INFLAMMATORY REACTIVE REPARATIVE and DEGENERATIVE CHANGES

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Inflammatory, reactive and degenerative changes in cervical smears are very common. The reason is not usually apparent, but there may be a specific infection, a post-partum sample, an IUCD or pessary, or a prior therapeutic procedure (e.g. laser, cautery, surgery, irradiation).

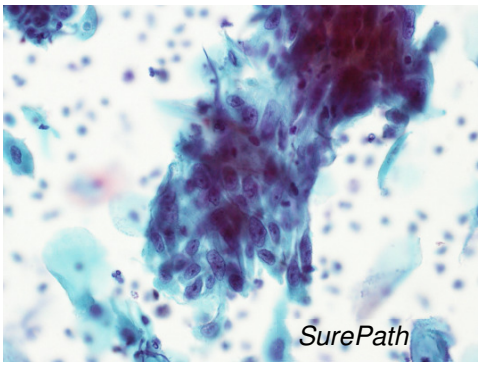
Minor reactive changes are not reported. Occasionally reactive changes result such significant cytologic atypia that they are difficult to differentiate from a neoplastic process. These these cases are reported as “ASC, possible high-grade”. Careful examination of cell and nuclear features and adherence to diagnostic criteria will reduce misinterpretation. Inflammation/infection/reaction can co-exist with neoplasia.

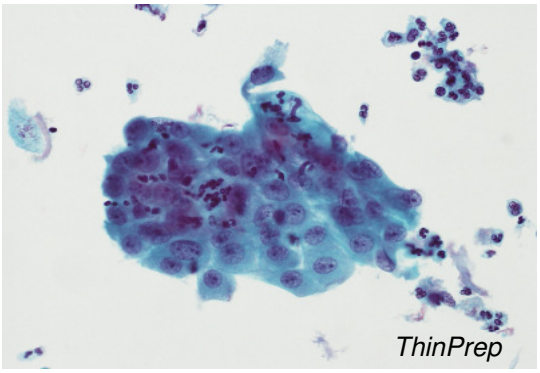
Inflammatory cells in cervical samples can come from any level of the genital tract. An increase of leucocytes occurs in women at various stages of the menstrual cycle and is of no clinical significance. Inflammatory cells in cervical cytology samples are such a non-specific finding that they are not usually helpful diagnostically, although should trigger a careful search for specific infections.

Most leucocytes in cervical cytology samples are neutrophils. Lymphocytes are much less common and usually seen in the lymphocytic cervicitis. Histiocytes can be physiological e.g. just before and during menstruation and are also common in postmenopausal women. .A true granulomatous reaction which includes epithelioid histiocytes as well as multinucleated histiocytes may occur as a foreign body reaction e.g. residual suture material, occasionally with IUCD’s or rarely because of genital tract tuberculosis.

Reactive epithelial cells need to be examined carefully to exclude a pre-neoplastic or neoplastic lesion.

Reactive cells are benign and retain good cell-to-cell cohesion with well-defined cell-to-cell borders, intracellular bridges, and a relatively ordered cell architecture and cell polarity. They typically occur in flat sheets, retaining good cell polarity with a streaming appearance. Inflammatory cells may or may not be present in these sheets or in the background.





Nuclei are variably increased in size. Nuclear membranes are smooth without irregularities. Because N:C ratios are increased, other nuclear characteristics are needed to distinguish these cells from pre-neoplastic/neoplastic lesions. Nuclei in reactive squamous cells resemble each other. In contrast, there can be considerable nuclear variation particularly in size, in reactive endocervical glandular cells. Nuclei in both epithelial types are metabolically active so may appear hyperchromatic with granular chromatin and prominent nucleoli.

Cells can be bi- or multinucleated and mitoses may be seen. In squamous cells, the cytoplasm may be denser, resembling metaplastic cells. Small soft-edged perinuclear halos are common in reactive squamous cells and need to be distinguished from the large sharp-edged large halos seen in koilocytes. Leucophagocytosis can occur (neutrophils ingested within the cytoplasm).

The increase in N:C ratios seen in reactive cells can be a cause for concern. In squamous epithelium the lack of variation between different nuclei (as seen in HSIL) helps to establish the benign reactive nature of the cells. In squamous epithelium, hyperchromatic crowded groups caused by an active cervicitis can be very difficult to distinguish from HSIL partly because it is harder to visualise individual nuclei to compare them in these crowded groups. This is a common reason for samples reported as "ASC, possible high-grade". An additional comment to alert the colposcopist to the differential diagnosis: HSIL vs. an active cervicitis, can usefully be included in the report. It can be even more difficult to distinguish marked reactive change from neoplasia in endocervical glandular cells because reactive glandular cells can look so variable and atypical.

Features seen in crowded sheets of HSIL but **not** typical of reactive cells include:
disorganised cell groups, abnormal mitoses, mitoses embedded within cell sheets, thick cell groups (4+ layers), and apoptotic debris in crowded cell groups

Repair occurs with regeneration of damaged epithelium. As with reactive change, repair can be cytologically atypical to the extent that some features may raise the suspicion of neoplasia. In reality there is a fine line between what constitutes reaction and what is repair. The features are very similar to reaction but are more marked – there are more cells resembling squamous metaplasia, the nuclear changes are more marked including high N:C ratios, presence of nucleoli and mitoses. Cohesion, cell architecture and polarity are retained. The presence of fibroblasts is unusual and suggests severe tissue damage. Repair is particularly difficult to assess when endocervical epithelium is involved. Over-diagnosis of marked reactive and reparative change in endocervical epithelium in the postpartum period as endocervical adenocarcinoma, is a recognised pitfall.

Degeneration is really common in epithelial cells in cervical cytology and needs to be identified. Fixation occurs rapidly with LBC samples so the degenerative changes seen have occurred in vivo. Endometrial cells that exfoliate and traverse the endocervical canal before being collected in a cervical sample are often partly degenerate. With reaction/repair the increase in cell activity and proliferation is accompanied by an increase in apoptosis and cell degeneration. Degenerate cells are also seen in increased numbers in atrophy. Features are:

i. Nucleus
- Swollen (hypochromatic) or shrunken (hyperchromatic, karyopyknosis) so N:C ratio varies
- Chromatin bland, marginated, smudged or breaks up (karyorrhexis, karyolysis)
- Nuclear ghosting e.g. in anucleate squamous cells
- Nuclear folds and creases

ii. Cytoplasm
- Cytolysis
- Cytoplasmic vacuolation
- Fragmented and broken cytoplasmic membranes
- Decreased intensity of staining
- Perinuclear halos where the nucleus has shrunk

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