Cutaneous Manifestation as Initial Presentation of Metastatic Breast Cancer: A Systematic Review

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PRACTICE POINTS

- Dermatologists may play a role in diagnosing breast cancer through cutaneous metastasis, even in patients without a history of breast cancer.
- Clinicians should consider breast cancer metastasis in the differential for any erythematous lesion on the trunk.

Metastatic breast cancer initially may present with cutaneous lesions. The goal of this systematic review was to evaluate available reports where the initial discovery of primary breast cancer occurred through the diagnosis of metastatic cutaneous lesions. We aimed to better understand these cases and the role of dermatologists in their diagnosis. A review of the literature for case reports and retrospective studies was conducted using the following databases: MEDLINE/PubMed, EMBASE, Cochrane library, CINAHL, and EBSCO. The PRISMA guidelines were utilized. Studies were included if they reported a cutaneous metastasis of a primary breast cancer in females. Studies were excluded if skin metastasis occurred in a patient with a history of breast cancer. Thirty-six publications were identified. Among these, 27 were case reports, and 9 were retrospective reviews. An enhanced understanding of how these cutaneous metastases present may be of clinical benefit to physicians, particularly dermatologists.

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reast cancer is the second most common malignancy in women (after primary skin cancer) and is the second leading cause of cancer-related death in this population. In 2020, the American Cancer Society

reported an estimated 276,480 new breast cancer diagnoses and 42,170 breast cancer–related deaths.¹ Despite the fact that routine screening with mammography and sonography is standard, the incidence of advanced breast cancer at the time of diagnosis has remained stable over time, suggesting that life-threatening breast cancers are not being caught at an earlier stage. The number of breast cancers with distant metastases at the time of diagnosis also has not decreased.² Therefore, although screening tests are valuable, they are imperfect and not without limitations.

Cutaneous metastasis is defined as the spread of malignant cells from an internal neoplasm to the skin, which can occur either by contiguous invasion or by distant metastasis through hematogenous or lymphatic routes.³ The diagnosis of cutaneous metastasis requires a high index of suspicion on the part of the clinician.⁴ Of the various internal malignancies in women, breast cancer most frequently results in metastasis to the skin,⁵ with up to 24% of patients with metastatic breast cancer developing cutaneous lesions.⁶

In recent years, there have been multiple reports of skin lesions prompting the diagnosis of a previously unknown breast cancer. In a study by Lookingbill et al, 6.3% of patients with breast cancer presented with cutaneous involvement at the time of diagnosis, with 3.5% having skin symptoms as the presenting sign. Although there have been studies analyzing cutaneous metastasis from various internal malignancies, none thus far have focused on cutaneous metastasis as a presenting sign of breast cancer. This systematic review aimed to highlight

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the diverse clinical presentations of cutaneous metastatic breast cancer and their clinical implications.

Methods

Study Selection—This study utilized the PRISMA guidelines for systematic reviews.⁷ A review of the literature was conducted using the following databases: MEDLINE/PubMed, EMBASE, Cochrane library, CINAHL, and EBSCO.

Search Strategy and Analysis—We completed our search of each of the databases on December 16, 2017, using the phrases cutaneous metastasis and breast cancer to find relevant case reports and retrospective studies. Three authors (C.J., S.R., and M.A.) manually reviewed the resulting abstracts. If an abstract did not include enough information to determine inclusion, the full-text version was reviewed by 2 of the authors (C.J. and S.R.). Two of the authors (C.J. and M.A.) also assessed each source for relevancy and included the articles deemed eligible (Figure 1).

Inclusion criteria were the following: case reports and retrospective studies published in the prior 10 years (January 1, 2007, to December 16, 2017) with human female patients who developed metastatic cutaneous lesions due to a previously unknown primary breast malignancy. Studies published in other languages were included; these articles were translated into English using

a human translator or computer translation program (Google Translate). Exclusion criteria were the following: male patients, patients with a known diagnosis of primary breast malignancy prior to the appearance of a metastatic cutaneous lesion, articles focusing on the treatment of breast cancer, and articles without enough details to draw meaningful conclusions.

For a retrospective review to be included, it must have specified the number of breast cancer cases and the number of cutaneous metastases presenting initially or simultaneously to the breast cancer diagnosis. Bansal et al⁸ defined a simultaneous diagnosis as a skin lesion presenting with other concerns associated with the primary malignancy.

