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CASE REPORT

Occult Invasive Lobular Carcinoma Presenting as an Axillary Skin Metastatic Lesion Underwent Neoadjuvant Endocrine Therapy and Surgical Resection: A Case Report and Review of Literature

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Introduction: Invasive lobular carcinoma (ILC) is the second most common type of breast cancer accounting for 5–15% of all breast cancer cases. It usually presents with nonspecific signs and symptoms. Occult breast cancer presenting as an axillary mass is rare, with prevalence of 0.3–1%, less likely with isolated cutaneous breast metastasis as a first presentation. There are limited data in the literature on patients who underwent endocrine therapy and complete surgical resection.

Case Presentation: A 54-year-old woman with left axillary skin swelling that had been persisting for 6 years was diagnosed with ILC 18 months ago presenting with an ulcerated axillary skin lesion and was managed with letrozole in another facility as she was estrogen receptor (ER) and progesterone receptor (PR) positive. She received letrozole for 18 months and had a partial response in the form of healing of the ulcer with persistent subcutaneous nodules. Her breast mammogram, ultrasound, and magnetic resonance imaging findings were unremarkable; however, there were few prominent left axillary lymph nodes. A biopsy of the left axillary lymph node was positive for malignancy, consistent with ILC. A skin punch biopsy of the axillary skin lesion showed ILC extending to the dermis with no background breast tissue. The patient underwent left modified radical mastectomy with excision of the left axillary skin lesion. The breast specimen comprised 0.4 mm of ILC as the primary malignancy and nine positive axillary lymph node malignancies. The patient received adjuvant radiotherapy and continued to receive letrozole. There were no signs of complications or recurrence during the follow-up period.

Conclusion: Ulcerated skin lesions in the axilla should raise concerns regarding breast cancer metastasis. In cases of isolated cutaneous breast metastases, surgical excision can be considered in combination with endocrine therapy.

Keywords: occult breast cancer, invasive lobular carcinoma, axillary skin lesions, breast cutaneous metastasis, neoadjuvant endocrine therapy

Introduction

Invasive lobular carcinoma (ILC) is the second most common invasive breast cancer, accounting for 5–15% of all reported breast cancer cases.[1] Diagnosis of ILC can be challenging, as physical examination is usually limited to nonspecific signs and symptoms, even with the help of mammography or ultrasound.[1]

Occult breast cancer (OBC) is defined as metastatic carcinoma mostly to the axillary lymph node, originating from a malignant primary breast cancer that is undetectable on clinical and radiological examinations.[2] OBC presenting as an axillary mass is rare, accounting for 0.3–1% of all breast cancers, and it represents a diagnostic challenge in terms of imaging and ascertaining the primary source.[3] Ectopic breast tissue (EBT) occurs when there is incomplete regression of the mammary tissue during embryogenesis along the milk line, with most of it in the axilla.[4] It consists of any

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combination of the breast parenchyma, areola, or nipple.[5] EBT is exposed to the same physiological and pathological changes that can occur in a eutopic breast, including carcinoma.[6]

Cutaneous breast metastasis is generally a rare and late sign that can occur through direct extension or via vascular or lymphatic routes.[7] It can also be the presenting sign in undiagnosed breast cancer, such as in our case, as a solitary axillary skin ulcerated nodule. Endocrine therapy is widely used for ILC because it is usually hormone receptor positive; however, its role as a neoadjuvant therapy is not well established.[1] In cases of isolated cutaneous metastasis with no signs of distant metastasis, surgical excision can be considered.[7]

In this report, we describe a case of isolated axillary cutaneous breast metastasis in the form of an ulcerated skin nodule with partial response to neoadjuvant endocrine therapy. The patient successfully underwent surgical excision with no signs of recurrence or other distant metastases on follow-up.

