LYMPH NODE TUBERCULOSIS- CURRENT SCENARIO

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ABSTRACT

BACKGROUND

Tuberculosis is one of the leading causes of mortality in India killing 2 persons every three minutes. The problem of drug resistance is now a major hindrance in our war against this disease. Much of the reported data worldwide is on pulmonary tuberculosis, hence this study to analyse the clinical and bacteriological characteristics in lymph node tuberculosis.
Aims and Objectives - 1) To study the clinical data and histopathological correlates in clinical suspects of lymph node tuberculosis. 2) To study the pattern of drug resistance in microbiologically confirmed cases of lymph node tuberculosis.

MATERIALS AND METHODS

84 cases of suspected lymph node TB were enrolled in the study. The clinical history regarding history of anti-tubercular treatment (ATT), contact history and associated disease was taken. Surgical specimens – biopsy and aspirates were obtained after informed consent and were processed.

RESULTS

1. We observed that in 66/84 (79%) of clinical suspects of lymph node tuberculosis there is histopathological evidence of granulomatous response.
2. We found 18/84 (22%) of cases to be culture positive and identified as Mycobacterium tuberculosis.
3. Of the culture isolates 23% (4) showed non granulomatous response in histopathology, of these patients, 75% (3) are HIV reactive and 25% (1) diabetic.
4. We observed that 5/18 (27.77%) cases to be resistant to atleast one of first line anti-tuberculous drugs.

CONCLUSION

Prompt diagnosis of lymph node tuberculosis is hindered by lack of gold standard diagnostic tests. Prognostic indicators for drug resistance includes previously treated patients, diabetics and HIV seropositive patients.

KEYWORDS

Lymph Node Tuberculosis, Extrapulmonary Tuberculosis, Drug Resistant Tuberculosis.

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BACKGROUND

Tuberculosis is an ancient infection that has plagued humans throughout history. It has been referred to in the Vedas as 'Rajayakshma'. There is clear evidence to show that the infection existed dating back to 8000 B.C., from skeletal remains of prehistoric humans in Germany.[1,2] India accounts for one-third of the global burden of tuberculosis.

The clinical manifestations of tuberculosis are of two types: Pulmonary and Extra-pulmonary forms of tuberculosis (EPTB), pulmonary being the commonest.

Extrapulmonary tuberculosis is defined as tuberculosis of organs other than the lungs, such as pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints, bones, tubercular meningitis, tuberculoma of the brain, etc. Diagnosis is based on one culture positive specimen from the extrapulmonary site; or histological evidence; or strong clinical evidence consistent with active extra pulmonary tuberculosis disease followed by a medical officer's decision to treat with a full course of anti-tuberculous therapy.

Extra pulmonary tuberculosis constitutes 15-20% of total cases of tuberculosis in immune hosts and 50% of total cases of tuberculosis in immune compromised hosts. The most common site of involvement of extra pulmonary tuberculosis is lymph node, followed by pleural effusion.[3]

The clinical presentation of extra pulmonary tuberculosis is atypical and includes a wide array of differential diagnosis. It is difficult to obtain samples for diagnosis and the yields are poor by conventional methods. For managing complications and for diagnosis surgical means may be required to procure tissue samples.[4]

In a descriptive analysis done in European Union (EU)/ European Economic Area (EEA) to study the burden and trends of extra pulmonary tuberculosis by Sandgren et al., in 2013 notification rates of tuberculosis from 2002 to 2011 decreased due to decrease in pulmonary tuberculosis but for extra pulmonary tuberculosis the notification rates remained stable (3.4/100000 in 2002 and 3.2/100000 in 2011). Hence

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they inferred that proportion of extra pulmonary tuberculosis showed a rising trend from 2002(16.4%) to 2011(22.4%). In their study 33.7% cases of extra pulmonary tuberculosis were culture confirmed. They concluded that while pulmonary tuberculosis showed a falling trend, extra pulmonary tuberculosis showed a rising trend.

MATERIALS AND METHODS

Study Design

Prospective Observational Study.

Inclusion Criteria

Patients clinically diagnosed as lymph node tuberculosis in whom treating doctor has suggested histopathological/ microbiological diagnosis in Respiratory Medicine/General Surgery departments at Government Medical College Hospital, Thoothukudi.

Exclusion Criteria

1. Patients clinically diagnosed as lymph node tuberculosis in whom the treating doctor has not suggested histopathological/microbiological diagnosis.
2. Patients currently on anti-tuberculous therapy for more than 2 weeks.
3. Patients not willing to participate in the study.

