Human Pathology (2014) **45**, 359–367

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Human PATHOLOGY

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Original contribution

Crohn enteritis–associated small bowel adenocarcinomas exhibit gastric differentiation☆

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Received 29 August 2013; accepted 18 September 2013

Keywords:
Crohn disease;
Small bowel adenocarcinoma;
Immunohistochemistry;
Pyloric gland metaplasia;
Gastric differentiation

Summary Primary small bowel adenocarcinoma is rare. Although generally similar to colonic adenocarcinoma, some small bowel adenocarcinomas exhibit unique morphologic features, particularly those arising in association with Crohn disease. In this study, 15 sporadic small bowel adenocarcinomas and 11 Crohn enteritis–associated small bowel adenocarcinomas were examined for histology and immunohistochemical profile including cytokeratins (CK) 7 and 20, intestinal markers CDX2 and MUC2, and gastric epithelial markers MUC5AC and MUC6. We found that Crohn enteritis–associated small bowel adenocarcinomas frequently resemble gastric tubular adenocarcinoma histologically. In addition, when compared to sporadic small bowel adenocarcinoma, the former expressed MUC5AC and MUC6 with much higher frequency (82% vs. 7% and 73% vs. 0%, respectively). Ten of 11 Crohn enteritis–associated small bowel adenocarcinomas (91%) were positive for at least one gastric-type marker (MUC5AC or MUC6). Expression of CK7 was also more frequent in Crohn enteritis–associated small bowel adenocarcinoma (73% versus 27%) while expression of CK20 was less frequent (64% vs. 100%). There was no difference between sporadic and Crohn enteritis–associated small bowel adenocarcinoma in expression of CDX2 (100% vs. 91%) and MUC2 (93% vs. 73%). These observations suggest that there is a difference in the morphologic and immunohistochemical characteristics of sporadic versus Crohn enteritis–associated small bowel adenocarcinoma, particularly in their expression of gastric-type mucin. The findings also suggest that gastric differentiation in Crohn enteritis–associated small bowel adenocarcinoma is related to gastric metaplasia, a common phenomenon in Crohn disease.

1. Introduction

While the small intestine comprises 90% of the mucosal surface of the gastrointestinal tract, primary small bowel adenocarcinoma (SBA) is remarkably rare, accounting for less than 2% of all gastrointestinal tumors [1]. Due to limited screening capabilities, vague presenting symptoms, and insensitivity of routine diagnostic imaging, these tumors are often diagnosed at late stage and thus carry a dismal prognosis with a reported 5-year survival of 26% [2,3].

SBAs are generally considered histologically similar to colorectal adenocarcinoma and are thought to arise out of a similar adenoma-carcinoma sequence [4]. However, when evaluating adenocarcinomas arising in Crohn enteritis, we have observed a tumor morphology similar to gastric tubular–type adenocarcinoma. In addition, despite the

☆ Disclaimer: There is no conflict of interest or commercial association to be disclosed.

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http://dx.doi.org/10.1016/j.humpath.2013.09.014

Table 1 Antibodies used for immunohistochemical analysis

Specificity (Clone)	Supplier	Dilution
CK7 (OV-TL 12/30)	DAKO	1:50
CK20 (K_s20.8)	DAKO	1:25
CDX2 (CDX2-88)	Biogenex, Fremont, CA	1:100
MUC2 (CCP58)	NovoCastra, UK	1:25
MUC5AC (CLH2)	NovoCastra, UK	1:25
MUC6 (CLH5)	NovoCastra, UK	1:25

seemingly similar pathogenesis, there is growing evidence that some SBAs have an immunophenotype distinct from colorectal adenocarcinoma. The classic immunohistochemical profile of well-differentiated colonic adenocarcinoma is reflective of the mucosa in which it arises. It is typically positive for intestinal markers CK20, CDX2, and MUC2 and is negative for CK7. In contrast, although limited in number, recent immunohistochemical studies of primary SBA have shown these tumors are often negative for CK20 (33%-52% negative), MUC2 (39%-56% negative), and CDX2 (40% negative) and positive for CK7 (35%-100% positive) [5–8]. In addition, there is also evidence that SBAs often aberrantly express gastric mucin MUC5AC and MUC6 (30%-40% and 26%-36% positive, respectively) [6–8].

It has been shown that a background of inflammatory bowel disease can affect the immunophenotype of the tumor in which it arises [9,10]. Long-term Crohn enteritis is a well-known risk factor for the development of SBA, and thus Crohn enteritis–associated SBA may also have unique immunophenotypic characteristics. To our knowledge, immunohistochemical studies directly comparing sporadic and Crohn enteritis–associated SBA have not been published. In the present study, sporadic SBAs are compared with those associated with Crohn enteritis for their expression of CK7 and CK20, intestinal markers CDX2 and MUC2, and gastric markers MUC5AC and MUC6. The results presented here demonstrate that unlike sporadic SBA, Crohn enteritis–associated SBA aberrantly expresses gastric markers with a significantly higher frequency. We propose this unique immunophenotype may be related to gastric-type metaplasia, a well-recognized change in Crohn enteritis.

2. Materials and methods

2.1. Case selection

Eleven cases of surgically resected Crohn enteritis–associated primary small bowel adenocarcinoma were retrieved from the surgical pathology archives at the

Table 2 Clinicopathologic features of sporadic and Crohn-associated small bowel adenocarcinomas

Case No.	Study Group	Age	Sex	Small bowel location	Size (cm)	pT	Crohn duration (years)	Gastric metaplasia	Tumor morphology
1	Crohn	65	F	Ileum	3	T4	Unknown	Yes	Gastric tubular
2	Crohn	47	M	Ileum	5	T4	25	Yes	Gastric tubular
3	Crohn	43	F	Ileum	Unknown	T2	22	Yes	Intestinal
4	Crohn	44	M	Ileum	5	T4	15	Yes	Gastric tubular/intestinal/mucinous
5	Crohn	43	F	Ileum	20	T3	10	Yes	Poorly differentiated
6	Crohn	49	F	Ileum	6	T4	32	No	Intestinal
7	Crohn	46	M	Jejunum	3.5	T4	20	No	Gastric tubular
8	Crohn	77	F	Ileum	2.5	T4	Unknown	Yes	Gastric tubular/mucinous
9	Crohn	42	M	Unknown	4	T4	36	Unknown	Signet ring/mucinous
10	Crohn	56	F	Ileum	8.5	T3	32	Yes	Gastric tubular/mucinous
11	Crohn	73	M	Ileum	5	T3	40	Yes	Gastric tubular
12	Sporadic	45	M	Jejunum	5	T3	–	No	Intestinal
13	Sporadic	83	M	Jejunum	3	T3	–	No	Intestinal
14 (Celiac)	Sporadic	69	F	Duodenum	1	T3	–	No	Intestinal
15	Sporadic	73	M	Duodenum	6.5	T4	–	No	Intestinal/mucinous
16	Sporadic	83	M	Ileum	3	T4	–	No	Intestinal
17	Sporadic	44	M	Ileum	5.5	T4	–	No	Intestinal/mucinous
18	Sporadic	53	M	Ileum	4	T4	–	No	Gastric tubular/mucinous
19	Sporadic	43	M	Jejunum	2.5	T4	–	No	Intestinal
20	Sporadic	80	M	Unknown	3	T4	–	No	Intestinal/gastric tubular
21	Sporadic	56	M	Unknown	5	T3	–	No	Intestinal
22	Sporadic	64	M	Unknown	2	T4	–	No	Intestinal
23	Sporadic	41	M	Ileum	1	T3	–	No	Intestinal/mucinous
24	Sporadic	57	F	Unknown	7	T3	–	No	Intestinal/gastric tubular/mucinous
25	Sporadic	60	M	Jejunum	14	T4	–	No	Intestinal
26 (FAP)	Sporadic	63	F	Jejunum	3	T4	–	Yes	Intestinal/gastric tubular