Cytology of Glandular Lesions

6

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Abstract

In this chapter the appearance of in situ and invasive glandular neoplasms of the cervix and their cytological mimics will be described.

Keywords

Endocervix • Adenocarcinoma in situ • Cervical glandular intraepithelial neoplasia • AIS • CGIN • Adenocarcinoma of the cervix

Introduction

Although the histological appearance of adenocarcinoma in situ of the endocervix (AIS) was described by Friedel and McKay in 1953, it was not until nearly 20 years later that Barter and Waters provided the first description of the cytological manifestations of AIS in conventional cervical cytology preparations, which were subsequently expanded and refined by other workers, and the cytological appearances suggestive of invasive cervical adenocarcinoma described [1–7]. More recently, defining criteria to separate normal or metaplastic from neoplastic endocervical cells and the cytological appearances in the two most commonly used liquid based cytology systems have also been described [8–14].

Cervical Glandular Intraepithelial Neoplasia (CGIN)/Adenocarcinoma In Situ (AIS)

The cytological appearance of CGIN/AIS in both conventional and liquid-based cervical cytology preparations reflects the histological appearances described in Chap. 3 and it is often the abnormal microarchitecture of crowded cellular groups that first draws attention at routine screening magnification.

Sheets of exfoliated cells from CGIN present as variable sized groups of crowded cells with frequent overlapping nuclei of uniform size and loss of the "honeycomb" pattern of normal endocervical cells (Fig. 6.1). At the margin of the cell groups there may be disrupted crypt openings

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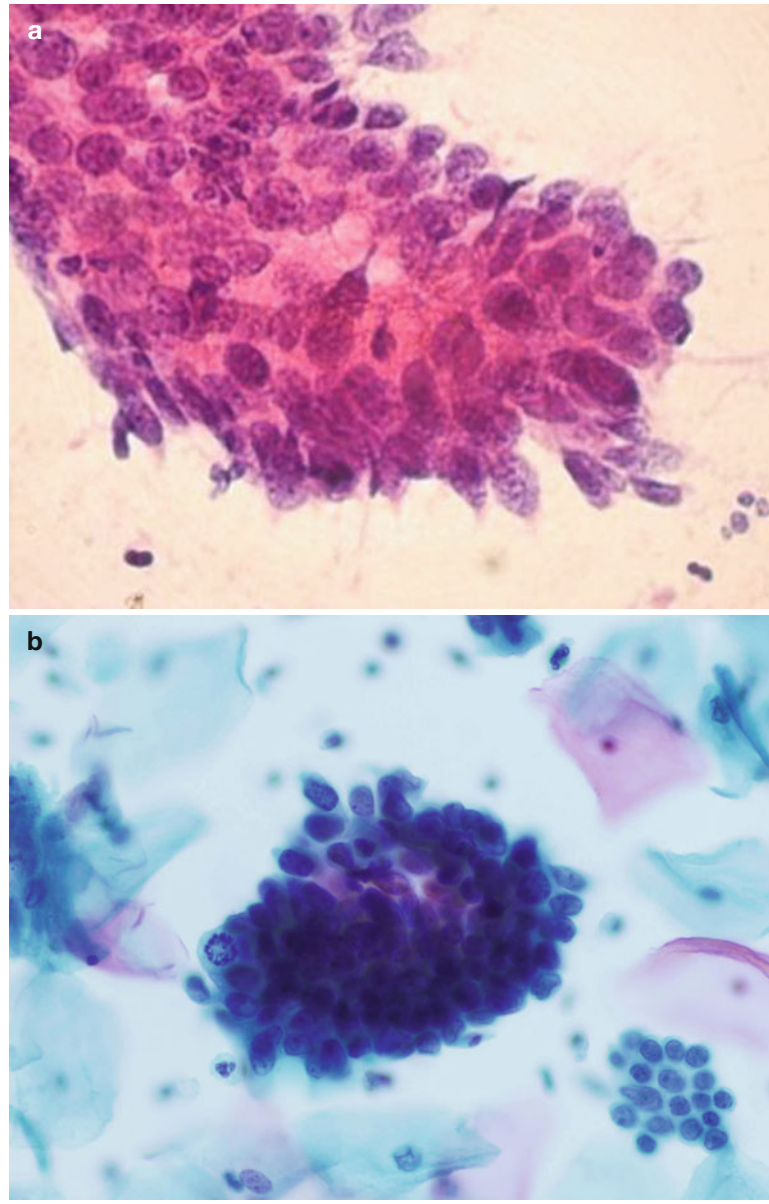


Fig. 6.1 A group of crowded disorganised atypical endocervical cells derived from adenocarcinoma in situ in a conventional cervical smear (**a**) and a SurePath LBC preparation (**b**)

and within the cell groups rosette formation, representing abortive attempts at glandular differentiation. Isolated rosettes may also be present (Fig. 6.2). In addition, at the margin of the cell groups, the nuclei of the constituent cells may lie at different levels (pseudostratification) and as a result of partial or complete loss of cytoplasm, bare nuclei or nuclei with tapering delicate cytoplasmic tags project from the crowded cell groups: an appearance first described as "feathering" by Pacey and colleagues in conventional cervical smears (Fig. 6.3). Although this appearance is less common and may be more subtle in liquid based cervical cytology preparations, it may still be a useful criteria to distinguish neoplastic glandular from squamous lesions in hyperchromatic crowded cell groups.

Cells derived from CGIN may also present as short strips with a straight or slightly curved contour in which there is pseudostratification of

nuclei with a common cytoplasmic border (Fig. 6.4). Especially in SurePath liquid based cytology preparations the dyskaryotic nuclei tend to fan out resulting in an appearance resembling a bird's tail or fish tail (Fig. 6.5).

Isolated or loosely cohesive small groups of neoplastic glandular cells may also be present in the background and as described above frequently have delicate cytoplasm which tends to taper from the nucleus resulting in a so-called "snake and egg" effect (Fig. 6.6).

Cell nuclei, whether in individual cells or groups of cells, are usually of similar size to that of normal endocervical cell nuclei, show minimal anisonucleosis, and are oval in shape with smooth nuclear membranes of variable thickness. Nuclear chromatin is of even distribution but varies from fine to coarse granularity resulting in a

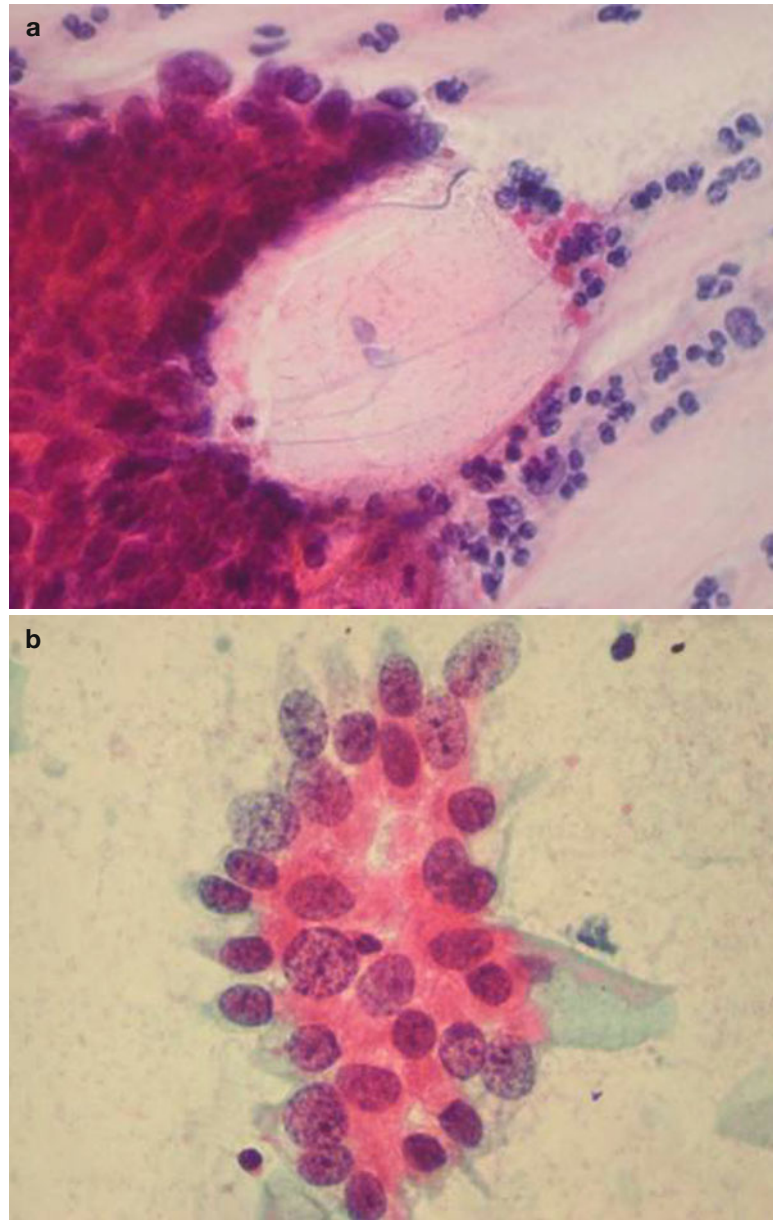
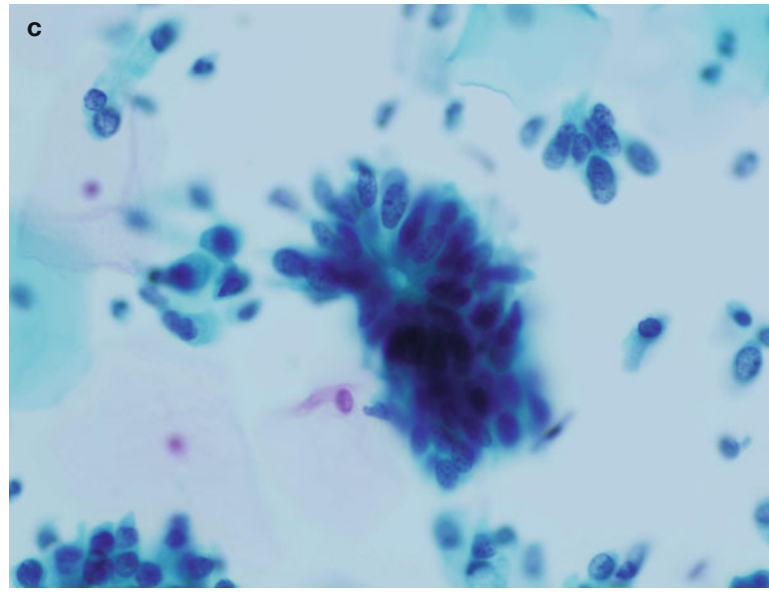


