

Dear editor,

We submit hereby a revised manuscript entitled “**The Subclavian Brachial Plexus Metastasis from Breast Cancer: A Case Report and Review of Literature**” (No. 77936). We have carefully studied the reviewer’s comments, concerns and suggestions, and have made appropriate revisions which are marked with yellow background in the revised manuscript.

In this revised manuscript, all concerns of the editor have been adequately addressed. In this “77936-Answering Reviewers” letter, the point-by-point responses to the editor’s comments and suggestions are provided. We greatly appreciate the constructive suggestions and comments from the editor and the reviewer, which is highly helpful for improving the quality of the manuscript. We sincerely hope that the revised manuscript would be suitable for publication in ***World Journal of Clinical Cases***. The following part is the point-by-point responses to the reviewer.

With best regards.

Zeng Zeng

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Response to Reviewer 1:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: In introduction: try to give an outline of your rare case instead of the details of the case which is already mentioned in abstract and clinical presentation section. In case presentation: -You should provide more details of the primary lesion (breast cancer type, grade, stage, hormonal receptors,...etc) -Provide the histopathology picture and the used immunohistochemistry to reach the final diagnosis and histopathology figure is important to be added. In discussion: - “Ultrasound with high frequency probe ($>10\text{MHz}$) is vital in detecting subcutaneous lesions. It can reveal the lesion's size, shape, depth of tissue and the blood supply and give out a tendency diagnosis “ Cite the related reference; I recommend this one 9 Klimonda Z, Karwat P, Dobruch-Sobczak K, Piotrkowska-Wr blewska H, Litniewski J. Breast-lesions characterization using Quantitative Ultrasound features of peritumoral tissue. Sci Rep. 2019 May 28;9(1):7963. doi: 10.1038/s41598-019-44376-z.) - “Metastatic lymph nodes are no exception, they have clear boundaries and regular shape. However, brachial plexus metastases do not have clear boundaries and regular shape. Second, lymph nodes have their fixed location, mostly within superficial soft tissues. While the brachial plexus nerve is located in the intermuscular space, associated brachial arteries and veins are always around them. Third, lymph nodes are often distributed in clusters and most lymph node metastasis is forward sentinel metastasis. Breast cancer mostly has axillary metastasis firstly” Try to provide sources; I recommend those (Kim J, Jeon JY, Choi YJ, Choi JK, Kim SB, Jung KH, Ahn JH, Kim JE, Seo S. Characteristics of metastatic brachial plexopathy in patients with breast cancer. Support Care Cancer. 2020 Apr;28(4):1913-1918. doi: 10.1007/s00520-019-04997-6. & Hasan A, Youssef A. Infiltrating duct carcinoma of the breast; histological difference between the primary

and the axillary nodal metastasis. *Revista de Senología y Patología Mamaria*. 2021 Jan 1;34(1):17-22. DOI: 10.1016/j.senol.2020.09.003 - Discuss the diagnostic challenge of metastatic carcinoma (histopathology and immunohistochemistry).

Response: We appreciate you and your reviewers for your valuable time in reviewing our work and providing important feedback. Your corrections and comments help us to improve the current version of our study. We considered each comment carefully and tried our best to address them. Below we provide a point-by-point response.

In introduction: try to give an outline of your rare case instead of the details of the case which is already mentioned in abstract and clinical presentation section.

Response: Thank you so much for your suggestions. We carefully revised the introduction part as “Breast cancer is the most threatening cancer in women worldwide. Bones, lungs, liver and lymph nodes are common predilection sites of breast cancer metastasis. Brachial plexus metastasis from breast cancer is extremely rare. So diagnosing this metastasis shows great challenging. We report a case of a 64-year-old woman who had subclavian brachial plexus metastasis 6 years after radical mastectomy. Ultrasound was the first exam to find the metastasis lesion both at brachial plexus and muscles. MRI and FDG-PET/CT gave further identification of brachial plexus metastasis. Pathology and immunohistochemistry results indicated lesions between pectoralis major and deltoid muscle as metastasis from breast cancer. The diagnosis has clinical importance for the next step of treatment whether by radiotherapy, chemotherapy or hormonal therapy”.

In case presentation: You should provide more details of the primary lesion (breast cancer type, grade, stage, hormonal receptors,...etc). Provide the histopathology picture and the used immunohistochemistry to reach the final diagnosis and histopathology figure is important to be added.

Response: Thank you so much for your suggestions. We added some details in

revised manuscript as follows “The patient primary lesion was invasive breast cancer(T₂N₁M₀), immunohistochemistry showed ER(+), PR(+), HER-2(+++)”. This patient had surgery of primary breast lesion in other hospital, so we did not have the histopathology picture of her primary breast lesion. However, we offered the metastatic lesion which had lesion punctuation under ultrasound guidance and the lesion was sent for pathology. Pathology pictures were included in figure 4. It showed ER(+,strong,90%), PR(+,moderate,10%), HER-2(3+), all these results were consistent with the primary right breast cancer characteristics, thus supporting lesion metastasis from breast cancer.