Results

The initial search of MEDLINE/PubMed, EMBASE, Cochrane library, CINAHL, and EBSCO yielded a total of 722 articles. Seven other articles found separately while undergoing our initial research were added to this total. Abstracts were manually screened, with 657 articles discarded after failing to meet the predetermined inclusion criteria. After removal of 25 duplicate articles, the full text of the remaining 47 articles were reviewed, leading to the elimination of an additional 11 articles that did not meet the necessary criteria. This resulted in 36 articles (Figure 1), including 27 individual case reports (Table 1) and 9 retrospective reviews (Table 2).

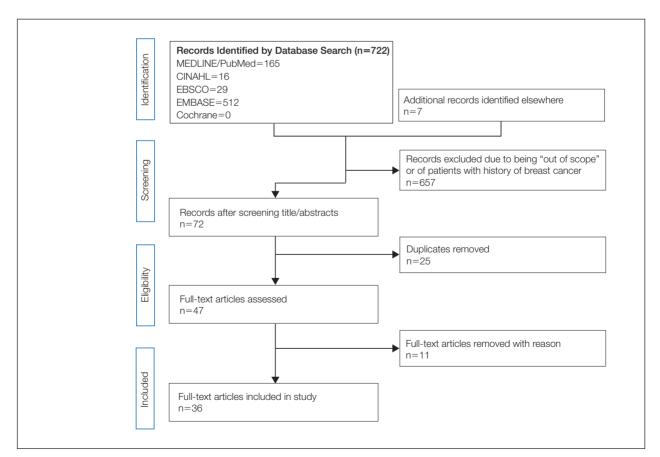


FIGURE 1. Diagram depicting study flow.

TABLE 1. Cutaneous Lesion Appearance for Each Case Report

Reference	Cutaneous lesion appearance	
Ahmed ⁹	Edematous rash on chest and neck with generalized thickening on breast	
Alani et al ¹⁰	Erythematous, indurated, ulcerated plaques with sharp demarcation	
Al Ameer et al ¹¹	Multiple erythematous macules and plaques on breast	
Bhattacharyya et al ¹²	Erythematous plaques with crusting, oozing, and indurated margins	
Carlos Ortega et al ¹³	Multiple erythematous nodules on face, neck, trunk, and abdomen	
Chandanwale et al ¹⁴	Multiple erythematous and papulovesicular linear lesions on the right chest along the T2-T3 dermatome	
Cullen Aravena et al ¹⁵	Multiple erythematous violaceous plaques on the chest wall, shoulder, arm, and scapular region with a carcinoma en cuirasse appearance	
Damaskos et al ²	Multiple erythematous, 0.5-mm, urticarial lesions	
Frances et al ¹⁶	Polychromatic, multilobulated, cystic-appearing nodule on nipple	
Gaitan-Gaona et al ¹⁷	Single ulcerated, 3-cm black nodule below breast	
Goodier and Jordan ¹⁸	Single violaceous nodule on the right lower eyelid	
Lee et al ¹⁹	Single erythematous mass protruding 6 cm with bloody discharge and crusting on left anterior chest	
Mahore et al ²⁰	Anterior chest: multiple indurated small nodules extending to left axilla Left arm: multiple keloidal indurated plaques	
Martí et a ²¹	Single black, irregular, ~1-cm nodule on the occipital scalp	
Mehenni et al ²²	Nodule resembling an angiomatous malformation of the lower eyelid	
O'Brien et al ²³	Multiple lesions resembling dermatofibromas of the neck and chest	
O'Brien et al ²⁴	Multiple erythematous, exophytic, friable nodules and swelling	
Oliveira et al ²⁵	Scaly papulonodular lesions with a carcinoma en cuirasse appearance	
Salati and Rather ²⁶	Diffuse erythema and nodularity with scaling of the left breast, neck, axilla, and arm	
Santiago et al ²⁷	Multiple erythematous, exophytic, papulonodular lesions	
Shagalov et al ⁵	Pink-brown, rubbery, indurated, 4-cm plaque in the right axilla	
Siqueira et al ²⁸	Single erythematous indurated plaque with central retraction on the intermammary region	
Uria et al ²⁹	Multiple erythematous, 0.5- to 1-cm papules on the chest	
Virmani et al ³⁰	Multiple erythematous, linear, vesicular papules along the T2-T3 dermatome in the axillary region	
de Souza Weimann et al ³¹	Multiple flesh-colored, 0.3- to 1-cm nodules with a fibrous consistency on the axilla, chest, and back	
Wu et al ³²	Single erythematous indurated nodule on the right middle finger	
Yaghoobi et al ³³	Left breast: multiple violaceous, lymphangioma circumscriptum–like papulovesicular lesions Right breast: multiple erythematous erysipelaslike lesions	

Approximately 13.7% of patients in the 9 retrospective reviews presented with a skin lesion before or simultaneous to the diagnosis of breast cancer (Figure 2).

Forty-one percent (17/41) of the patients with cutaneous metastasis as a presenting feature of their breast cancer fell outside the age range for breast cancer screening recommended by the US Preventive Services Task Force, 42 with 24% of the patients younger than 50 years and 17% older than 74 years (Figure 3).

Lesion Characteristics—The most common cutaneous lesions were erythematous nodules and plaques, with a few reports of black^{17,21} or flesh-colored^{5,20,31} lesions, as well as ulceration.^{8,17,32} The most common location for skin lesions was on the thorax (chest or breast), accounting for 57% of the cutaneous metastases, with the arms and axillae being second most commonly involved (15%) (Figure 4). Some cases presented with skin lesions extending

to multiple regions. In these cases, each location of the lesion was recorded separately when analyzing the data. An additional 5 cases, shown as "Other" in Figure 4, included the eyelids, occiput, and finger. Eight case reports described symptoms associated with the cutaneous lesions, with painful or tender lesions reported in 7 cases^{5,9,14,17,20,30,32} and pruritus in 2 cases. Moreover, 6 case reports presented patients denying any systemic or associated symptoms with their skin lesions. Sp. Multiple cases were initially treated as other conditions due to misdiagnosis, including herpes zoster 14,30 and dermatitis. 11,12

Diagnostic Data—Eighteen cases reported positive immunohistochemistry from cutaneous biopsy (Table 3), given its high specificity in determining the origin of cutaneous metastases, while 8 case reports only performed hematoxylin and eosin staining. One case did not report hematoxylin and eosin or immunohistochemical

TABLE 2. Characteristics and Content of Included Retrospective Reviews

Reference	Summary of study	Total CMs from breast	Diagnosed before or simultaneous to breast tumor
Atis et al ³⁴	CM patients seen at an outpatient clinic in a 6-y period; lesions examined with histopathology	n=4	n=2 diagnosed before (eczematous plaques from ductal carcinoma primary)
Bansal et al ⁸	CM patients diagnosed by FNA in a 1-y period; FNA found to be highly sensitive and specific as a diagnostic modality	n=28	n=3 diagnosed simultaneously
Benmously et al ³⁵	CM patients seen at a dermatology clinic in a 14-y period	n=3	n=2 diagnosed before (third patient, male, was excluded)
Chopra et al ³⁶	Histopathologic specimens of CM patients evaluated by a histopathology laboratory in a 5-y period	n=7	n=2 diagnosed simultaneously (erythematous plaques from primary ductal carcinoma)
El Khoury et al ³⁷	CM patients seen at a university medical center in an 8-y period; lesions examined with histopathology	n=41	n=4 diagnosed before
Fernandez-Flores ³⁸	Histopathologic specimens of CM patients evaluated by a pathology department in a 13-y period	n=22	n=9 diagnosed simultaneously
Gómez Sánchez et al ³⁹	CM patients diagnosed by histopathology at a dermatology department in an 18-y period	n=51	n=3 diagnosed before
Handa et al ⁴⁰	CM patients diagnosed by FNA in a 9-y period	n=23	n=1 diagnosed before
ltin and Tomaschett ⁴¹	CM patients seen at a dermatology department in a 6-y period	n=18 (1 patient had 2 independent breast cancers)	n=1 diagnosed before

Abbreviations: CM, cutaneous metastasis; FNA, fine-needle aspiration.

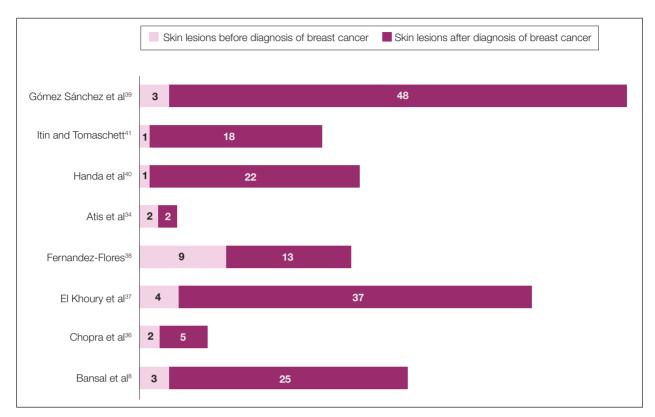


FIGURE 2. Summary of retrospective reviews comparing the number of skin lesions presenting as the primary finding of breast cancer.

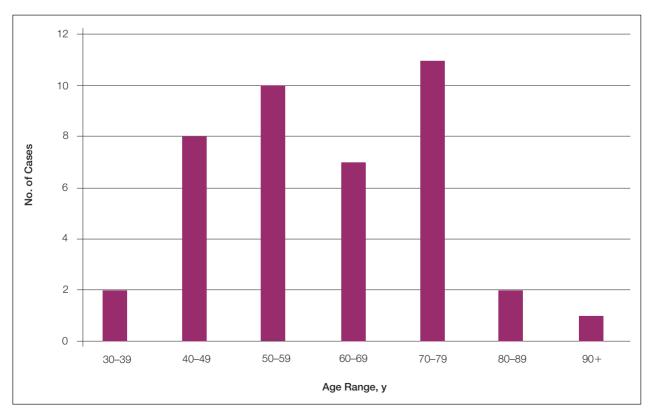


FIGURE 3. Number of reported cases by age group (N=41).

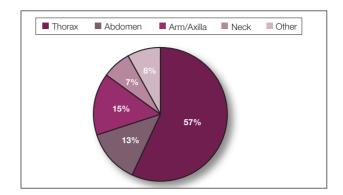


FIGURE 4. Location of cutaneous metastasis as primary presentation of breast cancer (N=61).

TABLE 3. Immunohistochemical Markers Reported in Each Case^a

	Immunohistochemistry ^a	
Reference	Positive	Negative
Alani et al ¹⁰	Strong positive: ER; weak positive: PR	EGF
Al Ameer et al ¹¹	AE1/AE3, CK7	ER, PR
Bhattacharyya et al ¹²	ER, GCDFP-15, AE1/AE3, CK7	ND
Carlos Ortega et al ¹³	ER, PR, GCDFP-15, EMA	ND
Cullen Aravena et al ¹⁵	HER2, mammaglobin, AE1/AE3, CK7, E-cadherin	ER, PR, CK20
Damaskos et al ²	ER (all cells), PR (few cells)	ND
Frances et al ¹⁶	ER, Bcl-2, E-cadherin	HER2, CK5-6, Ki-67, p63
Gaitan-Gaona et al ¹⁷	ER, PR	HMB-45
Lee et al ¹⁹	ER, PR	ND
Martí et al ²¹	ER, AE1/AE3, EMA; melanocyte positive: HMB-45, Melan-A	ND
Mehenni et al ²²	Hormone receptor positive	ND
O'Brien et al ²³	ER, PR, AE1/AE3, CK7	CK20, CD45, CD68, S100
Santiago et al ²⁷	ER, CK7, CAM5.2	PR, HER2
Shagalov et al ⁵	ER, PR, HER2, mammaglobin, AE1/AE3, GATA binding protein 3, intracytoplasmic mucicarmine stain	E-cadherin
Siqueira et al ²⁸	ER, PR, mammaglobin, AE1/AE3, CK7, 34BE12	CDX2, TTF-1
Uria et al ²⁹	GCPF-15, CK	LCA
de Souza Weimann et al ³¹	ER, mammaglobin, AE1/AE3, CK7	c-KIT, CK20, CD34, CDX2, WT1, LCA, TIF-1, p63, S100
Wu et al ³²	Strong positive: CK7, CK18; weak positive: PR, CEA	ER, HER2, AFP, CA-125, TTF-1, NSE, chromogranin A, synaptophysin, S100

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; EGF, epidermal growth factor; CK, cytokeratin; GCDFP, gross cystic disease fluid protein; ND, not determined; EMA, epithelial membrane antigen; HER2, human epidermal growth factor receptor 2; HMB, human melanoma black; TTF, thyroid transcription factor; LCA, leukocyte common antigen; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase.

^aThe following did not provide immunohistochemical information: Ahmed,⁹ Chandanwale et al,¹⁴ Goodier and Jordan,¹⁸ Mahore et al,²⁰ O'Brien et al,²⁴ Oliviera et al,²⁵ Salati and Rather,²⁶ Virmani et al,³⁰ and Yaghoobi et al.³³

