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Research Article

Etiological study of generalized lymphadenopathy in a tertiary care hospital

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ABSTRACT

Background: This study was done to know about the clinical biochemical as well as radiological profile of patients presented as generalized lymphadenopathy in a tertiary care centre and to know the different causes of generalized lymphadenopathy.
Methods: 116 patients of generalized lymphadenopathy were included this study based on the inclusion and exclusion criteria. Detailed history, physical examination and relevant systemic examination including detailed examination of lympho-reticular system were done as per a structured proforma and necessary lab investigations were done for confirming diagnosis.
Results: Among 116 patients of generalized lymphadenopathy 59.5% were non-malignant causes where 40.5% diagnosed as malignant causes. Among them tuberculosis consist of 39 (33.6%), NHL 18 (15.5%), reactive lymphadenopathy 16 (13.8%), CLL and HD 8 (6.9%) each, ALL 7 (6%), SLE 5(4.3%), Kikuchi's disease 4 (3.4%), AML and RA 3 (2.6%) each and castleman's disease, phenytoin lymphadenopathy, metastatic lung and breast carcinoma 1 (0.9%) each. Cervical groups of lymph nodes were most commonly involved 86 patients (74.1%) followed by axillary groups 73 patients (62.9%). Lymph nodes size <1.5cm were mainly due to reactive causes where size >1.5cm were due to malignant and non-malignant granulomatous cases. FNAC give definite diagnosis 80.9% malignant cases where 76.8% in non-malignant cases. HPE shown definite diagnosis in 100% cases both malignant and non-malignant diseases.
Conclusions: Tuberculosis is most common cause of generalized lymphadenopathy followed by lymphoma. And reactive lymphadenitis is also an important consideration.

Keywords: Generalized lymphadenopathy, Tuberculosis, Hodgkin and non-Hodgkin lymphoma, Reactive lymphadenitis, Chronic lymphoid leukemia, Kikuchi's disease, Systemic lupus erythematosus, Acute myeloid leukemia, Rheumatoid arthritis, Castleman's disease

INTRODUCTION

Lymphatic system is an important part of our immune system. Lymphadenopathy may be a presenting sign and symptom of patient's illness or may be an incidental finding in patients being examined for various reasons. It is the readiness with which particulate matter can enter the lymphatics, which gives these vessels and nodes their great importance as a pathway for spread of infection and cancer. The body has approximately 600 lymph nodes, but only those in the submandibular, axillary or inguinal regions may normally be palpable in healthy people. Lymphadenopathy is an abnormal increase in size and or altered consistency of lymph nodes. It is a clinical manifestation of regional or systemic disease and serves as an excellent clue to the underlying disease. There are various classifications of lymphadenopathy, but a simple and clinically useful system is to classify

lymphadenopathy as "generalized" if lymph nodes are enlarged in two or more noncontiguous areas or "localized" if only one area is involved.[1-3]

Distinguishing between localized and generalized lymphadenopathy is important in formulating a differential diagnosis. In primary care patients with unexplained lymphadenopathy, approximately three fourths of patients will present with localized lymphadenopathy and one fourth with generalized lymphadenopathy.[2,3]

Generalized lymphadenopathy is frequently associated with nonmalignant disorders such as tuberculosis, infectious mononucleosis (Epstein-Barr virus (EBV) or cytomegalovirus (CMV)], toxoplasmosis, AIDS, other viral infections, systemic lupus erythematosus (SLE), and mixed connective tissue disease and malignant disorders like lymphoma and leukemia. The size and texture of the lymph node(s) and the presence of pain are useful parameters in evaluating a patient with lymphadenopathy. Nodes <1.0 cm^2 in area (1.0 cm x 1.0 cm or less) are almost always secondary to benign, nonspecific reactive causes. In one retrospective analysis of younger patients (9-25 years) who had a lymph node biopsy, a maximum diameter of >2 cm served as one discriminant for predicting that the biopsy would reveal malignant or granulomatous disease. Another study showed that a lymph node size of 2.25 cm^2 (1.5 cm x 1.5 cm) was the best size limit for distinguishing malignant or granulomatous lymphadenopathy from other causes of lymphadenopathy. Patients with node(s) <1.0 cm^2 should be observed after excluding infectious mononucleosis and/or toxoplasmosis unless there are symptoms and signs of an underlying systemic illness.[4]

Our understanding of the epidemiology of lymphadenopathy in family practice is limited by the scarcity of relevant literature. Only one study provides reliable population-based estimates. Findings from this Dutch study revealed a 0.6 percent annual incidence of unexplained lymphadenopathy in the general population.[5]

