

Cytological evaluation of enlarged lymph nodes in metastatic disease: A hospital-based assessment

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ABSTRACT

Background: Lymphadenopathy is a heterogeneous entity with many underlying causes, ranging from self-limiting benign disease to severe neoplastic proliferations. Fine-needle aspiration is a cost-effective and reliable tool for initial investigation of enlarged lymph nodes. **Materials and Methods:** A study was conducted on 326 patients with metastatic disease in order to evaluate the efficacy of cytology in diagnosing malignancies metastasizing to the lymph node and predicting their primary origin as well as to find the relative frequency of different malignancies. The findings were also correlated with histopathology. **Results:** Cervical lymph nodes were the most frequently involved group, followed by axillary, supraclavicular, and inguinal lymph nodes. Squamous cell carcinoma (SCC) and adenocarcinoma were the most common cytological diagnosis. Among the cases with known primary tumors, head and neck was the most common site followed by breast carcinoma. Most common lymph node group to be aspirated in cases with unknown primary was cervical lymph node, and SCC was most frequently diagnosed cases. Sensitivity and positive predictive value of cytological diagnosis were calculated to be 100% and 93.1%, respectively. **Conclusion:** Fine-needle aspiration cytology has a very high sensitivity and positive predictive value and hence, a presumptive diagnosis can be made along with the detection of the primary site in case of metastatic disease.

Key words: Cytology, lymph node, metastasis, primary

INTRODUCTION

Lymph node enlargement is a very common presenting symptom. The cytological examination of lymph nodes is a simple, cost-effective procedure which may provide valuable information regarding the disease process, including both neoplastic and nonneoplastic conditions. Cytological examination of lymph node may be done either by fine-needle aspiration cytology (FNAC) or preparation of imprint/touch smears.

Fine-needle aspiration cytology has become a well-established method for the diagnosis of metastasis to the lymph nodes.^[1]

This simple technique has gained wide acceptance since it offers several advantage to patients and physicians alike. The technique is relatively painless and minimally invasive; produces fast results, and its accuracy can approach that of histopathology in providing a definite diagnosis.^[2] It is cost-effective and is now the first-line investigation technique for significantly enlarged lymph node. This method is applicable both to lesions that are easily palpable and to deeply located lesions under radiological guidance. The results of fine-needle aspiration (FNA) compare favorably with those of tissue biopsies; in some situations, the aspirate has qualities of a microbiopsy.^[3] The study done by Haque and Talukder concludes that before resorting to surgical intervention FNAC is a helpful procedure in the diagnosis of both neoplastic and nonneoplastic lesions of the lymph node. They reported sensitivity and specificity of 82.76% and 97.92%, respectively, for malignant lesions of the lymph node.^[4]

The aim of our study was to assess the efficacy of cytology in the diagnosis of malignancies metastasizing to the lymph nodes, predicting their primary origin and to find the

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relative frequency of different malignancies. The findings were also correlated with histopathology wherever possible.

MATERIALS AND METHODS

The present study was a retrospective and prospective study, conducted on 326 patients under investigation for lymphadenopathy. Only those cases of lymphadenopathy, which were positive for metastatic malignancy, were included in our study. A detailed clinical history and finding of physical examination were recorded. Of the total of 326 patients, 325 patients underwent FNA, of which 5 cases were aspirated under CT guidance, and imprint smears were submitted for evaluation in one patient. In 9 cases, two different lymph node sites were selected for aspiration, and in 3 cases imprint smears were also prepared in conjunction with FNAC, bringing the total number of samples analyzed to 338. The smears obtained were stained using Papanicolaou, hematoxylin and eosin and May–Grunwald–Giemsa stains. Histopathological correlation was possible in 73 cases where biopsies were available, either of the lymph node or the primary lesion. Statistical evaluation was carried out to determine the sensitivity and specificity of cytology as a diagnostic tool in lymphadenopathy.

