

Lymphadenopathy in adults

A clinicopathological analysis

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ABSTRACT

Objective: To describe the clinicopathological features of patients admitted to adult wards with a primary presenting feature of lymphadenopathy.

Methods: A retrospective study of all patients admitted to Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia between April 1996 through to March 2000.

Results: The patients mean age was 35.2 years (standard deviation 15.7 years) and 59.5% were females while 56.2% were Saudis. Swelling was the primary presenting symptom in 39.3% of the patients, while fever, night sweats, and pain occurred in 17.3%, 10.3% and 8.5% patients. There was considerable overlap between benign and malignant causes of lymphadenopathy but in 56.6% of patients, lymphadenopathy was the only sign. The cervical group of lymph nodes was the most commonly affected site. Hepatomegaly, splenomegaly and both organ enlargement occurred in 59 (22.9%) patients. The presence

of generalized lymphadenopathy and other physical signs (serositis and organomegaly) highly suggested a malignant process. Granulomatous lymphadenopathy due to tuberculosis was the most frequent pattern 98 (37.9%) followed by lymphoma 85 (32.9%). Tuberculosis was also more common in females than males (51% versus 19%). Among patients with Hodgkin's disease, nodular sclerosis was the most frequent (75%). Routine investigations did not discriminate between benign and malignant causes of lymphadenopathy. The overall mortality rate was 8.1%: with metastatic disease accounting for 52.4%.

Conclusion: There were significant similarities and differences between these findings and other previous studies in the Kingdom of Saudi Arabia and elsewhere.

Keywords: Lymphadenopathy, benign, malignant, tuberculosis, lymphoma.

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Lymphadenopathy (LA) is a commonly encountered clinical problem in all branches of medicine. Studies have shown that as many as 56% of patients examined for other reasons were found to have cervical LA.¹ In situations where this enlargement is a primary presenting sign, and cannot be readily explained, there is a need for thorough physical examination and a sensible approach to

management based on the common pattern in particular environments. A number of conditions, both benign and malignant are known to cause LA² and they manifest in various forms in different ages. It is well known that LA is a common problem in children and adolescents and often represents non-specific reactive hyperplasia.³ In adults, it is often believed to represent a malignant process.⁴ A number

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of reports from various parts of the world including 2 regions of the Kingdom of Saudi Arabia (KSA),^{5,6} have examined the histological pattern of LA but not the clinical features in detail. The present study examined the clinical and histological features of patients with primary presenting feature of lymphadenopathy admitted to the adult wards of Riyadh Medical Complex (RMC) in the central region of KSA. It specifically identified the important similarities and difference from previous studies.

Methods. All patients who presented to the adult wards of RMC between April 1996 through to March 2000 with LA as a primary clinical or radiological sign, or both, and subsequently underwent lymph node biopsy were reviewed retrospectively. Those who underwent lymph node biopsy routinely or as a staging procedure of malignancy were excluded. Also excluded were those erroneously admitted as LA but histological examination revealed another diagnosis. Where more than one biopsy was carried out, the definitive histological diagnosis was recorded. All charts were reviewed for the collection of demographic, clinical and routine laboratory and radiological data. The final histological diagnosis and outcome were also recorded. Mantoux test was carried out by intradermal injection of 5 units of purified protein derivative (PPD). Lymph node specimens were fixed in formalin and embedded in paraffin. Routine staining with hematoxylin-eosin was carried out. Special staining with Ziehl-Nielson, Reticulin, Gomari Methinamine silver and periodic acid schiff (PAS) were carried out where necessary.

Data was analyzed using the descriptive statistics module of Statistical Package for Social Sciences (SPSS) for windows version 10. Means and standard deviation (SD) were used to summarize continuous variables while percentages were used for categorical variables. Chi-square test was used to investigate the statistical significance between 2 categorical variables. The level of significance chosen was 5%.

