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A Report of Disseminated Carcinomatosis of the Bone Marrow Originating from Transverse Colon Cancer Successfully Treated with Chemotherapy Using XELOX plus Bevacizumab

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Key Words

Disseminated carcinomatosis of bone marrow · Chemotherapy · Transverse colon cancer · Disseminated intravascular coagulation

Abstract

A 61-year-old male, who had been admitted to another hospital due to disseminated intravascular coagulation (DIC), was referred to our hospital. Total colonoscopy, abdominal dynamic CT and positron-emission tomography revealed bone metastasis and multiple lymphocytic metastases from transverse colon cancer in addition to disseminated carcinomatosis of the bone marrow (DCBM). We immediately performed chemotherapy with XELOX + bevacizumab and denosumab against DCBM from transverse colon cancer in order to avoid radical surgery. In addition, we initiated the administration of recombinant human soluble thrombomodulin for 1 week to treat DIC. The patient was able to tolerate and receive 4 cycles of chemotherapy without any severe side effects. After receiving the 4 cycles of treatment, he recovered from DIC, and the bone and multiple lymphocytic metastases disappeared.

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Introduction

Disseminated carcinomatosis of the bone marrow (DCBM) is often associated with disseminated intravascular coagulation (DIC), and both are associated with poor prognoses. Most cases of DCBM are derived from gastric cancer; however, DCBM originating from colorectal cancer is relatively rare.

We herein report a case of DCBM originating from transverse colon cancer that was successfully treated with chemotherapy using XELOX + bevacizumab (BV) and recombinant human soluble thrombomodulin (rhTM).

Case Report

A 61-year-old male showed high levels of lactase dehydrogenase and alkaline phosphatase at a health checkup. He went to the clinic for an assessment of his general condition, and multiple lymphocytic metastases on an abdominal ultrasound and an elevation of the carcinoembryonic antigen level were detected. At the time of the medical visit, the patient only had back pain and did not report any inconveniences in his daily life activities. He had a history of hyperlipidemia and hypertension. When he came to our hospital, his peripheral blood examination showed multiple abnormal values (table 1). In addition, we diagnosed the patient with DIC (based on the DIC score calculated according to the DIC diagnostic criteria issued by the Japanese Association of Acute Medicine). A total colonoscopy (TCS) showed a stenosis of the transverse colon (fig. 1), and a signet ring cell carcinoma was detected on a biopsy. We found that the cancer was present throughout the transverse colon on a barium enema (fig. 2). Furthermore, a CT detected multiple lymph node metastases. Fluorodeoxyglucose (FDG)-positron-emission tomography (PET) also detected multiple lymph node metastases in addition to multiple bone metastases (fig. 3a–c). We performed a bone marrow puncture in order to make a diagnosis of the tumor and ultimately diagnosed the patient with DCBM originating from colon cancer (fig. 4). The same day, he was admitted to our department for treatment. We immediately initiated treatment with emergency chemotherapy consisting of XELOX + BV with an elemental diet. To treat the bone metastasis, denosumab was administered at an interval of 1 month for a total of 3 times before reevaluating the tumor. In addition, we administered anticoagulation therapy with rhTM to treat DIC (resulting from DCBM) for 1 week. We continued the chemotherapy for 4 cycles without any severe adverse events; we then reevaluated the tumor. The carcinoembryonic antigen level consistently decreased from 1,382 to 69.1 ng/ml. Although the primary lesion did not change in size on TCS or barium enema (fig. 5), the multiple metastases in the bone and lymph nodes clearly disappeared on CT and PET-CT (fig. 6a–c). Furthermore, the patient recovered from DIC caused by DCBM following the administration of chemotherapy and rhTM. We considered performing a resection of the primary lesion in order to reduce the tumor volume and enable oral intake.

Discussion

A diffusely infiltrative carcinoma was first reported by Jarcho [1] in 1936. Hayashi et al. [2] conducted a study of DCBM among 40 cases of disseminated carcinoma in Japan. The authors reported that most of the DCBM cases derived from gastric cancer (over 90%). DCBM is associated with 3 major symptoms: anemia, back pain and bleeding tendencies. The

hematological and blood biochemical findings of DCBM demonstrate severe anemia, leukoerythroblastosis and elevated levels of alkaline phosphatase and lactase dehydrogenase. In addition, the disease often occurs in association with DIC due to invasive bone marrow, and the metastases in the bone marrow are diffusely infiltrative rather than exhibiting a nodular pattern.

On the other hand, colorectal cancer is relatively rare as an origin of DCBM, with only 27 cases having been reported between 1984 and 2013 in Japan (table 2) [3–28]. The average patient age in these cases is 55 years, and the disease is as common in males as it is in females. The major symptoms are also the same as those of general DCBM. The frequency of lesions in the rectal colon is slightly higher than that of other primary lesions. With respect to the histological diagnosis, poorly differentiated carcinoma (13 cases), signet ring cell carcinoma (6 cases) and mucin-forming carcinoma (3 cases) are the most frequently observed, accounting for approximately 81% of cases. Although many patients with DCBM originating from colorectal cancer do not survive more than 100 days, chemotherapy regimens such as folinic acid, fluorouracil and oxaliplatin (FOLFOX) or folinic acid, fluorouracil and irinotecan (FOLFIRI) clearly improve survival. Therefore, it is possible to survive for more than 200 days in some cases. However, it is difficult to improve the prognosis of patients with DCBM originating from signet ring cell carcinoma, and the duration of survival remains short despite treatment with chemotherapy.

The present patient had DCBM originating from transverse colon cancer that occurred in association with DIC. We administered emergency chemotherapy consisting of XELOX + BV and denosumab to treat the patient's bone metastasis. In addition, we administered anticoagulation therapy with rhTM to treat DIC. The lymph node and bone metastases dramatically improved with these therapies and without any development of severe adverse events; the patient completely recovered from DIC. He survived for more than 100 days with a diagnosis of DCBM originating from signet ring cell carcinoma. To our best knowledge, this is the first report of such long-term survival. These results suggest that the administration of aggressive chemotherapy for DCBM originating from colon cancer may help to prolong overall survival.

We combined rhTM with chemotherapy to treat DIC resulting from DCBM in this case. Recently, rhTM has become widely used to treat DIC resulting from sepsis in Japan [29]. However, Akiyama et al. [30] reported that the use of anticoagulation therapy alone is not effective for DIC resulting from DCBM and recommended not only treatment against DIC, but also treatment with chemotherapy against the tumors of DCBM. Therefore, we considered chemotherapy to be the central therapy and used rhTM to support the chemotherapy.

The purpose of surgical resection of primary tumors is to prevent hemorrhaging, perforation and bowel obstruction. In many cases, it is not possible for patients to continue chemotherapy due to complications such as bleeding, perforation and bowel obstruction occurring without undergoing surgical resection of the primary tumor. Therefore, it is necessary to surgically remove the primary tumor in order to continue chemotherapy with few complications. In the past, some investigators have recommended performing a routine resection of the primary tumor in order to prevent the need for urgent surgical procedures due to local complications [31, 32]. Ruo et al. [33] reported that 30 (29%) out of 103 patients who were initially treated without bowel resection required subsequent operations for palliation of complications. Recently, some authors have suggested the use of elective resection of asymptomatic colorectal cancers, at least in a subset of patients with less advanced stage IV disease [33, 34]. Other authors have suggested a deferring resection of minimally symptomatic colorectal tumors because most of these patients succumb to progressive systemic disease instead of the complications related to the intact primary

lesion [33, 35]. However, surgical resection may delay the start of chemotherapy [35]. Generally, an interval of 4 weeks is required between surgery and the start of chemotherapy regimens, such as FOLFOX, FOLFIRI or XELOX. In most clinical trials, patients who have undergone surgery within 4 weeks are excluded. However, there is no apparent evidence to support this delay. Metastatic tumors can enlarge rapidly before the start of chemotherapy, possibly resulting in death. Because the significance of the postoperative 4-week delay before the start of chemotherapy is unclear, we evaluated the feasibility and safety of administering chemotherapy early in patients who have undergone colorectal surgery for colorectal cancer with synchronous multiple distant metastases [36–38].

In conclusion, we herein reported a case in which combination chemotherapy with XELOX + BV, denosumab, and rhTM was administered to treat DIC resulting from DCBM of the transverse colon cancer. The patient successfully survived DCBM for more than 100 days from the start of chemotherapy. As previously noted and to the best of our knowledge, this is the first case report of such long-term survival in a patient with DCBM originating from colorectal cancer. We are now considering surgical intervention targeting the primary lesion.

References

1 Jarcho S: Diffusely infiltrative carcinoma. A hitherto undescribed correlation of several varieties of tumor metastasis. Arch Pathol 1936;22:674.
2 Hayashi H, Haruyama H, Emura Y, Kaizuka I, Ozeki T: Disseminated carcinomatpsis of the bone marrow – study of a type of metastatic cancer and relationship of microangiopathic hemolytic anemia or disseminated intravascular coagulation (in Japanese). Jpn J Cancer Clin 1979;25:329–343.
3 Yanagawa M, Shibagaki F, Kono T, Okado A: A case of mucinous carcinoma of the ascending colon with DIC being aggravated by systemic bone metastasis (in Japanese). J Hyogo Assoc of Surg 1984;80:55–58.
4 Haratake J, Horie A: Clinicopathological examination of 12 autopsy cases of carcinomatosis of the bone marrow (in Japanese). Gan No Rinsho 1985;31:168–178.
5 Onodera H, Kawamura S, Miyake T, Mekawa K, Kanda M: A case of disseminated carcinomatosis of bone marrow from juvenile colon cancer (in Japanese). Gendai Iryo 1990;22:451–457.
6 Watanabe T, Ryu T, Yanagisawa M, Iizuka H: Metastatic bone marrow cancer from the stomach and colon. Progress in Acute Abdominal Medicine (in Japanese). 1990;10:488–491.
7 Hasegawa H, Kobayashi K, Iwahashi K, et al: A case of colon cancer presenting as disseminated carcinomatosis of the bone marrow (in Japanese). Shikwa-Gakuho 1991;91:193–198.
8 Yoshioka K, Shimizu H, Yokoo S, Adachi H: Disseminated carcinomatosis of bone marrow from submucosal carcinoma in adenoma of the rectum (in Japanese). Intern Med 1992;31:1056–1059.
9 Satoh N, Tamauchi T, Kobayashi I, Okamoto T, Mori S, Takeda H, Yokoyama S, Yashiro S: Microangiopathic hemolytic anemia associated with disseminated carcinomatosis of the bone marrow from abdominal neoplasmas (in Japanese). J Fukuroi Municipal Hospital 1999;8:98–104.
10 Kurata M, Takada Y, Kawamoto T, Yoshida S, Taniguchi H, Todorori T, Fukao K: Successful MTX-5FU sequential therapy for disseminated intravascular coagulation due to systemic bone marrow metastasis after operation (in Japanese). J Jpn Surg Assoc 2000;61;1256–1260.
11 Ianki N, Yoshiba H, Shibahara K, Funaki Y, Inada A, Mizuno K: A case of signet ring cell carcinoma of the ascending colon with myclocarcinosis (in Japanese). Gastroenterol Surg 2000;23:1729–1734.
12 Kikuchi Y, Hagisawa Y, Takahashi K, Hike K, Miura T, Urita Y, Hachiya A, Ida K, Miki K, Hasegawa C, Hamatani S, Miura M: A case of carcinomatosis of the bone marrow due to diffusely infiltrative colon cancer (in Japanese). Gastroenterol Endos 2002;44:1949–1954.
13 Uchida H, Hino N, Okamoto S, Taniyama K, Yamakida M: A case of rectal cancer complicated with bone marrow carcinomatosis and dsisseminated intravascular coagulation (in Japanese). The Kyosai Medical Journal 2002;51:236–240.
14 Nakazawa S, Ryo H, Yoshida K, Akiyama K, Yamashita Y, Kameoka S: A case of disseminated carcinomatosa of bone marrow from ascending colon cancer (in Japanese). Jpn Soc Gastroenterol Surg 2002;35:431–435.
15 Hirose Y, Matsushita T, Yamamoto H, Fuji H, Tanaka F: A case of juvenile colon cancer with bone marrow carcinosis (in Japanese). J Jpn Surg Assoc 2002;63:964–966.
16 Hirokawa F, Ono K, Hayashida M, Ochiai M, Shirai Y, Tomita Y: A case of disseminated carcinomatosis of the bone marrow from rectal and transverse colonic cancer (in Japanese). J Jpn Surg Assoc 2003;64:2238–2243.
17 Eshima Y, Ida S, Shigematsu M: A case of disseminated carcinomatosis of the bone marrow lumbago (in Japanese). Orthopedic Surg Traumatol 2005;54:77–80.

