

Original article

Role of Cytology in Metastatic Malignancies to Lymph Node: 7 Years Retrospective Study in Western Indian Population

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Abstract

Background: Infective lymphadenopathy, particularly due to tuberculosis, is common in developing countries like India. However, a significant percentage of cervical lymphadenopathies are malignant. Fine needle aspiration cytology (FNAC) plays a crucial role in diagnosing and classifying metastatic malignancies, often aiding in identifying primary tumor sites through cytomorphological features.

Methods: A retrospective-prospective study over seven years analyzed 2406 FNACs, of which 474 cases suspicious or positive for malignancy were included. Benign and inadequate samples were excluded. FNACs were performed on palpable and ultrasound-guided lymph nodes. Smears were stained with Giemsa and Pap stains, and follow-up histopathology was performed where feasible.

Results: Metastatic squamous cell carcinoma (SCC) was the most common malignancy (62%), predominantly in males (70%). Cervical lymph nodes (82%) were the most frequent FNAC site, with oral cavity and oropharynx as common primary sites. Rare metastases included melanoma of the penis and urogenital malignancies. Misdiagnoses occurred in chronic sialadenitis with sialolithiasis.

Conclusion:FNAC is an effective diagnostic tool for lymph node metastases, providing critical insights into primary sites. Awareness of cytomorphological patterns and clinical correlations enhances diagnostic precision, especially for rare malignancies.

Keywords - Fine Needle Aspiration Cytology (FNAC), Lymph Node Metastasis, Cytomorphological Patterns

Introduction:

In developing country like India, infective lymphadenopathy is quite common which is mostly due to high prevalence of tuberculosis. However, still a large percentage of cervical lymphadenopathies turn out to be malignant. There is an increasing emphasis on the accurate diagnosis and classification of metastatic malignancies utilizing less invasive techniques like FNAC and core needle biopsies. Determining the potential primary site of origin by using small samples is especially important in present era of expanding knowledge of tumour genomics and accompanying targeted therapies¹.

Determining the primary site can be challenging especially when there is no previous history of malignancy, or prior pathology is not available for comparison or there is unpredictable pattern of metastasis¹. FNAC, first described by Kun in 1847, is a simple, easy, cheap, quick, minimally invasive

and effective procedure which is used to assess the neck masses². It provides prompt information about the nature of the assessed lesion, performed either with or without USG assistance². This procedure has very few contraindications and risks and it is suitable for use in ambulatory settings².FNAC not only confirms the metastasis but also gives clue regarding the nature and origin of primary malignancy, prognosis as well as in the management of staging purposes. It is also useful for detection of recurrent and new metastasis³ In present study, we assessed the utility of FNAC in diagnosis of both malignant and nonmalignant lesions of lymph nodes in both suspected and unsuspected cases. We also emphasized the cytomorphology of all types of metastasis which were diagnosed on cytology. On the basis of both clinical findings and cytomorphology have helped identify the potential primary site.

Materials and Method:

A 7 years retrospective and prospective study was carried out in Cytopathology section of tertiary care centre. A total of 2406 FNACs were done. Out of these, 474 cases diagnosed as atypical, malignant or suspicious for malignancy on FNAC were included in this study. All reactive lymphadenitis, tuberculous lesions, acute suppurative inflammation, other benign lesions of lymph nodes and inadequate samples were excluded from study.

All palpable lymph node sites like cervical lymph node (level I, II, III, IV, V,VI), axillary and inguinal lymph nodes were studied. Standard fine needle aspiration procedure was performed after taking detailed clinical history and consent of the patient/

relative if required. For every case two air dried and two alcohol fixed smears were made and stained with both Giemsa and Pap stain respectively. For cystic swellings which yielded fluid, centrifuged and cytocentrifuged smears were prepared. And these samples had both air dried and wet fixed smears. For small difficult to aspirate swellings, USG guided FNAC was performed and further processing was done as per routine method. Follow up imaging findings and histopathology diagnosis were collected wherever possible and compared with cytological diagnosis.

