

Report

Cutaneous metastasis: clinicopathological study of 72 patients from a tertiary care center in LebanonJinane El Khoury¹, MD, Ibrahim Khalifeh², MD, Abdul-Ghani Kibbi¹, MD, and Ossama Abbas¹, MD

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Conflicts of interest: None.

Abstract

Background Cutaneous metastasis is the result of malignant cell spread from primary malignancy to the skin. This is not uncommon, and rates reported in the literature are as high as 10.4%. To the best of our knowledge, there are no studies assessing the epidemiologic, clinical, and histopathological features of cutaneous metastasis in our region.

Objective To assess the clinical and histopathological findings of all patients diagnosed with cutaneous metastasis at the American University of Beirut – Medical Center (AUB-MC) and to compare our findings with those published in the literature.

Methods Retrospective clinical and histopathologic evaluation of all cases diagnosed as cutaneous metastasis at AUB-MC between 1992 and 2010.

Results A total of 72 patients (50 females and 22 males) were identified. The mean age at diagnosis was 55.2 years. The most common primary cancer was breast cancer in women and laryngeal cancer in men. The most common clinical presentation was a single nodule in 27% of cases followed by multiple nodules in 23%. Cutaneous metastasis lesions were asymptomatic in the majority. The chest was the most commonly affected site. On microscopy, the majority of metastatic cases were adenocarcinomas (74%).

Conclusion This is, to our knowledge, the first study characterizing the epidemiological, clinical, and histopathological features of cutaneous metastasis in the Lebanese population. The clinical and histopathological features observed were in concordance with the published literature, with minor differences.

Introduction

Cutaneous metastasis results from the spread of malignant cells from a primary malignancy to the skin. This phenomenon is not uncommon, and it is commonly perceived as a sign of poor prognosis. Skin metastasis can be further subdivided into loco-regional, in-transit, and distant metastasis.^{1,2} Loco-regional skin metastasis occurs when tumor cells from a primary malignancy infiltrate an area located in the vicinity of the primary malignancy, whereas in-transit skin metastasis refers to seeding of tumor cells at the site of previous surgery or needle aspirate.^{1,2} Virtually any tumor can metastasize to the skin, with highest frequencies observed with breast cancer, followed by lung and colorectal cancers.³ To the best of our knowledge, there are currently no studies on cutaneous metastasis in the Middle East. Thus, the aim of this study is to assess the epidemiological, clinical, and histopathological features of all patients diagnosed with cutaneous metastasis at the American University of

Beirut – Medical Center (AUB-MC) and to compare our findings with those published in the literature.

Materials and methods

All the cases labeled as cutaneous metastasis from 1992 to 2010 were retrieved from our database. We included all cases arising from solid malignancies and malignant melanoma. Lesions arising from hematological malignancies were excluded. Histologic sections of all cases were reviewed and diagnoses confirmed by two dermatopathologists (I.K. and O.A.). The diagnosis of cutaneous metastasis was established on the basis of histopathological examination. Clinical information collected included age, sex, morphology, and location of the lesions as well as associated symptoms. We also noted the type of primary malignancy, presence of concomitant systemic metastasis, and interval between the primary tumor and metastasis. Similarly, histological features reviewed included the histological type of the metastasis, degree of differentiation, distribution and tumor circumscription,

epidermotropism, desmoplastic reaction pattern, necrosis, ulceration, and lymphovascular invasion. The presence of inflammation was graded as absent, sparse, moderate, or heavy, and the predominant cell type was noted. When available, the immunohistochemical staining profile was also reviewed. Institutional Review Board approval was granted (DER.OA.02).

Results

Clinical features

The clinical features of patients as well as classification of subtype of skin metastases (loco-regional, in-transit, and distant) are summarized in Table 1. A total of 72 patients were included in the study (50 women and 22 men). The mean age of the patient population was 55.2 years, ranging from 19 to 81 years. The distribution of cutaneous metastasis according to gender and primary malignancy is summarized in Table 2. The most common primary cancer to metastasize to the skin was breast cancer in women (81% of cases) and laryngeal cancer in men (18% of cases).

Of the 72 cases, we could retrieve adequate data on clinical presentation on 70 patients. The clinical presentation was highly variable, ranging from solitary nodules, papules, or plaques to grouped nodules, papules, and plaques as well as ulcers and wound dehiscence (Fig. 1). A solitary nodule was the most common clinical presentation observed in 27% of cases ($n = 19$), followed by multiple nodules in 23% of cases ($n = 16$). Two patients (patients 10 and 49) had breast cancer skin metastasis in a “peau d’orange” appearance. Other characteristic clinical presentations described in breast cancer were the erythematous cellulitis-like patch seen in one patient (patient 36) and the “en cuirasse” type observed in another patient (patient 48). Notably, the lesions were most commonly asymptomatic (Table 1).

Regarding anatomical distribution of lesions, they were confined to one location in most patients. Interestingly, lesions were distributed over two anatomical locations in seven patients. Nearly 50% localized to the chest ($n = 36$) (Fig. 2), making it the most common site of metastasis in our study population; the majority was metastatic breast cancer. The second most common anatomical location was the head and neck (18 cases). Again, the majority of lesions were metastatic breast cancer, and the scalp was a site of predilection. The head and neck was the preferential anatomical location of laryngeal cancer metastasis (three of four cases). The back was the site of metastasis in roughly 10% of the cases, with breast cancer being the most common type, followed by lung cancer and oropharyngeal carcinoma. Primary cancers arising from the gastrointestinal tract preferentially metastasized to the

abdomen. Two patients presented with umbilical lesions (patient 26 had colon cancer that presented as a single “Sister Mary Joseph” nodule, and patient 45 had gastric cancer that presented as multiple grouped nodules over the umbilicus). Metastasis to the limbs was rare and was seen in two cases, one of which was from a primary renal cell carcinoma, whereas the other was metastatic lung cancer.

