

UC Davis

Dermatology Online Journal

Title

Noninflammatory presentation of cutaneous breast cancer: a retrospective case series at a single academic institution with review of the literature

Permalink

<https://escholarship.org/uc/item/5cc5c8xw>

Journal

Dermatology Online Journal, 28(4)

Authors

Peach, Aaron
Blaise, Brittany
Parker, Jordan
et al.

Publication Date

2022

DOI

10.5070/D328458515

Copyright Information

Copyright 2022 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

Noninflammatory presentation of cutaneous breast cancer: a retrospective case series at a single academic institution with review of the literature

Aaron Peach MD, Brittany Blaise MD, Jordan Parker MD, Rebecca Larson MD

Affiliations: Division of Dermatology, School of Medicine, Southern Illinois University, Springfield, Illinois, USA

Corresponding Author: Aaron Peach, Southern Illinois University School of Medicine, 2301 Cherry Hills Drive, Apartment 3, Springfield, IL 62704, Tel: 618-558-6510, Email: aaron.p.peach@gmail.com; Rebecca Larson, Division of Dermatology, Southern Illinois University School of Medicine, 751 North Rutledge Street, PO Box 19644, Springfield, IL 62794, Tel: 217-545-8000, Email: rlarson@siumed.edu

Abstract

Breast cancer with skin involvement is an uncommon clinical presentation of this malignancy. Breast cancer overall has a relatively high mortality rate and wide variety of presentations, making skin involvement by breast cancer a necessary consideration in the differential diagnosis for many types of breast lesions. A retrospective review of our own small academic dermatology outpatient clinic, between August 2006 and January 2020, found four cases of noninflammatory breast cancer with skin involvement diagnosed through biopsy by our dermatologists. This review was approved by the local Institutional Review Board. Of the four patients identified, three were female and one was male. One patient had prior history of invasive ductal carcinoma in remission before recurrence was diagnosed. Another patient had a history of melanoma in situ before diagnosis with breast cancer. Patients were treated with various combinations of surgery, radiation, and hormone therapy. These four cases are presented here in detail, which emphasize the role of the dermatologist in recognizing various cutaneous manifestations of noninflammatory breast cancer in order to make a timely diagnosis.

Keywords: breast cancer, cancer, case report, noninflammatory, series

Introduction

Breast cancer with skin involvement is an uncommon presentation of the second most common type of cancer in women [1]. Cutaneous

involvement can result from direct invasion of the tumor, metastasis through lymphatics or blood vessels, or iatrogenic direct seeding [2]. For the purpose of Classification of Malignant Tumors (TNM) staging, breast cancer with skin involvement via direct invasion is classified as either inflammatory breast cancer or breast cancer with noninflammatory skin involvement [3].

Per the Centers for Disease Control and Prevention, breast cancer is diagnosed in 250,000 women and 2,300 men annually in the U.S. and rates have been trending down from 1999-2017 [1,4]. Despite some decline, breast cancer remains the second most common cause of cancer death among women, and the most common cause of cancer death in Hispanic women in the U.S. [1]. Mortality rates for breast cancer of Black women are also disproportionately greater than that of White women [1]. Locally advanced breast cancer represents 5-10% of new breast cancer diagnoses in the U.S. and 60-70% of new diagnoses worldwide. Of new breast cancer cases, 1-2% of tumors have skin involvement limited to histologic examination without macroscopic changes [5,6]. This small subset of cases are not typically considered a part of "classic" breast cancer with skin involvement. Although cutaneous involvement from breast cancer is relatively uncommon, breast cancer is the most common solid organ tumor producing cutaneous manifestations, accounting for 33% of all cutaneous metastases [7].

We performed a retrospective case series review of patients identified in the outpatient Southern Illinois University dermatologic clinic with breast cancer

with noninflammatory skin involvement. Included cases were detected through cutaneous breast examination and diagnosed with subsequent skin biopsy completed by a dermatologist. This review was approved by the local Institutional Review Board. Our retrospective case series found four cases of noninflammatory breast cancer diagnosed between August 2006 and January 2020, which are presented and discussed here.

