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Case Study – Cervical cytology

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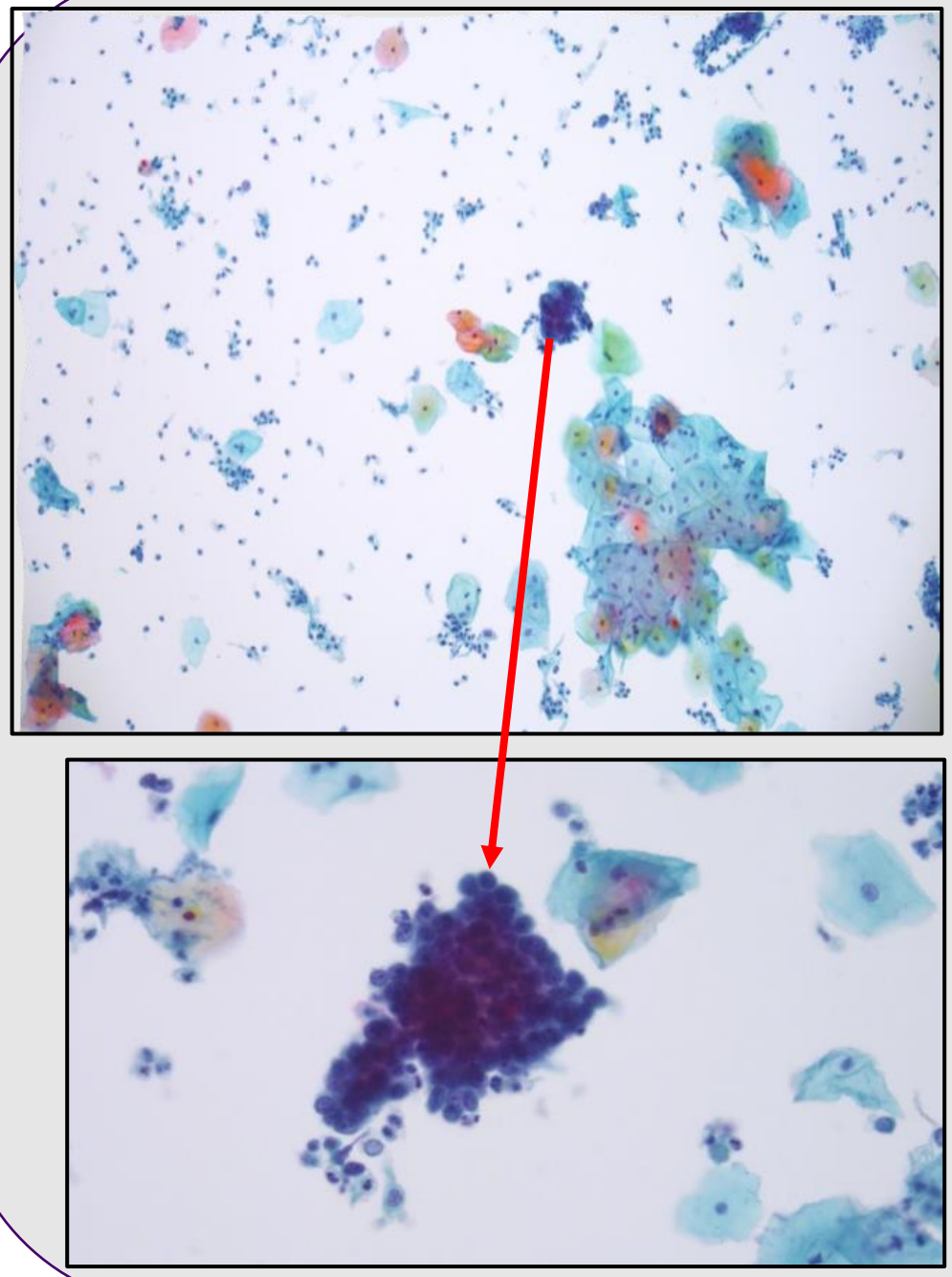
Clinical information

- 42-year-old female
- LMP day 19
- Previous cervical screening history
- 2 moderate dyskaryosis >20y ago
- followed by - 11 x neg cytology
- Current HPV test = positive (subtype 18)

Cervical cytology

- The overall cytology appearance consists of squamous cells, numerous sheets of endocervical cells, hyperchromatic crowded cell groups (HCCGs) and inflammatory exudate
- The squamous cells present are a mixture of orangeophilic superficial cells with hyperchromatic nuclei and intermediate cells many of which contain cytoplasmic glycogen.
- On low power screening there are quite a few darkly stained microbiopsies present. On high power these HCCGs revealed 3D groups of metaplastic type cells with dense cytoplasm, overcrowding, abnormal nuclei showing features of hyperchromasia, high N:C ratio, irregular nuclear membranes with chromatin clumping, pleomorphism suggestive of high grade dyskaryosis, possible ?crypt involvement.
- On further screening bare nuclei with uneven chromatin and irregular nuclear membranes are identified in the background.
- There are numerous sheets of endocervical type cells present with regular honeycomb and palisade architecture. In some of the HCCGs with abnormal nuclei it is difficult to distinguish between squamous or glandular in origin although overall features favour HG squamous dyskaryosis with possible crypt involvement.



Cervical cytology

- Presence of squamous, mainly intermediate type cells (glycogen laden)
- Inflammatory exudate including polymorphs in the background however there is no blood or debris suggestive of diathesis.
- Darkly stained clusters of metaplastic type cells (microbiopsies/HCCGs)
- Microbiopsies showing features of overcrowding with hyperchromatic high grade dyskaryotic cells

