HSIL). The nuclei in this fragment have only mild irregularities in their contours and the nuclei are all around the same size.

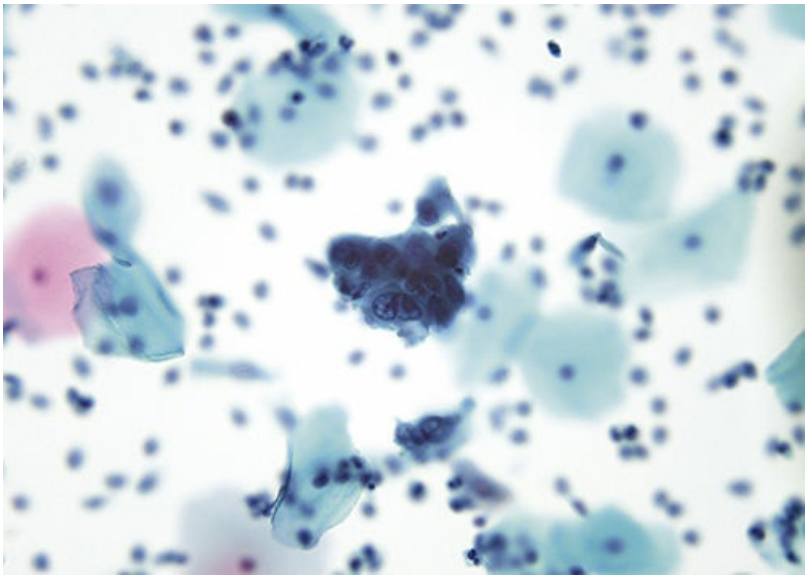

FIGURE 1.2.5 High-grade squamous intraepithelial lesion (HSIL). These atypical cells have more cytoplasm than in the previous figures, but have enlarged nuclei with hyperchromasia, are pleomorphic, and demonstrate nuclear size variation. The N/C ratios are more compatible with HSIL than LSIL.

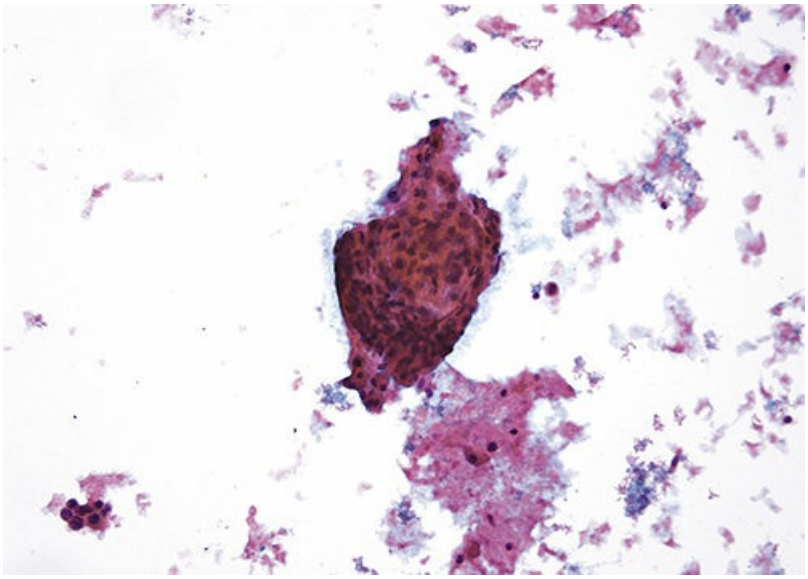

FIGURE 1.2.6 Squamous cell carcinoma. This tissue fragment contains cells with pink cytoplasm, indicating keratinization. While this could represent atypical parakeratosis, the cells have dark and crowded nuclei, and the background contains abundant necrosis.

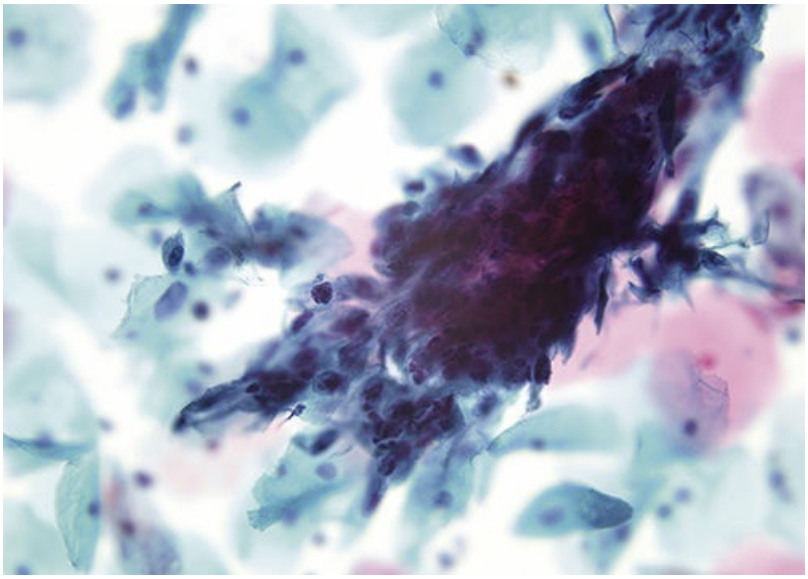

FIGURE 1.2.7 Squamous cell carcinoma. The cells in this fragment are enlarged and have large nuclei and high N/C ratios. The nuclei are dark and have markedly irregular nuclear borders. There is prominent variation in nuclear size. While HSIL is in the differential, the features are concerning for a possible squamous cell carcinoma.

