

Diagnostic Utility of FNAC for Metastatic Lymph Node Malignancies – A Two-year Study at a Tertiary Care Center

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ABSTRACT

Introduction: Lymphadenopathy more than one cm for longer than a week is always pathological until proved otherwise. Enlarged superficial lymph nodes (LNs) are easily amenable to evaluation by Fine Needle Aspiration (FNA) technique. FNAC confirms the presence of metastatic disease and on detailed cytological examination of the cellular morphology and architecture, a definite clue to the nature and origin of the primary/ occult tumor can also be made. FNAC is of considerable value in disease staging and documentation of recurrence. **Materials and Methods:** Present was a retrospective, cross sectional study conducted at Department of Pathology, at a Tertiary Care Center over a period of two-years from July 2018 to June 2020. **Results:** A total of 946 LN aspirates were obtained over a period of two-years, out of which 136 were diagnosed as metastatic deposits of malignancy that were included in present study. Age of patients ranged from one-year to 88-years. Maximum number of cases were obtained in 61-80 years of age (41.91%). The male to female ratio was 1.72:1. Metastatic lesions were most commonly observed in supraclavicular LN (48%), followed by cervical LN (32%). Most common tumors metastasizing to LNs originated from head, neck & face region (HNF) (56 cases – 41.17%). Most common tumor metastasizing to LN was Squamous Cell Carcinoma (50%), followed by Adenocarcinoma (14.70%). **Conclusion:** FNAC proves to be very helpful in diagnosing and subtyping of metastatic LN malignancies, in developing countries like India, where usually patients present in late stages of malignancy.

Keywords: FNAC, Lymph node, Malignancy, Metastatic, Squamous Cell Carcinoma

INTRODUCTION

Lymph nodes (LNs) are an integral component of the immune system and are affected by a multitude of pathological lesions. They are local circumscribed collections of lympho-reticular tissue invested by a fibrous capsule¹ and are located at anatomically constant points along the course of lymphatic vessels² and are grouped as cervical, axillary, mediastinal, retroperitoneal, iliac and inguinal lymph nodes. Lymphadenopathy more than one cm for longer than a week is always

pathological until proved otherwise.³ In developing countries like India, Tuberculous lymphadenopathy is most common in adults and reactive lymphadenopathy in children. However, lymphadenopathy may be the first sign of internal malignancy in a patient.

Enlarged superficial LNs are easily amenable to evaluation by Fine Needle Aspiration (FNA) technique. Fine Needle Aspiration Cytology

(FNAC) technique was introduced by Greig and Grey and since 1960 it is being extensively used as a diagnostic tool for rapid evaluation of many superficial lesions. FNAC is most cost effective, simple, safe, reliable, relatively non-invasive and repeatable.⁴ The cyto-morphological features collaborate with Histopathology and has qualities of a micro-biopsy.⁵ Drawbacks of FNAC also exist like sampling error and micrometastasis.² The diagnostic yield of FNAC can be improved if it is accompanied by radiological guidance like Ultrasonography and Computed Tomography scan.⁶

The use of FNAC for the diagnosis of metastatic malignancies in the LN at all age groups is very well established at all the diagnostic centers in Urban as well as Rural areas. FNAC confirms the presence of metastatic disease and on detailed cytological examination of the cellular morphology and architecture, a definite clue to the nature and origin of the primary/ occult tumor can also be made. FNAC is of considerable value in disease staging and documentation of recurrence. More than 90% of lymph node metastasis are diagnosed in first FNAC itself.⁷

In India, LN malignancy is predominately metastatic in nature with incidence of 65.7-80% and primary lymphomas range from 2-15.3%.⁸ Confirmatory positive report of LN metastasis obviates the need of un-necessary surgical intervention for the patient.

Present study was under taken with the aims to study the different cyto-morphological types of metastatic epithelial and non-epithelial lymph node malignancies in all age groups, at a tertiary care center.