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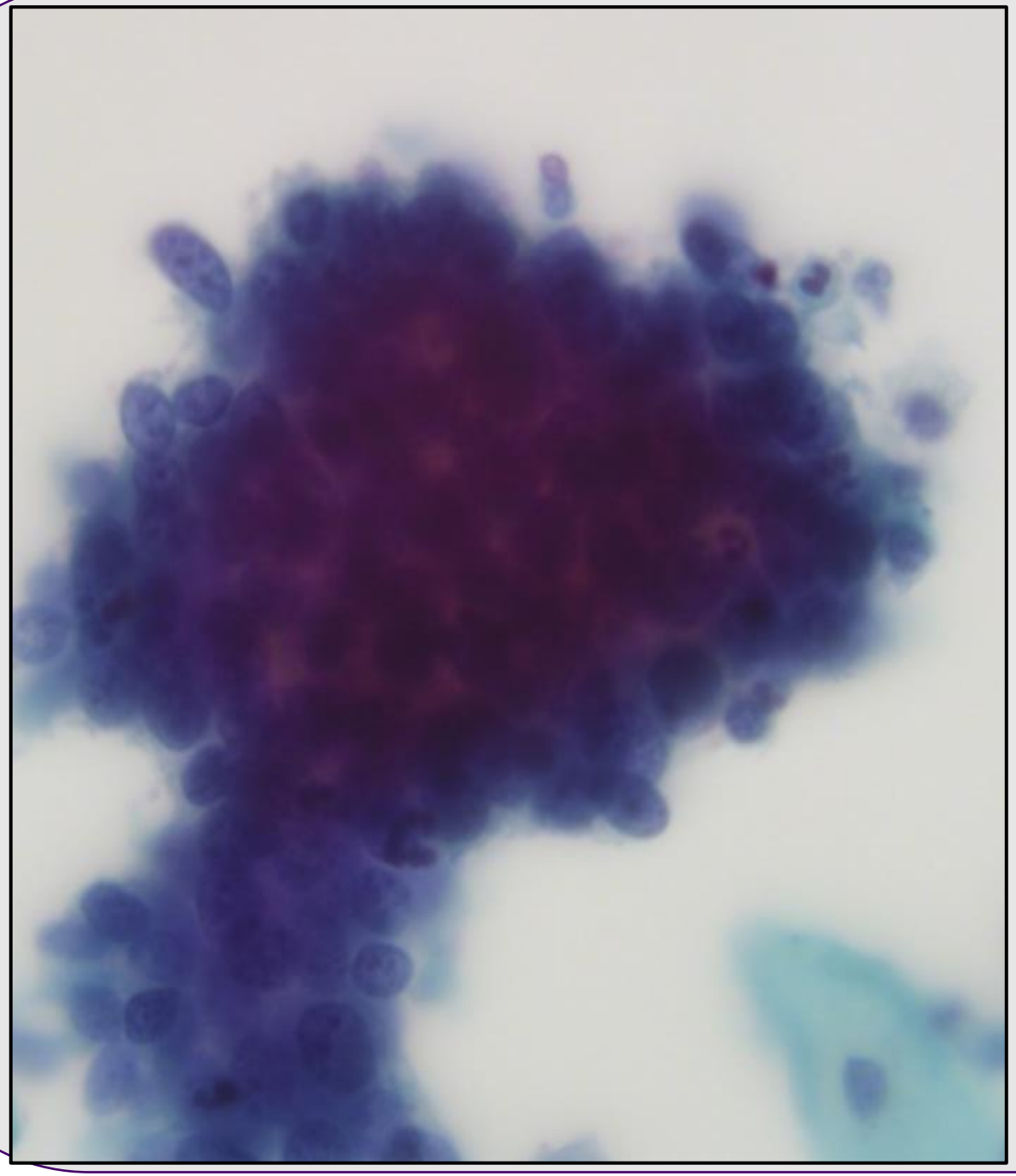

Cervical cytology

- Atypical three-dimensional cell groups showing increased N:C ratio, crowded, coarse granular chromatin and nuclear pleomorphism and jumbled architecture, jagged border, suggestive of severe dyskaryosis with possible crypt involvement.