The time from diagnosis of the primary cancer to diagnosis of the cutaneous metastasis was assessed in years (mean time to metastasis for each primary cancer is summarized in Table 3). The time to metastasis ranged from 0 to 28.02 years. Interestingly, the cutaneous lesions preceded and led to discovery of the primary malignancy in nine patients (four cases of breast cancer, two cases of unknown primary cancer, and one case each of gastric cancer, renal cell carcinoma, and lung cancer). The mean time to metastasis in breast cancer was 2.93 years. The longest interval was seen in a 78-year-old man known to have follicular thyroid carcinoma who presented 28 years after the diagnosis of his primary malignancy with a single slow growing nodule over the lateral aspect of the neck (patient 58). As expected, the majority of patients had stage IV metastatic disease at the time of diagnosis ($n = 45$). Interestingly, 16 patients did not have systemic metastasis at the time of appearance of their skin lesions.

Three patients had skin metastasis of unknown origin. Patient 21 was a 73-year-old man who presented with multiple firm nodules over the chest of 1-month duration. The biopsy from these nodules was consistent with a well-differentiated adenocarcinoma. Unfortunately, the patient was lost to follow-up, and a work-up was not performed in our center. However, in view of his age and of the fact that he had multiple nodules, the possibility of cutaneous metastasis from a systemic adenocarcinoma was favored over a primary adnexal tumor. Patient 43 was an 81-year-old man who presented to the clinic with multiple firm dermal nodules over the chest and proximal upper extremities. He underwent extensive imaging studies that revealed brain, liver, and bone metastasis as well as focus within the lung parenchyma that could have represented the primary cancer. Unfortunately, the patient quickly deteriorated and passed away within weeks of diagnosis before having had the possibility to get tissue confirmation of the primary tumor. Patient 62 was a 65-year-old man who presented with a single nodule over the left temporal area that had been slowly growing over three weeks. His lesion was biopsied and was consistent with a moderately differentiated adenocarcinoma. His systemic work-up revealed multiple systemic metastases to the liver, bone, and conjunctiva but failed to elucidate his primary malignancy.

Table 1 Clinical Characteristics of the patients

Patient no.	Age	Gender	Skin lesions		Time to metastasis (years)	Type of primary malignancy	Type of metastasis ^a
1	57	Male	Multiple nodules	Suprasternal notch	0.5	Laryngeal cancer	LR
2	53	Female	Ulcerated plaque	Chest and back	2	Breast cancer	LR
3	75	Male	Single nodule with telangiectasia	Scalp	1.59	Lung cancer	LR
4	48	Female	Single nodule	Chest	4	Breast cancer	LR
5	44	Female	Single nodule	Chest	1.42	Breast cancer	LR
6	27	Female	Multiple nodules	Scalp and shoulder	–	Breast cancer	DM
7	37	Female	Single plaque	Chest	–	Breast cancer	LR
8	71	Female	Multiple plaques	Chest	26.6	Breast cancer	LR
9	40	Female	Multiple nodules	Scalp, neck, and chest	0.92	Breast cancer	DM
10	65	Female	Large plaque, peau d'orange	Chest	3.33	Breast cancer	LR
11	52	Female	Multiple nodules	Chest	4.5	Breast cancer	LR
12	76	Female	Single nodule	Chest	5.17	Breast cancer	LR
13	58	Female	Multiple nodules	Chest and scalp	1	Breast cancer	LR
14	52	Female	Multiple nodules	Chest	1.33	Breast cancer	LR
15	71	Female	Single eroded plaque	Hand	0	Renal cell carcinoma	DM
16	52	Female	Single nodule	Shoulder	0	Breast cancer	DM
17	54	Female	Multiple papules	Chest	0.25	Breast cancer	LR
18	55	Male	Multiple papules	Chest	0.17	Breast cancer	DM
19	50	Female	Multiple annular plaques	Back	–	Breast cancer	DM
20	81	Female	Multiple plaques	Chest	0	Breast cancer	LR
21	73	Male	Multiple nodules	Chest	0	Unknown primary	N/A
22	58	Female	Multiple nodules	Chest	4.25	Breast cancer	LR
23	67	Female	Single nodule	Chest	0	Breast cancer	LR
24	72	Male	Multiple ulcerated nodules	Chest	2.59	Laryngeal cancer	DM
25	63	Female	Multiple papules	At site of scar/chest	1.25	Breast cancer	IT
26	60	Female	Single ulcerated nodule	Umbilicus	0.08	Colon cancer	DM
27	58	Female	Multiple nodules	Back and chest	5.84	Breast cancer	DM
28	55	Male	Multiple nodules	Back and chest	0.42	Lung cancer	LR
29	39	Female	Multiple papules	Neck	4.67	Breast cancer	DM
30	39	Male	Single nodule	Abdomen	1.5	Malignant melanoma	DM
31	34	Female	Multiple nodules	Scalp and neck	–	Breast cancer	DM
32	54	Female	Single plaque	At site of scar/chest	2.5	Breast cancer	IT
33	52	Female	Multiple papules	Chest	–	Breast cancer	LR
34	32	Female	Single nodule	Scalp	–	Breast cancer	DM
35	52	Female	Multiple ulcerates papules	Chest	–0.08	Breast cancer	LR
36	31	Female	Cellulitis-like patch	At site of scar/chest	–	Breast cancer	IT
37	42	Female	Multiple papules	Pubic area	3.58	Ovarian cancer	DM
38	27	Male	Single nodule	Perianal	2.51	Rectal cancer	LR
39	56	Female	Single papule	Chest	–	Breast cancer	LR
40	42	Female	Multiple papules	Chest	2.33	Breast cancer	LR
41	53	Female	Multiple plaques	Chest	2.75	Breast cancer	LR
42	50	Female	Multiple plaques	At site of scar/chest	2.5	Breast cancer	IT
43	81	Male	Multiple nodules	Chest	0	Unknown primary	N/A
44	73	Male	Single papule	Chest	2.33	Adenocarcinoma of the parotid	DM
45	57	Male	Multiple nodules	Umbilicus	0	Gastric cancer	DM
46	48	Female	Multiple plaques	Chest	4.92	Breast cancer	LR
47	46	Female	Single plaque	Chest	0.08	Breast cancer	LR
48	75	Female	Single plaque en cuirasse	Chest	2.16	Breast cancer	LR

