Original Article

Cutaneous metastases of internal malignancies: A clinicopathologic study

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ABSTRACT

Background: Secondary tumor deposits in the skin represent advanced malignancy and are of uncommon occurrence. The clinical presentation of these lesions is variable, and the clinical impression is rarely correct, except in cases of known primary malignancies. **Aim:** To summarize the clinical and histopathological findings in biopsy-proven cutaneous metastases. **Methods:** The present study has analyzed 14 cases of cutaneous metastases from internal malignant neoplasms, excluding hematolymphoid neoplasms. The clinical parameters analyzed include presentation of deposits and their relation to the primary tumor. The histological features of cutaneous metastases were compared with the primary tumors and the frequency of common features in them were evaluated. **Results:** Cutaneous metastases from internal organ malignancies showed a prevalence rate of approximately 2%. Eight cases (56%) presented as primary manifestations of the tumor; biopsy evaluation in these cases suggested the possible primary tumor site and triggered further evaluation and imaging studies. Four patients, undergoing treatment for a known malignant tumor, had recurrence of the tumor in the form of cutaneous metastatic deposits. In the remaining two patients, cutaneous metastases of the tumor appeared simultaneously with the primary neoplasm and represented a higher stage of malignancy. **Conclusions:** Skin biopsy findings were significant in all cases. The morphological patterns of cutaneous metastases corresponded with the primary tumors and their evaluation helped localize unknown primary malignancies. In cases with known primaries, cutaneous metastases upstaged the malignancy and affected the prognosis.

Key words: Internal malignancy, skin, metastasis

INTRODUCTION

Cutaneous metastasis from an internal malignancy is a relatively uncommon phenomenon with the reported incidence ranging from 0.7 to 10.4% among various reported case series.[1] These metastatic deposits indicate a higher stage of malignant disease and like any other metastatic tumor deposits in a patient being treated, signify the lack of response of the malignant disease to treatment.[2,3] As skin metastases can be suspected and detected earlier, compared to metastases in other organs; the clinician should be cognizant with the various appearances of such lesions, and the pathologist should be aware of the various patterns of metastatic deposits in the skin. The biopsy evaluation of such deposits often yields information as to the probable site of the primary tumor, based on the histological appearance of tumor deposits. The information can be further refined by using histochemical stains and immunohistochemical studies on the biopsy sections.[4-8] Accurate recognition of cutaneous metastases on biopsy examination, in cases of unknown primary tumor, initiates relevant clinical and radio imaging investigations for confirming the site and type of primary neoplasm.

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METHODS

Cases of metastatic tumor deposits in the skin were collated from the archives of the Histopathology laboratory, in the Department of Pathology. Only cases with solid internal malignant tumors recorded consecutively from 2002 to 2007 in the archives were included, and cases of hematolymphoid neoplasms and melanomas were excluded from the study. Cases with direct extension of primary malignancy into the overlying skin were also excluded. In all cases, the histopathology of the primary tumor was available. These cases were retrospectively analyzed with respect to the clinical information obtained from the patient files and histopathology requisition forms. The initial clinical impressions and final histological skin biopsy diagnoses were analyzed comparatively. The histological features, especially those suggesting the primary tumor site, were evaluated in these cases, along with the secondary morphological changes in the skin tissue. The significance of special stains (performed for mucin in five cases) and immunohistochemistry (performed in one case) were also evaluated. In addition, a clinical diagnostic workup was undertaken subsequently.