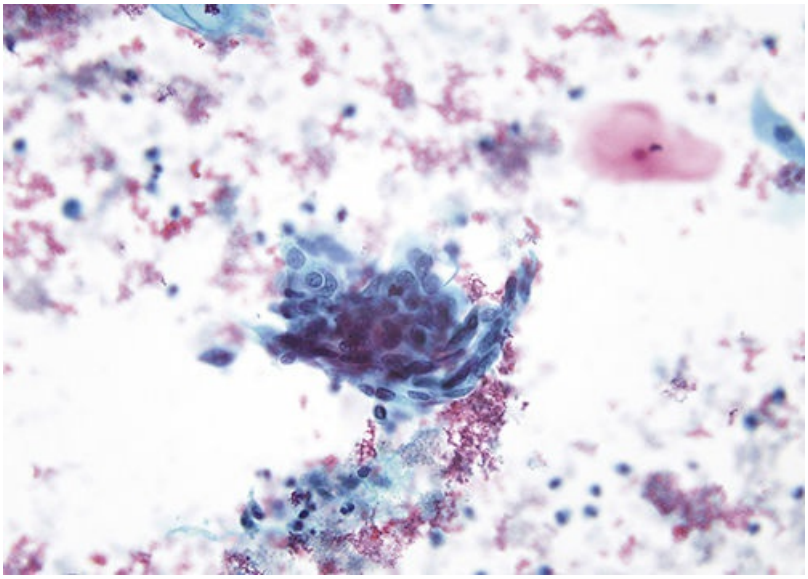

FIGURE 1.2.8 Squamous cell carcinoma. The cells have high N/C ratios and irregular nuclear shapes. They are crowded and disorganized within the fragment. They could represent HSIL, but the presence of "clinging diathesis" (necrotic granular debris attached to the fragment) raises suspicion for squamous cell carcinoma.

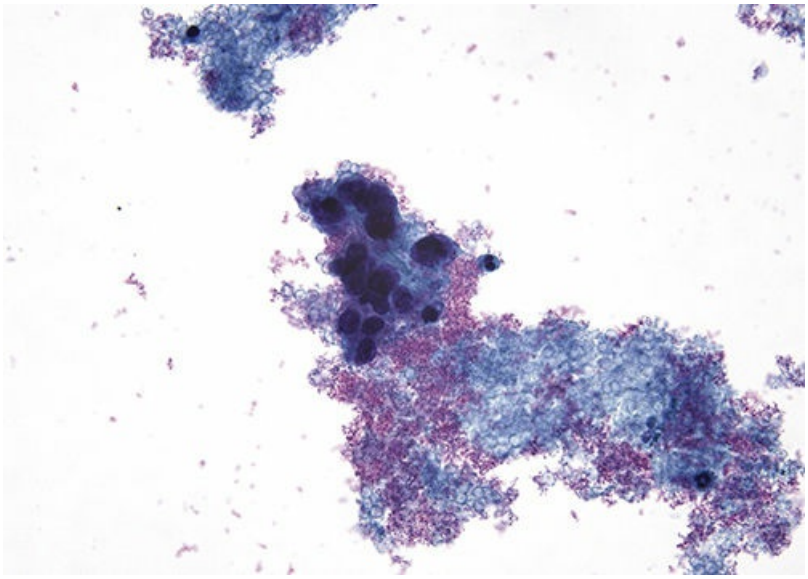

FIGURE 1.2.9 Squamous cell carcinoma. These cells appear as carcinoma would be seen elsewhere in the body: large cells with enlarged nuclei, high N/C ratios, hyperchromasia, anisonucleosis, and markedly irregular nuclear contours.

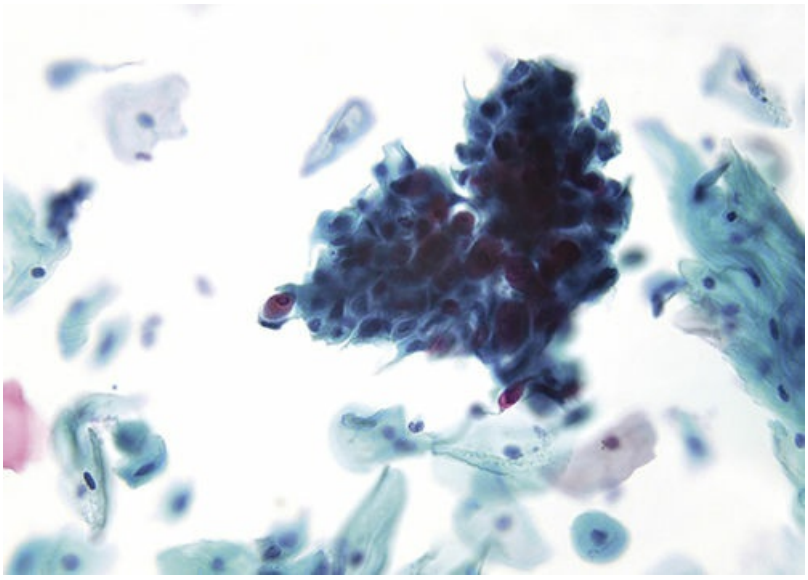

FIGURE 1.2.10 Squamous cell carcinoma. This fragment contains cells with crowded, hyperchromatic nuclei. Some of the cells demonstrate frank keratinization, a feature that favors a squamous cell carcinoma over HSIL.

