Virchows Arch (1998) 432:315–322

ORIGINAL ARTICLE

Keiko Ishii · Noriko Hosaka · Toshihiko Toki
Masanobu Momose · Eiko Hidaka · Shinichi Tsuchiya
Tsutomu Katsuyama

A new view of the so-called adenoma malignum of the uterine cervix

Received: 16 June 1997 / Accepted: 16 December 1997

Abstract Adenoma malignum of the uterine cervix (mucinous type of minimal deviation adenocarcinoma, mucinous MDA), is a unique neoplasm that is difficult to diagnose owing to the deceptively benign appearance of the tumour cells. The present study was undertaken to explore the phenotypic expression of this tumour compared with those of non-neoplastic cervical tissues and of cervical carcinomas of various types. Ten cases of mucinous MDA, 50 cases with non-neoplastic cervical tissues, 13 of cervical adenocarcinoma including the mucinous (endocervical or intestinal type) and endometrioid types, and 2 of mucoepidermoid carcinoma were examined by various histochemical staining methods, including those for gastric mucins, pepsinogen, lysozyme, chromogranin A and carcinoembryonic antigen. The results revealed that mucinous MDA characteristically exhibited gastric phenotypes. The presence of gastric metaplasia was also demonstrated in 9 cases of mucinous MDA and in 5 of the other cases examined. The 7 endocervical-type adenocarcinomas also included 4 that expressed gastric phenotypes, and 2 of the 3 intestinal-type adenocarcinomas showed the same properties focally. These results indicate the presence of a group of lesions expressing gastric phenotypes in the uterine cervix and suggest a close relationship between these lesions. Cervical adenocarcinomas expressing gastric phenotypes are probably derived from MDA.

Key words Adenoma malignum · Minimal deviation adenocarcinoma · Uterine cervix · Mucin · Histochemistry

K. Ishii · S. Tsuchiya
Division of Clinical Pathology, Nagano Cancer Detection Centre, Matsumoto 390, Japan

N. Hosaka · M. Momose · E. Hidaka · T. Katsuyama (✉)
Department of Laboratory Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390, Japan,
Tel.: (+81)-263-37-2805, Fax: +81-263-34-5316,
e-mail: tkatsuy@gipac.shinshu-u.ac.jp

T. Toki
Department of Obstetrics and Gynecology, Shinshu University School of Medicine, Matsumoto, Japan

Introduction

Adenoma malignum was first reported by Gusserow in 1870 [6]. A century later, Silverberg and Hurt [24] proposed the term "minimal deviation adenocarcinoma (MDA)" for adenoma malignum. Since then, the definition of MDA has been expanded to include any cell type, including the endometrioid type [14]. However, Gilks et al. [5] recommended restricting the designation "adenoma malignum" to tumours of the mucinous type. This tumour is characterized by minimal cellular and structural atypia; consequently, pathological diagnosis is difficult, especially in its early stage. The present study was undertaken to characterize the histochemical properties of adenoma malignum (mucinous MDA) by employing a battery of methods, including those for targeting mucosubstances.

Materials and methods

All cases examined in this study were collected from the pathology file of Shinshu University Hospital over a period of 3 years (1994–1996). Ten cases of mucinous MDA were included. They were diagnosed according to pathological criteria [17], which require that each is a "very highly differentiated adenocarcinoma" in which the majority of the epithelial cells resemble benign endocervical epithelium, even though a minor component of less well differentiated tumour may be present. Although the bulk of the tumour tissue was very highly differentiated in these 10 cases, some less well differentiated foci were found in 7 cases. The clinicopathological data for these cases are summarized in Table 1. These patients ranged in age from 16 to 57, with an average age of 42.6 years. One patient had an accompanying Peutz-Jeghers syndrome. All materials were surgically removed because of a pathological diagnosis reached by biopsy and/or cytology. An ovarian mucinous cystadenoma was found in 1 case.

The histochemical properties of these 10 cases were compared with those of endocervical samples obtained from 50 other cases. Of these 50, 31 cases were biopsy specimens (including 26 cases of chronic cervicitis with polyp and 5 of squamous dysplasia); the other 19 cases were hysterectomy materials removed because of leiomyoma or adenomyosis. These 19 included 4 cases with cervical glandular hyperplasia (tunnel cluster). In addition, 13 cases of cervical adenocarcinoma [10 of the mucinous type (3 intestinal

Table 1 Ages and pathological data for 10 cases of mucinous MDA (*MDA* minimal deviation adenocarcinoma, *TL* typical lesion, *LWDL* less well differentiated lesion, *LN* lymph node, *P* post-peritoneum)

