

[ CASE REPORT ]

## Primary Cardiac Leiomyosarcoma: A 27-Month Survival with Surgery and Chemotherapy

Koji Nakashima, Haruhiko Inatsu and Kazuo Kitamura

### Abstract:

The patient was a 39-year-old man hospitalized due to the presence of a cardiac mass and heart failure. Emergency tumor resection and mitral valve replacement were performed. The pathological findings of the tumor led to a diagnosis of cardiac leiomyosarcoma. After the operation, multiple metastases were found. The patient underwent three courses of chemotherapies: adriamycin, ifosfamide, dacarbazine, and mesna (MAID therapy), gemcitabine plus docetaxel, and sunitinib. During MAID therapy, the patient underwent resection of gastrointestinal metastases twice due to gastrointestinal hemorrhaging. Although he died 27 months after the initial treatment, use of multimodal therapy was effective in achieving a longer survival for the patient.

**Key words:** cardiac neoplasm, leiomyosarcoma, surgery, chemotherapy

(Intern Med 56: 2145-2149, 2017)

(DOI: 10.2169/internalmedicine.6965-15)

### Introduction

Primary cardiac leiomyosarcoma is very rare, and it also has a poor prognosis. Although radical surgery is the best intervention for achieving a good outcome, complete surgical resection is sometimes difficult due to distant metastasis. Although in these cases, surgical resection and palliative chemotherapy may be effective, their actual effectiveness remains unclear.

### Case Report

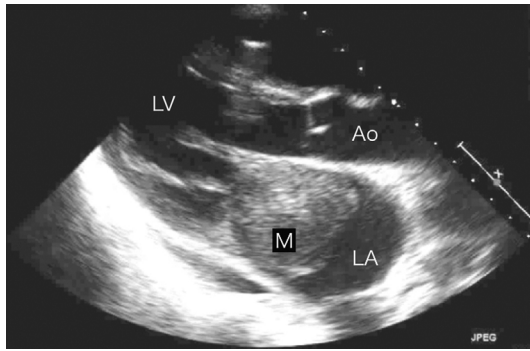
A 39-year-old man was admitted to a local hospital with effort dyspnea. Before admission, he had suffered from fatigue for 7 months and productive coughing at night for a month. A cardiac tumor was detected by echocardiography, and he was transferred to our hospital for diagnosis and treatment. His blood pressure and pulse rate at admission was 89/58 mmHg and 88/min, respectively. Fig. 1 shows the patient's echocardiography on admission. The cardiac mass involved the left atrium, and it invaded the mitral valve. The hemodynamic abnormalities included a mitral stenosis-like appearance (peak flow velocity of mitral valve, mean mitral valve gradient and measurement of systolic pulmonary ar-

tery pressure was 3.67 m/s, 23 mmHg and 99 mmHg, respectively). Fig. 2 shows the chest enhanced computed tomography (CT) findings on admission. An extracardial expanding mass was observed. In abdominal CT, an upper abdominal mass measuring 3 cm in size was detected. Due to the patient's indications of unstable hemodynamics, he could not receive detailed examinations, and an emergency operation was performed on the day after admission. The intraoperative findings demonstrated that a left atrial tumor had invaded the left auricle and expanded beyond the pericardium. The tumor within the left auricle was resected, and the mitral valve was replaced. Figs. 3 and 4 show the pathological findings. In a macrographic view, a white mass was observed, and Hematoxylin-Eosin staining demonstrated sheet-like spindle cells with elongated- to irregular-shaped hyperchromatic nuclei, or unusually large nuclei. Immunohistochemistry showed strong positivity for vimentin and smooth muscle actin. Thus, the tumor was diagnosed to be cardiac leiomyosarcoma. After the operation, the patient's vital signs normalized and his general condition improved. Thereafter, he was examined for systemic metastasis by positron emission tomography-computed tomography (PET-CT). PET-CT showed multiple metastases in the stomach, small intestine, right vastus lateralis muscle, and left gluteus maximus muscle. Fig. 5 shows images obtained from double balloon en-