RESULTS

Of the total of 326 cases, 246 (75.5%) were males, and 80 (24.5%) were females. The male: female ratio was noted to be 3.1:1. The largest number of cases was in the age group of 51–60 years (110 patients) followed by 41–50 years (88 patients). Among the males, the peak incidence of lymphadenopathy was noted at age 51–60 years, whereas in females the peak was observed a decade earlier at 41–50 years of age.

Fine-needle aspiration and imprint smears from various lymph node groups in the body that were included in our study are depicted in Table 1.

On cytological evaluation of lymph nodes from different anatomical regions or groups, it was seen that the cervical lymph nodes were the most frequently aspirated (69.2% cases)

followed by axillary (13.1% cases), supraclavicular (10.4% cases), and inguinal (4.8% cases). Among males, cervical lymph nodes were the most frequently involved group (83.7%). However, among females, the most frequently aspirated lymph nodes were in the axillary region (42.7%). Mediastinal lymph nodes were analyzed in 4 cases, by guided aspiration. Other lymph node groups included 2 cases of mesenteric lymph node enlargement and one each of preauricular and occipital lymph nodes.

The breakup of cytological diagnosis is given in Table 2. In general, incidence of squamous cell carcinoma (SCC) was the highest (174 cases, 53.4%), followed by 87 cases (26.7%) of adenocarcinoma. Nine cases were diagnosed as small cell carcinoma, four as mucoepidermoid carcinoma, two as melanoma, and there was 1 case each of spindle cell tumor, fibrosarcoma, undifferentiated pleomorphic sarcoma, papillary serous cystadenocarcinoma, and bronchoalveolar carcinoma. Fibrosarcoma and undifferentiated pleomorphic sarcoma were diagnosed on cytohistological correlation. A diagnosis of poorly differentiated carcinoma was rendered in 45 cases (13.8%), where it was not possible to type the malignancy on the basis of cytology. The most common cytological diagnosis among males was SCC while it was adenocarcinoma in female patients.

Of 326 patients with metastatic malignancy included in our study, biopsies of metastatic lymph nodes were done in 11 patients only, where cytohistological correlation was available. Cytology of lymph node aspirate was correlated with histopathology of primary tumor site in another 62 patients undergoing histopathological examination of the tumor. Hence, cytohistological correlation was available in a total of 73 patients. A concordant cytological correlation was obtained in all of these cases except 5 cases (1 case of infiltrating ductal carcinoma breast and 4 cases of poorly differentiated carcinoma).

The primary site of malignancy could be found in 179 (54.9%) patients only; while it could not be established in 147 patients (45.1%). Of 179 cases [Table 3] with known primary, 97 cases (54.2%) of metastasis could be traced to

Table 1: Analysis of anatomical LN regions aspirated

LN groups	Male (%)	Females (%)	Total (%)	Most common cytological diagnosis	Most common primary tumor sites
Cervical	211 (83.7)	21 (25.6)	232 (69.2)	SCC, adenocarcinoma	Larynx, tongue
Supraclavicular	19 (7.5)	16 (19.5)	35 (10.4)	Adenocarcinoma, small cell carcinoma	Lung, breast
Axillary	9 (3.6)	35 (42.2)	44 (13.1)	Adenocarcinoma	Breast, lung
Inguinal	11 (4.4)	5 (6.1)	16 (4.8)	SCC, adenocarcinoma	Skin, thigh, penis
Mediastinal	2 (0.8)	2 (2.4)	4 (1.2)	*	*
Mesenteric	0	2 (2.4)	2 (0.6)	SCC, adenocarcinoma	Colon, unknown
Preauricular	0	1 (1.2)	1 (0.6)	SCC	Lower eyelid
Occipital	0	1 (1.2)	1 (0.6)	Muco-epidermoid carcinoma	Parotid gland
Total	252**	83**	335** (100)		

*In mediastinal LN; 1 case of adenocarcinoma from endometrium, 1 case each of small cell carcinoma and bronchoalveolar carcinoma from lung and 1 case of SCC from tongue were found. **Since in 9 cases two different LN sites were selected for aspiration, therefore, the total number of LNs examined increased to 335. SCC: Squamous cell carcinoma, LN: Lymph node