Result:

Age Bracket	Female	Male	Total	%
1-10	0	1	1	0.2%
11-20	2	4	6	1.3%
21-30	8	21	29	6.1%
31-40	32	51	83	17.5%
41-50	42	78	120	25.3%
51-60	24	91	115	24.3%
61-70	24	63	87	18.4%
71-80	9	21	30	6.3%
81-90	1	2	3	0.6%
Grand Total	142	332	474	100.0%

Table 1 : Age bracket with gender distribution

Site of FNAC	Total	%
Cervical lymph nodes	389	82%
Axillary lymph nodes	41	9%
Inguinal lymph nodes	38	8%
Other	6	1%

Table 2: Distribution of site of FNAC

*Other- Infra-clavicular, intra-mammary, parotid, postauricular, preauricular

Level of Cervical lymph node	Right	Left	Bilateral	Total	%
I	19	21	4	44	9%
II	101	78	11	190	40%
III	22	14	5	41	9%
IV	36	43	2	81	17%
V	31	19	2	52	11%

Table 3: Distribution of levels of cervical lymph nodes

lymph node	Right	Left	Bilateral	Total	%
Axillary	25	16	0	41	
Inguinal	18	13	7	38	
Other	3	3	0	6	

Table 4: Distribution of lymph nodes according to side

Cytodiagnosis	No of cases	%
Atypical cells	2	0.4%
Suspicious for Carcinoma	2	0.4%
Suspicious of malignancy	1	0.2%
Metastasis of Carcinoma	469	98.9%
Total	474	100%

Table 5: Broad diagnosis given on cytology

Specific diagnosis on Cytology	Primary malignancy known	Primary malignancy not known	Total
Adenoca	6	13	19
ADENOSQUAMOUS		1	1
Anaplastic ca	1		1
Atypical Cells seen		1	1
Duct Ca	17	15	32
Follicular ca	1		1
HDC	17	53	70
Melanoma	1	3	4
MTC	1	2	3
NPCa	1		1
PDC	2	3	5
PTC	2	11	13
RCC		2	2
SCC	105	190	295
Suspicious for 1) HL 2) Mets of melanoma		1	1
UDC	6	19	25
Grand Total	160	314	474

Table 6: Distribution of specific diagnosis given on cytology with clinical and/ or radiological history of primary malignancy

Primary site on histopathology	Concordant	Discordant	Grand Total
Brain	1		1
Breast	29		29
GIT	11		11
GUT	15		15
Kidney	1		1
Larynx	22		22
Lung	17		17
Lymph node		1	2
ORAL CAVITY	71		71
OROPHARYNX	64	1	65
SALIVARY GLAND		1	1
Skin	7	1	7
Thyroid	13		13
Grand Total	251	4	255

Table 7: Distribution of concordant and discordant cases with primary site diagnosed on the basis of histopathology

Cyodiagnosis Vs Histodiagnosis	Reactive lymphadenitis	Nasopharyngeal Carcinoma	Chronic sialoadenitis	Epidermal Cyst	Grand Total
Atypical Cells seen	1				1
SCC				1	1
UDC - SCC		1	1		2
Grand Total	1	1	1	1	4

Table 8: Comparison of discordant cases on cytology with histopathology diagnosis

Majority cases were males (70%) than females with male to female ratio of 2.3:1 (Table:1)

Most common age group was 41-50 years (25.3%) followed by 51-60 years (24.3%) (Table:1)

Most common site of FNAC was right level II cervical lymph node (21.3%) followed by left level II cervical lymph node (16.5). In 24 cases (5%) bilateral cervical lymph nodes were metastatic with level II being most common site involved. There were seven cases with bilateral inguinal lymph nodes. All axillary lymph nodes were associated with breast lumps except three cases in whom there was no any palpable breast lump. These three lymph nodes were diagnosed as metastasis of high grade carcinoma on cytology.

There were 314 cases (66%) where the history of primary malignancy was not known. Out of these, 32 cases (6.7%) were suspected of malignancy on the basis of clinical and radiological findings. 282 cases (59.5%) were primarily diagnosed as metastasis to

lymph nodes on cytology where primary malignancy was not suspected at all. 160 cases (33.8%) had history of primary malignancy and had presented with lymph node swelling.

Cytological features:

