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Original Research Article

A study on incidence and etiology of cervical lymphadenopathy in community

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ABSTRACT

Background: The etiologies for cervical lymphadenopathy fall under a wide range spectrum and usually, history and physical examination alone may lead to a diagnosis. Posterior cervical LAP may occur with Epstein-Barr virus (EBV) infection, tuberculosis, lymphoma, or head and neck malignancy (either lymphomas or metastatic squamous cell carcinoma). However, a stepwise methodological approach to LAP can lead to an accurate diagnosis with minimal discomfort to the patient and also less time-consuming for the clinician.
Methods: In this series, 320 cases were studied with taking a detailed clinical history, physical examination, and investigations. After a physical examination and reaching a clinical diagnosis, confirmation was done by fine needle aspiration cytology (FNAC) and biopsy.
Results: Incidence of tuberculous LAP is much higher in lower socioeconomic class groups people versus middle or higher socioeconomic class groups. Incidence of tuberculous LAP is higher in urban areas compared to rural areas due to overcrowding, and poor sanitation.
Conclusions: Tuberculosis is a potentially serious infectious disease, one of the commonest diseases affecting lymph nodes. It is curable with anti-tubercular drugs if administered as per the accepted regimen.

Keywords: Tuberculosis, Lymph node, Pulmonary, Lymphoma, HIV, Biopsy, FNAC

INTRODUCTION

The human body has approximately 500–600 lymph nodes distributed throughout the body, with clusters found in the underarms, groin, neck, chest, and abdomen. Lymph nodes play the role of filtering the lymph fluid as it circulates throughout the body. Lymph node enlargement of the neck may be an incidental finding during a routine checkup or maybe a patient's complaint. Rather than being a disease by itself; it may be a sign of one of many possible underlying diseases. It may be localized, limited, or generalized in location and/ or acute, subacute, or chronic in duration. The etiologies for cervical lymphadenopathy (LAP) fall under a wide range spectrum and usually, history and physical examination alone may lead to a diagnosis. Posterior cervical LAP may occur with Epstein-Barr virus (EBV) infection, tuberculosis, lymphoma, or head and neck malignancy (either lymphomas or metastatic squamous cell carcinoma). However, a stepwise methodological approach to LAP can lead to an accurate diagnosis with minimal discomfort to the patient and also less time-consuming for the clinician.

The prime function of the lymph node is to deal with any kind of antigen, whether this is in the form of microorganisms or other particulate material, or even

soluble antigen. The lymph nodes contain T and B cells along with antigen presenting cells (APCs) which are called the dendritic cells. They form the part of the immune system and function to fight off the disease and infections. LAP refers to the lymph nodes that are abnormal in size (>1 cm) consistency or number. In general, there are two well-established mechanisms of LAP: hyperplasia that occurs in response to immunologic or infectious stimuli; and infiltration which is the result of infiltration by various cell types, including malignant cells, lipid cells, or glycoprotein-laden macrophages.

When this occurs, lymph nodes may be palpable on clinical examination. Thus, LAP is the term used to describe the clinical sign of swelling of the lymph nodes. The pathologic term for inflammation of the lymph nodes is lymphadenitis. The neck contains nearly 2/3rd of the total lymph nodes of the body as the lymph nodes are strategically placed along the drainage of tissue and body fluids. Cervical LAP is usually significant as it is associated with various etiology and there is a high index suspicion of the spread of infection and malignancy. When cervical LAP is detected, a cause can sometimes be determined by careful medical history, thorough physical examination, judicious selection of laboratory tests, and, if necessary, a lymph node biopsy. Various diagnostic modalities like fine needle aspiration cytology (FNAC), ultrasonography (USG), computerized tomography (CT), and positron emission tomography (PET) CT neck are now available to diagnose underlying diseases in case of cervical lymphadenitis. These investigating tools have high sensitivity and specificity for cervical LAP. The standard modality in the workup of a neck mass is fine-needle aspiration cytology (FNAC). FNA can be used for both cytology and culture (in cases in which a suspected infectious neck mass does not respond to routine conventional antibiotic therapy). If FNAC is unsuccessful or if sufficient information is not obtained from an initial FNA, the FNA should be repeated before the open biopsy. The etiology and clinical presentation of cervical LAP are certainly different in different groups of populations. Understanding prevalent conditions and presentations of LAP in the population will make it possible to establish a sound clinical protocol in the evaluation and diagnosis of this condition preventing delay in treatment.

