

Utility of Fine-Needle Aspiration Cytology in Diagnosis of Cutaneous and Subcutaneous Metastasis

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Abstract

Introduction: Cutaneous metastasis (CM) is an uncommon clinical presentation and poses trouble in diagnosis. However, it is remarkable and can occur due to a known or an unknown primary tumor. Despite the fact that clinical assessment helps in the diagnosis, Fine-needle aspiration cytology (FNAC) is a modest, basic, and quick principle line of investigation for the finding of CM. **Materials and Methods:** It was a retrospective study conducted in the department of pathology at a tertiary care teaching hospital. The study was conducted from January 2010 to May 2020. All cases of CM that has been diagnosed by FNAC were included. **Results:** During the study period, a total of 37 cases of CM were observed, constituting 0.15% of all FNACs. The age of the patients ranged from 35 to 74 years, and the male: female ratio was 1.05:1. Primary tumor was known in all 37 cases. Among males, lung carcinoma was the more common whereas breast was the most common organ of primary among females. The most common lesion was a single nodule (27 cases), with predominant site being chest wall (32.5%), and the most common tumor at microscopy was metastatic adenocarcinoma. **Conclusion:** FNAC is a fast and safe procedure that can be utilized as a first line of investigation in diagnosing metastatic skin lesions. Basic assessment of cytomorphology alongside significant clinical subtleties could help in recognizing the site of an unknown primary.

Keywords: Adenocarcinoma, cutaneous metastasis, fine-needle aspiration cytology, lung carcinoma, squamous cell carcinoma

INTRODUCTION

Cutaneous metastasis (CM) denotes tumor invasion of the skin from a known or obscure primary and conveys a poor prognosis. Early determination is significant to provide treatment to such patients. Literature review shows that the rate of CM ranges from 0.7% to 10.4%.^[1-17] It can be manifested as a late secondary lesion or an early recurrent lesion to a known primary and rarely the only manifestation of an unknown primary. The rate of CM increases with age and more so after 50 years. The most common malignancies to show secondaries to skin are breast, lung, and gastrointestinal tract (GIT). Patient benefit demands early diagnosis which requires high clinical suspicion.^[2]

CM with unknown primary poses a diagnostic challenge to a clinician and pathologist. Fine needle aspiration cytology (FNAC) is an out patient technique, it is simple and reliable. When applied this technique will help to differentiate CM from primary cutaneous tumours.^[13-14] The present study is to establish the utility of FNAC in the diagnosis of CM lesions.

MATERIALS AND METHODS

It is a retrospective study conducted in the department of pathology at a tertiary care teaching hospital. All cases of CM that has been diagnosed by FNAC in our institute from January 2010 to May 2020 were included. Patients with primary malignant adnexal tumors were excluded.

Sample size was calculated using the following formula: $n = Z^2 \cdot apq / d^2$ where $Z\alpha$ is 1.96, $P = 70\%$, $q = 100 - 70 = 30$, and $L = 15$. With the above formula, the minimum sample size was 35, but during the study period, we were able to collect 37 samples. Demographic profiles of the patient such as age, sex, site, and primary tumors were retrieved from the cytology request and medical record sections. Cutaneous location

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of the lesion was confirmed by radiological examination. Cytology slides were retrieved from the pathology archives and reanalyzed. It is our practice that, for every case, we do FNAC using a 23G needle with a 5-ml disposable syringe attached. Two or three passes were required for adequate material. Five to six slides were prepared. Air-dried smears were used for Leishman's staining. Alcohol-fixed wet smears were used for hematoxylin and eosin stain and Papanicolaou (PAP) staining using standard protocol. The study is approved by the institutional ethical committee bearing no. 532/I/11/12 dated December 2, 2020.

Statistical analysis

Statistical analysis was performed using frequency and percentage.

RESULTS

During the study period, a total of 24,129 FNACs were performed, out of which 37 cases of CM were observed, constituting 0.15%. The age of the patients ranged from 35 to 74 years. The diseases are common after the fourth decade, with 26 cases in the age range of 35–74 years [Table 1]. Males were slightly more affected than females (male: female: 1.05:1). Among females, breast carcinoma was the most common primary site, constituting 35%, whereas lung carcinoma was most common in males accounting for 24%. Chest wall is the most common site of occurrence in 32.5% followed by back in 8 (21%).