Case Synopsis

Case 1

A 76-year-old woman with history of stage I triple-negative invasive ductal carcinoma of the left breast treated with lumpectomy, chemotherapy, and radiation 24 years prior, presented to our clinic with thickening of her lumpectomy scar a few months prior. She had normal yearly mammograms before this visit. On examination, she had an indurated and retracted pink plaque with overlying scale at the site of her scar. Besides recurrent breast cancer, other diagnoses to consider would be hypertrophic scar (less likely given the amount of time from lumpectomy to presentation and the fact that the lesion was still growing), dermatofibrosarcoma protuberans (less likely due to patient's sex and older age), and squamous cell carcinoma. The site was biopsied with a 4mm punch (**Figure 1**). Pathology showed an intradermal infiltrative neoplasm with



Figure 1. Case 1 clinical image. Indurated and retracted pink plaque on the left inframammary breast at site of lumpectomy scar.

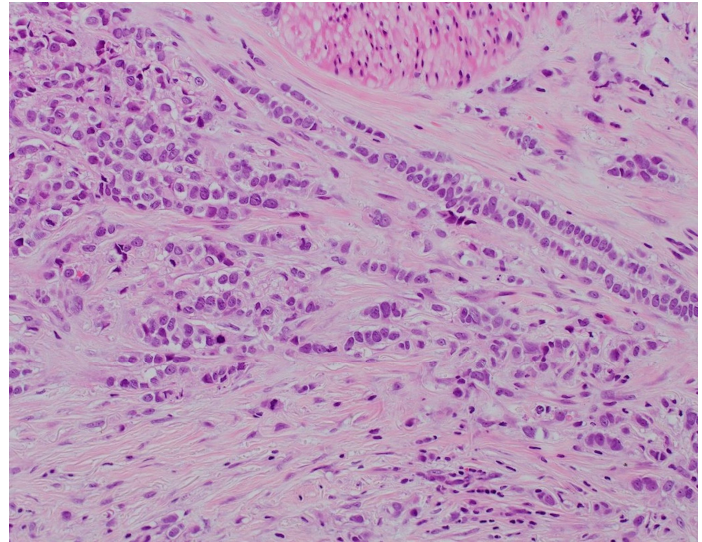


Figure 2. Case 1 biopsy specimen. Hematoxylin and eosin stain demonstrating intradermal proliferation of numerous small epithelial aggregates and cords. Dense collagen is laid down between the tumor cells, 200x.

cords of epithelial cells (**Figure 2**) which stained positive for cytokeratin 7, mammaglobin, estrogen receptor, and progesterone receptor. She was diagnosed with invasive ductal carcinoma, stage IIb and treated with mastectomy. There were multipositive margins and she was sent for proton therapy. Currently, she is doing well on anastrozole daily.

Case 2

An 83-year-old woman with history of melanoma in situ, reported a one-year history of a firm bump beneath her left breast. She had normal annual mammograms prior to this visit. On examination, there was a 3x4cm fixed, firm subcutaneous nodule with a 2cm reddish firm plaque centrally on the inframammary fold. Besides breast cancer, other diagnoses considered included dermatofibroma (less likely due to location and lack of trauma to area), dermatofibrosarcoma protuberans (less likely given patient's older age), and infiltrative basal cell carcinoma. The nodule was biopsied with a 6mm punch (**Figure 3**). Pathology showed an intradermal proliferation of small epithelial aggregates and cords with frequent central lumen formation (**Figure 4**) that stained positive for cytokeratin 7, estrogen receptor, and progesterone receptor. She was diagnosed with invasive ductal carcinoma, stage IIb,



Figure 3. Case 2 clinical image. Fixed, firm subcutaneous nodule on the left inframammary fold.

and treated with radical mastectomy and radiation. She declined anti-estrogen therapy.

