

# Clinicopathological study of cardiac tamponade due to pericardial metastasis originating from gastric cancer

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Supported by KOBAYASHI MAGOBE Memorial Medical Foundation

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Received: 2005-05-02 Accepted: 2005-07-19

**Key words:** Gastric cancer; Pericarditis carcinomatosa; Cardiac tamponade; Chemotherapy

Kobayashi M, Okabayashi T, Okamoto K, Namikawa T, Araki K. Clinicopathological study of cardiac tamponade due to pericardial metastasis originating from gastric cancer. *World J Gastroenterol* 2005; 11(44): 6899-6904  
<http://www.wjgnet.com/1007-9327/11/6899.asp>

## Abstract

**AIM:** To review the cases reported in the literature, examined their clinicopathological features, and evaluated the efficacy of different therapeutic modalities for this rare condition.

**METHODS:** A search of the MEDLINE database revealed 16 cases of pericarditis carcinomatosa (PC) originating from GC reported in the literature between 1982 and 2005. Additional detailed data were obtained from the authors of these studies for subsequent clinicopathological investigation. We have also described about a case study from our own clinic.

**RESULTS:** The mean age of cases with pericarditis carcinomatosa originating from GC was 54 years. Females were diagnosed at a younger age (46.3 years) compared to males (58 years). The mean survival period after diagnosis was 4.5 mo. No statistical differences in the length of survival time were found between different therapeutic modalities, such as drainage, and local and/or systemic chemotherapy after drainage. However, three cases who underwent systemic chemotherapy survived for more than 10 mo. Cases that developed metachronous cardiac tamponade for more than 2 years after the diagnosis of GC generally survived for a longer period of time, although this was not statistically significant. Multivariate analysis revealed that low levels of carcinoembryonic antigen (CEA), and CEA and/or cancer antigen 19-9 (CA 19-9) were associated with longer survival.

**CONCLUSION:** Cases with low levels of CEA, and CEA and/or CA 19-9 should undergo systemic chemotherapy with or without local chemotherapy after drainage.

## INTRODUCTION

Malignant pericardial effusion typically develops slowly and can spontaneously regress or remain stable. Some cases, however, may progress to cardiac tamponade<sup>[1]</sup>. Pericardial effusion can be caused by common primary malignancies that metastasize to the pericardium, such as lung cancer, lymphoma, breast cancer, and leukemia<sup>[2-4]</sup>. Cardiac tamponade due to pericarditis carcinomatosa (PC) originating from a primary gastric cancer (GC) is a rare condition. It is usually detected during the terminal stages of GC; however, it is also detected during cardiac emergencies. There are several reports of cardiac tamponade due to GC; however, most of them are only case reports. Due to the limited number of cases seen in a single institute, we performed a clinicopathological study of the cases of PC originating from GC reported in the literature, including a case from our hospital, and investigated the best therapeutic modality for this rare condition.

## MATERIALS AND METHODS

A search of the MEDLINE database revealed 16 cases of PC originating from GC reported in the literature and meeting proceedings between 1982 and 2005 (Table 1)<sup>[5-15]</sup>. Cases in which PC was synchronous with GC and its recurrence were included. In addition, we asked the authors of these studies to review the available medical records to obtain more information about the cases.

A 36-year-old female patient, diagnosed with Kruckenberg's tumor, who consulted our clinic for further examination, was included in this case study. Endoscopic examination revealed GC of the antrum. The patient underwent distal gastrectomy with lymph node dissection. Histological examination showed that signet-ring cell carcinoma was mostly confined within the mucosal layer and had slightly invaded the muscular layer. Histology also showed lymph node metastases in a wide area with

