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Original Research Paper



Pathology

DIAGNOSIS OF PERSISTANT PERIPHERAL LYMPHADENOPATHY BY FINE NEEDLE ASPIRATION CYTOLOGY

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ABSTRACT

Aim and Objectives: The present research was carried out to study the prevalence and cytological features of peripheral persistent lymphadenopathy and also correlate cytological findings with its

histopathological diagnosis.

Method: In this study, total 2022 aspirates of persistent peripheral lymphadenopathy were studied from 2016 patients. Detailed clinical examination, aspiration biopsy cytology and histopathology in the available cases were done to reach the definite diagnosis.

Results: Out of total 2022 aspirates, 67 (3.31%) aspirates were inadequate for cytological interpretation while 97 (4.80%) aspirations were inconclusive though adequate. Cases in which aspirates were showing reactive change formed a large group 520 (25.73%) and in this group sensitivity and specificity was 94.4% and 100% respectively. Inflammatory lesions of lymph nodes were most common and tuberculosis alone constituted 764 (37.78%) cases. In only 14 (0.69%) cases leukemic infiltration was seen, out of which only 2 cases were available for histopathological study that confirmed the cytological diagnosis. 54 cases of lymphoreticular malignancy were diagnosed, out of which 42 were non-Hodgkins' lymphoma and remaining 12 were Hodgkins' disease. Metastatic deposits in the lymph nodes were seen in 492 (24.33%) cases, out of these, maximum numbers of cases were of squamous cell carcinoma.

Conclusion: Aspiration cytology is very much useful, easy, economical and time saving procedure in diagnosing many conditions responsible for the lymphadenopathy but limitations of aspiration biopsy should always be kept in mind. It is not a substitute for histopathology but a supplementary procedure for it.

KEYWORDS : Peripheral Lymphadenopathy, Persistent, Cytology, Histopathology, Aspirates, Tuberculosis, Lymph nodes

INTRODUCTION

Lymphadenopathy (LAP) is the term to describe the conditions in which lymph nodes become abnormal in size, consistency, and number [1]. It is a commonly encountered clinical problem which has a multiple causes [2]. The lymphadenopathy persisting for a long time, possibly without an apparent cause is called as the persistent lymphadenopathy. However the persistent peripheral lymphadenopathy without an obvious cause after the history and physical examination presents a diagnostic dilemma [3].

The etiologies of peripheral lymphadenopathy are numerous, it is frequently due to a local or systemic, benign, self-limited, infectious disease. However, it could be a manifestation of underlying malignancy [1]. Whenever the issue of a malignancy is raised or a patient does not respond to an empirical trial of antibiotics, and lymphadenopathy persists, a morphologic analysis of the lymph node is inevitable [4, 5]. In persistent or suspicious lymphadenopathy, there is a need for a rapid, simple and accurate diagnostic tool. Considering that the frequency of nonspecific benign self-limiting lymphadenopathy is high, [6] the number of patients requiring a diagnostic or therapeutic surgical biopsy is correspondingly low [7]

In adults with persistent lymphadenopathy, fine-needle aspiration cytology (FNAC) is used extensively as an initial diagnostic tool [8,9]. Pioneering works in this technique has been done by Franzen and Zajicek [10], who toiled hard to make this technique a popular one throughout the world. In the cytology section of Pathology Department, Indira Gandhi Government Medical College, Nagpur, fine needle aspiration is being done since a long time as a routine diagnostic procedure. Aspiration biopsies are being done from various sites like lymph nodes, breasts, thyroid, abdominal lumps, prostate etc. During the course of present study, limitations of FNAC were kept in mind. Cytology studies the morphology of the cells and never the architecture of the lymph node or the relation of one to each other. This technique is complementary to the traditional gold standard biopsy procedure and not a substitute for it.

MATERIALS AND METHODS

All the patient referred to the cytology section from the clinical outpatient department as well as the patients admitted in the wards with clinical diagnosis of localized or generalized persistent peripheral lymphadenopathy and those having lymph node of size more than 2 cm with minimum duration of 3 weeks were included in the study. In this cross-sectional study, total 2022 numbers of aspirations from 2016 patients were studied during the period of four years.

Before aspiration lymph node, thorough knowledge of the anatomy of area is required aspiration was done in such a way that needle tract would probably be included in a subsequent incision if need arises. Written consent of the patient was taken. The procedure was described in detail to the patient so that she/he would cooperate during the actual procedure. On the selected cases, the same lymph node was biopsied from where FNAC was done. A detailed clinical history and presenting complaints were noted. General and systemic examination was carried out.

