BENIGN NON-INFECTIOUS CONDITIONS IN CERVICAL CYTOLOGY

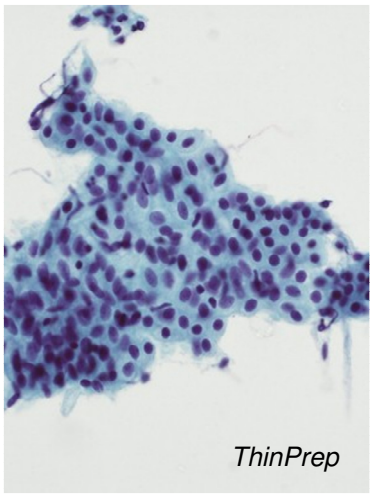
Notes updated: 04.07.14

ATROPHY

- less oestrogen results in a thinner more fragile less mature squamous epithelium and reduced mucus secretion from endocervical cells.
- seen to a variable degree in postmenopausal women, postpartum, after oophorectomy, in vaginal epithelium after total abdominal hysterectomy and in some women on Depo Provera.
- can lead to chronic irritation and reaction of cervical/vaginal epithelial cells associated with chronic inflammation (atrophic cervicitis/vaginitis) which can cause a brown PV discharge clinically.

In Atrophy: Typically see sheets of atrophic squamous cells and numerous parabasal cells, both in sheets and as small round single cells.

- squamous metaplastic cells may also be present and can be difficult to distinguish from parabasal cells (latter tend to be larger and have slightly more cytoplasm)
- cells may show degenerative features such as karyopyknosis. Autolysis may result in naked nuclei.
- small, keratinised degenerate squamous cells may be present and should be examined carefully to ensure that small, well-differentiated abnormal keratinised high-grade squamous cells are not overlooked.
- the degree of atrophy varies considerably from one post-menopausal woman to another, but tends to be fairly constant over time for an individual woman.

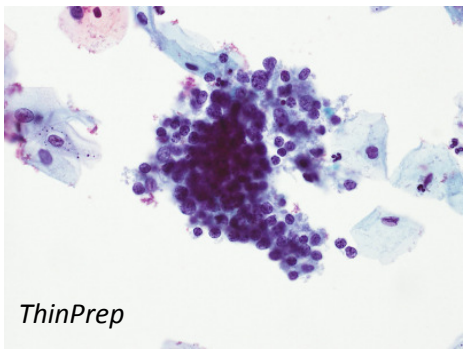

ThinPrep

In Atrophic cervicitis: a variable degree of reactive change is seen in epithelial cells.

- can result in epithelial atypia and as atrophic epithelial cells already have a high N:C ratio, distinction from HSIL or even invasive SCC can be difficult.
- the background contains bacteria, neutrophils and histiocytes of variable size (single or multinucleated)
    - a granular precipitate is common. With LBC, may be removed by processing or remain either in clumps or clinging to cell groups.
    - spherical structures termed “blue blobs” are either degenerating parabasal cells (look like large abnormal bare nuclei) or inspissated mucus.

LYMPHOCYTIC CERVICITIS (Chronic follicular cervicitis)

- Sub-epithelial lymphoid follicles can be represented in a cytology sample if there is erosion or ulceration of the epithelium or if the epithelium is thin and easily disrupted as in atrophy.
- most commonly seen cytologically in middle-aged postmenopausal women.
- See a polymorphous lymphoid cell population with scattered tingible body macrophages. Latter are very helpful if present but are not always seen.


ThinPrep

- In LBC the lymphocytes are usually single or in loosely non-cohesive small clusters.
- DD includes HSIL (larger cells, often some clusters, more nuclear pleomorphism, squamous differentiation), Small cell (neuroendocrine) carcinoma (significant nuclear abnormalities, one cell type, diathesis), poorly differentiated SCC with very small cells (pleomorphism, some squamous differentiation, diathesis, clumping and clearing of nuclear chromatin), and lymphoma.

- Lymphoma must be considered if a monomorphic lymphoid population is present. This is rare in the cervix and usually occurs in the context of more widespread previously identified disease.
- Chlamydia has been associated with lymphocytic cervicitis but the association is not specific enough to be helpful diagnostically.

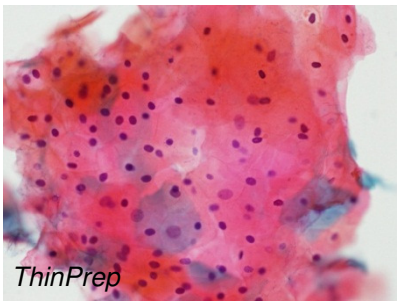
HYPERKERATOSIS and PARAKERATOSIS

In **hyperkeratosis**: see sheets and clusters of keratinous debris and anucleated squamous cells.

