J Tokyo Wom Med Univ
86(3) 116~122 (2016)

Report

A Case of Undifferentiated Small Intestinal Carcinoma with Pan-peritonitis

Yoshizumi DEGUCHI[1,2], Takayuki SATO[1,2], Hiroyasu SUGA[1,2], Shinobu SUZUKI[3], Takao NAKAGAWA[1] and Eiji ISOTANI[2]

[1]Department of Emergency and Critical Care Medicine, Isesaki Sawa Medical Association Hospital
[2]Emergency and Critical Care Center, Tokyo Women's Medical University Medical Center East
[3]Department of Pathology, Isesaki Sawa Medical Association Hospital

(Accepted March 18, 2016)

Undifferentiated cancer of the small intestine carries a poor prognosis and has rarely been reported. A 63-year-old man presented with intermittent pain of the left lower abdomen that had been left untreated. Blood tests showed inflammation and high levels of tumor markers. Contrast-enhanced CT of the abdomen showed a small intestinal tumor with a diffuse thickened wall, and fat tissue, peritoneal inflammation, and peritoneal fluid were observed around the tumor. Acute pan-peritonitis due to perforation caused by a small intestinal tumor was diagnosed. Perioperative findings in the jejunum 100 cm from the ligament of Treitz showed a 3-cm, mass and at 20 cm anal side of this mass, there was a 6 cm tumor invading into the sigmoid colon with perforation. Swollen lymph nodes of mesenterium and omentum, and a gastric tumor were also obserbed. Dissection and radical surgery were performed. Histopathologically, primary undifferentiated small intestinal carcinoma was diagnosed. The postoperative course was good and postoperative chemotherapy with an oral anticancer agent, S-1 was started after the patient resumed eating solid food. He was discharged on postoperative day 23, but readmitted with peritonitis carcinomatosa on postoperative day 75 and subsequently died on postoperative day 118.

Key Words: small intestinal cancer, undifferentiated cancer, S-1

Introduction

Primary small intestinal carcinoma is very rare, and undifferentiated small intestinal carcinoma is particularly rare, with very few reported cases of long-term postoperative survival[1)~3)]. We report a case of undifferentiated small intestinal carcinoma where the subjective symptom of left lower abdominal pain went untreated and peritonitis developed.

Case Report

Patient: A 63-year-old man.

Past medical history and family history: Nothing of note.

Life history and occupation: Corporate management; Smoking history: 20/day for about 40 years; Drinking history: Social drinker.

History of the present illness: Left lower abdominal pain appeared on December 25, 2012, and intermittent pain persisted. On January 8, 2013, he visited a nearby urology department with the complaint of oliguria. Urology failed to find a problem, but black stool was noted and abdominal ultrasound indicated a pseudo-kidney sign, and thus he was referred to our department for a suspected tumor of the gastrointestinal tract.

Present illness at admission: At admission, the patient was lucid, with a blood pressue of 94/74 mmHg, pulse of 50/min with a regular heart beat,

✉ : Yoshizumi DEGUCHI Emergency and Critical Care Center, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishi-Ogu, Arakawa-ku, Tokyo, 116-8567 JAPAN
E-mail: yoshizumi08@gmail.com

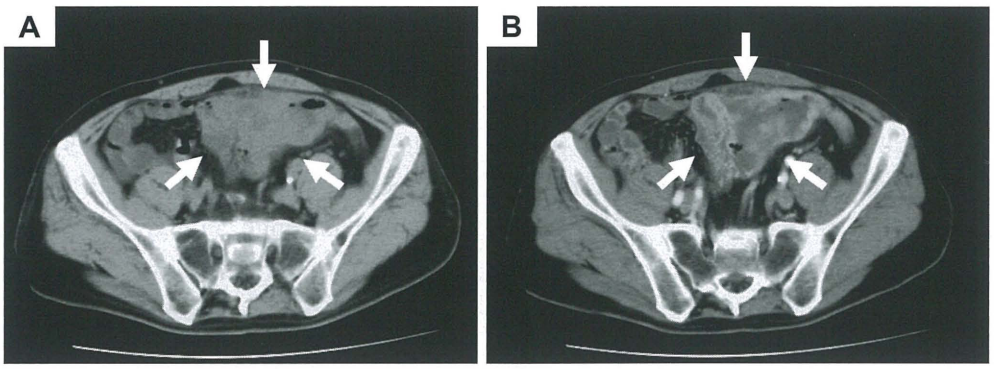

Fig. 1 Abdominal CT shows a diffuse thickening of intestinal wall and large tumor (arrows, A: plain, B: enhanced).