Fig. 6.2 Disrupted crypt opening ('torn open gland') at the edge of a group of cells derived from adenocarcinoma in situ in a conventional cervical smear (**a**) and rosette formation in a conventional cervical smear (**b**) and a SurePath LBC preparation (**c**)

Fig. 6.2 (continued)



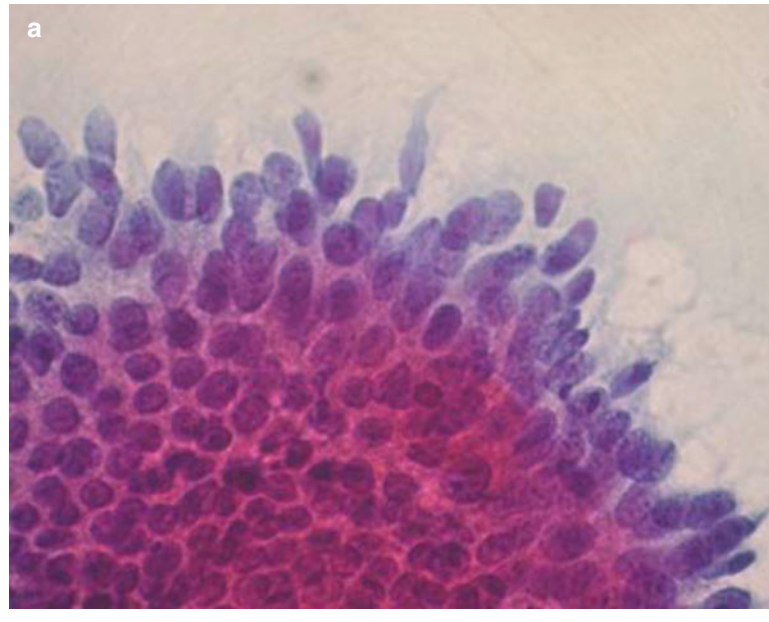


Fig. 6.3 "Feathering" in adenocarcinoma in situ in a conventional cervical smear (**a**) and a SurePath LBC preparation (**b**). Note the bare nuclei and nuclei with tapering delicate cytoplasmic tags projecting from the cell group

Fig. 6.3 (continued)

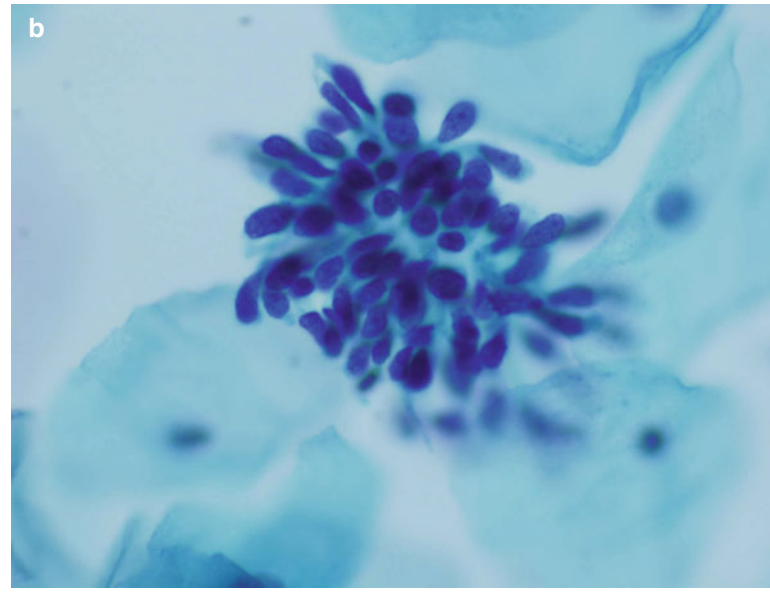
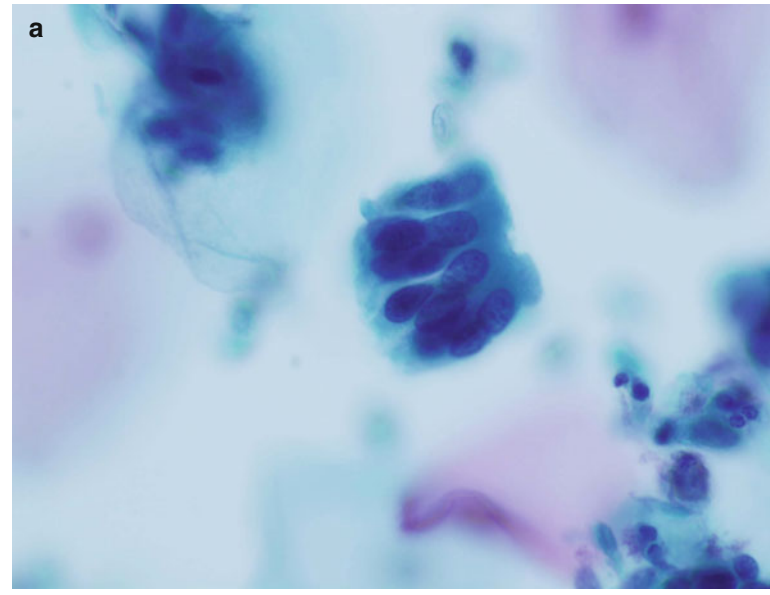


Fig. 6.4 Strips of cells from adenocarcinoma in situ with characteristic nuclear pseudostratification and a common cytoplasmic border (**a**, **b**). SurePath LBC



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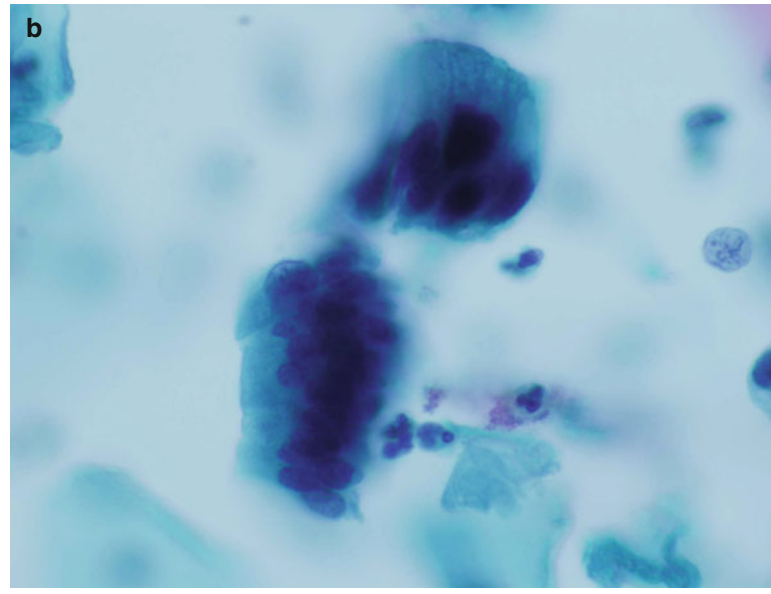


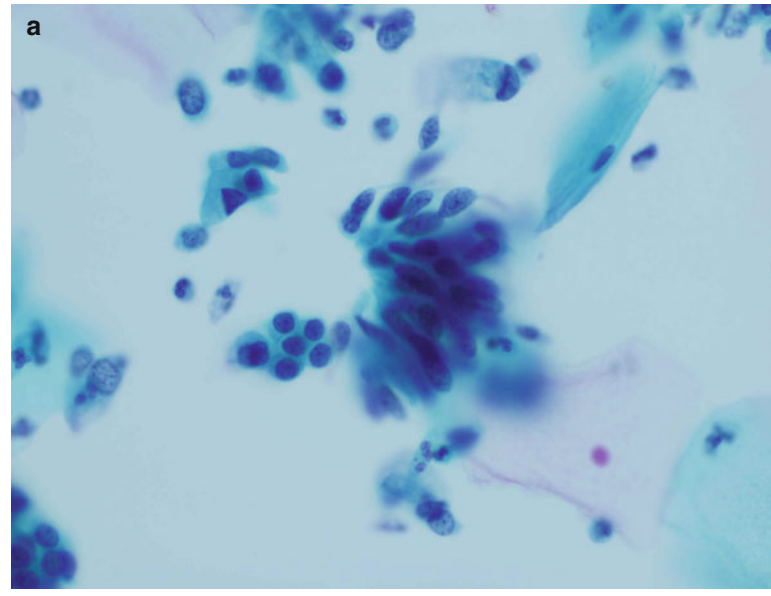
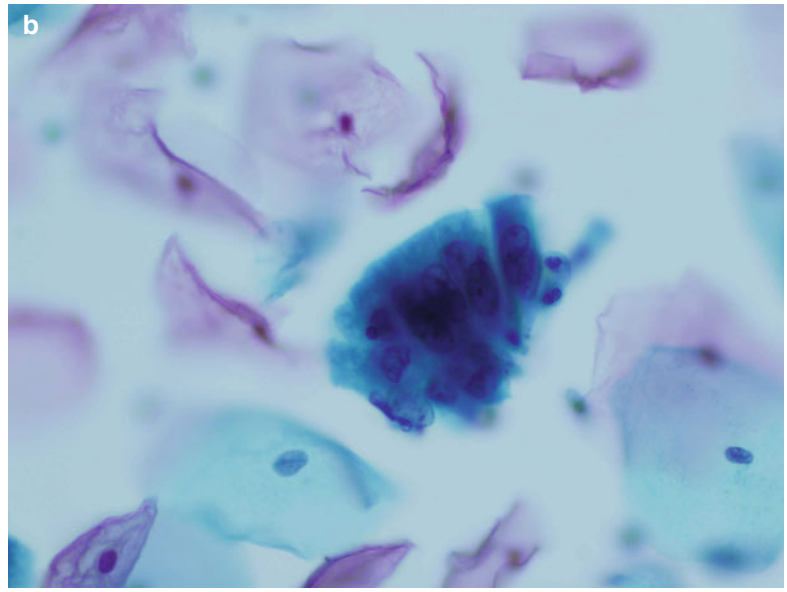


Fig. 6.5 Slightly curved pesudostratified strips of cells from adenocarcinoma in situ resembling a bird's tail or fish tail (**a**, **b**). SurePath LBC

Fig. 6.5 (continued)



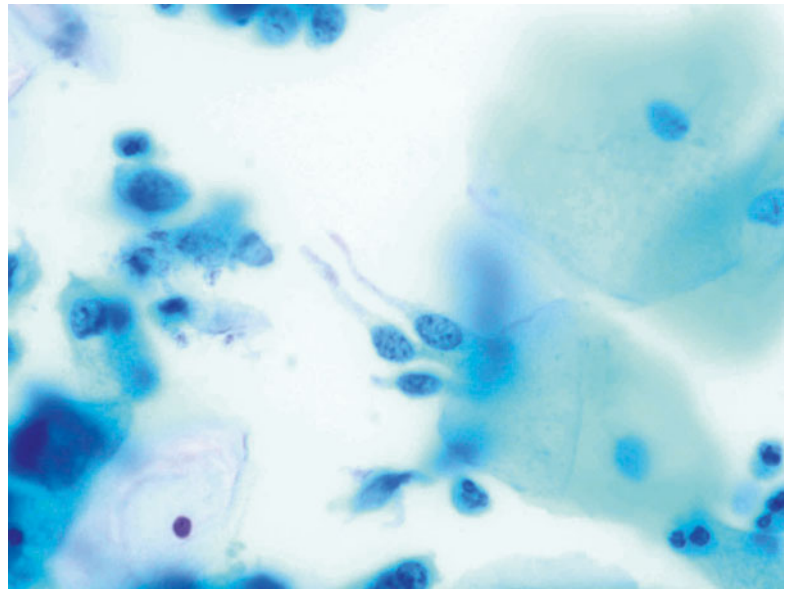


Fig. 6.6 Neoplastic glandular cells with tapering delicate cytoplasm – "snake and egg" appearance. Note the characteristic fine and coarse granular nuclear chromatin. SurePath LBC

"salt-and-pepper" appearance. Mitoses and apoptotic bodies are frequently identified in crowded cell groups and may be present in exfoliated strips of neoplastic endocervical cells.