Case Presentation

A 54-year-old postmenopausal married Sudanese woman presented to our facility with a history of left axillary skin swelling for 6 years that had been diagnosed 18 months earlier at another facility as an ILC; her condition was managed with letrozole. Although she had initially presented with an ulcerating skin lesion in the left axilla (Figure 1) 18 months earlier, she had noticed a swelling 6 years earlier but had not sought medical advice until it had started to ulcerate. A biopsy of the lesion revealed the presence of an ILC. She was treated with daily administration of oral letrozole (2.5 mg). During the 18-month interval until she presented to us, the ulcer had healed. However, she was concerned regarding the persistent swelling in the left axilla. She did not feel any masses in her breasts, and there were no changes in the skin or nipple discharge. A systemic review was unremarkable. Her personal and family histories were negative for breast cancer and other malignancies. Her medical history included type II diabetes mellitus, hypertension, and stage I chronic kidney disease. Examination of the left axilla revealed a 2-cm firm, irregular, non-mobile mass without any ulceration. There were no breast skin changes or nipple discharge, and no breast masses were observed. She had bilateral accessory axillary breasts that were soft with no masses.

Radiology

On mammography, the left breast and left axilla were unremarkable. However, in the right breast, we found a stable, lobulated isodense mass measuring 10.0 × 8.0 × 8.0 mm that had been present in the right upper outer quadrant of the mid-to-posterior breast since 5 years before her presentation to us. Bilateral accessory breast tissue was observed, primarily on the left side.

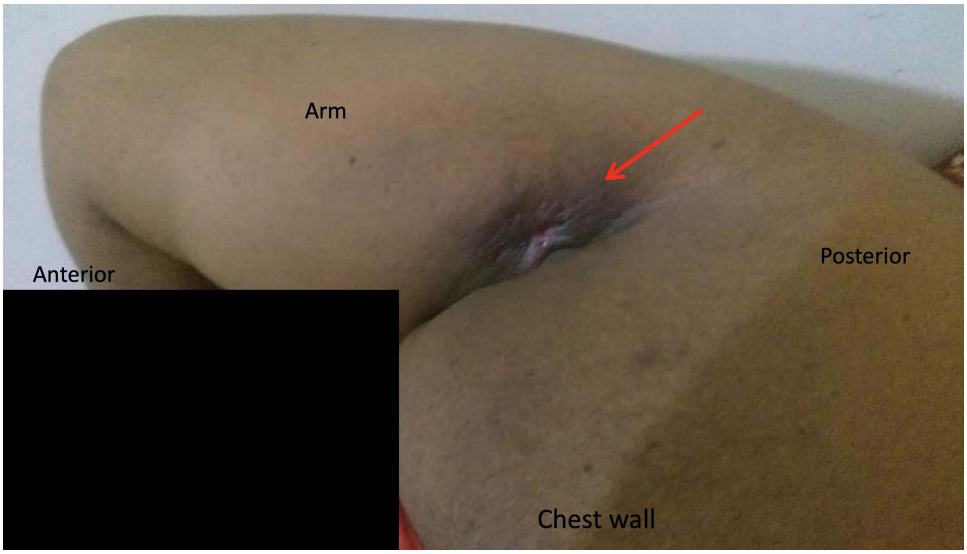

Figure 1 Ulcerating skin lesion in the left axilla.

Ultrasonography of the left breast was unremarkable. The left axilla had multiple abnormal lymph nodes with diffuse cortical thickening; the largest one measured 12.1 × 7.3 mm with cortical thickness up to 4.5 mm. In the right breast, we found a well-defined lobulated hypoechoic mass measuring 8.9 × 3.9 × 5.9 mm in the right upper quadrant mid-breast; it had an elastography strain ratio up to 2.9. There were a few prominent right axillary lymph nodes with focal cortical thickening measuring up to 3.0 mm; the accessory breast tissues were unremarkable.

Contrast-enhanced magnetic resonance imaging (MRI) of the breast showed no suspicious masses, abnormal enhancement, or architectural distortions. The areola, retroareolar, and skin were unremarkable. There were multiple abnormal left axillary lymph nodes in association with a thickened cortex; the largest lymph node measured 1.3 cm. The right axillary lymph nodes were observed to have a preserved fatty hilum.

Histopathology

Histopathological analysis of the left axillary lesion at another facility revealed the presence of an ILC of nuclear grade I/III. The tissues were positive for ER (80%), positive for PR (40%), negative for HER2/neu, with a low Ki-67 index (5–10%); further, the expression of mammaglobin was positive, gross cystic disease fluid protein 15 (GCDFP-15) was negative, and E-cadherin was negative with no breast parenchyma surrounding the lesion.

