Clinics in Dermatology (xxxx) **xx**, xxx

ELSEVIER

Clinics in Dermatology

Cutaneous metastases: A great imitator

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Abstract Neoplastic cells originating from a primary cancer can uncommonly spread to the skin, where they suggest a poor prognosis for the patient. In women, melanoma, breast, ovarian, oral cavity, and lung are the most common primary sources; in men, melanoma, lung, colon, and squamous cell carcinoma of the head and neck predominate. The classic presentation of cutaneous metastases is a firm, painless, flesh-colored to an erythematous dermal nodule (or nodules); however, several other presentations, including inflammatory, cicatricial, and bullous lesions, have been reported. Cutaneous metastases may also mimic benign conditions such as lipomas, hemangiomas, or cellulitis. A high degree of clinical suspicion is necessary, and the diagnosis is confirmed by biopsy, which may also be used to establish the primary malignancy if unknown, as the histopathologic appearance of the metastatic tissue may mimic the primary tumor. Treatments include excision of the metastases, chemotherapy, immunotherapy, radiation, and/or palliative care.

Introduction

Cutaneous metastases may be defined as lesions of neoplastic cells that have originated from a primary cancer elsewhere in the body.[1–3] These uncommon presentations of a malignancy account for only 2% of all skin cancers.[4] On average, 1% to 10% of patients who develop metastatic disease to any organ of the body will develop cutaneous metastases.[3] Although uncommon, these metastases are of clinical importance and portend a poor prognosis.[3] Cutaneous metastases may be the first indication of a primary internal malignancy and occur in up to 22% of patients.[4] They may sometimes mimic other benign skin conditions, such as lipomas and cellulitis.[3] (Tables 1 and 2.)

The variation in the prevalence of cutaneous metastases results from the type of primary cancer. Metastatic melanoma is responsible for the greatest incidence of cutaneous metastases, which can be present in up to 45% of patients with metastatic disease.[3] Sex-related differences in the prevalence of primary cancers correlate with their frequency of cutaneous metastases. In women, breast cancer is the most common source of metastatic skin disease, representing 70% of all causes, followed by ovarian (3.3%), oral cavity (2.3%), lung (2%), and large intestine (1.3%).[1] In men, lung cancers are the most common source of cutaneous skin disease (11.8%), followed by large intestine (11%), oral cavity (8.7%), kidney (4.7%), breast (2.4%), esophagus (2.4%),

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https://doi.org/10.1016/j.clindermatol.2019.10.004
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Table 1 Common clinical presentations of cutaneous metastases

Clinical presentation	Clinical description	Associated primary malignancy
Dermal or subcutaneous nodules	1- to 3-cm firm, adherent nodule(s) in the dermis or subcutis	Any, but the most common presentation is periumbilical Sister Mary Joseph nodule in ovarian and gastrointestinal
Inflammatory carcinoma (carcinoma erysipeloides)	Erythematous, rapidly expanding patch with well-defined border	Breast > lung, ovary, gastrointestinal
Alopecia neoplastica	Nodules or plaques with associated alopecia	Lung, breast > all others
Mammary Paget disease	Dermatitis of the nipple and areolar skin	Breast
Carcinoma en cuirasse (scirrhous carcinoma)	Morpheaform or sclerodermoid; may also appear indurated, fibrous	Breast > prostate
Carcinoma telangiectodes	Erythematous patch with telangiectasias	Lung
Sclerodermoid	Indurated dermal plaques	Breast, lung, melanoma

">" : entity more predominant > entity less predominant.

and pancreas, stomach, or liver cancers (0.8%).[1] In children, leukemia, rhabdomyosarcoma, and neuroblastoma are responsible for the largest proportions of cutaneous metastases.[3]

The presentations of cutaneous metastases are variable and based on the type of primary internal malignancy; however, the most classic presentation is a firm, painless, erythematous nodule or nodules.[3] On average, cutaneous metastases appear within 36 months of the primary tumor being identified and may appear along with other organ metastases.[4]