For clinical diagnosis all the relevant investigations, aspiration of the lymph node and cytological diagnosis were done. The FNAC was performed by cytopathologist, using a 22 G needle attached to 20 ml disposable plastic syringe. If needed multiple sites were aspirated. The aspirated material was smeared on slides. Slides were immediately fixed in 95% ethyl alcohol for wet fixation and after air dried for dry fixation. Prepared Slides were stained with papanicolau stain (dry fixation) and Hematoxylin & Eosin (wet fixation). These two stains were routinely used in all the cases while one of the air-dried smears was stained with May Grunwald Giemsa. Remaining dried smears was kept for AFB staining in all the suspected cases of tuberculous lesion.

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Histological diagnosis: 1) Final diagnosis: Lymph node biopsies were then done with specified criteria's given by Symmers and St. C. Senr [11] and Henry et al [12]. After removal of lymph node, gross description was noted. 2) Method of aspiration biopsy: The method of aspiration biopsy used in the present study is the same as that described by Franzen and Zajicek [10], and their colleague. At the end of the study data were analyzed.

Observations and Results

The total number of lymphadenopathy cases attending the cytology OPD during the study period was 2022 (25.71%) out of the total number of aspirations 7864 (excluding the cervical smears and fluid cytology) done during the same period. 2022 aspirations were done in 2016 number of cases among them 917 (45.49%) were male and 1099 (54.51%) were female. The male to female ratio was 1:1.19. The prevalence of persistent peripheral lymphadenopathy was highest in the age group of 21-30 years and lowest in the age group of >71 years as shown in table 1.

Table 1: Age wise distribution of the 2016 cases of lymphadenopathy

Age group (Years)	No. of patients	Percentage
00-10	254	12.60%
11-20	402	19.94%
21-30	475	23.56%
31-40	303	15.03%
41-50	206	10.22%
51-60	222	11.01%
61-70	127	6.30%
>70	27	1.34%
Total	2016	100%

In 6 cases aspiration was done from two different anatomical sites. The most common site of clinical presentation of lymphadenopathy was cervical group (1245; 61.57%) followed by axillary group (12.86%), (Table 2).

Table 2: Distribution of anatomical site of aspiration in 2022 number of aspirates

Site of aspiration		No. of aspirates	Percentage
Cervical	Unilateral	1102	54.50%
	Bilateral	143	7.07%
	Total	1245	61.57%
Submandibul	Submandibular		8.21%
Supracla-	Right	55	3%
vicular	Left	71	3.51%
	Total	126	6.23%)
Axillary	260	12.86%	
Inguinal	125	6.18%	
Epitrochlear	18	0.89%	
Generalized	82	4.06%	
Total	2022	100%	

Out of total 2022 aspirates, 67 (3.31%) aspirates were inadequate for cytological interpretation. The inadequate aspirations were showing scanty cellularity. From the table 3, it is clearly evident that tuberculous lymphadenitis heads the list (37.78%) followed by reactive lymphadenitis group (25.73%) and metstatic group (24.33%). 54 cases of lymphoreticular malignancy were diagnosed, out of which 42 (77.78%) were non-Hodgkins' lymphoma and remaining 12 (22.22%) were Hodgkins' disease.

Table 3: Various cytological diagnosis according to the diagnostic criteria

Cytological Diagnosis	No. of patients	Percentage
Reactive	520	25.73%

37.78% 764 Tuberculous Granulomatous 3 0.15% Lymphoreticular malignancy 54 2.67% Leukaemic infiltrate 14 0.69% Filarial 11 0.54% Metastatic 492 24.33% 97 Inconclusive 4.80% Inadequate 67 3.31% Total 2022 100%

Metastatic deposits in the lymph nodes were seen in 492 cases (24.33%). Out of these maximum numbers of cases were of metastatic deposits of squamous cell carcinoma (267; 54.27%) followed by adenocarcinoma deposits (161; 32.72%) as shown in figure 1.

Figure	1:	Various	types	of	metastatic	lesions	to	the	lymph
node									



Figure 2 shows that FNAC was useful in staging the known malignancy in 424 (86.18%) cases and detecting the occult primary malignancy in 68 (13.82%) number of cases.