In discussion: “Ultrasound with high frequency probe (>10MHz) is vital in detecting subcutaneous lesions. It can reveal the lesion’s size, shape, depth of tissue and the blood supply and give out a tendency diagnosis “ Cite the related reference; I recommend this one 9 Klimonda Z, Karwat P, Dobruch-Sobczak K, Piotrkowska-Wr blewska H, Litniewski J. Breast-lesions characterization using Quantitative Ultrasound features of peritumoral tissue. Sci Rep. 2019 May 28;9(1):7963. doi: 10.1038/s41598-019-44376-z.)

Response: Thank you so much for your suggestions. We had already added this reference in our manuscript. The following new references were included:

Klimonda Z, Karwat P, Dobruch-Sobczak K, et al. Breast-lesions characterization using Quantitative Ultrasound features of peritumoral tissue. Sci Rep. 2019 May 28;9(1):7963. doi: 10.1038/s41598-019-44376-z. PMID: 31138822; PMCID: PMC6538710.

“Metastatic lymph nodes are no exception, they have clear boundaries and regular shape. However, brachial plexus metastases do not have clear boundaries and regular shape. Second, lymph nodes have their fixed location, mostly within superficial soft tissues. While the brachial plexus nerve is located in the intermuscular space, associated brachial arteries and veins are always around them. Third, lymph nodes are often distributed in clusters and most lymph node metastasis is forward sentinel

metastasis. Breast cancer mostly has axillary metastasis firstly” Try to provide sources; I recommend those (Kim J, Jeon JY, Choi YJ, Choi JK, Kim SB, Jung KH, Ahn JH, Kim JE, Seo S. Characteristics of metastatic brachial plexopathy in patients with breast cancer. Support Care Cancer. 2020 Apr;28(4):1913-1918. doi: 10.1007/s00520-019-04997-6. & Hasan A, Youssef A. Infiltrating duct carcinoma of the breast; histological difference between the primary and the axillary nodal metastasis. Revista de Senología y Patología Mamaria. 2021 Jan 1;34(1):17-22. DOI: 10.1016/j.senol.2020.09.003

Response: Thank you so much for your suggestions. We had already added this reference in our manuscript. The following new references were included: Kim J, Jeon JY, Choi YJ, et al. Characteristics of metastatic brachial plexopathy in patients with breast cancer. Support Care Cancer. 2020 Apr;28(4):1913-1918. doi:10.1007/s00520-019-04997-6. Epub 2019 Jul 30. PMID: 31363905.

Discuss the diagnostic challenge of metastatic carcinoma (histopathology and immunohistochemistry).

Response: Thank you so much for your suggestions. In the discussion part, we added as follows “In the absence of breast lesions, diagnosis of metastatic cancer will be challenging and even delayed. When we diagnose a disease, we need to think logically, including understanding the patient’s past and current disease history, because these are important basis for diagnosis. Physical examination and extensive investigations are needed when diagnosing metastatic carcinoma. Multidisciplinary team also shows great value in diagnosing”.

The following new references were included:

Alfian Sulai DD, Krishnasamy T, Nik Mahmood NRK. Diagnostic challenge in silent metastatic invasive breast carcinoma: dysphagia as the only symptom. BMJ Case Rep. 2021 Jul 21;14(7):e239997. doi: 10.1136/bcr-2020-239997. PMID: 34290001; PMCID: PMC8296809.

Response to Reviewer 2:

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The case report highlights a rare type of brachial plexus metastasis from a previously treated breast cancer. The case description is brief and neat. The figures are adequate and clear. The authors must add a few more citations related to variations of brachial plexus trunks which could mislead the radiologic assessment of the metastasis. for example: Nayak S.;Somayaji, Nagabhooshana; Vollala, Venkata Ramana; Raghunathan, Deepthinath; Rodrigues, Vincent; Samuel, Vijay Paul; Alathady Malloor, Prasad, A rare variation in the formation of the upper trunk of the brachial plexus - A case report. Neuroanatomy Volume 4, Pages 37 - 38. Shetty, S.D., Satheesha Nayak, B., Madahv, V., Braganza, C.S., Somayaji, S.N. A study on the variations in the formation of the trunks of brachial plexus | [Estudio sobre las variaciones en la formación de los troncos del plexo braquial] International Journal of Morphology 29(2), pp. 555-558

Response: Thank you so much for your valuable suggestions. After reading your suggestions carefully, we have added citations related to variations of brachial plexus trunks which could mislead the radiologic assessment of the metastasis. In discussion part, we have added “Brachial plexus is the plexus of nerves which can supply the upper limb. It is made by the union of ventral rami of C5, C6, C7, C8 and T1 spinal nerves. Brachial plexus has roots, trunks, cords, divisions and branches. The roots and trunks variation of brachial plexus are rare, however, the origin and distribution of the branches of brachial plexus are very common. More attention should be paid to these variations which can mislead to the assessment of the metastasis”. Changes of these in our manuscript are in highlights accordingly (see details in our revised manuscript).

The following new references were included:

Satheesha NAYAK, Nagabhooshana SOMAYAJI, Venkata Ramana VOLLALA, et al. A rare variation in the formation of the upper trunk of the brachial plexus-A case report. *Neuroanatomy*. 2005;4:37-38.

Shetty, S. D., Nayak, B. S., Madahv, V., et al. A study on the variations in the formation of the trunks of brachial plexus. *Int. J. Morphol.* 2011;29(2):555-558.