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## **A pattern of lymphadenopathies seen in a tertiary care hospital in Lahore, Pakistan**

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## A pattern of lymphadenopathies seen in a tertiary care hospital in Lahore, Pakistan

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**Aim:** This cross sectional study was conducted to assess various clinicopathological parameters in 1785 patients from various regions of Punjab.

**Materials and methods:** These cases were collected from Gulab Devi Chest Hospital, Lahore, Pakistan. The data were collected from all patients during a period of 2 years, from June 2006 to June 2008. All the cases were diagnosed after routine hematoxylin and eosin staining.

**Results:** Our observations revealed that the most prevalent lymphadenopathy in these patients was tuberculous lymphadenitis 53% (n = 946), and the most common group of lymph nodes involved is cervical lymph nodes. A significant association was observed between tuberculosis and gender ( $P < 0.01$ ) as 69.13% (n = 654) of the females presented with tuberculous lymphadenitis that was seen only in 30.86% (n = 292) of the males. Hodgkin's lymphoma was seen in 72 (4.03%) and non-Hodgkin's lymphoma in 27 (1.51%) patients. These lymphomas were seen more in the male patients as compared to the female ones ( $P < 0.008$  and  $< 0.043$ , respectively). However, in the remaining lymph nodes non-specific inflammatory conditions of the lymph nodes (non-specific lymphadenitis, non-caseating granuloma and reactive hyperplasia), were seen with no difference in the distribution of disease in male or female, P value  $< 0.636$ ,  $< 0.8267$ , and  $< 0.7507$ , respectively. A significant association was observed between metastatic lymph nodes and gender P value being  $< 0.01$  as 68.70% (n = 90), were males whereas 31.29% (n = 41) were females.

Mean age of the patients with tuberculosis was 34 years. On the other hand, both Hodgkin's and non-Hodgkin's lymphomas were seen more prevalent in the second and third decades of their lives. Mixed cellularity and diffuse small cell lymphoma were the commonest histopathological subtypes among Hodgkin's and non-Hodgkin's lymphoma, respectively.

**Conclusion:** Tuberculosis is more common in females ( $P < 0.01$ ) whereas lymphomas ( $P < 0.008$  in Hodgkin's lymphoma and  $P < 0.043$  in non-Hodgkin's lymphoma) and metastatic carcinoma are more common in males ( $P < 0.01$ ). The commonly occurring histopathological subtypes of both Hodgkin's (mixed cellularity) and non-Hodgkin's lymphoma (diffuse small cell) in our study differ from those in Western countries.

**Key words:** Tuberculous lymphadenopathy, cervical lymphadenopathy, Hodgkin's lymphomas, non-Hodgkin's lymphoma, metastatic carcinomas

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## Introduction

Tuberculosis kills about 2 million people each year (1) and is more prevalent in developing countries (2). The diagnosis of tuberculosis is mostly clinical, and wherever facilities are available, it is diagnosed by histopathological means of lymph node biopsy (2). Clinical diagnosis is easy when features like matting, ulceration, sinuses, caseation, and liquefaction are present. However, in early cases and some of the late cases these features are absent, resulting in diagnostic difficulties (3). Sometimes cases diagnosed as chronic non-specific lymphadenitis show positive cultures of mycobacteria; this is because early tuberculous cases could not be recognized on histopathology since the formation of granuloma and emergence of classical histological picture is a late phenomenon (4). Infectious agents, immunological reactions, and various other stimuli may cause reactive changes in lymph nodes. While some of these reflect the underlying abnormality of the immune system and cell control process, others are related to viral infections (5).

Hodgkin's lymphoma is relatively rare and its incidence varies with geographic location (6). WHO classified Hodgkin's lymphoma into 5 subtypes as lymphocyte rich, nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte predominance (7,8). Hodgkin's lymphoma is characterized histopathologically by the presence of Classic Reed-Sternberg cells and/or its variants (9). The annual incidence of non-Hodgkin's lymphoma is increasing by 3% to 4% in different parts of the developed countries (10). It constitutes a large and heterogeneous group of malignant tumors (11). Secondary lesions in lymph nodes are in the form of metastases (5). Tumor cells spread from primary tumors to form distant metastatic deposits by both lymphatic and blood routes (12). The present study is an attempt to assess various clinicopathological parameters in 1785 patients with lymphadenopathies, from various regions of Punjab.

## Materials and methods

This is a cross sectional study conducted in the department of Morbid Anatomy and Histopathology

at University of Health Sciences, Lahore. It included a total of 1785 cases of lymphadenopathy, collected from Gulab Devi Chest Hospital during a period of 2 years, from June 2006 till June 2008. The cases were diagnosed on the basis of routine hematoxylin and eosin staining.

