Role of FNAC in Extramammary Tumors Metastatic to the Breast

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Abstract

Background: Metastasis to the breast of an extra-mammary origin is very rare. FNAC plays an important role in differentiating non-mammary breast metastasis from primary malignancy. This study aimed to analyze the cytomorphological criteria and its pitfalls in differentiating metastatic lesion of the breast from primary malignancy. Methodology: Retrospective analysis of 891 FNACs of the breast was performed for a time span of 3 years. A total of 12 cases were diagnosed on FNAC as secondary neoplasms to the breast. Clinical and radiological data, along with Pap and MGG stained smears of each case were examined and correlated with the histopathology of the primary tumor. Statistical analysis was carried out. All cases of primary breast malignancies were excluded from our study. Results: In 10 out of 12 cases, primary malignancies were identified as Plasma cell myeloma (one case), B-acute lymphoblastic leukemia (two cases), acute myeloid leukemia (one case); chronic myeloid leukemia (one case), Burkitt’s lymphoma of the ovary (one case), Diffuse large B-cell lymphoma (one case), esophageal squamous cell carcinoma (one case), spindle cell sarcoma (one case) and squamous cell carcinoma of the cervix (one case). The remaining two cases in our study were misdiagnosed on cytology as metastasis and turned out to be breast primaries on histopathology. Conclusion: Our case series highlights the importance of FNAC to differentiate secondary lesions from primary breast malignancy and thus helps to avoid unnecessary surgery to the patient. It emphasizes on the need to keep in mind the possibility of metastatic breast neoplasms in the presence of unusual cytological features on FNAC.

Keywords: Breast, extra-mammary tumor, FNAC, metastasis

INTRODUCTION

According to Globocan India 2018, a world health organization (WHO) initiative, breast cancer is now considered the most common malignancy affecting Indian women accounting for about 25% of the malignancies seen.[1] The most common primary breast carcinoma is invasive ductal carcinoma (IDC) which accounts for 80% of the cases.[2] Breast as a site of metastasis is an uncommon entity. The majority of the cases metastasizing to the breast are primaries from the contralateral breast.

Fine needle aspiration cytology (FNAC) is a valuable tool in the evaluation of breast lesions as the first line of investigation and also for suspected recurrence in breast malignancy. It is simple, safe, cost-effective, and relatively less invasive with reported specificity of 89.8% to 100% and sensitivity of 43.8% to 95%.[3] Metastatic involvement by extramammary primary is extremely rare and accounts for less than 2% of breast malignancies.[4] Among the non-mammary *primaries, hematological malignancies and melanomas are the most common cancers followed by lung, ovary, soft tissue sarcomas, and prostate carcinomas showing metastasis to the breast.[5] Metastasis from gastrointestinal tumors like the esophagus, stomach, and colo-rectum is very rare.[6] Clinically, these lesions present as firm, rounded, freely mobile masses without any fixation to surrounding parenchyma. On mammography, they show single or multiple well-circumscribed nodules with irregular margins, in the absence of microcalcification and spiculations.[7]

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Accurate diagnosis is mandatory to differentiate breast metastasis from primary carcinoma as they have different treatment protocols. Failure to make this differentiation can result in unnecessary mastectomy and sentinel lymph node dissection. Extramammary metastasis is often a marker for disseminated malignancy and it indicates a poor prognosis.

This study aims to analyze the cytomorphological criteria and its pitfalls in differentiating metastatic lesion of the breast from primary malignancy.

**MATERIALS AND METHODS**

An observational and retrospective cross-sectional study was conducted on metastatic malignancies to the breast, diagnosed on FNAC. These cases were obtained from the files of the Department of Cytopathology from January 2016 to December 2018. The study was conducted with approval from the ethics committee of the institute.

Clinical data including age and sex of the patient along with features of the breast lump such as laterality and number were noted. Findings were correlated with the radiological data of each case. History of known primary malignancy and presence of systemic metastasis in sites other than breast was also evaluated.

FNAC procedure was performed by direct palpation or under ultrasound guidance using 22G to 24G needle. Five to six smears were prepared with the aspirated material in each case. Air-dried and alcohol fixed smears were stained with May-Grunwald-Giemsa (MGG) and Papanicolaou stain, respectively. Smears were evaluated for cellularity, patterns, cellular details, mitosis, necrosis, and presence of benign breast tissue.

