Author’s response to reviews

Title: Successful management of refractory pleural effusion due to systemic AL amyloidosis by vincristine adriamycin dexamethasone chemotherapy: a case report

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Version: 2 Date: 17 February 2010

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Feb. 17th, 2010

The Editor

Journal of Medical Case Reports

re: “Successful treatment of refractory pleural effusion due to systemic AL amyloidosis by vincristine adriamycin dexamethasone chemotherapy: a case report” by Toshikazu Araoka, Hiroya Takeoka, Keisuke Nishioka, Masaki Ikeda, Makiko Kondo, Azusa Hoshina, Seiji Kishi, Makoto Araki, Rokuro Mimura, Hideharu Abe and Toshio Doi; MS: 1956480305333764

Dear Editor:

We are most grateful to you and the reviewers for the helpful comments on the original version of our manuscript.

In the attached document, we describe the changes made in response to your and reviewer’s comment point by point.

We have included the ethnic origin and nationality of the patient; this information “a 68-year-old man” has been revised as “a 68-year-old Japanese male” on page 2 in the abstract and on page 4 in the case presentation section, and the side effects of VAD chemotherapy are included in the discussion section.
Further, we have discussed the mechanism of the infiltration cardiomyopathy and the reason that VAD chemotherapy is effective in the improvement of cardiac function in discussion section. We have avoided the conclusive suggestion about the effect and prognosis both of pleurodesis and VAD chemotherapy. Moreover, we have added the clinical course between the diagnosis and initial management and today.

In abstract section, we have added the new sentence “vincristine adriamycin dexamethasone” for abbreviation of VAD because original version of our manuscript includes “VAD” as abbreviation.

The revised manuscript contains a number of important changes, which we believe this revised manuscript is suitable for publication in the Journal of Medical Case Reports.

In the revised version of our paper, we have added the new 2 references which are “Migrino RQ, Harmann L, Woods T, Bright M, Truran S, Hari P: Intraventricular dyssynchrony in light chain amyloidosis: a new mechanism of systolic dysfunction assessed by 3-dimensional echocardiography. Cardiovasc Ultrasound 2008, 6:40” and “Tazawa K, Matsuda M, Yoshida T, Gono T, Katoh N, Shimojima Y, Ishii W, Fushimi T, Koyama J, Ikeda S: Therapeutic outcome of cyclic VAD (vincristine, doxorubicin and dexamethasone) therapy in primary systemic AL amyloidosis patients. Intern Med 2008, 47:1517-1522”. These 2 recent articles are required to supplement our discussion.

We have addressed all the comments by you and reviewer 1 and 2, as indicated on the attached pages, and we hope that our explanations and revisions are satisfactory.

To answer your comments and those of reviewers 1 and 2, the revised version of our paper is more than 2,000 words and includes 15 references. We hope that this increase in word count is acceptable, and the revised version of our paper is now suitable for publication in the Journal of Medical Case Reports and we look forward to hearing from you at your earliest convenience.

Best regards.

Sincerely,

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We are grateful to reviewer 1 for the critical comments and useful suggestions that helped us to improve our paper. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

Reviewer 1

Comment #1: The reviewer asks the possible effect of VAD chemotherapy on the possible myocardial infiltration

Response

We have added the new sentence “Infiltrative cardiomyopathy revealed in an echocardiogram may be caused by the amyloid deposition, which has the potential to alter regional cardiac mechanics, resulting in LV dyssynchrony and cardiac decompensation (Migrino RQ, et. al. Cardiovasc Ultrasound 2008, 6:40). Although the mechanisms by which VAD ameliorate the infiltrative cardiomyopathy are still unclear, a recent report suggests that the reduction of amyloid depositions resulting from decreased precursor protein may be the mechanism by which VAD exert their therapeutic effects (Tazawa K. et. al. Intern Med 2008, 47:1517-1522). The cardiac function of this patient remained unchanged after administration of VAD chemotherapy; however, a similar pathogenic mechanism may be involved in the development of refractory pleural effusion without cardiac decompensation.” on page 9-10 and “Hence, amyloid depositions in the parietal pleura may be directly reduced by VAD chemotherapy. However” on page 10 in the discussion section.

Further, we have revised from “Although his lower extremity edema had not improved, there were no recurrences of pleural effusion until discharge from the hospital (Figure C and D)” to “However, the edema in his lower extremities showed no improvement, and no obvious change was seen in cardiac indices; pleural effusion did not recur until he was discharged from the hospital (Figures C and D)” on page 7 in the case presentation section.