Results. There were 258 cases, 145 (56.2%) Saudi nationals and 113 (43.8%) were of other nationalities. The mean age was 35.2 years (SD = 15.7). There were 153 (59.3%) females and 105 (40.7%) males giving a sex ratio of 0.69. **Table 1** shows the distribution of the presenting symptoms in relation to the histological diagnosis. Local swelling was the most frequent symptom in 195 (75.6%) cases and the only symptom in 87 (33.7%) cases. Fever, which occurred in 85 (32.9%) cases, was always associated with other symptoms. Other common symptoms were night sweats, pain and weight loss. There was no clear difference in the pattern of symptoms between benign and malignant disorders. Duration of symptoms varied from one day to 3 years with a median of 60 days. Lymphadenopathy was localized in 141 patients (54.7%), limited in 30 (11.6%) and generalized in 87(33.7%). Lymphadenopathy is considered to be localized if only one group of lymph nodes is involved, limited if 2-3 groups of lymph nodes are involved and generalized if more than 3 groups of lymph nodes are involved.² **Tables 2 & 3** show the distribution according to histological diagnosis and extension. The most frequent site was the cervical group of

Table 1 - Presenting symptoms of patients with lymphadenopathy in relation to histological diagnosis.

Symptoms	Diagnosis							N* (%)
	Tuberculosis N=98 (%)	Lymphoma N=85 (%)	Metastasis N=17 (%)	Sarcoidosis N=6 (%)	Kikuchi's Disease N=7 (%)	NSRH N=36 (%)	Others N=9 (%)	
Swelling	83.7	74.1	58.8	50	85.7	69.4	66.7	195 (39.3)
Fever	28.6	40.0	11.8	16.6	71.4	27.8	55.6	85 (17.1)
Night sweats	24.5	16.5	29.4	-	42.8	13.9	-	51 (10.3)
Pain	8.2	28.2	35.3	33.3	-	5.6	-	42 (8.5)
Weight loss	7.1	21.2	11.8	0	14.3	0	22.2	30 (6.3)
Cough	8.2	15.3	-	16.6	14.3	5.6	22.2	27 (5.7)
Others (related to cause)	5.1	14.1	11.8	-	-	5.6	22.2	23 (4.8)
Unrelated symptoms	9.2	17.6	14.2	50	14.3	19.4	11.1	43 (8.7)

N - number, NSRH - non-specific reactive hyperplasia, * - includes multiple response

Table 2 - Causes of lymphadenopathy in relation to its extension.

Diagnosis	Localized (%)	Limited (%)	Generalized (%)
Tuberculosis	63.8	16.7	3.4
Hodgkin's Disease	5.7	20	29.9
Non-Hodgkin's Lymphoma	0	6.7	49.4
Metastatic	3.5*	3.4	12.6
Kikuchi's Disease	2.8	10	-
Sarcoidosis	0.7	16.7	-
Non-specific reactive Hyperplasia	19.9	20	2.3
Others	3.5	6.7	2.3
Total	141 (100)	30 (100)	87 (100)
*All localised metastatic lymphadenopathy were nasopharyngeal in origin			

lymph nodes accounting for 121 (46.9%). Benign causes tended to be localized (90.8%) as opposed to malignant causes, which are often generalized (92%). In 146 patients (56.6%) there were no other physical signs other than LA. Hepatomegaly, splenomegaly and hepato-splenomegaly occurred in 8 (3.7%), 17 (6.6%) and 34 (13.2%) patients. Serositis was present in 21 (8.1%) patients on presentation. Other common signs were skin rash 7 (2.7%) and neurological signs 7 (2.7%). Also, 74.1% of patients with lymphoma and all cases with metastatic disease had other signs, but only 8.2% of patients with tuberculosis, 19.4% of patients with non-specific reactive hyperplasia (NSRH) and none with Kikuchi's disease had other signs.

