

Diffuse Cutaneous Breast Cancer Metastases Resembling Subcutaneous Nodules With No Surface Changes

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PRACTICE POINTS

- Although breast cancer has the highest rate of cutaneous metastasis among internal malignancies, cutaneous metastases occur in only a small minority of breast cancer patients.
- Cutaneous metastases from breast cancer typically do not carry as poor a prognosis as those in other internal malignancies.
- The clinical presentation of cutaneous metastases from breast cancer can be varied. In our patient, the metastases were subtle and resembled subcutaneous nodules lacking surface changes, thus making them best detectable by palpation.
- While oncologists can use the response of cutaneous metastases to treatment as an indicator of systemic response, the cutaneous response may be poorer due to the skin's relatively weaker blood supply.

Cutaneous metastases typically occur in only a small minority of breast cancer patients. Clinical appearance can vary, but lesions often present as isolated dermal nodules with superficial discoloration or a change in texture on the chest ipsilateral to the primary breast malignancy. We report the case of a woman with metastatic adenocarcinoma of the breast presenting with diffuse cutaneous nodules with no surface changes. The nodules were almost undetectable clinically and had minimal elevation, making them difficult to detect, especially without palpation. A punch biopsy showed positive cytokeratin immunostaining consistent with the markers for the primary breast cancer. A review of the literature on cutaneous metastases from breast adenocarcinomas also is provided.

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Cutaneous metastases from solid tumors in general occur at a rate of about 1% per primary tumor.¹ In breast cancer, cutaneous metastases occur at a rate of about 2.5% per primary tumor. Because of the high incidence of breast cancers relative to other internal malignancies, breast cancer accounts for almost 33% of all cutaneous metastases.² Infiltrating ductal carcinoma accounts for almost 70% of cutaneous metastases from breast cancers, whereas lobular carcinoma accounts for about 15%.

Cutaneous metastases may be the first presenting sign of primary malignancy. In one retrospective study, 6% of breast carcinomas (N=992) initially presented with only skin manifestations.³ Clinical appearance can vary, but cutaneous metastases from breast adenocarcinomas often present as isolated dermal nodules with superficial discoloration or changes in texture. The most common location of cutaneous metastases is on the chest ipsilateral to the primary breast malignancy.⁴ We present a case of metastatic adenocarcinoma of the breast presenting with diffuse cutaneous nodules with no surface changes.

Case Report

A 64-year-old woman who was otherwise in good health presented to her primary care physician for evaluation of recent-onset fatigue. Laboratory testing revealed that she was mildly anemic with mild thrombocytopenia and lymphocytosis. She was referred to a hematologist, who ordered flow cytometry and cytogenetic testing. Blood abnormalities were not considered severe enough to warrant a bone marrow biopsy, and she was monitored clinically for the next 2 years.

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Two years after the initial presentation, the primary care physician performed a breast examination that was unremarkable, but enlarged axillary lymph nodes up to 15 mm were discovered in the right breast during routine breast ultrasonography. Additionally, she noted that she had experienced unintentional weight loss of 10 lb over the past year. The hematologist suspected a low-grade lymphoma and performed a bone marrow biopsy. The immunohistochemistry of the bone marrow specimen was consistent with an estrogen receptor-positive, progesterone receptor-negative, human epidermal growth factor receptor 2-negative invasive lobular breast carcinoma, which was then confirmed in the right breast on magnetic resonance imaging. The patient denied any history of prior radiation treatment, but she disclosed a family history of breast cancer in her cousin.

Several weeks after the bone marrow biopsy, an oncologist found that the patient also had an abdominal mass and bone metastases of the primary breast cancer. Colonoscopy confirmed metastases to the colon that subsequently led to obstruction and ultimately required a right hemicolectomy. The patient's oncologist started her on anastrozole, an aromatase inhibitor (AI), for treatment of the metastatic breast cancer and zoledronic acid, a bisphosphonate, along with calcium and vitamin D for the bone involvement.

Shortly after, during a routine annual skin examination, the patient's dermatologist (H.T.N.) discovered 3 soft, fixed, subcutaneous-appearing nodules—one on the right chest that was 15 mm in diameter, one on the left mid back that was 7 mm, and one on the left upper anterior thigh that was 10 mm. They were discrete with well-defined borders but had only minimal elevation,

making them difficult to detect clinically, especially without palpation. The nodules were not visibly apparent because they were flesh-colored with no surface discoloration or texture changes. The patient remembered that the lesions had appeared gradually several months prior, predating the breast cancer diagnosis, and were not associated with pain, itching, or burning, so she was not alarmed by their appearance and never sought medical attention. The dermatologist (H.T.N.) recommended a biopsy at the time of the skin examination, but the patient declined.

