

Spectrum of Cutaneous Metastasis in Visceral and Haematolymphoid Malignancies: A Cross-sectional Study at a Tertiary Care Centre in Kolkata, West Bengal, India

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ABSTRACT

Introduction: Cutaneous Metastasis (CM) is the spread of malignant cells from a primary site of malignancy to the skin. The incidence of CM ranges from 0.5% to 9% of all patients with cancer. CM may be the first sign of clinically silent visceral cancer or can even be a clue to tumour recurrence and heralds a poor prognosis requiring intense chemoradiotherapy.

Aim: To study the spectrum of CM of internal malignancies, including haematolymphoid neoplasms.

Materials and Methods: This cross-sectional study was conducted at Department of Pathology, Command Hospital Kolkata, West Bengal, India, over a period of two years from April 2020 to March 2022 and data was analysed over the next six months. A total of 16 patients who developed CM secondary to underlying solid organ or haematological malignancy were analysed. Categorical variables were summarised as percentages. Data in tables were presented as the frequency of variables (categories) or as absolute numbers.

Results: The parameters studied included the primary site of malignancies, the frequency of various histological types at the primary site, and the common cutaneous metastatic regions. The mean patient age was 55.25 years (ranges 24-72 years) with no gender predilection (M:F=1:1). The most common primary cancer site was the kidney and the oral cavity 4 each (25%), followed by breast, lung, and haematolymphoid malignancy, 2 each (12.5%), and 1 each of thyroid and gallbladder (6.25%). The most common site of CM was the head, abdomen, and epigastric wall 07/16 each (43.75%). The majority of the CM were identified as adenocarcinoma on histopathology.

Conclusion: The CM occurs rarely and can be the initial presentation of an occult internal malignancy or may suggest recurrence if diagnosed later. Renal cell carcinomas and squamous cell carcinomas of the oral cavity are the tumours that have a high predisposition for CM, and hence these patients require close follow-up and surveillance.

Keywords: Adenocarcinoma, Internal malignancy, Primary site, Skin metastasis

INTRODUCTION

The CM involves the spread of malignant cells from a primary tumour site to the skin. The incidence of CM is reported in the literature as 0.5%-9% and represents only 2% of all skin tumours [1-5]. CM may be the first sign of clinically silent visceral cancer (37% in men and 6% in women) or present as tumour recurrence. Skin metastases from internal malignancies have variable clinical appearance and presentation and often masquerade as inflammatory dermatosis. This causes delay and failure in diagnosis [5]. The development of CM occurs by several different pathways: haematogenous spread, lymphatic spread, direct contiguous tissue invasion, and iatrogenic implantation [6-8]. The mechanism for CM can be viewed as a sequence of steps: initial steps being vessel formation (angiogenesis), cell attachment followed by invasion (matrix degradation and cell motility) and skin homing secondary to certain chemokine-induced upregulation of dermal receptors [3,9,10].

Furthermore, the metastatic cascade provides three basic patterns of distribution of metastases: Mechanical tumour stasis (anatomic proximity and lymphatic drainage), site-specific (selective attachment of tumour cells to a specific organ), non selective (independent of mechanical and organ-specific factors). There are four main morphologic patterns of CM involving the dermis: nodular, infiltrative, diffuse, and intravascular [11,12]. Generally, cutaneous metastases herald a poor prognosis. The average survival time of patients with skin metastases is approximately 7.5 months [13]. In the present study, Immunohistochemical (IHC) studies helped identify underlying malignancies when primary tumours were unknown. Various IHC markers used in the present study were Pan Cytokeratin (CK), CK7,

CK20, CD10, Cluster Differentiation 45 (CD45), GATA3 binding protein (GATA3), Gross Cystic Disease Fluid Protein (GCDFP), Thyroid Transcription Factor (TTF1), CD3, and CD20.

By analysing the spectrum of CM of internal malignancies including haematolymphoid neoplasms, the present study aimed for a better understanding of the pathophysiology of cutaneous metastasising tumours that can be attempted, and this may lead to the opening of new horizons for clinicians to implement effective management guidelines.

MATERIALS AND METHODS

The present cross-sectional study evaluated the clinicopathological findings of total of 16 patients who presented with CM between April 2020 and March 2022 at the Department of Pathology, Command Hospital Kolkata, West Bengal, India. Detailed history and relevant clinical examinations were carried out in all cases.

