



Visceral Malignancies Presenting as Cutaneous Deposits – A Cytopathologist's Stance

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Abstract

Introduction: Cutaneous metastases can occur in a wide variety of internal malignancies and may be the first indication of an underlying malignancy or recurrence in a patient with a known primary and in rare instances can arise from a second primary.

Aim: This study is designed to analyze cases of cutaneous metastasis from a known or unknown primary and evaluate usefulness of Fine Needle Aspiration Cytology (FNAC) as a diagnostic modality.

Materials and Methods: This is a prospective study conducted in a tertiary care hospital. We studied the cases according to their age, sex, the clinical presentations, site, the treatment provided and the cytopathological findings.

Results: This study comprises of eight cases of cutaneous metastatic deposits from various primary visceral malignancies at different sites-scalp, anterior abdominal wall, chest with varied presentations. The patients have undergone treatment and were referred to surgery and radiotherapy department for further management.

Conclusion: Cutaneous metastasis is a manifestation of the disease due to either hematogenous or lymphatic spread. This study also reiterates that fine needle aspiration biopsy is a very helpful and cost-effective modality in determining the nature of such lesions. So, the study of their clinical profile and cytopathological findings paves way for early diagnosis of primary lesion or recurrence and better management.

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Keywords: Cutaneous; Cytology; FNAC; Metastasis; Underlying malignancy

Introduction

Cutaneous metastases are uncommon presentations of an underlying malignancy [1]. Data from autopsy series indicate an incidence of 0.8% to 5% [2,3]. In most of the cases they occur in patients known to have some malignancy, rarely they may be the first manifestation of an underlying condition. Cutaneous metastasis in visceral cancers pretends to a poor prognosis and often is a hallmark of a widely spread malignancy. Among all skin tumors, 2% comprises of the metastatic deposits in skin [4]. The incidence of cutaneous metastasis increases with age and more so after the fifth decade of life. In patients with malignant disease this metastatic deposit in skin is present in 0.7% to 9% patients. Sometimes it can be confused with various inflammatory conditions of skin [5]. Primary malignancies of the breast, lung, and gastrointestinal tract have a greater propensity to metastasize to the skin [3,6].

The most common sites of skin metastases are the chest and abdomen [7]. Often cutaneous metastases go unrecognized clinically as they may be mistaken for certain dermatological conditions. A high index of clinical suspicion is required for an early diagnosis to enable prompt treatment. Skin metastases are believed to be a manifestation of systemic spread and terminal stage of malignancy with limited survival period. Fine-Needle Aspiration Cytology (FNAC) is an important tool for diagnosis of these conditions [6]. It has been underutilized and even more so in the diagnosis of metastatic skin lesions. The role of Fine Needle Aspiration Cytology (FNAC) as non-invasive first line of investigation is a simple and cost-effective method [7]. FNAC is a diagnostic procedure with high sensitivity and specificity and it can be done on the daily Out-Patient Department (OPD) basis using simple palpation of nodular cutaneous lesions. The diagnosis can be achieved rapidly after the

aspiration [7,8]. Many times, it has been seen that these skin deposits are the main presenting features before the diagnosis of the primary tumor [8]. Gupta et al. and Schneider et al. emphasized on the usefulness of FNAC in establishing the presence of such metastatic disease [9-11]. We carried out the current study to delineate the significance of cutaneous metastasis and usefulness of FNAC for the proper diagnosis of these lesions. Later on, which was confirmed by biopsy and histopathological examination.

Aims and Objectives

Our main objectives were to evaluate the patients with cutaneous lesion by the help of Fine Needle Aspiration Cytology (FNAC).

