

Peer Review File

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Reviewer A

Comment 1: Very good case presentation and systemic review. This description must contribute to diagnosis and care for male occult breast cancer patients.

Reply 1: Thank you very much for your comment.

Changes in text: none

Reviewer B

Comment 1: Interesting case and systemic review.

Reply 1: Thank you for all your comments.

Changes in text: none

Comment 2: Need to stress/emphzise what new perspective this case brings given there are already 11 cases published on the same topic. Is your article of better quality in description, imaging, pathology, discussion of management? Does it add new points to the literature? Does is provide any new perspective? Please emphasize why this is worth to be a valuable read.

Reply 2: We believe our case showed the exhaustive search of the primary tumor and the confirmation with biopsy, preventing morbidity with early surgery, as we believe a misdiagnosis would have led our patient to overtreatment. Thus, the major surgery was performed after the confirmation of the OBC. Also, the neoadjuvant and adjuvant therapy to prevent recurrence. The more innovative proposal in this case, is the genetic study of the patient to recognize the risk of recurrence, the development of other related primary tumors and the familiar risk, performing a better follow-up.

Changes in text: (Page 12, lines 203-211) Limitations of our study include the small number of cases we found, and that we should not meta-analyze a case report systematic review. However, in this study we highlight and recommend an exhaustive performance of different images for the first suspicion of the primary tumor to make an early diagnosis. Also, the confirmation with biopsy to decide the complete multidisciplinary management, considering the histological aggressiveness of HER2 and the consequent morbidity and mortality of the patient. The genetic counseling is innovative in our case and it should be mandatory even in low-genetic-risk patients to study completely the risk of recurrence or development of another primary tumor, and the familiar risk of

breast or other related cancers in both men and women, improving the follow-up.

Comment 3: In lines 56-57 "lymph node conglomerate measuring 78x34 mm with echogenic images concerning calcification" Can you clarify? Do you meant there were ecogenic foci in the lymph nodes suggesting calcifications? Was a mammogram attempted at all at time of diagnostic work up? Can you provide images of the breast in fused PET/CT, to include the axilla? Also, if allowed MRI images of the breast would be extremely helpful, either MIP or axial post contrast subtraction imaging.

Reply 3: All suggestions were included in our article to clarify the results in the ultrasound, show the PET/CT scan and make sure it is clear why we did not perform a mammogram. Unfortunately, the MRI images are not available to be published because those were taken at another hospital.

Changes in text: (Page 3, lines 55-58) A mammary and axillary ultrasound was performed reporting fatty mammary parenchyma without evidence of lesions, but an axillary lymph node conglomerate that measured 78x34 mm and presented hyperechogenic images inside suggesting calcification.

(Pages 3-4, lines 61-63) Mammogram was not performed due to small mammary tissue that difficult the development and the quality of the image, and other studies showed no abnormalities.

(Page 4, lines 73-74)

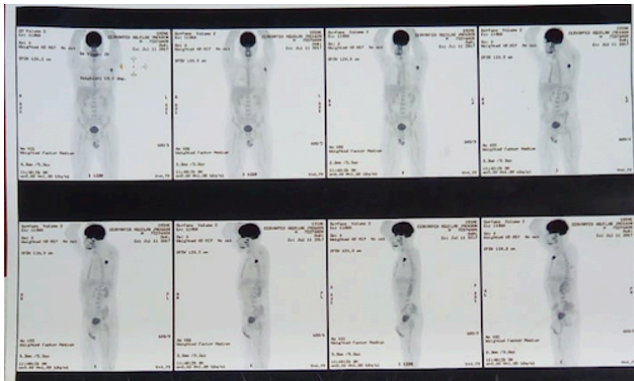


Figure 1. PET-CT scan with hypermetabolic activity in the left axillary region

Comment 4: Line 110 "Any patient underwent a genetic consult"-- Do you meant to say "All patients underwent a genetic study"

Reply 4: Completely right, we wanted to express no patient but ours, underwent genetic consultation.

Changes in text: (Page 8, line 123) No patients underwent a genetic counseling

Reviewer C

Comment 1: line 63: please indicate why an incisional biopsy was performed for tissue diagnosis. the standard of care is an ultrasound-guided core needle biopsy to avoid multiple surgeries.

Reply 1: Thank you very much. You are completely right, we did not specify how the incisional biopsy was taken, so we corrected it in the text.

Changes in text: (Page 4, lines 66-68) An incisional ultrasound-guided core needle biopsy of lymphadenopathies...

Comment 2: line 76: diagnosis should be ypT0N2M0 ("y" needs to be placed in front when its s/p neoadjuvant chemotherapy)

Reply 2: Corrected as suggested

Changes in text: (Page 6, lines 86-87) Breast cancer was classified as ypT0pN2M0 stage IIIB.

Comment 3: line 78: should be discussed both in the case report AND in the discussion was a modified radical mastectomy was performed. for occult breast cancers presenting with axillary adenopathy, the standard is ALND + appropriate systemic therapy + (whole breast radiation or mastectomy). mastectomy is not superior to whole breast radiation in these cases. it has been widely proven in the female breast cancer literature, and so far, there is not enough data in men specifically with occult primary to determine superiority/inferiority of WBRT vs mastectomy.

Reply 3: As the literature is not conclusive in men, we struggled in the decision of management of this case. Reason why, we took the case to the breast surgery / oncology / radiotherapy board, and decided chemotherapy followed by ALND, radiotherapy, mastectomy and trastuzumab. Axillary radiotherapy was performed after pathologic examination of the ALND specimen showed one positive lymph node after chemotherapy. This finding was considered a partial response of the tumor. Also, due to HER2 aggressiveness positive factor and the lack of breast targeted radiotherapy, the board considered mastectomy for local control even though we have an OBC patient. We can explain this, as an OBC might become a visible breast cancer with local and distant progression. Adjuvant Trastuzumab therapy was performed as it would have been done in a woman with HER2 positive tumor.

Changes in text: (Pages 5-6, lines 81-92) Neoadjuvant Adriamycin and Cyclophosphamide chemotherapy was administered in four cycles with sequential Paclitaxel and Trastuzumab, and lymph node axillary dissection three

weeks after completion of chemotherapy. During surgery, a left axillary lymph node conglomerate was observed with adenopathies between 5 and 10 mm. In the specimen, sixteen lymph nodes were resected and one presented involvement of poorly differentiated carcinoma foci with areas of necrosis. Breast cancer was classified as ypT0pN2M0 stage IIIB. The patient case was taken to the breast surgery, oncology and radiotherapy board and a partial response of the tumor was considered. Reason why, radiotherapy was performed in the axillary region. As a primary tissue should have been controlled too, the patient was taken to a left modified radical mastectomy. The histopathological study of the mastectomy specimen was negative for the residual tumor. The patient received adjuvant management with Trastuzumab for nine months until completing eighteen doses.

Comment 4: lines 191-192: Disease-free survival cannot be attributed to mastectomy (as WBRT would have given the same disease-free survival), and this patients risk of distant metastases is greater than his risk of local recurrence.

Reply 4: We also agree with you, and we might have taken attributions to our experience and not according to the evidence. We decided to delete our affirmation and confirm that we need association studies to verify it.

Changes in text: (Page 12, lines 95-96) More studies are needed to attribute surgical mastectomy or breast radiotherapy of OBC to disease-free and overall survival.