Cutaneous metastases
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Cutaneous metastases from carcinoma are relatively uncommon in clinical practice, but they are very important to recognize. Cutaneous metastasis may herald the diagnosis of internal malignancy. Early recognition can lead to accurate and prompt diagnosis and timely treatment, but a high index of suspicion is required because the clinical findings may be subtle. The recognition of cutaneous metastases often dramatically alters therapeutic plans, especially when metastases signify persistence of cancer originally thought to be cured. Some tumors metastasize with predilection to specific areas. Recognition of these patterns can be useful in directing the search for an underlying tumor.

Pathophysiology

The breast, stomach, lung, uterus, large intestine, and kidneys are the most frequent organs to produce cutaneous metastases. Cancers that have the highest propensity to metastasize to the skin include melanoma (45% of cutaneous metastasis cases), breast (30%), nasal sinuses (20%), larynx (16%), and oral cavity (12%). Because breast cancer is so common, cutaneous metastasis of breast cancer is the most frequently encountered type of cutaneous metastasis in most clinical practices. Although some tumors are very common, they may not necessarily eventuate in metastasis in a manner that parallels their incidence in the overall population. For example, prostate cancer is very common, but cutaneous metastasis from prostate carcinoma is relatively uncommon.

The incidence of cutaneous malignancy varies. In some autopsy studies of patients with metastatic carcinoma, as many as 9% of individuals were noted to have cutaneous metastases. Other studies suggest a range of 3-4%. A 2003 meta-analysis estimates a rate of cutaneous metastasis of 5.3%.
**History**

- In most cases, cutaneous metastases develop after the initial diagnosis of the primary malignancy (eg, metastases of breast carcinoma involving the chest wall several years after a mastectomy). In a very small percentage of patients, metastases may be discovered at the same time or prior to the diagnosis of a primary tumor (eg, lung and renal cell carcinoma presenting as scalp metastases in a man who otherwise appears well and gives no history of prior malignancy).
- Patients may present with rapidly developing nodules or tumors. Although asymptomatic in most instances, pain and tenderness may be noted. Any rapidly developing or eruptive lesions should warrant careful consideration of the possibility of metastasis. The term carcinoma of unknown primary site (CUPS) is used when dealing with a metastasis that occurs before primary tumor diagnosis. In dealing with cutaneous CUPS, the age, the sex, and the affected skin region of the patient as well as the histology of the lesion are important clues that are useful in determining a likely primary tumor. Immunohistochemistry can be invaluable in identifying the tissue of origin.

**Physical**

- Most cutaneous metastases occur in a body region near the primary tumor. The most common presentation of cutaneous metastases is nodules. The nodules are often nonpainful, round or oval, firm, mobile, and rubbery in texture. The nodules are usually flesh colored, although they may also be other colors (eg, from flesh colored to brown or blue-black). Often, the nodules from the metastases of renal cell carcinoma and occasionally thyroid carcinoma are red and purple. They vary in size from barely perceptible lesions to large tumors. Multiple nodules appear rapidly before growth slows down.
- Carcinoma may engender a brisk inflammatory response mimicking cellulitis. This pattern is referred to as inflammatory breast carcinoma. When many telangiectatic blood vessels are encountered, the pattern is referred to as carcinoma telangiectodes. Occasionally, the skin may have an orange peel–like appearance (peau d'orange), and/or changes in the local blood flow may occur. In other cases, the skin may feel firm and have a breastplatelike appearance, which is referred to as carcinoma en cuirasse.
- Breast cancer is one of the most common malignancies to spread to the skin. The most common sites of cutaneous metastasis are the chest and abdomen.
- The most likely site for cutaneous metastases in women is the chest; less common sites include the scalp, the neck, the upper extremities, the abdomen, and the back.
- Occasionally, patients with metastatic breast cancer may have a firm, scarlike area in the
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Cutaneous metastases usually occur on the scalp. When this occurs on the scalp, hair may be lost, and the clinical appearance may mimic alopecia areata, except that the skin exhibits marked induration on palpation. This condition is known as alopecia neoplastica, as shown in the images below.