Case no.	Age (years)	Histopathology
1	57	TL with gastric and intestinal metaplasia
2	41	TL 9/LWDL 1[a], endometrial involvement, metastasis (LN, P)
3	43	TL 8/LWDL 2 with gastric metaplasia, endometrial involvement, mucinous cystadenoma in right ovary
4	50	TL with gastric metaplasia
5	49	TL 7/LWDL 3 with gastric metaplasia, endometrial involvement
6	50	TL 8/LWDL 2 with gastric metaplasia
7	47	TL with gastric metaplasia
8	45	TL 6/LWDL 4 with gastric metaplasia, metastasis (LN)
9	28	TL 8/LWDL 2 with gastric metaplasia, endometrial involvement, metastasis (P)
10	16	TL 7/LWDL 3 with gastric metaplasia, metastasis (LN, P), mucinous cystadenoma in right ovary (Peutz-Jeghers syndrome)

[a] Relative proportion of the typical and less well differentiated lesions within the whole tumour tissue

Table 2 Significance of immunostaining and sources of antibodies (*CEA*, carcinoembryonic antigen)

Antigens	Localization	Antibodies (and their sources)
Gastric gland mucous cell mucin	Gastric gland mucous cell mucin	HIK1083 (Dr. K. Hotta, Kitasato University, Isehara, Japan)
Lysozyme	Gastric gland neck cells [8]	Anti-lysozyme (Dako, Los Angeles, Calif.)
Chromogranin A	Endocrine cells	Anti-chromogranin A (Dako)
Pepsinogen I	Chief cells & mucous neck cells	Anti-pepsinogen I (Dr. K. Miki, Tokyo University, Tokyo, Japan)
Pepsinogen II	Chief cells, mucous neck cells & pyloric gland cells	Anti-pepsinogen II (Dr. Miki)
Keratan sulphate	Endometrial epithelia [22]	Anti-keratan sulphate (Seikagakukogyo, Tokyo, Japan)
CEA		Anti-CEA (IBL, Fujioka, Japan)
Forssman	Goblet cells of the large intestine [9]	Anti-Forssman (Dr. K. Uemura, Shinshu University, Matsumoto, Japan)

and 7 endocervical type) and 3 of the endometrioid type] and 2 of mucoepidermoid carcinoma were also studied.

All materials had been fixed in 10% phosphate-buffered formalin for 24–72 h, dehydrated through graded alcohols, cleared in xylene and embedded in paraffin. Serial sections were cut at 3 μm and stained by the following methods: haematoxylin-eosin (HE) for histological observation, alcian blue pH 2.5/periodic acid–Schiff (AB/PAS) [26] to differentiate neutral from acid mucin, high iron diamine/alcian blue pH 2.5 (HID/AB) [26] to differentiate sulpho- from sialomucin, galactose oxidase/cold thionine Schiff/paradoxical concanavalin A staining (GOCTS/PCS) [11, 20] to identify gastric surface mucous cell mucin (by GOCTS) and gland mucous cell mucin (by PCS) and periodic acid/sodium borohydride/potassium hydroxide/PAS (PA/SB/PH/PAS) [2] to identify 8-*O*-acetylated *N*-acetylneuraminic acid (8-*O*-acetylated NeuAc), which is the hallmark of goblet cells of the large intestine. In addition, adjacent sections were stained immunohistochemically by the indirect immunoperoxidase method for various antigens, including gastric gland mucous cell mucin (by monoclonal antibody HIK1083 [7]), lysozyme, chromogranin A, keratan sulphate and carcinoembryonic antigen (CEA). Pepsinogens I and II [21] and Forssman antigen [31] were stained by the avidin–biotin peroxidase complex method. In the staining methods using HIK1083, anti-CEA, anti-pepsinogen I and anti-pepsinogen II antibodies, hydrated tissue sections were digested with a 0.2% trypsin solution before exposure to the antibodies [4]. Before exposure to the anti-Forssman antibody, tissue sections were first placed for 15 min in 1% NaOH in 70% ethyl alcohol and then digested for 18 h at 37°C in a solution of sialidase (from *Arthrobacter ureafaciens*; Nakarai, Kyoto, Japan) [19]. HIK1083, anti-pepsinogen I and anti-pepsinogen II antibodies and anti-Forssman antibody were kindly provided by Prof. Kyoko Hotta (Department of Chemistry and Biochemistry, Kitasato University, Isehara, Japan), Dr. Kazumasa Miki (Department of Internal Medicine, Tokyo University, Tokyo, Japan) and Dr. Keiichi Uemura (Department of Lipid-Biochemistry, Shinshu University, Matsumoto, Japan), respectively. The significance of the immunostaining and the sources of the antibodies are listed in Table 2.

