

Gemcitabine with Paclitaxel Therapy Against Mesocolic Leiomyosarcoma: A Case Report

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Abstract. A 65-year-old man complained of lower right abdominal pain, and an intra-abdominal mass was identified. An intra-abdominal hemorrhage was discovered during a thorough examination and emergency surgery was performed. The tumor was ruptured and was fragile, making it difficult to perform extirpation; thus, an ileocecal resection was performed. The histopathological diagnosis of the tumor was leiomyosarcoma, and recurrence was observed during the early postoperative period. The patient underwent surgery twice; each time there was a recurrence, but complete resection could not be obtained, and paclitaxel and gemcitabine chemotherapy was performed. A temporary effect was observed, and control of disease progression lasted approximately five months. Standard chemotherapy for leiomyosarcoma has not been established, but this method could become a therapeutic strategy for leiomyosarcoma.

Mesocolic leiomyosarcoma is resistant to chemotherapy and radiation therapy, and effective therapy other than surgical treatment has not been established. However, the early discovery of this disease is difficult, and the disease has usually progressed significantly by the time subjective symptoms appear. Here, we report on the use of paclitaxel and gemcitabine that appeared to be effective against mesocolic leiomyosarcoma, which grows extremely quickly and is unresectable.

Case Report

A 65-year-old patient had repetitive lower right abdominal pain from July 2010. A gastro-intestinal endoscopy was performed at a local hospital, but abnormalities were not

found. However, with abdominal ultrasonography and abdominal computed tomography (CT), a mass was identified in the lower right abdomen, and the patient was subsequently referred to our Department. The day after magnetic resonance imaging was performed, the patient experienced severe abdominal pain and was immediately admitted to the hospital on September 10, 2010 (Figure 1). At the time of admission, the patient complained of severe pain in the chest, abdomen, and lumbar region, and was fairly lucid, with a blood pressure of 90/60 mmHg and a pulse rate of 120/minute. Palpebral conjunctiva anemia was observed, and the abdomen was slightly swollen.

Abdominal palpation showed that the abdominal area was elastic soft, but general tenderness and coldness of the limbs were observed. Blood biochemistry test results are shown in Table I. Marked anemia and marked acidosis were detected. Abdominal X-ray showed a gasless region in the right abdomen, and also confirmed gas in the small intestine. From the abdominal CT observations, we determined this to be an intra-abdominal hemorrhage due to a ruptured tumor, and emergency surgery was performed (Figure 2).

Upon laparotomy, we found approximately 4 Lt. of intra-abdominal bleeding. A soft tumor approximately 20 cm in diameter was found on the right mesentery with a hematoma adhered to its surface. Bleeding from the ruptured tumor was found on the dorsal side of the hematoma. It appears that this was the feeding artery from the superior mesenteric artery region, but its identification was difficult. The tumor itself was fragile, and extirpation was extremely difficult. Thus, we performed ileocecal resection. The resected specimen showed that the tumor was encapsulated, and the interior portion consisted of a mixture of solid and cystic components (Figure 3).

Histopathological findings showed atypical spindle cell proliferation that indicated differentiation into smooth muscle. Immunohistochemical examination indicated that the tumor was α -smooth muscle actin (SMA)-positive, Anti -CD117 (c-KIT)-negative, and S-100 protein (S-100)-negative, and the tumor was subsequently diagnosed as a leiomyosarcoma (Figure 4).

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Figure 1. Computed tomographic image of the irregularly-shaped tumor (triangles), with a size of 162×141×90 mm, of the right abdominal cavity. A mixture of multilocular low-high signals was present in the tumor, and the portions with high signal were considered hemorrhagic changes.



Figure 2. Computed tomographic image showing fluid collection with a high absorption value around the liver (a). The tumor was enlarged due to an internal hemorrhage, and it was considered that the tumor had ruptured (b).

Table I. Laboratory data upon admission.

Parameter value		Blood gas at O ₂ 5-l face mask	
RBC	206×10 ⁴ /μl	pH	6.953
Hb	6.5 g/dl	pCO ₂	50.6 Torr
Hct	19.0 %	pO ₂	185.7 Torr
Plt	25.0×10 ⁴ /μl	HCO ₃	10.9 mEq/L
WBC	141×10 ² /μl	B.E.	-19.4 mEq/L
AST	14 U/l		
ALT	12 U/l		
LDH	293 U/l		
T.bil	0.76 mg/dl		
BUN	24.0 mg/dl		
Cre	0.84 mg/dl		
Na	139 mmol/l		
K	4.1 mmol/l		
Cl	106 mmol/l		
CK	40 U/l		
CRP	1.75 mg/dl		

RBC: Red blood cell count, Hb: hemoglobin, Hct: hematocrit, Plt: platelet count, WBC: white blood cell count, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, T.bil: total bilirubin, BUN: urea nitrogen, Cre: creatinine, Na: creatinine, K: potassium, Cl: chloride, CK: creatine kinase, CRP: C reactive protein.