In cases with a known primary, the biopsy, surgical specimens, and immunohistochemistry (IHC) of the primary malignant mass were examined. The histopathology slides of breast biopsy (available in 7 cases) were reviewed and compared with the cytological material. In the case of hematolymphoid malignancies, immunophenotyping (IPT) of the bone marrow was performed for further characterization.

In addition, cases diagnosed as extra-mammary metastasis to the breast on histopathological samples were also examined. These were cross-referenced with the cytology records to identify cases diagnosed as extramammary metastasis on histopathology and reported as otherwise on cytology. No such cases were identified.

For statistical analysis, a two by two contingency table was prepared (Table 1) and the sensitivity, specificity, positive, and negative predictive value of FNAC in extra-mammary metastasis to the breast was calculated.

All cases with primary breast cancer were excluded. Patients were followed up for a period of 6 months to 2 years.

**Observation and Results**

A total of 891 FNAC from breast masses were performed over a period of three years and twelve cases were diagnosed cytologically as extramammary tumors metastasizing to the breast.

There were ten female and two male patients in the age group of 20-70 years. Clinically, 7 cases showed solitary breast lesions, 1 case showed multiple lesions, and the remaining 4 cases were found to be bilateral tumors. Eight out of twelve cases had a known primary at the time of diagnosis. Two of
The treatment plan for 9 out of 10 cases was available. Since the involvement of the breast indicates Stage IV malignancy, most of the patients received chemo-radiotherapy according to NCCN guidelines in each case according to its primary malignancy. Follow up of 7 patients was available for up to 2 years. These patients are alive and well. The remaining 5 cases were lost to follow up.

Statistical analysis

Out of the total 891 breast FNACs performed, 10 cases showed extramammary metastasis to the breast, whereas 2 cases were misdiagnosed as metastasis on cytology and turned out to be primary tumors of the breast on histopathology. The remaining 879 did not show evidence of extramammary metastasis on both cytology and histopathology. There were no cases that were missed on cytology and diagnosed as extramammary metastasis on histopathology.

To evaluate the diagnostic accuracy of FNAC in non-mammary metastasis to the breast, we calculated the sensitivity and specificity, which was 100% and 99.7%, respectively. A positive predictive value of 83.3% and a negative predictive value of 100% was also determined for the same.

Discussion

Metastasis to the breast from an extra-mammary neoplasm is an extremely rare phenomenon with the reported incidence varying from 0.5 to 6.6% in various studies.\cite{5,9} Our series also showed an incidence of 1.2% highlighting the infrequent occurrence. The rarity of breast as a site of metastasis in comparison to other body organs is believed to be due to large areas of fibrous tissue and relatively less vasculature.\cite{10,11}

Increased reports of metastasis at unusual sites including breast in recent times are due to multiple factors such as better radiological modalities for early detection of asymptomatic lesions, increased overall survival of cancer patients owing to the multidisciplinary approach, targeted, and specific treatment which acts predominantly on the primary tumor but may not be as effective on the metastatic lesions.\cite{12}

In our study, 33% of cases presented with the breast as the initial site of malignant disease, which was in concordance with other studies reporting a range of 11-33%.\cite{7,9,14} According to the literature, common malignancies metastasizing to the breast are of hematolymphoid origin, malignant melanoma, rhabdomyosarcoma, ovarian, and bronchogenic carcinoma.\cite{5,7,13}

58% of our cases were metastasis from hematolymphoid malignancies [Figure 1]. Shukla et al. and Mandal et al. had comparative findings with our study, having hematolymphoid origin tumors as the commonest metastasis to breast.\cite{5,13}

Metastasis to the male breast is an uncommon entity, reported most commonly from prostatic adenocarcinoma.\cite{7,14} We had two extra-mammary metastasis in the male breast. Both showed hematolymphoid [Figure 1c] type malignancy- metastasis from plasma cell myeloma in one and chronic myeloid leukemia in another case was suggested [Figure 1d].

