Clinicopathologic Correlation of Cutaneous Metastases

Experience From a Cancer Center

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Objective: To analyze the clinical, histopathologic, and immunohistochemical characteristics of skin metastases.

Design: Retrospective analysis (January 1, 1990, to December 31, 2005).

Setting: Comprehensive cancer center.

Patients: Fifty-one patients (21 men and 30 women) with biopsy-proven skin metastases and correlative clinical data.

Interventions: Four dermatopathologists reviewed a random mixture of metastases and primary skin tumors. Immunohistochemical studies for 12 markers were performed on the metastases, with skin adnexal tumors as controls.

Main Outcome Measures: Clinical characteristics of cutaneous lesions, clinical outcomes, histologic features, and immunohistochemical markers.

Results: Eighty-six percent (43 of 50) of the patients had known stage IV cancer, and skin metastasis was the presenting sign in 12% (6 of 50). In 45% (21 of 47) of the biopsies, the lesions were not suspected of being metastases owing to unusual clinical presentations. Seventy-six percent of the patients died of disease (median survival, 5 months). On pathologic review, many metastases from adenocarcinomas were either recognized or suspected, but the primary site was not easily identified based on histologic findings alone. Metastases from small cell carcinomas and sarcomas were histologically misinterpreted as primary skin tumors. Immunohistochemical analysis using a panel including p63, B72.3, calretinin, and CK5/6 differentiated metastatic carcinoma from primary skin adnexal tumors.

Conclusions: Cutaneous metastases can have variable clinical appearances and can mimic benign skin lesions. They are usually seen in patients with advanced disease, but they can be the presenting lesion. Although many metastatic adenocarcinomas can be recognized based on histologic findings alone, immunohistochemical analysis is an important diagnostic adjunct in some cases.

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Cutaneous metastases from internal organ malignancies or soft tissue sarcomas are uncommon findings in clinical dermatology and dermatopathology. However, with an increasing incidence of cancers, dermatologists and dermatopathologists are more likely to encounter or even be the first physicians to discover the malignancy. Clinically, the lesions do not have a uniformly characteristic appearance. Histologic features vary depending on the type of originating malignancy and, in some instances, require differentiation from a primary cutaneous tumor. Several series have reported the clinical appearances and histologic changes of cutaneous metastasis. The studies provide detailed and excellent illustrations of the histologic features based on the organs of origin and histologic types. However, most studies have included malignant melanomas or lymphomas and direct extension and local recurrences. This study summarizes the clinical, histologic, and immunohistochemical findings in biopsy-proven cutaneous metastases observed at the Fox Chase Cancer Center between January 1, 1990, and December 31, 2005. The cases selected were restricted to metastases from internal organ malignancies and soft tissue sarcomas, with exclusion of melanomas, hematologic malignancies, direct tumor extension, and local recurrences. We emphasize unusual clinical presentations, clinical outcomes in patients, and the practicality of recognizing cutaneous metastases and their origins in a daily dermatopathology practice, where a detailed clinical history is often not available, and we suggest an immunohistochemical panel that may facilitate differentiation from skin adnexal tumors.
METHODS

Biopsy-proven skin metastases with available histologic slides were selected from the pathology files at the Fox Chase Cancer Center (January 1, 1990, to December 31, 2005). All the cases had detailed demographic information, and most had clinical follow-up data. Metastases from hematologic malignancies or skin tumors (including melanomas), direct extensions to the skin, and local recurrences in the scar of a previous surgery were excluded. Three patients were included in a previous publication on genitourinary malignancies.8 This study was conducted according to the Fox Chase Cancer Center institutional review board–approved protocol. Hematoxylin-eosin–stained slides were reviewed for all cases. To test the practicality of recognizing skin metastases and their origins in the setting of a routine dermatopathology practice, 4 dermatopathologists (C.C., X.X., R.E., and J.S.) independently reviewed the histologic slides of 41 skin metastases. These cases were randomly mixed with 28 cases of primary skin adnexal tumors. No clinical history was provided. The pathologists were required to provide a diagnosis as to whether the cases represented metastasis or primary skin tumors and the site of origin for metastasis.

