NCPTS
National Cervical Pathology Training Service

ATYPICAL AND ABNORMAL ENDOMETRIAL CELLS IN CERVICAL CYTOLOGY SAMPLES
Cytomorphology for Year 1-2 Registrars

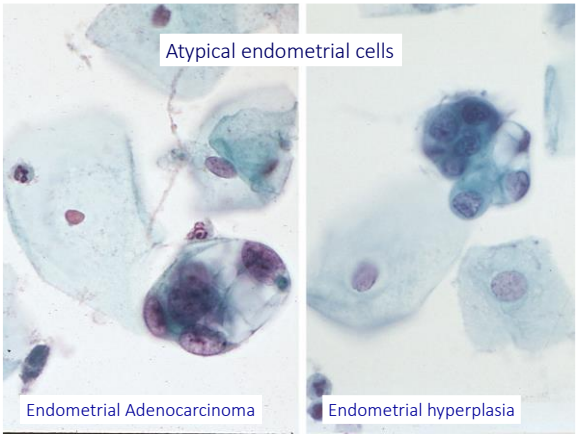
Overview

- reported as either atypical endometrial cells or as abnormal glandular cells consistent with endometrial adenocarcinoma
- all cases require specialist investigation with urgent referral if adenocarcinoma is identified

ATYPICAL ENDOMETRIAL CELLS

- always reported at any age and always referred for specialist investigation
- cells are reported as atypical mainly because of nuclear enlargement and greater nuclear variability compared with normal endometrial cells. Nucleoli may be slightly more prominent and cell groups may be less tightly clustered.

- raises the possibility of malignancy but can also be caused by atypical endometrial hyperplasia, endometrial polyps, chronic endometritis or an IUCD
- category also used when the features are very suspicious of endometrial carcinoma but are not quite sufficient for a definite diagnosis



- The distinction between atypical endometrial hyperplasia (with or without atypia) and well-differentiated endometrial adenocarcinoma is not reliable by cytology

- Atypical glandular cells are difficult to assess, and it may not be possible to determine whether they are endocervical or endometrial in origin. Such cases are reported as *atypical glandular cells* and referred for investigation.

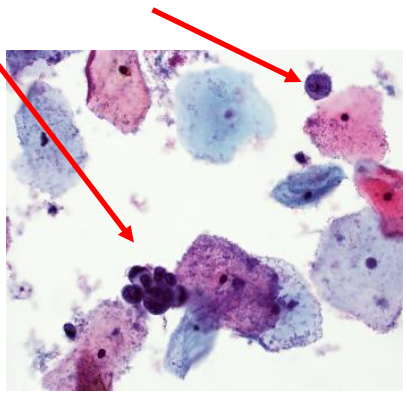
ABNORMAL GLANDULAR CELLS CONSISTENT WITH ENDOMETRIAL ADENOCARCINOMA

- endometrial adenocarcinoma is much more frequent than endocervical adenocarcinoma
- most present with abnormal bleeding, usually in those who are postmenopausal
- endometrial carcinoma is often associated with a hyper-oestrogenic state which may be reflected in the maturity of the other cells in the cytology sample, but this is not always the case and some samples will be atrophic.

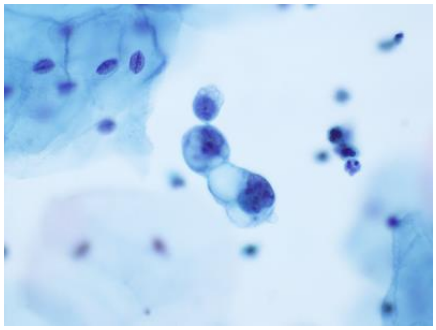
Cytomorphology of endometrial carcinoma

- is a wide spectrum of different tumour types as well as a range in the degree of differentiation - reflected in cytology samples.
- if poorly differentiated, may only be able to report a case as carcinoma, or even as a malignant neoplasm NOS, without being able to specify the site of origin. Not usually a problem because the site of origin is usually evident clinically or radiologically and confirmed on histologic biopsy.

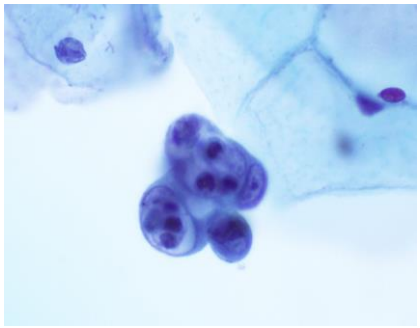
- Endometrial carcinoma cells are usually exfoliated from the uterine cavity so are seen as small rounded 3-D clusters. Cells are often partly degenerate.