Sample Size

84 patients who attended outpatient department of Thoracic Medicine/ General Surgery departments satisfying inclusion/ exclusion criteria were enrolled in the study.

Method of Study

Patients clinically diagnosed as lymph node tuberculosis meeting the inclusion criteria were selected for the study. Detailed case history including demographic details, history of contact with a case of pulmonary tuberculosis, history of respiratory symptoms, duration of swelling, history of ENT ailments, history of treatment for tuberculosis obtained.

General examination and systemic/local examination carried out. Size, shape, consistency and fixity of lymph node swelling noted. Blood investigations including random blood sugar, complete blood count including Erythrocyte Sedimentation Rate, ELISA for HIV and other necessary investigations for the individual patient done. Patients in whom alternative diagnosis of lymph node secondaries (hard node swelling with a mass lesion in CXR), lymph node swelling secondary to pharyngitis or ear infection was obvious from history and clinical examination to the treating doctor were excluded from the study.

Patients enrolled in the study were subjected to surgical excision/debridement under local/general anaesthesia after informed consent as required. The specimens were transported in sterile glass bottles in Kirchner's medium to the microbiology laboratory and in formalin to the histopathology laboratory.

Laboratory Methods

Extra pulmonary specimens in general are paucibacillary in nature and hence their processing methods require milder decontamination. Hence the specimens are inoculated into media made selective by incorporating polymyxin B, amphotericin B, carbenicillin, vancomycin and trimethoprim to inhibit growth of other microorganisms (PACT).

The tissue specimens are cut into small pieces using sterile scissors and transferred into a sterile tissue grinder tube and homogenised with 5 ml of sterile water. A direct smear is made from the homogenate. The smear is prepared and read using modified Ziehl-Neelson method.

The homogenate is centrifuged for 15 minutes and the supernatant decanted. 5% sulphuric acid solution is added to the deposit and centrifuged at 3500 rpm for 15 minutes. After discarding the supernatant, the deposit is mixed with 0.2 ml sterile water and inoculated onto two slopes of Lowenstein– Jensen media and incubated at 37^0 Celsius.

The cultures are read weekly and typical colonies of M.tuberculosis are rough, buff, tough, nonpigmented (cream coloured) and slow-growers i.e. Colonies appearing after one or two weeks after inoculation.

Niacin test, inhibition by para-nitrobenzoate and catalase test are done for species identification. Mycobacterium tuberculosis yield positive niacin test (pink colour), positive catalase test (bubbles seen) and inhibited by PNB.

Drug susceptibility is tested by 1% proportion method. Resistance is defined as mycobacteria with greater than 1% of the population exhibiting growth in the presence of the lowest concentration of drug tested.

RESULTS

Case Definition

A patient is defined as having lymph node tuberculosis if either granulomas are present in histopathology or LJ culture shows growth and identified as mycobacterium tuberculosis or both.

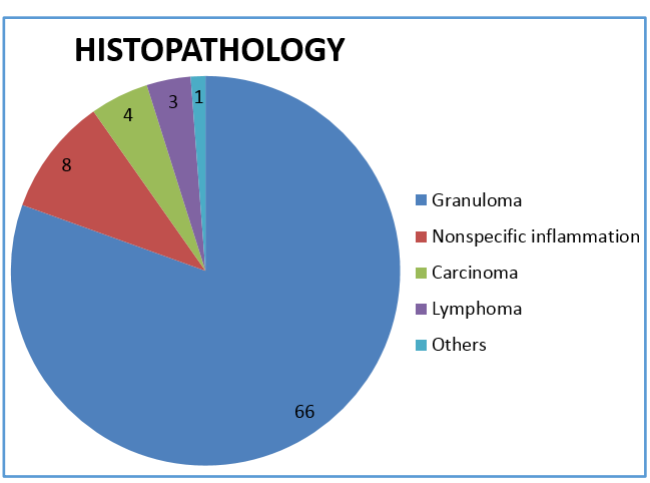

Figure 1. Histopathological Patterns

Supportive Evidence	Contact History present	Contact History Absent	Constitutional Symptoms Present	Constitutional Symptoms Absent	Anaemia Present	Anaemia Present	ESR > 40 mm/hour	ESR ≤ 40 mm/hour
Tuberculosis	15	57	66	6	54	18	63	9
Non tuberculosis	2	10	8	4	7	5	9	3