All cases of metastasis of SCC presented with cystic swelling which yielded hazy, blood mixed fluid or pus like aspirate. On cytology there were many singly scattered malignant polygonal cells with central, large hyperchromatic nuclei with irregular membrane. Cell in typical squamous cell carcinoma showed individual cell keratinization. Background showed many mixed inflammatory cells composed of polymorphs, histiocytes with many of them engulfing the keratinous material, few lymphocytes, along with keratinous material admixed with necrotic material in

background. All these features with no individual cell keratinization was seen in non-keratinizing SCC. In cases of high grade carcinoma, many of them had clusters of malignant cells with high grade nuclei with no typical features of any particular malignancy. Metastasis of adenocarcinoma showed clusters of cells with glandular pattern having high nuclear cytoplasmic ratio with eccentric hyperchromatic nuclei. Cytoplasm showed vacuoles in few cells. In cases of nasopharyngeal carcinoma metastasis, typical presentation of nasal blockage and cytology showing large polygonal cells with vesicular nuclei and prominent macro-nucleoli could clinch the diagnosis except for one case where the cells were single, discrete with few nuclei showing hyperchromasia and dense blue cytoplasm which were mistaken as atypical lymphoid cells of diffuse large B cell lymphoma. Hence, differential diagnosis was given as Non-Hodgkin's Lymphoma and Nasopharyngeal carcinoma. However, histopathology follow up showed nasopharyngeal carcinoma. In case of papillary thyroid carcinoma metastasis on cytology typical follicular arrangement with papillary nuclear feature and presence of intranuclear grooves with background lymphocytes could diagnose the malignancy. And since in same setting thyroid FNAC was also done showing similar features, we could confirm the diagnosis. One 70 years male patient presented with level II lymph node swelling along with oral ulcer in bilateral buccal mucosae. He was suspected of squamous cell carcinoma due to typical presentation. However, cytology was suspicious for metastasis of PTC. Since the smears showed predominantly histiocytes along with very few clusters of cells with typical PTC nuclei. On histopathology follow up this patient had left buccal mucosa squamous cell carcinoma with papillary thyroid carcinoma in thyroidectomy specimen along with metastasis to lymph node. All these patients had hemosiderin laden macrophages in the background. One case showed abundant fluffy material along with many plasmacytoid cells having stippled nuclear chromatin, the features typical of medullary thyroid carcinoma. On further palpation there was no clinically palpable nodule in thyroid, hence serum calcitonin level was advised which showed extreme rise level. Follow up histopathology was diagnostic of medullary carcinoma thyroid. One case showed repetitive follicular arrangement with microfollicle

formation and itrafollicular colloid along with necrotic material and scattered lymphocytes in background. This patient was a known case of follicular carcinoma thyroid and typical cytological features could diagnose it as metastasis of follicular carcinoma thyroid.

Two case had many papillary fragments along with fibrovascular cores and foamy macrophages. Both these cases were young males presented with abdominal pain, operated cases of papillary carcinoma of kidney. CT scan showed multiple metastatic deposits in abdomen, liver, lung and lymph nodes. On the basis of history, imaging findings and cytology, the diagnosis of metastasis of papillary RCC was given.

There was a 62 year old female, known, operated case of hysterectomy with salphingo-oophorectomy along with pelvic dissection two years back, presented with multiple lymph nodes in axillary and cervical region. Axillary lymph node was largest in dimension, hence aspiration was taken from it. On cytology smears were cellular with many malignant polygonal and few spindle cells with high grade nuclear features. Many tumour giant cells along with frequent mitoses was also seen. Background showed necrosis. Follow up CT scan showed multiple tumour deposits in abdomen, pelvis, liver, lung and lymph nodes was present. The diagnosis was given as high grade carcinoma. Histopathology follow up was MMMT.

One 21 years old female presented with supraclavicular swelling showed many polygonal cells with delicate cytoplasm and central round, vesicular nuclei with prominent nucleoli along with tegroid background. Features were suspicious for metastasis of germ cell tumour. However, this patient was lost to follow up.

There was a 40 years old male with left level Ib swelling which was diagnosed on FNAC as undifferentiated carcinoma due to presence of clusters of cells with high nuclear cytoplasmic ratio and nuclear irregularity. Histopathology follow up of this case showed extensive acute on chronic inflammation of submandibular gland with metaplasia of glandular cells.

There was a 23 year old male, presented with bilateral inguinal swelling since one month which yielded 3cc brownish aspirate. He also had penile ulcer. Smears from inguinal lymph nodes showed

many macrophages with brown black, coarse granular pigment in cytoplasm. Background showed abundant necrotic material and similar pigment extracellularly. There were very occasional single cells with binucleation but did not have prominent macronucleoli. To rule out hemosiderin pigment and to confirm that the pigment is melanin, pearls Prussian blue stain and melanin bleach were performed on cytology smears. Pearls Prussian blue was negative and melanin bleach cleared both intracellular and extracellular pigment thus suspecting the malignant etiology. Hence the diagnosis of suspicious for melanoma was given on cytology. Histopathology confirmed it as melanoma of penile ulcer.

