Peer Review File

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Reviewer A

The authors present a successful therapeutic alternative. I congratulate the authors for conducting the case, but I must say that, as it is a case report, the conclusions must be more cautious for reasons already well known.

We appreciate the reviewer's careful analysis of our work and have revised the manuscript according to the comments.

Reply #: As the reviewer pointed out, we could not draw a definitive conclusion in terms of p-AKT because of the nature of case reports. We have added the following sentence in the Discussion section (see page 13, line 2-4).

Changes in the text: A prospective study is warranted to clarify the significance of p-AKT as a biomarker for sensitivity to eribulin.

minor review is required:

Comment 1. *page 2, line 18 has no reference.*

Reply 1: As requested, we have adde a reference (1). (see page 5, line 3)

Change in the text: Uterine leiomyosarcoma (U-LMS), arising from the myometrium, is a rare type of tumor accounting for approximately 3% of all uterine malignancies (1).

Comment 2. *page 3, line 39. Generally, we should use references because it is not necessary to use references in the case description.*

Reply 2: As requested, we have added references (2, 3, 10, 12) (see page 10, line 17).

Changes in the text: Most of these patients receive palliative chemotherapy primarily with the GD regimen or a doxorubicin-containing regimen (2,3,10,12) (Table 1).

Reviewer B

This is a remarkable case of a rare cancer with a rare pattern of metastasization. It is also very interesting for the possible role of p-AKT as a biomarker for response to eribulin.

We appreciate the reviewer's careful analysis of our work, and have revised the manuscript according to the comments.

Major points:

Comment 1. *Page 2, line 2; page 3, line 52: the authors mention that eribulin achieved a durable response for 17 months. However, in the Case Presentation section, it is mentioned that the patient underwent 15 cycles of eribulin, administered every 21 days. This correspondes to roughly 10.5 months, not 17 months, before the patient experienced new progressive disease. Were there pauses in between the cycles? Treatment delays? Please clarify.*

Reply 1: The case presentation was not appropriate. Therefore, we have added the following sentence in the appropriate section (see page 8, line 14-15).

Changes in the text: Unfortunately, several pauses of treatment with eribulin were needed due to neutropenia and personal reasons.

Comment 2. *This manuscript reports a patient with metastatic disease who has had multiple lines of treatment. A discussion of the real benefit for the patient regarding the sequence and timing for the lines of treatment administered is warranted, especially in what the patient's symptoms are concerned. The authors have enumerated the lines of treatment, but have not described the benefit in terms of quality of life.*

Reply 2: As mentioned, we did not show the patient's symptoms and quality of life clearly. We have added the following three sentences (see page 7, line 10-14, page 8-9, line 18-1 and page 9, line 6-8).

Changes in the text: Given the poor response to the AI regimen, which was not effective against easy fatigability caused by the cardiac metastasis, the patient was next treated with the GD regimen (i.e., gemcitabine 900 mg/m2 on days 1 and 8, docetaxel 70 mg/m2 on day 8) every 3 weeks.

As a result, her quality of life recovered to status reported prior to the relapsed cardiac metastasis.

Treatment with trabectedin and pazopanib did not improve the symptoms related to the cardiac tumor and quality of life.

Comment 3. *Page 2, lines 33-35: colonic metastasization of a uterine leiomyosarcoma is a rare event on an already rare disease. Was this the inital presentation of the patient's uterine leiomyosarcoma? Also, can you please provide the pathology report for the colonic metastasis? What I find striking in this case is that the tumour metastasized both to the colon and the heart. As is mentioned in the Introduction to this manuscript, the colon and the heart are not the most frequent sites of metastasis in uterine leiomyosarcomas. Perhaps this patient's tumor had a specific biology. This should be addressed and discussed in the manuscript.*

Reply 3: We intended to confirm the initial presentation of U-LMS. However, we could not find appropriate information, because she had been diagnosed and treated 30 years earlier. In

terms of colonic metastasis, we could confirm the findings of the pathological report. Therefore, we added a new sentence in the Case Presentation section (see page 6, line 4-5). As mentioned, this tumor has an undetermined biological feature, which is a scientifically interesting. We also added a sentence regarding this point (see page 10, line 9-13).

Changes in the text: The resected tumor was compatible with metastatic LMS, which was pathologically diagnosed in a tertiary referral hospital.

This case presented with extremely rare conditions; the tumor metastasized to the colon and the heart. Such tumors may have an undetermined biological feature. Thus, further investigations (e.g., RNA sequencing) may be needed to clarify their biological profile.