1.3 High-Grade Squamous Intraepithelial Lesion (HSIL) Versus Endocervical Adenocarcinoma

	High-Grade Squamous Intraepithelial Lesion (HSIL)	Endocervical Adenocarcinoma
Age	Any age	Any age
Location	Cervix (also vagina, anus, and vulva)	Cervix
Signs and symptoms	None; detected on routine screening or on colposcopy	Dyspareunia; bleeding; vaginal discharge; mass on colposcopy; may be asymptomatic
Etiology	Premalignant lesion more commonly associated with high-risk HPV types	HPV infection, most commonly HPV 16 and/or 18; may be associated with adenocarcinoma in situ
Cytomorphology	• Cellular fragments and/or dispersed single cells (Figures 1.3.1 and 1.3.2) • High N/C ratio due to increased nuclear size and decreased amounts of cytoplasm (Figure 1.3.3) • Hyperchromatic nuclei without nucleoli (Figure 1.3.4) • Nuclear border irregularities (Figure 1.3.5) • Anisonucleosis may be present (Figure 1.3.5) • Dense, opaque cytoplasm in individual cells	• Malignant cells in fragments or present singly (Figures 1.3.6 and 1.3.7) • Three-dimensional fragments with columnar cells (Figures 1.3.8 and 1.3.9) • Enlarged cells with large nuclei and high N/C ratios (Figures 1.3.8 and 1.3.9) • Nuclear contour irregularities may be present • Anisonucleosis (Figure 1.3.9) • Prominent nucleoli (Figure 1.3.10) • Necrosis may be present
Special studies	HPV studies	None; a cytomorphologic diagnosis

Molecular alterations	Under investigation; mostly driven by HPV oncogenes	Under investigation
Treatment	Complete excision	Depends on stage; conization, hysterectomy, pelvic lymph node dissection, and/or chemoradiation
Clinical implications	May progress to squamous cell carcinoma if incompletely excised	Depends on stage; best if complete surgical removal is possible

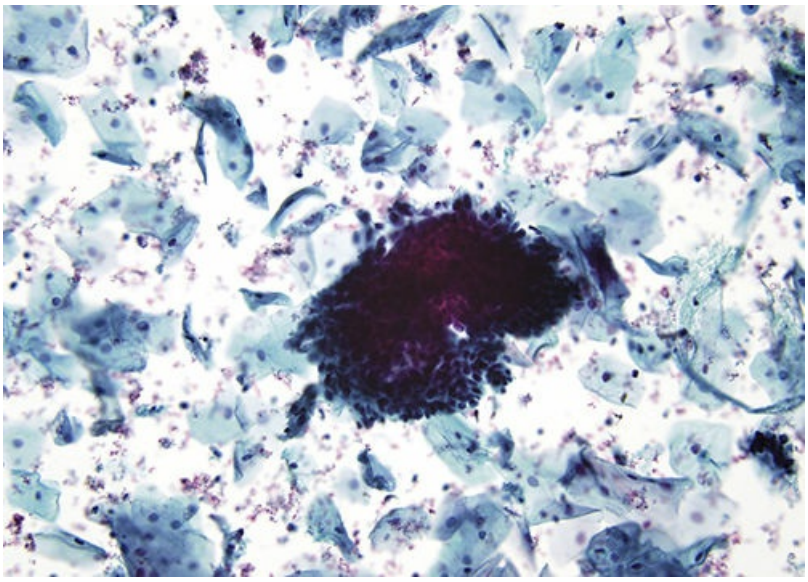

FIGURE 1.3.1 High-grade squamous intraepithelial lesion (HSIL). The cells in this tissue fragment have enlarged, crowded, and hyperchromatic nuclei. Examination at higher magnification is required to assess the nature of this hyperchromatic crowded group, but the amount of hyperchromasia is concerning for HSIL.

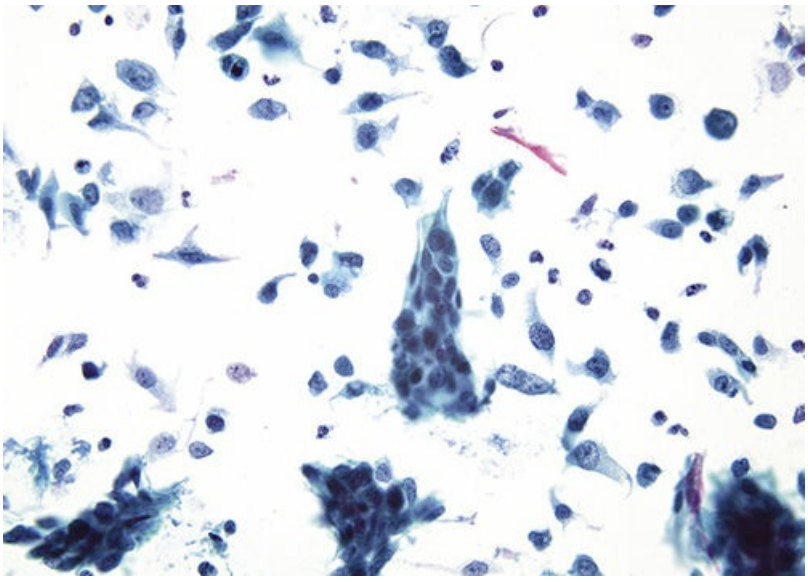

FIGURE 1.3.2 High-grade squamous intraepithelial lesion (HSIL). This field contains small fragments of HSIL as well as dispersed HSIL cells. The cells have high N/C ratios and dark chromatin. HSIL cells may look elongated in some preparations, emulating the columnar shapes of cells with glandular differentiation.

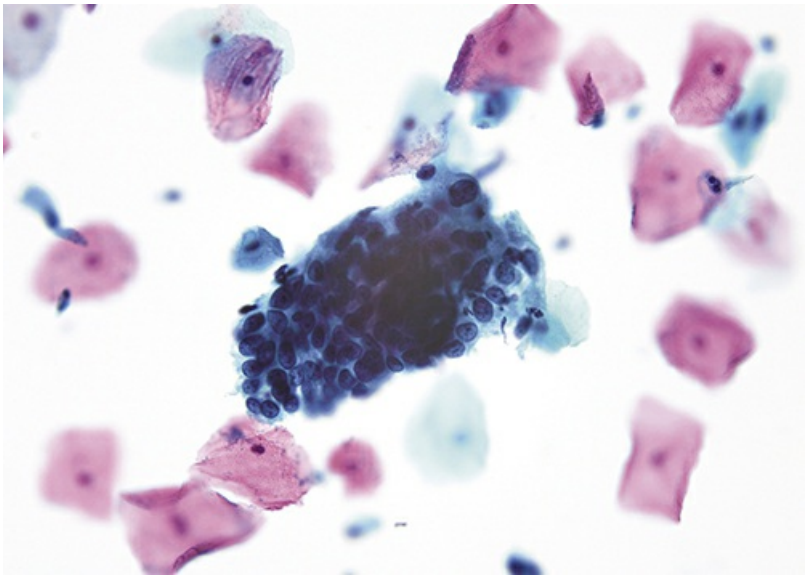

FIGURE 1.3.3 High-grade squamous intraepithelial lesion (HSIL). This fragment contains numerous crowded, dark nuclei. The nuclei are oval shaped and vary in size.

