Histopathological Analysis of Non-Neoplastic Superficial Lymphadenopathies

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ABSTRACT

Background

Lymphadenopathies are the clinical manifestation of enlargement of lymph nodes which are a common occurrence and are processes of lymph nodes in response to a variety of exogenous and endogenous stimulants. The vast majority of enlarged lymph nodes are non-neoplastic.

Objective

The objective of the study is to analyze the spectrum of non-neoplastic lesions of superficial lymphadenopathies with their histomorphological features.

Method

This was a retrospective hospital based study done in the department of Pathology. All cases of superficial lymph node biopsies received during a period of 7 years were retrieved and divided into 2 broad categories: neoplastic and non-neoplastic. The latter group is the material for the present study. The diagnosis was made on morphological basis.

Result

Of all the 268 superficial lymph node biopsies, 25.4% (68 cases) were neoplastic and 74.6% (200 cases) were non-neoplastic. The non-neoplastic cases were further categorized into non-infectious 60.5% (121 cases) and infectious 39.5% (79 cases). Neck node (70%) was the most common site of involvement. There were 102 male and 98 female patients with male to female ratio 1.04:1. The age range of the patients was 2 years to 83 years with a mean of 27.16 years and most common being 11-20 years 29% (58 cases). Majority of the cases were non-specific reactive lymphadenitis 84.3% (102 cases) followed by tuberculosis 36.5% (73 cases).

Conclusion

The major cause for the superficial lymphadenopathy was found to be non-neoplastic etiology with slight male predominance. Reactive lymphadenitis was the leading cause unlike the studies done in other Asian and Tropical countries where tuberculosis was more common.

KEY WORDS

Lymphadenopathies, non-neoplastic, reactive lymphadenitis, tuberculosis

INTRODUCTION

Lymphadenopathy is defined as an abnormality in the size or character of lymph node caused by the invasion or propagation of either inflammatory cells or neoplastic cells into the node.[1] The etiology and pathogenesis of many lymphadenopathies are still unknown; thus, the category remains heterogeneous and poorly defined.[2] It is broadly categorized and easily recalled as the mnemonic acronym "MIAMI", representing Malignancies, Infections, Autoimmune disorders, Miscellaneous and unusual conditions, and Iatrogenic causes.[3] The basic question pathologists first attempt to answer when studying lymph node biopsies is to comment whether the process is reactive or neoplastic.[4,5] The most common causes of lymphadenopathies are non-neoplastic rather than neoplastic.[6] The main aim of this study is to analyze the histopathological spectrum of non-neoplastic lesions of superficial lymph node biopsies.

METHODS

This was a retrospective hospital based study conducted in the Department of Pathology, Manipal Teaching Hospital, Pokhara, a tertiary care center, from January 2008 to December 2014. Prior approval was taken from institutional ethical committee. During the study period, a total of 268 cases of superficial lymph node excision biopsies were retrieved from the departmental data bank and were divided into neoplastic and non-neoplastic categories. Only 200 cases of superficial lymph node biopsies under non-neoplastic category were enrolled in the current study. The lymph nodes removed as a part of bigger specimen such as bowel, breast, gall bladder, thyroid and larynx etc and deep seated lymph nodes e.g., mesenteric and retroperitoneal nodes were excluded from the study. All the slides were reviewed. The stains studied were routine H&E stain and special stains like reticulin stain, Ziehl Neelsen stain, Periodic Acid Schiff (PAS) stain wherever required. The cases under the study were further categorized according to demographic profile (age and gender), site and histopathological diagnosis. The statistical analysis was performed using SPSS, version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, a total number of 268 superficial lymph node biopsies were reported, which were divided into 2 broad categories viz., neoplastic (68 cases, 25.4%) and non-neoplastic (200 cases, 74.6%). The non-neoplastic groups were analyzed in the present study. There were 102 male patients and 98 female patients with male to female ratio of 1.04:1.

Neck node was the most common site comprising of 140 cases (70%) followed by axillary node 41 cases (20.5%) and the inguinal node 17 cases (8.5%). Supraclavicular node involvement was 11 cases (5.5%) followed by submandibular and submental nodes 4 cases (2%) each (Table 1).

Table 1. Site distribution of all non-neoplastic superficial lymphadenopathy (n= 200).

Site	Number of cases (n)		%
Neck	Cervical	117	70
	Supraclavicular	11	
	Submandibular	4	
	Submental	4	
	Post-auricular	3	
	Occipital	1	
Axillary	41		20.5
Inguinal	17		8.5
Epitrochlear	1		0.5
Mid-arm	1		0.5

The age range of the patients was 2 years to 83 years with a mean of 27.16 years. Most of the patients in this study were in the age group of 11-20 years comprising of 58 cases (29%) followed by 21-30 years with 47 cases (23.5%) and less than 10 years with 33 cases (16.5%). Amongst males, majority i.e. 35 cases (34.3%) were between the age group of 11-20 years followed by 20 cases (19.6%) in less than 10 years while amongst females, maximum number of cases were in the age group of 21-30 years (n=30, 30.6%) followed by 11-20 years (n=23, 23.5%) (Table 2).