Results

The results obtained by histochemistry are summarized in Table 3. The mucosal surface and mucous glands were lined by a single layer of mucin-containing tall columnar epithelial cells with basal nuclei, which tended to move to the centre of the cytoplasm in the secretory phase of the menstrual cycle. The normal cervical lining cells and the glandular epithelia showed almost the same histochemical properties: the cytoplasmic mucins of these cells were seen to be faintly basophilic with HE (Fig. 1a), exhibited intense alcinophilia with AB/PAS (Fig. 1b) and stained predominantly for sulphomucins with HID/AB (Fig. 1c) throughout the menstrual cycle. Signs of reactivity for gastric mucins,8-*O*-acetylated NeuAc, lysozyme, chromogranin A, pepsinogen I, pepsinogen II, keratan sulphate, CEA and Forssman antigen were consistently absent from normal or inflamed cervical epithelia and tunnel clusters.

The typical lesions of mucinous MDA consisted mostly of abnormally shaped tubules. These showed papillary infolding and irregular branching and were lined by mildly atypical cells with slightly angular basal nuclei. Mitoses were found only rarely. These typical lesions occurred not only in the superficial portion of the tumours in the upper region of the mucosa, but also within the invasive or metastatic lesions. They were not found lining the luminal surface of the cervical canal. A stromal reaction, such as mild oedema and inflammatory cell infiltration, was found only occasionally and, even when present, it was not pronounced.

Small foci consisting of less well differentiated lesions overtly diagnosed as adenocarcinoma were found

Table 3 Occurrence of mucin and antigens in the normal cervical mucosa, mucinous MDA, other types of cervical carcinoma and gastric metaplasia (*Gmc* gland mucous cell, *Ect* endocervical type, *Mec* mucoepidermoid carcinoma, *Itt* intestinal type, *Emt* endometrioid type, *Gt* gastric phenotype, *nGt* non-gastric phenotype, *PA/SB/PH/PAS* periodic acid/sodium borohydride/potassium hydroxide/PAS, *PCS* paradoxical concanavalin A staining, *u* sulphomucin, *i* sialomucin, *u/i* sulphomucin predominates over sialomucin, *i/u* sialomucin predominates over sulphomucin; number of + signs indicates the intensity of the reaction, +++ being the most intense)

	Cervical mucosa	Mucinous MDA		Other types of cervical carcinoma					Gastric metaplasia
	Gmc	TL	LWDL	Ect		Mec	Itt	Emt	
				Gt	nGt				
No. of cases	50	10	7	4	3	2	3	3	14
Mucosubstances[a]									
Acidity	u/i	i/u	i/u	i/u	i	i	i/u	u[c]	–
PA/SB/PH/PAS	–	–	–	–	–	–	–	++	–
PCS	–	+/–	–/+	–/+	–	–	–	–	+++
Antigens									
Gastric gland mucous cell mucin (HIK1083-reactive mucin)	–	+/–	–/+	–/+	–	–	–	–	+++
Lysozyme	–	++/–	+/–	–/+	–	–	–	+/–	+/–/–
Pepsinogen I	–	–	–	–	–	–	–	–	–
Pepsinogen II	–	+/–	–/+	–/+	–	–	–	–	+/–
Keratan sulphate	–	–	–	–	–	–	–	+[c]	–
Chromogranin A[b]	–	+/–	–	–	–	–	+	–	++/–
Forssman	–	–	–	–	–	–	++/–	–	–
CEA	–	–	–/+	–/+	+/–	–	++/–	–	–

[a] Results obtained with methods characterizing mucosubstances were evaluated according to the reactivity of the cytoplasm

[b] + or – in the line of chromogranin A indicates the presence or absence of positive endocrine cells

[c] Results were evaluated according to the reactivity of the apical surface

in 7 of 10 cases. The tumour cells showed a high N/C ratio, and nuclear atypia and mitoses were evident. These atypical tubules were consistently accompanied by a stromal reaction with oedema and inflammatory cell infiltration. They occurred in the peripheral region of the tumour and were found not only in the mucosa, but also within invasive or metastatic lesions. Then occupied 10–30% of the entire lesion in 7 cases.

In addition, examples of gastric metaplasia, so designated because of their expression of a gastric phenotype and their lack of cellular and structural atypia, were found in 9 of 10 cases. The gastric metaplasia was consistently located in the upper region of the mucosa, but not in the mucous cells lining the cervical canal. The metaplastic cells formed rather small, round tubules, and showed no mitoses and no stromal reaction. As shown in Fig. 2, these tubules were frequently gathered into lobular arrangements connected to the larger lumina, which resembled a duct. The apical cytoplasm of the cells forming the tubules remained clear with HE (Fig. 3a). The gastric metaplasia was mostly located in the vicinity of a MDA lesion, but in 1 case was found in both the cervical tissue and an endometrial polyp. In case 1, a small number of goblet cells lined the metaplastic tubules. Gastric metaplasia was also found in 2 of the 50 control cases and in 3 of the other types of carcinomas (1 of endocervical and 2 of intestinal type adenocarcinoma).