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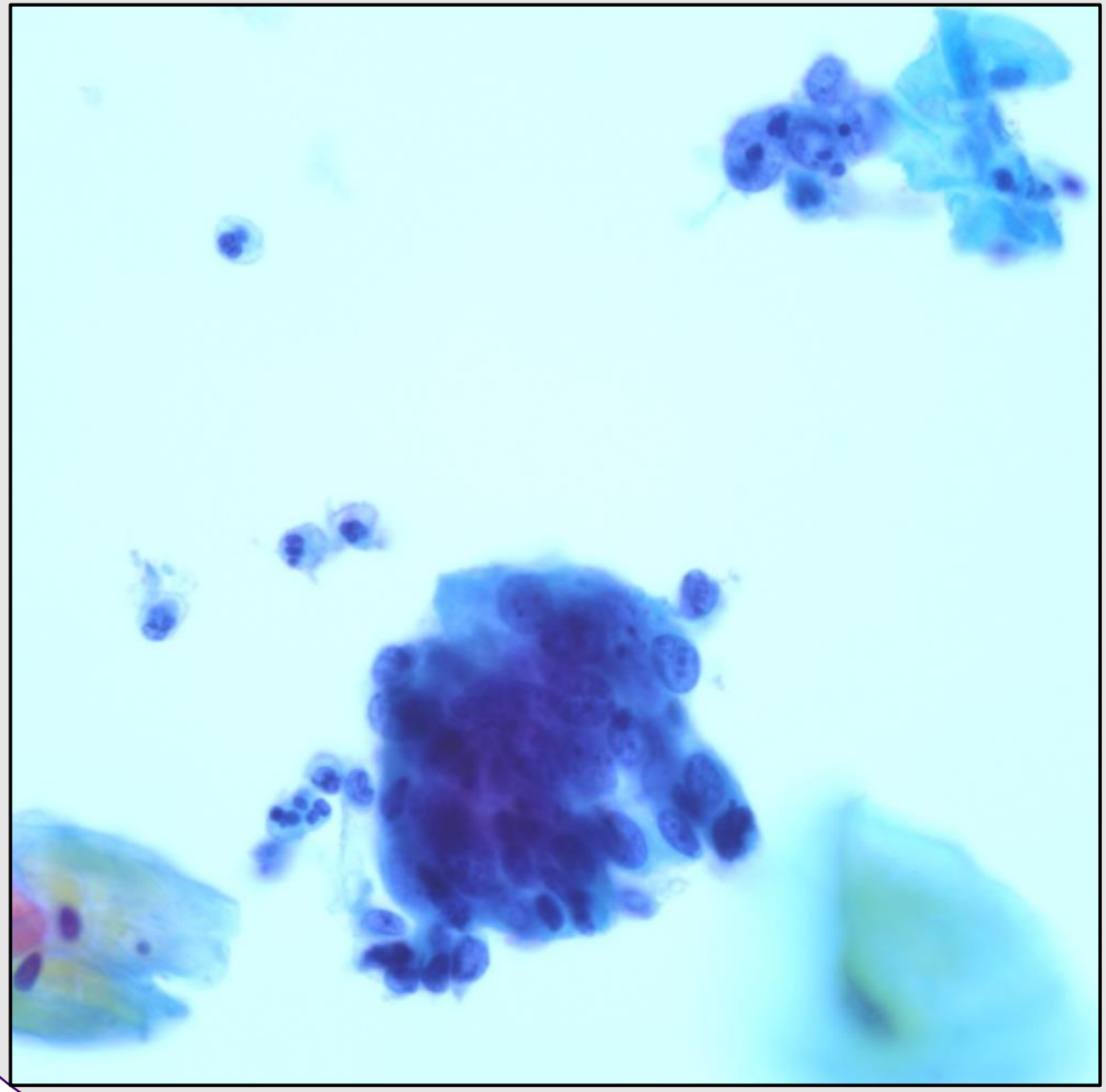
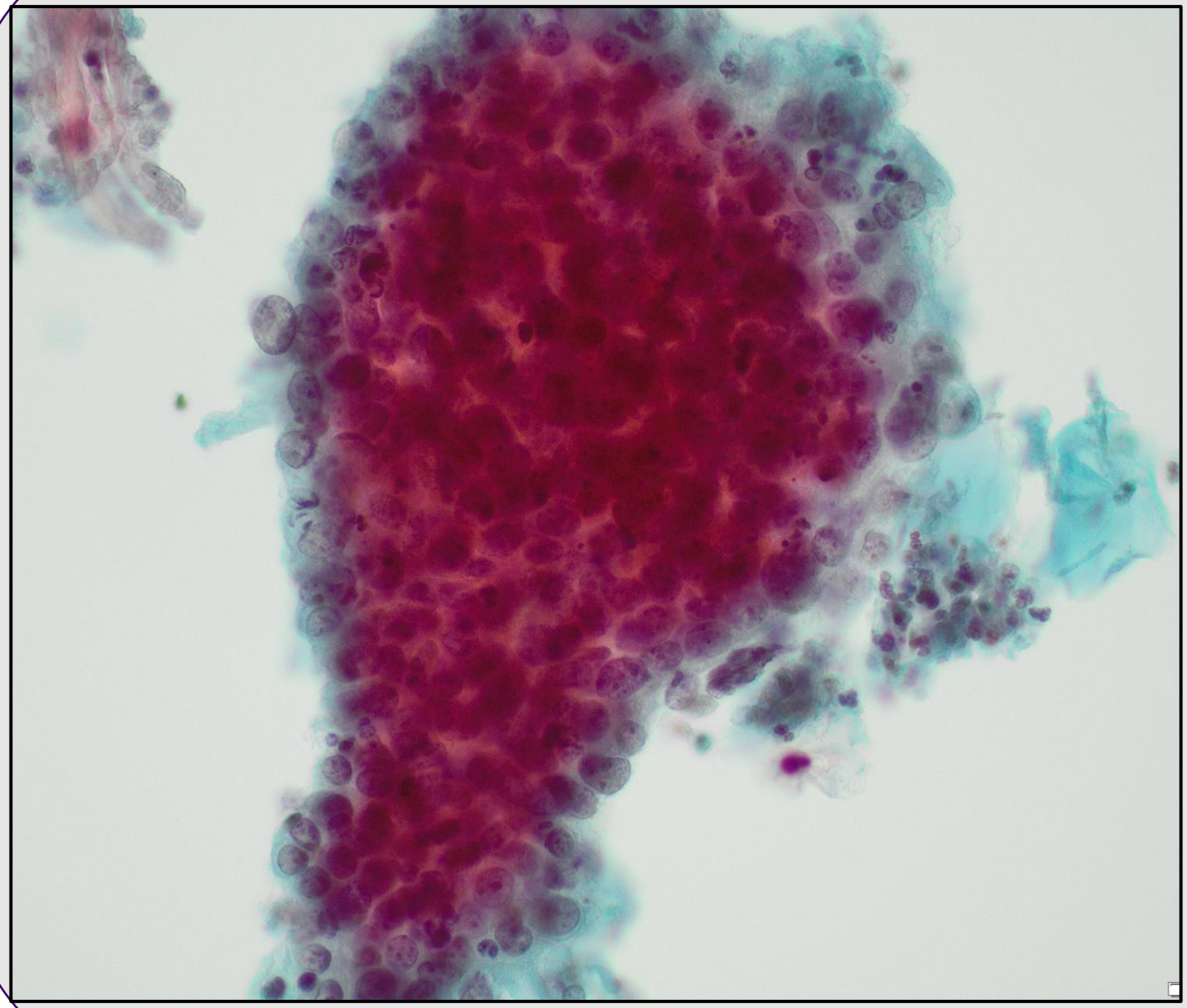


Cervical cytology

- Crowded group of cells with hyperchromasia, chromatin clumping, multiple nucleoli, pseudo stratification, subtle hint of possible glandular architecture.



Cervical Cytology

- Atypical cell group with overcrowding of nuclei, multiple enlarged nucleoli, pleomorphism, irregular border, difficult to assess the origin of cell type

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Cervical cytology report

- Primary screener report - High grade dyskaryosis (severe)
- Checker and consultant BMS – High grade dyskaryosis, severe
- Internal Report comment by CBMS – possible crypt involvement

Pitfalls:

- HCCGs are a known pitfall for missed dyskaryosis in screening samples as they may be mistaken on low power for a variety of benign mimics such as inflammatory or reactive metaplastic squamous cells, reserve cell hyperplasia, Tuboendometrioid metaplasia (TEM), endometrial cells for example especially where these are present elsewhere in the sample. *It is important to screen all darkly stained microbiopsies on high power to identify any potential atypia*
- ?Origin of atypical cells in HCCGs; squamous vs glandular. This can be very challenging in some cases. Each case should be assessed individually and seeking further opinions from colleagues may be useful before issuing the final report. The final report wording should reflect the difficulties in identifying the origin of the abnormal cells and offer a differential diagnosis where appropriate.

