NCPTS
National Cervical Pathology Training Service

GLANDULAR LESIONS OF THE CERVIX
Cytomorphology for Year 1-2 Registrars

ADENOCARCINOMA IN SITU (AIS)

DEFINITION

- Adenocarcinoma in situ (AIS) is a precancerous intraepithelial lesion of endocervical epithelium
- It is the glandular equivalent of HSIL in squamous epithelium

OVERVIEW

- No one single feature is sufficient for the cytological diagnosis of AIS. The diagnosis should only be made using collective parameters.
- Architectural features are far more important than individual cell criteria when diagnosing AIS and can often be appreciated at screening magnification (10X objective)
- Most AIS cases are well-differentiated but there is a range to poorly differentiated cytology which is still AIS

ADENOCARCINOMA IN SITU: THE DETAILS

Background Clean, i.e. no tumour diathesis. May be blood or inflammation.

Number of atypical cells Generally increased endocervical cells present, but varies widely depending on sampling technique, and location and size of the lesion.

Arrangement of aggregates: need more than one group to make the diagnosis

1. Abundant large irregularly shaped sheets. Bizarre shapes, with irregular borders.
2. Feathering or a common border at edges of sheets, or palisaded nuclei with cytoplasmic tags
3. Tightly crowded groups with overlapping nuclei
4. Strips and rosettes showing pseudostratification
5. Gland openings, papillary groups, luminal edges, branching, strip off sheets
6. Thickness rarely more than 3 cells thick (compared with HSIL where HCG's = 4+ cells thick)

- Note: Attached stroma or presence of cilia are usually benign features

Cell features: look for unpredictable variation

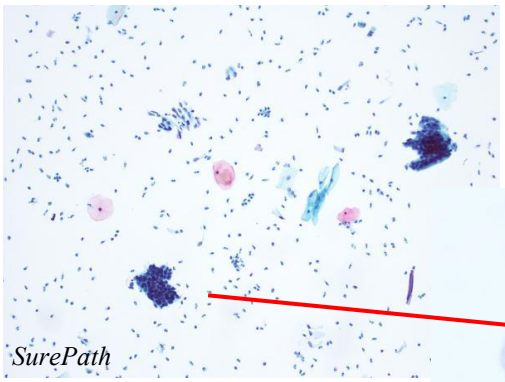
1. Single cells uncommon or absent
2. Hyperchromatic crowded nuclei. Mild increase in nuclear size. Abnormal shapes.
3. Chromatin uniform and finely stippled or moderately granular
4. Micronucleoli may be present, but usually difficult to find
5. Cytoplasm may be indistinct. Honeycomb pattern often absent.
6. Mitotic figures, especially if abnormal.
7. Apoptotic debris (need to distinguish from degenerating neutrophils)

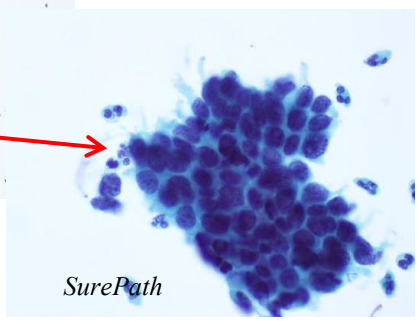
The above features characterize well-differentiated AIS (majority). Less differentiated cases show looser syncytial groups, with larger more pleomorphic nuclei and prominent nucleoli.

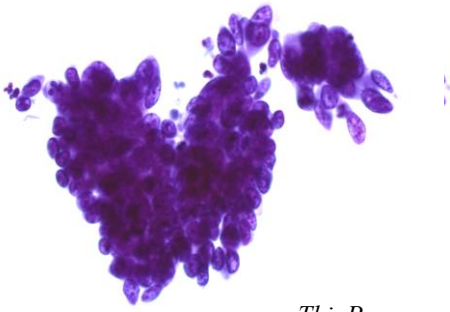
Differences between ThinPrep and SurePath

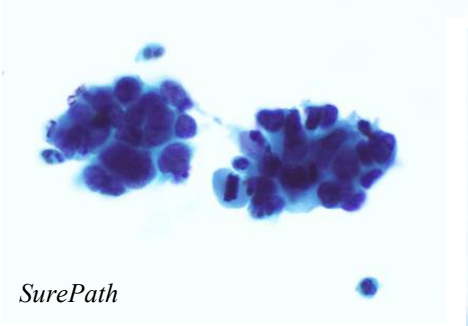
The different processing systems used with ThinPrep and SurePath affect the appearance of AIS.