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissues. Antibodies used included B72.3 (Biogenex, San Ramon, Calif); BerEP4, cytokeratin (CK) 7, CK20, ER, PR, p63, and CK5/6 (DAKO, Carpinteria, Calif); Brst-2, CA19.9, and CA125 (Signet, Dedham, Mass); calretinin (Zymed, San Francisco, Calif); and CD15 (BD Transduction, Brea, Calif). Antigen retrieval and primary and secondary antibody staining were performed according to the laboratory’s routine protocol. All the staining was performed using TechMate 1000 (Ventana Medical Systems Inc, Tucson, Ariz) except for p63 and CK5/6, which was performed using a DAKO autostainer. A stain result was recorded as positive when more than a few cells showed definitive staining. Cases with only rare positive cells were scored as negative. Focal positivity was defined as staining in less than 10% of the tumor cells. The immunohistochemical staining was performed on 32 cases of cutaneous metastases with available tissue blocks, including metastatic lung (n=8), breast (n=6), colon (n=3), pancreatobiliary (n=3), gastric (n=2), ovarian (n=3), bladder (n=2), prostate (n=1), kidney (n=2), and thyroid (n=1) carcinomas and those of unknown primary site (n=1). For comparison, the same staining was also performed on 25 cases of primary benign and malignant skin adnexal tumors, including chondroid syringoma (n=3), spiradenoma (n=2), hidradenoma (n=2), sebaceous carcinoma (n=3), porocarcinoma (n=2), mucinous carcinoma (n=1), apocrine carcinoma (n=1), low-grade eccrine carcinoma (n=7), and poorly differentiated adnexal carcinoma (n=4).

Statistical analysis was performed using the chi² test. P<.05 was considered statistically significant. A recursive partitioning analy-

Figure 1. Clinicopathologic correlation of cutaneous metastases. A metastatic lung carcinoma to the chest closely simulating a keratoacanthoma (A). Biopsy demonstrated a metastatic adenocarcinoma with diffuse growth in the dermis (B) (hematoxylin-eosin, original magnification ×40) composed of malignant glands with large eosinophilic cells (C) (hematoxylin-eosin, original magnification ×400). Multiple flesh-colored cysts on the scalp with appearances similar to piliar cysts (D). Biopsy showed an adenocarcinoma involving the entire dermis (E) (hematoxylin-eosin, original magnification ×40), with well-formed glands containing abundant necrosis (inset) characteristic of colonic carcinoma. A metastatic cholangiocarcinoma to the umbilicus simulating impetigo (F). Histologically, the tumor showed uncommon findings of epidermotropism (G: hematoxylin-eosin, original magnification ×100; and H: hematoxylin-eosin, original magnification ×400).
CLINICAL FEATURES AND FOLLOW-UP

The 51 patients (21 men and 30 women) were aged 37 to 86 years (mean, 62 years; median, 62 years) at the time of skin metastasis. The metastases originated from diverse primary sites. In men the most common origin was the lungs, whereas in women it was the breasts. In women, metastatic lung cancer was the second most common cause of cutaneous metastasis, reflecting the rising mortality rate of lung cancer in women.\(^9\) In 4 cases, the site of origin was not certain despite extensive clinical workup (metastasis of unknown primary site).

Forty-five (88%) of 51 cases of skin metastasis were seen in patients with known systemic malignancy. However, it was the presenting lesion in 6 patients who had a subsequent diagnosis of a primary malignancy (1 case each of breast, lung, colon, and esophageal and 2 cases of ovarian carcinoma). The interval between diagnosis of primary malignancy and development of skin metastasis in the 41 patients with known clinical primary malignancy ranged from 1 to 177 months (mean, 36 months). Most cases presented within a short interval of 3 years. The longest interval of 177 months was in a patient with stage I breast cancer who subsequently developed pleural effusion suggestive of disseminated malignancy. At the time of skin metastasis, most patients (47/50; 94%) had stage III (4 patients) or IV (43 patients) disease. For the 6 patients with skin metastasis as the presenting lesion, the internal malignancy was discovered simultaneously in 1 and within 1 month in the other 5.