Materials and Methods

This is a prospective study conducted in a tertiary care hospital comprising of eight cases. All patients presented with wide-ranging clinical features in relation to the primary origin of carcinoma and location of cutaneous lesion were included in the study. Pertinent clinical history, examination findings, and details of other investigations performed were taken into account. Informed consent was taken. 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 Hematoxylin and Eosin (HE), May Grunwald Giemsa (MGG) and Papanicolaou (PAP) stains. Using light microscopy, cytopathological findings were reported. Tru-Cut biopsy from the cutaneous nodules of the clinically stable and willing patients were done and sent for histopathological confirmation. Immunohistochemistry was done where possible. Our cases presented with cutaneous lesions. Informed consents were taken from all the patients.

Results

Case 1

A 55-year-old male presented with nodule over the temporal region (Figure 1A). The nodule was firm, nonulcerated and gradually increasing in size. The patient was hepatitis-B positive and there was complaint of weight loss and abdominal distension.

Radiological investigation revealed a homogenous mass of intermediate echogenicity. Fine needle aspiration was performed on the nodule. Aspirates were cellular, with atypical epithelial cells having hyperchromatic nucleus, high N:C ratio arranged in acini and also in sheets (Figure 1B). Findings were suggestive of a metastatic deposit from a carcinoma. Excisional biopsy from the swelling was done and sent for histopathological assessment.

Clinical, radiological, cytopathological corroboration leads to the diagnosis of multiple metastatic deposits of cholangiocarcinoma which was later confirmed by histopathological diagnosis.

Case 2

A 43-year-old female presented with an ulcerated nodule in the anterior abdominal wall (Figure 2A). The patient complained of intermittent jaundice. There was no other complaint.

Fine needle aspiration was performed on the nodule. Aspirates from the nodule were cellular, with atypical ductal cells in sheet, clusters or singly. Cells show nuclear pleomorphism, irregular

membrane and high N:C ratio (Figure 2B). Features were in keeping with adenocarcinoma. Radiological examination revealed a mass in the gall bladder. Tru-Cut Biopsy from the swelling was done and sent for histopathological assessment.

Clinical, radiological, cytopathological corroboration leads to the diagnosis of multiple metastatic deposits of gall bladder adenocarcinoma which was later confirmed by histopathological diagnosis.

Case 3

A 65-year-old male presented with nodules on the scalp, left upper chest, upper extremity. The nodule on the scalp was noticed first, followed by nodules on the left upper chest and left upper extremity (Figure 3A). The nodules were firm, nonulcerated and gradually increasing in size. The patient complained of intermittent jaundice. There was no other complaint.

CT abdomen showed a well-defined mild enhancing hypodense lesion in uncinat process of pancreas.

Fine needle aspiration was performed on the nodules on the scalp and left arm. Aspirates from the nodules were cellular, with atypical cells in monolayer having monomorphic nucleus, nuclear pleomorphism, disorganized clusters with some acinar arrangements seen (Figure 3B). The cytological features indicated a neoplastic lesion favoring malignancy.

Tru-Cut biopsy from the swelling of extremity was done and sent for histopathological assessment.

Clinical, radiological, cytopathological corroboration led to the diagnosis of multiple metastatic deposits of pancreatic carcinoma which was later confirmed by histopathological diagnosis as pancreatic acinar cell carcinoma.

Case 4

A 56-year-old male presented with diffuse chest wall lesion (Figure 4A). Patient complained of mild cough.

CT thorax showed a rounded or irregular region of increased attenuation (Figure 4B). Fine needle aspiration was performed on the nodules on the chest wall. Aspirates from the lesion revealed atypical cells having high N:C ratio, hyperchromatic nuclei and irregular nuclear membrane, foamy or vacuolated cytoplasm, open chromatin, inconspicuous nucleoli (Figure 4C). FNAC suggested presence of a carcinoma. Excisional biopsy from the lesion was done and sent for histopathological assessment. Clinical, radiological, cytopathological corroboration led to the diagnosis of multiple metastatic deposits of lung carcinoma which was later confirmed by histopathological diagnosis as squamous cell carcinoma of lung.

Case 5

A 50-year-old male presented with nodule on the scalp for last seven months (Figure 5A). The nodule was soft to firm and gradually increasing in size.