Case 3

An 89-year-old man with a history of basal cell carcinoma and lentigo maligna, presented to the clinic with a left breast nodule of six months' duration. On examination, there was a 4×4.5cm reddish, non-tender, nodule beneath the left areolar surface. In addition to breast cancer we considered nodular basal cell carcinoma, squamous cell carcinoma, and dermatofibrosarcoma protuberans (less likely due to patient's sex and older age). Shave biopsy was performed and pathology showed proliferation of atypical basaloid cells arranged in irregular nests with peripheral palisading. He was diagnosed with nodular basal cell carcinoma and referred to the general surgery department for excision. Excision pathology found invasive ductal carcinoma with lymphovascular invasion that stained positive for estrogen receptor and progesterone receptor. He was diagnosed with invasive ductal carcinoma, stage IIa. The patient was treated with tamoxifen but declined radiation therapy.

Case 4

A 67-year-old woman with history of basal cell carcinoma reported a 3-month history of a growing nodule on her right breast. She had a normal mammogram one year prior. On exam, there was a 1.4×1.2cm fixed, firm, pink nodule on the outer quadrant of the areola. Breast cancer, dermatofibrosarcoma protuberans, and nodular

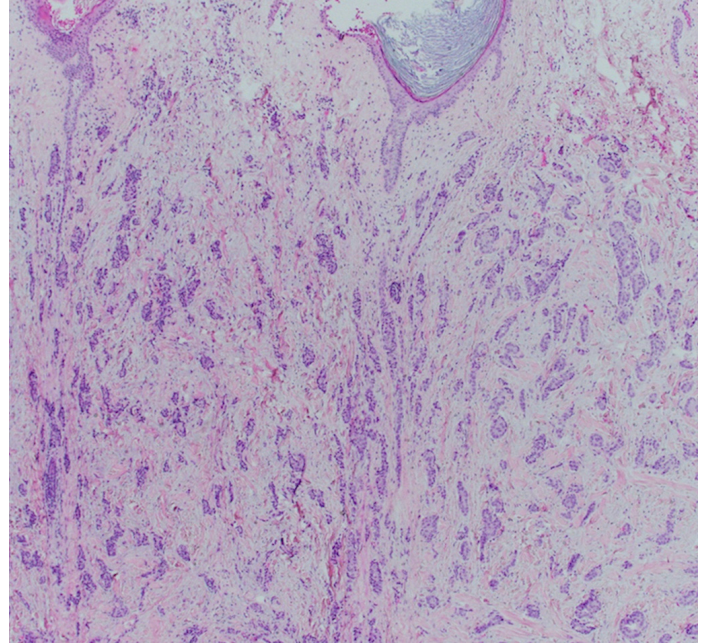


Figure 4. Case 2 biopsy specimen. Hematoxylin and eosin stain demonstrating intradermal proliferation of numerous small epithelial aggregates and cords, frequently with central lumen formation. Luminal spaces are lined by 1-2 layers of cuboidal-to-low columnar cells with round to oval vesicular nuclei, 40×.

basal cell carcinoma were considered. A 6mm punch biopsy was performed, and results revealed extensive cellular infiltrate which stained positively for estrogen receptor and progesterone receptor. She underwent further testing with MRI-guided biopsy and was diagnosed with invasive ductal carcinoma. She underwent right-sided lumpectomy and sentinel lymph node biopsy, of which two of five nodes returned positive for invasive carcinoma with mixed ductal and lobular features. She was staged IIa and is currently undergoing adjuvant radiation.

Case Discussion

Table 1 shows a summary of the clinical characteristics of the presented patients. Previous studies have demonstrated the broad spectrum of presentation within the subset of breast cancer with noninflammatory skin involvement [2,5,6,8-10]. Noninflammatory skin involvement has been described as nodular, telangiectatic, ulcerative, zosteriform, pigmented, or purpuric, with nodular being the most common morphology documented [2,11]. Cutaneous lesions are commonly discrete,

Table 1. Patient demographics and disease characteristics.

