

Histopathological Spectrum of lymphadenopathy in children: A 5 year study

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Introduction

The term “Lymphadenopathy” refers to lymph nodes that are abnormal in size, consistency or number. The body contains approximately 600 lymph nodes, but only those in the submandibular, axillary and inguinal regions may be palpable in healthy people. There are various classifications of Lymphadenopathy, but a simple and clinically useful system is to classify Lymphadenopathy as “generalized” if the lymph nodes are enlarged in two or more noncontiguous areas, or “localized”, if only one area is involved. [1]

In pediatric age group, lymph node enlargement is a common clinical finding. It may represent normal age related physiological changes or transient response to

various benign local or generalized infections originating from the upper respiratory tract or skin. A biopsy is often included in patients with an unexplained localized Lymphadenopathy and a worrisome clinical picture or in those with generalized Lymphadenopathy. [2] In developing countries like India, acute upper respiratory infections, suppurative skin infections and tuberculosis are the major causes for regional Lymphadenopathy. [3] This study was aimed to determine the different causes of Lymphadenopathy in children needing biopsy and to study the different histological patterns and correlation with FNAC wherever possible.

Materials and Methods

This was a retrospective study of lymph node biopsies over 5 years in our department. A total of 78 lymph node biopsies were studied from 2011 to 2015. Details of these cases with respect to age, sex, clinical presentation, clinical diagnosis, investigations and histopathological findings in lymph nodes were obtained from departmental records. Detailed review of these cases was done. Sections from formalin fixed, paraffin embedded blocks and stained with hematoxylin and eosin stains were reviewed along with special stains wherever necessary. The study was approved by institutional ethical committee. Eligibility criteria adopted in our study: 1) Inclusion criteria: Children aged 0 to 12 years who had undergone lymph node biopsy, either core needle or excisional received in our pediatric pathology section. 2) Exclusion criteria: Cases with autolytic changes, poorly preserved tissues and cases where biopsies were inadequate for opinion.

Results

Table 1: Histopathological diagnosis of Lymph Node Lesions

Type of Lesion	Male	Female	Total	Percentage (%)
Benign	35	32	67	90.54
Malignant	6	1	7	9.46
Total	41	33	74	100

Total number of lymph node biopsies was 78 but four cases were excluded (as per exclusion criteria). Histopathological diagnosis of total lymph node lesions are given in **Table 1**.

Out of 74 lymph node lesions, 33 cases (44.6%) were of granulomatous lymphadenitis, 20 (27.02%) of reactive lymphadenitis, 5 (6.76%) cases of dermatopathic lymphadenitis, 4 (5.41%) cases of descriptive of benign etiology, 2 (2.70%) cases of non-specific inflammatory pathology, and 1 (1.35%) case each of Cat-Scratch disease, BCG adenitis and normal lymph node. There were 7 (9.46%) cases of malignant lymph node lesions, all these cases were primary malignancies (**Table 2**).

Table 2: Age distribution of different causes of lymphadenopathy

Age (years)	Reactive Lymphadenitis	Tuberculosis Lymphadenitis	Others (Dermatopathic, cat scratch, BCG Adenitis, Normal, Nonspecific, Descriptive)	Hodgkin	Non - Hodgkins	Hematolymphoid Malignancy	Total Cases
0-3	3	5	3	1	1	1	10
4-6	5	6	4	1	1	-	12
7-9	8	6	4	1	1	-	15
10-12	4	16	3	-	-	-	9
Total	20	33	14	3	3	1	74

The overall mean age of presentation was 7.47 years. The majority of the patients were in the age group of 10 – 12 years constituting 26 cases (35.14%), followed by the age group of 7 – 9 years consisting of 18 cases (24.32%). There was a slight male predominance with male to female ratio of 1:0.8.