18 Makino T, Mishima H, Ikenaga M, Tsujinaka T, Takeda M, Mano M: A case of signet cell carcinoma of the sigmoid colon showing a rapid development of systemic bone marrow metastasis after operation (in Japanese). J Jpn Surg Assoc 2005;66:124–128.
19 Tajima T, Mukai M, Hinoki T, Ootani Y, Sato S, Nakasaki H, Makuuchi H: A case of poorly differentiated carcinoma of the ascending colon with rapid postoperative progression suggesting disseminated carcinomatosis of the bone marrow (in Japanese). Jpn Soc Gastroenterol Surg 2006;39:265–270.
20 Ohnishi K, Ueda N, SendaK, Nakagawara H, Yoshimatsu Y, Sawa T: A case of disseminated carcinomatosis of bone marrow due to recurrence of signet ring cell carcinoma in juvenile colon cancer (in Japanese). J Jpn Surg Assoc 2007;68:136–141.
21 Nakazaki T, Nonaka Y, Shindo H, Tamura K, Taniguchi H, Nakano S: A case of juvenile colon cancer with bone marrow carcinosis (in Japanese). J Jpn Surg Assoc 2007;68:394–397.
22 Kosuge M, Ogawa M, Watanabe M, Eto K, Yokoyama M, Yanaga K: A case of poorly differentiated adenocarcinoma of the transverse colon in which MTX/5-Fu therapy was effective for disseminated inteavascular coagulation syndrome due to carcinoma of bone marrow (in Japanese). J Jpn Surg Assoc 2007;68:943–947.
23 Kobayashi K, Abe M, Ueda N, Sato T, Azuma M, Hanatate F, Shimizu Y, Ikeda Y, Matubara T, Matsunami H: A case of poorly differentiated rectal adenocarcinoma causing disseminated inteavascular coagulation syndrome due to carcinomatosis of bone marrow after a Modified FOLFIRI-induced pathological CR (in Japanese). J Jpn Soc Coloproctol 2009;62:65–71.
24 Nonaka K, Sha S, Ito M, Nonaka K, Yamanaka N: A case of poorly differentiated adenocarcinoma of the rectum with disseminated carcinomatosis of the bone marrow successfully treated with mFOLOX-6/bevacizumab (in Japanese). Nihon Shokakibyo Gakkai Zasshi2010;107:1151–1158.
25 lsozaki Y, Yamanishi M, Utsunomiya S, Yamaguchi S, Okita M, Matsumoto N, Nagao Y, Oyamada H, Kokura S, Naito Y, Yoshikawa T: A case of disseminated carcinomatosis of bone marrow with disseminated intravascular coagulation caused advanced colon cancer treated by mFOLFOX6 (in Japanese). Gan To Kagaku Ryoho 2011;38:1705–1708.
26 Yamauchi M, Okamoto Y, Doi M Shinozaki K: mFOLFOX6 for treatment of anal canal cancer with disseminated carcinomatosis of bone marrow – a case report (in Japanese). Gan To Kagaku Ryoho 2011;37:2209–2211.
27 Hmaguchi Y, Arimitu T, Babazono Y, Seo S, Oike F, Mitsuyoshi A: A case of rectal cancer showing rapid development of disseminated carcinomatosis of bone marrow postoperatively. J Jpn Surg Assoc 2011;72:444–447.