After excluding 6 patients who had less than 1 month of follow-up and unknown survival status, the remaining 45 had follow-up ranging from 0.25 to 93.5 months (mean, 13.3 months; median, 9 months). These patients included 3 who died within 1 month of follow-up. Overall, a high percentage of patients (76%; 34/45) died of disease. For these patients, the interval between the diagnosis of skin metastasis and death ranged from 0.25 to 50 months (mean, 9.4 months; median, 5 months). Ten patients who were alive with persistent disease were followed up for 6.5 to 39 months (mean, 18.4 months; median, 15.5 months). One patient with no evidence of disease at 93.5 months after the development of skin metastasis had stage IV breast carcinoma at the time of skin metastasis.

Typically, it is believed that a metastasis manifests as a firm nodule in the skin; however, the clinical presentation of the skin metastases in this series was highly variable. We retrieved a clinical diagnosis in 47 of the 51 cases; only 55% (26/47) were submitted as skin metastasis. From the other clinical diagnoses recorded, it is clear that skin metastases can often mimic other clinical entities. In 7 (15%) of 47 cases, the diagnosis was rash. Four other cases had a descriptive diagnosis of erythema, induration, pain, or edema. The remainder were diagnosed as malignant melanoma (n=1), basal cell carcinoma (n=1), keratoacanthoma (n=1), subcutaneous nodule (n=1), skin nodule (n=1), nodules (n=1), mass (n=1), skin lesion (n=1), and hernia (n=2).

As illustrated and discussed in Figure 1 and Figure 2, metastases can closely simulate various skin tumors and even benign skin conditions. In 35 cases the skin metastasis was a single lesion, whereas in 16 there were 2 or more lesions. In most patients, the lesions were distributed in a single anatomical region; however, 4 patients had lesions located in 2 different anatomical sites. The upper trunk and the abdomen were the most frequent sites for metastasis, followed by the head and neck (particularly the scalp). The umbilicus was also a common
Figure 3. Metastases mimic primary cutaneous tumors. A metastatic small cell carcinoma of the lung showed diffuse dermal infiltrate (A) (hematoxylin-eosin, original magnification ×20) composed of aggregates of small blue cells (B) (hematoxylin-eosin, original magnification ×100) with vesicular nuclei (C) (hematoxylin-eosin, original magnification ×400) that was difficult to distinguish from a Merkel cell carcinoma. A metastatic leiomyosarcoma to the skin closely simulates a primary skin spindle cell sarcoma (D: hematoxylin-eosin, original magnification ×20; E: hematoxylin-eosin, original magnification ×200; and F: hematoxylin-eosin, original magnification ×400).

Figure 4. Morphologic similarity between metastatic carcinoma and skin adnexal tumors. A metastatic clear cell renal cell carcinoma (A) (hematoxylin-eosin, original magnification ×200) showed histologic similarity to a clear cell nodular hidradenoma (B) (hematoxylin-eosin, original magnification ×200) and a sebaceous carcinoma (C) (hematoxylin-eosin, original magnification ×200). A metastatic lung cancer (D: hematoxylin-eosin, original magnification ×40; and E: hematoxylin-eosin, original magnification ×400) and a high-grade primary skin adnexal carcinoma (F: hematoxylin-eosin, original magnification ×40; and G: hematoxylin-eosin, original magnification ×400) both showed diffuse growth of solid sheets of poorly differentiated tumor cells in the dermis.
metastases to the extremities were uncommon. It seems that breast cancer tends to metastasize to the upper trunk, lung cancer to the head and neck and the trunk, and colon cancer to the abdomen.

HISTOLOGIC FINDINGS

Histologic sections most commonly showed infiltrate of tumor cells in the entire dermis, some with extension into the subcutaneous tissue. Several cases showed tumors predominantly in the subcutaneous tissue. Two common patterns were observed. One was a nodular, cellular growth with scanty intervening stroma (Figure 1B and C). The other pattern showed strands of tumor cells infiltrating a fibrotic dermis (Figure 2B and D). In most cases the epidermis was not involved. In several cases the tumors abutted the epidermis, with only rare cases (2 lung carcinomas and 1 cholangiocarcinoma) exhibiting tumor cells in the epidermis (epidermotropism) (Figure 1G and H). Lymphatic invasion was identified in approximately 25% of the cases. In several cases the tumor was composed mostly of intralymphatic emboli, with or without associated infiltrative strands of tumor cells in the surrounding dermis. Interestingly, lymphatic invasion seemed to be more commonly seen in metastatic lung cancer (3 of 9 patients) and genitourinary tract carcinomas (2 of 2 cases of bladder carcinoma, 1 of 2 cases of renal cell carcinoma, and 1 of 1 case of prostatic adenocarcinoma). Furthermore, in 3 of 4 cases with diffuse intralymphatic tumor emboli, the lung was the primary site.

To assess the accuracy of identifying skin metastasis in a daily dermatopathology practice, without the assistance of detailed clinical information, the slides of 41 cutaneous metastases were randomly mixed with those of 28 cases of primary cutaneous tumors that were predominantly adnexal tumors. Four dermatopathologists (C.C., X.X., R.E., and J.S.) independently reviewed the slides without knowing the clinical history. Twenty-seven (66%) of 41 cases were correctly identified as metastases by all 4 pathologists. An additional 6 cases were recognized as metastases by 3 of them. These cases were metastatic adenocarcinomas from various organ sites. However, 2 metastatic pulmonary small cell carcinomas and 4 metastatic sarcomas were misinterpreted as primary skin tumors by most of the pathologists. The metastatic small cell carcinoma closely simulated Merkel cell carcinoma (Figure 3A-C). Without a clinical history, the metastatic sarcomas were practically indistinguishable from primary skin sarcomas (Figure 3D-F). In the absence of a pertinent clinical history, it seemed to be difficult to ascertain the primary site of the metastatic carcinomas. One metastatic breast lobular carcinoma and 1 metastatic renal cell carcinoma (clear cell type) were correctly recognized by all 4 pathologists. An additional 8 cases were assigned the correct site of origin by 2 or more pathologists. However, for most of the cases, the organ of origin was not accurately predicted. Several primary skin adnexal tumors were interpreted as metastases, including clear cell hidradenoma (n=2), sebaceous carcinoma (n=2), and high-grade adnexal carcinoma (n=2). Morphologically, sebaceous carcinoma and clear cell hidradenoma can simulate a metastatic clear cell renal cell carcinoma (Figure 4A-C). A high-grade adnexal carcinoma can be difficult to differentiate from a metastasis (Figure 4D-G).

IMMUNOHISTOCHEMICAL STUDIES

To identify a panel of immunohistochemical markers that may assist in differentiating metastases from primary skin adnexal tumors, 12 antibodies were tested in 32 metastatic and 25 skin adnexal tumors. Six markers (B72.3, calretinin, p63, CK5/6, BerEP4, and CK20) were differentially expressed between metastases and primary skin adnexal tumors, with statistical significance (Table 1). However, none is sensitive or specific enough to be used as a single marker to differentiate the 2 groups. P63 staining was negative in 78% (25 of 32) of the metastatic carcinomas but positive in 96% (24 of 25) of the skin adnexal tumors. When used as a single marker, a positive p63 stain had the highest sensitivity (96%) for primary adnexal tumors, and a negative p63 stain has the highest positive predictive value (96%) for metastasis. This result is consistent with recently published studies. Nevertheless, we found a substantial number (7 of 32; 22%) of metastatic carcinomas expressing p63. Both cases of metastatic bladder carcinoma showed strong and diffuse p63 staining. Positive staining was also seen in 2 of 6 breast, 2 of 8 lung, and 1 of 2 gastric carcinomas. On the other hand, a cutaneous mucinous carcinoma was mostly negative for p63. As a result, if p63 were to be used as a single marker, 22% of metastases would be misclassified as skin adnexal tumors.