Table 2. Age and sex distribution of non-neoplastic superficial lymphadenopathy.

Age group (yrs) / Sex	Male (n)	Female (n)	Total (n)
<10	20	13	33
11-20	35	23	58
21-30	17	30	47
31-40	9	10	19
41-50	5	8	13
51-60	10	5	15
61-70	2	6	8
71-80	3	3	6
>81	1	0	1
Total (n)	**102**	**98**	**200**

In the current study, histological diagnosis of all 200 cases were tabulated in table 3, out of which 121 cases (60.5%) had a non-infectious etiology and the remaining 79 cases (39.5%) had an infectious cause. Among 121 cases of non-infectious category, 102 cases (84.3%) were reported as non-specific reactive lymphadenitis, out of which, follicular hyperplasia were seen in 73 cases, sinus histiocytosis in 24 cases and paracortical hyperplasia in five cases. The second cause under this category was Dermatopathic lymphadenopathy (DL) (n=6, 3%) followed by Sacoidosis

Table 3. Categorization and diagnosis of all cases (n=200).

Lesions		Frequency (n)		%
Non-infectious (n=121)				
Reactive lymphadenitis	102	Follicular hyperplasia	73	51
		Sinus Histiocytosis	24	
		Paracortical expansion	5	
Dermatopathic lymphadenopathy		6		3
Sarcoidosis		3		1.5
Necrotic node		2		1
Castleman's disease		2		1
Kikuchi fujimoto's disease		2		1
Non-specific granulomatous LA		2		1
RDD		1		0.5
Lipid LN		1		0.5
Infectious (n=79)				
Tuberculosis		73		36.5
Cat scratch disease		3		1.5
Fungal granulomatous LA		1		0.5
Nocardia		1		0.5
Acute lymphadenitis		1		0.5
Total		200		100

LA: Lymphadenitis, RDD: RosaiDorfman disease, LN: Lymphadenopathy.

(n=3, 1.5%). Among the infectious lymphadenopathy, tuberculosis (TB) was the most common etiology (n=73, 36.5%). Other infectious lesions found were three cases (1.5%) of cat scratch disease (CSD) and one case (0.5%) each of fungal granulomatous lymphadenitis, Nocardia and acute lymphadenitis.

The age and sex distribution of different histological diagnosis of all the non-infectious and infectious cases in the study is shown in table 4 and 5 respectively.

DISCUSSION

Lymphadenopathies, manifested clinically by the enlargement of lymph nodes, are a common occurrence and are processes of lymph nodes in response to a variety of exogenous and endogenous stimulants.[2] The vast majority of enlarged lymph nodes are non-neoplastic. The ratio of non-neoplastic to neoplastic lymph node lesions varies greatly with the kind of medical practice in which they present. In general medical practice, malignancies represent only about 1.1% of lymph node lesions, whereas at referral centers their frequency may be 40 to 60%.[2] Benign cases represent the proliferation of lymphocytes and cells of the monocyte-macrophage system usually in response to antigenic stimulus or infiltration of lymph nodes by inflammatory cells in various infections or by metabolite laden macrophages in storage diseases.[6]

In the present study, 200 of 268 cases (74.6%) were reported as non-neoplastic cause of superficial lymphadenopathies among which, 121 cases (60.5%) were of non-infectious category while in the remaining 79 cases (39.5%) infectious cause has been demonstrated similar to the study conducted by Chhabra et al.[6] In other study done by Williamson also had related findings in which 186 of 220 cases (84%) were non-neoplastic amongst which 112 (63%) patients were diagnosed with non-specific or reactive etiology.[7] Another study done in primary care practice has shown that more than two-third of patients with lymphadenopathy have either no specific causes or associated upper respiratory illnesses (viral or bacterial).[8] In the other series, the percentage of non-specific reactive lymphadenopathies among the non-neoplastic cases ranged from 35.6 to 65.6%.[6,9]

In one study, maximum numbers of patients with non-neoplastic superficial lymphadenopathy were in the age group of 10-30 years (55.2%) and also mentioned that males and females were almost equally affected with slight male preponderance.[6] The current study also showed similar picture with 52.5% in the age group of 11-30 years and male to female ratio being 1.04:1.