METHODS

All patients of generalized lymphadenopathy admitted the medical wards who fulfilling inclusion and exclusion criteria are included to my study. This study was undertaken over a period of one year. Valid consent was taken from all the patients who were included this study. Proper history from all patients were taken and relevant examination of all systems specially lymphreticular system were done. According the patients profile relevant investigations (Like CBC, LFT, LDH, HIV serology, CXR, Mantoux Test and Sputum for AFB, USG, Whole abdomen, CT chest and abdomen, FNAC, LN biopsy and Special investigation if needed like Microbiological stains, cultures, tumour markers, bronchoscopy, GI endoscopy, etc.) were done to diagnose the cases. All data were then analysed statistically.

Inclusion criteria

- Patients over 12 years of age admitted in Medicine Wards.
- Patients presenting with generalized lymphadenopathy.

Exclusion criteria

- HIV positive.
- Cases of generalized lymphadenopathy with a confirmed diagnosis to explain this presentation.
- Patients <12 years of age.

RESULTS

Among 116 patients Male 64 (55%), Female 52 (45%), M: F ratio was 1.23: 1. Mean age of 35.16 and a standard deviation of ±16.45 years, maximum patients were between the age group of 12 years to 40 years (63.8%).

Out of 116 patients, patients were presented with fever, dyspnea, swelling, weight loss, fatigability, night sweat, bleeding manifestation, skin rash and other features were 67.2%, 37.9%, 56%, 61.2%, 59.5%, 37%, 9.5%, 24.1%, 27.9% respectively. Among the following symptoms in relation of different diseases fever (x^2=10.695, p=0.4691), easy fatigability (p=0.5388), dyspnea (p=0.3661) were not statistically significant but significant weight loss (x^2=22.554, p=0.0204), lymph nodes swelling (x^2=23.793, p=0.0136), night sweat (x^2=25.023, p=0.0090), prominent bleeding manifestation (x^2=90.758, p<0.0001) and prominent skin rash (x^2=53.499, p<0.0001) were statistically significant.

Among 116 cases, on physical examination pallor, icterus and edema was present 48.3%, 14.7%, 17.2% cases respectively.

Among the 116 patients, cervical groups of lymph nodes were most commonly involved 86 patients (74.1%) followed by axillary groups 73 (62.9%) patients, inguinal groups 68 (58.6%) patients , epitrochlear lymph node 23 (19.8%) patients, and popliteal group 10 (8.6%) patients.

Among all patients lymph nodes size <1.5 cm mostly were due to reactive lymphadenopathy, lymph nodes size 1.5 – 3 cm were mainly due to malignant diseases (52.1%) and non-malignant granulomatous cases (43.7%) and lymph nodes size >3cm were due to mainly non-malignant granulomatous cases (64.1%) and malignant cases (35.9%). Lymph nodes size in different regions was statistically significant for diagnosis of different cases of generalized lymphadenopathy (p<0.0001) except in popliteal region (p=0.4582).

Matted lymph nodes were mainly seen in cervical followed by inguinal regions. Matted lymph nodes in non-malignant granulomatous and malignant cases were

75.4% and 24.6% respectively. These matted lymph nodes were statistically significant in cervical region (p<0.0001) and inguinal region (p=0.0321).

Among 116 patients soft lymph nodes were mostly due to reactive lymphadenitis and firm lymph nodes were due to malignant and non-malignant granulomatous disease and hard lymph nodes were due to malignant diseases. Lymph nodes consistency in different regions was statistically significant for diagnosis of different cases of generalized lymphadenopathy (p<0.0001) except in popliteal region (p=0.1249).

Among the patients lymph nodes with sinus were seen commonly in cervical followed by inguinal region and axillary region. These lymph nodes with sinus were seen mainly non-malignant granulomatous cases (87%). Lymph nodes with sinus in different regions were statistically not significant (p>0.05) except in cervical region (p=0.0445).

Among 116 patients of generalized lymphadenopathy pleural effusion were present among 24 patients (20.7%).There were mediastinal widening among 46 patients (39.7%) and 7.8% patients had pulmonary infiltrates. Among the chest X-ray abnormality mediastinal widening in distribution of different cases was statistically significant (x^2=29.803, p=0.0017) but pleural effusion, pulmonary infiltrates were statistically not significant (p>0.05).