Materials and Methods:

Present was a retrospective, cross sectional study conducted at Department of Pathology, at a Tertiary Care Center over a period of two-years from July 2018 to June 2020. Retrospective existing data of 3181 records was collected from Cytology section, out of which 946 were FNAC done from peripheral lymphadenopathy in all age groups of both the sex. Patients referred for FNAC of enlarged superficial LNs, more than one cm in size and more than one-week duration, from Surgery, Respiratory Medicine, ENT, Paediatrics and Medicine were included in the

present study. All Haemato-lymphoid neoplasms were excluded. Cytospin smears were prepared in cases of liquefactive necrosis of metastasis yielding fluid aspirate.

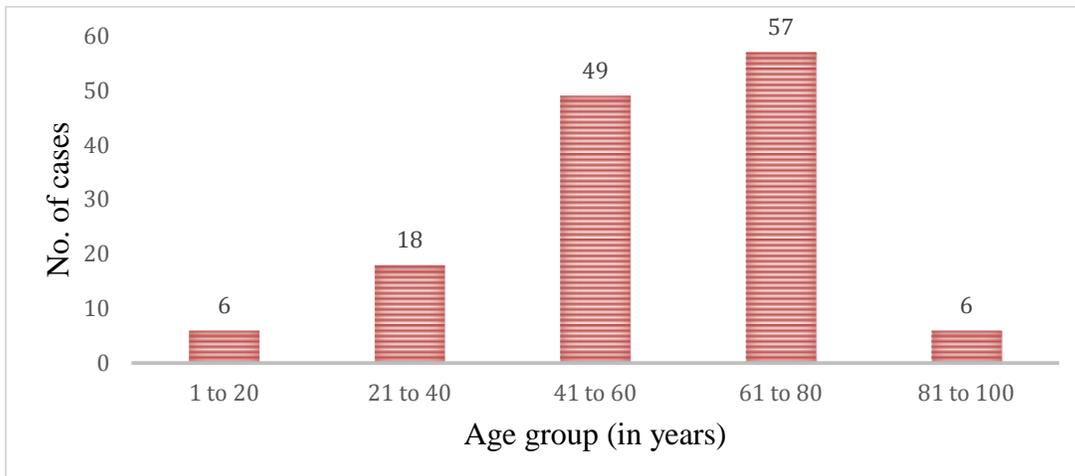
The clinical profile of each patient including age, sex, site and duration of illness was studied in detail. Consent of the patients was obtained in each case. FNAC was performed using a 23-gauge needle attached to a 5 ml disposable syringe. Minimum two passes were given. Smears were prepared on clean glass slides as per standard techniques, and the smears were either wet fixed by immersing the slides in 95% ethanol or air dried. Wet fixed smears were stained by Hematoxylin and Eosin (H&E) and Papanicolaou's (Pap) stains. Air dried smears were stained by Giemsa (MGG) stain. Wherever needed, special stains like Periodic Acid Schiff (PAS), Ziehl Neelsen (ZN) and Auramine-rhodamine stain for Fluorescent Microscopy (FM) were also performed on air-dried slides and studied.⁹ Every case was studied in detail by Senior Cytopathologist. Architecture, cellular morphology and background were studied and was reported as positive for metastatic deposits of epithelial/ non-epithelial malignancy. Also, subtyping of the malignancies into Squamous Cell Carcinoma (SCC), Adenocarcinoma, Small cell carcinoma, Melanoma, Poorly-differentiated malignancy or Lympho-reticular malignancy, was done. In cases of occult primary, mention of the most likely site of origin of malignancy was also documented.

Results:

A total of 946 LN aspirates were obtained over a period of two-years, out of which 136 were diagnosed as metastatic deposits of malignancy that were studied and following results were obtained.

