Cutaneous Metastasis of Unknown Origin: Dermatologic Features and Pathology

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Abstract

Background: Skin metastases are rare yet crucial indicators of advanced disease. They can mimic various skin conditions, making them challenging to diagnose.

Aims and Objectives: To investigate the incidence rate of biopsy-confirmed cutaneous metastasis and explore the clinical presentation, workup, and diagnostic techniques for skin metastases.

Materials and Methods: Local study involving comprehensive laboratory tests, pathological examination, and immunohistochemistry to identify primary tumors and confirm diagnoses.

Results: Nodules were the most common manifestation of skin metastases, particularly in breast carcinoma. The chest wall and abdomen were frequent sites of involvement. Pathological examination and immunohistochemistry played a critical role in confirming diagnoses, revealing various histopathologic patterns. Immunohistochemical markers assisted in determining tumor origin but required careful interpretation. Monitoring tumor behavior over time provided insights into nature and origins.

Conclusion: Comprehensive workups including laboratory testing, pathology, and immunohistochemistry are essential for accurate diagnosis and management of skin metastases. Careful monitoring of tumor behavior can provide valuable information about its nature and origins.

Keywords: Diagnosis, Skin metastasis, Unknown Primary

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Introduction

Skin metastases are infrequently encountered in the everyday clinical setting of dermatology; however, they hold significant clinical importance as they typically signify the presence of advanced disease. Cutaneous metastases imitate various underlying diseases, making their diagnosis challenging. It is observed in approximately 0.7%–0.9% of individuals diagnosed with cancer.[1] They can manifest as the initial indication of metastatic spread from an internal malignancy,[2] or serve as a warning sign of cancer recurrence long after the treatment of the primary tumor.[3] A high level of clinical suspicion is therefore required.

A study conducted by Dumlao *et al.* in 2022 on the clinical and histopathologic profile of Filipino patients from a tertiary hospital revealed an incidence rate of only 0.12%

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for biopsy-confirmed cutaneous metastasis throughout 7 years.[4]

The patterns of cutaneous metastases exhibit variations between women and men, and among the various types of malignancies. These metastases can be asymptomatic or accompanied by pain and tenderness. They often appear as rapidly expanding, painless nodules within the dermis or subcutaneous tissue while the surface epidermis remains intact.[5] However, they can also resemble inflammatory skin conditions, adding to the complexity of diagnosis.

In this article, we provide a practical method for utilizing available clinical and pathological information to classify skin metastases. It focuses on frequently encountered entities, placing particular emphasis on distinguishing between clinical and pathological differential diagnoses and providing helpful clues for identification. In addition, it specifically addresses metastases of unknown primary origin.

Clinical Presentation

Cutaneous metastases commonly arise from primary tumors such as melanoma, breast, and squamous cell carcinoma of the head and neck.[6] Cutaneous metastases are usually firm in consistency due to the involvement of the dermis or lymphatic structures, or they may appear erythematous. These clinical clues help exclude certain nonvascular conditions from the list of potential differential diagnoses, such as cysts and fibromas. The presence of pigmentation is most commonly associated with cutaneous metastases originating from melanoma.[7] Cutaneous metastases are usually limited to a single anatomical region; however, occasionally, they may be located in various anatomical sites. The upper trunk and abdomen are the most frequent sites of metastases, followed by the head and neck. The umbilicus is also a frequent site of metastases. Metastases to extremities are rare. Metastases may present at the same time as the primary tumor (synchronous) or months to years after the primary tumor (metachronous).[8]

Majority of cutaneous metastases present as single nodules. However, melanoma and carcinomas of unknown origin often manifest as multiple nodules.[8] The presence of locoregional melanocytic metastases can be attributed to angiotropism, an extravascular migratory phenotype that serves as a significant marker and prognostic factor for metastasis in melanoma.[9] The face and scalp are the most commonly affected areas, suggesting that blood vessels and nerve patterns may influence the spread of metastases.[10] These patterns have also been observed in cancers originating from the stomach, lungs, prostate, ovaries, larynx, palatine tonsils, pancreas, colon, parotid gland, thyroid, and uterus.

In patients diagnosed with breast carcinoma, the incidence of cutaneous manifestations of the disease is reported to be 23.9%.[11] The chest wall and abdomen are the most frequently affected sites for breast carcinoma cutaneous manifestation (BCCM), although they can also occur in the extremities and the head/neck region. Given the high prevalence of breast carcinoma, BCCMs are the most observed metastases encountered by dermatologists.