- Lung cancer is the most frequently encountered metastasis in men. The most common site for cutaneous metastases in men is the chest, followed by the abdomen and the back. Other areas (in decreasing order of frequency) include the scalp, the neck, the face, the extremities, and the pelvis. For women, the most common areas (in decreasing order of frequency) are the chest, the abdomen, the back, and the upper extremities.
- Gastrointestinal cancers (usually colon and stomach cancer) often metastasize to the abdomen and the pelvis. Gastrointestinal carcinomas may spread along the urachus and produce nodules at the umbilicus. The presentation of nodules at the umbilicus has been referred to as a Sister Mary Joseph nodule. Sister Mary Joseph was a nurse at the Mayo Clinic who helped prepare patients prior to operation for gastrointestinal surgery. She noted that the nodules at the umbilicus were an ominous sign of extensive involvement of colorectal carcinoma.
- About 60,000 Americans develop malignant melanoma each year, but only 9000 deaths are attributed to malignant melanoma annually in the United States. When malignant melanoma metastasizes, the skin is commonly involved. In men, melanomas are likely to metastasize to the chest, the extremities, and the back. A large portion of female patients have metastases to the lower extremities. Metastases of melanoma may simulate blue nevi and may be epidermotropic or simulate primary cutaneous melanoma. A zosteriform appearance reportedly is rare.
- Cutaneous metastases from squamous cell carcinoma in the oral cavity usually remain in the local area, most often affecting the neck and the face.
- Renal cell carcinoma may metastasize to the scalp, to operative scars, or on many other surfaces. Because of the prominent vascular supply of renal cell carcinoma, lesions may mimic a hemangioma or a pyogenic granuloma.
- Metastases from the ovary and the uterus are seen in the skin of the lower abdomen, the groin, or the upper thigh.
- Common cutaneous metastasis sites and their probable primary sites are as follows:
  - Metastasis to scalp - Breast, lung, kidney
  - Metastasis to neck - Oral squamous cell carcinoma
  - Metastasis to face - Oral squamous cell carcinoma, renal cell, lung
  - Metastasis to extremities - Malignant melanoma, breast, lung, renal, intestinal
  - Metastasis to chest - Breast, lung, malignant melanoma
  - Metastasis to abdomen - Colon, lung, stomach, breast, ovary
  - Metastasis to umbilicus - Stomach, pancreas, colon, ovary, kidney, breast
  - Metastasis to pelvis - Colon
  - Metastasis to back - Lung

Causes
Metastases arise as disconnected extensions of a primary tumor. This occurs when cancerous cells break away from a primary tumor and spread elsewhere. By definition, this makes the primary tumor malignant. Determining whether a primary neoplasm will metastasize is difficult because of many factors, but, generally, the larger and faster a neoplasm grows, the more likely it will metastasize.

The mechanism for metastasis varies, and several different pathways are thought to be important. Regional spread through tissue most often occurs through body cavities, especially the peritoneal cavity. Transplantation can be caused by mechanical transport of tumor fragments by instruments during surgery or other invasive procedures but rarely occurs. Lymphatic and vascular routes are the most common pathways, although differentiating the routes is difficult because they are interconnected. Lymphatic spread is the most common pathway for the initial spread of carcinoma. Hematogenous spread is commonly associated with metastasis from sarcomas, although carcinomas may also use this pathway.

Cells may have a predictable metastatic spread, but unusual sites of metastasis may be encountered. The use of sentinel lymph node studies is an attempt to define likely paths of metastasis to identify whether metastasis has occurred. Unfortunately, for some tumors like melanoma, there is as of yet no clear evidence that lymphatic spread is the predominant mode of metastasis. Although sentinel node studies may provide useful information on prognosis, this does not enhance overall survival.

Many steps have to be met for metastasis to occur. The primary tumor has to be large enough to release a sufficient amount of neoplastic cells into the circulatory or lymphatic system. These cells need certain properties, such as cell suspension and mitotic rate, to survive while in circulation. Most single neoplastic cells released are destroyed by the immune system, whereas clusters of 6 or 7 cells have a better chance of metastases. To establish metastases once the neoplastic cells are in the circulation system, the neoplastic cells need to attach and penetrate vessel walls. The most common attachment sites are based on the circulatory path, but the neoplastic cells also have affinities to certain target tissues. Once attachment occurs, a thrombus forms around the neoplastic cells through endothelial cell injury. This thrombus serves as protection for the neoplastic cells. The new metastasis establishes itself and obtains nutrition initially through diffusion and then it forms its own vessels.

