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Original

A Clinicopathological Study of Primary Small Intestinal Cancer with Emphasis on Cellular Characteristics

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Abstract: We examined the clinicopathological profiles and cellular characteristics of 10 cases of surgically resected primary small intestinal cancers (excluding duodenal cancers). Histological examination revealed nine adenocarcinomas and one sarcomatoid carcinoma. Invasion depth was subserosal in five cases, serosal in four cases and to the adjacent transverse colon in the remaining case. Metastasis was present in lymph node in seven cases, in distant organs in six, and in the peritoneum in seven cases. Of the 10 cases, 7 underwent postoperative chemotherapy, and 6 of the eight traceable patients died from the disease (mean period of survival: 386 days). Histomorphologically, eight of nine adenocarcinomas showed an intestinal phenotype (unclassifiable in the other) in the upper layer, while in the lower layer, there showed an intestinal phenotype and five a non-intestinal phenotyp. Immunohistochemistry revealed a mean positive rate in the upper / lower layers as follows: 93% / 86% and 38% / 29% by intestinal markers CDX2 and MUC2; 19% / 28% and 13% / 32% by pancreatobiliary markers CK7 and MUC1; and 4% / 19% and 2% / 9% by gastric markers MUC5AC and MUC6, respectively. Thus, the intestinal phenotype predominated in almost all small intestinal cancer in this study, although some showed a transformation to non-intestinal or hybrid phenotypes with tumor progression. Flexible management for the diversity and transformation of cellular characteristics is therefore recommended treating and diagnosing small intestinal cancers.

Key words: small intestinal cancer, clinicopathological study, cellular characteristics, intestinal phenotype

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Introduction

Cancer of the small intestine is often not detected until it reaches an advanced stage due to the late presentation of symptoms and the difficulty in performing endoscopic examinations. Many cases are also unsuitable for radical resection or have postoperative cancer recurrence, making chemotherapy frequently appropriate as an adjuvant or multidisciplinary therapy. However, there are no established chemotherapy regimens specific to small intestinal cancer as this cancer is extremely rare, comprising $<2\%$ of all cases of gastrointestinal malignancies[1, 2] and successful results have not yet been obtained[3].

The need for "personalized medicine" is being increasingly considered. This involves medication selection and regimen determination based on the sensitivity of an individual's cancer cells to anti-cancer drugs or cancer cell-specific characteristics such as the presence of tumor-associated antigens. Although small intestinal cancer is generally considered to resemble colon cancer histomorphologically, the keratin profiles and genetic abnormalities of this disease differ from those of colon cancer[4–8]. The study focused on the cellular characteristics of small intestinal cancer, since few such studies have been done.

The aim of this study was to clarify the cellular characteristics of small intestinal cancer by histomorphological and immunohistochemical analyses. We expect that the results will be useful when considering the histogenesis of small intestinal cancer as well as for its diagnosis and treatment.

Materials and Methods

Case selection

We reviewed 65 cases of malignant small bowel neoplasms (excluding duodenal tumors), which were surgically resected during the 7 years from September 2003 to September 2010 at the authors' facilities. Among these, 26 cases (40%) were reported as metastatic carcinomas to the small intestine, 23 as peritoneal dissemination of abdominal malignancy, and 3 as metastasis from lung cancer. The remaining 39 primary tumor cases included 10 cases of carcinoma (15%) (9 adenocarcinoma and 1 sarcomatoid carcinoma), 12 cases (18%) of malignant lymphoma, 8 cases (12%) of gastrointestinal stromal tumor (GIST), 3 cases (5%) of leiomyosarcoma, 1 case (2%) of neuroendocrine tumor (carcinoid), and 5 unclassified cases (8%) as follows; one case in which the tumor was mainly located in the terminal ileum, but also involved the cecum; one in which a tumor equally involved the jejunum and pancreas; two in which a primary ileal carcinoma was suspected, but another carcinoma was observed concurrently in another organ (colon); and one in which it was difficult to distinguish whether the tumor was a recurrence of gastric cancer after more than 5 postoperative recurrence-free years or a primary jejunal carcinoma. The subject of the present study were the 10 carcinoma cases

Clinicopathological study

14 clinicopathological factors—age, sex, chief complaint, localization, size, tumor marker, macroscopic type, histological type, invasion depth, presence of lymph node metastases, presence of distant metastases and / or peritoneal dissemination, chemotherapeutic regimen, and prognosis were studied.