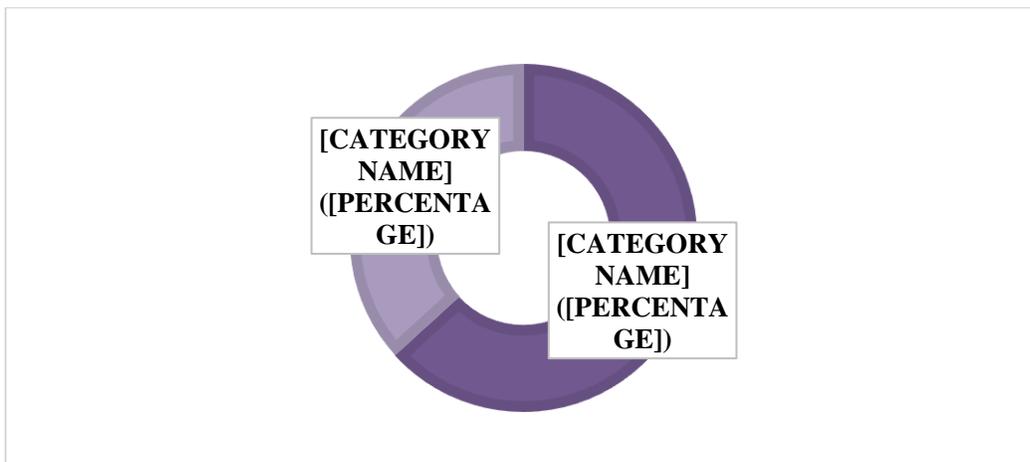
Age of patients in present study ranged from one-year to 88-years. Youngest patient was one-year male patient, diagnosed as neuroblastoma with metastasis to cervical LN (primary lesion in brain). Two patients in present study were 88-years male. One with metastatic deposits of SCC in cervical LN and the other had metastatic deposits of Melanoma of foot to inguinal LN. Maximum number of cases were obtained in 61-80 years of age (41.91%), followed by 41-60 years (36.02%). (Fig 1)

Figure 1: Age-wise distribution of cases (n=136)



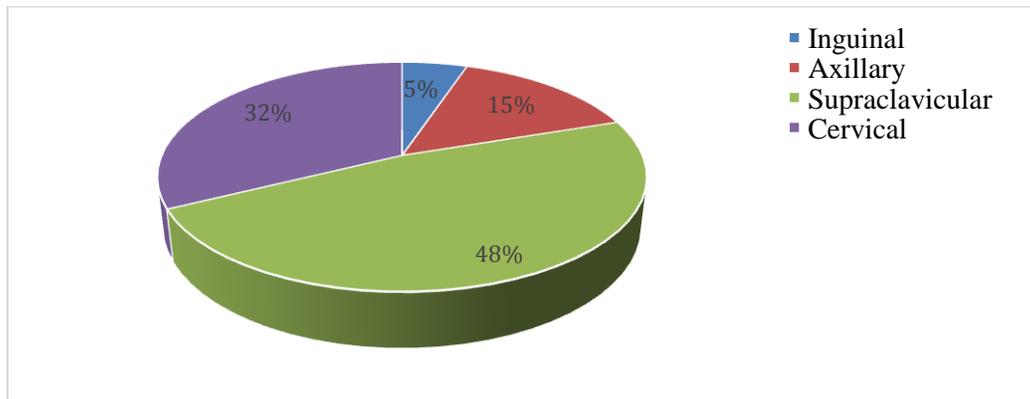
There were 86 males (63%) and 50 females (37%) in present study, with the male to female ratio of 1.72:1. (Fig 2)

Figure 2: Sex-wise distribution of cases (n=136)



Metastatic lesions were most commonly observed in supraclavicular LN (48%), followed by cervical LN (32%). Least common involvement was of Inguinal LN (seven cases - 5%) with metastatic deposits of melanoma (four cases) and Ewing’s Sarcoma (three cases) (Fig 3). Maximum of SCC metastatic deposits were seen in supraclavicular LN.