Similar to the other studies, neck was found to be the commonest site of superficial lymphadenopathy in our study (70%).[6,10] In the study conducted by Tiwari et al. in Central Nepal, cervical node (49%) was the most commonly affected superficial lymph node followed by supraclavicular (13%) and submandibular (9%) nodes.[11] In the current study, cervical node (58.5%) was the most involved node whereas involvement of supraclavicular and submandibular node were 5.5% and 2% respectively.

The present study showed non-specific reactive hyperplasia as the most common cause (51%) of non-neoplastic lymphadenopathy. A pathologic entity as heterogeneous and loosely defined as nonspecific reactive lymphadenopathy may exhibit a variety of morphologic patterns. This is because each of the major lymph node tissue components may be involved in the reactive process, resulting in partial effacement of the original architecture and the formation of new histologic patterns. Although clearly defined patterns are not usually observed, several attempts have been made to classify them. According to the predominance of various lymph node components, the major patterns of reactive lymphoid proliferations are follicular, paracortical expansion, diffuse, sinusal and mixed.[12] Follicular hyperplasia is the most common pattern of reactive lymphadenopathy.[13] In our data, among the reactive lymphoid hyperplasia, majority i.e. 71.6% (73 cases) were follicular hyperplasia, subsequently 23.5% (24 cases) were sinus histiocytosis and 4.9% (5 cases) were paracortical hyperplasia (Table 3). These findings were similar to the other study conducted by Roy et al. in South India where it was found that majority were follicular

Table 4. **Age and sex distribution of all the non-infectious cases (n=121).**

Lesions	Sex	Age group (Yrs)									
		<10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	>81	Total
RL	M	19	26	7	3	3	4	2	2	1	67
	F	9	10	7	4	2	1	2	-	-	35
DL	M	-	-	-	-	-	2	-	-	-	2
	F	1	-	1	1	-	-	1	-	-	4
Sarcoidosis	M	-	-	-	-	-	-	-	-	-	-
	F	-	-	-	1	1	-	1	-	-	3
CD	M	-	1	-	-	-	-	-	-	-	1
	F	-	-	1	-	-	-	-	-	-	1
Kikuchi Fujimoto's disease	M	-	-	-	-	-	-	-	-	-	-
	F	-	1	-	-	1	-	-	-	-	2
Necrotic node	M	-	-	-	-	-	-	-	-	-	-
	F	-	-	1	-	-	-	-	1	-	2
Non-specific granulomatous LN	M	-	1	-	-	-	-	-	-	-	1
	F	-	-	-	-	-	-	-	1	-	1
RDD	M	-	-	-	-	-	-	-	-	-	-
	F	-	-	1	-	-	-	-	-	-	1
Lipid LN	M	-	-	-	-	-	-	-	1	-	1
	F	-	-	-	-	-	-	-	-	-	-
Total		**29**	**39**	**18**	**9**	**7**	**7**	**6**	**5**	**1**	**121**

RL: Reactive lymphadenitis, DL: Dermatopathic lymphadenopathy, CD: Castleman's disease.

Table 5. **Age and sex distribution of all infectious cases (n=79).**

Lesions	Sex	Age group (Yrs)									
		<10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	>81	Total
TB	M	-	7	9	6	1	3	-	-	-	26
	F	3	12	19	4	4	2	2	1	-	47
CSD	M	1	-	1	-	1	-	-	-	-	3
	F	-	-	-	-	-	-	-	-	-	-
FG LA	M	-	-	-	-	-	-	-	-	-	-
	F	-	-	-	-	-	1	-	-	-	1
Nocardia	M	-	-	-	-	-	-	-	-	-	-
	F	-	-	-	-	-	1	-	-	-	1
Acute LA	M	-	-	-	-	-	1	-	-	-	1
	F	-	-	-	-	-	-	-	-	-	-
Total		**4**	**19**	**29**	**10**	**6**	**8**	**2**	**1**	**-**	**79**

TB – Tuberculosis, CSD – Cat scratch disease, FG LA – Fungal granulomatous lymphadenitis, LA – Lymphadenitis.

hyperplasia (66.2%) followed by sinus histiocytosis (6.3%) and paracortical hyperplasia (3.5%) among 287 cases of reactive nodes.[14]

Reactive lymphadenitis may be particularly common in younger individuals, but may be observed in all ages.[13] Hanif G et al. found reactive lymphadenitis as the common cause of lymphadenopathy in paediatric age group with more male predominance.[15] In the current study, it was more common in males and more in the age group of 11-20 years which is similar to one study conducted in South India.[14]

In the current study, TB was the second most common cause for the lymph node enlargement comprising of 73 cases (36.5%) among the total non-neoplastic lymphadenopathy and a leading cause among the infectious lymphadenopathy affecting 92.4% which is similar to the other study.[6] Whereas several previous studies revealed high prevalence of tuberculous lymphadenitis in countries like Pakistan, India and Bangladesh and also other tropical countries.[16-18] This variation in the incidence may be due to sampling bias as it is a tertiary care center and most of the cases are being treated in the private sector on the basis of cytological diagnosis.