RESULTS

A majority of the patients were female (11 out of a cohort of 14 patients). The three male patients had skin metastases from primary gastric carcinoma, colon carcinoma, and neuroendocrine carcinoma of the lungs, respectively. The female patients showed skin metastases originating from breast carcinoma (seven cases), ovarian carcinoma (two cases), gall bladder carcinoma (one case), and lung adenocarcinoma (one case). A skin nodule was the most common clinical presentation (nine cases). The size of the lesions varied from 0.5 – 3 cm. The regional localization in cases of breast carcinoma included — sternum (two cases), chest wall (three cases), axillary skin (one case), and skin of upper arm (one case). Both cases of ovarian adenocarcinoma had skin deposits localized to the abdominal skin; one case showed involvement of the umbilical skin, the other case presented with multiple deposits involving the lower abdomen, inguinal areas, and thighs. Cases of colonic adenocarcinoma and gall bladder carcinoma had deposits on the abdominal skin as well. The case of signet ring cell carcinoma of the stomach, however, had widespread skin deposits on the scalp, face, neck, and trunk. The case of lung adenocarcinoma showed secondary deposits involving the abdominal skin, whereas, the deposits of lung neuroendocrine carcinoma involved the sternal region. In all cases except three, the skin deposits were solitary; the exceptions included ductal carcinoma breast (Case No. 9), serous carcinoma ovary (Case No. 10), and signet ring cell carcinoma of the stomach. The clinical features are summarized in Table 1.

In eight cases (56%), cutaneous metastasis was the presenting sign of silent primary growth; in two cases of invasive ductal carcinoma of the breast, the metastatic deposits appeared simultaneously along with the primary tumor. In four cases (three cases of breast carcinoma and one case of gallbladder carcinoma), the skin deposits appeared 1–6 months after the initiation of treatment for primary tumor [Table 1]. Such treatment comprised of radical surgery combined with radiotherapy, and chemotherapy in breast carcinoma cases.

A prebiopsy clinical diagnosis of cutaneous metastasis was made in six cases where the primary site was already known. These six cases included four patients already diagnosed with primary tumor and undergoing treatment for the same and two patients where skin lesions appeared simultaneously along with the primary breast malignancy. In the remaining eight cases, the primary site was unknown. In one case of widespread ovarian carcinoma deposits, the clinical impression was of cutaneous metastases from unknown primary or lymphoma, and in case of signet ring cell carcinoma of stomach, the clinical suspicion went towards lymphoma or sarcoidosis. Lymphoma was also the clinical diagnosis in the solitary cutaneous deposit of neuroendocrine carcinoma of the lungs. In three cases, the clinical diagnoses were primary skin tumors: adnexal tumor (two cases) and squamous cell carcinoma (one case), although in two cases, the clinical diagnosis did not even include a neoplasm and hidradenitis suppurativa and umbilical hernia, respectively, were suspected [Table 1].

The histological patterns found in the cases have been described in detail in Table 2. The fine morphological details are shown in Figures 1–6. The deposits of lung adenocarcinoma and colonic adenocarcinoma showed infiltrating glandular structures and sheets of moderately pleomorphic tumor cells, with vesicular nuclei and prominent nucleoli. The mucin stains (PAS and Mayer's mucicarmine) showed intra-cytoplasmic

Table 1: Detailed clinical features, impressions, and final biopsy diagnoses of cutaneous metastases