We found that adding other markers into a panel of immunohistochemical stains was helpful in increasing the sensitivity and specificity. A recursive partitioning analysis was used to identify the best panel of markers for this sample of 57 tumors. B72.3 was expressed in most (26/31; 84%) metastatic carcinomas, except for 2 renal cell, 1 lung, 1 papillary thyroid, and 1 breast carcinoma. This positivity was particularly helpful in 2 cases of metastatic bladder carcinoma that were diffusely positive for p63 and CK5/6, 2 lung and 2 breast carcinomas with positivity for p63, and 1 gastric carcinoma with strong and diffuse positivity for p63 and CK5/6. In adnexal tumors, 72% (18/25) were negative for B72.3. The staining in the positive cases was mostly focal, except for diffuse and strong staining in a cutaneous mucinous carcinoma. Using B72.3 positivity as an additional criterion, all p63+ metastases were correctly classified. However, 7 skin adnexal tumors remained misclassified because of their expression of B72.3. Calretinin and CK5/6 were tested as additional markers. Calretinin was negative in 72% (23/32) of the metastatic carcinomas. Most of the positive cases were metastatic pancreatobiliary (3 of 3) and lung (5 of 8) carcinomas. In contrast, 64% (16 of 25) of the skin adnexal carcinomas were positive for calretinin. CK5/6 was positive in 14 (44%) of 32 metastatic carcinomas. However, most (5 of 6) metastatic breast, bladder (2 of 2), and gastric (2 of 2) carcinomas showed significant CK5/6 expression. The expression was also frequently seen in metastatic lung and pancreatobiliary carcinomas. CK5/6 expression was not seen in metastatic colon (0 of 3) or renal cell (0 of 2) carcinomas. All adnexal tumors showed CK5/6 positivity. We found that the constant positivity for CK5/6 and the frequent expression of calretinin in skin adnexal tumors were useful in the panel. As shown in Figure 5, by adding calretinin + and CK5/6 + as additional criteria, all skin...
table 1. Immunohistochemical Staining Results on Cutaneous Metastases and Skin Adnexal Tumors*

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<th>Tumor Type</th>
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<th>Calretinin</th>
<th>P63</th>
<th>CK5/6</th>
<th>BerEP4</th>
<th>Brst2</th>
<th>CA19.9</th>
<th>CK7</th>
<th>CK20</th>
<th>CD15</th>
<th>Lysozyme</th>
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<td>24</td>
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<td>12‡</td>
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χ² = 8.53
χ² P value = <.001

Abbreviation: ND, not determined.

*Data are given as the number of cases with positivity for the given marker (number of cases with staining in <10% of tumor cells). The numbers in parentheses further specify cases that showed focal (<10% of tumor cells) positivity.

†For metastases, B72.3, Brst2, CK20, and CD15 were determined in 31 cases.
‡For skin adnexal tumors, BerEP4, CA19.9, CK7, and CK20 were tested in 24 cases; Brst2 in 23 cases; CD15 in 22 cases; and lysozyme in 15 cases.

adnexal tumors except 2 (1 sebaceous carcinoma and 1 mucinous carcinoma) were correctly classified.

In summary, as shown in Figure 5, most metastasis and skin adnexal tumors had distinct combinational expression patterns of the following 4 markers: p63, B72.3, calretinin, and CK5/6. Two adnexal carcinomas (1 sebaceous and 1 mucinous) showed overlapping patterns with metastases. In general, p63 negativity strongly favored metastases. For p63-positive tumors, a combined pattern of p63, B72.3, calretinin−, and CK5/6− favored metastases.