Among 116 patients' hepatomegaly and splenomegaly were present 31% and 25.9% respectively. 42.2% patients had retroperitoneal lymph nodes and 12.1% had ascites. Retoperitoneal lymphadenopathy (x^2=36.360, p=0.0001) and hepatomegaly (x^2=22.724, p=0.0193) were statistically significant in relation to different diseases but splenomegaly and ascites were statistically not significant (p>0.05).

Out of 116 patients 57.8% had anemia, 34.5% patients were presented with increased total leukocyte counts, 47.4% patients had thrombocytopenia and 8.6% had abnormal cells on peripheral blood smear. Among them 82.8% had increased ESR. Anemia (x^2=22.899, p=0.0183), increased TLC (x2=48.338, p<0.0001) and thrombocytopenia (x^2=23.592, p=0.0146) were statistically significant in distribution of different cases but increased ESR was not statistically significant (x^2=12.901, p=0.2998).

Among 116 patients bilirubin were increased 23.3% patients, SGOT, SGPT were increased 19.8% patients and 23.3% patients had increased ALP.

Among 116 cases LDH increased in malignant and non-malignant cases were 53.2% and 30.4% respectively. LDH is mainly increased in lymphoma leukemia and tuberculosis. Increased LDH was statistically significant in distribution of different diseases (x2 =29.323, p=0.0020).Among 39 cases of tuberculosis, sputum for AFB was positive in 7 (17.9%) patients and MT were positive in 30 (76.9%) cases and MT is statistically significant diagnosis of TB lymphadenitis (x^2=79.893, p<0.0001).

Out of 116 cases FNAC give definite diagnosis 80.9% malignant cases where 76.8% in non-malignant cases. HPE shown definite diagnosis in 100% cases both malignant and non-malignant diseases. Among 47 malignant cases FNAC give proper diagnosis 100% in acute leukemia, 80.8% in lymphoma, 62.5% in CLL, 100% in metastatic carcinoma and HPE give 100% definite diagnosis in all malignant cases.

Out of 69 non-malignant cases FNAC showed proper diagnosis in 84.6% TB cases, 76% reactive lymphadenopathy, 20% other granulomatous diseases and HPE give 100% definite diagnosis in all non-malignant cases. Accuracy of FNAC in diagnosis of malignant diseases was 80.8% where in non-malignant diseases it was 76.8% and overall 78.4%.

Table 1: DD of generalized lymphadenopathy: total population (n=116).

Malignant disease		Non-malignant disease	
ALL	7 (6%)	Kikuchi's DS	4 (3.4%)
AML	3 (2.5%)	Phenetoin LN	1 (0.9%)
Castleman'SDS	1 (0.9%)	RA	3 (2.5%)
CLL	8 (6.9%)	Reactive LN	16 (13.9%)
HD	8 (6.9%)	Sarcoidosis	1 (0.9%)
NHL	18 (15.5%)	SLE	5 (4.3%)
MET breast CA	1 (0.9%)	TB	39 (33.6%)
MET lung CA	1 (0.9%)		
Total	47 (40.5%)	Total	69 (59.5%)

Among 116 patients 40.5% diagnosed as malignant causes where 59.5% were non-malignant causes. Among them tuberculosis consist of 39 (33.6%), NHL 18 (15.5%), reactive lymphadenopathy 16 (13.8%), CLL and HD 8 (6.9%) each, ALL 7 (6%), SLE 5 (4.3%), Kikuchi's disease 4 (3.4%), AML and RA 3 (2.6%) each and Castleman's disease, phenytoin lymphadenopathy, metastatic lung and breast carcinoma 1 (0.9%) each (Table 1 and Figure 1).

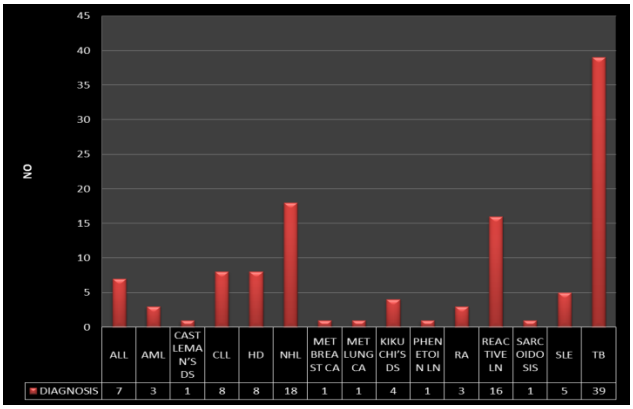

Figure 1: Diagnosis of generalized lymphadenopathy of the cases.

