Treatment with Corticosteroid for Pericardial Effusion in a Patient with Advanced Synchronous Esophageal and Gastric Cancers following Chemoradiotherapy

Satoshi Osawa\textsuperscript{a} Takanori Yamada\textsuperscript{a} Takeji Saitoh\textsuperscript{b} Takashi Kosugi\textsuperscript{c} Tomohiro Terai\textsuperscript{a} Yasuhiro Takayanagi\textsuperscript{a} Yasushi Hamaya\textsuperscript{a} Ken Sugimoto\textsuperscript{a} Mutsuhiro Ikuma\textsuperscript{a}

\textsuperscript{a}First Department of Medicine, \textsuperscript{b}Division of Cardiology, Internal Medicine III, and \textsuperscript{c}Department of Radiology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Key Words
Pericardial effusion · Chemoradiotherapy · Radiation-induced pericarditis · Esophageal cancer · Late toxicity

Abstract
Severe late toxicity following chemoradiotherapy in esophageal cancer, especially cardiac toxicity, is sometimes difficult to treat and is associated with mortality. However, there is little published information with regard to patients with delayed pericardial effusion following chemoradiotherapy and its management. We herein report the case of a 63-year-old man with advanced synchronous esophageal and gastric cancers. This patient presented with pericardial effusion with cardiac tamponade after definitive chemoradiotherapy and was successfully treated with corticosteroid after pericardiocentesis. No instances of pericardial and pleural effusions were observed during the 2-year follow-up period until his death from cancer relapses.

Introduction
Chemoradiotherapy is a treatment of choice for patients with esophageal cancer. Reports indicate that it is comparable to surgery in terms of therapeutic outcome [1–3]. As the survival rate after chemoradiotherapy increases, management of the late adverse
effects of radiation becomes increasingly important [4–6]. Since patients with esophageal cancer receive a wide range of irradiation to the mediastinum and heart, they may develop postirradiation complications such as cardiac and pulmonary toxicities that have been reported in Hodgkin’s disease [7]. Severe late toxicity, especially cardiac toxicity, is sometimes difficult to treat and associated with mortality. However there is little published information with regard to patients with delayed pericardial effusion following chemoradiotherapy in esophageal cancer and its management. Here, we report a patient with advanced synchronous esophagus and gastric cardia cancers who presented with severe pericardial effusion as late toxicity. He was successfully treated with corticosteroid therapy following pericardial drainage.

Case Report

A 63-year-old man initially presented with dysphagia. He had a past history of surgery and radiotherapy for meningioma. Hematological tests revealed the levels of all tumor markers, namely squamous cell carcinoma antigen, carcinoembryonic antigen, and carbohydrate 19-9, to be in the normal range. The patient was diagnosed to have synchronous esophageal ulcerative tumor in the middle thoracic esophagus (fig. 1a) directly invading the thoracic aorta, accompanied by a gastric ulcerative tumor in the cardia (fig. 1b), concomitant with metastasis to the paraesophageal and abdominal lymph nodes. An endoscopic forceps biopsy specimen revealed moderately differentiated squamous cell carcinoma in the esophagus and well-differentiated adenocarcinoma in the stomach under microscopic examination. The patient was subsequently diagnosed with stage III (T4N1M0) esophageal carcinoma and stage III (T3N1M0) gastric carcinoma according to the TNM classification of the International Union against Cancer. He was treated with definitive chemoradiotherapy using a daily low dose of nedaplatin (CDGP) (10 mg/day) and a continuous infusion of 5-FU (500 mg/day) for 20 days. Fractionated radiotherapy was performed since initiating chemotherapy and a total dose of 66 Gy was delivered at the rate of 2 Gy per fraction. Initially, both tumors could be encompassed in a single radiation field that included the celiac nodes (fig. 2). The field was changed to avoid spinal cord irradiation following a dose of 40 Gy, and only thoracic macroscopic lesions were irradiated with a margin of at least 1 cm. An additional two cycles of maintenance chemotherapy were performed for 5 days following chemoradiotherapy with CDGP (20 mg/day) and 5-FU (750 mg/day). Both tumors showed a clinically complete response (fig. 1c, d).

