Author’s response to reviews

Title: Multiple Intraneural Glomus Tumors In Different Digital Nerve Fascicles

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Author’s response to reviews:

Dear Prof. Jean-Philippe Brosseau:

Thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. The response to your comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely, Hui Lu M.D. Department of orthopedics

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Replies to the Editor Comments:

1) Regarding the histological characterization of the Glomus Tumor (Figure 4)a) Please provide all immunohistochemistry images for weak or negative staining (cytokeratin, CD31, EMA, KI-67, S100, CgA) along with their respective positive control and scale bar on each images.
Answer: We add the negative staining and scale bar on each images. For the sake of the number of pathological photos, we have chosen KI-67, S100, hope you will understand.

b) Better describe a rational for the use of each markers and what differential diagnosis they are ruling out

Answer: we add the section. “CD34 for vascular tumors (+), CK(pan) for tumors of epithelial origin (−), CD31 for endothelial cells and tumor angiogenesis (−), Desmin for mesenchymal tissues origin (small quantity +), EMA for epithelial origin (weak +), Ki-67 for cell proliferation in tumours (+2%) , S-100 for nervous tissue origin (−) , SMA for tumors of smooth muscle origin (+), Nestin for nervous tissue origin (+) , CgA for tumors of neuroendocrine cells origin (−), and Syn for tumors of neuroendocrine cells origin (+).” See in page 5, line 74–81.

2) In the discussion section, please discuss differential diagnosis encompassing clinical, radiological and histological characterization and cite appropriate literature.

Answer: we add the section. “Pacinian corpuscles neuroma was pain and swelling tumor in finger with or without history of trauma, subcutaneous plane, spherical, gray and in clusters lesions can be observed in pathological study[13]. Giant cell tumor of tendon sheath is a common benign with incentives, multiple nodules tumor arising in the tendon sheath. In treatment, the elimination of the tumor lesions including soft tissue and bone is favored. synovial cells and a few multinucleated giant cells can be observed in pathological study[14]. Enchondroma was the most common benign tumour of the tubular bones in hands. The treatment was usually surgery[15].” See in page 7 ,line 105–114.

Replies to Olga Gutkowska (Reviewer 1): The Abstract:

1. Please, give the extract location of the tumors: "Surgical incision revealed the presence of two glomus tumors within different fascicles" of the ulnar digital nerve of the middle finger.

Answer: Thanks ,we add what you pointed out. See in page 2, line 23.

Background:

2. "Glomus tumors originating from digital nerves are extremely rare". In my opinion, it is not justified to say that glomus tumors "originate from" the nerve as they do not derive from nervous tissue . Please, change to "originate within" or "arise in".
Answer: Thanks, we change to “originate within”, see in page 2, line 32.

3. "Previous studies have reported four cases of solitary intraneural glomus tumors [1-6]" - Were there four cases or six cases, as the literature reference indicates? Please, correct.

Answer: Thanks, we correct it to “six”, see in page 2, line 33.

4. "This study describes two intraneural glomus tumors within one finger". Were both tumors located in different fascicles of the same digital nerve? This should be stated clearly, rather than referring to "one finger".

Answer: Thanks, we change to “This study describes two intraneural glomus tumors located in different fascicles of the same digital nerve.” see in page 3, line 36~37.

Case presentation:

5. "Results of the cold sensitivity test were negative, demonstrating an increase in localized pain on exposure of the affected finger to cold water, based mainly on the patient's medical history" - This sentence provides conflicting information. You state that the results were negative and describe a positive result. Please, correct.

Answer: we change the sentence to “The results of the cold sensitivity test were negative, which demonstrating an increase in localized pain on exposure of the affected finger to cold water.” See in page 3, line 46~48.

6. "Contrast enhancement" should be written instead of "enhancement" throughout the manuscript.

Answer: We replaced them.

7. Please, give all tumor dimensions in mm, rather than using either mm or cm.

Answer: we change them to mm.
8. "It was diagnosed as middle finger ulnar abnormal signal, neurogenic tumor? Hemangioma to be discharged." The meaning of this part of the test is unclear. Please, rewrite.