Colposcopy findings

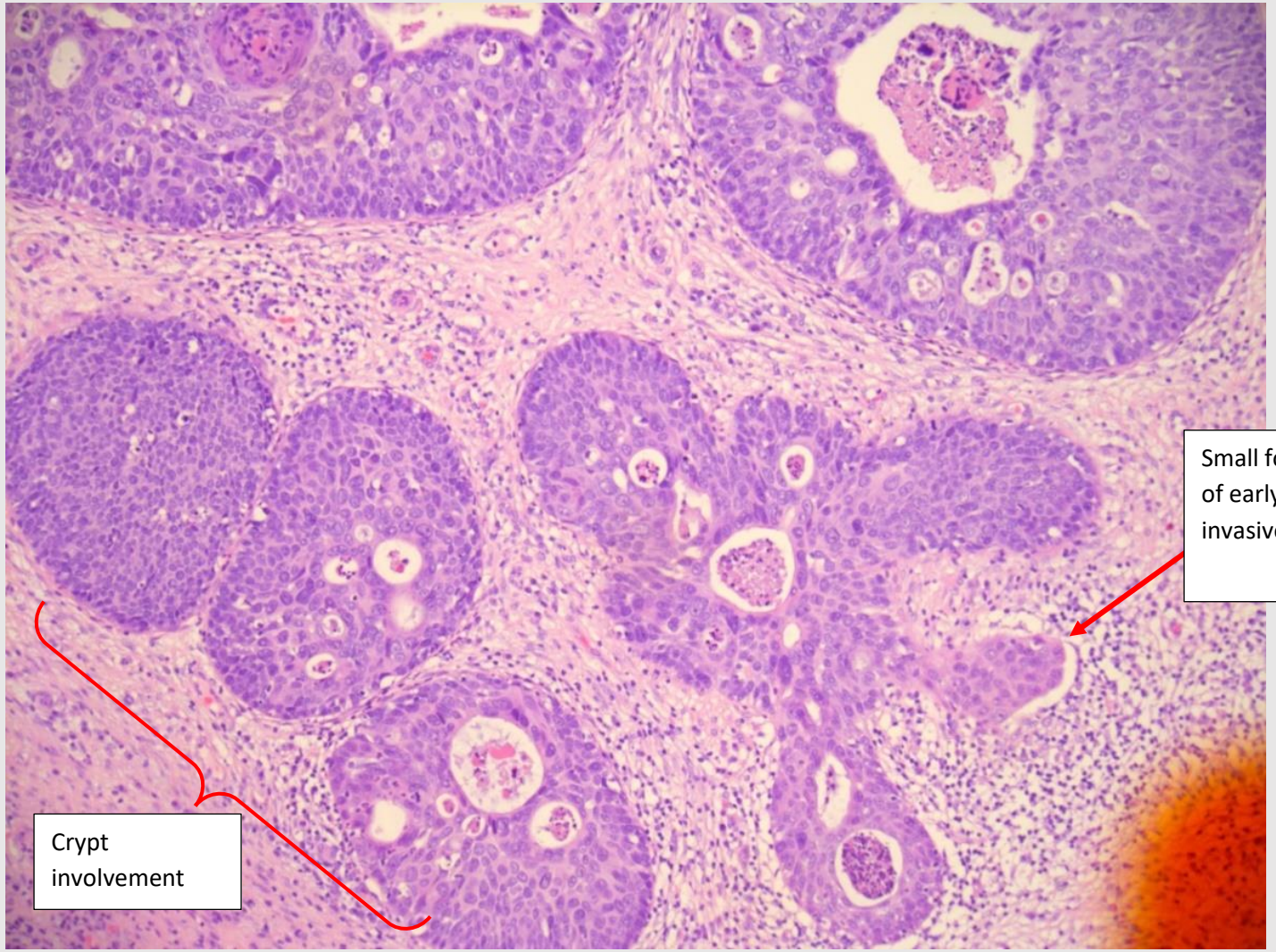
- Colposcopy opinion : HG CIN
- Directed biopsy: CIN3 with HPV Cervicitis

- The patient attended for follow up treatment in the form of a LLETZ due to the biopsy findings.

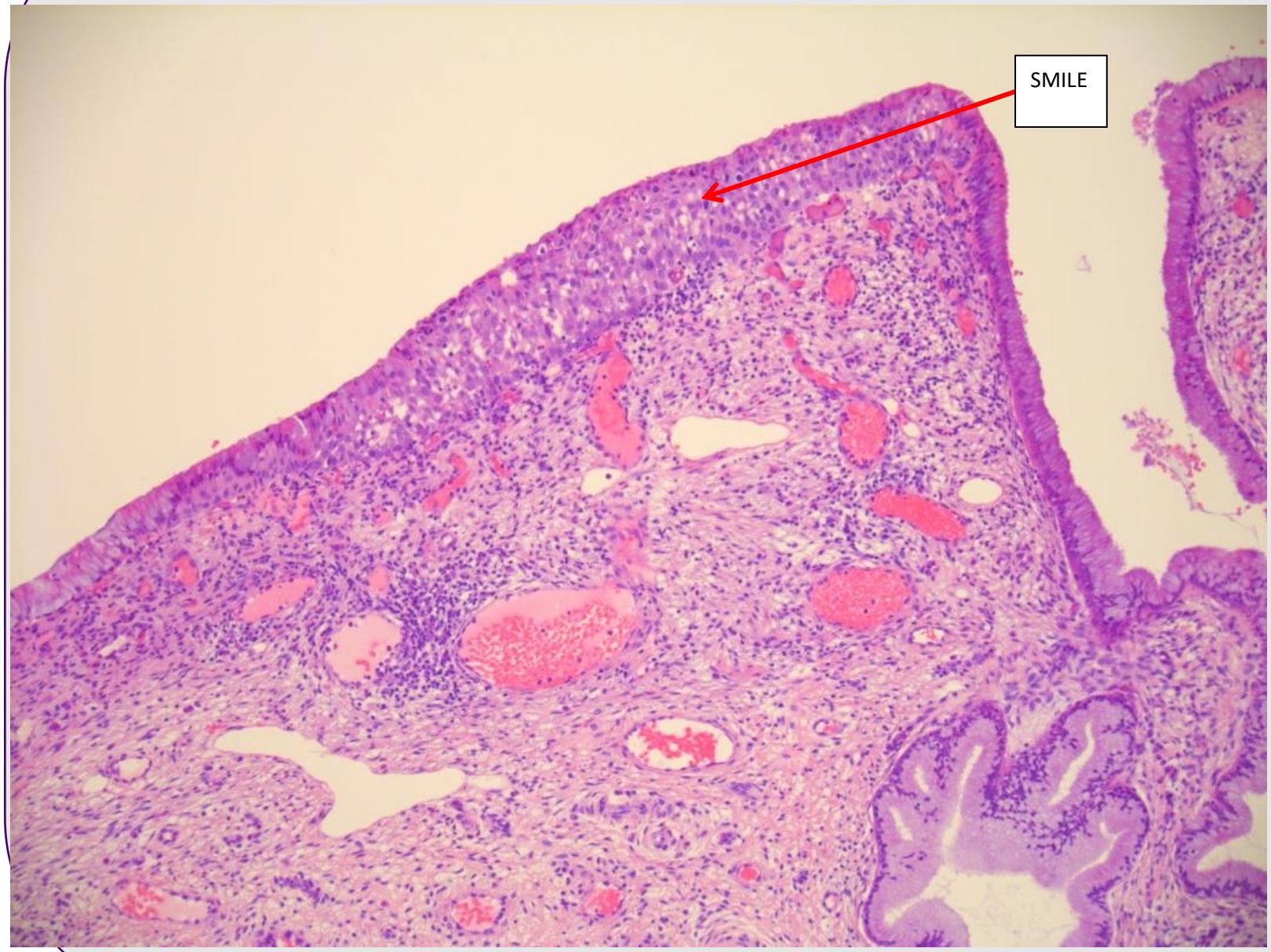
Large Loop Excision of the Transformation Zone (LLETZ)