Patient	Age	Sex	Morphology	History of breast cancer	History of melanoma in situ	Immunohistochemical stains	Diagnosis	TNM staging	Treatment
1	76	F	Indurated and retracted pink, scaly plaque	+	-	(+)ER, PR, CK7, mammaglobin	IDC	IIb	Radiation and anastrozole
2	83	F	Firm nodule with central red plaque	-	+	(+)ER, PR, CK7	IDC	IIb	Radical mastectomy and radiation
3	89	M	Red nodule	-	+	(+)ER, PR	IDC	IIa	Tamoxifen
4	67	F	Pink nodule	-	-	(+)ER, PR	IDC	IIa	Lumpectomy, sentinel lymph node biopsy, radiation

F, Female; M, Male; +, present; -, absent; ER, estrogen receptor; PR, progesterone receptor; CK7, cytokeratin 7; IDC, invasive ductal carcinoma.

painless, mobile nodules that present suddenly, possibly with several lesions at once [5]. Though both inflammatory and noninflammatory breast cancer can present with edema, erythema, and *peau d'orange* changes, these characteristics are more localized and painless in noninflammatory cases [6]. Our patient series, though small, is consistent with the most common morphologies of cutaneous noninflammatory breast cancer. In our cases, solitary, pink-to-red-brown, firm nodules and plaques represented direct skin invasion by breast cancer. Although these lesions are most often asymptomatic, symptoms can include pruritus, pain, stinging, and color and textural change [10]. Because the presentation of breast cancer with skin involvement is diverse, it is important to consider this in the differential diagnosis for breast lesions, especially if a patient has a history or clinical suspicion for malignancy.

Our first patient's history of breast cancer leads one to consider breast cancer as a leading diagnosis. There are a few possible explanations for the recurrence of her breast cancer. One is the well-documented, although rare, risk of iatrogenic seeding following the initial core needle biopsy prior to lumpectomy [12-14]. A study performed by Diaz et al. found that histological displacement of tumor cells occurred in 37% of core needle biopsies, but evidence of tumor displacement declined as the

interval from biopsy to surgical excision increased [15]. One retrospective study of 58 patients who underwent skin-sparing mastectomy showed that three of 11 patients diagnosed with stereotactic needle biopsy had clinical recurrence of their breast cancer at the needle entry site [12]. These studies suggest seeding of tumor cells can occur with needle biopsy but with decreased tumor cell survival rates, and this does not always lead to clinical disease.

Nonetheless, due to the risk of recurrence, some surgeons advocate for surgical resection of the needle biopsy tract at time of mastectomy [12]. For clinical scenarios in which this is not feasible, Hoorntje et al. suggest radiotherapy to be performed to these areas after surgery [16]. Others argue that the biopsy be taken with a vacuum-assisted device to reduce local recurrence rates [17].

Another explanation for our first patient's breast cancer recurrence is the spread of neoplastic cells to the skin via her initial lumpectomy. Chances of this are decreased by negative surgical margins, but recognizing that margin control is not exhaustive, there could have been residual neoplastic cells remaining at the time of her initial surgery that grew gradually with direct spread to the skin.

It is prognostically relevant to note that our first patient had a history of triple-negative breast cancer and her recurrence stained positive for estrogen

receptor and progesterone receptor. Various studies report receptor conversion rates between primary and recurrent tumors to be between 10-26.9% for estrogen receptor, 25-40% for progesterone receptor, and 3-22.4% for human epidermal growth factor receptor two [18-20]; conversion from negative to positive staining is generally a good prognostic sign [21].

Our second patient's history of melanoma in situ and third patient's history of lentigo maligna raise an interesting point about the risk of developing a second primary cancer given this history. In a study of 90,075 melanoma in situ patients, Ulanja et al. found a positive correlation between melanoma in situ and a second primary malignancy, with relative risk increasing both over time and with increasing number of melanoma in situ lesions. Interestingly, this study showed an increased risk of breast cancer only when patients had ≥ 3 melanoma in situ lesions [22]. Alternatively, a Swedish study followed 3,766 patients with melanoma in situ and reported a significant risk of developing breast cancer, particularly 1-4 years after diagnosis and in women under 60 years old [23]. Studies have shown that estrogen receptors are expressed by melanoma and breast cancer cells [23], suggesting there may be some degree of hormonal influence for both cancer types. There is also a strong familial association between germline CDKN2A mutations and risk of developing melanoma and breast cancer [24,25]. Though the risk of developing certain cancers seem to be higher among melanoma in situ patients, it is unclear how breast cancer risk is affected by a personal history of melanoma.