Table 1 (Continued)

Patient no.	Age	Gender	Skin lesions		Time to metastasis (years)	Type of primary malignancy	Type of metastasis ^a
49	77	Female	Peau d'orange	Chest	0	Breast cancer	LR
50	51	Female	Single plaque	Chest	2.33	Breast cancer	LR
51	59	Female	Multiple papules	Scalp	–	Breast cancer	DM
52	19	Female	Multiple nodules	Neck	0.67	Alveolar rhabdomyosarcoma	LR
53	56	Male	Single nodule	Scalp	1.33	Malignant melanoma	N/A
54	73	Female	Single nodule	Chest	0.33	Breast cancer	LR
55	57	Female	Single nodule	Chest	2.08	Breast cancer	LR
56	44	Female	–	Abdomen	12.17	Mandibular mucoepidermoid cancer	DM
57	53	Male	Multiple nodules	At site of scar/chest	4.17	Follicular thyroid cancer	IT
58	76	Male	Single nodule	Neck	28.02	Follicular thyroid cancer	LR
59	65	Female	Single plaque	Shoulder	3.17	Breast cancer	DM
60	48	Female	Single nodule	Upper extremity	0	Lung cancer	DM
61	65	Male	Ulcer	At site of scar/neck	2.25	Laryngeal cancer	IT
62	65	Male	Single nodule	Face	0.02	Unknown primary	N/A
63	77	Female	Wound dehiscence	At site of scar/abdomen	0.08	Endometrial cancer	IT
64	41	Male	Ulcer	Back	0.75	Oropharyngeal cancer	DM
65	29	Male	Single nodule	Back	0.27	Mesothelioma	LR
66	61	Male	Ulcerated nodule	Neck	0.66	Laryngeal cancer	LR
67	60	Male	Single nodule	Ear	0.16	Renal cell carcinoma	DM
68	50	Female	Ulcerated plaque	Chest	2.24	Breast cancer	LR
69	59	Male	Single nodule	Lip	2	Rectal cancer	DM
70	48	Female	–	Abdomen	2.32	Rectosigmoid cancer	DM
71	58	Male	Multiple nodules forming a plaque	Neck	0	Gastric cancer	DM
72	70	Female	Single nodule	Pubic area	4.42	Vulvar cancer	LR

^aLR, locoregional metastasis; IT, in-transit metastasis; DM, distant metastasis.

Table 2 Cutaneous metastasis distribution

Primary cancer	Number of cases	Total, %
Cutaneous metastasis in female patients		
Breast carcinoma	41	82
Colorectal cancer	2	4
Ovarian carcinoma	1	2
Vulvar carcinoma	1	2
Endometrial carcinoma	1	2
Lung carcinoma	1	2
Renal cell carcinoma	1	2
Other	2	4
Cutaneous metastasis in male patients		
Laryngeal carcinoma	4	18
Lung carcinoma	2	9
Melanoma	3	14
Renal cell carcinoma	1	5
Follicular thyroid carcinoma	2	9
Colorectal carcinoma	2	9
Oropharyngeal carcinoma	1	5
Gastric carcinoma	2	9
Unknown primary	3	14
Other	2	9

Histopathologic findings

Histopathologic examination of 76 biopsies revealed most commonly a diffuse infiltration of the dermis with tumor cells. Most histopathological cases exhibited a pan-dermal diffuse infiltrate of pleomorphic cells; however, some showed a distribution confined to the upper dermis, and others had a deeper location extending into the subcutis. Several additional patterns were identified including: presence of a single nodule in the dermis or subcutis; diffuse nodular pattern (tumor cells were arranged in scattered nodules throughout the dermis); and intravascular pattern (malignant cells were strictly confined to the intravascular compartment) (Table 4). The majority of cases were metastatic adenocarcinomas (74%), although several other types were observed, including squamous cell carcinoma, follicular thyroid carcinoma, melanoma, renal cell carcinoma, and mucoepidermoid carcinoma (Figs. 3–8).

Epidermotropism was noted in 14 cases (18%) and was mostly focal (Fig. 9). Necrosis was not a very prominent feature with only 12 cases showing this feature

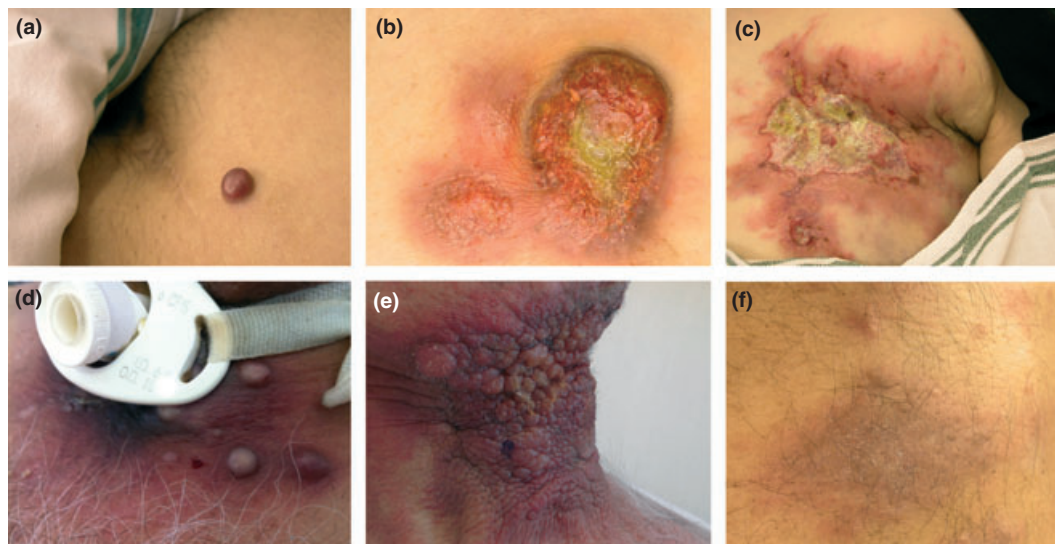


Figure 1 Clinical findings in patients with cutaneous metastasis: (a) metastasis from malignant melanoma presenting as a single nodule over the trunk; (b,c) skin metastasis from breast carcinoma presenting as multiple ulcerated nodules over the nipple in (b) and a large ulcer over the right breast with surrounding erythema in (c); (d) metastasis from laryngeal carcinoma presenting as multiple nodules over tracheostomy site; (e) skin metastasis from gastric carcinoma presenting as a cauliflower-like plaque over the neck; (f) metastasis from unknown origin presenting as a dusky eczematous patch over the trunk

