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ORIGINAL ARTICLE

Trefoil factor family 2 protein: a potential immunohistochemical marker for aiding diagnosis of lobular endocervical glandular hyperplasia and gastric-type adenocarcinoma of the uterine cervix

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Abstract

Gastric-type adenocarcinoma (GA) is an aggressive subtype of cancer of the uterine cervix. Several immunohistochemical markers for gastric mucins, such as mucin 6 (MUC6) and *N*-acetylglucosamine α1 → 4galactose → R (αGlcNAc-R), which is recognized by HIK1083 antibody, have been introduced for diagnosis of GA and lobular endocervical glandular hyperplasia (LEGH). However, MUC6 is also expressed in normal endocervical glands and HIK1083 antibody has limited availability. Trefoil factor family 2 protein (TFF2) is secreted by gastric, but not normal endocervical glands. Here, we evaluated TFF2 immunostaining for detection of a gastric immunophenotype in endocervical glandular lesions. We compared TFF2, αGlcNAc-R, and MUC6 expression in 103 endocervical glandular lesions: LEGH ($n = 23$), adenocarcinoma in situ/microinvasive adenocarcinoma (AIS–MIA) ($n = 29$), and invasive adenocarcinoma (usual type [UA], $n = 26$; GA, $n = 11$; intestinal type [IA], $n = 2$; signet ring cell type [Sig], $n = 2$; and mucinous adenocarcinoma not otherwise specified [NOS], $n = 10$). TFF2 and αGlcNAc-R expression was completely concordant in each subtype: LEGH (100%), AIS–MIA (44.8%), UA (26.9%), GA (90.9%), IA (100%), Sig (0%), and NOS (20%). TFF2 staining scores were significantly correlated with those of αGlcNAc-R in these lesions. TFF2 and αGlcNAc-R immunoreactivity was present in cytoplasmic mucins and luminal secretions. TFF2 and αGlcNAc-R were not expressed in the normal endocervical glands. MUC6 was frequently expressed in normal endocervical glands and endocervical glandular lesions. Endocervical adenocarcinomas sometimes stained only for MUC6. TFF2 is a promising immunohistochemical marker and its identification in uterine cervical secretion is a potentially useful diagnostic test for endocervical glandular lesions with gastric differentiation.

Keywords Cervical adenocarcinoma · Gastric type · LEGH · Gastric mucin · TFF2 · αGlcNAc

Introduction

The incidence of endocervical adenocarcinoma is increasing, currently comprising 20–25% of uterine cervical carcinomas [1]. According to the 2014 World Health Organization Classification (WHO) of Tumours of Female Reproductive Organs [2], the commonest type of endocervical adenocarcinoma is classified as usual-type adenocarcinoma (UA). It represents ~ 90% of endocervical adenocarcinomas and is associated with high-risk human papillomavirus (HPV) infection in the same way as uterine cervical squamous cell carcinoma. Several recent studies have described endocervical gastric-type adenocarcinoma (GA), an uncommon variant of non-HPV-related endocervical mucinous adenocarcinoma with the histological and immunohistochemical profile of gastric mucosa and aggressive clinical behavior [3–5]. This category includes minimal deviation adenocarcinoma, also known as adenoma malignum, which is an extremely well-differentiated variant [2]. Additionally, lobular endocervical glandular hyperplasia (LEGH), which simulates gastric pyloric mucosa, has been reported as a potential precursor of GA [6–11].

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Previous studies of GA and LEGH have been introduced several immunohistochemical markers for detecting the gastric phenotype: carbonic anhydrase (CA)-IX [12, 13], cytokeratin (CK)7 [14], mucin (MUC)6 [8], *N*-acetylglucosamine α1 → 4galactose → R (αGlcNAc-R), which is recognized by the monoclonal antibody HIK1083 [6, 15–18], trefoil factor family 2 (TFF2) [17], and claudin 18 [19, 20]. The only normal human tissues in which CA-IX is abundantly expressed are stomach and gallbladder epithelia [21]. However, CA-IX is frequently expressed in LEGH and GA and less often in a wide range of endocervical adenocarcinoma other than GA [12, 13]. It is the most widely expressed gene in response to hypoxia, this expression being almost exclusively associated with tumors but not the corresponding normal tissues [22]. CK7 is frequently expressed in gastric carcinomas [23]; however, it is also expressed in normal endocervical columnar cells [24]. In the stomach, both MUC6 and αGlcNAc-R are expressed in gastric gland mucous cells [25, 26], αGlcNAc-R being a sugar residue that binds to MUC6 [15, 27]. Importantly, normal endocervical mucous cells express MUC6 [17, 28], but not αGlcNAc-R [17]. The HIK1083 antibody, which recognizes αGlcNAc-R, is reliable for identification of the immunophenotype of gastric gland mucous cells [25, 26]; however, its availability is limited.