The maximum number of cases (325; 42.54%) showed epithelioid cell granuloma without caseation necrosis and acid fast bacilli (AFB) positivity was maximal in the third group showing only caseous necrosis in 129 cases (87.16%), (Table 4). Of these cases showing only caseation, 5 patients were HIV positive and these were not available for further follow up.

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Cytological Cases	No. of findings	AFB Positivity
Epithelioid granuloma with caseation necrosis	291 (38.09%)	108 (37.11%)
Epithelioid granuloma without caseation	325 (42.54%)	66 (20.31%)
Caseation necrosis only	148 (19.37%)	129 (87.16%)
Total	764	303 (39.66%)

Table 4: Cytological findings of tuberculous lymphadenitis (N=551)

Out of the total 1858 aspirates (excluding the inadequate and inconclusive group), in only 234 cases histopathology was done. The cyto-histopathological correlation of the lymph nodes is shown in table 5. Maximal biopsies were done in the lymphoreticular malignancy group where histopathological

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proof was mandatory.

Table 5:	Cyto-histopathological	correlation	ot	the	lymph
nodes as	spirates				

Cytological Diagnosis		No. of Cases	Histopatho Diagnosis	No. of Cases	
Tuberculosis		69	Tuberculosis		70
Reactive		73	Reactive	Sinus Histiocytosis	29
				Follicular Hyperplasia	19
				Nonspecific reactive	20
				Kimura's disease	01
				Kikuchis' disease	01
				Total	70
Granulomatous		03	Granulo- matous	Cat scratch disease	01
				Sarcoidosis	01
				Candida Lymphadenitis	01
				Total	03
Hodgkins'	disease	08	Hodgkins' o	lisease	08
Non- Hodg	kins' lymphoma	34	Non- Hodgl	kins' lymphoma	36
Leukemic i	nfiltrate	02	Leukemic in	nfiltrate	02
Metastatic	Metastatic Squamous cell carcinoma		Metastatic	Squamous cell carcinoma	17
	Adenocarcino ma	07		Adenocarcino ma	07
	Melanoma	02		Melanoma	02
	Papillary carcinoma thyroid	01		Papillary carcinoma thyroid	01
	Hurthle cell carcinoma''	01		Hurthle cell carcinoma''	01
	Ductal carcinoma breast	23		Infiltrating duct carcinoma	23
	Total	45		Total	45
Total		234	Total	-	234

Table 6: Diagnostic accuracy of FNAC as compared to histopathology for the reactive lymphadenitis group

	A A	_	
Cytological	Cytology	Cytology	
categorization of	consistent with	inconsistent with	
smears	histopathology, No	histopathology, No	
	of cases, (%)	of cases, (%)	
Benign (N=71)	69 (94.52%)	2 (2.74%)	
Malignant (N=34)	34 (100%)	0 (0.00%)	
Total (N= 105)	103 (96.26%)	2 (1.87%)	

DISCUSSION

In the present study, total 2022 aspirations of persistent peripheral lymphadenopathy cases were studied from 2016 patients; to test efficiency and overall utility of aspiration biopsy in clinically suspected cases of lymphadenopathy. The maximum number of patients were found in the age group of 21-30 years which is comparable with those of Shah et al [13] and Shilpa et al [14]. The sex-wise distribution shows a slightly higher prevalence in females, with male: female ratio of 1:1.19. This finding is correlated with the other studies [15, 16]. The most common site for FNAC was cervical region (61.57%) followed by axillary region (12.86%), similar findings were also observed in previous studies [13, 14, 17]. The generalized lymphadenopathy constituted 4.06% of cases. Inadequate aspirates showed scanty cellularity i.e. 3.31% and which is lower than the inadequacy rates reported by previous workers [18, 19].

Tuberculous lymphadenitis is one of the most common types of lymphadenopathy in developing countries. Likewise in

current study most common cytological diagnosis was tuberculous lymphadenitis (764; 37.78%) which is comparable with the earlier studies [13, 14, 17]. The high rate may be due to low socio-economic status, illiteracy, incomplete treatment and resistance. Among the tuberculosis cases, only 69 were available for the biopsy. Except one case all cases correlated with the cytological diagnosis. One case showed necrosis and on histopathology it was diagnosed as Kikuchi's disease. One case was diagnosed as BCG adenitis in which a 1-year male child came with the history of left axillary lymphadenopathy and vaccinated 4 weeks back. 3 patients presented with the non-tubercular granulomatous lymphadenitis and all these were followed up. These patients did not respond to the shortterm anti-Koch's treatment and later were biopsied for histopathology study. Out of 3 cases, the specific pathology was-1 case of Cat Scratch Disease, 1 case of Sarcoidosis and 1 of fungal (candida) infection. In the case with fungal infection, PAS stain was done for localization of the budding form of candida.