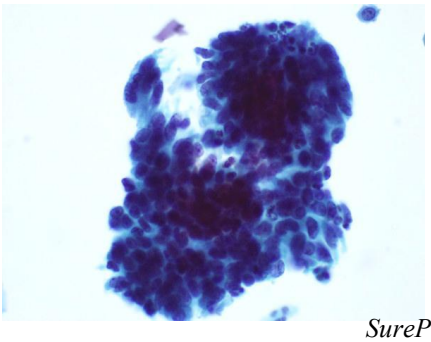
- In ThinPrep, normal and abnormal glandular groups round up in the fixative fluid. The cells may appear small and crowded. Small, rounded groups of cells need close examination at high power, as this is a high-risk pattern and the changes seen in AIS can be subtle.
- In SurePath, glandular groups can appear more stretched out so learning to recognize what AIS looks at in SurePath samples requires specific experience with this LBC type.

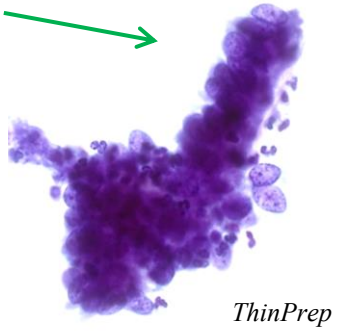






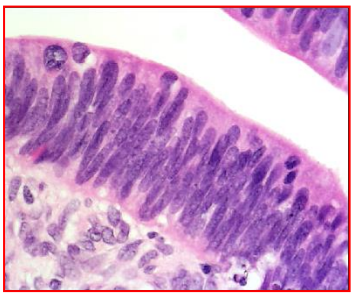


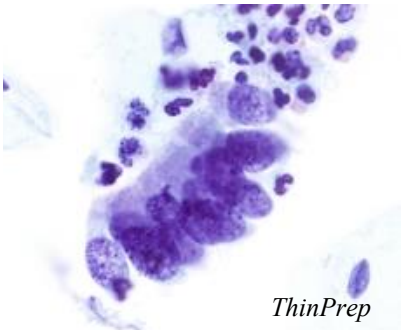




AIS: Irregular crowded groups.

Large and small irregularly shaped crowded groups of atypical cells are common in AIS. The groups can be small with rounded up edges. The cells are cohesive with nuclei being crowded and overlapped. The groups often have well-defined cytoplasmic borders which give a smooth edge and may form a communal border. Specific shapes such as papillary-like formations, abnormal strips, strips coming off the group edge (green arrow), common borders and rosettes are seen.

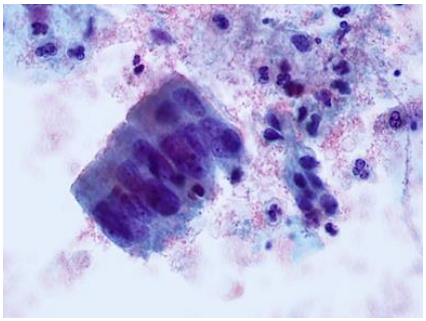


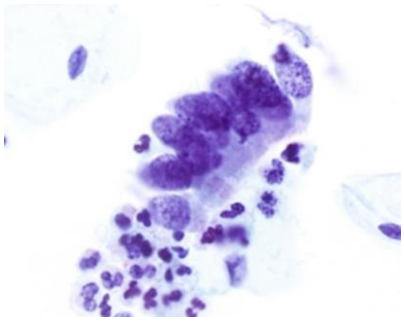


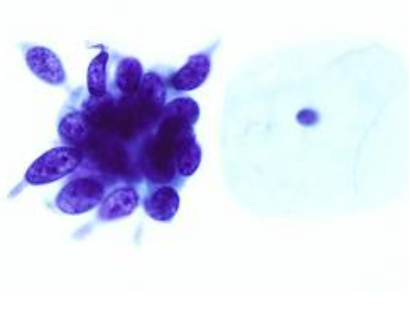
AIS: Retention of cell polarity

Centre: Histology of endocervical AIS showing elongated overlapping neoplastic nuclei with a distinct polarity from the basal to apical portion of the cells.

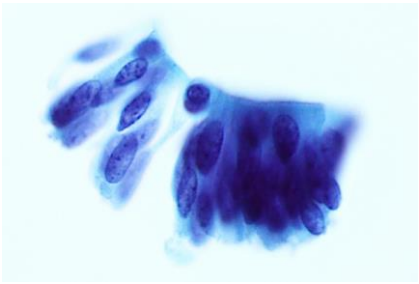
Right and Left: Pseudostratified strips of AIS with the same orientation.