**COMMENT**

METASTASIS MAY MIMIC PRIMARY SKIN TUMOR OR DERMATOSIS

This review of the clinical findings revealed a variety of presentations and prebiopsy diagnoses. In this series, before biopsy, metastasis was suspected in approximately 50% of the cases. This is much lower than the 81.8% reported in a recent study. In contrast to the common belief that metastatic lesions are usually skin nodules or tumors that are distinct from primary skin lesions, we found that some metastases, particularly when they are a single lesion, can closely simulate a benign cyst, keratoacanthoma, basal cell carcinoma, or melanoma. One of us (S.R.L.) has encountered 2 cases with small, innocuous nodules that were clinically indistinguishable from an epidermal inclusion cyst. The lesions were biopsied only because of somewhat firm consistency and a concern for potential metastasis in high-risk patients. In a review of cutaneous metastasis, McKee stated that nodular metastatic lesions are easily and often misdiagnosed as simple cysts or benign connective tissue lesions. The presence of multiple lesions in the same anatomical region and the clinical history of a systemic malignancy will help in formulating a differ-
ent diagnosis. Several case reports have also documented cutaneous metastasis mimicking pyogenic granuloma, granular cell tumor, a benign cyst, and cutaneous angiosarcoma.

Equally deceiving are the lesions masquerading as benign dermatoses. It is important to recognize them to avoid prolonged empirical anti-inflammatory therapy that will result in the delay of a correct diagnosis. Many of our cases presented as a rash that clinically simulates or is indistinguishable from a dermatitis, including eczema, herpes zoster, intertrigo, or contact dermatitis. We have observed recurrent breast cancer with early involvement of deep lymphatic vessels presenting as erythematous, blanchable, nonindurated macules mimicking intertrigo, contact dermatitis, or inflammatory breast cancer. Individual case reports have described metastases simulating cutaneous vasculitis and erythema annulare centrifugum. There are multiple reports on zosteriform metastasis. Therefore, atypical or persistent nodular lesions in patients with a history of systemic malignancy should be considered for biopsy to rule out metastasis. Cancer patients with atypical or unusual inflammatory dermatoses should undergo skin biopsy because of the possibility of metastasis.

**HISTOLOGIC DIFFERENTIATION BETWEEN METASTASES AND PRIMARY SKIN TUMORS**

Four dermatopathologists independently reviewed slides of metastases that were randomly mixed with slides of benign and malignant skin adnexal tumors. The results show that most metastatic adenocarcinomas were correctly diagnosed. Conversely, some adnexal tumors were mistaken as metastases. The lesions that are particularly difficult to diagnose are (1) high-grade porocarcinoma vs metastatic poorly differentiated non–small cell carcinoma of the lung or high-grade transitional cell carcinoma of the urinary tract; (2) low-grade ductal carcinoma of the skin adnexa vs metastatic low-grade ductal carcinoma of the breast or salivary gland; and (3) basaloïd adnexal carcinoma in the axilla vs metastatic breast carcinoma or metastatic basal cell carcinoma. Certain metastatic tumors may closely simulate skin primary tumors, including metastatic small cell carcinoma as Merkel cell carcinoma, metastatic systemic sarcoma as primary skin sarcoma, papillary thyroid carcinoma as primary papillary adnexal tumors, clear cell renal cell carcinoma as either seboceous carcinoma or clear cell hidradenoma, and metastatic mucinous carcinoma as primary cutaneous mucinous carcinoma. In general, metastatic lobular breast carcinomas and moderately differentiated colonic carcinomas with typical tumor necrosis are among the easiest to recognize. The site of the primary tumor often requires correlation with clinical history.

**IMMUNOHISTOCHEMICAL DIFFERENTIATION BETWEEN METASTASES AND PRIMARY SKIN TUMORS**

As discussed previously herein, in some cases a morphologic distinction between metastatic and primary tumors can be difficult. Two previous studies emphasized the values of either p63 alone or a combination of p63 and CK5/6 in this differentiation. However, urothelial carcinomas are known to be strongly positive for p63 and CK5/6. In the present study, we also found this dual positivity in some of the metastatic gastric, lung, and breast carcinomas. We found that additional markers, including B72.3 and calretinin, further differentiate the primary from metastatic tumors. The combination of all 4 markers in a sequential analysis distinguished most tumors. The remainder of the markers listed in Table 1 did not contribute additionally in this sequential analysis. Table 2 summarizes the general characteristics of the 4 markers, with emphasis on the utility in differentiating metastatic adenocarcinomas and skin adnexal tumors.