Nodules are the most common presentation of BCCMs. These may be solitary or multiple in number, with skin-colored to erythematous appearance. In general, these are asymptomatic, but in some cases, may be associated with pain, tenderness, and ulceration. This cutaneous presentation coincides with the findings made by Dumlao *et al*.[4] where 92.2% of patients presented with multiple lesions, predominantly skin-colored to erythematous nodules, which were asymptomatic. In cases of extensive cutaneous involvement, cutaneous metastases may mimic other cutaneous diseases and show a distinct pattern.[12]

Carcinoma erysipeloides is also known as inflammatory metastatic carcinoma. It may initially be misdiagnosed as cellulitis or erysipelas, given its presentation with erythematous, elevated, tender patches or plaques that are warm to touch and may have a leading edge. The affected region might display a visibly elevated border and swelling due to blockage of lymphatic vessels.[13,14]

Carcinoma en cuirasse, also known as scirrhous carcinoma, presents as firm, scattered, and reddened plaques with increased tissue density on the chest wall. Occasionally, the skin might take on a yellowish hue and exhibit a tough, fibrous texture.[15]

Telangiectatic carcinoma presents as noticeable dilation of blood vessels (telangiectasia) and papulovesicular lesions that resemble a type of vascular abnormality called lymphangioma circumscriptum. It is commonly found on the chest but can also emerge on the facial area.[16]

Alopecia neoplastica is characterized by circular, indurated regions of hair loss on the scalp, resulting from the

dissemination of cancer cells through the bloodstream. The alopecic scalp area shows erythema, possibly accompanied by scaling, and in some instances, it may conceal a lump beneath the skin or showcase numerous visible dilated blood vessels on the surface. Intense itching has also been observed, sometimes leading to an inaccurate identification of eczema. In instances of documented cancer cases, specific areas of hair loss on the scalp persist beyond the resolution of secondary effects from chemotherapy.[17]

An additional pattern involves the zosteriform manifestation of cutaneous metastasis. This pattern comprises two components: the first pertains to the morphology, which resembles vesicles seen in herpes infections, while the second relates to their dermatomal distribution. Numerous cases of dermatomal metastases were initially misdiagnosed as herpes zoster due to the presence of spontaneous pain resembling herpes zoster in patients displaying zosteriform metastases. Consequently, a significant portion of these individuals were initially administered antiviral medications.[15,18]

Clinical Workup

While clinical clues can provide some indication of the potential location of the primary tumor, it is still advisable to conduct a comprehensive battery of diagnostic laboratory tests. These tests can provide valuable insights and help confirm the suspected origin of the tumor. Relying solely on clinical clues may not always be sufficient for an accurate diagnosis, making thorough laboratory investigations a prudent approach.

In the National Institute for Health and Care Excellence guideline, a patient who presents with metastatic malignancy (in the form of tumor masses or effusions) identified on clinical examination or by imaging, without an obvious primary site, is regarded as having "malignancy of undefined primary origin." The initial diagnosis of metastatic cancer is usually made based on the detection of tumor masses or effusions on clinical examination or by imaging, often on a background of recognized but nonspecific symptoms.[19] Table 1 shows the investigations for the initial diagnostic phase.

Table 1: Investigations for the initial diagnostic phase from the National Institute for Health and Care Excellence (2010)

Detailed clinical history and physical examination
Blood tests (e.g., complete blood count, liver function tests, renal function tests)
Imaging studies
CT scan of the chest, abdomen, and pelvis
PET scan
MRI of specific areas, if indicated
Histopathological examination
FNAC or core needle biopsy of accessible tumor masses
Biopsy of other involved sites, such as lymph nodes or effusions, if feasible
Immunohistochemistry and molecular profiling
Analysis of tumor markers and immunohistochemical staining to help determine the likely origin of the tumor
Molecular profiling for specific mutations or genetic alterations that may guide treatment decisions
Additional investigations as deemed necessary based on individual patient factors and clinical judgment

CT: Computed tomography, PET: Positron emission tomography, MRI: Magnetic resonance imaging, FNAC: Fine-needle aspiration cytology

Pathological Examination and Immunohistochemistry

When cutaneous metastases are suspected, a punch or excisional biopsy is recommended for a definitive diagnosis. Hussein outlined several distinguishing characteristics that can help differentiate cutaneous metastasis from primary skin malignancies, as follows: the presence of tumor cells within lymphatic and blood vessels, the presence of tumor cells in the deep dermis and subcutaneous fat, and the identification of neoplastic cells dispersed among collagen bundles.[20] Furthermore, six basic histopathologic patterns of cutaneous metastasis have been described: nodular, infiltrative (interstitial), diffuse, intravascular, bottom-heavy, and top-heavy patterns.[21,22]

Tumors are identified in the dermis as a deposit of atypical cells. Cutaneous metastases typically spare the epidermis, and when observed under low magnification, they often display a characteristic bottom-heavy appearance.[20-22] This refers to the presence of cellular infiltrates in the deep part of the dermis, which have a broad-based or pyramidal architecture.[23]

Mitotic figures and vascular invasion of neoplastic cells are often observed. Although less differentiated cells to the primary tumor are often seen in cutaneous metastasis, a thorough microscopic examination typically reveals significant clues. For instance, melanoma commonly exhibits pigmentation in at least some neoplastic cells. Squamous cell carcinoma is characterized by the formation of keratin pearls, while adenocarcinomas usually display gland formation. Thyroid cancer may present colloid bodies, colon cancer can be associated with mucinous cells, and other tumors may exhibit distinctive indicators regarding their origin.

Moreover, the cutaneous patterns discussed previously may also present distinctly on biopsy. Telangiectatic metastatic carcinoma displays clusters of abnormal

tumor cells and red blood cells, accompanied by dilated blood vessels within the papillary dermis. In carcinoma erysipeloides, metastatic cancer cells are densely packed within enlarged superficial and deep lymphatic vessels. Carcinoma en cuirasse is presented by fibrosis with few neoplastic cells interspersed in the collagen bundles, occasionally showcasing a distinctive arrangement reminiscent of an "Indian file" pattern. Zosteriform metastases display a notable invasion of the epidermis by neoplastic cells arranged in nests or lines. This can lead to the development of localized formations of vesicles both within and beneath the epidermis, resulting from the separation of tumor cells and edema of the dermis. In addition, a mild infiltration of lymphocytes and plasma cells is observed around these blood vessels.[11,12] Histopathological examination of the scalp lesion in a case of alopecia neoplastica showed a reduction in the number of hair follicle cells, alongside the presence of metastatic adenocarcinoma cells dispersed among collagen fibers and surrounding hair follicles.[24]

Hence, when presented with a case of a potential metastasis, one of the initial steps is to compare its histological appearance with previously diagnosed malignant neoplasms, if applicable, as this can aid in identifying the source.[25] In cases where tumors are poorly differentiated or anaplastic, screening immunohistochemical studies can be highly beneficial.

Neoplastic cells, which exhibit positive staining with cytokeratin (CK) markers such as AE1/AE3 and CAM 5.2, suggest the likelihood of a carcinoma, as shown in Table 2. Staining with CD45/leukocyte common antigen indicates a lymphoid origin for the neoplastic cells. For melanomas, positive staining can be observed with markers such as S-100, Melan-A, Mart-1, HMB-45, and SRY-related HMG-box 10 (SOX-10). In cases where initial screening studies and clinical correlation have not yielded conclusive results in identifying the tumor's origin, more detailed immunohistochemical investigations [Figure 1] can be performed, as thoroughly discussed by Habermehl and Ko.[26]

Table 2: Screening immunophenotypes of undifferentiated neoplasm[25]

Tumor Type	AE1/AE3, Cam 5.2	Vimentin	LCA	S100
Carcinoma	+	-/+	-	- (R+)
Lymphoma	-	-	+	-
Melanoma	- (R+)	+	-	+
Sarcoma	- (R+)	+	-	-/+

+: Always positive, -/+: mostly negative, R+: rare positive cells, -: negative, LCA: leukocyte common antigen