Cutaneous metastases from internal malignancies generally signify a poor prognosis. The average length of survival in patients, when skin metastases are diagnosed, is approximately 7.5 months.[1] In addition, they are often an indication of a widely spread visceral malignancy, and 76.6% of patients had extensive metastasis to lymph nodes and other organs at the time of diagnosis.[5]

The location of the metastasis may serve as a helpful clue in diagnosing a primary malignancy, as metastases commonly appear near the site of the primary malignancy.[3] Due to the possibility of detecting asymptomatic visceral cancers, an understanding of the clinical presentations and proper diagnosis of cutaneous metastases is vital in establishing timely treatment of the primary malignancy. Additionally, physicians treating patients with internal malignancies should be suspicious of new skin lesions, as the dismal prognosis of cutaneous metastases may affect treatment decisions.

Pathogenesis

A primary malignancy can metastasize to the skin through several pathways: direct invasion, hematogenous spread, lymphatic spread, or implantation.[1] The process is thought to involve detachment of neoplastic cells from the primary tumor, intravasation into a vessel, circulation of neoplastic cells, stasis, extravasation into the new site, and proliferation.[6]

The three typical patterns of presentation seen in cutaneous metastases are mechanical tumor stasis, site-specific metastasis, and nonselective spread.

In mechanical tumor stasis, the metastatic disease appears in close anatomic proximity to the initial tumor. This presentation commonly occurs when cells spread through the lymphatic route or through direct invasion. Breast carcinoma and squamous cell carcinoma of the head and neck are examples of malignancies that often spread to the skin by direct invasion.[3] Site-specific metastasis arises when neoplastic cells have a predilection for specific organs. Finally, nonselective metastasis occurs when the neoplastic cells metastasize without a specific organ preference.[6]

Malignancies metastatic to the skin

Breast

Cutaneous metastases from breast carcinoma are the most common type of cutaneous metastases. In the largest published case series,[2] skin involvement was observed in 23.9% of all patients with breast carcinoma.

Cutaneous metastases from breast carcinoma most commonly present as hardened, asymptomatic nodules.[1,2] They are generally skin-colored; however, they may also be pink or red-brown.[1] On occasion, these nodules may erode, ulcerate, and become infected.[7] The common sites of metastasis are on the thoracic wall and abdomen, but the extremities and the head-and-neck region can also be affected. These metastases can mimic a variety of benign dermatologic conditions, necessitating histologic confirmation.[8] Additionally, other clinical presentations include erysipeloid infiltration, sclerodermiform, inflammatory carcinoma en cuirasse, telangiectasias, neoplastic alopecia, and palpebral nodules.[1,9] These lesions can mimic conditions such as cellulitis and mastitis.

Lung

Cutaneous metastases occur in only 2.5% of primary lung cancers; however, lung cancers account for 12% of all cutaneous metastases in men and are also a common cause of