CT Scan revealed a well-defined soft tissue density swelling at the midline frontal region. Fine needle aspiration was performed on the nodules. Aspirates from the nodules revealed a cellular smear with microfollicles having enlarged overlapping nuclei with irregular contours and fine chromatin (Figure 5B). Features were consistent with metastatic deposit from a thyroid carcinoma. Tru-Cut biopsy could not be done as the patient did not agree. Later on, biopsy was

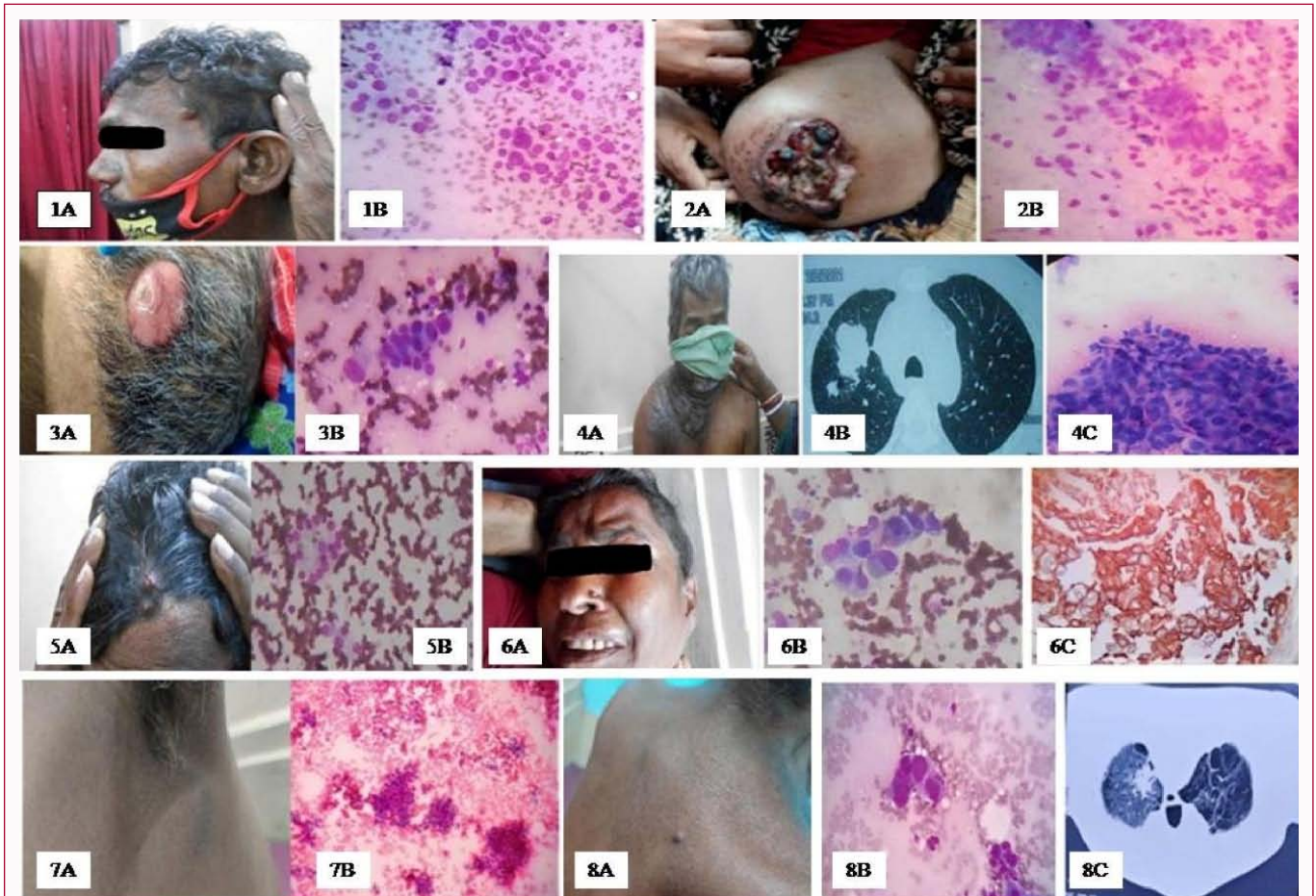


Figure 1: A) Cutaneous nodules over temporal area. B) Ulcerated cutaneous swelling.
Figure 2: A) Sheet of atypical cell (LG 100x). B) Cellular smear with sheet of atypical cells (LG 400x).
Figure 3: A) Scalp swelling. B) Disorganised cluster of atypical cells (LG 400x).
Figure 4: A) Diffuse cutaneous lesion. B) CT thorax showing rounded area of increased attenuation. C) Smear showing cluster of atypical cohesive cells (LG 400x).
Figure 5: A) Scalp swelling. B) Microfollicles having atypical cells (LG 400x).
Figure 6: A) Nodules on face. B) Smears showing loose cluster of clusters of atypical cells (LG 400x). C) Strong her2neu positivity (100x).
Figure 7: A) Blackish nodules. B) Smears showing cluster of atypical cells showing nuclear Pleomorphism (LG 100x).
Figure 8: A) Black skin swelling. B) Cells having hyperchromatic nuclei, high n:c ratio of foamy cytoplasm. C) CT thorax showing rounded enhancing soft tissue density in right upper lobe of lung.

done under GA. Clinical and radiological corroboration lead to the diagnosis of metastatic deposits of thyroid follicular carcinoma which was confirmed by histopathological examination.

Case 6

A 45-year-old female presented with nodules on face. The nodules were firm, nonulcerated and gradually increasing in size (Figure 6A). Patient has a history of breast carcinoma and had undergone modified radical mastectomy of the left breast 2 years back.

Fine needle aspiration was performed on the nodules on the face. Aspirates from the nodules revealed atypical cells in loose clusters having high N:C ratio, hyperchromatic nuclei and irregular nuclear membrane, open coarse chromatin and prominent nucleoli (Figure 6B).