Three months after this event, on December 15, 2010, an 11×15 cm tumor on the inferior aspect of the liver was discovered with abdominal CT, and resurgery was performed with the diagnosis of recurrence. Aside from the inferior aspect of the liver, the tumor was also present on the mesentery of the small intestine. The tumor on the mesentery was extirpated with partial resection of the small intestine, but complete extirpation of the tumor on the inferior aspect of the liver was impossible. The residual tumor was treated with heat therapy upon the patient's request, but there were no effects, and it had further enlarged according to CT one month later. In addition, because the patient had lost his appetite and body weight due to compression by the tumor, a salvage operation was performed on March 10, 2011. We extirpated the tumor as

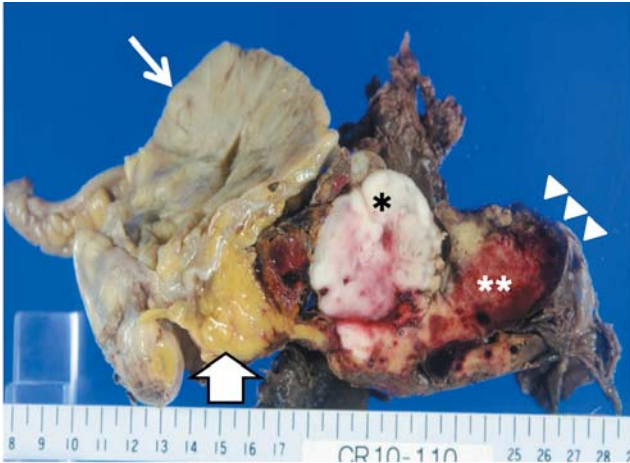


Figure 3. Resected specimen. Tumor was found on the mesentery (broad arrow). The tumor was encapsulated (triangles), and the inside contained a mixture of hard solid parts(*) and soft parts(**). Narrow arrow: Ascending colon.

much as possible and performed gastro-jejunostomy (bypass method). The residual intra-abdominal tumor remained only on the inferior aspect of the liver, and the patient was consequently able to consume food (Figure 5a).

On March 23, 2011, the patient started therapy of gemcitabine (1,250 mg/m², days 1 and 8), and paclitaxel (175 mg/m², day 8) with three per cycle on an outpatient basis. After completing four cycles of treatment, a reduction tendency in the tumor and cystic changes of its interior were observed (Figure 5b). However, after completion of nine cycles, there were no changes in the tumor on the inferior aspect of the liver, and a new lesion had appeared on the liver. Disseminated lesions were also observed on the abdominal wall, and the patient was diagnosed with progressive disease (Figure 5c). The regimen was subsequently changed to gemcitabine and docetaxel, but CT after four cycles showed increased liver metastasis and liver lesions. Furthermore, chemoembolization (degradable starch microspheres; 300 mg + mitomycin C; 4 mg) against the liver lesions was performed three times without any effect, and the patient passed away on March 6, 2012. The survival period was 18 months after the emergency surgery for the ruptured tumor, and 12 months after initiation of chemotherapy.

Discussion

Small tumors that develop in the abdomen have poor subjective symptoms, and early discovery of these tumors is rare. In particular, mesenteric tumors are extremely rare (1, 2), and it has been shown in Japan that malignant mesenteric tumors are usually sarcomas. The prognosis of advanced soft