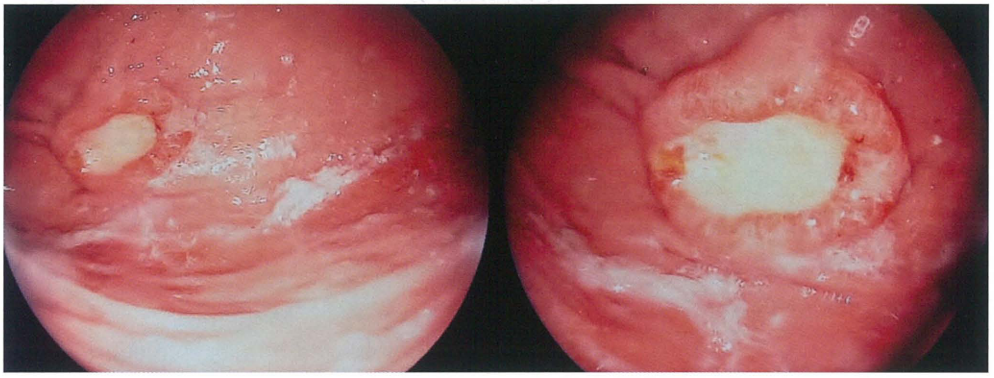

Fig. 2 A type 2 tumor is found on the greater curvature of gastric body by gastroendoscopy.

and temperature of 36.2 ℃. Height was 167.4 cm and weight was 65.1 kg. The patient said he had lost about 4 kg of weight in several months. He did not have palpebral conjunctival pallor or yellowness of the bulbar conjunctiva, and his skin was moist. There were no anomalies in chest auscultation. The abdomen was mildly distended. A mass with a 6-cm diameter was palpable in the left abdomen, and he complained of tenderness and spontaneous pain.

Blood test findings at admission: Inflammatory response and tumor markers were elevated, with WBC 11,200 /μL, CRP 6.48 mg/dL, CEA 6.8 ng/mL, and CA 19-9 104.0 U/mL. Other biochemical test data did not show any anomalies.

Thoracoabdominal X-ray findings at admission: No pleural effusion, no abnormal shadowing in the lung field; the abdomen showed niveau formation in the small intestine.

Abdominal contrast-enhanced CT findings: There was diffuse tumor-like thickening of the small intestine wall in the left lower abdomen, and we also observed irregularity of the surrounding adipose tissue and peritoneum, a large number of enlarged lymph nodes along the superior mesenteric vein, enlargement believed to be metastasis in the left adrenal gland, and a moderate amount of ascites (Fig. 1).

Upper gastrointestinal endoscopy findings: A Borrmann Type II tumor with a diameter of 2 cm was observed toward the anterior wall of the greater curvature of the stomach, and biopsy results were group 5 and poorly differentiated adenocarcinoma was suspected (Fig. 2).

Lower gastrointestinal endoscopy findings: No abnormal findings, other than two Isp polyps observed in the sigmoid colon.

These results gave a diagnosis of malignant tumors of the small intestine and suspected perforation peritonitis; the patient was hospitalized with fasting and intravenous infusion, and underwent

open abdominal surgery on hospital day 8.

Intraoperative findings: A moderate amount of turbid ascites was observed in the abdominal cavity. A tumor measuring 3 cm was observed in the jejunum, about 100 cm from the ligament of Treitz, and a tumor measuring 6 cm had directly infiltrated into the sigmoid colon at 20 cm further to the anal side. An enlarged lymph node measuring 4 cm was observed in the mesentery. An enlarged lymph node measuring 3 cm was also found in the omentum. Blunt dissection of the small intestine where the sigmoid colon was infiltrated showed a pinhole-like perforation in the center of the tumor. The small intestinal tumor was excised en bloc along with the lymph nodes, followed by end-to-end anastomosis. The site of tumor infiltration in the sigmoid colon was resected and the omental lymph node was dissected; then, 2 cm of tumor in the gastric body was partially resected, and a drain was placed in Douglas' pouch and in the inferior surface of the liver, to conclude the surgery.

Histopathological findings: The 6-cm tumor that had directly infiltrated into the sigmoid colon had an ulcer accompanied by partial perforation, and exhibited a comparatively clearly-defined nodule with a periphery elevated in the manner of an embankment. The tumor nodule was solid, filled with an array of atypical cells having a large and irregular nucleus, clearly-defined nucleolus, and a wide amphophilic cytoplasm. The tumor cells had no clear, specific trend in their arrangement. Some mitotic figures were also seen, and some were found to have succumbed to necrosis. Tumor growth spanned the full thickness of the wall, and there was exposure below to the delaminated surface and serosal surface. Lymphatic invasion was also observed. The tumor nodule measuring 3 cm that was observed in the jejunum, about 100 cm from the ligament of Treitz orad of there included an ulcer, and there was growth of a tumor exhibiting similar histological signs. Tumor growth here spanned from the mucosa to the subserosal layer. The 2-cm tumor nodule of the stomach also included an ulcer, and exhibited growth of a tumor showing similar histological signs from the mucosa to the muscle layer, with clearly-defined nodule formation with a periphery elevated in the manner of an embankment. The greatest tumor diameter was in the small intestine, where the depth of invasion spanned the full thickness, with growth infiltrating into a broad range, and lymphatic invasion also observed; however, the tumor nodule of the stomach was confined to between the mucosa and muscle layer. Thus, we concluded that the 6-cm tumor of the small intestine was the primary lesion. Immunostaining showed that the tumor cells were slightly positive for cytokeratin (AE1/AE3). They were negative for UCHL-1, CD20, CD30, epithelial membrane antigen (EMA), and desmin.

Thus, these histological signs and immunostaining results indicate small intestine primary undifferentiated carcinoma (Fig. 3). According to 8th edition of the Japanese Classification of Colorectal Carcinoma, the carcinoma was classified as SE, N3, H0, P3, M1, and Stage IV.

He followed a favorable course, other than developing postoperative wound infection, and was started on fluids on postoperative day 5; on postoperative day 7, he gained the ability to eat sanbugayu (Japanese porridge), and on postoperative day 23, he was started on an oral anticancer agent, S-1 and discharged.

On postoperative day 75, he was re-hospitalized with a fever and abdominal pain.

Abdominal contrast-enhanced CT findings: A 63-mm tumor was observed in the nearby mesentery after the small intestinal carcinoma surgery, and this was also found to be surrounded by lymph node metastasis and nodules believed to be peritoneal dissemination. A 65 × 48-mm tumor was also found in the sigmoid colon. The left adrenal tumor had increased in sized as compared to the previous CT (Fig. 4).

Lower gastrointestinal endoscopy findings: A Borrmann Type II tumor occupied the majority of the lumen in the sigmoid colon about 37 cm from the pectinate line. This corresponding to the site of direct invasion of the small intestinal carcinoma at the time of the previous surgery, and biopsy results showed poorly differentiated carcinoma, which was

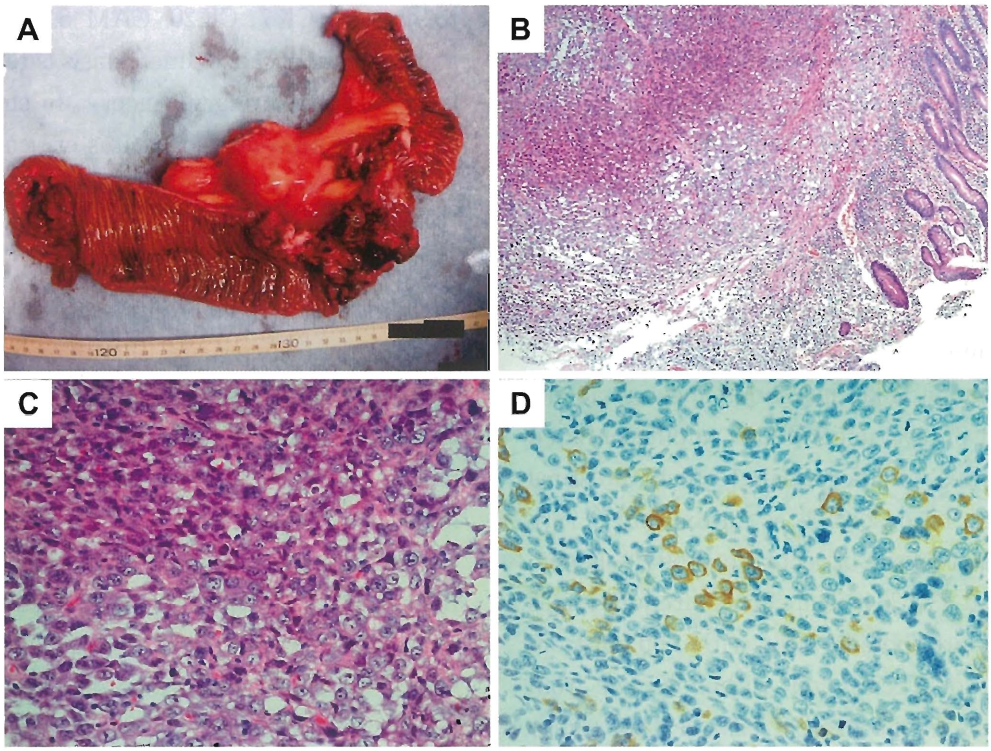

Fig. 3 Macroscopically, a type 2 tumor is observed in the jejunum (A), and microscopically, atypical cells with large irregular nucleus are diffusely infiltrated and form a solid line irregularly. Further immunohistochemical studies show the lesion to be slightly positive for cytokeratin (AE1/AE3) (B: HE×50, C: HE×200, D: cytokeratin (AE1/AE3)×200).

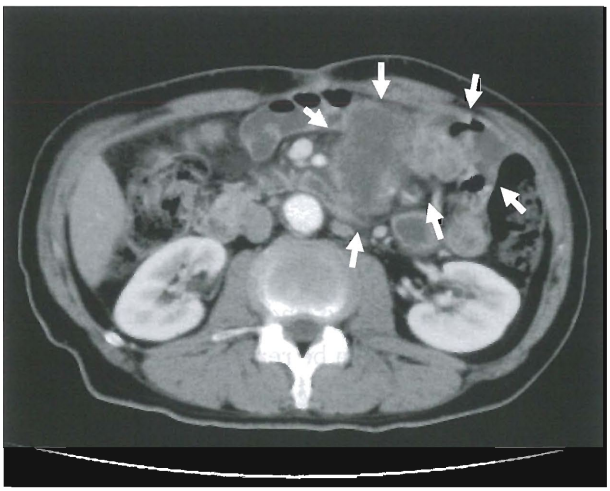

Fig. 4 Enhanced abdominal CT on postoperative day 75, showed multiple recurrent tumor, lymph node metastasis on the mesenterium and peritoneal dissemination (arrows,).

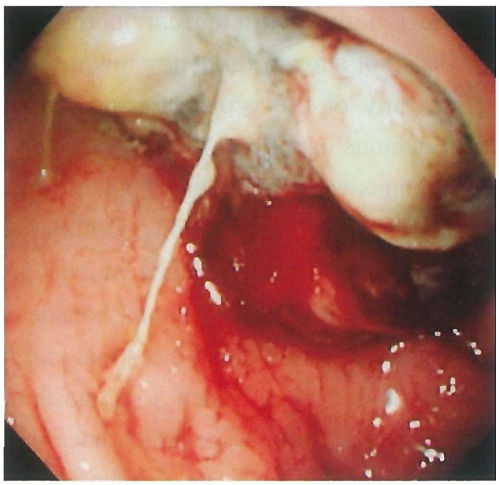

Fig. 5 Type Ⅱ tumor recurrence was found in the sigmoid colon by colonoscopy.

believed to be recurrence of the small intestinal carcinoma (Fig. 5).

On postoperative day 84, he underwent a small intestine bypass surgery and colostomy, and regained the ability to eat, but later, peritonitis carcinomatosa led to left abdominal wall infiltration, and he died on day 118 after the first surgery.