Laboratory Studies

The diagnosis of metastatic carcinoma hinges on histopathologic evaluation of involved skin. Tumors may show characteristics of the underlying tumor, or they may have a more anaplastic appearance. In the situation of an anaplastic tumor, immunohistochemical marker studies and ultrastructural examination may help delineate the tissue of origin.

Punch or excisional biopsy usually provides sufficient tissue for diagnosis. Fine-needle aspiration cytology can also be useful in certain circumstances.

Carcinoma immunophenotypes, with the location and antibody positivity/negativity, are as follows, with (+) indicating "always positive" and (-) indicating "negative but with rare exceptions." Additionally, CK is isoenzymes of creative kinase, TTF is thyroid transcription factor, Ber-EP4 is antihuman epithelial antigen, WT-1 is Wilms tumor protein, CEA is
carcinoembryonic antigen, ER is estrogen receptor, and CA is cancer antigen.

- Breast - CK7 (+), CAM 5.2 (+), vimentin (-), TTF-1 (-), Ber-EP4 (+), WT-1 (-), DPC4 (-)
- Lung adenocarcinoma - CK7 (+), CAM 5.2 (+), CEA (+), Ber-EP4 (+), WT-1 (-), DPC4 (-)
- Colorectal - CK20 (+), CAM 5.2 (+), CK17 (-), CK19 (+), CEA (+), TTF-1 (-), Ber-EP4 (+), S100 (-), WT-1 (-), DPC4 (-)
- Gastric - CAM 5.2 (+), vimentin (-), TTF-1 (-), ER (-), Ber-EP4 (+), WT-1 (-), DPC4 (-)
- Prostate - CK7 (-), CK20 (-), CAM 5.2 (+), CD5/6 (-), CK17 (-), CEA (-), vimentin (-), TTF-1 (-), ER (-), Ber-EP4 (+), S100 (-), WT-1 (-), DPC4 (-)
- Pancreas - CK7 (+), CAM 5.2 (+), vimentin (-), TTF-1 (-), ER (-), Ber-EP4 (+), S100 (-), WT-1 (-), DPC4 (-)
- Renal - CK7 (-), CK20 (-), CAM 5.2 (+), CEA (-), TTF-1 (-), CA125 (-), ER (-), CD10 (+), WT-1 (-), DPC4 (-)
- Neuroendocrine - CK20 (-), CK5/6 (-), CA125 (-), ER (-), Ber-EP4 (-), WT-1 (-), DPC4 (-)
- Squamous cell carcinoma - CK7 (-), CK20 (-), CK5/6 (+), CA17 (-), TTF-1 (-), CA19.9 (-), CA125 (-), ER (-), Ber-EP4 (-), CD10 (-), S100 (-), WT-1 (-), DPC4 (-)
- Merkel cell carcinoma - CK7 (-), CK20 (+), CK5/6 (-), CEA (-), CEA (-), CA125 (-), Ber-EP4 (+), CD10 (-), S100 (-), WT-1 (-), DPC4 (-)

Immunohistochemical screening studies can be used in cases in which no clues point to a particular type of underlying cancer. Immunohistochemical markers and the cellular tissue of origin are as follows:

- Cytokeratins AE1/AE3 and CAM 5.2 - Epidermis and appendageal tumors
- Desmin - Smooth muscle tumors
- Vimentin - Mesenchymal cells, melanoma, lymphoma, sarcoma
- Carcinoembryonic antigen - Glandular or gastrointestinal tumors
- S-100 - Melanocytic tumors, tumors of eccrine or apocrine glands
- CD34 - Vascular tumors, dermatofibrosarcoma protuberans, angiosarcoma
- Chromogranin - Neuroendocrine cells
- Prostate-specific antigen - Prostate carcinoma

Screening immunophenotypes for undifferentiated neoplasms are as follows:

- Carcinoma - AE1/AE3 (positive), vimentin (negative), LCA (leukocyte common antigen) (negative), S-100 (negative)
- Sarcoma - AE1/AE3 (negative), vimentin (positive), LCA (negative), S-100 (negative)
- Lymphoma - AE1/AE3 (negative), vimentin (negative), LCA (positive), S-100 (negative)
- Melanoma: AE1/AE3 (negative), vimentin (positive), LCA (negative), S-100 (positive)

Imaging Studies
- MRI, CT, and ultrasonography can be used in select cases to gauge the extent of metastases or to identify metastases if biopsy samples are inconclusive. Imaging studies are also of value when performing a biopsy is dangerous because of proximity to vital organs.

