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Case Report

Cutaneous Metastases as a Clinical Presentation of Occult Breast Carcinoma

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Abstract

Cutaneous metastases as a primary presentation of occult breast carcinoma (OBC) is a rare sign of this type of malignant disease. Cutaneous metastases (CM) are neoplastic infiltrations of the skin that originate from distant malignant tumors. We described the diagnosis and treatment of a woman in her mid-50s who presented with extensive papulonodular pruritic skin lesions that started a year ago mostly in the right breast chest wall, right axillary region, and right arm. The patient denied a history of breast lumps. Skin biopsy revealed cutaneous metastases of a high-grade invasive ductal carcinoma of the breast with extensive dermal lymphatic invasion. Further investigation indicated that the cells were positive for cytokeratin 7 and GATA3 and negative for p63 confirming their breast origin. Immunohistochemistry analysis revealed that the tumor was estrogen-receptor negative, progesterone-receptor negative, and human epidermal growth factor receptor 2 positive. The patient was treated with carboplatin, docetaxel and trastuzumab. Evaluation after 6 cycles of chemotherapy showed stable disease.

Keywords: Occult Breast Carcinoma, Cutaneous Metastases, Breast Carcinoma

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Introduction

Breast carcinoma (BC) is the leading cause of cancer in women worldwide with 2 296 840 cases in 2022 (1). According to the Global Cancer Observatory, BC in Guyana represents the 33.3 % of all cases of malignant disease in 2022 and the first cause of death (1). We can distinguish between different groups of breast carcinomas according to their molecular profile: those that express Estrogen Receptor (ER) and/or Progesterone Receptor (PR) (70-75%), those that express Epidermal Growth Factor Receptor 2 (Her2) (15%) and tumors that do not express any of these three markers, triple-negative breast cancer (TNBC) (10–20%) (3). BC is widely recognized as a heterogeneous disease in terms of both primary tumor metastatic capacity and the time to metastatic spread. Common risk factors influencing the metastatic process of BC include tumor size, histologic grade, nodal stage, and receptor status. The main targets for metastasis in BC are the bones, lungs, liver, and brain (4,5). Patients with metastatic BC have bone metastases in up to 60–75% of cases, lung metastases in up to 32–37%, liver metastases in up to 32–35%, and brain metastases in up to 10% (4,5).The molecular subtypes of BC are associated with metastases to the targeted organs: Luminal A (ER+, PR+/-. HER2-, Ki-67 low) with preferential bone metastases. TNBC subtypes, present a smaller tropism to the bone, are usually present in the brain and lungs, and rapidly recur. The HER2 subtype mostly metastasizes to visceral organs (4,5).

For cutaneous metastases from BC, immunohistochemical evaluation should focus on the expression of the following markers typical of BC:

- Mammaglobin and Gross cyst disease fluid protein (GCDFP): Mammaglobin is the most sensitive marker for BC, whereas GCDFP is the most specific. These

markers are expressed in most luminal type of breast cancer and HER2-positive tumors but are less sensitive in triple-negative tumors (35% and 16%, respectively). Both markers are expressed in cutaneous metastases of adnexal origin.

- GATA3: GATA3 is a transcription factor involved in the differentiation of various tissues, including mammary luminal epithelium. However, it is also expressed in urothelial, trophoblastic, salivary, and pancreatic tumors.
- SOX10: SOX10 is a transcription factor involved in the differentiation and survival of neural crest cells. SOX10 has been found positive in 66%–74% of triple-negative and metaplastic tumors but only in 5% of non-triple-negative tumors (7).

Regardless of tumor type, dissemination of tumor cells precedes the initial stage of the metastasis cascade (8). The dissemination process includes the initial steps of the invasion and metastasis cascade, which allows malignant tumor cells to acquire properties that enable them to leave the primary site and migrate to distant tissues (8). One of the most important assumptions that has led scientists to study the organ-specificity of tumor metastasis, and BC in particular, is the assumption that the nature of the primary tumor cell and its spread subsequently determines different metastatic properties, organotropism, and response to therapy (8). Metastasis is a process by which an original primary tumor develops into a distal secondary tumor (9). Metastasis is highly complex and involves multiple cellular mechanisms including division from the primary tumor, invasion, evasion of immune surveillance, and regulation of the tissue microenvironment. In particular, epithelial–mesenchymal transition (EMT) is required for metastasis in most cancers (9).The immediate process of tumor metastasis is a complex process that involves several sequential stages: local invasion with exit from the surrounding tissues of the primary tumor, invasion into the blood or lymphatic vessels (intravasation); survival in the bloodstream as circulating tumor cells (CTCs); exit of CTCs from the circulatory system (extravasation); adaptation to the microenvironment in the form of disseminated tumor cells, and transformation into cells initiating metastasis with the final formation of macrometastases (3,10). Sequencing of 617 breast cancer samples identified 9 genes (TP53, ESR1, GATA 3, KMT2C, NCOR1, AKT1, NF1, RIC8A and RB1) that were more frequently mutated in metastatic breast cancer than in early BC (3,10). Although relatively uncommon, cutaneous metastases from BC represent the most frequent form of skin metastases and pose a significant clinical and therapeutic challenge (11). Cutaneous metastases (CM) is defined as a neoplastic lesion arising from a primary malignancy that affects the dermis or subcutaneous tissue. Their reported incidence ranges from 0.7% to 9%, accounting for only 2% of all skin cancers, and they occur in up to 10% of cancer patient (11,12,13).