Discussion

The small intestine accounts for 75 % of the entire gastrointestinal tract in terms of length, and 90 % in terms of total mucosal surface area, but malignant tumors rarely occur in the small intestine, and

the frequency of primary small intestinal malignant tumors is about 1 to 3 % of all gastrointestinal tract malignant tumors[4]. According to Yao et al[5], the frequency of small intestine malignant tumors by tissue type is 32.6 % cancer, 30.4 % malignant lymphoma, and 29.1 % gastrointestinal stromal tumor (GIST). Thus, primary small intestinal cancer is said to be about 0.2 % of all gastrointestinal tract cancer[6]. According to Ikeguchi et al[7] and Hiramitsu[8], the most common small intestine cancer is adenocarcinoma, at 87.5 %, and 6.3 % is undifferentiated carcinoma; thus undifferentiated small intestinal carcinoma can be described as an extremely rare disease. In terms of site of occurrence, 56.7 % is jejunal cancer and 43.3 % is ileal cancer; frequent sites of occurrence are thought to be within 60 cm from the ligament of Treitz and within 40 cm from Bauhin's valve. In the present case, a 3-cm tumor was found in the jejunum about 100 cm from the ligament of Treitz, and a 6-cm tumor also had infiltrated directly into the sigmoid colon from 20 cm toward the anal side.

The Japanese Classification of Colorectal Carcinoma defines undifferentiated carcinoma as when "cancer does not show a tendency toward differentiating into any of the types of cancer-adenocarcinoma, mucinous carcinoma, signet ring cell carcinoma, squamous cell carcinoma, or adenosquamous carcinoma—and does not exhibit glandular cavity formation or have clearly-evident mucus production[9][10]. This means that the histopathological findings for undifferentiated small intestinal carcinoma would make it difficult to reach a diagnosis simply from an HE-stained tissue specimen, because large or small polynuclear cells or spindle cells grow without assuming a certain structure. In many reports, a definitive diagnosis of undifferentiated small intestinal carcinoma was reached by immunostaining with multiple antibodies[11]. The tumor cells in the present case were EMA negative, but only slightly positive for AE1/AE3, and appeared epithelial in nature. They were negative for UCHL-1, CD20, CD30, EMA, and desmin, thus ruling out malignant lymphoma and non-epithelial tumor. Undifferentiated carcinoma is positive for other cytokeratins (CK7, CK20, CAM 5.2, etc.)[12][13]. With small intestinal cancer, metastasis is ten times more frequent than primary cancer[14]. In small intestinal cancer has been diagnosed, it is critically important to differentiate between primary cancer and metastasis. Since the 2 small intestinal tumors and the gastric tumor of the present case were exposed to the lumen, careful consideration was needed to determine the primary site. Generally, intramural metastasis of the gastrointestinal tract is when a metastasis forms under the mucosa or serosa, separated from the primary tumor, via the submucosal layer, lymphatic network, or venous network; the primary tumor and the metastasis are histopathologically identical, and there should be no continuity between the tumors. Macroscopically, there is said to be submucosal tumor-like elevation. When the present case is considered on the basis of these facts, Together with the gastric tumor and with a large number of lymph node metastases, the 3-cm tumor was considered to be non-continuous metastasis that had formed in the small intestine apart from the primary 6-cm tumor that showed identical history and had been perforated.

Clinical symptoms of small intestine malignant tumors overall include abdominal pain, vomiting, bleeding, palpable masses, ileus, anemia, and abdominal bloating, but in reported cases of small intestine cancer in Japan, abdominal pain, vomiting, and other ileus symptoms as well as bloody stool have caused patients to undergo surgery before a definitive diagnosis can be reached, due to acute abdomen. In the present case, frequent abdominal pain had gone untreated since the year prior, and progressed into peritonitis. Blood biochemistry do not include any useful tumor markers for undifferentiated small intestinal carcinoma, but the present case exhibited high values for both CEA and CA 19-9. Metastasis to the stomach or sigmoid colon is thought to have lead to the increase in these tumor markers. Elevated soluble IL-2 receptor is also observed in tumor-bearing conditions and blood diseases such as malignant lymphoma, and therefore reports have also noted it would be an auxiliary diagnosis of undifferentiated small intestinal carci-

noma[15]. In terms of treatment strategies for primary small intestinal cancer in the future, we feel it is most important that it be discovered in the early stages, when there is no lymph node metastasis. Testing generally includes intraoral or enema contrast examination, endoscopy, ultrasound diagnosis, CT, MRI, angiography, and the like. However, these tests rarely provide a definite diagnosis before surgery. In CT and MRI findings, small intestinal cancer often exhibits afferent wall thickening, with uneven density in the tumor. It is considered necessary to confirm the site of occurrence by first diagnosing the presence of a tumor with ultrasound diagnosis, CT, or MRI and then identifying the feeding vessels by angiography. Recent improvements in endoscopic technology, such as double-balloon endoscopes and capsule endoscopes, and the spread of PET have raised the frequency of discovery of small intestinal cancer[16]. Double-balloon endoscopy or capsule endoscopy in the small intestine relies greatly on the practitioner's skills, and the examination takes time, but there is great potential for these new diagnostic procedures.