TFF peptides are mucin-associated peptides secreted by mucous cells and participate in mucosal barrier function and repair of damaged mucosa [29]. TFF2 is co-secreted with MUC6 by gastric gland mucous cells. TFF2 binds to MUC6 via lectin interactions with αGlcNAc-R and contributes to complex multimeric assembly, crosslinking, and packaging of MUC6 [30, 31]. TFF2 is not secreted by normal endocervical mucous cells but is expressed aberrantly, as is αGlcNAc-R, in LEGH [17].

The purpose of this study was to evaluate the utility of TFF2 immunostaining for detecting a gastric immunophenotype in endocervical glandular lesions including endocervical adenocarcinoma and LEGH and to compare it with that of αGlcNAc-R immunostaining.

Material and methods

Tissue samples

The study cohort comprised 111 consecutive patients who had undergone hysterectomy or conization and been histologically diagnosed as having LEGH or endocervical adenocarcinoma at Shinshu University Hospital from 1996 to 2016. Hematoxylin and eosin (H&E)-stained sections from all patients were reviewed by two pathologists (S.A. and H.O.) and the histological subtypes determined according to the 2014 WHO classification of tumors of the uterine cervix [2]. Two patients with endometrioid adenocarcinoma and one with clear cell adenocarcinoma of the uterine cervix were excluded, as were five patients for whom no specimens suitable for immunohistochemical analysis were available. There were no patients with serous or mesonephric adenocarcinoma of the uterine cervix. The remaining 103 patients (age range, 27–77 years; median age, 44 years; East Asian ethnicity) comprising 23 with LEGH, 29 with adenocarcinoma in situ and microinvasive adenocarcinoma (AIS–MIA) corresponding to FIGO 2014 stage IA [32], and 51 with invasive adenocarcinoma (IAC) were enrolled. The 51 IAC patients were further subdivided into 26 UAs, 11 GAs, two intestinal-type (IA), two signet ring cell-type (Sig) adenocarcinomas, and 10 mucinous adenocarcinoma, not otherwise specified (NOS). Normal endocervical glands were also evaluated in 84 of the 103 samples.

Immunohistochemical analysis

All specimens were fixed in 10% neutral buffered formalin and embedded in paraffin. Serial paraffin sections of 3-μm thickness were prepared from representative blocks from each case. These sections were stained with H&E for histological examination and subjected to immunohistochemical staining to evaluate expression of TFF2 (1:10, clone GE16C; Novus Biologicals, Littleton, CO, USA), αGlcNAc-R (1:10, clone HIK1083; Kanto Chemical, Tokyo, Japan), and MUC6 (1:100, clone CHL5, Leica Biosystems Newcastle, Newcastle Upon Tyne, UK). The paraffin sections were deparaffinized, rehydrated, and placed in a 0.3% hydrogen peroxide solution in methanol for 30 min at room temperature to block endogenous peroxide. Antigen retrieval using a microwave was performed at 650 W for 25 min with Tris–EDTA buffer (pH 8.6). Primary incubation was manually performed overnight at 4 °C. Immunohistochemical staining was performed using an immuno-enzyme polymer method with 3,3′-diaminobenzidine as the chromogen: Novolink Polymer (Leica Biosystems, Wetzlar, Germany) for TFF2 and Histofine Simple Stain MAX PO Multi (Nichirei Biosciences, Tokyo, Japan) for αGlcNAc-R. The sections were counterstained with hematoxylin, dehydrated, and mounted. A section of the gastric pyloric mucosa was used as a positive control. Immunoreactivity was assigned a score based on the approximate proportions of positive staining in the lesions as follows: 0 (< 5%), 1 (5–24%), 2 (25–49%), 3 (50–74%), and 4 (≥ 75%). A lesion was considered positive when at least 5% of the tumor cells displayed immunohistochemical staining, irrespective of the intensity.

