Author’s response to reviews

Title: Acquired immunodeficiency associated with thymoma: A case report

Authors:

Takahisa Kawamura (ta.kawamura@scchr.jp)
Tateaki Naito (t.naito@scchr.jp)
Haruki Kobayashi (h.kobayashi@scchr.jp)
Kazuhisa Nakashima (ka.nakashima@scchr.jp)
Shota Omori (s.omori@scchr.jp)
Kazushige Wakuda (k.wakuda@scchr.jp)
Akira Ono (a.ono@scchr.jp)
Hirotsugu Kenmotsu (h.kenmotsu@scchr.jp)
Haruyasu Murakami (ha.murakami@scchr.jp)
Masahiro Endo (m.endo@scchr.jp)
Toshiaki Takahashi (t.takahashi@scchr.jp)

Version: 1 Date: 25 May 2019

Author’s response to reviews:

Dr. Linda Gummlich
Editor
BMC Cancer

25 May 2019

Dear Dr Gummlich,

Thank you very much for considering our manuscript entitled “Acquired immunodeficiency after radiotherapy for thymoma: A case report” by Kawamura et al. I am pleased to read the constructive comments raised by the Reviewers and the Editor. We have considered their comments very carefully and have made appropriate revisions to avoid any misunderstandings and to clarify the context.
I have uploaded the modified version (R1). We sincerely hope that our manuscript is now suitable for publication and look forward to hearing from you at your earliest convenience.

Sincerely yours,

Tateaki Naito, M.D, Ph.D.

Division of Thoracic Oncology, Shizuoka Cancer Center
Shizuoka, Japan
Tel: 81(55)989-5222; Fax: 81(55)989-5634
E-mail: t.naito@scchr.jp

Response to the Editor

Thank you for your advice. We appreciate your comments and have made appropriate amendments to the revised manuscript.

Editor’s comment:

1. Please remove the header "Acquired immunodeficiency after irradiation for thymoma" from each page of the manuscript.

Response #1:

We have removed the header from each page of the manuscript.

Editor’s Comment:

2. The individual contributions of ALL authors to the manuscript should be specified in the Authors’ Contributions section. Guidance and criteria for authorship can be found here:

http://www.biomedcentral.com/submissions/editorial-policies#authorship
Currently, many of the authors are missing from the contributions

Response #2:
Response to the review comments

To Reviewer #1

Thank you for your feedback. We agree with your comments and have made appropriate revisions in accordance with your advice.

Reviewer #1’s comment:

This paper by Kawamura et al deals describes a patient with thymoma and immunodeficiency possibly caused by radiation of the thymoma. There is no discussion that the patient is suffering from a immunodeficiency syndrome, but it remains unclear whether it is mainly caused by irradiation or part of the paraneoplastic Good syndrome. It would be helpful to have the pre-operative CD4 values, if low it would be clear whether the immunodeficiency syndrome was caused by Good Syndrome or irradiation. I understand that the authors where not aware of this problem before they started irradiation. I think it is more probable that the patient already suffered from Good syndrome and irradiation caused worsening of immunodeficiency. The message of this paper should not that this immunodeficiency syndrome is only caused by irradiation, but that in all thymoma cases routinely CD4 levels have to be measured frequently over the time, irrelevant of the immunoglobulin levels are within the range or not. To my personal experience Good syndrome is more frequent than expected because it is mostly overlooked. Correct diagnosis would give the opportunity to start early replacement therapy with i.v. immunoglobulins as recommended for primary immunodeficiency syndrome also treating the paraneoplastic Good syndrome to avoid complications by other necessary therapies e.g. irradiation, chemotherapy, surgery. The authors should change the discussion to alert this interesting problem.

Response:

Thank you for your advice. We completely agree with your suggestion. As you have pointed out, it is unclear whether immunodeficiency is mainly caused by irradiation or is a result of Good syndrome. Unfortunately, the CD4 values before radiotherapy were not available for this case. We have amended our approach in the Discussion to highlight that Good syndrome in patients with thymoma is more frequent than expected because it is mostly overlooked.

