A challenging diagnosis of occult breast cancer in men: a case report

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Abstract: We present a case of a 38-year-old male patient with a left axillary metastatic mass without evidence of the primary lesion. Needle aspiration biopsy was performed showing a human epidermal growth factor receptor 2 (HER2) positive occult breast cancer (OBC). The patient underwent neoadjuvant chemotherapy and radical modified mastectomy followed by radiotherapy and systemic therapy. Genetic studies were negative, and the follow-up showed no relapse. OBC is defined as a mammary gland neoplasm that presents as a metastatic disease without clinical or radiological manifestation of the primary tumor. The incidence of OBC in men is unknown and is limited to case reports. A systematic review was performed including eleven case reports with twelve patients ranging from 29 to 83 years old. Estrogen and progesterone receptors were positive in seven patients of which two patients were also HER-2 positive; one patient presented only progesterone receptors, two presented only HER-2 positive and two were triple-negative. Operative management, hormonal therapy, chemotherapy, and radiotherapy were performed together or apart depending on the attending and the patient's preferences. No one reported mortality due to malignant disease. OBC is a rare pathology in men and requires a high diagnostic suspicion in patients with an axillary or thoracic metastatic disease without an evident primary neoplasm. The genetic study is necessary to determine mutations and evaluate the risk of relapse and the high risk of primarily associated neoplasm in the patient and family.

Keywords: Occult breast cancer (OBC); men; axillary adenopathy; metastatic disease; case report

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Introduction

Occult breast cancer (OBC) is a mammary gland neoplasm that presents as a metastatic disease without clinical or radiological manifestation of the primary tumor (1). The most frequent finding is axillary or thoracic adenopathy presented as a painful mass, the reason why patients consult (1). The incidence of OBC in men is unknown and is limited to case reports. OBC is a challenge for the physician due to the need to rule out all the most prevalent cancers in men before the diagnosis. This study aims to present a case of a 38-year-old male patient with human epidermal growth factor receptor 2 (HER2) positive OBC and the corresponding systematic review of cases that described related clinical and histopathological features,

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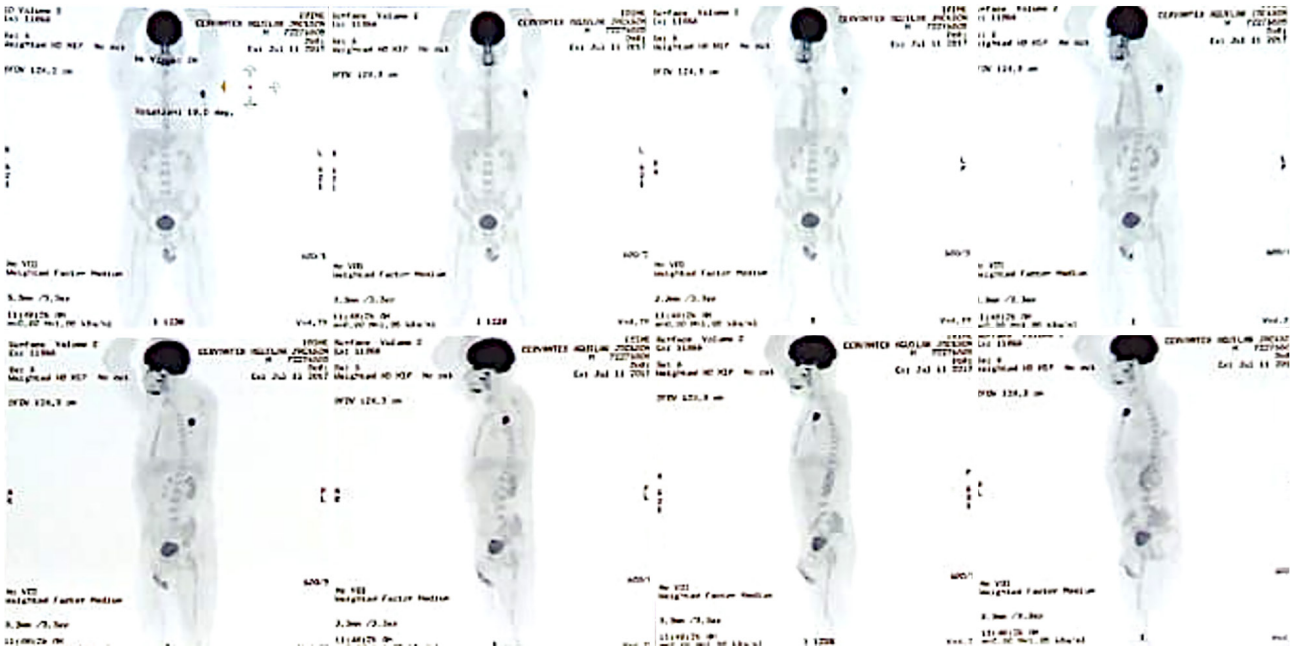

Figure 1 PET-CT scan with hypermetabolic activity in the left axillary region. PET-CT, positron emission tomography-computerized tomography.

management, clinical course, and follow-up. We present the following case in accordance with the CARE reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-21-44/rc).