Ultrasound-guided core needle biopsy of the left axillary lymph node, right breast mass, and right axillary lymph node was performed. The left axillary lymph node was positive for malignancy, consistent with ILC of the breast; immunohistochemical staining revealed the node to be ER positive, PR positive, HER2/neu negative, pan-cytokeratin positive, evaluation of high molecular weight cytokeratin (HMWCK) positive, and mammaglobin positive and have a Ki-67 index < 5%. The right breast mass showed adenosis, microcalcification, and pseudoangiomatous hyperplasia and was negative for malignancy. The right axillary lymph node showed an unremarkable lymphoid tissue.

A skin punch biopsy of the left axillary lesion showed the ILC extending into the dermis with a morphology similar to that of the left axillary lymph node, with no breast tissue in the background. Immunohistochemical staining was positive for pan-cytokeratin, ER, PR, GATA-3, and GCDFP-15 and negative for E-cadherin.

Computed tomography (CT) of the chest, abdomen, and pelvis and a bone scan showed no sign of metastasis.

The case was then discussed in a multidisciplinary team meeting, and we planned to proceed with left modified radical mastectomy (MRM) with left axillary skin lesion excision, as we were dealing with either primary left ectopic breast ILC with lymph node involvement with partial response to hormonal therapy or OBC and axillary lymph node involvement associated with isolated axillary skin metastasis with partial response to hormonal therapy. After discussing the options with the patient, she decided to undergo left MRM with left axillary skin lesion excision. The patient had uneventful recovery with no complications and was discharged on postoperative day 5.

The breast tissue specimen comprised a 0.4-mm residual ILC in the central upper portion of the left breast with a negative margin, and positive lobular carcinoma in situ was present. Nine lymph nodes showed macrometastasis; the largest measured 9 mm, with >2 mm focal extranodal extension and lymphovascular invasion. The axillary skin was infiltrated by the ILC with no breast parenchyma on the background with a negative margin.

She received adjuvant radiotherapy with no complications and continued letrozole 2.5 mg daily. She was offered adjuvant chemotherapy; however, the patient declined it, stating that she planned to do a follow-up abroad. She was last evaluated 6 months after the surgery and was in a good condition, with a healed scar with no signs of local recurrence or distant metastasis. Unfortunately, we do not have long term result due to the patient wished to continue her follow-up abroad.

Discussion

ILC is the second most common type of invasive breast cancer after invasive ductal carcinoma and accounts for 5–15% of all reported breast cancer cases.[1] There are multiple histological variants of ILC, which affects prognosis of the disease, including classic, solid, alveolar, mixed, tubulo-lobular, and pleomorphic lobular carcinoma.[8] Tubulo-lobular variants may exhibit the best prognosis, as they are usually of low histological grade and are often node-negative.[9] In contrast, pleomorphic ILC variants generally have the worst prognosis, as they usually present at an advanced stage of the disease with large tumors and lymphovascular invasion.[10]

The diagnosis of ILC can be challenging as physical examination is usually limited by nonspecific signs, and patients often present with no palpable masses.[1] Even with the help of mammography or ultrasonography the diagnosis can be difficult because these imaging modalities have low sensitivity (57–81% and 68–98%, respectively) for detecting ILC than for other invasive breast cancers.[1] One of the common indicators in mammography is microcalcification; however, ILC has a low chance of presenting with microcalcification.[1] In fact, it was reported to range from 1 to 28% of the ILC to have microcalcification, which makes it difficult to detect these lesions.[1] MRI has sensitivity of 93% for detecting ILC.[11] This high level of sensitivity was attributed to increased neovascularization in the tumors.[12] It also helps to detect multifocal, multicentric, and presence of any contralateral disease.[1] It can also reveal other tumor foci in ipsilateral breast up to 16% and the presence of contralateral breast disease in 58% of patients with ILC, which were not present on the initial mammogram imaging.[1]

Lobular carcinoma in situ (LCIS) carries a 12-fold risk of developing breast cancer in the general population, which is significant.[13] Holland et al reported that there was no increase in local recurrence of ILC in patients who have LCIS present in the specimen.[14] In addition, Schnitt et al have compared ILC and IDC and noted that the presence and extent of LCIS did not increase the chance of local recurrence, unlike ductal carcinoma in situ (DCIS).[15] In a study involving 131 patients with ILC, Hussien et al reported that the presence of LCIS did not affect overall survival or local recurrence.[13]