28 Higashiyama A, Kudo M, Nagasako T, Kawamura N, Abiko S, Yamamoto Y, Takano M, Gotoh J, Tamaki T, Meguro J, Yonekawa M, Kawamura A, Tanino M: Successful chemotherapy of carcinomatosis of the bone marrow with disseminated intravascular coagulation from a rectal carcinoma found by eosinophilia (in Japanese). Nihon Shokakibyo Gakkai Zasshi 2011;108:1244–1251.
29 Yamakawa K, Fujimi S, Mohri T, Matsuda H, Nakamori Y, Hirose T, Tasaki O, Ogura H, Kuwagata Y, Hamasaki T, Shimazu T: Treatment effects of recombinant human soluble thrombomodulin in patients with severe sepsis: a historical control study. Crit Care 2011;15R123.
30 Akiyama M, Suzuki Y, Yamaguchi T, Tamai H, Kariya K, Takami H, Yoshida Y: Blood coagulation and anticoagulant therapy for cases of disseminated carcinomatosis of the bone marrow with a disseminated intravascular coagulation (in Japanese). Jpn J Cancer Clin 1993;39:1819–1824.
31 Joffe J, Gordon PH: Palliative resection for colorectal carcinoma. Dis Colon Rectum 1981;24:355–360.
32 Longo WE, Ballantyne GH, Bilchik AJ, Modlin IM: Advanced rectal cancer. What is the best palliation? Dis Colon Rectum 1988;31:842–847.
33 Ruo L, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD: Elective bowel resection for incurable stage IV colorectal cancer: Prognostic variables for asyptomatic patients. J Am Coll Surg 2003;196:722–728.
34 Rosen SA, Buell JF, Yoshida A, Kazsuba S, Hurst R, Michelassi F, Millis JM, Posner MC: Initial presentation with stage IV colorectal cancer: how aggressive should we be? Arch Surg 2000;135:530–534.
35 Benoist S, Pautrat K, Mitry E, Rougier P, Penna C, Nordlinger B: Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. Br J Surg 2005;92:1155–1160.
36 Yoshida Y, Hoshino S, Shiwaku H, Beppu R, Tanimura S, Tanaka S, Yamashita Y: Early start of chemotherapy after resection of primary colon cancer with synchronous multiple liver metastases: a case report. Case Rep Oncol 2011;4:250–254.
37 Yoshida Y, Hoshino S, Shiwaku H, Beppu R, Tanimura S, Tanaka S, Yamashita Y: Early start of chemotherapy after resection of brain metastasis from colon cancer with synchronous multiple liver metastases: a case report. Case Rep Oncol 2012;5:290–294.
38 Yoshida Y, Hoshino S, Aisu N, Naito M, Miyake T, Tanimura S, Yamashita Y: Pilot study of the early start of chemotherapy after resection of primary colorectal cancer with distant metastases (Pearl Star 01). World J Surg Oncol 2013;11:39.