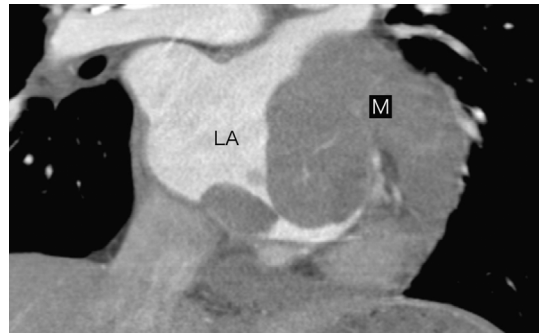
First Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Japan

Received: December 17, 2015; Accepted: May 6, 2016; Advance Publication by J-STAGE: August 1, 2017

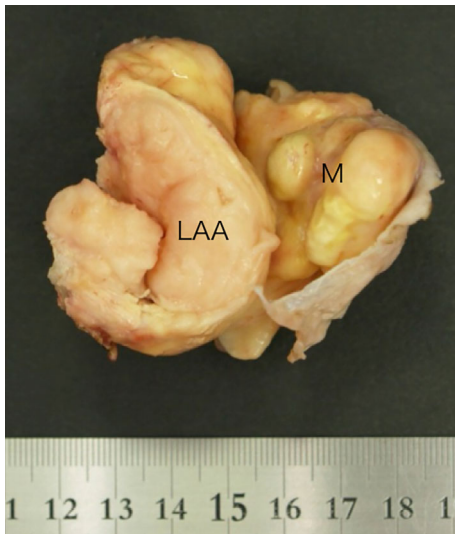
Correspondence to Dr. Haruhiko Inatsu, [inacchi@med.miyazaki-u.ac.jp](mailto:inacchi@med.miyazaki-u.ac.jp)



**Figure 1.** Echocardiography on admission. The cardiac mass is involved in the left atrium and mitral valve failure is observed. M: mass, LA: left atrium, LV: left ventricle, Ao: aorta

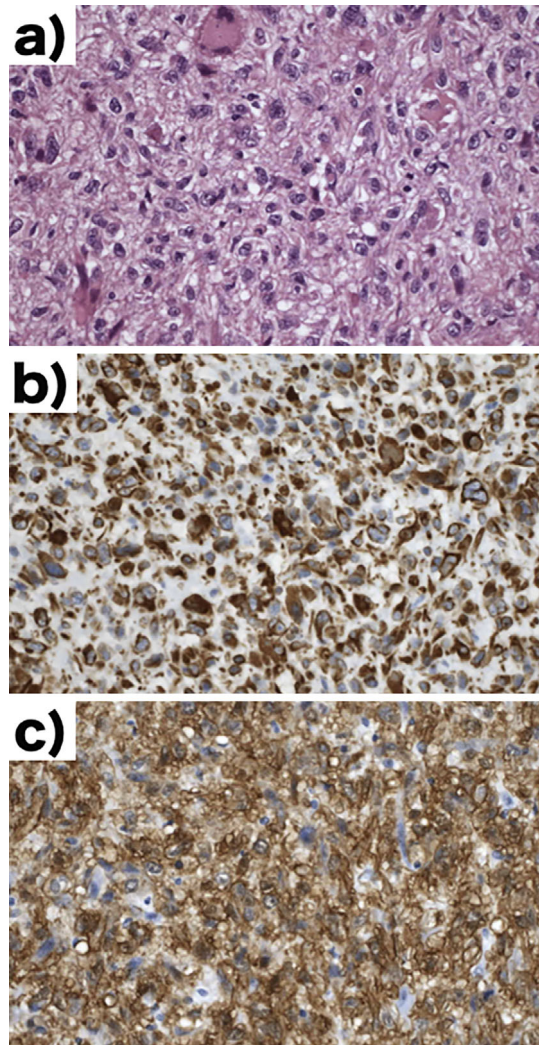


**Figure 2.** Chest enhanced computed tomography on admission. An extracardial expanding mass is observed. M: mass, LA: left atrium