Answer: We change it to” It was diagnosed as middle finger ulnar abnormal signal, neurogenic tumor or hemangioma.” See in page 4, line 57~58.

9. "(...)while the other tumor was removed leaving the radial nerve fascicle intact." This description is confusing, because you wrote previously that both tumors were located on the ulnar side of the finger. Please, rewrite to avoid ambiguity.

Answer: we change the sentence to “Two solitary tumors were observed within different fascicles of the same digital nerve. (Figure 2). One tumor was excised along with a segment of the surrounding one nerve fascicle with tumor, while the other tumor was removed leaving another nerve fascicle intact.” See in page 4, line63~65.

10. "A tumor (0.4 cm × 0.25 cm in size) was observed in the area of the fiber." The description of the location of both lesions is unclear. Please, correct and provide adequate description.

Answer: we change the sentence to” A tumor (4 mm × 2.5 mm in size) was wrapped by nervous fibers.” See in page 5, line70.

Discussion

11. In my opinion, some general information about glomus tumor should be added at the beginning of "Discussion": what type of cells it is built from, where it is usually found and how it is diagnosed.

Answer: We add the “Glomus tumor is a rare benign tumor that most frequently occurs in the glomus body in the subungual regions of digits[8]. The typically cell components were glomus cells, vasculature, and smooth muscle cells[9]. Within the glomus tumor family, the glomus tumor itself consists predominantly of glomus cells. The glomangioma shows high density of vascularity[10] and the glomangiomyoma shows elongated smooth muscle cells in pathological manifestation[11]. The clinical diagnosis of glomus tumor is made based on examination. Typical symptoms of a glomus tumor are localized pain and cold sensitivity [12].” see in page 6, line 90~98.

Figure legends:
12. Figure 3: A - intraoperative image of the two lesions; B - image after complete resection of the lesions

Answer: Thanks, we change them.

13. Figure 4: Please, give information about the type of staining and magnification for each of the pictures in Figure 4

Answer: we add the section “FIGURE 4 Pathologic findings indicated multiple intraneural glomus tumors with proliferated nervous fibers. (A) Tumor 40X10 HE stain. (B) Nervous fibers 40X10 HE stain. (C) Tumor 20X10 HE neurofilament stain (D) Tumor was wrapped by nervous fibers. 5X10 HE neurofilament stain. Immunohistochemistry results were as follows: (E) CD34 (+)40X10, (F) SMA (+)40X10, (G) Nestin (+)40X10, (H) Syn (+)40X10, (I) Ki-67 (-)40X10 and (J) S100 (-)20X10.”

Replies to Anja Harder (Reviewer 2):

This is a very interesting and well written case report of a rare manifestation of a glomus tumor. The data are well documented. I have some remarks for minor revision concerning a more precise description of the tumor itself:

1. Are there signs of malignancy in histology (atypical features, mitoses (count), pleomorphism)?

Answer: We add the sentence of “The atypical features, mitoses and pleomorphism were normal.” see in page 5, line 73~74.

2. Can a glomangioma and a glomangiomyoma be ruled out? Are there oncocytic features?

Answer: We add the section of “Within the glomus tumor family, the glomus tumor itself consists predominantly of glomus cells. The glomangioma shows high density of vascularity and the glomangiomyoma shows elongated smooth muscle cells in pathological manifestation.” See in page 6, line 94~97.

3. Is a family history ruled out?

Answer: The patient had no family history of cancer and hereditary disease. See in page 3, line 45~46.
4. It would really great if you could provide an analysis of a MIR143-NOTCH gene fusion, but if this is too complicated, then please provide better histological photographs including neurofilament stain. I would recommend to skip the synaptophysin staining (I think is just very weak) and better show a second HE stain of the tumor cell arrangement as well as a neurofilament stain to demonstrate nerve attachment.

I have no major concerns.

Answer: we add the NF stain of the tumor cell and nerve attachment. see in Figure 4. Sorry, we cannot provide the analysis of a MIR143-NOTCH gene fusion.