Analysis of cellular characteristics

We conducted histological and immunohistochemical analyses for determining the cellular characteristics of adenocarcinoma cases.

Histological analysis

We classified the neoplastic glands histomorphologically into intestinal and non-intestinal phenotypes. The intestinal phenotype was characterized by similarities with colorectal adenomas or cancers showing tall columnar epithelium with pseudostratified, spindle nuclei and chromophilic (basophilic or acidophilic) cytoplasm. Goblet and paneth cells were also considered as related findings. On the other hand, the neoplastic glands lacking these characteristics were classified into the non-intestinal phenotype. For each case, 1 or 2 slides including all layers of the tumor were selected and observed by dividing the lesions into upper and lower layers. The upper layer was considered as a relatively early stage lesion of the tumor and the lower layer as the invasive front. In cases involving a mixture of intestinal and non-intestinal phenotype, the dominant appearance was agreed upon by multiple observers (K.N, N.O, T.M).

Immunohistochemical analysis

Immunohistochemical staining was performed using an avidin-biotin complex detection system (BenchMark XT / LT automated slide stainer ; Ventana Medical Systems, Inc., Tucson, AZ, USA). We prepared 3-μm sections for immunostaining from formalin-fixed, paraffin-embedded blocks used in the histological analysis. Markers included MUC1 (Ma695, Leica Biosystems Newcastle Ltd, Newcastle, UK ; diluted ×100), MUC2 (Ccp58, Leica Biosystems ; diluted ×200), MUC5AC (CLH2, Leica Biosystems ; diluted ×200), MUC6 (CLH5, Leica Biosystems ; diluted ×50), CK7 (OV-TL12 / 30, DAKO North America, Inc. CA, USA ; diluted done), CDX2 (EPR2764Y, Nichirei Bioscience Inc, Tokyo, Japan ; diluted done), CA19-9 (C241 : 5 : 1 : 4, Leica Biosystems ; diluted ×200), and CEA (COL-1, Nichirei Bioscience Inc, Tokyo japan ; diluted done). Positive staining at the apical membrane of tumor cells was considered significant for MUC1, nuclear-positive staining for CDX2, and cytoplasmic staining for the remaining markers. MUC2 and CDX2 were recognized as intestinal phenotypic markers, MUC1 and CK7 as pancreatobiliary phenotypic markers, and MUC5AC and MUC6 as gastric phenotypic markers. All markers were evaluated by the proportion of positive cells in numerical values separately for the upper and lower layers of the lesions,

which almost represented the proportions in the whole tumor.

Results

Clinicopathological characteristics (Table 1)

The patients included 6 males and 4 females with a mean age of 62 years (age range:

Table 1 Clinicopathological characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (ys.)	34	66	37	63	65
Sex	male	female	male	female	male
Chief complaint	ileus	ileus	ileus	abd tumor	ileus
Localization	ileum	ileum	jejunum	ileum	jejunum
Macroscopic type	ulcerated	ulcerated	ulcerated	ulcerated	ulcerated
Microscopic type	tub > muc	tub	tub	muc > tub	tub > por
Dominant phenotype					
upper layer	intestinal	intestinal	intestinal	intestinal	intestinal
lower layer	non-intestinal	non-intestinal	non-intestinal	intestinal	non-intestinal
Invasion depth	ss	se	ss	ss	ss
Lymph node metastasis	+	+	−	+	+
Distant metastasis	−	+	+	+	−
Peritoneal dissemination	−	+	+	−	+
Chemotherapy	TS-1	TS-1	TS-1 → UFT	TS-1	none
Outcome (days after surgery)	1460 alive	500 alive	416 dead	88 dead	551 dead