According to the American Joint Committee on Cancer, current TNM classification of breast cancer with direct extension to skin beyond the dermis is locally advanced with T4 grouping, regardless of tumor size and lymph node status [26]. Classification of Malignant Tumor guidelines further classify any breast cancer tumor with ulceration and/or ipsilateral satellite nodules and/or edema of the skin, which do not meet the criteria for inflammatory carcinoma as T4b [26]. Although early TNM classification staged breast cancer with direct

noninflammatory skin involvement is generally higher, recent studies suggest the feature of skin involvement itself is not prognostic but is rather an associated symptom of a locally advanced process [27]. A small, retrospective study by Tada et al. showed that although patients with skin invasion were older with larger tumor size and more invasive cancer, skin involvement had no impact on survival in node-negative invasive breast cancer [28].

Although it is suggested that locally advanced tumors make up 5-10% of breast cancer diagnoses in the U.S. [5], there is not, to our knowledge, sufficient epidemiologic data on cases diagnosed in the dermatological setting. As evidenced by our first, second, and fourth patients' recent normal mammogram findings, our anecdotal data shows that negative annual mammograms should not rule out the possibility of a breast cancer diagnosis. This elucidates the importance of dermatologists considering breast cancer in their differential diagnosis for a skin lesion, especially on the breast.

Conclusions are limited by the small number of patients reviewed from a single clinic. More robust series describing characteristics in a larger number of cutaneous breast cancer patients will likely provide additional insight into how this entity can present and most effectively be detected.

Conclusion

Rarely, skin involvement may be the first sign of breast malignancy. This report highlights the dermatologist's vital role in diagnosing breast cancer to reduce morbidity and mortality by performing a thorough cutaneous breast examination. It would be useful to further study the epidemiology, prognostic implications, and treatment outcomes of breast cancer with noninflammatory skin involvement to better understand how to care for patients with this diagnosis.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