Inclusion criteria: All patients (all age groups, both genders) with CM of any site, of any primary known or occult malignancy (skin, visceral malignancy, haematolymphoid neoplasms) were included in the study.

Exclusion criteria: Exclusion of cases of primary cutaneous malignancies like malignant melanoma and cases of direct cutaneous involvement from the primary site or tumours arising in a previous scarred or surgical site was done.

Study Procedure

The CM was confirmed by Fine Needle Aspiration Cytology (FNAC) or histopathology. There were cases that presented with CM initially and FNAC, along with clinical and imaging correlation,

helped ascertain the primary tumour site. In other cases with CM in a known primary site tumour, the recurrence was suggestive and necessitated the use of aggressive therapy. The primary site of the tumour, site of CM, and cytology or histopathology of the CM site tumour were noted. In some cases, IHC was performed on either the cell block made from cytology specimens or on biopsies to locate the primary cancer site. Various IHC markers used in this study were Pan Cytokeratin (CK), CK7, CK20, CD10, CD 45 (CD45), GATA3 binding protein (GATA3), GCDFP, TTF1, CD3, and CD20.

Fine needle aspiration was performed by standard technique using a 22 G needle attached to a 10 mL disposable syringe fitted onto a Cameco syringe handle. Two to three passes were taken to obtain adequate material, and 3 to 6 slides were prepared. Both wet and air-dried smears were made from the aspirated material. Wet smears were stained with Leishman and Giemsa and Papanicolaou (PAP) stains. Trucut biopsy from the cutaneous nodules was attempted if there was any discrepancy in cytology diagnosis that required histopathological confirmation. Trucut biopsy was also attempted initially in cases with an occult primary. IHC was attempted in most cases, and Immunocytochemistry (ICC) was tried on cell blocks prepared from cytology (FNAC) specimens in a few cases. IHC was used only in cases where the primary diagnosis was not known or in cases where the FNAC done did not clearly rule out a CM from the primary lesion.

STATISTICAL ANALYSIS

Categorical variables were summarised as percentages. Data in tables were presented as the frequency of variables (categories) or as absolute numbers. For data pertaining to age, the range with maximum and minimum values, and median age were calculated.

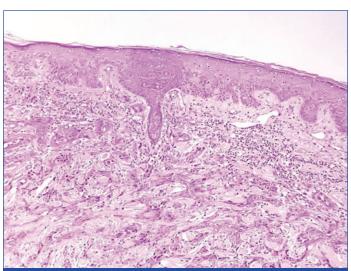
RESULTS

The demographic profile is mentioned in [Table/Fig-1]. The CM emerged from diverse primary sites. Among 16, 11 patients were >50 years of age and 5 (31.25%) were ≤50 years of age. The mean age of the present study population was 55.25 years. Out of 16, 8 (50%) patients were males and 8 (50%) were females, suggestive of no gender predilection with the occurrence of CM. The most common site of CM observed in the present study was the head and neck region and epigastric region/anterior abdominal wall 07/16 each (43.75%). This was followed by CM deposits in the chest/axilla 2 cases (12.5%) [Table/Fig-2].

S.	Age (in years)/	Cutaneous metastatic site	Known/oc- cult primary malignancy	FNAC/Histopathology (HPE) finding: Metastatic deposits	Primary site
1	65/F	Scalp	Occult	Follicular carcinoma	Thyroid
2	28/F	Scalp	Occult	Invasive duct carcinoma	Breast
3	61/F	Lumbar region/ lower back	Occult	Adenocarcinoma	Lung
4	54/M	Neck	Known	Squamous cell carcinoma	Oral cavity
5	53/M	Supraclavicular/ neck	Known	Renal cell carcinoma	Kidney
6	58/F	Epigastric	Known	Renal cell carcinoma	Kidney
7	63/M	Epigastric	Occult	Renal cell carcinoma	Kidney
8	46/M	Abdominal/ epigastric	Known	Adenocarcinoma	Lung
9	62/F	Epigastric	Known	Adenocarcinoma	Gallbladder
10	48/F	Abdominal/ Epigastric	Known	Renal cell carcinoma	Kidney
11	72/M	Submental/Neck	Known	Squamous cell carcinoma	Oral cavity
12	49/F	Chest	Known	Invasive duct carcinoma	Breast

13	61/M	Axilla	Known	Squamous cell carcinoma	Oral cavity
14	69/M	Submandibular/ Neck	Known	Squamous cell carcinoma	Oral cavity
15	24/F	Lumbar region/ lower back	Occult	Diffuse large B cell lymphoma (DLBCL)	Lymph node
16	71/M	Scalp	Occult	Plasma cell neoplasm/Solitary plasmacytoma	Bone marrow

[Table/Fig-1]: Demographic profile of the patients with visceral malignancies who presented with Cutaneous Metastasis (CM).