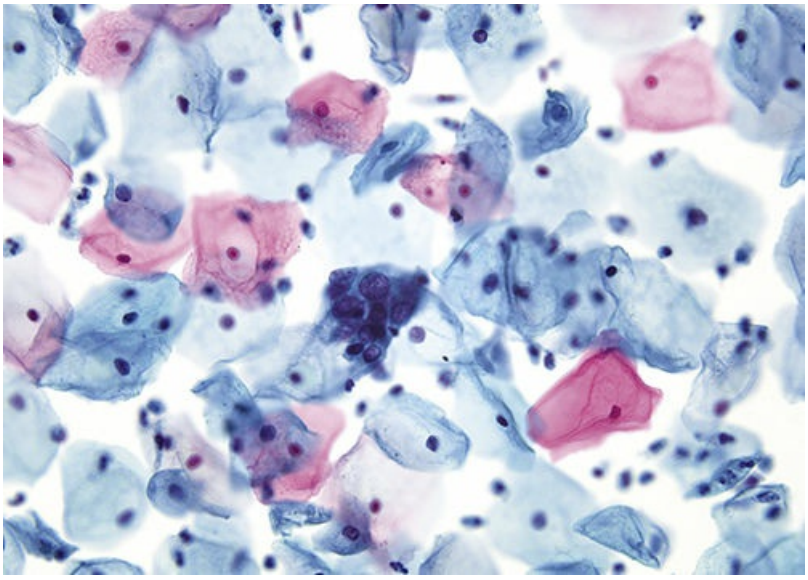

FIGURE 1.3.4 High-grade squamous intraepithelial lesion (HSIL). The nuclei in this small fragment of HSIL have prominent variation in size and mild nuclear contour irregularities. Nucleoli are absent and should not be seen in HSIL.

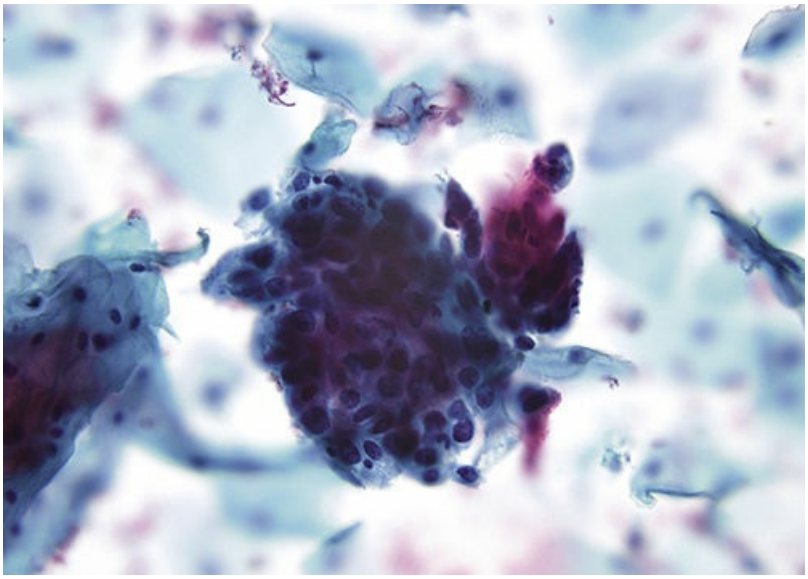

FIGURE 1.3.5 High-grade squamous intraepithelial lesion (HSIL). This fragment emulated a squamous cell carcinoma, as some nuclei have markedly irregular borders, nuclear size variation is prominent, and some cells adjacent appear to be keratinized. Despite being rare, keratinizing HSIL lesions do exist.

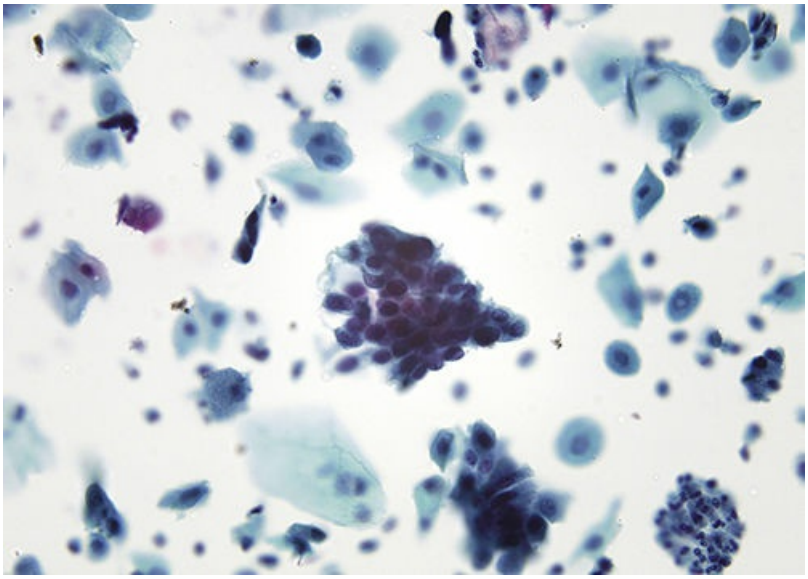

FIGURE 1.3.6 Endocervical adenocarcinoma. A small fragment of cells emulates HSIL. The cells are small, with high N/C ratios and dark nuclei. There is little size variation between the nuclei.

