International Journal Dental and Medical Sciences Research (IJDMSR)
ISSN: 2393-073X Volume 4, Issue 10 (October - 2020), PP 26-36
www.ijdmsr.com

Retrospective study of clinical and epidemiological characteristics of Tubercular Lymphadenitis in a tertiary care center of Bihar

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ABSTRACT:- Tuberculosis (TB) still continues to be a leading cause of mortality and morbidity among infectious diseases and affects millions each year. Extrapulmonary tuberculosis contributes a significant proportion of all TB cases especially among HIV patients and tubercular lymphadenopahy is the most common presentation. The diagnosis of tubercular lymphadenopathy involves various modalities. In this study, retrospective evaluation of laboratory and clinical data for a period of 3 years in AIIMS, Patna, was done to evaluate the accuracy of different diagnostic techniques used in the diagnosis of tuberculous lymphadenopathy. We also look for various demographic and clinical conditions that may be associated with tuberculous lymphadenopathy. In this study, a female predominance was seen among cases and involvement of cervical lymph nodes was most commonly seen. Histopathological examination and CBNAAT showed high sensitivity and specificity in diagnosing TB lymphadenopathy. Z-N stain had poor sensitivity and a negative test can't exclude the diagnosis. Cigarette smoking and contact with an active pulmonary tuberculosis case were found to be statistically significant risk factors. Clinical suspicion based on the patient's demographic and clinical profile and a combination of various diagnostic modalities may play a crucial role in the diagnosis of TB lymphadenopathy and will serve the ultimate goal of TB eradication by 2025.

I. INTRODUCTION

Tuberculosis (TB) is an ancient disease of humankind and continues to be one of the major infectious diseases causing mortality and morbidity to millions throughout the world reflected by the Global TB report of W.H.O stating that there are an estimated 10 million new cases in the year 2018 [1]. Tuberculosis is an infectious disease caused by acid-fast bacteria *Mycobacterium tuberculosis* and is manifested pathologically as granulomatous inflammation with formation of granulomas or sometimes cavities or other lesions. India as a developing country contributes a major proportion (27%) of the global TB burden with an estimated 2.69 million new cases in the year 2018 [1, 2].TB continues to be most killing infectious disease globally with an estimated 1.2 million deaths in non-HIV patients and 251,000 deaths in HIV infected patients [1]. The Government of India has launched the National Tuberculosis Eradication program with a goal of Elimination of TB in India by 2025 [3].

Extra Pulmonary Tuberculosis (EPTB) contributes to 15-20% of total cases of TB and in India. The prevalence of EPTB is estimated from 8.3- 13.1% in various districts according to cohort analysis by central TB division, Ministry of Health & Family Welfare, India [4, 5]. EPTB contributes to 10-50% of all TB cases among HIV negative patients and 30-80% in HIV infected patients. Tubercular lymphadenitis is the most common type of EPTB contributing to almost 40% of cases and in India, it contributes 15- 20% of all TB cases [6-9].

Tuberculous lymphadenitis commonly involves cervical lymph nodes and mimics other pathological conditions like metastasises, lymphoma, non-specific lymphadenitis and sarcoidosis, etc. Therefore, it can be presented with a variety of symptoms like fever, weight loss, fatigue, and slow-growing painless mass or masses and a small portion of cases may present with sinus formation [10-12]. The incidence of EPTB is rising in recent decades due to the spread of HIV and the improvement in socioeconomic conditions [13]. A study conducted by Rai *et al*. showed an increase in the prevalence of EPTB cases from 9.59% in 2009 to 20.75% in 2011 [14].

Drug resistance in TB is a continuous and growing threat to public health and WHO global TB report shows that 3.4% of new TB cases and 18% of previously treated cases were multi-drug resistant TB in the year 2018 [1]. A study conducted by Kant S *et al*. shows a rising trend of MDR isolates in patients with EPTB in India. [15].