Paraffin embedded blocks were collected from this 500 bedded tertiary care hospital. From each block, 3-5 micron thick sections were prepared using a Leica Rotary Microtome. One section of each case was collected on frosted slides and stained with conventional hematoxylin and eosin stains. The sections were examined by at least 2 pathologists to reach a final diagnosis.

## Statistical analysis

The data were entered and analyzed using SPSS 16.0. Mean  $\pm$  S.D is given for quantitative variables. Frequencies and percentages were given for qualitative variables. Pearson chi-square was applied to observe associations between qualitative variables. A P value of  $<0.05$  was considered to be statistically significant.

## Results

Among the total lymph nodes included in this study ( $n = 1785$ ), 87.11% ( $n = 1555$ ) were inflammatory in nature, 7.33% ( $n = 131$ ) were metastatic, 4.03% ( $n = 72$ ) were Hodgkin's lymphoma, and 1.51% ( $n = 27$ ) were non-Hodgkin's lymphoma. Sites of lymph nodes involved by various pathological conditions of lymph node are listed in Table 1.

## Gender

A significant association was observed between tuberculosis and gender with a P value  $<0.01$  as 69.13% ( $n = 654$ ) of the females presented with tuberculous lymphadenitis whereas only 30.86% ( $n = 292$ ) of the males were affected. No significant association was observed between non-specific lymphadenitis and gender, the P value being  $<0.636$ , as it was seen in 50.68% ( $n = 185$ ) males and 49.31% ( $n = 180$ ) females. No significant association was observed between reactive hyperplasia and gender, the P value being  $<0.7507$  as it was found in 56.69% of the males and in 43.30% of the females. No significant association was observed between non-tuberculous

Table 1. Various pathological conditions of the lymph nodes along with the sites of lymph nodes involved.

Site	Pathological conditions in lymph nodes						
	T.B n (%)	N-C. Granuloma n (%)	Ch.non.sp lymphadenitis	R.H n (%)	Chol. Granuloma n (%)	Lymphomas n (%)	Metastatic nodes
Cervical	649(68.60)	84 (70)	284(77.80)	89(72.95)	0(0)	43(59.72)	60(45.80)
Axillary	68(7.18)	9(7.5)	36(9.86)	21(17.21)	1(50)	9(12.5)	21(16.03)
Inguinal	8(0.84)	0(0)	14(3.83)	1(0.81)	0(0)	0(0)	3(2.29)
Submandibular	56(5.91)	10(8.33)	8(2.19)	7(5.73)	1(50)	1(1.38)	2(1.52)
Submental	7(0.73)	1(0.83)	3(0.82)	1(0.81)	0(0)	0(0)	0(0)
Supraclavicular	151(15.96)	14(11.66)	18(4.93)	3(2.45)	0(0)	16(22.22)	45(34.35)
Preauricular	3(0.31)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Mediastinal	1(0.10)	2(1.66)	1(0.27)	0(0)	0(0)	1(1.38)	0(0)
Paratracheal	1(0.10)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Occipital	1(0.10)	0(0)	1(0.27)	0(0)	0(0)	0(0)	0(0)
Postauricular	1(0.10)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Mediastinal	0(0)	0(0)	0(0)	0(0)	0(0)	1(1.38)	0(0)
Pelvic	0(0)	0(0)	0(0)	0(0)	0(0)	1(1.38)	0(0)
Total	946 (60.83)	120 (7.71)	365 (20.44)	122 (12.89)	2 (0.21)	72 (4.03)	131 (7.33)

Abbreviations: T.B.=Tuberculosis, N.C. Granuloma= Non-caseating granuloma, Ch.non.sp lymphadenitis= Chronic non-specific lymphadenitis, R.H.= Reactive hyperplasia, Chol Granuloma= Cholesterol granuloma.

granulomatous lymphadenitis and gender, the P value being  $<0.8267$  as it was seen in 52.5% (n = 63) of females and 47.5% (n = 57) of males. There were 2 cases of cholesterol granuloma; both were in females (100%). Among the lymphomas, Hodgkin's disease was found to be more common, 72.72% (n = 72), than non-Hodgkin's lymphoma, 27.27% (n = 27). A significant association was observed between Hodgkin's lymphoma and gender type, the P value being  $<0.008$  as Hodgkin's lymphoma was seen more in males as 72.22% (n = 52) as compared to females, 27.77% (n = 20).