Discussion:

Incidence of metastasis in lymph nodes ranges from 65.4% to 80.4% **4**.

FNAC plays very important role in diagnosing metastatic malignancies in lymph nodes.

In our seven years study overall incidence of squamous cell carcinoma was higher i.e. 62% with predominant involvement in males. Almost all these patients had history of tobacco chewing and few of them were smokers too. Tobacco chewing and smoking are proven carcinogens **5**. Other studies have also similar findings of males being more commonly affected than females **5**.

Maximum cases were in 41-60 yrs age range which is similar to the observation done by **Gazala et al** and **Agrawal et al** **4,5**

Maximum aspirations were from cervical lymph nodes with axillary lymph nodes being second most common site of aspiration. Other studies have also similar observation **4,5**

In our study second most common malignancy given on cytology was high grade carcinoma (70 cases (14%), since the cytomorphology was difficult to type the malignancy.

Squamous cell carcinoma was the most common malignancy found on histology follow up from these high grade carcinomas. Since the smears from these did not show any keratinization along with no significant clinical history to clinch the diagnosis and cytomorphology showed very high grade nuclei along with few showing nucleoli. Hence these cases were put under high grade carcinoma with few of them were called as possibly non keratinizing squamous cell carcinoma. Other studies observed that

adenocarcinoma being the second most common malignancy diagnosed on cytology **5**.

In our study oral cavity cancer was most common finding accounting to 71 cases (27.8%) followed by oropharynx (65 cases, 13.7%). In India oral cavity cancer is the most common cancer and our observation is concordant with this fact **5**. In females breast malignancy was most common malignancy found in our study which is again concordant with the fact that Breast malignancy is most common malignancy in females in India.

Other studies observed that lung malignancy was most common finding which is discordant with our observation **4**.

Many a times distinction between metastatic adenocarcinoma and poorly differentiated squamous cell carcinoma is difficult, especially when there is absence of keratinization and nuclei showing vesicular chromatin with prominent nucleoli. In our study we put such difficult to type cases into high grade carcinoma and poorly differentiated carcinoma with few of them were given as possibility of non-keratinizing SCC. Even the malignancies from urinary bladder and endometrium would have been difficult to type but since there was history of malignancy and metastasis was suspected clinically and radiological investigations, we could diagnose them as metastasis of high grade carcinoma from these two sites.

In case of cystic change in lymph nodes due to metastasis of squamous cell carcinoma or PTC (10-20% cases), serous papillary carcinoma from ovary and endometrium **6,7**, which can be due to necrosis or abscess formation, the chances of false negative diagnosis increases since it becomes difficult to differentiate these malignancies from benign lesions like infection, abscess, tuberculous lymphadenitis, sialadenitis, salivary adenoma **8**, branchial cleft cyst, dermoid, teratoma, epidermoid **9,10,11**. The aspirations from such cystic swelling often become hypocellular due to presence of fluid. Hence repeat aspiration should be done from residual swelling for better cellularity. The regular smears, centrifuged and cytocentrifuged smears should be carefully examined for any malignant cells of squamous cell carcinoma or PTC.

The smears showing background mixed inflammatory cells composing of polymorphs, histiocytes, lymphocytes, foreign body giant cells,

and/ or granulomas should also be carefully examined to look for malignant SCC cells. The presence of keratinous debris, foreign body giant cells indicate possibility of keratinizing SCC⁸. In present study one case of epidermoid cyst was misdiagnosed as SCC which could be due to nucleated squamous cells with keratinous debris seen in background.

Metastasis of PTC to cervical lymph nodes occurs in 30-50% of patients with PTC¹².

Some patients present only with cervical lymph node swelling without any clinically palpable thyroid nodule⁶. Only 20-40% of patients with cervical lymph nodes metastasis can be diagnosed preoperatively using USG¹². And it is very crucial to detect metastasis of PTC to lymph nodes for surgical management¹². USG guided FNAC is the standard preoperative diagnostic modality in suspected cases of lymph node metastasis ¹².

There is an observation that atypical histiocytoid cells are predominantly found in cystic metastasis of PTC to lymph nodes and represent diagnostic pitfall leading to false negative diagnosis due to lack of typical nuclear features of PTC¹². In our study there was one 70 yr old man presented with oral ulcer on both right and left buccal mucosa, histopathology suggestive of SCC, along with cervical lymph node swelling which on FNAC was called as suspicious for metastasis of PTC. The patient did not have any clinically palpable nodule in thyroid and history of oral ulcer was misleading, even the swelling was cystic and fluid was aspirated. The smear were hypocellular, showing many histiocytes. There were very occasional clusters of cells with papillary nuclear features and hence the diagnosis of PTC was made. In our case we did get many histiocytes, however atypical histiocytes were not seen. This patient was operated for oral lesions and thyroid which confirmed that he had both synchronous malignancies with metastasis of PTC to cervical lymph node.