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**Table 2. Summary of Immunohistochemical Markers**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>General Characteristics</th>
<th>Metastatic Carcinomas</th>
<th>Adnexal Tumors</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>P63</td>
<td>Homologue of p53, expressed in basal cells of skin and mucosa, myoepithelial cells of breast, salivary gland, and prostate. Positive in SCC of various sites, urorheal carcinomas, BCC, skin adnexal tumors.</td>
<td>Negative in the published literature&lt;sup&gt;10,11&lt;/sup&gt;, Negative in 25/32, positive in 2/2 urothelial, 2/8 lung, 1/2 gastric, and 2/6 breast carcinomas</td>
<td>Positive in all adnexal tumors in the published literature&lt;sup&gt;10,11&lt;/sup&gt;, Positive in 24/25</td>
<td>Most useful marker; however, should not be used as the only one</td>
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<tr>
<td>B72.3</td>
<td>A tumor-associated glycoprotein, expressed in many adenocarcinomas; used in lung carcinoma vs mesothelioma and seen in apocrine skin adnexal tumors.</td>
<td>Positive in 26/31</td>
<td>Negative in 18/25; focal positive in 6/25, 1 mucinous carcinoma diffusely positive</td>
<td>Positivity helpful in metastatic carcinomas that are positive for p63 and CK5/6</td>
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<tr>
<td>Calretinin</td>
<td>Calcium-binding protein expressed in mesothelial, epithelial, and stromal cells; used in adenocarcinomas vs mesothelioma and in testicular and ovarian sex cord–stromal tumors; no report on skin adnexal tumors.</td>
<td>Negative in 23/32, positive in 9 (pancreas, lung, occasional breast)</td>
<td>Positive in 16/25</td>
<td>Negativity helpful in metastatic carcinomas that are positive for p63 and CK5/6</td>
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<tr>
<td>CK5/6</td>
<td>Intermediate-sized cytokeratin, expressed in skin and squamous mucosa, myoepithelial cells of breast, salivary gland, and prostate. Positive in SCC, BCC, thymoma, salivary gland tumors, biphasic mesothelioma, and some urothelial, endometrial, pancreatic, breast, and ovarian carcinomas.</td>
<td>Negative in the published literature&lt;sup&gt;11&lt;/sup&gt;, Negative in 14/32, positive in 18/32</td>
<td>Positive in the published literature&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Consistent expression in skin tumors useful in a panel of markers</td>
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Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.
Immunoreactivity for calretinin in skin adnexal tumors has not been reported in the literature. In the present study, many skin adnexal tumors (64%) were positive for calretinin. In most cases, the staining was seen in a subpopulation of the tumor cells. There does not seem to be a differential expression pattern between benign and malignant tumors. Strong calretinin expression was also seen in endogenous skin adnexal structures, including all apocrine glands and some eccrine glands, but not in eccrine ducts.

In summary, the detailed clinical, histologic, and immunohistochemical studies of 51 cases of biopsy-proven cutaneous metastasis accumulated during a 16-year period from a cancer center showed that patients may present with unusual clinical lesions that closely simulate primary skin diseases. Metastatic adenocarcinomas can often be diagnosed or suspected based on histologic pattern alone. However, there are difficult cases that require clinicopathologic correlation and immunohistochemical studies. A combined panel of p63, B72.3, calretinin, and CK5/6 will be helpful in this differentiation.

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Author Contributions: Dr Wu had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sariya, Pasha, Zhang, Lessin, and Wu. Acquisition of data: Sariya, Adams-McDonnell, Cusack, Xu, Elenitsas, Seykora, Baldassano, Lessin, and Wu. Analysis and interpretation of data: Sariya, Ruth, Lessin, and Wu. Drafting of the manuscript: Sariya and Wu. Critical revision of the manuscript for important intellectual content: Sariya, Ruth, Adams-McDonnell, Cusack, Xu, Elenitsas, Seykora, Pasha, Zhang, Baldassano, Lessin, and Wu. Statistical analysis: Ruth. Obtained funding: Wu. Administrative, technical, and material support: Sariya, Adams-McDonnell, Xu, Elenitsas, Pasha, Zhang, Baldassano, and Wu. Study supervision: Sariya and Wu.

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