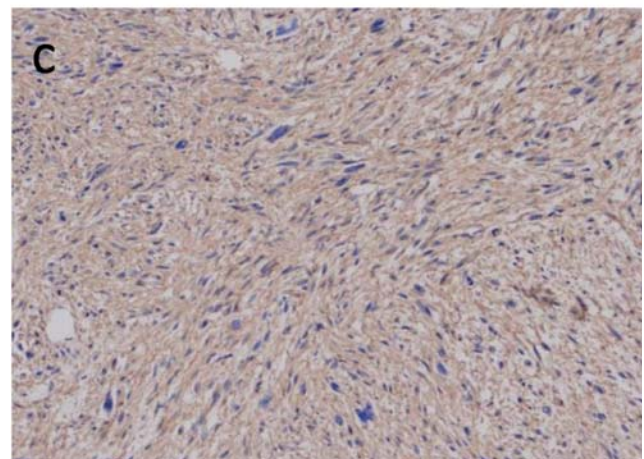
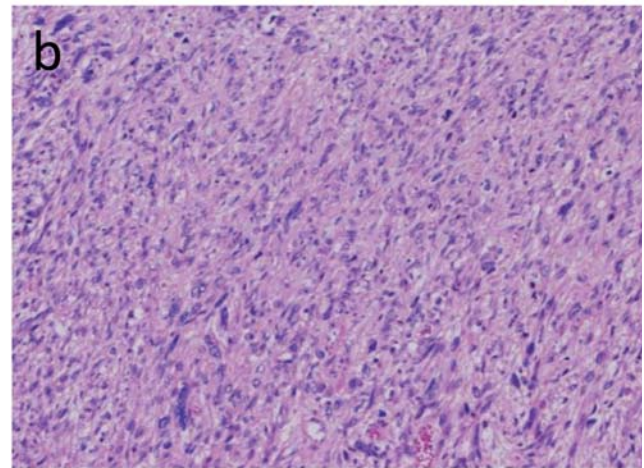
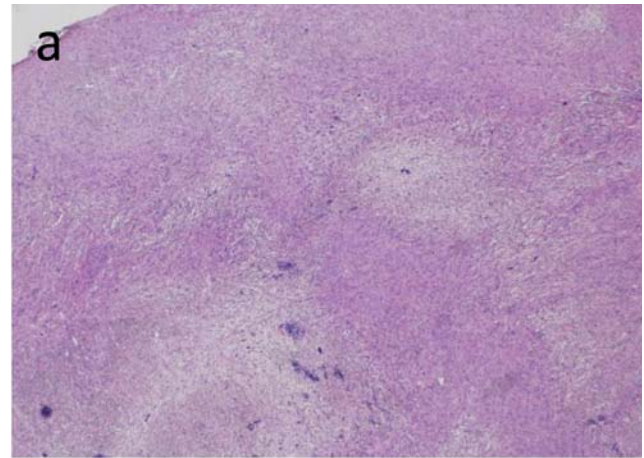


Figure 4. Hematoxylin and eosin (H&E) staining of the tumor showed atypical spindle cell proliferation that indicates differentiation into the smooth muscle. Immunostaining showed positive staining only for α -smooth muscle actin (α -SMA), Anti-CD117 (c-KIT) and S-100 protein (S-100). a: H&E staining, low-power field, b: H&E staining, high-power field, c: α -SMA staining.