Table 1. Supportive Evidence in Lymph Node Tuberculosis versus the Exclusion

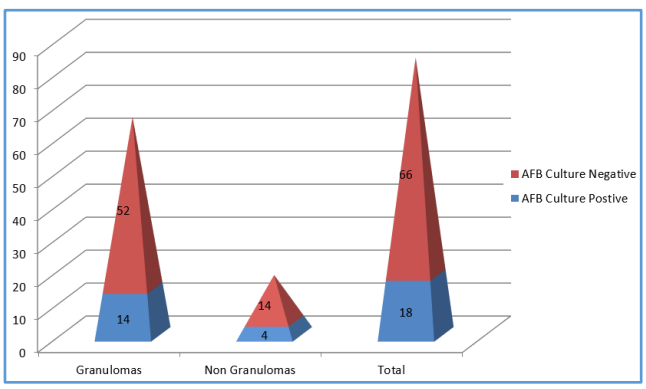

Figure 2. Comparison of Histopathological Pattern and AFB Culture

Gender Distribution	Lymph Node TB	%
Male	26	36.48
Female	46	63.51
Total	72	100
Fishers Exact Test		P value 0.011

Table 2. Gender Distribution in Lymph Node Tuberculosis

L J Culture Status	New Cases	%	Previously Treated Cases	%
Culture positive	13	20.31	4	50
Culture negative	51	79.68	4	50
Total	64	100	8	100
P value Chi Squared Test	0.0055			

Table 3. L J Culture Result in New and Previously Treated Patients

1. We observed that 86.8% (72/84) of clinical suspects of lymph node tuberculosis met the case definition of lymph node tuberculosis on histological and microbiological grounds. The other diagnosis includes carcinoma, nonspecific inflammation and acute inflammation.
2. The supportive evidence of contact history, constitutional symptoms, anaemia and elevated ESR had a marginal role in separating cases from other diagnosis.
3. In our study most of the patients of lymph node tuberculosis were in the age group of 11-20 years(45.78%) closely followed by 21-30 years(36.14%).
4. Lymph node tuberculosis is more common in females with a male to female ratio of 3:5.
5. In our study population new cases constituted 82.4% and previously treated patients 17.5%.
6. We observed that in 79% (66/84) of clinical suspects of lymph node tuberculosis there is histopathological evidence of granulomas.
7. In the histopathological examination, 79% showed granulomas, 10.5% nonspecific inflammation, 4.3% carcinoma, 2.6% lymphoma, 0.8% acute inflammation, 0.8% necrotic material.
8. Of the 10.5% nonspecific inflammation, 50% showed culture positivity in LJ medium and identified as mycobacterium tuberculosis.
9. We found 22% (18/84) of cases to be culture positive and identified as Mycobacterium tuberculosis. Of the culture isolates 4 showed non granulomatous response in histopathology, of these patients, 75% (3) are HIV reactive and 25(1) % diabetic.
10. We observed that 27.77%(5/18)cases to be resistant to at least one of first line anti-tuberculous drugs
11. We found that of the resistant isolates 25% were multi drug resistant, 25% poly drug resistant, 50% monoresistant.
12. The drug resistance rate is 17.6% in new cases and 55.5% in previously treated cases of which multidrug resistance is 0% in new cases and 22% in previously treated cases.
13. The resistance rate in HIV positive patients is 37.5% and in HIV negative patients is 24.7%
14. The resistance rate in diabetics is 33.4% and the resistance rate in nondiabetics is 25.4%.

DISCUSSION

Lymph node tuberculosis, the most common form of extra pulmonary tuberculosis was known as the King's evil during the Middle Ages. It was believed that royal touch cured scrofula and the gift of gold coin from the king prevented further scrofulous attacks.[5] Historically lymph node TB is more common in children.

Multiplicity, matting and caseation are the three clinching points favouring the diagnosis of tuberculous lymphadenitis. If the offending node is below the deep fascia through which it may break through it results in a

subcutaneous caseous collection (collar-stud abscess). As the disease process reaches the surface, skin gets involved producing scrofuloderma or tuberculous dermatitis.

Lymph node tuberculosis may be a part of primary or post primary disease. In children with lymph node TB 50-80% have radiographic evidence of active pulmonary tuberculosis which is in concordance with Walgren's calendar for primary tuberculosis published in 1948. In striking contrast in adults with tuberculous lymphadenitis only 30% show chest x ray abnormality and the abnormality is usually of old healed tuberculous lesion and the lymph node disease is part of post primary or reactivation disease. The possible events in lymph node TB are compression of surrounding tissue, caseation and breakdown and healing of eroded nodes causing fibrotic remnants. Even though mortality is uncommon, morbidity and chronic illness is common.

