

## CLINICO-CYTOLOGICAL AND HISTOPATHOLOGICAL CORRELATION OF LYMPHADENOPATHY IN PEDIATRIC PATIENTS

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Received: 02 December 2021, Revised and Accepted: 25 January 2022

### ABSTRACT

**Objective:** The aim of the present study was to evaluate the cytomorphological and histopathological (wherever possible) patterns of lymph node (LN) lesions along with clinical correlation in the pediatric population.

**Methods:** This was a prospective study conducted on 100 pediatric patients (aged <12 years) who presented with lymphadenopathy (LAP). Fine-needle aspiration cytology (FNAC) was performed on all cases out of which only 22 underwent surgical excision and histopathological examination. Aspirated material was stained with May-Grunwald Giemsa, Papanicolaou, Z-N stain (wherever required) and for histopathology, Hematoxylin and eosin stain was used.

**Results:** Majority number of patients was in the age group of 5–8 years (44%). Cervical LN s were most commonly involved (71%). Out of the total 100 cases, 91% were benign, 3% was malignant and 6% were inadequate. Most common cytologically diagnosed entity was non-specific reactive lymphadenitis (68%). There was one case of reactive lymphadenitis on cytology that proved to be Hodgkin lymphoma on histopathology. Two cases of generalized LAP given as atypical lymphoproliferative lesion on cytopathology proved to be acute lymphoblastic leukemia/lymphoma on further investigation. The cytomorphological findings were found to be concordant with histopathology in 21 cases out of 22 with a diagnostic accuracy rate of 95.45%.

**Conclusion:** FNAC is especially helpful as LN biopsy is a difficult and invasive procedure in children. Although excision biopsy is the gold standard, FNAC is preferred as first-line investigation. Along with cell block analysis and ancillary techniques, it provides an excellent diagnostic accuracy.

**Keywords:** Fine needle aspiration cytology, Paediatric lymphadenopathy, Lymphadenitis.

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### INTRODUCTION

Lymphadenopathy (LAP) is defined as an abnormality in the size or character of lymph node (LN) caused by the invasion or propagation of either inflammatory or neoplastic cells into the nodes [1]. LNs are not considered significantly enlarged until their diameter exceeds 1 cm for cervical and axillary nodes and 1.5 cm for inguinal nodes. However, palpable supraclavicular nodes are always considered abnormal [2]. In the majority of the pediatric cases, the enlarged LNs are due to reactive causes and are self-limiting. Hence, it is neither possible nor desirable to perform an excision biopsy in all these cases. Also, excision biopsy is an invasive procedure requiring anesthesia and is associated with potential complications [3]. Fine needle aspiration cytology (FNAC) is being increasingly used in pediatric patients as it promotes rapid diagnosis with minimum intervention. The cytomorphological features collaborate with histopathology and have the qualities of a micro-biopsy [4,5].

We conducted this study to evaluate the cytological and histopathological (wherever possible) patterns of LN lesions with clinical correlation in the pediatric age group.

### METHODS

The study was conducted in Department of Pathology, GMC Patiala after approval from the ethics committee of the institute. This was a prospective study conducted on 100 cases in pediatric age group below 12 years presenting with LN swelling.

Informed consent was taken from the accompanying parent or guardian for inclusion into the study. The clinical history and laboratory data of these patients were recorded. Physical examination was carried out regarding size, location, number, consistency, mobility, presence of matting, and other local changes such as redness or discharge.

For cytological examination - Smears were stained with May-Grunwald Giemsa, Papanicolaou and Hematoxylin and eosin (H and E) stains. Special stains such as PAS, ZN stain was done as and when required.

For histopathological examination - Slides were prepared and stained with H and E and special stains as and when required.

Data was analyzed and represented in terms of sensitivity, specificity, negative predictive value, positive predictive value, diagnostic accuracy, and Chi-square test was used to determine the p-value and p<0.05 indicates significance.

### RESULTS

A study of 100 pediatric patients with LAP was conducted in the Department of Pathology, Government Medical College, Patiala in a time period of 2 years with proper history, thorough physical examination, and relevant investigations. The study showed that out of total of 100 cases, 91% of cases were benign, 3% of cases were malignant and 6% of cases were inadequate (Table 1).