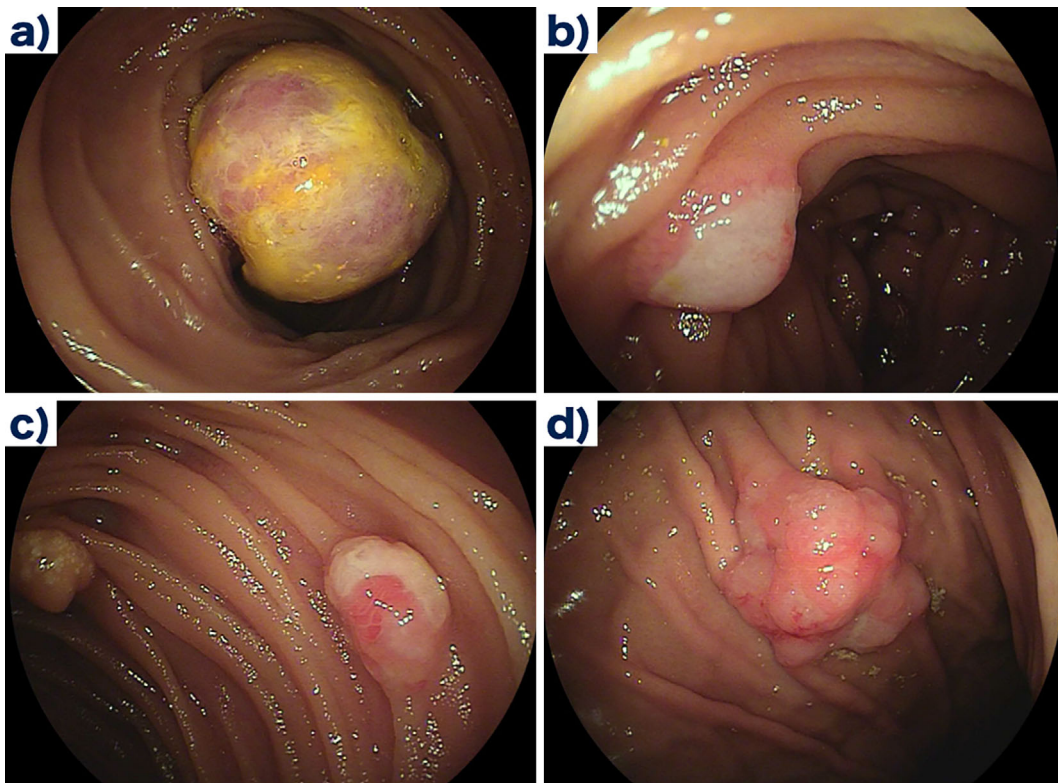


**Figure 3.** Resected left atrial tumor with left auricle showed a white smooth surface and a randomly-distorted appearance. M: mass, LAA: left atrial auricle

doscopy (DBE). DBE revealed multiple masses in the stomach, with a poly-nodular and submucosal tumor-like appearance, and in the jejunum, with a giant mass in the lumen and a submucosal tumor-like appearance. These multiple and submucosal tumor-like appearances were the typical findings of a metastatic gastrointestinal tumor. Biopsy results showed findings that were similar to the cardiac pathological findings, and multiple metastases of cardiac leiomyosarcoma were diagnosed. The patient received combination chemotherapy of adriamycin (DXR), ifosfamide (IFM), dacarbazine (DTIC), and mesna (MAID therapy every four weeks: DXR 20 mg/m<sup>2</sup>/day, day 1-3; IFM 2,500 mg/m<sup>2</sup>/day, day 1-3; DTIC 300 mg/m<sup>2</sup>/day, day 1-3; mesna 2,400 mg/m<sup>2</sup>/day, day 1-4). Although MAID therapy showed a partial response in abdominal CT as per the Response Evaluation Criteria In Solid Tumors (RECIST; version 1.0), gastrointestinal hemorrhaging occurred after 3 courses. DBE identified the small intestine metastases as the cause of hemorrhaging. Eight metastatic lesions in the small intestine were resected by open abdominal surgery. Because the hemorrhaging stopped after



**Figure 4.** (a) Hematoxylin and Eosin staining (×400) showed the growth of sheet-like spindle cells with elongated- to irregular-shaped hyperchromatic nuclei or unusually large nuclei. Mitosis was observed in an 8/10 high power field. Immunohistochemical studies showed strong staining of vimentin (b) and  $\alpha$ -smooth muscle actin (c). MIB-1 labeling index is 44.1% (324/734).