Figure 3: Site-wise distribution of cases (n=136)



Most common tumors metastasizing to LNs originated from head, neck & face region (HNF) (56 cases – 41.17%), that included tongue, alveolus, maxilla, buccal mucosa, nasal cavity, palate and larynx. Most common tumor metastasizing to LN was SCC (50%), followed by Adenocarcinoma (14.70%) (Fig 4,5). Poorly differentiated malignancy was found in 11.76%, which had difficulties in knowing the primary site of origin. Maximum of which, belonged to HNF, followed by lung. Primary origin for five cases (3.67%) of poorly differentiated malignancy was not known. Apart from SCC, adenocarcinoma and poorly differentiated malignancies from lung, metastatic deposits of small cell carcinoma were also seen in supraclavicular and cervical LNs.

5.88% cases were of metastatic deposits of thyroid malignancy to supraclavicular LNs.

Metastasis to supraclavicular LNs, from primary thyroid malignancy, was seen in (eight cases) 5.88%. It included papillary carcinoma (five cases)

(Fig 5L), medullary carcinoma (two cases) and anaplastic carcinoma (one case).

Metastatic deposits of melanoma (2.94%) from foot and vulva (Fig 4E) were seen in inguinal LNs. Salivary gland malignancy (2.94%) was also obtained with metastasis to cervical LNs. Cytomorphological features suggestive of metastatic mucoepidermoid carcinoma – two cases, metastasis of acinic cell carcinoma and pleomorphic adenoma ex-carcinoma (one case each). Germ cell tumor (GCT) metastasis was seen in three cases (2.2%). These included dysgerminoma of ovary, seminoma of testes and mixed-GCT of testes (one case each). Least commonly, metastatic deposits of Syringo-ecrine carcinoma from vulva and malignant nodular hidradenoma of neck was seen in 1.47% cases.

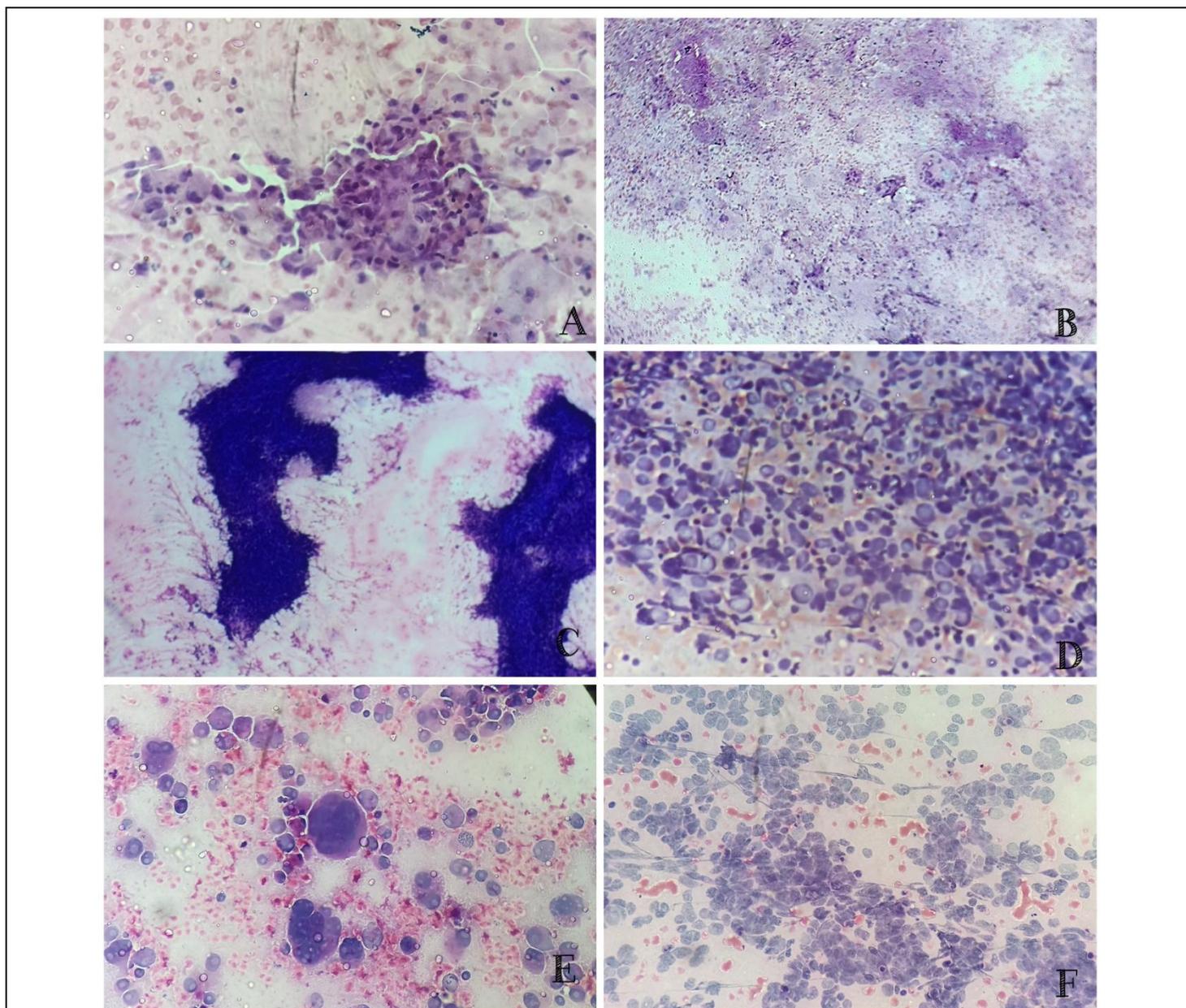
5.88% cases were of Small Round Cell Tumors (SRCTs) which included Neuroblastoma (2.2%) (Fig 4F), Ewing’s sarcoma (2.2%) and Retinoblastoma (1.47%). (Table 1)

