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Trefoil Factor 2 (TFF2) as a Surrogate Marker for Endocervical Gastric-Type Carcinoma

Kiyokawa Takako, MD[*], **Lien Hoang, MD**[†], **Cristina Terinte, MD**[§], **Anna Pesci, MD**[‖], **Sarit Aviel-Ronen, MD**[¶], **Isabel Alvarado-Cabrero, MD**[#], **Esther Oliva, MD**[‡], **Kay J. Park, MD**[##], **Robert A. Soslow, MD**[##], **Simona Stolnicu, MD**[††]

[*]Department of Pathology, The Jikei University School of Medicine, Tokyo, Japan

[†]Department of Pathology, Vancouver General Hospital, Vancouver, BC, Canada

[§]Department of Pathology, Regional Institute of Oncology, Iasi, Romania

[‖]Department of Pathology, Ospedale Sacro Cuore Don Calabria, Negrar, Italy

[¶]Department of Pathology, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel

[#]Department of Pathology, Hospital de Oncología Mexico City, Mexico City, Mexico

[‡]Department of Pathology, Massachusetts General Hospital, Boston, MA

[##]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY.

[††]Department of Pathology, University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Romania

Abstract

Gastric-type carcinoma (GAS) is the most common HPV-independent endocervical adenocarcinoma (ECA), characterized by an aggressive behavior. TFF2 is a mucin-associated peptide expressed in normal gastric but not endocervical glands. This study was carried out to investigate whether TFF2 could be a surrogate marker to separate GAS from other types of ECA.

ECAs from 9 international institutions were reviewed for consensus histotype. Of them, expression of TFF2 was immunohistochemically examined compared to that of HIK1083, using whole sections of 50 ECAs (10 GASs and 40 non-GASs) and 179 ECAs (24 GASs and 155 non-GASs) with tissue microarrays (TMAs). TMAs were assessed to simulate assessment of immunohistochemical stains in small biopsies. Both markers were similarly scored and any cytoplasmic/membranous staining of more than 5% of tumor cells was considered positive.

Of 50 ECAs with whole sections, TFF2 was significantly more frequently expressed in GASs (8/10) compared with non-GASs (5/40) ($p<0.01$). In 179 ECAs with TMAs, TFF2 was also significantly more frequently expressed in GASs (7/24) compared with non-GASs (4/155) ($p<0.01$). There was no significant difference in specificity among the two markers. Double

Corresponding author: Simona Stolnicu, Department of Pathology, University of Medicine, Pharmacy, Science and Technology of Targu Mures, 38 Gheorghe Marinescu Street, Targu Mures 540139, Romania, stolnicu@gmx.net, Telephone: +40265215551, Fax: +40744765716.

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positivity for TFF2 and HIK1083 in ECAs was highly specific in separating GASs from non-GAS ($p<0.01$). A significantly smaller percentage of GASs were TFF2 positive in TMAs than in whole sections ($p<0.01$).

Our results suggest that TFF2 is a promising marker, along with HIK1083, to confirm a diagnosis of GAS. This marker may be negative in small biopsies, indicating the necessity of using other exclusionary markers in combination with rigorous morphologic review and extensive sampling in resection specimens.

INTRODUCTION

The incidence of endocervical adenocarcinoma (ECA) has been increasing and has recently been reported to represent approximately 25% of all invasive carcinomas of the uterine cervix worldwide.[1-3] Unlike cervical squamous cell carcinoma, which is almost invariably associated with human papilloma virus (HPV) infection, recent studies have documented that ECA is etiologically divided into HPV-associated and HPV-independent types. Our group has recently established a new histological classification of ECA reflecting the importance of HPV in the pathogenesis of most but not all ECAs. The International Endocervical Criteria and Classification (IECC) group reported that the most common histotype is usual-type, which is HPV-associated.[4] Gastric-type carcinoma (GAS) is a distinct subtype of ECA, being the second most common histotype and the most frequent HPV-independent type, that has aggressive behavior.[4-8] Postulated precursors of GAS include atypical lobular endocervical glandular hyperplasia (LEGH) and gastric-type adenocarcinoma in situ.[9]