Single nodule was observed in 27 (73%) cases, more than one nodule were noted in 7 (20%) cases, and in 2 cases (5.5%), papule was noted and 1 case had ulcer (2.5%) [Figure 1a-d].

Adenocarcinoma (including invasive ductal carcinoma-no special type) was the most common microscopic pattern in 24 (65%) of cases followed by squamous cell carcinoma in 8 (21.5%) cases. Two cases (5.5%) of NHL and one each case of hepatocellular carcinoma, follicular carcinoma, and pleomorphic sarcoma were noted. In the present study distant metastasis was observed in three cases (1. Carcinoma lung to right leg, 2. Carcinoma carvix to neck, 3. Soft tissue sarcoma of thigh to face).

In all the cases, the primary tumor was known. Out of 37 cases, in 35 cases, CM was the late manifestation, and in 2 cases, it has preceded the primary malignancy. The clinical and pathological details of cutaneous and subcutaneous metastasis are shown in Table 2.

Table 1: Age distribution of cases	
Age (years)	Number of cases, n (%)
31-40	1 (3)
41-50	11 (30)
51-60	15 (40)
61-70	7 (19)
71-80	3 (8)

Smears from adenocarcinoma showed clusters of tumor cells with increased nuclear-to-cytoplasmic ratio, hyperchromatic, pleomorphic nuclei with prominent nucleoli, and moderate [Figure 1e-h] cytoplasm. Tumor cells are also arranged in glandular pattern. Squamous cell carcinoma shows scattered to clusters of tumor cells with vesicular, pleomorphic nuclei with basophilic cytoplasm [Figure 1i-k]. Cases from lymphoma showed scattered monomorphic lymphoid series cells with occasional cells showing nuclear indentation [Figure 1l]. Metastasis from the thyroid showed tumor cells arranged in microfollicular pattern. Hepatocellular carcinoma cells showed glandular cells with abundant granular cytoplasm. Smears from sarcoma showed spindle cells with malignant nature.

DISCUSSION

Skin is the largest organ in the body, however it is the rare site of metastasis with a prevalence of 0.7%–10.4%.^[3-16] Lookingbill *et al.*^[11] and Spencer *et al.*^[17] in their autopsy study on visceral malignancy observed a higher incidence of 9%–10%. In the present study, we have observed a prevalence of 0.17% and our findings were consistent with Sharma *et al.*^[6] and within the range reported in the literature^[3-16] [Table 3].

CM is of diagnostic challenge and carries a poor prognosis. In some cases, it will be the first indication of metastasis in an adequately treated cancer, or the first manifestation of an occult primary. Occurrence of CM simultaneously with the primary tumor will alter the staging and treatment plan.^[7]

CM can occur at any age; in the literature, it has been observed in the range of 2–90 years; and in the present study, it was in the range of 35–74 years and is consistent with the literature^[3-15] [Table 3]. Males are commonly affected than females and the same was also observed in the present study. In contrast, Mendonca *et al.*^[11] and Nibhoria *et al.*^[10] observed female predominance. Chaudhury *et al.*^[9] and Sharma *et al.*^[12] in their study observed no gender difference.

Incidence of tumor metastasis to skin correlates with the frequency of occurrence of primary tumors in each gender. Among the females, breast was the most common primary organ and same also been observed in the present study.^[3-7,9-11,13-15] In a study, Chaudhury *et al.*^[9] observed hematological and Sharma *et al.*^[12] observed GIT as the most common primary organ among females. With respect to males, the primary organ varies among studies. In the present study, lung is the most common primary site and our findings were in consistent with Srinivasan *et al.*,^[3] Gupta and Naran,^[4] Sharma *et al.*,^[6] Karki *et al.*,^[8] Mendonca *et al.*,^[11] Nibhoria *et al.*,^[10] Handa *et al.*,^[13] and Rajasree Varma *et al.*^[15] In a separate study, by Bansal and Naik^[5] and Bansal *et al.*^[7] observed that GIT has the most common primary organs among males. In a study, Chaudhury *et al.*^[9] observed that hematological malignancy as the most common primary site. Gupta *et al.*^[14] observed that gallbladder as the most common primary site.

