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Original Article

Cutaneous Metastases of Internal Malignancies: A Retrospective Study from a Tertiary Care Centre in Sub-Himalayan Region

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Abstract
Background: *Cutaneous metastases (CM) are perceived as a sign of advanced disease and are regarded as a grave prognostic indicator.*
Materials and Methods: *Cases of metastatic tumor deposits in the skin from internal malignant malignancies and lymphomatoid malignancies were recorded from 2014-2016 from the old records of our college*
Results: *Fourteen cases of cutaneous metastases were recorded: 7 males and 7 females. The age range was 40 to 73 years, with a mean of 56.2 years. Firm multiple nodules were the most relevant clinical presentation in 42.85% of the cases. In 4 cases (28.5 %), cutaneous metastasis was the presenting sign and in rest 10 patients (71.4%) the cutaneous lesions appeared after treatment of malignancies. Most common primary malignancy metastasizing to skin was breast The most common site of metastasis was abdomen in 42.8 % cases, followed by lower back, extremities were rarely involved. Distant metastasis was seen in 35.7 % cases.*
Conclusion: *Cutaneous metastases are important to recognize because they may help in diagnosing an unknown carcinoma, recurrence of malignancy. Generally cutaneous metastases are poor prognostic signs.*
Keywords: *Cutaneous metastases, Renal cell carcinoma, Carcinoma breast.*

Introduction

Cutaneous metastases (CM) is defined as noncontiguous spread of a cancer to dermis or subcutaneous tissue. It is a relatively uncommon phenomenon with an incidence ranging from 0.7 to 10.4% among various reported case series.[1] As skin metastases can be suspected and detected earlier, compared to metastases in other organs; the clinician and the pathologist should be aware with the various appearances of such lesions, and the various patterns of metastatic deposits in the skin. Cutaneous involvement by cancer can occur by different routes: haematogenous, lymphatic, direct contiguous tissue invasion and iatrogenic implantation..[2] The mechanisms underlying tumour metastasis by lymphohaematogenous route are complex and incompletely defined. A tumour needs to detach from the primary tumour, invade, and intravasate into a blood or lymphatic vessel; survive in the circulation; extravasate; and

finally invade and proliferate at the secondary site.[3] Metastasis to the skin commonly affect the anterior chest, abdomen head and neck.[4] However, it may occur at almost any location. It usually present as painless nodules but may mimic as benign entities as well.

Methods

Cases of metastatic tumor deposits in the skin were collated from our old record of dermatologic patients. Cases with internal malignant malignancies and lymphomatoid malignancies were recorded from January 2014- December 2016. 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.

Results

There were 14 patients 7males and 7 females. The age ranged from 40 -73 years with the mean age of 56.2 years. The 7 male patients who showed skin metastases; three cases were originating from, non –Hodgkin lymphoma (NHL) and one case each from adenocarcinoma colon, renal cell carcinoma (RCC) (Fig.1), lung carcinoma (Fig.2) and breast . Three female patients showed skin metastasis originating from breast carcinoma (Fig.3) and one each from ovaries, endometrium, cervix(Fig4.) and RCC (Fig.5). The clinical features are summarized in Table 1

