HPV-related cervical glandular lesions

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Abstract

The prevalence of premalignant and malignant endocervical glandular lesions is increasing in both relative and absolute terms. The majority of premalignant and malignant endocervical glandular lesions are aetiologically related to HPV infection. Neuroendocrine carcinomas of the cervix are also HPV related neoplasms that have an aggressive behaviour. This review concentrates on the latest classification and terminology of cervical glandular lesions and neuroendocrine carcinomas, their morphology and differential diagnosis and includes important practice points.

Keywords cervical glandular intraepithelial neoplasia (CGIN); endocervical glandular; HPV; invasive carcinoma; neuroendocrine carcinoma; p16

Introduction

The relative and absolute incidence of invasive adenocarcinoma of the cervix and the precursors is increasing in many developed countries, whilst the incidence of squamous cell carcinoma shows a declining trend.[1] This maybe partly relative compared to squamous carcinoma, because of a reduction in the latter in developed countries secondary to organized cervical screening programmes. Better recognition of glandular lesions by pathologists and a higher prevalence of human papillomavirus (HPV) infection and/or a change in the distribution of HPV types are possible reasons for the absolute increase.[2] Most of the adenocarcinomas in the World Health Organisation (WHO) classification[3] are HPV related [Table 1].

Premalignant and early invasive lesions are usually detected cytologically by cervical cancer screening programmes. An increasingly recognized minority of adenocarcinomas of the cervix do not show a causative association with HPV. This may show a relative increase as HPV vaccination results in decrease of papillomavirus related cervical neoplasia.

Premalignant endocervical glandular lesions

Cervical glandular intraepithelial neoplasia (CGIN) is the term used in the United Kingdom for endocervical glandular lesions that are the precursor of usual-type cervical adenocarcinoma. The use of CGIN terminology is endorsed in the NHS Cervical Screening Programme publication 20 'Histopathology Reporting in Cervical Screening — an Integrated Approach'.[4] High grade CGIN is synonymous with adenocarcinoma in situ (AIS) and both terms are accepted in WHO classification. Low grade CGIN is a term that is used for lesions with cytological atypia less than high grade CGIN and is synonymous with endocervical glandular dysplasia (EGD). In this review, the term CGIN will be used in preference to glandular dysplasia or AIS. Stratified mucin-producing intraepithelial lesion (SMILE)[5] is a preneoplastic glandular lesion of the cervix that shows stratified epithelium containing atypical cells with mucin containing vacuoles in all layers.

CGIN is considered as a precancerous lesion of invasive cervical adenocarcinoma. Convincing evidence includes the fact that CGIN is usually diagnosed in populations 10—20 years younger than those with invasive adenocarcinoma. It frequently coexists with invasive adenocarcinoma and both CGIN and invasive adenocarcinoma contain similar high risk HPV (hrHPV). Most CGIN and adenocarcinomas are associated with HPV18 followed by HPV16 and 45. Other hrHPV (31 and 59)[6] are rarely found.

HPV-related cervical glandular lesions

Cervical glandular intra epithelial neoplasia (CGIN)
Adenocarcinoma
- Endocervical adenocarcinoma, usual type
- Villoglandular carcinoma
- Endometrioid carcinoma
- Adenocarcinoma admixed with neuroendocrine carcinoma
- Invasive SMILE (Stratified mucin-producing intraepithelial lesion)

Modified from WHO classification of tumours of the uterine cervix

Table 1

Morphology and immunohistochemistry

There are a variety of morphological types of CGIN [Table 2].

The commonest type of high grade CGIN is characterized by columnar epithelium showing nuclear hyperchromasia, nuclear pseudo-stratification, enlargement and rounding of nuclei and loss of mucin. The normal glandular lobularity can be exaggerated. Mitotic activity is conspicuous and the mitotic figures appear 'suspended' in the supranuclear cytoplasm. Basal apoptotic bodies are conspicuous. (Figure 1). This pre-neoplastic epithelium is usually present at the squamocolumnar junction and is seen in surface and glandular epithelium. Sharp and abrupt transition from normal endocervical epithelium to the abnormal cells of CGIN is a typical and often eye-catching feature. High grade CGIN is always strongly and diffusely (block) positive for p16 and show increased proliferation index with Ki67.

Terminology of premalignant endocervical glandular lesions

- High grade cervical glandular intra epithelial neoplasia (CGIN) or adenocarcinoma in situ (AIS)
- Low grade cervical glandular intra epithelial neoplasia (CGIN) or endocervical glandular dysplasia (EGD)
- Stratified mucin-producing intraepithelial lesion (SMILE)

Table 2

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Please cite this article in press as: Ganesan R, HPV-related cervical glandular lesions, Diagnostic Histopathology (2017), https://doi.org/10.1016/j.mpdhp.2017.11.012

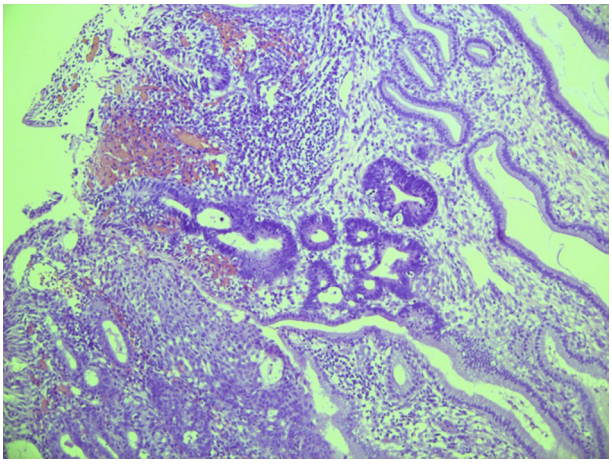

Figure 1 High grade CGIN showing hyperchromasia, nuclear pseduostratification, mitotic activity and abrupt junction with normal endocervical mucinous epithelium (×10 magnification). The inset shows the apoptotic bodies that are typically seen in high grade CGIN (×40 magnification).

