GYNAECOLOGICAL PATHOLOGY

The developing spectrum of gastric-type cervical glandular lesions

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Summary

Adenocarcinoma of the cervix is less common than squamous cell carcinoma, although its relative prevalence is increasing. Oncogenic (high-risk) human papillomavirus (HPV) infection is implicated in the development of approximately 90% of all cervical adenocarcinomas. Of the remaining non-HPV associated tumours, the most frequent is gastric-type adenocarcinoma (GAS), which is recognised by the World Health Organization as a form of mucinous adenocarcinoma of the cervix. Minimal deviation adenocarcinoma (MDA) of mucinous type (adenoma malignum) is considered an extremely well differentiated variant of GAS and is encompassed within the category of GAS. The concept of gastric-type cervical glandular lesions has emerged over recent decades and our understanding of the full spectrum of benign, premalignant and malignant lesions is still evolving. Established benign lesions, which are rare, include simple gastric metaplasia and lobular endocervical glandular hyperplasia (LEGH) (complex gastric metaplasia). Postulated premalignant lesions comprise atypical LEGH and gastric-type adenocarcinoma *in situ* (gAIS); these are probably related lesions for which the umbrella term 'gAIS' has been proposed. The term 'gastric-type' derives from the morphological resemblance of the glandular epithelium to that seen in the stomach and pancreaticobiliary tree; intestinal metaplasia with goblet cells and neuroendocrine cells are present in some cases. A gastric immunophenotype has been demonstrated using markers of pyloric gland mucin, MUC6 and HIK1083. Uncommonly, gastric-type cervical glandular lesions involve multiple sites in the female genital tract and it may be problematic to discern whether these represent independent synchronous or metastatic lesions. There is also an association between gastric-type cervical lesions and Peutz–Jeghers syndrome. Awareness of the spectrum of gastric-type lesions is important, as the diagnostic features of both gAIS and GAS, particularly well differentiated examples, may be subtle, and p16 immunohistochemistry is usually negative. GAS has a much poorer prognosis than HPV-associated cervical adenocarcinoma, with propensity for presentation at advanced stage and wide dissemination to unusual sites such as the ovary, omentum and peritoneum. Although uncommon, GAS is likely to increase in relative prevalence with the introduction of HPV vaccination and precursor lesions will not be detected by primary HPV-based screening programs.

Key words: Cervix; gastric-type lesions; gastric-type adenocarcinoma; gastric-type adenocarcinoma *in situ*; lobular endocervical glandular hyperplasia.

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INTRODUCTION

Effective cervical cancer screening programs in developed countries have led to a significant decline in the incidence of squamous cell carcinoma (SCC) of the cervix.^{1–5} By comparison, cervical SCC remains a leading cause of cancer death in less affluent nations.⁶ Adenocarcinoma of the cervix is less common than SCC, but the relative incidence of adenocarcinoma is increasing as the rate of SCC declines, particularly in young women,^{3–5} and currently, adenocarcinoma is estimated to account for up to 25% of all cervical cancers.^{1,7} Most cervical adenocarcinomas are causally related to persistent infection with oncogenic (high-risk) human papillomavirus (HPV).^{8,9} A recent multinational European study assessed HPV prevalence in 461 cervical adenocarcinomas using centralised pathology review and sensitive HPV testing and found 90% of cases to be HPV positive, with HPV types 16, 18 and 45 accounting for 98% of all HPV positive cases.¹⁰ Of the remaining small subset of non-HPV associated adenocarcinomas, the most common is so-called gastric-type adenocarcinoma (GAS), which represents the malignant end of an emerging spectrum of benign, premalignant and malignant gastric-type cervical glandular lesions, the characteristics of which have been elucidated in a series of recent publications.^{11–28} The latest edition of the World Health Organization (WHO) Classification of Tumours of the Female Genital Tract has been modified to include GAS as a subtype of mucinous adenocarcinoma of the cervix.²⁹ Minimal deviation adenocarcinoma (MDA) of mucinous type, also known as adenoma malignum, now denotes the rare, extremely well differentiated variant of GAS and, as discussed later, is best subsumed under the umbrella term GAS. Most cases of GAS are less well differentiated than prototypic MDA, although a spectrum of differentiation is often seen within an individual tumour.²⁹ Table 1 depicts the 2014 WHO classification of adenocarcinoma of the cervix. Other non-HPV related cervical adenocarcinomas include most clear cell carcinomas (a minority are HPV-related¹⁰) and mesonephric adenocarcinoma, both of which are less frequent than GAS.

Within the spectrum of gastric-type cervical glandular lesions, the best understood are the benign and malignant entities, whereas knowledge of the premalignant category is evolving. The aim of this review is to provide a comprehensive overview of the entire spectrum of gastric-type cervical glandular lesions, reflecting on historical aspects but

Table 1 WHO classification of glandular tumours of the uterine cervix

Adenocarcinoma
Endocervical adenocarcinoma, usual type
Mucinous carcinoma, NOS
Gastric-type ^a
Intestinal type ^a
Signet-ring cell type
Villoglandular carcinoma
Endometrioid carcinoma
Clear cell carcinoma ^a
Serous carcinoma
Mesonephric carcinoma ^a
Adenocarcinoma admixed with neuroendocrine carcinoma

^a Established or postulated to be non-HPV related.

also highlighting recent developments. Although uncommon, these lesions are likely to increase in prevalence as a consequence of national HPV vaccination programs and precursor lesions will not be detected by primary HPV-based screening programs.

GENERAL COMMENTS REGARDING CERVICAL GASTRIC-TYPE LESIONS

The concept of gastric-type cervical glandular lesions has emerged over the past one to two decades and is largely attributable to work by Japanese authors.^{12–21} Table 2 lists the entities currently considered to comprise this group. All lesions share a somewhat distinctive morphology, characterised by glandular epithelium resembling gastric foveolar and pyloric epithelium or that lining the pancreaticobiliary tree. Classically, the epithelial cells are columnar with basally located nuclei and abundant apical eosinophilic cytoplasm. This characteristic 'pale pink' cytoplasm differs to that of normal endocervical glands, which is usually basophilic (Fig. 1). Some examples show more obvious cytoplasmic mucin, resulting in very pale staining or cleared cytoplasm. Like gastric and pancreaticobiliary epithelium, cervical gastric-type lesions contain neutral cytoplasmic mucin when stained with Alcian blue/periodic acid-Schiff (PAS).³⁰ This results in predominantly red staining with Alcian blue/PAS compared with purple-violet staining seen in normal endocervical glands due to their admixture of neutral and acid mucins, although, in our experience, mucin staining patterns may overlap and therefore be unreliable in practice. Immunohistochemical markers MUC6 and HIK1083, both of which detect pyloric gland mucin, may be used as an aid to confirm gastric-type differentiation,^{12,13,31} although these are not essential for diagnosis, which can usually be achieved based

on morphology, supplemented by a panel of more readily available markers (discussed below). Importantly, p16 is negative or exhibits mosaic-type (non-block) staining, HPV is not detected by molecular methods and a subset of GAS exhibit mutation-type p53 staining. This contrasts with usual type cervical adenocarcinoma, which is characterised by mucin-poor cells demonstrating diffuse block-type p16 immunoreactivity and almost invariably exhibits wild-type staining with p53.³² It is also worth noting that all lesions within the 'gastric' spectrum may contain variable numbers of goblet cells. In view of this, labelling these lesions 'gastrointestinal' may be more accurate; however, the 'gastric-type' terminology has become entrenched and is in widespread use, as reflected by the 2014 WHO classification.²⁹ Also noteworthy is the occasional presence of neuroendocrine cells, which we have observed in benign, pre-malignant and malignant gastric-type lesions.

BENIGN ENDOCERVICAL GLANDULAR LESIONS EXHIBITING GASTRIC DIFFERENTIATION

Lobular endocervical glandular hyperplasia (LEGH) (complex gastric/pyloric metaplasia)

LEGH was first described by Nucci *et al.* in 1999¹¹ as a pseudoneoplastic cervical lesion for which the principal consideration in the differential diagnosis was MDA. Almost simultaneously, Mikami *et al.* described three cases of florid endocervical glandular hyperplasia with intestinal and pyloric metaplasia.¹² Examination of the photomicrographs in these two publications demonstrates that both are describing the same lesion.²² Mikami *et al.* noted that the glandular epithelium resembled gastric pyloric glands and demonstrated predominantly PAS positive neutral cytoplasmic mucin and a gastric pyloric immunophenotype with positive staining with HIK1083.¹² His group expanded upon these initial observations, reporting a series of nine cases of LEGH and labelling this a metaplastic process with a pyloric gland phenotype.¹⁴

LEGH is an uncommon lesion, with the incidence among Japanese women estimated to be 0.7% in a series of 1169 consecutive hysterectomy specimens in a single institution,¹⁴ although as only limited sampling of the cervix is performed in hysterectomy specimens, the true incidence may be higher. An association with Peutz–Jeghers syndrome (PJS) has been reported.³³ Clinically, LEGH is detected in women with a mean age in the range of 45–48 years^{11,12} and is usually found incidentally in a hysterectomy or cervical loop excision specimen. Sometimes patients present with symptoms which

Table 2 Endocervical glandular lesions postulated to exhibit gastric differentiation

Category	Lesion
Benign	Lobular endocervical glandular hyperplasia/complex gastric (pyloric) metaplasia Simple gastric (pyloric) metaplasia ^a Tunnel cluster (type A)
Possible <i>in situ</i> /pre-malignant	Atypical lobular endocervical glandular hyperplasia/adenocarcinoma <i>in situ</i> of gastric-type ^a
Malignant	Gastric-type adenocarcinoma ^b Mucinous variant of minimal deviation adenocarcinoma (adenoma malignum) ^b

^a These lesions have been speculated to exist but there is little published literature.

^b These comprise a spectrum of cervical adenocarcinomas exhibiting gastric differentiation and the umbrella term gastric-type adenocarcinoma is preferred.

Fig. 1 This example of gAIS exhibits the pale pink cytoplasm characteristic of all gastric-type lesions. Goblet cells are also evident and there is a relatively low degree of nuclear atypia. The intervening benign endocervical glands show contrasting blue-tinged cytoplasm (arrowed).

suggest MDA, for example increased watery or mucoid vaginal discharge and/or a cervical mass.¹¹ Radiological studies may also raise concern for MDA.¹⁴ On computed tomography/magnetic resonance imaging (CT/MRI), LEGH appears as a multicystic lesion and while this may result in consideration of MDA,³⁴ the latter more commonly exhibits a predominantly solid pattern on imaging, which should enable distinction from LEGH.^{35,36}

Macroscopically, LEGH forms grossly visible cysts, usually located within the upper endocervix, close to the internal os and rarely with extension to involve the endometrium.^{22,25,35} Histology shows a distinctly lobular architecture in most cases with a proliferation of small round glands, often surrounding a central dilated duct (Fig. 2A); the lesion is generally confined to the inner half of the cervical wall, although occasional involvement of the outer half occurs.

Some examples lack the characteristic lobular architecture in places, although this is usually present at least focally. The glands are lined by columnar cells with pale eosinophilic cytoplasm and basally located uniform small nuclei.¹¹ Occasionally, intestinal metaplasia with goblet cells is observed (Fig. 2B) and in some cases neuroendocrine cells may be present; the latter may be visible histologically in the form of eosinophilic cytoplasmic granules or may only be identified immunohistochemically (see below).¹² The intervening stroma is usually unremarkable, although occasionally there is mild inflammation surrounding the glands.^{11,22} Cytologically, cervical smears from LEGH show glandular cells with 'golden-yellow' cytoplasmic mucin. This finding, once considered diagnostic of MDA, simply reflects a gastric phenotype^{13,37} but should prompt further investigation.

As with other gastric-type cervical lesions, LEGH shows immunoreactivity with HIK1083 and MUC6, although this may be focal. HIK1083 is regarded as a more specific but less sensitive marker than MUC6 and the former is not widely available.²⁵ The nuclei are usually negative for oestrogen receptor (ER) and progesterone receptor (PR)^{14,38} (Fig. 2C,D), although occasional reactivity with both may occur. This contrasts with normal endocervical glands and other benign cervical glandular lesions, which usually express hormone receptors (excluding mesonephric remnants/hyperplasia, which are negative).²⁵ Carcinoembryonic antigen (CEA) is generally negative or only focally positive apically, in contrast with the cytoplasmic immunoreactivity seen in most adenocarcinomas.^{11,25} As discussed, chromogranin or synaptophysin positive neuroendocrine cells may be seen.^{14,22}

Currently, in the absence of features warranting a designation of 'atypical LEGH' (discussed below), LEGH is considered to be a benign lesion. This is supported by the two published series detailed above, in which a total of 16 patients with LEGH showed no disease recurrence after follow-up averaging 3.4 and 4 years.^{11,12} A recent molecular study demonstrated genetic aberrations in 11 of 19 (58%) LEGHs. Eight cases had *GNAS*

Fig. 2 LEGH. (A) Lobular aggregates of glands surrounding a dilated duct, (B) LEGH with goblet cells, (C) positive MUC6, and (D) negative ER staining in LEGH.

mutations and *KRAS* and *STK11* mutations were identified in one and two cases, respectively.³⁹ These frequent genetic aberrations suggest that a proportion of non-atypical LEGH may represent a neoplastic rather than a metaplastic process.³⁹ Several reports have documented the co-existence of LEGH with GAS.^{15,18,19} These observations and the molecular data suggest LEGH may be a neoplastic entity with a capability of developing into a premalignant or malignant lesion, although mechanisms underlying this transformation or the exact risk of progression is unknown. Subsequent management following a diagnosis of LEGH on a loop excision should be based upon the patient's wishes for fertility preservation and clinical and radiological findings, for example the presence or absence of a significant cervical mass or profuse watery discharge.²²

Simple gastric (pyloric) metaplasia (SGM)

SGM denotes architecturally normal endocervical glands lined by columnar cells displaying the characteristic pale pink cytoplasm previously described and exhibiting a gastric immunophenotype. The glandular epithelium comprises a single layer of cells with basally located, uniform bland nuclei. This is an extremely uncommon, poorly defined and likely under-recognised entity, particularly given the subtle morphological features. In a study examining the mucin staining properties of normal cervical glandular epithelium, pyloric-type mucin was detected using HIK1083 in only two of 278 cases (0.7%).³¹ The significance of SGM is currently unknown, although it has been proposed to represent an early phase of LEGH.²² In a recent report of nine cases of cervical gastric-type adenocarcinoma *in situ* (gAIS) (discussed below), we found SGM to co-exist in two cases.²⁸ Furthermore, we noted that the degree of nuclear atypia in gAIS is often subtle and, at the low end of the spectrum, gAIS may be difficult to distinguish from SGM, particularly as validated criteria or biomarkers for this distinction have not yet been established. In view of the morphological overlap of SGM and gAIS, it is possible that these lesions represent a continuum and, similar to the postulated link between atypical LEGH and GAS, another pathway of carcinogenesis leading to GAS.