Tubercular lymphadenitis can be diagnosed by a variety of diagnostic modalities like Culture, Acid fast stain (Z-N stain), Fine Needle Aspiration (FNA), and radiological techniques like CT scan and MRI. Modern molecular tests like CBNAAT provide an excellent option for a fast, easy, and reliable method of diagnosis [16]. A study conducted by Khan *et al*. found that LED-FM microscopy has only 40% sensitivity in detecting EPTB samples compared with GeneXpert [17]. A combination of FNA and PCR was found to increase the sensitivity

and specificity in diagnosing tuberculous lymphadenitis [18]. Even after all these advancements in diagnostics TB lymphadenitis is challenging to diagnose and manage mostly due to lack of clinical suspicion and limitations of available diagnostic methods especially in resource-limited settings in developing countries [19].

Various socio-economic and demographic characteristics are associated with tubercular lymphadenitis and analysis of such characteristics may be crucial in finding various risk factors associated with such infections [20].

To best of our knowledge, no study has previously reported the recent clinical, diagnostic and epidemiological factors associated with this disease from Bihar state and hence, we conducted this study on patients reporting at one tertiary care hospital facility with the following aims and objectives-

I. Diagnostic accuracy of different methods in detecting TB lymphadenitis.
II. To investigate the demographic factors associated with patients with TB lymphadenitis.

III. MATERIAL AND METHODS-

Study Design- Hospital-based Retrospective study

Study Population- Patient attending in the OPD or admitted in different wards of All India Institute of Medical Sciences, Patna

Study Duration- 3 years (January 2017 to December 2019)

Selection of cases- All patients who presented with swelling of lymph nodes (i.e. lymphadenitis) in different OPDs or were admitted in different wards were included in this study if they fulfilled the inclusion and exclusion criteria.

Inclusion criteria

Patients presenting with lymphadenopathy irrespective of sex, caste, religion, socio-economic status, duration & severity of illness were included in the study.

Exclusion criteria

Diagnosed cases of malignancies from any primaries presented with lymphadenopathy.

IV. METHODS-

Laboratory and hospital records were retrospectively collected and evaluated for all the patients who fulfilled the inclusion and exclusion criteria. We looked for Z-N stain reports and CBNAAT reports and also looked for histopathological and radiological reports of those patients along with the demographic data and associated clinical conditions. Smear microscopy reports of such patients were looked for the presence or absence of acid-fast bacilli (AFB). CBNAAT reports were evaluated for the detection of *M. tuberculosis* along with rifampicin resistance. Histopathological examination like Fine Needle Aspiration (FNA) cytology or excision biopsy reports were looked for the presence of granuloma. Reports from radiological tests like USG, CT-scan, or MRI were evaluated for the presence of matting of lymph nodes or hypoechoic lesions due to necrosis. Hospital records were also looked for various demographic factors like age, sex, residence, occupation, smoking habits, and associated clinical conditions like previous PTB, diabetes mellitus, etc for all the patients included in this study.

Statistical analysis-

All the relevant data were plotted using Microsoft Excel 2007 and were presented as tables and bar or pie graphs. Percentages or ratios were calculated using the MS Excel sheet. Chi-square test and McNeemer test was done to compare various categorical variables and diagnostic tests. Sensitivity and specificity were calculated using MedCalc (v. 19.1.3)

V. RESULTS-

During this study, a total number of 4850 presumptive TB cases were analyzed out of which 468 (9.6%) were EPTB cases. Among those EPTB cases, 34 (7.3%) were presumptive cases of tuberculous lymphadenitis. **[Fig-1]**

Out of those presumptive tubercular lymphadenitis cases 12 (35.3%) were male and 22 (64.7%) were female (i.e. male: female ratio= 12:22= 1:1.8) and among the CBNAAT confirmed cases 9 were female and 2 were male (i.e. Male: Female ratio= 1:4.5). **[Table-1 & Fig-2]**

