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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