Clinically, metastasis to the breast from extra-mammary primary usually presents as palpable, rapidly growing,
Table 2: Clinical and radiological details of cases

| Case no. | Age/sex | U/L or B/L breast | Radiology | Cytological diagnosis | Known Primary | Primary site | Other site of metastasis | Final histopathological diagnosis |
|----------|---------|-------------------|-----------|-----------------------|--------------|-------------|--------------------------|----------------------------------|
| 1.       | 67/M    | U/L               | -         | Malignant recurrent plasma cell myeloma [Figure 1c] | Yes          | Bone Marrow | -                        | Multiple Myeloma                 |
| 2.       | 49/F    | U/L               | Soft tissue density in retro areolar region and extends to involve overlying skin. P/O breast primary | Spindle cell tumor [Figure 2a] | Yes          | Soft tissue | Lung | Undifferentiated Spindle cell sarcoma |
| 3.       | 48/F    | B/L               | Solitary rounded lesion having benign appearance | Malignant round cell tumor. P/O granulocytic sarcoma | Yes          | Bone marrow | -                        | Acute Myeloid Leukemia-M4         |
| 4.       | 33/F    | U/L               | No detectable mammographic changes | Involvement by acute lymphoblastic leukemia [Figure 1b] | Yes          | Bone marrow | -                        | B-Acute Lymphoblastic Leukemia    |
| 5.       | 46/F    | U/L               | -         | Squamous cell carcinoma [Figure 3] | Yes          | Cervix      | Lung | Squamous cell carcinoma    |
| 6.       | 40/F    | U/L               | Ill defined soft tissue opacities with specks of micro calcification suggestive of metastasis | Malignant- Metastasis from Esophagus [Figure 1a] | Yes          | Esophagus    | -                        | Poorly differentiated squamous cell carcinoma |
| 7.       | 35/F    | B/L               | Solitary rounded lesion having benign appearance | Malignant round cell tumor P/O Non Hodgkin’s lymphoma | No           | B/L Ovary   | -                        | Burkitt’s lymphoma                |
| 8.       | 22/F    | B/L               | Mass with infiltrating margins and axillary lymph nodes involved suggesting primary breast carcinoma with nodal metastasis | P/O - Non Hodgkin’s lymphoma or Poorly differentiated carcinoma | No           | Axillary lymph node | - | DLBCL-ABC                       |
| 9.       | 72/F    | U/L               | -         | Malignant round cell tumor | Yes          | Bone Marrow | -                        | B-Acute Lymphoblastic Leukemia    |
| 10.      | 26/M    | B/L               | -         | Granulocytic sarcoma [Figure 1d] | Yes          | Bone Marrow | -                        | Chronic Myeloid Leukemia-myeloblastic crises (L) MRM- Malignant Phylloides |
| 11.      | 56/F    | U/L               | -         | ?Metastatic carcinoma ?Malignant Phylloides tumor [Figure 2b] | No           | Breast      | -                        |                                    |
| 12.      | 38/F    | U/L               | Heterogeneous lesion with few solid and cystic areas? Fibroadenoma ? Neoplasm | P/O Stromal tumor | No           | Breast      | -                        | Giant cell tumour of soft tissue breast |

FNAC=Fine-Needle Aspiration Cytology, HPE=Histopathological examination, U/L=Unilateral, B/L=Bilateral, P/O=Possibility of, NHL=Non-Hodgkins Lymphoma, IHC=Immunohistochemistry, MRM=Modified Radical Mastectomy

well-circumscribed rounded mass without overlying skin involvement or nipple retraction. On mammography, metastatic breast lesions have non-specific and deceptive features which makes it difficult to distinguish it from primary breast lesions. In our case series, 3 cases were reported as benign, 2 cases as primary breast malignancy, and only one case as metastatic lesion on mammography.

Hence, FNAC plays a key role as a first-line diagnostic procedure with a reported sensitivity of 43.8% to 95%, but the cytomorphological diagnosis of an extramammary tumor is not always straightforward. The reasons may be a confusing clinical picture, non-specific mammographic findings, and/or tumors involving the breast in the clinical setting of genetically determined multiple primary malignancies. Hence, along with cytomorphological features, it may be necessary to use ancillary studies to arrive at the correct diagnosis.