Case presentation

A 38-year-old male patient with no relevant medical or family history consulted due to the appearance of a painless left axillary mass without other symptoms since a month ago. On physical examination, findings of a mobile, soft, and non-attached to deep planes 5 cm × 7 cm lymph node conglomerate in the left axillary region without changes in the skin. A mammary and axillary ultrasound was performed reporting fatty mammary parenchyma without evidence of lesions, but an axillary lymph node conglomerate that measured 78 mm × 34 mm and presented hyperechogenic images inside suggesting calcification. Chest CT-scan was negative for adenomegalies or mediastinal masses, however, reported the left lymph node conglomerate that measured 57 mm × 48 mm× 98 mm. The breast magnetic resonance imaging (MRI) was negative to focal lesions or alterations on muscle tissues. 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.

Positron emission tomography-computerized tomography (PET-CT) scan was performed with evidence of a high-grade hypermetabolic conglomerate in the left axillary region with an SUV of 10.8 without pathological findings in the breast or mediastinum (*Figure 1*). An incisional ultrasound-guided core needle biopsy of lymphadenopathies was performed and confirmed involvement of a non-special moderately differentiated ductal carcinoma of the mammary gland, with a positive immunohistochemical profile for CK-7, GATA-3, GCDFP-15, and mammaglobin. Estrogen (ER) and progesterone receptors (PR), and CK-20 were negative while HER-2 (3+) was positive, and a Ki-67 cell proliferation index was 30% (*Figure 2*). It was considered metastatic infiltration due to moderately differentiated ductal carcinoma of the mammary gland.

