

July 20, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 27093-case report.doc).

**Title:** Glomus tumors of the fingers: expression of vascular endothelial growth factor

**Author:** Sittisak Honsawek, Pravitt Kitidumrongsook, Pobe Luangjarmekorn, Kawee Pataradool, Voranuch Thanakit, Adisorn Patradul

**Name of Journal:** *World Journal of Orthopedics*

**ESPS Manuscript NO:** 27093

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Dear authors, you have written a very nice manuscript. Well organized, concise and interesting. Good work! I can suggest that you may discuss more deeply the importance of VEGF expression, search if there could be any difference in the expression of that growth factor in benign and malignancy forms or in the other forms of glomus tumors such as glomangiomas. You also need to include more references to explain and support the importance of VEGF expression in vascular tumors

Response: We have improved our manuscript as the reviewer's suggestion, in page 8 and 9.

"Glomangioma and glomangiomyoma are classic variants of the common feature of glomus tumors. The typical histological appearances of the glomus tumors comprise angiocentric uniform sheets of cells with oval nuclei, forming a perivascular collar around vessels. The three different tumor variants are differentiated by their histological characteristics. The common or solid form includes lobules, strands, and broad sheets of rounded, uniform glomus cells with indistinct capillaries in the walls of surrounding large blood vessels. Whereas glomangiomas exhibit prominent vascular structures with dilated veins surrounded by clusters of glomus cells, and glomangiomyomas consisted of prominent vascular and elongated, spindle smooth muscle cells [7]. In malignant forms, glomangiosarcoma, pleomorphic tumor cells with marked nuclear atypia and frequent mitotic figures are found in variable numbers [8]. Angiogenesis has been implicated in the progression from benign to malignant tumors. The contribution of angiogenesis and VEGF expression in glomus tumors as yet has not been completely elucidated. It is not yet clear whether there is any difference in VEGF expression between benign and malignant forms of glomus tumors."

"Angiogenesis may result in the reconstruction of nutrition for the expanding tumor and could enable further proliferation. However, prospective longitudinal studies with larger sample size are warranted to define the precise role of VEGF in glomus tumors."

"In conclusion, increased VEGF expression was observed in glomus tumors. VEGF could contribute to the process of promoting tumor angiogenesis and might be important in the pathogenesis

of glomus tumors. ”

(2) The authors reported the expression of VEGF, a major actor of angiogenesis, in five finger glomous tumors. The paper is comprehensibly written and the text is quite concise. Though, some adjustments will improve this article.

General comments: - the authors should better describe the clinical presentation of glomous tumors, detailing the site of occurrence of these unusual tumors. More specifically they should mention that glomous tumors occur usually in the dermis and that visceral sites may also be involved (add references ex: Ghigna MR et al. "A quite exceptional cause of recurrent hemoptysis" *Chest*. 2013 Nov;144(5):1724-8; Kihara A et al "Glomus tumor of the liver presenting as a cystic lesion" *Pathol Int*. 2014 Jun;64(6):295-7).

- the differential diagnosis should also be detailed; histologically glomous tumors incorporate: "classic" form, "glomangioma" and "glomangiomyoma"; in addition malignant forms are described. The author should mention the histological features of glomous tumors and mention if in reviewing literature there is any difference in the expression of VEGF according to histological subtype and malignancy.

Response: We have improved our manuscript as the reviewer's comments, in page 7-10, and Table 1.

"Although frequently found in the dermis, glomus tumors may occur in deep soft tissue or visceral sites throughout the body including lung, gastrointestinal, and liver [4, 5]."

"Glomangioma and glomangiomyoma are classic variants of the common feature of glomus tumors. The typical histological appearances of the glomus tumors comprise angiocentric uniform sheets of cells with oval nuclei, forming a perivascular collar around vessels. The three different tumor variants are differentiated by their histological characteristics. The common or solid form includes lobules, strands, and broad sheets of rounded, uniform glomus cells with indistinct capillaries in the walls of surrounding large blood vessels. Whereas glomangiomas exhibit prominent vascular structures with dilated veins surrounded by clusters of glomus cells, and glomangiomyomas consisted of prominent vascular and elongated, spindle smooth muscle cells [7]. In malignant forms, glomangiosarcoma, pleomorphic tumor cells with marked nuclear atypia and frequent mitotic figures are found in variable numbers [8]. Angiogenesis has been implicated in the progression from benign to malignant tumors. The contribution of angiogenesis and VEGF expression in glomus tumors as yet has not been completely elucidated. It is not yet clear whether there is any difference in VEGF expression between benign and malignant forms of glomus tumors."

"4. Ghigna MR, Fadel É, Bellini R, Rohnean A, Palazzo L, Dorfmueller P, Darteville P, Thomas de Montpréville V. A quite exceptional cause of recurrent hemoptysis. *Chest* 2013;144:1724-1728

5. Kihara A, Fukushima J, Horiuchi H. Glomus tumor of the liver presenting as a cystic lesion. *Pathol Int* 2014;64:295-297

7. Mravic M, LaChaud G, Nguyen A, Scott MA, Dry SM, James AW. Clinical and histopathological diagnosis of glomus tumor: an institutional experience of 138 cases. *Int J Surg Pathol* 2015;23:181-8.

8. Park JH, Oh SH, Yang MH, Kim NI. Glomangiosarcoma of the hand: a case report and review of the literature. *J Dermatol* 2003;30:827-33."

(3) This is a report of vascular endothelial growth factor in glomus tumors of the fingers. The topic of this manuscript is interesting and it deserves serious consideration for publication. The high VEGF expression in the glomus tumors of the fingers has not been reported in other literatures. But the disadvantage is that the number of clinical cases is too small. In summary, I would suggest publishing the manuscript

Response: We have improved our manuscript as the reviewer's suggestion, in page 9.

"Angiogenesis may result in the reconstruction of nutrition for the expanding tumor and could enable further proliferation. However, prospective longitudinal studies with larger sample size are

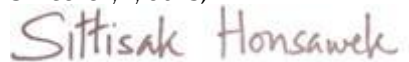
warranted to define the precise role of VEGF in glomus tumors.”

“In conclusion, increased VEGF expression was observed in glomus tumors. VEGF could contribute to the process of promoting tumor angiogenesis and might be important in the pathogenesis of glomus tumors.”

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Orthopedics*.

Sincerely yours,

A handwritten signature in dark ink that reads "Sittisak Honsawek". The signature is written in a cursive, slightly slanted style.

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