Clinicocytomorphological spectrum of palpable Lymphadenopathies in Kumaon region of Uttarakhand

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Abstract

Background: To study the cytological patterns of lymphadenopathy in our setting to determine the demographic parameters and the clinical presentation of the various causes of lymphadenopathy in adults and children and the diagnostic utility of FNAC in the evaluation of lymphadenopathy. This would help the doctors attending patients in this region to have a basic idea about prevalence of different clinical profiles of palpable lymphadenopathy for easier case detection and better therapeutic outcome.

Material & Methods: FNAC was performed using a 22 or 23 gauge needle attached to 20 ml disposable plastic syringe mounted on a syringe holder for single hand grip was used, Slides will be fixed in 95% ethyl alcohol for cytological evaluation using Papanicolaou staining (PAP) and Hematoxylin and Eosin (H&E) stain. Smears are kept air-dried for May–Grünwald–Giemsa staining and Ziehl Neelsen stain.

Results: Out of 665 cases, 372 cases (55.9%) were males while 293 cases (44.1%) were females. Male to female ratio is 1.3: 1. Out of total, 76.1% cases were benign and 23.9% cases were malignant.

Keywords: FNAC, Lymphadenopathy, Reactive, Granulomatous, Kumaon

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2394-6792.2016.00072.7

Introduction

Lymphadenopathies are reactive processes of lymph nodes in response to a variety of exogenous and endogenous stimulants. Lymphadenopathy is a common manifestation of many diseases which are categorized as "MIAMI" representing malignancies, infections, auto-immune disorders, miscellaneous and iatrogenic causes.[1]

Lymphadenopathy is a clinical manifestation of regional or systemic disease which serves as an excellent clue to the underlying disease[5]. It can arise either from benign or malignant causes depending upon the geographical condition and socioeconomic set up.[2]

Government medical college, Haldwani is a newly established medical institute in Kumaon region of Uttarakhand and this prompted us to study the cytological patterns of lymphadenopathy in our setting to determine the demographic parameters and the clinical presentation of the various causes of lymphadenopathy in adults and children and the diagnostic utility of FNAC in the evaluation of lymphadenopathy. This would help the doctors attending patients in this region to have a basic idea about prevalence of different clinical profiles of palpable lymphadenopathy for easier case detection and better therapeutic outcome.

Material and Methods

The criteria for patient selection were as follows:

1. All patients referred to the department of pathology, Government Medical College, Haldwani for FNAC of lymph nodes in the study period.
2. USG/CT SCAN guided FNAC will be included.
3. FNAC from lesions which were clinically not diagnosed as lymph nodes but turned out as lymphoid tissue on cytology.

The criteria for patient exclusion are as follows:

- Patient not willing/not giving consent.
- The FNAC of the swelling provisionally diagnosed as lymph node but on cytology found to be of non-lymphoid origin.
- Patient with acute suppurative lesions in lymph node will be excluded.
- Non-diagnostic aspirates.

The study is approved by the ethical committee of the institution.

After taking an informed valid written consent, the patient will be clinically examined in detail. All medical reports will be studied. The patient will be explained the procedure in full detail. The procedure (FNAC) will be performed without any anaesthesia using a 22 or 23 gauge needle attached to 20 ml disposable plastic syringe mounted on a syringe holder for single hand grip was used, Slides will be fixed in 95% ethyl alcohol for cytological evaluation using Papanicolaou staining (PAP) and Hematoxylin and

Eosin **(**H&E) stain. Smears are kept air-dried for May–Grünwald–Giemsa staining **(**MGG) and Ziehl Neelsen stain (ZN stain).

Results

- Total 692 cases were referred to department of pathology for FNAC of clinically suspected palpable lymph nodes during the study period.
- Out of these, 665 cases (96.1%) were found to be lymph node while 23 cases (3.3%) were found to be non-lymphoid after FNAC and 4 cases (0.6%) yielded non-diagnostic material. These total 27 cases were excluded from the study.
- Out of 665 cases, 372 cases (55.9%) were males while 293 cases (44.1%) were females. Male to female ratio is 1.3: 1.
- Out of total 665 cases of lymphadenopathy, 76.1% cases were benign and 23.9% cases were malignant.