Distinguishing GAS from ECAs of HPV-associated type as well as from other HPV-independent ECAs, such as clear cell-type, can be difficult in some settings, particularly when one has only biopsy material to examine. High-risk HPV status determined by RNA in situ hybridization (HPV-ISH) is a reliable method to distinguish GAS from HPV-associated ECAs, though it may be more costly than immunohistochemistry and not available in most laboratories. MUC6 is a sensitive, but not specific marker for gastric-type differentiation among ECAs, while HIK1083 is a specific marker for GAS, but it is not highly sensitive and is not widely available.[4] Other “positive markers” of gastric pyloric differentiation are currently unstudied. Recently, TFF2, a mucin-associated peptide expressed in normal gastric glands but not in normal endocervical glands, has been reported to be expressed in GAS and LEGH, and less commonly in ECAs of non-GAS types.[10-12] This study was carried out to validate whether TFF2 could be a surrogate marker to separate GAS from other types of ECA, and to compare its usefulness in diagnosis of GAS with that of HIK1083.

MATERIALS AND METHODS

Institutional approval for this study was obtained from each of the participating centers.

Patient Selection

Slides from 409 invasive ECAs with at least a 5-year follow-up were collected from 9 international institutions. All Hematoxylin-Eosin (H&E) slides with tumor present (an

average of 12 slides per case) were reviewed and a histological consensus was reached in every case with at least two and as many as four expert pathologists reviewing slides at a multiheaded microscope.

Tumors were classified based on the IECC[4]. In situ carcinomas, squamous cell carcinomas, adenosquamous carcinomas, tumors with a neuroendocrine component, carcinosarcomas, and any tumor demonstrating clinical, macroscopic, or microscopic features, suggesting a lower uterine segment, uterine corpus, or adnexal primary origin were excluded. Tumors treated with neoadjuvant chemotherapy and/or radiotherapy were also excluded. Types of specimens included were conizations/trachelectomies/hysterectomies, exenterations with lymph node dissection, while biopsies and LEEP specimens were excluded.

Immunohistochemistry using whole sections and tissue microarray (TMA)

Of 409 cases, 10 consecutive GASs and 40 non-GASs from patients treated at single institution (The Jikei University School of medicine) between 2001 and 2012 were immunohistochemically analyzed for expression of TFF2 and for HIK1083. Formalin-fixed, paraffin-embedded tumor tissue were sectioned at a thickness of 4 micrometer and the sections were deparaffinized and rehydrated. For TFF2 expression, polyclonal antibody TFF2 constructed by Kaise et al was used as a primary antibody with the methods described previously.[13] For HIK 1083 expression, a mouse monoclonal antibody HIK1083 (1:10, Kanto Chemical, Tokyo, Japan) was used as the primary antibody after pretreatment with CC1 (Ventana Medical Systems, Tucson, Arizona, USA) at 100℃ for 60 min. Immunostaining was performed in an automated stainer using the BenchMark-ultra with i-View DAB kit. A section of the normal gastric pyloric mucosa was used as positive control for both antibodies.

In order to simulate staining in a small biopsy, in 179 of 409 ECAs, expression of TFF2 was also immunohistochemically analyzed using TMAs and the results were compared with that of HIK1083 in 179 matched cases, which were among those included in previous studies.[4] The TMAs were constructed using previously described methods.[14,15] Each tumor was represented by three 0.6mm cores (120 cases) except those from Japan which were represented by a single 3mm core (59 cases).

Stains were scored by 2 study pathologists (T.K. and S.S. for TFF2; R.A.S. and S.S. for HIK1083), reaching a consensus. Disagreements were extremely rare and were adjudicated by re-reviewing stated criteria for positivity, as described below. In some cases in the TMA, only 1 or 2 cores remained on the stained slide and were still considered eligible for scoring. For both TFF2 and HIK1083, the percentage of any cytoplasmic/ membranous staining of tumor cells was scored as follows: score 0: <5%; score 1+: 5% to 10%; score 2+: 11% to 25%; score 3+: 26% to 75%; score 4+: >75%; and those with score 1+ to score 4+ were considered positive.

Statistical analysis

Statistical analysis was performed using chi-square test with and without Yate’s correction.