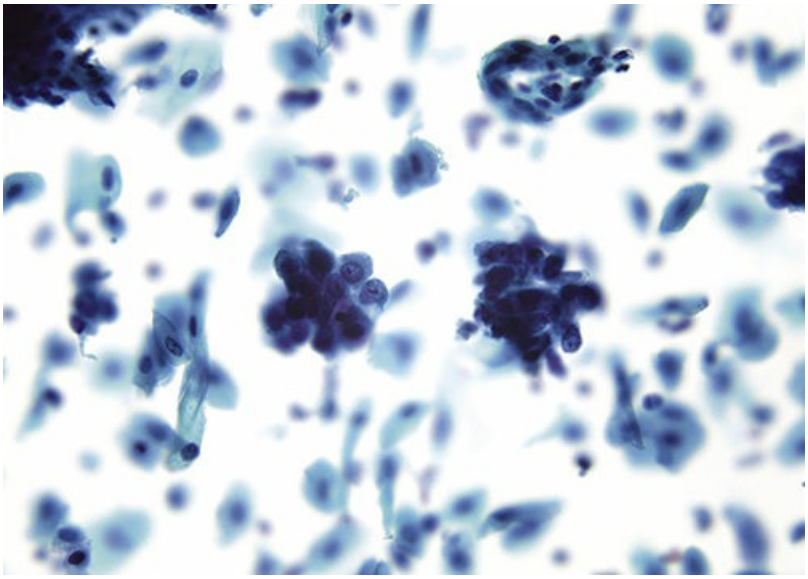

FIGURE 1.3.7 Endocervical adenocarcinoma. The hyperchromatic cells in this field have little size variation, oval-to-elongated nuclei, and high N/C ratios. While HSIL remains in the differential, the presence of elongated nuclei and nucleoli (though small) should cause consideration of an adenocarcinoma.

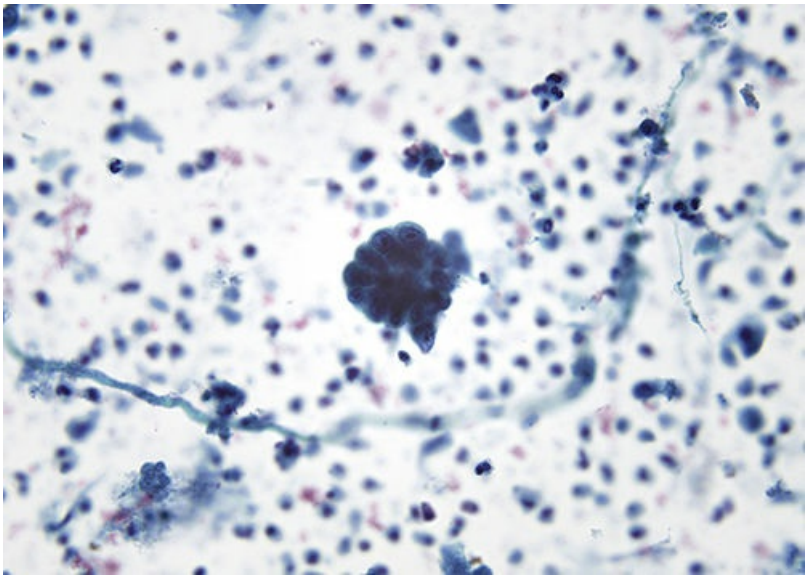

FIGURE 1.3.8 Endocervical adenocarcinoma. This tissue fragment has a smooth, scalloped border that is not usually seen with squamous differentiation. The cells are three-dimensional and have small nucleoli, additional features that are more suggestive of glandular differentiation.

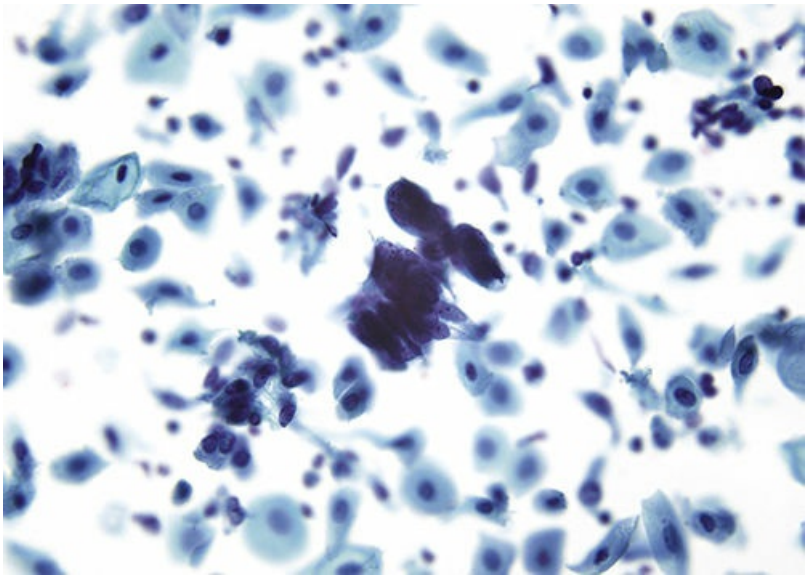

FIGURE 1.3.9 Endocervical adenocarcinoma. These cells are columnar and have large, hyperchromatic, elongated nuclei. The differential diagnosis includes endocervical adenocarcinoma as well as adenocarcinoma in situ.