The appearances described above relate to the usual or endocervical type of CGIN. In intestinal type CGIN individual cells with prominent solitary cytoplasmic vacuoles (goblet cells) are present and an extremely useful clue as to the neoplastic nature of the process (see Chap. 3) (Fig. 6.7). In endometrioid type CGIN the overall microarchitectural and cytomorphological features are similar to those of usual type CGIN but the individual cells have small even sized nuclei which are rounded rather than oval [15] (Fig. 6.8).

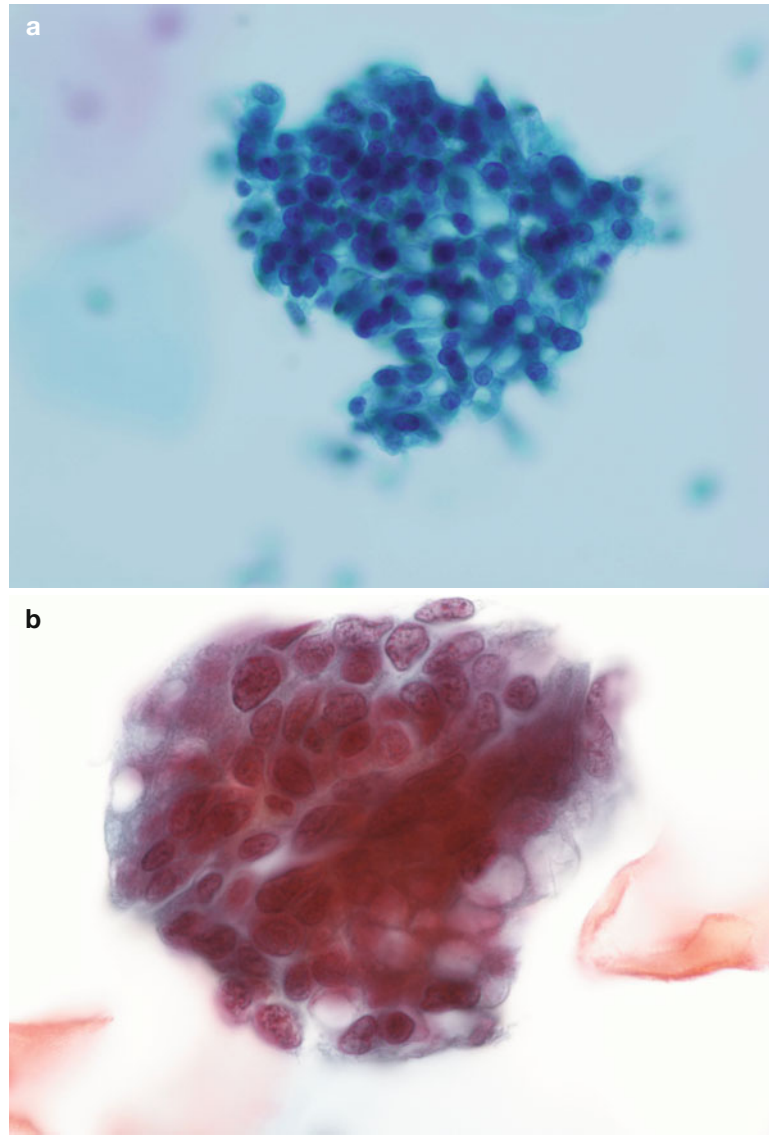


Fig. 6.7 Intestinal type adenocarcinoma in situ with characteristic goblet cell formation (**a**, **b**). SurePath LBC

Mimics of CGIN

There are a number of conditions which may in part cytologically mimic CGIN and cause diagnostic confusion, reflected in the generally reduced sensitivity and specificity of cytological detection of CGIN compared with CIN [16–21]. Furthermore, CGIN and CIN may coexist resulting in a mixed cytological pattern in cervical cytology preparations [16].

Endocervical Crypt Involvement by High Grade CIN (CIN 2/3) (HSIL)

The cytological appearance of endocervical crypt involvement by high grade CIN has been described by Selvaggi and is similar in both conventional and liquid-based cervical cytology preparations [22, 23].

Exfoliated cells from crypts involved by high grade CIN may present one of two patterns. The

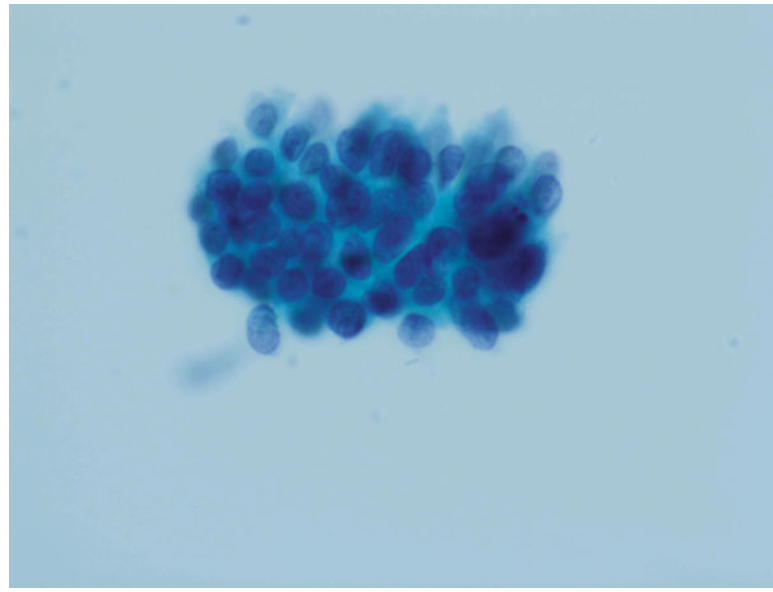


Fig. 6.8 Endometrioid type adenocarcinoma in situ. A disorganised crowded group of small glandular cells with even sized rounded nuclei. SurePath LBC

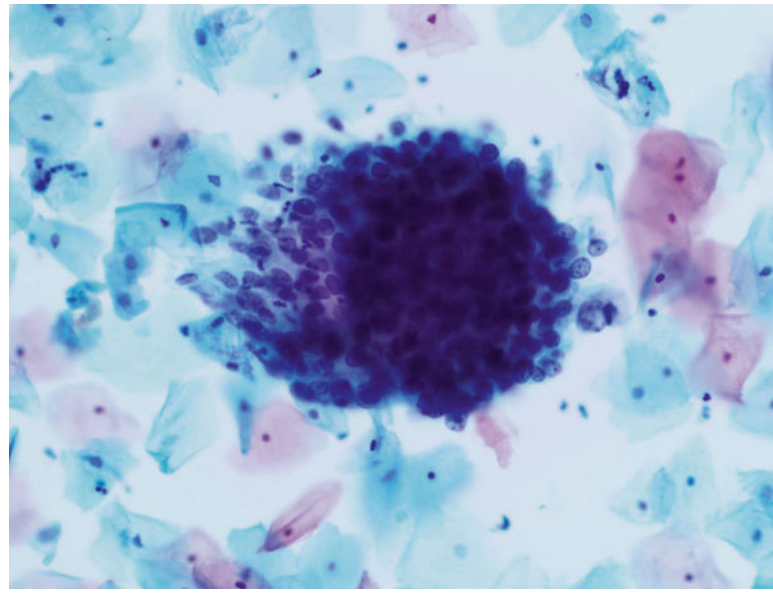


Fig. 6.9 High grade CIN involving an endocervical crypt. An oval cluster of abnormal cells with smooth cell borders. Note the transition from totally disorganised cells in the centre, lacking any honeycomb pattern, to flattened disorganised cells at the periphery. SurePath LBC

type A pattern designated by Selvaggi consists of oval clusters of abnormal cells with smooth cell or slightly irregular borders in which the cells at the periphery are flattened or disorganised and those within the centre totally disorganised often with a spindling or whirling arrangement, in contrast to the residual honeycomb pattern of CGIN; the constituent cells show an increased nuclear/cytoplasmic ratio and hyperchromatic nuclei with granular chromatin (Fig. 6.9). The type B pattern consists of sheets of columnar cells with peripheral palisading and nuclear pseudostratification, suggestive of CGIN, but with nuclear features of squamous differentiation. The latter is characterised by evenly distributed chromatin or chromatin clumping and clearing, variation in

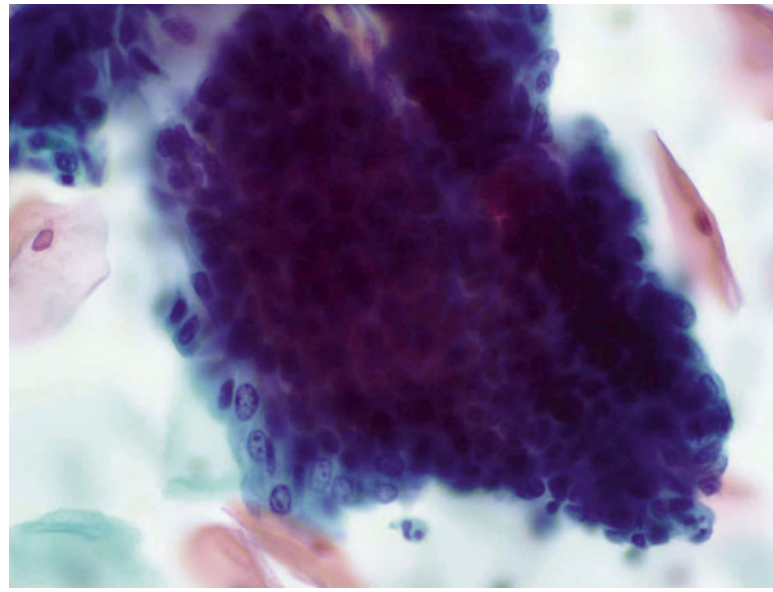


Fig. 6.10 High grade CIN involving an endocervical crypt. Sheets of columnar cells with peripheral palisading and nuclear pseudostratification, suggestive of CGIN, but nuclear features of squamous differentiation, no feathering and intact cytoplasm. SurePath LBC

size and shape of peripheral nuclei, irregularity of nuclear outlines with occasional notches and micronucleoli, which contrasts with the "salt and pepper" pattern of chromatin, relatively uniform nuclear size, shape and outline, and prominent nucleoli in neoplastic endocervical cells. Furthermore if palisaded or pseudo-stratified cells are present at the periphery of groups of cells derived from crypts involved by CIN, the cytoplasm is usually intact and dense with smooth edges and does not show the wispy cytoplasmic tags typical of CGIN (Fig. 6.10). Apoptosis and mitoses are clearly visualized in both entities and do not permit reliable distinction.

Inflammatory Change in Endocervical Cells and Benign Endocervical Polyps

In many women with cervicitis or a benign endocervical polyp, cytology samples are entirely normal but in some cases endocervical cells may show reactive changes consisting of crowded cell groups with dense cyanophilic or eosinophilic cytoplasm, maintenance of internuclear spacing, anisonucleosis in round or ovoid nuclei, hyperchromasia and prominent nucleoli [12, 24, 25] (Fig. 6.11).

Occasionally polypoid tissue fragments from endocervical polyps appear in cervical cytology samples, comprising an inner core of numerous small dark stromal cells, covered by a layer of columnar cells with basal nuclei and tissue fragments from lower uterine segment polyps, which typically have a low gland to stroma ratio, present as small vessels running in various directions connected by thin sheets of small ovoid cells with indistinct cytoplasm [26].

Microglandular hyperplasia, as described below, is sometimes seen in cytology samples from a polyp.

Cervical Endometriosis and Lower Uterine Segment Sampling

Although spontaneous endometriosis of the cervix has been described, it is uncommon unless there has been a previous operative procedure such as a loop or cone biopsy or trachelectomy, superficial endometriosis then resulting from direct implantation at the site of injury during a subsequent menstrual period; alternatively endocervical brush samplers or spatulae with elongated tips may directly sample the lower uterine segment and harvest endometrial glands and stroma as intact tissue fragments [24, 27–35].

In conventional and liquid based cervical cytology samples, endometrial cells from the cervix are well preserved and are arranged in large sheets or strips showing gland openings and nuclear

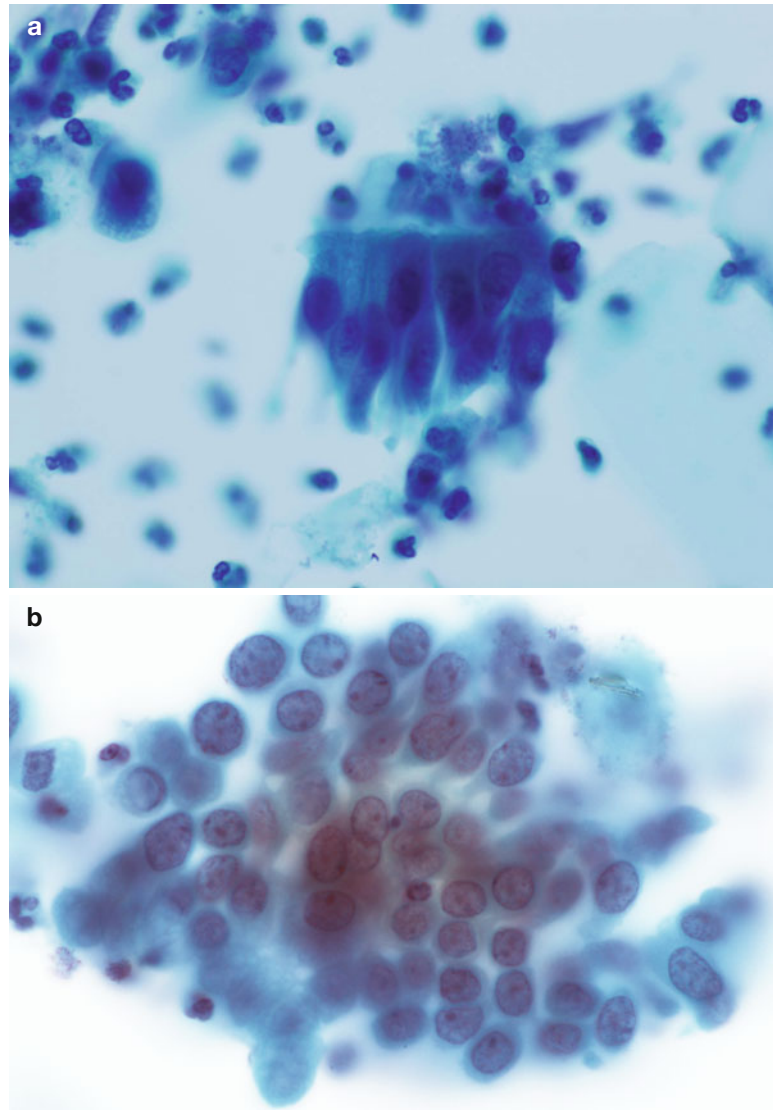


Fig. 6.11 Reactive changes in endocervical cells viewed in strips (**a**) and sheets (**b**)

stratification respectively composed of cuboidal cells with a high nuclear/cytoplasmic ratio, relatively hyperchromatic nuclei with irregular contours and coarse chromatin; prominent nucleoli and mitoses may be found (Fig. 6.12). These features, together with the exfoliation pattern described, carry the risk that the cells may be mistaken for dyskaryotic endocervical cells. The latter cells, however, typically present as sheets of monotonous cells with crowded overlapping nuclei and the sheets have more striking architectural abnormalities.

Endometrial stromal cells may also be present, either in loose groups with ragged edges or admixed with the epithelial cells. Stromal cells are oval or round with rounded or reniform nuclei and scanty ill-defined cytoplasm, which is more abundant during the secretory phase of the cycle. The presence of stromal cells enables the diagnosis of endometriosis to be made [24, 28]. In conventional smears in particular the specimen may also be heavily blood stained. Directly sampled tissue from the lower uterine segment consists of tubular structures with well demarcated outlines composed of small uniform cuboidal cells with a peripheral rim of elongated delicate stromal cells orientated along the long axis of the tubular structure; these characteristic features are readily

identified at low power routine screening magnification. Such structures are often likened to "elephant trunks" (Fig. 6.13).

Tubal and Tuboendometrioid Metaplasia

Tubal metaplasia refers to replacement of epithelium at Mullerian-derived sites, such as the endometrial cavity or endocervix, by benign epithelium resembling that of the fallopian tube; in addition, tubal metaplasia frequently includes cells of endometrial type, so-called tuboendometrioid metaplasia. Tubal metaplasia has been found in between 31 and 100 % of adequately sampled cervices removed for both neoplastic and non-neoplastic reasons and tubal or tuboendometrioid metaplasia has been reported in 26 % of cervices removed after cone biopsy [27, 36–38].

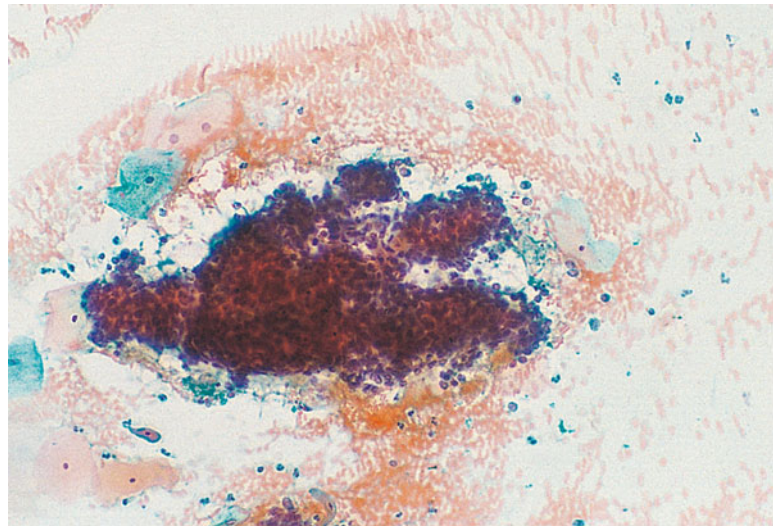


Fig. 6.12 Endometriosis of the cervix. A large sheet of cuboidal endometrial cells showing gland openings and nuclear stratification on a haemorrhagic background in a conventional smear (From Smith [84] with permission)

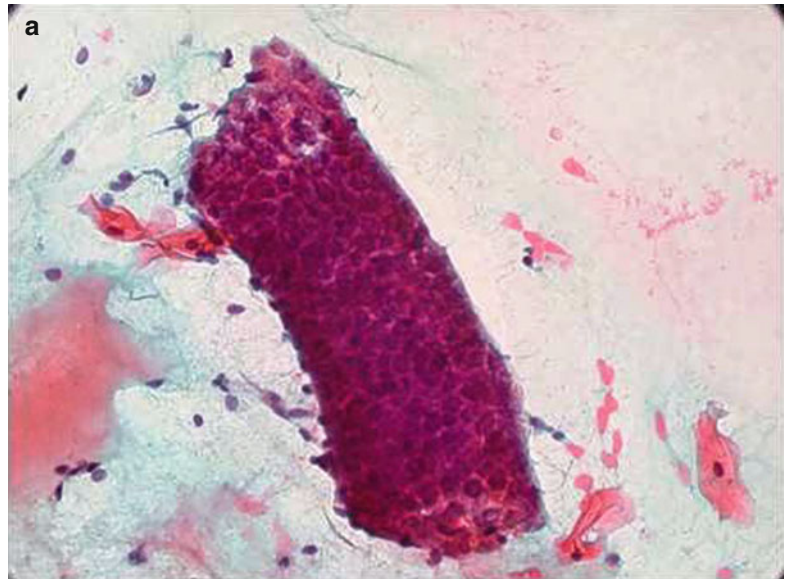
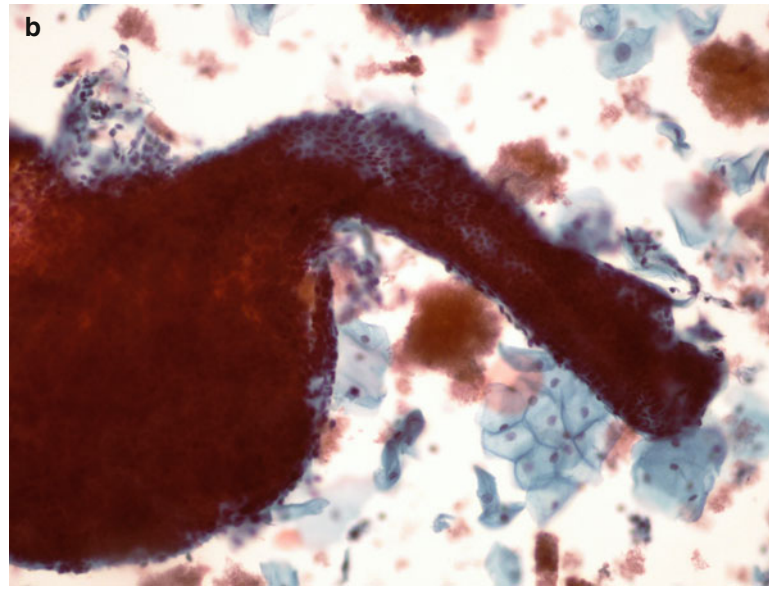


Fig. 6.13 Directly sampled tissue from the lower uterine segment in a conventional cervical smear (**a**) and SurePath LBC preparation (**b**)

Fig. 6.13 (continued)



Tubal and tuboendometrioid metaplasia tends to be multifocal and involve upper endocervical crypts rather than the lower endocervix and surface epithelium. Therefore it is more likely to be encountered in cervical cytology specimens following the use of brush devices for liquid based cytology sampling [38, 39]. Endometriosis may also occur in the same group of patients, as already described, although it is a less frequent event.

