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Differential expression of MUC2 and MUC5AC in benign and malignant glandular lesions of the cervix uteri

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Abstract The expression of mucin genes in the normal glandular epithelium of the endocervix has been well characterized. However, mucin gene expression in neoplastic or particular non-neoplastic glandular cervical lesions has not been addressed. This immunohistochemical study was carried out to analyze the expression of MUC2 and MUC5AC in neoplastic and non-neoplastic glandular lesions of the cervix. Monoclonal antibodies were used on paraffin-embedded sections from 41 adenocarcinomas, 2 adenosquamous carcinomas, 13 adenocarcinomas in situ (ACIS), 3 glandular dysplasias, 8 endometrioses, 5 tubal metaplasias, 17 squamous metaplasias, 3 microglandular hyperplasias and normal tissue of the endocervix, endometrium and fallopian tube. The patterns of expression of MUC2 and MUC5AC were different and in principle contrary. Focal MUC2 expression was observed almost exclusively in neoplastic lesions (36%) and not in normal epithelia and non-neoplastic lesions, the one notable exception being immature metaplasia. In contrast, strong expression of MUC5AC was observed in both normal endocervical epithelium (100%) and neoplastic lesions (73%). The expression of MUC5AC, however, was diminished in most neoplastic glandular lesions. Co-expression of MUC2 and MUC5AC was consistently documented in the lesions with intestinal differentiation. In contrast, cases of tubal metaplasia and endometriosis were negative for MUC2 and MUC5AC. These results indicate that discrimination of mucin gene expression may be helpful in discriminating lesions of the cervix.

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Introduction

Adenocarcinoma in situ (ACIS) of the cervix is characterized by the replacement of the endocervical glands by neoplastic epithelial cells. First described by Friedell in 1953 [7] and subsequently shown to have a propensity for late recurrence and the development of invasive adenocarcinoma [22], ACIS represents approximately 9–25% of adenocarcinomas of the cervix [5, 14], which account for 8–26% of cervical carcinomas [11, 20, 21]. Patients with ACIS have a similar epidemiologic profile to those with invasive adenocarcinoma of the endocervix [3, 4, 16]. However, ACIS generally occurs a decade or two earlier than invasive adenocarcinoma [10]. It is also important because there is an increase in the absolute and relative number of adenocarcinomas of the cervix, rising at an annual rate of approximately 2% [15, 19]. For these reasons, it is important to recognize ACIS in biopsy materials and to differentiate them from benign mimics.

ACIS is divided into four types based on its differentiation: endocervical, endometrioid, intestinal and mixed types [3, 4, 6, 14]. Endocervical and intestinal types are mucinous in nature while endometrioid differentiation should be associated with a loss of its mucinous phenotype. A lot of neoplastic proliferations originate from the Muellerian epithelium that is well known for its ability to differentiate towards endocervical, endometrial, tubal and intestinal epithelia, which is well documented in surface epithelial tumors of the ovary and endometrial carcinomas. We speculated that expression of certain mucin genes may be altered in association with various types of Muellerian differentiation.

In many instances, ACIS is discovered incidentally in surgical or cytology material. The diagnosis is often difficult as it must be distinguished from benign mimics.

Diagnostic difficulties often occur when attempting to distinguish tubal metaplasia and endometriosis involving the cervix [2, 13] from ACIS. These two relatively common simulators of ACIS continue to receive attention in the literature and are well characterized [2, 13]. However, as reported recently, both superficial cervical endometriosis and tubal metaplasia continue to cause diagnostic difficulties. We speculated that these metaplasias would lack expression of MUC2 and MUC5AC because they are composed of a non-mucinous epithelium.

There have been recent advances in mucin biology with the identification (using expression cloning) of at least 12 human mucin genes that collectively produce mucin glycoproteins [1, 8, 9, 17, 23]; in the past, pathologists have recognized these using conventional Alcian blue histochemistry. We focused on MUC2 and MUC5AC, because MUC5AC and rarely MUC2 have recently been shown to be expressed in the normal endocervix [8, 9, 17]. In addition, MUC2 is the major intestinal mucin and, therefore, we felt it may be important in the intestinal type of metaplasia, which is the most well-documented heterologous type of metaplasia/differentiation.

As mentioned, because the endocervical epithelium is mucinous while both the endometrial and tubal epithelia are not, we thought it would be worthwhile to compare MUC2 and MUC5AC profiles of neoplastic and metaplastic lesions of the endocervix. In addition, a comparison with those of endometriosis and tubal metaplasia might be diagnostically helpful. To date, we are unaware of any studies that have specifically examined the expression of MUC2 and MUC5AC in specific cervical lesions and, therefore, regardless of the results, we felt it important to evaluate these lesions for MUC2 and MUC5AC expression.

Materials and methods

Anatomical pathology studies

Anatomical studies included histopathological, histochemical and immunocytochemical methods.

Selection of cases

Using routine hematoxylin and eosin stained sections, we selected 91 cases of cervical glandular and squamous lesions. The cases consisted of neoplastic conditions that included invasive adenocarcinomas (41) which were classified using the current World Health Organization (WHO) classification scheme, ACIS (3 endocervical, 1 intestinal and 9 endometrioid), glandular dysplasias (3) and the neoplastic simulators endometriosis (8) and tubal metaplasia (4). In addition, we examined cases of microglandular hyperplasia (3) and squamous metaplasia (17). Sections of normal endocervix (65), endometrium (25) and tubal epithelium (15) were used as controls.

Routinely processed, formalin-fixed, paraffin-embedded tissue blocks were retrieved from the Division of Gynecologic Pathology at Brigham and Women's Hospital, Boston, Mass., and several referring institutions.

Histochemical studies

Alcian-blue staining (pH 2.5), which was hyaluronidase resistant, was used to better visualize the extracellular and the intracellular mucin in each case studied. In addition, this histochemical stain helped distinguish mucin from other non-mucinous proteinaceous accumulations.

Immunocytochemical studies

The identity of the mucin in each of the cases was investigated with antibodies to MUC2 and MUC5AC. Anti-MUC2 (Research Diagnostics, Inc., Flanders, N.J.), a murine monoclonal antibody (clone Ccp58) to a synthetic peptide corresponding to a site on the MUC2 human core protein that was non-reactive with MUC5AC, was used at a dilution of 1:100–1:200. Anti-MUC5AC (Research Diagnostics Inc), a murine monoclonal antibody (clone 45M1) to a peptide core corresponding to a site on the MUC5AC human core protein that was non-reactive with MUC2, was used at a dilution of 1:100–1:200. Paraffin-embedded sections were deparaffinized, rehydrated and processed for antigen retrieval using citrate pretreatment (0.1 mol/l sodium citrate buffer, pH 6.0) followed by microwave heating for 10 min. Sheep anti-mouse IgG was used as a secondary antibody (1:250 dilution). Antigen binding sites were then revealed by incubating with peroxidase polymerizing diaminobenzidine (DAB) producing insoluble brownish–black staining at sites of antigen presence. Sections of normal colonic mucosa (MUC2) and normal gastric mucosa (MUC5AC) were used as positive controls and also served as negative controls for one another.

Immunoreactivity patterns were studied by two pathologists independently who categorized both the distribution and intensity of staining of positive cells. The distribution was categorized as absent (no staining), sporadic (rare, single cells, less than 5% of cells), focal (no diffuse staining, maximum 30%), multifocal (incomplete diffuse staining, 30–80%) and diffuse (virtually 100%). Intensity was scored using a 3-point system: 1 being weak, 2 being medium and 3 being strong.

Results

Sections of normal cervical glandular epithelium were consistently positive with Alcian blue, and the histochemical reaction was present both within the glandular cells and extracellularly. These glands also revealed a diffuse and strong pattern of immunoreactivity for MUC5AC (Fig. 1a). However, no immunoreactivity was observed with MUC2. In the adjacent normal ectocervical epithelia and in the cells of mature metaplasias, no mucins were detected with the methods used in this study. Furthermore, no expression of MUC2 or MUC5AC was observed in the control sections of endometrial or tubal epithelium. All results are summarized in Table 1 and Table 2.