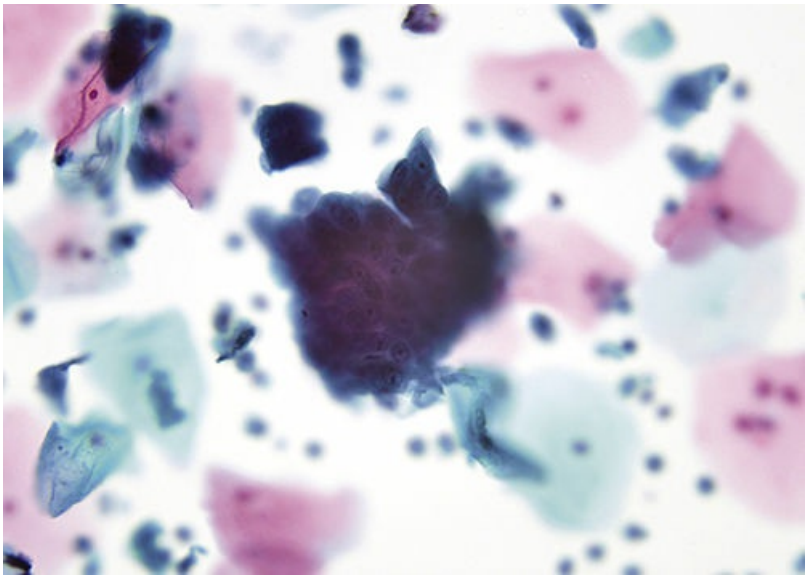

FIGURE 1.3.10 Endocervical adenocarcinoma. This tissue fragment is three-dimensional and contains cells with prominent nucleoli. Some cells have a columnar shape. The differential diagnosis includes endocervical adenocarcinoma as well as cells with marked reactive atypia.

1.4 Squamous Cell Carcinoma Versus Endocervical Adenocarcinoma

	Squamous Cell Carcinoma	Endocervical Adenocarcinoma
Age	Any age	Any age
Location	Cervix (also vagina, anus, and vulva)	Cervix
Signs and symptoms	Dyspareunia; bleeding; vaginal discharge; mass on colposcopy; may be asymptomatic	Dyspareunia; bleeding; vaginal discharge; mass on colposcopy; may be asymptomatic
Etiology	Progression of HSIL secondary to HPV infection (usually high-risk subtype)	HPV infection, most commonly HPV 16 and/or 18; may be associated with adenocarcinoma in situ
Cytomorphology	• Malignant cells in fragments or present singly (Figure 1.4.1) • Enlarged cells with large nuclei and high N/C ratios (Figure 1.4.2) • Nuclear contour irregularities (Figure 1.4.3) • Anisonucleosis (Figures 1.4.2 and 1.4.3) • Cells may be keratinizing, with pink cytoplasm and irregular cytoplasmic extensions and pyknotic nuclei • Necrosis may be present (Figures 1.4.4 and 1.4.5)	• Malignant cells in fragments or present singly (Figures 1.4.6 and 1.4.7) • Three-dimensional fragments with columnar cells (Figure 1.4.7) • Enlarged cells with large nuclei and high N/C ratios (Figure 1.4.8) • Nuclear contour irregularities (Figure 1.4.2) • Anisonucleosis (Figure 1.4.9) • Prominent nucleoli (Figure 1.3.10) • Necrosis may be present (Figure 1.4.10)
Special studies	None; a cytomorphologic diagnosis	None; a cytomorphologic diagnosis
Molecular alterations	Most commonly mutations in PIK3CA, KRAS, and EGFR	Under investigation

Treatment	Depends on stage; conization, hysterectomy, pelvic lymph node dissection, and/or chemoradiation	Depends on stage; conization, hysterectomy, pelvic lymph node dissection, and/or chemoradiation
Clinical implications	Depends on stage; best if complete surgical removal is possible	Depends on stage; best if complete surgical removal is possible

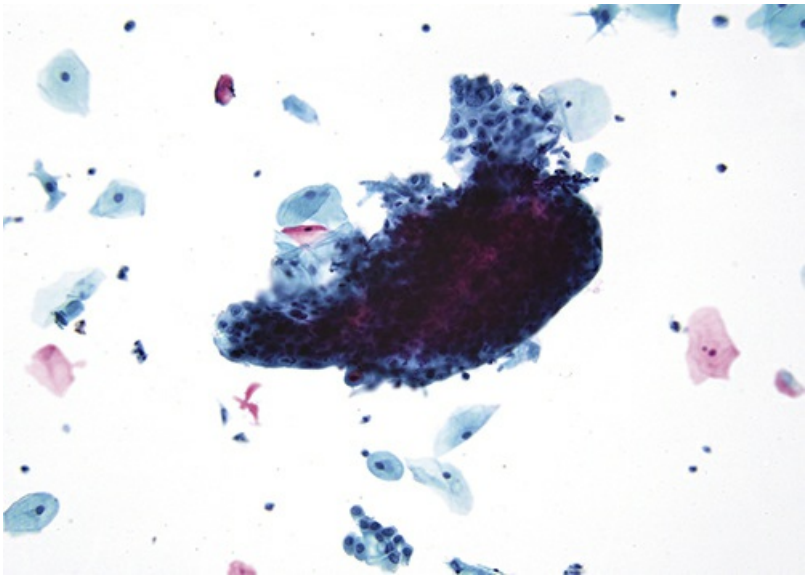

FIGURE 1.4.1 Squamous cell carcinoma. The nuclei in this fragment are hyperchromatic and crowded. The cells have significant anisonucleosis and carcinoma is suspected. An examination at higher magnification will help determine whether these cells have squamous or glandular features.