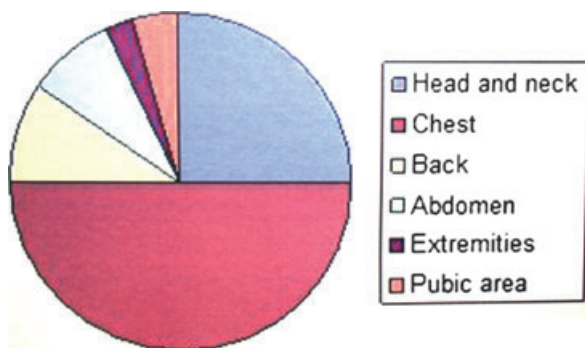


Figure 2 Anatomical distribution of cutaneous metastasis

Table 3 Mean time to metastasis in years

Primary cancer	Mean time to metastasis (years)
Breast carcinoma	2.93
Colorectal cancer	1.73
Ovarian carcinoma	3.58
Vulvar carcinoma	4.42
Endometrial carcinoma	0.08
Lung carcinoma	0.67
Renal cell carcinoma	0.08
Laryngeal carcinoma	1.50
Melanoma	1.00
Follicular thyroid carcinoma	16.09
Oropharyngeal carcinoma	0.75
Gastric carcinoma	0.00

(16%). A desmoplastic reaction pattern was a very commonly observed feature seen in 60 of 76 cases (79%). Lymphovascular invasion was detected on hematoxylin and eosin staining in approximately 76% of cases and was generally easier to identify at the tumor periphery. Indian filing was seen in 47% of the cases, mostly in moderate to poorly-differentiated tumors in which the infiltrate consisted mostly of strands of single cells dissecting collagen bundles. Transepidermal elimination of the malignant cells was noted in one patient (patient 37), a case previously reported by Abbas *et al.*⁴

As for the inflammatory infiltrate, it was absent in 25 cases and scarce in 33 cases (33% and 43% respectively). The infiltrate was predominantly lymphocytic in the majority of cases and predominantly lymphoplasmacytic in 13%. The presence of neutrophils and eosinophils were noted in nine and four cases, respectively.

Several interesting observations were made. Patient 69 was known to have rectal cancer, and on histopathology we noticed diffuse dermal infiltrate embedded in a rich mucinous stroma (Fig. 10). Moreover, the presence of signet cells was noted. On immunohistochemistry, the tumor stained positive for cytokeratin (CK) 20 and negative for CK7. The finding of mucin deposition within the stroma of the tumor was also seen in patient 44 who had a metastatic adenocarcinoma of the parotid.

As for immunohistochemical staining, breast carcinoma cases generally exhibited positivity for estrogen, progesterone, and HER2 staining. Cases of cutaneous

Table 4 Histological characteristics of the 76 biopsies from 72 patients

Patient no.	Type of metastatic carcinoma	Pattern and location	Epidermotropism	Circumscription	Degree of inflammation and cell type	Additional histological findings
1	Squamous cell carcinoma	Superficial dermal	Absent	Well circumscribed nodule	Sparse, presence of neutrophils	
2	Adenocarcinoma	Diffuse superficial and mid dermal	Present	Poorly circumscribed	Moderate, lymphocytic	
3	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Moderate, lymphoplasmacytic with neutrophils	
4	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
5	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Absent	
6	Adenocarcinoma	Diffuse pan dermal reaching the subcutis	Absent	Poorly circumscribed	Absent	
7	Adenocarcinoma	Superficial dermal	Present	Poorly circumscribed	Sparse, lymphocytic	
8	Not identifiable	Deep dermal	Absent	Poorly circumscribed	Sparse, lymphoplasmacytic	
9	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Absent	
10	Adenocarcinoma	Dermal, within vessels	Absent	Well circumscribed	Moderate, lymphocytic	Necrosis
11	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse	
12	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Absent	
13	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
14	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Absent	
15	Renal cell carcinoma	Dermal, diffuse, and nodular	Present	Poorly circumscribed	Moderate, lymphocytic	Ulceration of the epidermis and necrosis, also presence of clear cells
16	Adenocarcinoma	Deep dermal	Absent	Well circumscribed	Sparse, lymphocytic	
17a	Adenocarcinoma	Dermal, diffuse, and nodular	Absent	Poorly circumscribed	Absent	
17b	Adenocarcinoma	Superficial dermal	Present	Well circumscribed	Heavy, lymphoplasmacytic	
17c	Adenocarcinoma	Dermal, within vessels	Absent	Well circumscribed	Moderate, lymphoplasmacytic	
17d	Adenocarcinoma	Dermal, within vessels	Absent	Well circumscribed	Moderate, lymphoplasmacytic	
17e	Adenocarcinoma	Dermal, within vessels	Absent	Well circumscribed	Moderate, lymphoplasmacytic	
18	Not identifiable	Dermal, diffuse, and nodular	Absent	Poorly circumscribed	Absent	
19	Adenocarcinoma	Diffuse pan dermal	Present	Poorly circumscribed	Sparse, lymphocytic	
20	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
21	Adenocarcinoma	Diffuse pan dermal reaching the subcutis	Absent	Poorly circumscribed	Sparse, lymphocytic	
22	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Absent	
23	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Moderate, lymphocytic	
24	Squamous cell carcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
25	Adenocarcinoma	Diffuse pan dermal	Absent	N/A	Sparse, lymphocytic	
26	Adenocarcinoma	Dermal, diffuse, and nodular	Absent	Poorly circumscribed	Heavy, lymphocytic	
27	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
28	Not identifiable	Deep dermal	Absent	Poorly circumscribed	Absent	
29	Adenocarcinoma	Dermal, diffuse, and nodular	Absent	Poorly circumscribed	Absent	
30	Melanoma	Single nodule in the dermis	Absent	Well circumscribed	Sparse, lymphocytic, presence of eosinophils	Necrosis
31	Adenocarcinoma	Deep dermal reaching the subcutis	Present	Poorly circumscribed	Absent	
32	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	Presence of clear cells
33	Adenocarcinoma	Diffuse pan dermal	Present	Poorly circumscribed	Moderate, lymphocytic	Ulceration of the epidermis
34	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Absent	