Statistical analysis

Statistical analysis was performed using Spearman's rank method for examining correlations between TFF2 and αGlcNAc-R staining scores and Wilcoxon rank sum test for the significance of differences between TFF2 and αGlcNAc-

R staining scores. The Mann–Whitney *U* test was used to assess the statistical significance of differences of TFF2, αGlcNAc-R, and MUC6 staining scores in LEGH, AIS, UA, GA, and NOS. A p value < 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using Statcel version 4 software (OMS Publishing, Tokorozawa, Japan).

Results

None of the normal endocervical glands from the 84 specimens for which they were available were positive for TFF2 or αGlcNAc-R; however, the endocervical glands from 70 of 84 specimens (83.3%) were positive for MUC6 (Table 1). TFF2, αGlcNAc-R, and MUC6 were generally detected in LEGH, GA, and IA; however, some specimens of AIS–MIA (31.0%), UA (46.2%), GA (9.1%), and NOS (60%) stained only for MUC6 (Table 1). Both specimens of Sig were positive only for MUC6 (Table 1).

The frequency of TFF2 and αGlcNAc-R expression in each type of endocervical glandular lesion was completely concordant: LEGH (100%), AIS–MIA (44.8%), UA (26.9%), GA (90.9%), IA (100%), Sig (0%), and NOS (20%) (Table 1). Spearman's rank method showed an excellent correlation between TFF2 and αGlcNAc-R immunostaining scores: $r = 0.923$ for LEGH ($p < 0.0001$), $r = 1.000$ for AIS–MIA ($p < 0.0001$), and $r = 0.995$ for IAC ($p < 0.0001$). The Wilcoxon rank sum test revealed no significant difference between TFF2 and αGlcNAc-R staining scores.

The Mann–Whitney *U* test revealed that expression of TFF2 and αGlcNAc-R was significantly stronger in LEGH than AIS–MIA ($p < 0.0001$), GA ($p < 0.05$), UA ($p < 0.0001$), and NOS ($p < 0.0001$). Additionally, TFF2 and αGlcNAc-R expression in GA was significantly higher than in AIS–MIA ($p < 0.005$), UA ($p < 0.001$), and NOS ($p < 0.01$) (Fig. 1). Expression of MUC6 was similar to that of TFF2 and αGlcNAc-R in LEGH, AIS–MIA, GA, and UA (Fig. 1).

Both TFF2 and αGlcNAc-R were detected in the cytoplasmic mucin and luminal secretions of endocervical glandular lesions, and their localization was similar; additionally, MUC6 was detected in the cytoplasm (Figs. 2 and 3). In LEGH, TFF2, αGlcNAc-R, and MUC6 expression was mainly observed in the mucous cells lining the clustered small tubules adjacent to the central dilated glands (Fig. 2). TFF2, αGlcNAc-R, and MUC6 expression was often diffuse; the mean staining scores were 3.6 (range 1–4) for TFF2, 3.3 (range 1–4) for αGlcNAc-R, and 3.7 (range 1–4) for MUC6 (Fig. 1). In AIS–MIA, TFF2, αGlcNAc-R, and MUC6 expression was often focal (Fig. 2); the mean staining scores were 0.7 (range 0–4) for both TFF2 and αGlcNAc-R and 1.2 (range 0–4) for MUC6 (Fig. 1). In IAC, GAs often showed diffuse expression of TFF2, αGlcNAc-R, and MUC6 (Fig. 3) and had the highest mean staining scores for TFF2 (mean score 2.3; range 0–4), αGlcNAc-R (mean score 2.2; range 0–4), and MUC6 (mean score 2.4; range 1–4) (Fig. 1). In UA, the tumor cells usually had less cytoplasmic mucin and expression of TFF2, αGlcNAc-R, and MUC6 was usually focal (Fig. 3). The mean staining scores in UA were 0.4 (range 0–2) for TFF2, 0.3 (range 0–2) for αGlcNAc-R, and 0.7 (range 0–1) for MUC6 (Fig. 1). In IA, expression of TFF2, αGlcNAc-R, and MUC6 was also focal (Fig. 1), mainly being observed in columnar or cuboidal cells with abundant cytoplasmic mucin, but not in goblet cells (Fig. 3). In NOS, the histology was usually poorly differentiated adenocarcinoma, TFF2- and αGlcNAc-R-positive cells were sporadically observed, and MUC6-positive cells were often focally observed (Fig. 1).