Case No.	Age (years) / sex	Lesion type	Site of lesion	Lesion surface	Time of appearance	Clinical impression	Final diagnosis
1.	40/F	Nodule	Left upper arm	Skin colored, erythematous	Simultaneous appearance	?Metastatic tumor deposit	CD: Ductal carcinoma breast
2.	48/M	Papules - nodules	Upper body (scalp, face, neck, trunk)	Skin colored, erythematous	First manifestation	?Lymphoma ??Sarcoidosis	CD: Signet ring cell adenocarcinoma stomach
3.	55/F	Nodule	Abdominal wall	Skin colored	Six months after radiotherapy and chemotherapy	?Metastatic tumor deposit	CD: Gallbladder adenocarcinoma
4.	67/M	Nodule	Sternal region	Erythematous	First manifestation	?Lymphoma	CD: Neuro-endocrine carcinoma lung
5.	72/M	Nodule	Abdominal wall	Erythematous	First manifestation	?Skin adnexal tumor	CD: Adenocarcinoma colon
6.	81/F	Ulcerated - indurated	Sternum	Ulcerated	First manifestation	?Squamous cell carcinoma	CD: Ductal carcinoma
7.	50 / F	Ulcerated -indurated	Abdominal wall	Ulcerated	First manifestation	?Skin adnexal tumor	CD: Adenocarcinoma lung
8.	55 / F	Nodule	Left axillary skin	Ulceration and scar	First manifestation	?Hidradenitis suppurativa	CD: Ductal carcinoma breast
9.	49 / F	Papules	Chest wall	Erythematous	5 months post mastectomy	?Metastatic tumor deposit	CD: Ductal carcinoma breast
10.	62 / F	Papules	Lower abdomen	Erythematous	First manifestation	?Metastatic tumor deposit ?Lymphoma	CD: Serous adenocarcinoma ovary
11.	73 / F	Nodule	Umbilicus	Erythematous	First manifestation	?Umbilical hernia ?Umbilical adenoma	CD: Serous adenocarcinoma ovary
12.	70 / F	Papule	Sternum	Erythematous	Simultaneous appearance	?Metastatic tumor deposit	CD: Ductal carcinoma breast
13.	60 / F	Nodule	Chest	Erythematous	one month post mastectomy	?Metastatic tumor deposit	CD: Lobular carcinoma breast
14.	64 / F	Nodule	Chest	Erythematous	three months post mastectomy	?Metastatic tumor deposit	CD: Ductal carcinoma breast

CD: cutaneous deposits, sex: M for male, F or female

positivity. The cutaneous deposits of gallbladder carcinoma had characteristic infiltrating glandular formations, having low architectural dysplasia with high cytological dysplasia [Figure 6]. Signet ring cell carcinoma deposits showed diffusely invading dyscohesive cells with a signet ring cell morphology and abundant mucin positive cytoplasm.

Dermal fibrosis and vascular prominence were present in all the lesions, vascular tumor emboli were present in Case No.9; secondary inflammatory changes were present in cases with surface ulceration (Cases 6 and 7).

In all cases of cutaneous metastases, a possibility of primary skin neoplasm (including benign and malignant adnexal tumors) was excluded, based on the typical histological patterns described for the primary skin tumors. In cases of close differential diagnoses between metastatic deposits and primary skin tumors, it was so mentioned in the histopathology report. In all the cases, following the aforementioned diagnosis, the histopathology reports contained a suggestion of the probable site / sites of the primary tumor.

DISCUSSION

Cutaneous metastases are uncommon findings. Reported incidences range from 0.7 – 10.4% of visceral cancer cases.[1-3] In this study, only 14 out of a total of 712 patients with internal malignancies, attending the hospital during the five-year study period, presented with cutaneous metastases, thus showing a prevalence rate of approximately 2%.

Cutaneous metastasis may be the first indication of the silent primary growth. In our study, skin metastasis was the presenting sign in 56% (8 of 14). This is higher than the 12% reported in a recent study.[9] Due to their relative rarity, and especially in patients where skin metastasis clinically presents as the first manifestation of an unknown primary, the clinical diagnosis can vary widely, ranging from primary skin tumor to inflammatory / non-neoplastic diseases, as has been our experience. In this series, a pre-biopsy clinical diagnosis of cutaneous metastases was considered in only seven out of 14 cases (50%), and among the cases without any known primary tumor (eight cases), such a clinical impression was considered only in one case.