- A rectangular shaped loop biopsy measuring 25mmx23mmx11mm received in 1 piece and examined in 9 slices
- Microscopy report shows, **CIN3** in 4 slices with extension into crypts.
- Stromal invasion present within block 6 and there is a small bud of atypical cells showing paradoxical maturation. The features are those of a small focus of **squamous cell carcinoma (SCC)** (too small to grade).
- **Stratified mucin-producing intraepithelial lesion (SMILE)**present in block A5

Large Loop Excision of the Transformation Zone (LLETZ)

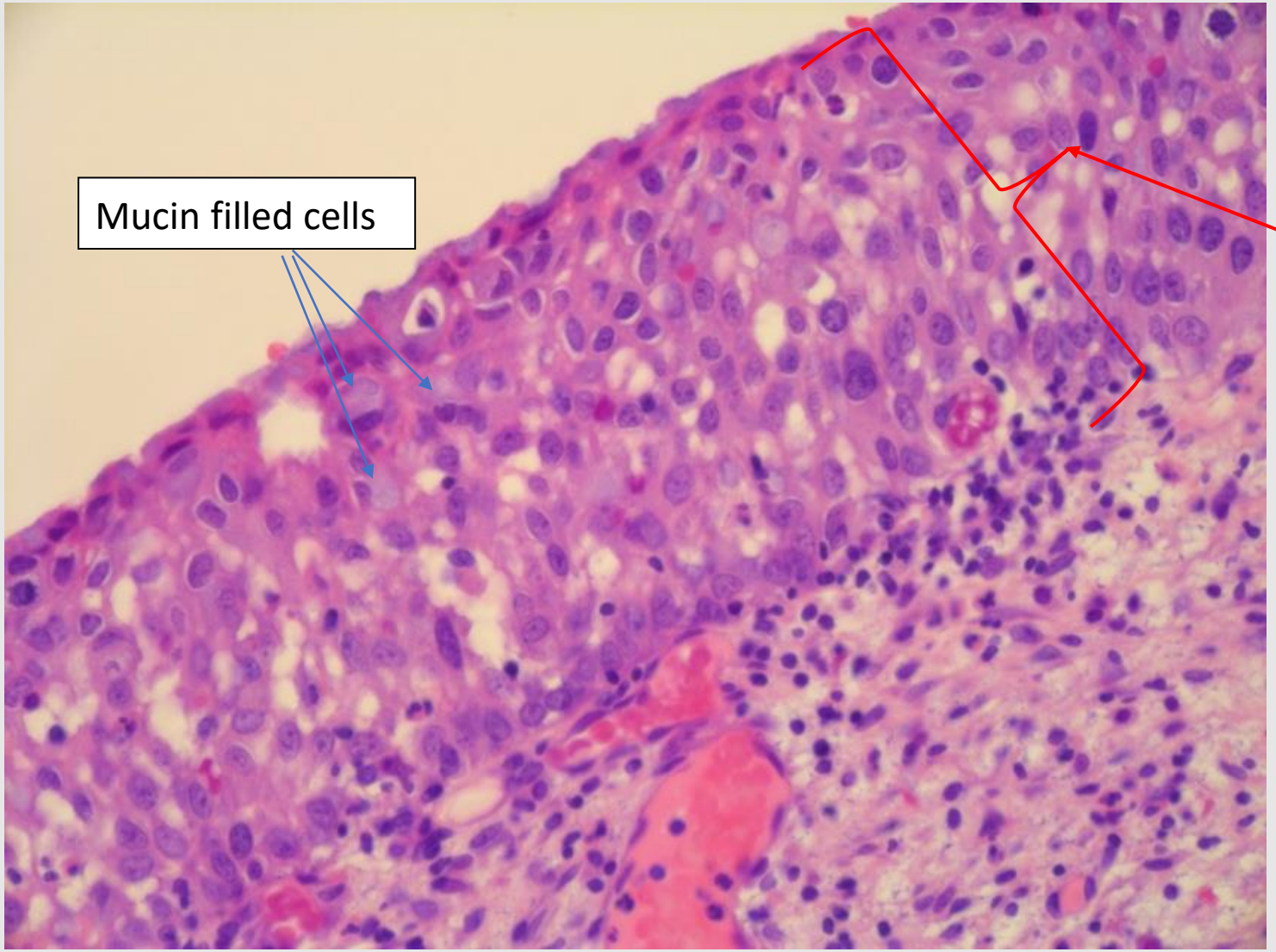


- The image showing gland crypt involvement
- Focally a small bud of atypical cells showing paradoxical maturation was identified; a feature of a small focus of squamous cell carcinoma (SCC) arising from a gland involved by HG CIN



Large Loop Excision of the Transformation Zone (LLETZ)

- The image showing multilayered stratified, immature epithelial cells with intracytoplasmic mucin, feature of SMILE lesion.