The histochemical reactivity of these lesions will be described in the order of differentiation of the lesions.

The gastric metaplasia found here was histochemically characterized by abundant neutral mucins (Fig. 3b, c) and the organoid differentiation [4] of the metaplastic cells. The metaplastic cells lining the clustered small tubules contained mostly gastric gland mucous cell mucins (Fig. 3d, e), but were not stained by GOCTS. Some of the cells also stained for pepsinogen II, indicating their

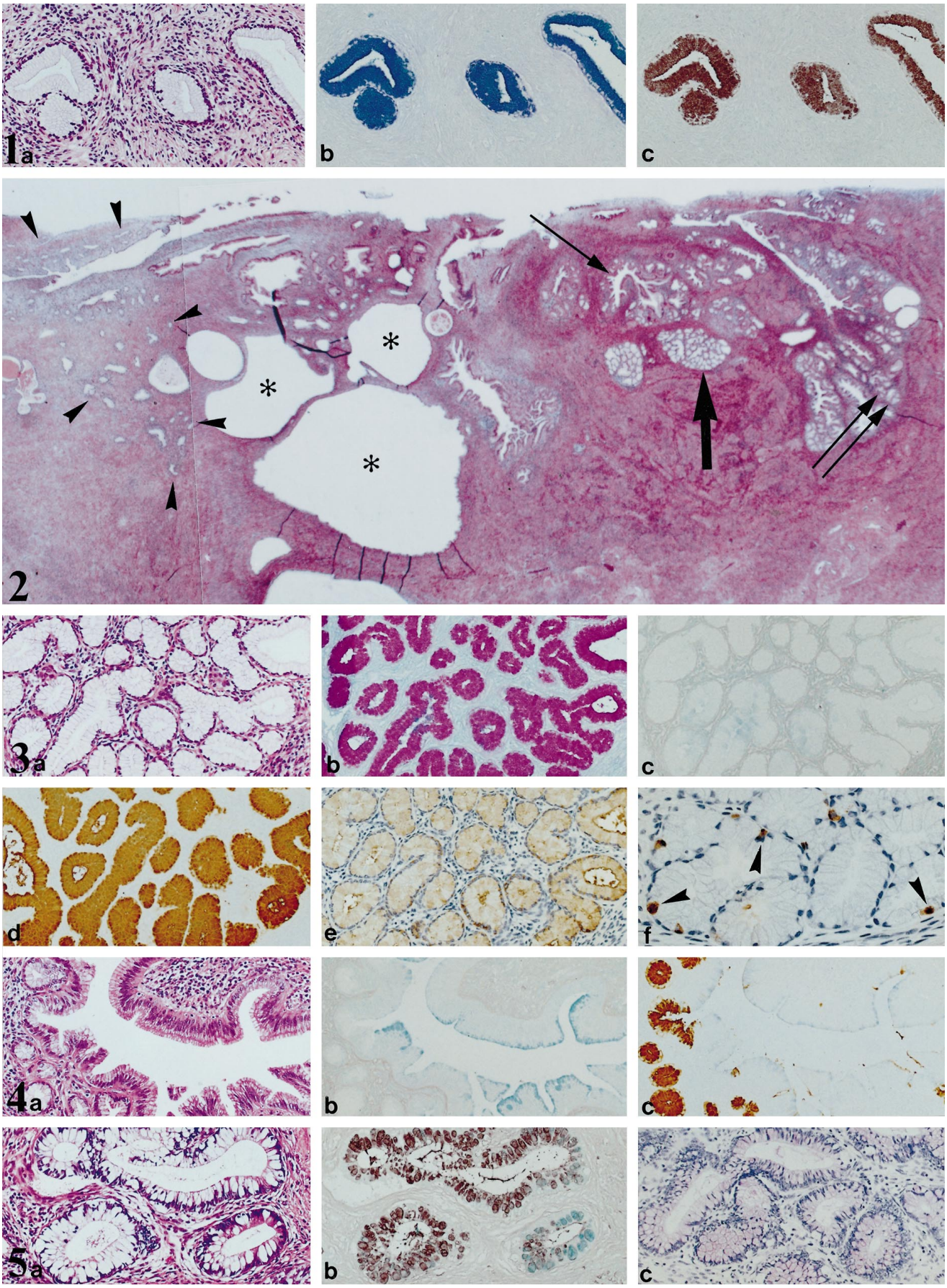
Fig. 1 **a–c** Histochemistry of normal cervical glands found in a control case. The cytoplasmic mucins stained **a** faintly basophilic with HE and **b** blue with AB/PAS; **c** they were stained for sulphomucin with HID/AB ▶