Table 2: Histological findings, biopsy impressions, and primary tumor

Case No.	Histological findings	Biopsy impression	Primary tumor
1.	Small sheets, trabeculae, and tubules in the dermis and subcutaneous tissue	Ductal carcinoma deposits	Invasive ductal carcinoma breast
2.	Diffuse dermal infiltration of signet ring carcinoma cells in dermis along with fibrosis	Signet ring cell carcinoma deposits ? Gastric ?? Breast	Signet ring cell carcinoma stomach
3.	Simple glandular structures, marked cellular heterogeneity, anaplasia, and focal necrosis	Gallbladder adenocarcinoma deposits	Gallbladder adenocarcinoma
4.	Sheets, trabeculae, and nests of poorly differentiated cells with coarse nuclear chromatin	Neuroendocrine carcinoma deposits ?GIT ??Lung	Neuroendocrine carcinoma lung
5.	Complex fusing glandular structures with few goblet cells	Adenocarcinoma deposits ? GIT ?? Lung	Adenocarcinoma colon
6.	Trabeculae and small sheets in dermal tissues with ulceration	Ductal carcinoma breast deposits	Invasive ductal carcinoma breast
7.	Well-formed glands focally fusing and few sheets	Adenocarcinoma deposits ? Lung ? Ovary ? GIT	Adenocarcinoma lung
8.	Tubules and trabeculae in dermis and fibrosis	Ductal carcinoma breast deposits	Invasive ductal carcinoma breast
9.	Nests, small sheets, and trabeculae with focal irregular lumina	Ductal carcinoma breast deposits	Invasive ductal carcinoma breast
10.	Fusing glands and nests with focal clear cell change	Adenocarcinoma deposits ? Ovary ? Lung ? GIT	Serous adenocarcinoma ovary
11.	Papillary configurations, with focally glandular and solid pattern	Papillary adenocarcinoma deposits ? Papillary serous adenocarcinoma ovary	Papillary serous adenocarcinoma ovary
12.	Tubules and trabeculae in dermis with fibrosis	Ductal carcinoma breast deposits	Invasive ductal carcinoma breast
13.	Indian file pattern with dyscohesive cells	Lobular carcinoma breast deposits	Invasive lobular carcinoma breast
14.	Trabeculae and focal tubules	Ductal carcinoma breast deposits	Invasive ductal carcinoma breast

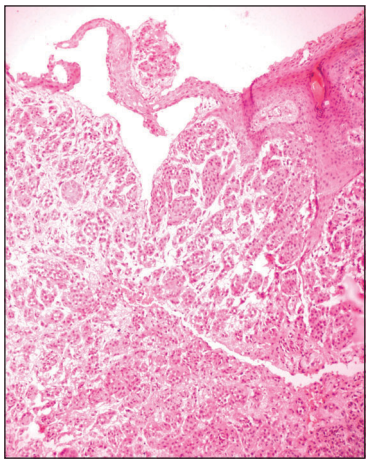

Figure 1: Photomicrograph of cutaneous metastatic deposits of ductal carcinoma breast showing fusing trabeculae and tubules involving the dermis, with surface ulceration. (H&E, x100)

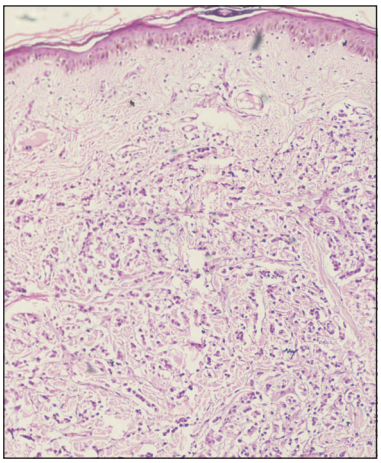

Figure 2: Photomicrograph of cutaneous metastatic deposits of lobular carcinoma breast showing dyscohesive and uniform cell population, focally forming an Indian file pattern, and extensively involving the dermal tissues. (H&E, x200)

