

Acral Cutaneous Metastasis From a Primary Breast Carcinoma Following Chemotherapy With Bevacizumab and Paclitaxel

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PRACTICE POINTS

- Cutaneous involvement of internal malignancy typically occurs late in the disease course but can occasionally be the first extranodal sign of metastatic disease.
- Acral cutaneous metastasis from internal malignancies typically is unilateral, involving only one extremity; however, this case demonstrates involvement on both the hands and feet.
- This case supports a chemotherapy-related etiology of acral cutaneous metastasis of a primary breast cancer.

Acral cutaneous metastasis from internal malignancy is rare, and the pathogenesis is not completely understood. We present the case of a 54-year-old black woman with a history of breast cancer diagnosed 2 years prior who developed multiple cutaneous metastases to acral sites involving the palmar and plantar surfaces of the hands and feet. This case represents an unusual metastatic pattern of breast carcinoma that arose after treatment with bevacizumab, an angiogenesis inhibitor that binds vascular endothelial growth factor A. We propose that bevacizumab-induced vascular changes localized to acral skin may have contributed to the metastatic pattern seen in our patient.

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Cutaneous metastasis of internal malignancy is a relatively uncommon phenomenon, with an overall incidence of 5.3% in cancer patients.¹ Cutaneous involvement typically occurs late in the course of disease but can occasionally be the first extranodal sign of metastatic disease. Breast cancer has the highest rate of cutaneous metastasis, most often involving the chest wall¹; however, cutaneous metastasis to the acral sites is exceedingly rare. The hand is the site of 0.1% of all metastatic lesions, with only 10% of these being cutaneous lesions and the remaining 90% being osseous metastases.² Herein, we report a case of multiple cutaneous metastases to acral sites involving the palmar and plantar surfaces of the hands and feet.

Case Report

A 54-year-old black woman with a history of stage IV carcinoma of the breast was admitted to the university medical center with exquisitely painful cutaneous nodules on the hands and feet of 5 weeks' duration that had started to cause difficulty with walking and daily activities. The patient reported that the breast carcinoma had initially been diagnosed in Nigeria 2 years prior, but she did not receive treatment until moving to the United States. She received a total of 4 cycles of chemotherapy with paclitaxel and bevacizumab, which was discontinued 6 weeks prior to admission due to pain in the lower extremities that was thought to be secondary to neuropathy. One

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The authors report no conflict of interest.

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week after discontinuation of chemotherapy, the patient reported increasing pain in the extremities and new-onset painful nodules on the hands and feet. Treatment with gabapentin as well as several courses of antibiotics failed to improve the condition.

She was admitted for symptomatic pain control and a dermatology consultation. Physical examination revealed multiple firm, tender, subcutaneous nodules on the volar surfaces of the soles, toes, palms, and fingertips (Figure 1). A nodule also was noted on the scalp. A punch biopsy of a nodule on the right fourth finger revealed a dermal carcinoma (Figure 2). On immunohistochemistry, the tumor stained positive for cytokeratin 5/6, cytokeratin 7, and gross cystic disease fluid protein 15. It did not demonstrate connection to the epidermis or adnexal structures. Although the tumor did not express estrogen or progesterone receptors, the findings were compatible with metastasis from the patient's primary breast carcinoma with poor differentiation. A biopsy of the primary breast carcinoma was not available for review from Nigeria.

Comment

The majority of cases reporting acral cutaneous metastasis from internal malignancies are unilateral, involving only one extremity. Several hypotheses have been provided,

including spread from localized trauma, which causes disruption of blood vessels and consequent extravasation and localization of tumor cells into the extravascular space.³ The distal extremities are particularly vulnerable to trauma, making this hypothesis plausible.