However, 14 months after the chemoradiotherapy, the patient was readmitted to our hospital presenting with dyspnea and chest pain. His blood pressure fell to 92/68 mm Hg accompanied by a pulse rate of 116 bpm. A paradoxical pulse was observed. Chest radiograph indicated an enlarged cardiac silhouette with a left pleural effusion (fig. 3a). Computed tomography (CT) scan revealed pericardial effusion and a small amount of bilateral pleural effusion (fig. 4a). Echocardiography indicated an enlarged pericardium and collapsed ventricles with a left ventricular ejection fraction of 63%. According to these findings pericardial and pleural effusions were diagnosed. Pericardiocentesis and pericardial drainage were then performed. Pericardial fluid analysis showed a specific gravity of 1.033, protein 4.8 g/dl, and LDH 336 IU/l. Cultures and cytologic examinations of fluid specimens were repeatedly negative for bacteria and cancer cells. Pericardial drainage was performed for 5 days. However, the pericardial and left pleural effusions increased again. Pleural fluid composition was similar to that of pericardial fluid and its cytology was negative for cancer cells. Therapy with 40 mg prednisolone daily was started 30 days after pericardiocentesis. Immediately after adding steroid, the patient’s condition improved dramatically and a chest radiograph showed a decrease in cardiomegaly as well as pleural effusion (fig. 3b). Steroid was gradually reduced every 2 weeks since then.

As local recurrence of both the esophageal and the gastric tumors was revealed by endoscopy 7 months after the treatment for pericardial and pleural effusion, chemotherapy using S-1 was performed. During a follow-up period of 2 years, no increases in the cardiothoracic ratio were observed on chest radiography (fig. 3c) and CT (fig. 4b). The patient survived until May 2008, after which he died from esophagorespiratory fistula and tumor bleeding.
Discussion

We present a case of cardiac tamponade with pericardial effusion following chemoradiotherapy for advanced synchronous middle esophageal and cardial cancers, and successful treatment with corticosteroid therapy combined with pericardiocentesis. When pleural and pericardial effusions occur following chemoradiotherapy for esophageal or cardial cancer, the possibility of treatment-related complications must be considered by the physicians. Few clinical reports discussing late cardiac toxicity management following chemoradiotherapy in esophageal cancer therapy exist till date. The present case suggests the feasibility of steroid therapy as an alternative treatment for refractory pericardial effusion following chemoradiotherapy.

Delayed complications following mediastinal radiotherapy or chemoradiotherapy include pericarditis, myocardial fibrosis, coronary artery disease, valvular abnormalities, conduction disturbances, and pulmonary fibrosis [8, 9]. Benign pericardial effusion following radiation therapy for esophageal or cardial cancer is considered a relatively rare event and accurate incidence data were not obtained until recently. A recent retrospective study revealed pericardial effusion to be the commonest cardiac toxicity in esophageal cancer patients with a crude incidence of 27.7% (28 of 101 patients) and median time at onset was 5.3 months (range 1.0–16.7 months) following chemoradiotherapy. In this study the actual incidence at 18 months was 48% (95% confidence interval 34–63) [10]. Treatment of pericardial effusion is not necessary in asymptomatic patients, whereas Ishikura et al. reported severe pericarditis (grade ≥3) in 10% (8 of 78 patients) and a few patients died as a result of heart failure despite pericardiocentesis or pericardial window placement [4].

It may be necessary to determine whether the effusion is associated with cancer relapses on observing such an effusion for the first time. In our case, repeated cytologic examinations of fluid specimens gave negative results for cancer relapse. External irradiation with a total dose of 66 Gy, delivered at the rate of 2 Gy per fraction, was performed in this case. It is known that a total dose greater than 35–40 Gy, daily fractionation in excess of 2 Gy, and volume of heart irradiated have been associated with an increased incidence of effusion [8]. As both lower esophageal cancer and cardial cancer were irradiated in our case, the field of irradiation involved a certain portion of the heart. It was suggested that the increased radiation volume and dose induced severe pericarditis. Daily low dose of CDGP and continuous infusion of 5-FU were given with radiation therapy in our case. Some chemotherapeutic agents have cardiotoxic effects. Doxorubicin is a well-known cardiotoxin that mainly affects the myocardium [11]. 5-FU also has a cardiotoxic effect [12] and is commonly used to treat esophageal cancer. However, it is not known whether it interacts with radiation to potentiate cardiotoxicity. In our recent clinical study, daily low dose of CDGP and 5-FU together with radiation for esophageal cancer did not seem to increase late cardiac toxicity [13]. To date, no other clinical factors have been found to influence the risk of pericardial effusion significantly following chemoradiotherapy for esophageal cancer, and high-dose radiation to the pericardium is the only significant risk associated with pericardial effusion [10, 14].