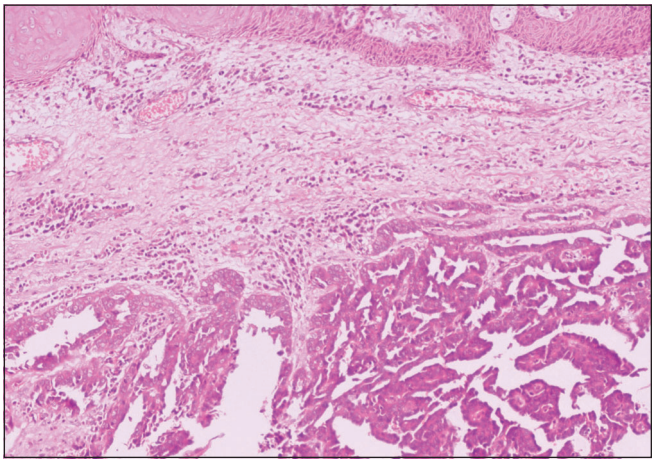

Figure 3: Photomicrograph of cutaneous metastatic deposits of ovarian papillary serous adenocarcinoma showing complex papillary structures in the dermal tissues. (H&E, x200)

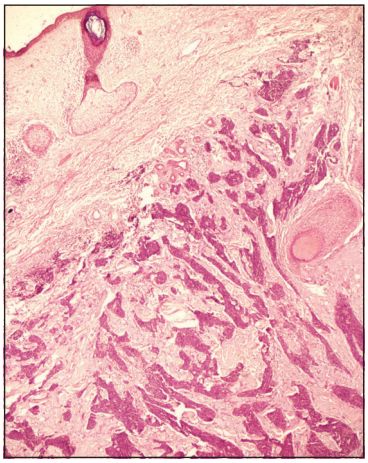

Figure 4: Photomicrograph of cutaneous metastatic deposits of neuroendocrine carcinoma lung showing nests and trabeculae of tumor cells with uniform nuclei and coarsely granular nuclear chromatin in the dermal and subcutaneous tissues. (H&E, x100)

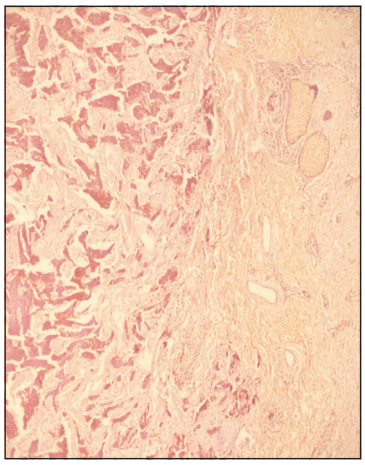

Figure 5: Photomicrograph of cutaneous metastatic deposits of neuroendocrine carcinoma lung showing positivity for chromogranin by immunohistochemistry (IHC) staining in the same case, depicted in Figure 4. (IHC, Chromogranin, x100)

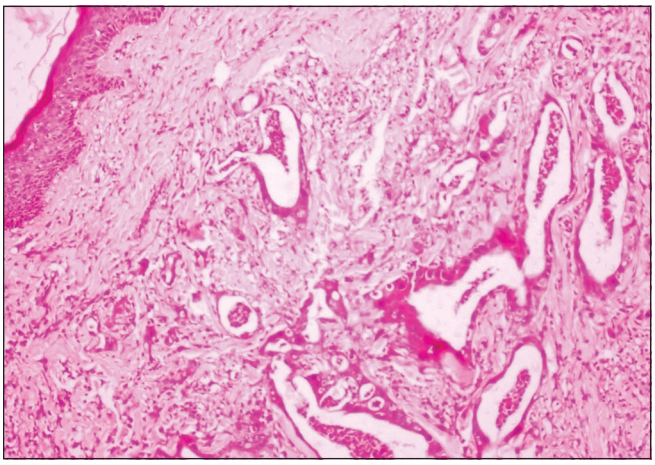

Figure 6: Photomicrograph of cutaneous metastatic deposits of gall bladder carcinoma showing simple glandular structures, but marked cellular heterogeneity and nuclear atypia. (H&E, x200)

Two cases even had non-neoplastic clinical diagnoses of hidradenitis suppurativa and umbilical hernia. In one recent study, 45% of skin metastases were not suspected clinically.[9]