**Table 1** Reported cases of cardiac tamponade due to pericarditis carcinomatosa from gastric cancer.

Case	Author	Year	Sex	Age	Hist <sup>1</sup>	T	ly	v	n	Time interval <sup>2</sup>	Symptom	AST	ALT	ALP	LDH	CEA	CA19-9	Treatment <sup>3</sup>	Survival <sup>4</sup>
1	Ohtomo	1982	F	33	ud	2	3	NA	NA	0	Cough	31	26	297	365	NA	NA	D	5.0
2	Koide	1984	M	67	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	D	2.0
3		1984	F	65	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	D	5.0
4	Usami	1989	F	44	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	L	1.3
5	Moriyama	1995	M	64	por	>2	NA	NA	>1	2.5 mo	Chest pain	38	11	4.2KA	832	240.1	26.7	S + L	1.5
6	Orihata	1996	M	51	sig	2	0	0	0	27.5 mo	Dyspnea	417	283	281	921	2.3	1 100	L	3.0
7	Sakusabe	1998	M	42	por	2	2	0	0	77 mo	Hypotension	25	35	142	154	0.6	2.7	L	3.5
8	Unno	1998	F	48	sig	NA	NA	NA	NA	7 mo	Dyspnea	51	56	503	235	0.7	47	L	1.5
9	Sakai	1999	M	45	sig	1	3	NA	3	0	Dyspnea	14	18	299	211	1.7	8.6	D	2.5
10	Kobayashi	2000	M	44	sig	1	2	1	2	19 mo	Dyspnea	22	94	456	216	2.5	56	S + L	5.0
11	Hiramatsu	2002	M	51	por	2	2	1	2	26 mo	Fatigue	1 224	1 087	NA	NA	3.0	27.9	S	10.0
12	Saitoh	2003	M	68	tub1	1	2	0	2	4 mo	Hypotension	NA	NA	NA	NA	12.5	238	S	2.5
13		2003	M	69	sig	2	3	3	2	50 mo	Cough	44	58	307	377	3.6	15.5	S + L	14.0
14	Sakusabe	2005	M	69	tub1	2	1	2	0	13 mo	Dyspnea	NOR	NOR	NOR	NOR	5.7		S	2.5
15	Suto	2003	F	52	sig	2	3	2	1	26 mo	Dyspnea	N	N	N	N	N	178.4	D	4.0
16		2003	M	68	tub2	3	3	2	3	32 mo	Dyspnea	N	N	N	N	41.6	894.1	D	1.0
17	Author		F	36	sig	2	2	1	2	27.5 mo	Vomit	95	152	312	272	0.76	9.78	S + L	13.0

NA: data not available, NOR: within normal range

<sup>1</sup>Hist: Histology, ud: undifferentiated carcinoma, por: poorly differentiated adenocarcinoma, sig: signet-ring cell carcinoma, tub1: well differentiated tubular adenocarcinoma, tub2: moderately differentiated tubular adenocarcinoma

<sup>2</sup>Time interval: time interval from the diagnosis of gastric cancer to the onset of cardiac tamponade

<sup>3</sup>D: drainage only, L: local chemotherapy, S: systemic chemotherapy

<sup>4</sup>Survival: survival after onset of cardiac tamponade (months)

Cases 11, 13 and 14 were cited from meeting proceedings.

massive permeation into the lymphatic vessels. The patient underwent postoperative chemotherapy of sequential methotrexate plus 5-fluorouracil. Twenty-seven and a half months after the operation, she developed nausea and laboratory data showed elevated levels of aspartate aminotransferase (95 IU/L), alanine aminotransferase (152 IU/L) and alkaline phosphatase (312 IU/L). An abdominal CT scan revealed massive pericardial effusion and left pleural effusion. The patient underwent pericardiocentesis and left pleural centesis. Cytological examination of the fluid revealed signet-cell carcinoma. After drainage, 10 mg of cisplatin was infused into the pericardial space. The pericardial effusion subsequently disappeared. She underwent injection chemotherapy into the pleural space (135 mg cisplatin) and systemic chemotherapy (cisplatin and sequential methotrexate plus 5-fluorouracil) until the pericardial effusion reappeared 9.5 mo later. Pericardiocentesis was performed again and 150 mg cisplatin was infused into the pericardial space. She also underwent systemic chemotherapy, however, died 13 months after the onset of PC.

Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Multivariate Cox regression analysis was used to identify factors independently associated with mortality. For multivariate analysis, all factors were dichotomized: gender (male, female), time interval between diagnosis of gastric cancer and diagnosis of cardiac tamponade (<24 mo including synchronous cases, >24 mo), carcinoembryonic antigen (CEA) levels (<5.0, >5.0 ng/mL), cancer antigen 19-9 (CA 19-9, <40 U/mL, >40 U/mL), and systemic chemotherapy

(done, not done). Using the Pearson's  $\chi^2$  test, differences in proportions were evaluated.  $P < 0.05$  was considered statistically significant.

## RESULTS

The clinicopathological features of cardiac tamponade due to PC originating from GC are presented in Table 2. More than half of the patients were males, an occurrence similar to that generally seen in GC. The mean age of the 17 cases was 54 years (range, 33-69 years). Females diagnosed with cardiac tamponade tended to be younger (mean, 46.3 years; range, 33-65 years) as compared with the males (mean, 58 years; range, 42-69 years). Of the 17 cases, 14 died within 6 mo of diagnosis. Figure 1 shows the Kaplan-Meier survival curve for all the 17 cases. The mean survival after the diagnosis of PC was 4.5 mo (range: 1.0-14.0 mo). Histological data was obtained for 12 of the cases. Of these, 11 were of the less differentiated type. Eleven of the twelve cases also showed lymphatic permeation, and nine showed lymph node metastasis.

The different treatments used after the diagnosis of cardiac tamponade and the survival of the corresponding cases are shown in Table 3. Six cases underwent pericardiocentesis only, and the mean survival after the diagnosis of cardiac tamponade was 3.3 mo. Eleven cases underwent local infusion chemotherapy targeting the pericardial space and/or systemic chemotherapy following pericardiocentesis. The mean survival periods of the cases treated with local chemotherapy, systemic chemotherapy, and combined local and systemic chemotherapy were

**Table 2** Clinicopathological analysis of cardiac tamponade due to PC from GC

Male:female	11:6
Mean age (yr; n = 17)	54.0 (range: 33-6)
Male	58.0 (range: 42-69)
Female	46.3 (range: 33-65)
Histological types (n = 14)	
sig	7
por	3
ud	1
tub	3
T (n = 13)	
1	3
2	9
3	1
ly (n = 12)	
0	1
1	1
2	5
3	5
v (n = 10)	
0	3
1	3
2	3
3	1
n (n = 12)	
0	3
1	2
2	5
3	2

The histological types, "T", "ly", "v", and "n", are defined in the General Rules for the Gastric Cancer Study by Japanese Research Society for Gastric Cancer<sup>[26]</sup>. sig: signet-ring cell carcinoma; por: poorly differentiated carcinoma; ud: undifferentiated carcinoma; and tub: tubular adenocarcinoma.

For T which represents depth of cancer invasion, 1: mucosal and submucosal layer; 2: proper muscular and subserosal layer; 3: expose to serosal layer; and 4: invasion to the adjacent organ.

For ly and v which represent lymphatic permeation and venous permeation, respectively, 0: none; 1: slight; 2: moderate; and 3: massive.

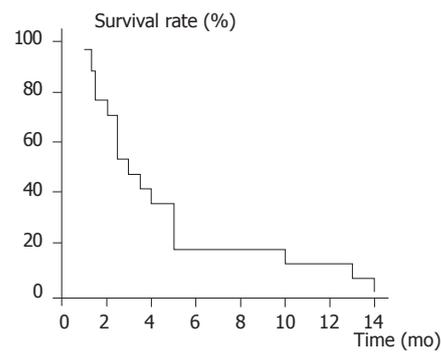
**Table 3** Treatment and corresponding mean survival time after the diagnosis of cardiac tamponade

