Pulmonary Cutaneous Metastasis: A Case Report and Review of Common Cutaneous Metastases

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RELEASE DATE: December 2009
TERMINATION DATE: December 2010
The estimated time to complete this activity is 1 hour.

GOAL

To understand cutaneous metastasis to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Evaluate the current statistics and epidemiology concerning cutaneous metastatic disease.
2. Outline the clinical manifestation of cutaneous metastatic disease.
3. Describe the more common cutaneous metastasizing carcinomas (ie, breast, lung, and colorectal cancer).

INTENDED AUDIENCE

This CME activity is designed for dermatologists and general practitioners.

CME Test and Instructions on page 311.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: November 2009.

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Drs. Beachkofsky, Wisco, S. S. Osswald, M. B. Osswald, and Hodson report no conflict of interest. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest. The staff of CCME of Albert Einstein College of Medicine and *Cutis*® have no conflicts of interest with commercial interest related directly or indirectly to this educational activity.

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The literature on cutaneous metastatic disease can be difficult to interpret because of inconsistent study design and analysis among authors. Furthermore, one should be careful when reviewing the statistics in the literature, as reported patient populations tend to vary and are not representative of the whole population. However, certain trends are notable and should be reported. Diagnosis of cutaneous metastatic disease carries a grave prognosis. We describe a patient with pulmonary cutaneous metastasis and provide a

review of the literature on nonmelanomatous solid tumor malignancies that most commonly have cutaneous metastases. The review will focus on epidemiology, clinical presentation, histology and immunohistochemical staining, and prognosis and management. The most common cutaneous metastasizing carcinomas—breast, lung, and colorectal cancer—also are discussed.

Cutis. 2009;84:315-322.

CASE REPORT

A 48-year-old Taiwanese woman with a history of stage IV non–small cell lung cancer and known brain metastases presented to the dermatology clinic for evaluation of a painful mass on the left side of her chest. During her first cycle of chemotherapy, the patient noted a rapidly growing, painful lesion on the left side of the chest wall that developed over the course of one week. She had no other remarkable medical, surgical, social, or family history. Physical examination revealed a solitary, 2-cm, subcutaneous nodule that was firm, tender, and mobile with an overlying slightly bluish hue (Figure 1). Excision biopsy of the lesion was performed with removal of a 2.5-cm, soft, gray nodule. Histology showed a well-circumscribed subcutaneous nodule composed of small and large glandular structures with pleomorphic cells, atypical mitosis, and focal areas of central necrosis consistent with adenocarcinoma (Figure 2). The histologic features of the lesion were compared to a previously resected metastatic brain lesion and were found to be similar and consistent with metastatic disease from a primary lung source. Unfortunately, the disease rapidly progressed and the patient died within a few months.

COMMENT

The facts and figures provided in reports on cutaneous metastatic disease often can be difficult to interpret. There are many inconsistencies in study design and analysis. Furthermore, the raw data are published in few studies, making accurate meta-analysis difficult. For example, some studies include hematopoietic and melanomatous malignancies, while other studies include one, both, or neither. Also, patient populations vary, ranging from metastatic disease as a whole to only cutaneous metastatic disease, and the methodology for describing tumor location varies from specific tumor site identification to regional groupings. However, it is important to note that not all reported cases of cutaneous metastatic disease are biopsy proven and therefore are subject to misdiagnosis, which is an inconsistency with the greatest possible impact. Thus, the purpose of this article is to present a review of the data regarding nonhematopoietic nonmelanomatous cutaneous metastases from the most commonly reported cutaneous metastasizing carcinomas.

Epidemiology

A recent meta-analysis reported that the incidence of cutaneous metastasis from all visceral malignancies is approximately 5%.[1] While meta-analysis is limited by the interstudy design, this number falls well within the previously reported range of incidence of less than 1% to more than 10%.[2-8] Cutaneous metastasis occurs most commonly between the fifth and seventh decades of life and affects women more often than men.[3,9,10] Minimal data are available on prevalence among different ethnic groups. Commonly, patients with cutaneous metastasis have known metastatic