In tropical areas, tuberculosis (TB) is the most common benign cause of posterior triangle LAP in adults and children. Tuberculous lymphadenitis is among the most frequent presentations of extra-pulmonary tuberculosis (TB). Tuberculous lymphadenitis in the cervical region is known as scrofula.[1] This syndrome can also be caused by nontuberculous mycobacteria.

TB is responsible for up to 43 percent of peripheral LAP in resource-limited settings.[2] In rural India, the prevalence of tuberculous lymphadenitis in children up to 14 years of age is approximately 4.4 cases per 1000.[3] In the United States, about 20 percent of patients with TB have the extra-pulmonary disease, and lymphadenitis is a presenting symptom in about 30 to 40 percent of cases.[4-6] In a Danish report including more than 480 patients with TB between 2007 and 2016, lymphadenitis was observed in 13.5 percent of cases.[7] The human immunodeficiency virus (HIV) epidemic has been associated with an increase in the total incidence of TB and an increased proportion of miliary, disseminated, and extra-pulmonary TB cases (up to 50%) including lymphadenitis.[8]

In resource-rich countries, most cases of tuberculous lymphadenitis occur among adult immigrants from tuberculosis (TB)-endemic countries.[9,10,11] This was illustrated by case series of tuberculous lymphadenitis in France and Germany in which about 70 percent of cases occurred in immigrants; in the German study, two-thirds of patients had immigrated >3 years prior to diagnosis.[9,10] In a subsequent review of more than 480 cases reported from Denmark (a low TB incidence country with 4.8 cases per 100,000 population in 2017) between 2007 and 2016, more than 90 percent of patients with tuberculosis lymphadenitis were immigrants.[7] Furthermore, the molecular analysis demonstrated a high proportion of unique genotypes, suggesting reactivation disease.[7]

In the United States, the rate of tuberculous lymphadenitis is higher among individuals of Asian Pacific Island descent and in females.[2,5,12] Rarely, tuberculous lymphadenitis can also occur in travelers to endemic areas.[13,14] Tuberculous lymphadenitis occurs more frequently in women than in men.[1]

Previously, tuberculous lymphadenitis was considered a disease of childhood.[3] However, the peak age of onset in developed countries has shifted from childhood to ages 20 to 40 years.[13] In contemporary series, the median age has been approximately 40 years in developed countries (range 1 to 88 years).[9,11,16,21] In resource-limited countries where TB is endemic, extra-pulmonary TB occurs in up to 60 percent of HIV-infected patients with TB and is frequently accompanied by signs of pulmonary involvement.[17-19] Most extra-pulmonary TB cases (including tuberculous lymphadenitis) occur among patients with HIV at CD4 counts <300 cells/µl (usually below 100 cells/µl).[8,20] A Danish study described not only HIV infection but also other factors such as alcohol abuse, homelessness, diabetes, and renal insufficiency as risk factors for tuberculous lymphadenitis.[7]

METHODS

This prospective observational study includes 320 patients who attended the outpatient department (OPD) in District Tuberculosis Hospital, Mehsana and a few private hospitals in Mehsana from December 2014 to March 2020 after proper consult regarding ethical approval.

In this series, 320 cases were studied with taking a detailed clinical history, physical examination, and investigations to determine: to study the etiology and various clinical

presentations of posterior triangle cervical LAP, and to correlate pathological findings with the clinical diagnosis.