Table 2 Cutaneous metastases by primary malignancy

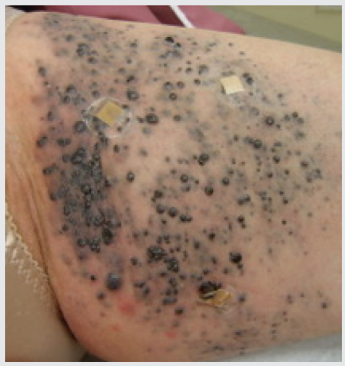
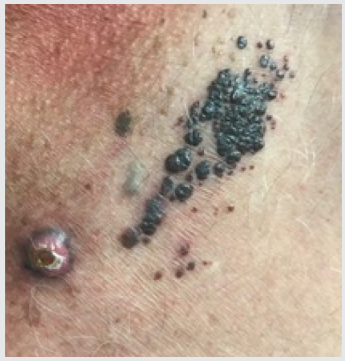
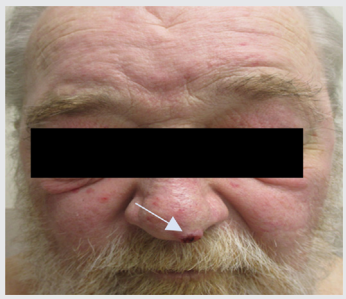
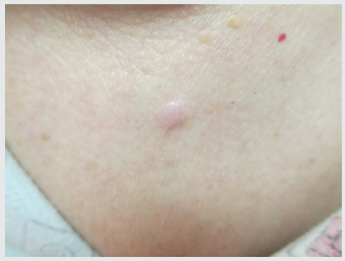
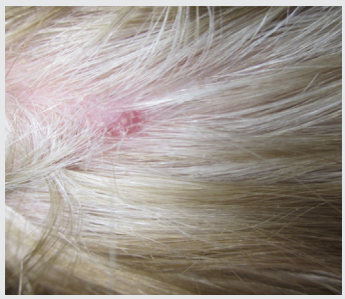
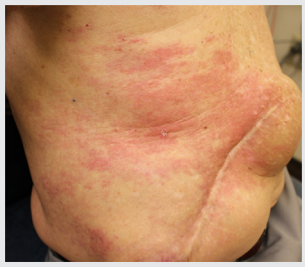
Primary malignancy	Image	Most common site	Common clinical presentation
Breast[1]	 Metastatic breast nodules on the left side of the chest and flank	Thoracic wall, abdomen	Multiple 1- to 3-cm firm nodules in the dermis or subcutis
Melanoma[11]	 Metastatic melanoma on the right thigh  Metastatic melanoma on the left cheek	Men: chest, back > extremities Women: extremities	Single or multiple variably pigmented papules and nodules
Squamous cell carcinoma head and neck[17]		Above the diaphragm, most commonly on the neck	Single or multiple nodules or erythematous macules; painless, often mimicking infection or primary squamous cell carcinoma
Lung[10]	 Metastatic lung as nodule on the nose	Chest wall, abdomen	Well-localized cluster of firm, palpable, red to violaceous nodules

Table 2 (*continued*)

Primary malignancy	Image	Most common site	Common clinical presentation
Colon[21]		Perineum, abdomen	Small subcutaneous or intradermal nodules, often appearing at the site of a surgical scar or colostomy
Ovary[4]		Abdomen, chest	Multiple flesh-colored nodules
Urinary bladder[23]		Umbilicus, pubis	Variable
Endocrine[20]	  Metastatic medullary thyroid carcinoma to chest (a) and scalp (b)	Face, scalp, neck	Itchy, nontender, slowly growing erythematous nodular lesions
Esophageal (most commonly squamous cell carcinoma)[27]		Abdominal wall	Variable, often appearing after invasive procedures
Gastric	 Metastatic cholangiocarcinoma to abdomen	Abdomen, umbilicus	Nodules

Vivian Shi, MD, and Melody Maarouf, MD, University of Arizona Dermatology, and Michael Warso, MD, University of Illinois, Department of Surgery, provided the photographs. Reproduced with their permission.
">" : entity more predominant > entity less predominant.

cutaneous metastases in women.[1,3,10] Lung and pleural metastases to the skin typically present as a cluster of painless, firm, reddish dermal, or subcutaneous nodules or even a solitary mass. Nodules appear flesh-colored, violaceous, or telangiectatic.[4] They may also be ulcerated, hemorrhagic, or vascular in appearance.[1,3,4,9] This vascular, red appearance is more typical for lung carcinoma metastases and is less commonly seen in other types of cutaneous metastases.

