Envoi SPECIALIST PATHOLOGISTS *inside insights*

Update No.6 - 2017 *Dr Mark Bettington*

Anal intraepithelial neoplasia

Definition: Anal intraepithelial neoplasia (AIN) is a dysplastic lesion of the anal squamous epithelium.

Aetiology: AIN is driven by infection with human papilloma virus (HPV).

Pathogenesis: HPV infection can be classified as either productive or integrated. Low risk HPV genotypes (predominantly 6 and 11) take on the productive form in which the HPV DNA remains in an extra-nuclear location and results in the koilocytic appearance of the cells. High risk genotypes (predominantly 16 and 18) typically take on the integrated form with integration of HPV DNA into the host DNA which acts as the driver of neoplasia.

Nomenclature: Pathogenic considerations are the basis for the newer two-tiered LAST (Lower Ano-genital Terminology) classification system, identical to that used for reporting cervical squamous lesions.

- Low grade squamous intraepithelial lesion (LSIL) – previously condyloma acuminatum and AIN 1
- High grade squamous intraepithelial lesion (HSIL) – previously AIN 2 and 3.

Pathology: HPV associated lesions of the anus can be either polypoid or flat.

1) Polypoid lesions.
   - Most polypoid lesions are condyloma acuminata (Fig 1).
   - Most condyloma are low grade although up to 15% can harbour foci of HSIL. When HSIL is present in a condyloma a careful inspection of the anal canal is required to exclude concurrent flat dysplasia
   - Condyloma acuminata have a verrucous growth pattern with hyperkeratosis and koilocytosis. Koilocytes are keratinocytes with voluminous clear cytoplasm and centrally placed nuclei with irregular nuclear contours and a thick nuclear membrane.

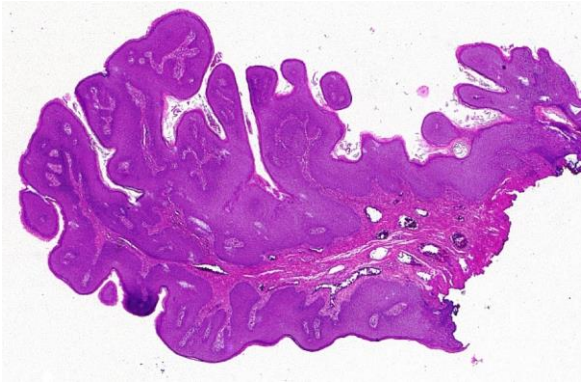

Fig 1. Condyloma acuminatum

2) Flat lesions.
   - Can represent low or high grade SIL.
   - Low grade flat dysplasia is recognised by koilocytes at the epithelial surface and increased proliferation in the basal compartment. The nuclear changes are mild.
   - High grade dysplasia is recognised by nuclear crowding, increased nuclear to cytoplasmic ratio and abnormal mitoses, including mitoses near the epithelial surface (Fig 2).

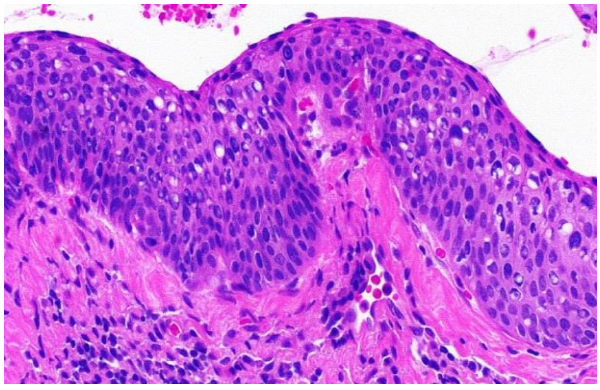

Fig 2. Flat high grade dysplasia (HSIL)

Ancillary testing: At present immunohistochemistry for p16 is the only recommended ancillary test for AIN and is most useful in the categorisation of borderline LSIL/HSIL lesions. Strong block positive p16 staining is a surrogate marker for high risk HPV and indicates HSIL whereas lack of block positive staining is seen in LSIL. Other tests, such as HPV DNA are not indicated at this time.

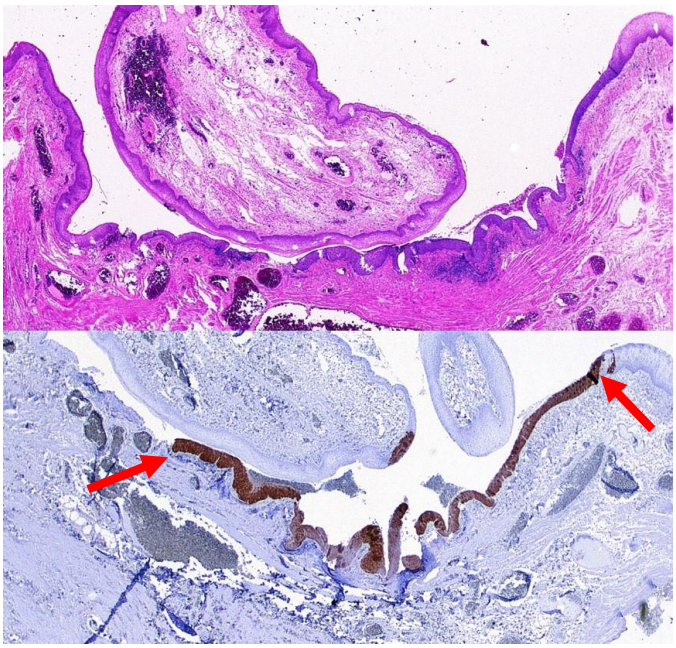

Fig 3. High grade squamous intraepithelial lesion in a haemorrhoidectomy specimen. Strong block staining with p16 (between red arrows).

Differential diagnosis: There are three major diagnostic uncertainties in AIN.

1) Low grade versus high grade SIL. p16 immunohistochemistry is the most effective method for resolving this issue.
2) Flat and papillary immature squamous metaplasia versus high grade dysplasia.
3) Condyloma acuminatum versus a non-HPV driven lesion (e.g. a verruciform fibroepithelial polyp). This can be problematic in some cases. The identification of koilocytes on the H&E is the best indicator of an HPV driven lesion, however some chronic condylomata will have no definite koilocytes. In these cases the distinction can be impossible, and this will be indicated in the report. Other tests such as HPV DNA are not helpful in this regard as they test for high risk strains of HPV which are not present in 85% of condylomata.

Risk of progression to squamous cell carcinoma: The natural history of AIN is difficult to ascertain as most progression data is generated from patient cohorts under active treatment/surveillance. In these series progression from HSIL to squamous cell carcinoma is low (around 1%/year) but the risk is higher in smokers, the immunosuppressed and probably in patients whose HSIL is not treated.

Note: There is a current large US based multi-institutional trial (the Anal Cancer HSIL Outcomes Research - ANCHOR trial) underway comparing the impact of observation to excision/destruction of HSIL.

Incidental HSIL in haemorrhoidectomy specimens: HSIL is identified in around 2% of haemorrhoidectomy specimens and invasive SCC in 0.26%. Although it has not been specifically studied, these patients are at risk of HSIL elsewhere in the anal canal.

References:

Dedicated issue on anal squamous neoplasia in: Seminars in Colon and Rectal Surgery. 2017 June 28(2).