A significant association was observed between non-Hodgkin's lymphoma and gender, the P value being  $<0.043\%$ . In non-Hodgkin's lymphoma males were affected in 74.07% (n = 20) of the cases, and females in 25.92% (n = 7). As regards the metastatic lymph nodes males were involved in 68.70% (n = 90) cases, whereas females were involved in 31.29% (n = 41) of the cases.

### Age

Mean age of tuberculous patients was 34 years, with the youngest patient being 3 years of age and the

oldest 65 years. Mean age of patients with non-specific lymphadenitis was 34 years with the youngest patient 3 years of age and the oldest 65 years. The age range of the patients with reactive hyperplasia in the present study was from 6 to 75 years and mean age was 40.5 years. Mean age of patients with non-tuberculous granuloma was 32 years, with the youngest patient 4 years old and oldest 60 years. There were 2 cases of cholesterol granuloma: one in a 14 year old and the other in a 26 year old. Hodgkin's lymphoma was seen more commonly in the second and third decades of life. Mean age was 44.5 years, with the youngest patient 4 years of age and the oldest 85 years. Non-Hodgkin's lymphoma was also seen more commonly in the second and third decades of life. Mean age was 35 years, with the youngest patient being 5 years of age and the oldest 65 years. The mean age of patients with metastatic nodes was 49 years, with the youngest patient being 13 years old and the oldest 85 years. Clinical features of the pathological conditions are given in Table 2.

Among Hodgkin's lymphoma, mixed cellularity was the most common subtype, seen in 43.05% (n =

Table 2. Clinical features of lymphadenopathies included in this study.

Clinical features	H L n (%)	NHL n(%)	T.B n(%)	Inf. Conditions n(%)	Metastatic n(%)
Cough	24(33.33)	11(40.74)	520(54.96)	125(20.52)	50(38.16)
Fever	47(65.27)	17(62.96)	712(75.26)	200(32.84)	55(41.98)
Swelling	31(43.05)	11(40.74)	751(79.38)	174(28.57)	36(27.48)
Hepatosplenomegaly	2(2.77)	2(7.4)	0(0)	0(0)	0(0)
Chest pain	5(6.94)	2(7.4)	0(0)	0(0)	20(15.26)
Anorexia	8(11.11)	1(3.7)	303(32.02)	0(0)	2(1.52)
Weight loss	16(22.22)	2(7.4)	416(43.97)	0(0)	21(16.03)
ATT	4(5.55)	2(7.4)	49(5.17)	0(0)	
Pleural effusion	1(1.38)	4(14.81)	19(2.00)	0(0)	22(16.79)
Mediastinal widening	6(8.33)	3(11.11)	0(0)	0(0)	0(0)
Dyspnea	8(11.11)	5(18.51)	73(7.71)	0(0)	35(26.71)
Opacities	0(0)	0(0)	101(10.67)	83(13.62)	
Smoking	0(0)	0(0)	8(0.84)	6(0.98)	18(13.74)
Hemoptysis	0(0)	0(0)	4(0.42)	0(0)	2(1.52)
Night sweats	0(0)	0(0)	3(0.31)	0(0)	0(0)
Hoarseness of voice	0(0)	0(0)	0(0)	0(0)	9(6.87)
Dysphagia	0(0)	0(0)	0(0)	0(0)	3(2.29)

HL; Hodgkin's lymphoma, NHL; Non-Hodgkin's lymphoma, T.B; Tuberculosis, Inf; Inflammatory.

31) patients, followed by nodular sclerosis in 26.38% (n = 19), lymphocyte rich in 19.44% (n = 14), lymphocyte depleted in 8.33% (n = 6), and lymphocyte predominance in 2.77% (n = 2). Among the non-Hodgkin's lymphoma, diffuse small cell lymphoma was the most commonly seen subtype, i.e. 48.14% (n = 13), followed by diffuse large cell lymphoma 37.03% (n = 10), mantle cell lymphoma 7.40% (n = 2), follicular lymphoma 3.70% (n = 1), and plasmacytoid lymphoblastic lymphoma 3.70% (n = 1). Among the various types of tumors metastasizing the lymph nodes large cell carcinoma and poorly differentiated carcinoma were the commonest, both comprising 19.84% (n = 26) each, followed by adenocarcinoma in 13.74% (n = 18), small cell carcinoma in 11.45% (n = 15), non-small cell carcinoma and anaplastic tumor in 7.63% each (n = 10), and many other tumor types.