In general tuberculous lymphadenitis is most common in cervical region, but inguinal, axillary, mediastinal, mesenteric and intramammary involvement also occurs.[6]

The common sites of tuberculous lymphadenitis in head and neck region are-

- Anterior and posterior cervical
- Submandibular
- Preauricular
- Submental[7]

The differential diagnosis includes chronic septic lymphadenitis, Hodgkin's disease, secondary carcinomatous deposits.

The lack of gold standard for diagnosis for extrapulmonary tuberculosis is striking in the metanalysis by Stephen D Lawn et al.[8]

Torticoli et al.[9] in 2012 in their study in Italy used-

1. Culture(both solid and liquid) or
2. Suggestive radiology/histology with documented positive response to tuberculosis treatment as gold standard.

Armand et al[10] in 2011 from France used culture in both solid and liquid media as gold standard. (n=32)

Causse et al.,[11] from Spain in 2011 included tissue biopsies, CSF, gastric aspirates, pleural fluid, purulent exudates in their analysis and used solid and liquid media culture as gold standard. (n=41)

Friedrich et al.[12] from South Africa in 2011 used liquid culture as gold standard in their analysis.

Hillemann et al.[13] from Germany in 2011 used solid and liquid culture as gold standard for tuberculosis diagnosis in samples of tissue, gastric as pirate and urine in their analysis.

Ligthelm et al.[14] from South Africa in 2011 used a composite gold standard of

1. Positive Cytology + AFB and/or
2. Culture of MTB

Moure et al.[15] from Spain in their analysis of lymph node, abscess aspirates, lymph nodes and pleural fluid used solid and liquid culture as the gold standard.

In India, Vadwai et al.[16] in 2011 used a composite gold standard of-

1. Smear
2. Culture
3. Clinical
4. Radiology and
5. Histology

In the studies which used solid and liquid culture as the sole gold standard criterion for diagnosis have a lower positivity rate. And the ideal gold standard would be a combination of clinical, microbiological and clinical response to tuberculosis treatment in follow up.

The lack of gold standard in diagnosis of extrapulmonary tuberculosis makes the assessment of prevalence of drug resistance particularly difficult.

In India, A K Maurya et al.[17] in 2012 reported patterns of drug resistance in extra pulmonary tuberculosis in North India. In their study they included 756 patients with clinical diagnosis of extra pulmonary tuberculosis of various sites including lymph node tuberculosis, cold abscess, pleural fluid, genitourinary tuberculosis, ascitic fluid, biopsy materials, pus, pericardial fluid, synovial fluid and bone marrow aspirates. Of the clinical suspects of extra pulmonary tuberculosis 30.1% (n=165) were positive for mycobacteria by BACTEC culture. They included only the culture positive cases for further analysis. 74.5% of their study population were new patients (no treatment or less than one month of treatment against tubercle bacilli) and 25.5% were had previous history of treatment, history of contact was present in 25.4% of patients, 11.5% patients were having a history of diabetes mellitus and 1.8% of cases were HIV positive.

They subjected the culture isolates for drug susceptibility testing for first line anti-tuberculous drugs including isoniazid, rifampicin, ethambutol and streptomycin. They observed higher presence of resistant strains in patients with history of prior treatment with antituberculous drugs. 61.8% of new cases were susceptible to all drugs and 57.2% of previously treated cases were susceptible to all drugs. They observed that on the whole 39.9% of extra pulmonary tuberculosis cases were resistant to first line anti-tubercular drugs.

In our study we observed that lymph node tuberculosis has a higher degree of drug resistance in previously treated patients and HIV seropositive patients. These groups can be considered as risk factors for drug resistance in lymph node and can be targeted for drug susceptibility testing (DST).

CONCLUSION

The main focus of international and national control strategies is on pulmonary tuberculosis it being the transmissible form of disease. However extra pulmonary tuberculosis including lymph node adds significantly to the

burden of disease and requires early, accurate diagnosis. Prompt diagnosis is hindered by the difficulty in obtaining adequate, representative samples, high rates of contamination and lack of gold standard diagnostic tests, the yield of conventional cultures being low. The disease in specific reference to lymph node has a higher degree of bad prognostic indicators particularly drug resistance in previously treated patients, diabetics and HIV seropositive patients. There is a need for large multi centric epidemiologic trials to study the risk factors and patterns of drug resistance in extra pulmonary tuberculosis and direction of resources towards high risk individuals for drug susceptibility testing.

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