  - Cells are usually single or in small clusters
  - nuclei are typically eccentric and variably pleomorphic with prominent nucleoli (called “cherry red” because of their colour and prominence)
  - Nuclei are generally smaller than seen with endocervical carcinoma, but poorly differentiated endometrial carcinomas may have large nuclei. Conversely, cells and their nuclei can be very small because of partial degeneration. Small nuclei still have malignant features but the variation between malignant nuclei is happening on a small scale too, so can be subtle.



  - the cytoplasm is pale and vacuolated and there may be ingested neutrophils, a sign of degeneration. The cytoplasm is more abundant than in normal endometrial cells.
  - a characteristic appearance is indentation of the nucleus which is pushed to one side of the cell by a large cytoplasmic vacuole
  - the number of malignant cells varies greatly. Well-differentiated lesions shed fewer cells than poorly differentiated lesions. Small cells in very small numbers are easily overlooked.



  - Low power clues are important to trigger a search for small numbers of malignant cells
  - The background may be clean or contain finely granular endometrial debris forming membranous sheets that may contain neutrophils or histiocytes.
  - Endometrial debris often consists of very small particles of debris which can have a distinctive “bitty” look
  - Prominent emperipolesis (engulfment of cells and debris) should prompt a thorough examination of the nuclei of the cells concerned for malignant characteristics. Engulfment of other cells, neutrophils and debris is a feature of cell degeneration not malignancy per se but is common in endometrial carcinoma.

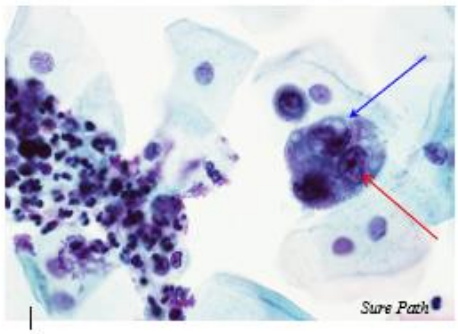
- The architecture of cell groups varies widely reflecting the range of different endometrial malignancies. Cell groups may have glandular or papillary architecture, show 3-D clusters and cell balls, present as single cells or large cell clusters

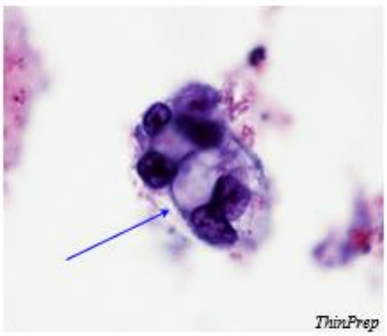
- Most malignancies of endometrial origin seen in cervical cytology are carcinomas. With carcinosarcoma it is the epithelial component that is usually shed and seen in cervical cytology samples. Stromal tumours such as endometrial stromal sarcomas can occasionally be seen.

- As endometrial malignancies usually present as exfoliated cells in cervical cytology samples, some degree of cell degeneration is common. Interpreting the effects of degeneration and distinguishing between degenerative and malignant features can be very challenging.

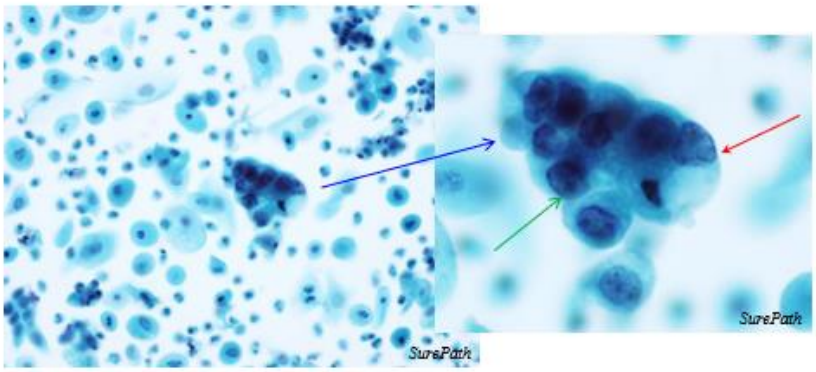
- Where the endometrial malignancy directly invades the endocervix or presents as a polypoid mass that protrudes down into the endocervical canal, the tumour may be directly scraped by the sampling device. The appearance then differs from that of exfoliated material in that:
  - the amount of abnormal material is greater
  - cell preservation is often better
  - the cells are not as rounded up into balls but present in flatter sheets.

The combination of the right clinical setting, the sample background and the characteristic appearance of the malignant endometrial cells often allows a confident cytologic diagnosis of endometrial carcinoma. Malignant cells must be clearly identified before making a definite diagnosis.