The management of ILC involves a multidisciplinary approach involving surgery, systemic therapy, and radiotherapy.[1] Management is usually tailored to the stage of presentation and ILC subtypes.[16] Early breast cancers are usually managed with upfront surgery,[1] while neo-adjuvant therapy is considered to reduce tumor burden in advanced disease.[1] Breast-conserving surgery (BCS), in the form of wide local excision with clear margins, is usually performed.[1] Fodor et al compared 235 patients with ILC who underwent either BCS or mastectomy and concluded that there was no difference in terms of distant metastasis-free survival and cancer-specific survival between the two groups for 15 years.[17] In addition, axillary lymph node status is important which influences surgical planning. Axillary ultrasound (AUS) has a sensitivity of detecting LN metastases ranging from 36 to 68% in patients with ILC.[18] Thus far, sentinel lymph node biopsy has been the standard method for assessing the axilla.[18] Formal axillary lymph node dissection should be performed in patients with nodal involvement.[13]

The management of ILC also depends on its distinct biological profile, as it is usually strongly positive for both the estrogen receptor (ER) and progesterone receptor (PR), negative for human epidermal growth factor receptor 2 (HER-2), and has a low mitotic rate.[16] Additionally, E-cadherin is usually lost, resulting in the proliferation of disclosive cells in single-file strands.[16] Up to 95% of ILC have positive ER receptors, and about 70% express PR receptors, which is higher than in IDC.[1] Hence, the role of neoadjuvant chemotherapy (NAC) in ILC is limited, as these tumors respond poorly to chemotherapy and are unlikely to improve the rate of breast conservation surgery.[1,16] Lips et al performed an analysis of two large NAC trials including 676 patients, 75 of whom had lobular histology.[19] They concluded that ILC is less responsive to NAC than IDC and explained that it is owing to the difference in molecular characteristics between the groups, particularly in ER, PR, and HER-2.[19] Owing to the biological profile of ILC being luminal A type, the chance of a pathological complete response (pCR) is lower (11%) than that of IDC (25%).[1]

Endocrine therapy is widely used for ILC because it is usually strong hormone receptor positive.[1] It is used in the adjuvant setting because of its high correlation with reducing the risk of recurrence, and can also be used in the neoadjuvant setting to downstage tumors and potentially allow BCS.[20] Filho et al analyzed the effectiveness of adjuvant letrozole versus tamoxifen in patients with ILC in the BIG 1–98 trial.[21] Over the 8-year follow-up period, the disease free survival (DFS) and overall survival were lower for tamoxifen, 66% and 74%, than for letrozole, 82% and 89%, respectively.[21] Endocrine therapy is not as well documented as neoadjuvant treatment for breast cancer; however, reported studies suggest that it is preferable to chemotherapy.[1] Dixon et al reported in a retrospective study of 61 patients with ILC that they had a 66% reduction in tumor volume following 3 months of neoadjuvant letrozole with a successful BCS rate of 81%.[22] The results of two randomized control trials of neoadjuvant endocrine treatment with ER-positive disease in postmenopausal patients indicate a higher probability of response in correlation with the ER status.[23,24] There is still no consensus regarding the optimal duration of neoadjuvant endocrine therapy.[25] Fontein et al reported a better reduction in size for ER-positive breast cancer patients after 6 months of neoadjuvant exemestane

therapy than for those with a 3-month therapy duration.[25] Another Phase II clinical trial of neoadjuvant letrozole therapy evaluated a maximum response rate of 4.2 months.[26]

Few studies have investigated the role of adjuvant radiotherapy in patients with ILC with some evidence of improved survival outcome, which is beneficial[16] in reducing locoregional recurrence and prolonging survival.[16] Some of the indications eligible for adjuvant radiotherapy following mastectomy include positive surgical margins, four or more positive axillary lymph nodes, skin involvement and stage T3–4 tumors.[16]