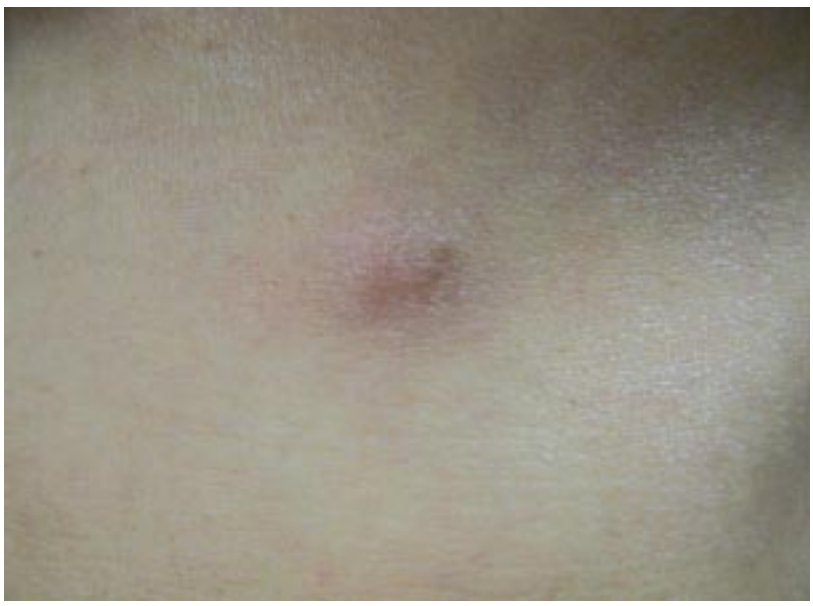

Figure 1. Solitary, 2-cm, subcutaneous nodule on the left side of the chest wall that was firm, tender, and mobile with an overlying slightly bluish hue.

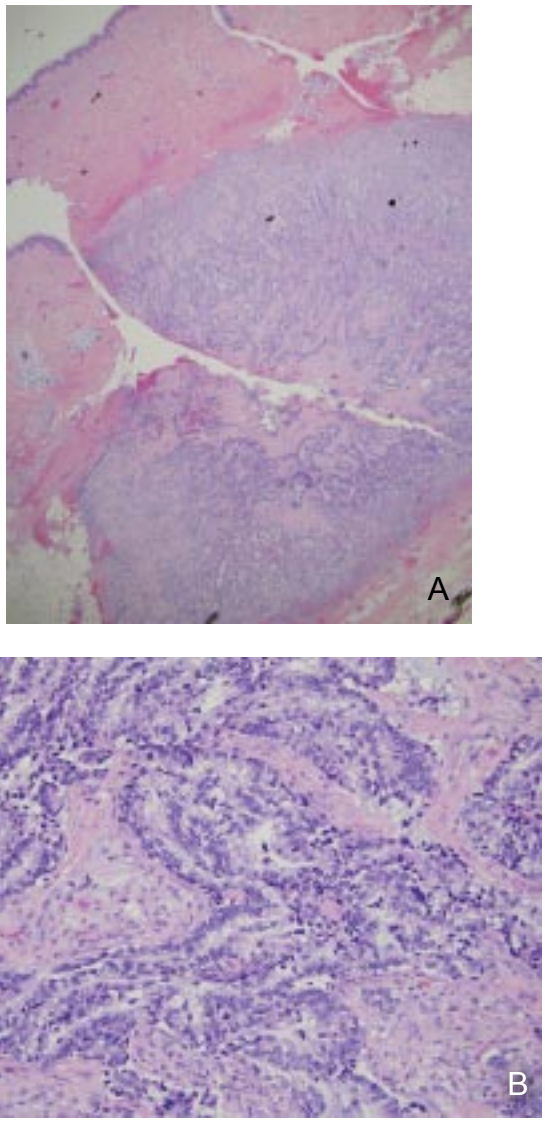

Figure 2. Biopsy of the nodule on the left side of the chest wall (A and B)(H&E; original magnifications ×2 and ×20, respectively).

disease. Less than 1% of patients present with cutaneous metastatic disease before the primary cancer is found.[11]

Breast carcinoma consistently has been reported as the tumor with the highest incidence of cutaneous metastasis. It is responsible for cutaneous metastatic disease in 24% of cases.[1] While other commonly reported tumors include lung, colorectal, ovarian, and renal cell carcinomas, each occur in less than 5% of cases.[1,2,4] Ranking by gender is inconsistent between individual studies. However, a review of the literature by Nashan et al[2] reported the most common cutaneous metastasizing carcinomas in women and men (in descending order of incidence): breast, colorectal, lung, and ovarian carcinomas in women, and lung, colorectal, renal, and gastrointestinal tract carcinomas in men.