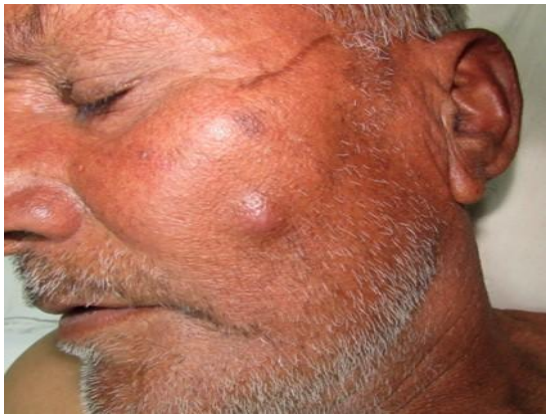

Fig. 1 Distant metastasis on face in renal cell carcinoma

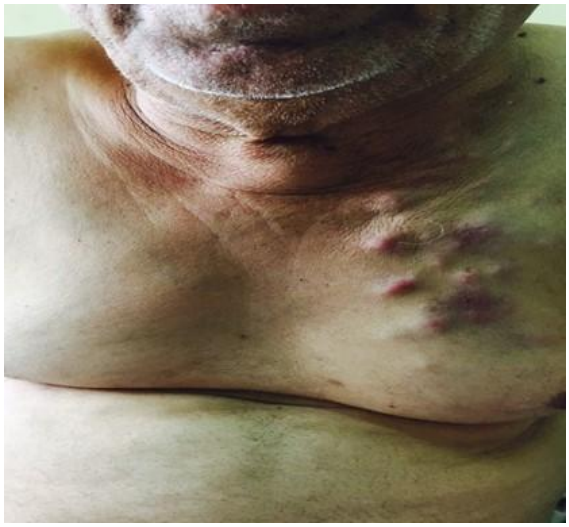

Fig.2 Metastatic nodules in carcinoma lung

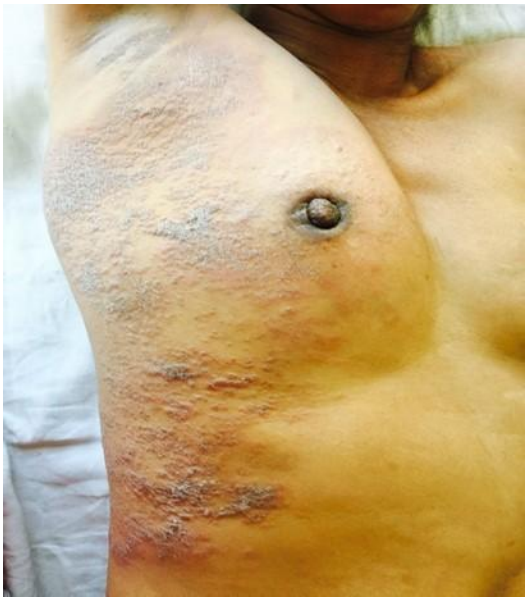

Fig.3 Carcinoma erysipeloides in ca breast

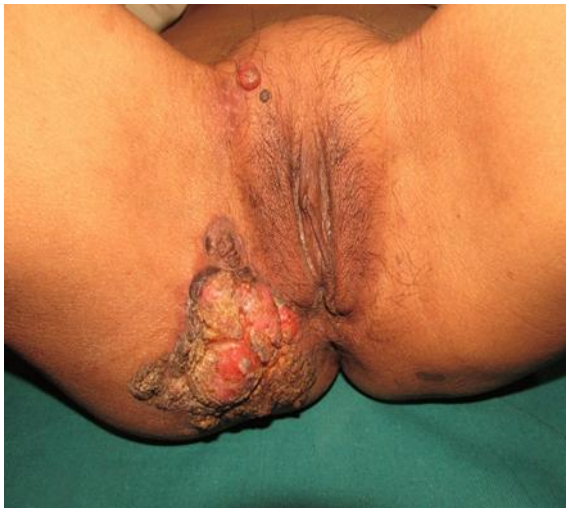

Fig.4 ulcerative plaque in carcinoma cervix

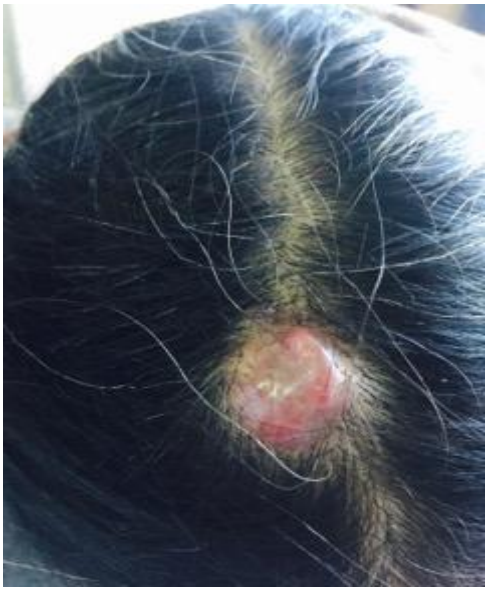

Fig.5 Scalp metastasis in renal cell carcinoma

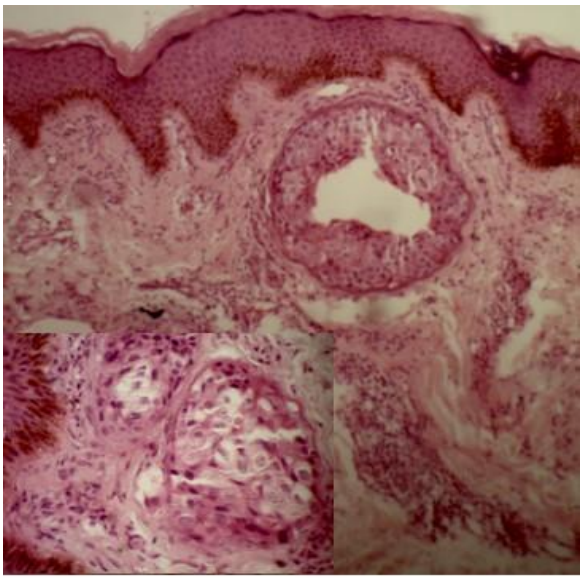

Fig.6 Histopathology H&E stain (10X)showing nests of mitotic cells in carcinoma erysipeloides, inset (40X) mitotic emboli in lymphatics