[Table/Fig-2]: Cutaneous deposits of malignant glands in the dermis lined by cells having high N: ratio, coarse vesicular chromatin with prominent nucleoli (H&E, 400X)

There were 4 cases each of renal cell carcinoma and squamous cell carcinoma (25% each), 3 cases (18.75%) with cutaneous metastatic deposits of adenocarcinoma (02 lung and 01 gallbladder origin), 2 cases each of ductal carcinoma of the breast and haematolymphoid malignancies (12.50%), and one case of follicular carcinoma of the thyroid (6.25%) [Table/Fig-3].

Primary site	Histological diagnosis	Frequency	Percentage (%)
Kidney	Renal cell carcinoma	04	25.0
Breast	Invasive duct carcinoma	02	12.5
Lung	Adenocarcinoma	02	12.5
Oral cavity	Squamous cell carcinoma	04	25.0
Gallbladder	Adenocarcinoma	01	6.25
Thyroid	Follicular carcinoma	01	6.25
Haematolymphoid malignancy	B-NHL and plasma cell neoplasm/Solitary plasmacytoma	02	12.5
Total		16	100%

[Table/Fig-3]: Distribution of primary site malignancies along with the histomorphology of the primary site cancer.

NHL: Non hodokin's lymphoma

In males, squamous cell carcinoma was the most common primary site tumour to present as CM (50%), whereas in females, it was the primary site of the breast and kidney (25% each) that metastasised more commonly to the skin.

All four oral cavity cases, three out of four kidney tumours, one each of breast, lung, and gallbladder were already diagnosed cases on treatment that developed CM later. On the other hand, both the haematolymphoid neoplasms recorded presented initially as cutaneous deposits of occult malignancies. One of these was a young woman diagnosed on FNAC of an abdominal wall mass as high-grade Non Hodgkin's Lymphoma (NHL), which was later confirmed on biopsy as Diffuse Large B-Cell Lymphoma (DLBCL), and detailed imaging {Computed Tomography (CT) of the abdomen and chest} showed generalised lymphadenopathy. [Table/Fig-4]

represents cytology smears of an abdominal nodule in a case of high-grade NHL. The smears are highly cellular and show cutaneous lymphoma deposits.

[Table/Fig-4]: Aspirate smear from abdominal skin nodule showed monomorphic population of atypical lymphoid cells with inset showing these lymphoid cells having high ratio and open chromatin against the background lymphoglandular bodies (Leishman and Giemsa, 400X).

The second haematological occult case was of plasma cell neoplasm presenting as a scalp nodule in an elderly male [Table/Fig-3].

The CM to the scalp in a case of carcinoma breast, which was an occult primary is represented in [Table/Fig-2]. The patient underwent a mastectomy that confirmed the present initial diagnosis. Overall, the findings of scalp metastatic carcinoma breast in a young 28-year-old lady were quite intriguing.

The other scalp nodule metastasis case was of an elderly lady of 65 years. She was apparently asymptomatic except for a history of an enlarging nodule in the occipital region that developed over a period of three months. FNAC from the scalp nodule showed follicular epithelial cells arranged in follicles and clusters with colloid in the background. The differentials considered on cytomorphology were of an adnexal tumour; however, the presence of colloid favoured a tumour of follicular cell origin. Immediately, ultrasonography of the thyroid glands was done, which revealed a solitary nodule in the right lobe. She underwent total thyroidectomy that confirmed follicular carcinoma of the thyroid [Table/Fig-5a-d].

The present cohort had one elderly female who presented with metastatic deposits of adenocarcinoma in the lower back. Later clinical work-up and imaging revealed a lung mass.

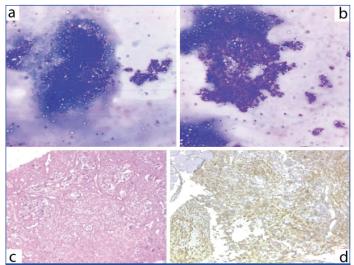
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[Table/Fig-5]: Aspirate smears from scalp nodule were cellular and (a,b) Aspirate showed epithelial cells arranged predominantly in microfollicular pattern (Leishman and Giemsa, 400X). (c,d) Aspirate smears from thyroidectomy specimen confirmed Follicular carcinoma (H&E, 400X).

Biopsy confirmed non small cell carcinoma lung, favouring adenocarcinoma.

The last of the present occult CM cases was of a 63-year-old male who presented with epigastric wall deposits of renal cell carcinoma. FNAC of the abdominal wall nodule suggested metastasis of renal cell carcinoma, which was later confirmed by nephrectomy. The most common CM deposits seen were from underlying primary visceral adenocarcinoma that included tumours of the lung, kidney, breast, gallbladder, and thyroid 10/16 (62.50%). This was followed by squamous cell carcinomas 4/16 (25%).

Another tumour known to show cutaneous involvement is renal cell carcinoma of the kidney. Three out of the four renal cell carcinomas metastasised to the abdominal wall/epigastric region, and one case metastasised to the neck. FNAC followed by biopsy confirmed the cutaneous RCC deposits [Table/Fig-6a-d]. On FNAC, the differentials considered were metastatic adenocarcinoma versus renal cell carcinoma. Since all four cases were known renal cell carcinomas, a synchronous or metachronous dual malignancy was not the present first diagnosis. All underwent trucut biopsy that confirmed renal cell carcinoma deposits. IHC was done, which showed the tumour cells to be positive for CD10 and negative for CK7 and CK20.



[Table/Fig-6]: (a,b) Aspirate smears from epigastric nodule shows tumour cells in cohesive clusters with high N: ratio, coarse chromatin and prominent cytoplasmic vacuolations (Leishman and Giemsa, 400X). Haematoxylin and Eosin stained (400X magnification) section (c) from nephrectomy specimen confirmed clear cell carcinoma which showed membranous and cytoplasmic positivity for CD10 immunostain (d).

DISCUSSION

Cutaneous metastasis (CM) refers to the infiltration of cancer cells in the skin and subcutis, originating usually from internal known visceral malignancy. It is an uncommon occurrence and if seen, suggests disease progression [14,15]. Metastasis to the skin occurs in advanced stages of internal malignancy. It is commonly due to lymphatic or haematogenous embolisation, contiguous spread, or rarely by iatrogenic implantation of malignant cells following surgical procedures. CM can be divided into three different groups [16]. The first and largest group represents cutaneous metastases originating from primary cutaneous malignant tumours, such as primary skin malignant melanoma, squamous cell carcinoma, Merkel cell, and adnexal carcinomas. The second group comprises metastatic involvement from internal malignancies [17-19]. The last group is manifestations of systemic haematolymphoid neoplasms (leukaemia and lymphomas) in the skin. Since, skin metastases reflect systemic dissemination of a primary malignancy, they are associated with a poor prognosis [20].

The incidence of CM increases with age, especially after the fifth decade of life [21]. In the paediatric age group, skin metastasis associated with neuroblastoma or leukaemia is common [12]. In

the present study, 11 patients (68.75%) were over 50 years of age, and five patients (31.25%) were 50 years of age or younger. This finding was consistent with a study conducted by Rolz-Cruz G and Kim CC [21]. The mean age of patients in this cohort was 55.25 years, with an age range of 24-72 years. The youngest patient with CM was a 24-year-old female with metastasis from occult high-grade non Hodgkin lymphoma to the lower back. This finding was in line with studies conducted by Teyateeti P and Ungtrakul T, and Kwon HM et al., where the mean age and age range of cases were 55/34-72 years and 58.6/26-87 years, respectively [22,23]. The male-to-female ratio in the present study was 1:1, consistent with studies conducted by Teyateeti P and Ungtrakul T, and Betloch-Mas I et al., showing a male-to-female ratio of 0.94:1 and 1.1:1 respectively [22,24].