Modalities	n	Mean survival (mo)
Drainage only	6	3.3
Drainage+chemotherapy		
Local only	4	2.3
Systemic+local	4	8.4
Systemic only	3	5.0

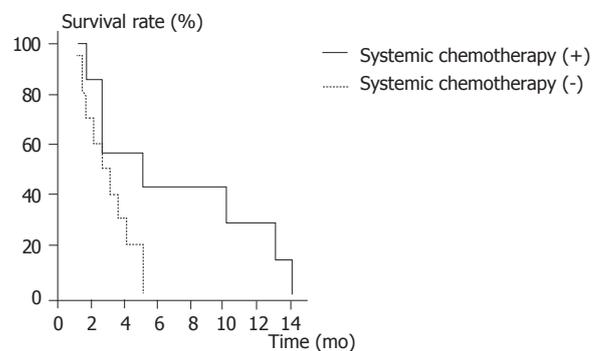
Local: local infusion chemotherapy into pericardial space.

2.3, 5.0, and 8.4 mo, respectively. All the three cases who had survived for more than 10 mo underwent systemic chemotherapy (two cases: local and systemic; one case: systemic only).

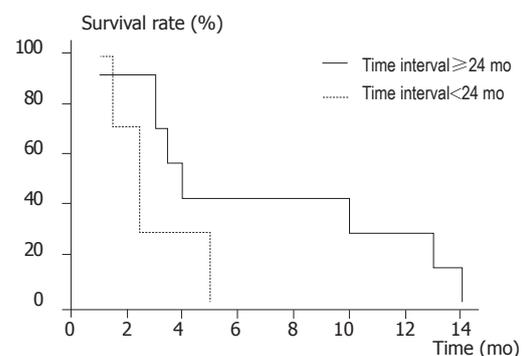
Statistical analyses of the prognostic factors are presented in Table 4. Cases treated with systemic chemotherapy tended to survive longer (6.9 mo) than those who were not treated with systemic chemotherapy ( $P = 0.0579$ ; Figure 2). The mean survival period of the cases that developed cardiac



**Figure 1** Kaplan-Meier survival curve of all cases (n = 17).



**Figure 2** Kaplan-Meier survival curve according to administration of systemic chemotherapy. The cases treated with systemic chemotherapy were more likely to survive longer ( $P = 0.0579$ ) than those who were not treated with systemic chemotherapy.



**Figure 3** Kaplan-Meier survival curve according to time period between the diagnosis of gastric cancer and diagnosis of cardiac tamponade. The cases in whom cardiac tamponades were diagnosed for more than 24 mo after the diagnosis with gastric cancer were more likely to survive longer than those in whom cardiac tamponade was diagnosed for less than 24 mo after the initial diagnosis of gastric cancer. However, there was no statistical difference between the two groups ( $P = 0.1130$ ).

tamponade within 2 years after the diagnosis of primary GC, including one synchronous case, was 2.9 mo. This was shorter than the cases in which the onset of cardiac tamponade occurred 2 years after the diagnosis of GC (6.9 mo). However, there were no statistical differences between the two groups ( $P = 0.1130$ ; Figure 3). The mean

**Table 4** Clinical characteristics of cardiac tamponade due to pericarditis carcinomatosa from GC

Characteristics	n	Survival rate (%)			Median survival in months (range)	P values
		1 mo	5 mo	10 mo		
Overall	17	94.2	17.7	11.8	4.5 (1.0-14.0)	
Gender						
Male	11	90.9	18.2	9.1	4.3 (1.0-14.0)	
Female	6	-	16.7	-	5.0 (1.3-13.0)	0.7614
Time interval						
<24 mo	7	-	0.0	0.0	2.9 (1.5-5.0)	
>24 mo	7	85.7	-	28.5	6.9 (1.0-14.0)	0.1130
CEA (ng/mL)						
<5	9	-	-	22.2	6.3 (1.5-14.0)	
>5	4	75.0	0.0	0.0	1.9 (1.0-2.5)	0.0071
CA 19-9 (U/mL)						
<40	6	-	33.3	16.7	7.4 (1.5-14.0)	
>40	6	-	0.0	0.0	2.8 (1.0-5.0)	0.1074
CEA and/or CA 19-9						
Normal	5	-	0.0	0.0	8.6 (2.5-14.0)	
High	8	87.5	0.0	0.0	2.6 (1.0-5.0)	0.0244
Systemic chemotherapy						
Done	7	-	42.9	28.6	6.9 (1.5-14.0)	
Not done	7	90.0	0.0	0.0	2.8 (1.0-5.0)	0.0579