RESULTS

Expression of TFF2 and HIK1083 in whole sections

Using whole slide sections, 10 GASs and 40 non-GASs were studied. The non-GASs included 37 usual-type, 1 mucinous NOS-type, 1 clear cell-type, and 1 endometrioid-type (Table 1). Of the 10 GASs, eight were positive for TFF2 (80%; one score 1+, two score 2+, and five score 3+) and 7 (70%; two score 1+, one score 2+, three score 3+, and one score 4+) for HIK1083 (Fig.1, Fig.2); seventy percent (7/10) of GASs were positive for both markers (double positive); eighty percent (8/10) for at least one of two markers. Among seven double positive GASs, luminal secretion in the neoplastic glands was also stained for TFF2 in two cases, and for HIK 1083 in another case. There was no evidence to suggest the correlation between the positivity for either of the markers and the degree of architectural/cytological atypia of the tumors. Of 40 non-GASs, 5 (12.5%; three score 1+, and one each score 2+ and score 3+) were positive for TFF2 and 14 (35%; seven each score 1+ and score 2+) for HIK1083, with only one case (2.5%) being double positive. Of interest, the latter case had a consensus diagnosis of HPV-associated mucinous carcinoma based on review of H&E slides, although it was negative for high-risk HPV in situ hybridization, calling into question the H&E diagnosis. One clear cell-type ECA was negative for TFF2 while it was positive (score 1) for HIK1083. Both markers were significantly more frequently expressed in GASs compared with non-GASs ($p<0.01$ for TFF2 and $p<0.05$ for HIK1083). Positive and negative predictive values of TFF2 for GAS were 61.5% and 94.6%, respectively. Positive and negative predictive values of HIK1083 for GAS were 33.3% and 89.6%, respectively. In most of GASs positive for TFF2, less than 50% of tumor cells were stained and the distribution of staining cells was variable within a tumor. There was no significant difference in specificity or sensitivity among the two markers. Double positivity was significantly frequent in GASs compared with non-GASs ($p<0.01$), and the specificity of double positivity for the diagnosis of GAS was 97.5%.

One double positive GAS had atypical LEGH/gastric AIS adjacent to invasive carcinoma which was also positive for both markers. Normal endocervical glands adjacent to carcinoma in the present study showed positivity for neither of them.

Expression of TFF2 and HIK1083 in TMAs

TMAs were assessed to simulate assessment of immunohistochemical stains in small biopsies. Of 179 ECAs, 128 were usual-type, 24 GAS, 7 clear cell-type, 3 endometrioid-type, and 17 other HPV-positive types (such as 7 invasive stratified mucin producing-type, 3 intestinal mucinous-type, 1 mucinous NOS-type, and 6 adenocarcinomas NOS-type). Our previous study confirmed that none of those ECAs of GAS, endometrioid-type, or clear cell-type were HPV positive, although 33% of GAS and 17% of clear cell-type were p16-positive[4]. Of 24 GASs, seven cases were positive for TFF2 (29%; one score 2+/1+, and 6 score 3+/4+) and 10 cases for HIK1083 (42%; 10 score 3+/4+) (Table 2) (Fig. 3, 4, 5; together, 50% (12/24) were positive for either or both marker(s). Of seven TFF2 positive GASs, six scored 3+/4+ and the remaining one was 2+, while all 10 HIK1083 positive GASs showed 3+/4+ staining. Of 155 non-GASs, four (2.5%) were positive for TFF2, all of which were of usual-type with two each showing score 2+ and score 1+. In contrast, two (1.3%) of

155 non-GASs were positive for HIK1083, one usual-type and one intestinal mucinous-type, all being score 3+/4+. Both markers were significantly more frequently expressed in GASs compared with non-GASs ($p<0.01$). There was no significant difference in specificity among the two markers though HIK1083 had higher sensitivity ($p<0.05$) in separating GASs from non-GASs. The frequency of TFF2 expression in GASs in the TMAs was significantly lower compared with that using whole sections ($p<0.01$), while no such difference was found with HIK1083. Double positivity was significantly frequent in GASs (20.8%, 5/24) compared with non-GASs (0.6%, 1/155, usual-type) ($p<0.01$), and the specificity of double positivity for the diagnosis of GAS was 99.4%.

DISCUSSION

The present study has shown that TFF-2 expression is specific for gastric-type differentiation in GAS in resection specimens and is a promising surrogate marker to separate GAS from other types of ECA; it shares the same degree of specificity with HIK1083. It has also revealed that double positivity for TFF-2 and HIK1083 is highly specific for the diagnosis of GAS, and is extremely rare in non-GASs, regardless of specimen size.