Although immunohistochemical studies provide valuable insight into determining the primary tumor, results must be interpreted with caution. Several pitfalls to immunohistochemical studies exist. For instance, while CK 5/6 staining is typically associated with cutaneous apocrine carcinoma, it has also been observed in metastatic squamous cell carcinoma. Similarly, CK 7 staining tends to be diffuse in metastases but may show focal staining in primary cutaneous adnexal carcinoma, although this pattern is not absolute.[27] Gross cystic disease fluid protein and mammaglobin are commonly employed as immunohistochemical indicators of breast origin. Their staining appears in the cytoplasm and displays variability, necessitating a thorough review of the entire stained slide. Nonetheless, these markers are not as effective in detecting triple-negative (TN) tumors, with sensitivities of less than 35% and 16%, respectively. Consequently, their diagnostic value for TN tumors is limited.[28] Cyclooxygenase 2 staining is associated with tumors of the mid-gut (ileum and appendix), gut, colorectal adenocarcinoma, and gastroesophageal adenocarcinoma; however, staining of adenocarcinoma of the lung and endometrioid adenocarcinoma can also occur, underscoring the importance of interpreting immunohistochemical markers in conjunction with other findings.[29] In cases where an epithelial carcinoma of unknown primary is identified, CK 7 and 20 stains can provide a valuable characterization of tumors. CK7 is uniquely found in the simple epithelium of internal organ cavities and transitional epithelium. While lung and breast epithelial cells may display CK7 expression, glandular epithelia in the colon and prostate lack CK7 expression.[30] CK20 is specific for colonic, urothelial, and Merkel cell carcinoma.[31] Additional testing, such as thyroid transcription factor-1 and other markers, may be performed as necessary. Fortunately, as of this time of writing, most of the stains mentioned in the algorithm[26] can be accessed at tertiary medical institutions within the Philippines. Nevertheless, it is worth noting that staining for p40, CK10, SOX10, and Merkle Cell Polyomavirus was not available.

Taking into account the history, clinical presentation, pathological and immunohistochemical findings of a case, the tumor origin of cutaneous metastasis often becomes clear. However, rare cases where a precise diagnosis regarding whether a tumor is primary or metastatic remains elusive are also reported. Until more advanced diagnostic methods are developed, the biological behavior of the tumor ultimately becomes the determining factor in such cases. Monitoring the tumor's behavior and progression over time can provide valuable insights into its nature and origin [Figure 2].