Fig. 2 Low-power view of a metaplastic lesion. Only a few normal cervical glands are present (*upper left corner*, *arrowheads*); one of these glands was shown in Fig. 1. The mucous glands of gastric metaplasia, indicated here by a *thick arrow*, are also shown in Fig. 3. A duct-like lumen (*thin arrow*) surrounded by mucous glands; its histochemical properties are shown in Fig. 4. The example of intestinal metaplasia in the *right corner* (*double arrows*) is shown in Fig. 5. Dilated glands are also found in the gastric metaplasia

Fig. 3 **a–f** Histochemistry of metaplastic mucous glands resembling gastric pyloric glands (from serial sections). Cytoplasmic mucins stained **a** faintly eosinophilic by HE and **b** red by AB/PAS: they were almost negative to HID/AB (**c**), strongly positive to PCS (**d**) and positive for HIK1083 (**e**). **f** Some cells (*arrowheads*) were positive for chromogranin A

Fig. 4 **a** A duct-like lumen in a metaplastic lesion. **b** Lining cells stained for sialomucin with HID/AB and weakly positive for GOCTS, whereas mucous glands stained intensely with PCS (**c**). This structure resembles those seen in the pyloric mucosa and is designated organoid differentiation. Prepared from serial sections

Fig. 5 **a** Goblet cells in intestinal metaplasia. The cytoplasmic mucins stained **b** for sialo- or sulphomucins by HID/AB and **c** for 8-*O*-acetylated NeuAc with PA/SB/PH/PAS. Prepared from serial sections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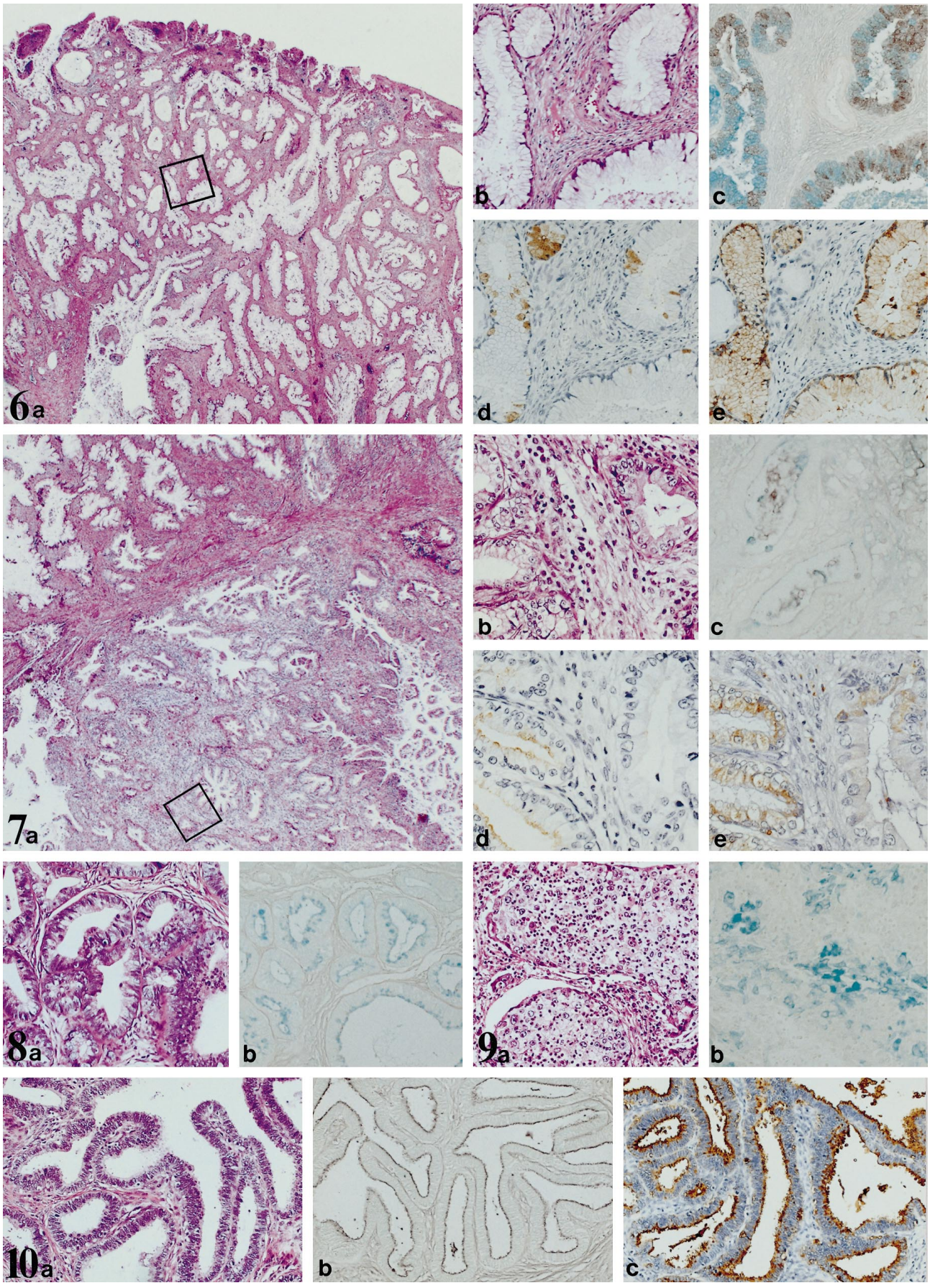
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differentiation into gastric gland mucous cells, especially those of the pyloric gland. Epithelial cells containing chromogranin A were also scattered among HIK1083-positive cells (Fig. 3f). In contrast, the metaplastic cells lining the duct-like lumina (Fig. 4a) contained sialomucins (Fig. 4b), stained with GOCTS (Fig. 4c), but lacked reactivity for the markers of gastric gland mucous cells, suggesting differentiation into surface mucous cells. Lysozyme was demonstrated most frequently at the glandular side of the junction between the glandular cells and the surface mucous cells. The goblet cells (Fig. 5a) found in 2 metaplastic lesions – 1 control case and 1 of mucinous MDA – were stained for acid mucins (Fig. 5b) and 8-*O*-acetylated NeuAc (Fig. 5c). Pepsinogen I, keratan sulphate and CEA were consistently absent from these metaplastic cells.

In the lesions classed as typical lesions of mucinous MDA (Fig. 6a), the tumour cells contained abundant mucins (Fig. 6b); these stained for sialo- or sulphomucins (Fig. 6c). PCS- and HIK1083 (Fig. 6d)-reactive mucins and lysozyme (Fig. 6e) were also demonstrated in all cases, but the proportion of positive cells varied from site to site and from case to case. The more differentiated the lesion, the stronger was the reaction for the gastric gland mucous cell mucins. The GOCTS reactivity of tumour cells was faint or absent. Pepsinogen II, but not pepsinogen I, was also positive in some cells in 8 cases. Chromogranin A-reactive cells, however, were found in all cases. CEA reactivity occurred only focally in 2 cases and was restricted to cells that lacked gastric phenotypes.

In the lesions classed as less well differentiated lesions overtly diagnosed as adenocarcinoma (Fig. 7a), the tumour cells contained a small amount of mucins (Fig. 7b, c). Cells reactive with PCS, HIK1083 (1 case), pepsinogen II (2 cases) (Fig. 7d) and lysozyme (7 cases) all occurred occasionally (Fig. 7e). Chromogranin A-containing cells were absent. In contrast, these lesions were often positive for CEA, but only focally.

The mucous cells of endocervical type adenocarcinoma (Fig. 8) and of mucoepidermoid carcinoma (Fig. 9) stained predominantly for sialomucins, but lacked reactivity for 8-*O*-acetylated NeuAc. In 4 of the 7 cases of endocervical-type adenocarcinoma we found cells expressing gastric phenotypes. In these 4 cases, carcinoma cells containing PCS and HIK1083-positive mucins, lysozyme, pepsinogen II and chromogranin A occurred in proportions that varied from site to site in a given case and from case to case. Focal gastric metaplasia was found in 1 of these 4 cases adjacent to the carcinoma tissues. In addition, the typical lesions of mucinous MDA were also found in the superficial portion of the tumours in all 4 cases, although they occurred only focally. In contrast, mucous cells of mucoepidermoid carcinomas never showed these gastric properties. CEA-positive cells were found focally in all 7 cases of endocervical-type adenocarcinoma, though the 2 mucoepidermoid carcinomas were both CEA-negative.

The three cases of intestinal-type adenocarcinoma were rich in goblet cell-type tumour cells, which characteristically showed staining for 8-*O*-acetylated NeuAc and Forssman antigen. Chromogranin A-reactive cells were also found occasionally. In 2 of these 3 cases, several carcinoma tubules contained cells showing reactions for PCS, HIK1083, anti-lysozyme antibody and anti-chromogranin A antibody. In addition, in 1 case, pepsinogen II was demonstrated in these tubules. In these 2 cases, focal gastric metaplasia was also found adjacent to the carcinoma tissues. The other case, which entirely lacked any expression of a gastric phenotype, showed more marked cellular and structural atypia and reacted strongly for CEA in most of the carcinoma tissues.