While evaluating cytology smears in such cases, our first goal is to exclude any primary breast lesion such as pre-malignant carcinoma-in-situ or invasive carcinomas along with its variants. Presence of any atypical ductal epithelial cells or foci of ductal carcinoma in situ raises the possibility of a primary lesion. However, the presence of a dispersed population of undifferentiated small cells, malignant cells of hematopoietic origin, dysplastic keratinized cells, pleomorphic spindle cells, and cells with neuroendocrine morphology should alert one to rule out metastasis before labeling lesion as breast primary.[7]

In our series, eight cases had a known primary at the time of breast FNAC and this information played a significant
Table 3: Cytomorphological Features

| Case          | Case 1 [Multiple Myeloma] | Case 2 [Undifferentiated Spindle cell sarcoma] | Case 3 [AML-M4] | Case 4&9 [B-ALL] | Case 5 [Squamous cell carcinoma] | Case 6 [Squamous cell carcinoma] | Case 7&8 [NHL] | Case 10 [CML-myeloblastic crises] | Case 11 [Malignant Phyllodes] | Case 12 [Giant cell tumor soft tissue breast] |
|---------------|---------------------------|-----------------------------------------------|-----------------|------------------|----------------------------------|----------------------------------|----------------|-----------------------------------|----------------------------------|-----------------------------------------|
| **Arrangement of cell** | Relatively monotonous, discohesive cells | Loose cohesive clusters | Dispersed | Dispersed population | Small, cohesive clusters | Cohesive cluster | Discohesive cells | Discohesive, polymorphic population | Cohesive clusters and sheets | Singly scattered with few fragments |
| Size and shape of cells | Medium to large cells plasmacytoid cells | Spindle to cigar shaped cells with high N: C ratio and | Medium to large cells | Medium sized atypical, monotonous population of cells | Medium to large cells having high N: C ratio | Polygonal cells with high N: C ratio | Small to medium sized cells | Predominantly large cells | Proliferation of spindle shaped stromal cells with aggregates of epithelial cells | Spindle cells along with multinucleate giant cells |
| Cytoplasm     | Moderate amount of pale cytoplasm and paranuclear halo | Scant cytoplasm | Moderate amount of pale cytoplasm | Scant rim of pale cytoplasm | Moderate amount of eosinophilic cytoplasm | Moderate amount of refractive, orangish cytoplasm | Scant amount of cytoplasm | Moderate amount of pale cytoplasm | Moderate amount of pale cytoplasm | Moderate pale cytoplasm |
| Nuclear features | Eccentrically situated, round to oval nucleus with coarse nuclear chromatin | Moderately pleomorphic, hyperchromatic | Irregular nuclear membrane, fine nuclear chromatin with prominent nucleoli | Irregular nuclear membrane, coarse chromatin and inconspicuous nuclei (+/-) | Pleomorphic cells, round to oval nucleus with open nuclear chromatin, prominent nucleoli | Pleomorphic, hyperchromatic nucleus | Monomorphic round nucleus, coarse chromatin, and prominent nucleoli | Pseudomorph, irregular nuclear membrane, fine chromatin with 1 or more prominent nucleoli | Stromal cells with mild atypia. Epithelial cells marked anisonucleosis, irregular nuclear membrane, coarse chromatin | Bland spindle cells with elongated nucleus and inconspicuous nucleoli |
| Binucleation/ Multinucleation | Binucleation + | Multinucleation + | - | - | - | - | - | Multinucleate tumor giant cells | Multinucleation + |
| Mitosis       | - | + | + | + | - | + | - | Few myeloid precursors, neutrophils and eosinophils + | - | - |
| Necrosis      | - | - | - | - | + | + | - | - | - | - |
| Other         | Plasmablasts + | - | Apoptotic bodies seen | - | - | - | - | - | - | - |
| Normal breast tissue | - | - | + | + | + | + | - | + | + | + |

