Dear Editor and Reviewer,

Thank you very much for the reviewer’s valuable comments on our manuscript entitled "Malignant meningioma with jugular vein invasion and carotid artery extension: A case report and review of literature".

We have carefully addressed the comments raised by the reviewer and revised the manuscript, the amendments are highlighted in yellow in the revised manuscript. Point by point responses to the reviewer’s comments are listed below this letter.

Moreover, thanks for the comments given by the company's editor-in-chief. Regarding the language editing and polishing, we consulted the English language-editing teacher of the International Scientific Editing Company, who thought that there were still some language problems in my manuscript. The language of the manuscript has been edited again by them. The International Scientific Editing Company is dedicated to helping non-native English speakers write and publish in English and has helped many articles[1, 2] to be published successfully. We hope that the revised version of the manuscript will be acceptable for publication in "World Journal of Clinical Cases".

We look forward to hearing from you soon.

Yours sincerely

Jiping Su

Replies to Reviewer's Comments

Reviewer #1:

1. 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Clinical and pathological aspects: yes, but Regarding the circulating of meningioma tumor, no supportive document, mainly, the journey to the host organ has not been, by specific neural antibody, such as Neurofilament, supported. 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? Please read the answer to question 5.

Answer:

Thank you very much for the comments.

The update of WHO classification in 2016 has implemented molecular markers for several brain tumour types. However, no molecular specific markers have yet been established for meningioma. Although some of important genetic alterations can be investigated by specific antibodies, for example neurofibromin (NF2), progesterone receptors(PR), TNF receptor-associated factor 7 (TRAF7), Kruppel-like factor 4 (KLF4)[3, 4], they are still in research and exploration stage and not absolute specific markers of meningiomas.

In this case, the immunohistochemistry showed vimentin (+), EMA (+),CD34 (−), S-100 (−),PR (−),CK (−), P40 (-),SMA (+), TTF-1 (−), calponin (+), desmin (−),D2-40 (−), E-CAD (−), and Ki-67 (+ [50%]). The pathology consultation from the First Affiliated Hospital of Sun Yat-sen University showed that the tumor cells were positive for vimentin, CD99, INI-1, and EMA; desmin was slightly positive in some of the cells; Ki67 expression varied between 10% and 30%; and was negative for S-100, PR, GFAP, CD34, Syn, NSE, MyoD1 and myogenin.

Studies on markers of meningiomas[5, 6] suggest that meningiomas mainly contain mesenchymal and epithelial cellular structures. Epithelial membrane antigen

(EMA) is a glycoprotein expressed in the dura mater epithelium[7]. It has been reported that in meningiomas the positive rate of EMA expression is 100%[8], and EMA and vimentin are strongly positive[9].Vimentin is a kind of mesenchymal silk protein, which is expressed in mesenchymal tissues and mesenchymal tumors. Positive vimentin expression indicates that the cell is in the immature stage with low degree of cell differentiation[10]. Both EMA and vimentin are important markers for meningiomas.

S-100 is an acid calcium binding protein of the nervous system. S-100 and glial fibrillary acidic protein (GFAP) are markers that exist in astrocytes and astrocyte-derived tumors. They are highly expressed in gliomas, but low in meningiomas[7]. Therefore, the combined detection of Vimentin, EMA, S-100, and GFAP is beneficial to the differential diagnosis of meningiomas and gliomas. In addition, CD34 is used to differentiate hemangiopericytoma (positive) from meningiomas (negative)[11].

Ki-67 is a non-histone nuclear antigen, expressed in the G1, S, G2, and M phases of the cell proliferation cycle, and is used to show the proliferation trend of tumors. The poorer the tissue differentiation, the more cells in a proliferating state, and the higher the expression of Ki-67. It is a commonly used antigen to detect the degree of tumor malignancy[12].

In benign meningiomas, ER (Estrogen receptor), PR(Progesterone receptor) and AR (Androgen receptor) have a certain correlation[13]. The PR positive rate is higher in meningiomas with a lower WHO grade, while the PR positive rate is lower in malignant meningiomas[14].

Based on these and more studies, the immunohistochemical antigen staining combined with clinical information in this case, the diagnosis of malignant meningioma has been strongly explained.

2. 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author

self-cite, omit, incorrectly cite and/or over-cite references? Yes for clinical aspects. Regarding migration, “Circulation” is used 12 times with a referral as Reference 9. Mathiesen T.,et al. Meningiomas engaging major venous sinuses. World Neurosurg 2014; 81(1):116-124 In fact no background on the Circulating tumor cells are provided.

Answer:

Thank you very much for the comments. Indeed, as the reviewer described, the theme of reference 9 (Mathiesen T.,et al. Meningiomas engaging major venous sinuses. World Neurosurg 2014; 81(1):116-124) is not that malignant meningiomas invade the circulatory system, but that it contains relevant descriptions in introduction part. It is described in the introduction as follows: "Their potential of invading the sinus walls and affecting bridging veins are common denominators that complicates radical surgery. The several series of differently located venous meningiomas have had reported….." Although it contains relevant descriptions, we agree with the reviewer’ s opinions and choose more appropriate references[15-17] to reinsert for a more powerful explanation that meningiomas invade the circulatory system.

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