Cutaneous metastases presented as nodule in 42.85% cases, plaques in 35.71%(out of which 60% were ulcerated), papuloplaque in 21.42% and noduloplaque in 14.28 %.The size of the lesions varied from 0.5– 8 cm. Lesion count varied from a single lesion to about 50 in number.

In 4 cases (28.5 %), cutaneous metastasis was the presenting sign of silent primary growth, while in rest 10 patients (71.5%) the cutaneous lesions appeared after a period ranging from 6 month to 10 years of the treatment in the form of surgery, chemotherapy or radiotherapy.

Metastasis was in anatomical close site in 57.1%,distant in 35.7% and metastasis was both local and distant in 7.1% cases. Abdomen was the commonest site involved followed by lower back. The different sites involved are shown in table 2

Histopathologically 57.1 % of primary tumours showing metastasis were adenocarcinoma , 21.4 % were lymphoid malignancy and 7.1% each were serosal, small cell and squamous cell carcinoma. The histological patterns found in the cases have been described in detail in Table1.

Table 1 clinical features of the patients with cutaneous metastases of malignancies

SERIAL NO.	AGE/SEX	LESION TYPE	NO. OF LESION	SITE OF LESION	TIME OF APPEARANCE (In months)	HISTOLOGY	UNDERLYING MALIGNANCY
1	68/F	ulceronecrotic plaques	m	abdomen ,back andthighs	48	Moderately differentiated endometroid adenocarcinoma.	ca-endometrium
2	41/M	erythematous subcutaneous nodules and plaques	m	Abdomen, back	0	atypical lymphoid cells infilterating deep dermis & S/C tissue ,rimming of atypical lymphoid cells around adipose tissue , & around adnexal structures	NHL
3	65/M	erythematous to skin coloured subcutaneous nodules	m	upper chest	8	small cell carcinoma	ca-lung small cell
4	48 /M	erythematous subcutaneous nodules	s	scalp	0	Invasive ductal nests of mitotic cells	Breast carcinoma
5.	73/M	erythematous subcutaneous nodules	m	face, lower back	24	adenocarcinoma fibrocollagenous tissue infilterated by tumor epithelial	RCC

		and plaques				cells arranged in nests,cords ,glands	
6	60/F	erythematous noduloplaque	s	scalp	18	adenocarcinoma Fibrocollagenous tissue infilterated by tumor epithelial cells arranged in nests,cords ,glands ,pleomorphic with large nuclei	RCC
7	65/M	nodules	m	abdomen	36	Complex fusing glandular structures with few goblet cells	adenocarcinoma colon

SERIAL NO	AGE/ SEX	LESION TYPE	No. of lesion	SITE of lesion	TIME OF APPEARANCE	HISTOLOGY	FINAL DIAGNOSIS
8.	70/F	Noduloplaque over perigenital area	m	perigenital area	0	moderately differentiated sccinterlacing bands and lobules of squamous epithelium well demarcated by fibrocollagenous septa	Carcinoma cervix
9.	42/F	erythematous papules and plaques	m	right side chest upto flank	0	invasive ductal carcinoma nests of mitotic cells with central vacuolation . sheets trabeculae and tubules in dermis and scubcutaneoustissue.malignant thrombi are seen in the lymphatics.	carcinoma right breast
10	48/F	eryhthematous papules and plaques	m	right side of chest and abdomen	12	invasive ductal carcinoma nests of mitotic cells with central vacuolation . sheets trabeculae and tubules in dermis and scubcutaneoustissue.malignant thrombi are seen in the lymphatics.	carcinoma right breast
11	57/M	ulcerated plaques	m	buttocks and low back	120	cutaneous metastasis nhlinfilterate of predominantly large lymphocytes and plasmacytoid cells in dermis and subcutaneous tissue	NHL
12	5O/F	erythematous papuloplaques	m	right side of chest	6	invasive ductal carcinoma nests of mitotic cells with central vacuolation . sheets trabeculae and tubules in dermis and scubcutaneous tissue.	carcinoma right breast
13	40/F	erythematous ulcerated plaques	m	right thigh and leg	9	adenocarcinoma fusing glands and nests with focal clear change	carcinoma ovary
14	60/M	skin coloured to erythematous nodules	m	Back ,abdomen, face	6	cutaneous metastasis of nhlinfilterate of predominantly large lymphocytes and plasmacytoid cells in dermis and subcutaneous tissue	NHL

