Journal of Clinical and Translational Research
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Glioblastoma multiforme of spinal cord – case series in a tertiary cancer centre

Aswin Nagarajan, Ramya Ravichandar

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1st Editorial decision
17-Aug-2021

Ref.: Ms. No. JCTRes-D-21-00127
GLIOBLASTOMA MULTIFORME OF SPINAL CORD – CASE REPORT SERIES IN A TERTIARY CANCER CENTRE
Journal of Clinical and Translational Research

Dear Dr. Nagarajan,

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. Please pay particular attention to the comments of reviewer 1, who remarked that you failed to properly classify the malignancy.

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 Sep 16, 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
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Reviewers' comments:

Reviewer #1: Spinal glioblastoma is indeed a rare form of glioblastoma. Diagnosis of glioblastoma should be based on both histological description and molecular features. The authors did not include any molecular description of the tumors that will support the diagnosis of glioblastoma. There are several test that should be done to confirm their diagnosis. One important test that should be requested is H3K27M. Diffuse midline glioma, H3 K27M-mutant has been defined since the 2016 revision of the WHO classification of CNS tumors. It mostly represents pontine gliomas but it can appear elsewhere in midline structures (spinal cord or thalamus). There has been changes on diagnosis of pediatric tumors based on the latest WHO classification 2021. Glioblastoma is no longer used in the setting of pediatric-type of neoplasm.

Reviewer #2: The authors wrote an interesting case series about a rare entity within the field of neuro-oncology: primary spinal glioblastoma. It highlights the variety of survival among these patients. However, the manuscripts needs some major revisions to clarify a few points and need to better discussed in the discussion section. Please find my comments below.

Major comments
1. Please refer to the CBTRUS report/ SEER database in the introduction, if you speak about the incidence of a GBM in the spinal cord, in stead of a case report (reference [1])
2. Please be consistent in all cases you describe, what were the neurological deficits before surgery, how was the MRI before surgery, and how were those two things after surgery. If unchanged just say that, but try to be complete and consistent in the order you describe the case.
In case 3, for example:
- a 13 year-old female child (no need to use the word child here)
- I can hardly imagine she was suffering from incontinence for 1 month, did she gradually worse with unsteadiness of gait, and subsequently developed incontinence?
- Be aware of lower case and upper case when writing and be clear: Clinically the strengths of the upper???? limbs was 3/5 (were all muscles affect equally?) and the lower limbs was 0/5, the sensation and ....plantar reflex showed a Babinki sign on both feet. The MRI before surgery showed..... She underwent a laminectomy and .... The MRI post-operative showed .... Histology and molecular analysis showed ...
- in this case you used cGy, instead of Gy, again try to be consistent in all cases

3. In the light of WHO classification of 2021 (and also of 2016), reports about CNS tumors

need a more than just the histology description, mention at least the IDH, 1p/19q and MGMT status.

4. The Discussion needs to rewritten, in order to clarify a few points that are brought up
- " The CSF cytology is routinely done since there is chance of 26% metastasis due to leptomeningeal dissemination which is attributed to relatively thin parenchyma in the spinal cord and short distance to the subarachnoid space [6]"
Do you mean, it should be done?
And, 26% is a very specific percentage, while you are referring to a case report [6]. So I think this should be rephrased into: "...CSF metastases can occur in up to 26%" with the same reference, or use a reference that describes a larger series.
- " Microscopically it shows features ..." this part is about the histology, please mention that. In addition, how about the molecular features in spinal GBM. Please add.
- Since the spinal GBM carries poor prognosis, multimodality treatment is recommended which includes maximal safe surgery, radiotherapy, chemotherapy and immunotherapy [7]. First, it should be mentioned that there is no standard of care of spinal GBM. But in consensus: surgery is the first step, after that the Stupp regimen could be given, in line with GBM in the brain. Second, reference [7] describes only brain GBM, mainly in children and does not mention immunotherapy!