Table 1: Distribution of cases according to primary site (n=136)

Diagnosis (%)		Primary site	No. of cases	Percentage(%)	
Epithelial Malignancy	SCC (50%)	Head, Neck & Face	48	35.3	
		Lung	16	11.76	
		Occult	04	2.9	
	Adenocarcinoma (14.70%)	Breast	14	10.29	
		Colon	03	2.2	
		Lung	02	1.47	
		Stomach	01	0.73	
	Poorly Differentiated Malignancy (11.76%)	Head, Neck & Face	08	5.88	
		Lung	03	2.2	
		Occult	05	3.67	
	Thyroid Malignancy (5.88%)			08	5.88
	Melanoma (2.94%)	Foot	03	2.2	
		Vulva	01	0.73	
	Salivary gland malignancy (2.94%)			04	2.94
	Small cell carcinoma (2.2%)		Lung	03	2.2

	Germ Cell Tumor (2.2%)	Testes	02	1.47
		Ovary	01	0.73
	Adnexal tumors (1.47%)	Vulva	01	0.73
		Neck	01	0.73
Small Round Cell Tumors	Neuroblastoma	Brain	03	2.2
	Ewing's Sarcoma	Leg	03	2.2
	Retinoblastoma	Eye	02	1.47

Figure 4: Microphotographs of the Metastatic malignant lesions to LNs

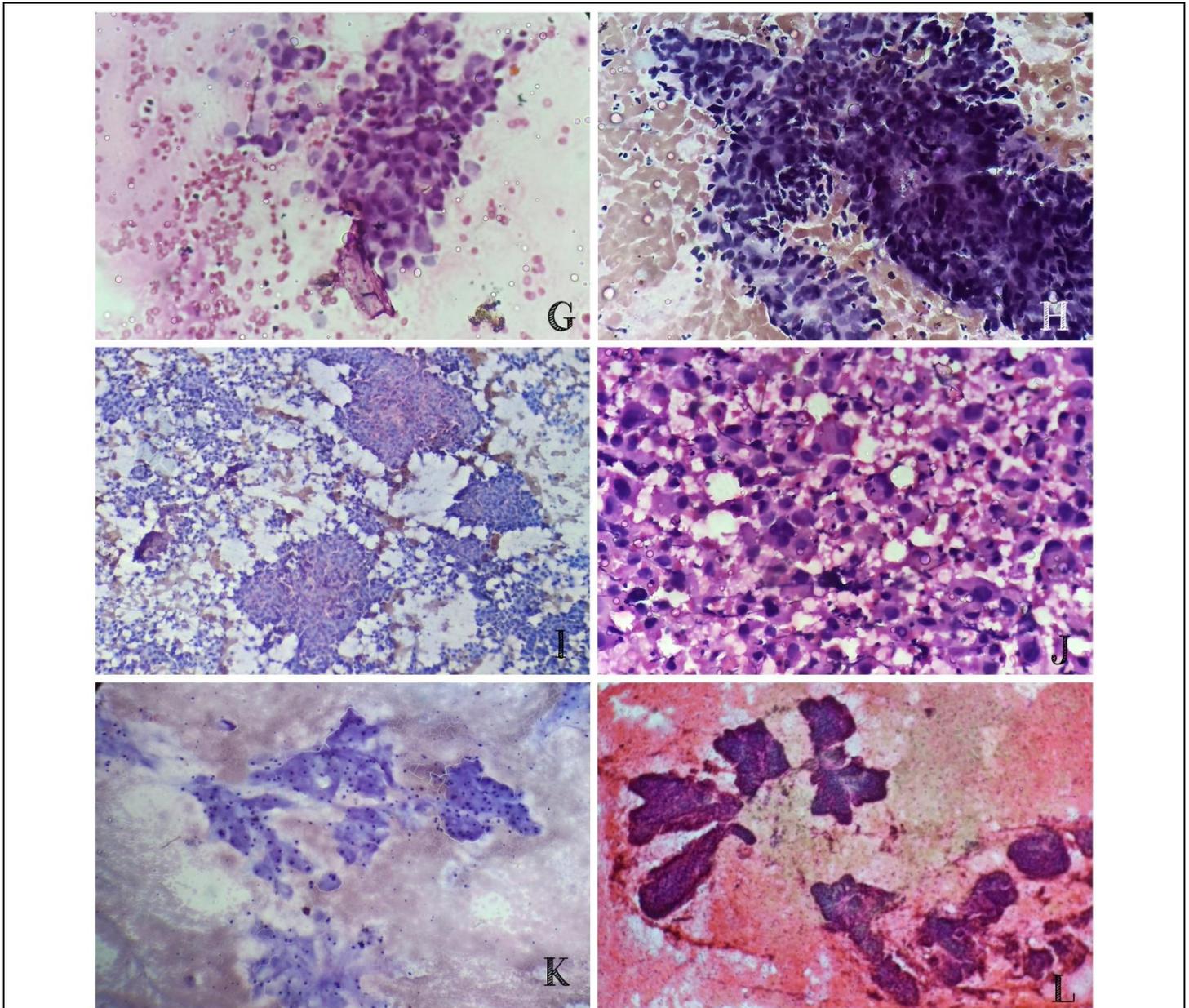


A – Metastatic Well-differentiated SCC to cervical LN (H&E, 400x)

B – Metastatic SCC with extensive necrosis and giant cell reaction (H&E, 200x)

- C – Metastatic SCC lung to axillary LN (MGG, 200x)
- D – Metastatic Poorly-differentiated malignancy to cervical LN (MGG, 200x)
- E – Metastatic Melanoma to Inguinal LN (MGG, 400x)
- F – Metastatic Neuroblastoma to cervical LN (H&E, 200x)

Figure 5: Microphotographs of the Metastatic Adenocarcinoma to LNs



- G – Metastatic Gastric Signet-ring Adenocarcinoma to Virchow's LN (H&E, 400x)
- H – Metastatic Colonic Adenocarcinoma to Virchow's LN (H&E, 400x)
- I – Metastatic Ductal Carcinoma to axillary LN (H&E, 200x)
- J – Metastatic Adenocarcinoma Lung to cervical LN (H&E, 400x)
- K – Metastatic Mucinous Carcinoma Breast to axillary LN (MGG, 200x)
- L – Metastatic Papillary Carcinoma Thyroid to cervical LN (H&E, 200x)