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

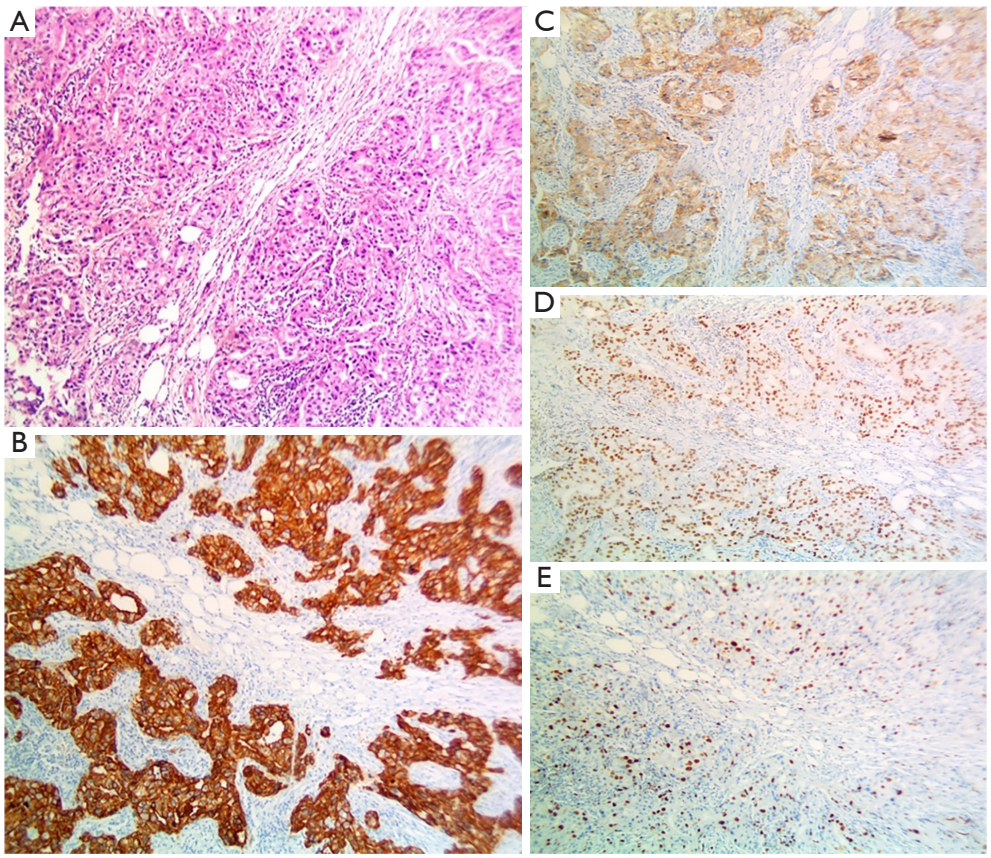

Figure 2 Incisional biopsy histology and immunohistochemical profile at 10× photomicrograph. (A) HE staining with moderately differentiated non-special type ductal adenocarcinoma. (B) CK-7 with strong cytoplasmic and membrane reactivity (IHC staining); (C) HER-2 with complete membrane reactivity in 90% of tumor cells (IHC staining); (D) GATA-3 favoring carcinoma of the breast as the primary tumor (IHC staining); (E) Ki-67 with nuclear reactivity of 30% in tumor cells (IHC staining). HE, haemotoxylin and eosin; IHC, immunohistochemistry; HER-2, human epithelial factor receptor 2.

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.

Genetic studies with the 30-gene GENCELL PHARMA™ panel were performed, with all gene mutations negative, including *BRCA1* and *BRCA2*. On a 3-year follow-up, the patient had no clinical or radiological signs of recurrence.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Systematic review

The present analysis was conducted according to the 2009 preferred reporting items for systematic review. Search strategies included two separate reviewers and the following terms: ("male AND occult breast cancer") OR ("male AND occult breast cancer AND case report ") OR ("male

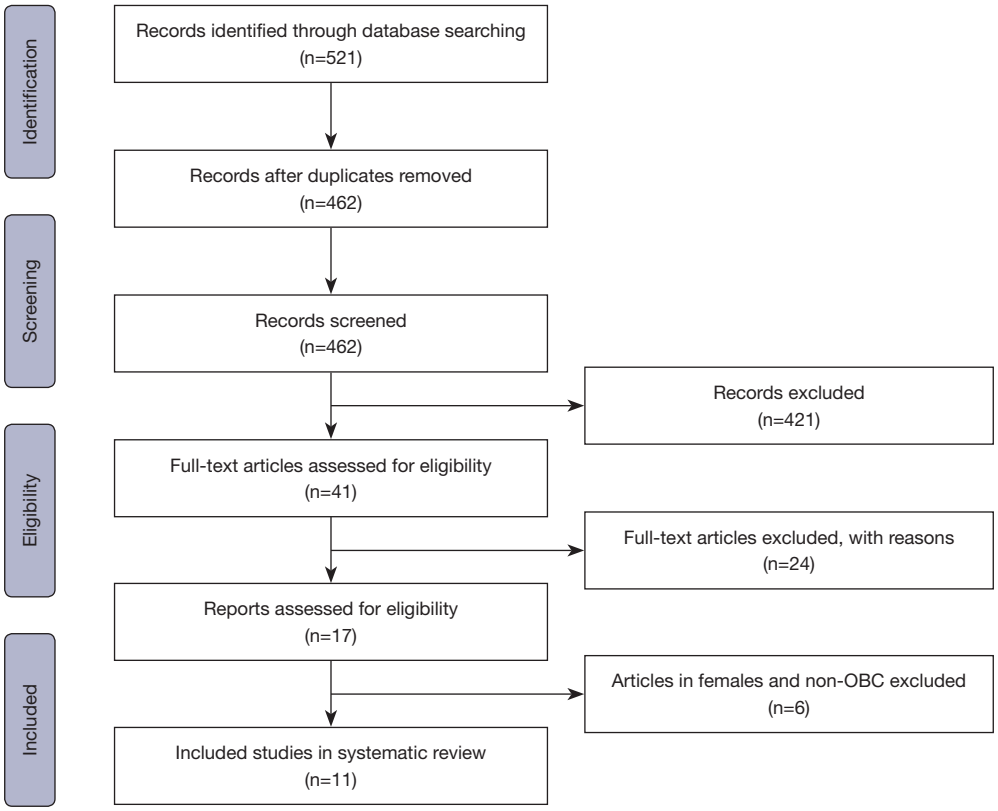

Figure 3 PRISMA diagram for literature search. OBC, occult breast cancer.