Table 1 Frequency of TFF2, αGlcNAc-R, and MUC6 expression in LEGH, AIS–MIA, IAC, and normal endocervical glands

Diagnosis (number of cases)	Immunohistochemistry				
	TFF2/αGlcNAc-R	MUC6	TFF2/αGlcNAc-R and MUC6	TFF2/αGlcNAc-R only	MUC6 only
LEGH ($n = 23$)	23 (100%)	23 (100%)	23 (100%)	0 (0%)	0 (0%)
AIS–MIA (n = 29)	13 (44.8%)	18 (62.1%)	9 (31.0%)	4 (13.8%)	9 (31.0%)
IAC ($n = 51$)	21 (41.2%)	41 (80.4%)	20 (39.2%)	1 (2.0%)	21 (41.2%)
UA (n = 26)	7 (26.9%)	18 (69.2%)	6 (23.1%)	1 (3.8%)	12 (46.2%)
GA (n = 11)	10 (90.9%)	11 (100%)	10 (90.9%)	0 (0%)	1 (9.1%)
IA (n = 2)	2 (100%)	2 (100%)	2 (100%)	0 (0%)	0 (0%)
Sig (n = 2)	0 (0%)	2 (100%)	0 (0%)	0 (0%)	2 (100%)
NOS (n = 10)	2 (20.0%)	8 (80.0%)	2 (20%)	0 (0%)	6 (60%)
Normal endocervical glands ($n = 84$)	0 (0%)	70 (83.3%)	0 (0%)	0 (0%)	70 (83.3%)

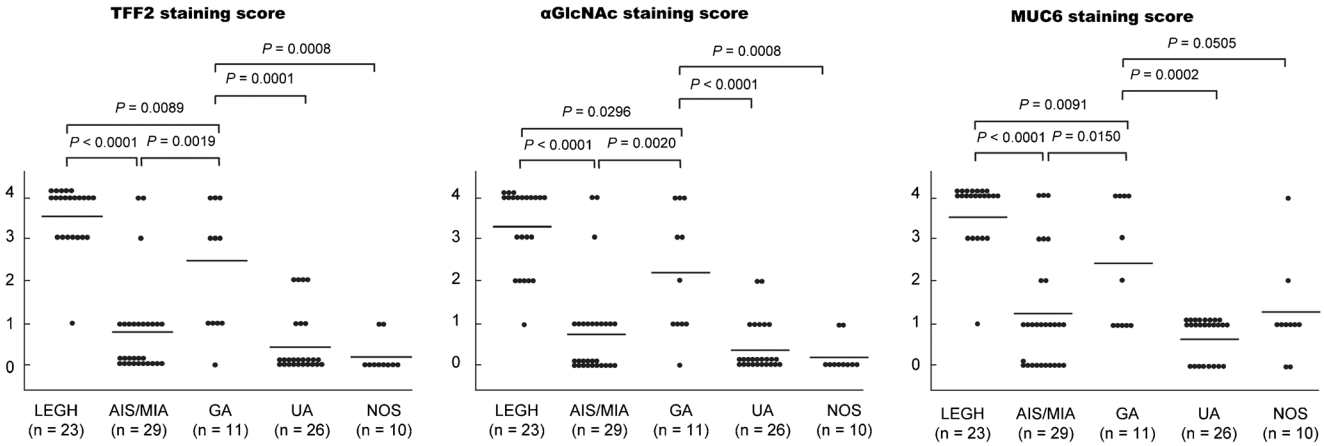

Fig. 1 Staining scores for TFF2, αGlcNAc-R, and MUC6 in LEGH and endocervical adenocarcinoma. The Mann–Whitney *U* test revealed that expression of TFF2 and αGlcNAc-R was significantly stronger in LEGH than in AIS–MIA, GA, UA, and NOS. Additionally, TFF2 and αGlcNAc-R expression in GA was significantly stronger than in AIS–MIA, UA, and NOS. Expression of MUC6 was similar to that of TFF2 and αGlcNAc-R in LEGH, AIS–MIA, GA, and UA. Bars represent the mean values of the staining scores.