There is little published information with regard to delayed pericardial effusion management following chemoradiotherapy. Once delayed radiation cardiopulmonary toxicity occurs, there is no specific treatment other than steroids, diuretics, vasodilators, pericardiocentesis, pleurocentesis, pericardial window placement, and so on. There are only two clinical case reports in which radiation-induced pericardial effusions were successfully treated by steroid therapy: one was a case of breast cancer [15] and the other a
case of Hodgkin’s disease [16]. The pathology of radiation-induced heart disease is well characterized in an experimental rabbit model. Myocardial and pericardial fibroses, which appear to result from microcirculatory insufficiency and subsequent ischemia, dominate the late stage of radiation-induced heart disease [17, 18]. In this experimental model, early administration of methylprednisolone or ibuprofen decreases the incidence of pericardial effusion, reduces myocardial fibrosis, and improves survival [19]. Another clinical report indicated that rapid withdrawal of high-dose corticosteroids may activate subclinical radiation injury in the lungs and heart in Hodgkin’s disease [20]. Therefore, steroid treatment is a candidate for promising means of improving radiation-induced pericardial effusion.

Pericardial effusion following chemoradiotherapy may sometimes be self-limited and asymptomatic, but is also sometimes difficult to treat and associated with mortality. Further clinical experience is necessary to establish the initiation of steroid therapy in treating pericardial effusion following chemoradiotherapy in the clinical setting. It is also important to determine the optimal dose of radiation, because the higher radiation dose did not increase survival or local/regional control and the dose of 50.4 Gy was recommended for patients treated with concurrent 5-FU and cisplatin chemotherapy according to the INT 0123 trial [21, 22]. Possible future treatments also include the use of new chemotherapeutic agents with both systemic and radiosensitizing activity so as to reduce toxicity.
Fig. 1. Endoscopic findings in esophageal and gastric cancers. a An esophageal lesion was demonstrated endoscopically as an ulcerative tumor in the middle thoracic esophagus. This was pathologically diagnosed as a moderately differentiated squamous cell carcinoma. b A gastric lesion was demonstrated as an ulcerative tumor in the cardia. It was pathologically diagnosed as a well-differentiated adenocarcinoma. Complete response was observed for the esophageal (c) and gastric cancers (d) 12 months following chemoradiotherapy, and was confirmed by endoscopic biopsy.
**Fig. 2.** Initial radiation field described as planning target volume. Initially, both esophageal and cardial cancers could be encompassed in a single radiation field.

**Fig. 3.** Chest radiographies of the pericardial and pleural effusions. 

- **a** The pretreatment chest radiograph indicated an enlarged cardiac silhouette with a left pleural effusion 14 months after initiating chemoradiotherapy.
- **b** A chest radiograph after 8 days of corticosteroid administration (40 mg/day) indicated improvement in the enlarged cardiac silhouette and pleural effusion.
- **c** No recurrence of the effusions was observed 9 months after initiating steroid therapy.
Fig. 4. CT scan findings of the pericardial and pleural effusions. a The pretreatment CT scan revealed pericardial effusion and a small amount of bilateral pleural effusion 14 months after chemoradiotherapy. b The posttreatment CT scan indicated no recurrence of either pericardial or bilateral pleural effusions 12 months after initiating steroid therapy.
References

