

A ten-year histopathological study of generalised lymphadenopathy in India

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Abstract

Background: Lymphadenopathy is a rather common clinical finding in a primary healthcare setting, and may be due to inflammatory lesions and tumours. Correlation between clinical findings and laboratory data is essential in arriving at a diagnosis. This study was undertaken to study the histopathology of generalised lymphadenopathy in India, as well as the demographics of the study population.

Method: This study was conducted for a period of 10 years (August 1997–July 2007), of which eight years were retrospective, from August 1997–July 2005, and two years were prospective, from August 2005–July 2007. The source of data for this study was patients seeking medical attention, who, on clinical examination, were found to have generalised lymphadenopathy. A representative node was excised for histopathology. Tissues were routinely processed, stained with haematoxylin and eosin, and examined by means of light microscopy.

Results: Of the 244 lymph node biopsies analysed in this study, 75 cases (30.73%) were reactive lymphadenitis, 142 cases (58.19%) showed granulomatous lymphadenitis, one case (0.40%) was Hodgkin's lymphoma, eight cases (3.27%) were non-Hodgkin's lymphoma, and 18 cases (7.37%) were metastatic malignancy.

Conclusion: In this study, the most common cause of generalised lymphadenopathy was granulomatous lymphadenitis, followed by reactive lymphadenitis. Among the neoplastic lesions, metastatic malignancy accounted for most cases.

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Introduction

The body contains approximately 600 lymph nodes, but only those in the submandibular, axillary and inguinal regions may be palpable in healthy people. "Lymphadenopathy" refers to nodes that are abnormal in size, consistency or number. There are various classifications of lymphadenopathy, but a simple and clinically useful system is to classify lymphadenopathy as "generalised" if the lymph nodes are enlarged in two or more noncontiguous areas, or "localised", if only one area is involved. In primary care patients with unexplained lymphadenopathy, approximately three-fourths of patients will present with localised lymphadenopathy, and one-fourth will present with generalised lymphadenopathy.¹ This study set out to investigate lymphadenopathy in the Indian primary healthcare context, with regard to aetiology, as well as demographics.

Method

Clinical records were retrieved for the retrospective cases from August 1997–July 2005, and for the prospective

cases from August 2005–July 2007, a total duration of 10 years. All patients sought medical attention, and on clinical examination, were found to have generalised lymphadenopathy. A representative node was excised from these patients. Lymph node biopsies that were performed to document metastatic spread to regional lymph nodes in cases of known malignancy, e.g. axillary nodes in breast carcinoma, and biopsies from cases of localised lymphadenopathy were not included in the study.

Cervical lymph nodes were most frequently biopsied (97.5%). For the prospective cases, the specimens were fixed in 10% formalin for 24 hours, after recording the gross morphological features. The size, shape, colour, and consistency of the nodes, as well as the presence of necrosis and matting, appearance on cut section, and appearance of the capsule were noted. The nodes were sectioned at 5-mm intervals and submitted for processing. Four- to five-micron-thick sections were cut with a microtome, and stained with haematoxylin and eosin. Special stains, such as Ziehl-Neelsen, reticulin, periodic acid-Schiff and Van Gieson,

were employed whenever indicated by the pathologist. For the retrospective cases, the respective paraffin blocks were retrieved, and the sections were cut and stained in a similar manner.

After tabulating the results according to age and sex distribution, statistical methods like the X (chi) square test were applied, the p-value was calculated, and the statistical significance was noted.

Results

Of the 244 lymph node biopsies analysed in this study, 75 cases (30.73%) were reactive lymphadenitis, 142 cases (58.19%) showed granulomatous lymphadenitis, one case (0.40%) was Hodgkin's lymphoma, eight cases (3.27%) were non-Hodgkin's lymphoma, and 18 cases (7.37%) were metastatic malignancy. (Refer to Table I).

The age range of the study population was from one year to 81 years. Most cases were seen in the age group 11-20 years (71 cases, 29.09%), and the least cases were seen in the age group over 70 years (four cases, 1.64%). (Refer to Table II.)

It was observed that there was a slight female preponderance for generalised lymphadenopathy (128 cases, 52.45%), as compared to men with the disease (116 cases, 47.54%). Statistically, the distribution of cases and sex correlation was found to be not significant (p-value > 0.05).