Discussion

We compared the immunohistochemical expression of TFF2, αGlcNAc-R, and MUC6 in normal mucosa, LEGH, and adenocarcinoma of the uterine cervix and found TFF2 and αGlcNAc-R immunoreactivity in the cytoplasmic mucin and luminal secretion in LEGH and adenocarcinoma tissues, but not in normal endocervical mucosa, whereas we found MUC6

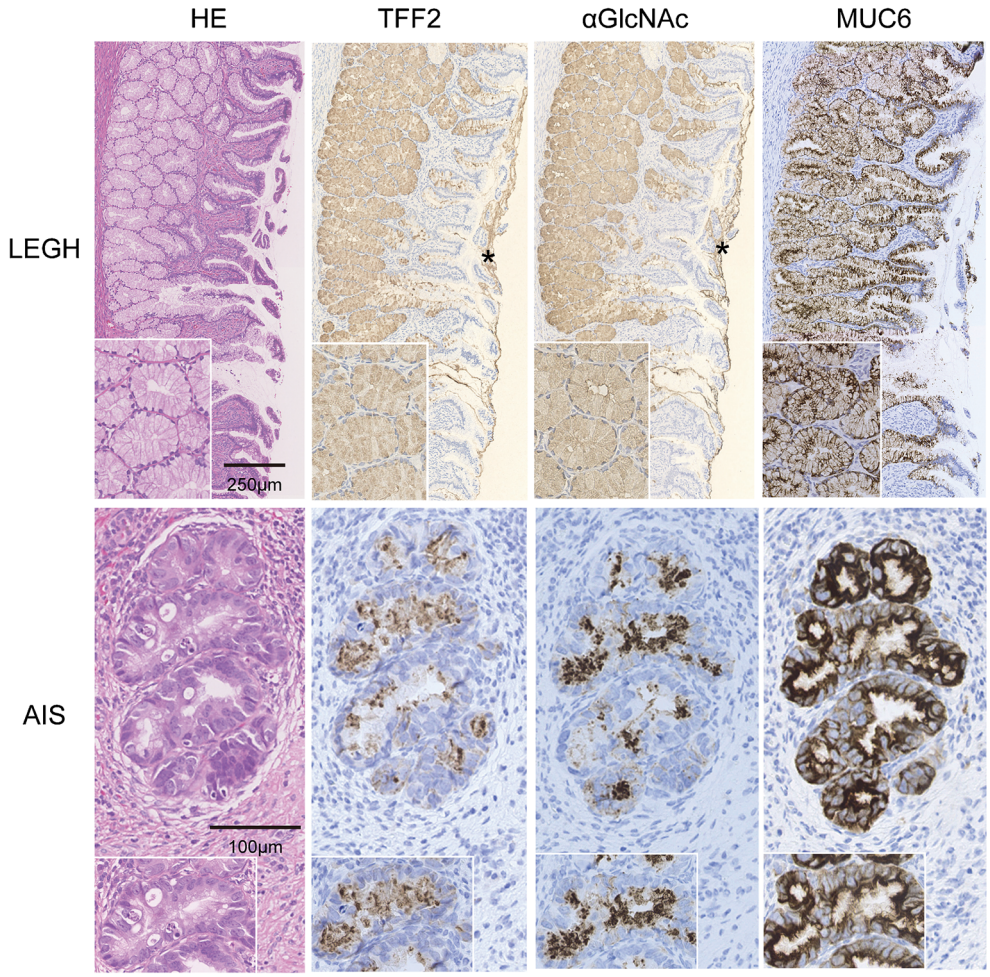

Fig. 2 TFF2, αGlcNAc-R, and MUC6 expression in LEGH and AIS. LEGH showing cluster of mucous glands with a papillary configuration on the surface. TFF2 and αGlcNAc-R were detected in the cytoplasmic mucin of mucous glands and luminal secretions (asterisk) and MUC6 was detected in the cytoplasm. AIS showing nuclear enlargement and irregularity and conspicuous nucleoli with a variable amount of apical mucin. TFF2 and αGlcNAc-R were detected in the cytoplasmic mucin and luminal secretions, their localization being similar. MUC6 was detected in the cytoplasm. Scale bar in inset = 250 μm in LEGH and 100 μm in AIS