The most common presenting symptom was fever in 22 (29.7%) cases, followed by loss of weight and appetite in 13 (17.6%) cases, cough in 8 (10.8%) cases, pain in abdomen and abdominal distension in 7 (9.5%) cases. The cervical region was the commonest site of involvement in 47 cases (63.51%), followed by axillary in 9 cases (12.16%), mesenteric in 6 cases (8.12%), inguinal in 6 cases (8.12%), mediastinal in 4 cases (5.41%). There was 1 case (1.35%) each of carinal and splenic lymph node. Most of the patients had localized lymphadenopathy (93.24%). Only 5 patients (6.76%) had generalized lymphadenopathy. The majority of the lymph nodes were within the range of 1-2 cm (60.91%)

followed by < 1 cm (30.91%), and only 3 (2.72%) were greater than 3 cm in size.

The criteria followed for the diagnosis of tuberculous lymphadenitis was the presence of caseous necrosis with epithelioid cell granulomas along with availability of special stain studies viz. Acid fast bacilli (AFB) & Gomori's Methenamine Silver (GMS). There were 33 cases (44.6%) cases of tuberculous lymphadenitis diagnosed on H&E stained sections **Fig 1(a)**. The largest lymph node measured 3.5 cm in size. Out of these, 3 cases were AFB positive and 4 were mantoux positive. Cytology diagnosis was available for 8 cases of which 4 were concordant with the histopathological diagnosis of tuberculous lymphadenitis.

The diagnosis of reactive lymphadenitis was considered when lymph node showed preserved architecture along with follicles of varying sizes containing germinal centers. In this study, 20 (27.02%) cases were of reactive lymphadenitis. The youngest patient was 6-months male and the oldest was 12 years female. The mean age of presentation was 6.95 years. Cytological diagnosis was available for 9 cases of which 8 were correlating with the histopathological diagnosis of reactive lymph node. One case was discordant on Cytopathological diagnosis, and was given as hematomalymphoid malignancy. The cases of reactive lymphadenitis were commonly presented as localized lymphadenopathy and cervical lymph node (65%) was the commonest site of involvement.

Patients with various skin diseases may show signs of regional adenopathy. Diagnosis of dermatopathic lymphadenitis was considered when lymph node architecture is distorted by focal nodular expansions of the subcapsular paracortical areas by aggregates of histiocytes; inter digitating reticulum cells, and

langerhans cells with elongated grooved nuclei. Admixed with histiocytes are small lymphocytes, many of which have folded nuclei. Melanin is usually present in the cytoplasm of cells and as extracellular deposits **Fig 1(b)**. In our study 5 (6.75%) cases were diagnosed as dermatopathic lymphadenitis. The youngest patient was 1.5-years-old male, while the oldest patient was 11-years-old female. Male to female ratio was 1.5:1. Size of largest lymph node was 2 cm. All the patients had localized lymphadenopathy, 4 (80%) patients were having cervical lymphadenopathy and 1 (20%) patient was having inguinal lymphadenopathy.

In our study, there was a single case of Cat-Scratch lymphadenitis diagnosed on histopathology **Fig 1(c)**. It was an 11.5-years-old female, with localized cervical lymphadenopathy having 1.5 cm lymph node. Patient presented with fever. No investigations were available. Special stains for AFB and GMS were negative. Cytology diagnosis of this case was not available for correlation.

We had a single case of BCG lymphadenitis in 6 months old child presented 6 months post BCG vaccination. Child presented with 2.5 cm sized left axillary lymph node. No investigations were available of the child. FNAC was also not done.

In our study, there were 2 (2.7%) cases with non-specific inflammatory etiology presented in a 5-years-old male with a 0.5cm and one with a 8-years-old female with 2cm tender cervical lymphadenopathy. Microscopy in both the cases showed mixed inflammatory infiltrate comprising of neutrophils, lymphocytes, macrophages and plasma cells. No granulomas or atypical cells were identified in both. There were 4 (5.4%) cases where no definite diagnostic pathology was found hence descriptive report was given. It includes 3 males and 1

female. One patient, a 6-years-old male, known case of thalassemia major, on regular transfusions was found having normal splenic lymph node on histology.