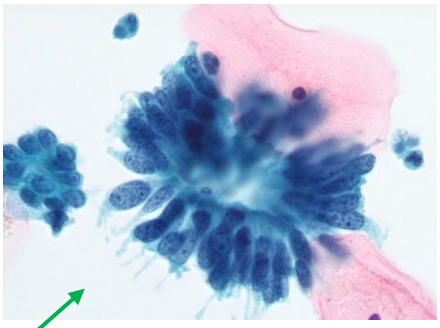


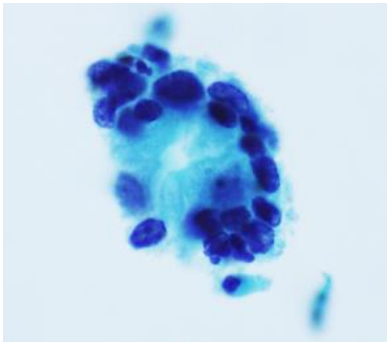




ThinPrep





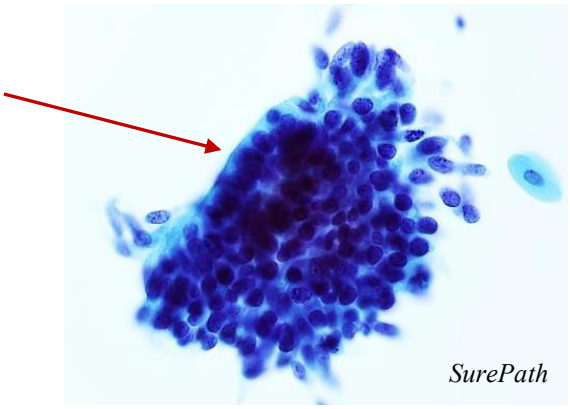


SurePath

AIS: Strips and Rosettes

Strips where cell polarity is maintained are common in AIS. Look for pseudostratification and nuclear abnormality, particularly hyperchromasia in AIS. AIS strips are often curved, with the luminal border at the concave edge. The basal part of the cell expands when the attachment to the basement membrane is lost during sampling, because of the enlarged basal nuclei. Note the feathering (green arrow)

Rosettes are less frequently seen but are a characteristic architectural appearance in AIS. There is mucin in the apical portion of the cells adjacent to a central lumen with nuclei radiating out at the periphery of the cluster.



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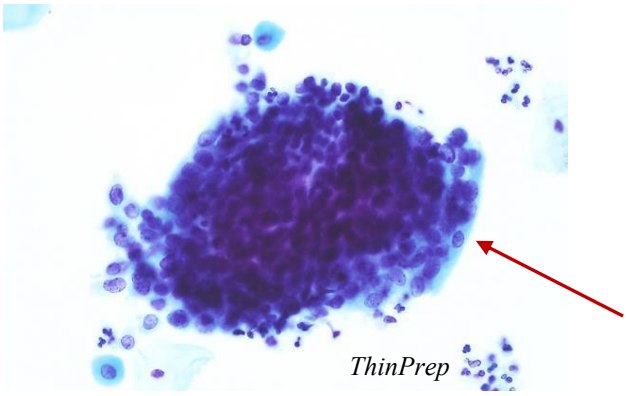
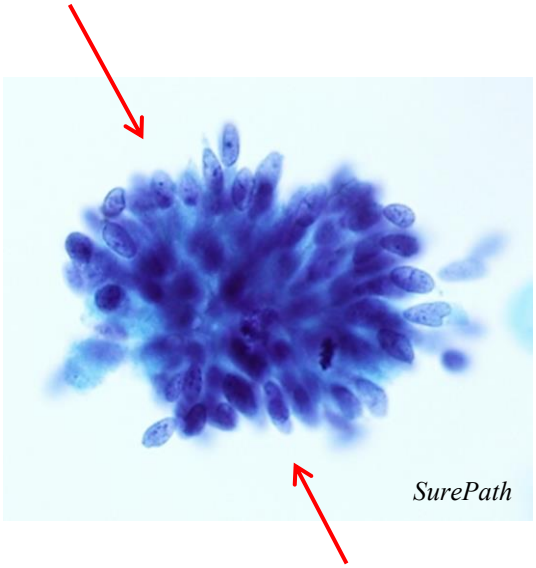