In the endometrioid adenocarcinomas, the carcinoma cells lacked cytoplasmic mucins (Fig. 10a) and a gastric phenotype, but showed staining for sulphomucins (Fig. 10b) and keratan sulphate (Fig. 10c) on the apical surface. CEA was consistently negative.

Discussion

The present study revealed that mucinous MDA characteristically express gastric phenotypes.

The expression of gastric phenotypes, especially those of the pyloric mucosa, was demonstrated by the use of a battery of histochemical stains. The substances related to the pyloric mucosa that were demonstrated in this study included neutral mucins, GOCTS-reactive mucins, gastric gland mucous cell mucins, pepsinogen II (but not pepsinogen I) and lysozyme. These markers have been used previously to identify gastric phenotypes in carcinoma tissues [1, 8, 13, 15, 19, 22].

The typical lesions of mucinous MDA showed minor structural and cellular atypia, were found not only in the superficial portion of the tumours, but also in invasive and metastatic lesions, showed properties characteristic of the pyloric mucosa, contained predominantly acid mucins, contained abundant lysozyme, and stained only occasionally for CEA. The tumour cells frequently revealed properties characteristic of gastric epithelia, although the expression was not as consistent as in the examples of gastric metaplasia and the combination of

◀ **Fig. 6 a–e** The typical lesions of mucinous MDA in case 2. **a** Papillary epithelial infolding is evident. **b–e** Higher magnification views of the region enclosed by the square. **b** The cytoplasm was abundant and **c** stained for sialo- or sulphomucins with HID/AB, **d** stained focally for HIK1083, and **e** stained consistently positive for lysozyme

Fig. 7 a–e The less well differentiated lesions of mucinous MDA in case 8. **a** Typical lesions are also found (*upper left corner*). **b–e** Higher magnification views of the region enclosed by the square. **b** Tumour cells showing definite cellular atypia and stromal reaction; **c** they contained minimal amount of mucins (HID/AB) and stained faintly for **d** pepsinogen II and **e** lysozyme

Fig. 8 a Endocervical-type adenocarcinoma, lacking expression of gastric phenotypes. **b** The cytoplasm stained for sialomucin with HID/AB

Fig. 9 a Mucoepidermoid carcinoma. **b** Signet-ring-like mucous cells stained for sialomucin with HID/AB

Fig. 10 a Endometrioid adenocarcinoma. Apical surface stained **b** for sulphomucin with HID/AB and **c** for keratan sulphate

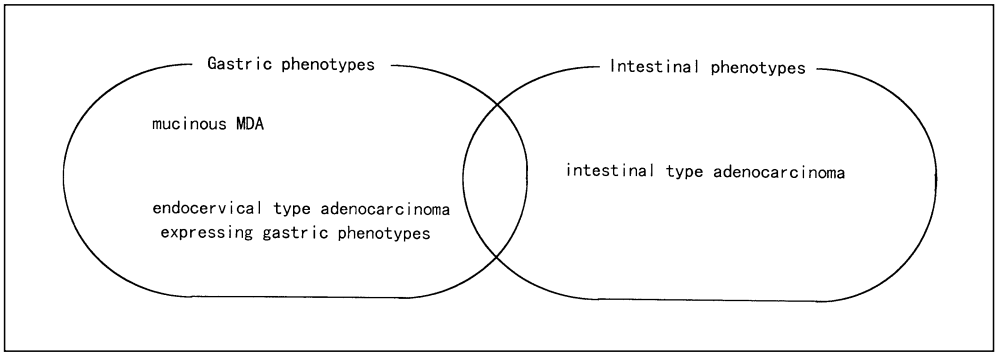

Fig. 11 Relation between two types of cervical adenocarcinoma expressing gastric or intestinal phenotypes (*MDA* minimal deviation adenocarcinoma)

markers actually demonstrated was found to vary from site to site and from case to case.

The less-well-differentiated lesions found in cases of mucinous MDA differed from the typical lesions of mucinous MDA by showing definite cellular and structural atypia, a marked stromal reaction, little mucin production, focal expression of gastric properties, reactivity for acid mucins and frequent expression of CEA.