There were 3 cases of Hodgkin’s lymphoma; all were males with cervical lymph node involvement, presented with localized lymphadenopathy. Largest lymph node was 4 cm. FNAC diagnosis was available for 1 case, concordant with the histopathological diagnosis of Hodgkin’s lymphoma **Fig 2(a, b, c)**. Also, there were 3 cases of non-hodkins lymphoma; all were males with cervical lymph node involvement **Fig 3(a)**. FNAC diagnosis was available for 1 case, concordant with the histopathological diagnosis of Non-Hodgkin’s lymphoma. There was a female patient, presented with generalized lymphadenopathy involving mediastinal, abdominal and axillary lymph nodes. Axillary lymph node biopsy showed histological features of hematomalymphoid malignancy, and was advised further workup **Fig 3(b)**.

Discussion

In our study, age group selected was 0 to 12 years, which is similar to Studies done by Mohan MS et al [4] and Reddy MP et al[3]. Other studies had selected different age groups as in, 1 to 18 years in study by Maria A et al [5] and 1 month to 18 years in a study by Gwili NM et al[2].

In our study, sex ratio was found to be (M: F) 1.2:1, which is similar with the study of Al-Tawfiq JA et al[6]. Who had sex ratio of 1.6:1. Other studies have slightly higher sex ratio. Study by Gwili NM et al[2] had sex ratio of 2.4:1, Maria A et al[5] had sex ratio of 3.3:1, Darnal HK et al[7] had sex ratio of 2:1 and Mohan MS et al[4] it was 2.4:1.

Cervical lymph nodes were most commonly affected 47 (63.51%) in our study. The findings in our study are

similar with findings of Gwili NM et al[2]. They found 49 cases (77.78%) of cervical lymphadenopathy and 5 cases (7.94%) of axillary lymphadenopathy. Similar findings were observed in a study by Maria A et al[5] (77.27%). Axillary lymph nodes were the second most commonly affected site in our study (12.16%), which is similar with study done by Gwili NM et al[2]. Maria A et al[5] found inguinal nodes as second most common site (13.64%).

In our study, there were 67 (90.54%) cases of benign lymph node lesions and 7 (9.46%) cases of malignant lymph node lesions. Similar studies conducted had different percentages of benign and malignant lymph node lesions. Study by Gwili NM et al[2] had 24(51.1%) cases of benign lymph node lesions and 23(48.9%) cases of malignant lymph node lesions. Maria A et al[5] had 17 (77.27%) cases of benign lymph node lesions and 5 (22.73%) cases of malignant lymph node lesions and study by Darnal HK et al[7] had 36 (85.71%) cases of benign lymph node lesions and 6 (14.29%) cases of malignant lymph node lesions.

Histopathological diagnosis of pediatric lymph node lesions had different percentages for different diagnoses in various studies (**Table 3**)

Histopathological Diagnosis	Darnal HK et al[7]	Reddy MP et al[3]	Maria A et al [5]	Gwili NM et al[2]	Present study
Granulomatous	21.43%	57.44%	32%	8.5%	37.84%
Reactive	52.38%	36.18%	45%	25.5%	27%
Dermatopathic	2.38%	0%	0%	4.3%	6.76%
BCG adenitis	0%	0%	0%	0%	1.35%
Cat-Scratch disease	0%	0%	0%	0%	1.35%
Malignant	14.29%	6.38%	23%	48.9%	9.46%
Others	9.52%	0%	0%	12.8%	9.48%

The most common non-neoplastic lesion in our study was tuberculous lymphadenitis 28 (41.79%) cases, similar with a study by Khan NK et al^[8] who found 32 (37.2%) cases of tuberculous lymphadenitis. Maria A et al^[5] 7 (32%) cases and Damal HK et al^[7] 9 (21.43%) cases, had little lesser percentage of tubercular lymphadenitis as compared with our study. Khan RA et al^[9] in their study described tuberculosis as still one of the leading health problems in developing countries, with vast social and massive economic implications. In India about 1.5% of the population is affected with tuberculosis. It is the most common presentation of extra-pulmonary tuberculosis, accounting for 30-40% of cases in reported series. The onset of tuberculous lymphadenitis is insidious. Patients present with enlarged, usually painless lymph nodes, most commonly affecting the cervical region. It has been found that females are more likely to suffer from the disease. They had a male to female ratio of 1: 1.22. Present study also had similar findings with male to female ratio of 1:1.5, whereas it was 2:1 in a study done by Darnal HK et al^[7] and it was 1:0.7 in a study done by Maria A et al^[5]

In our study, there was a single case of Cat-Scratch lymphadenitis in 11.5 years- old female, with localized cervical lymphadenopathy. Its incidence was 1.35% in our study, whereas study by Nunes Rosado FG et al^[10] showed higher incidence of 7 (20 %) cases and they concluded bartonella affects older age children (mean age 9.8 years) and lymph nodes other than cervical.

