Author’s response to reviews

Title: Diffuse Cavernous Hemangioma of the skull misdiagnosed as skull metastasis in breast cancer patient: one case report and literature review

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Version: 2 Date: 29 Nov 2018

Author’s response to reviews:

Dear editor,

Many thanks for your email with encouraging news regarding our manuscript. We also thank the reviewers and their constructive suggestions and comments. We have revised our manuscript accordingly and would like to re-submit it for your consideration. Our point-by-point answers to the reviewers’ comments are attached below and the amendments are highlighted in yellow in the revised manuscript, and other changes such as grammar, spelling, and syntax using track changes.

We hope that the revised manuscript is now acceptable, and I am looking forward to hearing from you soon.

Sincerely,

Xiaoying Xue, MD
Professor and Chief
Our responses to the reviewers’ comments

Reviewer #1

Isaac Chen (Reviewer 1): The authors present a single case of a primary intraosseous cavernous hemangioma (PICH) in a patient with prior breast cancer. The patient developed a mass on the right side of the head that was initially painless. However, it was initially associated with headaches and bilateral upper eyelid edema. Imaging showed an extensive lesion affecting the bilateral frontal and right temporal/parietal skull. There was also evidence of intracranial extension causing mass effect and cerebral edema. After a biopsy was performed, the diagnosis of PICH was obtained, and the patient was treated with radiation. This led to (presumably) a decrease in the size of the lesion and improvement in symptoms.

Comments:

- This an interesting case with very evocative imaging findings. However, it is very difficult to read in its current format. The manuscript would benefit from extensive proofreading to improve its grammar, spelling, and syntax.

We thank the reviewer for this positive remark. This manuscript has been edited and proofread by AI Yi Ping medical information consultation Co. Ltd. Jinan, China.

- What is etiology of the patient's eyelid edema? Is this an inflammatory response to the PICH?

We fully understand the reviewer’s concern. Based on the CT and MRI findings, the headache and upper eyelid edema of the patient were considered to be caused by the local invasion of the skull lesions. We have added such information in Case presentation section, line 11-12, page 4.

- The physical examination description should include a full neurological exam.

We fully agree and have added neurological exam in Case presentation section, the first paragraph, line 12-13, page 3.

- The CT shows areas of the skull where bone signal is nearly completely gone. Were these areas of the skull soft on physical exam?
We fully understand the reviewer’s concern. On physical exam, these areas of the skull was solid, we have added this information in Case presentation section, line 9, page 3.

- In Figure 1, it appears that the lesion extends to the orbital roof. Inclusion of lower cuts would be helpful to see the extent of the lesion in the orbital/maxillofacial bones.

We fully agree and have add lower cuts in Fig.5 of revised manuscript.

- What type of biopsy was performed? Open versus needle core?

We thank the reviewer and the suggestion, and have added this information in the second paragraph of Case presentation, line 8, page 4.

- Given the extensive nature of the lesion, it seems likely that the radiation field was quite extensive, perhaps even approaching whole brain radiation. Inclusion of the radiation plan would be helpful.

We fully agree and have added radiation plan in Case presentation section, the second paragraph, line 13-18, page 4.

- The authors state that "the head CT showed that the area of the biopsy area (right temporoparietal area) was reduced" at the end of radiotherapy. Does this mean that the PICH had decreased in size at the time of the last fraction? If so, this imaging should be shown as another figure. Also, imaging at the time of subsequent follow-up should also be shown to document decrease in the size of the PICH, decreased cerebral edema, and less brain shift, which the authors imply happened.

We fully understand the reviewer’s concern. First, we apologize profusely for our mistake. In reality, the CT image provided in Fig.1 (corrected to Fig.5 in our revised manuscript), which was acquired using a 64 row CT scanner, was performed at the end of radiotherapy. The CT image before the radiotherapy was obtained using a 16 row CT scanner, which was used for radiotherapy positioning (as illustrated in Fig.1 in our revised manuscript). We concluded that the head CT image exhibited no significant change compared to that before the radiotherapy. We therefore provided the clearer and more typical CT image, which was scanned after completion of radiotherapy. In our revised manuscript, we have corrected this. Upon physical examination, the size of the lump at biopsy site (the primary right frontal, temporal, and dorsal scalp) was slightly reduced on physical examination, but the head CT exhibited no significant change compared to pre-radiotherapy CT images (Fig.5). We concluded that this may due to poor soft tissue resolution on CT images. The symptoms of discomfort in the head and eye swelling were relieved. Unfortunately, as the patient resides in another city, far from our hospital, we performed only a telephonic follow-up. The CT scan during the 1 year follow-up was performed at an outside institution and was not available for inclusion in this report. Recently, we have
attempted to persuade this patient to undergo a follow-up examination at our hospital (Case presentation section, the second paragraph, line 18-21, 23-26, page 4).

- In the Discussion, the authors state "The hemangiomas in skull always present as a single mass, multiple lesions is rare." This statement is inherently contradictory. If rare multiple lesions exist, then skull hemangioma are NOT always present as a single mass.

We are sorry for this, and have revised it in the Discussion and Conclusions section, the first paragraph, line 13-14, page 5.

- In the Discussion, the authors state that "extensive cranial hemangioma has not been reported previously." How is "extensive" defined? Is this qualitative or quantitative? Has this term been used or defined in prior literature?

We are sorry for this, and have revised it as “Diffuse Cavernous Hemangioma” throughout the manuscript. “Diffuse Cavernous Hemangioma” has been used in many prior literatures.( e.g. 1. Wang HT, et al. Diffuse cavernous hemangioma of the rectosigmoid colon. Tech Coloproctol 2005 Jul;9 (2): 145-8; 2. Djouhri H et al. Diffuse cavernous hemangioma of the rectosigmoid colon: imaging findings. J Comput Assist Tomogr 1998 Nov-Dec (6): 851-5. etc)

- Given the cerebral edema, was the patient treated with steroids (e.g., dexamethasone)? If so, were the steroids able to be weaned after radiation?

We fully understand the reviewer’s concern. Based on the T2/FLAIR imaging of MRI, the cerebral edema was not remarkable, and the patient had a slightly headache, so she did not treated with steroids.

- If the patient did not have recurrence of her breast cancer, what was the reason why her serum tumor markers were elevated. Are the authors implying that PICH can lead to elevations in tumor markers? If so, this should be discussed more.

We fully understand the reviewer’s concern. We have added such information in the Discussion and Conclusions section, the fourth paragraph, line 6-7 and 15-17, page 7.

Reviewer #2

Jian Guan (Reviewer 2): The article described a case of extensive cranial hemangioma of the skull in a breast cancer patient, which could be easily misdiagnosed as skull metastasis. Meanwhile, author has reviewed several literatures. I recommend that the manuscript should ask a native English speaking colleague to copyedit the paper. Author should summarize the characteristics of extensive cranial hemangioma based on literatures. Additionally, manuscript should increase the research development of etiology according to recent studies.
We thank the reviewer and the suggestion. This paper has been copyedited. We have summarized the characteristics of extensive cranial hemangioma and increased the research development of etiology according to recent studies, also added these in the first and last paragraph of Discussion, line 5-13 page 5, and line 18-20, page 7.