In immature metaplasias, rare cells distributed within the metaplastic epithelium exhibited mucins on Alcian-blue staining. These cells were immunoreactive for MUC5AC and surprisingly MUC2 as well (Fig. 1b). Cases of microglandular hyperplasia also revealed a strong Alcian-blue staining in the glandular cells, which were also immunoreactive for MUC5AC. In contrast, MUC2 expression was not observed in these lesions. Of note was the absence of mucin in the reserve cell population around the glandular structures in both of these lesions.

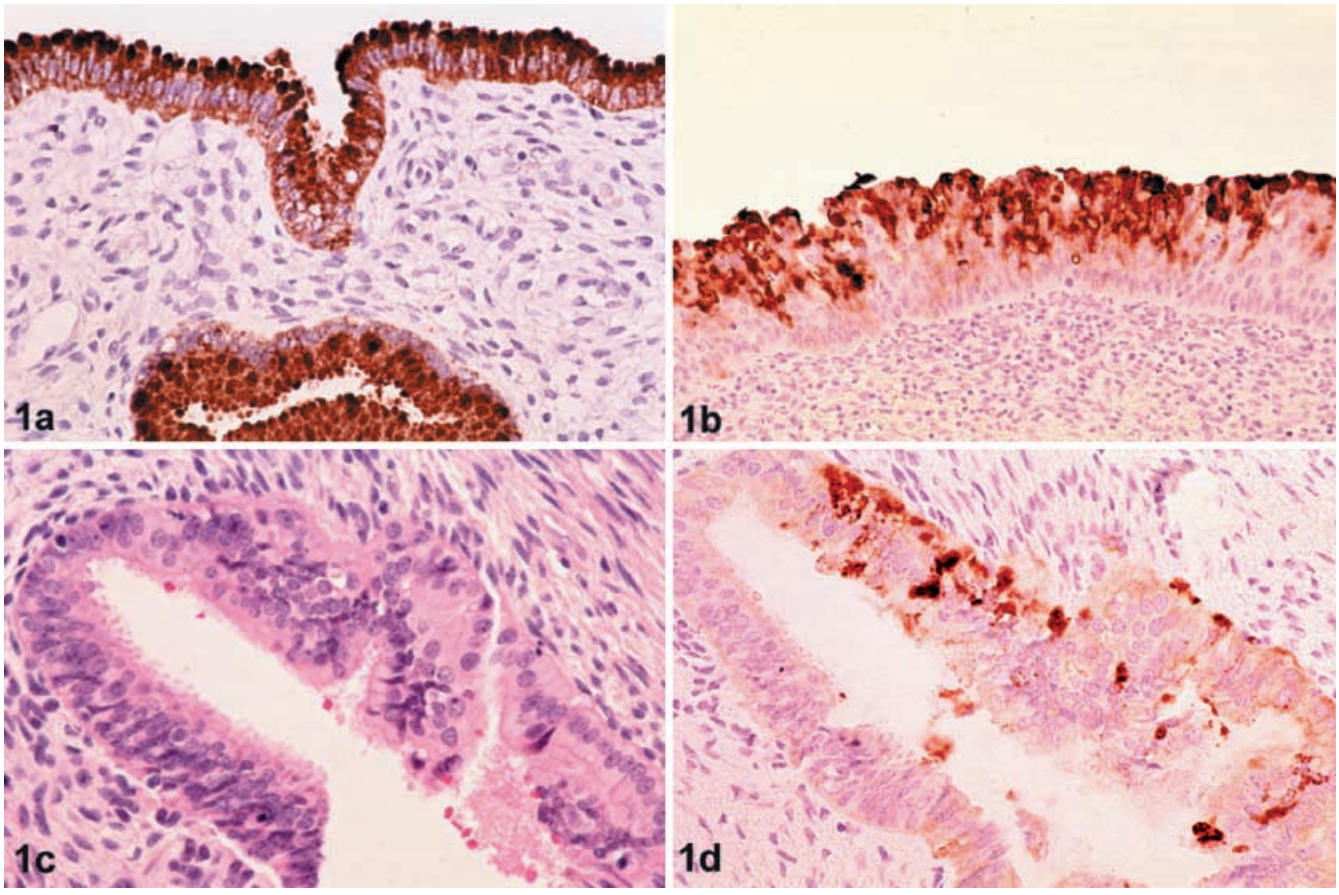


Fig. 1 **a** Strong expression of MUC5AC in normal glandular epithelium. **b** Partial expression of MUC2 in immature metaplasia. **c**, **d** Tubal metaplasia with sporadic expression of MUC5AC (**d**)

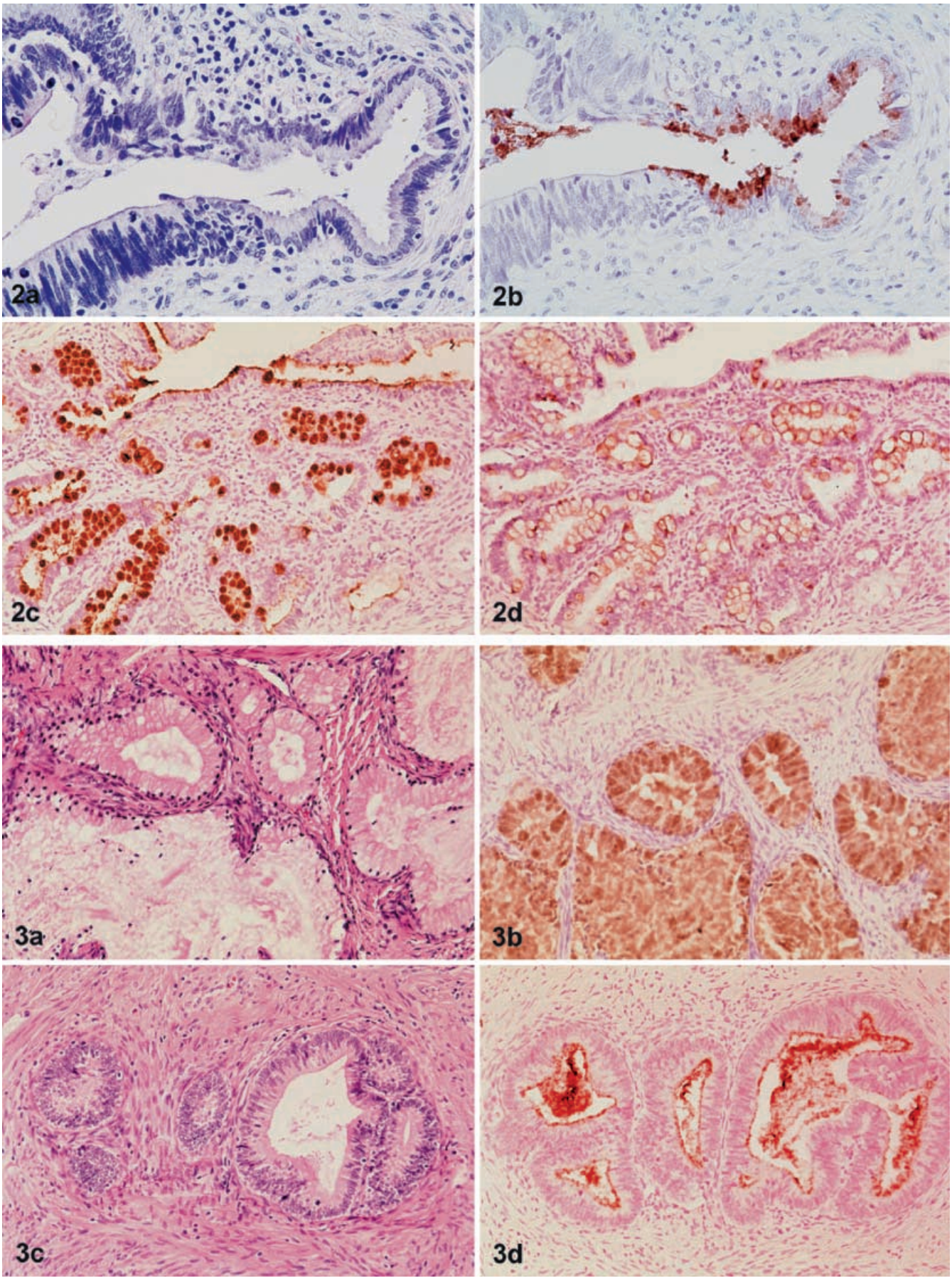
Table 1 Mucins in normal endocervical epithelium and benign lesions