Granulomatous LA due to tuberculosis, based on the presence of caseating granuloma, positive acid fast bacilli or complete response to antituberculous drugs, was the most frequent diagnosis occurring in 98 (37.9%) patients followed by lymphoma in 85 (32.9%) patients. Non-specific reactive hyperplasia occurred in only 36 (14%) patients. Kikuchi's Disease and sarcoidosis occurred in 7 (2.7%) and 6 (2.3%) of patients. The proportion of females with tuberculosis was statistically significantly higher than their male counterpart (51% versus 19% $p < 0.01$) irrespective of nationality. But a statistically higher proportion of non-Saudis have tuberculosis ($p < 0.05$).

Table 3 - Histological diagnosis in relation to age in patients with lymphadenopathy.

Age group	Tuberculosis (%)	Hodgkin's Disease (%)	NHL (%)	Metastasis (%)	Kikuchi's Disease (%)	Sarcoidosis (%)	NSRH (%)	Others (%)
<20	9.2	32.5	4.4	11.8	-	-	44.4	11.1
20-29	33.7	25	6.7	5.9	57.1	16.7	25	33.3
30-39	29.6	10	17.8	29.4	14.3	16.7	13.9	22.2
40-49	17.3	20	17.8	29.4	28.6	33.3	11.1	11.1
50-59	8.2	5	22.2	-	-	33.3	2.8	11.1
60-69	2	2.5	13.3	11.8	-	-	2.8	-
≥70	-	5	17.8	11.8	-	-	-	11.1
Total	98 (100)	40 (100)	45 (100)	17 (100)	7 (100)	6 (100)	36 (100)	9 (100)
NHL - Non-Hodgkin's lymphoma, NSRH - Non-specific reactive hyperplasia								

Also, 23 of the 98 (23.5%) patients with caseating granuloma were positive for acid-fast bacilli. The percentage of patients with lymphoma was higher in males ($p > 0.0001$). Nodular sclerosis was the most frequent pattern (75%) among 40 patients with Hodgkin's disease (HD), mixed cellularity (20%) and lymphocyte depletion (5%). The diagnoses classified as 'others' are dermatopathic LA (3 patients), and one each of Rosai-Doffman Disease, angioimmunoblastic LA, dystrophic calcification, sinus histiocytosis, cryptococcal LA (in a patient with acquired immune deficiency syndrome) and suppurative LA.

Mantoux test was positive in 73 of 79 patients with tuberculosis (92.4%), in 6 of 64 patients with lymphoma (9.4%), in 2 of 8 (25%) patients with metastasis and in one of 6 (16.7%) with sarcoidosis and none in those with Kikuchi's disease. The complete blood count (CBC) was abnormal in a higher proportion in one or more of the elements in 87 of 156 (55.8%) patients with benign disorders compared to 71 of 102 (69.6%) of those with malignant disorders ($p < 0.05$). Also the results of liver function tests were less abnormal in patients with benign disorders compared to patients with malignant disorders (19.2% versus 44.1%, $p > 0.01$). Serology for the human immunodeficiency virus was carried out on 30 patients and it was positive in only one patient (3.3%).

Follow-up. There were 21 deaths recorded during a 6-48 month follow-up period giving a mortality rate of 8.1% or 81 per 1000. One patient died during hospitalization and 2 of the 40 with Hodgkin's disease (5%), 6 of 45 with non-Hodgkin's lymphoma (13.3%) and 11 of 17 (64.7%) of the patients with malignant disease also died. The remaining patients were either fully treated or transferred to other hospitals. None of the patients with NSRH died or developed a malignant condition.