ThinPrep

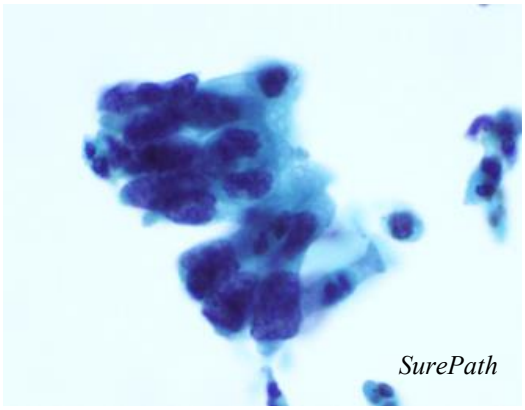
AIS: Common (communal) borders

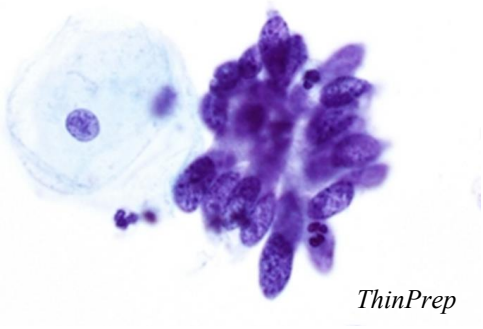
This is a very helpful feature when considering a group of abnormal crowded, overlapped and hyperchromatic cells as it helps to identify the group as glandular.



AIS: Feathering.

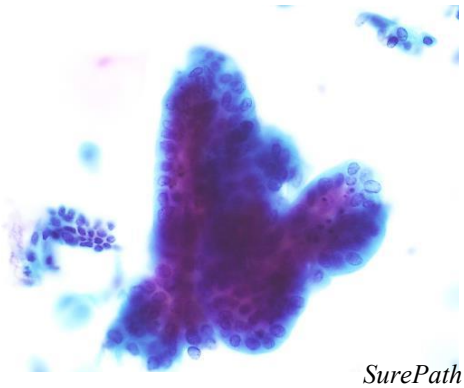
"Feathering" is the appearance of elongated and splayed-out nuclei around the periphery of glandular clusters, named because of the resemblance to the tail feathers of a bird. Feathering is characteristic on low power and a strong indicator of AIS when present but only occurs in 10-20% of cases. The nuclei lie at different levels at the edge of the cell cluster. The cytoplasm may appear as small cytoplasmic tags or be lost with nuclei appearing pulled out and attenuated.

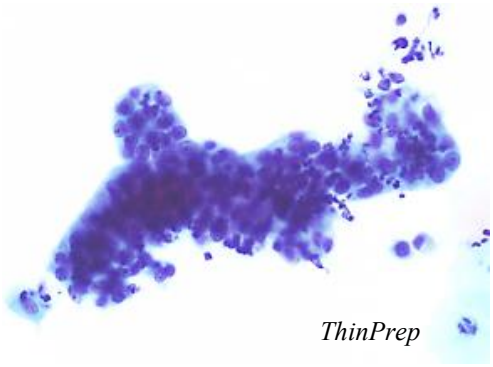




AIS: Nuclear chromatin

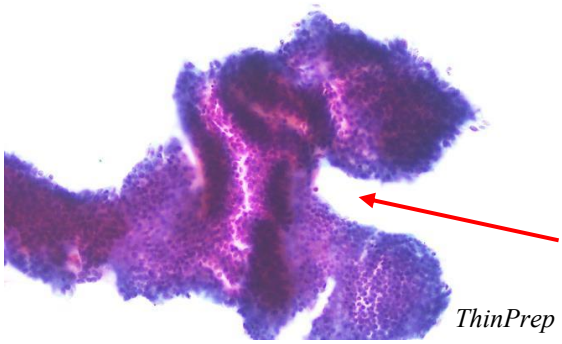
AIS nuclei are typically hyperchromatic and usually have a stippled appearance although these nuclear changes can be subtle with very well-differentiated AIS. If present, nucleoli are small and inconspicuous.