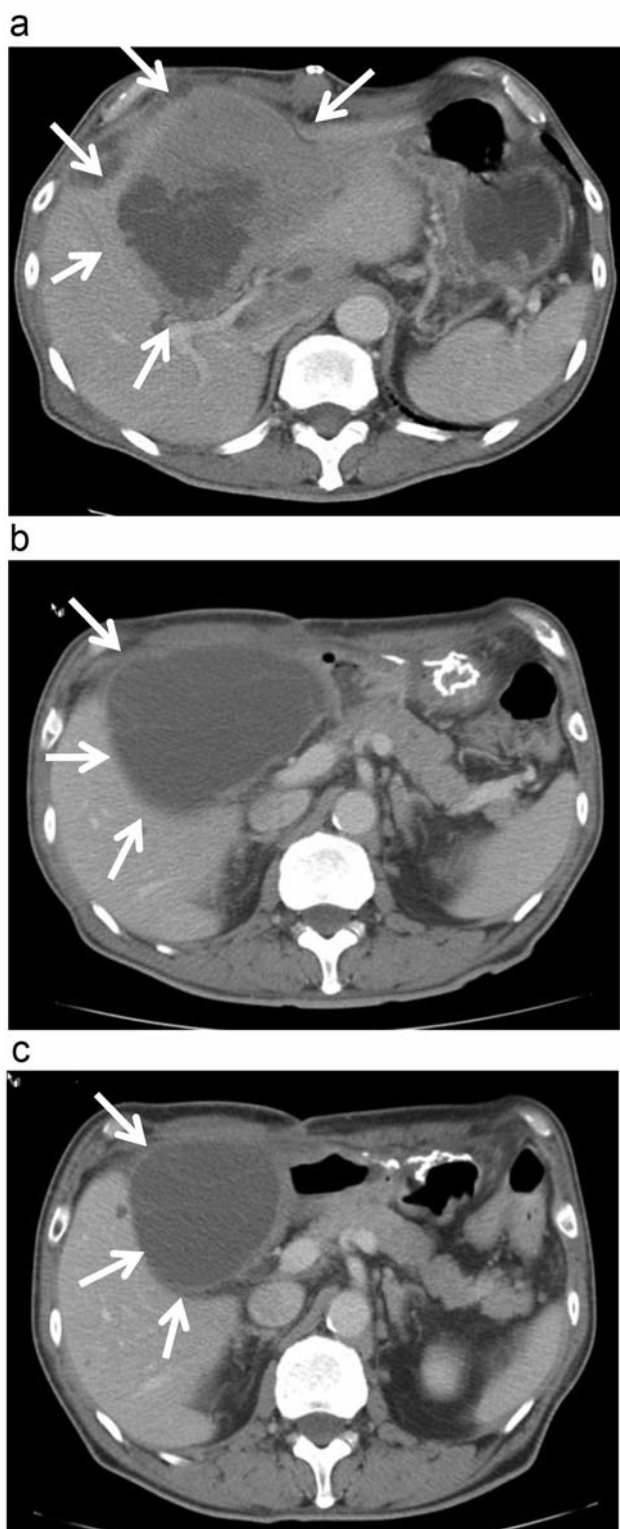


Figure 5. a: Residual tumor present on the inferior aspect of the liver before chemotherapy. b: The tumor was slightly reduced in size, and the majority of the interior showed cystic changes at two months after chemotherapy. c: The tumor was further reduced in size, but new lesions in the liver and on the peritoneum were found at five months after chemotherapy.

tissue sarcomas (STS) remains poor. As a general rule, surgical resection is used for treatment, but performing R0 resection is often difficult (3). In addition, there are only few reports that indicate the efficacy of treatments such as chemotherapy, radiation therapy, chemoradiotherapy, and hyperthermic chemotherapy towards this type of cancer. There are no clear treatment guidelines established for leiomyosarcoma (4), and hence we performed hyperthermic therapy, general chemotherapy, and embolization against liver metastasis, but only gemcitabine with paclitaxel showed a positive effect.

Anthracyclines, ifosfamide, gemcitabine, and trabectedin have been reported as treatment drugs for STS, especially leiomyosarcoma (5). Most reports were pertaining to leiomyosarcoma in the urological and gynecological fields. The efficacy of these drugs was unfavorable, with 25% efficacy for doxorubicin alone, and 17% efficacy for ifosfamide alone (6).

Recently, the utility of treatment with concomitant usage of gemcitabine and docetaxel as second-line therapy has been reported (7, 8). From the positive results of this concomitant therapy in uterine leiomyosarcoma (9) and from a French sarcoma group study (10), it was suggested that these drugs have high sensitivity.

Paclitaxel is mainly known to provide good responses against cancer such as breast cancer, gastric cancer, and uterine carcinosarcoma. Donald *et al.* reported that control of disease progression was achieved against uterine leiomyosarcoma in 30% of cases(11). There was a report from Japan that also showed marked tumor reduction using concomitant therapy with gemcitabine and paclitaxel against lung metastasis of leiomyosarcoma. From such reports, we decided to use gemcitabine with paclitaxel as first-line therapy and gemcitabine with docetaxel as second-line therapy. We observed a tumor-reducing effect, and control of disease progression lasted for approximately five months. However, there were no digestive or neurological symptoms, and the quality of life was satisfactory. We cannot affirm that this treatment was effective against mesocolic leiomyosarcoma, but at the very least, it was markedly effective against the primary lesion. Testing various treatment methods may lead to a breakthrough in treatment of refractory tumors.

In addition, molecular-targeted drugs have been developed, and their effects on various types of carcinoma have recently been reported. For instance, there is a good example that imatinib, a tyrosine kinase inhibitor, is markedly effective against gastrointestinal stromal tumors (12). Furthermore, although this pertains to metastatic breast cancer, eribulin mesylate (Halaven[®]) is clinically used for patients who previously received anthracycline and taxane. This new inhibitor of microtubule dynamics was also effective towards xenografts of leiomyosarcoma cells (13).

Many subtypes of STS have been found to express various tyrosine kinase receptors and pro-angiogenic growth factors, which are considered to play a role in tumor pathogenesis and angiogenesis (14). If gene expression profiling becomes clear in leiomyosarcoma, which is a non-epithelial tumor similar to STS, antibodies against these factors may allow for new clinical therapeutic strategies.

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