M male,F –female, m(multiple),s-single, NHL (non hodgkins lymphoma), SPTCL(subcutaneous panniculitis like T cell lymphoma)

Table 2 –showing sites of involvement in cutaneous metastasis

Sites involved	Number of patients n (%)
Scalp, face	4 (28.5)
Chest	4 (28.5)
Abdomen	6 (42.8)
Back	5 (35.7)
Lower limb	2 (14.2)
Perineum	1 (7.1)

Discussion

Cutaneous metastases (CM) is a rare finding. The incidence reported in the literature range from 0.7–10.4% of visceral cancer cases.[1],[2],[3]. Skin metastases may indicate the recurrence of malignancy after treatment. CM can arise at any age, the commonest age reported is during or after the fifth decade.[4] Most of our patients were in the range of 40-70 years.

The period of interval between the onset of symptoms of the primary malignancy and the onset of cutaneous metastases ranged from 6 months to 10 years. The shortest duration was 6 months in the case of carcinoma breast and the longest was 10 years in the case of non-hodgkin lymphoma. On an average cutaneous metastases appear within first three years of primary malignancy.[5] In our study, skin metastasis was the presenting sign in 28.5% (4 of 14). This is higher than the 12% reported in a recent study. [6] Male breast carcinoma because of less subcutaneous fat have early metastasis. Another female with carcinoma breast also probably never noticed the lump in her breast only presented to hospital when visible lesions appeared on the skin. Likewise case 2 and 8 never had any complaint from their primary and only presented when they developed cutaneous lesions.

CM lesions are usually multiple and may range from 1 to 100. [7] In our study only one patient of renal cell carcinoma had a solitary lesion rest 13(92.8%) patients presented with multiple lesions upto 50. Rarity of solitary lesion could be

because normally cutaneous metastasis occurs in later stages of disease when it has become widely disseminated in the lymphohaematogenous route.

Skin-coloured to erythematous nodules at multiple sites were the most common clinical presentation of cutaneous metastases seen in 57.1% patients. We also observed plaques, papuloplaques, noduloplaques, and ulcers. Erysipeloidlesions in carcinoma breast were due to involvement of cutaneous lymphatics which show malignant embolus. These are quite commonly misdiagnosed as erysipelas and contact dermatitis and are often prescribed multiple courses of antibiotics and steroids.

'Soil-seed' hypothesis has been put forward by Stephen wherein he stated that tumour cells act as seed and soil is the chemokine milieu in tissue. A premetastatic niche is formed in metastatic site by the growth factors secreted by primary tumour.[8] CM is not common with all malignancy, secondaries are commonest from melanoma and breast,followed by lung, colon, stomach, upper aerodigestive tract, kidney and uterus .[9] In this study, most common neoplasm to produce cutaneous metastases was carcinoma breas t(28.5%) and NHL(21.4%) followed by RCC in 14.2% patients. According to various studies CM from breast malignancy is seen in 26.5 % cases,[10] in RCC in 3.4%.[11]CM from gynaecological malignancies are very rare with a reported incidence of 0.1 to2 %.[12] In our study in addition to ovarian cancer we had CM from endometrium and cervix. According to a study by Epstein and Mac Eachern NHL cutaneous metastatic lesions are seen in approximately13.9 % patients.[13]

Survival period in patients with cutanenous metastasis is said to be around 3 months. [14] Early death in these patients could be due to undetected secondaries in visceral organs and high-grade malignant nature of the primary tumor. In our study, 4 out of 14 patients (28.6%), were lost to follow-up, and among the remaining 10 patient six patients (42.8%) expired in the period of 1-6 months and rest four are continuing the treatment. As the study period was quite short we cannot assess the survival rate . Shortest survival period (1 month) was seen in a patient who had a recurrence of NHL and 3 months in RCC male patient. In general survival is better in localized cutaneous metastasis in breast carcinoma with no other organ involvement.