- Superficial squamous cells may have cytoplasmic keratohyaline granules.
- Clinically the appearances are of leucoplakia on the cervix/vagina. The dense white appearance is due in part to the increase in overall thickness of the epithelium (acanthosis) and in part to keratinisation.
- Hyperkeratosis is usually due to chronic superficial abrasion of the cervix as in uterine prolapse, and can also occur with cervical infections.
- Uncommonly, hyperkeratosis can overlie a squamous intra-epithelial lesion. This is problematic for the colposcopist who will not be able to visualise the lesion because of the leukoplakia. All cytology samples with hyperkeratotic material should be screened thoroughly for abnormal squamous cells.
    - If no abnormal cells are found, the appearances are too non-specific to recommend early repeat smears or colposcopy.
- There is no specific Bethesda code for hyperkeratosis and whether it is commented on in reports or not, varies.

In **parakeratosis:** keratinised cells are nucleated. Cells have dense glassy bright orange cytoplasm (keratinised) and can present as single cells, small sheets or keratin pearls.

- Parakeratosis is very important as it can occur at all levels of the squamous spectrum of disease i.e. from benign conditions (e.g. atrophy), in association with infection, commonly with HPV infection, in preneoplastic lesions and in squamous cell carcinoma.
- These entities are distinguished by the appearance of the nuclei which must be carefully examined in all parakeratotic material.


ThinPrep

In normal degeneration, as the nucleus becomes more pyknotic it becomes smaller and darker so that in a sheet, the smaller nuclei are darker. If the larger nuclei are also darker than the smaller nuclei in a parakeratotic group, examine carefully for the possibility of a high-grade squamous lesion.

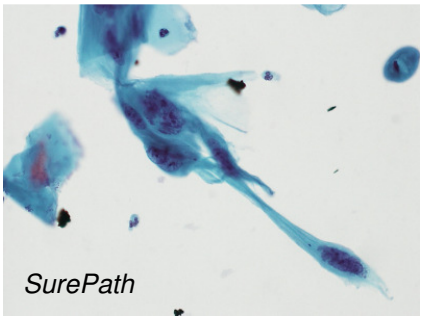
- Typical parakeratosis: cells have round to oval pyknotic nuclei with a low N:C ratio. This benign appearance may still overlie a squamous intra-epithelial lesion so look for abnormal cells.
- Atypical parakeratosis: more nuclear variability. Is a common manifestation of HPV infection but can occur with any degree of intra-epithelial or invasive squamous lesion.
- Assess the degree of squamous abnormality on the basis of nuclear changes. The N:C ratio can be difficult to use to classify the degree of abnormality and at the high end of the spectrum, distinction between keratinisng HSIL and SCC can be very difficult. Colposcopy may be necessary to rule out SCC.
- Miniature keratinised squamous cells with small irregular hyperkeratotic nuclei may be the only manifestation of squamous cell carcinoma in a cytology sample.

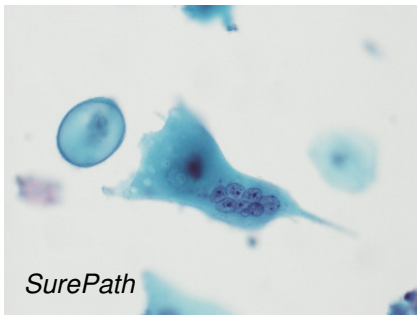
RADIATION and CHEMOTHERAPY EFFECTS

Radiation can cause short term (about 6 months) and long term effects on cells, which can be bizarre and mimic carcinoma, dysplasia, and/or HPV. Clinical information is essential.