After a physical examination and reaching a clinical diagnosis, confirmation was done by FNAC and Biopsy. Lymph node biopsy was the most important of these.

Inclusion criteria

Patients with inflammatory LAP and infective LAP; patients with the above two etiologies who gave consent for LN biopsy were included in the study.

Exclusion criteria

Patients with LAP due to other etiologies, secondary neck masses, and lymphomas were excluded from the study.

Name, age, sex, religion, address, and occupation of the patients were noted. Cases were taken at random.

Criteria for socioeconomic status are decided by the income of the patients. They were divided into 3 income groups according to their monthly income: up to Rs. 30 for low-income group; Rs. 3000-6000/month middle income group; and >Rs. 6000/month higher income group

Nutritional value of the patients was well-nourished or malnourished.

Whether he/she belongs to a rural or urban area and living condition is overcrowded or not.

A complete clinical examination was carried out. In the local examination, importance was given to the site, size, laterality, number, secondary changes, and level of the cervical lymph. The systemic examination was n also carried out. An attempt was made to find out the primary tumor in cases of lymph nodes suspicious as secondaries in the neck. Those patients with cytological findings of tuberculosis underwent a battery of investigations which included a chest X-ray and three samples of sputum for acid-fast bacillus (AFB) to exclude pulmonary tuberculosis. Monteux's test and erythrocyte sedimentation rate (ESR) were carried out in all the patients with positive FNAC findings. Those with FNAC findings suggestive of reactive lymphadenitis were treated with ten days of antibiotic therapy and were followed after two weeks to see the size of the node. After making a clinical diagnosis, further investigations were carried out to confirm the diagnosis. Routine investigations included hematological and radiological. FNAC was put in the front line for diagnosis and to get a cytological diagnosis at hand. Lymph node biopsy was carried out meticulously; it was studied grossly and sent to the pathologist for expert opinion. Further tests were carried out on the basis of histopathological diagnosis (e.g. secondaries in the neck), contrast radiological investigations, and endoscopy carried out in relevant cases. Those patients with cytological or histopathological confirmed tubercular lymphadenitis were referred to the directly observed therapy (DOTS) clinic for anti-tubercular therapy (ATT) with four drugs regimen for the initial two months and then two drugs continuation for four months. The information was complied with, analyzed, and tabulated to get statically and comprehensive results. After a clinical diagnosis was made, investigations were done to confirm the diagnosis. Blood examination ESR, total white cell count, differential count, hemoglobin percentage, and Monteux test was done by standard method and erythema of more than 12 mm after 48 hours is taken as positive. The presence of Langerhans type of giant cells was taken as the criteria for diagnosing tuberculosis of lymph nodes. All the specimens were processed by a standard procedure like fixing in formalin, slicing by microtome, and staining by gram's and Zeihl-Neelson (ZN) stain. All the slides were examined under 10X, 60X, and 100X power using a standard microscope. Aspiration material from cold abscess was stained by gram stain and special stain. Biopsy procedure lymph node biopsy was infiltrating 1% lignocaine. If multiple lymph nodes are their large lymph node was biopsied. If anterior and posterior groups were involved, the posterior group was preferred. The lymph node is taken along with the capsule. Care was taken in the supraclavicular area regarding homeostasis.

All patients were given anti-tuberculous drugs using the DOTS strategy with 2 months of intensive therapy and 4 months of continuation phase therapy with drugs isoniazid, rifampicin, ethambutol, and pyrazinamide.

RESULTS

The workup of palpable lymph nodes is a common clinical task for general practitioners. Most of the causes of cervical lymph adenopathy (CLA) are benign and may resolve spontaneously. It can be, on the other hand, a sign of malignancy or systemic disease, thus understanding the differential diagnosis is of paramount importance.

Table 1: Causes of lymphadenopathy.

Number of the patients	Tuberculous LN enlargement (%)	Non-tuberculous LN enlargement (%)	Fungal infection (%)
320	256 (80)	58 (18.12)	6 (1.88)

In this study, the total number of cases studied were 320. From the Table 1 it can be seen that tuberculous LAP is the commonest cause of cervical LAP with 80% followed by chronic non-specific LAP with 18.12%.