The present study also revealed the presence of gastric metaplasia in the uterine cervix. This showed no cellular or structural atypia, no stromal reaction, predominantly neutral mucins, organoid differentiation simulating the gastric pyloric mucosa, chromogranin A-reactive endocrine cells and no CEA reactivity. Metaplastic tubules appeared mostly in the upper region of the cervical mucosa, but did not displace the superficial lining cells. It should be noted that gastric metaplasia was found not only in cases of mucinous MDA, but also in 2 of the control cases. Gastric metaplasia has been reported in other organs, such as the duodenum [12], pancreas [15, 29], gallbladder [28, 29] and small intestine [12]. It is noteworthy that the metaplastic tissues consistently expressed the properties of the pyloric mucosa and that neither chief cells nor parietal cells were present [12], a finding consistent with the lesions representing gastric metaplasia of the uterine cervix. Metaplasia usually involves transformation to a tissue type found within the same germ layer, transdermal metaplasia seldom being reported [30]. Thus, there remains the possibility that these metaplasia-like tissues are aberrant ones. Whether the markers employed here to indicate gastric phenotypes would be expressed in the developing genital tissues or cloaca remains to be explored.

In most cases of mucinous MDA, gastric metaplasia, typical lesions of mucinous MDA and less well differentiated lesions coexisted. This finding indicates the possible occurrence of dedifferentiation from gastric metaplasia to typical lesions of mucinous MDA and on to less well differentiated lesions.

In this study, metaplastic goblet cells were found in association with gastric metaplasia in 1 control case and in 1 case of mucinous MDA. The intestinal-type adenocarcinomas, however, contained numerous goblet cells and also expressed gastric properties in a focal manner. These findings suggested that both intestinal-type adenocarcinoma and mucinous MDA are extreme forms expressing either gastric or intestinal phenotypes. As demonstrated here, there can be adenocarcinomas expressing both gastric and intestinal phenotypes (Fig. 11). It is interesting that 8-*O*-acetylated NeuAc, which is a marker of goblet cells lining the large intestine, was demonstrated in almost all the metaplastic, as well as the neoplastic, goblet cells in the cervical lesions.

The presence of Grimelius-positive cells has been reported as a possible indication of precursor lesions of adenoma malignum [3, 5, 9]. The reports cited describe only neuroendocrine cells, which were identified by immunostaining for chromogranin A in this study. The present study, however, showed that these cells formed part of gastrointestinal phenotypes and were not necessarily the precursor of mucinous MDA.

All 10 cases of mucinous MDA exhibited properties of gastric mucosa, but further study is required to determine whether all cases actually express a gastric phenotype. We have revealed two groups of endocervical type adenocarcinoma: one expressing gastric phenotype and the other lacking it. The histological and histochemical features of the former group coincided with those of the less well differentiated lesions seen in cases of mucinous MDA. It seems likely that this group represents a dedifferentiated form. The second group, nevertheless is probably made up of genuine endocervical-type adenocarcinomas and is characterized by almost exclusive sialomucin production, frequent CEA reactivity, no expression of gastric mucins, lysozyme or chromogranin A, no goblet cells or 8-*O*-acetylated NeuAC, no keratan sulphate and frequent squamous metaplasia.

The signet-ring-like mucous cells seen in cases of mucoepidermoid carcinoma resembled those seen in endocervical-type adenocarcinoma lacking gastric phenotypes, but they lacked CEA. Endometrioid adenocarcinoma, in contrast, showed no CEA, positive keratan sulphate [23], no expression of gastric mucins, lysozyme or chromogranin A and neither goblet cells nor 8-*O*-acetylated NeuAC.

Previous authors have emphasized the significance of the demonstration of CEA in adenoma malignum [18, 27]. However, in the present study, CEA was almost absent in the typical lesions seen in mucinous MDA. In our view, therefore, CEA is not a useful marker for the diagnosis of mucinous MDA.

Adenoma malignum occurs in association with Peutz-Jeghers syndrome [3, 5, 16, 25], which is a hereditary disease and characteristically accompanied by hamarto-

matous polyposis of gastrointestinal tract. Ovarian mucinous tumours are also associated with adenoma malignum [10, 16, 32], and ovarian mucinous cystadenomata express gastrointestinal phenotypes [22] almost exclusively. The so-called endocervical type cells have the appearance of either gastric surface mucous cells or gastric gland mucous cells. The significance of the relationships between mucinous MDA and these two disorders remains to be clarified.

Acknowledgements We thank Drs. Kenzo Ono and Mariko Ohshiro, Department of Pathology, Tosei General Hospital, Seto, Japan and Dr. Ohi Harada, Department of Pathology, Iida Municipal Hospital, Iida, Japan, for providing the materials examined, and Mr. Ikuo Matsuyama, Ms. Taeko Yamamoto and Ms. Aki Ikeda, Nagano Cancer Detection Centre, Matsumoto, Japan, for technical assistance.

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