Similar to this study, Biswas et al. and Khajuria et al. also found peak incidence of TB lymphadenitis in 2nd – 3rd decades of life though the percentage in our study is low.[19,20] In the current study, TB lymphadenitis was observed more commonly in females which was similar to other studies.[19,21]

Histologically, out of 73 cases, eight cases (11%) had positive acid fast bacilli on Ziehl Neelsen stain which was similar to the study conducted by Chhabra et al.[6] Whereas in several other studies, the frequency of demonstration of bacilli on Ziehl Neelsen stain was varying.[22] Rest of the cases of TB was diagnosed on the basis of caseating epithelioid cell granulomas and Langhan's giant cells.

After the two major causes, the next common cause for the superficial lymphadenopathy was found to be DL comprising of 3% of all the cases which is less in frequency in comparison to other similar studies.[6] The diagnosis was based on the histological findings of expansion of paracortical zone and presence of histiocytes containing phagocytosed melanin pigment, positive for Masson Fontana in their cytoplasm. The differential diagnosis with the mycosis fungoides was of particular concern as it is a cutaneous disorder that can be associated with dermatopathic lymphadenitis.[23]

Similar to the other studies, sarcoidosis were seen in three cases histologically showing diffuse architectural effacement of lymph node by compact, sharply demarcated, lymphocyte poor, reticulin rich epithelioid cell granulomas and asteroid bodies.[6] All these cases were negative for AFB staining. However, it is difficult to differentiate this disease from tuberculosis only on the basis of AFB staining because of very low AFB positivity on tissue sections of tuberculous cases. Clinical correlation is of prime importance for its diagnosis.[6]

A total of three cases of lymph node biopsies showed partial distortion of lymph node architecture with the presence of stellate abscess encircled by epithelioid histiocytes.[24] With these histological findings and clinical correlation, diagnosis of Cat Scratch disease (CSD) was made.

Castleman's disease (CD) of hyaline vascular type, usually presents as a solitary lymphadenopathy in young patients, most commonly in the mediastinum (60%), and also in abdomen, neck, lung, axilla, mesentry, broad ligament, retroperitoneum, soft tissue of the extremities, nasopharynx, leptomeninges, adrenal paradrenal and parotid.[25] In this study, two cases of lymph node biopsies were diagnosed as CD, hyaline vascular type. Both the cases presented as cervical lymphadenopathy in below 30 years of age similar to the study done by Ghosh et al. and Mallik et al.[25,26] Histologically, all these cases showed characteristic picture with increased number of large follicles with presence of hyalinization and vascular proliferation in their germinal center. Vessels penetrating into the follicles may give "lollipop appearance" and arrangement of the lymphocytes in surrounding mantle zone gives classical "targetoid appearance".[6,25]

In the current study, two cases (1%) of Kikuchi Fujimoto's disease were reported similar to the study conducted by Chhabra et al.[6] Histologically, both the nodes showed large discrete areas of necrosis with abundant nuclear debris and lack of granulocytes in the areas of necrosis. Absence of neutrophils and follicular hyperplasia differentiated these cases from lymphadenitis caused by CSD and other bacterial infections.[27]

Rosai Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is seen more commonly in the children, adolescents and young adults, though older adults also affected.[28] The disease mainly involves cervical and submandibular lymph nodes,[29] but involvement of mediastinal and retroperitoneal lymph nodes also has been described.[30,31] In the current study, only one case of lymph node biopsy was diagnosed as RDD and was seen in a young female of 25 years who presented with enlarged axillary lymph node. Histologically, lymph node showed distorted architecture with dilated sinuses containing numerous histiocytes with phagocytic properties.

Two cases were diagnosed as necrotic lymph node where histology showed multiple fragmented bits of necrotic tissue only. No viable tissue identified and AFB stains in both the cases were negative.

As it is a hospital based study and it may not represent the whole population of Western Nepal. Moreover, as already mentioned, there is a high possibility of sampling bias as it is a tertiary care center and most of the cases are treated on the basis of cytological diagnosis.

CONCLUSION

The major cause for the superficial lymphadenopathy was found to be non-neoplastic etiology with slight male predominance. Neck node was found to be the commonest site involved with majority of the age group affected being 11-20 years. Among the various diagnoses, reactive lymphadenitis was the leading cause unlike the studies done in other Asian and Tropical countries where TB was more common. Reactive lymphadenitis was seen more in younger age group and in males. TB was diagnosed mostly in the second and third decade with female preponderance as in other similar studies.

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