Cervical Glandular Neoplasia – diagnosis, detecting invasion and distinguishing benign mimics

Session description
Learning objectives:

- Criteria for recognition of CGIN and SMILE
- Mimics of CGIN and SMILE
- How to distinguish CGIN and SMILE from mimics
- Features of invasion

- Before commencing this session you should have:
  - Read the NHSCSP Publication No 10 – Histopathology reporting in cervical screening – an integrated approach
  - Read NHSCSP guidance – Histopathology reporting handbook
  - Have a basic knowledge of cervical intraepithelial neoplasia

Adenocarcinoma in situ

The 2020 edition (5th edition) of the WHO classification of the tumours of the female genital tract has divided epithelial tumours of the cervix on the basis of their association with HPV infection. This change allows the accurate assessment of cervical cancer screening by HPV testing and the role of HPV vaccination. The glandular neoplasms of the cervix are divided into HPV-associated and HPV-independent adenocarcinomas. Their precursors are similarly divided into HPV-associated and HPV-independent groups.

Cervical glandular intraepithelial neoplasia (CGIN)

High grade cervical glandular intraepithelial neoplasia (HGCGIN) is the term used in the UK for endocervical glandular lesions that are precursors of usual-type, HPV associated endocervical adenocarcinomas. The synonymous term is AIS (adenocarcinoma in situ).

HG CGIN is characterized by a set of well-established architecture and cytological features. Architecturally the normal gland profile is maintained and the normal glandular luminal outlines are preserved. Intraglandular papillae or cribriforming may occasionally minimally be present. Glands may be partially or completely involved by HGCGIN. There is abrupt transitioning from normal to abnormal epithelium. The cells have variable cytoplasm with little or no mucin. The nuclei are enlarged, hyperchromatic, psuedostratified and crowded. Mitosis are frequent. They are located apically, a feature sometimes referred to as ‘suspended’ mitoses. Basal apoptotic bodies are seen.

CGIN is usually located at the transformation zone although it may be located higher up in the endocervical canal. It may show intestinal differentiation with goblet cells. Sometimes CGIN is subtyped as intestinal, endometrioid and tubal, based on morphology. The WHO classification (2020) does not subtype CGIN.

Stratified mucinous intra-epithelial lesion (SMILE)

The WHO classification (2020) refers to SMILE as an important subtype of AIS/CGIN. It is characterized by stratified epithelium composed of cells with clear or vacuolated cytoplasm throughout the thickness of the epithelium. The presence of intracellular mucin creates even spacing of nuclei. This feature is especially noticeable in the basal and middle layers. Nuclear hyperchromasia is seen. SMILE is often coexistent with high grade CIN and CGIN or invasive carcinoma.

Benign mimics of CGIN

- Metaplasia and ectopias
  - Tuboendometrioid metaplasia
  - Endometriosis
  - Prostatic metaplasia
  - Mesonephric remnants
- Glandular hyperplasias
  - Diffuse laminar endocervical glandular hyperplasia
  - Microglandular hyperplasia
  - Mesonephric hyperplasia
- Reactive and inflammatory lesions
  - Diathermy artifact
  - Mitotically active endocervical glands
  - Inflammatory atypia
  - Arias Stella effect
- Benign neoplasms
  - Mullerian papilloma
  - Villous adenoma

The common benign mimics of CGIN are reactive atypia, mitotically active endocervical glands, tubal or tubo-endometrioid metaplasia, endometriosis mesonephric remnants and intestinal metaplasia.

Reactive atypia can mimic CGIN as large hyperchromatic nuclei can be seen. Reserve cell hyperplasia can mimic stratification and intraepithelial lymphocytes can be interpreted as apoptotic bodies. The absence of mitotic activity and apoptotic bodies along with even distribution of chromatin in these nuclei are a pointer to the benign nature. Immunochemistry for p16 is patchy or mosaic – it will not show block positivity.