**Figure 5.** Double balloon endoscopy findings. (a) In the jejunum, a giant mass is located in the lumen. (b) (c) In the jejunum, a multiple submucosal tumor-like appearance was seen. (d) In the stomach, a poly-nodular and submucosal tumor-like appearance was seen.

surgical resection, MAID therapy was resumed. However, after nine more courses of MAID, gastrointestinal hemorrhaging occurred again. A new intra-gastric mass with bleeding was identified by upper gastrointestinal endoscopy, and it diagnosed to indicate a progression of disease. Because the size of the mass was large (50 mm), it was resected by partial gastrectomy. After recovering from surgery, the patient underwent second line chemotherapy with gemcitabine (GEM) plus docetaxel (DTX) (GEM+DTX therapy every three weeks: GEM 900 mg/m<sup>2</sup>, day 1, 8; DTX 60 mg/m<sup>2</sup>, day 8). Four months after the start of GEM+DTX therapy, PET-CT revealed cardiac recurrence and new metastatic bone, lung, stomach, adrenal gland, and intramuscular lesions. A chest X-ray revealed pleural effusion and an enlargement of the cardiac silhouette due to cardiac recurrence. The patient received third line chemotherapy with sunitinib. After the start of sunitinib administration, the enlargement of cardiac silhouette improved and the amount of pleural effusion decreased. However, 2 months after the start of sunitinib, he suffered from uncontrolled worsening of general fatigue and dyspnea, and cardiac recurrence and heart failure was identified as the cause of his symptoms. Although he received palliative care, he died suddenly 27 months after initial treatment.

## Discussion

Primary cardiac leiomyosarcoma is very rare, and it is re-

ported in less than 0.25% of all cardiac tumors (1) since its first description by Weir et al. in 1941 (2). It typically presents in the patient's 40's, with no sex predilection. Making a preoperative diagnosis of malignant cardiac tumor by echocardiography is difficult, due to difficulty in differentiating it from myxoma, the most common benign tumor of the heart. In the present case, a definitive preoperative diagnosis could not be obtained; however, surgery was urgently required to improve his symptoms and circulation dynamics. Although multiple metastases were found after surgery, sudden death due to heart failure was able to avoid.

Primary cardiac leiomyosarcomas have a poor prognosis, and the mean survival time without treatment is reported to be 6 months from the time of diagnosis (3). Primary cardiac leiomyosarcoma is usually asymptomatic until it reaches an advanced stage, and the diagnosis is often delayed until the emergence of clinical symptoms due to heart failure and embolism. Although radical surgery is the best intervention for achieving a good outcome, complete surgical resection is difficult to achieve in many cases, and local recurrence or metastasis often occurs even in cases of complete resection. In a study by Donsbeck et al. (4) with twenty-four cases of primary cardiac sarcoma (including six cases of leiomyosarcoma), complete macroscopic resection was successful in only 33% of 24 cases, and death due to local recurrence occurred in 50% of complete macroscopic resection cases.

Despite the high incidence of distant metastasis, surgical resection relieves symptoms adequately and offers palliation.

**Table. Cases Surviving for Longer than 24 Months with Available Data Regarding the Treatment and Outcome.**

Age (y)	Sex	Site	Size (cm)	operation	re-operation	chemotherapy (chemotherapy drug)	radiation therapy	follow-up	out come	references
67	ND	RV	ND	radical	No	No	No	3y	Alive, NED	12
24	M	LA	7	radical	Yes	Adjuvant (VCR, ACT, IFM, DXR)	Yes	7y	Dead	13
29	F	LV	3.5	radical	No	No	No	24mo	Alive, NED	14
25	M	LA	9	radical	Yes	Adjuvant (DXR, IFM, VBL, ACT)	Yes	7y	Dead	14
16	M	RA	10	radical	No	Adjuvant (IFM, VCR, ACT, DXR)	No	34mo	Alive, NED	15
45	M	LA	ND	radical	No	Adjuvant (IFM, DXR)	No	24mo	Dead	16
36	M	ND	ND	trans-plantation	No	NAC (DXR, IFM)	No	37y	Alive, NED	17
43	F	LA	ND	radical	Yes	Adjuvant (DXR, IFM)	No	45mo	Dead	18
21	F	LA	7	radical	No	Adjuvant (DXR, IFM, CDDP)	No	24mo	Alive, WD	19
3mo	M	RA	4.8	radical	No	Adjuvant (IFM, VP16)	No	18y	Alive, NED	20, 21
49	M	LV	3	radical	No	No	No	3y	Alive, NED	22
42	F	LV	2.5	radical	No	Adjuvant (DXR, DTIC, CPA)	No	2y	Alive, NED	23
3mo	M	RA	5.3	radical	No	No	No	96mo	Alive, NED	24
33	F	LA	8	radical	Yes	Adjuvant (DXR, IFM)	Yes	41mo	Alive, WD	25
56	M	RA	5	radical	Yes	ND	ND	42mo	Alive, WD	26
48	F	LA	ND	radical	Yes	Adjuvant (unknown)	No	3y	Alive, NED	27
47	M	RA	5	radical	No	Adjuvant (DXR, IFM)	No	8y	Dead	28