AND occult breast cancer AND case report AND HER2") in OVID, MEDNAR, Embase, Scopus, Web of Science, PubMed, and CENTRAL databases. The search was not limited to location or date of publication. A hand search of the reference list of the articles selected was performed. All cases in English and Spanish that reported male patients with OBC were included. Gray literature was excluded.

A total of 521 articles were found, duplicates were removed for an evaluation of 462 studies. All studies different for case reports were excluded and 41 articles remained. Out of these, 17 studies were assessed eligibility by two reviewers, and articles that did not correspond to OBC in men were excluded. Finally, 11 studies were identified and included in the systematic review (*Figure 3*).

The information extracted included: first author's last name, country, publication year, number of patients, baseline characteristics of the patients, tumor characteristics and staging, histopathological and immunohistochemical evaluation, imaging, management, and follow-up.

The overall quality of the cases was good to moderate. Most cases reported an adequate description of the patient's past medical history, laboratory image investigation, and treatments, however, a few cases did not report convincing evidence of follow-up.

Ages ranged between 29 and 83 years old. ER and PR were positive in seven patients of which two patients were also HER-2 positive; one patient presented only progesterone receptors, two presented only HER-2 positive and two were triple-negative. Most of the patients had no family history or risk factors to develop breast cancer, however, 9 out of 12 patients, were diagnosed in stage III and IV. No patients underwent a genetic counseling.

Operative management, hormonal therapy, chemotherapy, and radiotherapy were performed together or apart depending on the attending and the patient preferences: 2 patients were only treated with surgery, 2 patients were not operated on and managed only with chemotherapy, 2 patients underwent surgery and radiotherapy, 2 more patients were managed with surgery and radio and chemotherapy, one patient underwent surgery and received hormone and chemotherapy, and 3 patients underwent all four therapies together. All data is reported in *Table 1*.

Table 1 Systematic review of case reports of male patients with occult breast cancer

First author	Country	Year	Number of patients	Age (year)	Risk-factors	Clinical manifestation	Imaging	Biopsy	Hormonal therapy	Chemotherapy	Radiotherapy	Surgery	Primary tumor in pathology specimen	Type of tumor	TNM	ER	PR	HER2	Genetics test	Follow-up
Namba (2)	Japan	2002	1	78	N/A	Left axillary and supraclavicular node	TAC and RNM no evidence of primary lesion	Yes	No	Yes	No	No	N/A	Poorly differentiated adenocarcinoma	cT0N3M0, stage IIIB	Negative	Positive	N/A	No	N/A
Gu (3)	China	2008	1	72	Any	Right axillary node	Ultrasound: axillary nodes	No	No	No	No	Modified radical mastectomy and axillary dissection	No	Ductal carcinoma	pTxN2M1, stage IV	Negative	Negative	Positive	No	29 months: relapse free, alive
Gonzalez-Perez (4)	Spain	2012	1	73	Mother with breast cancer	Left retroareolar mass	MRI: osteolytic lesion in the left condyle	Yes	No	Yes	Yes	Left mastectomy with axillary node dissection	Yes	Ductal carcinoma	pT4bN3 M1, stage IV	Positive	Positive	Negative	No	3 years: relapse free, alive
Hur (5)	Korea	2012	2	59	Any	Right axillary mass	PET-CT scan: increased uptake on the right axillary area	Yes	Yes	Yes	No	Skin sparing right mastectomy with axillary node dissection	No	Metastatic carcinoma	pTxN2M1, stage IV	Positive	Positive	Negative	No	Any signs of recurrence
				45	Any	Left axillary node	Mammography, breast ultrasound and MRI: negative	Yes	Yes	Yes	Yes	Left axillary node dissection	N/A	Metastatic adenocarcinoma	pTxN2M0, stage IIIA	Positive	Positive	Negative	No	Any signs of recurrence
He (6)	Korea	2015	1	40	Any	Left axillary node	Ultrasound: multiple hypoechoic solid masses with irregular margins in the left axillary cavity MRI: negative PET-CT scan: increased lesions in the left axillary and high metabolic activity in the bone marrow (non-malignant lesions)	Yes	Yes	Yes	Yes	Modified radical mastectomy and axillary dissection	No	Moderately differentiated adenocarcinoma	pT0N3M0, stage IIIC	Positive	Positive	Positive	No	30 months: relapse free, alive
Kuninaka (7)	Japan	2017	1	67	Any	Left anterior chest wall eczema-like and mass approximately 3 cm in diameter	CT scan: multiple subcutaneous nodules in the left chest and in the right axilla and neck	Yes	No	Yes	No	No	No	Metastasis adenocarcinoma	cTxNxMx	Positive	Positive	Positive	No	15 months: relapse free, alive
Zhang (8)	China	2017	1	84	Any	Palpable nodule in the right axilla	Ultrasound: irregular hypoechoic solid mass in the right axilla cavity Brain, abdomen and pelvis CT scan: negative Bone scan: negative	Yes	No	Yes	No	Modified radical mastectomy and axillary dissection	No	Poorly differentiated adenocarcinoma likely from the breast	pT0N1M0, stage IIA	Negative	Negative	Negative	No	>2 years: relapse free, alive
Xu (9)	China	2017	1	29	8 pack-year smoking	Growing painless half peanut-sized nodule in the left axilla	Ultrasound: 3 hypoechoic solid masses in the left axillary cavity Chest CT scan: multiple enlarged lymph nodes in the left axillary and infraclavicular regions PET-CT scan: increased uptake in the left axilla and infraclavicular regions	No	No	Yes	Yes	Axillary neoplasm resection and left axillary lymph node dissection	No	Metastatic lymph node with infiltrating ductal carcinoma	pT0N3aM0, stage IIIC	Negative	Negative	Positive	No	Any signs of recurrence