In our study, there were 7 cases (9.46%) of malignant lymph node lesions. Out of which, Hodgkin's and Non-Hodgkin's lymphoma had 3 (42.85%) cases each with all males and 1 (14.3%) female with hematolymphoid malignancy. Similar observations were made by Reddy MP et al^[3], where malignant lesions were 6.38% of

total. Damal HK et al^[7] had 9.52%, little higher prevalence than our study, whereas studies by Maria A et al^[5] had 23%, Hanif G et al^[11] had 19.5 %, Khan NK et al^[8] had 19.7% and that by Gwili NM et al^[2] had 48.9% malignant lesions, higher than our study. In our study, M:F ratio for malignant lesions was 6:1, where as it was 3:1 in studies conducted by Hanif G et al^[11] and Roy A et al^[12]. All the studies are in accordance with our study of male preponderance.

In our study, all the cases of malignancies were of primary malignancy; there was no case with secondary malignancy or metastasis. Similarly all cases in a study by Maria A et al^[5] and Reddy MP et al^[3] were of primary malignant lesions. In a study by Kamat GC^[13], there were eight cases of non-Hodgkin's lymphoma, out of which anaplastic large-cell lymphomas accounted for four cases (50%), follicular lymphomas accounted for three cases (37.5%), and small lymphocytic lymphoma accounted for a single case (12.5%).

FNAC has appeared a promising technique for the evaluation of etiology of lymphadenopathy because of low cost, and can be easily performed. However, histopathological evaluation of lymph node biopsy specimen is considered the "gold standard." Although FNAC can diagnose most of the benign diseases and many lymphoma cases, it cannot provide sufficient material for further evaluation of lymphoma, on which the therapeutic decisions are based.^[14]

Conclusion

Tuberculous lymphadenitis was the most common cause of lymphadenopathy followed by Reactive lymphadenitis in our study. Lymph node biopsy plays an important role in establishing the cause of lymphadenopathy specially to rule out malignant causes in paediatric age group. This study highlights the

importance of lymph node biopsy with a accurate correlation of clinical, radiological and FNAC investigations in diagnosing generalised lymphadenopathy.

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Legends Figures

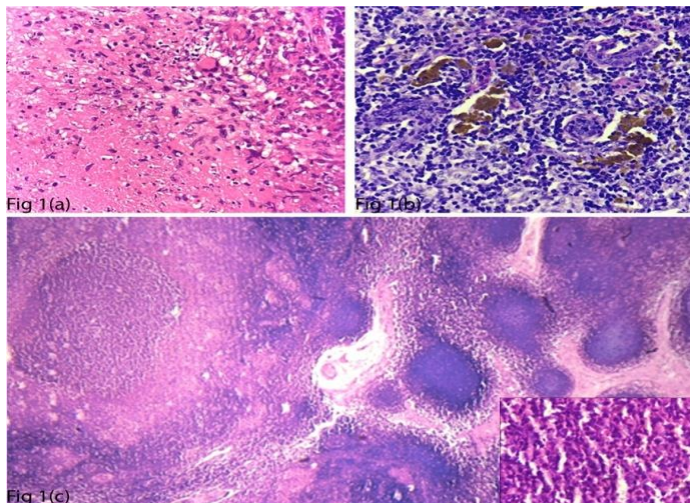


Fig 1(a): H&E stained section of tuberculosis lymphadenitis showing necrotizing granuloma consisting of epithelioid cells, Langerhan’s giant cells, lymphocytes and caseous necrosis (H&E, X400)

Fig 1(b): H&E stained section of Dermatopathic lymphadenitis showing reactive lymphoid follicles, prominent blood vessels and foci of dark brown granular pigment. (H&E, X400)

Fig 1(c): H&E stained section of Cat-Scratch lymphadenitis showing reactive lymphoid follicles of varying sizes. Foci of abscesses are seen in the center of the follicles (Inset). (H&E, X40).