- Follow-up smears from patients treated with radiotherapy for cervical cancer are taken to detect disease recurrence and may contain:
  1. Benign cells showing radiation effect
  2. Malignant cells affected by radiation
  3. Malignant cells unaffected by radiation. In persistent cancer, most malignant cells show little radiation effect.
- Radiation effect is well documented. The effects of chemotherapy are less well defined but appear to share some of the features seen following radiation treatment.
- Radiation causes short term acute (about 6 months) and long term chronic changes which can persist for years, even for a lifetime.
- Smears should not be taken within the first 8 weeks following radiation as viable tumour cells may still occur along with degenerating tumour cells. At about 8 weeks the smear will rapidly become clear of tumour cells.
- Nonspecific degenerative changes (pyknosis, karryorrhexis, karyolysis) signify cell destruction.
- There will still be a background of diathesis including blood, fibrin, mixed leucocytes, and necrosis along with features of regeneration and repair. Severe ulceration and granulation tissue may result in macrophages (including multinucleated giant forms), epithelioid histiocytes, capillaries, and fibroblasts/myofibroblasts, which are elongated with pleomorphic nuclei.
- In the longer term (chronic), the features of repair and granulation will disappear.
- The epithelial changes are similar in both the acute and chronic stages.
  - large to giant squamous cells (macrocytes). The cells are enlarged with a corresponding large nucleus so the N:C ratio remains low (i.e. normal for the cell type).
  - the cells may appear indistinct, pale and “washed out”.
  - the nuclear membrane may appear wrinkled or folded. Perinuclear halos seen.
  - the cytoplasm may be polychromatic/vacuolated/contain ingested cells and debris.
  - bizarre forms e.g. tadpole cells and multinucleation are common.
  - the chromatin may appear granular or smudged. Is evenly distributed.
  - cytoplasm vacuoles, both large and/or small, are common

  Similar effects may be seen in glandular cells.


SurePath


SurePath

- If the ovaries have been removed or are inactive, the background will be atrophic.
- A contracted scarred stenotic vagina can result, which is difficult to visualise colposcopically.
- Hormone replacement therapy may be given to some patients who have had radiation for treatment of cervical carcinoma although there is understandably reluctance to use oestrogen in any situation where a tumour could be oestrogen dependent. This limits the use of vaginal oestrogen to resolve the atrophy before taking samples for cytology.

Using cervical cytology to detect tumour recurrence can be notoriously difficult particularly after treatment for squamous cell carcinoma. Samples are often sparsely cellular and markedly atrophic, and can be very difficult to interpret. Cervical cytology is not sensitive for detecting tumour recurrence but can be specific if the appearances are definite. The differential diagnosis is usually:

Recurrent carcinoma with radiation change vs *radiation change only*

- The most important feature when considering tumour recurrence is the presence of abnormal cells with **high N:C ratios**.
- Chromatin distribution can also be helpful – even if benign, uneven if malignant
- Traps:
  1. tissue fragments of stromal cells with disturbing nuclei
  2. sheets of repair cells with very active nuclei
  3. large numbers of histiocytes with active nuclei (often multinucleated).

The diagnostic difficulty is compounded by the fact that SIL lesions can occur in the post-radiation period, sometimes called "radiation dysplasia". This is a very difficult area for cytologic assessment.

- Mild radiation dysplasia is a relatively common finding (up to 25% of cases) and can be associated with both acute and chronic radiation changes.
- Any suspicion of high-grade dysplasia or recurrence would be referred back for further clinical assessment and colposcopy.
- Any grade of dysplasia occurring within the first three years post-radiation carries a higher risk of tumour recurrence.

Some oncologists recommend NOT taking post-radiation smears, preferring to follow patients clinically. This is because of the difficulties in detecting recurrence that is not apparent clinically and because a significant clinical dilemma results if a false positive report is issued, even if only a possibility of recurrent cancer is raised.

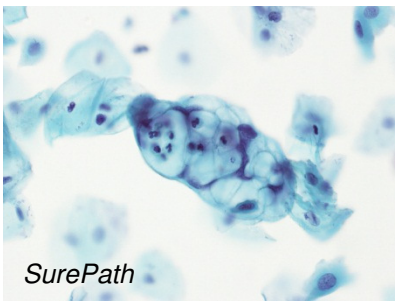
Chemotherapy can cause changes in squamous epithelial cells that mimic SIL, either LSIL or HSIL

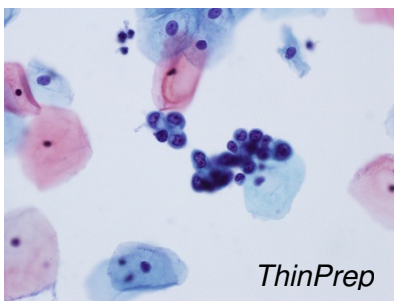
e.g. cell/nuclear enlargement, hyperchromasia, coarse granular chromatin, variations in nuclear size/shape.

- atrophy may occur with long term treatment
- the changes seen may persist after the drug has been withdrawn.

IUCD EFFECTS

Can cause endometritis, cervical microglandular hyperplasia, or cervicitis due to irritation by IUCD threads. Frequently associated with actinomyces.


SurePath


ThinPrep

- IUCD cells are probably of endometrial origin: High N/C ratios, uni/multinucleated, nucleoli and degenerative changes are common. May have large cytoplasmic vacuoles.
- Normal endometrial cells can be shed at any time of the menstrual cycle. May show degenerative changes
- Endocervical cells may look reactive or hyperplastic. Can be shed singly or in large papillary fragments.