1. Kleinberg L, Forastiere AA: Chemoradiation in the management of esophageal cancer. J Clin Oncol 2007;25:4110–4117.
2. Kleinberg L, Gibson MK, Forastiere AA: Chemoradiotherapy for localized esophageal cancer: regimen selection and molecular mechanisms of radiosensitization. Nat Clin Pract Oncol 2007;4:282–294.
3. Ohtsu A: Chemoradiotherapy for esophageal cancer: current status and perspectives. Int J Clin Oncol 2004;9:444–450.
4. Ishikura S, Nihei K, Ohtsu A, Boku N, Hironaka S, Mera K, Muto M, Ogino T, Yoshida S: Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003;21:2697–2702.
5. Kume kawa Y, Kaneko K, Ito H, et al: Late toxicity in complete response cases after definitive chemoradiotherapy for esophageal squamous cell carcinoma. J Gastroenterol 2006;41:425–432.
6. Morota M, Gomi K, Kozuka T, Chin K, Matsuura M, Ouchi M, Ito H, Yamashita T: Late toxicity after definitive concurrent chemoradiotherapy for thoracic esophageal carcinoma. Int J Radiat Oncol Biol Phys 2009;75:122–128.
7. Cosset JM, Henry-Amar M, Pellae-Cosset B, Carde P, Girinski T, Tubiana M, Hayat M: Pericarditis and myocardial infarctions after Hodgkin’s disease therapy. Int J Radiat Oncol Biol Phys 1991;21:447–449.
8. Gaya AM, Ashford RF: Cardiac complications of radiation therapy. Clin Oncol (R Coll Radiol) 2005;17:153–159.
9. Marks IB, Yu X, Vujaskovic Z, Small W Jr, Fozl R, Ancher MS: Radiation-induced lung injury. Semin Radiat Oncol 2003;13:333–345.
10. Wei X, Liu HH, Tucker SL, Wang S, Mohan R, Cox JD, Komaki R, Liao Z: Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with definitive chemoradiation therapy. Int J Radiat Oncol Biol Phys 2008;70:707–714.
11. de Graaf H, Dolsma WW, Willemsen PH, van der Graaf WT, Sleijfer DT, de Vries EG, Mulder NH: Cardiotoxicity from intensive chemotherapy combined with radiotherapy in breast cancer. Br J Cancer 1997;76:943–945.
12. Becker K, Erckenbrecht JF, Haussinger D, Frieling T: Cardiotoxicity of the antiproliferative compound fluorouracil. Drugs 1999;57:475–484.
13. Osawa S, Furuuta T, Sugimoto K, et al: Prospective study of daily low-dose nedaplatin and continuous 5-fluorouracil infusion combined with radiation for the treatment of esophageal squamous cell carcinoma. BMC Cancer 2009;9:408.
14. Sasamoto R, Tsuchida E, Sugita T, Matsumoto Y, Abe E, Sasai K: Risk factors for enlargement of cardiac silhouette on chest radiography after radiotherapy for esophageal cancer. Radiat Med 2006;24:431–437.
15. Biran S: Corticosteroids in radiation-induced pericarditis. Chest 1978;74:96–98.
16. Keelan MH Jr, Rudders RA: Successful treatment of radiation pericarditis with corticosteroids. Arch Intern Med 1974;134:145–147.
17. Stewart JR, Fajardo LF: Radiation-induced heart disease: an update. Prog Cardiovasc Dis 1984;27:173–194.
18. Fajardo LF, Stewart JR: Pathogenesis of radiation-induced myocardial fibrosis. Lab Invest 1973;29:244–257.
19. Reeves WC, Cunningham D, Schwiter EJ, Abt A, Skarlatos S, Wood MA, Whitesell L: Myocardial hydroxyproline reduced by early administration of methylprednisolone or ibuprofen to rabbits with radiation-induced heart disease. Circulation 1982;65:924–927.
20. Castellino RA, Glatstein E, Turlow MM, Rosenberg S, Kaplan HS: Latent radiation injury of lungs or heart activated by steroid withdrawal. Ann Intern Med 1974;80:593–599.
21. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA, Kelsen DP: INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167–1174.
22. Hong TS, Crowley EM, Killoran J, Mamon HJ: Considerations in treatment planning for esophageal cancer. Semin Radiat Oncol 2007;17:53–61.
S.O. wrote the manuscript. T.Y., K.S. and M.I. contributed to the paper design and coordination. T.S. contributed to the assessment of cardiology. T.K. contributed to the planning of irradiation. T.T., Y.H. and Y.T. were involved in chemoradiotherapy, treatment for delayed complications, and follow-up. All authors have read and approved the final manuscript.