GAS has a distinct morphology and a few studies have reported good interobserver reproducibility in its recognition using digital microscopic photographs by general surgical pathologists or biopsy/ excision specimens by expert gynecologic pathologists.[16,17] Preoperative biopsy specimens containing limited tumor cells still represent a diagnostic challenge. GAS tends to grow in an endophytic pattern to form a firm, bulky cervix, which may complicate the acquisition of sufficient tumor cells to make a definitive diagnosis. Commonly encountered problems in the diagnosis of GAS in routine practice include distinguishing it from the much more frequently encountered HPV-associated ECAs (i.e. usual-type ECA), HPV-positive mucinous ECAs because of intracytoplasmic mucin in both types and clear cell-type ECA because of frequently similar morphology such as cytoplasmic clearing and crisp cytoplasmic membranes. Compared with usual-type ECA, GAS is significantly associated with a bulky cervical mass, deep stromal invasion, lympho-vascular space invasion, parametrial invasion, ovarian metastasis, positive ascitic fluid cytology, high stage, increased risk for disease recurrence, disappointing disease-specific survival at 5 years, and chemotherapy resistance.[5-8, 18,19] Thus, the diagnostic accuracy in recognizing GAS in a preoperative biopsy is especially important, as ovarian conservation in patients with GAS may not be recommended and omentectomy should be considered as part of surgical treatment. When ECA is found in a biopsy specimen and the differential diagnosis includes GAS, TFF2 immunohistochemistry may be helpful for assignment of histotype.

In the present study, none of the clear cell-type ECAs expressed TFF2, indicating that it may be a candidate marker to distinguish GAS from clear cell-type ECA. Clear cell-type ECA is a relatively rare histotype, and is characterized by histological features that are similar to clear cell-type carcinomas elsewhere in the gynecologic tract; the tumor cells grow in tubulocystic, papillary, and/or solid architecture with minimal cellular stratification, and the cells have clear or eosinophilic cytoplasm, frequently with a hobnail shape. The nuclei are

generally uniform in appearance, with occasional exceptions, although they are individually atypical and occasionally feature prominent nucleoli. The mitotic index is usually low (on average 5 mitotic figures per 10 high power fields). Cytoplasmic boundaries are often prominent due to displacement of cytoplasmic organelles by glycogen as well as frequent projection of interdigitating cytoplasmic process into the irregular expanded intercellular spaces.[20] These features are easily recognizable in excision (loop electrosurgical excision, cold knife cone, trachelectomy, hysterectomy) specimens in which generous tumor tissue is available, but they are potentially misinterpreted by pathologists as GAS (and vice versa) when encountered in a small biopsy specimen with a paucity of tumor cells. Like GAS, clear cell-type ECA may display clear, foamy, or pale eosinophilic cytoplasm, distinct cellular borders, and rounded nucleoli with a distinct nucleolus. Although GAS is typified by cytoplasmic mucin, clear cell-type ECAs may rarely have similar findings.[21] Several studies have reported that GAS may express markers typically present in clear cell-type carcinomas such as HNF-1 beta and napsin A, indicating that these markers are not useful in differential diagnosis.[4-6,22] As both clear cell-type ECA and GAS are HPV-independent and estrogen and progesterone receptors-negative, HPV-ISH and immunohistochemistry have no diagnostic value in distinguishing between these two types. The results of the present study indicate that the positivity for TFF2 with or without that for HIK1083 favors GAS over clear cell-type while negativity for TFF2 does not exclude it, when encountered with ECAs in which the morphological differential diagnoses are between GAS and clear cell-type.

In a previous study by Asaka et al, the authors found TFF2 expression in 10/11 GASs and 11/40 in non-GASs using whole sections.[12] The current study investigated a larger number of GASs, but we report less frequent staining for TFF2, which were assessed to simulate assessment of immunohistochemical stains in small biopsies. This can be explained by the observation that TFF2 positive tumor cells were often seen in limited areas of GASs in whole sections. Based on these findings, it should be emphasized that extensive sampling might be required to find positive staining for TFF2. HIK1083 expression in GAS using TMAs (42%) was also less frequent than in whole sections (70%), which compares favorably to that reported in the literature (75%−100%).[5,12]

Certainly, the small sample number of clear cell-type ECAs as well as mucinous NOS-type examined was a limitation of the present study, as both of them are the potential morphological mimics of GAS. Although both histotypes are rather rare in ECAs, further studies are needed to compare a greater number of both types of ECAs with GASs before the impact of TFF2 staining in separating GASs from them can be accurately assessed.