Clinical Presentation

Cutaneous metastases in adults generally develop near the site of the primary tumor, which is thought to be due to local lymphatic and/or hematologic spread. In a meta-analysis by Krathen et al,[1] the most common sites for metastasis were the chest (28%) and abdomen (20%), followed by the extremities (12%), neck (11%), posterior aspect of the back (11%), scalp (7%), pelvis (6%), and face (5%). The face and scalp have shown preferential involvement for distant cutaneous metastases in multiple series,[1,3-6] possibly due to tumor-induced chemokine expression in these locations.[12] Notably, renal cell carcinoma has been emphasized in the literature for its predilection to metastasize to the scalp, commonly the first sign of metastatic disease[8,13] and often the presenting sign of the underlying primary cancer.[5] While the clinical manifestations can vary dramatically, lesions most often appear as solitary nodules. However, grouped nodules, erythematous plaques, nonhealing ulcers, and infiltrated scars also may be noted.

Histology

Histologic analysis of cutaneous metastases often reveals a nonspecific adenocarcinoma, a squamous cell pattern, or an undifferentiated tumor pattern that can represent a variety of primary locations. Most lesions are restricted to the dermis with some infiltration of the surrounding subcutaneous tissue and present as either a nodular growth with scanty intervening stroma or strands of tumor cells infiltrating a fibrotic dermis.[14] Various histologic stains can be valuable tools for identifying the primary tumor site[15] and should be considered. It has been reported that when pathologists use only hematoxylin and eosin stain and have no clinical information, they can only correctly identify biopsied lesion specimens as metastatic in 66% of cases and can only further identify the primary origin in 44% of cases.[14,16]

Many immunohistochemical stains have been studied for use as adjuncts, including but not limited to Ber-EP4, B72.3, calretinin, carcinoembryonic antigen (CEA), CDX-2, cytokeratin (CK) 5/6, CK7, CD10, CK19, CK20, E-cadherin, epithelial membrane antigen, estrogen receptor (ER)/progesterone receptor (PR), gross cystic disease fluid protein–15 (GCDFP-15), Her-2 (human epidermal growth factor receptor 2), HMB-45 (human melanoma black), Melan-A/MART-1 (melanoma antigen recognized by T cells), p63, smooth muscle actin, S-100 protein, TAG-72 (tumor-associated glycoprotein), and thyroid transcription

factor–1 (TTF-1).[14,16-18] The most common stains described to be useful in identifying cutaneous metastases include CK7, CK20, ER/PR, S-100 protein, and TTF-1.

Prognosis and Management

The development of cutaneous metastases is an extremely poor prognostic event. Studies have shown that the median time from development of cutaneous metastases to death ranged from 1 to 34 months depending on the tumor type.[4,9,10] Survival rates of 36% at one year, 23% at 3 years, 18% at 5 years, and 3% at 10 years also have been reported.[10]

Treatment of cutaneous malignancies generally is aimed at improving the patient's quality of life and minimizing discomfort or disfigurement; however, aggressive treatment may be pursued in specific patients. In general, surgical excision is indicated when the removal of the metastases and the primary tumor would meet these goals. Given the poor mean survival time for certain patients with cutaneous metastases, aggressive therapy with radiation or chemotherapy may not always be warranted. Palliative care is always appropriate, and with cutaneous metastasis, wound care for ulcerated lesions should be provided because of the risk for infection.

Common Causes of Cutaneous Metastases

Cutaneous metastases secondary to primary visceral carcinomas may occur; however, breast, lung, and colorectal cancer account for the majority of published cases. Details on these common sources of nonhematopoietic nonmelanomatous cutaneous metastasizing carcinomas are provided in the Table.

Breast Carcinoma—Breast cancer is the most common cancer in women in the United States and is the second greatest cause of cancer mortality in women.[33] The median age at diagnosis for breast cancer is 61 years and the median age at death is 69 years. Tumor staging at the time of diagnosis was reported as follows: 60% primary site (localized); 33% spread to regional lymph nodes or directly beyond the primary site; 5% metastatic disease (distant); and 2% unknown.[19] The primary risk factors include family history and hormone exposure.[34,35] Most cutaneous metastases develop on average 47 to 60 months after a formal diagnosis of breast cancer.[3,10] Multiple studies found that up to 6.3% of patients with breast cancer will already have skin involvement, including local extension and metastases, at the time of diagnosis and 3.5% will be diagnosed because of the cutaneous involvement.[4,11] Additionally, cutaneous metastases from breast cancer have been reported to account for more than 80% of cases of cutaneous metastatic disease in women and are the first sign of extranodal disease in 24% of women with breast cancer, indicating progression to stage IV.[4]

Cutaneous metastases from breast cancer most commonly present on the chest, back, scalp, upper extremities, abdomen, and neck. Lesions have been described most commonly as nodular, inflammatory, ulcerative, and pagetoid.[4,11] Rarely, metastases to the scalp resemble patches of alopecia areata favoring a diagnosis of alopecia neoplastica.[36] Additionally, 4 clinical patterns also have been reported almost exclusively related to breast cancer: carcinoma erysipelatoides (inflammatory carcinoma), Paget disease, carcinoma telangiectaticum, and carcinoma en cuirasse. These patterns typically are associated with skin involvement through direct extension rather than cutaneous metastasis.[20]