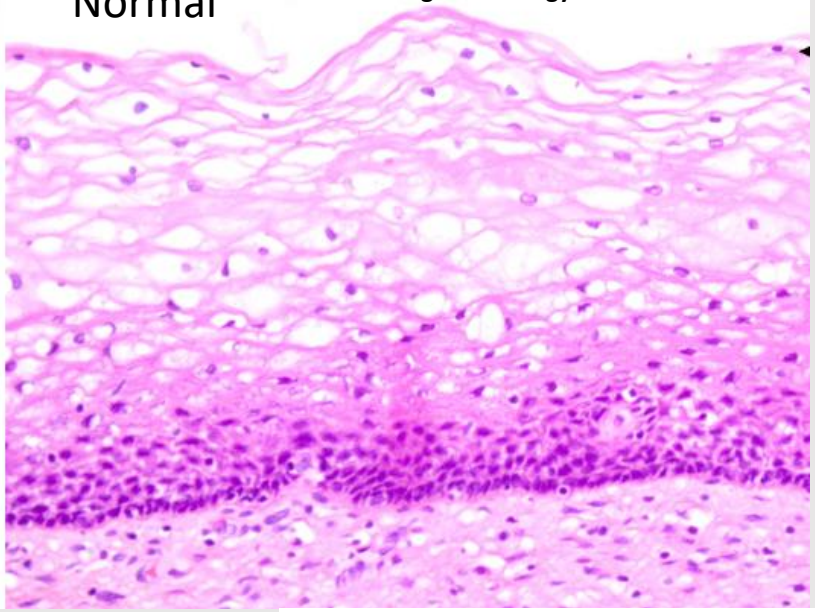


LLETZ – Shows full thickness lack of maturation, with atypical mucin filled abnormal intraepithelial cells and vacuolation scattered throughout the full thickness of the epithelium: these morphological features are consistent with SMILE

- Image showing: Stratified, immature epithelial cells with varying quantities of intracytoplasmic mucin

Normal

Image: PathologyOutlines.com



Normal: full thickness maturation of squamous cells with normal ‘basket weave pattern’ in intermediate and superficial layers representative of cytoplasmic glycogen stores

SMILE

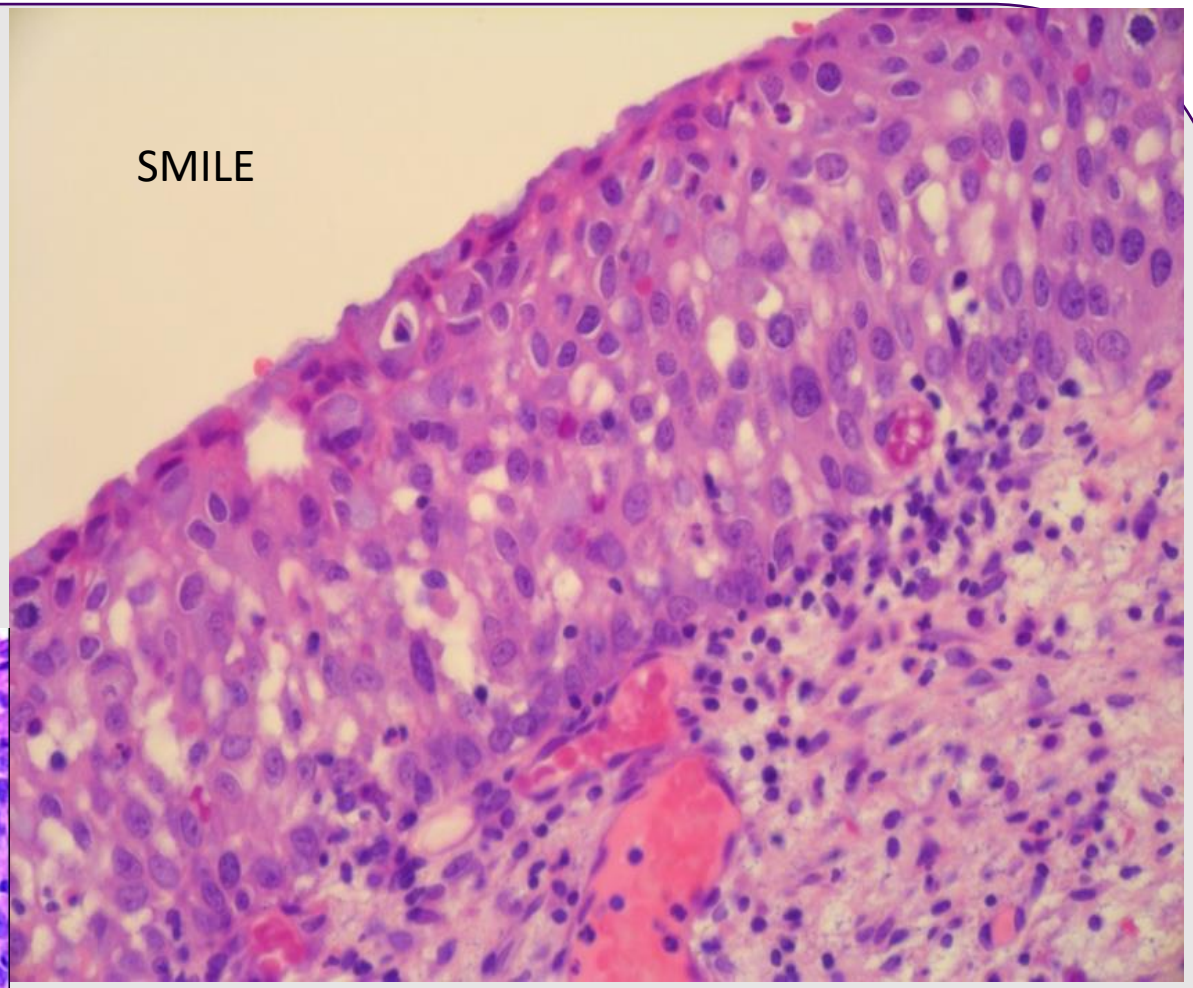
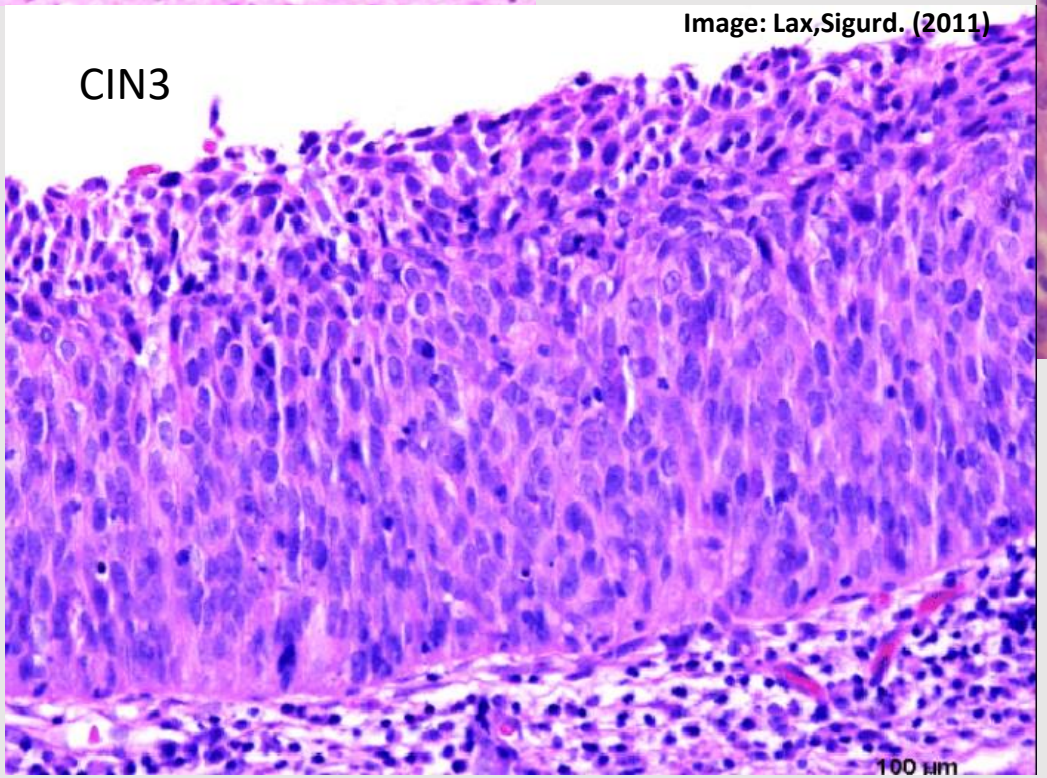