Minor comments
1. title: CASE REPORT SERIES, change into case series
2. language, please see some the typo's below
- p1, line 29: 1-5 % of all glioblasoma, change into glioblastoma
- p1, line 37-38: Magnetic Resonance Imaging (MRI) of the entire spine including brain is generally advised in this condition, in would recommend to say: the entire neuroaxis, including the brain, or the entire spine and the brain. Now it reads like the brain is part of the entire spine.
- p 2, line 21-22: He underwent laminectomy and partial excision of the lesion in a private hospital outside in the month of august 2018. Please rephrase, because: did he have surgery in another hospital or was it before or after August 2018. In addition, August is obviously a month. For example: " ...of the lesion in a another (private) hospital in August 2018."
- Discussion: The common features include pain, neurological deficits, sensory disturbances, bowel and bladder disturbances,etc. Remove etc. and change it into: the most common features are pain, weakness, sensory deficits and bowel and bladder dysfunction. The sentence thereeafer, do you mean, " One or more of these features were present in all patients reported in this series." ?

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Title: change "case reports" to "case series"
Page 1, line 31: change "age" to "life"
Line 35: change "seedling" to "seeding"
Line 48: "A 32-year-old male…" is the correct form.
In case 1: please mention the temozolomide dose used concurrently with RT and adjuvant to it and number of adjuvant cycles. Also, what do you mean by "anti-edema precautions"? If you

mean corticosteroid use, please clarify.
The fact that this patient has remained disease-free for such a long time, is very interesting. Were the initial pathology blocks sent for re-review by another pathologist?
In Case #2, did the patient succumb to illness due to the progressive disease or because of treatment related adverse effects like edema as stated? The authors have to clarify this issue.
Case #3, line 53, change "power" to "muscle force"
What was the result of pre-op MRI in this case? Please omit or change this sentence: "The MRI spine was suggestive of C7 - D7 laminectomy and excision of the lesion in November 2018." and explain the initial lesion and the surgical procedure like the previous cases.
Figure 4 shows a very large treatment field. What was the exact size and extension of the initial tumor for case #3, and did she or any other one of your mentioned cases experience acute or late radiation related toxicities?

Authors' response

REBUTTAL LETTER
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We are grateful for your commentary and suggestions, which we have addressed to the fullest extent as indicated below for your comments Reviewers' comments:

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Answer: Discussion. Page 3. Lines 27,28,29

Reviewer #2: The authors wrote an interesting case series about a rare entity within the field of neuro-oncology: primary spinal glioblastoma. It highlights the variety of survival among these patients. However, the manuscripts need some major revisions to clarify a few points and need to better discussed in the discussion section. Please find my comments below.

Major comments

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2. Please be consistent in all cases you describe, what were the neurological deficits before surgery, how was the MRI before surgery, and how were those two things after surgery. If unchanged just say that, but try to be complete and consistent in the order you describe the case.

In case 3, for example:

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- Be aware of lower case and upper case when writing and be clear: Clinically the strengths of the upper???? limbs was 3/5 (were all muscles affect equally?) and the lower limbs was 0/5, the sensation and ....plantar reflex showed a Babinki sign on both feet. The MRI before surgery showed..... She underwent a laminectomy and .... The MRI post-operative showed .... Histology and molecular analysis showed ...
- in this case you used cGy, instead of Gy, again try to be consistent in all cases Answer: Case 3. Page 2. Lines 28,29,30,31,32.
  Page 3. Lines 1,2,3,4,5,6,7.

3. In the light of WHO classification of 2021 (and also of 2016), reports about CNS tumors need a more than just the histology description, mention at least the IDH, 1p/19q and MGMT status.

Answer: Discussion. Page 3. Lines 33,34,35,36.

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26% metastasis due to leptomeningeal dissemination which is attributed to relatively thin parenchyma in the spinal cord and short distance to the subarachnoid space [6]" Do you mean, it should be done? And, 26% is a very specific percentage, while you are referring to a case report [6]. So I think this should be rephrased into: "...CSF metastases can occur in up to 26%" with the same reference, or use a reference that describes a larger series.
Answer: Discussion. Page 3. Lines 29,30,31.

- " Microscopically it shows features ..." this part is about the histology, please mention that. In addition, how about the molecular features in spinal GBM. Please add.

Answer: Discussion. Page 3. Lines 33,34,35,36.