Discussion:

LN that are clinically suspicious for metastasis are one of the most common indications for FNAC. FNAC has a significantly lower risk of subsequent complications, including tumor recurrence, as compared to excisional biopsy.⁷ Enlarged LN are accessible for FNAC and are important to diagnose secondary or primary malignancies.⁸

In present study, LN metastasis was seen in 14.37% of the total LN aspirates. While it was found to be 90% in the studies done by Wilkinson AR, et al⁸ and 84% in Sharma M. study.¹⁰ Age group, in present study, ranged from very early to elderly advanced, with maximum number of cases in 61-80 years of age. Pathy PC¹¹ found third to sixth decade age group to be most commonly involved and Ghartimagar D¹² had more than 60 years of age to be most common. In our study, males outnumbered females with 63%, which was in concordance with the others.^{7,8,10,11} This may be due to increased use of tobacco and alcohol in males, as compared to that of females. In the study done by Ghartimagar D¹², females were involved the most.

In present study, supraclavicular LN metastasis was found to be the most common (48%), followed by cervical LNs (32%). But, cervical nodes were most commonly seen to be involved in other studies done in the literature.^{7,8,10,11,12} It is very important to look at the neck level of involvement especially in working up the head and neck oncology in general. As in cancers of oral cavity and submandibular gland, Level 1 nodes (nodes in the submandibular and submental triangles of the neck) are commonly involved, while Level 2 nodes (nodes along the upper one-third of the sternocleidomastoid muscle) are involved in nasal, pharyngeal and laryngeal cancers.⁷ Most commonly tumors from HNF were seen to metastasize to supraclavicular and cervical nodes. This was in accordance with the studies done by Bagwan I⁷ and others.^{8,10,11}

In the present study, 50% aspirates showed metastasis of SCC to the lymph nodes. In differentiated SCC, tight clusters or loosely scattered single cells showing various degrees of keratinization are seen. Most of the aspirated cells tend to be mature but a careful search for hyperchromatic irregular nuclei showing more malignant features is important for a confident diagnosis, as this can be easily confused with the

branchial or epidermal cyst aspirate with its content of mature squamous cells.⁷ The less differentiated squamous carcinomas are more difficult to diagnose but cells with abundant dense opaque cytoplasm, arranged in mosaic sheets with occasional keratin pearl formation and giant cell reaction to keratin are useful diagnostic clues.

Many metastatic nodes undergo liquefaction necrosis with central cavitations. FNA smears of these nodes reveal abundant neutrophils, histiocytes, necrotic debris and stray individually scattered keratinized cells. The differential diagnosis includes an acute suppurative pathology, a Warthin's tumour, infected branchial cleft cyst, epidermoid cyst and necrotizing squamous carcinoma. In such cases, re-aspiration from the edge of the mass rather than from the center is more contributory.⁷ The tumour cells of non-keratinizing variant of squamous carcinoma appear in sheets and have round to oval nuclei with coarse granular chromatin and prominent nucleoli. Studies in literature^{7,8,10,11} also shows SCC to be the most common metastatic malignancy.

When a tumor looks very bizarre or anaplastic in a setting of an occult primary, sites such as upper aero-digestive tract, lung, thyroid and pancreas should be seriously considered as the likely sources of the primary.

Metastatic adenocarcinomas of the head and neck region may originate from salivary glands, thyroid, breast, lung, kidney, prostate and gonads. The individual cells are large cuboidal to columnar with abundant lacy cytoplasm, often with a pale blue extra cellular mucinous fluid background. Some cells may even exhibit vacuoles with definite signet ring cell morphology. The nuclei are round to oval with irregularly thickened nuclear membranes and prominent nucleoli. Sometimes getting it difficult to rule out a poorly differentiated squamous carcinoma.⁷ Adenocarcinoma was most commonly seen, followed by SCC to metastasize to LN in the study done by Ghartimagar D, et al¹² Metastatic clear cell carcinoma should raise the suspicion of a primary in the kidney or the salivary gland (myoepithelial cell tumors). Aspirates with papillary branching, three-dimensional groups of cells may originate from thyroid, salivary glands, breast, lung and rarely ovary. Psammoma bodies have been in thyroid, lung, pancreas and ovarian metastasis.⁷