	Number of cases	MUC2	MUC5AC	Alcian blue
Normal endocervical epithelium	65	0/65	65/65	65/65
Immature squamous metaplasia	5	5/5	5/5	5/5
Mature squamous metaplasia	12	0/12	0/12	0/12
Microglandular hyperplasia	3	0/3	3/3	3/3
Endometriosis	8	0/8	1/8	0/8
Tubal metaplasia	4	0/4	0/4	0/4

The glandular epithelial cells of endometriosis and tubal metaplasia showed a virtual absence of MUC2 and MUC5AC immunoreactivity. A single case of endometriosis, however, did reveal weak apical staining for MUC5AC that appeared to be limited to the glycocalyx. Furthermore, rare single cells within glands exhibiting tubal metaplasia were also positive with Alcian blue and MUC5AC (Fig. 1c–d). But these positive cells were recognizable histologically as residual normal endocervical cells on routine hematoxylin and eosin sections.

In comparison with the benign lesions in which MUC2 was observed only in rare cells within foci, immature metaplasia, sporadic or focal MUC2 expression was frequently present within ACIS and adenocarcinomas of the endocervial and endometrioid types. In addition, it was consistently observed in a multifocal pattern in the lesions with intestinal differentiation (Fig. 2d).

Expression of MUC5AC was maintained in most cases of ACIS and invasive adenocarcinomas; however, in comparison with normal endocervix there was an appreciable loss in expression of MUC5AC in ACIS (54%, Fig. 2a, b) and more frequently in cases of adenocarcinoma (61%). This loss of expression was most prominent within more poorly differentiated areas of invasive adenocarcinomas. Interestingly, a single case of glandular dysplasia exhibited a similar loss of MUC5AC expression. The immunocytochemical and histochemical distribution of MUC5AC and Alcian blue also differed between the differentiation patterns in cases of ACIS and invasive adenocarcinoma. Cases with


2a
2b
2c
2d
3a
3b
3c
3d

endometrioid differentiation revealed a moderate apical pattern of expression (two of three cases, Fig. 3c, d), whereas endocervical and intestinal types revealed a strong cytoplasmatic staining pattern (three of three cases, Fig. 2c, Fig. 3a, b).

Cases of adenosquamous carcinomas exhibited a pattern of immunoreactivity with MUC2 and MUC5AC, which was similar to the pattern observed in ACIS and invasive adenocarcinomas. The major caveat being the immunoreactivity was limited to areas of clear-cut glandular differentiation. We also observed a similar pattern of immunoreactivity in a single lymph-node metastasis from a case of adenosquamous carcinoma. Finally, the single mesonephric carcinoma studied revealed no expression of mucin either histochemically or immunohistochemically.

Discussion

The normal mucinous epithelium of the endocervix consistently expresses MUC5AC both intensely and diffusely at the protein level but rarely expresses MUC2 [1, 8, 9]. Therefore, our observation that MUC5AC expression is absent in normal tubal and endometrial epithelia presents a potentially useful immunocytochemical method for discriminating them from the neoplastic endocervical lesions of ACIS and invasive adenocarcinoma involving the cervix. Expression of MUC2, although less prominent in ACIS and invasive adenocarcinoma than MUC5AC, may also be useful in certain instances because it was not observed in endometriosis and tubal metaplasia.