Treatment is generally small intestinal resection including lymph node dissection when resection is possible, but in practice, many cases are advanced and they often end up in palliative surgery. Even in the present case, the primary tumor was resected in the first surgery, and yet there was widespread lymph node metastasis, and we observed direct infiltration into the sigmoid colon as well as left adrenal metastasis, and thus this was not radical surgery. In the second surgery, as well, we observed a remnant that had become a lump in the abdominal cavity, and recurrent tumors, and surgery was confined to bypass and colostomy. There is no standard regimen at present for chemotherapy for small intestinal cancer, but there are reports where adjuvant chemotherapy was attempted on the basis of regimens for stomach cancer and colon cancer[17]. S-1 is an oral anticancer agent that blends 5-chloro-24-dihydroxypyridine, a competitive inhibitor of dehydropyrimidine dehydrogenase, which is a 5-fluorouracil (5-FU)-degrading enzyme, into tegafur, which is a prodrug of 5-FU, thus intensifying the anti-tumor effects of the 5-FU; it reportedly is often effective in stomach cancer and colon cancer. Recent years have seen reports where chemotherapy with S-1 was performed after surgery for small intestinal mucinous adenocarcinoma or undifferentiated carcinoma and yielded recurrence-free survival[18)19)]. S-1 has advantages in particular in that it does not exhibit adverse events and allows for medication to be administered on an outpatient basis, without adversely affecting the patient's QOL. On this basis, we obtained informed consent in the present case to perform oral chemotherapy with S-1, but this did not lead to long-term survival. There are very few reported cases of long-term survival with undifferentiated small intestinal carcinoma, which has a poor prognosis, and according to Pridgen et al, the three-year survival rate, five-year survival rate, and 10-year survival rate are reportedly 34.0 %, 23.9 %, and 12.5 %, respectively[20].

Testing methods for early diagnosis have been established in recent years, and reports of cases of radical surgery are expected to increase.

References in this paper represent a search from 1977 to August 2014 with the keywords "small intestinal cancer", "undifferentiated cancer", and "S-1" in the Igaku Chuo Zasshi.

The authors declare no conflicts of interest.

References

1) **Ackman FD**: Carcinoma of the small intestine. Can Med Assoc J **32** (6): 634–639, 1935
2) **Harries DJ, Harrison CVPR**: Primary carcinoma of the small intestine. Br Med J **1** (3878): 923–962, 1935
3) **Nakamura T, Otani Y, Kokuba Y et al**: A case of primary undifferentiated small intestinal carcinoma with neuroendocrine cell differentiation observed in association with multiple small intestine metastases. J Jpn Surg Assoc **61** (12): 3271–3275, 2000
4) **Ogata S, Kazuto M, Kurayama H et al**: A study of five cases of malignant small intestinal tumors in the classroom. J Jpn Soc Gastroenterol Surg **19**: 722–725, 1986
5) **Yao H, Yao K, Matake H et al**: Summary of the last five years (1995-1999) of Japanese case reports of small intestine tumors. Stomach and Intestine **36**: 871–881, 2001
6) **Kurakane K**: Clinical statistical discussion of primary jejunal and ileal cancer in Japan. Saishin Igaku **34**: 1053–1058, 1979