Image: Lax,Sigurd. (2011)

CIN3



CIN3 vs SMILE: there are overlapping features present in both CIN3 and SMILE with abnormal cells showing lack of maturation through the full thickness of the epithelium however in SMILE lesions abnormal mucin filled cells and irregular vacuolation are also present throughout all levels of the involved epithelium

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SMILE is a difficult entity to diagnose therefore Histopathologists may use immunohistochemical stains to aid with the diagnosis such as:

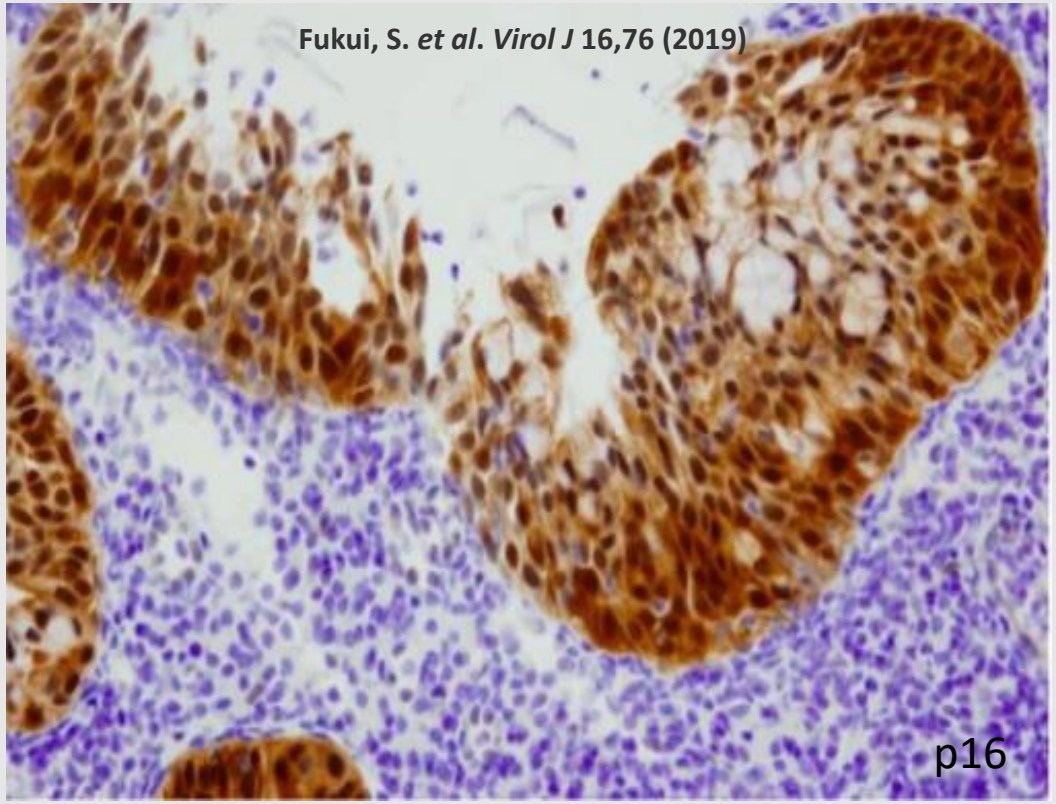
Positive stains

- Ki67 (MIB1) – high index
- P16 – Block type staining
- Mucicarmine – intracytoplasmic staining
- Diastase-PAS
- Alcian Blue