One year after the appearance of the first skin lesions, 14 more nodules (Figure 1) progressively erupted on the ipsilateral and contralateral chest (Figure 2A), axillae, arms, shoulders, back (Figure 2B), and thighs (Figure 2C). At this point, the dermatologists performed a punch biopsy on a lesion on the back to confirm the suspicion of cutaneous metastasis of the primary breast cancer. The biopsy showed interstitial dermal proliferation of atypical cells between collagen bundles and stained strongly positive for cytokeratin 7, an epithelial protein common in breast adenocarcinoma (Figure 3). Further immunohistochemical staining returned metastatic estrogen receptor-positive, progesterone receptor-negative, human epidermal growth factor receptor 2-negative invasive lobular breast carcinoma. Therefore, the markers for the cutaneous metastases were consistent with the markers for the original breast cancer.

After 1 year of treatment with anastrozole, the patient's internal metastases had not changed considerably, but the cutaneous metastases continued to grow—the lesion on the left thigh doubled from 10 to 20 mm in diameter, and new nodules developed on the chest, back, arms, and legs. One year and a half after the initial lesions

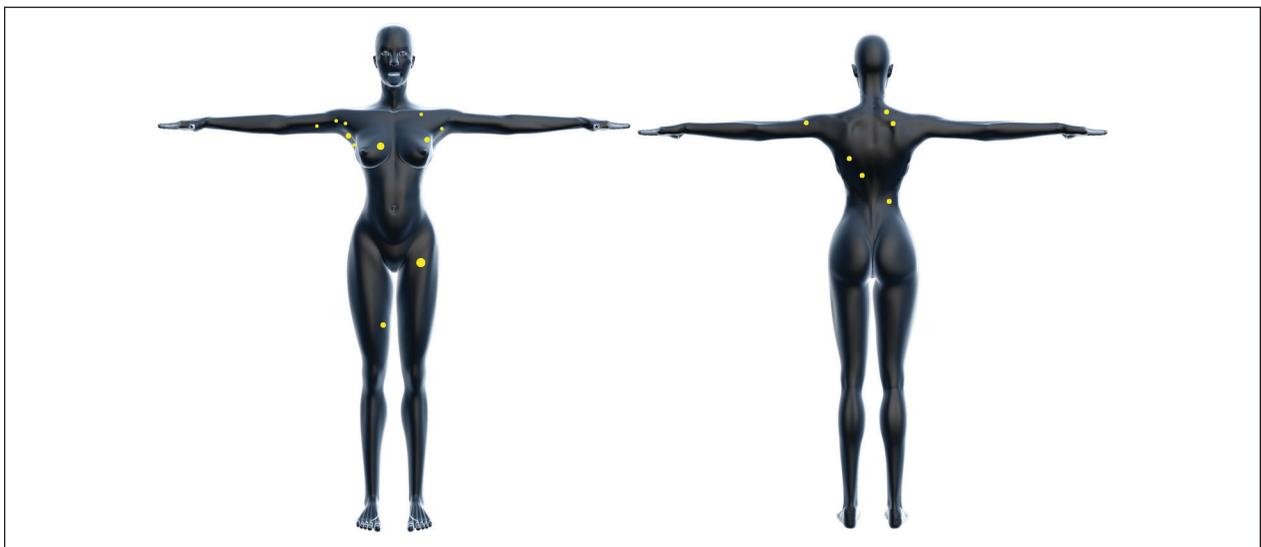


FIGURE 1. Map of all cutaneous metastases (indicated in yellow) present 1 year after the appearance of the initial metastases. Lesions were present on the ipsilateral chest, contralateral chest, axillae, arms, shoulders, back, and thighs.



FIGURE 2. Cutaneous metastasis of a primary adenocarcinoma of the breast. Lesions sites included the right chest (A), back/shoulder (B), and left thigh (C)(arrows).