- Since the spinal GBM carries poor prognosis, multimodality treatment is recommended which includes maximal safe surgery, radiotherapy, chemotherapy and immunotherapy [7]. First, it should be mentioned that there is no standard of care of spinal GBM. But in consensus: surgery is the first step, after that the Stupp regimen could be given, in line with GBM in the brain. Second, reference [7] describes only brain GBM, mainly in children and does not mention immunotherapy! Answer: Discussion. Page 4. Lines 1,2,3.

Minor comments

1. title: CASE REPORT SERIES, change into case series

Answer: Page 1. Title

2. language, please see some the typo's below

- p1, line 29: 1-5 % of all glioblasoma, change into glioblastoma

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Answer: Case 1. Page 1. Line 21 Case 2. Page 2. Line 8.
Case 3. Page 2. Line 31

- p 2, line 21-22: He underwent laminectomy and partial excision of the lesion in a private hospital outside in the month of august 2018. Please rephrase, because: did he have surgery in another hospital or was it before or after August 2018. In addition, August is obviously a month. For example: " ...of the lesion in a another (private) hospital in August 2018." Answer: Case 2. Page 2. Lines 12,13

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Answer: Page 1. Title
Grammar: Answer: Page 1. Line 29.
Page 2. Lines 1, 21
Page 3. Lines 11,21,22
Page 4. Lines 10,11,14,15,16,24.

Page 1, line 31: change "age" to "life"
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Line 35: change "seedling" to "seeding" Answer: Introduction. Page 1. Line 14.

Line 48: "A 32-year-old male…" is the correct form.
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In case 1: please mention the temozolomide dose used concurrently with RT and adjuvant to it and number of adjuvant cycles. Also, what do you mean by "anti-edema precautions"? If you mean corticosteroid use, please clarify.
Answer: Case 1. Page 2. Lines 2,3.

The fact that this patient has remained disease-free for such a long time, is very interesting. Were the initial pathology blocks sent for re-review by another pathologist?
Answer: Usually, two pathologists will review the slides and the blocks and give the final report before initiation of the treatment. Hence, the diagnosis was confirmed .

In Case #2, did the patient succumb to illness due to the progressive disease or because of treatment related adverse effects like edema as stated? The authors have to clarify this issue.
Answer: Case 2. Page 2. Lines 24,25,27,28.

Case #3, line 53, change "power" to "muscle force" Answer: Case 3. Page 3. Line 1.

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Answer: Case 3. Page 2. Lines 30,31,32.
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Figure 4 shows a very large treatment field. What was the exact size and extension of the initial tumor for case #3, and did she or any other one of your mentioned cases experience acute or late radiation related toxicities?
Answer: Case 3. Page 3. Line 12.
Discussion. Page 4. Lines 30,31.

2nd Editorial decision
15-Sep-2021

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Please understand that the editorial board has stipulated that compliance with the current classification criteria of GBM is a hard prerequisite for publication of the study. The reviewer who keeps pointing that out is a global expert whose expert opinion bears a lot of critical mass. It is also in the interest of the authors that the correct tumor is being addressed in the manuscript. Knowledge of and compliance with the most recent criteria is a testament to the quality of your work. We therefore want to extend one more opportunity to you to bring the manuscript in agreement with putative classification standards.

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.

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However, although I realize that molecular testing was not done, this lacks a proper classification and histology might be glioblastoma, molecular features might show it is a different entity which might explain the long-term survival of one of the cases.
In the Discussion section, this is just partly explained and the paragraph about molecular features in GBM, describes incorrect features, based on a paper published in 2014. Since then, the classification has changed twice: A GBM is by definition an IDH wild-type tumor and

MGMT hypermethylation is present in only 50% of the cases.

The reference to the Stupp trial is the wrong one: Stupp, Mason, van den Bent, et al, NEJM, 2005 is the one that describes the nowadays standard of care for brain GBM

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Answer: Page no 4. Lines 1,2,3,4,5,6,7,8,9,10,11,12,13,16.

Page no 5. Reference 8.

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Thanks a lot.

3rd Editorial decision
12-Nov-2021

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GLIOBLASTOMA MULTIFORME OF SPINAL CORD – CASE REPORT SERIES IN A TERTIARY CANCER CENTRE
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: