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REVIEW

Cutaneous Metastases of Internal Tumors☆,☆☆

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Abstract Cutaneous metastases are relatively rare in clinical practice and their diagnosis requires a high index of suspicion because clinical findings can be subtle. These metastases reveal the presence of disseminated malignant disease and can lead to the diagnosis of unsuspected internal tumors or the spread or recurrence of an already diagnosed tumor. Early recognition of cutaneous metastases can facilitate prompt and accurate diagnosis resulting in early treatment; however, they are generally indicative of a poor prognosis. Some tumors have a predilection to metastasize to specific areas. Recognition of these patterns provides essential information that can guide the search for the underlying tumor.

PALABRAS CLAVE
Metástasis cutáneas;
Cascada metastásica;
Nódulo;
Diseminación;
Patrones metastásicos;
Inmunohistoquímica

Metástasis cutáneas de origen visceral

Resumen Las metástasis cutáneas son relativamente raras en la práctica clínica. Su diagnóstico requiere un alto índice de sospecha, pues los hallazgos clínicos pueden ser sutiles. Las metástasis cutáneas ponen de manifiesto la presencia de un tumor maligno diseminado y pueden permitir el diagnóstico de neoplasias internas no conocida o indicar la diseminación o recurrencia de otras ya diagnosticadas. Su reconocimiento temprano puede llevar a un diagnóstico preciso y rápido, con el consiguiente tratamiento oportuno, aunque en la mayoría de los casos son indicativas de un pronóstico infausto. Algunos tumores tienen predilección por metastatizar en áreas específicas. El reconocimiento de esos patrones es esencial para dirigir la búsqueda del tumor subyacente.

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Introduction

The presence of metastases is one of the characteristics of malignant tumors that is a threat to the life of the patient and incontrovertibly signals the existence of a systemic disease.[1] Considerable advances have been made in recent years in our understanding of how tumor cells circulating in the blood and in the lymphatic system are able to interact with and pass through the endothelium to reach distant sites, and of the properties that determine whether the cells of these disseminated tumors are able to survive and whether they will remain in a latent state or will be able to form macrometastases.[2] New discoveries concerning early metastatic seeding, parallel progression, self-seeding of circulating tumor cells from the primary tumor, and the induction of premetastatic niches in organs at a distance from the primary tumor are now at the forefront of research.[3]

Skin metastases (SMs) are the result of infiltration of the skin by proliferations of cells from distant malignant tumors.[4,5] The early detection of metastases within the body often requires sophisticated additional tests; however, SMs are usually easily observed on careful, targeted physical examination. Up to a third of SMs are diagnosed before or simultaneously with the primary tumor, and the role of the dermatologist in establishing an adequate clinical suspicion[6,7] is essential.[8] The early clinical recognition of SMs is crucial, as it can lead to the diagnosis of a previously unidentified primary malignant tumor, provide evidence of the dissemination of a previously known tumor, or be an early sign of recurrence of a malignant tumor apparently in remission. The diagnosis of SMs can therefore alter the staging of a malignant disease, with the consequent therapeutic and prognostic implications[9]; their presence will often lead to drastic changes in the management plan, particularly when the metastases indicate the persistence of a tumor thought to be in remission.[10] Furthermore, SMs are easy to biopsy, which facilitates tests of sensitivity of the primary tumor to specific treatments, such as inhibitors of epidermal growth factor or of c-kit/CD117.[11]

Some tumors appear to have a predilection to metastasize to certain areas. Recognition of these patterns can help to target the search for an unknown underlying tumor.[12]

The recent presentation in various countries of a number of retrospective studies of SMs reflects current international interest in this subject.[13]

Etiology and Pathogenesis

Metastases arise when neoplastic cells break away from a primary tumor and disseminate to other sites.[14,15] Several mechanisms involving various pathways are implicated in the development of metastases.[16,17] Hematogenous and lymphatic spread are the most common, although separation of these 2 pathways can be difficult as they are interconnected. Lymphatic spread is the most common initial route of propagation of the majority of malignant tumors and its role in the determination of metastatic patterns is a subject of current research.[18] Regional spread usually occurs through the body cavities, in particular the peritoneal cavity. Tumor-cell transplant due to the mechanical transport of fragments of tumor on surgical instruments during surgery or other invasive procedures can happen but is rare.[19,20]

Traditionally it has been postulated that a series of steps must occur for a metastasis to develop. First, the primary tumor must be large enough to release a sufficient number of neoplastic cells into the circulatory or lymphatic systems. The majority of free neoplastic cells are destroyed by the immune system, whereas groups of 6 or 7 cells appear to have a greater likelihood of forming a metastasis.[21] These cells, in turn, must have certain properties, such as cellular suspension and an adequate mitotic index, in order to survive.[22] Development of a clone with metastatic potential is initially favored by the activation of specific oncogenes[23,24] and the loss of tumor suppressor genes.[25,26] For neoplastic cells in the circulatory system to become established, they must pass through the vessel walls. After the cells adhere to the vessel wall, a thrombus forms around them due to a lesion of the endothelial cells. This thrombus serves to protect the neoplastic cells. The metastasis becomes established and initially obtains its nutrients by means of diffusion phenomena[27]; later it will form its own vessels (angiogenesis).[28,29] In this classical model of cancer development, the metastases correspond to the final stage of the metastatic cascade. However, recent studies suggest a different model, which predicts that the expression of proteins that regulate epithelial-mesenchymal transition promote oncogenesis concomitantly with metastatic spread. In this alternative model, cell spread from the primary tumor can occur at any time during development of the cancer[30] (Fig. 1).

Epidemiology

The true incidence of SMs is unknown. However, the incidence appears to be higher in some recent studies compared with historical series, although this may due to higher rates of biopsy and diagnosis rather than a true increase in the incidence.[31] SMs are a rare finding in clinical practice, and their prevalence varies between 0.7% and 9% of patients with internal tumors, depending on the series.[32]

In theory, any malignant tumor can spread to the skin. However, in practice, a direct relationship has been found between the frequency of different malignant tumors and the appearance of SMs, with the most common malignant tumors in each sex being those that most frequently give rise to SMs. Thus, breast cancer in women, lung cancer in men, and adenocarcinomas of the digestive tract in both sexes are the most common origins of SMs.[33]

A meta-analysis published in 2003 reviewed 1080 cases of SM in 20 380 cancer patients, and reported an estimated SM rate of 5.3%.[34] In a classic study from 1972, Brownstein and Helwig[12] examined the distribution of SMs in 724 male and female patients. In men, the most common malignant tumors that metastasized to the skin were carcinoma of the lung (24%), colorectal carcinoma (19%), melanoma (13%), and oral squamous cell carcinoma (12%), whereas, in women, the most common tumors were breast cancer (69%), colorectal carcinoma (9%), melanoma (5%), and carcinoma of the ovary (4%). The area most commonly affected was the anterior chest wall; the lower limbs were the least common sites. In men, around 75% of SMs were observed on the head

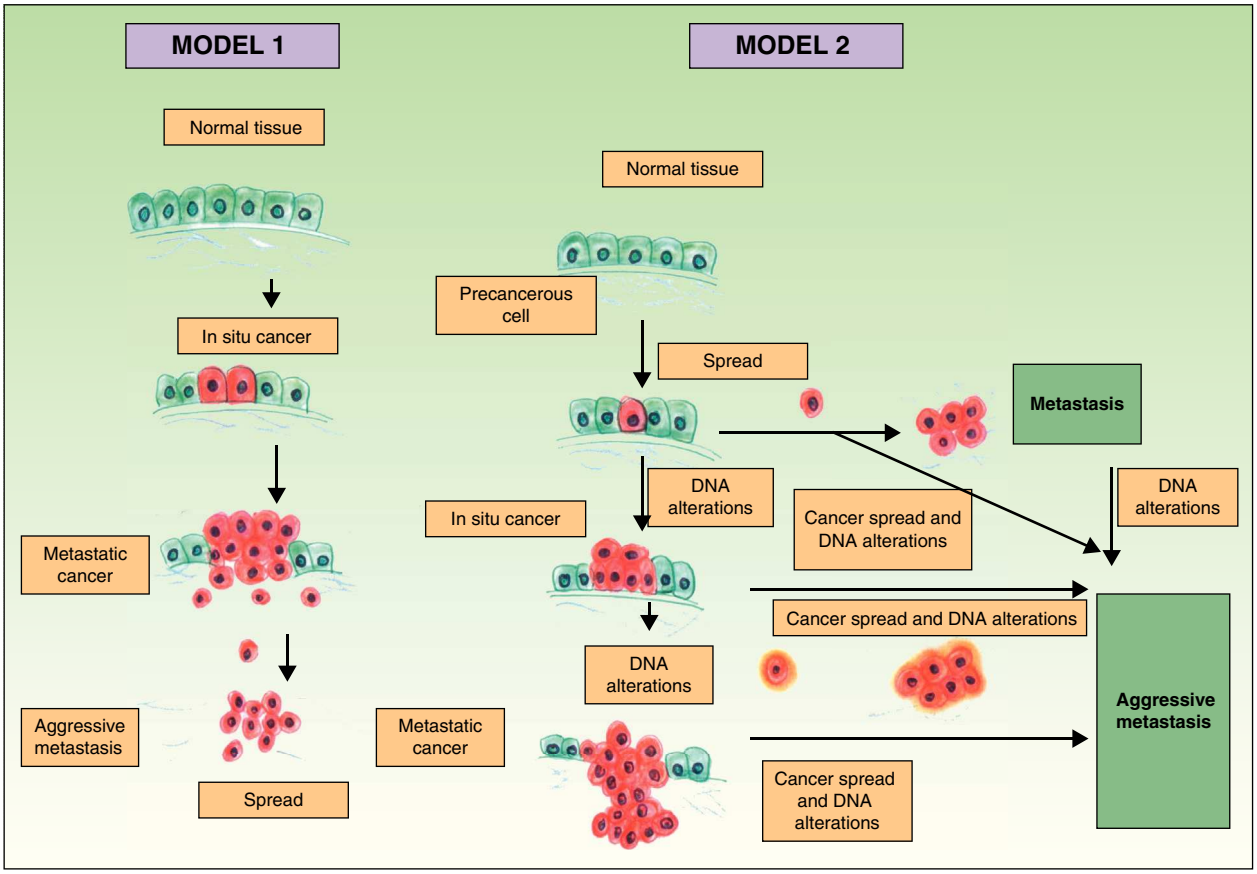

Figure 1 Pathogenesis of skin metastases. Diagram that compares the classical model of metastasis production with the most recent hypotheses. Source: Sánchez-García I.[30]

and neck, whereas, in women, 75% of cases were found on the anterior chest wall and on the abdomen. In general, the back was an uncommon site for SMs.[35]

In women the most common site of SMs is the thorax, followed by the abdomen, the back, the upper limbs, the scalp, and the neck; in men, the thorax is also the area most commonly affected, followed, in descending order of frequency, by the abdomen, the back, the scalp, the neck, the face, the upper and lower limbs, and the pelvis. The frequency of SMs by age and sex is summarized in Table 1. SMs are very rare in children. The most common primary tumors that produce SMs in this age group are rhabdomyosarcoma and neuroblastoma.[36]

Clinical Presentation

In the majority of cases, SMs develop after diagnosis of the primary tumor. However, in a notable proportion of patients (up to a third of cases), the metastases are discovered prior to[37] or simultaneously with[38] the primary tumor.

SMs tend to appear in a body region close to the primary tumor. Presentation is typically in the form of rapidly growing, mobile, round or oval nodules of firm or elastic consistency[39]; they may be ulcerated.[40] However, they can present as any primary or secondary skin lesion[41] (Fig. 2). The nodules are usually skin-colored, although metastatic nodules from renal cell or thyroid carcinoma often have

Table 1 Frequency of Skin Metastases According to Age and Sex (in Decreasing Frequency).

Age	Men	Women
< 40 y	Melanoma	Breast cancer
	Colon cancer	Carcinoma of the colon
	Lung cancer	Ovarian cancer
> 40 y	Lung cancer	Carcinoma of the breast
	Colon cancer	Carcinoma of the colon
	Squamous cell carcinoma of the oral cavity	Lung cancer
		Carcinoma of the ovary
	Melanoma	Melanoma

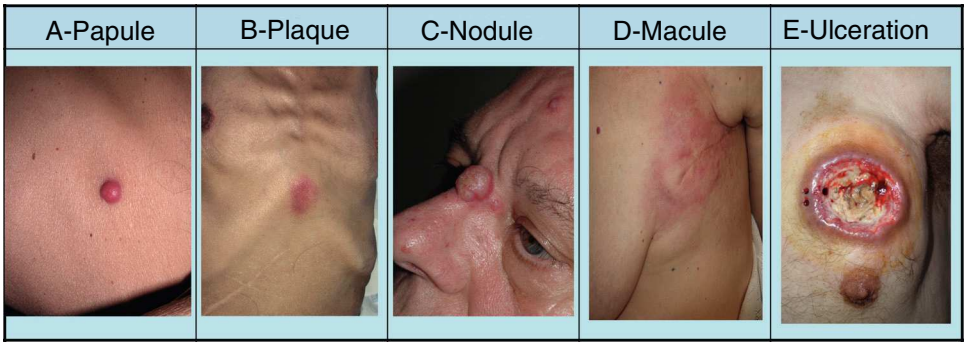

Figure 2 Skin metastases can manifest as primary or secondary skin lesions. A, Metastasis from a gastric adenocarcinoma. Papule of 7 mm diameter on the abdomen. B, Metastasis from an adenocarcinoma of the ovary presenting as a plaque. C, Metastasis from a urothelial carcinoma of the bladder presenting as a nodule. D, Metastasis from an adenocarcinoma of the breast. The lesion started as a macule over the mastectomy scar. E, Ulcerated infiltrated plaque corresponding to a metastasis from an adenocarcinoma of the lung.

a characteristic reddish or violaceous discoloration[42,43] (Fig. 3). Some recent studies report that skin metastases present most often as a single nodular lesion, whereas older studies more commonly reported multiple nodules.[44] This may be because more SMs are now diagnosed earlier.

Although most SMs are asymptomatic, patients may describe pain, particularly with lesions in certain areas, such as subungual metastases.[45]

Gastrointestinal cancers (specifically, colorectal and gastric carcinomas) often give rise to metastases on the abdomen and pelvis. These carcinomas can spread along the urachus to produce umbilical nodules known as Sister Mary Joseph's nodules.[46] SMs from squamous cell carcinoma of the oral cavity usually arise in the same body region, and most frequently affect the face and neck. Renal cell carcinoma, among others, typically metastasizes to the scalp and, because it is a highly vascular tumour, the lesions may be confused with hemangiomas or pyogenic granulomas. SMs from hepatocellular carcinoma often develop on the fingers, palms, soles, or the back, while those from gastric carcinoma tend to develop on the head and neck.[47] Thus, the site of an SM can suggest a possible origin (Table 2).

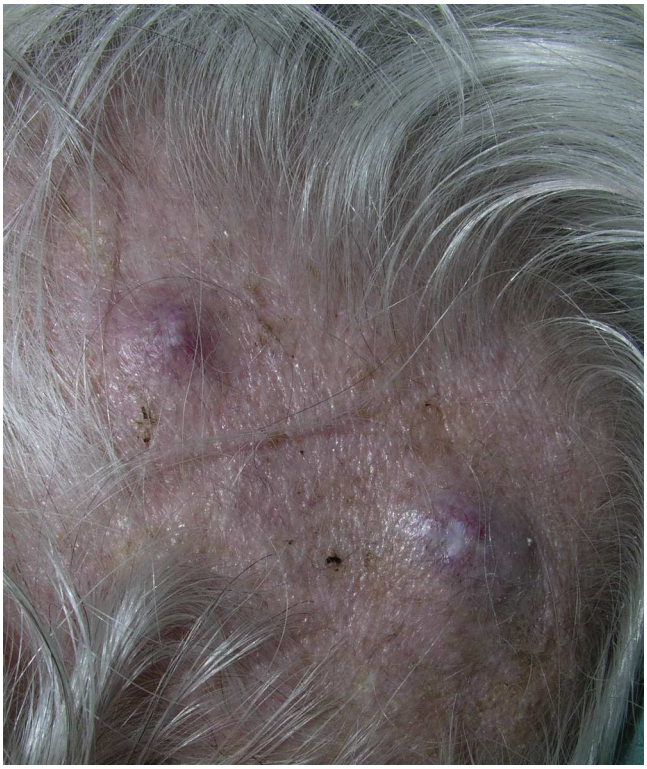

Figure 3 Metastases from a follicular thyroid carcinoma. Violaceous nodules on the scalp with superficial telangiectasias.

Specific Clinical Forms of SMs

A very large number of specific clinical forms of SMs have been described. Erysipeloid or inflammatory carcinoma is often observed in patients with adenocarcinoma of the breast and is not uncommon in other types of cancer (pancreas, rectum, lung, ovary, and parotid).[48,49] It presents as well-defined erythematous lesions that are hot and tender, similar to erysipelas.[50] Lymphatic obstruction by the neoplastic cells can give rise to localized lymphedema with peau d'orange. Lymphedema can cause the skin to become fibrous and yellowish, with a similar appearance to carcinoma en cuirasse[51] or scirrhous carcinoma. This clinical form presents as indurated erythematous plaques that infiltrate the chest wall. It is usually observed in metastases from breast cancer, although it can be a form of presentation of a primary breast tumor or of SMs of other origins.[52] The main differential diagnosis of this presentation is with infectious disorders. Erysipeloid carcinoma localized to the breast can be difficult to distinguish from mastitis. Persistent inflammation that does not respond to conventional therapy must therefore be carefully evaluated to exclude metastatic infiltration, particularly when there is no fever or leukocytosis.[53]

Telangiectatic carcinoma, described by Weber[54] in 1933 in a patient with metastatic breast cancer, is characterized by the appearance of nodules, papules, or purpuric plaques on the chest wall,[55] usually in the proximity of a surgical scar.[56,57]

Zosteriform or herpetiform metastases present as papules, vesicles, nodules, or blisters affecting individual dermatomes,[58,59] mimicking herpes zoster[60,61] (Fig. 4).

Table 2 Most Common Primary Tumors Giving Rise to Skin Metastases According to the Site of the Metastases.

Site of the Skin Metastases	Most Common Primary Tumors
Scalp	Breast, lung, and kidney
Neck	Oral squamous cell carcinoma
Face	Oral squamous cell carcinoma, renal cell, and lung
Chest	Breast and lung
Abdomen	Colon, lung, stomach, breast, and ovary
Umbilicus	Stomach, pancreas, colon, kidney, ovary, and breast
Pelvis	Colon
Lower abdomen, groin, or thigh	Ovary and uterus
Limbs	Breast, lung, kidney, and bowel
Back	Lung

Although their etiology and pathogenesis are not fully understood, most hypotheses suggest there is spread of the tumor cells from the cutaneous lymph vessels to the sensory nerves, via which they reach the dorsal root ganglia.[62,63]

Clown nose is considered to be the result of an SM arising on the tip of the nose, typically from a carcinoma of the lung or breast.[64]

Alopecia neoplastica is defined as hair loss secondary to invasion of the scalp by malignant cells. It can present as 1 or more plaques of scarring alopecia that are often indurated and have a bluish or violaceous color. These plaques must be differentiated from alopecia areata[65] (Fig. 4). The neoplastic cells can destroy the hair follicles by producing fibroplasia induced by the release of inflammatory mediators that bring inflammatory cells into the area, and/or by substitution of the normal cells.[66] Breast cancer is the underlying primary malignant tumor in 84% of patients with alopecia neoplastica.[67]

Paget's disease of the nipple and areola is a skin sign associated with an underlying adenocarcinoma of the breast in 100% of cases.[68] This skin condition is produced by epidermotropic SMs due to the spread of an intraductal tumor along the lactiferous ducts to reach the overlying skin.

Subungual metastases merit special consideration. These metastatic lesions are usually painful and often need to be differentiated from infectious disorders, in particular acute paronychia, or from glomus tumors[69] (Fig. 4). Presentation as painless dactylitis has been reported.[70]

Sister Mary Joseph's nodule or umbilical metastasis is widely described in the literature. This form of metastasis presents as single or multiple, indurated umbilical or periumbilical nodules that can sometimes ulcerate or have a

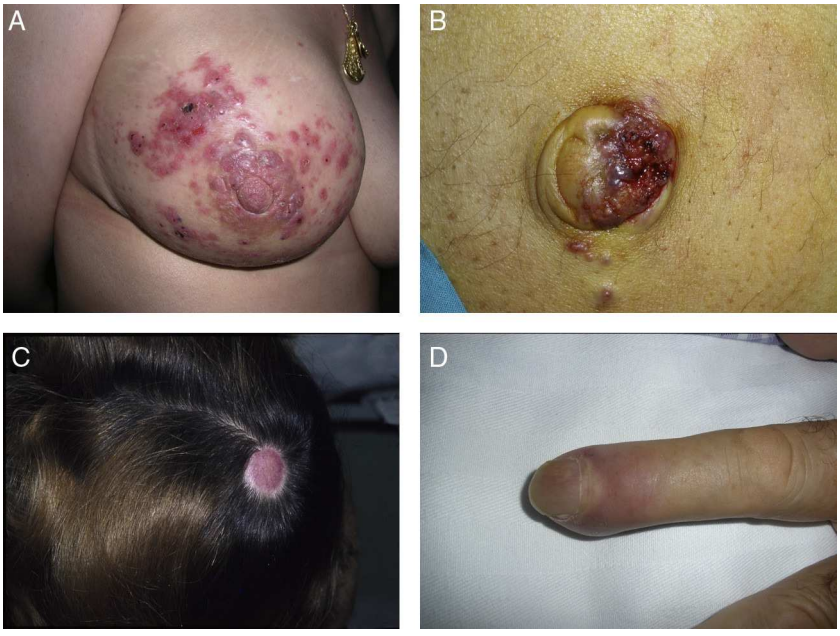

Figure 4 Unusual skin metastases. A, Zosteriform metastases from a ductal adenocarcinoma of the breast. Clusters of infiltrated papules, some confluent and some ulcerated, in a metameric distribution. B, Umbilical metastasis (Sister Mary Joseph's nodule); multiple, confluent, ulcerated papules and nodules in the umbilical and periumbilical regions. C, Alopecia neoplastica. Plaque of alopecia over a metastasis from a ductal adenocarcinoma of the breast in a woman. D. Subungual metastasis. Metastasis from a squamous cell carcinoma of the lung presenting as a painful inflammatory nodule that deformed the distal phalanx of the second finger of the left hand.

friable appearance (Fig. 4). Although the site of the primary tumor is unknown in approximately 29% of cases,[71] the majority of umbilical metastases come from tumors that arise in the stomach, ovary, colon, rectum, or pancreas.[72] The proposed pathogenesis of metastases in the umbilical region includes both contiguous infiltration and spread via the blood or lymph.[73]

Finally, clinically occult metastases are those with no detectable clinical findings but which are discovered as incidental findings on a histopathological examination performed for some other reason.[74]

Differential Diagnosis

The differential diagnosis of SMs is very broad and includes many more disorders in addition to those mentioned above. First we must consider primary skin tumors,[75] both benign (dermatofibroma, pyogenic granuloma,[76] epidermal cyst,[77] adnexal tumors[78]) and malignant (basal or squamous cell carcinoma, melanoma, Merkel cell tumor, angiosarcoma[79]). Other skin diseases to be considered are eczema, erythema annulare centrifugum,[80] erythema multiforme [target-shaped SMs], and vasculitis.[81]

Diagnosis

A detailed medical history and complete physical examination are essential to establish the initial diagnostic suspicion.

The histopathology of SMs may reveal the same characteristics as the tumor of origin, or there may be a more anaplastic appearance. Immunohistochemistry can help to determine the possible origin in the case of undifferentiated tumors. Incisional or excisional skin biopsy is essential to reach a diagnosis. Cytology study by fine-needle aspiration biopsy can be useful in certain circumstances.[82,83] The pattern observed and the microscopic appearance of the tissue often suggest its origin.[84]

In some cases, such as renal cell carcinoma, characteristic histological findings will identify the primary tumor, but the majority of SMs can only be classified in general terms as adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma. It is also necessary to differentiate between metastatic skin lesions and primary skin tumors; as these 2 types of lesion frequently have very similar morphological patterns, immunohistochemical markers can be very useful for their differentiation. Table 3 summarizes the results of the literature review published by Sarya et al.[85] in 2007.

Certain histological features differentiate metastases from primary tumors. Characteristics suggestive of SMs include the presence of neoplastic cells within the lymph and blood vessels, localization of the lesion in the deep reticular dermis and hypodermis, and the presence of neoplastic cells running along the bundles of collagen.[86] Metastatic tumors typically develop as round nodules located in the dermis or hypodermis, and are not usually in contact with the epidermis. This Grenz zone is much more common in metastatic lesions. Fibrosis and inflammation may be evident (Figs. 5 and 6).

Immunohistochemical markers and, sometimes, ultrastructural studies are valuable tools for establishing the origin of SMs.[87] Fig. 7 shows the diagnostic algorithm that should be applied for undifferentiated SMs. The basic recommended battery of markers includes CD45 (for lymphoid tumors), pancytokeratin AE1/AE3 (for the majority of carcinomas), S100 (for melanoma) and CD34 (for vascular tumors and leukemia). The second recommended battery of markers includes lymphoid markers (CD3 and CD20), epithelial markers such as epithelial membrane antigen and carcinoembryonic antigen, chromogranin (neuroendocrine tumors), prostate specific antigen and acid phosphatase (carcinoma of the prostate), thyroid transcription factor

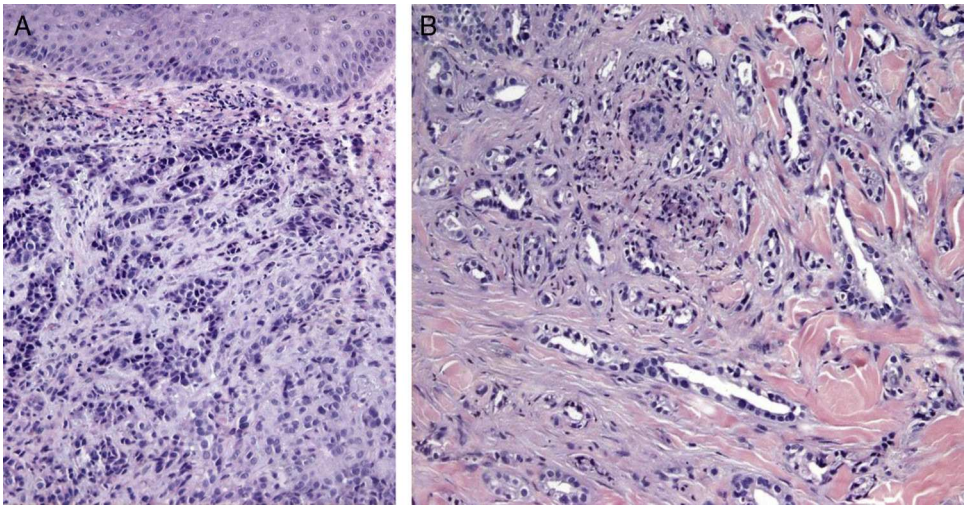

Figure 5 Histological images of skin metastases. A, Dermal metastasis from a poorly differentiated carcinoma of unknown origin. Infiltration of the dermis by cords and nests of epithelioid cells (hematoxylin-eosin, original magnification x10). B, Dermal metastasis from a moderately differentiated adenocarcinoma of the pancreas. Glandular lumens lined by a layer of epithelial cells can be seen between the dermal collagen bundles (hematoxylin-eosin, original magnification x10).

Table 3 Summary of the Immunohistochemical Markers Useful for the Differentiation Between Skin Metastases and Primary Skin Tumors, and Synopsis of the Data Obtained in the Series by Sarya et al.

Antibodies	General Characteristics	Metastatic Carcinomas	Adnexal Tumors	Usefulness
p63	Homolog of p53, expressed in the basal cells of the skin and mucosas and in the myoepithelial cells of the breast, salivary glands, and prostate Positive in SCC at various sites, urothelial carcinoma, BCC, adnexal tumors, 30% of lung cancers, and some pancreatic, biliary, gastric, ovarian, breast, hepatic, renal, colon, and thymus cancers	Negative in the published literature Negative in 25/32, positive in 2/2 from urothelial tumors, 2/8 from lung tumors, 1/2 from gastric tumors, and 2/6 from carcinomas of the breast	Positive in all cases published in the literature Positive in 24/25	Most useful marker However, it should not be used alone
B72.3	Tumor-associated glycoprotein. Expressed in many adenocarcinomas. Useful to differentiate lung cancer from mesothelioma and in adnexal tumors of apocrine origin	Positive 26/31	Negative in 18/25, focally positive in 6/25, and diffusely positive in 1 mucinous carcinoma	Positivity useful in metastatic carcinomas that are positive for p63 and CK5/6
Calretinin	Calcium-binding protein expressed in mesothelial, epithelial, and stromal cells. Used to differentiate adenocarcinoma from mesothelioma and in sex-cord stromal tumors of the testis and ovary	Negative in 23/32, positive in 9 (pancreas, lung, breast sporadically)	Positive in 16/25	Negativity useful in metastatic carcinomas that are positive for p63 and CK5/6
CK5/6	Intermediate-sized cytokeratin expressed in the skin, squamous mucosa, myoepithelial cells of breast, salivary glands, and prostate Positive in SCC, BCC, thymoma, salivary gland tumors, biphasic mesothelioma, and some urothelial, pancreatic, endometrial, breast, and ovarian tumors	Negative in the published literature Negative in 14/32, positive in 18/32	Positive in the published literature Positive in 25/25	Consistent expression in skin tumors. Useful in the panel of markers

Source: Sarya et al.[85] Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

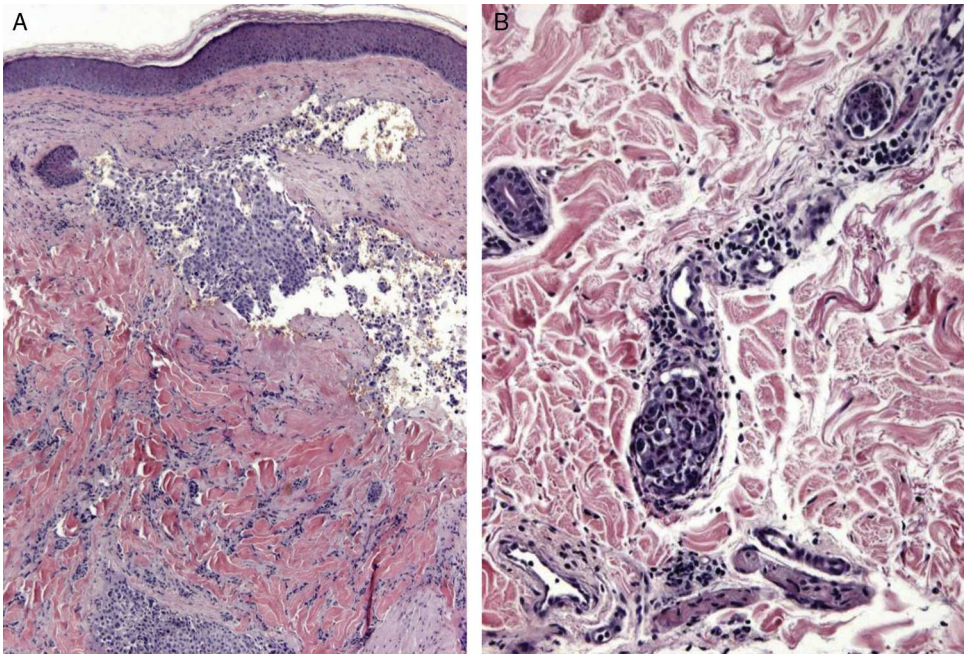

Figure 6 A, Dermal metastasis from a carcinoma of the ovary. Dilated dermal blood vessels occupied by atypical epithelial cells (hematoxylin-eosin, original magnification x20). B, Extensive dermal and vascular infiltration (lymphangitis carcinomatosa) by a poorly differentiated carcinoma.

(carcinoma of the lung), Wilms' tumor protein (carcinoma of the ovary), CDX2[88] (intestinal carcinomas), and Hep Par1[89] (hepatocellular carcinoma).[90] The immunophenotypes of the main tumors that metastasize to the skin are summarized in Table 4.

Ultrastructural studies can be useful in the identification of certain undifferentiated tumors. Desmosomes may be observed in carcinomas, cytoplasmic vacuoles in adenocarcinomas, melanosomes in melanomas, and neurosecretory granules in neuroendocrine tumors. However, ultrastructural studies are long and costly techniques that are not available in the majority of centers and require highly specialized staff; immunohistochemical studies therefore tend to be more useful in clinical practice.

Positron emission tomography (PET) gives a large number of false positives.[91] PET-computed tomography is more

Table 4 Immunophenotypes of the Metastases of the Principal Carcinomas.

Primary Tumor	Immunohistochemical Markers[a]
Breast	CK7 (+), CAM 5.2 (+), vimentin (−), TTF-1 (−), Ber-EP4 (+), WT-1 (−), DPC4 (−)
Adenocarcinoma of the lung	CK7 (+), CAM 5.2 (+), CEA (+), Ber-EP4 (+), WT-1 (−), DPC4 (−)
Colon and rectum	CK20 (+), CAM 5.2 (+), CK17 (−), CK19 (+), CEA (+), TTF-1 (−), Ber-EP4 (+), S100 (−), WT-1 (−), DPC4 (−)
Stomach	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 (−), DPC 4 (+)
Kidney	CK7 (−), CK20 (−), CAM 5.2 (+), CEA (−), TTF-1 (−), Ca-125 (−), ER (−), CD10 (+), WT-1 (−), DPC4 (−)
Neuroendocrine	CK20 (−), CK5/6 (−), Ca-125 (−), ER (−), Ber-EP4 (−), WT-1 (−), DPC4 (−)
Squamous cell carcinoma	CK7 (−), CK20 (−), CK5/6 (+), CK17 (+), TTF-1 (−), CA19.9 (−), Ca-125 (−), ER (−), Ber-EP4 (−), CD10 (−), S100 (−), WT-1 (−), DPC4 (−)

[a] (+) indicates ''always positive'' and (−) ''negative, with rare exceptions''. Abbreviations: Ber-EP4, human epithelial antigen; CA, carcinoid antigen; CEA, carcinoembryonic antigen; CK, cytokeratin; ER, estrogen receptors; TTF, thyroid transcription factor; WT-1: Wilms' tumor protein.

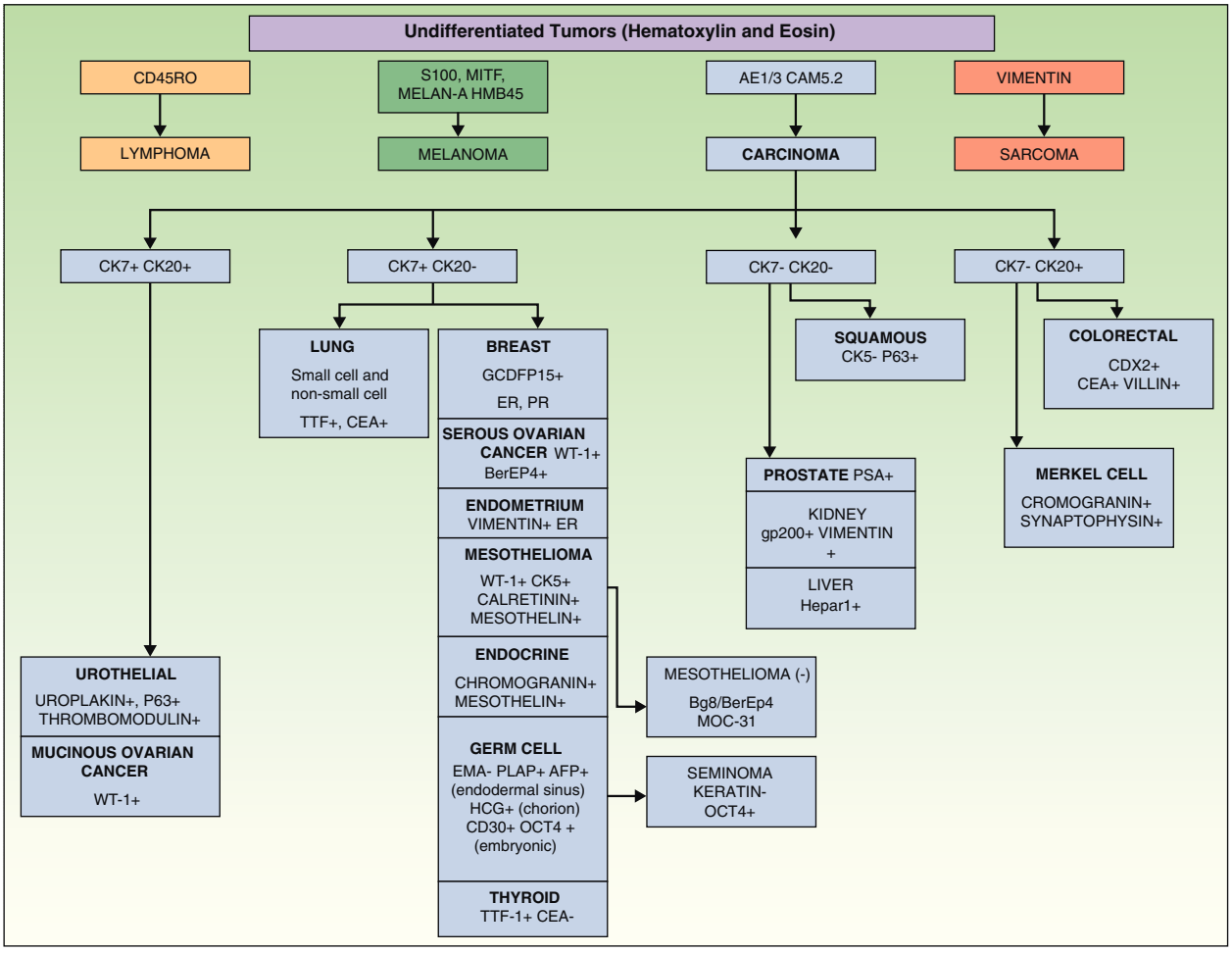

Figure 7 Diagnostic algorithm for undifferentiated skin metastases using immunohistochemical markers.