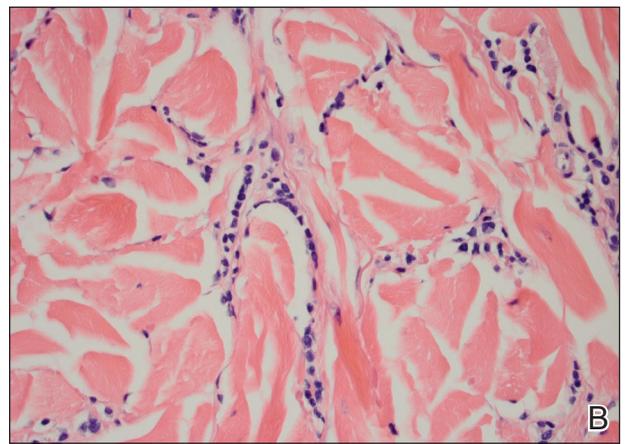
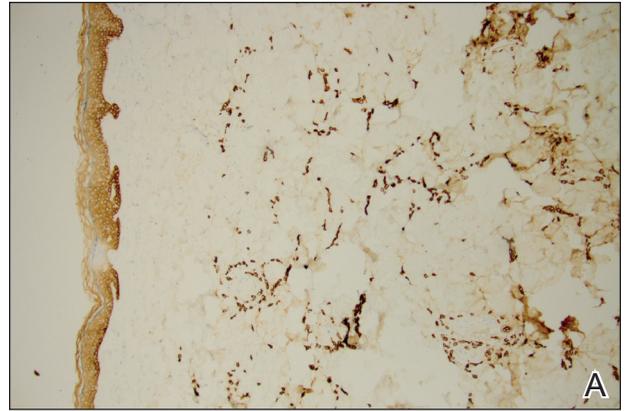


FIGURE 3. A biopsy from a lesion on the back showed interstitial dermal proliferation of atypical cells between collagen bundles (A)(H&E, original magnification $\times 400$) and strong positive staining with cytokeratin 7 (B)(original magnification $\times 100$).

were documented, several nodules had disappeared and several new ones appeared. The remaining nodules remained relatively constant in size.

After stopping anastrozole, the patient was enrolled in a research trial using bortezomib, a chemotherapeutic agent typically used for multiple myeloma, as well as fulvestrant, an estrogen receptor antagonist; however, because of continued progression of the metastatic cancer, the patient was removed from the trial and switched to the established regimen of everolimus, a chemotherapeutic agent, and exemestane, another AI. Everolimus eventually was stopped, but the patient continued on exemestane as monotherapy. In addition to development of pleural disease, the cutaneous metastases continued to progress. The patient did not receive any local treatment for her cutaneous metastases.

Comment

Typically, cutaneous metastases of breast cancer manifests as a 1- to 3-cm, asymptomatic, firm, pink to red-brown nodule on the chest ipsilateral to the primary tumor.

There may be more than 1 nodule, and ulceration may be present.^{5,6} In addition to nodular metastases, which make up 47% of cases (N=305), other common presentations include alopecia neoplastica (12%), telangiectatic carcinoma (8%), melanomalike lesions (6%), carcinoma erysipeloides (6%), subungual lesions (5%), carcinoma en cuirasse (4%), and zosteriform metastases (4%).⁶

Although nodular metastases are the most common type of cutaneous breast cancer metastases, our case is unique in that the patient had soft nodules dispersed to both arms and legs, and the nodules had no surface changes. Although cutaneous metastases can present as flesh-colored nodules,⁷ they typically have an erythematous base, a slight change in coloration, or induration. Additionally, cutaneous metastases most often are few in number and appear in close proximity to the primary breast adenocarcinoma.⁸ Without the detection of a slight soft elevation on palpation, our patient's nodules were practically indistinguishable from the normal skin.

Among common internal cancers, breast cancer is the most likely to metastasize to the skin at a rate of 2.42% per primary tumor (Table 1).¹ Cutaneous metastases from lobular carcinomas are much rarer than those from ductal carcinomas.⁴ The metastases also are most often located locally on the chest ipsilateral to the primary malignancy. Distant metastases are relatively rare. In a review of 212 cases of breast cancer patients with skin metastases, only 9 had involvement of the legs and only 4 had involvement of the contralateral chest.⁴ Our patient had involvement of the ipsilateral chest, both arms and legs, and the contralateral chest.

