Cutaneous metastases of internal malignancies are relatively rare in clinical practice, but they are an entity that should remain in a clinician’s differential diagnosis when evaluating cutaneous lesions. Cutaneous metastases rarely present as the first sign of an internal malignancy; rather, they typically serve as a poor prognostic factor of an aggressive underlying malignancy. Skin metastases most commonly arise as multiple, solid, painless nodules, localizing near the site of the primary tumor, with the pathology most commonly consistent with adenocarcinoma. Differentiating between clinicopathologic entities to determine the source of the metastatic tumor can be very challenging. Immunohistochemical (IHC) staining plays a key role in conjunction with the patient’s history and clinical presentation. Two entities that share a significant histological overlap are metastatic ductal mammary carcinoma and primary cutaneous sweat gland carcinoma. Proper diagnosis is of utmost importance to determine appropriate treatment for the patient. Here, we present a case of adenocarcinoma metastatic to the skin in a patient with no known history of primary carcinoma. This case exemplifies the need for clinicians to consider the rare entity of cutaneous metastasis when evaluating patients, as well as diagnostic challenges and the importance of IHC staining in determining the origin of the primary tumor.

CASE REPORT

A 63-year-old Caucasian female presented to clinic in November 2014. Her medical history was significant for anxiety, arthritis, diabetes, gastroesophageal reflux, and hypertension, and her dermatology history was significant for xerosis and allergies. Medications included aspirin, amlodipine, atenolol, enalapril, multivitamin, hydrochlorothiazide, metformin, pravastatin, alprazolam, ranitidine, and sertraline. Her surgical history was significant for a left breast biopsy performed several years ago and reported to be negative.

The physical examination at her initial 2014 visit was unremarkable, except for an erythematous, well-circumscribed, non-tender, freely mobile subcutaneous nodule measuring 1.2x1.5cm on the left lateral superior chest (Fig. 1). She reported no change in the lesion at her annual examination in 2015, 2016, or 2017. The patient was referred for excision of the lesion at her 2017 appointment due to its unusual clinical appearance.

An in-office excision was performed in January 2018. The pathology result reported an intradermal malignant epithelioid neoplasm arranged in nests and cords with a sclerotic fibrous...
stroma (Fig. 2), consistent with adenocarcinoma. The deep margins were involved, and perineural invasion was noted. The differential diagnosis was consistent with metastatic ductal breast carcinoma versus primary eccrine ductal adenocarcinoma. The pathology was reactive for pankeratin (Fig. 3), CEA (Fig. 4), EMA (Fig. 5), and Ber-EP4 (Fig. 6), Ki-67 index of 20 percent (Fig. 7). CK 5/6, p40 and podoplanin were negative. Additional immunostains revealed 100 percent reactivity of tumor cells to GATA3 (Fig. 8) and mammaglobin, which are estrogen receptor proteins. A p63 stain was negative. The staining pattern was consistent with metastatic adenocarcinoma of the breast. A conservative re-excision with radiological evaluation was recommended by the dermatopathologist.

The patient underwent a PET scan, which did not show evidence of a primary tumor or remote appearing metastatic disease. Lab work was unremarkable except a mildly elevated alanine aminotransferase at 34 IU/L (normal 0-32 IU/L). An MRI of the area showed a small cyst behind the nipple. A biopsy of the cyst showed fibrocystic change and was negative for in situ or invasive malignancy. The patient underwent re-excision of the original adenocarcinoma of the left lateral superior chest, which showed no evidence of residual malignancy.

**DISCUSSION**

A study of 4,020 patients with metastatic disease, noted cutaneous metastases in 10.4 percent of patients. Melanoma was the most common malignancy overall to present with cutaneous metastasis in both men and women. It is estimated that up to 45 percent of melanoma patients will develop cutaneous metastasis, which represents a significant percentage of patients with cutaneous metastasis.

Reingold examined 36 patients on autopsy and found the most common location of cutaneous metastasis to be the trunk, specifically the anterior chest, regardless of malignancy type. The results of this study were supported by additional reports, citing the trunk, head and neck as the most commonly affected locations. It is thought that cutaneous metastasis can occur either in contiguous sites of the primary tumor or in secondary locations due to extension of the tumor from the affected lymph node basin. Most cutaneous metastases are thought to arise from lymphatic spread. A rare exception to this observation is renal cell carcinoma, which, due to its vascular nature, has the propensity to metastasize hematogenously.

On gross examination, the tumors typically present as non-specific, 1-3 cm, solid, firm, non-painful nodules elevated above the skin surface with an intact epidermis. They typically arise in a cluster of nodules, as opposed to a single lesion, and do not have the classic indurated leathery appearance associated with cutaneous lesions of breast carcinomas. The color of the lesion has not been reported to provide much diagnostic value; melanoma metastases are pigmented in 36 percent of cases. Three out of four patients with renal cell carcinoma present with erythematous or purple lesions mimicking hemangiomas, which is consistent with the vascular nature of renal cell carcinoma.

Adenocarcinomas are the most common histologic finding of cutaneous metastatic lesions. In a report of 330 patients with internal malignancies presenting with cutaneous metastasis, 272 showed adenocarcinoma differentiation. The most common primary tumors associated with these findings are breast, lung, colorectal, and ovarian. In terms of breast carcinomas specifically, a report found 203 out of 206 carcinomas to be adenocarcinoma and cited ductal adenocarcinoma as the most common histological subtype. IHC analysis is a valuable tool used to differentiate between primary cutaneous lesions and cutaneous metastases from internal malignancies.