The CM typically develops after the initial diagnosis of the primary internal malignancy and often appears late in the course of the disease. It may indicate a recurrence of a previously treated tumour or could be the first presentation of an unrecognised malignancy, making it a critical finding [25]. When CM is the first presentation without a known primary origin, determining the primary tumour site can be a challenging task. Pathologists play a crucial role in this scenario, requiring morphology coupled with an appropriate IHC work-up to confirm the tumour's origin. Previous literature has shown that the incidence of occult malignancies presenting as CM varies from 15% to 30.3%, as reported by Fernandez-Flores A, Teyateeti P and Ungtrakul T, Kwon HM et al., Handa U et al., [11,22,23,25]. These findings align with the present study, where 25% of cases had initial skin involvement, subsequently confirmed by histomorphology, IHC, and clinicoradiological correlation. The FNAC in certain cases of known primary can reliably confirm cutaneous metastases [26]. It proves to be a rapid, minimally invasive technique that, when coupled with ICC, can help identify the unknown primary or confirm a known case. Authors used FNAC as a modality in certain cases, while biopsy took precedence in others, especially those with a silent primary.

According to studies conducted by Fernandez-Flores A on 78 biopsies from 69 patients, the abdominal wall was the most common site for CM, followed by the head and neck region [11]. In the present study, it was found that both the head and neck region and the abdominal wall were equally involved by CM. Nibhoria S et al., in their five-year study, reported nine cases out of a total of 1924 patients with internal malignancies presenting with cutaneous metastases, indicating a prevalence rate of approximately 0.5%. They reported the chest followed by the abdomen as the most frequent sites of metastasis [27].

The regional distribution of cutaneous metastases usually depends on the location of the primary disease and the mechanism of spread, which can occur through direct spread from adjacent non cutaneous structures, lymphatic or haematogenous spread, and infrequently through implantation following a surgical or diagnostic procedure [27]. Carcinomas of the kidney and lung tend to invade veins and often present as metastases at skin sites distant from the primary tumour. In the present study, out of four cases of renal cell carcinoma, one case metastasised to the neck and the remaining three to the abdominal wall. Of the two cases of lung carcinoma, one metastasised to the back and the other to the anterior abdominal wall. Two cases of breast carcinoma presented as a scalp nodule and a chest wall skin lesion. Out of four cases of squamous cell carcinoma of the oral cavity, three showed cutaneous metastases to the neck, while one had deposits in the axilla. Scalp metastases in females should raise suspicion of possible breast cancer, and in males, of lung malignancy [28]. One of the breast carcinoma cases had cutaneous metastasis in the scalp. However, cases of lung malignancies in the present study did not show scalp metastasis.

In the present study, the most common primary site malignancies were kidney and oral cavity (25%). Common primary tumour sites

differed between female and male patients. Among females, the most common primary site malignancies were breast and kidney, each amounting to 25% of cases. Among males, it was observed that oral cavity (50%), followed by kidney (25%), were the common primary malignancy sites. Studies conducted by Handa U et al., Kwon HM et al., and Fernandez-Flores A suggested that the most common site of primary malignancy was breast in women and lung in males [11, 23, 25]. Handa U et al., studied 138 cases retrospectively diagnosed with cutaneous and subcutaneous metastases on FNAC. Out of 101 cases with known primaries, Handa U et al., found that the most common cancer to metastasise to the skin was breast carcinoma (23 cases) in females, and in males, 12 cases of lung cancer metastasis were seen. Variations seen in the male cohort can be explained by multifactorial causes, with ethnic and geographical differences being the most probable. The histology of the most common primary malignancy was adenocarcinoma, followed by squamous cell carcinoma in the present cohort. The predominant histomorphology of adenocarcinoma is in concordance with study conducted by Handa U et al., who described 26 out of 138 cases as metastases of adenocarcinoma [25].

Limitation(s)

The major limitation in the present study was the small sample size and the heterogeneous cases reported, including two haematolymphoid neoplasms, which are known to have circulating malignant cells. Additionally, most patients who present with skin nodules first report to the Dermatology outpatient department. Being a cross-sectional study, the authors were unable to gather data on the initial dermatological description of the metastatic deposits.

CONCLUSION(S)

The CM can have variable clinical appearances and mimic many benign skin lesions. Skin manifestations before the primary tumour can make it difficult to determine the occult site based on morphology alone. However, the use of appropriate IHC markers along with clinicoradiological correlation can help confirm the diagnosis early, leading to timely therapeutic intervention. Large-scale prospective studies with follow-up details will help establish the outcomes of internal malignancies with CM. The present study has a small cohort of diverse cases that provide insight into the spectrum of associated CM and increase awareness among physicians and oncologists so that in the future, better treatment modalities can be established.

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