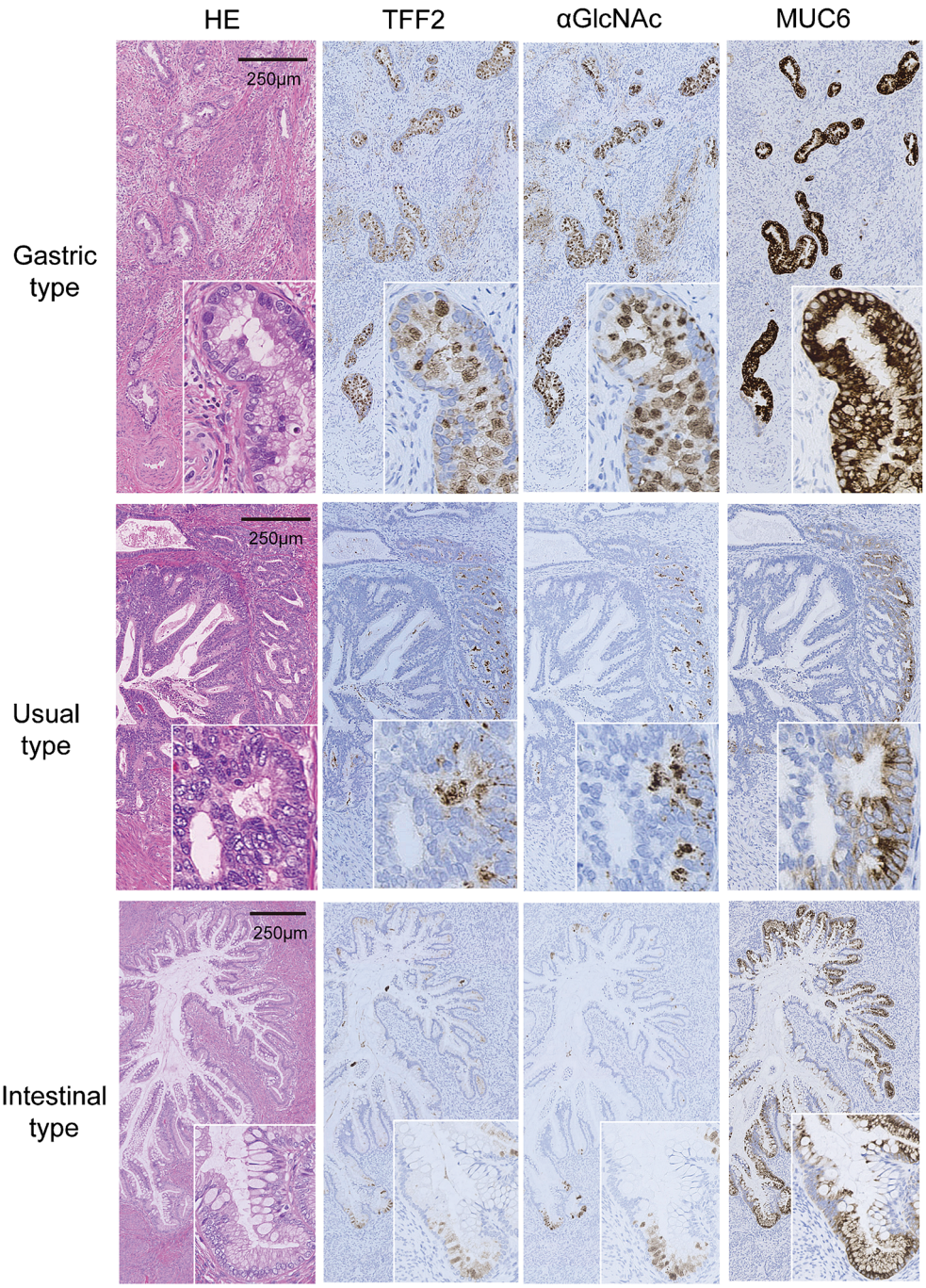

Fig. 3 TFF2, αGlcNAc-R, and MUC6 expression in GA, UA, and IA. GA showing clear, voluminous cytoplasm with a variable amount of cytoplasmic mucin. UA showing marked glandular confluence with cribriform structures that consist of columnar cells with a variable amount of cytoplasmic mucin. Tumor cells showing nuclear enlargement, stratification, and irregularity. IA showing complex glandular brunching, papillary structure, and nuclear enlargement and irregularity. In IA, tumor glands contain both columnar cells with a variable amount of apical mucin and goblet cells. TFF2 and αGlcNAc-R detected in the cytoplasmic mucin and luminal secretions and showing similar localization with each other. MUC6 detected in the cytoplasm. Scale bar in inset = 250 μm

immunoreactivity in normal mucosa, LEGH, and adenocarcinoma tissues. The frequencies and distributions of TFF2 and αGlcNAc-R expression were highly concordant in these lesions.