In conclusion, TFF2 is a promising “positive marker” of GAS and can be used with HIK1083 for distinguishing between GAS and other ECAs in the differential diagnosis. Double positivity for these markers in ECAs is specific for the diagnosis of gastric type. However, caution is advised since staining may be focal or negative.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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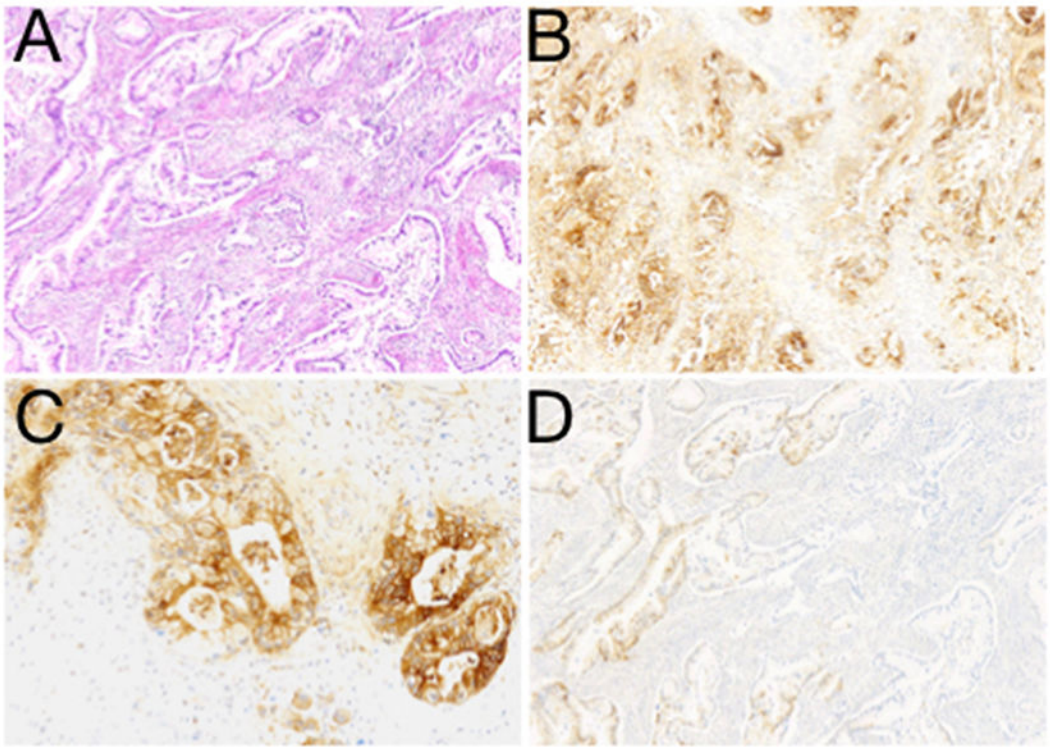

Figure 1:
Gastric-type carcinoma in whole section H&E (A); TFF2 staining of score 3 (B, C) with some foci showing patchy staining (D); in this case, tumor cells were negative for HIK1083.