- Fluorine 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging is useful in the staging of melanoma, especially for American Joint Committee on Cancer (AJCC) stages III and IV. 4

- Exciting recent developments include serologic testing for immune complexes. The serum TA90 immune complex assay developed at M.D. Anderson Cancer Center and licensed through Quest Diagnostics can predict the likelihood of melanoma recurrence with 70% sensitivity and 85% specificity. 5 Similar studies are being developed for other types of cancer to help identify patients at high risk for metastasis.

- A biopsy of the skin helps in confirming a diagnosis of tumor. The pattern noted and the microscopic appearance often suggest the likely tissue of origin.

**Histologic Findings**

The initial diagnosis can be made by examining frozen sections, but the final diagnosis should be reserved until permanent sections are included. Generally, the histologic features of the metastases are similar to the primary tumor, although metastases may be more anaplastic and exhibit less differentiation. Cases, such as renal cell carcinoma, can be identified through characteristic histologic findings, but, usually, metastases are only classified broadly as adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma. Note the images

Certain attributes distinguish metastases from the primary site. Some features include neoplastic cells in lymphatic and blood vessels, a large portion of neoplasm in the deep reticular dermis, and subcutaneous fat and neoplastic cells lined up between collagen bundles. Metastatic tumors are usually round, discrete tumor lobules in the dermis, with a Grenz zone, and are usually unassociated with the epidermis. Physical patterns vary among different carcinomas. Fibrosis and inflammation may be present. Vascular involvement is rare. Sometimes, unusual patterns can be identified. Some primary melanomas may arise in the dermis and simulate a metastasis. 6 On the other hand, some metastases may be epidermotropic and simulate a primary epidermal tumor.

Paget disease typically has a distinct clinical and histologic presentation, with involvement of the nipple or the areola. Symptoms may include an eczematous patch, with intense scaling, pain,
and bleeding in later stages. Paget disease may be a sign of underlying breast, genitourinary, or colon cancer, or it may be a primary neoplasm of indeterminate glands in the skin. In extraordinary situations, lesions may be pigmented and epidermotropic and simulate melanoma.

Determining the presence of metastases is important in staging. FDG-PET scanning may be particularly helpful in the staging of cutaneous malignant melanoma for AJCC stages III and IV to identify soft tissue metastases.

**Medical Care**

- Effective treatment depends on treatment of the underlying tumor. Palliative care is given if lesions are asymptomatic and the primary cancer is untreatable. This care includes keeping lesions clean and dry and debriding the lesions if they are bleeding or crusted. Hydrocolloid dressings may be used to help prevent secondary infection.
- Studies indicate that imiquimod 5% cream (Aldara) may lead to regression of metastasis in some cases of melanoma.
- Liquid nitrogen cryotherapy, photodynamic therapy, and conventional surgery also may be useful for palliation of skin metastasis.
- Short wavelength radiation therapy may be helpful to provide symptomatic relief for painful lesions, using superficial electron beam therapy. Cryotherapy with temperature probe control, carbon dioxide laser therapy,\textsuperscript{8,9} electrochemotherapy,\textsuperscript{10} and other treatment approaches may also be of value. Pulsed dye laser may be of value to reduce blood flow to highly vascularized metastases. Intrallesional chemotherapy and cytokines can be helpful, and topical retinoids or immune modulators, such as imiquimod, offer promise in select cases.

**Surgical Care**

In many cases, cutaneous metastasis can cause disfigurement or social embarrassment, or it can diminish the quality of the patient's life. Excision and removal of metastasis may be warranted to enhance the patient's quality of life, but they do little to increase survival. Simple excision is usually the treatment of choice.

**Medication**

Medical therapy is limited to treatment of the underlying neoplasm. Surgical approaches are generally most effective as a temporizing measure for cutaneous metastases. Medical
camouflage with cosmetics (eg, Dermablend) may be of value to disguise visible metastases for cosmetic purposes.