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Subacute neurological deficits and respiratory insufficiency due to intrathecal methotrexate

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Subacute neurological deficits and respiratory insufficiency due to intrathecal methotrexate
Journal of Clinical and Translational Research

Dear Dr. van der Meulen,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Nov 28, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The authors wrote an interesting case of acute methotrexate induced encephalopathy. This disease entity usually presents with stroke-like symptoms, such as aphasia, weakness, sensory deficits, ataxia, and seizure. It is not common that methotrexate neurotoxicity leads into severe symptoms like respiratory depression. It is important to increase awareness on the possibility of such toxicity from IT methotrexate. However, I have some questions for the authors.

-How often was the IT methotrexate given to the patient? Kindly include the time interval between treatments.
-Please clarify how long did the symptoms lasted before full recovery. Did he required prolong ventilatory support?
-It was mentioned that the patient was given dexamethasone with the IT MTX. Was there any adjustment with the steroids when his symptoms worsened?
-Did he continue with the clinical trial? Was the dexamethasone also discontinued after he stopped the IT methotrexate?

Minor comments:
Page 3 Line 18: put a space between 24 and hours. Place a comma after hours. then suggest to change to "he first developed..."
Page 3 Line 28: change semioval center to centrum semiovale (although similar meaning, I recommend to be consistent with the term use) Place a "but" before no gadolinium
Page 3 line 38: replace "by ruling out" to " the exclusion of"
Page 3 line 43: remove the comma after brain
Page 3 line 45: change semioval center to centrum semiovale.
Page 3 line 60: change "dosed" to "dose". Remove the comma before and after "over CNS irradiation"
Page 4 line 5: change "developing" to "the development of"
Page 4 line 19: suggest to change sentence to " At follow-up imaging, areas of high intensity can be seen mainly in deep white matter on T2 and FLAIR sequence which regress gradually..."

Reviewer #2: congratulations on the manuscript.
Subacute neurotoxicity due to MTX is seen with some frequency, up to 3.4% according to authors, I would suggest that you write a little more about the incidence described in the literature, as well as the treatments that have been tried in this situation, such as dextromethorphan.

Authors' response

Journal of Clinical and Translational Research
Editorial Office

Rotterdam, November 6th, 2021

Dear dr. Heger,

Thank you for considering our manuscript entitled ‘Subacute neurological deficits and respiratory insufficiency due to intrathecal methotrexate’ for potential publication in *Journal of Clinical and Translational Research*. We would like to thank the reviewers for their valuable comments to further improve the quality of our manuscript. Please find below our response to address the concerns of the reviewers.

All authors have seen and approved the revised manuscript. We declare that this manuscript, in whole or in part, has not been previously published or submitted concurrently to any other journal.

Yours sincerely,
On behalf of the co-authors

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Response to the reviewers' comments

Reviewer #1:

The authors wrote an interesting case of acute methotrexate induced encephalopathy. This disease entity usually presents with stroke-like symptoms, such as aphasia, weakness, sensory deficits, ataxia, and seizure. It is not common that methotrexate neurotoxicity leads into severe symptoms like respiratory depression. It is important to increase awareness on the possibility of such toxicity from IT methotrexate. However, I have some questions for the authors.

Comment 1: How often was the IT methotrexate given to the patient? Kindly include the time interval between treatments.

Response to comment 1: *The patient received eight intrathecal injections with methotrexate and dexamethasone, which was given in parallel with his systemic treatment. This is added on page 3 line 36-37: "His first IT-MTX was give one week after his first systemic chemotherapy, in total he received 8 injections within 7 months."*

Comment 2: Please clarify how long did the symptoms lasted before full recovery. Did he required prolong ventilatory support?

Response to comment 2: *We have extended the description of his recovery to: "His condition improved spontaneously within several hours and the following day he did not need any ventilation support and he did not have any neurological sequelae." on page 3, line 44-45.*

Comment 3: It was mentioned that the patient was given dexamethasone with the IT MTX. Was there any adjustment with the steroids when his symptoms worsened?

Response to comment 3: *Indeed at every occasion of intrathecal therapy dexamethasone was co-administered, immediately after injection of MTX. After he developed symptoms the intrathecal treatment was stopped, and no further dexamethasone was given. Since corticosteroids can be given in various ways, we added "IT" to the first time methotrexate and dexamethasone were given. Page 3, line 34-36: "This regimen was combined with prophylactic intrathecal (IT) administrated methotrexate (15mg) and IT dexamethasone (4mg)."*

Comment 4: Did he continue with the clinical trial? Was the dexamethasone also discontinued after he stopped the IT methotrexate?

Response to comment 4: *To address this, we added the changes in his systemic treatment after this incident: "The trial treatment was stopped and he switched to inotuzumab. No further intrathecal treatment was given." Page 3, line 51-52. Dexamethasone was only given as part of his further systemic treatment, please see also our response to comment 3.*

Comment 5: Minor comments:
Page 3 Line 18: put a space between 24 and hours. Place a comma after hours. then suggest to change to "he first developed..."
Page 3 Line 28: change semioval center to centrum semiovale (although similar meaning, I recommend to be consistent with the term use) Place a "but" before no gadolinium
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Page 4 line 19: suggest to change sentence to " At follow-up imaging, areas of high intensity can be seen mainly in deep white matter on T2 and FLAIR sequence which regress gradually..."

Response to comment 5: *We would like to thank the reviewer for bringing these language improvements to our attention. Allow us to respond to all changes in one comment. We changed all the suggestions accordingly, and we changed "semioval center" to "centrum semiovale" also in the abstract. Only the suggestions: for Page 3 line 60: change "dosed" to "dose"' was changed otherwise: "Dosed" was changed into "....multiple administrations..." See page 4, line 57.*

Reviewer #2:
Congratulations on the manuscript.

Comment 1: Subacute neurotoxicity due to MTX is seen with some frequency, up to 3.4% according to authors, I would suggest that you write a little more about the incidence described in the literature, as well as the treatments that have been tried in this situation, such as dextromethorphan.

Response to comment 1: *we agree that it is important to emphasize what can be done with respect to medical treatment to prevent neurotoxicity. This is mainly chemical meningitis and more rarely mucositis and bone marrow depression. Leukoencephalopathy after only intrathecal MTX treatment is rare. We added the following to the Discussion section: "It is important to administer IT corticosteroids together with MTX, and to use 15mg of folic acid, 24 hours after IT MTX to replenish folic acid depletion.[3]" Page 4, line 59-60. Focal neurotoxicity is very rare. The use of dextromethorphan or aminophylline has only been described in case-series and there is a lot of debate about is use. Currently, it is not recommended by international guidelines. Therefore it is beyond the scope of this case-report on when and how to use these agent.*

2nd Editorial response
12-Nov-2021

Ref.: Ms. No. JCTRes-D-21-00163R1
Subacute neurological deficits and respiratory insufficiency due to intrathecal methotrexate
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly

review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: