

Recent Advances in Imaging and Pathological Techniques for Diagnosing Tubercular Lymphadenitis (EPTB) In Children and Adolescents Up To 14 Years

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Abstract

Background: Lymphadenitis is the most common manifestation of extra pulmonary tuberculosis (EPTB), there is still a diagnostic challenge due to its similarity with other pathological conditions. Recent imaging techniques are very helpful in approaching the diagnosis of nodal tuberculosis. Further confirmation of diagnosis is done by staining for acid fast bacilli, fine needle aspiration cytology, and excisional biopsy & by histo-pathological analysis. High Resolution sonography contributes in diagnosis of various types of lymph nodes, and endobronchial ultrasound mainly useful for mediastinal and hilar lymph nodes. Recent advances like C.T. scan, MRI and PET-CT demonstrates site, pattern, and extent of disease. These imaging modalities can better differentiate between benign from malignant causes. The Ultrasound /C.T guided FNAC/ Biopsy further plays an important role in confirmation of diagnosis with staining /culture /histo-pathological analysis. It is also important to differentiate tuberculosis from non- tubercular mycobacterial lymphadenitis. HIV co-infection also plays important role in further increase the cases of lymphadenitis.

Keywords: extra pulmonary tuberculosis (EPTB), Cervical lymph nodal tuberculosis, fine needle aspiration cytology, biopsy, ultrasound.

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Received: October 2019

Accepted: November 2019

Introduction

The history of tuberculosis is almost as old as mankind. Hippocrates (460-377 BC) mentioned scrofulous tumors in his writing. The classic term scrofula derived from the latin word glandular swelling^[6]

In 1882, Robert Koch identified mycobacterium tuberculosis as etiological agent for tuberculosis^[2]

The disease was known as the king's evil in the middle ages because of widespread belief that it could be cured when the affected person was touched by royalty.^[4]

In England, Charles II was reported to have treated 10000 cases a year with his royal touch.

Initially considered to be involving pulmonary diseases, the tuberculosis can involve almost any organ^[3]

It is a very frequent cause of peripheral lymphadenitis in the developing world, more common in industrial area , among I/V drug users & immuno- compromised population especially due to HIV as co-infection^[9]

Cervical Lymph nodes are most commonly affected nodes in TB lymphadenitis 63 % cases, mediastinal and hilar 27 % , mesenteric nodes 10% and Axillary nodes 05 %.^[7]

More frequent Cervical group is in posterior triangle 51 % & deep upper cervical 48 % usually unilateral involving neck region.^[4] Mycobacterium avium intracellular for 10 % cases which in unlike tuberculosis, but least reported in

india^[10,12]

Our article provides a recent advances, of epidemiology, clinical presentation, pathogenesis, imaging techniques and current updates in pathological investigations for almost confirmatory diagnosis of lymph nodal tuberculosis.

The term extra pulmonary Tuberculosis (EPTB) has been used to describe the occurrence of tuberculosis at body sites than the lung.^[7]

Through TB is worldwide in distribution, but more prevalent in Asia & Africa.^[3]

India, china, Indonesia, South Africa & Nigeria ranked first to fifth in terms of number of cases.^[3]

India has the highest burden accounting almost one fifth of the global incidence.^[1]

A significant proportion of global tuberculosis cases are contributed by children throughout the world.^[4]

The extra pulmonary TB (EPTB) lymphadenitis is seen involving approximately 35 % cases. There is role of HIV as main contributing co-factor 6 % to 9 % of cases with or without involvement of other lymphoid tissue^[4, 5, & 6]

Subjects and Methods

In the developed countries, though decrease in incidence of pulmonary tuberculosis cases, but nodal tuberculosis still remains an important health issue.^[7, 8]

In a German study, the majority of the cases reported were immigrant of afghan, Pakistan & India origin and cervical lymph nodes were involved in 63.3 % of cases.

The causes of mycobacterial lymphadenitis include mycobacterial tuberculosis, *M. bovis* & *Africanum*. Currently, in developing like India and under developed countries, *M. tuberculosis* is most common cases of mycobacterial lymphadenitis.

Non tuberculous mycobacterial (NTM) may be mainly caused by mycobacterial avium intracellulare complex but frequently affects patients in their second decade and is more seen in developed countries.^[16]

Other NTM known to cause lymphadenitis are *M. scrofulaceum*, *M. kansasii*.

There is a female predominance in most of studies.

Cervical tuberculosis lymphadenitis is the commonest site of allages, followed by mesentery, mediastinal, hilar, axillary and inguinal region.

Demographic Profile

The demographic profile of patient with tubercular lymphadenitis shows that mean age was 8.2 years with over all affected girls (61.8%) more than boys (38.2%). In age groups of 0-5 years, the sex ratio is reversed & involved 17.8 % while 6-10 & 11-14 years age groups constitutes 34.4 and 47.6% respectively.

Out of total number of cases of EPTB during our study in a tertiary health care center, lymph nodes tuberculosis was commonest type & contributes about 81.4 % cases.

Cervical lymphadenitis was the most common type of lymph node involvement & affected in cases (80.4 %) followed by mesentery 21 cases (6.1%) & rest other sites involvement in 13.9 % only which involve inguinal, axillary, mediastinal & retroperitoneal etc respectively^[25]

Kent et al alleged that cervical tubercular lymphadenitis is the result of lympho-hematogenous spread of pulmonary tuberculosis. According to Powell, this entity is a hyper reaction of lymph nodes against previous pulmonary tuberculosis. There was unilateral involvement of lymph nodes seen, though in some cases Bilateral. Involvement also noted and the locations were Jugulo-carotial^[29], Supraclavicular, submandibular, axillary, mediastinal, and inguinal groups. Majority of patients showed several signs as asthenia, night sweats, mild fever & loss of appetite & weight.

None of the patient was detected as HIV positive/ Diabetic. The provisional diagnosis was obtained by clinico-radiological method while confirmation of diagnosis by FNAC / biopsy of lymph nodes & histopathological analysis in all patients. Sinus & fistula formation is seen in almost 10 % of the mycobacterial cervical lymphadenitis and accompanying pulmonary tuberculosis is reported in 18 % to 42 % of patients.

Pathogenesis

Tuberculous lymphadenitis is considered mainly a local manifestation of a systemic disease^[3] The organism enters the human body via the respiratory tract and spread through lympho- hematogenous spread. The bacilli lodge in terminal alveoli of lungs & multiply there and forming a Ghon's

focus. The lymphatics drain the bacilli engulfed by macrophages to the hilar & mediastinal lymph nodes & thus known as primary complex.^[8]

The peripheral lymphadenitis may be involved at the time of initial infection, as seen in young children & immune-compromised patient or may reflect a reactivation of a prior primary infection.^[2]

Iguchi H et al^[11] suggested the predominant pathway of spread of bacilli to cervical lymph nodes is from the lung parenchyma via supraclavicular lymph nodes & than upwards to the right lower cervical chain.

The chest radiographs reveals that 42 % (appx) of patients with tubercular lymphadenitis had evidence of pulmonary tuberculosis & 22.5 % of these had radiographically active disease. The alternate routes of spread to lymph nodes are also proposed such as Tonsils and adenoids. Other causes like caries teeth, middle ear & mastoid also affect the regional lymph nodes.^[13]

NTM is primary a disease of children & appears to be truly a localized disease. The bacteria enter the lymph nodes directly via oro- pharyngeal mucosa, salivary, tonsils, gingiva or conjunctiva. Surgery has an important role in treatment of NTM.^[13] Initially the nodes are discrete, periadenitis resulted in matting and fixation of the lymph nodes, later formation of caseous pus. This may perforate and indurated the overlying skin, may result in sinus formation.

Once the lesion is healed, resulted in calcification & scarring (Fibrosis).

Stages of Tubercular Lymphadenitis

Jones and Campbell in 1962 described the Stages of tubercular lymphadenitis as follows:-

1. Enlarged, firm mobile discrete lymph nodes.
2. Large rubbery nodes fixed to surrounding tissue.
3. Central softening abscess
4. Collar stud abscess formation
5. Sinus tract formation.

Clinical Features

The clinical manifestation of TB lymphadenitis mainly depends upon the anatomical location of the affected node and immune status of individual^[7]

The cervical lymph nodes are most frequently involved, followed by mediastinal, hilar, mesenteric, axillary, hepatic portal and inguinal lymph nodes.

The most common presentation is slowly enlarging painless lymph node/nodes in an asymptomatic patient. Some patients may show symptoms such as fever, night sweats, weight loss, and fatigue. These symptoms are more aggravated in HIV positive patients.

Females are more commonly involved than males. Cervical nodes in the submandibular and anterior upper cervical region are most commonly involved.

There is a history of tuberculosis contact in 21.8 % and tuberculosis infection in 16.1% of the cases. Cough is not a prominent feature of tuberculous lymphadenitis^[2]

Multiplicity, matting & caseation are three important findings of tuberculous lymphadenitis. Upto 57% of patients do not have systemic symptoms.^[3] Fistula

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formation was seen in nearly 10 % of the mycobacterial cervical lymphadenitis.^[6]

Tubercular mediastinal, hilar & right paratracheal lymphadenitis is also more common site in children, though peritoneal lymphadenopathy involve periportal, peripancreatic & mesenteric group in some cases^[9,23]

Patients with mediastinal & hilar node involvement are likely to have active pulmonary tuberculosis. M tuberculosis commonly involve jugulo –digastric, posterior triangle or supraclavicular lymph nodes^[24]

Non tubercular mycobacterium (NTM) usually seen in children between 1 to 5 years of age^[13]

NTM lymphadenitis commonly involves upper cervical lymph nodes, salivary glands and adjacent lymph nodes.

There a rapid enlargement of lymph nodes & may be associated with fistula formation.

Systemic symptoms are not a .prominent feature. Uncommon manifestations seen in some patients with mediastinal& abdominal lymph adenitis are dysphagia, trachea- esophageal fistula, jaundice chylothorax and cardiac tamponade.^[26]

Results

Table 1:

Clinico-Radiological features		
Patients (N=64)	Numbers	Percentage
Mean Age	8.2 years	
Sex		
Male	29	44.5%
Female	35	51.2%
Risk Factors		
HIV	None	
Diabetes	None	
Lymphnodal Localisations		
Jugulo-carotidian(upper)	35	54.9%
Supra-clavicular	3	4.9%
Sub-mandibular	5	8.5%
Submental	3	3.7%
Jugulo-carotidian (Mid/Lower)	5	7.3%
Mediastinal	5	7.3%
Axilla	1	2.4%
Mesenteric	4	6.1%
Inguinal	3	3.6%
Associated Findings		
Co-existing Lung infection	13	21%
Pleural effusion	2	2.4%

Diagnostic Methods

A thorough clinical history & physical examination is essential.

A. Radiological examination

- X Ray Neck, Chest and Abdomen
- USG/ guided FNAC
- CT Scan/Guided Biopsy
- MRI
- PET-CT scan
- Bronchoscopy
- Mediastinoscopy

Radiological

1. X-ray neck ,chest & abdomen

Normal x-ray chest –could not excluded the CTL diagnosis. Ghon’s focus, hilar, right paratracheal lymph nodes and pleural effusion can be detected

2. Ultrasound

Nodal size, shape (L/T Ratio) echogenicity, morphology of nodal hilum or cortex.

Excellent first line investigation & also play important role in USG guided Fine needle aspiration cytology^[17,20]

The combined grey scale imaging & FNAC has a sensitivity of 92 % & specificity 97 % in distinguishing benign from malignant disease .However ultrasound findings do not show Disease specific features of CTL. USG features are as a focal hypoechoic mass homogeneous initially, later demonstrate central necrosis.

Nodal matting Surrounding soft tissue edema

Reactive nodes including TB lymphadenitis demonstrate prominent vascularity confined to hilum, whereas malignant nodes demonstrate more peripheral capsular vascularity.

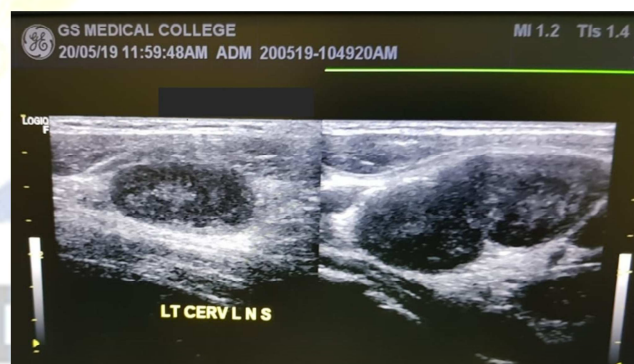


Figure 1: Cervical lymph node Solid and Matted

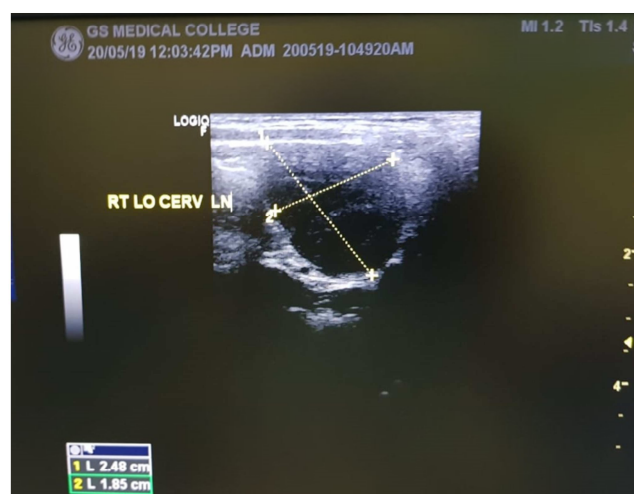


Figure 2: Cervical lymph node (Necrotic)

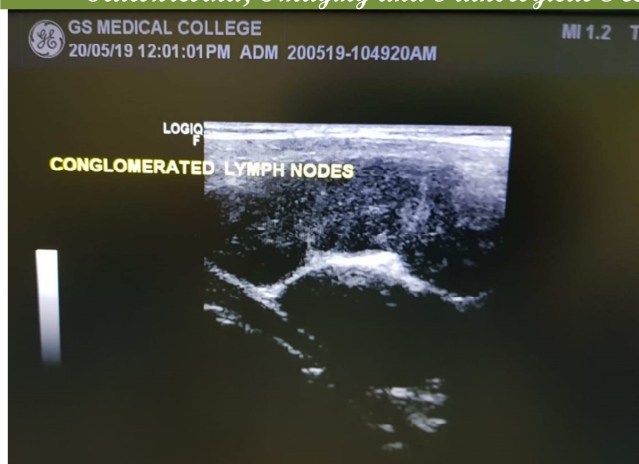


Figure 3: Conglomerated Lymph node

C.T. Scan

C T Scan demonstrates site, pattern and extent of disease .Three patterns are seen as early - Homogenous enhancement, mid –lymph node with central area of necrosis and late as Fibrocalcified lymph node.

Appearance variable depending upon degree of caseation present in the lymph node .initially lymph node appears enlarged with attenuation similar to muscle ,later central caseation develops & nodes become centrally low density & eventually frankly cystic.

They are usually matted together with only minor surrounding inflammatory changes.

CECT demonstrate mass of low attenuation with peripheral enhancement known as caseating granuloma .Nodal calcification develops in late TB stages.

MRI

Appearance similar to those of CT, ranging from homogeneous enlarged nodes to cystic transformation.^[21, 22, 23& 24] MR demonstrate central hypointensity& hyper intensity on T1 W & T2 W images with peripheral rim enhancement.

The diagnosis of tubercular lymphadenitis is established by histo-pathological examination along with acid fast bacilli (AFB) smear and AFB culture of lymph node material.