In this study of 320 cases, the disease commonly affected the 2nd and 3rd decades with 37.5% and 31.3% respectively. The next common age group in which cervical lymph adenopathy presented is the 4th decade with 21.9% of cases. In our country, tuberculous LAP commonly affects the younger age group. The commonest

age group affected is between 11-20 and 21-30 closely followed by 31-40 years.

Non-specific LAP commonly affects the age group of 11-20, 21- 30, and less commonly 1-10. But in western countries the pattern is different. The common age group affected is 0 to 10 years. The causative agent in this age group is atypical mycobacterium. In adults, the causative agent is most commonly the *Mycobacterium tuberculosis*. Only 5% are due to atypical mycobacterium. It cannot be assumed that all cervical LAP in children is caused by atypical mycobacteria. About 5-10% of childhood LAP is due to *Mycobacterium tuberculosis*. History of contact with tuberculosis. In the present study, there was no definite history of contact with tuberculosis in 82% of cases. A definite history was obtained in only 18% of cases (Table 3).

Table 2: Incidence according to the age.

Age	Number of patients	Percentage
0-10	8	2.5
11-20	120	37.5
21-30	100	31.3
31-40	70	21.9
41-50	10	3.1
51-60	7	2.2
>60	5	1.5

In this study of 320 cases, the disease commonly affected the 2nd and 3rd decades with 37.5% and 31.3% respectively. The next common age group in which cervical lymph adenopathy presented is the 4th decade with 21.9% of cases. In our country, tuberculous LAP commonly affects the younger age group. The commonest age group affected is between 11-20 and 21-30 closely followed by 31-40 years. Non-specific LAP commonly affects the age group of 11-20, 21- 30, and less commonly 1-10. But in western countries the pattern is different. The common age group affected is 0 to 10 years. The causative agent in this age group is atypical mycobacterium. In adults, the causative agent is most commonly the *Mycobacterium tuberculosis*. Only 5% are due to atypical mycobacterium. It cannot be assumed that all cervical LAP in children is caused by atypical mycobacteria. About 5-10% of childhood LAP is due to *Mycobacterium tuberculosis*. History of contact with tuberculosis. In the present study, there was no definite history of contact with tuberculosis in 82% of cases. A definite history was obtained in only 18% of cases (Table 3).

In the present study, there is comparatively an increased incidence of tuberculous cervical LAP in females than in males. In the present study, though very small, the sex incidence was as follows - males 40% and females 60% (Table 4).

The increased incidence in females may be because of the wide prevalence of malnourishment in females. The other factors influencing the higher incidence in females are overcrowding, lack of education, early marriage, pregnancy, large families, and poor socioeconomic conditions.

Table 3: History of contact with TB groups.

Type of the patients	Number of the patients	Percentage
Patients with definite history of contact with Tb groups	262	82
Patients without definite history of contact with TB groups	58	18

Table 4: Incidence of lymphadenopathy according to sex.

Sex	Number	Percentage
Male	128	40
Female	192	60

Incidence of tuberculous LAP is much higher in lower socio-economic class group people (75%) versus middle socioeconomic class group (22%). The higher socioeconomic class group has the lowest incidence of tuberculous LAP (3%) (Table 5).

The higher incidence in the lower socioeconomic class is due to overcrowding, poor sanitation, education, and large families.

Table 5: Incidence of tuberculous lymphadenopathy among different income groups.

Income group	Number of patients	Percentage
Low (<3000/month)	240	75
Middle (3000-6000/month)	70	22
High (>6000/month)	10	3

Incidence of tuberculous LAP is higher in urban areas compared to rural areas due to overcrowding, and poor sanitation (Table 6).

Table 6: Incidence of tuberculosis lymphadenopathy among different geographical groups.