OBC is defined in the literature as the clinical presentation of metastatic carcinoma mostly to the axillary lymph node, originating from a malignant primary breast cancer that is undetectable by clinical examination and radiological findings.[2] OBC presenting as axillary mass is a rare disease accounting for 0.3–1% of all breast cancers and it represents a diagnostic challenge in terms of imaging and ascertaining the primary source.[3] Carcinomas of the lung, thyroid, colon, rectum, stomach, and pancreas rarely present solely as axillary lymph node metastasis.[27] Hence, immunohistochemical markers can be useful in differentiating metastatic breast cancer from other cancers.[27] ER and PR status have high sensitivity and specificity in differentiating primary breast cancer from others.[28] Other markers that can also be used are GSDFP-15, cytokeratin 7 (CK7), GATA-3, carcinoembryonic antigen (CEA), epithelial membrane antigen, and mammaglobin, which can help determine whether the breast is the primary site of malignancy.[2,27,29] In addition, cathepsin D, an aspartic protease, if observed in breast carcinoma metastases and indicates poor prognosis.[29] Kaufmann et al reported that the combination of GCDFP-15 and/or ER or PR had a sensitivity of 83% and a specificity of 93% for determining the breast as the primary source of metastasis.[28] Han et al have also reported that mammaglobin expression in the metastatic lymph nodes was an important marker with a sensitivity of 84% and a specificity of 85% for breast carcinomas.[30]

Cutaneous metastases are considered rare presentations and it is reported in less than 1% of cancer patients, and it usually implies an advanced systemic disease.[2] Lookingbill et al conducted a systematic review of 7316 patient with cancer and found 5% of them had cutaneous metastasis with about 0.8% of them having cutaneous metastasis as the first presentation.[31] Chuang et al reported breast cancer was the primary origin of cutaneous metastasis in 7.8% of cases.[32] Approximately 50% of breast cancer cutaneous metastasis are identified between 6 months and 4 years after the diagnosis of primary breast malignancy.[33] Hu et al reported that approximately one-third of patients with cutaneous breast metastasis did not have any other systematic involvement.[34] Cutaneous breast metastasis most commonly appears on the chest wall with the possibility of involvement of other sites such as the abdomen, back, head, neck, scalp, and upper extremity.[4] Clinically, nodular carcinoma is the most common manifestation of breast cutaneous metastasis ranging from 46 to 80% of reported cases.[35,36] The nodule can range in size from 1 to 3 cm and mostly they are asymptomatic, however, they can ulcerate, as in our case.[37] The less common clinical presentations include telangiectatic carcinoma, erysipeloid carcinoma, carcinoma en cuirasse, and alopecia neoplastica.[4] The presentation of cutaneous breast metastasis is generally a late sign that can occur through direct extension or via the vascular or lymphatic routes.[7] Mayer et al reported that 15% of cutaneous breast metastasis are from ILC.[38] It can also be a presenting sign in undiagnosed breast cancer, as in our case. It rarely presents as a solitary lesion, as it usually appears as a multiple nodule or rash with synchronous distant metastasis; thus, it can be considered a marker of distant metastatic disease.[7] Hence, we advise a full metastatic workup for any patient with cutaneous metastasis before considering definitive surgical management.

In our case, punch biopsy revealed cells infiltrating in a single file between the collagen bundles, with positive staining consistent with ILC. The differential diagnoses for such presentations include cutaneous breast metastasis, carcinoma arising from the EBT, and adnexal origin.[39] However, we were uncertain initially whether this represents cutaneous metastasis of a primary breast cancer or a primary breast cancer arising from EBT. EBT occurs in 2–6% of population when there is incomplete regression of the mammary tissue during embryogenesis along the milk line, with most of it in the axilla.[4] Ectopic breast carcinoma (EBC) occurs when a carcinoma arises from an EBT, and is quite rare, only 0.3% of breast cancers.[40] Histologically, it is necessary to have a normal adjacent breast parenchyma with a lack of lymphatic tissue to confirm the diagnosis of EBC and rule out a metastatic origin.[41] In our patient's initial presentation, she had no clinically or radiologically detected breast lesion, which put us on a dilemma whether we were facing a cutaneous breast metastasis with occult primary or EBC with axillary LN metastasis. After a multidisciplinary meeting and discussion of the patient's options and taking into consideration her partial response to neoadjuvant endocrine

therapy with no other evidence of distant metastatic disease, she underwent MRM with excision of the skin lesion. Pathological analysis revealed the presence of an OBC with a 0.4-mm ILC, with positive axillary LN and complete excision of the skin lesion. The skin lesion showed invasive lobular carcinoma infiltrating the skin, with no adjacent breast parenchyma or lymphatic tissue, thus confirming the presence of isolated cutaneous breast metastasis from occult breast ILC managed successfully with neoadjuvant endocrine therapy and complete surgical resection.