Table 2: Cytological diagnosis of the total number of cases and its correlation with histopathology

Cytological diagnosis	Number of cases in males (%)	Number of cases in females (%)	Total number of cases (%)	Commonest lymph node involved	Cytohisto pathological concordance (%)
SCC	160 (65.0)	14 (17.5)	174 (53.4)	Cervical	38/38 (100)
Adenocarcinoma	34 (13.8)	53 (66.3)	87 (26.7)	Axillary	8/8 (100), 17/18 (94.4)*
Small cell carcinoma	8 (3.25)	1 (1.3)	9 (2.8)	Supraclavicular	2/2 (100)
Muco-epidermoid carcinoma	2 (0.8)	2 (2.5)	4 (1.2)	Cervical, occipital	1/1 (100)
Malignant melanoma	1 (0.4)	1 (0.4)	2 (0.6)	Inguinal, axillary	-
Poorly differentiated carcinoma	38 (15.4)	7 (8.8)	45 (13.8)	Cervical	2/6 (33.3)
Spindle cell tumor	0	1 (1.3)	1 (0.3)	Supraclavicular	-
Fibrosarcoma, undifferentiated	2 (0.8)	1 (1.3)	3 (0.9)	Inguinal	-
pleomorphic sarcoma, papillary serous cystadenocarcinoma					
Bronchoalveolar carcinoma	0	1 (1.3)	1 (0.3)	Mediastinal	-
Total	246	80	326 (100)		

*Of 18 cases which were diagnosed as infiltrating ductal carcinoma breast (a type of adenocarcinoma) on cytology, 17 cases (94.4%) showed concordant result on histopathology.
SCC: Squamous cell carcinoma

Table 3: Anatomical sites of known primary tumors

Anatomical regions	Male (%)	Female (%)	Total (%)
Head and neck	87 (72.5)	10 (16.9)	97 (54.2)
Breast	00 (0)	36 (20.1)	36 (20.1)
Lung	23 (12.9)	05 (2.8)	28 (15.7)
Gastrointestinal tract	02 (1.1)	02 (1.1)	04 (2.2)
Female genital tract	00 (0)	05 (2.8)	05 (2.8)
Penis	02 (1.1)	00 (0)	02 (1.1)
Skin	03 (1.7)	01 (0.5)	04 (2.2)
Thigh	03 (1.7)	00 (0)	03 (1.7)
Total	120	59	179 (100)

the head and neck region. In the remaining 82 cases (45.8%), the primary tumors were seen in various other sites of the body, with a greater frequency of presentation in females (49 cases) as compared to males (33 cases).

In the head and neck region, most common primary sites were larynx and tongue (29 and 27 cases respectively), followed by tonsil (15 cases). Other sites were hypopharynx (7 cases), cheek (7 cases), soft palate (3 cases), salivary gland (3 cases), thyroid (3 cases) and one case each of eyelid, epiglottis, and oropharynx.

In other locations, the maximum number of primary tumors were noted in the breast (36 cases), followed by lung (28 cases), skin (4 cases), female genital tract (ovary-3 cases, cervix-1 case, endometrium-1 case), gastrointestinal tract (esophagus-2, colon-1, gall bladder-1), thigh region (3 cases), and penis (2 cases). The common primary tumor site in cervical group of lymph nodes was larynx and tongue while, for supraclavicular and axillary lymph nodes it was breast and lungs. Primary tumor site with respect to each group of lymph nodes is depicted in Table 1.

Of the 326 patients included in our study, primary site of the tumor could not be established in 147 patients (45.1%). The most common lymph node groups to be aspirated was cervical (85.3%) followed by supraclavicular (8.0%). Other involved groups were axillary, inguinal, and mediastinal.

It was noted that SCC was still the most common diagnosis (87 cases), the other being adenocarcinoma (32 cases), poorly differentiated carcinoma (27 cases), and a single case of spindle cell tumor which was present in supraclavicular lymph node [Tables 2].

