Detecting and interpreting glandular lesions in cervical cytology

Christine Waddell

Abstract

Abnormal glandular cells can appear in cervical samples not only from the cervix but from the whole of the genital tract from the fallopian tubes to the vulva, and from extra-uterine sources including primary tumours of the peritoneal cavity and metastases from distant sites. There is also a wide variation in morphology in benign, pre-malignant and malignant entities which on occasion challenge even the most experienced microscopist. This review outlines areas of difficulty with particular reference to liquid-based cytology, and provides guidance on how to approach a sample which has been identified by the primary screener as showing possible glandular abnormality.

Keywords adenocarcinoma; adenocarcinoma in situ; cervix; cervical glandular intraepithelial neoplasia; endometrial neoplasia; extra-uterine neoplasia; glandular neoplasia; liquid-based cytology; lower uterine segment sampling; malignant glandular cells; tubo-endometrioid metaplasia

Owing to diversity in presentation and in origin of both benign and malignant entities, and the existence of non-glandular lookalikes, interpretation of the glandular component in cervical samples is complex. This results in reduced accuracy in predictive value and in sensitivity when compared with squamous prediction.[1]

Terminology in glandular reporting

UK terminology for glandular reporting has just two main categories.

- '?Glandular neoplasia' for prediction of pre-invasive glandular lesions or more of the cervix, and for malignant glandular cells from uterine and extra-uterine sources, including metastases from distant sites.
- 'Borderline nuclear changes (BNC)' for endocervical predictions only to be used as a holding category in which findings are equivocal.[2,3] Usage is not consistent from centre to centre but it should be applied rarely. Although in current guidelines there is no specific 'BNC-?glandular' sub-category, this has been proposed by the British Society for Clinical Cytology (BSCC),[4] thus making the UK terminology more comparable with The Bethesda System (TBS) used in the USA (Table 1).[5]

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Cytological prediction of glandular lesions

The aim of cervical screening is to identify women at risk of developing cervical cancer. Initially, the focus of screening was the recognition of squamous dyskaryosis, and cytological features attributable to adenocarcinoma in situ (high-grade cervical intra-epithelial neoplasia (HG-CGIN)) were not published until 1970 when Barter and Waters described single abnormal cells in cytology from a case of what was then known as adenocarcinoma in situ (AIS).[6] From then on, for conventional cytology, evidence was gathered on which to base prediction of benign and potentially malignant conditions from all sites.[7,8] With the introduction of liquid-based cytology (LBC) in the mid-1990s these criteria are being revisited. With LBC nuclear details tend to be more pronounced and architectural features more subtle[9]; nevertheless, Belsley et al recently have concluded that the differences between conventional cytology and LBC are minimal.[10] Indeed, in the UK, although initially there was concern about the sensitivity and specificity of glandular reporting in LBC, post-pilot reports have shown no change in sensitivity and improved accuracy in discrimination between true glandular neoplasia and benign lookalikes.[11]

Normal glandular cytology and benign variants

On first considering a glandular prediction the microscopist must reflect: are the cells in question *really* glandular, and if so, are they *really* abnormal?[12] A good grasp of the spectrum of normality is required for both of these decisions before the final report can be compiled (Figures 1 and 2). Accounts of normal morphology are available in standard texts and atlases (see Further reading).

Normal endocervical glandular cells appear singly and in groups. Single cells are common in LBC and present in varying shapes and sizes, including triangular and cuboidal, as well as the classic tall columnar forms with basal vesicular nuclei. Cytoplasm is usually cyanophilic and consistency may vary from finely vacuolated to relatively dense. Cilia are common and occasionally large vacuoles may be seen. Discrimination, particularly between cuboidal glandular cells with dense cytoplasm and immature metaplastic cells, may be difficult but in practice this is of little consequence as long as their benign nature is recognized. Single benign glandular cells of either endocervical or endometrial origin when seen end-on, because of the spurious appearance of raised nucleocytoplasmic (N/C) ratio, may sometimes be misinterpreted as severe small cell squamous dyskaryosis.[4]

Endocervical cells may also be seen in single layered sheets in honeycomb formation with evenly sized and spaced round/oval vesicular nuclei. This architecture may be disturbed in reactive change with multinucleation, variation in size but not shape of nuclei and a modest degree of nuclear overlapping. N/C ratio may be slightly raised but overall the abundance of cytoplasm can be appreciated on focusing through the group of cells, noting in particular well formed cytoplasmic borders at the edges of the groups. Short palisaded strips of glandular cells with basal nuclei are common. On occasion, particularly with the SurePath method, they may be partially disrupted, producing strings or starburst formations joined usually at their luminal cytoplasmic margins.