Minor points:

Comment 1. *Page 2, lines 33-35: still not clear. It is mentioned that the patient had colonic metastasis in the beginning, and 10 years later also developed colonic metastasis? Again? Both times the colonic metastases were excised surgically? Please clarify.*

Reply 1: We apologize for the confusion. We have corrected the text (see page 6, line 2-10).

Changes in the text: A 69-year-old female with a medical history of U-LMS was treated with surgery and radiotherapy in 1992. Ten years later, she was diagnosed with colonic metastasis and underwent surgery. The resected tumor was compatible with metastatic LMS, which was pathologically diagnosed in a tertiary referral hospital. Nineteen years after the initial treatment, she suffered from chest pain, persistent atrial fibrillation, and hypotension. In May 2011, she was diagnosed with a metastatic cardiac tumor (41 x 34 mm) located in the right ventricle, which blocked the right ventricular outflow tract. The patient underwent marginal surgical resection to prevent sudden death.

Comment 2. *Page 2, lines 36-38: in the beginning of symptoms, was the atrial fibrillation paroxysmal or persistent? Did it subside/resolve with the excision of the metastatic cardiac tumour? In the pathology exam, was there invasion of the right atrium? Were the margins clear of tumour (this is important considering that there was a cardiac tumour relapse later on)? It would be interesting to understand whether there was a clear, causal relationship between the metastatic cardiac tumour and the development of atrial fibrillation.*

Reply 2: We asked the doctor who referred the patient to our hospital to address these questions. We have modified the text accordingly (see page 6, line 12-17).

Change in the text: The boundary between the tumor and surrounding tissue was unclear; as a result, the surgical margin was positive. It was impossible to confirm whether the tumor infiltrated the right atrium directly. After the operation, the symptoms originating from the cardiac tumor were improved, including atrial fibrillation. Atrial fibrillation may be induced by right atrial pressure load.

Comment 3. *Page 2, lines 38-39: it seems to me that this patient's case was reported in the past whilst on an earlier phase of the disease, as is mentioned in the Discussion (page 3, line*

36). This reference is not as clear here on the Case Presentation section. Please give a more clear reference.

Reply 3: As requested, we added reference 4 (Japanese literature) in the Case Presentation section (see page 6, line 12).

Comment 4. *Page 7, Figure 3: the legend does not seem to be correct. The first sentence seems to refer to panel A, and the text after "(A)" seems to refer to panel B. Please correct.*

Reply 4: We have corrected the figure legends as advised (see Page 18, line 1-4).

Change in the text: (A) Computed tomography (CT) of the chest showing a mass in the right ventricle (yellow arrows) prior to treatment with eribulin.
(B) CT revealing a reduction in cardiac tumor volume after 11 cycles of treatment with eribulin.

Comment 5. *Page 3, lines 13-14, 21: about the performance status. Is this scoring based on the Eastern Cooperative Oncology Group (ECOG) performance status scale? Please specify.*

Reply 5: We have changed the text as advised (see Page 8, line 8).

Change in the text: In May 2016, treatment with eribulin (1.1 mg/m2) was initiated; the dose was reduced by 20% because the patient's Eastern Cooperative Oncology Group (ECOG) performance status was 2.

Comment 6. *Page 8, Figure 4: as "M" was chosen to represent months in the abscissas axis in the graph, so the legend to months down in the abbreviations should come as "M", not "m". Please correct.*

Reply 6: We have corrected this as advised (see Page 18, line 9).

Change in the text: X, initiation of treatment with eribulin; M, months.

Comment 7. *Page 10, Table 1, No. 11: the authors had mentioned that the patient had colonic metastasization. However, in the table, number 11 (the present patient), in the "Sites of other metastasis" column, it is mentioned that the patient did not have any. Please correct.*

Reply 7: We have corrected the table as advised (see Table, number 12 (the present patient), in the "Sites of other metastasis").

Comment 8. *Page 3, lines 32-33: please consider adding the following case of a cardiac metastasis of a uterine leiomyosarcoma to your list of cases:*
Sripariwuth A, Xu B, Shih-Lin HS, et al. Multimodality Cardiac Imaging Assessment of a Large Metastatic Pericardial Leiomyosarcoma. CASE (Phila). 2018;2(4):156-162. Published 2018 Jun 28. doi:10.1016/j.case.2018.04.007

Reply 8: We have modified the text as advised (see Page 10, line 5), and table (see Table, number 10).

Change in the text: In the last decade, only 11 cases of cardiac metastasis of U-LMS have been reported in the literature (1-3,5-12) (Table 1).

Comment 9. *Page 3, line 54: "these effects are directly associated with an excellent outcome". The outcome does not seem to have been excellent. Please remove.*

Reply 9: As requested, we removed this sentence.