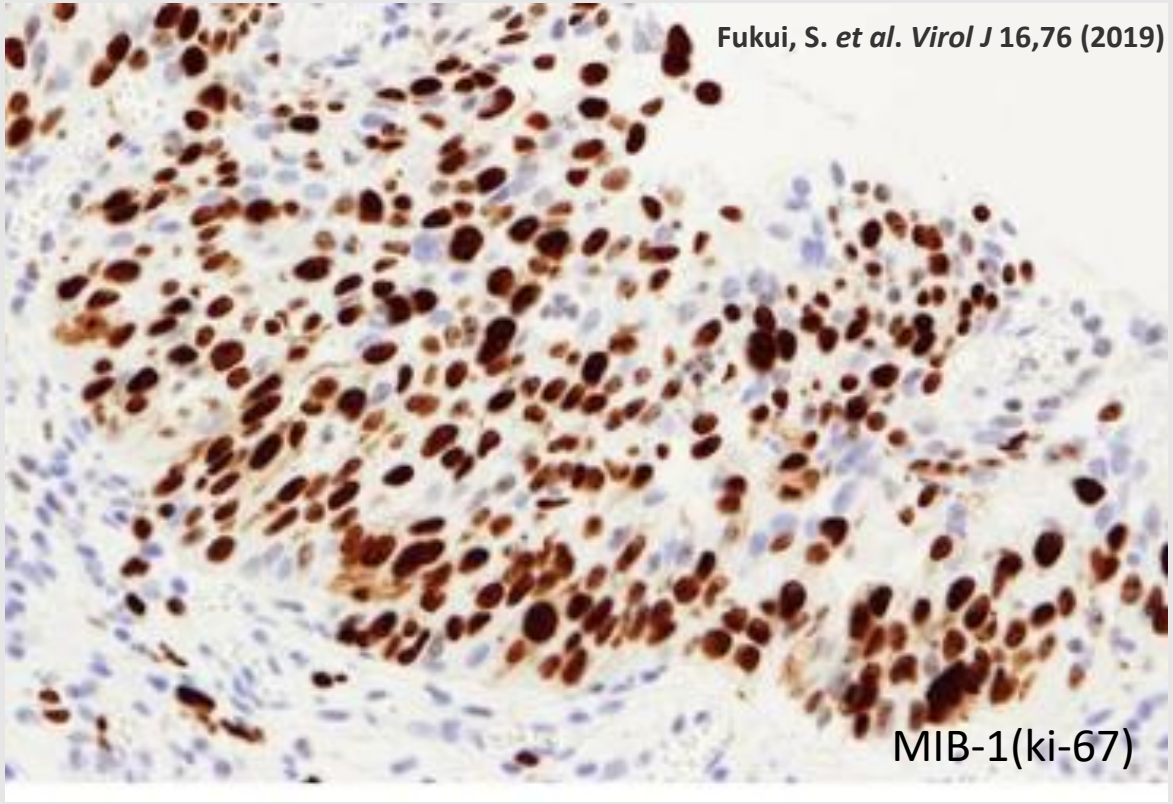
Negative stains

- P63 - may be positive in the basal portion of the lesion
- IMP3
- Keratins 5/14 – may be positive in the basal portion of the lesion

Examples of immunohistochemical stains to aid with SMILE diagnosis on histology:



Block type p-16 positivity.



MIB-1(Ki-67): Diffuse and strong positive staining

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Case discussion

- This patient had previous history of HG dyskaryosis that was treated and followed up with x10 yearly recalls according to the screening programme pathway at the time of reporting.
- Attending cervical screening regularly and had subsequent x11 negative cytology results
- Current cytology showed high-grade dyskaryosis with possible gland crypt involvement
- Subsequently referred to colposcopy and seen within 2-week high-grade referral period. Colposcopic opinion was high grade CIN. A directed biopsy was taken which showed CIN3 followed by LLETZ to treat the lesion.
- The treatment LLETZ showed early Invasion, SMILE and CIN3. SMILE is often found in association with CIN and CGIN although in this case no CGIN was identified.
- As the LLETZ showed only a very small area of early invasion arising from a gland crypt not to the surface making the features of invasion unlikely to be identified in the recent cytology slide.

Further case discussion

- In this case the patient was treated adequately with complete excision of SMILE and invasive disease.
- The subsequent patient management was based on the presence of invasive disease identified as this supersedes the complete excision of the SMILE lesion.
- The subsequent screening sample tested negative for HR-HPV, with management of recall for repeat screening in a further 6 months' time as per invasive follow up protocol.
- This patient will remain on annual screening to complete 10 years post invasive disease follow up as per NHSCSP guidance.
- Currently no cancer audit review available as this case originated at an external Trust and we are awaiting further correspondence.

Stratified mucin-producing intraepithelial lesion (SMILE)

- SMILE diagnosis is a rare premalignant lesion that is considered a variant of adenocarcinoma in situ (AIS) and may cause diagnostic difficulties to the Histopathologist due to overlap in morphological features with high-grade CIN and glandular abnormalities. Due to these similar morphological features some studies describes SMILE lesions as a form of high-grade reserve cell dysplasia. The WHO classifies SMILE as a subtype of high grade CGIN/AIS.
- Due to overlap in cytological features with HG dyskaryosis and glandular abnormality, cytologically SMILE cannot be confirmed or identified with any certainty and remains a purely histological diagnosis.
- There is little information available on the detection of HPV integrated into the SMILE lesion.
- In the NHSCSP SMILE cases are managed as per the protocol for CGIN as it is classed as a glandular lesion. After treatment and clear excision margins: Rpt TOC cytology at 6 and 18-month post treatment intervals: if negative then return to repeat in 36 months. If the excision margins are not clear then the patient is offered repeat treatment or alternatively followed up on 6, 12 month and then x9 yearly recalls.

Stratified mucin-producing intraepithelial lesion (SMILE) in summary

- SMILE is seen in 0.6% of cervical samples in one of the study (Histopathology 2015;66:658)
- SMILE often co-exists with other preinvasive lesions, including SIL (up to 93%) and AIS (up to 42%) as well as invasive carcinoma (up to 10%) (Hodgson A, *et al*, 2017; PathologyOutlines.com)
- High association with AIS (92%) compared to SIL (58%) (Hum Pathol 2016;55:174)

More research, case studies and literature is required to have better understanding of SMILE.

References

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