Features were suggestive of a metastatic deposit from a carcinoma. IHC for ER, PR and Her2neu were done on cytological smears. The malignant cells were positive for ER, PR and Her2neu (Figure 6C).

Clinical, radiological, cytopathological corroboration led to the diagnosis of multiple metastatic deposits of breast carcinoma which

was later confirmed by histopathological diagnosis as deposit from breast carcinoma.

Case 7

A 55-year-old female presented with blackish nodules on upper extremity (Figure 7A). The nodules were firm, nonulcerated and gradually increasing in size.

After clinical examination there was suspicion that the nodules might be the metastatic deposit of breast carcinoma and the patient was sent for FNAC.

Fine needle aspiration was performed on the nodules. Aspirates from the nodules revealed atypical cells in clusters having high N:C ratio, hyperchromatic nuclei and irregular nuclear membrane, open coarse chromatin and prominent nucleoli (Figure 7B). The diagnosis of a metastatic deposit from a carcinoma was given.

Tru-Cut biopsy from the swelling was done and sent for histopathological assessment.

Clinical, radiological, cytopathological corroboration led to the diagnosis of multiple metastatic deposits of breast carcinoma

which was later confirmed by histopathological diagnosis as breast carcinoma.

Case 8

A 62-year-old male presented with multiple nodules in back and the upper extremity (Figure 8A). The nodules were soft to firm and gradually increasing in size. Patient had complaint of persistent cough, breathlessness and hemoptysis.

Fine needle aspiration was performed on the nodules on the back. Aspirates from the nodules revealed cohesive cells having high N:C ratio, hyperchromatic nuclei and irregular nuclear membrane, foamy or vacuolated cytoplasm, fine chromatin, variable prominent nucleoli. FNAC suggested a carcinoma favoring adenocarcinoma (Figure 8B). Afterwards CT thorax was advised which showed a rounded enhancing soft tissue density in the right upper lobe of lung (Figure 8C).