- Distinction from HSIL or neoplasia can be very difficult, and overcalls can occur particularly if the history of an IUCD is not known.

TAMOXIFEN

- widespread use in treatment of women with breast carcinoma.
- in post-menopausal women, has a weak oestrogen-like proliferative effect on cervical/vaginal epithelium.
- May affect cervical cytology in 2 ways:
  1. Endometrial abnormalities: increased incidence of both hyperplasia and endometrial carcinoma
  2. "Small blue cells" seen in smears taken from women on tamoxifen. Are probably reserve cells that are also seen in women not on tamoxifen but often stand out in the oestrogenised smears of women on tamoxifen. Need to be accurately distinguished from both endometrial cells and HSIL cells.
    - Nuclear size is similar to an endometrial cell, but nuclear contours are regular and smooth (endometrial cells often have nuclear grooves)
    - reserve cells have no cytoplasm whereas endometrial cells have a small rim
    - form loose cellular aggregates whereas endometrial cells are typically in tightly cohesive 3-dimensional clusters.

ENDOCERVICAL POLYPS

- Endocervical polyps can originate in any area of the endocervical canal. Can be covered by endocervical cells or squamous metaplastic cells, and may show the full spectrum of squamous or glandular epithelial abnormality. Keratinisation can occur as a result of chronic irritation.

- Polyps are often inflamed and the surface epithelium can be very reactive. This results in atypical epithelial cells in cytology samples that can mimic squamous dysplasia and is a classic cause of false positive reports in cervical cytology.

CERVICAL ENDOMETRIOSIS

- can be difficult to determine if normal endometrial cells in cytology samples are a result of menstruation, endometrial pathology, or endometriosis.
- in endometriosis, endometrial cells are directly sampled so are well preserved and not as balled up as exfoliated cells from the uterine body, although some rounding up of groups can occur in the vial fluid of LBC samples. Also endometrial stromal cells are often present in the same sample in endometriosis, which is seen less commonly with exfoliated material.
- the most common situation in which cervical endometriosis occurs is in women who have had a previous cone or lletz cervical biopsy, as menstrual endometrial cells can seed the raw cervical stromal bed after the cone or lletz biopsy, before re-epithelialisation has occurred. Can also be a true metaplasia.
- DD can include cervical adenocarcinoma, Lower Uterine Segment cells (LUSC), HSIL, atrophy, repair, tubal or tubo-endometrioid metaplasia.

"EROSION" and ULCERATION

- historically, "erosion" was a clinical term used to describe what we now call the transformation zone.
- if true superficial erosion of the epithelium has occurred, superficial squamous cells are reduced with more basal and parabasal cells.
- If ulceration has occurred the full thickness of the epithelium is missing focally, but can re-epithelialize with healing.
- If tissue destruction is so extensive that repair cells cannot regenerate the epithelium, then repair is achieved by fibrosis. Fibroblasts and granulation tissue components including a mixed inflammatory cell population may be seen if cytology samples are taken.

- Eventually a scar is achieved.

NABOTHIAN CYSTS/FOLLICLES

- endocervical crypts can become plugged by mucus, inflammation or through the formation of metaplastic epithelium. May result in small cysts/follicles full of mucus.
- If a nabothian cyst is disrupted as a cytology sample is taken, necrotic debris and multinucleate giant cells with abundant foamy pink cytoplasm may be seen in the sample. These are multinucleated endocervical cells and should not contain phagocytosed material in the cytoplasm.

BASAL CELL HYPERPLASIA

- An increase in basal cells with basal cell hyperplasia, will not normally be seen cytologically as is covered by mature squamous epithelium.
- if the lower cell layers are exposed or sampled, the smear will contain many basal cells. Cytology will then resemble a post-natal/atrophic smear.
- Basal cells can have a prominent nucleolus as they are actively replicating.

RESERVE CELL HYPERPLASIA

- Reserve cell hyperplasia is relatively common in postmenopausal women but is seen uncommonly in cytology samples.
- Cells may be single, in dense clumps, or side-by-side in pairs, and the tip of one nucleus tends to overlap the edge of the next nucleus.
    - Nuclei resemble those of endocervical cells but are smaller, and may have a pointed tip at one end.
    - The chromatin is finely granular and a small nucleolus may be present.
    - numerous free oval nuclei may be seen.
    - Nuclear molding may be observed in dense clumps.

MICROGLANDULAR ENDOCERVICAL HYPERPLASIA

Is a localised proliferation of endocervical cells typically in younger women, with an association with oral contraceptive use and sometimes pregnancy. Usually an incidental finding on histology but cytologic features are poorly defined and can be a cause of overdiagnosis of AIS or adenocarcinoma.