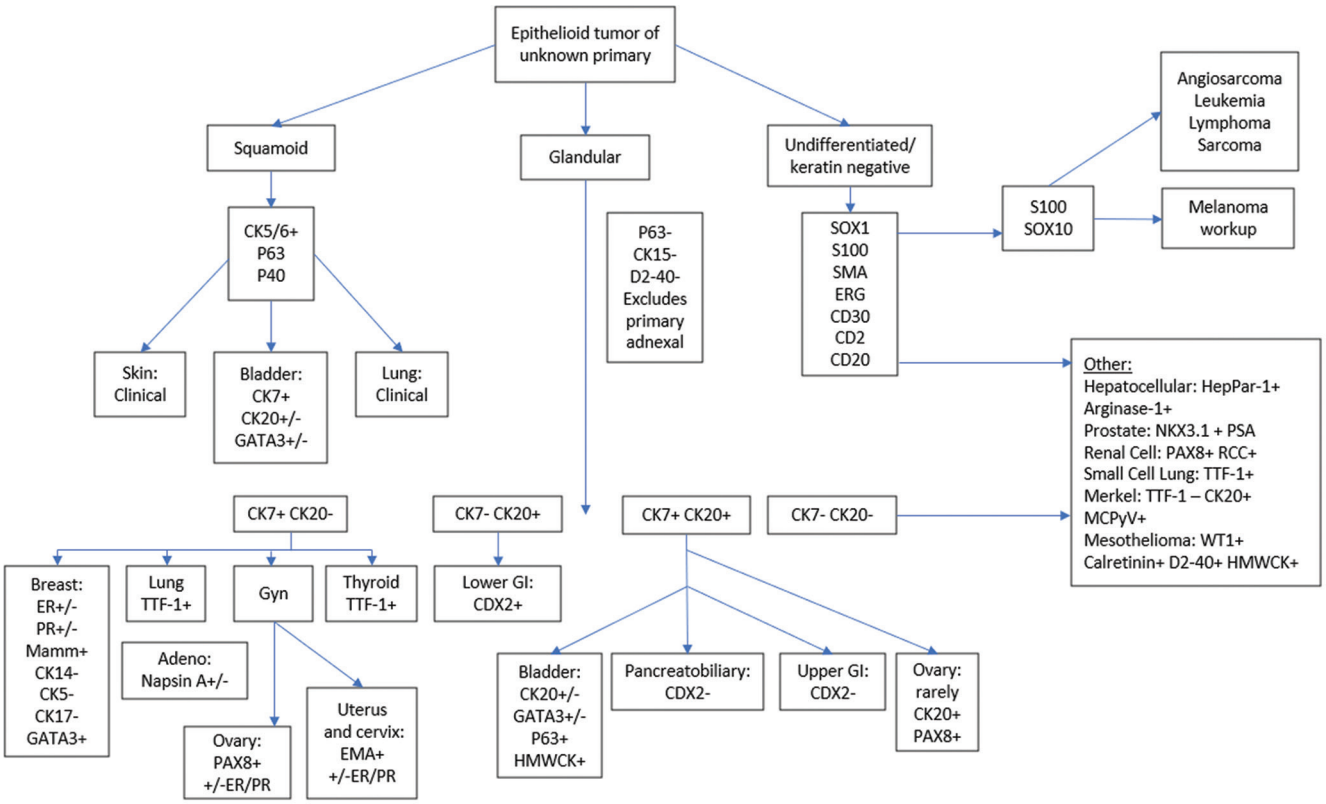

Figure 1: Summary of the workup algorithm for epithelioid cutaneous metastases to the skin lifted from Habermehl and Ko.[26] CD: Cluster of differentiation, CDX2: Caudal type homeobox 2, CK: Cytokeratin, EMA: Epithelial membrane antigen, ER: Estrogen receptor, ERG: ETS-related gene, GATA3: GATA binding protein 3, HepPar-1: Hepatocyte paraffin 1, HMWCK: High-molecular-weight cytokeratin, Mamm: Mammaglobin, MCPyV: Merkle cell polyomavirus, PAX8: Paired box gene 8, PR: Progesterone receptor, PSA: Prostate-specific antigen, RCC: Renal cell carcinoma, SMA: Smooth muscle actin, SOX10: SRY-related HMG-box 10, TTF-1: Thyroid transcription factor 1, WT1: Wilms tumor 1

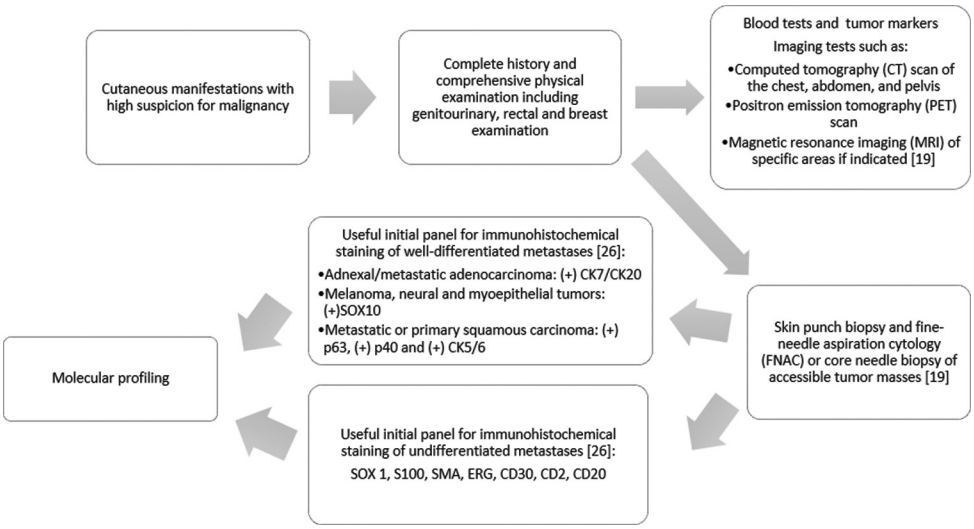

Figure 2: Proposed algorithm for cutaneous metastases of unknown origin adopted from the NICE guideline[19] and the workup algorithm for epithelioid cutaneous metastases from Habermehl *et al*.[26] Abbreviations: CD, cluster of differentiation; CK, cytokeratin; SOX10, SRY-related HMG-box 10; SMA, smooth muscle actin; ERG, ETS-related gene

Conclusion

The integration of clinical information, including the patient's medical history, presenting symptoms, imaging findings, and laboratory results, along with the results of immunohistochemical studies, provides a comprehensive approach to accurately identifying the primary tumor site. By considering the complete clinical

picture, health-care providers can make more informed decisions regarding the diagnosis and management of cutaneous metastasis.

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Conflicts of interest
There are no conflicts of interest.

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