Majority of the presumptive cases (n=31, 91.2%) belongs to age < 40 years. Among the CBNNAT confirmed cases, most (n=7, 63.6%) belong to age < 20 years. **[Table-1& Fig-2]**

Most of the presumptive cases were from pulmonary medicine (n=15, 44.1%) followed by general surgery (n=11, 32.4%), and these departments also contributed to majority (n=8, 72.7%) of the CBNAAT confirmed cases. **[Table-2& Fig-3]**

Most of the presumptive cases (n=22, 64.7%) showed involvement of cervical lymph nodes followed by axillary lymph nodes (n=4, 11.8%), and involvement of these 2 groups of lymph nodes is also seen in a majority (n=7, 63.6%) of the CBNAAT confirmed cases. **[Table-3 & Fig-4]**

Among the 34 tuberculous lymphadenitis cases, 3 (8.8%) were diagnosed positive based on Z-N stain smears, 11 (32.4%) were diagnosed by CBNAAT method, 13 (38.4%) were by hisptopathological examination and 11 (32.4%) were diagnosed as positive based on radiological findings. **[Table- 4 & 5]**

Considering CBNAAT as the reference standard for diagnosing tuberculous lymphadenitis the comparative sensitivity and specificity of Z-N staining, Histopathological examination and Radiological examination becomes (6.02%- 60.97%) &(78.05% - 99.89%), (30.79% - 89.07%) & (51.59% - 89.77%), (23.38% - 83.25%) & (56.30 % - 92.54%) respectively within 95% confidence interval (CI). **[Table-6& Fig-5]** No statistically significant association was found between AFB smear (Z-N stain) positivity and histopathological and radiological examinations ($p \geq .05$). **[Table-7 & 8]**

Among the various socio-demographic characteristics analyzed for tuberculous lymphadenitis cases, cigarette smoking, and positive history for contact with active pulmonary tuberculosis cases were found to be statistically significant ($p \leq .05$). **[Table-9]**

Table- 1: Age and Sex distribution of the patients

Age	Male (n=)	Female (n=)	Total (%)	Cumulative (%)
0-20	6	9	15 (44.1%)	44.1
21-40	5	11	16 (47.1%)	91.2
41-60	1	2	3 (8.8%)	100
Total	12	22	34	

Table- 2: Ward wise distribution of the patients

Ward	Male	Female	Total (%)
Pulmonary Medicine	5	10	**15 (44.1)**
Surgery	4	7	**11 (32.4)**
Others	3	5	**8 (23.5)**
Total	**12**	**22**	**34**

Table- 3: Anatomical sites involved in study subjects-

Site	Male	Female	Total (%)
Cervical	5	17	22 (64.7)
Axillary	2	2	4 (11.8%)
Mediastinal	1	0	1 (2.9)
Submandibular	2	1	3 (8.8)
Inguinal	1	1	2 (5.9)
Mesenteric	1	1	2 (5.9)
Total	12	22	34

Table-4: Diagnostic tests in Tubercular Lymphadenitis-

Diagnostic Test	No. Positive	Total	(%) Positive
CBNAAT	11	34	32.4
Z-N Stain	3	34	8.8
Histopathology	13	34	38.2
Radiology	11	34	32.4

Table-5: Comparative analysis of diagnostic tests against CBNAAT as a reference standard.

CBNAAT	Z-N stain	Histopathology	Radiology	No. of patients	Total (%)
Positive	Positive	Positive	Positive	3	11(32.4%)
Positive	Negative	Positive	Positive	3	
Positive	Negative	Positive	Negative	1	
Positive	Negative	Negative	Negative	4	
Negative	Negative	Positive	Negative	1	23 (67.6%)
Negative	Negative	Positive	Positive	3	
Negative	Negative	Positive	Negative	2	
Negative	Negative	Negative	Positive	2	
Negative	Negative	Negative	Negative	15	

Table-6: Sensitivity and Specificity of various diagnostic tests against CBNAAT as the reference standard.