Table 4 (Continued)

Patient no.	Type of metastatic carcinoma	Pattern and location	Epidermotropism	Circumscription	Degree of inflammation and cell type	Additional histological findings
35	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
36	Adenocarcinoma	Dermal, diffuse, and nodular	Absent	Poorly circumscribed	Moderate, lymphocytic	
37	Adenocarcinoma	Superficial dermal	Present	Poorly circumscribed	Sparse, lymphocytic	Transepidermal elimination of malignant cells
38	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Moderate, lymphocytic	
39	Adenocarcinoma	Diffuse pan dermal reaching the subcutis	Absent	Poorly circumscribed	Sparse, lymphocytic	
40	Adenocarcinoma	Dermal, diffuse, and nodular	Absent	Poorly circumscribed	Sparse, lymphocytic, presence of neutrophils	
41	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
42	Adenocarcinoma	Diffuse pan dermal reaching the subcutis	Absent	Poorly circumscribed	Moderate, lymphocytic	Presence of perineural infiltration
43	Adenocarcinoma	Single nodule in the dermis	Absent	Well circumscribed	Moderate, neutrophilic, presence of eosinophils	
44	Adenocarcinoma	Single nodule in the dermis	Present	Well circumscribed	Absent	Presence of mucin
45	Adenocarcinoma	Diffuse pan dermal reaching the subcutis	Absent	Poorly circumscribed	Moderate, neutrophilic, presence of plasma cells	
46	Adenocarcinoma	Dermal, diffuse, and nodular	Absent	Poorly circumscribed	Sparse, lymphocytic	Ulceration of the epidermis
47	Adenocarcinoma	Dermal, diffuse, and nodular	Absent	Poorly circumscribed	Sparse, lymphocytic	
48	Adenocarcinoma	Diffuse pan dermal	Present	Poorly circumscribed	Sparse, neutrophilic	
49	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
50	Adenocarcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, neutrophilic	
51	Adenocarcinoma	Diffuse pan dermal	Present	Poorly circumscribed	Sparse, lymphocytic	
52	Sarcoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
53	Melanoma	Deep dermal reaching the subcutis	Absent	Poorly circumscribed	Absent	Necrosis
54	Adenocarcinoma	Deep dermal reaching the subcutis	Absent	Poorly circumscribed	Sparse, lymphocytic	
55	Adenocarcinoma	Subcutaneous	Absent	Poorly circumscribed	Absent	
56	Other (mucoepidermoid carcinoma)	Mid dermal	Absent	Poorly circumscribed	Absent	
57	Other (follicular thyroid carcinoma)	Single nodule in the deep dermis	Absent	Well circumscribed	Absent	
58	Other (follicular thyroid carcinoma)	Subcutaneous	Absent	Well circumscribed	Absent	
59	Not identifiable	Diffuse pan dermal	Present	Poorly circumscribed	Absent	
60	Squamous cell carcinoma	Single nodule in the subcutis	Absent	Well circumscribed	Absent	
61	Squamous cell carcinoma	Diffuse pan dermal	Present	Poorly circumscribed	Absent	Ulceration of the epidermis and necrosis
62	Adenocarcinoma	Deep dermal reaching the subcutis	Absent	Well circumscribed	Absent	
63	Adenocarcinoma	Subcutaneous	Absent	Well circumscribed	Heavy, neutrophilic	Ulceration of the epidermis and necrosis
64	Squamous cell carcinoma	Diffuse pan dermal	Absent	Well circumscribed	Absent	Necrosis
65	Not identifiable	Subcutaneous	Absent	Poorly circumscribed	Absent	Necrosis
66	Squamous cell carcinoma	Diffuse pan dermal	Absent	Poorly circumscribed	Sparse, neutrophilic	Ulceration of the epidermis and necrosis

Table 4 (Continued)

Patient no.	Type of metastatic carcinoma	Pattern and location	Epidermotropism	Circumscription	Degree of inflammation and cell type	Additional histological findings
67	Other (renal cell carcinoma)	Diffuse pan dermal	Absent	Poorly circumscribed	Absent	Ulceration of the epidermis and necrosis, also presence of clear cells
68	Adenocarcinoma	Superficial dermal	Present	Well circumscribed	Sparse, lymphoplasmacytic	Presence of mucin deposition and signet cells
69	Adenocarcinoma	Mid to deep dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	
70	Adenocarcinoma	Deep dermal reaching the subcutis	Absent	Poorly circumscribed	Moderate, lymphocytic	Necrosis
71	Adenocarcinoma	Mid to deep dermal	Absent	Poorly circumscribed	Sparse, lymphocytic	Presence of signet cells
72	Squamous cell carcinoma	Deep dermal reaching the subcutis	Absent	Well circumscribed	Absent	Necrosis

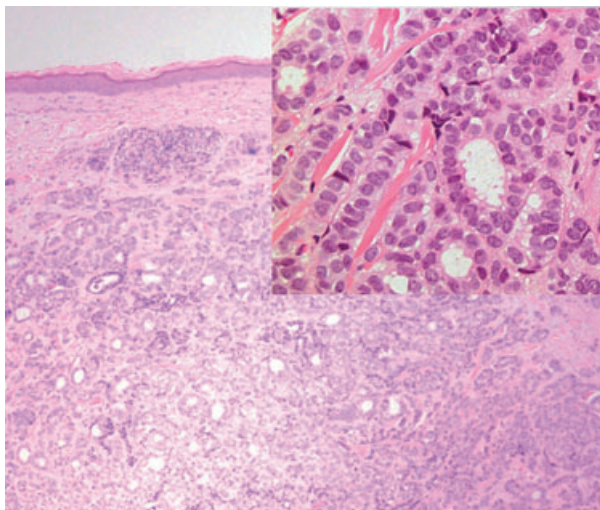


Figure 3 Histologic subtypes of cutaneous metastasis: adenocarcinoma, note the glandular structures in a well-differentiated metastatic adenocarcinoma (hematoxylin and eosin, original magnification ×4 and inset ×20)