Aspirates from lymph node in cases with metastatic SCC showed a necrotic background with cells having dense, eosinophilic cytoplasm and hyperchromatic, irregular nuclei [Figure 1a]. Histopathological examination of lymph nodes in these cases showed replacement of lymphoid population by keratinizing, malignant squamous cells [Figure 1b].

Adenocarcinoma was characterized by presence of cells that were arranged singly or in cohesive groups, ball-like clusters and acini with central lumina [Figure 1c]. Histopathology in these cases showed tumor cells arranged in a glandular pattern or nests, with hyperchromatic, eccentric nuclei, and intracytoplasmic vacuolation [Figure 1d].

Aspirate of metastatic muco-epidermoid carcinoma showed a dual population of mucoid and squamous cells, along with some clear cells. The background was characteristically dirty with necrotic debris and lymphoid cells [Figure 2a].

Bronchoalveolar carcinoma was defined by abundant cellular material with large, monolayered sheets and papillary structures. Individual cells were small, regular with mild nuclear pleomorphism, and well-defined cytoplasm. Intranuclear cytoplasmic inclusions were also present in some cells [Figure 2b].

Cytologically, aspirates from metastatic malignant melanoma showed highly atypical cells in sheets/dispersed in background. The cells were plasmacytoid or polygonal with well-defined cell margins, abundant cytoplasm, and pleomorphic nuclei with coarse chromatin and prominent

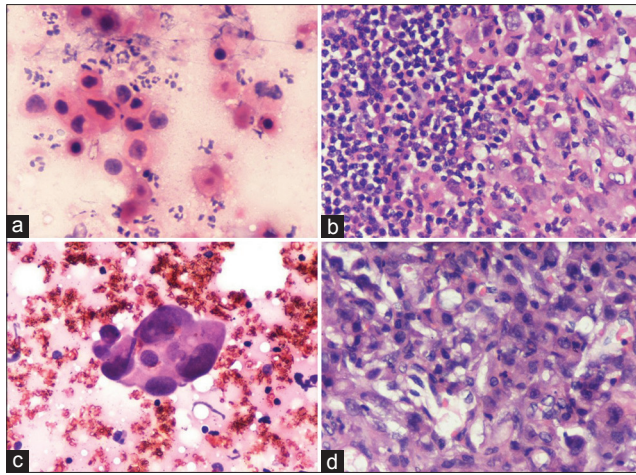


Figure 1: (a) Aspirate of squamous cell carcinoma (SCC) metastasizing to lymph node tumor cells with abundant, sharply demarcated, dense, deeply eosinophilic cytoplasm, and pyknotic nuclei (Papanicolaou, ×500). (b) Biopsy tissue showing metastatic SCC in lymph node, (H and E, ×500). (c) Fine needle aspiration-adenocarcinoma ovary in lymph node, showing tumor cells forming acinar structures, (Papanicolaou, ×500). (d) Section of lymph node showing metastatic adenocarcinoma. Tumor cells with hyperchromatic eccentric nuclei and intracytoplasmic vacuolation are seen, (H and E, ×500)

nucleoli. Bizarre, giant tumor cells were also seen in some smears. Melanin pigment was noted in few cells [Figure 2c].

Metastatic undifferentiated pleomorphic sarcoma yielded richly cellular smears which showed highly pleomorphic cells from bipolar spindle-shaped cells to round histiocytic cells with eosinophilic cytoplasm. The nuclei of the tumor cells showed pronounced atypia with irregular clumped chromatin granules and prominent nucleoli. Multinucleated giant cells, as well as cells with bizarre nuclei, were also seen. Atypical mitosis was also present [Figure 2d].

Pleomorphic tumor cells with high nuclear-cytoplasmic ratio and hyperchromatic nuclei, isolated or in groups were observed in smears of metastatic poorly differentiated carcinoma. Lymph node biopsy in these cases showed similar poorly differentiated cells with nuclear pleomorphism.