Diagnostic tests	Sensitivity (95% CI)	Specificity (95% CI)
Z-N Stain	6.02% to 60.97%	78.05% to 99.89%
Histopathology	30.79% to 89.07%	51.59% to 89.77%
Radiology	23.38% to 83.25%	56.30% to 92.54%

Table-7: Association between AFB positivity and Cytological examination in CBNAAT confirmed cases.

Hisopathological findings	AFB Positive	AFB Negative	p-Value	Remarks
Well defined Granuloma	2	9	.325892	Not Significant (NS)
Ill-defined Granuloma	1	1		
Total	3	10		

Table-8: Association between AFB positivity and Radiological examination in CBNAAT confirmed cases.

Radiological findings	AFB Positive	AFB Negative	p-Value	Remarks
Nodal matting is seen	2	6	.782252	Not Significant (NS)
Other than nodal matting	1	2		
Total	3	8		

Table-9: Socio-demographic characteristics associated with Gene Xpert MTB/RIF assay positivity among presumptive LNTB cases

Variable	Frequency	Xpert Positive	Xpert Negative	p-Value	Remarks
Age (in years)					
0-20	15	6	9	.397063	NS
21-40	16	5	11	.896876	NS
40-60	3	0	3	NA (Not applicable)	
Sex					
Male	12	2	10	.148748	NS
Female	22	9	13		
Residence					
Urban	15	4	11	.528871.	NS
Rural	19	7	12		
Marital status					
Married	15	5	10	.831657	NS
Un-married	19	7	12		
Occupation					
Manual labor	9	3	6	.941553	NS
Business	8	2	6	.611196	NS
Job	7	2	5	.810339	NS
Housewife	10	4	6	.538394	NS
Education					
Graduate or above	7	2	5	.810339	NS
10th or Above	19	5	14	.397063	NS
Primary	8	4	4	.222434	NS
Cigarette smoking					
Yes	18	9	9	.01965.	Significant
No	16	2	14		
Alcohol					
Yes	10	3	7	.849853	NS
No	24	8	16		
Contact with PTB					
Yes	14	8	6	.009734	Significant
No	20	3	17		
Debilitated condition					
Yes	5	2	3	.692278	NS
No	29	9	20		