Considering the overall rarity of metastases to acral sites, it is interesting that our patient developed multiple distal nodules on both the hands and feet. The rapid onset of cutaneous nodules shortly after a course of chemotherapy led the team to consider the physiologic effects of paclitaxel and bevacizumab in the etiology of the acral cutaneous metastases. Karamouzis et al³ described a similar case of multiple cutaneous metastases with a bilateral acral distribution. This case also was associated with chemotherapy in the treatment of breast cancer. The authors proposed hand-foot syndrome, a chemotherapy-related eruption localized to acral skin, as a possible mechanism for hematogenous spread of malignant cells.³ The pathogenesis of hand-foot syndrome is not well understood, but the unique anatomy and physiology of acral skin including temperature gradients, rapidly dividing epidermal cells, absence of hair follicles and sebaceous glands, wide dermal papillae, and exposure to high pressures from carrying body weight and repetitive minor trauma may contribute to the localization of signs and



FIGURE 1. Acral cutaneous metastasis with numerous painful subcutaneous nodules on the hands and feet (A–D).

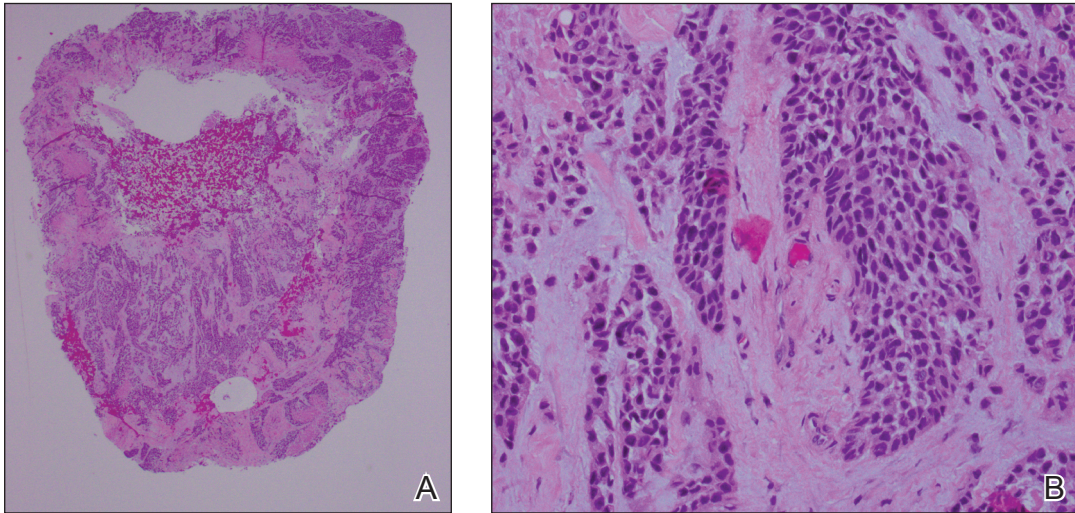


FIGURE 2. A punch biopsy of a nodule on the right fourth finger revealed a poorly differentiated metastatic carcinoma of the breast in the dermis (A and B)(H&E, original magnifications $\times 4$ and $\times 20$).

symptoms.^{3,4} Our case supports a chemotherapy-related etiology of acral cutaneous metastasis of a primary breast cancer; however, our patient did not have apparent signs or symptoms of hand-foot syndrome during the course of treatment. We propose that effects of bevacizumab on acral skin may have contributed to the development of our patient's metastatic pattern.

Bevacizumab, a monoclonal antibody to vascular endothelial growth factor A, has well-known vascular side effects. Unlike the inhibition of vascular endothelial growth factor A provided by the receptor tyrosine kinase inhibitors sorafenib and sunitinib, bevacizumab typically is not associated with hand-foot syndrome.⁵ However, several cases have been reported with chemotherapy-associated palmoplantar eruptions that resolved after withholding bevacizumab while continuing other chemotherapeutic agents, suggesting that bevacizumab-induced changes in acral skin contributed to the eruption.⁶ Specific factors that could contribute to acral metastasis in patients taking bevacizumab are endothelial dysfunction and capillary rarefaction of the acral skin, as well as hemorrhage, decreased wound healing, and changes in vascular permeability.^{5,7}

We present a rare case of acral cutaneous metastasis associated with bevacizumab, one of few reported

cases associated with a taxane chemotherapeutic agent.³ More cases need to be identified and reported to establish a causative association, if indeed existent, between acral cutaneous metastasis of breast carcinoma and the use of bevacizumab as well as other chemotherapeutic drugs.

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