There were 75 cases of reactive lymphadenitis, accounting for 30.73% of all lymph node biopsies. They constituted 34.56% of all non-neoplastic lesions causing generalised lymphadenopathy (75 out of 217). The maximum number of cases was found in the age group 11-20 (30 cases, 40%). Forty-three cases (57.40%) were found in men, and 32 cases (42.6%) were found in women. There was a male preponderance, with a male:female ratio of 1:0.74.

Out of 75 cases, 52 (69.3%) were follicular hyperplasia, 16 (21.40%) were sinus histiocytosis, and seven (9.3%) were paracortical hyperplasia.

In our study, granulomatous lymphadenitis was the most common cause of generalised lymphadenopathy. This is probably attributable to the high prevalence of tuberculosis in this part of India.² Out of 244 lymph node biopsies, there were 142 cases of granulomatous lymphadenitis, accounting for 58.19% of all biopsies, and 65.43% of all non-neoplastic lesions (142 out of 217), with most cases (46) in the age group 21-30 years.

There was a single case of Hodgkin's lymphoma, which accounted for 0.4% of all lymph node biopsies and constituted 11.11% of all lymphomas. This was present in a woman in the second decade of life. It was of mixed cellularity type.

Out of 244 lymph node biopsies, there were eight cases of non-Hodgkin's lymphoma, accounting for 3.27% of all cases. They constituted 29.62% of all malignant lesions causing generalised lymphadenopathy. The Hodgkin's

Table I: Histopathology of lymph node biopsies

Pathology	No of cases	%
Reactive	75	30.73%
Granulomatous	142	58.19%
Hodgkin's lymphoma	1	0.40%
Non-Hodgkin's lymphoma	8	3.27%
Metastasis	18	7.37%
Total	244	100%

Table II: Age distribution of different causes of generalised lymphadenopathy

Age (years)	Reactive	Granulomatous	HD	NHL	Metastasis	Total no of cases	%
< 10	10	10	0	1	0	21	8.61%
11-20	30	39	1	1	0	71	29.09%
21-30	12	40	0	0	0	52	21.31%
31-40	11	33	0	0	1	45	18.44%
41-50	5	9	0	3	1	18	7.38%
51-60	2	8	0	2	5	17	6.97%
61-70	4	3	0	1	8	16	6.56%
> 71	1	0	0	0	3	4	1.64%
Total	75	142	1	8	18	244	-
%	30.73%	58.19%	0.40%	3.3%	7.37%	-	100%

$\chi^2 = 129.81$, p-value < 0.001, highly significant

lymphoma:non-Hodgkin's lymphoma ratio was 1:8. The maximum number of cases (three) was found in the age group 41-50 years. Six cases were found in men, and two were found in women. There was a male predominance, with a male:female ratio of 3:1. Out of eight cases, four cases (50%) were anaplastic large cell lymphomas, three cases (37.5%) were follicular lymphoma, and a single case (12.5%) was small lymphocytic lymphoma.

There were 18 cases of metastatic lymph nodes out of 27 neoplastic lesions of the lymph node, which accounted for 66.66% of cases. The majority of cases were found in the age group 61-70 years (eight cases, 44.44%). The male:female ratio was 1:1. In both men and women, nine cases were found. Out of 18 cases, 12 had metastatic squamous cell carcinoma (66.66%) and six had metastatic adenocarcinoma (33.33%). No cases of metastatic sarcoma were seen in the present study, and this is not unexpected as sarcomas do not generally metastasise via the lymphatic route.

Discussion

As mentioned in *Harrison's Principles of Internal Medicine*,¹ which is Western literature, study researchers reported that 186 out of 220 patients (84%) referred for evaluation of lymphadenopathy had a benign diagnosis. The remaining 34 patients (16%) had a malignancy (lymphoma or metastatic adenocarcinoma).¹ In a study by Rao et al of

50 patients, lymphadenopathy due to malignancy was seen in 22 patients (44%), and non-malignant causes were present in 28 patients (56%).³ In our study, non-neoplastic lesions constituted 88.92%, and neoplastic lesions constituted 10.64% of all biopsies. Of the non-neoplastic lesions, 30.73% were reactive lymphadenitis, and 58.9% were granulomatous lymphadenitis. In contrast, in a study by Sibanda et al, the prevalence of reactive hyperplasia was 33%, and that of granulomatous lymphadenitis was 26.7%.⁴ Similarly, in a study by Oluwale et al, 29.3% of nodes were reactive, while 19.3% were granulomatous.⁵ In a study by Moore et al, 47.8% of nodes were reactive, and 36.3% were granulomatous.⁶ The higher incidence of granulomatous lymphadenitis in the present study is probably due to the high prevalence of tuberculosis in this part of India.² (Refer to Table III.)

In the present study, out of 75 cases of reactive lymphadenitis, 52 cases (69.3%) were follicular hyperplasia, 16 cases (21.4%) were sinus histiocytosis, and seven cases (9.3%) were paracortical hyperplasia. In a study by Reddy et al that included 63 cases of reactive lymph nodes, 54 cases (85.71%) were non-specific reactive hyperplasia, whereas nine cases (14.29%) were follicular hyperplasia.⁷ In the present study, lymphoreticular malignancies accounted for 3.67% of all cases, while metastatic disease accounted for 7.37% of all cases. In a study by Sibanda et al, 7% of cases were lymphomas and 12.4% of cases were metastatic

Table III: Comparison of histopathology in various studies

Study	Location	Non-neoplastic lesions			Neoplastic lesions		
		^a RH	^b GL	Others	Lymphoma	^c M	Others
Henry et al ¹	United States of America		84%			16%	
Sibanda et al ⁴	Zimbabwe	33%	26.7%	-	7%	12.4%	Kaposi's sarcoma: 9%
Amr et al ¹¹	Saudi Arabia		23%		35%	20.5%	-
Freidig et al ¹²	United States of America	31.74%	7.39%	Sarcoidosis: 22%	20.52%	4.05%	Miscellaneous: 18.85%
Oluwale et al ⁵	Nigeria	29.3%	19.3%	-	23.8%	24.5%	-
Chumakov et al ¹³	Russia	64.9%	20.2%	-	-	14.9%	-
Sinclair et al ⁸	United States of America	10.12%	8.86%	-	63.29%	17.72%	-
Rao et al ³	Hyderabad		56%			44%	
Moore et al ⁶	South Africa	47.8%	36.3%	Normal: 1.5% Miscellaneous infections: 2.4%	8.5%	2.62%	Kaposi's sarcoma: 0.07%
Present study	India	30.73%	58.19%	-	3.67%	7.37%	-

a = reactive hyperplasia, b = granulomatous lesion, c = metastasis

disease.⁴ In a study by Oluwale et al, lymphoma constituted 23.8% of cases, while metastasis was seen in 24.5% of cases.⁵ In a study by Sinclair et al, 63.29% of cases were lymphoma, while 17.72% of cases were metastatic deposits.⁸

In the present study, 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%). In a study by Strauss et al, 77% of cases were diffuse non-Hodgkin's lymphoma, 21% were nodular non-Hodgkin's lymphoma, 2% were nodular and diffuse non-Hodgkin's lymphoma, and 1% was unclassifiable.⁹

In the present study, there were 18 cases of metastatic malignancy, of which 12 cases (66.66%) were metastatic squamous cell carcinoma, and six cases (33.33%) were metastatic adenocarcinoma. In a study by Rao et al of 14 metastatic tumours, metastatic bronchogenic carcinoma was found in eight cases (57.15%), and metastasis from an unknown primary was found in three cases (21.43%), while metastases from carcinoma of the stomach, pancreas and testes contributed to one case each (7.14%).³

In the present study, out of 18 patients with lymph nodes with metastatic tumours, 16 (88.88%) were older than 50 years. In a study by Sriwatanawongsa et al, the incidence of secondaries after the age of 55 years was 75.8%, which is consistent with the present study.¹⁰

In our study, the most common cause of generalised lymphadenopathy was granulomatous lymphadenitis, followed by reactive lymphadenitis. Although this study relates to the histopathological study of lymphadenopathy in India, a similar incidence of reactive lymphadenitis, granulomatous lymphadenitis and neoplastic lesions has been found in studies conducted in other developing countries.^{3,4,6} Histopathological examination of lymph nodes is a simple and cost-effective investigation for identifying the cause of lymphadenopathy, and it helps in the appropriate management of patients.

Conclusion

This study highlights the importance of lymph node biopsy in diagnosing generalised lymphadenopathy. It has shown that in developing countries, such as India, tuberculosis is the leading cause of generalised lymphadenopathy. It is important for physicians to be aware of these findings, and wherever necessary, to advise that a lymph node biopsy be undertaken. A lymph node biopsy may also prove to be less expensive than multiple blood tests when investigating the cause of enlarged lymph nodes.

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