Table 1. Blood biochemical findings

WBC	4,000/μl	BUN	22 mg/dl
RBC	343×10⁴/μl	Cr	1.78 mg/dl
Hb	10 g/dl	Na	138 mEq/dl
Ht	29.30%	K	3.9 mEq/dl
Plt	8.6×10⁴/μl	Cl	100 mEq/dl
TBil	0.9 mg/dl	Glu	155 mg/dl
AST	53 IU/l	PT	21.8 s
ALT	23 IU/l	INR	1.98
LDH	537 IU/l	APTT	33.6 s
CK	508 IU/l	Fibrinogen	51 mg/dl
ALP	1,379 IU/l	AT III	82%
γ-GTP	13 IU/l	FDP	57 μg/dl
CRP	0.9 mg/dl	CA19-9	41 U/ml
		CEA	1,382.5 ng/ml

Table 2. Characteristics of DCBM in patients with colorectal cancer (Japan 1984–2013)

Characteristics		Patients, n	Chemotherapy	No. patients in chemotherapy	Survival	Outcome
Age						
Median	55					
Range	26–78					
Sex						
Male		16				
Female		11				
Primary lesion						
Cecum		2				
Ascending colon		5				
Transverse colon		4				
Descending colon		1				
Sigmoid colon		4				
Rectum		10				
Anal		1				
Histology						
Well		2	BSC	2	52±2	All dead
Moderately		2	BSC	2	20±9	All dead
Poorly		13	BSC	4	47±14	All dead
			mFOLFOX6	3	180±44	1 case alive
			mFOLFIRI	1	210	alive
			mFOLFOX6/BV	1	210	alive
			MTX/5-FU	2	124±79	All dead
			CPT11/CDDP	1	84	All dead
			UFT/LV/CP11	1	180	All dead
Signet		6	BSC	2	22±1	All dead
			XELOX/BV	1	118	alive
			5-FU	1	90	All dead
			MTX/5-FU	1	90	All dead
			CBDCA/5-FU	1	90	All dead
Mucinous		3	BSC	2	21±1	All dead
			5-FU	1	90	All dead
Carcinoid		1	BSC	1	390	All dead

BSC = Best supportive care; MTX = methotrexate; 5-FU = fluorouracil; LV = leucovorin; CPT11 = irinotecan; CDDP = cisplatin; CBDCA = carboplatin; UFT = tegafur–uracil; XELOX = oxaliplatin+ capecitabine.

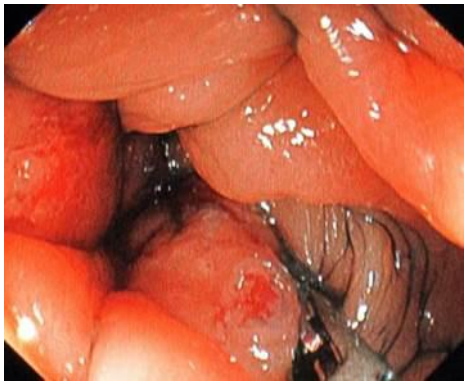

Fig. 1. Complete stenosis of the transverse colon on TCS.

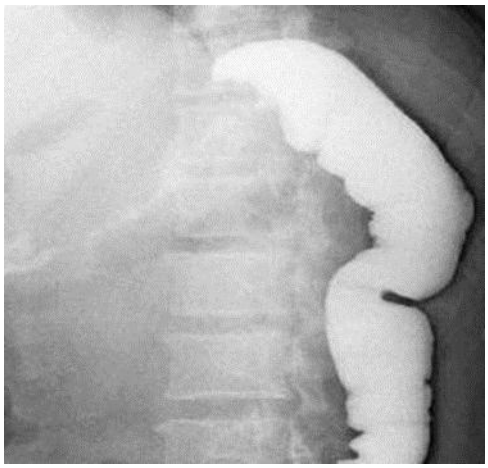

Fig. 2. Intense stenosis with transverse colon cancer observed during an enema.