Type A tunnel clusters

Tunnel clusters are lobular aggregates of closely arranged, rounded endocervical glands that are either non-dilated (type A) or dilated (type B) and lined by non-atypical and mitotically inactive glandular epithelium. These are an incidental finding, seen in approximately 10% of adult cervixes, type B being much more common than type A.²⁹ Kondo *et al.* demonstrated pyloric mucin using HIK1083 in some type A tunnel clusters and suggested that these could be related to LEGH, possibly representing an early form of this.⁴⁰

POSSIBLE *IN SITU* / PREMALIGNANT ENDOCERVICAL GLANDULAR LESIONS EXHIBITING GASTRIC DIFFERENTIATION

Atypical LEGH

As discussed, LEGH is considered a benign lesion.^{11,12} However, several reports have documented the existence of cytological and architectural atypia within LEGH, without evidence of stromal invasion and designated this 'atypical

LEGH' and a form of AIS.^{15,22} In the first description of atypical LEGH, Mikami *et al.* describe a lesion with the architecture of LEGH together with a combination of the following atypical features: (1) nuclear enlargement, (2) irregular nuclear contour, (3) distinct nucleoli, (4) coarse chromatin texture, (5) loss of polarity, (6) occasional mitotic figures, (7) apoptotic bodies and/or nuclear debris in the lumen, and (8) infolding of epithelium or distinct papillary projections with fine fibrovascular stroma.¹⁵ In that study, three cases of atypical LEGH (defined as LEGH exhibiting at least four of the above features) were identified in pure form and six in close association with MDA, either directly adjacent to or intermixed with the adenocarcinoma. The authors noted that both atypical LEGH and MDA lacked block-type staining with p16 and postulated an HPV-independent pathway of tumourigenesis. Figure 3 depicts atypical LEGH.

The premalignant potential of atypical LEGH has been further supported by molecular analysis. One study using comparative genomic hybridisation revealed recurrent chromosomal imbalances in LEGH (gains of chromosome 3q and loss of 1p, both also common to MDA) in three of 14 (21%) cases analysed; these three cases displayed cytological atypia, supporting the hypothesis that a proportion of LEGH are precancerous and precursors of GAS.²⁰

Atypical LEGH is an extremely uncommon lesion; in the study cited above demonstrating an incidence of LEGH of 0.7% in 1169 consecutive hysterectomy specimens, none of these showed features of atypical LEGH.^{14,15} No management guidelines exist for atypical LEGH. However, we concur with Meservee and Nucci who suggest complete surgical excision of atypical LEGH should be undertaken,⁴¹ noting that the lesion may be incompletely removed with cervical loop excision due to its location high in the endocervix.

Adenocarcinoma *in situ* of gastric-type (gAIS)

Several case reports and a recently published small series have drawn attention to another potential precursor of GAS, which has been designated 'adenocarcinoma *in situ* of gastric-type (gAIS)'.^{15,24,27,28} This uncommon form of AIS is HPV negative, displays a gastric phenotype and immunophenotype and shares many of the atypical cytological

Fig. 3 Atypical LEGH. The epithelium exhibits luminal infolding with nuclear enlargement, coarse chromatin, prominent nucleoli and mitotic activity.

features described above for atypical LEGH. It differs from atypical LEGH architecturally in that gAIS lacks the lobular architecture with clusters of small glands surrounding a dilated duct that typifies LEGH. Instead, glands involved by gAIS tend to retain the pre-existing normal endocervical glandular architecture, although they sometimes show increased intraglandular architectural complexity in the form of small luminal papillary infoldings that may bridge the gland lumen to create cribriform structures.²⁸ gAIS is also topographically distinct from atypical LEGH in that it tends to arise at the cervical transformation zone rather than high within the endocervical canal, although as discussed in the next paragraph it may extend more proximally. Despite these differences, in view of the shared cytological and immunohistochemical features and occasional co-existence in the same case, it has been proposed that gAIS and atypical LEGH are related entities within a spectrum of premalignant gastric-type lesions. In an attempt to develop more concise terminology, it has been proposed that both lesions be encompassed under the umbrella term 'gAIS'.²⁸

The reported cases of gAIS have been in patients aged 25–74 (mean age 53), an older mean age than HPV-related AIS.^{27,28} Most reported cases have been diagnosed following the identification of atypical glandular cells in a cervical smear in asymptomatic women; smaller numbers were incidental findings in a hysterectomy specimen or cervical excision undertaken for benign indications. gAIS is usually located at or just proximal to the transformation zone and in occasional cases, extension to the lower uterine segment and even the endometrium occurs. As discussed, the normal endocervical glandular architecture is preserved, although there is often increased intraglandular architectural complexity. A sharp demarcation between normal and abnormal glandular epithelium, either within the same gland or in directly adjacent glands, as is often observed in usual AIS, may occur in gAIS. Glands are lined by columnar cells with the pale pink cytoplasm typical of gastric-type lesions; this is subtly different to the blue-tinged cytoplasm of normal endocervical glands. Occasional cases show distinctive cytoplasmic microvacuolation imparting a 'foamy' appearance and a further morphological variant is a minor or predominant component of cells with cleared cytoplasm. Another feature, present in just over half of reported cases, is the presence of variable but generally small numbers of goblet cells. In gAIS, the nuclei are generally basally located and nuclear stratification is usually limited to the lower half of the epithelium. Nuclear atypia is generally low-grade with only mild nuclear enlargement and nuclear membrane irregularity, subtle derangement of nuclear chromatin and variably prominent nucleoli. In the 'foamy gland' variant in particular, the nuclei may be deceptively bland. Mitotic figures and apoptotic bodies are usually present but may be sparse; both mitotic figures and apoptotic bodies are less frequent than in usual (HPV-associated) AIS. Figure 4 depicts gAIS.

As mentioned, goblet cells in variable numbers are often present in gAIS and it is likely that there is a spectrum, with purely gastric lesions at one end and mixed 'gastrointestinal' at the other. Recent reports have described a subset of HPV negative intestinal-type AIS, which often occurs in older women^{42,43} and it is probable that these cases represent the predominantly 'intestinal' end of the same spectrum of lesions.

Immunohistochemically, gAIS usually expresses MUC6 and HIK1083, sometimes only focally. p16 is completely

negative or focally positive with a mosaic (non-block)-type pattern and a proportion of cases demonstrate mutation-type p53 staining. ER and PR are usually negative, although occasional cases are positive. PAX8 may similarly be positive or negative.²⁸

At present, the evidence supporting the premalignant potential of gAIS is largely observational. Published reports (and our own observations) have documented gAIS in close proximity to or intermixed with malignant glands of both early and widely invasive GAS.^{24,28} In addition, in one report, a case of undiagnosed gAIS predated the development of GAS by 6 years.²⁸ Unlike atypical LEGH, no molecular studies have been performed on gAIS. It should be noted that atypical LEGH or gAIS are not always identified in association with GAS. This may reflect the often extensive nature of GAS at diagnosis, with overgrowth of the precursor lesion, or the fact that some tumours arise *de novo*. Further study is required to ascertain the true malignant potential of the spectrum of proposed precursor lesions which, as mentioned, have been collectively designated under the umbrella term gAIS. Ideally, the development of a biomarker (such as p16 in usual AIS) would assist with accurate diagnosis. Currently, optimal management of gAIS is not well established, although we would recommend excision with clear margins. Bearing in mind the occasional extension of gAIS to the lower uterine segment and endometrium, a simple hysterectomy might be considered if fertility preservation is not an issue. It is reiterated that these potential premalignant lesions are not associated with oncogenic HPV infection and are far less common than HPV-associated usual AIS.

MALIGNANT ENDOCERVICAL GLANDULAR LESIONS EXHIBITING GASTRIC DIFFERENTIATION; GASTRIC-TYPE ADENOCARCINOMA (GAS), INCLUDING MINIMAL DEVIATION ADENOCARCINOMA (MDA)

Historical concepts

The mucinous variant of MDA of the cervix (adenoma malignum) is a rare and well-known neoplasm, which classically is characterised by extremely well differentiated mucinous glands with deceptively benign looking cytology. This results in a risk of under-diagnosis, particularly in small biopsies¹⁵; however, there is also a risk of over-diagnosis since there are several benign 'proliferative' endocervical glandular lesions which may result in consideration of MDA.⁴⁴ In 1998, Japanese authors reported the expression of gastric mucin in 10 cases of MDA using various histochemical and immunohistochemical markers, including HIK1083⁴⁵ and proposed the concept of a group of cervical glandular lesions exhibiting a gastric phenotype. Around the same time, studies demonstrated an absence of oncogenic HPV in MDA, suggesting that this neoplasm arises via an HPV-independent pathway, distinct from usual cervical adenocarcinomas.^{46,47} Subsequently, the term 'mucinous adenocarcinoma of gastric-type' was proposed, incorporating MDA within a spectrum of tumours exhibiting gastric differentiation.¹⁵ In a subsequent study, Kojima *et al.* further delineated the morphology and behaviour of adenocarcinomas exhibiting gastric differentiation, providing the first description of lesions occupying the more overtly malignant

Fig. 4 gAIS. (A,B) Glands retain pre-existing architecture or display mildly increased architectural complexity. Pale eosinophilic cytoplasm with interspersed goblet cells. (C,D) Basally located nuclei, limited nuclear stratification and a lesser degree of atypia than is seen in usual (HPV-associated) AIS. (E) Clear cell change and (F) foamy gland change in gAIS.

end of this spectrum.¹⁷ They described GAS composed of cells with voluminous clear or pale eosinophilic cytoplasm and distinct cell borders. Like MDA, no association with oncogenic HPV has been demonstrated in GAS.³² In view of the shared aetiological and immunohistochemical features, and the common co-existence of components resembling both MDA and GAS within the same tumour, the umbrella term GAS has been used to encompass this entire spectrum of neoplasia.²⁵ This is endorsed by the 2014 WHO tumour classification, which includes both MDA and GAS within the category 'mucinous carcinoma, gastric-type'.²⁹ Within this group, extremely well differentiated MDAs are now considered part of the GAS spectrum. Most tumours contain a more overtly malignant and less differentiated component. As discussed later, there is no difference in the outcome between classic well differentiated MDA and GAS and the umbrella term GAS is recommended. In the following sections, we describe the clinicopathological features of MDA and GAS but stress that these form part of a spectrum. Although GAS is relatively uncommon compared to usual-type adenocarcinoma, it represents the most frequent non-HPV related tumour and may be more prevalent among Japanese than Western populations; in the

former it may represent up to 25% of all cervical adenocarcinomas.^{21,25,48} Rarely, GAS has been reported to arise within the vagina.⁴⁹

Clinicopathological features of GAS

Early reported examples of MDA occurred in patients aged 25–72 years (average age 42).⁵⁰ In a more recent series incorporating the entire spectrum of GAS, patients ranged in age from 37 to 84 years (mean age 49).¹⁷ Common presenting symptoms reported in MDA include abnormal vaginal bleeding and watery vaginal discharge.⁴⁷ Clinical examination may reveal an enlarged, indurated cervix (so-called barrel cervix), although the cervix may appear macroscopically normal.⁵⁰ Macroscopically, these tumours typically involve the transformation zone and often extend to the vagina and/or parametrium.³⁵ Imaging generally demonstrates a predominantly solid neoplasm with or without an admixed cystic component.⁵¹

Histologically, 'pure' MDA is an extremely well differentiated mucinous adenocarcinoma composed of variably sized and abnormally shaped glands, sometimes described as 'claw-shaped', which infiltrate haphazardly and often deeply within the wall of the cervix.⁵⁰ Sometimes a proportion of the glands

are dilated. A stromal reaction to the infiltrating glands is characteristically subtle and often only seen focally. In such cases, establishing a malignant diagnosis may be impossible on a small biopsy specimen and can rely predominantly on the depth of cervical stromal involvement relative to benign glands or proximity of glands to thick walled blood vessels.^{23,25} Vascular and/or perineural invasion may be seen and facilitate a malignant diagnosis.⁵⁰ The glandular epithelium comprises mucin-rich columnar cells with basal nuclei exhibiting little or no pleomorphism, mitotic or apoptotic activity. Minor foci of less well differentiated glands with greater cytological atypia may be seen,^{45,50} corresponding to composite tumours composed of both MDA and GAS⁵² and reflecting the range of differentiation acknowledged to occur in tumours now designated GAS. In addition to the voluminous clear or pale pink cytoplasm (occasionally with a foamy appearance) and well-defined cell borders described by Kojima *et al.*, GAS exhibits a greater degree of cytological atypia than prototypical MDA, with nuclear enlargement, hyperchromasia and irregularity.^{25,29} Like MDA, GAS comprises variably sized, often angulated and dilated glands, which invade within a stroma sometimes lacking a desmoplastic response, although in many cases there is prominent stromal desmoplasia. Gland fusion, cribriform patterns, luminal papillae and solid areas may all be seen in GAS.²⁹ In addition to these features, we have observed examples of GAS with prominent neuroendocrine granules or with a component of signet ring cells. A further morphological variant we have observed is tumour 'dedifferentiation' into an undifferentiated, solid carcinoma which we have seen in occasional tumour recurrences. Both signet ring and undifferentiated patterns may pose a diagnostic challenge, particularly in the setting of tumour recurrence or metastasis. Mitotic and apoptotic activity is variable but is characteristically low compared with usual HPV-associated cervical adenocarcinoma. Figure 5 depicts the spectrum of morphology seen in MDA/GAS and Fig. 6 demonstrates some variant patterns.

Immunohistochemical features of GAS

There has been only a single study which has described in detail the immunophenotype of GAS.²⁶ Immunohistochemistry for gastric mucins HIK1083 and MUC6 may contribute to the diagnosis, although they are not necessary, since these markers are poorly sensitive, with sometimes only focal or even negative staining.^{22,48,53} These stains are also not specific, with focal expression observed in small numbers of usual-type cervical adenocarcinomas.^{17,53} GAS is generally positive with CK7 and CEA. CDX2, CA19.9, PAX8, CA125 and CK20 are positive in a proportion of cases and ER and PR are usually negative.^{26,38} In a proportion of cases, p53 exhibits mutation-type staining.²⁶ In comparison to usual cervical adenocarcinomas, p16 is usually negative or exhibits non-block-type (mosaic) immunoreactivity. However, a small subset of GAS has been documented to show diffuse p16 expression despite negative molecular testing for oncogenic HPV.^{26,48} Hepatocyte nuclear factor-1 beta is generally positive which should not result in misdiagnosis as a clear cell carcinoma.²⁶ Neuroendocrine markers may highlight a component of neuroendocrine cells, particularly in cases where neuroendocrine granules are visible on routinely stained sections. Figure 7 shows immunohistochemical staining in GAS.

Molecular pathology of GAS

The pathogenesis and molecular mechanisms involved in the development of GAS are currently unknown, although it is clear that HPV infection is not implicated in its development.^{21,22,29,32,46,47} GAS may rarely occur in patients with PJS. A serine threonine kinase gene, *STK11/LKB1*, has been identified as the tumour suppressor gene responsible for PJS⁵⁴ and somatic mutations of *STK11* have been demonstrated in six of 11 sporadic cases of MDA, suggesting a role of this gene in the pathogenesis of these tumours. Of note, cases with the *STK11* mutation had a significantly poorer prognosis than those without.⁵⁴ As previously stated, gains of chromosome 3q and loss of 1p have been detected in both MDA and atypical LEGH²⁰ and activating *GNAS* mutations, *KRAS* and *STK11* mutations in LEGH.³⁹ A number of other chromosomal aberrations have been described in MDA.²² Finally, in light of the observed mutation-type staining with p53 in a proportion of GAS, *TP53* mutation may play a role in tumorigenesis.^{26,29} It is possible that this mutation is acquired during the progression from *in situ* to invasive neoplasia, as most cases of gAIS in the recently published series exhibited wild-type staining.²⁸

Behaviour of GAS

In the original description of GAS, Kojima *et al.* found a significantly worse 5 year disease-specific survival compared to non-gastric-type adenocarcinomas (30% versus 77%).¹⁷ Similarly, Karamurzin *et al.* found the disease-specific survival at 5 years was 42% for GAS versus 91% for HPV-related adenocarcinomas.²³ The latter study showed that irrespective of the degree of differentiation and nuclear atypia, all lesions within the GAS spectrum exhibit aggressive behaviour, often with advanced stage at presentation compared with HPV-associated adenocarcinomas and a propensity for spread to unusual sites such as the peritoneum, omentum, adnexa, liver, brain and bone.^{22,23,50} This is distinct from usual type cervical adenocarcinomas, which usually remain localised to the pelvis until late in the disease course.²³ Analysis restricted to FIGO stage 1 tumours also indicates that GAS has worse disease-specific survival compared with adenocarcinoma of usual type.²³ This concurs with older studies where MDA was found to have a poor prognosis. Given the marked propensity of GAS for adnexal, omental and peritoneal dissemination, it may be that omentectomy should be considered in the surgical management of these neoplasms. Additionally, ovarian conserving surgery may be contraindicated.

Morphological overlap between GAS and HPV-related usual adenocarcinomas

Recently, Wada *et al.* have described a series of 13 cervical adenocarcinomas with components that morphologically resemble both usual-type adenocarcinoma and GAS within the same tumour.⁴⁸ Ten of 13 cases were negative for high-risk HPV by *in situ* hybridisation and exhibited positive HIK1083 staining and mutation-type p53 expression in both components. The remaining three cases displayed the opposite profile by molecular and immunohistochemical testing, being HPV positive, HIK1083 negative and exhibiting wild-type p53 immunoreactivity. The authors concluded that most of these cases represent GAS with a component morphologically resembling usual-type adenocarcinoma, with a smaller subset representing usual-type adenocarcinoma with areas of gastric-

Fig. 5 (A–E) Prototypical MDA. Haphazard, abnormally shaped glands invade widely within the cervix and lie in close proximity to thick-walled blood vessels (D, arrowed). (E) Mucin-rich, cytologically bland epithelium. (F,G) GAS with pale voluminous cytoplasm, well-defined cell borders and greater degree of nuclear atypia. (H) GAS displaying a mix of well-differentiated MDA-like glands (arrowed) alongside a more poorly differentiated component.

like morphology. Thus, usual-type cervical adenocarcinomas and GAS may exhibit morphological overlap but it is doubtful that genuine mixed tumours exist.

CLINICAL SYNDROMES ASSOCIATED WITH CERVICAL GASTRIC-TYPE LESIONS

Peutz–Jeghers syndrome (PJS)

PJS is an autosomal dominant disorder, best known for its association with mucocutaneous pigmentation and

hamartomatous gastrointestinal polyps.⁵⁵ PJS is also associated with a variety of neoplasms of the female genital tract including cervical GAS, ovarian mucinous neoplasms, ovarian sex cord tumour with annular tubules (SCTAT) and occasionally other ovarian sex cord-stromal tumours.^{22,50,52} An association with LEGH has also been documented.^{33,56} As discussed, *STK11* has been identified as the tumour suppressor gene responsible for PJS and somatic mutations of the same gene have been demonstrated in sporadic cases of GAS.⁵⁴ Recently, an ovarian mucinous tumour resembling

Fig. 6 GAS variant patterns. (A) Prominent neuroendocrine granules in GAS, with (B) chromogranin expression. (C) Signet ring cell pattern in GAS and (D) dedifferentiated GAS.

LEGH and with a pyloric gland immunophenotype has been described in a patient with PJS and the authors suggested that *STK11* mutation may play a role in the development of pyloric-type mucinous lesions at various anatomical locations.⁵⁷ One of us (WGM) has seen a similar ovarian mucinous neoplasm admixed with a SCTAT in a patient with PJS. There are currently no recommended gynaecological screening or clinical surveillance guidelines for PJS patients. The incidence of GAS in PJS patients is estimated to be 15–30%, with a mean age at diagnosis of 33 years⁵⁸ and it has been suggested that patients with PJS should undergo gynaecological surveillance including annual cervical cytology and transvaginal ultrasonography.⁵⁹ Among GAS, approximately 10% are associated with PJS⁵⁸ and it has been suggested that a diagnosis of GAS should prompt a comment in the pathology report noting the association with PJS.⁴¹

Synchronous mucinous metaplasia and neoplasia of the female genital tract

Gastric-type cervical glandular lesions may be associated with synchronous mucinous lesions (both metaplastic and neoplastic) in other parts of the female genital tract, including the endometrium, ovary and fallopian tube.²² Several published case reports and small series have documented the coexistence of a range of mucinous lesions, including mucinous metaplasia and neoplasia of the endometrium, fallopian tube and ovary and cervical LEGH or MDA/GAS. One patient also had a mucinous cystadenoma of the appendix and several patients had PJS.^{60,61} Another report documents a patient with PJS exhibiting multifocal mucinous lesions in the female genital tract and mucinous metaplasia of the urinary bladder. All these lesions and the patient's multiple hamartomatous polyps in the jejunum showed a pyloric phenotype,³³ supporting the proposed association of *STK11* mutation with multifocal mucinous proliferations of pyloric

type.⁵⁷ Although multiple mucinous lesions in the female genital tract are postulated to represent synchronous independent proliferations, in some cases it may be difficult to distinguish between synchronous and metastatic lesions. For example in a patient with a morphologically well differentiated cervical GAS and a bland ovarian mucinous neoplasm, it may be difficult or impossible to determine whether the ovarian lesion is a primary neoplasm or a bland metastasis.

Lynch syndrome

A single case of cervical GAS occurring in a patient with Lynch syndrome has been reported⁶² and one of us (WGM) has seen an additional case. This suggests that GAS may be an uncommon Lynch syndrome-associated tumour, although this should be confirmed by the documentation of additional cases. There is a well-known association between Lynch syndrome and a lower uterine segment location of endometrial carcinomas and it is possible that some of these represent cervical GAS with upwards extension to involve the lower uterine segment.

FUTURE EPIDEMIOLOGICAL AND SCREENING IMPLICATIONS

With the introduction of HPV vaccination, the incidence of HPV-associated cervical carcinoma is projected to decrease. In 2011, Brotherton *et al.* reported the first observed decline in biopsy proven high-grade cervical intraepithelial neoplasia/adenocarcinoma *in situ* in Victoria, Australia, following the implementation of a national vaccination program.⁶³ As the prevalence of HPV-related cervical neoplasia diminishes, the relative prevalence of GAS and other uncommon HPV negative adenocarcinomas will rise. The move to HPV-based cervical screening, where reflex cytology is only performed on cases which are positive for oncogenic

Fig. 7 GAS exhibiting positive staining with (A) MUC 6, (B) CEA, (C) CDX2 and (D) PAX8. (E) Diffuse mutation-type p53 and (F) negative p16 staining.

HPV, will effectively eliminate detection of HPV negative cervical adenocarcinomas via organised screening programs.⁹ Eight of 11 reported cases of cervical gAIS occurred in asymptomatic patients who came to clinical attention following abnormal cervical smears,²⁸ and although these numbers are small, such data are concerning as we transition to primary HPV-based screening.

In the context of primary HPV-based cervical screening, it may be worth considering alternative strategies for detecting gastric-type cervical lesions. In Japan there exists a commercially available latex agglutination test, which uses HIK1083 to screen for gastric mucin in cervical discharge. Omori *et al.* have shown this test to have excellent sensitivity and specificity for detection of cervical gastric-type lesions.⁶⁴ In 44 women with increased watery vaginal discharge, glandular cells with yellow mucin on cervical smear and/or a cystic appearance of the cervix on radiological imaging, all 26 women with a positive latex agglutination result had a gastric-type cervical glandular lesion, including LEGH, atypical LEGH and MDA/GAS on subsequent histology. None of the 18 patients with these symptoms or signs and a negative test result had a gastric-type lesion and all 31 asymptomatic control patients tested negative.⁶⁴ Tests such as this could be evaluated in an effort to improve detection of gastric-type lesions. This study also highlighted the

importance of increased watery vaginal discharge, yellowish cytoplasmic mucin in endocervical glandular cells on cervical cytology and a cystic appearance of the cervix on imaging as predictors of gastric-type lesions. Efforts should be made to increase practitioner awareness of these diagnostic clues.

PRACTICE POINTS FOR THE NON-SPECIALIST PATHOLOGIST

Pathologists need to be aware of gastric-type cervical lesions, especially the possible premalignant and malignant lesions, and be cognisant of various pitfalls in their diagnosis. gAIS may be an extremely subtle lesion, characteristically exhibiting less cytological atypia, mitotic and apoptotic activity than usual-type AIS. Without a high index of suspicion, the lesion may be overlooked or considered insufficient to justify a diagnosis of AIS; this may be reinforced by non-block-type p16 staining. Diagnostic clues include increased intra-glandular architectural complexity, pale pink rather than blue-tinged cytoplasm and scattered goblet cells. As discussed, there is considerable overlap between the lower end of the gAIS spectrum and SGM, particularly as validated criteria or biomarkers for this distinction have not yet been established.

Extremely well differentiated examples of GAS, previously designated MDA, are similarly subtle lesions which may be

difficult to distinguish from benign mimics such as LEGH or other benign glandular lesions, particularly in a small superficial biopsy. Appreciation of the low power architecture is critical and obviously best observed in a resection specimen. Compared with the orderly lobular arrangement of glands in LEGH, which are usually confined to the inner half of the cervical wall, GAS/MDA displays a haphazard arrangement of glands of varying sizes and shapes which widely infiltrate the cervical stroma, usually with at least a focal desmoplastic response.^{11,22} Vascular and/or perineural invasion and extension beyond the cervix, if present, assist in establishing a malignant diagnosis.⁵⁰ The various gastric-type lesions, benign and malignant, are usually negative with hormone receptors, although there are occasional exceptions; most of the other benign cervical glandular lesions, with the exception of mesonephric remnants/hyperplasia, are positive.

Additional criteria helpful in distinguishing LEGH from GAS/MDA include the location of the lesion in the cervix and the immunophenotype, although there is overlap between the benign and malignant lesions with regard to these parameters. As discussed, LEGH is often situated in the upper endocervix in the region of the internal os whereas GAS/MDA typically involves the transformation zone.³⁵ Immunohistochemically, GAS/MDA sometimes shows mutation-type p53 staining compared with wild-type immunoreactivity in LEGH.²² It has been reported that GAS/MDA can be distinguished from LEGH based upon the presence of smooth muscle actin positive stromal cells and absent or reduced numbers of ER positive stromal cells surrounding the infiltrating glands of GAS/MDA.³⁸ This reflects a desmoplastic stromal reaction with myofibroblasts replacing ER positive stromal cells. However, we find this of limited value and it is worth noting that gland rupture in LEGH may elicit a granulation tissue-like stromal reaction mimicking desmoplasia.²²

The more overtly malignant end of the GAS spectrum should not pose difficulties in terms of distinction from benign glandular proliferations, but awareness of the morphological features and immunohistochemical profile is required in order to avoid misdiagnosis as usual-type adenocarcinoma. In particular, a lack of block-type p16 staining and the presence of mutation-type p53 staining should prompt consideration of the possibility of GAS. The cleared cytoplasm of GAS may suggest a clear cell carcinoma (CCC). However, unlike CCC, GAS generally lacks a well-developed tubulocystic or papillary architecture, hobnail cells and stromal hyalinisation. As already discussed, hepatocyte nuclear factor-1 beta is generally positive in GAS which should not result in misdiagnosis as a CCC.²⁶ The latter is also characteristically positive with Napsin A but this marker has not been evaluated in GAS. The morphological resemblance of cervical GAS to tumours of pancreaticobiliary origin may generate diagnostic difficulty, particularly in the setting of tumour metastasis or recurrence and we make the point that although termed GAS on the basis of the presence of gastric-type mucins, the morphology often more closely resembles a pancreaticobiliary adenocarcinoma. Rare signet ring and undifferentiated patterns observed in GAS may pose a similar diagnostic challenge. In this setting, there is significant immunophenotypic overlap between GAS and pancreaticobiliary adenocarcinomas with respect to commonly used markers such as CK7, CK20, CEA, CA125, CA19.9 and CDX2. In this distinction, PAX8 may be a useful discriminatory marker. PAX8 was found to be positive in 32 of 47 (68%) cervical GAS and is negative in the vast majority of

gastrointestinal and pancreaticobiliary adenocarcinomas.^{26,65} Clinicoradiological correlation should also assist with this distinction.