OBC presents a diagnostic challenge, especially with the primary manifestations of systemic metastases. This study aimed to report a case of OBC that, mainly manifested as cutaneous metastases.

Case Presentation

A woman in her late 50s presented with extensive papulonodular pruritic skin lesions that started a year ago mostly in the right breast chest wall and subsequently throughout the left breast, right axillary region, and right arm with lymphedema without a history of breast lump.

Clinical Examination Findings

Multiple pink papulonodular lesions were seen throughout the skin in both breasts, mostly in the right breast, right arm associated with lymphedema and the back (Fig1,2 and 3).

Right and left Breast and axilla: No palpable mass or enlarged axillary nodes.

Figure 1. *Cutaneous metastases of occult breast cancer in chest wall.*

Figure 2. *Cutaneous metastases of occult breast carcinoma in right axillary region.*

Figure 3. *Cutaneous metastases of occult breast carcinoma in back.*

Mammography

Diffuse skin thickening involving both breasts. Increased opacification of the bilateral fibroglandular parenchyma. There was no evidence of architectural distortion. No breast or axillary mass was detected.

CT scan with contrast of the chest, abdomen, and pelvis: Revealed no metastasis.

The patient did not undergo PET-CT or bone scintigraphy because of the unavailability of the exam.

Breast MRI

No breasts mass. Skin thickening.

ECHO: LVEF 65%.

Biopsy Report

Biopsy, histology sections and immunohistochemistry (IHC) of skin lesions in the right chest wall indicated skin metastases of a high-grade invasive ductal carcinoma of the breast with extensive dermal lymphatic invasion, cytokeratin 7 (CK7) positivity, ER negative, PR negative, HER2 positive and GATA 3-protein gene (GATA-3) positivity. It was not possible to evaluate other IHC markers like Mammaglobin, GCDFG and SOX-10 due to unavailability.

Diagnosis

The results were consistent with those for breast cancer metastases. An invasive breast carcinoma of occult primary site (OBC) with cutaneous metastatic dissemination was diagnosed.

Therapeutic Interventions

Chemotherapy with Carboplatin/Docetaxel and anti-HER 2 targeted treatment with trastuzumab was initiated.

Pertuzumab, TDxD was not use due to unavailability.

Follow-Up and Outcome of Interventions

The patient was evaluated 5 months after treatment. The patient received 6 cycles. Clinical and imagenological assessments, including contrast -enhanced CT scan of thorax, abdomen and pelvis was performed. RECIST 1.1 criteria was used to evaluate response to treatment. She had a stable disease.

Side Effects

No side effects reported according to Common Terminology Criteria for Adverse Events (CTCAE v6.0).

Discussion

OBC is defined as the clinical presentation of metastatic carcinoma (mainly in the axillary lymph nodes) derived from a malignant primary breast tumor that is undetectable on clinical examination and radiological evaluation. A 2020 retrospective study of 164 patients reported that breast cancer had one of the highest incidences of cutaneous metastases (14). Histopathological examination and immunohistochemical findings of known breast cancer markers such as mammaglobin, GCDFG, SOX 10, ER, PR, CK7, and GATA 3 are necessary to confirm that the breast is the primary source, even when radiological investigations do not detect the tumor, as they have been found to lack sensitivity for OBC (7). There was not possible to indicate a comprehensive IHC panel for this patient, according to medical history, IHC results and clinical examination, it was concluded that cutaneous metastases of OBC was the diagnostic in this case. Huang *et al*. reviewed 572 patients with OBC in comparison with 117,217 patients with non-occult breast cancer. These authors also concluded that patients with OBC are diagnosed at a more advanced age, ER-negative status, PR-negative status, and HER-2-positive status, as observed in this case report (15). Ye *et al*. evaluated 691 patients with OBC; TNBC and HER2 enriched were more common in these cases (16). Da Costa *et al.* reported a case of cutaneous and bones metastases; luminal type with excellent responses to anastrozole (17). Other authors such as Weiman *et al.* described a 65-year-old female patient with normochromic papules on the trunk and upper limbs. The final diagnosis was cutaneous metastasis of ER positive OBC(18). Barbieri *et al.* reported OBC with metastases localized to the skin, lymph nodes, and bones, ER positive (19). These cases reports have different molecular patterns compared to this case report which was HER 2 enrich. Hachmi *et* al. retrospectively identified cases of OBC that were treated between 1996 and 2021. The study included 68 patients with a median age of 56 years, thirty-nine (57.4%) OBC were hormone receptor positive, 19 (33.3%) were HER2 positive and 13 (22.8%) tumors were triple negative (20).