Discussion. The overall mean age of the patients in this study is similar to other reports from other regions of KSA.⁵⁻⁷ The present study, like others from developing countries^{5,7-10} showed a high prevalence of tuberculosis. The age distribution of patients with tuberculous LA also conforms to the pattern in the developing world,¹⁰ with majority occurring before the age of 40 years. This however contrasts with the more recent pattern in the west where older patients are seen with tuberculous LA.¹¹ Our series showed a very high preponderance of females with tuberculosis. This is in consonance with what has been reported although in a ratio of 2:1 or less.^{6,8,10,12-14} The higher proportion of females in our series can be explained partly by the high prevalence of tuberculous LA in Indonesian females who usually work as housemaids in this Kingdom and who have

access to RMC like the Saudi nationals. The findings in this study conform to the recognized pattern of tuberculous LA in adults where generalized LA is very rare¹⁵ (3%) and most commonly involves the head and neck^{16,17} (86.4%). Mediastinal node involvement, per se, is uncommon in spite of this group being the most common primary regional site of drainage. A few patients (<8%) patients with tuberculous LA had a negative Mantoux test. This may be due to technical error in the administration of the tuberculin reagent but may also represent a true anergy.

Malignant lymphoma (NHL and HD) was the 2nd most common group of diseases accounting for 32.9% of cases. This figure is much higher than earlier figures published from other regions of the Kingdom.^{5,7} Riyadh Medical Complex being the only tertiary referral center for the Ministry of Health may explain this disparity but a real increase in the prevalence of these tumors may be contributory. Among patients with HD, nodular sclerosis was the most common histological type (75%) in contrast to reports from other parts of the Kingdom,^{5,6} and indeed from this region,¹⁸ 2 decades ago where mixed cellularity was the predominant pattern. This is also different from the pattern in other developing countries.¹⁹⁻²¹ Although inter-observer variation in classification may account for a small difference, we feel this magnitude represents a recent shift towards the pattern in the developed world.^{22,23} The age and gender distribution is in conformity with the recognized pattern in the west such as bimodal at 20-30 years and 40-50 years with a preponderance of males. One other notable difference between the results in this study and others from the Kingdom^{5,6} and elsewhere,^{2,24} is the low prevalence of NSRH (14%). This can partly be explained by the fact that our population excluded children where NSRH is a more common cause of LA and the decision to biopsy is more difficult.^{25,26} However, 69.5% of the patients in our series with NSRH were under 30 years of age.

This study also shows metastatic disease to be more likely in the older age group and to present with generalized LA in 64.7%. This is in agreement with other studies^{2,20} but further analysis shows a higher incidence (3.5%) of nasopharyngeal carcinoma occurring in the young and presenting as localized cervical LA. This underlines the importance of undertaking a thorough ear, nose and throat examination in patients presenting with isolated LA since biopsy in the setting of a carcinoma is believed to lead to spread of the disease and sinus tract formation.

Kikuchi's disease follows the recognized pattern namely, the disease is common in young females and affects the cervical group of lymph nodes. There

however seems to be an increase in the prevalence of the disease compared to a study of the same population a decade earlier when it accounted for 1.2% of all lymph node biopsies.²⁷ Sarcoidosis, believed to be rare among Saudis, occurred in only 2 of 145 Saudis (1.4%) in this study. This suggests that it may not necessarily be that rare, as some studies have also reported similar or higher figures.^{28,29} The high rate of positive Mantoux test (16.7%) in a condition believed to cause tuberculin anergy and in an endemic area for tuberculosis means that tuberculosis has to be excluded before a confident diagnosis of sarcoidosis can be made.

Although KSA is a low human immuno-deficiency virus (HIV)-seroprevalence area, the infrequent testing for HIV demonstrated in this study means that some cases might have been missed.

Finally, although a confident differentiation cannot be made between malignant and benign causes of LA, the presence of localized LA in a young female with a strongly positive Mantoux test strongly suggests the diagnosis of tuberculosis. The presence of generalized LA in a male with other physical signs on the other hand suggests a malignant process. NSRH is less common in adolescents and adults of this region than in other parts of the world.

In conclusion, LA differs in this region of KSA in being less likely to be due to non-specific reactive hyperplasia, more likely to be due to tuberculosis in females and more likely to be to be nodular sclerosis in type if due to Hodgkin's disease. Although a low sero-prevalence area for HIV, the infrequent testing in conditions that are associated with HIV infection means that some cases of HIV infection might have been missed.

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