We had two aspirates of follicular and papillary carcinoma thyroid metastatic to lymphnode. Both showed classic morphological patterns [Figure 3a and b]. The lymph nodes of patients with metastatic small cell carcinoma were populated by small tumor cells with nuclear molding and extensive necrosis [Figure 3c]. Histopathological examination of lung tissue in these cases showed a dense sheet of closely packed small cells with deep staining nuclei and scant cytoplasm [Figure 3d].

DISCUSSION

Lymph node aspiration has become an established method in the wide field of FNAC. It has a very important role in

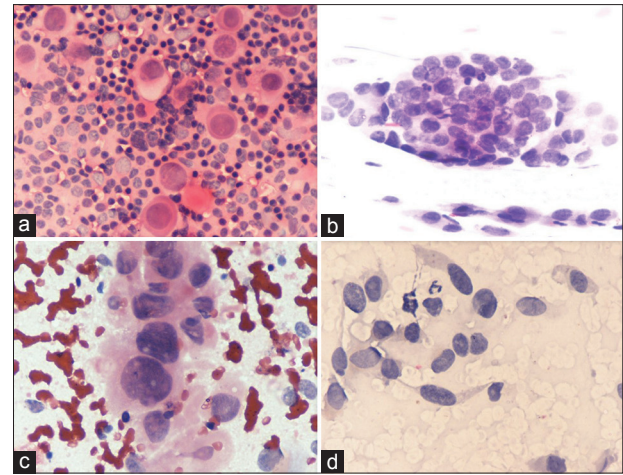


Figure 2: (a) Metastatic muco-epidermoid carcinoma showing squamous cells with large hyperchromatic nuclei and eosinophilic cytoplasm, and mucoid cells. Background shows lymphoid cells, (Papanicolaou, ×500). (b) Bronchioalveolar carcinoma-flat sheet of monotonous cells, (H and E, ×500). (c) Malignant melanoma metastatic to lymph node, showing highly pleomorphic nuclei with high nuclear-cytoplasmic ratio and prominent nucleoli, (Papanicolaou, ×500). (d) Metastatic undifferentiated pleomorphic sarcoma: smears show bipolar atypical spindle cells along with rounded cells, (Papanicolaou, ×500)

the diagnosis of malignant lymphadenopathies especially in a developing country like ours.^[5]

Overall incidence of malignancy especially SCC was found to be higher in males with a male: female ratio of 3.1:1. This may be due to the high incidence of smoking (especially bidi) and chewing of betel nut preparation which are proven carcinogens.^[6] Other studies hence also noted a higher male to female ratio.^[1,4]

The largest number of patients - 256 cases (78.5%) in our study belonged to fifth to seventh decade, very much similar to the findings of Agarwal *et al.*^[7] Furthermore, the maximum number of aspirations was obtained from cervical lymph nodes. This may be chiefly attributed to the large number of cases with metastatic head and neck malignancy (54.2% cases of known primary); another important reason is the easy accessibility of cervical lymph nodes for examination and evaluation. These observations coincide with other similar published reports.^[8-11]

In our study, SCC was the most common cytological diagnosis followed by adenocarcinoma. Our findings were in accordance with other pioneer workers.^[5,9,10,12]

Cancer of mouth/oropharynx is the most frequent cancer in males (12.48%) and third most frequent in females (5.52%) in India, a fact with which the findings of our study were concordant.^[13] Breast carcinoma was the second most common primary site to be involved. Breast carcinoma is the second most frequent cancer (20.01%) reported in females in India.^[13]