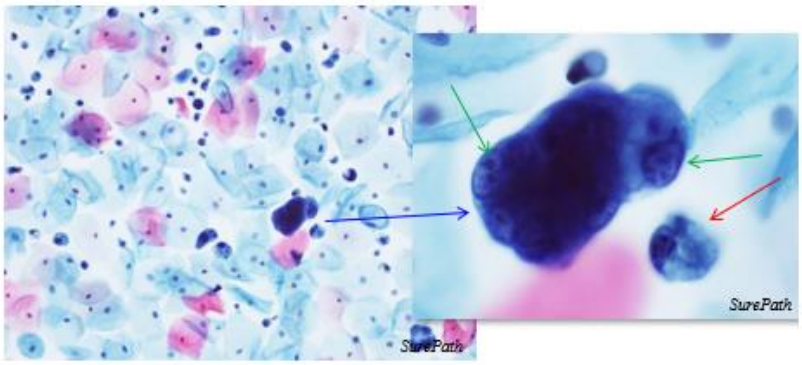




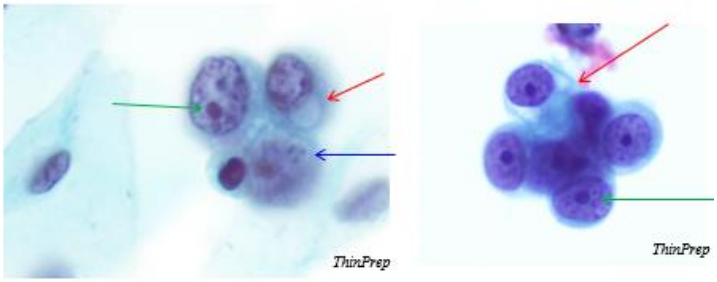
Far right: single and clustered malignant glandular cells with prominent nucleoli (red arrow), cytoplasmic vacuoles that compress the nucleus (blue arrows) and associated inflammatory debris.
Right: malignant glandular cells forming a rounded-up exfoliated cluster with prominent cytoplasmic vacuoles that indent adjacent hyperchromatic malignant nuclei



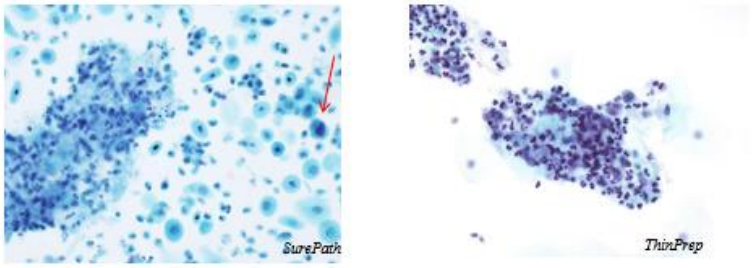
A rounded exfoliated cluster of endometrial adenocarcinoma occurring in an atrophic background. At high power there are eccentrically placed malignant nuclei which are indented by cytoplasmic vacuoles (red arrow). Prominent nucleoli are also present (green arrow).



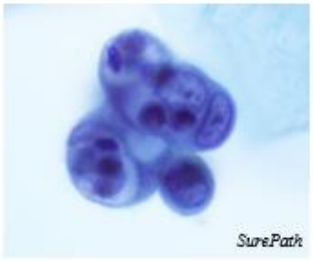
Exfoliated clusters and dissociated single cells of endometrial adenocarcinoma in an 80-year-old woman without epithelial atrophy. At high power malignant nuclei have highly abnormal chromatin with margination, thick irregular nuclear membranes and prominent nucleoli (green arrows). Cytoplasmic vacuoles displace and indent the nucleus (red arrow).

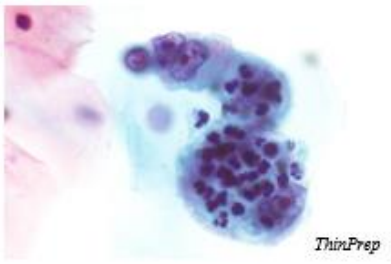


Endometrial adenocarcinoma.
Far right: marked nuclear pleomorphism with abnormal granular unevenly distributed chromatin. There is ingestion of a neutrophil (blue arrow).
Both cases show prominent nucleoli (green arrows) and cytoplasmic vacuoles (red arrows).



Clusters of granular debris, neutrophils and histiocytes are common and should trigger a careful search for malignant endometrial cells in a postmenopausal woman. There may or may not be partially degenerate malignant cells associated with the debris. More often, malignant cells are found elsewhere in the sample (red arrow).





Ingested neutrophils are common in the cytoplasm of malignant cells from an endometrial adenocarcinoma and may obscure the malignant nuclei. Ingested neutrophils are common but are not specific for endometrial adenocarcinoma and are a reflection of cell degeneration rather than malignancy per se.

Notes prepared by:
Margaret Sage
NCPTS cytopathologist
Updated 19/4/25