Histologic analyses are not always specific, as various histologic subtypes of breast cancer have been seen in cutaneous metastases, mainly invasive ductal adenocarcinoma with other variants such as lobular, mucinous/scirrhous, and undifferentiated types.[4] Sometimes sheets or columns of cells can be seen between the collagen bundles and signet ring cells occasionally are observed. Other patterns include adenoid and inflammatory.[8]

Immunohistochemical analysis with GCDFP-15, ER, and PR staining can be helpful adjuncts. When utilizing combined ER/PR immunohistochemical staining, sensitivity for breast cancer is 66% and specificity has been reported as high as 100%. The use of GCDFP-15 has shown a potential role in the diagnosis of breast cancer, with a sensitivity of 71% and specificity of 91%.[14] Additionally, in at least one report cathepsin D was observed to be useful because of the positive staining pattern seen in metastatic breast cancer.[21] Breast cancer metastases also sometimes contain melanin pigment and occasionally can stain positive with S-100 protein.[22,23]

Lung Carcinoma—Lung cancer is the most prevalent cause of cancer mortality worldwide for both men and women.[24] The median age at diagnosis for lung cancer is 71 years and the median age at death is 72 years. Tumor staging at the time of diagnosis was reported as follows: 15% primary site (localized); 22% spread to regional lymph nodes or directly beyond the primary site; 55% metastatic disease (distant); and 8% unknown.[19] The primary risk factor for approximately 90% of all lung cancers is cigarette smoking.[25]

On average, cutaneous metastases develop approximately 16 months after a formal diagnosis of lung cancer,[3,10] 0.3% of patients with lung cancer will already have cutaneous metastases at the time

Fast Facts for the Most Common Nonhematopoietic Nonmelanomatous Cutaneous Metastasizing Carcinomas[3-5,8-11,14,15,18-32]

Location for Cutaneous Metastases	Clinical Description of Lesion	Histologic Subtype	Median Age at Diagnosis, y	Patients With Skin Involvement at Time of Diagnosis, %	Patients Diagnosed Because of Cutaneous Metastases, %	Mean Interval Between Diagnosis and Development of Cutaneous Metastases, mo	Mean Time From Diagnosis of Cutaneous Metastases to Death, mo	Immunohistochemical Staining Considerations
Breast Carcinoma								
Chest, back, scalp, upper extremities, abdomen, neck	Solitary nodule, infiltrated scar, Paget disease, multiple nodules, erysipelaslike, plaque, ulcerated nodule(s)	Ductal, lobular, mucinous, scirrhous, undifferentiated	61	6.3	3.5	47–60	14–31	GCDFP-15, ER, PR, S-100 protein
Lung Carcinoma								
Chest, abdomen, back, scalp, face	Solitary nodule, multiple nodules, plaques, ulcerated nodules, infiltrated scars, erysipelaslike	Adenocarcinoma, squamous cell carcinoma, large cell carcinoma, small cell carcinoma	71	<1	<1	16	3–6	TTF-1, CK7, CK20
Colorectal Carcinoma								
Scalp, face, chest, back, abdomen, genitalia	Nodular, pedunculated, vascular, inflammatory, cystlike	Adenocarcinoma	71	<1	<1	17–31	4–18	CK7, CK20, CDX-2

Abbreviations: GCDFP-15, gross cystic disease fluid protein–15; ER, estrogen receptor; PR, progesterone receptor; TTF-1, thyroid transcription factor–1; CK, cytokeratin.

of diagnosis, and 0.2% will be diagnosed because of cutaneous metastases.[4,11] Cutaneous metastases from primary pulmonary cancers are the first sign of extranodal disease in 1% of patients with lung carcinoma.[4] Of all common primary malignancies known to produce cutaneous metastases, patients with lung cancers that metastasize to the skin have the shortest expected survival times following development of cutaneous metastases, averaging 2.9 to 6 months.[4,9,20] Cutaneous metastases from lung cancer commonly occur on the chest, abdomen, back, scalp, and face. Lesions have been described most commonly as a solitary nodule, multiple nodules, plaques, ulcerated nodules, infiltrated scars, and erysipelaslike.[4] Of note, solitary nodules tend to be firm with some variations in color from flesh colored to brown or blue-black.