- Centers for Disease Control and Prevention. Basic information about breast cancer. 2020. https://www.cdc.gov/cancer/breast/basic_info/index.htm. Accessed on November 7, 2020.
- Cho E, Kim MH, Cha SH, et al. Breast cancer cutaneous metastasis at core needle biopsy site. *Ann Dermatol*. 2010;22:238-40. [PMID: 20548926].
- Güth U, Huang DJ, Schötzau A, et al. Breast cancer with non-inflammatory skin involvement: current data on an underreported entity and its problematic classification. *Breast J*. 2010;19:59-64. [PMID: 20015652].
- U.S. Cancer Statistics Working Group. U.S. cancer statistics data visualizations tool, based on 2019 submission data (1999-2017): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. 2019. www.cdc.gov/cancer/dataviz. Accessed on November 7, 2020.
- Silverman D, Ruth K, Sigurdson ER, et al. Skin involvement and breast cancer: are T4b lesions of all sizes created equal? *J Am Coll Surg*. 2014;219:534-44. [PMID: 25026875].
- Güth U, Moch H, Herberich L, Holzgreve W. Noninflammatory breast carcinoma with skin involvement. *Cancer*. 2004;100:470-8. [PMID: 14745862].
- Mayer JE, Maurer MA, Nguyen HT. Diffuse cutaneous breast cancer metastases resembling subcutaneous nodules with no surface changes. *Cutis*. 2018;101:219-23. [PMID: 29718016].
- Oide T, Mitsuishi T. Pigmented macule - a skin manifestation of invasive breast cancer. *N Engl J Med*. 2017;377:1777. [PMID: 29091571].
- Lee HJ, Kim JM, Kim GW, et al. A unique cutaneous presentation of breast cancer: a red apple stuck in the breast. *Ann Dermatol*. 2016;28:499-501. [PMID: 27489436].
- Araújo E, Barbosa M, Costa R, Sousa B, Costa V. A first sign not to be missed: cutaneous metastasis from breast cancer. *Eur J Case Rep Intern Med*. 2020;7:001356. [PMID: 32015970].
- Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J Am Acad Dermatol*. 1993;29:228-36. [PMID: 8335743].
- Uriburu JL, Vuoto HD, Cogorno L, et al. Local recurrence of breast cancer after skin-sparing mastectomy following core needle biopsy: case reports and review of the literature. *Breast J*. 2006;12:194-8. [PMID: 16684314].
- Stolier A, Skinner J, Levine EA. A prospective study of seeding of the skin after core biopsy of the breast. *Am J Surg*. 2000;180:104-7. [PMID: 11044522].
- Chao C, Torosian MH, Boraas MC, et al. Local recurrence of breast cancer in the stereotactic core needle biopsy site: case reports and review of the literature. *Breast J*. 2001;7:124-7. [PMID: 11328321].
- Diaz LK, Wiley EL, Venta LA. Are malignant cells displaced by large-gauge needle core biopsy of the breast? *AJR Am J Roentgenol*. 1999;173:1303-13. [PMID: 10541110].
- Hoorntje LE, Schipper ME, Kaya A, et al. Tumour cell displacement after 14G breast biopsy. *Eur J Surg Oncol*. 2004;30:520-5. [PMID: 15135480].
- Loughran CF, Keeling CR. Seeding of tumour cells following breast biopsy: a literature review. *Br J Radiol*. 2011;84:869-74. [PMID: 21933978].
- Nguyen TH, Nguyen VH, Nguyen TL, Qiuyin C, Phung TH. Evaluations of biomarker status changes between primary and recurrent tumor tissue samples in breast cancer patients. *Biomed Res Int*. 2019;2019:7391237. [PMID: 31583246].
- Thompson AM, Jordan LB, Quinlan P, et al. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence In Tissues Study (BRITS). *Breast Cancer Res*. 2010;12:R92. [PMID: 21059212].
- Amir E, Miller N, Geddie W, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. *J Clin Oncol*. 2012;30:587-92. [PMID: 22124102].
- Shen J, Xu L, Shi J, et al. Prognostic value and influence of receptor conversion on treatment regimen in metastatic breast cancer at the first time of recurrence. *Oncol Res Treat*. 2020;43:620-7. [PMID: 32966998].
- Ulanja MB, Beutler BD, Antwi-Amoabeng D, et al. Second primary malignancies in patients with melanoma *in situ*: insights from the surveillance, epidemiology, and end results program. *Cancer Epidemiol*. 2021;72:101932. [PMID: 33773145].
- Wassberg C, Thörn M, Yuen J, Hakulinen T, Ringborg U. Cancer risk in patients with earlier diagnosis of cutaneous melanoma *in situ*. *Int J Cancer*. 1999;83:314-7. [PMID: 10495422].
- Potrony M, Puig-Butillé JA, Aguilera P, et al. Increased prevalence of lung, breast, and pancreatic cancers in addition to melanoma risk in families bearing the cyclin-dependent kinase inhibitor 2A mutation: implications for genetic counseling. *J Am Acad Dermatol*. 2014;71:888-95. [PMID: 25064638].
- Potrony M, Badenas C, Aguilera P, et al. Update in genetic susceptibility in melanoma. *Ann Transl Med*. 2015;3:210. [PMID: 26488006].
- Brierley JD, Gospodarowicz MK, Wittekind C. The TNM classification of malignant tumours. Brierley JD, Gospodarowicz MK, Wittekind C, editors. 8th ed. Wiley-Blackwell; 2017. p. 151-8.
- Güth U, Wight E, Schotzau A, et al. Breast carcinoma with noninflammatory skin involvement (T4b): time to abandon an historic relic from the TNM classification. *Cancer*. 2005;104:1862-70. [PMID: 16130140].
- Tada K, Morizono H, Iijima K, et al. Skin invasion and prognosis in node negative breast cancer: a retrospective study. *World J Surg Oncol*. 2008;6:10. [PMID: 18234087].