Peer Review File

Article information: https://dx.doi.org/10.21037/pcm-22-47

Reviewer A

The manuscript titled, "pathologically document brain necrosis: response to bevacizumab after irradiation for solitary fibrous tumour/haemangiopericytoma: case report and literature review," presents a well-written case of post-surgical and post-irradiation brain necrosis and relief of symptoms with DMSO and Bevacizumab. The novelty of the article is reduced some since recently it has become well accepted that Bevacizumab may relieve radiation-induced neurological symptoms. That said, the article has many meritorious points that will increase the healthcare's treatment of SFT/HPC. First it clearly demonstrates a case that characterizes radiation-induced necropsy carefully (as compared to surgery or recurrence related). It explains the rational behind why Bevacizumab may work at reversing radiation-induced symptoms as well as how it may treat SFT/HPC. It also highlights some of the uncertainty regarding timing and duration of treating post-irradiation necrosis with Bevacizumab. This article will encourage other to try Bevacizumab after radiation-induced necrosis of SFT/HPC cancer. Only minor suggested edits are recommended as numerated in chronological order below.
Reply: We were pleased with the Reviewers' assessment of our manuscript, saying that there were "many meritorious points that will increase healthcare's treatment of SFT/HPC", that it "characterises radiation-induced necropsy carefully", that it "explains how bevacizumab may work at reversing radiation-induced symptoms" and "how it may treat SFT/HPC". It also "highlights some of the uncertainty regarding timing and duration of treating post-irradiation necrosis with bevacizumab". They also state that "This article will encourage others to try Bevacizumab after radiation-induced necrosis of SFT/HPC" and that they recommended only minor suggested edits".

1. The slight male preponderance is not widely observed anymore. Recent papers suggest the incidence is equal amongst sexes.

Reply: Page 4 line 5. As requested, we mentioned there is an equal sex distribution.

2. In the introduction (line 14) the authors state SFT/HPC originate in the pericytes surround blood vessels. This has also been considered obsolete. The current findings suggest a mesenchymal cell with fibroblastic features.

Reply: Page 4 line 3. We removed reference to pericytes.

3. The reviewer would like to see more technical details of the case.
a. For example, page 2, line 35: "large left frontal tumour", how large? Please quantify

maximum diameter in cm.
Reply: Regarding tumour size: MRI brain 18/10/2019 - describes a left frontal tumour measuring approximately 75 x 65 x 70 mm (AP x TR x CC) and containing multiple non-enhancing central T2 hyperintense cystic regions, as well as multiple areas of intralesional susceptibility artefact consistent with haemosiderin deposition.
We added the tumour size on page 2, line 11 ("75mm maximal diameter") as well as page 5, line 12.
b. Page 2, Line 42: "not >10 per high-powered field", what was the mitotic rate exactly?
Reply: The mitotic rate was as follows: Histology report from 19/10/2019: "Mitotic activity is readily apparent in many areas, but does not exceed 5 per ten-high-power-fields."
Reply: we added this on page 5, line 11.
c. Page 3, Line 33: "symptoms responded promptly to dexamethasone", what symptoms specifically? Reply: Specific symptoms were mild right facial droop, morning headaches and difficulties with concentration. We added this on page 6, line 20.

d. Page 3, line 37: "Eventually," exactly how long was the patient on Dexamethasone before stopping?

Reply: "Exactly how long was the patient on Dexamethasone before stopping?"

"The patient was on Dexamethasone for 16 weeks; the bevacizumab overlapped with dexamethasone for 8 weeks (it took approx. 8 weeks until Bevacizumab became available)." We added this on page 6, final paragraph.

4." If the symptoms responded to Dexamethasone, why do you think Bevacizumab reversed the symptoms and not Dexamethasone?"

Reply: Actually, the symptoms responded to Dexamethasone promptly, but reoccurred on tapering the dose (the dose was subsequently tapered with 0.5 mg/week) then responded to Bevacizumab alone.

5. Discussion, line 3-5: "if they occur anywhere in the body they are labelled as SFT/HPC, not just intracranially".

Reply: We agree and have altered the text as suggested throughout.

6. "The authors need to be careful about claims that Bevacizumab can treat microscopic SFT/HPC disease along with radionecrosis (page 7, line 28-29)."

Reply: We have removed the statement that Bevacizumab may treat/kill microscopic SFT/HPC.

Reviewer B

1. -Page 3, line 4: Recommend that the authors include a detailed postoperative neurologic exam at the time of discharge, particularly in light of the described surgical morbidity.

Reply: Post craniotomy (19/10/2019) the patient was admitted to ICU, was intubated and sedated for days. She had brief episodes of delirium (intermittent visual hallucinations -responded to Haloperidol) between 23/10/19-26/10/19. This was inserted on page 5, line 7.