	Case 6	Case 7	Case 8	Case 9	Case 10
Age (ys.)	66	76	70	87	51
Sex	female	female	male	male	male
Chief complaint	ileus	ileus	abd pain	anemia	abd tumor
Localization	ileum	jejunum	jejunum	jejunum	ileum
Macroscopic type	ulcerated	ulcerated	ulcerated	ulcerated	protuberant
Microscopic type	tub	tub	por > muc	tub > muc	sar ca
Dominant phenotype					
upper layer	intestinal	intestinal	unclassifiable	intestinal	−
lower layer	intestinal	non-intestinal	unclassifiable	intestinal	−
Invasion depth	se	si	se	ss	se
Lymph node metastasis	+	−	+	+	unknown
Distant metastasis	+	−	+	+	unknown
Peritoneal dissemination	+	+	+	+	unknown
Chemotherapy	TS-1	TS-1 + CPT11	FOLFOX	none	none
Outcome (days after surgery)	550 dead	665 dead	50 dead	unknown	unknown

Abbreviations: tub; tubular adenocarcinoma, muc; mucinous (colloid) carcinoma, sar ca; sarcomatoid carcinoma
ss; subserosal invasion, se; serosal invasion, si; direct invasion to adjacent organs, +; present, −; absent

34–87 years). Intestinal obstruction (also called ileus) symptoms were the most frequent chief complaint. None of the case was complicated by specific inflammatory or hereditary diseases such as Crohn's disease or Peutz–Jeghers syndrome. High serum CA19-9 and CEA levels were found in 2 cases each (along with the growth of postoperative residual tumors, high serum CA19-9 and CEA levels were observed in 6 cases and 3 cases, respectively). Surgical methods were partial resection of the small intestine along with feeding arteries aimed at lymphadenectomy in all cases. All tumors were macroscopically advanced cancers showing protuberant type in 1 case (Case 10) and ulcerated type in the remaining 9 cases, with the latter frequently showing annular constriction. The mean tumor diameter was 7.3 cm (range : 3.0–21.0 cm). All tumors were solitary and there were no hamartomatous or adenomatous polyps in the surrounding mucosa. Histologically, the protuberant type (case 10) was sarcomatoid carcinoma, while the nine ulcerated types were tubular adenocarcinomas, including mucinous (colloid) carcinoma component in 4 cases. In addition, 2 cases (cases 2 and 9) showed an adenomatous component in the periphery, but those were indistinguishable from well-differentiated, low-grade adenocarcinoma. Invasion depth was subserosal in 5 cases and serosal in 4 cases, while invasion into the adjacent transverse colon was observed in one case (case 7). In addition, lymph node metastasis, distant organ metastasis, and peritoneal metastasis were observed in 7 cases, 6 cases, and 7 cases, respectively. Postoperative chemotherapy was administered to 7 patients of which 6 were treated by TS1 alone or by a combination of TS1 and other agents, and 1 by FOLFOX. Postoperative prognoses were traceable in 8 cases. Tumor-related death occurred in 6 patients and they were identified with a mean survival period of 386 days (range : 50–665 days). In the remaining 2 cases, one patient (case 2) is alive 500 days after the surgery with recurrence and another patient (case 1) is alive 1460 days after surgery without any recurrence (treated with adjuvant chemotherapy).

Cellular characteristics

All nine adenocarcinoma cases showed heterogeneous (composite or combined) cellular characteristics histomorphologically (Figure 1) ; however, when classifying the dominant features into intestinal and non-intestinal phenotypes for each layer, 8 cases were classified as intestinal and 1 case as unclassifiable in the upper layer, whereas 3 cases were classified as intestinal, 5 cases as non-intestinal, and 1 as unclassifiable in the lower layer (Table 1). The neoplastic glands of the non-intestinal phenotype were mainly composed of monolayer cuboidal epithelial cells with round nuclei and eosinophilic or clear cytoplasm showing characteristics of pancreaticobiliary or gastric phenotypes (Figure 1). A case of poorly differentiated adenocarcinoma showing medullary proliferation in most of the tumor was unclassifiable (case 8). In the immunohistochemical study, the proportional range of positive cells was wide for all markers in both layers, with the mean proportions in the upper / lower layers as follows (Table 2) : 93% / 86% and 38% / 29% for the intestinal phenotypic markers

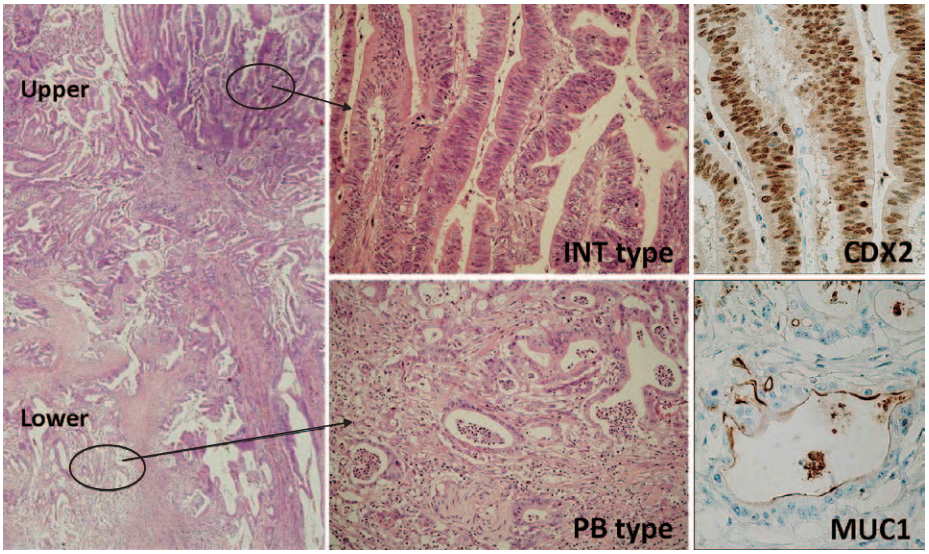

Fig. 1. Histological and immunohistochemical findings of small intestinal adenocarcinoma (case 1) Tumor shows a heterogeneous feature, although the intestinal (INT)-phenotype is dominant in the upper layer while the pancreatobiliary (PB) phenotype is dominant in the lower layer. Note the CDX2 nuclear staining in the former and MUC1 at staining at the apical membrane in the latter.

Table 2 Immunohistochemical study

	Intestinal maker		Pancreatibiliary marker		Gastric marker		Others	
	MUC2	CDX2	MUC1	CK7	MUC5AC	MUC6	CA19-9	CEA
Upper layer	38% (3-90)	93% (70-100)	13% (0-40)	19% (0-100)	4% (0-30)	2% (0-8)	77% (50-100)	84% (70-95)
Lower layer	29% (3-90)	86% (40-100)	32% (1-80)	28% (0-100)	19% (0-80)	9% (0-70)	94% (80-100)	93% (90-95)

(upper stand ; mean propotion of positive cells, lower stan ; range)

CDX2 and MUC2, respectively ; 13% / 32% and 19% / 28% for the pancreatobiliary phenotypic markers MUC1 and CK7, respectively ; and 4% / 19% and 2% / 9% for the gastric phenotypic markers MUC5AC and MUC6, respectively. The summarized data indicated that the expression of intestinal phenotypic markers were predominant in both layers, but that a mild increase in the expression of non-intestinal phenotypic markers was observed in the lower layer ; this seemed to correspond to the histomorphological results (Figure 1). Lymph node metastatic lesions showed similar histomorphological and immunohistochemical findings to those of the lower layer (data not shown).

Discussion

The efficacy of chemotherapy administered for small intestinal cancer remains unknown because this cancer is extremely rare and many such cancers are detected once in a locally

advanced or distantly metastasized status[1, 2, 9, 10], as also observed in this study. Personalized medicine involves medication selection and regimen determination based on the cancer cell-specific chemotherapeutic sensitivity or characteristic phenotypes (e.g., presence of tumor-associated antigens) to improve chemotherapy efficacy. We believe that our study on the cellular characteristics of small intestinal cancer will be beneficial for developing future such chemotherapeutic strategies against small intestinal cancer.