The most common sites of metastases in patients with HER 2 positives are visceral metastases. Currently, there are no specific guidelines for the systemic treatment of cutaneous metastases from breast cancer, and therapeutic strategies should follow the recommendations for advanced breast cancer. Patients with HER 2 positive diseases have a poor prognosis that improves with the use of targeted treatment. Therefore, this patient was treated with a combination of taxane/carboplatin + anti-HER 2 therapy (carboplatin 6AUC+ docetaxel 75mg/m^{2}sc+ trastuzumab 600mg s.c x 6cycles). Trastuzumab, which targets an extracellular domain in HER2, attenuates intracellular RAS/MEK/ERK and PI3K/AKT/mTOR signalling and induces Fc-receptor-mediated antibody-dependent cell-mediated cytotoxicity (ADCC). Its introduction has radically improved survival rates, which had been similarly dismal to those of TNBC. Pertuzumab was the second FDA approved humanized anti-HER2 agent. It targets a different extracellular domain and can prevent dimerization with other ERBB receptors (EGFR, HER2, and HER4), synergizing the arrest of downstream signaling (5). Anti-HER2 antibody drug conjugates (ADCs) have recently taken centre stage, where potent killer (cytotoxic) payloads are covalently bound to the monoclonal antibody via a cleavable synthetic linker. While the ADC is usually internalized, the cleavable linkers can also release the cytotoxic payload to adjacent tumor cells resulting in a potent “bystander effect (5).

The first-line therapy for HER2-positive advanced or metastatic breast cancer is a taxane plus the HER2-directed monoclonal antibodies Trastuzumab and Pertuzumab (the three-drug regimen is known as THP). The use of THP is based on the primary analysis of the 2012 phase 3 Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) trial, which established that combined with chemotherapy, dual HER2 blockade resulted in significantly longer progression-free survival than trastuzumab alone (median, 18.5 vs. 12.4 months; P<0.001) (21,22).

The results from Destiny-Breast 09 trial suggested that Trastuzumab Deruxtecan (TDxD) in combination with Pertuzumab may represent a new first line standard of care for patients with HER 2-positive metastatic breast cancer (23). The median progression-free survival as assessed by investigators was 40.7 months (95% CI, 36.5 to not calculable) with TDxD plus Pertuzumab and 20.7 months (95% CI, 17.3 to 23.5) with THP (hazard ratio for disease progression or death, 0.49; 95% CI, 0.39 to 0.61).

Skin-directed therapy for cutaneous metastases has the potential to improve disease response (24). There are various forms of skin-direct therapies: Electrochemotherapy (ECT) for CMs uses short electric pulses directed at the tumor to permeabilize cell membranes to increase the absorption

of either intralesional or intravenous chemotherapy. Photodynamic therapy (PDT) for CMs uses a nontoxic light to activate a topical or intravenous photosensitizer that interacts with tissue oxygen to generate toxic free radicals for its cytotoxic effects. Radiotherapy (RT) delivers ionizing radiation to the CMs and kills tumor cells by generating free hydroxyl radicals and causing direct DNA damage. Intralesional therapy (ILT) relies on the administration of an antineoplastic agent directly into or adjacent to the CM. Topical therapy (TT) is the application of an antineoplastic agent directly onto the CM (24). Spratt *et al* performed a meta-analysis of the efficacy of skin-directed therapy for cutaneous metastases. They found that breast carcinoma and melanoma represented 96.8% of the CMs analyzed. They had nearly identical objective responses of 54.5% (95% CI, 48.3% to 60.7%) and 54.0% (95% CI, 48.3% to 59.7%), respectively. Cabula et reviewed 125 patients with BC skin metastases who underwent ECT between 2010 and 2013.The response was evaluable in 113 patients for 214 tumors (median 1 per patient, range 1–3). The overall response rate after 2 months was 90.2 %, while the complete response (CR) rate was 58.4 %. In multivariate analysis, small tumor size ($P < 0.001$), absence of visceral metastases ($P = 0.001$), estrogen receptor positivity ($P = 0.016$), and low Ki-67 index ($P = 0.024$) were significantly associated with CR (25).

In a context with a lack of access to immunotherapy and financial restrictions the introduction of standards of care drugs is limited. The patient's response was stable disease.

Conclusions

Cutaneous metastases as a primary manifestation of OBC are a rare condition. Skin metastases, while uncommon, are significant indicators of BC and can mimic common skin conditions such as lymphedema. It was described a case with HER 2 positive cutaneous metastases of OBC with stable disease after systemic treatment.

Ethics statements: Consent to publish the case report was obtained. Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors declare no conflicts of interest.

Author Contributions

Conceptualization: Abel Ning Caballero, Latoya Gooding.

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Writing—Original Draft Preparation: Abel Ning Caballero.

Writing—Critical Review: Abel Ning Caballero.

Writing-Review & Editing: Abel Ning Caballero. Latoya Gooding

Visualization: Abel Ning Caballero, Latoya Gooding.

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