Author’s response to reviews

Title: A pediatric cancer patient with suspected chemical coping following high-dose opioid therapy: A case report

Authors:

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Author’s response to reviews:

Reviewer reports:
Reviewer #1: 1. Do you believe the case report is authentic? Yes

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.
Comments: I have no ethical concerns

3. Does the Introduction explain the relevance of the case to the medical literature? Yes

4. Does the article report the following information? Where information is missing, please specify.
   a. The relevant patient information, including:
      - De-identified demographic information (age, gender, ethnicity) - Partially
      - Main symptoms of the patient - Yes
      - Medical, family and psychosocial history - No
      - Relevant past interventions and their outcomes - No

   b. The relevant physical examination findings Yes

   c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at T = 0, follow up at T = 1 month.
   I think the authors should devise a timeline via a table/figure

   d. Diagnostic assessments, including:
      - Diagnostic methods
      - Challenges (e.g., financial, language/cultural)
      - Reasoning and prognostic characteristics (e.g., staging), where applicable Yes

   e. Types and mechanism of intervention Yes

   f. A summary of the clinical course of all follow-up visits Partially
5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented? Yes

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below. Yes

7. Is the Abstract representative of the case presented? Yes

8. Does the case represent a useful contribution to the medical literature? Yes

9. Additional comments for the author(s)?
The article "A pediatric cancer patient with suspected chemical coping following high-dose opioid therapy: A case report" by Miura et al. presents the case of a pediatric ALL patient suspected of chemical coping. The case is interesting and worth publishing; however, I think some changes are required prior to publishing.

1. I think the case report section should be better structured. Your description of the oncology part of the case is very brief. Also, you mention some things about the patient's pain treatment, but I am unclear as to what time period had passed between fentanyl dose escalations and oxycodone switch, how many times did you have to increase the fentanyl dose, if you treated this patient for pain with fentanyl only in the hospital or if he also went home with fentanyl, and so on and so forth. Perhaps a timeline of the case would help
   → We have provided the details in Table 1.

2. Page 7, rows 47-54 - "Considering the possibility of opioid overdose in response to complaints of nausea and fatigue, dose reduction was planned; however, he exhibited strong resistance." If I understood correctly, the patient exhibited significant nausea and fatigue, which is why you decided to reduce the dose. However, you do not explain that prior to this sentence. Also, I think the onset and the severity of these two symptoms should be included in the case presentation as they are important.
   → We have included the necessary details in Table 1.

3. At the beginning of page 8, you say that "Physically, his pain was considered to have alleviated;" - How did you assess that? Did you repeat the CT? Did you use any other assessment tools to diagnose chemical coping other than the team's opinion?
   Page 9, 1st line “his pain was considered to have alleviated”
   → CT revealed no findings that caused physically pain; his pain was considered to have alleviated
   (CT findings indicated no possible cause of pain, and his physical pain was considered to have alleviated.)

4. You mention that you tried giving Duloxetine to your patient, together with some other non-pharmacological measures. How long did you give the drug for?
   → We have provided the details in Table 1.
What was his analgesic need at that point?
Page 9, rows 5–6 Duloxetine, which exerts an antidepressive effect and adjuvant analgesic effect, was initiated at a dose of 10 mg/day.
   → Expected to use less opioid, duloxetine, which exerts an antidepressive effect and adjuvant analgesic effect, was initiated at a dose of 10 mg/day.

5. In the abstract, you mention that "opioid education was provided" for this patient. However, in
the case presentation I did not read anything about that - please reconcile.

Page 9, rows 17 Therefore, with the consent of the subject and his family,
→ An explanation on opioids in general and the possibility that the number of rescues will not decrease
for purposes other than analgesia (such anti-anxiety) was shared with the subject and family who
provided the consent,
(After providing a general explanation regarding opioids, the fact that the number of rescues might
remain unchanged for purposes other than analgesia (e.g., anti-anxiety effect) was understood by the
patient and his family who provided the consent…)

6. In the Discussions section, you state that "When chemical coping is suspected, it is important to
differentiate pseudo- addiction, opioid tolerance, and opioid-induced hyperpathia" and then proceed to
talk about the possibility of pseudo- addiction in your patient. I think you should add one-two
paragraphs discussing the possibility that your patient could have also had opioid tolerance or opioid-
induced hyperpathia at some point in his disease.
Page 11, rows 12 actual coping behavior, i.e., pressing the rescue dose button.
→ actual coping behavior, i.e., pressing the rescue dose button. However, the possibility of tolerance
and opioid-induced hyperalgesia could not be completely denied.
7. The importance of this case report should be emphasized more - how many other such cases
have been reported in the literature?
Page 3, rows 5–7: however, reports of pediatric cases are limited.
→ There are some pediatric opioid use-related tolerances and addictions; however, no mention of
chemical coping has been found.
Page 5, rows 15–16: there are few reports of chemical coping in children
→ There are some pediatric opioid use-related tolerances and addictions; however, no mention of
chemical coping has been found.

Minor observations:
- page 5, rows 22-23 - "and limited coping mechanisms are" instead of "and limited coping
  mechanism are"
- page 5, rows 29-30 - "opioids exhibited signs of chemical" instead of "opioids were determined
to exhibit chemical"
- page 7 rows 23-25 - "and the number of rescuing did not decrease in association with the
increase amount of continuous dosing" - please rephrase

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Comments: No
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f. A summary of the clinical course of all follow-up visits yes Comments: Yes

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9. Additional comments for the author(s)? None