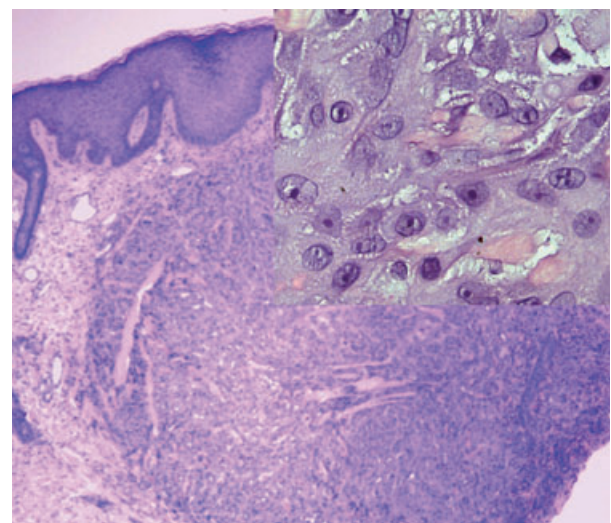


Figure 4 Histologic subtypes of cutaneous metastasis: squamous cell carcinoma, note the desmosomes on high power and the keratin clumps (hematoxylin and eosin, original magnification ×4 and inset ×20)

metastases from gastrointestinal origins showed positive staining for CK20, while CK7 was negative.

Discussion

Epidemiology and clinical presentation

Cutaneous metastasis from visceral tumors is rare, with an incidence reported between 0.2% and 10.4%.⁵⁻¹⁰ In a meta-analysis by Krathen *et al.*,⁷ the authors compiled data from seven studies comprising a total of 20,380 patients after excluding cutaneous primary neoplasms,

lymphomas, and leukemias. The overall incidence of cutaneous metastasis from a primary visceral tumor was found to be 5.3%. Naturally, the epidemiology of cutaneous metastasis varies within different population groups. In a retrospective study from Taiwan, the overall rate of cutaneous metastasis was found to be 1.2%, which is lower compared with cutaneous metastasis rates from Caucasians.¹¹ Moreover, breast cancer was found to have the highest rate of metastasis (2.42%), followed by lung (1.78%) and oral (1.75%) cancers.¹¹ This is in contrast

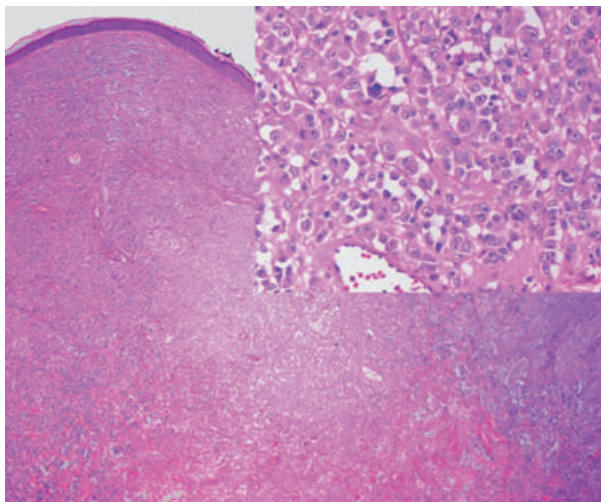


Figure 5 Histologic subtypes of cutaneous metastasis: malignant melanoma (hematoxylin and eosin, original magnification $\times 4$ and inset $\times 20$)

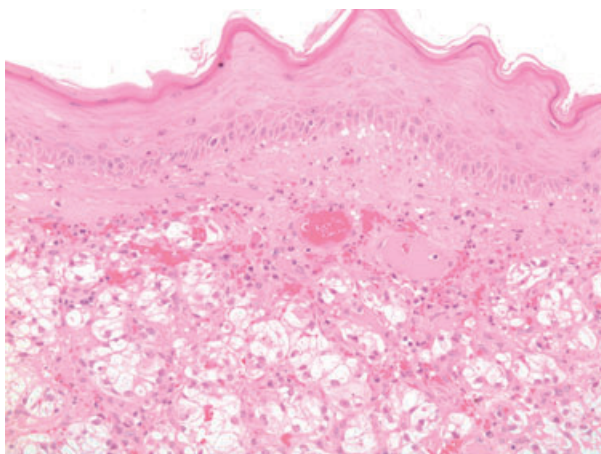


Figure 6 Histologic subtypes of cutaneous metastasis: renal cell carcinoma with atypical clear cells surrounded by a vascular stroma (hematoxylin and eosin, original magnification $\times 10$)

with results of studies conducted on Caucasians where rates of metastasis of breast cancer and oral mucosa carcinomas were found to be higher and differences between types of primaries much less pronounced.^{8,11-13} If melanoma is excluded, lung cancer is the most common source of cutaneous metastasis in men.¹⁴ Multiple series have found breast cancer to be the most common carcinoma to metastasize to the skin in women.^{5,15} In our series, breast cancer was much more common in women. In men, however, laryngeal cancer was the most common.

Although cutaneous metastasis can present at any age, patients with cutaneous metastasis most commonly pres-

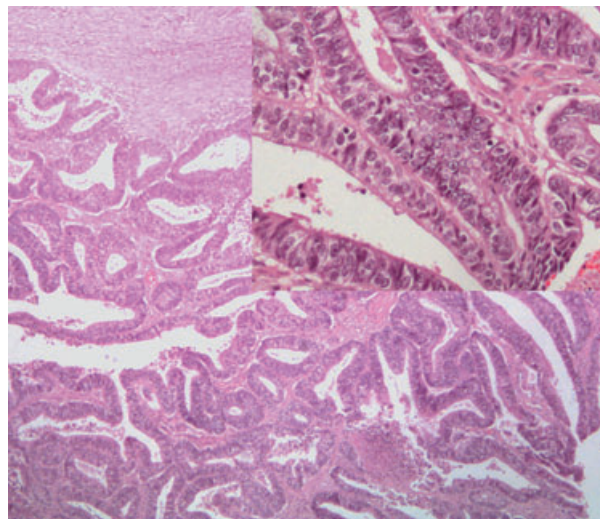


Figure 7 Histologic subtypes of cutaneous metastasis: endometrial carcinoma (hematoxylin and eosin, original magnification $\times 4$ and inset $\times 20$)

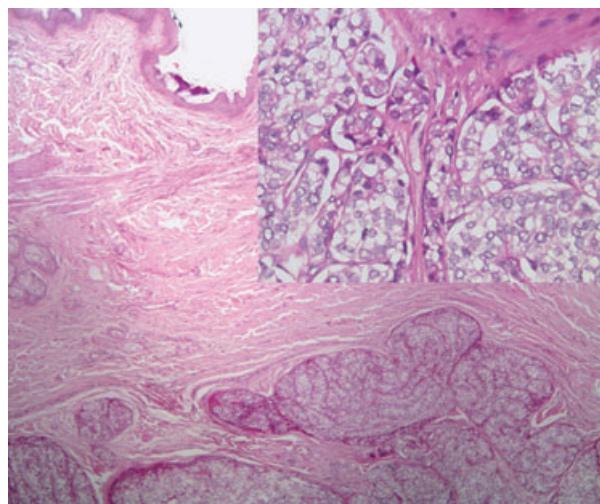


Figure 8 Histologic subtypes of cutaneous metastasis: follicular thyroid carcinoma (hematoxylin and eosin, original magnification $\times 4$ and inset $\times 20$)

ent between the fifth and seventh decade of life.¹² It is rare in children, perhaps echoing the overall lower rates of cancer in children. Our results are in accordance with the published literature, as we did not encounter children in our series. Our youngest patient was 19 years old at the time of diagnosis and suffered from alveolar rhabdomyosarcoma.

Cutaneous metastasis can have a wide spectrum of presentations. In a retrospective study by Mordenti *et al.*,¹⁶ 164 cases of skin metastasis from breast carcinoma were

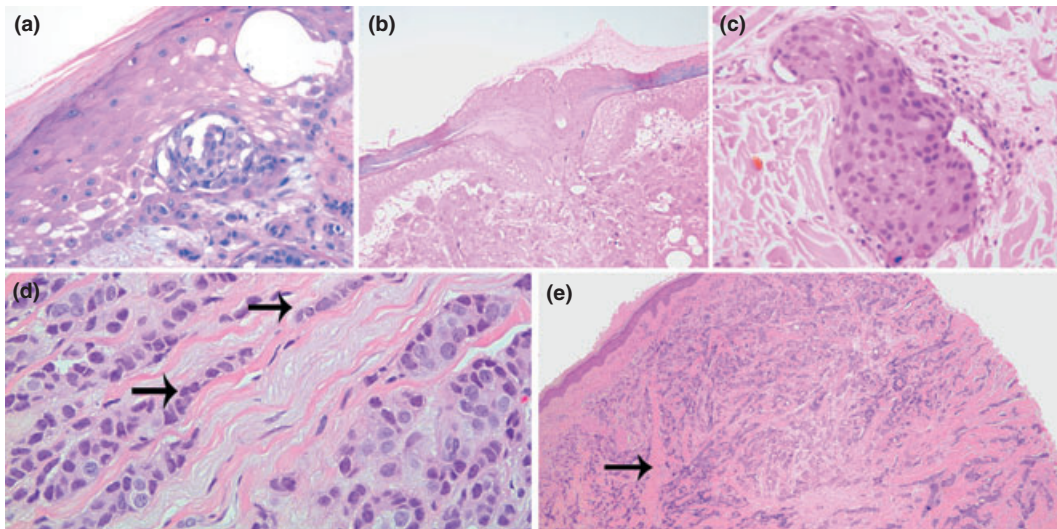


Figure 9 Histological findings in cutaneous metastasis from systemic diseases: (a) epidermotropism with tumor cells seen in the epidermis; (b) perforation of the tumor cells through the epidermis; (c) vascular invasion; (d) Indian filing with rows of atypical cells dissecting the collagen (arrows); (e) desmoplastic reaction pattern (arrows). Hematoxylin and eosin, original magnification (a) $\times 20$, (b) $\times 10$, (c) $\times 20$, (d) $\times 20$, (e) $\times 4$

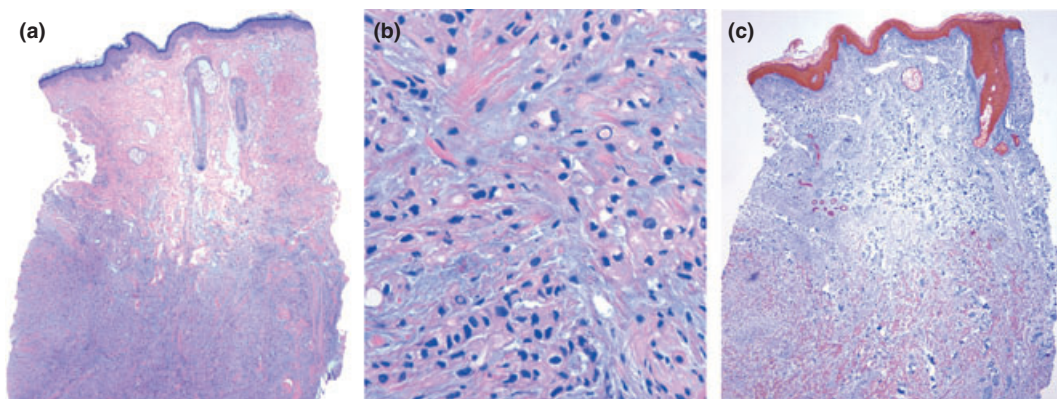


Figure 10 Patient 69 known to have rectal cancer shown on histopathology (a,b) a diffuse dermal infiltrate with scattered signet cells embedded in a rich mucinous stroma. (c) On immunohistochemistry, the tumor cells stained positive for cytokeratin 20. Hematoxylin and eosin, original magnification (a) $\times 4$, (b) $\times 10$, (c) cytokeratin 20, $\times 4$

examined. The most common findings were skin papules or nodules that were seen in 80% of the cases. Telangiectatic carcinomas were seen in 11% of the cases, erysipeloïd carcinoma in 3%, “en cuirasse carcinoma” in 3%, alopecia neoplastica in 2%, and zosteriform metastasis in 0.8%. In our study, the most common presentation was a single nodule followed by multiple firm nodules, a finding that echoes the results reported in the literature.^{12,16} Our series did comprise several classical presentations of breast metastasis such as carcinoma erysipeloïdes or “carcinoma en cuirasse.”