Table 1 (*continued*)

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First author	Country	Year	Number of patients	Age (year)	Risk-factors	Clinical manifestation	Imaging	Biopsy	Hormonal therapy	Chemotherapy	Radiotherapy	Surgery	Primary tumor in pathology specimen	Type of tumor	TNM	ER	PR	HER2	Genetics test	Follow-up
Wang (10)	China	2018	1	49	Smoking and drinking for >30 years	Painless quail egg-sized mass in the left axilla	Breast ultrasound: multiple hypoechoic solid masses in the left axilla PET-CT scan: increased uptake in the left axilla and infraclavicular regions	Yes	Yes	Yes	Yes	Left axillary lymph node dissection	No	Metastatic adenocarcinoma from the breast	pT0N3aM0, stage IIIC	Positive	Positive	Negative	No	N/A
Alsayed (11)	Saudi Arabia	2019	1	82	Any	Redness of the left lateral chest wall associated with painless mass in the left axilla	Ultrasound: solid and cystic lesion in subcutaneous tissue of the left axilla MRI: large complex tumor in the left axilla surrounded by multiple enlarged lymph nodes Thorax, abdomen and pelvis CT scan: negative Bone scan: negative	Yes	No	No	No	Left modified radical mastectomy and axillary dissection	Yes	Invasive ductal carcinoma	pT3N2Mx, stage IIIA	Negative	Negative	Negative	No	N/A
Sood (12)	India	2020	1	83	Chemotherapy and right axillary mass resection with ipsilateral conservative mastectomy 14 years ago: amelanotic melanoma	Right axillary mass	Bilateral mammogram: normal	Yes	No	Yes	No	En bloc excision of the mass with right axillary dissection	Yes	Solid papillary carcinoma in the specimen pathology	pT1bN0M0, stage IA	Positive	Positive	Negative	No	Three negative PET-CT scan till date

TNM, tumor, node, metastasis; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; N/A, not available; TAC, total area coverage; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computerized tomography.

Discussion

Breast cancer in men is a rare disease. OBC is defined as a mammary gland neoplasm without any symptoms or signs that could be identified on the interrogatory or the physical examination, nor diagnostic images (1). The first expression of OBC is usually metastatic adenopathy in the infra or supraclavicular fossa and is more frequently localized in the axilla (5), as in our case. The most common causes of malignant axillary lymph nodes include metastatic breast cancer, lymphoma, lung cancer, melanoma, and squamous cell carcinoma (3). This challenges the physician due to the need to rule out all the most prevalent cancers in men before the diagnosis.

In women, OBC has an incidence ranging from 0.3% to 0.8%, and in men, it is extremely rare, limited to case reports (13). Risk factors include a family history of breast cancer, obesity, cryptorchidism, orchitis, infertility, Klinefelter syndrome, previous chest radiotherapy, and changes in the estrogen index (14). In the articles reviewed, most patients were Asians with no relevant medical or family history, which lead to the study of habits, exposition to estrogen changing chemicals, and genetics associated with breast cancer in males.