**Table 5** Relative risk of death as analyzed by Cox proportional Hazards model

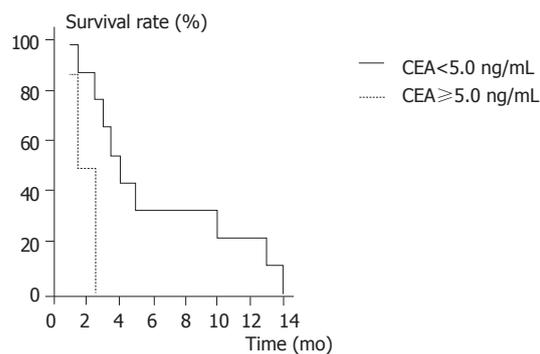
Variables	B value	Relative risk (95%CI)	P values
CEA			
<5.0 ng/mL			
>5.0 ng/mL	1.9	6.7 (1.2-36.6)	0.029
CEA and/or CA-19-9			
<5.0 ng/mL, <40 U/mL			
>5.0 ng/mL, >40 U/mL	1.6	4.9 (1.0-23.7)	0.049

95%CI: confidence interval.

survival periods of cases with high levels (>5.0 ng/mL) and normal levels (<5.0 ng/mL) of CEA were 6.3 and 1.9 months, respectively ( $P = 0.0071$ ; Figure 4). The mean survival periods of cases with high levels (>40 U/mL) and normal levels (<40 U/mL) of CA 19-9 were 2.8 and 7.4 months, respectively ( $P = 0.1074$ ). The cases in which either CEA and/or CA 19-9 were elevated at the time of cardiac tamponade had shorter survival periods (2.6 mo) as compared with the cases without CEA and/or CA 19-9 elevation (8.6 mo) ( $P = 0.0244$ ). Multivariate analysis also revealed that high levels of CEA and CEA and/or CA 19-9 were associated with poor survival ( $P = 0.029$  and  $0.049$ , respectively; Table 5).

## DISCUSSION

Secondary tumors of the heart and/or pericardium are rarely diagnosed in clinical practice. However, it is not uncommon to find these during autopsy cases. Secondary cardiac metastases most frequently arise from primary lung tumors. Primary GC rarely metastasize to the heart, with 4.3-7.7%<sup>[16-19]</sup> reported from autopsy investigations.

**Figure 4** Kaplan-Meier survival curve according to CEA levels. The cases with normal CEA levels had a longer survival period as compared to those with high CEA levels ( $P = 0.0071$ ).

We investigated 17 reported cases of cardiac tamponade due to PC originating from GC, and observed several characteristics specific to this condition. The mean age of the patients was 54 years, which was slightly younger than the average age reported for GC. Females tended to be diagnosed at a younger age than males. Histopathological results of 11 out of the 12 cases showed less differentiated tumors with massive lymphatic involvement. Raven<sup>[20]</sup> and Hanfling<sup>[21]</sup> reported that the hematogenous route was the most common metastatic pathway to the heart, while Warren and Gates<sup>[22]</sup> and Kline<sup>[23]</sup> believed that the cardiac lymphatic system was the major metastatic pathway to the heart. The fact that almost all cases showed massive lymphatic permeation suggested that the mechanism of pericardial metastasis might be through the lymphatic system.

