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Guanylyl Cyclase C Is a Specific Marker for Differentiating Primary and Metastatic Ovarian Mucinous Neoplasms

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Abstract

Distinguishing primary ovarian mucinous neoplasms from metastatic mucinous adenocarcinomas with ovarian involvement can be difficult, especially when characteristic gross and microscopic features are not present. CK7/CK20 expression appears to be more useful for distinguishing metastatic gastrointestinal adenocarcinomas from the lower tract. The addition of CDX2 for distinguishing metastatic upper gastrointestinal tract adenocarcinomas from primary ovarian mucinous neoplasms offers little advantage over CK7/CK20 coordinate expression. Guanylyl cyclase C (GCC) is a brush border membrane receptor for the endogenous peptides guanylin and uroguanylin, and the homologous diarrheagenic bacterial heat-stable enterotoxins that is selectively expressed by epithelial cells from the duodenum to the rectum, but not by normal epithelia of the stomach or esophagus, or normal extramucosal cells in humans. We studied 50 ovarian tumors: 27 primary ovarian mucinous neoplasms (7 cystadenomas, 10 borderline tumors, and 10 cystadenocarcinomas) and 23 metastatic mucinous adenocarcinomas with ovarian involvement (13 colorectal adenocarcinomas, 4 gastric adenocarcinomas, 6 appendiceal mucinous tumors (4 adenocarcinomas, 1 with neuroendocrine features, and 2 appendiceal mucinous cystadenomas). For primary ovarian mucinous neoplasms, 25 of 27 were negative for GCC. Twelve of thirteen cases of colorectal adenocarcinoma (except for 1 neuroendocrine adenocarcinoma) were positive for GCC. Three of four appendiceal mucinous adenocarcinomas were positive for GCC in both the primary and metastatic tumors (except for 1 neuroendocrine adenocarcinoma). Two of two appendiceal mucinous cystadenomas were positive for GCC. Of four cases of gastric adenocarcinoma with ovarian involvement, only one (primary tumor) exhibited focal GCC staining. These findings suggest GCC may be a useful marker for differentiating primary and secondary ovarian mucinous neoplasms.

Keywords

Ovarian Mucinous Neoplasms; Metastatic adenocarcinoma; Guanylyl Cyclase C

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Disclosure/Conflict of Interest

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Introduction

Ovarian epithelial tumors account for approximately half of benign ovarian tumors and 85–90% of malignant ovarian tumors [1]. When characteristic features are present, differentiating primary ovarian mucinous borderline tumor and mucinous adenocarcinoma from a metastasis can be relatively straightforward. Most often metastases originate in the large intestine, appendix, pancreas, biliary tract, stomach, lung, breast or cervix. Features favoring a primary ovarian mucinous neoplasm include unilaterality, size greater than 15 cm, smooth capsule and usually lack of extra-ovarian spread. Primary ovarian mucinous carcinomas most often arise in association with borderline mucinous tumors. Frequently there is confluent glandular or expansile invasion; however, they can exhibit destructive stromal invasion. Features that tend to favor metastatic mucinous adenocarcinomas to the ovary include bilaterality, smaller size (less than 10 cm), surface involvement, nodular involvement, and destructive stromal invasion [2–5].

Ovarian mucinous carcinomas that do not exhibit the aforementioned features usually require ancillary studies, including immunohistochemistry. Several studies have examined various immunohistochemical markers including CK7, CK 20, CDX2, beta-catenin, alpha-methylacyl-CoA racemase, Dpc4, carcinoembryonic antigen and others [6–10]. The combination of CK7, CK20, and CDX2, in addition to gross and microscopic features can be useful in distinguishing primary ovarian adenocarcinoma from a metastatic lesion. CDX2 is expressed in a variety of adenocarcinomas and therefore adds little to using co-expression patterns of CK7 and CK20 [11]. One study suggests that diffuse expression of CDX2, beta-catenin and racemase is virtually diagnostic of a metastatic colorectal carcinoma [12].

Guanylyl cyclase C (GCC) is a brush border membrane receptor for the endogenous peptides guanylin and uroguanylin, and the homologous diarrheagenic bacterial heat-stable enterotoxins. GCC is selectively expressed by epithelial cells from the duodenum to the rectum, but not by normal epithelia of the stomach or esophagus, or normal extramucosal cells in humans [13–17]. GCC is an intestinal tumor suppressor whose expression is regulated by CDX2 [18]. Its ligands inhibit enterocyte and colorectal cancer cell proliferation [19–21]. Expression of GCC universally persists after malignant transformation in colorectal tumors [9]. Using immunohistochemistry, GCC expression was identified in epithelial cells of the colon in cases of inflammatory bowel disease, tubular adenomas, intestinal metaplasia of the gastroesophageal junction with and without low and high-grade dysplasia, and in primary and metastatic colonic adenocarcinomas, including metastases to the lymph nodes and liver [22]. The aim of this study was to determine the distribution of GCC expression in primary ovarian mucinous neoplasms, including mucinous cystadenomas, mucinous borderline tumors and mucinous cystadenocarcinomas. In addition, GCC expression was evaluated in primary gastrointestinal adenocarcinomas with and without ovarian metastases.

Materials and Methods

With approval of the internal review board, the pathology files of the Thomas Jefferson University Hospital were searched between 1992 and 1996. Consecutive cases of primary ovarian mucinous neoplasms (mucinous cystadenomas, mucinous borderline tumors and mucinous cystadenocarcinomas) were procured from the files of the pathology department and all cases were reviewed blinded by the pathologists (VC, JPP and AB). In addition, the search included consecutive cases of primary gastrointestinal adenocarcinoma, with and without ovarian metastases. The primary ovarian mucinous neoplasms, gastrointestinal adenocarcinomas and metastatic adenocarcinomas were all stained with GCC as described below.

Sections (5 μ m) of formalin-fixed, paraffin-embedded tissues were mounted on Superfrost Plus-charged slides. Routine de-paraffinization from xylene to 95% alcohol was performed on a Leica Autostainer (Leica, Inc, Deerfield, IL). This process included a 30 min methanolic peroxide step to block endogenous peroxidase activity. Slides were then rehydrated and antigen recovery performed at 70% power in a 1050-W microwave oven (model # EM-F3400, Sanyo, Chatsworth, CA) in EDTA buffer (pH 8.0). Slides were microwaved for 2 intervals of 5 min each, with replenishment of evaporated buffer between exposures. After a 30 min cooling period, slides were washed in deionized water and placed in PBS for 5 min. Immunostaining was conducted using a DAKO autostainer (model # LV-1, DAKO Corporation, Carpinteria, CA). Slides were incubated for 15 min each with avidin and blocking solutions (Vector Laboratories, Burlingame, CA), followed by primary antibody (1:1000) for 60 min. After a PBS wash, biotinylated goat antirabbit IgG was applied to slides for 30 min, followed by Avidin Biotin Complex (Vector Laboratories) for 30 min. After another PBS wash, slides were incubated for 5 min in DAB solution (DAKO Corporation), washed in deionized water, counterstained with Harris hematoxylin (SurgePath, Richmond, IL), and dehydrated with xylene before mounting. Only cells exhibiting distinct apical membrane staining, independently of the level of expression, were considered positive for GCC expression. In contrast, weak cytoplasmic staining was not considered positive staining [22]. In some experiments, purified rabbit antibodies were preincubated with the immunizing peptide before immunostaining to confirm that staining reflected specific interaction with GCC. Cases known to express GCC were used as positive and negative controls.

Results

The patient population consisted of 50 women. Twenty-seven women had a primary ovarian mucinous neoplasm (Table 1). The median age of this group was 53 years (range, 27–79 years). The primary ovarian mucinous neoplasms were as follows: 7 mucinous cystadenomas, 10 mucinous borderline tumors, and 10 mucinous cystadenocarcinomas. The mean size of the primary ovarian mucinous neoplasms was 17.0 cm (median, 17 cm). Twenty-three women had a primary gastrointestinal adenocarcinoma to one or both ovaries (Table 2). The median age of the women with a primary gastrointestinal adenocarcinoma and ovarian metastasis was 53 years (age range 25–85 years). The primary sites were as follows: 13 colorectal adenocarcinomas (one of which was a neuroendocrine carcinoma), 4 gastric adenocarcinomas, 6 appendiceal mucinous neoplasms (4 adenocarcinomas [1 neuroendocrine], 2 mucinous cystadenomas). Concerning the four gastric adenocarcinomas, 1 of 4 cases had metastases to both ovaries. In 3 of 4 of metastatic gastric adenocarcinomas, information regarding the other ovary was not available. Of the patients with an appendiceal mucinous neoplasm, 2 had bilateral ovarian involvement while information regarding the remaining ovary on the third patient was not available. Information regarding the remaining ovary of the single case of metastatic appendiceal neuroendocrine carcinoma was not available.

GCC Expression in Primary Ovarian Mucinous Neoplasms

Of the 25 primary ovarian mucinous neoplasms examined, 23 (92%) were negative for GCC (Table 1; Fig. 1, 2). One case of ovarian mucinous cystadenocarcinoma and one case of borderline ovarian mucinous tumor was focally positive for GCC.

GCC Expression in Primary Gastrointestinal Adenocarcinomas

Of the 17 primary gastrointestinal adenocarcinomas examined, 16 (94%) exhibited generalized apical membrane staining for GCC (Table 2; Fig. 3, 4). One case of colorectal neuroendocrine carcinoma was negative for GCC. There were three cases of appendiceal

mucinous neoplasms, and all were positive for GCC. One case of appendiceal neuroendocrine carcinoma was negative for GCC. There were four cases of gastric adenocarcinomas, and only one (25%) was positive for GCC.

GCC Expression in Metastatic Adenocarcinomas

Twenty-five women had a primary gastrointestinal adenocarcinoma of which 16 (64%) had metastases to one or both ovaries (Table 2). Seven of eight (88%) metastatic colorectal adenocarcinomas exhibited apical membrane staining for GCC in primary tumors and metastases (Fig. 5, 6). The single case of metastatic colorectal neuroendocrine adenocarcinoma was negative for GCC in both primary tumor and metastases. There were four poorly differentiated gastric adenocarcinomas, all of which had metastases to the ovary. One case showed focal GCC positivity in the primary tumor but was negative in the metastasis. The remaining 3 cases of gastric adenocarcinoma were negative for GCC both in the primary tumor and metastases. The 3 cases of appendiceal mucinous neoplasm were positive for GCC in the primary tumor and metastases. The sole case of appendiceal neuroendocrine carcinoma was negative for GCC in both the primary and metastasis.

Discussion

Guanylyl cyclase C is a brush border membrane receptor selectively expressed by epithelial cells from the duodenum to the rectum, but not by normal epithelia of the stomach or esophagus, or normal extramucosal cells in humans [13–17]. GCC is an intestinal tumor suppressor whose expression is regulated by CDX2 [18]. Expression of GCC persists after malignant transformation in colorectal tumors [9]. We previously demonstrated GCC expression by immunohistochemistry in epithelial cells of the colon in cases of inflammatory bowel disease, tubular adenomas, intestinal metaplasia of the gastroesophageal junction with and without low and high-grade dysplasia, and in primary and metastatic colonic adenocarcinomas, including metastases to lymph nodes and liver [22]. The current study is the first to look at the expression of GCC in primary ovarian mucinous neoplasms and metastatic mucinous adenocarcinomas to the ovary.

GCC expression was predominantly negative in primary ovarian mucinous neoplasms, including mucinous cystadenomas, mucinous borderline tumors and mucinous cystadenocarcinomas. Only one case of mucinous borderline tumor and one case of mucinous cystadenocarcinoma were focally positive for GCC. These findings compare favorably to recent studies looking at CK7, CK20 and CDX2. CDX2 is a nuclear transcription factor that is involved in intestinal-type differentiation. CDX2 is expressed in a high proportion of colorectal adenocarcinomas (60–100%). The reported expression of CDX2 in primary ovarian mucinous tumors is broad and ranges from 0–100% [11]. Further, coordinate expression of CK7/CDX2 was seen in 36% of primary ovarian mucinous neoplasms in one study [11]. Regarding CK7 and CK20 expression, primary ovarian mucinous tumors and metastatic mucinous adenocarcinomas to the ovary can show overlapping expression patterns. Our experience is that 23 of 25 (92%) cases of ovarian mucinous neoplasms were negative for GCC. The two positive primary ovarian neoplasms, borderline tumor and cystadenocarcinoma were focally positive. Follow-up in our study ranged from 12 to 14 years. The primary ovarian mucinous neoplasm showed characteristic features on hematoxylin and eosin staining. None of the patients with a diagnosis of primary ovarian mucinous neoplasm (cystadenoma, borderline or cystadenocarcinoma) showed any evidence of primary gastrointestinal carcinoma.

Concerning the metastatic mucinous adenocarcinomas to the ovary, GCC expression varied depending on the primary site (Table 2). Indeed, 88% (7 of 8) of cases of colorectal adenocarcinoma were positive for GCC. Immunohistochemical staining showed that all of

these cases were globally positive for GCC in both the primary tumor and the metastasis. This finding is much higher than the reported range of CDX2 expression. Further, GCC expression in metastatic colorectal adenocarcinomas is consistently higher than that of coordinated CK7-/CK20+ expression patterns. In our series, the number of cases of mucinous tumors of the appendix was very small (n=3). However, a pattern similar to colorectal adenocarcinomas was seen. All three cases of mucinous adenocarcinoma of the appendix with ovarian involvement showed general GCC reactivity in both the primary and metastases. Of the four cases of poorly differentiated gastric adenocarcinoma with ovarian metastases, only one of the primary tumors focally stained with GCC, while the remaining gastric primary tumors and metastases were negative. This is consistent with our previous findings in which 5 poorly differentiated and 5 signet ring gastric adenocarcinomas were negative for GCC. Interestingly, 5 cases of intestinal-type gastric adenocarcinoma were positive for GCC [22]. GCC, similar to CDX2 and CK7/CK20, may not be optimal for distinguishing primary ovarian mucinous neoplasia from metastatic gastric adenocarcinoma.

Tissue-specific expression of GCC is activated, in part, by CDX2 [18]. Whereas CDX2 expression can be seen outside of the gastrointestinal tract, including ovarian mucinous neoplasms, urinary bladder adenocarcinomas, papillary thyroid carcinoma, and carcinoid tumors, guanylyl cyclase C expression in humans is selectively expressed in intestinal epithelial cells but not in extraintestinal parenchymal tissues [9, 11, 23, 24]. GCC appears to offer an advantage over CDX2 in differentiating primary ovarian mucinous from metastatic mucinous adenocarcinomas. However, GCC expression in extraintestinal tissue has not been studied by immunohistochemistry. We recently stained cell blocks from a small number of cases of peritoneal and pelvic wash fluids with metastatic adenocarcinomas (unpublished observation). Briefly, there were seven fluids with metastatic mucinous adenocarcinoma that were GCC positive including: esophageal, gastric (well-differentiated), appendiceal and colorectal. Twenty metastatic adenocarcinomas were GCC-negative including: breast, lung, ovarian mucinous neoplasms, pancreatic, and uterine adenocarcinomas.

This study is the first to examine the expression of GCC in primary ovarian mucinous neoplasms and mucinous adenocarcinomas metastatic to the ovary. GCC was not expressed in the majority of primary mucinous neoplasms of the ovary. Conversely, GCC was expressed in the majority of primary and metastatic intestinal adenocarcinomas, except for poorly differentiated gastric carcinomas. These observations suggest that GCC may be a useful marker to differentiate primary from metastatic mucinous neoplasms of the ovary.

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Figure 1.
Primary ovarian mucinous adenocarcinoma (H&E, 200X)

Figure 2.
Primary ovarian mucinous adenocarcinoma showing focal cytoplasmic reactivity with GCC
(GCC, 200X)

Figure 3.
Primary colorectal adenocarcinoma (H&E, 200X)

Figure 4.
Primary colorectal adenocarcinoma showing strong apical membrane staining and weak cytoplasmic staining (GCC, 200X)

Figure 5.
Metastatic colorectal adenocarcinoma to ovary (H&E, 200X)

Figure 6.
Metastatic colorectal adenocarcinoma to ovary showing strong apical membrane staining and weak cytoplasmic staining (GCC, 200X)

Table 1

Clinicopathologic features of patients with primary ovarian tumors.

AGE	DIAGNOSIS	SIZE (cm)	GCC
78	BORDERLINE MUCINOUS TUMOR	16	NEG
43	MUCINOUS CYSTADENOMA	8.5	NEG
44	MUCINOUS CYSTADENOMA	11	NEG
33	MUCINOUS CYSTADENOMA	14	NEG
50	MUCINOUS CYSTADENOMA	19	NEG
47	MUCINOUS CYSTADENOMA	14	NEG
27	MUCINOUS CYSTADENOMA	15	NEG
79	MUCINOUS CYSTADENOCARCINOMA	21	NEG
75	MUCINOUS CYSTADENOCARCINOMA	18	NEG
48	MUCINOUS CYSTADENOMA	6	NEG
37	BORDERLINE MUCINOUS TUMOR	22	NEG
48	MUCINOUS CYSTADENOCARCINOMA	19.5	NEG
78	BORDERLINE MUCINOUS TUMOR	26	NEG
79	MUCINOUS CYSTADENOCARCINOMA	15	NEG
46	BORDERLINE MUCINOUS TUMOR	19	NEG
75	BORDERLINE MUCINOUS TUMOR	25	POS
52	MUCINOUS CYSTADENOCARCINOMA	14	NEG
54	BORDERLINE MUCINOUS TUMOR	28	NEG
69	BORDERLINE MUCINOUS TUMOR	22	NEG
70	BORDERLINE MUCINOUS TUMOR	19	NEG
42	MUCINOUS CYSTADENOCARCINOMA	15	NEG
67	MUCINOUS CYSTADENOCARCINOMA	35	POS
38	MUCINOUS CYSTADENOCARCINOMA	7.5	NEG
77	MUCINOUS CYSTADENOCARCINOMA	1.3	NEG
72	MUCINOUS CYSTADENOCARCINOMA	15	NEG

Table 2

Clinicopathologic features of patients with primary gastrointestinal tumors.

Age	Diagnosis	OVARIAN METASTASIS	SIZE OF METASTASES (cm)	GCC
25	APPENDICEAL	Y	17, 12	POS [‡]
54	COLORECTAL	Y	6, 4.5	POS [‡]
36	COLORECTAL	N		POS
53	COLORECTAL	N		POS
57	APPENDICEAL	Y	21, *	POS [‡]
75	COLORECTAL	N		POS
65	COLORECTAL	N		POS
42	APPENDICEAL CARCINOID	Y	16, *	NEG ^ζ
46	COLORECTAL	N		
47	COLORECTAL	N		POS
53	COLORECTAL	N		POS
72	COLORECTAL	N		POS
48	COLORECTAL	Y	5.5, 13.5	POS [‡]
76	GASTRIC	Y	2.2, *	POS/NEG [‡]
42	COLORECTAL	Y	10, neg	POS [‡]
85	COLORECTAL	Y	2.2, *	POS [‡]
48	COLORECTAL	Y	3.5, neg	POS [‡]
32	GASTRIC	Y	biopsy, *	NEG ^ζ
32	GASTRIC	Y	1.5, *	NEG ^ζ
57	COLORECTAL	N		POS
68	GASTRIC	Y	12, 9	NEG ^ζ
52	APPENDICEAL	Y	18, 5.5	POS [‡]
85	COLORECTAL	Y	15, 3.5	POS [‡]
69	COLORECTAL	Y	3, *	POS [‡]
71	COLON CARCINOID	Y	5, 3	NEG ^ζ

* Patients in whom the status of the remaining ovary is not known

[‡]GCC positive in both the primary colorectal adenocarcinoma and the ovarian metastasis

[†] GCC positive in the primary adenocarcinoma and negative in the ovarian metastasis

[‡] GCC negative in both the primary adenocarcinoma and the ovarian metastasis