Majority number of patients were in the age group of 5–8 years (44%) (Table 2).

Table 1: Distribution of lesions

Lesions	Number of cases, n (%)
Benign	91 (91.00)
Malignant	3 (3.00)
Inadequate	6 (6.00)
Total	100 (100.00)

Table 2: Age distribution

Age groups (years)	Number of cases, n (%)
0-4	22 (22.00)
5-8	44 (44.00)
9-12	34 (34.00)
Total	100 (100)

Table 3: Gender distribution

Gender	Number of cases, n (%)
Female	33 (33.00)
Male	67 (67.00)
Total	100 (100)

Table 4: Site of lymphadenopathy

Site	Number of cases, n (%)
Cervical	71 (71.00)
Submandibular	12 (12.00)
Axilla	10 (10.00)
Inguinal	4 (4.00)
More than one group	3 (3.00)
Total	100 (100)

Table 5: Size of lymphadenopathy

Size (cm)	Number of cases, n (%)
<1	12 (12.00)
1-2	61 (61.00)
>2	27 (27.00)
Total	100 (100)

Table 6: Presentation of lymphadenopathy

Presentation	Number of cases, n (%)
Localized	97 (97.00)
Generalized	3 (3.00)
Total	100 (100)

Table 7: Consistency of lymph node

Consistency	Number of cases, n (%)
Firm	66 (66.00)
Soft	22 (22.00)
Matted	11 (11.00)
Hard	1 (1.00)
Total	100 (100)

Maximum patients were males (67%) with male to female ratio of 2.03:1 (Table 3).

Cervical group of LNs were most commonly involved (71%) followed by Submandibular group (12%) (Table 4).

Table 8: Tenderness of lymph node

Tenderness	Number of cases, n (%)
Present	33 (33.00)
Absent	64 (64.00)
Present with raised local temperature	3 (3.00)
Total	100 (100)

Table 9: Lymphadenopathy with associated symptoms

Symptoms	Number of cases, n (%)
Fever	65 (65.00)
Sore throat	24 (24.00)
Cough	28 (28.00)
Ear discharge	13 (13.00)
Loss of appetite/weight	15 (15.00)
More than one symptom	35 (35.00)

Table 10: Disease specific analysis of lymphadenopathy

Cause	Number of cases, n (%)
Idiopathic	28 (28.00)
Tonsillitis	24 (24.00)
Tuberculosis	16 (16.00)
Otitis media	13 (13.00)
Oro-dental infection	7 (7.00)
Scalp infection	5 (5.00)
Viral infection	4 (4.00)
Leukaemia	2 (2.00)
Hodgkin's lymphoma	1 (1.00)

Table 11: Analysis of investigations

Investigation	Number of cases, n (%)
Leucocytosis	40 (40)
Anaemia	44 (44)
ESR raised	37 (37)
Mantoux test positive	16 (16)
Lymphoblast on PBF	2 (2)

PBF: Peripheral blood film, ESR: Erythrocyte sedimentation rate

Table 12: Cytological diagnosis of lymph node lesions

Lesions	Number of cases, n (%)
Inadequate	6 (6.00)
Benign	
Non-specific reactive LAD	68 (68.00)
Granulomatous LAD	20 (20.00)
Acute suppurative LAD	4 (4.00)
Malignant	
Atypical lymphoid proliferation	2 (2.00)
Total	100 (100.00)

Most of the patients (61%) presented with significant enlargement of LNs between 1 and 2 cm. Only 27% of cases presented with size >2 cm (Table 5).

97 cases (97%) had localized LAP predominantly in cervical nodes and 3 cases had generalized LAP (Table 6). In generalized LAP, two out of three cases were of atypical lymphoid proliferation on FNAC. On further evaluation, they were diagnosed as Acute Lymphoblastic leukemia/lymphoma (ALL/L).

On palpation of LNs, 66% of the nodes were firm in consistency while matting was noted in 11% of the cases (Table 7).

Majority of patients had non tender LNs (64%) and three cases (3%) also had raised local temperature (Table 8).

Analysis of symptoms showed that most of the patients (65%) presented with fever followed by cough (28%) (Table 9). However, 35% of the patients presented with more than one symptom. Among the 65% of patients with fever, 4% cases also had history of rash suggesting viral etiology.

In the present study, the most common cause of LAP turned out to be idiopathic (28%) while specific diseases such as tuberculosis, viral lymphadenitis (LAD), ALL/L, and Hodgkin lymphoma (HL) were seen in 16%, 4%, 2%, and 1%, respectively (Table 10).

All the patients were subjected to routine investigations like TLC, DLC, ESR, Hb, Mantoux test, chest X-ray, and peripheral smear examination for the establishment of diagnosis. Analysis revealed that 40% of the patients had leucocytosis and 44% of the patients had anemia. ESR was raised in 37% of patients. Among 100 patients Mantoux test was done in 20 patients among which 16 were positive. Abnormal chest x-ray was seen in 15% of patients (Table 11).

The most common cytologically diagnosed entity was non-specific reactive LAD (68%) followed by granulomatous LAD (20%) (Table 12). Two cases (2%) were diagnosed as atypical lymphoid proliferation (Fig. 1) in which complete hematological workup was done in higher centers including bone marrow aspiration and immunophenotyping. It came out to be ALL.

On further evaluation of cases of granulomatous LAD, specific diagnosis of tuberculosis was made in 16 cases. Epithelioid granulomas can be seen in non tuberculoid lesions such as sarcoidosis, brucellosis, cat scratch disease, leprosy and occasional malignancies. So to rule out these diseases, Z-N stain was done on all cases of granulomatous LAD. Cytodiagnosis of tuberculosis was made by demonstration of epithelioid cells and langhans giant cells with or without necrosis (Fig. 2) along with positive acid-fast bacteria (AFB) stain (Fig. 3).

Table 13 shows 16 out of 20 cases of granulomatous LAD were AFB positive. Therefore, in the present study, tubercular LAD was the most common entity among granulomatous LAD. AFB positivity in the study was 73.33%.

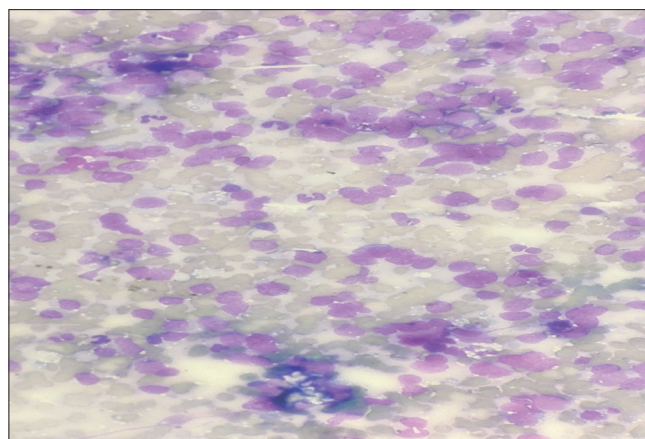
In the present study, cytological and histopathological correlation was available in only 22 cases out of 100 (22%) (Table 14). Maximum number of cases diagnosed in cytology was of reactive LAD which usually disappear after short antibiotic therapy. Hence, they were probably not subjected to any surgical excision or biopsy. Most of these patients were followed up in the out-patient department to check for any recurrence. The cytological findings were found to be concordant in 21 cases out of 22 with diagnostic accuracy rate of 95.45%. However, one case of reactive LAD (Fig. 4) on follow-up did not resolve after antibiotic treatment, so was subjected to excision biopsy which proved to be a case of Hodgkin lymphoma on HPE (Fig. 5).

**Table 13: Evaluation of granulomatous lymphadenopathy**

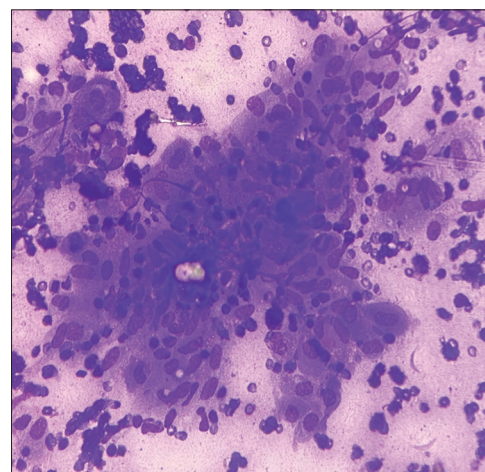
Cytological findings	Total cases	Number of cases	
		AFB stain positive, n (%)	AFB stain negative, n (%)
Epithelioid granuloma with necrosis	10	10 (100.00)	0
Epithelioid granuloma without necrosis	5	1 (20.00)	4 (80.00)
Only necrosis	5	5 (100.00)	0

AFB: Acid-fast bacteria

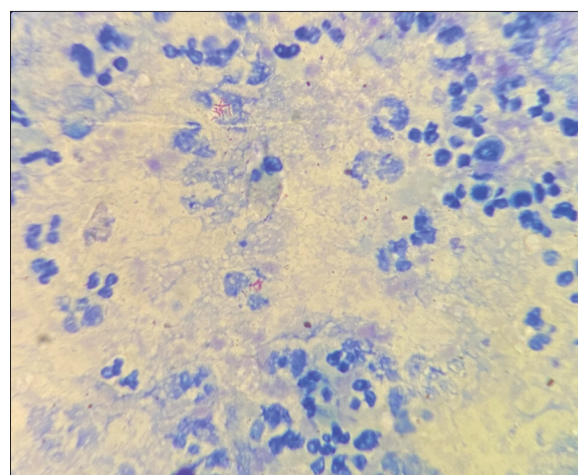
On statistical analysis, FNAC in the present study shows sensitivity, specificity, positive predictive value, negative predictive value, and



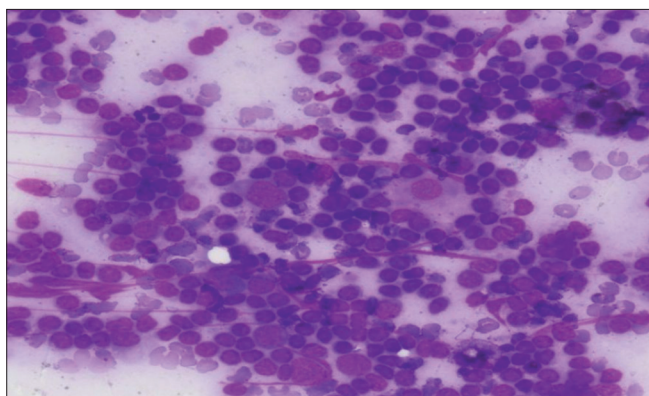
**Fig. 1: Fine-needle aspiration cytology of atypical lymphoproliferative lesion showing monomorphic lymphoid population which was further investigated and proved to be acute lymphoblastic, leukaemia/lymphoma. (May-Grunwald Giemsa 400x)**



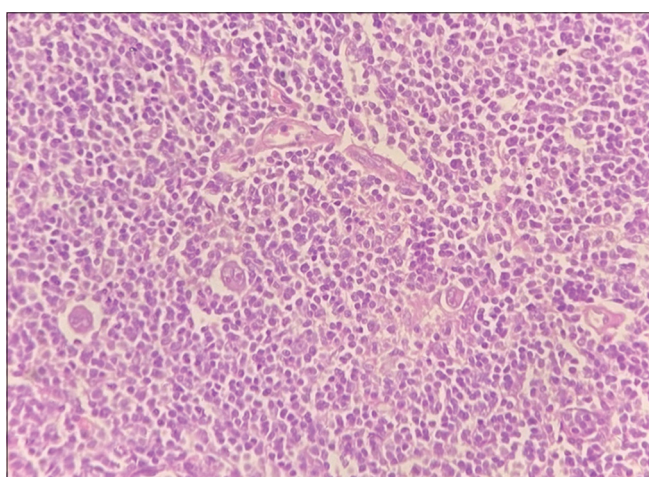
**Fig. 2: Fine-needle aspiration cytology smear of a granulomatous LAD showing granuloma comprising of epithelioid cells, lymphocytes, and giant cell. (May-Grunwald Giemsa, 400x)**



**Fig. 3: Z-N staining showing magenta colored, beaded, rod-shaped acid-fast bacteria (1000x)**



**Fig. 4:** Fine-needle aspiration cytology showing polymorphous population of lymphoid series of cell suggestive of reactive LAD (May-Grunwald Giemsa 400×)



**Fig. 5:** Histopathological examination of lymph node of Hodgkin's lymphoma showing monomorphic tumor cells, infiltration with eosinophils and classical Reed-Sternberg cell which on fine-needle aspiration cytology was reported as reactive LAD (H and E 400×)

diagnostic accuracy of 100%, 66.7%, 98.3%, 100%, and 95.45% respectively, as shown in Table 15.

As seen in Table 16, a clinical diagnosis of reactive LAP was made for 61 cases which on histopathology were confirmed as reactive LAD in 60 cases and Hodgkin's Lymphoma in one case. A clinical diagnosis of granulomatous LAP was made in 28 cases and on histopathological examination, 20 were confirmed as granulomatous LAD and eight were reactive LAD. A clinical diagnosis of inflammatory LAP was made in nine cases out of which four cases were confirmed as inflammatory LAD on histopathological examination while five cases were diagnosed as reactive LAD. Clinically, two suspected cases of malignancy were confirmed histopathologically.

Clinicopathological concordance was observed in 86% of cases. Statistical analysis was performed upon this correlation and p value came to be  $\leq 0.05$  (0.04) suggesting that it was significant (Table 16).

**DISCUSSION**

The present study consists of 100 cases of FNAC of LAP in pediatric age group with clinicopathological and cytohistopathological co-relation done. Histopathology was available in 22 cases. This is because majority of the cases were of reactive hyperplasia which regress after antibiotic therapy and does not require excisional biopsy and histopathological

**Table 14:** Correlation between histopathological and cytological diagnosis

Cytological diagnosis	Histopathological diagnosis		
	Total	Consistent	Inconsistent
Inadequate	6	-	-
Benign			
Non specific reactive	68	15	14
LAD			1 (hodgkin lymphoma)
Granulomatous LAD	20	5	5
Acute suppurative LAD	4	-	-
Malignant			
Atypical lymphoid proliferation	2	2	2
Total	100	22	21

**Table 15:** Statistical indices of present study

Indicators	Percentage
Sensitivity	100
Specificity	66.7
Positive predictive value	98.3
Negative predictive value	100
Diagnostic accuracy	95.45

**Table 16:** Comparison of clinically suspected cases and pathological proven cases

Clinical (diagnosis)	Pathological diagnosis		
	Total	Consistent	Inconsistent
Reactive LAP	61	60	1 (hodgkin's lymphoma)
	100%	98.36%	1.64%
Granulomatous LAP	28	20	8 (reactive LAD)
	100%	71.42%	28.58%
Inflammatory LAP	9	4	5 (reactive LAD)
	100%	44.44%	55.56%
Malignancy	2	2	-
	100%	100%	-
Total	100	86	14
	100%	86%	14%
$\chi^2$	8.52		
p	0.047		

LAP: Lymphadenopathy

evaluation. FNAC is particularly useful in such cases as it obviates the need for surgical intervention and also helps to rule out underlying serious systemic diseases.

Majority of the patients were in the 5-8 age group i.e. 44%. This is because normal peak lymphoid growth occurs in this age group. So with any ongoing antigenic stimulus, the lymphoid growth may exceed the normal limits. The results of the present study closely resemble the results of Ponder *et al.* [6], Reddy *et al.* [7], and Kondapalli *et al.* [8]. The cervical group of LN s was the most commonly involved (71%). This could be attributed to the predominant reporting population to our center being from low socio-economic group. They have high incidence of oropharyngeal, dental and scalp infections which results in enlargement of draining LN which is the cervical group. This could also be due to the rich lymphatic supply of the neck region and easy accessibility of cervical nodes for examination and evaluation [9]. These findings were in concordance with studies conducted by Ahmed *et al.* [10] and Vasuki *et al.* [11].

Frequency of distribution of benign lesions and malignant tumors was 91% and 3% respectively. The remaining 6% of the cases were inadequate to report. Hence, according to the present study benign

lesions were more common in pediatric age group. This observation was in concordance with the study done by Ahmed *et al.* [10] and Sawaimul *et al.* [12] in which the frequency of distribution of benign and malignant tumors was 90% and 10%, 96.80%, and 3.20%, respectively.