The 5-year relative survival rate for breast cancer patients varies based on the stage at diagnosis (99% in patients with localized cancer, 84% with regional lymph node involvement, 24% with distant metastases of any kind).⁹ In a study of 141 patients with cutaneous metastases in a Taiwanese medical center, Hu et al¹⁰ found that patients with breast cancer with only cutaneous metastases had a 5-year absolute survival rate of 38%. In the same study, patients with non-breast cancer metastasis including cutaneous metastasis had a 5-year survival rate of 15%.¹⁰ This data is summarized in Table 2.

Breast cancer metastasis to soft tissue (eg, the skin) typically indicates a better prognosis than breast cancer metastasis to a visceral organ or bone. In a study of 439 patients with metastatic relapse after surgical resection of a primary breast cancer, those who had soft tissue metastases had a median survival period of 39 months, whereas those who had visceral or bone metastases had a median survival period of 13 and 28 months, respectively.¹¹ Furthermore, cutaneous metastases from breast cancers do not necessarily indicate as poor a prognosis as skin metastases from other internal malignancies. Cutaneous metastases from other internal malignancies carry a relative risk of mortality of 4.3 compared to cutaneous metastases from breast cancer.¹⁰

TABLE 1. Cutaneous Metastasis Rates Of Primary Malignancies

Primary Tumor Site	Rate of Metastasis, %
Breast	2.42
Lung	1.78
Oral Mucosa	1.75
Colon/rectum	0.81
Stomach	0.80
Esophagus	0.74
Uterus/Cervix	0.31
Liver	0.30
Bladder/Ureter	0.22
Thyroid	0.20
Nasopharynx	0.16
Prostate	0.00
Overall	1.02

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TABLE 2. Five-year Breast Cancer Survival Rates By Cancer Type

Type of Breast Cancer	Five-year Survival Rate, %
Localized	99 ^{9,a}
Primary tumor with regional lymph node involvement	84 ^{9,a}
Primary tumor with skin metastases only	38 ¹⁰
Primary tumor with distant metastases of any kind	24 ^{9,a}
Primary tumor with cutaneous and visceral metastases	24 ¹⁰
Non-breast cancers with metastasis including the skin	15 ¹⁰

^aData is based on relative survival (ie, rates were compared to those of age- and sex-matched individuals without breast cancer).

Treatment of cutaneous metastases may be medically or cosmetically indicated. Standard treatments for cutaneous metastases from the breast include surgical excision, external beam radiotherapy, and systemic chemotherapy.⁶ While oncologists can use the response of cutaneous metastases to treatment as an indicator of systemic response to hormone therapy or chemotherapy,¹²

the response may be poorer due to the skin's relatively weaker blood supply.¹³

Our patient was first prescribed anastrozole, an AI. For metastatic hormone receptor–positive breast cancer, AIs are a first-line therapy in postmenopausal women. In one meta-analysis, AIs showed greater improvement of survival rates relative to other endocrine therapies such as tamoxifen, an estrogen receptor antagonist (hazard ratio of 0.87).¹⁴ After stopping anastrozole, the patient was prescribed fulvestrant, another estrogen receptor antagonist, along with a trial drug. In a randomized, double-blind, placebo-controlled trial, fulvestrant was found to be an effective second-line treatment after anastrozole for hormone receptor–positive breast cancer in postmenopausal women.¹⁵ Our patient was then started on everolimus, a chemotherapeutic agent, and exemestane, another AI. After first-line treatment with anastrozole, this regimen also has been found to be an effective second-line treatment with improved progression-free survival.¹⁶ For the bone metastases, our patient was treated with zoledronic acid, a bisphosphonate. In a meta-analysis, bisphosphonates were found to reduce skeletal-related complications by a median of 28% in breast cancer patients with bone metastases.¹⁷

Some promising new local treatments for cutaneous breast metastases include topical imiquimod and electrochemotherapy. In a small study of 10 patients whose malignancies were refractory to radiotherapy, imiquimod achieved a partial response in 20% (2/10) of patients.¹⁸ In another study, 12 patients received electrochemotherapy involving electroporation (applying an electrical field to increase cell membrane permeability and thus increase drug uptake) followed by local administration of bleomycin, an antineoplastic agent. Seventy-five percent (9/12) of the patients received a complete response with disappearance of the metastases.¹⁹

This case report provides a rare presentation of diffuse nodular cutaneous metastases of breast adenocarcinoma with no surface changes. The subtle clinical findings in our patient demonstrate the spectrum of clinical manifestations for cutaneous metastases. Our case also serves to highlight the need for close inspection of the skin, including palpation in patients with a history of internal malignancy.

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