AML-M4=Acute Myelomonocytic Leukemia, B-ALL=B-cell Acute Lymphoblastic Leukemia, NHL=Non-Hodgkin’s Lymphoma, CML=Chronic Myelogenous Leukemia, N: C ratio=nuclear-cytoplasmic ratio
role in reaching a diagnosis. Along with the clinical history, cytological features like presence of a dispersed population of malignant round cells suggestive of hematopoietic origin, premature myeloid series cells suggestive of granulocytic sarcoma, atypical bizarre and immature plasma cells suggestive of metastasis from myeloma, dysplastic and malignant squamous cells suggestive of metastasis from known primary squamous cell carcinoma and pleomorphic spindle cells without malignant breast epithelial cells suggestive of a metastatic lesion from sarcoma, played an important role in the diagnosis of metastatic lesion over breast primary.

The remaining 4 cases in our study, presented with breast as the initial site of malignant disease. On cytology, two of the four cases had a classical dispersed, monotonous population of tumor cells without the formation of true tissue aggregates, suggestive of malignant round cell tumor- Non-Hodgkin’s lymphoma. On further workup, they were confirmed to be an advanced stage primary nodal lymphomas.

The other two cases were misdiagnosed in our study, one case showed even distribution of multinucleated osteoclast-like giant cells with stromal cells that resembled the giant cell tumor of bone along with the presence of sheets of benign ductal cells and myoepithelial cells. This case was misinterpreted as metastasis, as on further histopathology it was proven to be primary giant cell tumor of the breast. When dealing with such cases it is important to consider the following differentials- primary breast malignancy with giant cells, giant cell-rich variants of osteosarcoma/leiomyosarcoma, and metastasis from a giant cell tumor of bone.[15,16] With respect to our case, the lack of malignant epithelial component (for carcinoma), absence of high-grade nuclear atypia (as seen in osteosarcoma/leiomyosarcoma), and no evidence of any primary bone malignancy helped us to make the diagnosis of giant cell tumor of the breast on histopathology.[15] This entity although rare must be borne in mind when encountered with giant cells on FNAC of the breast.

The second case showed atypical cytological features including high cellularity, presence of malignant spindle cells, focal crowding, nuclear abnormalities, bizarre multinucleated giant cells along with proliferative ductal cells. We misdiagnosed this case because of minimal stromal component which later turned out to be malignant phylloides on histopathology.

A variety of metastatic and primary lesions to the breast can present with spindle cell morphology. These lesions may range from inflammatory, benign proliferative to high-grade malignancies making their diagnosis very challenging. Phyllodes tumors (PT) with stromal overgrowth and metaplastic spindle-cell carcinoma (MC) represent the most common malignant spindle-cell lesions of the breast. The presence of a conspicuous, benign, non-neoplastic epithelial component would favor a phyllodes tumor, while a biphasic epithelial/mesenchymal phenotype would favor a metaplastic carcinoma.[17] Primary breast sarcomas and sarcomas metastatic to the breast are exceedingly rare and difficult to distinguish histologically from phyllodes tumor or metaplastic breast carcinoma. A history of previous sarcomas along with imaging and clinical correlation may help in making the diagnosis.[17]

Ancillary studies on cell block material and immunocytochemistry can play an important role to avoid such misdiagnosis. In most circumstances, sufficient material for these ancillary studies is not obtained. Working in close coordination with the clinician and rapid onsite evaluation can help to obtain adequate material for cell block, immunocytochemistry, flow cytometry, or other ancillary studies. Estrogen receptor, gross cystic disease fluid protein 15 (GCDFP-15), mammaglobin-A, and GATA3 are the most commonly used breast-specific immunomarkers but have variable sensitivities and specificities.[18] Hence, careful examination of cytomorphology and clinical history is key to an accurate diagnosis.

In conclusion, achieving optimal diagnosis in breast lesions requires a comprehensive approach that includes clinical history, radiographic findings, and careful assessment of cytological features. When unusual cytological features like malignant round cells, squamous cells- dysplastic or malignant, melanin pigment, or psammoma bodies are seen, we need to consider the possibility of metastatic lesions. The cytology of the metastasis depends upon the nature of the primary tumor and comparing it’s cytomorphology with the morphology of a known primary tumor can help to confirm or exclude the diagnosis.

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Conflicts of interest
There are no conflicts of interest.

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