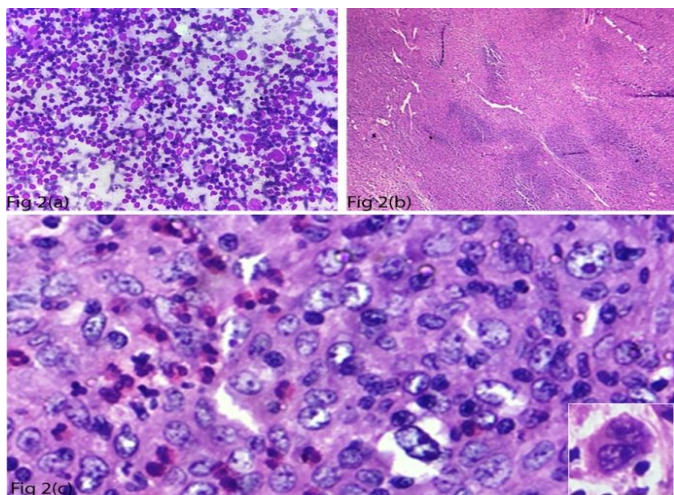


Fig 2(a): FNAC of lymph node - Hodgkin’s lymphoma showing monomorphic lymphoid cells, few large

atypical cells and RS cells (May-Grunwald Giemsa, X400)

Fig 2(b): H&E stained sections of Hodgkin’s lymphoma showing complete effacement of lymph node architecture. (H&E, X40)

Fig 2(c): H&E stained section of Hodgkin’s lymphoma showing scattered eosinophils, scanty lymphocytes with smudged nuclei and occasional large cells showing single nucleus with prominent nucleoli. (Inset RS Cell) (H&E, 400X)

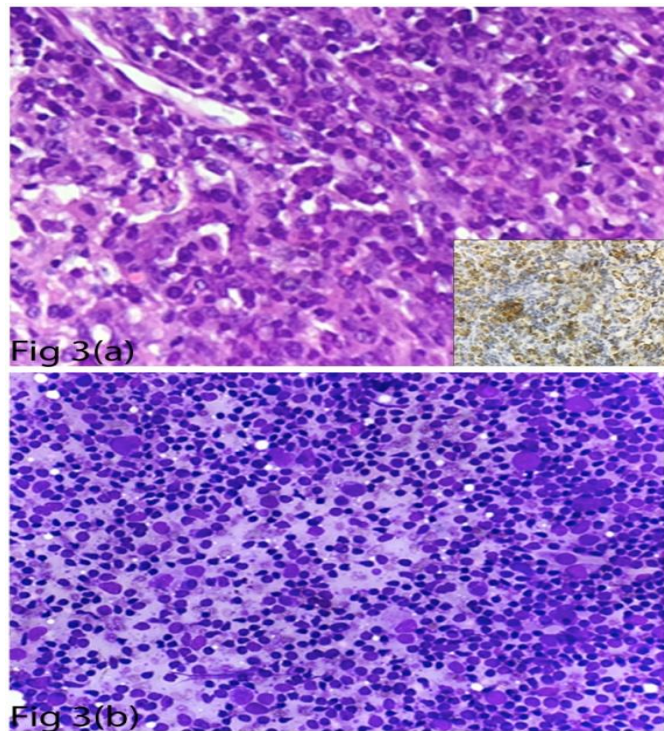


Fig 3(a): H&E section of Non-Hodgkin’s lymphoma showing large cells, these cells have moderate amount of eosinophilic cytoplasm and large vesicular nucleolus. (H&E, X400) (Inset: Immunohistochemistry – NHL-anaplastic large cell lymphoma, showing large cells diffusely positive for CD30 marker (X400)

Fig 3(b): FNAC of lymph node - Hematolymphoid malignancy showing monomorphic lymphoid cells and few large atypical cells.