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References

1. Adegoke O, Kulasingam S, Virnig B. Cervical cancer trends in the United States: a 35-year population-based analysis. *J Womens Health* 2012; 21: 1031–7.
2. Wang SS, Sherman ME, Hildesheim A, et al. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. *Cancer* 2004; 100: 1035–44.
3. Smith HO, Tiffany MF, Qualls CR, et al. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States – a 24-year population-based study. *Gynecol Oncol* 2000; 78: 97–105.
4. Mathew A, George PS. Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix – worldwide. *Asian Pac J Cancer Prev* 2009; 10: 645–50.
5. Shiliang L, Semenciw R, Mao Y. Cervical cancer: the increasing incidence of adenocarcinoma and adenosquamous carcinoma in younger women. *CMAJ* 2001; 164: 1151–2.
6. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108.
7. Australian Institute of Health and Welfare (AIHW). *Cervical screening in Australia 2012–2013. National Cervical Screening Program. Cancer Series No. 93, Cat No CAN 91*. Canberra: AIHW, 2015.
8. Pimenta JM, Galindo C, Jenkins D, et al. Estimate of the global burden of cervical adenocarcinoma and potential impact of prophylactic human papillomavirus vaccination. *BMC Cancer* 2013; 13: 553.
9. Pirog EC, Lloveras B, Molijn A, et al. HPV prevalence and genotypes in different histological subtypes of cervical adenocarcinoma, a worldwide analysis of 760 cases. *Mod Pathol* 2014; 27: 1559–67.
10. Holl K, Nowakowski AM, Powell N, et al. Human papillomavirus prevalence and type-distribution in cervical glandular neoplasias: results from a European multinational epidemiological study. *Int J Cancer* 2015; 137: 2858–68.
11. Nucci MR, Clement PB, Young RH. Lobular endocervical glandular hyperplasia, not otherwise specified: a clinicopathologic analysis of thirteen cases of a distinctive pseudoneoplastic lesion and comparison with fourteen cases of adenoma malignum. *Am J Surg Pathol* 1999; 23: 886–91.
12. Mikami Y, Hata S, Fujiwara K, et al. Florid endocervical glandular hyperplasia with intestinal and pyloric gland metaplasia: worrisome benign mimic of “adenoma malignum”. *Gynecol Oncol* 1999; 74: 504–11.
13. Ishii K, Katsuyama T, Ota H, et al. Cytologic and cytochemical features of adenoma malignum of the uterine cervix. *Cancer* 1999; 87: 245–53.
14. Mikami Y, Hata S, Melamed J, et al. Lobular endocervical glandular hyperplasia is a metaplastic process with a pyloric gland phenotype. *Histopathology* 2001; 39: 364–72.
15. Mikami Y, Kiyokawa T, Hata S, et al. Gastrointestinal immunophenotype in adenocarcinomas of the uterine cervix and related glandular lesions: a possible link between lobular endocervical glandular hyperplasia/pyloric gland metaplasia and ‘adenoma malignum’. *Mod Pathol* 2004; 17: 962–72.
16. Xu JY, Hashi A, Kondo T, et al. Absence of human papillomavirus infection in minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia. *Int J Gynecol Pathol* 2005; 24: 296–302.
17. Kojima A, Mikami Y, Sudo T, et al. Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am J Surg Pathol* 2007; 31: 664–72.
18. Nara M, Hashi A, Murata S, et al. Lobular endocervical glandular hyperplasia as a presumed precursor of cervical adenocarcinoma independent of human papillomavirus infection. *Gynecol Oncol* 2007; 106: 289–98.
19. Ohta Y, Suzuki T, Hamatani S, et al. Lobular endocervical glandular hyperplasia might become a precursor of adenocarcinoma with pyloric gland features. *Pathol Res Pract* 2008; 204: 683–7.