## Discussion

After decades of decline, tuberculosis has come back (13) and is still one of the most frequently occurring infectious disease worldwide (14). The

results of the present study showed that tuberculosis was the most common disease among the lymph nodes included in this study, making up 53% (n = 946) of all the 1785 cases. A study carried out by Khan et al. from Peshawar reported 37.2% of lymph nodes diagnosed as tuberculous; they also showed that cervical lymph node was most commonly involved site that is also similar to the results of the present study (15). Similar results were observed in another local study performed by Akmal et al. (6). The studies performed in Indian populations showed tuberculous lymphadenitis being the most common lymphadenopathy (2,4) Ilgazlı et al. also showed in their study from Turkey that the most common form of extrapulmonary tuberculosis is lymph nodes. In contrast Ilgazlı et al. revealed that the most common site of extrapulmonary tuberculous lymphadenitis was intrathoracic lymph nodes followed by cervical lymph nodes (16). In a Malaysian study, the most common lymph node pathology was reactive hyperplasia followed by metastatic lymph node (17). Like Asian and North African populations, in the U.S. tuberculous lymphadenitis was found to be more common in females as compared to males (18,19).

As far as the clinical features of inflammatory lymphadenitis are concerned, they may vary from painful to painless lymph nodes and are not much different from the features of tuberculous lymphadenitis (18,20). This is also true for our study. As regards the chronic (non-specific) lymphadenitis, it may be associated with regional bacterial and viral infection or chronic conditions such as rheumatoid arthritis. Another Pakistani reported that non-specific lymphadenitis was seen in only 9.3% of the patients. However, in the present study, this incidence was 20.44% (15). On the other hand, a Malaysian study showed a contrast to the present study in which only 2.18% cases were of non-specific lymphadenitis (17). As regards the reactive hyperplasia the results of the above mentioned studies were in contrast to our results (13.9%), whereas in the present study only 6.83% were diagnosed as reactive lymph nodes (17). Khan et al. from Peshawar reported reactive hyperplasia in 26.7% cases, which is in contrast to our results (15).

The association of Hodgkin's lymphoma with age, gender, and histological types in different countries is shown in Table 3 (6,21-24). In developed countries there is a bimodal distribution of the disease, with the first peak near 20 years of age and the second peak near 55 years of age (24,25). In contrast to the above mentioned studies, the present study and other studies reported from this region do not show any bimodal age distribution; they rather showed clustering of cases in the second and third decades of life (6,26). As regards the non-Hodgkin's lymphoma, Hu et al. showed that men are affected more commonly by non-Hodgkin's lymphoma (27). This is comparable to the present study ( $P < 0.043$ ). A study reported by Greiner et al. showed that diffuse large cell lymphoma constitutes nearly 30% of all

lymphomas and was the most common histological type, similar to the present study (28). Among the non-Hodgkin's lymphomas diffuse large cell type makes up 37.03% of all lymphomas, but in contrast to the above mentioned study it was the second commonest type in the present study (28). The commonest type in our study was diffuse small cell lymphoma, making up 48.14%. As far as the age of patients suffering from non-Hodgkin lymphoma is concerned Izarzugaza et al. showed that age adjusted incidence is increasing rather more rapidly in European adolescents as compared to European children under 15 years of age (11). Similarly in the present study, most of the patients were involved in the second and third decades of life. The distribution of metastatic lymph nodes among both sexes depends upon the tumor type (primary), as metastatic lymph nodes in patients with breast carcinoma will be seen more in female patients and vice versa (5).

### Conclusion

The most common lymphadenopathy in the present study is tuberculous lymphadenitis, and the most common group of lymph nodes involved is cervical lymph nodes among all the lymphadenopathies. Females were more affected by tuberculosis as compared to males ( $P < 0.01$ ). The second largest group of lymphadenopathy was of chronic non-specific lymphadenitis. In both Hodgkin's ( $P < 0.008$ ) and non-Hodgkin's lymphomas ( $P < 0.043$ ) males were more affected than females. Among the Hodgkin's lymphoma, mixed cellularity was the most common subtype and among the non-Hodgkin's lymphoma, diffuse small cell lymphoma was the most common subtype. Metastatic lymph nodes were also more common among males.

Table 3. Distribution of Hodgkin's lymphomas in different parts of the world according to gender, age and type (21-24).

Parts of the world	Gender	Age group	Types of HL
Local study in Pakistan	More in males	—	M.C.
Western Europe & U.S.	Equal in both sexes	Young adults	N.S.
Eastern Europe	Equal in both sexes	Children	N.S.
Middle East	More in males	—	—
Present study	More in males	Young adults	M.C.

HL Hodgkin's lymphoma, M.C. Mixed cellularity, N.S. Nodular Sclerosis.

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