Although not thought to be preneoplastic, it is important that the cytological appearances are recognized and not misinterpreted as indicating endocervical glandular dysplasia: in one study tubal metaplasia accounted for the smear appearances in 76 % of cases in which endocervical glandular dysplasia had been suggested [40].

The cytological appearances in both conventional smears and liquid based preparations have been described in detail [39, 41–43]. All three cell types found in normal fallopian tube epithelium should be present, namely ciliated cells, secretory non-ciliated cells and intercalary cells. Although the proportion of these cells varies greatly between individual samples, ciliated columnar cells with apical terminal bars are necessary for the diagnosis and typically present as aligned groups of cells with well demarcated cytoplasm, which contrasts with the pseudostratified edge, bare nuclei and tapering cytoplasm of AIS (Fig. 6.14).

The cells, which are smaller than endocervical cells, may be arranged in flat sheets, three-dimensional clusters, small poorly cohesive groups or occur singly. Their nuclei, which are oval, round or elongated and are usually basal in position, tend to be larger than those of endocervical cells and evenly spaced with finely granular nuclear chromatin which is slightly darker than that of endocervical cell nuclei. Nucleoli are more often visible in LBC preparations and are small and single.

Intercalary cells, exclusive to tubal metaplasia but less readily identified in cytology samples, have triangular dark staining nuclei and little cytoplasm, in contrast to the other cells which have varying amounts of granular or vacuolated cytoplasm. Mitoses are rare.

The differential diagnosis includes cervical endometriosis, endometrial cells from the lower uterine segment, microglandular and reserve cell hyperplasia, ‘reactive’ endocervical cells, and dyskaryotic cells from CIN 3 involving endocervical glands. Cilia are usually a feature of benign endocervical cells although a solitary case has been reported of histologically confirmed ciliated adenocarcinoma of the cervix with prior

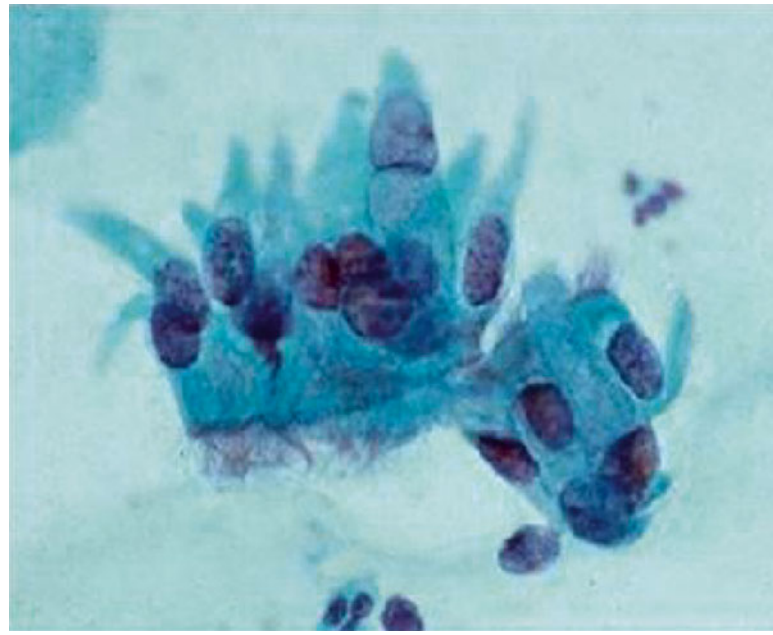


Fig. 6.14 Tuboendometrioid metaplasia in a SurePath LBC preparation. Note the cellular alignment, terminal bars and cilia

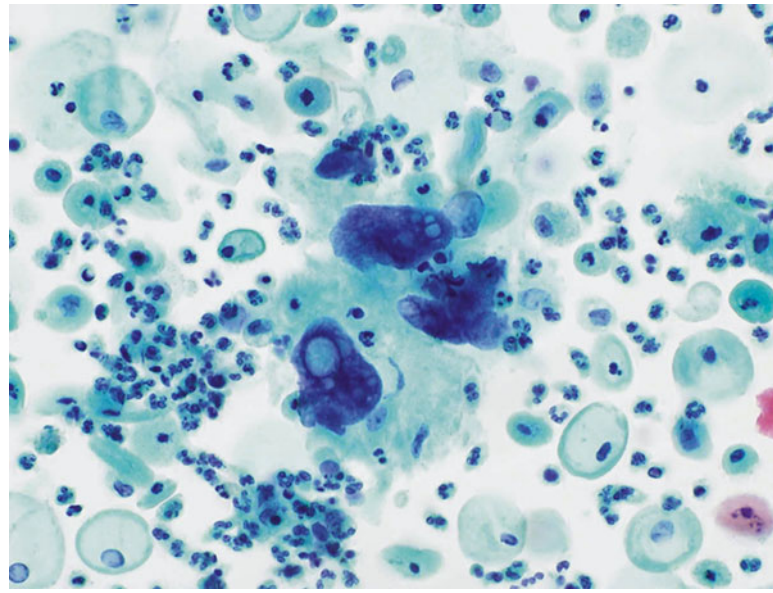


Fig. 6.15 Microglandular hyperplasia of the cervix in a SurePath LBC preparation. Small groups of glandular cells of variable size with bland nuclear features and abundant focally vacuolated cytoplasm (Courtesy of Dr C Waddell, Birmingham Cytology Training Centre)

liquid-based cervical cytology showing atypical, ciliated glandular cells that initially raised the diagnostic consideration of tubal metaplasia [44].

Microglandular Hyperplasia

The cytological appearances of microglandular hyperplasia reflect the histological appearances described in Chap. 2 and are characterised by bidimensional or tridimensional cellular clusters made up of cubic or cylindrical glandular cells with vacuolated cytoplasm; basaloid cells with dense cytoplasm, corresponding to immature squamous metaplasia; and subcylindrical reserve cells with small, round nuclei and scant cytoplasm. The clusters also show microlumina or fenestrated spaces, preserved polarity and absence of nuclear peripheral dispersion [45] (Fig. 6.15). Microglandular hyperplasia is a very common condition but is only likely to cause cytological confusion with endocervical or

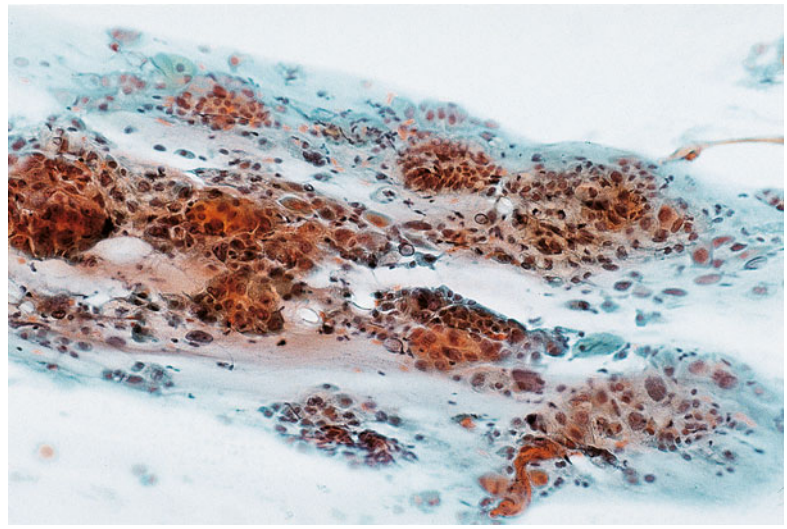


Fig. 6.16 Radiation change in endocervical cells in a conventional smear. Disorganised clusters of cells with loss of the normal honeycomb pattern, anisonucleosis, nucleolar enlargement, occasional multinucleation and abundant cytoplasm (From Waddell and Chandra [85] with permission)

endometrial neoplasia in the most florid papillary forms [39, 46–48].

Arias-Stella Change

Interpretative problems may arise during pregnancy if the endocervical glandular epithelium undergoes the type of extreme hypersecretory activity known as Arias–Stella change; it can also occur in other hyperprogestational states such as gestational trophoblastic disease and with high dose progestogen or ovulation inducing therapy [49].

The cytological features have been described in single case reports, and in one of these the cervical Arias-Stella reaction was associated with a cervical pregnancy [50, 51]. The atypical glandular cells occur singly, in syncytial clusters and cohesive sheets and are characterised by cyto- and karyomegaly, a high nuclear to cytoplasmic ratio, round to oval nuclei with finely granular or smudgy chromatin imparting a ground glass appearance, frequent intranuclear inclusions, and vacuolated or dense variable staining cytoplasm. Arias-Stella cells may be misinterpreted as malignant glandular cells if the history of pregnancy is not known [52].

Radiation Associated Changes

Although the cytological changes in cervical squamous cells after radiation therapy have been well described, the literature on the alterations in endocervical cells in response to radiation therapy is very limited. Frierson et al. studied the effect of radiation therapy for cervical cancer on endocervical cells in brush specimens at various times following treatment. Endocervical cells appeared as single cells or clusters lacking the honeycomb appearance of normal endocervical cells with lavender, mucin-filled cytoplasm. In samples taken within 6 months of treatment, the majority of endocervical cells were enlarged but usually had a normal nuclear/cytoplasmic ratio although the nuclei varied in size and had coarse chromatin, large nucleoli and were frequently multinucleated. Repair cells and multinucleated histiocytes were seen in 83 and 61 % of samples, respectively. Each of these cytological findings was less apparent in follow-up smears taken more than 6 months after the completion of radiotherapy. Awareness of these cytological changes in endocervical cells after radiation therapy should prevent the overdiagnosis of cancer in follow-up endocervical brush specimens [53] (Fig. 6.16).