We got two cases of mucoepidermoid carcinoma and one case each of acinic cell carcinoma and pleomorphic adenoma ex carcinoma of salivary glands, metastasizing to cervical nodes. There were eight cases of thyroid metastasis to supraclavicular LNs, in present study. Eun Bi Ryu¹³ also got four cases of metastatic papillary thyroid carcinoma to supraclavicular nodes.

In case of small cell carcinoma, the cells appear naked with scant cytoplasm and have ovoid nuclei, about twice the size of mature lymphocytes, with indistinct nucleoli. The chromatin is salt and pepper type. Nuclear dust, individual cell death and pyknotic nuclei are visible in the background. Nuclear moulding is a useful sign to look for.⁷ Generally mimic lymphoma on FNAC under these circumstances. Clinical history of generalised lymphadenopathy might be helpful in differentiation. There were three cases, in present study, of small cell carcinoma metastasizing from lungs to supraclavicular LNs. Ghartimagar D found two such cases.¹²

Melanomas, cytologically, are highly cellular with loosely scattered pleomorphic cells and binucleate and multinucleate forms. The cells have eccentrically placed nuclei, irregular nuclear outlines, intranuclear vacuoles and large prominent nucleoli. Melanin pigment is seen only in 25% of all aspirates.⁷ All the above mentioned features may not be present in every case. In the absence of intracytoplasmic pigment, melanomas are often mistaken for a spindle cell carcinoma, sarcoma or as an anaplastic carcinoma. Present study had four cases of melanoma which was in accordance with the two cases in Ghartimagar D study¹².

An uncommon tumour in neck nodes is metastatic seminoma. The tumour cells are usually scattered or in loose aggregates showing streaking effect. The cells are large, deeply stained and the nuclei have granular chromatin with prominent nucleoli. In the background, lymphocytes and histiocytes may be seen. Undifferentiated or embryonal carcinomas have a primitive or blastemal morphology.⁷ We have got one case of seminoma, metastasizing to cervical nodes. Other metastatic GCT found in our study was dysgerminoma and mixed-GCT (one case each).

Syringoid eccrine carcinoma is an extremely rare malignant adnexal tumor of eccrine origin, in the

head and neck region. Malignant nodular hidradenoma is a rare malignant, aggressive adnexal tumor, that can metastasize to regional lymph nodes and distant viscera, frequently reported on the HNF and rarely on the extremities. We got one case each of both these malignant adnexal tumors. Case reports for these lesions are documented in the literature.^{14,15}

All SRCTs are uniformly characterized by the presence of sheets of monomorphic cells with subtle architectural and cytomorphologic features that serves as clue to the correct diagnosis.¹⁶ In accordance to study done by Rekhi B, et al¹⁷, we reported eight cases of SRCT, in present study, metastasizing to supraclavicular (retinoblastoma and neuroblastoma) and inguinal LNs (Ewing's sarcoma).

The improved diagnostic ability of FNAC in diagnosing the malignant lesions of LNs is possibly due to increased experience, use of advanced radiological techniques, allied investigations and detailed history. Combination of this with easier availability of FNAC at all Institutional and Health Care Centers has gained unmatched importance of LN cytology.

Conclusion:

Many times, cytological diagnosis made on FNAC is the only accepted diagnosis and no further correlation with histopathology is done, especially in cases with advanced malignancies. As FNAC not only confirms the metastatic lesion but also gives the clue to the primary site of origin. It reduces the financial burden for the patients by avoiding the need for excisional biopsy. Moreover, FNAC is simple, quick, reliable and cost-effective. This proves to be very helpful in the developing countries like India, where usually patients present in late stages of malignancies. Hence, FNAC of LN lesions plays a vital role where there is availability of experienced hands and limited health care resources.

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