Fig-1: Distribution of Presumptive TB cases-

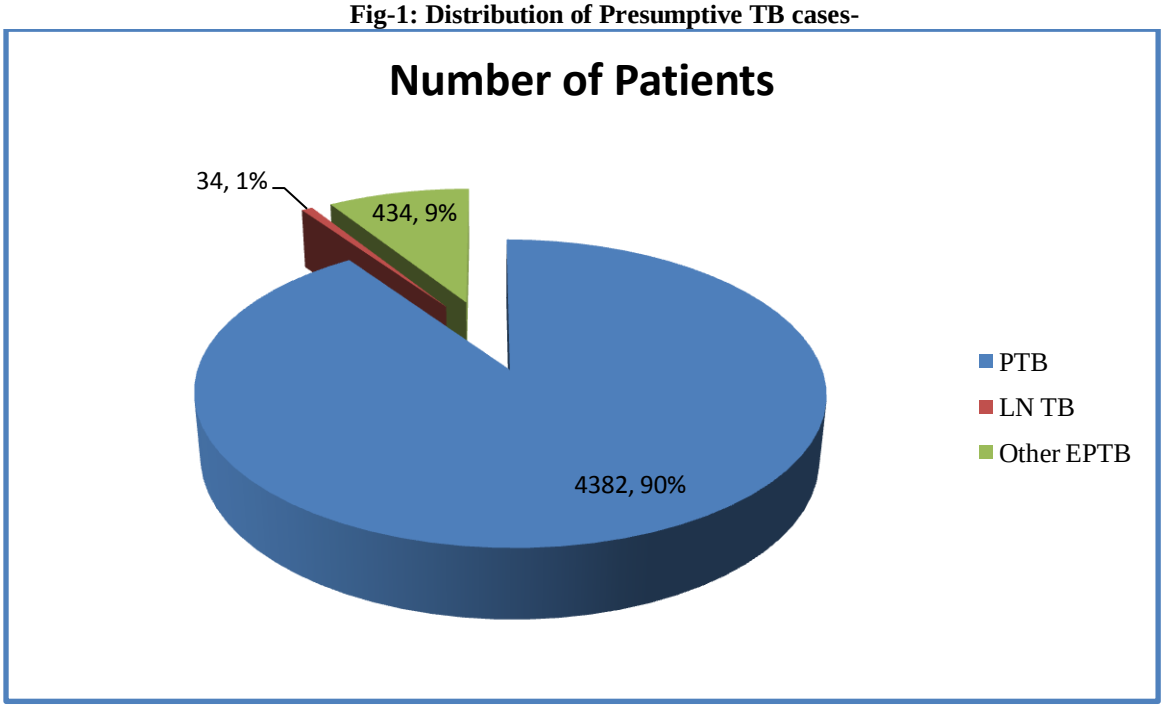


Fig: 2- Age and Sex wise distribution of CBNAAT confirmed cases

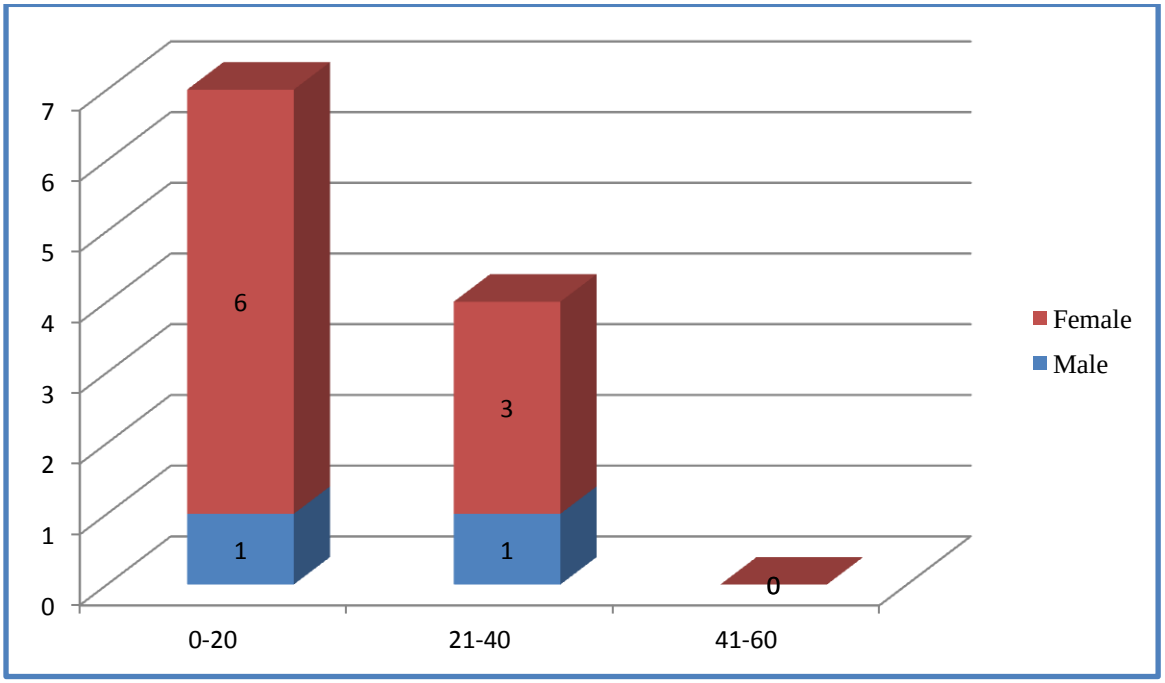