TFF2 and αGlcNAc-R were frequently expressed in AIS–MIA. The expression of αGlcNAc-R in AIS has previously been described [8, 33]. LEGH has been postulated to be a precursor of invasive endocervical GA [6–11]. AIS with gastric immunophenotype may also be a precursor of invasive endocervical GA, as proposed in a recent study [14], in which the immunohistochemical markers of CK7 and MUC6 were used to define gastric cell lineages.

In IAC, we detected gastric phenotypes on the basis of immunohistochemical expression of TFF2 and αGlcNAc-R not only in GA, but also in UA, IA, and NOS. Staining scores for TFF2 and αGlcNAc-R were significantly higher in GA than in AIS–MIA, UA, and NOS. These findings are in accordance with previous studies examining the expression of claudin 18, a comprehensive gastric-specific lineage marker, in both GAs and non-GAs [19, 20]. Histopathologically, GA has the following characteristics: (1) clear and/or pale eosinophilic cells; (2) voluminous cytoplasm; and (3) distinct cell borders [3]. However, tumor cells in UA with TFF2 and

αGlcNAc-R expression usually have less cytoplasmic mucin and lack the histopathological features of GA just described. Histological features of endocervical adenocarcinoma with gastric differentiation are yet to be re-evaluated on the basis of immunophenotype using cell lineage-specific markers.

In addition to GA and UA, both IAs also showed focal TFF2 and αGlcNAc-R expression. A similar finding has been reported in intestinal-type mucinous ovarian neoplasms, which reportedly frequently express gastric-specific claudin 18 [34]. On the basis of these findings, it has been speculated that endocervical adenocarcinoma expressing gastric and/or intestinal differentiation comprises a single spectrum designated endocervical adenocarcinoma of gastrointestinal type, the histology of which varies depending on degree of differentiation toward gastric or intestinal epithelium. Similar dual expression of gastric and intestinal immunophenotype has been recognized in gastric cancer [35, 36] and pancreatic intraductal papillary mucinous neoplasms [37].

We found that MUC6 was generally expressed in normal endocervical glands that are negative for TFF2 and αGlcNAc-R immunoreactivity. In addition, AIS–MIA, UA, GA, IA, and NOS sometimes stained only for MUC6, and Sig was positive only for MUC6. These findings suggest that MUC6 has limited specificity for detection of a gastric immunophenotype in endocervical glandular lesions, which is consistent with the findings reported by Stolnicu et al. [38].

Potential advantages of TFF2 are that it is a secreted protein and that antibody against it is widely available. In this study, we observed TFF2 in both luminal secretions and cytoplasmic mucin of tumor cells in LIGH, AIS–MIA, and IAC. Non-invasive means of detecting of TFF2, such as ELISA and agglutination testing of uterine cervical secretions, could contribute to screening and early diagnosis of LEGH and adenocarcinoma with GA.

One limitation of TFF2 and αGlcNAc-R is that both are markers for gastric glandular mucous cells but not for gastric surface mucous cells [25, 39]. In our previous study on LEGH, TFF2 and αGlcNAc-R were not expressed in cells with characteristics of gastric surface mucous cells [17].

In conclusion, both TFF2 and αGlcNAc-R are useful immunohistochemical markers for detecting gastric phenotype in endocervical glandular lesions. Moreover, non-invasive detection of TFF2, such as ELISA and agglutination testing of uterine cervical secretions, could contribute to screening and early diagnosis of uterine eondocervical glandular lesions with gastric phenotype.

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Compliance with ethical standards

This study was reviewed and approved by the medical ethics committee of the Shinshu University School of Medicine, Japan (project no. 1875, approved on 6 December, 2011).

Conflict of interest The authors declare that they have no conflict of interest.

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