Table 1

Types		**Benign**		**Malignant**		**Total**	
Sex		**F**	**M**	**F**	**M**		
Age (in years)	1 - 20	111	133	4	5	253	38.1%
	21 -40	106	86	8	16	216	32.5%
	41 - 60	28	24	11	61	124	18.6%
	61 - 80	9	8	14	39	70	10.5%
	81 - 100	1	0	1	0	2	0.3%
Total		255	251	38	121	665	100%

The above table shows age wise distribution of cases. Maximum number of cases 469 (70.5%) were encountered below 40 years of age and most of them were benign lesions (436, 86.2% of total benign lesions), while only 33 cases (7.1% of the total cases below 40 years of age) were malignant. As shown in the table, the number of cases of lymphadenopathy decreases from 253 cases (38.1%) in 1-20 years age group to 70 cases (10.5%) in 61-80 years age group and only 2 cases (0.3%) in > 80 years of age. Benign causes of lymphadenopathy found out to be most common in 1-20 years age group (244 cases, 48.2% of the total benign lesions) followed by 21-40 years age group (192 cases, 37.9%) while malignant causes are most common in 41-60 years age group(72 cases, 45.3% of the total malignant lesions) followed by 61-80 years age group(53 cases, 33.3% of the total malignant lesions). Malignant lesions found to be more common in males (121 cases, 76.1% of the total malignant lesions) than females (38 cases, 23.9% of the total malignant lesions).

Table 2

Benign					
	Male		**Female**		**Total**
RLN	148	29.25%	100	19.76%	248
TBLN	32	6.32%	49	9.68%	81
NECRO	9	1.78%	10	1.98%	19
GRAN	62	12.25%	96	18.97%	158
Total	251	49.60%	255	50.40%	506

Table 3

Age (in years)	**Male**	**Female**	**Total**	**%**
1-20	5	16	21	25.9
21-40	21	29	50	61.7
41-60	5	3	8	9.9
61-80	1	1	2	2.5
>80	0	0	0	0
Total	32(39.5%)	49(60.5%)	81	100

The above table shows all the benign causes of lymphadenopathy. Benign lesions found to be more common in females. Reactive hyperplasia found to be the most common cause in both males and females (248 cases, 49% of all benign lesions). Tubercular lymphadenitis included cases showing clusters of epithelioid cells, multinucleated giant cells, necrosis as well as acid fast bacilli (AFB) positivity with ZN staining and granulomatous lymphadenitis in the lesions that showed above features but AFB negative. Tubercular lymphadenitis comprised of 81 cases (16% of the total benign lesions) while granulomatous lymphadenitis comprised of 158 cases, 31.2% of the total benign lesions). They combined comprised 239 cases (47.2% of all benign lesions).

The above Table 3 shows the distribution of tubercular lymphadenitis. Tuberculosis found to be more common in females comprising 60.5% of all tubercular cases. Most common age group involved in both the sexes is 21-40 years comprising 50 cases, 61.7% of all tubercular cases. There is a decreasing number of tubercular cases with age.

Table 4

Granulomatous lymphadenopathy	AFB-	AFB +
239	158 (66.1%)	81 (33.9%)

ZN stain was performed in all cases of granulomatous lymphadenitis. Acid fast bacilli **(Fig. 3)** found to be positive in 81 cases (33.9% of all granulomatous cases), however in rest of 158 cases (66.1% of all granulomatous cases), acid fast bacilli could not be demonstrated on ZN stain. **(Table 4)**

	Primary		Metastatic				Total
	NHL	HL	SCC	Small Cell	ADENO	PDC	
F	7	4	12	0	4	11	38 (23.9%)
M	3	7	65	2	1	43	121(76.1%)
Total	10 (6.3%)	11 (6.9%)	77 (48.4%)	2 (1.3%)	5 (3.1%)	54 (34%)	159

The above table shows that the occurrence of metastatic lesions (86.8%, 138 cases) is much higher than primary malignant lesions **(Fig. 1, 2)**. Malignant lesions are more common in males (121 cases, 76.1%) than females (38 cases, 23.9%). Amongst the metastatic malignancies, squamous cell carcinoma found to be the most common both in males and females (77 cases,48.4% of all malignant cases) followed by poorly differentiated carcinoma (54 cases, 33.9%).

Table 6

Primary site	No. of cases
Larynx	34(24.6%)
Tongue	23(16.7%)
Lung	18(13.1)
Oral cavity	12(8.7%)
Pharynx	7(5.1%)
Breast	4(2.9%)
Penis	2(1.4)
Colon	1(0.7)
Mandible	1(0.7%)
Nasal cavity	1(0.7%)
Skin	1(0.7%)
Cheek	1(0.7%)
Unknown	33(23.9%)

Table shows the primary site of 138 cases with metastatic deposits in lymph nodes. Larynx found to be the most common primary site (34 cases, 24.6%), Tongue found to be the second most common primary site (23 cases, 16.7%). However primary site was not known in 33 cases, 23.9% cases.

