Comparison of the Chemosensitivity of the Primary Lesion and a Pancreatic Metastasis of Colon Cancer: A Case Report

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Abstract. *Pancreatic metastasis from colorectal cancer is rare, and accounts for less than 2% of all pancreatic metastases. There have been no studies that have reported the differences in the sensitivity to chemotherapy between the primary lesion and the pancreatic metastasis in colorectal cancer. We experienced a rare example of pancreatic metastasis from colorectal cancer, and report here the difference in the sensitivity to the antitumor drug. A 68-year-old female underwent colectomy for rectal carcinoma with a mass in the pancreatic tail and the liver. The patient also underwent a distal pancreatectomy and a segmental liver resection at the same time. v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) and tumor protein 53 (TP53) gene mutation analyses, in addition to the histopathological examinations, revealed tumors of the liver and the pancreatic tail as being metastases from the primary carcinoma. We employed a collagen gel droplet-embedded culture drug sensitivity test for both the primary lesion and the pancreatic metastasis. The sensitivity to oxaliplatin and FOLFOX (5-flurouracil, folinic acid and oxaliplatin) were lower in the pancreatic metastasis compared to the primary lesion. In conclusion, pancreatic metastasis from colorectal malignancy is rare, and the present results suggest that there are potential differences in the sensitivity to chemotherapy between the primary colorectal tumor and its pancreatic metastasis.*

Colorectal cancer (CRC) is the third most common type of cancer and the fourth leading cause of death due to cancer worldwide (1). In spite of progress made in chemotherapy for CRC, the outcomes of CRC with distant metastasis still remain poor. The pancreas is an uncommon location for solitary metastasis from other primary carcinomas (2). But in many autopsy series, the prevalence of pancreatic metastasis has been described as being as high as 1.6% to 11% (3, 4). The metastases usually derive from a primary tumor of the kidney, lung, breast, gastrointestinal tract (stomach, small bowel or colorectum) or from melanoma (5). There have only been 29 reported cases of a solitary resectable pancreatic metastasis from colorectal cancer (6). Although hepatic resection is a potentially curative therapy for liver metastases from CRC, the benefits of resection of pancreatic metastases are unclear.

The collagen gel droplet-embedded culture drug sensitivity test (CD-DST), using various types of malignant neoplasms, has been safely and widely applied in Japan (7-9). However, to date, CD-DST data for a pancreatic metastasis from CRC have not been reported. This case study was performed in order to evaluate the differences in the CD-DST results between the primary lesion and its pancreatic metastasis. An accumulation of this type of information may be helpful in the future in order to establish treatment modalities for unresectable metastatic pancreatic tumors, or may allow for resectable tumors to be treated with chemotherapy instead of surgical removal.

Case Report

A 68-year-old female in good general condition presented to our department in May 2011 complaining of constipation and tested positive for occult fecal bleeding. There was an adenocarcinoma of the rectum detected by colorectal endoscopy, and computed tomography also revealed an inhomogeneous mass in the pancreatic body, measuring 35 mm in the largest diameter, and in segment 6 of the liver, measuring 30 mm in the largest diameter (Figure 1).

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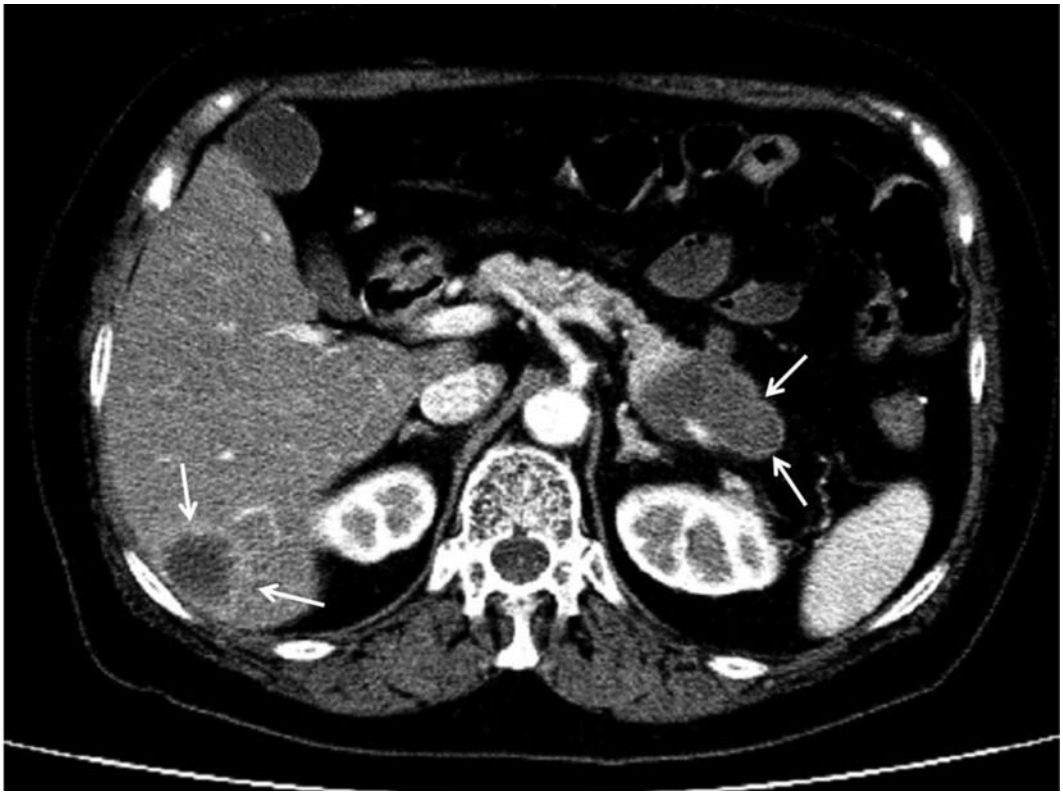

Figure 1. *Low density lesion seen in the tail of the pancreas and segment 6 of the liver, metastatic tumor from the rectal carcinoma as imaged by contrast-enhanced CT scan.*

Radiographically, no other masses were detected. At this point, it was uncertain whether the tumors in the liver and the pancreas were primary lesions or metastases from the rectal adenocarcinoma. In June 2011, the patient underwent a high anterior resection of the rectum. In a rapid diagnosis during the operation, the liver lesion was concluded to be a metastasis of the rectal adenocarcinoma, and therefore, a limited liver resection, together with resection of the pancreatic body and tail, were performed at the same time.

The rectal lesion was diagnosed histopathologically as moderately-differentiated adenocarcinoma invading into the serosal fat. The resected margins were free of tumor; however, 8 out of the 12 regional lymph nodes were positive for metastasis. The liver and pancreatic lesions showed the same morphological features in hematoxylin and eosin (H&E) staining. Immunohistological examinations revealed that the tumor cells of the rectal lesion, liver lesion and pancreas lesion were all negative for cytokeratin (CK) 7 and Mucin (MUC) 6, and all positive for CK20 and Caudal-type homeobox protein (CDX) -2. Because pancreatic metastasis of the colorectal carcinomas is rare, gene alterations of the *v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) and *tumor protein 53* (*TP53*) genes were further investigated in the rectal and pancreatic tumors. The presence of *KRAS* mutations in codons 12 and 13 were evaluated by a polymerase chain reaction (PCR)-based DNA heteroduplex assay followed by nucleotide sequencing as reported previously (10), and no *KRAS* alterations were found. The mutation hot-spots in exons 5 to 8 of the *TP53* gene were examined by direct sequencing of the PCR products, as described in a previous report (11), and the same one-nucleotide deletion followed by a stop codon (c.377del, p.Y126SfsX44) was found in both the rectal and pancreatic tumors (Table I). Taking the histopathological, immunohistochemical and genetic alteration findings into account, we considered the pancreatic tumor to be a metastasis from the rectal adenocarcinoma. As the preoperative diagnosis was a double primary cancer, we examined the chemosensitivity of both the rectal tumor and the pancreatic tumor using CD-DST to determine the most appropriate chemotherapy regimen for the patient. The results of the analysis are shown in Table II. The chemosensitivity of the metastatic pancreatic lesion was lower than that of the primary lesion for both oxaliplatin and FOLFOX (5-flurouracil, folinic acid and oxaliplatin). The pathological staging was T3 N2 M1, and based on the

Table I. *The differences in the results of the immunohistochemical and DNA mutation analyses between the primary lesion and the metastatic lesions.*

	Cytokeratin 7	MUC 6	Cytokeratin 20	CDX-2	*KRAS* mutation	*TP53* mutation
Rectum	–	–	+	+	–	c.377del, p.Y126SfsX44
Pancreas	–	–	+	+	–	c.377del, p.Y126SfsX44
Liver	–	–	+	+	Not investigated	Not investigated

MUC6: Mucin6; CDX-2: Caudal-type homeobox protein-2.

sensitivity testing, the patient underwent adjuvant chemotherapy with FOLFOX. The patient is alive and disease-free 8 months after surgery.

Discussion

The incidence of pancreatic metastases in autopsy series performed in patients with malignant neoplasms ranged from 1.6-11% (3, 4). In clinical studies among patients with solitary pancreatic masses, the frequency of pancreatic metastases ranged from 0.5 to 3% (12, 13). Renal cell carcinoma is the most common primary tumor, followed by lung cancer (adenocarcinoma and non-small cell lung carcinoma), lobular breast carcinoma, and more rarely, gastric cancer, melanoma, and soft-tissue sarcoma (2, 12, 14-17). Table III shows the details of the 30 cases with isolated metastasis to the pancreas from colorectal adenocarcinoma reported in the literature; only four cases of synchronous metastasis, including the present case, were identified out of 10 rectal adenocarcinoma cases. The treatment of colorectal cancer patients with an isolated distant organ metastasis, such as that to the brain, liver, lung, or local recurrence, by the resection of the metastases has been reported to have beneficial effects on patient survival (18-21). In patients with renal cell carcinoma, Reddy *et al*. (22) reported that the median survival after the resection of isolated pancreatic metastases was 4.8 years. However, the role of pancreatic resection for metastatic colorectal tumors is not well defined due to the paucity of such cases reported in the literature, and it is unclear whether these patients should be managed by a more conservative approach, such as chemotherapeutic management, and whether chemotherapy may offer the same results as pancreatic resection with less morbidity.

The response of recurrent disease to chemotherapeutic agents, such as 5-flurouracil, oxaliplatin and folinic acid (FOLFOX) or 5-flurouracil and folinic acid with irinotecan (FOLFIRI), has rarely been reported (14). Therefore, in the present study, we evaluated the chemotherapeutic sensitivity of cancer cells from both a primary rectal adenocarcinoma and a synchronous pancreatic metastasis using the CD-DST with multiple drug concentrations and contact durations. The

Table II. *Drug sensitivities as determined by the collagen gel droplet-embedded culture drug sensitivity test (CD-DST) in the rectal tumor and pancreatic metastasis.*

	Inhibition rate (%)	
	Primary lesion	Pancreatic metastasis
Irinotecan	36.8	27.5
Oxaliplatin	54.7	39.5
FOLFOX	63.3	53.1
FOLFIRI	42.1	41.4
5-flurouracil	30.7	41.1

FOLFOX: 5-Flurouracil+ folinic acid +oxaliplatin, FOLFIRI: 5-flurouracil+ folinic acid +irinotecan, The formula used to determine the inhibition rate is reported in the text.

CD-DST is a useful tool for the design of tailor-made chemotherapy regimens using the most suitable agents, doses, and schedules of administration (23), particularly in cases of rare tumors for which a standard chemotherapy regimen has not been established. The antitumor effect of the agents is determined by the inhibition ratio, which is calculated from the total volume of the colony that was in contact with the drug (T) and the total volume of the colony that was not in contact with the drug (C), according to the following formula: (1-T/C) ×100%. A value of more than 50% is indicative of good drug sensitivity. The primary rectal adenocarcinoma from the present patient exhibited good sensitivity to both oxaliplatin and FOLFOX, but the sensitivity to these chemotherapeutic agents was lower by more than 10% for the pancreatic metastasis. There have been no previous reports that the chemotherapy regimen was less effective for a pancreatic metastasis than for the primary colorectal carcinomalesion as determined by the CD-DST.

In conclusion, pancreatic metastases should be considerd when a patient with history of colorectal adenocarcinoma is presenting a pancreatic mass, and the present results suggest that there are potential differences in the sensitivity to chemotherapy between the primary colorectal tumor and its pancreatic metastasis.

Table III. *The nature and outcomes of pancreatic resections for colorectal metastasis: A review of the literature.*

Authors	Year	Site of primary tumor	Interval between tumors (months)	Site	Surgical procedure	Outcome	
						Dead	Alive
Present study	2012	Rectum	Synchronous	Tail	DP		7
Chao-Wei *et al*. (24)	2010	Rectum	24	Tail	DP		12
Norman *et al*. (6)	2010	Colon	108	Tail	DP	9	
Sperti *et al*. (14)	2009	Colon	48	Head	Wipple		31
		Colon	Synchronous	Head	PPPD		28
		Colon	10	Head	Wipple	17	
		Colon	36	Tail	DP		14
		Colon	24	Head	PPPD	10	
		Colon	Synchronous	Head	PPPD	15	
		Colon	Synchronous	Body	DP	5	
		Rectum	29	Tail	DP		30
		Rectum	80	Head	Enucleation	24	
Baierlein SA (25)	2008	Rectum	60	Head	PD	Not reported	
Gravalos C *et al*. (26)	2008	Colon	12	Head	PD		12
Bachmann *et al*. (27)	2007	Rectum	24	Tail	DP		1.5
		Rectum	30	Tail	DP		6
Shimoda *et al*. (28)	2007	Rectum	44	Head	PD	8	
Eidt *et al*. (29)	2007	Colon	12	Head	PPPD	105	
Matsubara *et al*. (30)	2007	Rectum	24	Head	Wipple	24	
Crippa *et al*. (31)	2006	Colon	7	Head	PPPD	13	
Torres-Villalobos *et al*. (32)	2004	Cecum	8	Tail	DP		6
Tutton *et al*. (33)	2001	Colon	23	Tail	DP		12
Pereira-Lima JC (34)	2000	Colon	36	Body	GJ	5	
Le Borgne *et al*. (17)	2000	Colon	60	Head	Wipple	12	
Yoshimi *et al*. (35)	1999	Colon	51	Tail	DP	24	
Inagaki *et al*. (36)	1998	Rectum	132	Body	DP		8
Harrison *et al*. (37)	1997	Colon	15	Head	Wipple	41	
		Colon	15	Head	Wipple	21	
Nakeeb *et al*. (38)	1995	Colon	34	Head	Wipple		43
Roland and van Heerden JA (5)	1989	Colon	Not reported	Tail	DP		27

DP: Distal pancreatectomy; GJ: gastrojejunostomy; PD: pancreaticoduodenectomy; PPPD: pylorus-preserving pancreaticoduodenectomy.

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