2. -Page 3, line 8: "Please provide mean doses to organs at risk, specifically the optic nerves, optic chiasm, retina, lens, brain stem".

Reply: These mean doses were: optic nerves (Right: 49.79Gy; Left: 31.38Gy, optic chiasm (39.94Gy), retina (not recorded), lens (Right 4.33Gy; Left 11.86Gy), brain stem (28.23Gy).
Reply: These data were inserted on page 5, line 21.

3. -Page 3, line 34: "The authors should provide more detail regarding the time interval between initiation of steroids and symptomatic response (prior to starting bevacizumab). What was the baseline neurologic exam prior to initiation of bevacizumab? Please provide the neurologic exam following initiation of steroids and state whether there was a partial or complete symptomatic response to steroids. Was there an MRI available prior to initiation of bevacizumab for comparison? The manuscript would greatly benefit from further detail on the clinical and radiographic course in order to determine whether the patient's improvement is due to steroids, avastin, or both".

Reply: We inserted (Last paragraph, page 6): The neurological exam prior initiating dexamethasone was unremarkable, except for mild right facial droop. There were no other cranial nerve abnormalities. Subjectively, the patient complained of difficulties in concentration, but examination of higher centres was unremarkable. The Mini Mental State Examination was also normal. Tone, power, reflexes, coordination and sensation were unremarkable. Unfortunately, there was no MRI in March 2021 prior initiation of steroids, nor prior to commencement of bevacizumab.

See also point 10, Reviewer B.

4. Page 3, line 46: Please correct MRI date "11/3/2022"

Reply: The MRI date is correct.

5. Page 5, line 9: Would strongly recommend adding citation (PMID 30828724 DOI 10.1093/neuonc/noz048)

Reply: Citation added as requested.

6. Page 5, line 16: Would discuss the spatiotemporal features of radionecrosis, particularly the increased frequency of radionecrosis among periventricular lesions (PMID 32488924 DOI 10.1634/theoncologist.2020-0085).

Reply: The following text has been inserted (page 11, second to last paragraph): “Characteristic spatiotemporal patters of radionecrosis are described, with a predilection for periventricular locations (Winter et al the oncologist). Such a periventricular location was observed in our case (see Figure 2, D and E)”.

7. Page 6, line 7: “Recommend further details regarding the acute and long term effects of steroids. The authors should highlight concerns that the immunosuppressive effects of steroids could undermine the efficacy of certain systemic agents (eg. Immunotherapy)”.

Reply: we believe that steroid effects are clinically well known, especially to practitioners in the field, and it is beyond the scope of this article. Also, as immunotherapy is not used in the treatment of SFT/HPC, we believe that this is also tangential to the manuscript and does not warrant inclusion.

8. Page 6, line 23: Recommend highlighting how bevacizumab has been applied to treat radionecrosis following radiation therapy for various intracranial tumor histologies.

Reply: we already provide a large section on this topic, including a number of recent review articles, commencing with paragraph 2, page 12.

9. Please cite more recent work showing the benefit of bevacizumab in the treatment of radionecrosis following SRS for primary CNS lymphoma (PMID: 35359747 DOI: 10.18632/oncotarget.28222).

Reply: Citation has been added as requested.

10. Page 7, line 22: The authors should acknowledge the challenge with attribution as it is unclear whether bevacizumab contributed to the clinical and radiographic response, as the patient had already received and improved with a course of steroids. More detail description of the clinical and radiographic evolution, with respect to medical interventions, is necessary.

Reply: we agree, and the following text has been inserted on page 7, last paragraph: “However, there was some difficulty in attributing the clinical and radiological improvement fully to Bevacizumab, since the patient had responded to steroids and there was a period during which the two drugs were being delivered simultaneously. Yet the overall picture favoured a Bevacizumab response”.

11. The authors should highlight case reports that have applied bevacizumab to treat radionecrosis following radiation therapy for other intracranial tumor histologies.

Reply: see response to point 8 above. This information is also available in the cited review articles.

12. Page 7, line 42: The authors should acknowledge that the patient was treated with a combination of steroids and avastin.

Reply: This has been added, eg, to the Abstract, Line 18: “The patient was treated initially steroids then with 10 cycles of bevacizumab..”. Also see response to point 10, above.

13. The figures have been partially rearranged as requested, but as mentioned above, there were no MRIs available from the time points of “post steroid (pre bevacizumab), post steroids + bevacizumab”, as suggested, and so the image of new Figure 3 would have been the only one available for the timeline (“long term follow up scan”), which was not useful.