Depending on the type of primary malignancy, cutaneous metastasis preferentially localized to a certain

anatomical site. For instance, breast carcinomas favor the thoracic region as a site of metastasis. The face, more specifically eyelids and nose, is another site of predilection for cutaneous metastasis from breast carcinoma.¹ Metastasis from gastrointestinal origin preferentially localizes to the abdomen. In a study on 75 cases of renal cell carcinoma, cutaneous metastasis localized to the torso in 40% of cases, scalp in 25%, and extremities in 10.7%.¹⁷ “Sister Mary Joseph” nodules or umbilical skin metastasis have been observed not only in ovarian cancer but also in gastrointestinal cancers and prostatic carcinomas.^{18,19}

Traditionally, skin metastasis is perceived as a sign of poor prognosis and advanced disease. It may be the

presenting sign of the internal malignancy in a minority of cases.^{5,20} In our study, skin metastasis heralded the diagnosis of a systemic malignancy in nine cases. Evaluating the prognostic characteristics of cutaneous metastasis in a Taiwanese population, Hu *et al.*²⁰ identified three different patient subsets. Patients having breast cancer with skin metastasis only showed significantly improved survival in comparison with the group of patients who had breast cancer with both skin and visceral metastasis ($P = 0.012$) and those who had other non-breast visceral cancer with skin metastasis ($P < 0.001$). Based on that, the authors concluded that the finding of cutaneous metastasis in a patient with breast cancer with no visceral involvement does not necessarily portend a dismal prognosis. Unfortunately, we were not able to obtain adequate data on survival in our population.

Histological findings

Microscopically, cutaneous metastasis is generally characterized by infiltration of the dermis and/or subcutaneous tissue with neoplastic cells, which usually resemble their malignancy of origin based on their degree of differentiation.³ For instance, a well differentiated skin metastasis from an adenocarcinoma will form glandular structures that closely resemble the primary malignancy. On the other hand, an undifferentiated tumor may not be clearly identifiable at first glance and will require additional immunohistochemical staining to help in achieving the correct diagnosis. Additional features such as lymphovascular invasion, necrosis, and a tumor-free “Grenz zone” may also be helpful.

In a study by Fernandez-Flores, 78 biopsies of cutaneous metastasis from 69 patients were examined. In that study, epidermotropism was not a very prominent feature (11.54%), whereas vascular invasion and necrosis were more commonly noted in 62.82% and 48.72% of the cases, respectively.⁵ Similarly, we found in our study that lymphovascular invasion was a prominent feature (76%), while epidermotropism and necrosis were only seen in 18% and 16% of cases, respectively. Moreover, Indian filing was an important feature that was seen mostly in moderately to poorly differentiated tumors. Similar to the study by Fernandez-Flores, we observed absent to mild inflammation around the tumor cells in the majority of the cases, supporting the view that evasion of the host-immune response is an important step in the metastatic cascade.⁵ The treatment of patients with cancer with chemotherapy is a confounding factor in the assessment of the degree of inflammation and degree of necrosis within the metastatic tumors. Indeed, the chemotherapeutic drugs may interfere with the immune response of the host and may by themselves induce necrosis of tumor cells. Unfortunately, one of the limitations of this study is the

lack of data on the temporal relationship between the biopsy time and intake of chemotherapy by patients.

The majority of the cases exhibited a desmoplastic reaction pattern around tumor cells. Desmoplasia is defined as the response of the host environment to signals produced by the tumor cells.²¹ On histological examination, this stromal reaction is described as collagenous or scar-like. The interaction between the tumor and its surrounding extracellular matrix is crucial to the metastatic cascade. A study by Koperek *et al.*²² showed that the presence of desmoplasia is an indicator of metastatic potential in medullary thyroid carcinoma. Moreover, in hepatic colorectal carcinoma, the desmoplastic reaction pattern was shown to promote tumor cell survival via α_v integrin binding and subsequent signaling.²³ In our study, the presence of desmoplasia is in accordance with the invasive nature of the tumor.

The use of immunohistochemical staining may prove useful to determine the site of origin of cutaneous metastasis, when the primary cancer is not known. However, these panels should be used judiciously as no antibody is on its own pathognomonic for a specific diagnosis. For instance, estrogen and progesterone reactivity is useful in the diagnosis of breast carcinomas; however, it may also be present in tumors of gynecological origin and in sweat gland tumors.²⁴ The immunohistochemical panel of CK7, CK20, and S-100 is a helpful tool that allows us to narrow the differential diagnosis of the primary tumor when further studies are needed. This is particularly true of tumors that exhibit an epithelioid pattern such as carcinomas and melanomas.¹⁰ Skin metastasis from carcinomas arising from the breast or lungs will typically exhibit positivity for CK7 and non-reactivity for CK20, whereas adenocarcinomas from intestinal origin will be negative for CK7 and positive for CK20.³ This panel will then help in the differentiation between adenocarcinomas of different origins (intestinal origin vs. breast and/or lung and melanoma). The usefulness of this immunohistochemical panel was supported by the findings of immunohistochemical staining observed in some of our cases in which immunohistochemistry was done, particularly cases of intestinal origin.

In summary, our study characterized the clinical and pathological findings of 72 patients with cutaneous metastasis in a Lebanese population. The clinical and histopathological features observed were in concordance with the published literature, with minor differences.

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