Stratified Mucin Producing Intraepithelial Lesion (SMILE)

To date there are no published accounts of the appearance of this entity in cervical cytology preparations, but a personal review of conventional and SurePath liquid based cervical cytology specimens that preceded the diagnosis of

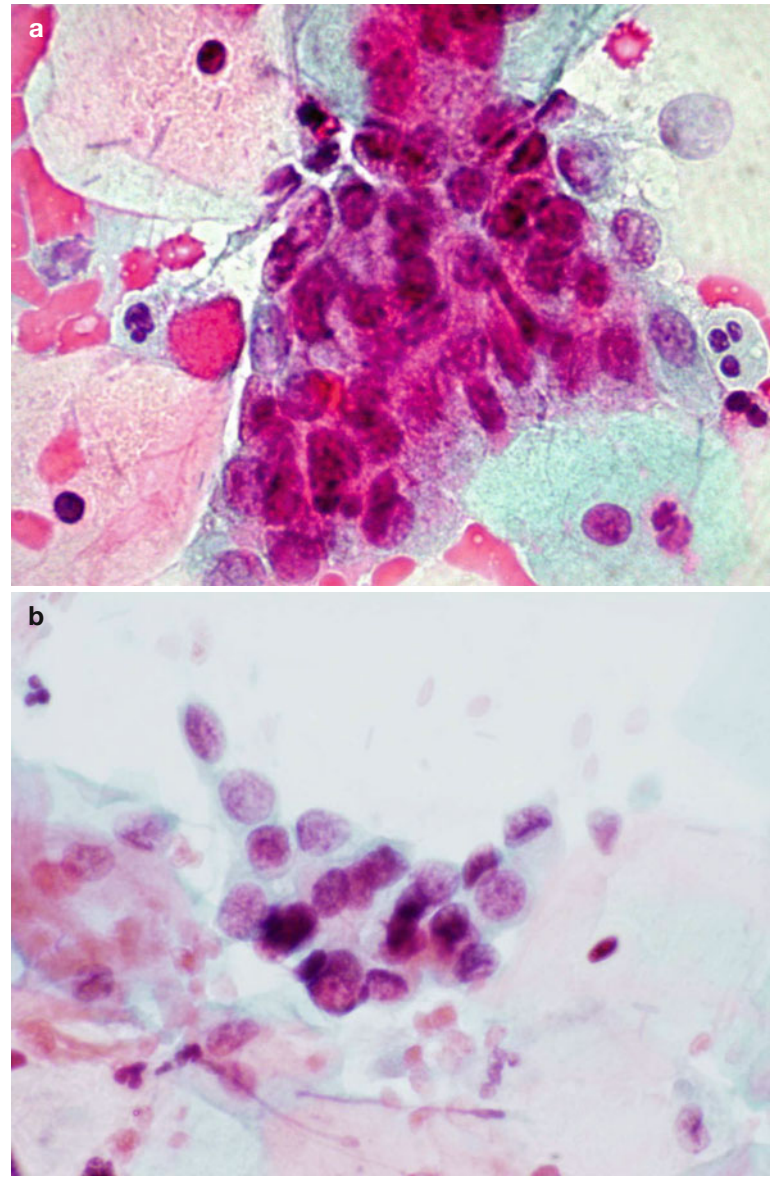


Fig. 6.17 Features consistent with origin from SMILE in a conventional smear (**a**) and SurePath LBC preparation (**b**). Crowded groups of neoplastic glandular cells with fine vacuolated cytoplasm

SMILE has identified hyperchromatic crowded groups of glandular cells with focal fine cytoplasmic vacuolation consistent with origin from SMILE (Fig. 6.17). These groups of cells were often associated with neoplastic squamous or endocervical glandular cells consistent with origin from CIN and CGIN respectively, which is frequently found in association with SMILE [54].

Invasive Adenocarcinoma

Endocervical Type Cervical Adenocarcinoma

A definitive diagnosis of endocervical adenocarcinoma cannot be made on cervical cytological preparations because the cytological features of adenocarcinoma in situ and invasive

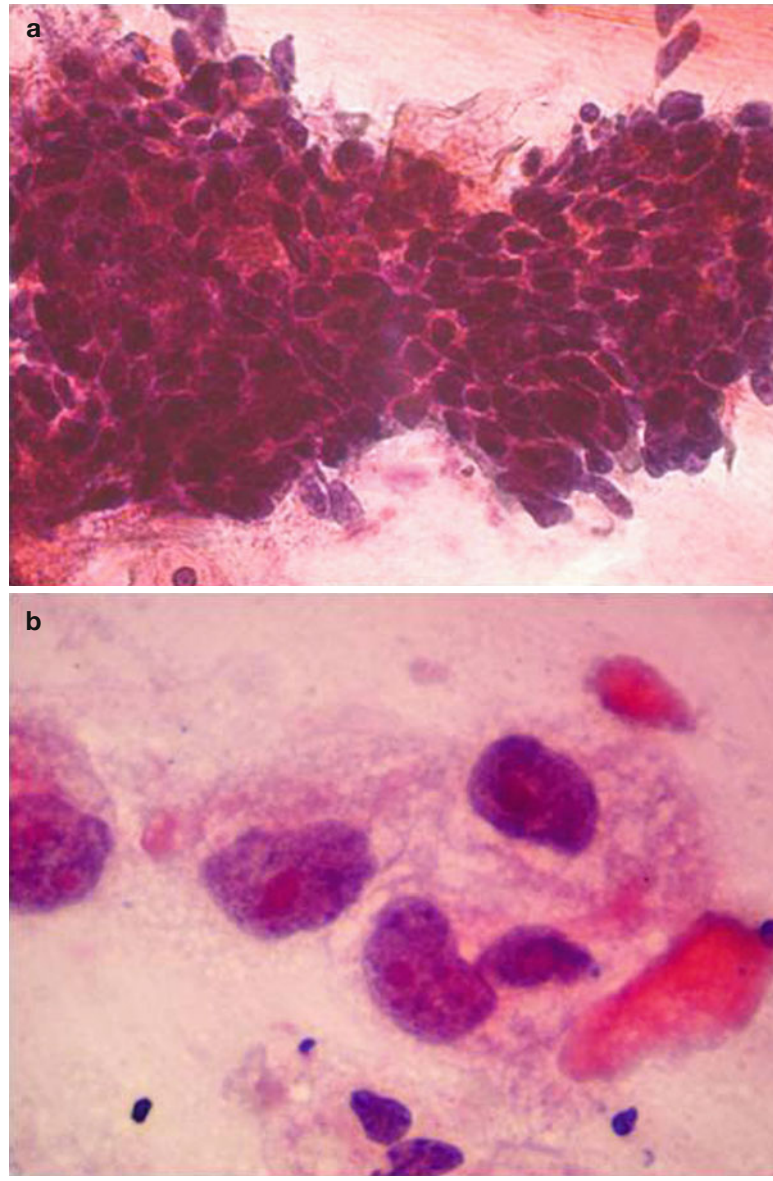


Fig. 6.18 Endocervical adenocarcinoma of the cervix in a conventional smear. Syncytial masses of large pleomorphic glandular cells (**a**) and dissociated neoplastic glandular cells with prominent irregular eosinophilic nucleoli (**b**)

adenocarcinoma overlap. However detailed analysis of conventional cervical smears from histologically confirmed cases of endocervical adenocarcinoma led Pacey and colleagues to suggest that syncytial masses of large pleomorphic glandular cells, small cells in very crowded sheets and papillary groupings of cells, when seen in conjunction with AIS, are suggestive of invasion. Dissociation of cells, variable nuclear pleomorphism dependent of the degree of differentiation of the tumour, an irregular chromatin pattern and inconspicuous-to-prominent nucleoli are also frequently present and in some cases a tumour diathesis in the smear background [4, 6] (Fig. 6.18). However although extreme nuclear crowding has been recognised as a feature suggestive of invasion in endocervical adenocarcinoma, other subtypes of cervical adenocarcinoma such as mucinous, endometrioid and serous or clear cell and glassy cell carcinoma have moderate or abundant cytoplasm respectively, and nuclear crowding is therefore not a reliable

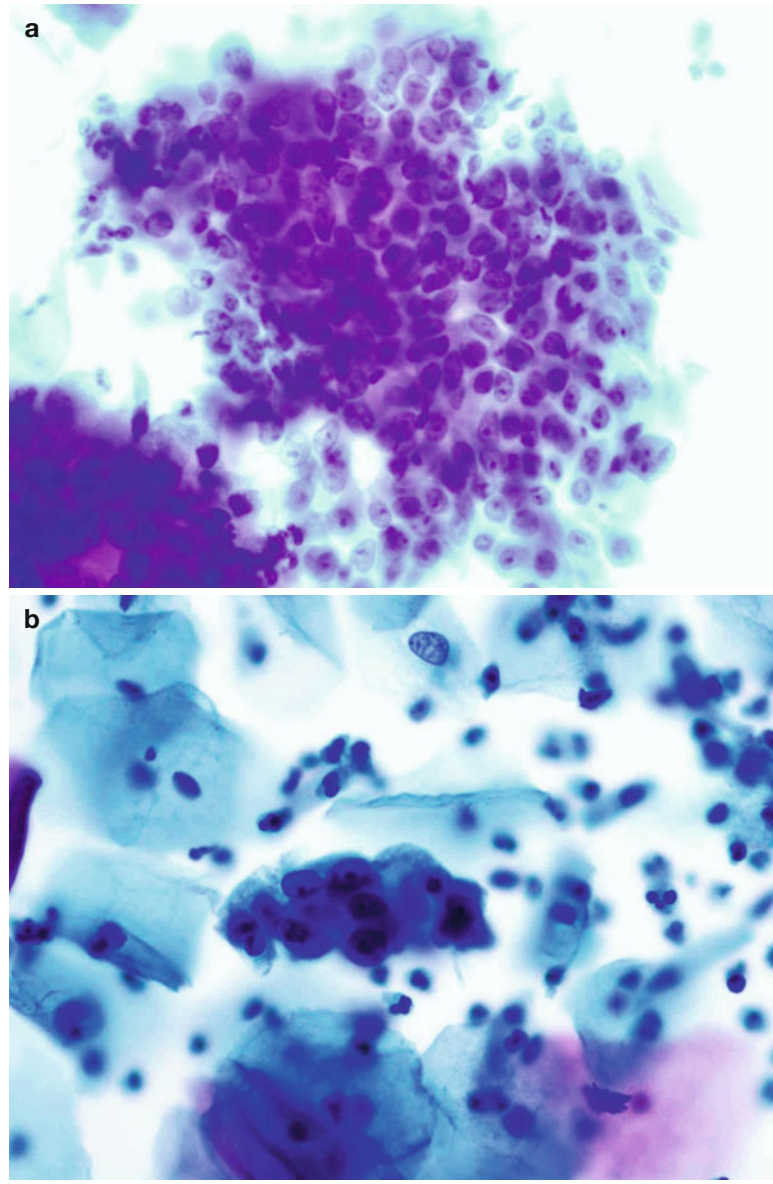


Fig. 6.19 Endocervical adenocarcinoma of the cervix in a SurePath LBC preparation. Syncytial masses of large pleomorphic glandular cells (**a**) and dissociated neoplastic glandular cells with prominent irregular nucleoli (**b**). Note the absence of tumour diathesis

morphological criteria for the diagnosis of these entities (see below).