Breast cancer is the most commonly diagnosed cancer in women and the second leading cause of cancer death in women. Breast carcinoma accounts for up to 73 percent of cutaneous metastatic carcinomas and about 25 percent of patients with breast cancer will develop cutaneous metastasis. Cutaneous metastasis from breast carcinoma typically presents as multiple lesions in a patient with a history of breast carcinoma. The most common location for cutaneous metastasis of breast carcinoma is the chest, but extramammary locations in order of decreasing prevalence are the lungs, bones, liver, adrenal, brain, skin, and kidneys. Cutaneous metastasis from breast carcinoma can present as a variety of lesions, including an asymptomatic plaque on the scalp with associated alopecia, fibrotic changes to the skin or a hard, leathery plaque. It may also present with a nodular appearance, with about 10 percent revealing ulceration. Approximately 10 percent of breast cancer metastases may be associated with inflammatory lesions, giving the appearance of cellulitis due to erythema and edema in the area. Inflammation is not unique to breast carcinoma, as other cancers, such as pancreas, rectum, lung, and ovary, have also been shown to appear as inflammatory.

Treatment of metastatic breast cancer involves a multidisciplinary approach, requiring surgical excision, intraläsional chemotherapy, and radiotherapy depending on the extent of the disease. Patients with metastatic breast carcinoma have a reported average life expectancy ranging from three to 31 months, supporting the statement that cutaneous metastasis represents advanced disease with a poor prognosis. IHC markers of mammary origin include estrogen (ER), progesterone (PR), gross cystic disease fluid protein 15 (GCDFP-15), the transcription factor GATA3 and mammaglobin. Although ER and PR can help identify tissue of mammary origin, these receptors also can be seen in eccrine carcinomas, making them unreliable differentiating IHCs. GCDFP-15 is a marker of breast carcinoma, however it lacks sensitivity and specificity and has not shown a statistically significant staining pattern between...
cutaneous metastatic breast carcinoma and eccrine carcinoma.2,8 Mammaglobin is a mammary epithelial marker that is considered more sensitive but less specific that GCDFP-15 in metastatic breast carcinomas.2 GATA3 is a transcription factor involved in the development of mammary glands, urinary bladder, and their associated neoplasms. It has been reported as a sensitive marker for breast carcinoma, staining up to 82 percent of metastatic breast carcinomas, as opposed to 11 percent of metastatic non-mammary adenocarcinomas. GATA3 can be considered more sensitive that mammaglobin and GCDFP-15 in the diagnosis of metastatic breast carcinoma.10

Primary cutaneous carcinomas of the eccrine gland are much rarer, only accounting for about 0.05 percent of all neoplasms of the skin. They present in middle-age patients as a solitary lesion, usually a plaque or nodule, typically on the scalp. They may or may not be painful or have associated alopecia. Primary eccrine carcinoma tends to be very aggressive, resulting in metastasis and high risk of mortality. These patients should be treated with Mohs micrographic surgery with consideration for radiation therapy. Chemotherapy is not widely used due to its low effectiveness.11 Cutaneous eccrine carcinoma usually does not present in a patient with a history of carcinoma. This may not always be the case and would result in a diagnostic challenge, as this entity can have significant histological overlap with metastatic breast carcinoma.8 Considering mammary ducts and eccrine glands are both derived from ectodermal appendages, it is of no surprise that much difficulty arises in distinguishing between the two histologically.2,12 The rarity of eccrine carcinoma contributes to the difficulty in defining IHC stains to help differentiate it from breast carcinoma, and a portion of the studies attempting to do so also include other appendagel neoplasms, which distorts the data.2

Commonly used markers in eccrine carcinoma include: cytokeratin 5/6, P63, ER, PR, podoplanin, carinoembryonic antigen (CEA), epithelial membrane antigen (EMA) and GCDFP-15.12 Eccrine carcinomas typically stain positive for pankeratins, CEA, EMA, S-100, but reportedly stain infrequently with GCDFP-15.8,13 CK 5/6 is a mixture of cytokeratins found to be positive much more frequently in eccrine carcinomas than metastatic breast. Therefore, it may help provide some insight in differentiating the two lesions.2,14 Mentrikoski found that a strong, diffuse staining of the nuclear transcription factor p63 is commonly expressed in eccrine carcinoma and can be considered as the most sensitive marker.2 Other reports state P63 can be considered the most useful marker, which would be negative in intramammary ductal carcinoma.12 The D2-40 antibody identifies podoplanin and is used to identify lymphatic endothelium. It has been reported to be a specific marker of eccrine carcinoma, however, it should be used as a third line marker. Podoplanin has been reported to stain negative in breast carcinomas, while staining a majority of adnexal carcinomas.8,14

CONCLUSION
Cutaneous metastases are rare entities but portend a poor prognosis. It is important to keep this diagnosis in mind and have a low threshold to biopsy, especially if a patient has a history of carcinoma. Multiple studies have attempted to find specific IHC markers to distinguish between these two entities, but have not been able to demonstrate a clear IHC panel to differentiate between the two. This prompts the need for further studies; until then, diagnosis should be made using clinical, histological and radiological correlation. The positive staining patterns of ER, PR and GATA3 with negative staining of p40, CK5/6 and podoplanin represented by our patient supported the diagnosis of metastatic ductal breast carcinoma over primary eccrine carcinoma. However, further workup revealed no primary tumor, posing a clinical challenge. Clinicians should take a multidisciplinary approach when caring for these patients and consult with oncology, surgery and radiology to determine a comprehensive monitoring schedule and treatment plan.

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