ND: no data, M: male, F: female, y: year, mo: month, d: day, RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, NAC: neo-adjuvant chemotherapy, DXR: adriamycin, DTIC: dacarbazine, IFM: ifosfamide, VCR: vincristine, ACT: actinomycin D, VP16: etoposide, CPA: cyclophosphamide: VBL: vinblastine, CDDP: cisplatin, WD: with disease, NED: no evidence of disease

While the combination of tumor excision and chemotherapy may be effective, the actual effectiveness remains unclear due to the rarity of leiomyosarcoma cases. A few cases of palliative chemotherapy alone, or surgery followed by palliative chemotherapy have been reported, with survival of 10 to 18 months (5, 6).

Adriamycin, epirubicin, and ifosfamide are some of the key drugs associated with response rates (RRs) of more than 20 percent for chemotherapy of metastatic soft tissue sarcoma. Many different combination chemotherapies including these key drugs have been studied, and were shown to have higher RRs and a longer progression free survival (PFS) than single regimens. The combination of adriamycin, ifosfamide, dacarbazine and mesna (MAID therapy) is one of the most commonly used multi-agent regimens. A study by Antman et al. (7), demonstrated that the response rate and time to progression of MAID therapy were 34% and 4 months, respectively.

Although gemcitabine and docetaxel each have modest activity, GEM+DTX has been shown to be more effective (8, 9), and Maki et al. reported in their randomized

phase II study, which included patients who had received prior chemotherapy, RRs, PFS, and the median overall survivals of GEM+DTX were 16%, 6.2 months, and 17.9 months, respectively (10).

Pazopanib is a multi-targeted orally active small molecule inhibitor of several tyrosine kinases. A worldwide randomized, double-blinded phase III study (the PALETTE trial), which compared pazopanib (800 mg daily) versus placebo in 369 patients of advanced soft tissue sarcoma, showed significantly higher median PFS (4.6 versus 1.6 months) and RRs (12.5 versus 10.7 months) in the pazopanib group (11). Based on these data, pazopanib is recognized as an important regimen for leiomyosarcoma; however, pazopanib had not been approved in Japan at the time that we treated this patient. Therefore, we used sunitinib, another multi-targeted tyrosine kinase inhibitor which shows activity against imatinib-refractory gastrointestinal stromal tumors (GIST). Although the activity of sunitinib for other types of non-GIST sarcoma has not been established, sunitinib improved the present patient's cardiac failure and pleural effusion.

Table shows similar cases that survived for over 24

months with the available data regarding treatment modalities and outcome (12-28). A long survival was reported 17 cases. In these cases, the rate of radical resection, cardiac reoperation, and perioperative chemotherapy were 100% (17/17), 35.3% (6/17), and 70.6% (12/17), respectively. The combination of radical surgery and chemotherapy tended to show a better outcome, and intensive therapy was also effective and improved their survival.

The present patient underwent two abdominal open surgeries for the treatment of gastrointestinal hemorrhaging due to small intestinal and gastric metastases. These operations resolved the gastrointestinal hemorrhaging, and the patient continued palliative chemotherapy. We believe that this multimodal therapy, which included one thoracic surgery, two abdominal surgeries, and three palliative chemotherapy regimens, were effective in achieving a 27-month survival period after initial treatment.

**The authors state that they have no Conflict of Interest (COI).**

#### Acknowledgement

We are grateful to the Department of Pathology and Surgery, Faculty of Medicine, University of Miyazaki.

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