So diagnosis of generalized lymphadenopathy following decreasing order- TB lymphadenopathy (33.6%), lymphoma (22.4%), reactive lymphadenitis (21.6%), acute leukemia (8.5%), CLL (6.9%), Kikuchi's disease (3.4%), metastatic cases (1.8%), Castleman's disease (0.9%), sarcoidosis (0.9%).

DISCUSSION

We are seeing so many cases of generalized lymphadenopathy referring from different primary healthcares to our apex institute and we study those patients admitted to our medical wards.

Most common presenting features of our patients were fever (67.2%) followed by weight loss (61.2%) and other features in decreasing order were- fatigability, swelling of lymph nodes, dyspnea, night sweat, skin rash and prominent bleeding manifestation and only 17% patients presented with B symptoms.

Taghipour ZS et al study revealed that cough, fever, night sweat, weight loss were statistically significant in relation to diagnosis of different cases which partially support our study.[6]

In our study among the 116 patients of generalized lymphadenopathy most common involved lymph node area was cervical groups in 86 (74.1%) patients, followed by axillary groups in 73 (62.9%) patients, inguinal groups in 68 (58.6%) patients, epitrochlear lymph node in 23 (19.8%) patients and popliteal group in 10 (8.6%) patients.

Different studies throughout the world also revealed that cervical groups of lymph nodes were most commonly involved which was similar to present study.[7-10]

Most of patients (86.9%) patients of epitrochlear lymphadenopathy were due to malignant causes in our study.

Selby CD et al study of the enlarged epitrochlear lymph nodes: an old physical sign revisited showed that enlargement of these nodes was common in most of the lymphoproliferative disorders except Hodgkin's disease.[11]

Among the patients of generalized lymphadenopathy in our study lymph nodes size <1.5cm were mainly due to reactive causes where size >1.5cm were due to malignant and non-malignant granulomatous cases.

Bedi RS et al. finding in the clinico-pathological study of superficial lymphadenopathy in Northern India supported this finding.[12] Another study from Switzerland published in 2010 also supported this finding.[13]

Pangalis conducted a study in which he analyzed lymph nodes of 220 patients of which biopsies produced no malignancies in lymph nodes smaller than 1 cm^2, 8% of the lymph nodes sized between 1-2.25 cm^2 were malignant, and 38% of patients whose lymph nodes were larger than 2.25 cm^2 were found to have a malignant disease.[14]

Another publication from Turkey published in 2011revealed that in patients aged 9-25, lymph nodes larger than 2 cm were predictive of granulomatous diseases or cancer.[15]

Matted lymph nodes in cervical, axillary and inguinal regions were mainly due to non-malignant granulomatous diseases (75.4%). In cases of TBLN matted lymph nodes were 69%.

In Dandapat et al study of peripheral lymph node tuberculosis revealed that matted lymph nodes seen in 55% of TBLN cases where Subrahmanyam et al study it was seen in 68% patients.[16,17] These lymph nodes with sinus were seen mainly non-malignant granulomatous cases (87%). Lymph nodes with sinus in different regions were statistically not significant ($p>0.05$) except in cervical region ($p=0.0445$).

In Dandapat et al study it was seen that lymph nodes with sinuses in TBLN cases was 13% where Subrahmanyam et al study it was 10.5% cases.[16,17]

USG examination of 116 cases showed that most common abnormality was retroperitoneal lymphadenopathy (42.2%) followed by hepatomegaly (31%) and splenomegaly (25.9%).

In CXR of 116 patients mediastinal widening (39.7%) was the most common finding followed by pleural effusion (20.7%).

Dursun Tatar et al study among TBLN patients showed that mediastinal lymph node involvement was found to be the commonest pulmonary manifestation of TBLN cases (141). Comparison of RPLN and MW was statistically significant (p<0.0001) but comparison between RPLN and MW in relation to different diseases was not statistically significant (p=0.0609).

In present study LDH was done all the patients and it was seen that LDH was increased in 25 (53.2%) malignant cases and 21(30.4%) non-malignant cases. In malignant cases LDH was increased 71.4% in ALL, 61.1% in NHL, 50% in HD, 37.5% in CLL and 33.3% in AML. In non-malignant cases it was increased mainly TBLN cases.

Kornberg et al showed that LDH was increased in 79% of ALL cases whereas in lymphoma cases it was increased in only 16% cases (18).

Bierman et al study shown that LDH increased in ALL and lymphoma were 87% and 86% respectively (19).