Less common, and sometimes co-existent with the 'usual type' CGIN, is the intestinal type CGIN. The lesional cells contain intestinal type mucin and goblet cells (Figure 2). Rarely they may have neuroendocrine and Paneth cells. Nuclear hyperchromasia, nuclear enlargement, coarsening of nuclear chromatin, mitotic activity and apoptosis are seen. Mucin containing vacuoles or goblets can replace the whole of the cytoplasm of the cell relegating the nucleus to the base. This can camouflage nuclear pseudostratification and assessment of atypia or hyperchromasia can become difficult. Whenever intestinal metaplasia is seen, care must be taken to assess the nuclei at closer examination. In addition to block positivity with immunohistochemistry for p16, cells of the Intestinal type CGIN may express CDX2 and CK20.[7] It is increasingly recognized that in some variants showing intestinal differentiation do not show diffuse (block) staining with p16.[8] Such lesions tend to occur in older women and the lack of p16 staining in intestinal type CGIN may be an indicator of a non-HPV associated glandular lesion.

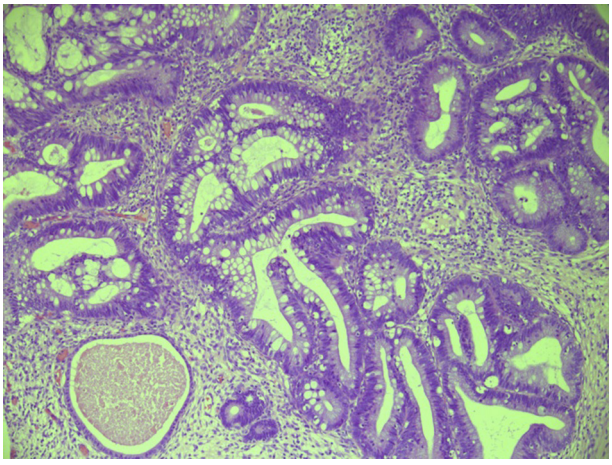

Figure 2 High grade CGIN showing prominent intestinal type differentiation co-existing with usual type CGIN (×20 magnification).

The cells constituting CGIN may have cilia or show tubal type morphology and this rare variant is known as tubal/ciliated CGIN.[9] It has features — nuclear hyperchromasis, pseudostratification and mitotic activity — and usually occurs in association with usual type CGIN. It shows diffusely (block) positive staining for p16.

SMILE occurs both in surface and glandular epithelium. It is commonly seen in association with high grade CGIN (Figure 3). The epithelium is stratified and mucin, usually in the form of discrete vacuoles, is present throughout the full epithelial thickness. There is associated nuclear hyperchromasia, atypia and mitotic activity. Block p16 staining and high Ki67 index are seen.

Lesions with nuclear atypia less than that seen in high grade CGIN are referred to as low grade CGIN. The criteria are not well defined and lesions show an overlap with reactive changes and high grade CGIN.[10] HPV DNA has been detected in low grade CGIN at a significantly lower rate than in high grade CGIN.

Differential diagnosis

Reactive atypia in endocervical cells vs CGIN: reactive changes in endocervical cells is usually in the form of randomly dispersed hyperchromatic, sometimes multinucleate cells. No mitotic activity is seen and p16 staining is negative or non-block in type (Figure 4).

Tubal or tubo-endometrioid metaplasia (TEM) vs tubal/ciliated CGIN: mild to moderate nuclear atypia and mitotic activity can be seen in both conditions. Apoptotic bodies are typically seen in CGIN. One must be careful not to mistake lymphocytes with perinuclear haloes, seen in TEM, for apoptosis. Block staining with p16 favours CGIN, patchy staining with p16 can be seen in TEM. Bcl2 positivity favours TEM.[11] Ki67 staining may not be helpful as tuboendometrioid metaplasia is hormone sensitive and can show mitotic activity in the proliferative phase of the menstrual cycle.

Endometriosis vs CGIN: both conditions can show nuclear pseudostratification and mitotic activity. In endometriosis, the patient usually has a history of previous cervical surgery, the glands are surrounded by endometrial stroma, there is no nuclear

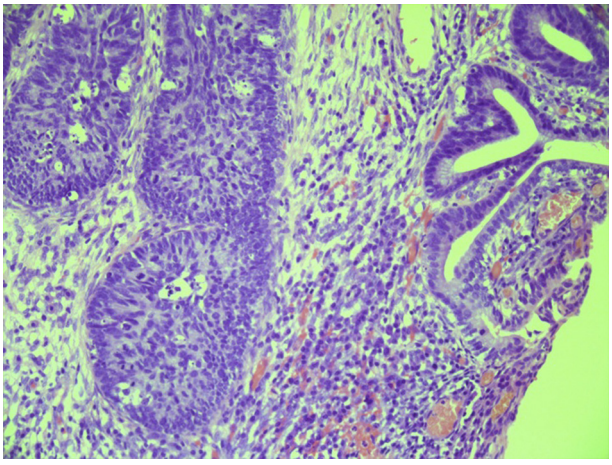

Figure 3 SMILE is seen in glandular epithelium and showing stratified epithelium with mucin vacuoles, nuclear hyperchromasia, atypia, apoptotic bodies and mitotic activity. The surface epithelium shows high grade CGIN (×20 magnification).

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