It is reported that mutations in the *BRCA1* or *BRCA2* genes were found in up to 40% of cases of male breast cancer, being the *BRCA2* the most common mutated gene (11). All physicians with a case of breast cancer in men, occult or not, should perform genetic counseling to the patients and their families. In this systematic review, any patient underwent a genetic study. In our case, a genetic study with a panel of 30 genes was performed, and specific mutations for *BRCA1* and *BRCA2* genes were negative so family members were not included in the genetic counseling. However, in cases with positive gene profile, would be important to include the patient and its family in screening programs for other cancers associated with the mutations found, and prevent advanced disease and mortality associated.

Diagnostic images have an important role, so they must be performed to find the primary tumor. The breast MRI let the physician discover hidden lesions in 59% of cases that have not been observed with other imaging modalities (12,15). In this review, any patient presented hidden lesions when studied with ultrasound, CT-scan, MRI, or PET-CT scan (2,8,10). Also, when patients underwent surgery, a primary tumor in the pathology of the specimen was only found in three cases (4,11,12), which represents the challenge of the diagnosis. In our patient, axillary ultrasound showed pathological lymph nodes and was used for guiding biopsy. Meanwhile, chest CT-scan and breast MRI did not show a primary hidden lesion, and the PET-CT scan showed a high-grade hypermetabolic lymph node conglomerate without pathological findings in the mediastinum.

Usually, in male breast cancer, ER and PR are expressed in more than 90% and 80% of cases, respectively. So, the identification of receptors is key for diagnosis, and evaluation to determine the necessity of hormonal therapy (5). In this review, ER and PR were positive in seven patients of which two patients were also HER-2 positive; one patient presented only progesterone receptors, two presented only HER-2 positive and two were triple-negative (3,7,9). Positive HER-2 breast cancer is seen in approximately 25–30% of cases and confers worse biological behavior (7,16). Our case was ER and PR negative, and HER-2 positive, which lead to discarding hormonal therapy.

The diagnosis of metastatic disease requires a panel of cytokeratins to consider the primary site of the malignant tumor (9). The CK-7 is usually expressed in up to 90% of cases, while CK-20 is usually negative (9). The GCDFP-15 has a positive predictive value and a specificity of 90% for breast carcinoma, and other markers such as GATA-3 and mammaglobin, have sensitivity but low specificity to favor mammary gland origin (17). The final diagnosis of our case was made after a histopathological and immunohistochemical evaluation of the specimen resected during the axillary lymph node dissection (ALND), and reactivity for CK-7, GCDFP-15, and GATA-3 with negative CK-20.

HER-2 amplification in breast cancer is an early event of tumorigenesis and is seen in nearly 50% of all *in situ* ductal carcinomas without any evidence of invasive disease (18-20). However, it is maintained during progression to invasive disease, and nodal and distant metastasis (19). The presence of HER-2 in our patient and the absence of ER and PR could be the explanation of the OBC as a ductal carcinoma without evidence of invasive primary tumor but nodal metastasis. However, it was only seen in two more cases of our review, and HER-2 was positive in a total of 4 patients, so further studies of the association are needed.

Treatment of breast cancer and OBC in men is based on the treatments given to women due to the rare incidence of the disease. Regarding surgical treatment, the conservative approach is not recommended in men and a modified radical mastectomy should be performed in all cases due to the

advanced stage in which male patients are usually diagnosed (5,21). Hereby, ten cases underwent surgery with ALND of which six patients were taken to mastectomy too. More studies are needed to attribute surgical mastectomy or breast radiotherapy of OBC to disease-free and overall survival.

The status of the axillary lymph nodes is one of the prognostic factors in patients with breast cancer, thus, postoperative radiation is recommended if mastectomy is not performed (9). In the literature, most of the patients were diagnosed in an advanced stage (III and IV) and needed directed therapies. For instance, our patient needed neoadjuvant chemotherapy with Adriamycin and Cyclophosphamide, and after ALND, Paclitaxel, and Trastuzumab due to partial response to neoadjuvancy, and the presence of HER-2 with negative ER and PR. In the three years follow-up, our patient continued without evidence of tumor relapse despite the aggressive HER-2 positive OBC. This could be related to the mastectomy surgical approach and the directed therapy with Trastuzumab.

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.

Conclusions

OBC is a rare pathology in men and requires a high diagnostic suspicion in patients with an axillary or thoracic metastatic disease without an evident primary neoplasm. All management should be based on the patient's findings, location of the metastasis, and immunohistochemical evaluation. The genetic study is necessary to determine mutations and evaluate the risk of relapse and the high risk of primarily associated neoplasm in the patient and family.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://asj.amegroups.com/article/view/10.21037/asj-21-44/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://asj.amegroups.com/article/view/10.21037/asj-21-44/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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