Berthier S et al study showed that LDH level elevations were seen in 60% of benign cases, 36% in malignant cases and undetermined in 4% (20).

In our study out of 116 cases FNAC give definite diagnosis 80.8% malignant cases where 76.8% in non-malignant cases. HPE shown definite diagnosis in 100% cases both malignant and non-malignant diseases. Among 47 malignant cases FNAC gave proper diagnosis 100% in acute leukemia, 80.8% in lymphoma, 62.5% in CLL, 100% in metastatic carcinoma and HPE give 100% definite diagnosis in all malignant cases. Out of 69 non-malignant cases FNAC gave proper diagnosis in 84.6% TB cases, 76% reactive lymphadenopathy, 20% other granulomatous diseases and HPE give 100% definite diagnosis in all non-malignant cases. Accuracy of FNAC in diagnosis of malignant diseases was 80.8% where in non-malignant diseases it was 76.8% and overall it was78.4%.

Comparison of HPE and FNAC in diagnosis of diseases were statistically significant (p<0.0001).

Thomas JO et al study of FNAC in management of peripheral lymphadenopathy showed that the overall accuracy rate of lymph node aspiration was 89.5%.[21]

Steel BL et al study of FNAC in diagnosis of lymphadenopathy showed that the most challenging lesions to assess using FNAC were lymphomas, accounting for 15 of the 23 false negatives. FNAC of nodes provides a high level of diagnostic accuracy, as shown by the 3.4% false-negative and 0.9% false-positive rates.[22]

Among 116 patients of generalized lymphadenopathy 40.5% diagnosed as malignant causes where 59.5% were non-malignant causes.

Among them tuberculosis consist of 39 (33.6%), NHL 18 (15.5%), reactive lymphadenopathy 16 (13.8%), CLL and HD 8 (6.9%) each, ALL 7 (6%), SLE 5 (4.3%), kikuchi's disease 4 (3.4%), AML and RA 3 (2.6%) each and castleman disease, phenetoin lymphadenopathy, metastatic lung and breast carcinoma 1 (0.9%) each.

So in our study that conducted in a tertiary care hospital concluded that diagnosis of generalized lymphadenopathy with following decreasing order- TB lymphadenopathy (33.6%), lymphoma (22.4%), reactive lymphadenitis (21.6%), acute leukemia (8.5%), CLL (6.9%), Kikuchi's disease (3.4%),metastatic cases (1.8%), Castleman's disease (0.9%) and Sarcoidosis (0.9%).

Studies of the developing countries revealed that tuberculosis was the most common cause that was similar with present study.[9,10]

Lymphoma was the 2nd most common cause in Ochicha O, Edino ST et al study of pathology of peripheral lymph node biopsies in Kano, Northern Nigeria that was similar to our study.[10]

Overall malignancy (40.5%) was a major cause of generalized lymphadenopathy in our study which contradicts several studies.[7,9]

Several studies also showed that malignancy was a major cause of lymphadenopathy that was similar to our study.[10,23]

Among malignant cases lymphoma was a major cause in our study that finding was also supported by different studies.[9,10,23] NHL was higher than HD in our study which also supported different studies.[24,25]

Reactive lymphadenitis was the 3rd most common cause in our study which contradicts several studies.[7,9]

Several studies throughout the world showed that reactive lymphadenitis was the most common cause followed by TB lymphadenopathy which contradicts our study.[6,8]

CONCLUSION

Males predominate in generalized lymphadenopathy cohorts across all age groups. Tuberculous infection is the commonest cause of generalized lymphadenopathy in India. Non malignant etiologies predominate as causes of generalized lymphadenopathy in our setting. TB lymphadenopathy is the most common cause of generalized lymphadenopathy followed by lymphoma and reactive lymphadenitis.

Cervical nodes are most commonly enlarged, irrespective of the etiology of lymphadenopathy. Lymph nodes size <1.5 cm in are predominantly benign reactive, while a size >1.5 cm are associated with benign granulomatous and malignant diseases. Epitrochlear lymphadenopathy has the strongest association with malignant causes. Sinus tracts are most common with cervical nodes and tuberculous etiology. Mediastinal widening and retroperitoneal lymphadenopathies are the commonest imaging associations. Elevation of LDH is associated with hematological malignancies and tuberculosis. Less than 20% patients with TBLN had co-existing pulmonary tuberculosis. FNAC is a safe and cost effective diagnostic tool with good sensitivity for all causes of lymphadenopathy.

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