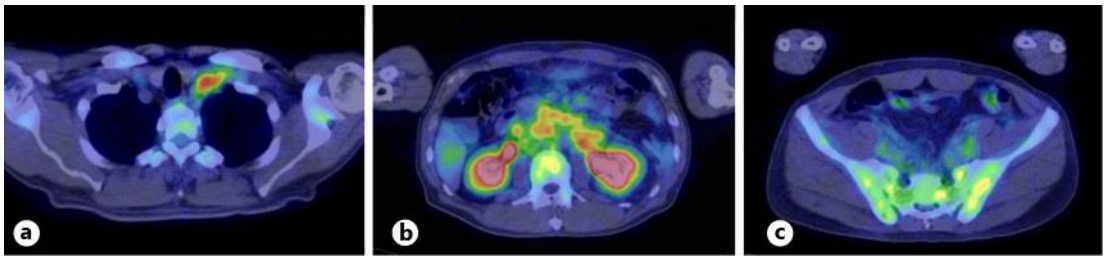

Fig. 3. a–c. Multiple areas of metastatic lymph node invasion and bone metastasis on PET-CT.

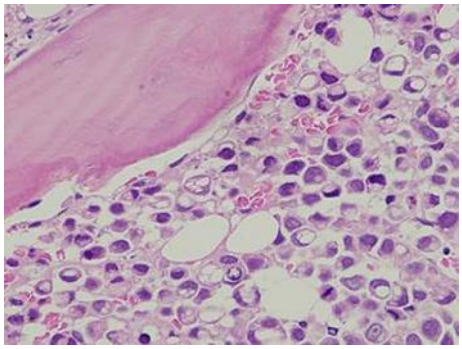

Fig. 4. Biopsy of bone marrow. Metastasis from a signet ring cell carcinoma (HE. ×400).

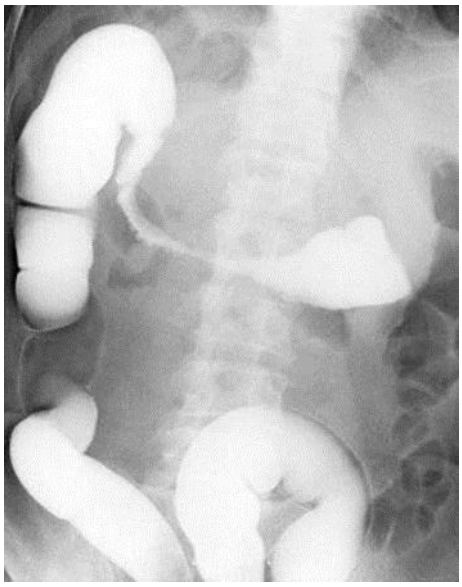

Fig. 5. Stenosis of the transverse colon did not develop during the enema.

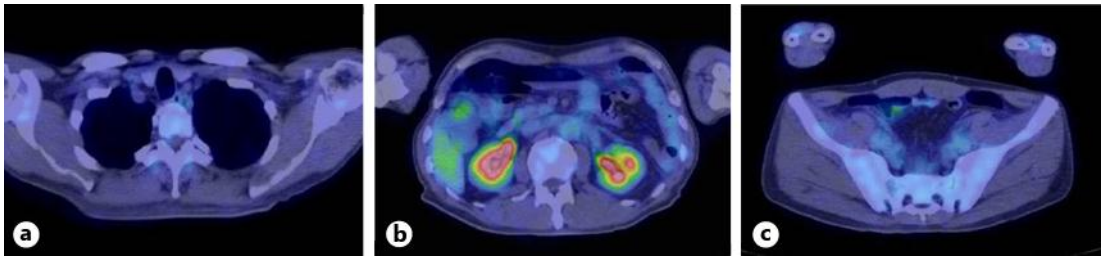

Fig. 6. a–c. Multiple areas of metastatic lymph node invasion and bone metastasis on PET-CT.