Most case of small intestinal cancer (adenocarcinoma) studied herein were histomorphologically heterogeneous. Hence, we were forced to evaluate the cellular characteristics based on dominant features along with the agreement of multiple observers, although several suggestive results were obtained. This study showed that intestinal phenotypic features were overwhelmingly predominant in the upper layer, which implies that small intestinal adenocarcinoma predominantly occurs with an intestinal phenotype. This is consistent with the description that histological features of small intestinal cancers are characterized by intestinal phenotypic adenocarcinoma similar to colon cancer[11]. On the other hand, features lacking intestinal phenotypic characteristics were dominant in the lower layer (invasive front), which suggested that small intestinal adenocarcinomas, originally developing with predominantly intestinal phenotypic characteristics, may lose those characteristics and add or change different phenotypes with invasive progression. Such phenomena are not surprising in carcinomas arising in transitional mucosa or mucosa showing frequent metaplastic changes[12, 13], and thus are seemingly inevitable also for small intestinal cancer. Immunohistochemically, the intestinal phenotype was predominant throughout the tumors because the positive rate of intestinal phenotypic marker CDX2 was overwhelmingly high in both layers compared to that of other markers, and the positive rates of pancreatobiliary phenotypic markers (MUC1 and CK7) and gastric phenotypic markers (MUC5AC and MUC6) only increased mildly in line with the histological features. Thus, these results suggest that selection of anti-cancer drugs centering on medications that are efficacious for intestinal phenotypic adenocarcinoma as well as combining medications that correspond to the transformation of cellular characteristics may increase their combined effects.

There are several histopathological differences between small intestinal cancer and colorectal cancer[4-8]. Poorly differentiated carcinoma and sarcomatoid carcinoma are sometimes observed in small intestinal cancers (case 8 and case 10 in this study)[9, 14-17], but such types are extremely rare in colorectal cancer. Small intestinal adenocarcinomas show expression of pancreatobiliary markers [e.g. keratin 7, MUC1, and CA19-9 (see Table 2)] at a higher rate compared to colorectal adenocarcinomas. Chen and Wang.[4] reported that all small intestinal adenocarcinomas showed a variable degree of CK7 expression (diffuse in 54% and focal in 46%) ; in contrast, only 4% in this study showed focal expression in secondary colorectal adenocarcinomas. We also confirmed that only 7 (4%) of 169 colorectal adenocarcinomas exhibited a MUC1 positive cell ratio of $>50\%$, while ratios this high were shown in 41 (70%) of 59 pancreatic adenocarcinomas and 3 (30%) of 10 small intestinal adenocarcino-

mas[18]. Moreover, genetic abnormalities of colorectal cancer (e.g., APC gene mutations) do not always apply to small intestinal cancers[5, 6, 19]. With regard to the histogenesis, it remains controversial whether an adenomacarcinoma progression sequence, which is well described in colorectal cancer, is the major pathway in small intestinal cancer because few study have been done involving early stage lesions. Although adenomatous component were observed in the tumor periphery in two of the present cases, the phenotype was still difficult to discriminate from well-differentiated, low grade adenocarcinoma (Chang *et al* described this as "peritumoral dysplasia"[9]). Thus, the adenomacarcinoma sequence was not proven in any case. In genetic susceptibility, no present cases involved hamartomatous or adenomatous polyps, suggestive of Peutz-Jeghers syndrome or familial adenomatous polyposis. Lynch syndrome was also not noted in any case, although the level of microsatellite instability (MSI) should be analyzed in future studies because high MSI rates of 10–25% have been already described in small intestinal cancers[11, 20-23].

In conclusion, this study of the clinicopathological features of small intestinal cancers suggested the need of chemotherapy as an adjunctive or multidisciplinary therapy. Most small intestinal cancers (adenocarcinomas) develop predominantly with intestinal phenotypic characteristics as a major characteristic, but they show intrinsically heterogeneous profiles. This could indicate the loss of intestinal phenotypic characteristics with tumor progression or an association with non-intestinal phenotypic characteristic. Higher case-number studies are now needed to better analyze the transformative effects on clinicopathological factors and prognoses. Indeed, flexible management for the diversity and transformation of cellular characteristics may be desirable when treating and diagnosing small intestinal cancers.

Ethical approval

This study has been approved by patients' agreement based on the informed consent and personal information was hidden in the investigations in the medical records.

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