Various reports disagree on the most common histologic subtype identified to metastasize to the skin. However, adenocarcinoma and squamous cell carcinoma are the most highly reported. When adenocarcinoma is observed, mucin-secreting glandular tissue occasionally can be observed.[8] Other histologic types of lung cancer with known cutaneous metastases include large cell and small cell carcinomas.[4,20]

Immunohistochemical staining does not play as important of a role in the diagnosis of cutaneous metastases of lung cancer compared to breast cancer because most patients with cutaneous metastases from a primary pulmonary source present at such an advanced stage that they commonly have other symptoms or other metastatic lesions that lead to diagnosis. However, in cases in which a primary source cannot be readily identified, there are a few immunohistochemical stains that may provide additional clues. Some studies have shown a predilection for lung cancer biopsy specimens to stain positive with TTF-1.[14,18] While these cases are limited, TTF-1 appears to be both sensitive and specific to lung carcinomas and thyroid tissue. Also, in some studies the use of a CK7 and CK20 staining panel was at least 95% effective in distinguishing pulmonary and colorectal adenocarcinomas, with lung carcinoma staining positive for CK7 and negative for CK20 and colon cancer staining negative for CK7 and positive for CK20.[18,26]

Colorectal Carcinoma—In 2008, colorectal cancer was both the third most common cancer and third most common cancer leading to death among men and women in the United States.[27] The median age at diagnosis for colorectal cancer is 71 years and the median age at death is 75 years. Tumor staging at the time of diagnosis was reported as follows: 39% primary site (localized); 37% spread to regional lymph nodes or directly beyond the primary site; 19% metastatic disease (distant); and 5% unknown.[19] Strong risk factors include familial adenomatous polyposis, hereditary nonpolyposis colon cancer, and personal or family history of adenomatous polyps.[37]

Cutaneous metastases develop on average 16.5 to 30.8 months after a formal diagnosis of colorectal cancer,[3,10] 0.5% of patients with colorectal cancer will already have cutaneous metastases at the time of diagnosis, and 0.4% will be diagnosed because of cutaneous metastases.[4,11] One study reported that cutaneous metastases from colorectal cancers occur in 2% of patients with colorectal cancer and are the first sign of extranodal disease in 2.6% of patients with metastatic colon cancer.[4]

Cutaneous metastases have been documented on the scalp, face, chest, back, abdomen, and genitalia. The lesions have been described as nodular, pedunculated, vascular, inflammatory, and cystlike.[5,11,28-30] The primary sites for metastases have been reported as follows: rectum (55%), sigmoid colon (17%), transverse colon (9%), rectosigmoid (7%), cecum (4%), and ascending colon (4%).[8] Histologically, cutaneous metastatic lesions typically are adenocarcinoma-like but may show papillary formations with tumor cells lying within large pools of mucin. In the more differentiated lesions, acinar structures tend to be larger with more basophilic nuclei, pleomorphic cells, and mitotic figures with basophilic/fibrotic connective tissue containing lymphocytes and histiocytes.[8,15]

Immunohistochemical analysis of cutaneous metastases staining negative for CK7 and positive for CK20 has been reported in multiple series with sensitivities ranging from 40% to 73%.[14,18,31,32,38] However, when differentiating cutaneous metastases of colorectal cancer and lung cancer, this pattern distinguishes at least 95% of cases.[26] Positive staining with CDX-2 reveals a sensitivity of 93% and specificity of 86%.[39] However, negative CK7 and positive CK20 staining remains more specific than positive CDX-2 staining.[40] Positive staining with CEA is highly sensitive but not specific, as this pattern also can be seen with breast, liver, and lung carcinomas. Cutaneous metastases from colorectal cancer typically do not stain with CK5/6, CD10, ER, PR, TTF-1, and S-100 protein. Thus, using these negative staining patterns in combination with a positive CEA staining pattern may be helpful in diagnosis when the primary cancer is unknown.[14]

CONCLUSION

Cutaneous metastatic disease, though rare, is a very concerning finding. It is much more common

to observe this finding in a patient with previously established disease, but it can be the first sign of an underlying malignancy and should not be missed. Excluding melanoma and lymphoma, the most common malignancies with cutaneous metastasis are breast, lung, and colorectal cancer. Histologic examination of new nodules or atypical dermatitis in patients with a history of these cancers or those at high risk for one of these cancers is always warranted. We hope this review will not only simplify this subject matter but also provide a resource to analyze concerning lesions for cutaneous metastases.

Acknowledgment—The authors would like to thank Milton Eisner, PhD, Surveillance Research Program, National Cancer Institute, Bethesda, Maryland, for his help with the statistical analysis of the online Surveillance, Epidemiology, and End Results (SEER) database.

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