In this study, our observation that MUC5AC expression is retained in many neoplastic glandular lesions of ACIS and invasive adenocarcinoma is intriguing because these lesions are believed to represent a spectrum of neoplastic transformation. Although the pattern of expression diminished with increasing nuclear atypia in ACIS and more poorly differentiated areas of invasive adenocarcinoma, the persistence of MUC5AC expression in many cases was at a level sufficient to identify these neoplasms as originating from endocervical glands. The expression of MUC5AC in adenosquamous carcinoma of the cervix is less dramatic but still a recognizable feature in the majority of even poorly differentiated tumors with a glandular component. The exception in our study was a mesonephric adenocarcinoma that is known to have a different histogenesis, i.e., Wolffian rather than Muellerian.

In contrast, expression of MUC2 in normal endocervical epithelium was not observed. Other studies have made similar observations [8, 9] and Audie et al. report its expression is an infrequent phenomenon being limited to rare cells [1]. Our observation of de novo MUC2 expression in neoplastic proliferations of the endocervical glands may have significance in its own right. This novel expression may herald genomic instability in the neoplastic cells, and therefore expression of MUC2 might accompany neoplastic transformation. The one possible exception might be cases of intestinal-type ACIS and invasive adenocarcinoma. Because of the existence of intestinal metaplasia and the possibility that these neoplasms may arise from this metaplastic epithelium, it is possible that MUC2 expression may precede neoplastic transformation in this setting. Further studies could better define the role of MUC2 expression in cases of intestinal metaplasia. It is also important to note intestinal differentiation in ACIS and adenocarcinoma appears to be an incomplete phenomenon. This is similar to the incomplete nature of intestinal differentiation in most mucinous tumors of the ovary (personal observation).

Finally, ACIS is often difficult to distinguish from both tubal metaplasia and endometriosis involving the cervix. Distinguishing morphologic features of ACIS included nuclear stratification with nuclear pleomorphism and the presence of mitotic activity. In contrast, endometriosis is characterized by the presence of endometrial glands that may exhibit significant cytologic pleomorphism that is typical of the normal cycling endometrium [2]. In addition, mitotic activity may be prominent in a reproductive woman in which the endometrial glands are hormonally responsive. In most instances, the presence of endometrial stroma in association with these glands will lead to their correct interpretation; however, in some cases, the stroma is inconspicuous or obscured by inflammation. In these cases, the diagnosis becomes more difficult and may require other means to establish the identity of the epithelium. This problem is best exemplified by the propensity of endometriosis to follow cervical conization, which is frequently associated with reparative changes of the cervical stroma and chronic inflammation. These post-conization stromal changes often make histologic recognition of endometriosis difficult. This study demonstrated that endometriosis is consistently negative using immunocytochemistry with antibodies against MUC2 and shows only rare, focal immunoreactivity for MUC5AC. This finding correlates well with the known MUC profile which has been reported by several investigators in that MUC gene expression is essentially absent in endometrial epithelia. Therefore, in these instances, immunocytochemistry using MUC2 and MUC5AC may be useful in the exclusion of a neoplastic glandular lesion.

Finally, in the single case of endometriosis that displayed weak MUC5AC immunoreactivity, the distribution was focal and limited to the apical portion of the endometrial glands. This distribution may represent an artifact of cross reactivity with the cilia and or the glycocalyx associated with this ciliated epithelium.

◀ **Fig. 2 a, b** Partial adenocarcinoma in situ (ACIS) with loss of MUC5AC expression (**b**). **c** Strong expression of MUC5AC in an intestinal differentiated ACIS. **d** Weak expression of MUC2 in an intestinal differentiated ACIS

Fig. 3 Endocervical adenocarcinoma with strong cytoplasmatic staining pattern (**a, b**) and endometroid adenocarcinoma with moderate apical staining of MUC5AC (**c, d**)

Table 2 Mucins in glandular dysplasia, adenocarcinoma in situ (ACIS) and glandular differentiated carcinomas. Numbers in parentheses indicate percentages