The histopathological features of the primary tumor are often reflected in CM. Skin biopsy examination helps to narrow down the primary tumor possibilities and in initiate specific radio-imaging and other relevant investigations concerning the patient's management, as early as possible. [15] In our case 4 and 9 invasion of dermis and subcutis by cords and nests of cells led us to suspect carcinoma breast(Fig6). The deposits of renal cell carcinoma showed presence of tumor cells in glandular configuration or in nests. In NHL deposits of atypical lymphoid cells in the dermis and subcutis with no epidermotropism give a clue to primary as in case 2.In case 8 squamous cell carcinoma histopathology helped us in diagnosing cervical malignancy. In some cases metastatic deposits may be undifferentiated and highly anaplastic, immunohistochemistry and ultrastructure may be of help. CM may mimic primary cutaneous malignancy. Primary cutaneous malignancy has epidermal, intraepidermal/intra-adenexal connection, but still if clear differenti-ation not possible then immunohistochemical staining panels can be helpful.[16] p63 is positive in primary cutaneous and adnexal tumors, and is always negative in the metastatic carcinoma to the skin. Podoplanin is positive in adnexal tumors and negative in metastatic adenocarcinomas. Mucin secreting primary cutaneous tumours secrete sialomucin hence stain positive with alcian blue at pH 2.5 whereas mucin from gastrointestinal adenocarcinoma is rich in sulfomucin and hence stain with alcian blue at pH 1 or 0.4. As seen in a study by Wong adenocarci-nomas (22.7%) were the commonest tumour showing CM followed by lobular carcinoma (4.7%), and non-adenocarcinoma (squamous cell carcinoma [12.2%] and malignant melanoma [5.2%]). [17]In our study adenocarcinoma was

primary tumour histopathologic variant in 57.1 % cases.

Cutaneous metastases are known to frequently occur in anatomical areas close to the primary tumour. [18] This is because most of the carcinomas spread through the lymphatic route to areas having common lymphatic drainage as that of the primary tumour. The abdomen was the predominant site involved in 42.8 % followed by back in our study. This is in contrast to study by Benmously et al .[19] This could be because in our study there were 35.7 % cases of primary in abdominal and pelvic organs ,breast and lung were involved in 28.3 % cases and there were 21.4 % cases of lymphomas in contrast to previous studies where breast and lung primaries outnumbered abdominal malignancies.

Distant metastasis was seen in 35.7 % cases. The scalp had been described as a common location for distant metastases.[20] Distant metastasis was seen in both RCC, male breast and lymphomas. Scalp CM are rare and have been reported in <2 % cases and usually recognized in lung (23.5%),colorectal (11.7%), liver and breast (7.84% each).In our study,28.3 % of cases had metastases to head and neck area. Scalp metastasis was seen in carcinoma male breast and a female with RCC, while distant metastasis on face was seen in a male patient of RCC and of NHL Extremities are rarely involved, only two patient of ours had CM to lower limbs. Distant metastasis in RCC could be because of highly vascular nature of the primary. Though the common route of haematogenous spread of RCC is through vena cava following renal vein, ultimately involving right atrium and lungs. Arteriovenous and systemic shunts, invasion of vertebral veins or Batson's plexus by primary facilitate the tumor's path to the head and neck region by overstepping lung filtration. Tumor-related growth factors, such as parathyroid-related protein and truncated fibronectin growth-promoting substance, may also play an important role in the localization of cutaneous metastasis in this region.

Site of CM may give a clue to the site of primary. Scalp metastasis is commonly seen in malignancy of breast, lung and kidney, face in oral, lung and kidney, chest in lung and breast malignancies, back in carcinoma lung, umbilicus in carcinoma stomach, colon, ovary, kidney or breast. Pelvis CM may be seen in colon malignancies. Although very rare metastasis in extremities may be seen in melanoma, breast, lung renal and intestinal cancers.

Conclusion

Cutaneous metastases indicate a sign of recurrenc e and widespread metastases. It is a poor prognos- tic factor and the survival period is also reduced. The skin is an infrequent site for metastasis and is only the 18th most common site, skin lesions provide an easily accessible tissue for biopsy and histopathologic examination. Systemic response to any therapeutic agent and relapse of internal malignancy can be assessed by the visible regression or recurrence of skin metastasis. Cutaneous metastases are important to recognize because they may precede internal visceral metastases, and their location and histopathology may help to diagnose an unknown primary. Early recognition helps in prolonging the survival of the patient.

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