7) **Ikeguchi M, Nishidoi H, Hiroshi K et al**: A case of undifferentiated ileal cancer—A study of 95 reported cases of primary jejunal and ileal cancer in Japan. J Jpn Surg Assoc **54**: 450–454, 1993
8) **Hiramitsu T, Masahi H, Nakanishi K et al**: A case of primary undifferentiated jejunal cancer. J Jpn Soc Gastroenterol Surg **42** (12): 1826–1830, 2009
9) **Japanese Society for Cancer of the Colon and Rectum**: Japanese Classification of Colorectal Carcinoma, (8th edition). Kanehara Shuppan, Tokyo (2013)
10) **Sasaki M, Hanatate F, Yamamura K et al**: A case of undifferentiated small intestinal carcinoma with anemia as chief complaint. J Jpn Soc Gastroenterol Surg **21** (10): 2435–2438, 1988
11) **Gadoya M, Suzuki Y, Hazama K et al**: A case of undifferentiated primary small intestine cancer. J Jpn Soc Gastroenterol Surg **36** (11): 1615–1620, 2003
12) **Usuda M, Nakano T, Hirano T et al**: A case of undifferentiated small intestinal carcinoma onset with unidentified fever. J Jpn Surg Assoc **68** (10): 2543–2547, 2007
13) **Arase K, Higurashi A, Yamada T et al**: A case of primary undifferentiated small intestinal carcinoma accompanied by bilateral adrenal metastasis. J Jpn Surg Assoc **72** (5): 1156–1161, 2011
14) **Matsuoka T, Katsuragi K, Matsuzaki T et al**: A case of undifferentiated small intestinal carcinoma accompanied by multiple small intestinal intramural metastasis. J Jpn Soc Gastroenterol Surg **41** (1): 123–128, 2008
15) **Seishima R, Nagase T, Nakagawa M et al**: A case of undifferentiated small intestinal carcinoma accompanied by multiple small intestinal metastases and lymph node metastases in the pancreatic head. J Jpn Surg Assoc **71** (6): 1544–1549, 2010
16) **Ideguchi K, Obayashi K, Ueda H et al**: Two cases of small intestinal malignant tumor. J Kyoto Pref Univ Med **122** (4): 237–243, 2013
17) **Inaba M, Kataoka M, Yasuhara I et al**: A case of triplicate cancer including primary undifferentiated small intestinal carcinoma. J Jpn Soc Gastroenterol Surg **43** (11): 1159–1164, 2010
18) **Gunji N, Gohongi T, Iida H et al**: A case of jejunal cancer accompanied by lung metastases and peritoneal dissemination where preoperative TS-1 therapy was successful. J Jpn Soc Gastroenterol Surg **40** (11): 1839–1844, 2007
19) **Maruyama T, Horiuchi S, Enomoto T**: A case of small intestinal cancer accompanied by peritoneal dissemination treated with S-1 therapy. J Jpn Soc Gastroenterol Surg **37**: 1249, 2004
20) **Pridgen JE, Mayo CW, Dockerty MB**: Carcinoma of the jejunum and ileum exclusive of carcinoid tumors. Surg Gynecol Obstet **90**: 513–524, 1950

腹膜炎で発症した小腸未分化癌の1例

[1]伊勢崎佐波医師会病院救急医療科
[2]東京女子医科大学東医療センター救急医療科
[3]伊勢崎佐波医師会病院病理検査科

出口（デグチ） 善純（ヨシズミ）[1,2]・佐藤（サトウ） 孝幸（タカユキ）[1,2]・須賀（スガ） 弘泰（ヒロヤス）[1,2]
鈴木（スズキ） 忍（シノブ）[3]・中川（ナカガワ） 隆雄（タカオ）[1]・磯谷（イソタニ） 栄二（エイジ）[2]

小腸腫瘍のなかでも非常に稀で予後不良の小腸未分化癌の1例を経験した．症例は63歳男性．左下腹部の間欠痛が続いていたが放置していた．来院時血液検査で炎症反応と腫瘍マーカー高値を認めた．腹部造影CT所見では小腸壁のびまん性腫瘤状肥厚があり，周囲の脂肪織や腹膜の不整と中等量腹水を認め小腸腫瘍による穿孔性腹膜炎と診断した．開腹するとトライツ靭帯から約100 cmの空腸に径3 cm大の腫瘤を，その肛側20 cmの部分に径6 cmの腫瘤を認めた．後者はS状結腸に浸潤しており，ピンホール状の穿孔を伴っていた．腸間膜や大網にリンパ節腫脹を認めた．小腸腫瘍をリンパ節とともに一塊に切除し端々吻合した．S状結腸の腫瘍浸潤部位を切除し大網のリンパ節切除，胃体部の腫瘍を部分切除した．病理検索では小腸未分化癌が原発巣と考えられた．術後経過良好で経口摂取可能となったため23日目より経口抗がん剤S-1を開始し退院したが，術後75日目に癌性腹膜炎で再入院し術後118日目に死亡した．