TABLE 4. Final Breast Cancer Diagnosis for Each Case

Reference	Breast cancer diagnosis	
Ahmed ⁹	Adenocarcinoma	
Alani et al ¹⁰	Lobular breast carcinoma	
Al Ameer et al ¹¹	Inflammatory breast carcinoma	
Bhattacharyya et al ¹²	Breast carcinoma	
Carlos-Ortega et al ¹³	Breast carcinoma	
Chandanwale et al ¹⁴	Breast carcinoma	
Cullen Aravena et al ¹⁵	Ductal breast carcinoma	
Damaskos et al ²	Lobular breast carcinoma	
Frances et al ¹⁶	Mucinous carcinoma	
Gaitan-Gaona et al ¹⁷	Ductal breast carcinoma	
Goodier and Jordan ¹⁸	Mucinous adenocarcinoma	
Lee et al ¹⁹	Ductal breast carcinoma	
Mahore et al ²⁰	Ductal breast carcinoma	
Martí et al ²¹	Ductal breast carcinoma	
Mehenni et al ²²	Lobular breast carcinoma	
O'Brien et al ²³	Lobular breast carcinoma	
O'Brien et al ²⁴	Lobular breast carcinoma	
Oliviera et al ²⁵	Ductal breast carcinoma	
Salati and Rather ²⁶	Ductal breast carcinoma	
Santiago et al ²⁷	Ductal breast carcinoma	
Shagalov et al ⁵	Lobular breast carcinoma	
Siqueira et al ²⁸	Adenocarcinoma	
Uria et al ²⁹	Lobular breast carcinoma	
Virmani et al ³⁰	Breast carcinoma	
de Souza Weimann et al ³¹	Breast carcinoma	
Wu et al ³²	Ductal breast carcinoma	
Yaghoobi et al ³³	Inflammatory breast carcinoma	

staining. Table 4 lists the final breast cancer diagnosis for each case.

As per the standard of care, patients were evaluated with mammography or ultrasonography, combined with fine-needle aspiration of a suspected primary tumor, to give a definitive diagnosis of breast cancer. However, 4 cases reported negative mammography and ultrasonography. ^{13,22,28,31} In 3 of these cases, no primary tumor was ever found. ^{13,22,31}

Comment

Our systematic review demonstrated that cutaneous lesions may be the first clinical manifestation of an undetected primary malignancy. These lesions often occur on the chest but may involve the face, abdomen, or extremities. Although asymptomatic erythematous nodules and plaques are the most common clinical presentations, lesions may be tender or pruritic or may even resemble benign skin conditions, including dermatitis, cellulitis, urticaria, and papulovesicular eruptions, causing them to go unrecognized.

Nevertheless, cutaneous metastasis of a visceral malignancy generally is observed late in the disease course, often following the diagnosis of a primary malignancy. ¹⁴ Breast cancer is the most common internal malignancy to feature cutaneous spread, with the largest case series revealing a 23.9% rate of cutaneous metastases in females with breast carcinoma. ⁶ Because of its proximity, the chest wall is the most common location for cutaneous lesions of metastatic breast cancer.

Malignant cells from a primary breast tumor may spread to the skin via lymphatic, hematogenous, or contiguous tissue dissemination, as well as iatrogenically through direct implantation during surgical procedures.³ The mechanism of neoplasm spread may likewise influence the clinical appearance of the resulting lesions. The localized lymphedema with a peau d'orange appearance of inflammatory metastatic breast carcinoma or the erythematous plaques of carcinoma erysipeloides are caused by embolized tumor cells obstructing dermal lymphatic vessels.^{3,11} On the other hand, the indurated erythematous plaques of carcinoma en cuirasse are caused by diffuse cutaneous and subcutaneous infiltration of tumor cells that also may be associated with marked reduction in breast volume.³

A primary breast cancer is classically diagnosed with a combination of clinical breast examination, radiologic imaging (ultrasound, mammogram, breast magnetic resonance imaging, or computed tomography), and fineneedle aspiration or lesional biopsy with histopathology. Given that in 20% of metastasized breast cancers the primary tumor may not be identified, a negative breast examination and imaging do not rule out breast cancer, especially if cutaneous biopsy reveals a primary malignancy. Histopathology and immunohistochemistry can thereby confirm the presence of metastatic cutaneous lesions and help characterize the breast cancer type involved, with adenocarcinomas being most commonly implicated. Although both ductal and lobular adenocarcinomas stain positive for cytokeratin 7, estrogen

receptor, progesterone receptor, gross cystic disease fluid protein 15, carcinoembryonic antigen, and mammaglobin, only the former shows positivity for e-cadherin markers.³ Conversely, inflammatory carcinoma stains positive for CD31 and podoplanin, telangiectatic carcinoma stains positive for CD31, and mammary Paget disease stains positive for cytokeratin 7 and mucin 1, cell surface associated.³ Apart from cutaneous biopsy, fine-needle aspiration cytology can likewise provide a simple and rapid method of diagnosis with high sensitivity and specificity.¹⁴

Conclusion

Although cutaneous metastasis as the presenting sign of a breast malignancy is rare, a high index of suspicion should be exercised when encountering rapid-onset, out-of-place nodules or plaques in female patients, particularly nodules or plaques presenting on the chest.

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