Then Tru-Cut biopsy from the swelling and the lung lesion were done and sent for histopathological assessment.

Clinical, radiological, cytopathological corroboration led to the diagnosis of multiple metastatic deposits of lung carcinoma which was later confirmed by histopathological diagnosis as adenocarcinoma of lung.

Discussion

Cutaneous metastases from internal malignancy may develop following surgery for a primary neoplasm or simultaneously with the primary tumor or may arise from an unknown primary. The most dreadful aspect of cancer is the propensity for distant metastatic dissemination of cancer cells from which the patient eventually dies. Cutaneous metastasis from visceral cancers regardless of the histological type or the organ of primary malignancy usually represents a diffuse metastatic disease with a dismal prognosis [12]. Cutaneous metastasis is not common. Handa et al. in their series of 138 cases showed male predominance and showed that elderly people were commonly affected [13]. In our study also males were more than female and metastatic deposits were mainly seen in the fourth to sixth decade of life. The deposits were usually found on the skin over the chest [13]. Here also the metastasis from lung carcinoma was on the chest wall skin. Cutaneous metastatic deposits were the first symptoms in all our cases except one. After diagnosis of carcinoma by FNAC other radiological examinations true cut biopsy from lung was done to confirm the diagnosis. Min Lu et al. in their study of cutaneous deposit of cholangiocarcinoma showed male predominance and the commonest site of cutaneous metastasis is the scalp occurring in elderly men [14]. In our study the patient was male aged 55 years and metastasis was found on the scalp. The metastatic deposits from gastrointestinal tract that is gall bladder carcinoma, cholangiocarcinoma and pancreatic adenocarcinoma were seen where cutaneous nodules were the chief complaints of the patients and later on further evaluation led to the origin of the visceral malignancy. There were two cases of cutaneous deposits from breast carcinoma one had history of previous modified radical mastectomy and in the other case it was the first presenting symptom.

Cutaneous metastases may occur by direct extension, local invasion through lymphatics/body cavities, or distant metastasis *via* the hematogenous or lymphatic route [15-17]. The complex molecular mechanisms responsible for tumoral metastasis to the skin are not completely understood. It is believed that certain chemokines and

their receptors have a role to play [18]. Interactions between dermal/epidermal factors and tumor cells have a plausible role in the skin-homing mechanism of neoplastic cells [17]. FNAC proves to be an efficient and quick method of microscopic confirmation and reduces the numbers of surgical biopsies [18]. FNAC is done on an outpatient basis with routinely available equipment's. It is inexpensive, less traumatic, and a rapid procedure as compared to punch biopsies. The turnover time for the report is just 4 h to 6 h. Since the diagnosis is rapidly available on FNAC, appropriate therapy for the patient can be started earlier. There are no allied complications following the procedure [10]. Metastatic skin deposit may be single or multiple. Most cases are multiple and appear as firm, nonulcerated nodules [19]. In our studies also both single and multiple skin nodules were noted. When solitary, they may be misdiagnosed as primary skin tumors. The common sites of cutaneous metastases are the scalp, abdomen, and chest, followed by the back and extremities [19]. Here also we also got cutaneous metastasis in chest wall, abdomen and scalp. In metastases from an unknown primary, the abdominal wall is the most preferred site [20]. Our abdominal skin deposit was from unknown primary of gall bladder carcinoma. The pattern of spread is related to the mode of dissemination and the anatomic proximity of the primary neoplasm [21]. Saeed et al. saw that the mean age of presenting cutaneous metastasis was 62 years. But in our 8 cases the mean age was 43 years [22]. Cutaneous metastases tend to occur close to the region of primary cancer [20]. Cutaneous metastases among breast and lung cancer patients usually involves the chest wall [23].