Comment 10. Pages 3-4, lines 54-1: many other factors might have contributed to the long survival the patient experienced after the cardiac metastasis relapse, for example, having had other chemotherapy regimens. If the authors intend to say that eribulin contributed to this long survival, please rephrase the sentence.

Reply 10: As requested, we corrected the text in Discussion section (see page 11-12, line 18-3).

Changes in the text: Possible reasons for the 5-year survival of this patient after the detection of the cardiac metastasis relapse are the successful treatment with eribulin and the sequential administration of several chemotherapeutics. Moreover, the functions of her major organs were maintained during the clinical course.

Comment 11. *Page 4, lines 3-5: this information seems to correspond to reference number 19, not 18. Other references in the text are misnumbered too. Please review and correct your list of references.*

Reply 11: We apologize for our mistakes. We have corrected the list of references.

Comment 12. *Page 4, lines 3-5: this information does not seem to be correct according to the study by Wozniak et al. (2021). The authors from this study state that "the presence of TP53 mutation showed a positive correlation with PFS [P = 0.036; HR, 0.51 (95% CI, 0.26–0.93)] but had no impact on OS". Also, I could not find a reference to the impact a mutation in the MUC16 gene had in the eribulin-treated cohort in this paper. Furthermore, I could not find a reference to what the "cell surface associated" gene might be.*

Reply 12: We apologize for our mistakes. As requested, we revised the sentences in the Discussion section (see page 12, line 5-7).

Changes in the text: However, it appears that wild-type *tumor protein p53* and mutated *alpha-thalassemia/mental retardation, X-linked (ATRX)* were associated with shorter PFS in patients with LMS who received eribulin (18).

Comment 13. *Page 4, lines 3-5: please use the abbreviation and its correct meaning for all genes studied by Wozniak et al. (2021). For example, mucin 16 (MUC16).*

Reply 13: As requested, we revised the sentences in the Discussion section (see page 12, line 5-7).

Changes in the text: However, it appears that wild-type *tumor protein p53* and mutated *alpha-thalassemia/mental retardation, X-linked (ATRX)* were associated with shorter PFS in patients with LMS who received eribulin (18).

Reviewer C

The authors described a case with cardiac metastasis from uterine leiomyosarcoma who received eribulin.
Cardiac metastasis should be rare and successful treatment using eribulin was impressive.

We appreciate the reviewer's careful analysis of our work, and have revised the manuscript according to the comments.

Comment 1. The authors concluded that the expression levels of p-AKT in U-LMS may be a good predictive biomarker for response to treatment with eribulin. Why did the authors choose GD treatment and pazopanib before the eribulin treatment?

Reply 1: We initiated treatment with eribulin for this patient from May 2016. As we described in the Discussion section, in 2016, eribulin was approved for the treatment of patients with unresectable/metastatic sarcoma in Japan. Therefore, we could not administer eribulin as second- and third-line treatment after the AI regimen. In addition, our research on resistance to eribulin was published in 2019. We modified the text accordingly (see page 8, line 6, page 10-11, line 17-2).

Changes in the text: In May 2016, treatment with eribulin (1.1 mg/m2) was initiated;

In addition, it has been revealed that pazopanib improves PFS in patients with LMS (13). Therefore, we selected the AI regimen, GD regimen, and pazopanib as first-, second-, and third-line treatments for this patient, respectively.

Comment 2*. Surprisingly, in our patient, the reduction in tumor volume induced by eribulin was sustained for 17 months and... Therefore, the patient survived for 5 years after the detection of the cardiac metastasis relapse. I can't understand why the patient can survive for 5 years after the detection of the cardiac metastasis relapse due to the 17 months treatment of eribulin. 17 months and 5 years are very different.*

Reply 2: As mentioned, achievement of a durable response with eribulin was not the only cause of this outcome. We have corrected the text in the Discussion section (see page 11-12, line 18-3).

Changes in the text: Possible reasons for the 5-year survival of this patient after the detection

of the cardiac metastasis relapse are the successful treatment with eribulin and the sequential administration of several chemotherapeutics. Moreover, the functions of her major organs were maintained during the clinical course.

Comment 3. *If possible. please add the CT or MRI at initial cardiac metastasis. Why was initial cardiac metastasis able to be resected? Tumor size or site?*

Reply 3: This has been published in Reference 4 (Japanese literature). Therefore, in this manuscript, we focused on the clinical course of relapsed cardiac metastasis. Please consider it. We have corrected the text in the Case Presentation section (see page 6, line 7-10).

Changes in the text: In May 2011, she was diagnosed with a metastatic cardiac tumor (41 x 34 mm) located in the right ventricle, which blocked the right ventricular outflow tract. The patient underwent marginal surgical resection to prevent sudden death.