Revisions:

1. We changed the title of “Acquired immunodeficiency after radiotherapy for thymoma” to “Acquired immunodeficiency associated with thymoma” in the revised version (title
We also simplified the conclusion: “In conclusion, we reported a case of acquired cellular immunodeficiency in a patient with thymoma. Our findings suggest that physicians need to be aware of severe infections due to immunodeficiency in patients with thymoma.” (Discussion and Conclusions section, lines 9–11, page 8) and changed the Background and Conclusion section in the Abstract to “immunodeficiency that may have been induced by radiotherapy for thymoma” to “immunodeficiency with thymoma”. (Abstract section, line 3, page 3, and line 2, page 4.)

2. We have added text to deal with the issue that it remains unclear whether immunodeficiency is mainly caused by irradiation because the CD4 values before radiotherapy were not available in this case: “However, a direct relationship between radiotherapy and immunodeficiency was not proven because the CD4+ cell count before radiotherapy was not measured in this case.” (Discussion and Conclusions section, lines 14–16, page 7). Furthermore, based on your advice, we added the following speculation: “A previous report suggested that cellular immunodeficiency associated with thymoma was not uncommon, but it is frequently overlooked. In this case, it was possible that the patient already had undiagnosed cellular immunodeficiency before radiotherapy.” (Discussion and Conclusions section, from line 16, page 7 to line 1, page 8).

3. We also describe the importance of regular measurement of CD4 levels to detect thymoma-related immunodeficiency in clinical practice in accordance with your suggestion: “In thymoma cases, CD4 levels may have to be measured frequently over time, irrelevant of whether the immunoglobulin levels are within the range or not. Correct diagnosis would provide the opportunity to start early replacement therapy with intravenous immunoglobulins, as recommended for the treatment of primary immunodeficiency syndrome, as well as treatment of the paraneoplastic Good syndrome to avoid complications induced by therapies such as radiotherapy, chemotherapy, and surgery.” (Discussion and Conclusions section, lines 2–8, page 8).

We believe that incorporation of your advice and suggestions has significantly improved our manuscript. Thank you very much once again for taking the time to review our manuscript.

To Reviewer #2

Thank you very much for your constructive feedback. We agree with your comments and have made appropriate revisions according to your advice.

Reviewer #2’s comment:

1. Conclusions of the article is that radiation was the proximate cause of immunodeficiency, but no baseline immune functions were performed prior to radiotherapy to support that hypothesis.
Response #1: As you have pointed out, it is unclear whether immunodeficiency is mainly caused by irradiation or other therapies because the baseline immune functions before radiotherapy were not available in this case. Therefore, we have changed the Discussion section in the revised manuscript as follows:

“However, a direct relationship between radiotherapy and immunodeficiency was not proven because the CD4+ cell count before radiotherapy was not measured in this case.” (Discussion and Conclusions section, lines 14–16, page 7.)

Reviewer #2’s comment:

2. It is well known that patients with thymoma alone (with or without prior therapy) have immunodeficiencies in gamma globulin (Good’s Syndrome) and lymphopenia, especially CD4. A paper by Khawaja et al (J. Clin Immunol (2012) looked at 79 patients with thymoma with immunological testing. low CD4+ counts were seen in over 30%.

Response #2: Thank you for your feedback and useful comments. We have cited your suggested reference and have added suitable text to the Discussion as follows:

“A previous report suggested that cellular immunodeficiency associated with thymoma was not uncommon, but is frequently overlooked [Khawaja et al]. In this case, it was possible that the patient already had undiagnosed cellular immunodeficiency before radiotherapy.” (Discussion and Conclusions section, from line 16, page 7 to line 1, page 8.)

Reviewer #2’s comment:

3. The authors note that symptoms occurred after the radiation, but he may have had the immunodeficiency for some time, but it was not until he was infected that it was elucidated.