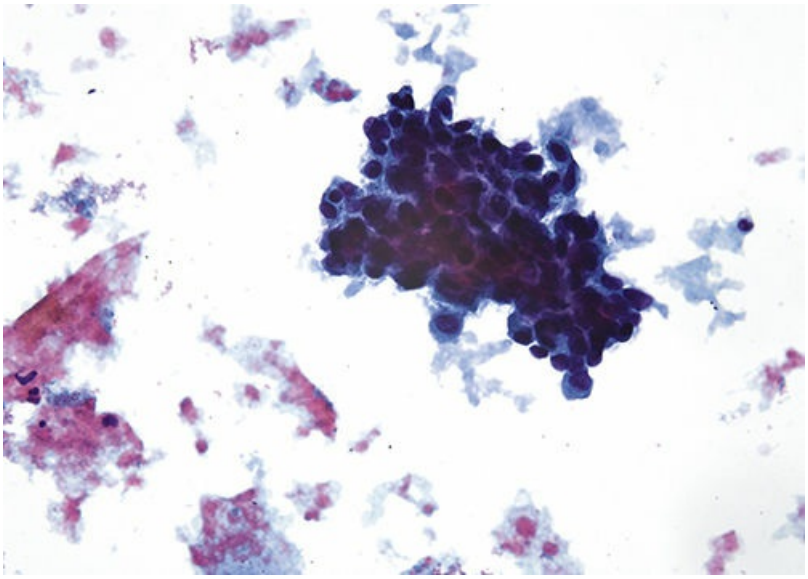

FIGURE 1.4.2 Squamous cell carcinoma. These carcinoma cells have dark, enlarged nuclei with markedly irregular borders. They have polygonal cytoplasm, which favors a squamous cell carcinoma over an adenocarcinoma. There is abundant necrotic debris in the background.

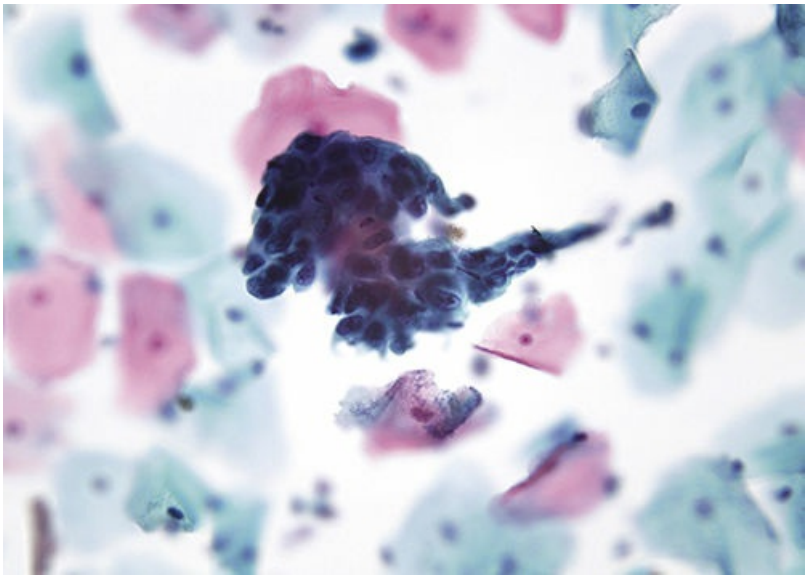

FIGURE 1.4.3 Squamous cell carcinoma. These cells resemble HSIL but have severe nuclear atypia: nuclear enlargement and anisonucleosis. The cytoplasm appears dense and opaque, favoring a squamous cell carcinoma over an adenocarcinoma.

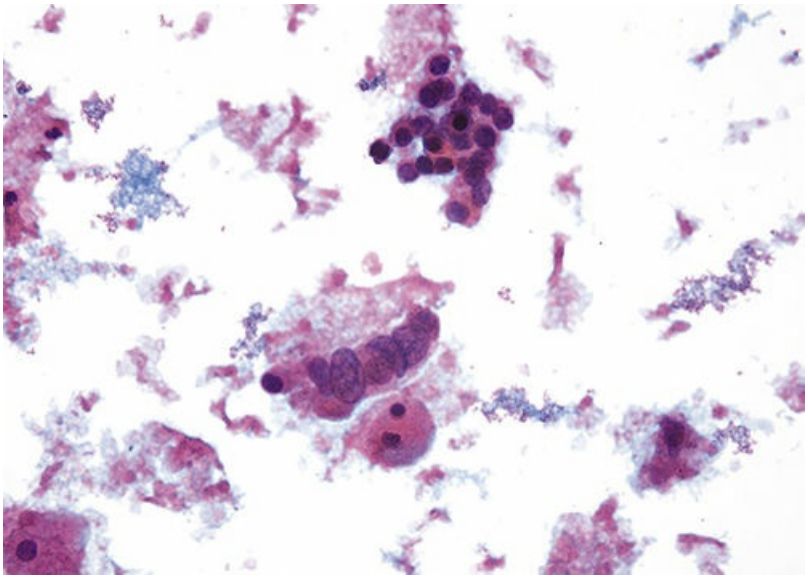

FIGURE 1.4.4 Squamous cell carcinoma. Two small fragments of malignant cells are seen amid necrotic debris. One fragment contains cells with enlarged, elongated nuclei that suggests a glandular differentiation. However, these cells are from a patient with squamous cell carcinoma. It can be difficult to differentiate a squamous cell carcinoma from an adenocarcinoma in some situations, although squamous cell carcinoma is found more often.

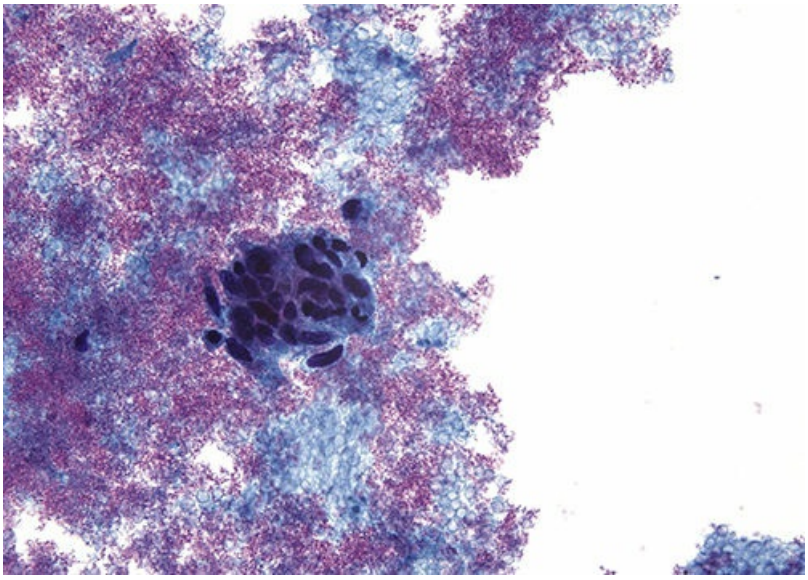

FIGURE 1.4.5 Squamous cell carcinoma. Cells with dark, elongated nuclei are found in a background of granular debris. The elongated nuclei may cause one to consider a glandular lesion, but elongated nuclei can be found in HSIL and squamous cell carcinoma.