Comment #2: The reviewer asks the course of the patient between the diagnosis and initial management (in 1999) and today.

Response

In the revised version of our paper, we have added the new clinical course of this patient. We have revised the sentence “and had been successfully managed by intermittent MP chemotherapy.” to “After diagnosis, he was successfully managed with 21 courses of intermittent MP chemotherapy for seven years” on page 4 in case presentation section.

Further, we have added further information; this new clinical course “There has been no recurrence of pleural effusion for six months after ambulation.” Has been
revised as “Pleural effusion did not recur for six months after the patient became ambulatory. However, the patient had a recurrence of right pleural effusion and was managed with VAD chemotherapy. Although his right pleural effusion did not increase for one month receiving VAD chemotherapy, the recurrence occurred immediately after VAD chemotherapy. Hence, in 2006, the patient underwent chemical pleurodesis for recurrent right pleural effusion. After pleurodesis, his pleural effusion has not been increased by receiving intermittent MP chemotherapy in 2010.” on page 7-8 in the case presentation section.

Comment #3: The reviewer demonstrates that the effect of management by VAD chemotherapy is speculatively described and is not conclusively mentioned.

Response

We have erased the sentence “This procedure alleviates the symptoms for a short term but does not improve their prognosis” and added the new sentence “Although pleurodesis temporarily alleviates the symptoms, its effectiveness for improving the prognosis of systemic AL amyloidosis remains to be clarified.” on page 4 in the introduction section.

Further, we have changed the word from “We used chemotherapy for the first time to successfully to treat refractory pleural effusion” to “We used chemotherapy for the first time to successfully to manage refractory pleural effusion” on page 4 in the introduction section.

Moreover, we have revised the sentence from “Unfortunately, pleurodesis is an invasive technique and carries risks associated with infection and pneumothorax. Furthermore, pleurodesis cannot improve the poor prognosis of refractory pleural effusion” to “Although pleurodesis represents the gold standard for the treatment of massive recurrent pleural effusion, this procedure is invasive and may be associated with the risks of infection and pneumothorax [2]. Hence, to manage the refractory pleural effusion, we administered VAD chemotherapy as an initiation therapy before pleurodesis.” on page 8-9 in the discussion section.

In the conclusion section, we have changed the words from “This treatment was effective and afforded” to “This treatment may be effective and afforded” on page 11, further, changed the word from “we conclude that VAD chemotherapy is clinically” to “we suggest that VAD chemotherapy is clinically” on page 12.

Comment #4: The reviewer demonstrates the title should be changed from “Successful treatment” to “successful management” or “response”

Response

We have changed the title from “Successful treatment” to “successful management”.

We are grateful to reviewer 2 for the important comments and vital suggestions.
that helped us to improve our paper. As indicated in the responses that follow, we have taken all these comment and suggestions into account in the revised version of our paper.

Reviewer 2

Comment #1: The reviewer suggests that “cannot improve the poor prognosis of refractory pleural effusion” should be rephrased or erased.

Response

We have changed the conclusive sentence from “This procedure alleviates the symptoms for a short term but does not improve their prognosis” to “Although pleurodesis temporarily alleviates the symptoms, its effectiveness for improving the prognosis of systemic AL amyloidosis remains to be clarified.” on page 4 in the introduction section.

Further, we have erased the sentence “Furthermore, pleurodesis cannot improve the poor prognosis of refractory pleural effusion” on page 8 in discussion section.

Moreover, we have revised the sentence from “Unfortunately, pleurodesis is an invasive technique and carries risks associated with infection and pneumothorax. Furthermore, pleurodesis cannot improve the poor prognosis of refractory pleural effusion” to “Although pleurodesis represents the gold standard for the treatment of massive recurrent pleural effusion, this procedure is invasive and may be associated with the risks of infection and pneumothorax [2]. Hence, to manage the refractory pleural effusion, we administered VAD chemotherapy as an initiation therapy before pleurodesis.” on page 8-9 in the discussion section.

Comment #2: The reviewer suggest that we should mention about the increase in risk of the side effect of VAD chemotherapy in the revised version of our paper.

Response

We have added the new sentence “However, whether VAD chemotherapy can be used as initial therapy before pleurodesis remains to be clarified because doxorubicin, vincristine, and dexamethasone, which are included in the VAD regimen, can cause cardiac toxicity, neuropathy, and infection, respectively. Therefore, VAD chemotherapy should be administered after careful consideration.” on page 9 in the discussion section.