Response #3: Thank you for your comment. Accordingly, we have added the following text to the Discussion of the revised manuscript:

“In this case, it was possible that the patient already had undiagnosed cellular immunodeficiency before radiotherapy.” (Discussion and Conclusions section, from line 16, page 7 to line 1, page 8.)

“In thymoma cases, CD4 levels may have to be measured frequently over time, irrelevant of whether the baseline immunoglobulin levels are within the range or not. Correct diagnosis would provide the opportunity to start early replacement therapy with intravenous immunoglobulins, as recommended for the treatment of primary immunodeficiency syndrome, as well as treatment of the paraneoplastic Good syndrome to avoid complications induced by therapies such as
radiotherapy, chemotherapy, and surgery.” (Discussion and Conclusions section, lines 2–8, page 8.)

Reviewer #2’s comment:

4. The associated of opportunistic infections in thymoma patients is not uncommon, because of altered immune system (Tarr et al (Medicine (2001))) but listeria is uncommon and that by itself may be worth noting.

Response #4: We agree with your opinion that listeria infection in thymoma patients is uncommon and that it may be notable when it manifests by itself. We have cited your suggested reference in the revised manuscript.

“Furthermore, he had oral candidiasis and Listeria meningitis, which may reflect a dysfunction in T-cell-mediated immunity [Tarr et al].” (Discussion and Conclusions section, lines 4–5, page 7.)

Reviewer #2’s comment:

5. Authors state that the patient had prior systemic therapy including amrubicin and an "Investigational drug". What was that drug and when was chemotherapy given in context to this presentation? Why might they not also contribute to immunosuppressive theory?

Response #5:

The investigational drug was a PI3K and mTOR inhibitor. In this case, all chemotherapies including the "Investigational drug" were administered 2 years before irradiation. Therefore, we speculated that radiotherapy mostly contributed to the immunosuppression observed in this patient. We corrected “an investigational drug” to “phosphoinositide 3-kinase/ mammalian target of rapamycin inhibitor”. (Case presentation section, line 12, page 5)

Reviewer #2’s comment:

6. No details on the CD4 counts over time (mentioned that "remained low").

Response #6:

We have added the CD4 counts over time after discharge to the revised manuscript, as follows:
“His CD4+ cell count has remained <150 cells/µl during the 15-month follow up after discharge (after 3 months, 79 cells/µl; 6 months, 107 cells/µl; 9 months, 146 cells/µl; 12 months, 132 cells/µl).” (Case presentation section, lines 15–17, page 6)

We believe that incorporating your advice and suggestion has improved our manuscript significantly. Thank you very much once again.

To Reviewer #3

Thank you very much for your constructive feedback. We agree with your comments and have made appropriate revision according to your advice.

Reviewer #3’s comment:

1. The authors should add the counts of B, T CD8 and NK cells (page 6, line 35).

Response #1:

We have added the counts of B and T CD8 cells to the revised manuscript. Unfortunately, we did not measure the counts of NK cells in this case.

We added the counts as follows: “129 CD8+ cells/µl with a CD4+/CD8+ ratio of 0.84 (normal range, 0.40–2.30), and 2% B cells (11 cells/µl).” (Case presentation section, lines 11–12, page 6.)

Reviewer #3’s comment:

2. This case report should be discussed: Prolonged severe immunodeficiency following thymectomy and radiation: a case report.


as well as this review: Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature.


Response #2:
Thank you for your constructive advice. We have added the two suggested references to the revised manuscript.

Revisions:

1. “One possible explanation is the large reduction in volume caused by radiotherapy also induces a similar systemic immune response, leading to acquired immunodeficiency [Wickemeyer et al.].” (Discussion and Conclusions section, lines 12–14, page 7.)

2. “Furthermore, he had oral candidiasis and Listeria meningitis, which may reflect a dysfunction in T-cell-mediated immunity [Tarr et al].” (Discussion and Conclusions section, lines 4–5, page 7.)

Thank you very much for your advice and suggestions, which we believe have significantly improved our manuscript.