Table 2: Clinical and pathological details of cutaneous and subcutaneous metastasis

Organ	Male	Female	Site of cutaneous	Type of lesion	FNAC diagnosis
Breast	0	13	Chest wall (6) Axilla (2) Neck (1) Back (3) Scalp (1)	Nodule (10) MN (1) Papule (2)	IDC-NST (13)
Lung (9)	9	0	Chest wall (3) Arm (2) Back (2) Scalp (1) Leg (1)	Nodule (5) MN (3) Ulcer (1)	Adenocarcinoma (4) SCC (4) Mucinous adenocarcinoma (1)
Oral cavity (2)	2	0	Chest wall (1) Arm (1)	Nodule (2)	SCC (2)
Colon (2)	1	1	Abdomen (1) Back (1)	Nodule (2)	Adenocarcinoma (2)
Gallbladder (2)	1	1	Abdomen (1) Chest wall (1)	Nodule (1) MN (1)	Adenocarcinoma (1) Papillary adenocarcinoma (1)
Lymph node (2)	2	0	Abdomen (1) Chest wall (1)	Nodule (1) MN (1)	NHL (2)
Liver (1)	1	0	Abdomen (1)	MN (1)	Hepatocellular carcinoma (1)
Tonsil (1)	1	0	Face (1)	Nodule (1)	SCC (1)
Pancreatic (1)	1	0	Abdomen (1)	Nodule (1)	Adenocarcinoma (1)
Thyroid	0	1	Back (1)	Nodule (1)	Follicular carcinoma (1)
Maxillary sinus (1)	1	0	Back (1)	Nodule (1)	Poorly differentiated (1)
Cervix (1)	0	1	Neck (1)	Nodule (1)	SCC (1)
Soft tissue (1)	0	1	Face (1)	Nodule (1)	Pleomorphic sarcoma (1)

FNAC: Fine-needle aspiration cytology, MN: Milker's nodule, IDC-NST: Invasive ductal carcinomas-no special type, NHL: Non-Hodgkin's lymphoma, SCC: Squamous cell carcinoma