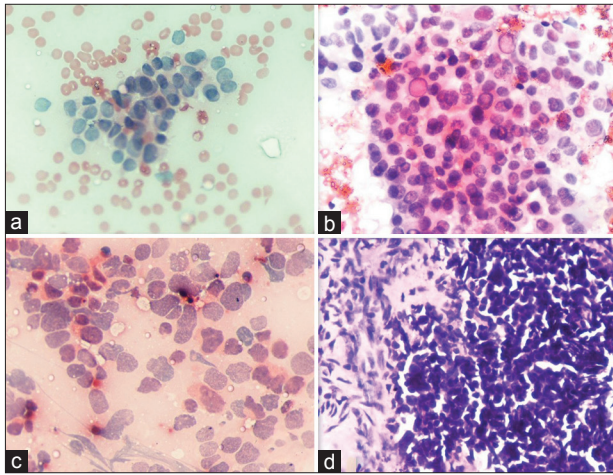


Figure 3: (a) Metastasis from follicular carcinoma of the thyroid showing cluster of epithelial cells with microfollicles, (Papanicolaou ×500). (b) Metastatic papillary carcinoma thyroid, showing prominent intranuclear inclusions, (Papanicolaou, ×500). (c) Metastatic small cell carcinoma. Small, round tumor cells with molding, lying singly and in loosely cohesive groups, (Papanicolaou, ×500). (d) Small cell carcinoma lung (histopathology), showing a dense sheet of closely packed small cells, (H and E, ×500)

The primary site of the tumor could not be established in 147 patients in our study. The reasons for this were either referral of the patient to a higher center, death of the patient or inability to detect primary site even after extensive investigation including ultrasonography, computed tomography and magnetic resonance imaging. Positron emission tomography scan was not done as it is an expensive procedure and not easily available to all patients. Most common lymph node group to be aspirated in cases of unknown primary was again the cervical group, similar to the findings of other studies.^[14] The most common cytological diagnosis in this category was again SCC, with a fair number of cases of adenocarcinoma and poorly differentiated carcinoma as well. Cytological features and the lymph node group involved were correlated with the clinical features to search for the unknown primary in these cases.

Of 179 patients with known primary tumors metastasizing to lymph node, it was possible to make a cytohistological correlation in 73 cases. In the remaining 106 cases, histopathological data were not available for correlation due to several reasons. In the majority of cases, the primary was located in head and neck region. Hence, the initial treatment comprising of radiotherapy was administered based on cytological diagnosis alone. Surgical resection was done only in clinical advanced cases where tissue was available for histopathology. The other reasons for this limitation were referral of patients to other advanced centers for treatment, noncompliance of patient for follow-up, or death of the patient.

We observed a concordance rate of 93.1% on cytohistological correlation. The findings were very much comparable

to other studies.^[5,10] Of the 5 discordant cases, 4 had a cytological diagnosis of poorly differentiated carcinoma which were diagnosed as SCC on histology. One case which was considered as infiltrating ductal carcinoma of the breast on cytology was typed as lobular carcinoma on histology.

Statistical analysis showed that the overall sensitivity of cytological diagnosis in our study was 100%, and positive predictive value was 93.1%. Sensitivity was 100% because only those cases that were positive for metastatic malignancy were included in our study. The results were comparable to other data in previous studies.^[4,9,10,15,16] However, in patients of poorly differentiated carcinoma, sensitivity was 100% but predictive value was only 33%. Poorly differentiated tumors were difficult to interpret on FNAC. In such cases, routine stains alone are insufficient and immunostaining is required to reach a final diagnosis and avoid discrepancies.^[17]

The accuracy of cytology, immunocytochemistry, and transmission electron microscopy using biopsy results as the gold standard in diagnosing tumor category are 78% by cytology and 91% by the latter.^[18] But in a resource-challenged environment like ours, FNAC still remains the most acceptable, cheap, and easily accessible modality with no/minimal complication for the diagnosis of metastatic lymphadenopathy.

In the end, we conclude that cytology has a high efficacy of diagnosis. It also has the added advantage of being able to predict the primary site (where origin of the tumor is unknown) in several cases. The latter is beneficial to the treating surgeon and extremely helpful in deciding the line of therapy. Because of the high rate of accuracy of cytological diagnosis, it precludes the need for biopsy/surgery, which is a boon, as it saves precious resources, time and avoids trauma to the patients. We should stress, however that FNAC is not a substitute for conventional histopathology. It should be regarded as an essential component of preoperative/pre-treatment diagnosis, when correlated clinicoradiologically and with other investigations.

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