The cytological features of endocervical adenocarcinoma in LBC preparations are similar to those in conventional smears except that nuclear morphology is better preserved and mitoses are more obvious, while tumour diathesis is less evident and if present corresponds to that seen in invasive squamous lesions: in SurePath preparations it tends to be bluish grey in colour and often closely associated with the malignant cells, so-called 'clinging diathesis', whilst in ThinPrep specimens lysed blood, a universal component of diathesis, is located at the periphery of the cell deposit and appears red in colour [10, 14] (Fig. 6.19).

Endometrioid Adenocarcinoma of the Cervix

The cytological appearances of this rare subtype of cervical adenocarcinoma, which some believe

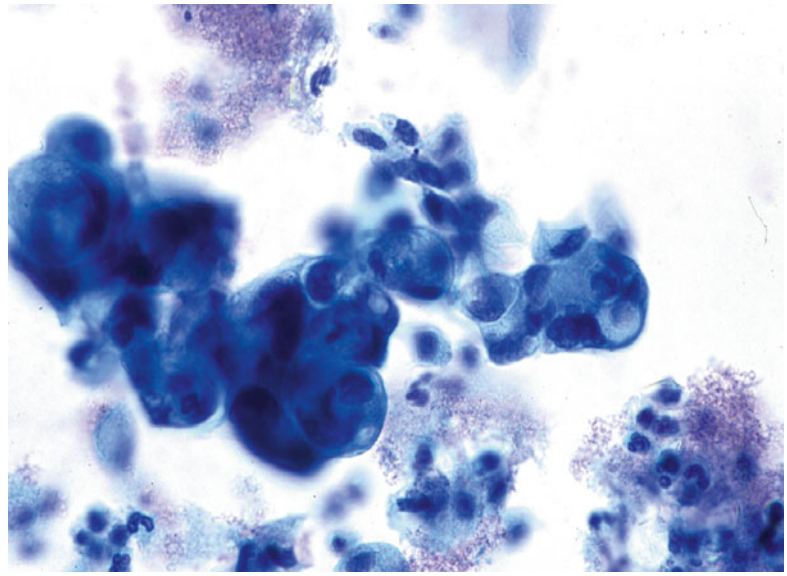


Fig. 6.20 Endometrioid adenocarcinoma of the cervix in a SurePath LBC preparation. Note the cuboidal or columnar cells with eccentric nuclei and occasional vacuolated cytoplasm, small nucleoli and dense cyanophilic cytoplasm. Compare with Fig. 6.17

is simply a variant of endocervical type cervical adenocarcinoma (see Chap. 5), are very similar to those of endometrioid adenocarcinoma of the endometrium being characterised by cuboidal or columnar cells with eccentric nuclei and occasional vacuolated cytoplasm, small nucleoli and dense cyanophilic cytoplasm (Fig. 6.20).

In tumours arising from the cervix, as opposed to the endometrium, there may be a tumour diathesis [55, 56].

Minimal Deviation Adenocarcinoma

The diagnosis of minimal deviation adenocarcinoma (MDA), and its putative precursor lesion lobular endocervical glandular hyperplasia (LEGH), is difficult and rarely made in cervical cytology preparations, reflecting the minimal and often focal cytological atypia seen in histological sections. In the majority of reported cases, the diagnosis has been made in retrospect on review of conventional cervical smears that preceded the biopsy diagnosis; to date the appearance in liquid based cytology preparations has not been described. In conventional cervical smears an abundance of glandular material consisting of flat honeycomb sheets with focal disorganisation, abundant lacy or vacuolated cytoplasm and nuclei enlarged up to twice normal size with fine or coarsely granular chromatin and occasional conspicuous nucleoli are features suggestive of origin from minimal deviation adenocarcinoma [57, 58]. In addition cytoplasmic mucin of cells derived from MDA and LEGH shows golden-yellow Papanicolaou staining in contrast to normal endocervical mucin which stains pink, and the cells themselves are immunoreactive to HIK1083 in keeping with their gastric pyloric phenotype [59, 60] (Fig. 6.21). Cells derived from LEGH may be distinguished from cells derived from MDA by the presence of intranuclear cytoplasmic inclusions [61].

Villoglandular Cervical Adenocarcinoma (VGA)

The cytological features of this uncommon type of cervical adenocarcinoma in conventional cervical smears were first described in 1996 and subsequently confirmed in other small series [62–65].

Characteristic cytological features include many large cohesive groups and sheets of endocervical glandular cells showing nuclear crowding and loss of the normal honeycomb pattern; the presence of long villous fronds and papillae

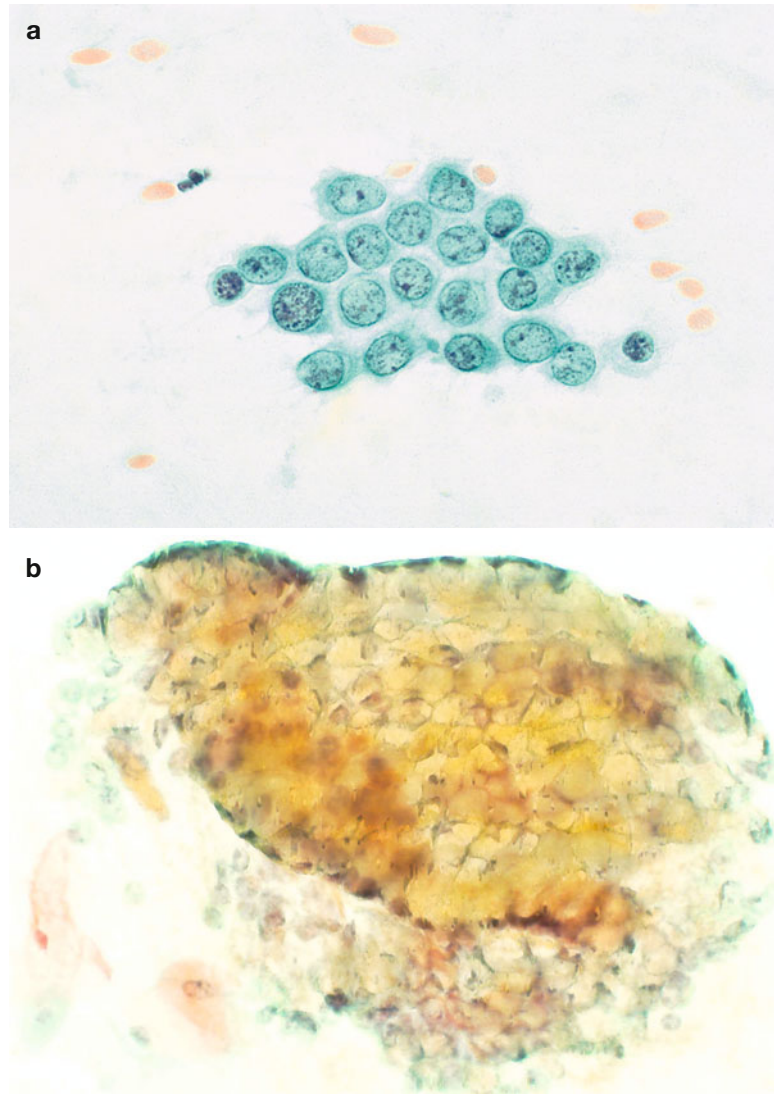


Fig. 6.21 Minimal deviation adenocarcinoma of the cervix in a conventional cervical smear. Endocervical cells retain the honeycomb pattern but show focal disorganisation, nuclear enlargement with minor variation in shape, fine or coarse granular chromatin, and finely vacuolated cytoplasm (**a**). Yellow stained cytoplasmic mucin in a flat sheet of endocervical cells with subtle disorganisation of the honeycomb pattern (**b**) (From Waddell and Chandra [85] with permission)

lined by columnar cells with intact smooth cytoplasmic borders and minimal to moderate cytological atypia; and strips and three-dimensional ball-like clusters of cells with smooth, intact communal cytoplasmic rims and flattened cells at the periphery. Cell nuclei are small, ovoid and hyperchromatic with granular evenly distributed chromatin and absent or inconspicuous nucleoli. Apoptotic bodies and scattered mitoses are present.

Similar appearances are seen in liquid based cytology preparations but nuclear membrane irregularity and nucleoli are more often identified as a result of better cell preservation [66]. The differential diagnosis of VGA includes adenocarcinoma in situ, papillary CIN 3 and CIN 3 involving endocervical glands, papillary squamous and squamotransitional neoplasms, directly sampled endometrial cells and reactive endocervical cells. However, the above constellation of features, and in particular the branching papillary fronds with smooth as opposed to "feathered" borders and characteristic architectural and nuclear features should permit an accurate diagnosis (Fig. 6.22).