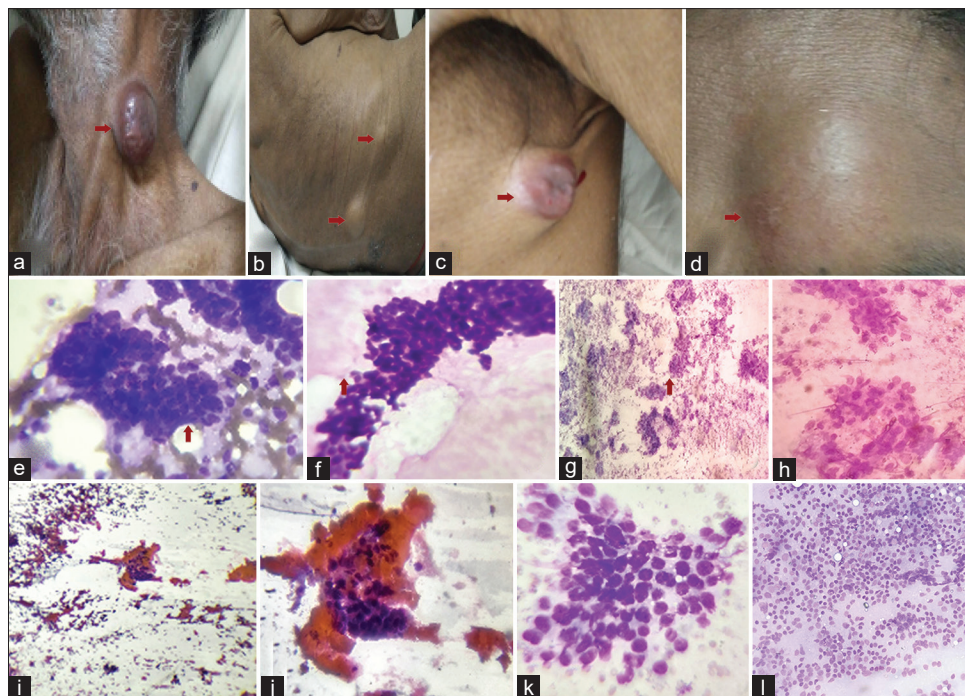


Figure 1: Clinical photograph of cutaneous metastatic lesion, note the single nodule (a and d), multiple nodules (b), and ulcerative lesion (c). (e and f) Microphotograph showing clusters of ductal cells with malignant features (red arrow) (Giemsa $\times 40$). (g) Microphotograph showing clusters of glandular cells with malignant features in the background of necrotic material (arrow) (Giemsa, $\times 10$). High magnification of the same image (h) (Giemsa, $\times 40$). (i) Microphotograph showing clusters of malignant squamous cells in a dirty background (arrow) (Papanicolaou stain, $\times 10$). High magnification of the same image (j) (Papanicolaou stain, $\times 20$). Microphotograph showing clusters of squamous cells with malignant nature (Giemsa, $\times 40$). (k) Microphotograph from a case of cutaneous metastasis of lymphoma showing mono- to biomorphic population of lymphoid series cells (Giemsa, $\times 40$) (l)

Table 3: Comparison of clinical and pathological findings of cutaneous and subcutaneous metastasis with published literature

Authors	Number of cases	Prevalence	Age	Sex	C/F	Multiple nodules	Primary known	Unknown primary	Site	MC primary		Microscopy
										Male	Female	
Srinivasan <i>et al.</i> (1993) ^[3]	38	-	-	Male>female	SN	1	34	4	Chest and abdomen	Lung	Breast	-
Gupta and Naran (1999) ^[4]	146	0.8	34-82	Male>female	SN	8	135	11	Abdomen and chest wall	Lung	Breast	Adenocarcinoma
Bansal and Naik (1998) ^[5]	70		2-74	Male>female	SN				Abdomen	GIT	Breast	Adenocarcinoma
Sharma <i>et al.</i> (2009) ^[6]	95	0.17	4-96	Male>female	SN	8	63	32	Chest and abdomen	Lung	Breast	Adenocarcinoma
Bansal <i>et al.</i> (2011) ^[7]	83	-	2-74	Male>female	SN	2	83	0	Chest and abdomen	GIT	Breast	Poorly differentiated
Karki <i>et al.</i> (2011) ^[8]	19	0.9	40-85	Male>female	SN	4	17	2	Chest	Lung	Lung	SCC
Chaudhury <i>et al.</i> (2013) ^[9]	16	4.2	4.5-80	Male=female	SN	2	14	2	Chest and back	Ovary	Hematological	Adenocarcinoma
Mendonca <i>et al.</i> (2015) ^[11]	17	-	27-70	Female>male	SN	1	15	2	Chest	Lung	Breast	Adenocarcinoma
Sharma <i>et al.</i> (2016) ^[12]	16	-	31-76	Male=female	SN	2	13	3	Abdomen and chest	Breast and GIT	GIT and lung	Adenocarcinoma
Nibhoria <i>et al.</i> (2013) ^[10]	9	0.5	30-72	Female>male	SN	0	19	-	Abdomen and chest	Lung	Lung	SCC
Handa <i>et al.</i> (2017) ^[13]	138	-	5-86	Male>female	SN	33	101	37	Chest and abdomen	Lung	Breast	Adenocarcinoma
Gupta <i>et al.</i> (2018) ^[14]	25	0.4	18-72	Male>female	SN	-	19	6	Abdomen and chest	Gallbladder	Breast	Adenocarcinoma
Rajasee Varma <i>et al.</i> (2018) ^[15]	128		15-90	Male>female	-	-	89	39	Chest and abdomen	Lung	Breast	Adenocarcinoma
Present study (2020)	37	0.15	35-74	Male>female	SN	7	37	-	Chest and back	Lung	Breast	Adenocarcinoma

SCC: Squamous cell carcinoma, GIT: Gastrointestinal tract, SN= Single nodule, C/F= clinical features, MC= Most common

In the present study, the most common site of involvement was chest followed by abdomen and our findings are in consistent with the literature.^[3-15] Due to the lymphatic spread of tumour, CM occurs near to primary organ however due to the haematogenous spread of tumor distant sites can be involved. Metastasis occur by both lymphatic and haematogenous route. When occur by lymphatic route surrounding and near by skin is involved. Example for lymphatic route are carcinoma lung and breast metastasizing to back. Gastrointestinal carcinoma to umbilicus and renal cell carcinoma to lumbar region. Distance metastasis occur due to hematogenous route. In the present study three cases showed distant metastasis. Gupta *et al.*^[14] in their study observed three cases of distant metastasis: carcinoma cervix metastasizing to arm, renal cell carcinoma metastasizing to shoulder, and testicular cancer metastasizing to back. Nibhoria *et al.*^[10] observed only a case of carcinoma cervix showing metastasis to thigh.

Clinically CM occurs as a single nodule and rarely as multiple lesions. The morphological spectra of clinical appearance described in CM were papules, nodules, plaque, tumors, telangiectatic lesions, and ulcers.^[13] In the present study, thirty cases were single lesions and seven cases had multiple lesions. Morphologically predominantly were nodules (34 cases) followed by 2 cases of papules and one case of ulcerative lesion were observed and our findings were consistent with literature^[3-15] [Table 2]. In a study by Ayyamperumal *et al.*,^[16] multiple sites were common than single lesions.

Among 37 cases, 35 had a prior history of malignancy, and in two cases, CM was diagnosed along with the primary tumor. None of the cases were unknown in the present study. Our findings were similar to Bansal *et al.*^[7] and Nibhoria *et al.*^[10] However, many authors have dealt with unknown primary cases.^[3,4,6,8,9,11-15] The comparison of clinical and pathological findings of cutaneous and subcutaneous metastasis with published literature is shown in Table 3.

CM occurring as single nodule and unknown primary are diagnostic challenge to dermatologist and pathologist. In this situation, primary adnexal tumor forms the close differential diagnosis, and can be differentiated on the basis of morphology and with the help of special stains and immunohistochemistry. Adnexal tumors with clear cell morphology such as hidradenoma or sebaceous neoplasm mimic like renal cell carcinoma. Renal cell cancer will be periodic acid-Schiff-positive and diastase-sensitive reaction. Metastatic squamous cell carcinoma will show positive reaction on PAP stain and negative oil red O stain and thus can be differentiated from adnexal tumor with squamous cell differentiation. Most difficult is to differentiate metastatic adenoicarcinoma with adnexal tumor showing sweat gland differentiation. Metastatic tumor will show signet ring cells, extracellular mucin along with three-dimensional clusters of tumor cells.^[13] Most of the primary adnexal tumors will also have intermingled benign component.^[10]

Carcinomas have more propensities for metastasis than sarcoma. Carcinomas such as lung, breast, GIT, germ cell tumors, melanomas, and hematolymphoid malignancy were common. Sarcomas such as Ewing's sarcoma, osteosarcoma, leiomyosarcoma, epithelioid sarcoma, chondrosarcoma, and angiosarcoma have been reported with CM. In the present study, we have observed only one case of pleomorphic sarcoma metastasizing to face.^[13]

FNAC also helps in predicting the probable primary site of metastasis, in cases of unknown primary. Signet ring cells with intra and extracellular mucin points the primary towards GIT. Card-like arrangements of single cells suggest carcinoma breast. Cells with microfollicle arrangements suggest thyroid. Melanoma will show brownish pigment with prominent eosinophilic nucleoli with spindle to plasmacytoid cells. Cytoplasmic elongation with abundant cytoplasm is seen in transitional cell carcinoma. In difficult cases, immunohistochemistry will help to predict the unknown primary.^[10,15]

CONCLUSION

CM is a rare entity and lung carcinoma in male and breast carcinoma in females, were the most common primary organ and chest being the most common secondary site. CM with unknown primary will cause diagnostic challenge. FNAC is a fast and safe procedure that can be utilized as a first-line of examination in diagnosing metastatic skin lesions. Basic assessment of cytomorphology alongside significant clinical subtleties could help in recognizing the site of an unknown primary.

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Conflicts of interest

There are no conflicts of interest.

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