The reactive lymphadenitis forms the second largest group after tuberculous lymphadenitis with 520 cases out of 2022 aspirates which are comparable with studies done by Shrivastav et al [20] and Khajuria et al [21]. Of these 520 reactive cases, specific diagnosis in infectious mononucleosis and Kimuras' disease were given in 1 case each, rest were given as reactive or non-specific reactive lymphadenitis. In this, a 16-year male presented with cervical lymphadenopathy and fever since 5 days. FNAC was done and it revealed excessive proliferation of plasmacellular elements with conspicuous frequency of plasmoblasts and immunoblasts. Later on serologically it was confirmed and diagnosed as infectious mononucleosis. In the 2^{nd} case, a 32 years female presented with cervical lymphadenopathy that revealed activated lymphocytes, abundant eosinophils, plasma cells and occasional polykaryocytes. This was diagnosed as Kimuras' disease and later confirmed histologically. 73 out of 520 cases were subsequently biopsied, as there was no clinical correlation available. Histopathologically confirmation was obtained in 69 cases; however the specific diagnosis was missed in 4 cases. Histopathologically, 2 cases turned out to be Non-Hodgkins' lymphoma and remaining 2 cases turned out to be tuberculous lymphadenitis. Rest of the reactive lymphadenitis was subdivided into the various lesions histopathologically as: 29 cases of sinus histiocytosis; 19 as follicular hyperplasia; 1 case of Kimuras' disease; rest 20 as non-specific reactive lymphadenitis. So in this particular group, positive predictive and negative value was 100% and 97.18% respectively. Sensitivity and specificity was 94.44% and 100% respectively. This can be explained by the observation of Stitch [22] and Stewart et al [23] that in cases of lymphoma, superficial nodes may show reactive change.

54 cases of lymphoreticular malignancy were diagnosed, out of which 42 were non-Hodgkins' lymphoma and remaining 12 were Hodgkins' disease. The prevalence of Hodgkins' disease is in accordance with those of Mehrotra et al [24] and Parate et al [25]. Out of 42 non-Hodgkins' lymphoma diagnosed, specific diagnosis of Burkitt's lymphoma was given in one case (2.39%). In all these 42 cases biopsy was performed and histopathology confirmed the cytological diagnosis. In only 14 (0.69%) cases leukemic infiltration was seen, out of which only 2 cases were available for histopathological study that confirmed the cytological diagnosis.

The aspirates of metastatic deposits in the lymph nodes (excluding leukemic infiltration) form the third largest group (492; 24.33%), which is correlated with the other studies [13, 14,17]. It was may be due to different study population, genetic factors, environmental factors and habitual factors like smoking and tobacco consumption. Also because our hospital is tertiary care centre and we get number of referred cases. So

we get more cases of metastatic malignancy in lymph node. Out of 492 cases, squamous cell carcinoma deposits were commonest (267; 54.27%), this finding is correlated with the study done by Mamatha et al (56%) [26] and Mohan et al (52.8%) [27]. Adenocarcinoma was found in 161 (32.72%) cases, this prevalence of metastasis of adenocarcinoma correlated well with the Parate et al study [25]. Among the metastatic cases, 45 were subsequently available for histopathologic study. Cytological findings of metastatic malignancy were confirmed in all 45 cases. Thus, malignancy was correctly diagnosed in 100% cases which are similar to the study done by Bharadwaj et al [15] and Raghuveer et al [18].

Out of total 2022 aspirates, 97-aspirates material was adequate for interpretation, but not specific cytopathology could be diagnosed from these smears. In these fine needle aspiration biopsies / histopathology was advised or a descriptive report was given.

CONCLUSION

Aspiration cytology is very much useful, easy, economical and time saving procedure in diagnosing many conditions responsible for the lymphadenopathy but limitations of aspiration biopsy should always be kept in mind. It is not a substitute for histopathology but a supplementary procedure for it. Also, FNAC can differentiate a neoplastic from a nonneoplastic process and therefore influence patient management preventing patient from being subjected to unnecessary surgery.

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