There is no defined therapy for pericardial metastasis. Most reports describing therapeutic modalities for cardiac tamponade due to malignant pericarditis were based on cases in which lung cancer was the primary tumor. Drainage of the malignant effusion either by percutaneous pericardiocentesis or by pericardiectomy should be performed if this condition is diagnosed. The prognosis of cardiac tamponade caused by malignant pericarditis is grave and survival is limited. Fraser *et al*<sup>[24]</sup> reported the prognosis of 21 cases and more than half of the 21 cases originated from lung cancer. Seven patients treated with pericardiocentesis and provided with supportive care had a median survival time of 3 wk. Eight patients treated with pericardiocentesis and either radiotherapy and/or intrapericardial or systemic chemotherapy had a median survival period of 3.5 mo. Six patients treated with pericardiocentesis and pericardiectomy with or without radio- or chemotherapy had a median survival period of 6 mo. Moreover, Appelqvist *et al*<sup>[1]</sup> reported the prognosis of three cases of pericardiectomy. Among them, two cases had primary lung cancer, while the primary tumor was of unknown origin in the third case. The case who did not undergo treatment only survived for 5 wk, the case treated with radiotherapy survived for 7 wk, and the case treated with systemic chemotherapy survived for 9 mo<sup>[1]</sup>.

To our knowledge, there are no reports investigating the different therapeutic modalities available for the treatment of cardiac tamponade originating from GC. Our review of the literature showed that the therapeutic modalities in 6 cases were only the drainage of malignant effusion, while the 10 cases underwent chemotherapy after the drainage. In addition, the chemotherapy treatment varied in the cases with the routes of administration of anti-cancer agents (e.g., intrapericardial infusion and/or systemic administration), the type of anti-cancer agents, and the dose of anti-cancer agents. More than half of the cases treated with local chemotherapy received various doses of cisplatin. We found that there were no complications caused by local chemotherapy in our review of the literature, and cisplatin was the most frequently used agent for local chemotherapy. The agents used for local chemotherapy should be less irritable to the heart. As the number of cases was limited, we were unable to determine which treatment was the most effective for this condition. However, we did find that cases treated with systemic chemotherapy tended to survive longer than those who were not ( $P = 0.0579$ ).

The period of time from the diagnosis of gastric cancer to the onset of cardiac tamponade may influence prognosis. When the time period was less than 2 years, the survival was 2.9 mo, and if the time period was over 2 years, the survival increased to 6.9 mo. The cases with high levels of either of the tumor markers CEA or CA 19-9 had a shorter survival period than those with low levels of either of these markers.

Honda *et al.*<sup>[25]</sup> reported a case of cardiac tamponade originating from lung cancer, in which the malignant cardiac effusion was controlled by weekly paclitaxel therapy. Sakusabe *et al.*<sup>[15]</sup> also reported that weekly administration of paclitaxel was effective for the control of malignant pericardial effusion originating from GC. There are many reports demonstrating that malignant ascites arising from GC can be controlled by paclitaxel in patients diagnosed with peritonitis carcinomatosa of GC. We confirmed that the level of paclitaxel in malignant ascites remained effective until 72 h after systemic administration (submitted for publication). Paclitaxel may, therefore, be a promising agent for systemic chemotherapy, and should be considered for the treatment of malignant pericardial effusion.

In summary, we were unable to reveal which therapy was the best for extending the life expectancy in cases of PC originating from GC. However, the cases with systemic chemotherapy survived for a longer period of time compared to the cases treated with drainage only or with local chemotherapy. The cases that developed cardiac tamponade due to PC arising from GC more than 2 years after the diagnosis, and the cases in which the levels of CEA and CA 19-9 were not elevated may have a possibility of surviving for a longer period of time. Such cases should undergo chemotherapy following emergency pericardiocentesis. While a specific chemotherapeutic strategy has not yet been developed for these cases, the use of paclitaxel for systemic, and cisplatin for local

chemotherapy may be promising for the treatment of cardiac tamponade caused by PC arising from GC.

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Science Editor Kumar M and Guo SY Language Editor Elsevier HK