Discussion

In our study, maximum number of cases 469 (70.5%) were encountered below 40 years of age and most of them were benign lesions (438, 86.6% of total benign lesions), while only 33 cases (6.6%) were malignant. The number of cases of lymphadenopathy decreases from 253 cases (38.1%) in 1-20 years of age to 70 cases (10.5%) in 61-80 years of age and only 2 cases (0.3%) in > 80 years of age. Similar results were obtained by Hafez and Tahoun[6] who found only three cases and Chawala N *et al* (2012)[5] who found no patient above 80 years during study period. This may be because with age immune response is compromised and lymph nodes become non-palpable because of fibrosis and fatty infiltration. As the age advances, number of cases decrease but the percentage of malignant cases increases from 1.4% (9 cases) in 1-20 years of age-group to 10.8% (72 cases) in 41-60 years and 16.4% (109 cases) in 61-80 years of age-group. It is similar to that found by Mitra *et al*[3], Hafez and Tahoun[6]. This can be explained by a NIH study published in 2013. The research says that in older people there is accumulation of age-associated changes in a biochemical process that helps control genes may be responsible for some of the

increased risk of cancer. They identified DNA methylation sites across the human genome that changed with age. They demonstrated that a subset of those sites-the ones that become increasingly methylated with advancing age are also disproportionately methylated in a variety of human cancers.[9]

In the present study, collectively benign causes of lymphadenopathy found to be more common (506 cases, 76.1%) than malignant causes (159, 23.9%). This is in concordance with Ahmad *et al*(2005)[11] who also found benign lesions more common comprising 86.4% of the total 1000 cases. Priyanka and colleagues[10] studied lymph node aspirates of 1050 patients and they found 965 (91.9%) benign and 85 (8.1%) malignant lesions. Similarly, Chawala N *et al* (2012)[5] found 83% cases to be benign. In study by Biswas *et al*[8], 71.6% cases were benign. But countered by study of Qadri *et al*[4] who found 38.2% of all cases to be metastatic lesions & Hafez and Tahoun[6] found 69.4% cases to be malignant.

In the present study, benign causes found to be most common in 1-20 years of age. Reactive hyperplasia found to be the most common cause in both males and females (248 cases, 49% of all benign lesions) followed by granulomatous lymphadenitis which comprised of 158 cases, 31.2% of the total benign lesions). This is in concordance with study of Chawla N *et al* (2012)[5], Ahmad *et al* (2005)[11], Khan *et al*[12] and Hafez and Tahoun[6] who found reactive hyperplasia in 41.7%, 53.6%, 55.05%, 30.6% respectively but contrary to that found by Nirmala C *et al*[7] who found granulomatous lymphadenitis in 45.5% of cases as the most common cause, Shrivastava *et al*[14] also found tuberculosis as most common etiology comprising 39.33% of total cases and Qadri *et al*[4] found metastatic malignancy(603 cases, 38.2%) as the single most common cause of lymphadenopathy in their study followed by reactive lymphoid hyperplasia(583 cases, 36.9%).

In the present study, tubercular lymphadenitis showed a female preponderance comprising 49 out of 81 cases, 60.5% while the rest 32 cases, 39.5% were males. Age group of 21-40 years was most commonly involved in both the sexes comprising 50 cases, 61.7% of all tubercular cases. This is in concordance with the findings of Paliwal N *et al*[18] where females comprised 53.9% of all tubercular cases, Biswas *et al*[8] who found young middle aged females more affected by tuberculosis comprising 63.4.%. Shrivastava *et al*[14] found that tubercular lymphadenitis outnumbered other causes of lymph node enlargement in young adults and middle aged patients (232 out of total 502 cases, 46.21%) with female preponderance. Bhaskaran *et al*[16] also found maximum number of granulomatous lymphadenitis in the age group of 21-30 years with a decreasing trend in elderly and there was a female preponderance of cases. Priyanka C *et al*[10] also noted female preponderance in tuberculosis with male to female ratio being 1:1.38 but in contrast, Thakur *et al* found male predominance. Malnutrition, poverty, ignorance, stigma and gender inequities are still common in some settings in India can result in women becoming ill with tuberculosis; threats such as rising tobacco use and diabetes among women also result in increased TB burden. As observed by Ahmad *et al*(2005)[11], Bhaskaran *et al*[16], Shrivastava *et al*[14] that there is a decreasing number of tubercular cases with advancing age, in our study also we observed similar trend with only 10 out of 81 cases, 10.3% in patients over 40 years.