It has been observed that many carcinomas spread through the lymphatic route to areas having common lymphatic drainage as that of the primary site.[10] In the present cohort of cases as well, the cutaneous deposits from breast carcinoma have mainly localized to the skin of the chest wall and sternum. Other cutaneous deposits have also shown corresponding patterns of skin localization [Table 1], except for the case of signet ring cell carcinoma, indicating a wide lymphohematogenous spread. One study has also evaluated the mechanisms responsible for the cutaneous metastasis and concludes that such mechanisms include factors other than chemokine receptors CCR10 and CXCR4, because their expressions by tumor cells are neither necessary nor sufficient for the formation of skin metastases.[11]

The morphological features of the primary tumor are often reflected in cutaneous metastatic deposits and an attempt to suggest the possible primary site on skin biopsy evaluation helps the clinician in narrowing down the primary tumor possibilities and in initiating specific radio-imaging and other relevant investigations concerning the patient's management, at the earliest.[9]

Metastatic carcinomas are usually differentiated from primary skin carcinomas because of the latter's typical histological patterns, the epidermal connection, intraepidermal / intra-adnexal (in-situ component) tumor or the presence of a benign counterpart.[1,2] In cases where distinction between metastatic and primary skin tumors is difficult, a variety of immunohistochemical staining panels can be helpful.[4-8] The positivity for cytokeratin 7 (CK 7), gross cystic disease fluid protein (GCDFP), estrogen receptor (ER), and progesterone receptor (PR) favors breast primary, whereas, thyroid transcription factor-1 (TTF-1) positivity favors lung adenocarcinoma or small-cell carcinoma, as well as, thyroid primary, and is not described in the primary cutaneous tumors.[5,12] P63 is a useful marker of primary cutaneous tumors as it is positive in most of the adnexal tumors, including carcinomas, and is always negative in the metastatic carcinoma to the skin. Therefore, in tumors with tubular differentiation, positivity for p63 (especially when > 25% of tumor cells are positive) strongly supports a primary cutaneous adnexal tumor and negativity favors metastatic adenocarcinoma.[6-8] Podoplanin is another marker, demonstrable by immunohistochemistry, which is positive in adnexal tumors and negative in metastatic adenocarcinomas.[13]

In case of tumors with extracellular mucin secretion, the histochemical stains play a part, as most skin tumors with mucin secretion contain sialomucin staining with alcian blue at pH 2.5, but not at pH of 1.0 or 0.4, whereas, the metastatic gastrointestinal adenocarcinomas secrete mucin rich in sulfomucin, and therefore, stain with alcian blue at pH 1 and 0.4.[12]

Our study being a retrospective one possesses some limitations. The patients being reported in the study are the cases who were alarmed by the skin lesions and the clinician considered these lesions to be significant enough for differential diagnoses. Therefore, a biopsy was performed and the result was a skin metastasis. However, it is likely that some of the skin lesions in the cases of visceral malignancies were not considered significant enough and therefore not biopsied. Hence, the sample size of skin metastases in our study may be lesser than the true occurrence of such lesions. The description of clinical appearances and the timing of skin lesions depend upon the filling of the medical records and the histopathology requisition forms by the doctors and nurses, and it is likely that some of the clinical profiles of the patients in our study may be under-represented due to under-reporting of the complete clinical picture in the medical records. Our ongoing correspondence with the clinical departments including the Dermatology department assures us that the chances of such under-reporting are miniscule, however, it cannot be completely discounted.

In all cases of cutaneous metastases, we label the lesion as such, followed by the most likely primary tumor site, and type, if possible, from the biopsy interpretation aided by special studies. In cases where one likely possibility is not evident, we recommend all the possible sites of the primary tumor. In the present study, the skin biopsy impression was confirmed by the primary tumor detection in all cases. In eight cases, where the primary was unknown; the histopathology report favored one primary location in three cases, and two to three possibilities were put to the clinicians in the remaining five cases. The biopsy suggestions based upon the histological patterns were helpful in all the cases.

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