Current recommendations for patients with OBC with negative MRI findings include axillary lymph node dissection (ALND) plus whole breast radiotherapy (RT) with or without nodal RT or ALND plus mastectomy with or without RT.[42] In cases of axillary metastasis in OBC, MRM may be necessary for the localization, excision, and biological characterization of the primary tumor.[43] Patients who did not undergo mastectomy were reported to have worse survival than those who did.[44,45] However, histological examination in one-third of these patients fails to detect the primary tumor even with 3–4 mm thin sections as the tumor size is smaller than the interval section, such as in our patient, where it was only 0.4 mm.[3] This led physicians to investigate other treatment options for these patients.[46] Watchful waiting has been suggested as an alternative to a mastectomy.[43] Merson et al analyzed 60 patients with axillary metastasis from OBC who underwent either mastectomy or watchful waiting, and concluded that there was no statistically significant difference between the groups in terms of survival.[47] Frattaroli et al reported a case in which the patient refused to undergo mastectomy. After 8 years of follow-up, the breast lesion was mammographically evident, and the patient underwent BCS with hormonal treatment and radiotherapy.[43] Van Ooijen et al reported observations of the breasts of patients with OBC, with surgical therapy undertaken only if it became clinically evident.[48] Only 2 of 14 cases presented after a median time of 7.5 years.[48] In contrast, Ellerbroek et al reported 57% chance of appearance of primary breast cancer within 5 years for OBC in the non-treated breasts.[44] Limited resections, such as blind outer quadrantectomy, were also introduced as an option for these patients, but these efforts failed to lead to better outcomes.[27] Alternative treatment plans for these patients include breast irradiation coupled with ALND along with appropriate adjuvant systemic therapy.[49] Varadarajan et al conducted a retrospective study on eight patients with isolated axillary nodal metastasis who were treated with ALND, all of whom received chemotherapy and radiotherapy, and six patients received hormonal therapy as well. During the follow-up period of 57 months, none of the patients developed distant metastases.[49]

In patients with cutaneous breast metastasis, a thorough staging workup should be conducted, including computerized tomography of the chest, abdomen, pelvis, and brain, as well as bone scans and tumor markers, to detect any signs of other distant metastases before making any treatment decisions.[7] Cutaneous metastasis is a late finding that reflects an advanced systemic disease.[37] Treatment with the aim to improve symptoms and quality of life, management includes systemic chemotherapy, radiotherapy, and immunotherapy.[37] Local treatment that focuses on controlling symptoms, includes use of imiquimod, traztuzumab injection, and debridement, in case of bleeding.[37] Local surgical excision can be considered in cases of isolated cutaneous metastasis with no signs of other distant metastases.[7]. da Costa et al reported regression of cutaneous metastasis in a case of occult breast ILC treated with anastrozole alone.[2]

Conclusion

Ulcerated skin nodules in the axillary region should raise concerns regarding breast malignancy metastasis. A thorough breast and axillary assessment should be performed using detailed clinical examinations and breast imaging including breast ultrasonography, mammogram, and MRI to evaluate the primary lesion, as cutaneous breast metastasis could be the first presentation. A thorough detailed assessment of other distant metastatic lesions should be conducted, including CT of the chest, abdomen, and pelvis as well as a bone scan to rule out other distant metastases. Neoadjuvant endocrine therapy can help control ILC progression and, in some cases, induce disease regression. In cases of isolated cutaneous breast metastases, surgical excision can be considered after ruling out other distant metastases. Further studies are needed to assess the benefit and duration of neoadjuvant endocrine therapy as well as the role of surgery in patients with limited cutaneous breast metastasis.

Abbreviations

ILC, invasive lobular carcinoma; MRM, modified radical mastectomy; BCS, breast-conserving surgery; SLNB, sentinel lymph node biopsy; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor

2; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; OBC, occult breast cancer; EBC, ectopic breast carcinoma; EBT, ectopic breast tissue; ALND, axillary lymph node dissection; RT, radiotherapy; GCDFP-15, gross cystic disease fluid protein 15; HMWCK, evaluation of high molecular weight cytokeratin; MRI, magnetic resonance imaging; CT, computed tomography; DCIS, ductal carcinoma in situ; AUS, axillary ultrasound; DFS, disease free survival; CK7, cytokeratin 7.

Disclosure

The authors report no conflicts of interest in this work.

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