Those cases were included under tubercular lymphadenitis that showed clusters of epithelioid cells, multinucleated giant cells, necrosis as well as acid fast bacilli (AFB) positivity with ZN staining and granulomatous lymphadenitis in the lesions that showed above features but AFB negative. They combinedly comprised 239 cases (47.2% of all benign lesions). Acid fast bacilli were found to be positive in 81 cases (33.9% of all granulomatous cases), however in rest of 158 cases (66.1% of all granulomatous cases), acid fast bacilli could not be demonstrated on ZN stain. The sensitivity of ZN stain is 33.9% in our study which is more than that found by Thakur *et al*[15] who found smear positivity for Mycobacteria by conventional ZN method to be 26.7% (24/90). However, Bhaskaran *et al*[16], Mudduwa and Nagahawatte[17] and Ahmad *et al*(2005)[11,] Priyanka C *et al*[10] found sensitivity of 53.3%, 53.84% and 46.34%, 44.54% respectively which are comparatively higher than our study. Paliwal N *et al*[18] aspirated 318 cases of clinically suspected tubercular lymph nodes and found total 176 cases of tubercular lymphadenitis on cytomorphology. Out of 176 cases, 125 cases showed AFB positivity giving 71% sensitivity. They increased the sensitivity of ZN stain by repeating the stain on decolorized smears or repeat smears wherever cytology suggested tuberculosis. They also concluded that microbiological assessment is necessary for confirming tubercular pathology as high bacterial load is required for AFB positivity. Sensitivity is lower in our study because our hospital caters tertiary care facility to the entire Kumaon region so most of the patient load is formed by ignorant people from hills who lack awareness about the disease and many of them are treatment defaulters who have already taken incomplete course of anti-tubercular drugs previously. This can also be explained by the fact that the concentration of organisms in the sample has a direct relationship to the sensitivity of the ZN stain and a concentration of $>10^4$ organisms/ml increases the probability of positive smear.[19] So variation in sensitivity can also be attributed to the type of material pulled out as AFB are seen mostly in purulent aspirate smears which do not show granulomas, necrosis or epithelioid cells.[20] Neelima and Prem Latha[23] found sensitivity of 98.18% in HIV seropositive patients. This can be attributed to higher

bacillary load in immunocompromised patients. The overall acid-fast bacilli positivity in fine needle aspiration smears can vary from 37.4% to 59.4%.[20,21,22]

Amongst the metastatic malignany, deposits of squamous cell carcinoma found to be the most common comprising 77 cases, 48.4% of all malignant cases. This is in concordance with study of Chawala N *et al*[5]., Mitra *et al*[3], Hafez and Tahoun[6], Biswas *et al*[8], Shrivastava *et al*[14], Ahmad *et al* (2005)[11], and Qadri *et al*[4] who found metastatic squamous cell carcinoma to be 50%, 40.1%, 45.2%, 45.9%, 65%, 53.8% and 32.2% respectively.

In the present study, amongst the metastatic malignancies in lymph node aspirates, Larynx found to be the most common primary site (34 cases, 24.6%).Tongue found to be the second most common primary site (23 cases, 16.7%), however primary site was not known in 33 cases(23.1%). This is similar to the other studies in India including studies by Ahmad *et al*(2005)[11] who found that most of the metastatic squamous cell carcinoma had a primary in the oral cavity (49%) similarly Ahmad *et al*(2011)[24] found oropharynx, including the oral cavity and pharyngolarynx as the most common primary site, 55 cases (32.2%). Shrivastava *et al*[14] and Wilkinson *et al*[25] also found high rates of oral cavity, pharynx and larynx to be the primary sites. It may be due to high rate of tobacco use in India which is the common etiological factor for cancers of respiratory and upper aerodigestive tract. This is in contrast to that found by Mitra *et al*[3] who found lungs (65 out of 147, 44.2%) to be the most common primary site.

Conclusion

FNAC is a cheap, reliable, accurate, quick and cost effective method of categorizing lymphadenopathies in benign and malignant categories. The knowledge of the pattern of lymphadenopathy in a given geographical region is essential for making a confident diagnosis.

It gives fair idea to the clinician to find the occult primary in cases where no malignancy was suspected clinically. FNAC should be used earlier and more frequently to shorten the diagnostic interval in diseases like tuberculosis which have a good cure rate with medical treatment without the need of surgical biopsy which is more invasive. FNAC technique is used as a triage to distinguish between cases of lymphadenopathy so that appropriate treatment and investigations can be done and the patients with malignancies can be diagnosed and referred early without delay. So in developing country like India with large population and limited resources, cheap and simple procedure like FNAC should be used for diagnosis of lymphadenopathies.

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