Clinically, metastatic nodular lesions may mimic lipomas, pilar cysts, epidermal inclusion cysts, keratoacanthomas, dermatofibromas, pyogenic granulomas, or hemangiomas. It is important to note that, unlike epidermal inclusion cysts or dermatofibromas, metastatic nodules do not typically have a central punctum, spontaneous drainage, or a central scar on dermatoscopy. Less common clinical presentations of lung cutaneous metastases include inflammatory carcinoma

(erythema erysipeloides), alopecia neoplastica, zosteriform lesions, and telangiectatic carcinoma.[1,3]

The most common cutaneous surfaces affected are the chest wall and the abdomen.[1,9] Cutaneous metastases may also appear at a thoracotomy site or incision and are notoriously heterogenous.[3] These metastases have been found in such remote areas as the scalp, head, chin, neck, abdomen, and extremities.[1–4,10] The average survival time from the appearance of skin metastases from the lung ranges from 3 to 5 months.[10]

Melanoma

Cutaneous metastases occur in 18% of all patients with a primary extracutaneous melanoma and 45% of those with a primary cutaneous melanoma.[3,9] Metastases are detected as the first manifestation of melanoma in 2% to 8% of patients and are seen as the initial progression in 56% of patients.[11] The average time from the date of diagnosis of the primary melanoma to the onset of regional and distant skin metastases is 1.3 to 2.9 years, respectively.[11] The presence of cutaneous metastasis from a primary cutaneous or extracutaneous melanoma is a poor prognostic criterion.[12]

Cutaneous metastasis from a primary melanoma can be categorized as satellite (<2.0 cm adjacent to or deep to and completely discontinuous from a primary melanoma with unaffected stroma occupying the space between), in-transit (>2.0 cm from primary melanoma but not beyond the regional nodal basin), or distant metastases (>2.0 cm from primary melanoma and beyond the regional nodal basin)[12]

The most common clinical presentation is variably pigmented papules and/or nodules, either solitary or grouped.[2,9,11] Lesions often appear in the same anatomic region as the primary malignancy.[11] Additional clinical presentations include carcinoma erysipeloides, ulcerated lesion, keratinous cyst, keratoacanthoma, nonhealing abscess, pedunculated nodule, erysipeloid patch, or a sclerodermiform lesion.[11,13] Metastatic melanoma may also have associated paraneoplastic phenomena in the skin. A case of paraneoplastic systemic sclerosis associated with metastatic melanoma has been decribed.[14] The most common sites of metastases are the extremities and scalp.[15] In women, the extremities are the most common anatomic sites of metastases; in men, back and chest involvement is more common.[1]

Cutaneous melanoma metastases may mimic other epithelial and mesenchymal neoplasms, such as hemangiomas, dermatofibromas, melanocytic nevi, and dermatofibrosarcoma protuberans.[11,15] Spitz nevi, squamous cell carcinomas, pigmented actinic keratoses, basal cell carcinoma, talon noir, Paget disease, solar lentigos, and tinea nigra can also appear similar to cutaneous melanoma metastases. Lastly, cutaneous melanoma metastases may appear similar to a persistent abscess, cellulitis, or morpheaform lesions.

Squamous cell carcinomas: Head and neck

Metastatic disease to skin from squamous cell carcinomas of the head and neck (SCCHN) is uncommon, and 75% of SCCHN metastases appear within 18 months of the diagnosis of the primary tumor.[16] In prior studies, dermal metastases have been reported in 0.8% to 3% of patients.[16,17]

Unlike breast, lung, or colonic cutaneous metastases, metastatic SCCHN is much more heterogenous in its clinical presentation. SCCHN cutaneous metastases most often present as painless, solitary, or grouped nodules or erythematous macules; however, they also frequently mimic infectious skin lesions, such as erythema annulare, contact dermatitis, tinea, or erysipelas. Less common clinical presentations include ulcers, erythematous patches, or plaques.[18] SCCHN metastases can appear clinically similar to psoriasis, lichen simplex chronicus, prurigo nodularis, lichen sclerosus, syphilis, discoid lupus erythematosis, seborrheic keratoses, amelanotic melanoma, poromas, chronic abscesses, actinic keratoses, lichen planus, Merkel cell carcinoma, nummular dermatitis, sporotrichosis, and a multitude of other conditions. SCCHN metastases can even masquerade as a primary cutaneous squamous cell carcinoma.[16–18]