A. Pathological

- Tuberculin Test (PPD)
- Staining for acid fast bacilli (Ziehl –neelsen)
- Fine needle aspiration cytology especially in children presenting with a suspicious neck swelling (17).Aspirated material is allocated for cytological examination, acid fast bacilli (AFB) staining, mycobacterium culture & or molecular testing.
- Lymph node biopsy – excisional preformed CT guided, Endbronchial ultrasound EBUS, mediastinoscopy guided biopsy (23).Gahlot et al concluded that EBUS-TBNA is highly accurate diagnostic yield 92 % and safe procedure for diagnosing mediastinal lymphadenopathy & granulomatous lymphadenitis common with TB.^[13]

- Culture presence of 10-100 bacilli per cubic mm of specimen is enough for positive culture report.
 - Molecular test – TB Genexpert ,PCR is a fast and useful.^[18]
 - Sputum smear & culture – positive sputum culture are uncommon (0-14 %) in setting of tuberculosis lymphadenitis
 - Blood culture –are rarely positive for M tuberculosis
- Histopathology – diagnostic of M.TB cervical lymphadenitis, Langherhans giant cells, caseating necrosis, granulomatous inflammation & calcification can be seen.

Differential Diagnosis

- Infections due to other Mycobacteria , bacterial , viral , fungal
- Non- specific reactive hyperplasia
- Toxoplasmosis, sarcoidosis
- cat –scratch disease
- cystic hygroma
- Kikuchi disease – idiopathic histolytic necrotizing lymphadenitis
- Malignancy
- Primary – Hodgkin lymphoma, non- Hodgkin lymphoma
- Secondary – metastatic nodal (cervical)
- Necrotic metastases – nasopharyngeal
- carcinoma
- Infectious mononucleosis

Discussion

The lymph nodal tuberculosis has increased over last two decades and represents 30 % of extra pulmonary tuberculosis with predominance of cervical group approx. 62%

The present study also confirms the high prevalence of EPTB in children in the 51.2% contribution by females & 44.5% by boys.

The proportion of tuberculosis in children caused by EPTB in our study was 36 % which is much higher than in adult population.

Marais et al also observed disease to be common in females 50.5 % than boys 49.5 %.

The high proportion of TB in female children is probably due to better social status of boys in indian society.

Scrofula comes from the latin word for brood sow^[14,15] kings evil (in Middle Ages), it was believed that royal touch of king of England or France could cure the disease.^[24]

In India, HIVsero-positive prevalence in tuberculosis patient varies from as low as 2 % in Delhi, 3. 2% in Aligarh & as high as 5.89% in Mumbai & 18.6 % in Pune.^[7]

The overall accuracy in detection of lymph nodal tuberculosis by FNAC & excisional biopsy is approx... 85.25 %^[29, 31]

Our major strength of getting success in detection &

treatment through DOTS centers under RNTCP programme. Which emphasize the need to access the accurate diagnosis, prompt effective free treatment through health centers & adherence in poor endemic areas carrying majority of load of the disease.^[30]

Conclusion

TB is a major health problem in developing countries like India, where tuberculosis is a systemic disease & lymphadenitis is the most – common extra pulmonary manifestation of the disease in children/adolescents as chronic painless mass in neck, their diagnosis is required a high index of suspicion, detailed history, clinical evaluation and utilization the variety of different imaging modalities like chest-x-ray, ultrasound, CT scan, MRI, and PET – CT scan (24) to approach the diagnosis & further confirmation is done by FNAC / Excisional biopsy & Histo-pathological correlation. Tuberculous adenitis is best treated with anti-tubercular therapy extended from 6 to 9 months or more, sometimes surgical treatment is also required in selected complicated cases (27, 30).

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How to cite this article: Kulshrestha V. Recent Advances in Imaging and Pathological Techniques for Diagnosing Tubercular Lymphadenitis (EPTB) In Children and Adolescents Up To 14 Years. Asian J. Med. Radiol. Res. 2019;7(2):113-17.
DOI: dx.doi.org/10.21276/ajmrr.2019.7.2.24

Source of Support: Nil, **Conflict of Interest:** None declared.