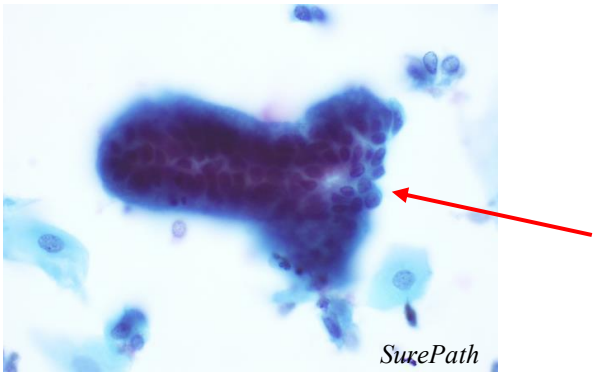




AIS: Papillary-like structures

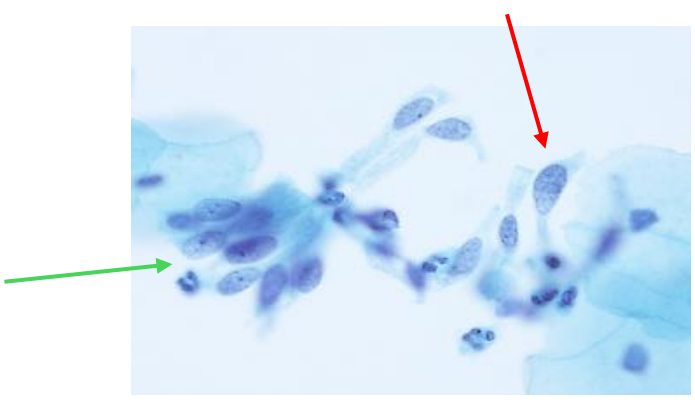
These can be seen in both AIS and in adenocarcinomas from various primary sites. An inner stromal core is uncommon in cytology and papillary-like configurations are usually identified by a common surface border covering three sides of the cluster.





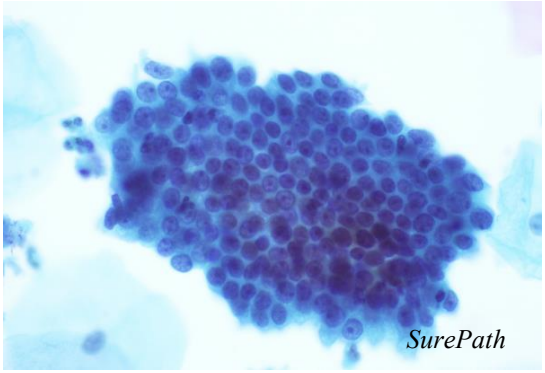
AIS: Gland openings

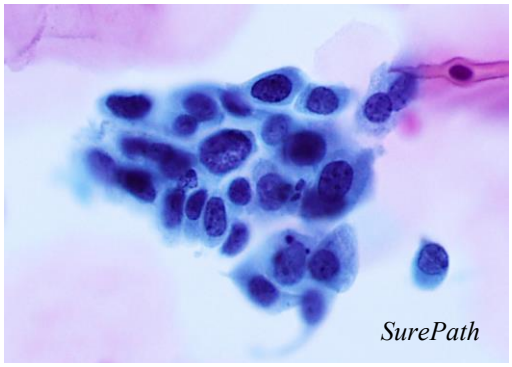
Glandular lumina are occasionally observed within crowded groups shed from endocervical AIS. These lumina will be within the surface epithelium and lead into endocervical crypts (red arrows).



Nuclear enlargement

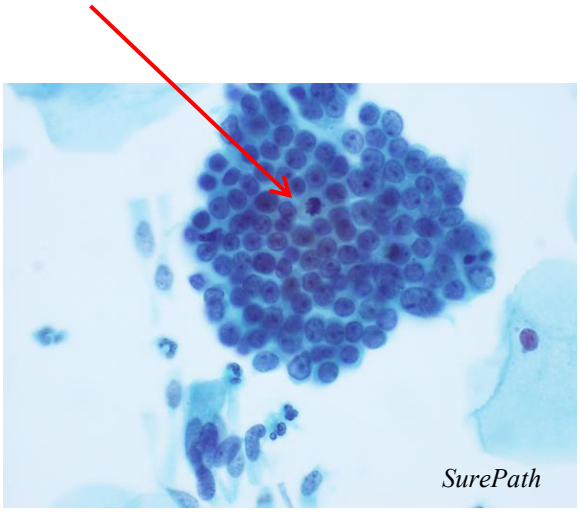
Bulging nuclei in endocervical cells from AIS cause an appearance called “frying pan” cells, or “egg-in-snake”. The nucleus (red arrows) is wider in diameter than the cross-section of both ends of the cell where there is cytoplasm only. The nuclear enlargement causes nuclei to splay out at the basal edge of a short strip in the photo on the right (green arrow), giving a wedge-shaped architecture.