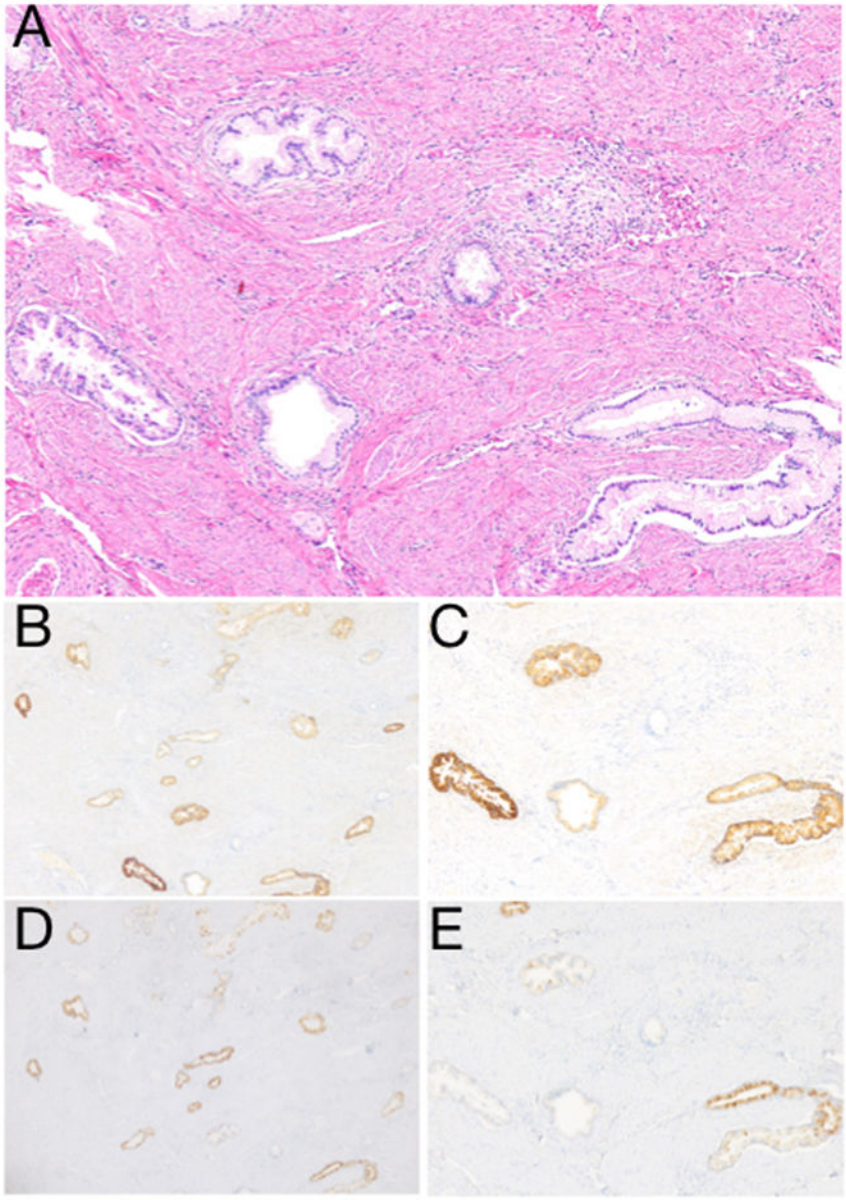

Figure 2:
Gastric-type carcinoma in whole section H&E (A); TFF2 staining of score 3 (B, C); HIK1083 staining of score 3 (D, E).

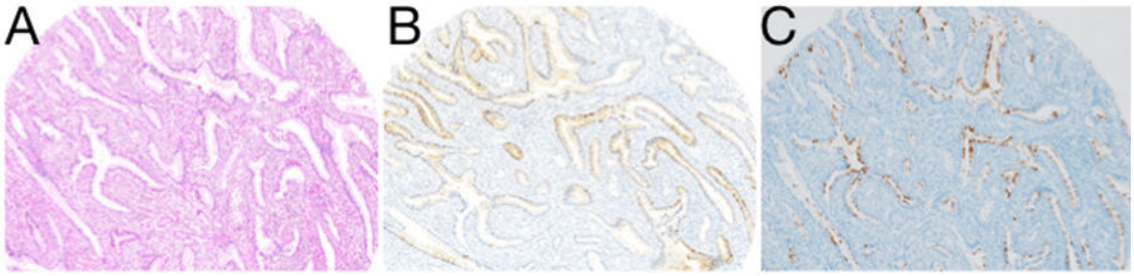

Figure 3:
Gastric-type carcinoma in TMA H&E (A); in this case, tumor cells were positive (score 4) for both TFF2 (B) and HIK1083 (C).