Fig: 3- Ward wise distribution of CBNAAT confirmed cases-

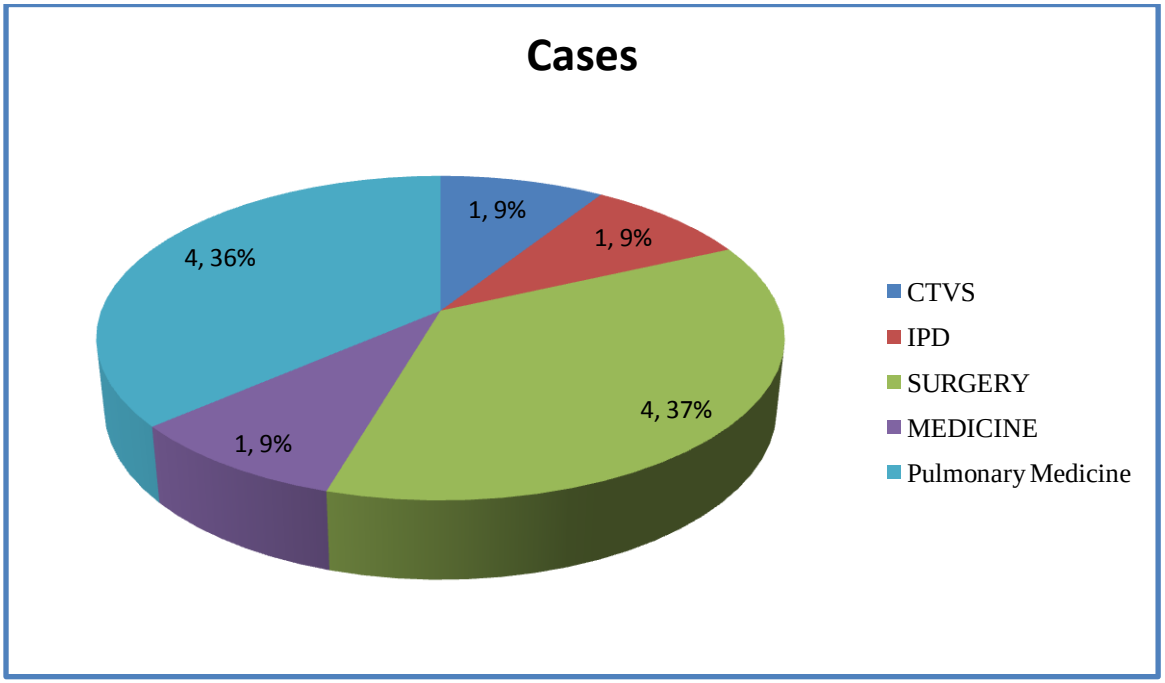


Fig: 4- Anatomical site involved in CBNAAT confirmed cases-