Metastases from SCCHN tend to be close to the site of the primary tumor and lymph node metastases, as seen with most cutaneous metastases of internal origins. The majority of SCCHN metastatic lesions occur above the diaphragm, with 98% found on the head, neck, or chest wall.[17] This site is also common for metastases from lung, breast, or endocrine primary tumors. Metastases to the abdomen and lower extremities that can be seen with gastrointestinal carcinomas and metastatic melanoma are extremely rare with an SCCHN primary, and only a few reported cases exist in the literature.[17]

Although SSCHN disease stage does not appear to correlate with the occurrence of cutaneous metastases, the presence of cutaneous metastases is a very poor prognostic factor with an average survival time of 3 to 7 months in these patients.[17] This is a comparable survival time to other cutaneous metastases from internal malignancies. Treatment of metastatic SCCHN is difficult and depends on the location involved and extent of metastasis. A multidisciplinary approach is often warranted.

Colon

Cutaneous metastases of rectal adenocarcinoma are seen in fewer than 4% of all patients with rectal cancer; however, there are infrequent reports of isolated colorectal metastases to the skin without evidence of visceral disease.[19]

Skin manifestations of colorectal cancer, which can be varied in appearance, present as solitary or multiple nonspecific nodules. They most often appear on the perineal region and abdominal wall; for instance, the Sister Mary Joseph nodule represents metastasis to the umbilicus.[20] They can also be located on a surgical scar or colostomy site as a small subcutaneous or intradermal nodular lesion.[2,21] The nodules are usually asymptomatic and tend to be firm, rubbery,

and painless. Clinically, they may resemble infundibular cysts, lipomas, neurofibromas, granulomas, condyloma acuminatum, scars, erythema annulare centrifugum, allergic contact dermatitis, and benign soft tissue tumors.[21] Histopathologically, cutaneous metastases are centered in the dermis, often spread out to the subcutaneous tissues. The epidermis is usually, but not always, spared with a thin band of papillary dermis of compressed collagen separating the tumor from the epidermis. These lesions are composed of well to poorly differentiated mucin-producing cells arranged in glandular solid, or single-cell patterns.[1]

Ovarian

Cutaneous metastases from a primary ovarian cancer occur in 3.5% to 4% of patients, and adenocarcinoma and serous cystadenocarcinoma of the ovary are most often associated with the presence of cutaneous metastatic disease.[1] Patients typically present with multiple, painless, flesh-colored nodular lesions located on the lower part of the abdomen or chest.[1,3,4] Some patients may also develop metastatic lesions at an incisional site, which may be misconstrued as a hypertrophic scar or keloid.[1] Less common presentations include an umbilical Sister Mary Joseph nodule, erythematous herpetiform lesions, erysipeloid lesions, and scarred or indurated plaques.[1,4,22] Nodular ovarian cutaneous metastasis may mimic adnexal neoplasms, epidermal inclusion cysts, herpes zoster, seborrheic keratoses, abscesses, and lipomas. Erysipeloid lesions may mimic conditions such as erysipelas, cellulitis, mastitis, abscesses, radiation dermatitis, and erythema migrans. Scarred or indurated lesions may be mistaken for scars, hypertrophic scars, keloids, dermatofibromas, dermatofibrosarcoma protuberans, sarcoidosis, morphea, or a foreign body reaction. Isolated presentations include an inflammatory metastatic carcinoma of the thighs, vulva, and breast; lymphatic carcinomatosis presenting as scleroderma; and a dermatitislike eruption.[1]