Type of lymphadenopathy	Number of patients	Percentage
Tuberculous	256	80
Urban	192	75
Rural	64	25
Non-tuberculous + fungal infection	64	20
Urban	51	80
Rural	13	20

DISCUSSION

Neck swellings are often seen in routine clinical practice, and the clinician should be able to determine the etiology of a mass using organized, efficient diagnostic methods. The first goal is to determine if the swelling is benign or malignant; malignant swellings are more common in adult smokers older than 40 years. Etiologies can be grouped according to whether the onset/duration is acute (e.g. infectious), subacute (e.g. squamous cell carcinoma), or chronic (e.g., thyroid), and further narrowed by patient demographics.

If the history and physical examination do not lead to an obvious cause, imaging and surgical tools are helpful. Contrast-enhanced computed tomography (CECT) is the initial diagnostic test of choice in adults. CT angiography is recommended over MR angiography for the evaluation of pulsatile neck masses. If imaging rules out the involvement of any underlying vital structures, a fine-needle aspiration biopsy can be performed, providing diagnostic information via cytology, Gram stain, and bacterial and acid-fast bacilli cultures. The sensitivity and specificity of fine-needle aspiration biopsy in detecting a malignant lesion range from 77% to 97% and 93% to 100%, respectively.[22] A history of environmental exposure to tobacco, alcohol, and ultraviolet radiation increases the suspicion of metastatic carcinoma of the internal organs, head, and neck as well as skin malignancies. Immune deficient patients, like those with AIDS, have wide differential causes of LAP and malignancies like Kaposi's sarcoma; however, non-Hodgkin's lymphoma should always be taken into consideration.[17,18] A family history of malignant disorders may raise the physician's suspicion of distinct etiologies of LAP such as breast carcinomas, melanoma, and dysplastic nevus syndrome. Also, if LAP lasts less than two weeks or over one year without increasing in size, the probability of malignancy is quite low.

Infectious mononucleosis (IM) affects patients of all ages; however, it is more frequent before adolescence.[23] Approximately 90% of adults all over the world are seropositive for this viral disease, although only 25-30% of them have become clinically ill.[23] In general practice, less than one percent of patients with LAP have the malignant disease, often due to leukemia in younger children and Hodgkin's disease in adolescents. It has been reported that the prevalence of malignancy is 0.4% in patients under 40 years and 4% in those over 40 years of age in the primary care setting.[24] The prevalence rises to 17% in referral centers and soars to 40-60% in highly suspicious patients.[24] Be that as it may, the location of LAP changes the possibility of malignancy. Hodgkin's disease is rare before 10 years old and a small male dominance is present, especially in childhood.[25] The EBV infection in combination with an immune deficiency is a risk factor for increasing Hodgkin's disease, particularly in less-developed countries and with low socioeconomic conditions.[25] Non-Hodgkin's lymphoma, the fourth most common worldwide malignancy in males with a frequency of 6.7% is another cause.[26]

This study includes an observation of patients from a single community to determine the incidence and etiology of the area where patients were not randomized to different groups. Because social phenomena cannot be controlled or used for laboratory experiments, generalizations made by this study are not very reliable.

CONCLUSION

Tuberculosis is a potentially serious infectious disease, one of the commonest diseases affecting lymph nodes. It is curable with anti-tubercular drugs if administered as per the accepted regimen. Clinical symptoms in cervical LAP have limited significance and clinical behavior can be highly variable. Dependence on clinical evidence alone would lead to erroneous diagnoses in a considerable number of cases. FNAC can be deemed as a frontline investigation with further investigations on the basis of FNAC results. However, histopathological examination remains the most dependable diagnostic tool. Most of the diseases are medically curable with a limited role for surgery in non-neoplastic lesions. It is important to have a high index suspicion in the head and neck region and an otolaryngologist must aware of the possible pathologies in cervical LAP. Then only an early diagnosis can be possible with a simple investigation and thus a better outcome of cervical LAP.

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