- Typically see enlarged oval-shaped nuclei with finely granular chromatin and small nucleoli. Cytoplasm usually abundant and finely vacuolated. Nuclear crowding and overlapping is frequent and degenerative changes can cause the cells to appear hyperchromatic.

METAPLASIAS

Squamous metaplasia is the normal physiological process that occurs at the squamocolumnar junction where endocervical glandular epithelium is gradually replaced by squamous epithelium.

Tubal metaplasia is common. It occurs in the endocervical canal where normal endocervical epithelium is replaced by epithelium normally seen in the fallopian tube. This includes ciliated glandular cells. IS a common diagnostic pitfall in AIS diagnosis.

- Usually small strips or tightly cohesive groups. Cells with cilia and terminal bars greatly facilitate the diagnosis when present but are not always seen.

Tubo-endometrioid metaplasia is less common and also occurs in the endocervix.

Endometrial metaplasias (tubal, eosinophilic, papillary, squamous) occur in the endometrium but may still be a source of metaplastic cells seen in cervical cytology samples.

Transitional metaplasia occurs mainly on the ectocervix in peri/post-menopausal women and can be misinterpreted as HSIL. Cells are bland and parabasal-like with elongated nuclei, often with a prominent longitudinal nuclear groove.

FOLIC ACID and/or Vitamin B12 DEFICIENCY

- May see both nuclear and cytoplasmic enlargement but typically the cytoplasmic enlargement predominates
- nuclear changes are usually minor and the N:C ratio is extremely low so cells are not of concern.
- see marked enlargement of intermediate squamous cells (macrocytes) to a diameter of 70 microns or larger, nuclear enlargement to 14 microns or more (low N:C ratio).
- cytoplasmic vacuolisation and multinucleation may be seen in a small number of cells. Also phagocytosis, clumping and folding of nuclear chromatin. May see nucleoli.
- Women who develop megaloblastic anaemia during pregnancy may show these changes.
- Folic acid changes are occasionally erroneously reported as ASC-US.

PSAMMOMA BODIES

- Seen rarely in cervical cytology samples.
- Associated with a wide range of benign and malignant conditions of the ovary, peritoneum, endometrium and cervix.
    - Benign: IUCD's, ovarian inclusion cysts, ovarian cystadenofibroma, endosalpingiosis, chronic salpingitis, TB endometritis, tubo-ovarian adhesions
    - Malignant: Serous tumours of ovary including serous adenocarcinoma, endometrial carcinoma, even SCC of cervix.
- Majority are benign but association with malignancy increases with age.
    - Incidence of malignancy still sufficiently high at any age to warrant further investigation of the genital tract if psammoma bodies are identified.
    - Age of the patient and the other cells present in the same cytology sample, are the best predictors of malignancy.

CHANGES SEEN POST-LLETZ /CONE BIOPSY

- Smears are not recommended until at least 6 months post-lletz or cone biopsy because healing and regeneration makes cytologic interpretation too difficult.
- Surgical trauma to the cervix results in an initial acute phase of degeneration followed by regeneration.
- Laser treatment is followed by rapid regeneration with little or no evidence of necrosis in the smear.
- cryotherapy and cautery can result in necrosis for some weeks after the treatment.
    - Active squamous metaplasia and repair may be seen.
    - Endometrioid, tubo-endometrioid, or tubal metaplasia is reasonably common
    - Hyperchromatic crowded groups with overlapping nuclei may be large and constitute a high-risk pattern which must be carefully examined to exclude HSIL. These groups are sometimes reported as ASC-H and can be a source of over diagnosis.
- Cone biopsy can shorten the length of the endocervical canal. Sheets of lower uterine segment endometrial cells are then sampled and appear in cervical cytology samples. These are high N:C cells and may have mitoses if the endometrium is proliferating, and need to be distinguished from a high-grade lesion.

GLANDULAR CELLS POST-HYSTERECTOMY

Benign endocervical-type cells that are indistinguishable from cells sampled from the endocervix, may be seen in vaginal vault samples from women who have had a hysterectomy. Several potential reasons:

- A frequent association is previous radiotherapy or chemotherapy – probably a metaplastic reaction
- May be mucinous/goblet cell metaplasia in response to atrophy
- Prolapsed fallopian tube (after vaginal hysterectomy)
- Adenosis occurring after traumatic stimulation of mesenchymal cells also postulated

Important to exclude adenocarcinoma, particularly if the hysterectomy was done for glandular neoplasia.

Dr Margaret Sage
Cytopathologist, NCPTS