Genito-urinary

The overall incidence of cutaneous metastases from any type of urologic cancer is 1.1% to 2.5%.[23] Transitional cell carcinomas are the most common bladder tumors that metastasize to the skin.[1] Cutaneous metastases from the bladder are frequently present in the pubic or umbilical region, on the scrotum, and on the legs.[1,9] The presenting lesions vary between patients but commonly include single nodule or multiple nodules, lesions resembling contact dermatitis, red-to-violet papules, cystic lesions, rubbery subcutaneous nodules, indurated plaques, plaques similar to cellulitis, zosteriform lesions, or keratoacanthomalike tumors.[1] Similar to the majority of other malignancies, most cases of cutaneous metastases from transitional cell carcinoma present during the advanced stages of diseases, which leads to a poor prognosis.[23]

Thyroid

Cutaneous metastases of thyroid cancers are rare; papillary carcinoma is reported most frequently, followed by follicular, anaplastic, and medullary carcinoma.[1] Cutaneous manifestations are mostly seen in disseminated disease and rarely are a manifestation of occult thyroid cancer.[20,24,25] The median survival in patients with thyroid cancer after the diagnosis of skin involvement is 19 months.[20]

Metastases may present as pruritic, nontender, slow-growing, erythematous, single of multiple nodular lesions on the scalp, face, or neck in patients with a history of thyroid cancer.[1,20] The scalp is the most common site of skin metastases in thyroid cancer, with ulceration being uncommon.[26] Other sites of metastasis can include the postthyroidectomy scar, sacral area, abdominal wall, chest, scrotum, chin, and shoulder.[1] Rare cases of carcinoma erysipeloides associated with long-standing anaplastic thyroid carcinoma and multiple pulsatile nodules on the face, suggesting Kaposi sarcoma, have also been observed.[1,26]

Esophagus

Less than 1% of patients with metastatic disease have cutaneous involvement. Cutaneous metastases from esophageal neoplasia are very rare, and they have been mainly described from esophageal adenocarcinoma with an average survival time of 3 months after the development of cutaneous metastases.[27,28] Cutaneous metastases occur most commonly on the abdominal wall, often after invasive procedures for diagnostic or therapeutic purposes.[29] Metastatic lesions may also occur on the skin of the extremities and back,[30] on the lips, and frontal or temporal regions of the scalp.[28] The clinical presentation of cutaneous metastatic lesions is variable; they can manifest as solitary, fixed, painless, subcutaneous nodules; erythematous papules; areas of alopecia (like alopecia areata); erysipeloid or zosteriform lesions; angiomatous lesions; and, rarely, keratoacanthomalike lesions.[28,31]

Gastric

Gastric carcinoma is a common source of cutaneous metastases.[1] Cutaneous metastases usually appear late in the disease course but may be the presenting sign.[32] Gastric cancer commonly metastasizes to the umbilicus, resulting in a Sister Mary Joseph nodule. Metastases have also been reported to appear on the head and neck area, axilla, chest, and the fingertips.[2,33]

Cutaneous metastases secondary to gastric cancer can manifest as multiple discrete, slow-growing, hard nodules[33]; however, several other patterns have also been described. These include cellulitis/erysipelaslike erythematous plaques, inflammatory metastatic carcinoma, carcinoma en cuirasse, and zosteriform lesions.[1,32,34] There are other reports of metastatic signet-ring cell carcinoma of the gut, presenting as firm nodules, indurated plaques, vegetative lesions, and carcinoma erysipeloides.[35]

Conclusions

The most common presentation of cutaneous metastases appears in the form of painless, subcutaneous, firm nodules, often near the site of the primary malignancy, surgical scar, or metastatic lymph node, generally confirmed by histopathologic examination. Metastatic disease to the skin confers a very poor prognosis, and about half of the patients will expire within 6 months after diagnosis despite intervention. Prompt recognition of cutaneous metastases can prevent unnecessary diagnostic workup or treatment and provide insight into disease prognosis. Treatment of cutaneous metastases will vary on a case-by-case basis and symptomatology but includes excision of the lesion, chemotherapy, immunotherapy, radiation, and/or palliative care.

Acknowledgments

Clinical photographs provided by permission: Vivian Shi, MD, and Melody Maarouf, MD, University of Arizona Dermatology, and Michael Warso, MD, University of Illinois Department of Surgery.

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