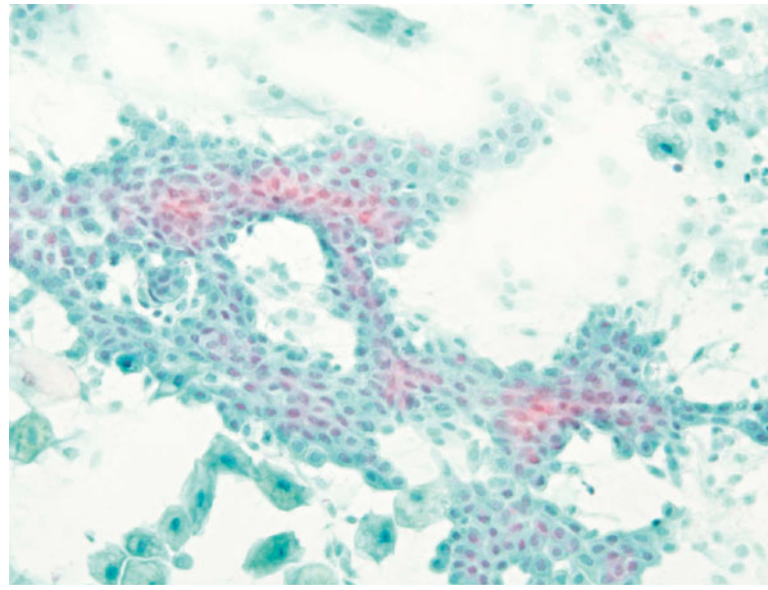


Fig. 6.22 Villoglandular adenocarcinoma of the cervix in a cystoscopy urine sample from a patient with tumour directly infiltrating the bladder. Note the branching papillary fronds composed of glandular cells showing only minor atypia (From Waddell and Chandra [85] with permission)

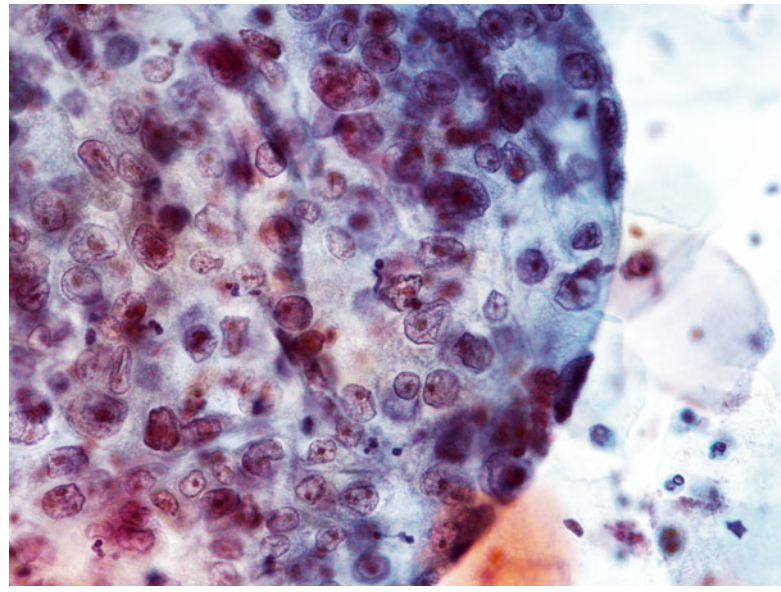


Fig. 6.23 Clear cell carcinoma of the cervix. A sheet of pleomorphic glandular cells with prominent nucleoli, sharply defined nuclear borders, prominent nucleoli and finely granular or clear cytoplasm. SurePath LBC

Clear Cell Carcinoma

Clear cell carcinoma of the cervix in young women was previously associated with prenatal exposure to diethylstilboestrol but following discontinuance of the use of this drug for the management of miscarriage in the early 1970s, this rare cervical tumour now tends to be seen more often in elderly women (see Chap. 4). The cytological appearance in cervical smears was first described in 1978 and more recently the appearance in liquid based cytology preparations [67–70]. Tumour cells present as single or clusters of cells showing anisonucleosis with variable amounts of finely granular or near optically clear cytoplasm and round or ovoid nuclei with delicate nuclear borders, finely granular chromatin and prominent, sometimes multiple, eosinophilic nucleoli (Fig. 6.23).

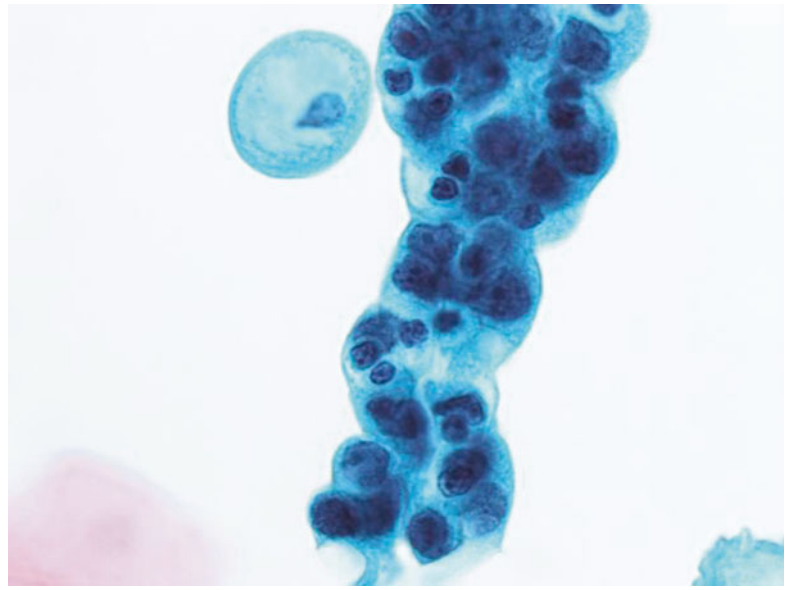


Fig. 6.24 Serous carcinoma of the cervix. Three-dimensional papillary group of cells showing nuclear pleomorphism, prominent nucleoli and cytoplasmic vacuolation. SurePath LBC (Courtesy of Manchester Cytology Training Centre)

Serous Carcinoma

Primary serous carcinoma of the cervix is very rare and most cases of cervical serous carcinoma represent either direct spread from a primary tumour of the endometrium or metastasis from the ovary or fallopian tube [71]. Cytomorphologically primary serous carcinoma of the cervix is of similar appearance to serous carcinoma of the ovary consisting of multilayered sheets of pleomorphic glandular cells, papillary fragments, tight balls and dissociated markedly atypical cells with vacuolated cytoplasm, prominent nucleoli and occasional associated psammoma bodies. Abundant tumour diathesis is usually found in primary serous carcinoma of the cervix but is scanty in cases of serous ovarian carcinoma metastatic to the cervix [72, 73] (Fig. 6.24).

Adenosquamous Carcinoma

Cervical cytology preparations from adenosquamous carcinoma of the cervix reflect the histological appearances and consist of dissociated or syncytial aggregates of atypical malignant epithelial cells showing features of both squamous and glandular differentiation associated with tumour diathesis; in some cases only one type differentiation may be apparent or predominate [16, 74–76].

Glassy Cell Carcinoma

Glassy cell carcinoma is considered to be a variant of adenosquamous carcinoma since ultrastructurally there is evidence of both glandular and squamous differentiation [77]. The cytological features in both conventional smears and liquid based preparations have been described [78, 79]. The tumour cells tend to be numerous and arranged in groups with a syncytial appearance or in sheets and clusters. A few single tumour cells may also be present. They are larger than severely dyskaryotic squamous cells and show marked anisokaryosis. The nuclei are large and hyperchromatic, the chromatin having a finely granular appearance. Large irregular nucleoli are often present. A moderate amount of cytoplasm is present which may have a finely granular appearance (Fig. 6.25). Inflammatory cells, including eosinophils, may be conspicuous in the background and may be seen closely associated with tumour cells.

The cytological features can be confused with poorly-differentiated large cell non-keratinizing squamous carcinoma, the nuclei of which tend to

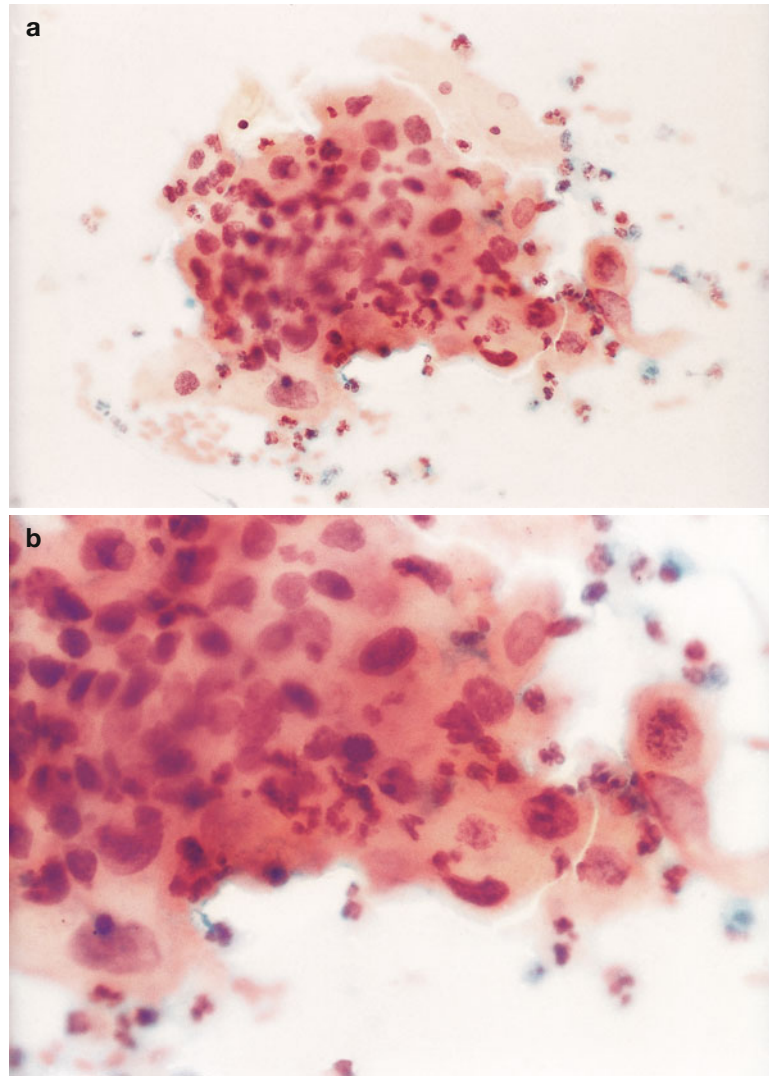


Fig. 6.25 Glassy cell carcinoma of the cervix. Medium (**a**) and high power (**b**) views of a conventional smear. A syncytial sheet of tumour cells, larger than severely dyskaryotic squamous cells, showing marked anisokaryosis and moderate amounts of finely granular cytoplasm (From Smith [84] with permission)

have coarser chromatin and less nucleolar abnormality, and with atypical reparative cells which do not full the nuclear criteria of malignancy. Misdiagnosis as a low-grade squamous abnormality can occur if the sheets of cells have bland nuclear features, leading to delay in diagnosis [80].

Adenoid Cystic Carcinoma and Adenoid Basal Carcinoma

These tumours are rarely diagnosed in cervical cytology samples, either because no tumour cells are present reflecting the fact that the overlying mucosa is usually intact or because the tumour cells present are misinterpreted as benign or abnormal endometrial cells. The cells are small, tend to be arranged in irregularly shaped three-dimensional groups and sheets, and have small uniform hyperchromatic nuclei, occasional small nucleoli and scanty cytoplasm. They may also form cords and acini, some of which contain globules of hyaline material if derived from an adenoid cystic carcinoma.

The differential diagnosis includes endocervical adenocarcinoma, endometrial adenocarcinoma, small cell neuroendocrine carcinoma, in which nuclear moulding and frequent mitoses are

seen, and severe squamous dyskaryosis, in which the cells tend to be larger and less uniform.

If the tumours occur in association with in situ or invasive squamous neoplasia both tumour cell types may be present in the same smear [81–83].

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