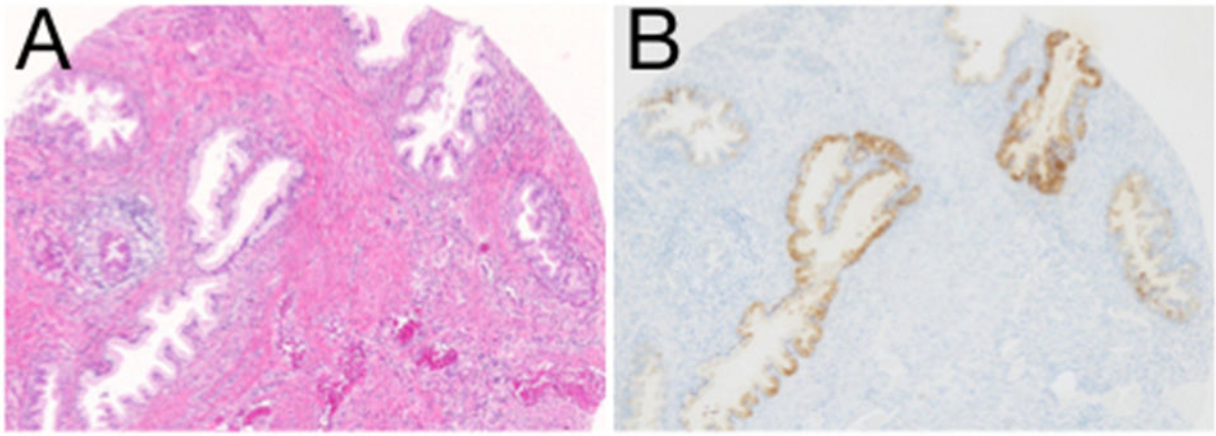

Figure 4:
Gastric-type carcinoma in TMA H&E (A); HIK1083 staining of score 4 (B).

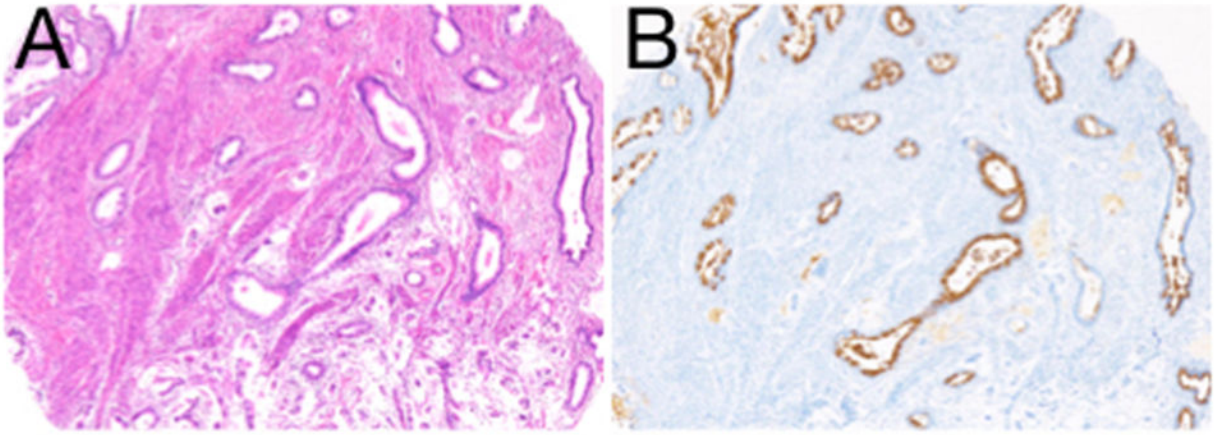

Figure 5:
Gastric-type carcinoma in TMA H&E (A); HIK1083 staining of score 4 (B).

Table 1.

TFF2 and HIK1083 expression of ECAs in whole sections

		TFF2		HIK1083	
Total		**n=50**		**n=50**	
GAS		80.0% (8/10)	] *	70.0% (7/10)	] **
Non-GAS		12.5% (5/40)		35.0% (14/40)	
	Usual	10.8% (4/37)		32.4% (12/37)	
	Mucinous, NOS	100% (1/1)		100% (1/1)	
	Clear cell	0 (0/1)		100 % (1/1)	
	Endometrioid	0 (0/1)		0 (0/1)	

ECAs: Endocervical adenocarcinomas; GAS: gastric-type carcinoma; Non-GAS: Non- gastric-type carcinoma

* <0.01

** <0.05

Table 2.

TFF2 and HIK1083 expression of ECAs in TMAs

		TFF2		HIK1083	
Total		**n=179**		**n=179**	
GAS		29.2% (7/24)	] *	41.7% (10/24)	] *
Non-GAS		2.6% (4/155)		1.3% (2/155)	
	Usual	3.1% (4/128)		0.8% (1/128)	
	Mucinous, intestinal	0 (0/3)		33.0% (1/3)	
	Mucinous, NOS	0 (0/1)		0 (0/1)	
	iSMILE	0 (0/7)		0 (0/7)	
	NOS	0 (0/6)		0 (0/6)	
	Clear cell	0 (0/7)		0 (0/7)	
	Endometrioid	0 (0/3)		0 (0/3)	

ECAs: Endocervical adenocarcinomas; TMAs: Tissue microarrays

GAS: gastric-type carcinoma; Non-GAS: Non-gastric-type carcinoma

iSMILE: invasive stratified mucin producing carcinoma

* <0.01