Lymph node status in metastasis of medullary carcinoma thyroid is also crucial, since management is decided accordingly along with serum calcitonin levels and USG findings ¹³.

The cytological patterns of medullary thyroid carcinoma may mimic papillary thyroid carcinoma, anaplastic carcinoma or follicular carcinoma. Its diagnosis heavily relies on experienced pathologist^{14,15} In our case better cellularity and

examination by experienced pathologist and presence of abundant amyloid in background could diagnose the metastasis of MTC despite no clinically palpable nodule in thyroid and no relevant clinical history.

In our study there were seven cases of Marjolin's ulcer due to post burn, scar due to road traffic accident and chronic wound respectively since many years, all presented with inguinal lymph node swelling. All these were positive for metastasis of SCC. Marjolin's ulcer represents malignant degeneration occurring in post burn, scars or chronic wound with incidence being 0.77% - 2% and contributing to overall 2% of all SCC and 0.03% of basal cell carcinoma in the skin. Lymph node metastasis from primary cutaneous SCC is an infrequent event occurring in less than 5% cases¹⁶. However, once it crosses the outlining of scar it metastasizes to regional lymph nodes and at presentation, regional lymph nodes are involved in 20-36% of the patients¹⁷.

Spread of urinary bladder cancer primarily occurs to pelvic and retroperitoneal lymph nodes, bones, lung, liver and peritoneum ¹⁸. Involvement of cervical lymph node is extremely rare. We had one known treated case of high grade urothelial carcinoma metastasizing to supraclavicular lymph node.

The epithelial changes in chronic sialoadenitis and sialolithiasis show marked nuclear atypia in the form of nuclear enlargement, hyperchromasia along with squamous or oncocytic metaplasia¹⁹. We had one such case with submandibular swelling diagnosed as undifferentiated carcinoma on cytology and histopathology follow up was acute on chronic sialoadenitis with multiple large stones. In this case the swelling was hard, immobile, located in submandibular region suspecting clinically malignant and cytomorphology showing extensive nuclear atypia with high nuclear cytoplasmic ratio and hyperchromatic nuclei led to diagnose it as carcinoma.

Melanoma of penis is extremely rare accounting less than 1% of the primary penile malignant tumours²⁰. It commonly occurs between 6th and 7th decades²⁰. There are very few case reports on melanoma penis as per global literature²¹. Glans penis is the most common site accounting to 55%. They have poor prognosis as compared to cutaneous melanomas and bilateral inguinal lymph node metastasis does not produce a greater survival benefits²¹. Due to its

rarity, there are very few articles on cytomorphology of melanoma (Radhika et al). Radhika et al have studied cytomorphology of metastasis of melanoma to lymph nodes. They observed that presence of pigment laden macrophages was the most common finding accounting to 83% followed by presence of melanin pigment (77%). In our case both pigment laden macrophages and extracellular pigment were seen. Special stains of melanin bleach could remove the melanin from extracellular and intracellular site indicating the utility of special stains on cytology smears.

Conclusion:

FNAC has its potential pitfalls in diagnosis of chronic sialoadenitis with sialolithiasis which can be misdiagnosed as malignancy. The involvement of levels of lymph nodes, relevant clinical history along with cyto-morphological features can clinch the potential primary site. Cystic transformation of

lymph nodes in adult males and cytomorphology showing abundant necrotic material, cyst macrophages, siderophages and or polymorphs, with or without keratinous debris/granuloma should be suspected as metastatic malignancies where primary can be oral cavity or thyroid. Examination of oral cavity and USG thyroid are recommended to arrive at a diagnosis. Melanoma of penis is extremely rare and metastasis occurs in inguinal lymph nodes. Hence full awareness of spectrum of cytomorphology of melanoma along with clinical history gives a greater precision in diagnosis. Special stains like Pearls Prussian blue stain and melanin bleach can be helpful to lead the cytopathologist to a diagnosis. Metastasis of urogenital malignancies to cervical lymph node is rare. Clinical correlation along with cyto-morphological features are important for prognosis and management of the patients.

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