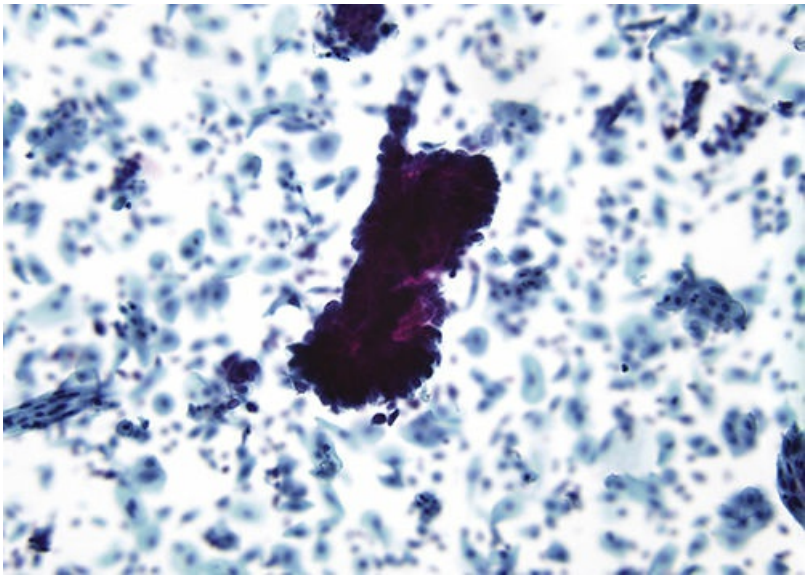

FIGURE 1.4.6 Endocervical adenocarcinoma. The field is cellular and this fragment of adenocarcinoma contains overlapping, hyperchromatic nuclei. Some edges of the fragment have a feathery appearance because the nuclei are elongated and palisaded along the fragment edges.

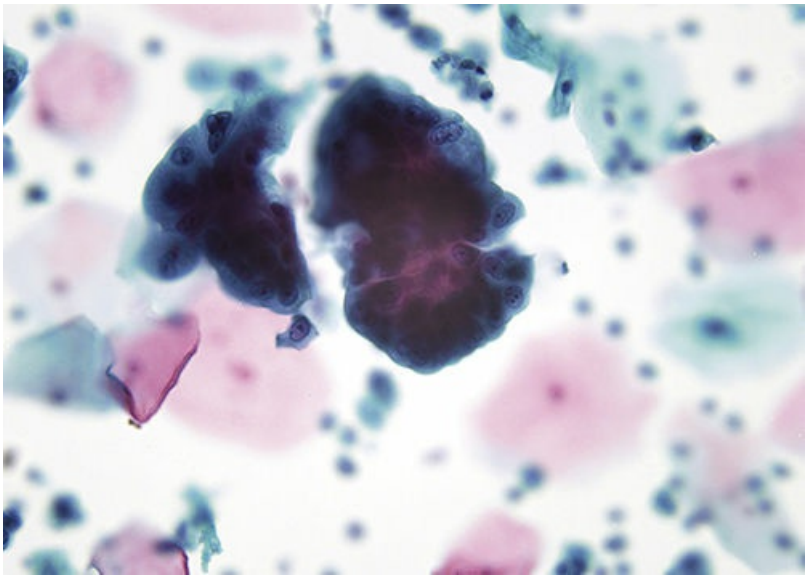

FIGURE 1.4.7 Endocervical adenocarcinoma. The nuclei seen here have irregular contours and are of different sizes. One clue to the glandular differentiation of these cells is the tissue fragment's smooth edges. Fragments of squamous cell carcinoma are more likely to have jagged edges.

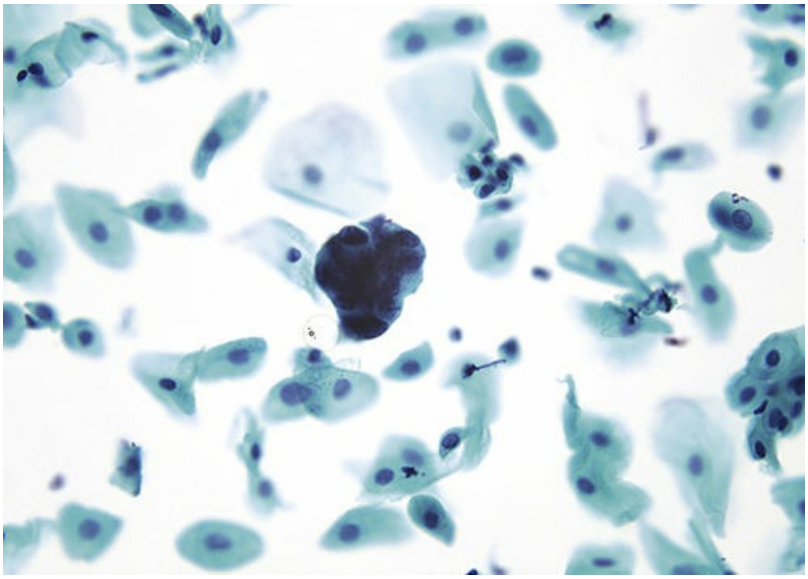

FIGURE 1.4.8 Endocervical adenocarcinoma. This small fragment contains cells with very dark nuclei and irregular nuclear contours. The tissue fragment contains smooth edges.