20. Kawauchi S, Kusuda T, Lui XP, *et al.* Is lobular endocervical glandular hyperplasia a cancerous precursor of minimal deviation adenocarcinoma?: a comparative molecular-genetic and immunohistochemical study. *Am J Surg Pathol* 2008; 32: 1807–15.
21. Kusanagi Y, Kojima A, Mikami Y, *et al.* Absence of high-risk human papillomavirus (HPV) detection in endocervical adenocarcinoma with gastric morphology and phenotype. *Am J Pathol* 2010; 177: 2169–75.
22. Mikami Y, McCluggage WG. Endocervical glandular lesions exhibiting gastric differentiation: an emerging spectrum of benign, premalignant and malignant lesions. *Adv Anat Pathol* 2013; 20: 227–37.
23. Karamurzin YS, Kiyokawa T, Parkash V, *et al.* Gastric-type endocervical adenocarcinoma. An aggressive tumour with unusual metastatic patterns and poor prognosis. *Am J Surg Pathol* 2015; 39: 1449–57.
24. Stewart CJR, Frost F, Leake R, *et al.* Foamy gland changes in gastric-type endocervical neoplasia. *Pathology* 2015; 47: 653–8.
25. McCluggage WG. Recent developments in non-HPV-related adenocarcinomas of the lower female genital tract and their precursors. *Adv Anat Pathol* 2016; 23: 58–69.
26. Carleton C, Hoang L, Sah S, *et al.* A detailed immunohistochemical analysis of a large series of cervical and vaginal gastric-type adenocarcinomas. *Am J Surg Pathol* 2016; 40: 636–44.
27. Yuan CT, Lin MC, Kuo KT, *et al.* Gastric-type adenocarcinoma in situ of uterine cervix: cytological and histopathological features of two cases. *Virchows Arch* 2016; 469: 351–6.
28. Talia KL, Stewart CJ, Howitt BE, *et al.* HPV-negative gastric type adenocarcinoma in situ of the cervix: a spectrum of rare lesions exhibiting gastric and intestinal differentiation. *Am J Surg Pathol* 2017; 41: 1023–33.
29. Kurman RJ, Carcangiu ML, Herrington CS, *et al.*, editors. *WHO Classification of Tumours of Female Reproductive Organs*. Lyon: International Agency for Research on Cancer, 2014.
30. Hayashi I, Tsuda H, Shimoda T. Reappraisal of orthodox histochemistry for the diagnosis of minimal deviation adenocarcinoma of the cervix. *Am J Surg Pathol* 2000; 24: 559–62.
31. Zhao S, Hayasaka T, Osakabe M. Mucin expression in non neoplastic and neoplastic glandular epithelia of the uterine cervix. *Int J Gynecol Pathol* 2003; 22: 393–7.
32. Park KJ, Kiyokawa T, Soslow RA, *et al.* Unusual endocervical adenocarcinomas: an immunohistochemical analysis with molecular detection of human papillomavirus. *Am J Surg Pathol* 2011; 35: 633–46.
33. Kato N, Sugawara M, Maeda K, *et al.* Pyloric gland metaplasia/differentiation in multiple organ systems in a patient with Peutz-Jegher's syndrome. *Pathol Int* 2011; 61: 369–72.
34. Yoden E, Mikami Y, Fujiwara K, *et al.* Florid endocervical glandular hyperplasia with pyloric gland metaplasia: a radiologic pitfall. *J Comput Assist Tomogr* 2001; 25: 94–7.
35. Sasajima Y, Mikami Y, Kaku T. Gross features of lobular endocervical glandular hyperplasia in comparison with minimal-deviation adenocarcinoma and stage 1b endocervical-type mucinous adenocarcinoma of the uterine cervix. *Histopathology* 2008; 53: 487–90.
36. Takatsu A, Shiozawa T, Miyamoto T, *et al.* Preoperative differential diagnosis of minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia of the uterine cervix: a multicenter study of clinicopathology and magnetic resonance imaging findings. *Int J Gynecol Cancer* 2011; 21: 1287–96.
37. Hata S, Mikami Y, Manabe T. Diagnostic significance of endocervical glandular cells with “golden-yellow” mucin on pap smear. *Diagn Cytopathol* 2002; 27: 80–4.
38. Mikami Y, Kiyokawa T, Moriya T, *et al.* Immunophenotypic alteration of the stromal component in minimal deviation adenocarcinoma (‘adenoma malignum’) and endocervical glandular hyperplasia: a study using oestrogen receptor and alpha-smooth muscle actin double immunostaining. *Histopathology* 2005; 46: 130–6.
39. Matsubara A, Sekine S, Ogawa R, *et al.* Lobular endocervical glandular hyperplasia is a neoplastic entity with frequent activating GNAS mutations. *Am J Surg Pathol* 2014; 38: 370–6.
40. Kondo T, Hashi A, Murata S-I, *et al.* Type A tunnel clusters of gastric phenotype. *Histopathology* 2007; 50: 843–50.
41. Meserve EE, Nucci MR. Peutz-Jeghers syndrome: pathobiology, pathologic manifestations, and suggestions for recommending genetic testing in pathology reports. *Surg Pathol Clin* 2016; 9: 243–68.
42. Howitt BE, Herfs M, Brister K, *et al.* Intestinal-type endocervical adenocarcinoma in situ. An immunophenotypically distinct subset of AIS affecting older women. *Am J Surg Pathol* 2013; 37: 625–33.
43. Talia KL, Cretney A, McCluggage WG. A case of HPV-negative intestinal-type endocervical adenocarcinoma in situ with coexisting multifocal intestinal and gastric metaplasia. *Am J Surg Pathol* 2014; 38: 289–91.
44. McCluggage WG. New developments in endocervical glandular lesions. *Histopathology* 2013; 62: 138–60.
45. Ishii K, Hosaka N, Toki T, *et al.* A new view of the so-called adenoma malignum of the uterine cervix. *Virchows Arch* 1998; 432: 315–22.
46. Ferguson AW, Svoboda-Newman SM, Frank TS. Analysis of human papillomavirus infection and molecular alterations in adenocarcinoma of the cervix. *Mod Pathol* 1998; 11: 11–8.
47. Toki T, Zhai YL, Park JS, *et al.* Infrequent occurrence of high-risk human papillomavirus and of p53 mutation in minimal deviation adenocarcinoma of the cervix. *Int J Gynecol Pathol* 1999; 18: 215–9.
48. Wada T, Ohishi Y, Tsunehisa K, *et al.* Endocervical adenocarcinoma with morphologic features of both usual and gastric types. Clinicopathologic and immunohistochemical analyses and high-risk HPV detection by in situ hybridisation. *Am J Surg Pathol* 2017; 41: 696–705.
49. Talia KL, Scurry J, Manolitsas T, *et al.* Primary vaginal mucinous adenocarcinoma of gastric type arising in adenosis: a report of 2 cases, 1 associated with uterus didelphys. *Int J Gynecol Pathol* 2012; 31: 184–91.
50. Gilks CB, Young RH, Aguirre P, *et al.* Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. *Am J Surg Pathol* 1989; 13: 717–29.
51. Park SM, Lee JH, Lee YH, *et al.* Adenoma malignum of the uterine cervix: imaging features with clinicopathologic correlation. *Acta Radiol* 2013; 54: 113–20.
52. McCluggage WG, Harley I, Houghton JP, *et al.* Composite cervical adenocarcinoma composed of adenoma malignum and gastric type adenocarcinoma (dedifferentiated adenoma malignum) in a patient with Peutz-Jeghers syndrome. *J Clin Pathol* 2010; 63: 935–41.
53. Ichimura T, Koizumi T, Tateiwa H, *et al.* Immunohistochemical expression of gastric mucin and p53 in minimal deviation adenocarcinoma of the uterine cervix. *Int J Gynecol Pathol* 2001; 20: 220–6.
54. Kuragaki C, Enomoto T, Ueno Y, *et al.* Mutations in the STK11 gene characterise minimal deviation adenocarcinoma of the cervix. *Lab Invest* 2003; 83: 35–45.
55. Schoolmeester JK, Erikson LA. Cervical minimal deviation adenocarcinoma in Peutz-Jeghers syndrome. *Mayo Clin Proc* 2017; 92: e7–8.
56. Hirasawa A, Akahane T, Tsuruta T, *et al.* Lobular endocervical glandular hyperplasia and peritoneal pigmentation associated with Peutz-Jeghers syndrome due to a germline mutation of STK11. *Ann Oncol* 2012; 23: 2990–3.
57. Kim EN, Kim GH, Kim J, *et al.* A pyloric gland phenotype ovarian mucinous tumour resembling lobular endocervical glandular hyperplasia in a patient with Peutz-Jeghers syndrome. *J Pathol Transl Med* 2017; 51: 159–64.
58. Banno K, Kisu I, Yanokura M, *et al.* Hereditary gynecological tumours associated with Peutz-Jeghers syndrome (Review). *Oncol Lett* 2013; 6: 1184–8.
59. Giardiello FM, Trimpath JD. Peutz-Jeghers syndrome and management recommendations. *Clin Gastroenterol Hepatol* 2006; 4: 408–15.
60. Seidman JD. Mucinous lesions of the fallopian tube. A report of seven cases. *Am J Surg Pathol* 1994; 18: 1205–12.
61. Mikami Y, Kiyokawa T, Sasajima Y, *et al.* Reappraisal of synchronous and multifocal mucinous lesions of the female genital tract: a close association with gastric metaplasia. *Histopathology* 2009; 54: 184–91.
62. Moat M, O'Donnell RL, McCluggage WG, *et al.* Gastric-type adenocarcinoma of the cervix in a patient with Lynch syndrome: a case report. *Gynecol Oncol Rep* 2014; 10: 41–3.
63. Brotherton JML, Fridman M, May CL, *et al.* Early effect of the HPV vaccination program on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet* 2011; 377: 2085–92.
64. Omori M, Hashi A, Ishii Y, *et al.* Clinical impact of preoperative screening for gastric mucin secretion in cervical discharge by HIK1083-labelled latex agglutination test. *Am J Clin Pathol* 2008; 130: 585–94.
65. Laury AR, Perets R, Piao H, *et al.* A comprehensive analysis of PAX8 expression in human epithelial tumours. *Am J Surg Pathol* 2011; 35: 816–26.