Diathermy artifact can show markedly stratified and strikingly elongated hyperchromatic epithelial cells. These cells do not show mitotic activity or apoptotic bodies. In difficult cases, immunochemistry for p16 and Ki67 can be used.

Mitotically active glands can be present and be mistaken for CGIN. However mitoses do not have an apical location and are not associated with nuclear stratification, cytological atypia or apoptotic bodies.

Tubo endometrioid metaplasia (TEM) is characterized by replacement of mucinous endocervical cells with cells resembling those seen in the fallopian tube or in the endometrium. This is commonly seen in post-surgical (post loop) specimens. The cells show prominent nuclear stratification, columnar outlines, relatively high nuclear to cytoplasmic ratio and may even show segmental involvement of glands. Mitotic activity may be present. The periglandular stroma may have an endometrial stroma like appearance. Stromal alterations such as oedema can also be seen and cause concern for invasive adenocarcinoma. In most instances, morphology is adequate to diagnose TEM. In difficult cases a panel of immunostains including p16, ER, PR, bcl2, Ki67/MiB1 and PAX2 is helpful. Typically, TEM shows patchy staining with p16, diffuse staining with Bcl2 and a low proliferative index. ER and PR are typically positive. PAX2 has been shown to stain TEM but not CGIN.

Endometriosis may be present either superficially or deep in the cervical wall. A higher incidence has been reported in patients with a history of prior events including

cervical biopsy, vaginal delivery and endometrial sampling. Mitotic activity may be conspicuous in endometriotic glands. This, in combination with, periglandular stromal alterations can give cause for concern. Similar to TEM, endometriosis shows patchy staining with P16, diffuse staining with Bcl2 and a low proliferative index. ER and PR are typically positive.

Intestinal metaplasia has been rarely reported in normal glands. Some pathologists advocate that intestinal metaplasia in the cervix is always indicative of a preneoplastic lesion. Nuclear changes can be subtle. P16 staining is helpful as block positivity favours CGIN.

Mesonephric remnants are seen as rounded glands generally arranged in a lobular pattern around a duct like structure. The lining cells are low cuboidal, lack mucin and do not show mitotic activity. Inspissated eosinophilic secretions are seen. The cells are CD10 and GATA 3 positive and do not show block staining with p16.

Mimics of SMILE

Immature metaplasia is the main mimic. In immature metaplasia, the mucinous cells are confined to the upper or upper and middle layers. In SMILE, mucin producing cells are seen throughout the epithelium. SMILE should be suspected by the finding of abundant cytoplasm in the cells and the spacing of the nuclei in the middle and lower layers. SMILE shows brisk proliferative activity, high proliferative index and block staining with P16.

Colonisation of endocervical glands by high-grade CIN can mimic SMILE. p63 is positive in CIN and negative in SMILE.

Features of invasion

The features of infiltrative stromal invasion are:
Fragmented glands with tiny finger like processes extending into this stroma with detached cell clusters and isolated cells
Paradoxical differentiation i.e. apparently squamous appearing buds or nests arising from CGIN
Stromal response including oedema, chronic inflammatory cells and desmoplastic response
Lymphovascular invasion

There are features to suggest invasion when an overtly infiltrative growth pattern is not seen. These include
Confluent architecture that distorts the normal lobular architecture.
Complex architecture including branching of glands, intra glandular papillary growth and cribriform arrangement
Presence of solid areas
Extension beyond normal crypt field
Abutting on deep thick walled vessels and nerves

A pattern based (Silva) classification has shown relation between patterns of invasion and nodal involvement in HPV associated cervical adenocarcinomas. It has been shown to be reproducible among pathologists and maybe of use in planning patient management at MDT.

- Pattern A tumours are characterised by well-demarcated glands frequently forming clusters or groups with relative preservation of lobular architecture and lacking destructive stromal invasion or lymphovascular invasion
- Pattern B tumours demonstrate localised destructive invasion with or without lymphovascular invasion.
- Pattern C tumours show diffusely infiltrative glands and associated desmoplastic response with or without lymphovascular invasion.