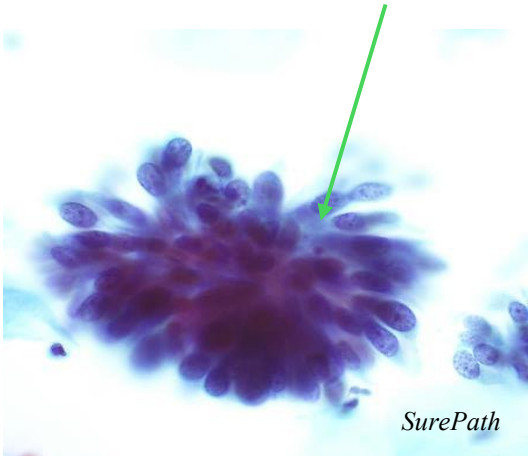
AIS: Pleomorphism

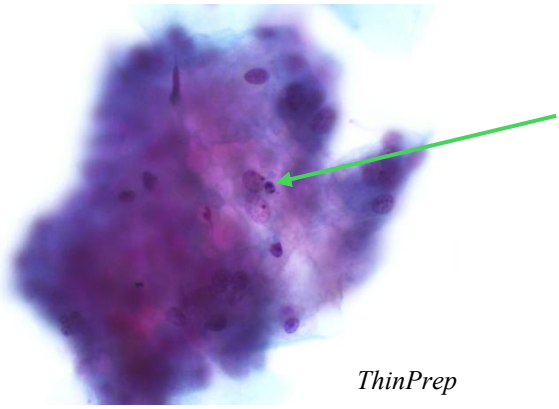
The degree of nuclear pleomorphism varies in AIS. Most AIS cases are well-differentiated (left) but poorly differentiated AIS also occurs (right). The possibility of invasive endocervical adenocarcinoma needs to be considered in a poorly differentiated case but it but may still be an in-situ lesion.



AIS: Mitoses and Apoptotic debris

Mitoses and apoptotic debris/remnants of nuclei are relatively common findings in AIS. Mitoses are seen above (red arrows). Apoptotic debris is identified as variably sized and shaped blue/black granular material among cell groups below (green arrows). It is important to distinguish apoptotic debris, which may have different internal shades of colour from the degenerating lobes of neutrophils which are only black.





MIMICS OF AIS

A range of benign, reactive, preneoplastic and malignant lesions can mimic AIS. A brief list is provided here – these will be discussed in more detail in the *Difficult endocervical lesions* module in Year 3.

1. Normal cells from the endocervical canal
    - **High sampling** of cells from the lower uterine segment
2. Benign/reactive changes
    - **Reactive endocervical cells**
    - **Tubal metaplasia**
    - **Cervical endometriosis**
3. In situ high-grade lesions
    - **HSIL**, particularly if involving glands
4. Malignant lesions
    - **Endocervical adenocarcinoma**
    - **Endometrial carcinoma**, particularly if invading the cervix and directly sampled

AIS vs. INVASIVE ENDOCERVICAL ADENOCARCINOMA

Cytology is not particularly good at distinguishing between AIS and invasive endocervical adenocarcinoma because there is an overlap of appearances. The following comments provide a brief introduction to distinguishing AIS from endocervical adenocarcinoma.

AIS versus Invasive Endocervical Adenocarcinoma: no single feature is definitive

- AIS is usually well-differentiated – consider invasion if pleomorphic
- Single malignant cells are more common with invasive lesions, particularly if abundant
- Large variable secretory vacuoles are not usual in AIS
- Conspicuous prominent nucleoli are not common in AIS
- There is usually evidence of diathesis with invasive adenocarcinoma – “clinging” fibrillary cyanophilic and orangeophilic material around groups of malignant cells – not seen with AIS.
- AIS frequently coexists with invasive endocervical adenocarcinoma

SUMMARY

AIS often presents a striking appearance when observed at a low-power screening magnification with irregular crowded cell groups with nuclear crowding but retained basal nuclear polarity and hyperchromasia.

On higher magnification, AIS cells can be recognised as tightly packed sheets 1-3 cells thick, cell strips with pseudostratification, feathered/frayed edges and common borders, oval to elongated nuclei with increased N/C ratios, and stippled fine to coarse granular chromatin. Apoptotic debris and abnormal mitotic figures may also be observed.

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Updated 4/8/25