Distribution of positive cells	Number of cases	MUC2			MUC5AC		
		Absent	Sporadic, focal, multifocal	Diffuse	Absent	Sporadic, focal, multifocal	Diffuse
Glandular dysplasia	3	3 (100)	0	0	1 (33)	0	2 (67)
ACIS	13	7 (54)	6 (46)	0	0	7 (54)	6 (46)
Endocervical	3	2 (67)	1 (33)	0	0	3 (100)	0
Intestinal	1	0	1 (100)	0	0	1 (100)	0
endometrioid	9	5 (56)	4 (44)	0	0	3 (33)	6 (67)
Adenocarcinoma	41	27 (66)	14 (34)	0	10 (24)	6 (15)	25 (61)
Endocervical	13	10 (77)	3 (23)	0	4 (31)	0	9 (69)
Intestinal	3	0	3 (100)	0	0	0	3 (100)
Endometrioid	19	12 (63)	7 (37)	0	4 (21)	3 (16)	12 (63)
Serous	1	0	1 (100)	0	0	1 (100)	0
Mesonephric	1	1 (100)	0	0	1 (100)	0	0
Poorly differentiated	4	4 (100)	0	0	1 (25)	2 (50)	1 (25)
Adenosquamous carcinoma	2	1 (50)	1 (50)	0	0	0	2 (100)
Lymph-node metastasis	1	0	1 (100)	0	0	0	1 (100)

Tubal metaplasia, however, is characterized by the presence of three cell types: ciliated, non-ciliated and intercalated cells [13], which can be difficult to recognize within an inflammatory background, particularly following a biopsy or cervical conization. Rarely, mitotic figures may be encountered but generally the absence of mitoses will lead to the correct interpretation of this phenomenon. In contrast to endometriosis, tubal metaplasia is thought to have its origin from endocervical glands and is not thought to be an implantation process. Because it is endocervical in origin, one might expect the pattern of MUC5AC and MUC2 expression to be retained. In our study, however, it was observed that MUC5AC expression is rare, while MUC2 expression was not observed. Again this pattern may be useful as a contrast to neoplastic glandular lesions of the endocervix. In addition, the MUC5AC sporadic/focal immunoreactivity in some cases of tubal metaplasia may be misleading because these glands exhibited incomplete tubal metaplasia on routine hematoxylin and eosin staining. The residual endocervical cells and not the metaplastic cells were immunoreactive. These antibodies therefore may also be useful in distinguishing tubal metaplasia from ACIS.

The persistence of MUC5AC expression in immature squamous metaplasia reveals a similar phenomenon. The luminally positioned, residual endocervical cells expressed MUC5AC in an identical manner to normal endocervical cells. In contrast, the metaplastic squamous cells expressed variable amounts of MUC5AC characterized by reduction in expression in cell layers further from the identifiable residual endocervical cells. In addition, the expression of MUC2 in cells of immature metaplasias is a surprising phenomenon that could be explained by changes in the expression of mucins during the metaplastic process, although this needs further investigation.

Recently, a small series of ACIS cases arising in tubal metaplasia has been reported by Schlesinger and Silverberg [18]. In these instances, the immunocytochemical distinction of tubal type epithelium from endocervical would have little relevance. However, the nature of this newly described entity bears further investigation in order to characterize its biology and identify its malignant potential. It is important that cases such as these be examined with loss of heterozygosity studies to confirm a clonal nature and possibly examine them for human papilloma virus because of its presence in the overwhelming majority of cases of adenocarcinomas of the cervix [6, 12].

Table 3 Expression of MUC2 and MUC5AC in differential diagnosis of glandular cervical lesions

Diagnosis	MUC2	MUC5AC
Endometriosis	–	–
Tubal metaplasia	–	–/+
Adenocarcinoma in situ	–/+	+
Adenocarcinoma	–/+	+/–

In conclusion, immunocytochemistry with monoclonal antibodies to MUC2 and MUC5AC is useful in establishing the endocervical nature of glandular lesions involving the cervix (Table 3). In addition, there are sufficient differences in their expression within certain metaplasias of the cervix that make them potentially useful in discriminating benign entities from malignancies. Finally, MUC2 and MUC5AC also appear useful in discriminating endometriosis from endocervical glandular neoplasms. This discrimination may be particularly useful in post-conization specimens.

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