In our study, gall bladder carcinoma metastasized in abdominal skin and lung carcinoma to the chest wall and on the back. In contrast, malignancy of the gastrointestinal tract is likely to involve the abdominal area. However, the regional distribution of this may not always be predictable and sometimes related to metastatic spread mechanism [24]. The incidences of various tumors that metastasize to skin correlates with a frequency of occurrence of the primary malignant tumor in each gender [24]. A review by Schwartz reported cutaneous metastatic disease as the first sign of internal cancer that was most commonly seen with cancers of the lung, kidney, and ovary [25]. We have also seen that first symptom of metastatic deposit from lung carcinoma was skin of chest wall and back. Karki et al. studied [10] patients with cutaneous metastasis and found that common sites for it were chest wall followed by abdomen and scalp [26]. In our series chest wall, abdomen and scalp were the sites of metastasis. The commonest tumor type was adenocarcinoma followed by squamous cell carcinoma [26]. We also got predominantly adenocarcinoma as primary tumor.

Most cutaneous metastases appear as mobile solitary or multiple, flesh-colored dermal or subcutaneous nodules which are variable in size and are usually painless [26,27]. Other presentations include telangiectatic violaceous papulovesicles, alopecia neoplastica, non-ulcerative papules, erythematous-infiltrating plaques, and zosteriform metastasis [28]. In this study we came across single and multiple mobile painless skin nodules which were gradually increasing in size.

Clinically, cutaneous metastases may mimic primary adnexal tumors. On cytology, the distinction between primary adnexal tumors and cutaneous metastases can be made by morphologic features, histochemical stains, and immunostains. Distinguishing between primary cutaneous mucinous carcinoma and metastatic mucinous adenocarcinoma is a challenge. Morphological features such as 3-dimensional papillae, pools of extracellular mucin, and signet cells

are fairly reliable indicators of metastasis [29]. Cutaneous metastases from thyroid cancer are rare. When they do occur, they are found in the head and neck area, particularly the scalp [30]. A number of cases of follicular thyroid carcinoma with scalp metastases have been reported [30]. Scalp metastases from thyroid carcinoma result from malignant cells migrating along the external carotid artery [31]. Alternatively, tumor cells may be transmitted through the valveless vertebral venous system, thereby bypassing the lungs [31]. We also described the case of follicular carcinoma of thyroid with metastasis to scalp which was the presenting feature. In cases of cutaneous metastasis with an unknown primary, the aim of cytologic diagnosis is to identify the site of primary tumor. The cytological features of metastatic nodules in all cases correlated well with primary neoplasm. Adenocarcinoma from various organs was the most common morphological lesion to metastasize. The use of immunostains may help to suggest the possible primary site in cases with an unknown primary tumor, and also plays a role in confirming the known previous malignancy. Various working algorithms involving panels of immunostains have been recommended. The primary panel comprising of CK, S-100, vimentin, and LCA may be followed for determining the tumor cell lineage. Depending on the results, further panels can be employed. Immunopanel with up to 10 markers to determine the primary site in metastatic adenocarcinoma employing CDX2, CK7, CK20, TTF-1, CEA, MUC2, MUC5AC, SMAD4, ER, and GCDFP-15 have been advocated [32]. The patients with cutaneous metastasis usually first go to the dermatologist. So, the dermatologist plays a very important role with the clinical diagnosis of the skin lesion [33]. A combination of cytomorphological findings with ancillary immunocytochemistry and other clinical diagnostic workup with close collaboration between the cytologist and the treating clinician holds the key for the timely and proper management of the patients.

Conclusion

Cutaneous metastases from internal malignancies are rare and may have an unpredictable presentation. The FNAC plays an important role for the detection and confirmation of cutaneous metastases from visceral malignancies. It can be recommended as a first line of investigation preferably with IHC panel as a microscopic proof of cutaneous metastases. It is a safe and rapid procedure. Early diagnosis of cutaneous metastasis by FNAC helps the clinician in proper management of the patients.

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