In the present study, inadequate/unsatisfactory material was found in 6% (6 cases) comparing well with findings in other studies conducted by Handa *et al.* [13] and Sawaimul *et al.* [12]. In most of the cases, cytological material was insufficient to give any definite diagnosis or smears contained only blood. Among the benign lesions, majority of the cases were of non-specific reactive hyperplasia (67%) followed by granulomatous LAD (20%) and acute suppurative LAD (4%). The results of the present study were in concordance with Singh *et al.* [13] who observed 71% cases of reactive LAD, 25.8% of granulomatous LAD, and 3.5% of acute suppurative LAD. Similar results with non-specific reactive LAD as predominant pattern were seen in studies by Handa *et al.* [13] and Aggarwal *et al.* [15]. On cytohistological correlation, there was one false-negative case where a case of Hodgkin's lymphoma was missed and reported as reactive LAD on cytology. Since a focal area of LN is sampled on FNA, representative area may be missed. Detailed clinical history and physical examination should always be carried out to avoid false-negative diagnosis in such cases. FNA is more accepted for the diagnosis of Hodgkin lymphoma than for Non-Hodgkin lymphoma and it may be diagnostic in high-risk surgical candidates and in patients where masses are inaccessible.

Amongst granulomatous LAD, tubercular LAD constituted the largest group (16%). Similar findings were reported by Singh *et al.* [14]. In a country like India where tuberculosis is highly prevalent, FNA offers an easy, quick, and effective means for making early diagnosis and preventing further transmission and spread of disease [9]. As the confidence of clinician increases, as indicated on cytology reports the excision biopsy can be avoided [16]. AFB positivity in the study was 73.3%. The detection of AFB was more in smears containing necrotic material with or without granulomas. Many cases show caseous necrosis along with polymorphs and histiocytes. ZN stain should be performed in all such cases of acute necrotizing lymphadenitis.

About 4% of the cases in the study showed features of acute suppurative lymphadenitis. In such cases, FNA is diagnostic and is also helpful in obtaining material for culture and sensitivity. ZN staining should be done in all cases of suppurative lymphadenitis to rule out tuberculosis [9]. About 2% of the cases were diagnosed as atypical lymphoid proliferation on FNAC and they were investigated on hematological lines. Bone marrow aspiration and immunophenotyping were done and it proved to be a case of ALL/L. FNA cytology can be particularly useful in cases of lymphomas to obtain samples for cytogenetic analysis.

The sensitivity of FNAC in the present study was 100%. When it is compared with the studies of other authors the sensitivity was comparable with studies by Singh *et al.* [14], Malhotra *et al.* [17] and Kondapalli *et al.* [8] where the reported sensitivity was 97.5%, 94.49%, and 100%, respectively.

In the present study comparison between cytological and histopathological diagnosis was available in 22% of cases; with concordance in 95.45% of cases and discrepancy in 4.55% of cases. The results of the present study were in accordance with the studies conducted by Mohan *et al.* [18] and Prathima *et al.* [19].

## CONCLUSION

FNAC is a simple bedside investigation which is a safe, affordable, effective and non-invasive technique with high patient acceptance, especially in pediatric age group as excision biopsy is difficult in children. FNAC acts both as a screening as well as a diagnostic procedure in various clinical conditions. Even though excision biopsy is the gold standard, FNAC is preferred as a first-line investigation and along with cell block analysis and application of ancillary tests (including immunocytochemistry), it helps to achieve an excellent diagnostic accuracy.

## AUTHORS CONTRIBUTION

Dr. RIYA MAHAJAN: Collection of data and writing of manuscript; Dr. POONAM SINGAL: Writing of manuscript; Dr. HARJINDER AND DR RAMESH KUMAR KUNDAL: Analysis of data and proof reading of manuscript; Dr. SHIVANSHU KUNDAL: Collection of data and statistical analysis; Dr. PRIYASI MONGA: Collection of data.

## CONFLICT OF INTEREST

None.

## AUTHORS FUNDING

None.

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