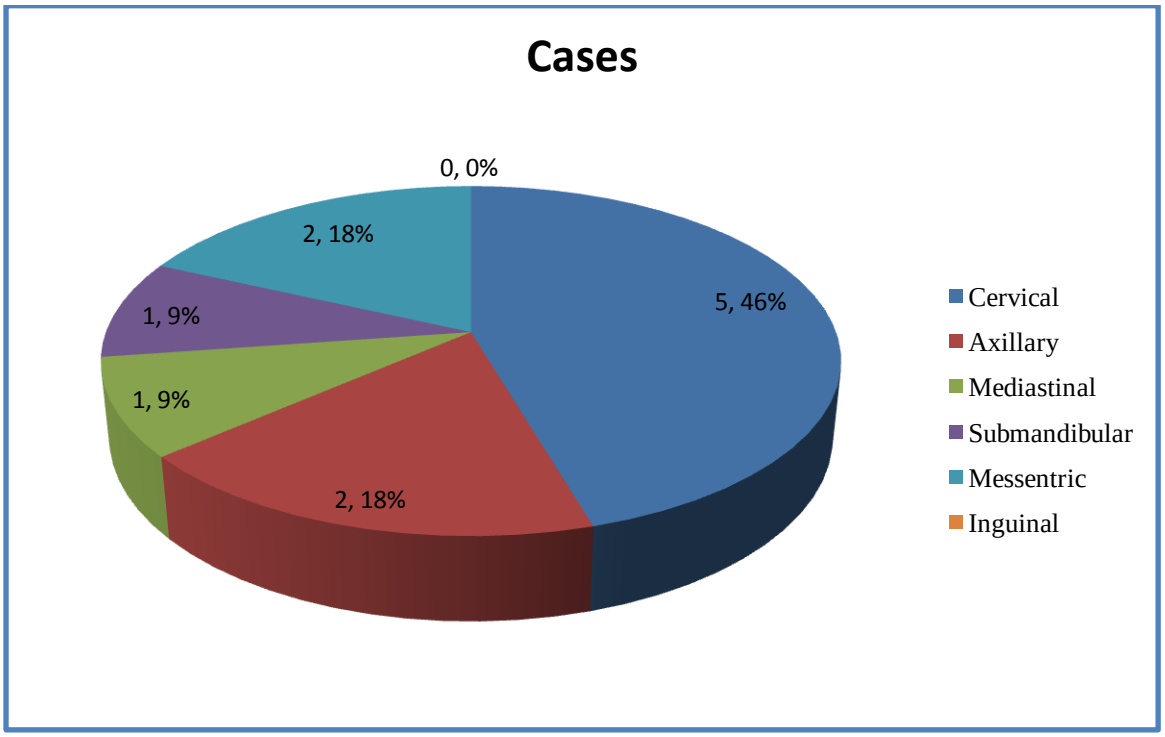
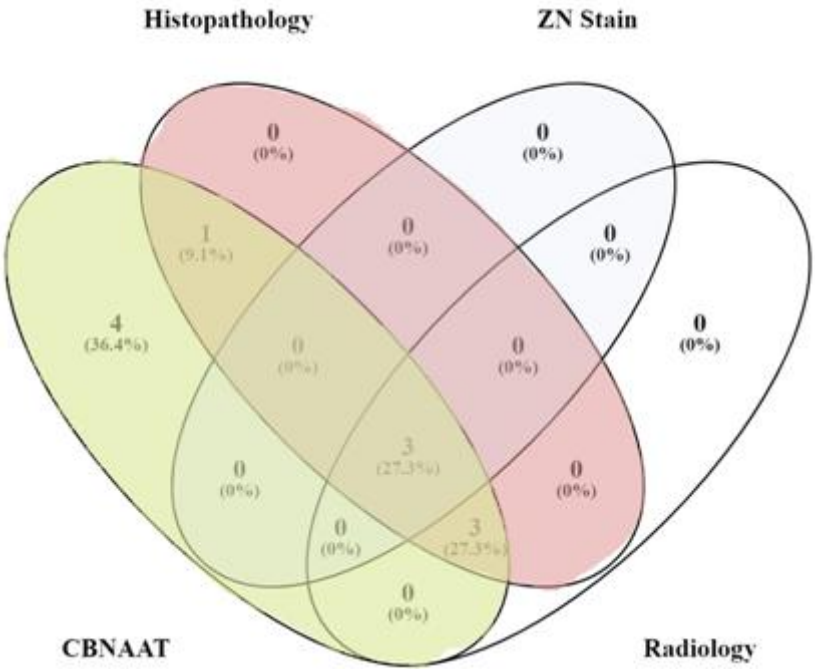


Fig: 5- Venn diagram showing case detection by different methods in CBNAAT confirmed cases.