useful.[92] However, PET may understage tumors in some cases, and small metastases or cerebral lesions may be missed.[93]

Prognosis

The presence of metastatic disease in the skin usually implies widespread systemic disease with a high mortality, although the prognosis varies considerably depending on the type of primary tumor.[94,95] SMs in the absence of other distant metastases only occur in 6.4% to 7.8% of cases.[96] However, it would appear that recent advances in chemotherapy have considerably increased survival.[97]

It is estimated that mean survival after the diagnosis of SMs is 50% at 6 months. A number of survival analyses of patients with SMs have been published, those of Benmously et al.[98] and Schoenlaub et al.[97] being particularly relevant All the analyses report a better survival in cases of breast cancer than in other types of cancer.[99,100]

The mean interval between the diagnosis of a primary tumor and the appearance of SMs varies between 2 and 3 years, but periods of up to 22 years have been reported. Recent studies indicate that this interval varies depending on the type of primary tumor.[101,102] In 141 patients analyzed by Hu et al.,[103] the mean interval between the excision or treatment of the primary tumor and the appearance of SMs was longer in patients with breast cancer (47.2 months) than in those with other tumors, such as lung cancer (15.7 months), colorectal cancer (16.5 months), or stomach cancer (19.8 months). According to some studies, lung cancer is the tumor that most rapidly metastasizes to the skin.[104,105]

Treatment

The therapeutic approach to SMs is based on appropriate management of the primary tumor, if it has been identified.[106] As the presence of SMs implies the coexistence of other metastatic lesions in most cases, chemotherapy directed against the tumor of origin is usually the only option that might achieve complete remission.[107] Surgery and radiation therapy are often used to treat SMs due to the ease of access to the majority of these lesions; however, no clear increase in survival has been demonstrated, and the aim of such treatments is often only palliative.[108] It has been suggested that surgery might improve survival in cases of SM from lung cancer[109] or gastric cancer.[110,111] Radiation therapy has achieved complete responses and lasting palliation in some cases of metastases from renal cell carcinoma.[112] In

1 study, pulsed brachytherapy achieved local control in 41 (89%) of 46 cases of SMs from breast cancer.[113] The topical application of 6% miltefosine solution to SMs from carcinoma of the breast achieved good control of the SM in comparison with placebo in a randomized study.[114] In another study, 10 patients with SM from breast or colon cancer were treated with intratumoral injections of recombinant single-chain antibodies targeted to ErbB2/HER2, with complete remission in 4 cases.[115]

The results after intralesional immunotherapy with interferon alfa or interleukin 2[116] have been variable.[117,118] Reports of metastatic melanoma treated with imiquimod have also been published.[119]

Other locally ablative procedures, such as electrochemotherapy,[120] electrocoagulation, electroporation, and electrovaporization,[121] have also been used successfully. In particular, electrochemotherapy with bleomycin is an option in multiple skin and subcutaneous metastases. One study of electrochemotherapy with bleomycin included 174 tumor nodules in 52 patients with breast cancer[122]; complete responses were observed in 80% and partial remission in 20% after repeated application. Electrochemotherapy with cisplatin has also been evaluated in the treatment of SMs from breast cancer, but was less successful.[123]

No specific chemotherapy has been shown to be the most effective for the systemic treatment of SMs. Observations of SMs that have regressed after systemic chemotherapy are limited to case reports, such as a patient with SMs from cancer of the pancreas treated with gemcitabine,[124] and a patient with urothelial carcinoma of the bladder treated with cyclophosphamide, methotrexate, and 5-fluorouracil.[125] Case reports of SMs from carcinomas of unknown origin treated with cisplatin, gemcitabine, vinorelbine, and paclitaxel have also been published.[126,127] Determination of the expression of certain molecules such as EGF, Her-2/neu kinase, and c-kit tyrosine kinase is very important as it will provide possible targets for systemic therapy. In addition, drugs targeted against stromal function and angiogenesis could prove useful.[128]The palliative treatment of SMs includes adequate management of the pain, pruritus, possible bacterial superinfection, and, in some cases, of the unpleasant smell that these lesions can produce.[129–132]

Conclusions

The majority of tumor recurrences are diagnosed on the basis of a detailed medical history and complete physical examination, combined with the relevant imaging studies. As SMs are usually asymptomatic, active screening is essential.

SMs can play a crucial role in alerting the physician to a possible tumor recurrence or may even be the first sign of previously unknown tumor. The site and distribution of the skin lesions can suggest the organ of origin.

Histological and immunohistochemical study of SMs is required in order to identify the primary tumor.

Early detection of SMs is essential in order to start appropriate treatment. Although strong scientific evidence of a survival benefit is lacking, case reports and certain preliminary publications would suggest that early diagnosis improves life expectancy.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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