Endometrial cells also appear in small clusters but exfoliated forms lack the honeycomb pattern, have less cytoplasm and their

Terminology in glandular reporting

Current UK terminology	2008 UK Proposed BSCC terminology	2001 USA The Bethesda System (TBS)
Negative	Negative	Within normal limits (WNL) including benign atypia
Borderline Nuclear Changes (BNC) (no sub-category for glandular prediction)	Borderline Nuclear Changes in endocervical cells (BNC-G) (for endocervical prediction only)	Atypical glandular cells - not otherwise specified (AGC NOS) (for abnormality from all sites)
?Glandular neoplasia (no site-specific sub-category)	?Glandular neoplasia Cervical glandular intra-epithelial neoplasia (CGIN) and cervical adenocarcinoma	AGC favour neoplasia (from all sites)
	Non-cervical adenocarcinoma — endometrial, other	Adenocarcinoma in situ (AIS) Adenocarcinoma (from all sites)

Table 1

nuclei vary in shape but not size. In the late menstrual phase, groups may appear with dense stromal cores and peripheral epithelial cells (the top hat formation). Papillary clusters of endometrial cells may be problematic in samples taken in the early menstrual phase and with intra-uterine contraceptive device (IUCD) use. Appreciation of the normality of the nuclei and especially the presence of bean-shaped nuclear forms helps in correct interpretation.

Tubo-endometrioid metaplasia and isthmic (lower uterine segment) sampling

With the use of the Cervex brush, particularly in post-loop or cone biopsy cervices, direct sampling of endometrial cells from the uterine isthmus is likely. These are cuboidal and so have a higher N/C ratio than their columnar counterparts. They also undergo cyclical change with mitotic activity in the proliferative phase. As a result, on occasion, discrimination between benign endometrial cells and neoplastic endocervical cells is challenging (Table 2).

In tubo-endometrioid metaplasia (TEM) crowded clusters of glandular cells are common, and pseudostratified strips of cuboidal cells and sometimes mitotic figures may be seen, raising the possibility of endocervical neoplasia. The most useful features to confirm the benign nature of such cell groups are the presence of well formed cytoplasmic borders and cilia (Figure 3).[13,14]

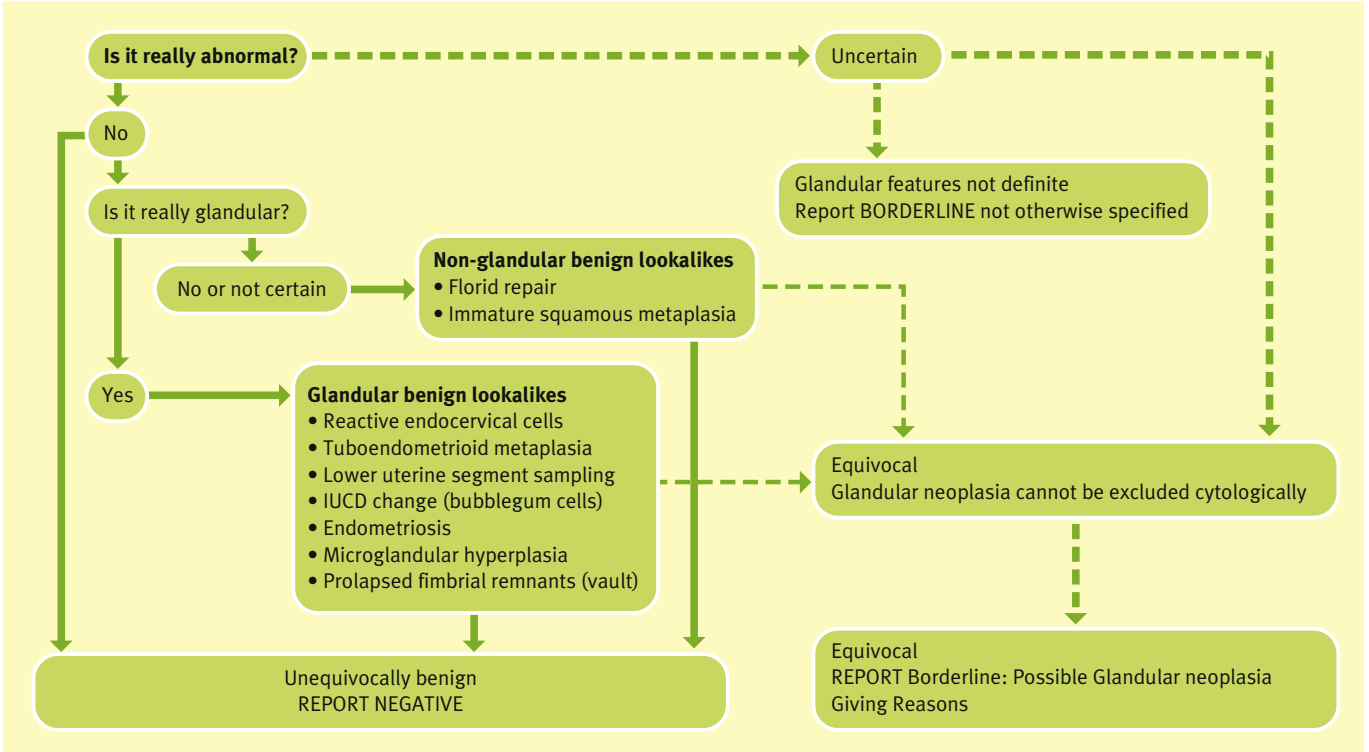

Figure 1 Decision tree 1 in cytological prediction of ?glandular neoplasia in cervical samples — opinion negative or borderline nuclear changes.