VI. DISCUSSION-

In the current study, the prevalence of tuberculous lymphadenopathy was found to be 7.3% among patients with presumptive EPTB. Studies from various authors have established that tuberculous lymphadenopathy is the most common type of EPTB [6, 8]. The low prevalence found in this study is due to low case reporting of TB lymphadenopathy cases due to a lack of patient health-seeking behavior and difficulty in clinical diagnosis in many of such cases. A study conducted by Purohit *et al.* showed that only 12% of patients in central India seek medical advice in EPTB cases mostly due to lack of awareness [21, 22].

In this study, there is a female predominance (M: F ≅ 2) in presumptive and laboratory-confirmed cases of tuberculous lymphadenopathy. A study conducted by Das *et al.* also showed a female predominance (68%) in tuberculous cervical lymphadenopathy where the male: female ratio was (13: 27 i.e. 1: 2.1) which is in harmony with this study [23]. The female predominance may be due to the difference between health care seeking behavior among males and females regarding their physical appearance as shown in a study by Dandapat *et al* [24].

In this current study patients within the age of 40 years contribute the majority of presumptive cases (91.2%). Tuberculous lymphadenopathy was once considered a disease of childhood but recent studies by various authors showed that its mean age has now shifted to 20-40 years in most developed and developing countries [25]. In a study conducted by Das S *et al.*57.1% of the patients with head and neck tuberculosis were in the age group of 15-24 years [26]. This study result is in harmony with those studies.

Cervical lymph nodes are most commonly (63-77%) involved in tuberculous lymphadenopathy [27, 28]. In this study, 64.7% presumptive cases of tuberculous lymphadenopathy and 46% of laboratory-confirmed cases showed involvement of cervical lymph nodes and this corresponds to finding with other authors [29].

In developing countries, tuberculosis may be an important reason for lymphadenopathy involving lymph nodes other than cervical especially mediastinal lymph nodes [30-32]. In developed countries, lymphomas may be the most prevalent cause of such lymphadenopathy but in developing countries and resource-restricted settings, a trial course of Anti-Tubercular treatment may be given to look for size reduction which also supports the diagnosis and eliminates the need of invasive diagnostic procedures [33, 34].

In this study, cases of presumptive tuberculous lymphadenopathy were diagnosed using various methods among which acid fast staining using Ziehl-Neelsen stain is the most frequently used technique especially in resource-limited settings in developing countries [35]. Though easy to perform and available but the diagnostic yield is very low especially in EPTB cases. A study conducted by Mittal *et al.* found that 13.58 % (11/81) patients with EPTB were positive for Z-N stain and this corresponds to this current study where 8.8% of the presumptive cases were positive for Z-N stain smear [36]. In a study conducted by Chakravorty *et al.* the highest sensitivity of Z-N stain was found to be 21.1% which is in harmony with this study where the sensitivity ranges from 6% to approximately 61% [37].

In this study, histopathological procedures include FNA (Fine Needle Aspiration) and Excision biopsy. Although excision biopsy has been used traditionally for diagnosing tuberculous lymphadenitis, FNA provides a less invasive, less painful and reliable alternative diagnostic method [38]. The sensitivity and specificity of histopathological techniques in this current study is up to 89%. In a study conducted by Lau *et al*. the sensitivity and specificity of FNA were found to be 77% and 70% respectively [39]. The sensitivity of excision biopsy was estimated to be 96% in a study done by Knox *et al* [40]. These study results correspond to our current study.
Histopathological examination is of special importance where lymphadenopathy can be due to NTM (Non-Tubercular Mycobacteria) infections. In a study conducted by Izuzquiza *et al*., FNA detected 66.7% of NTM associated tuberculous lymphadenopathy [41]. CBNAAT has it's limitation in detection of NTMs [42]. Hence histopathological procedures will continue to play a crucial role in the initial diagnosis of tuberculous lymphadenitis and it should be confirmed using other sophisticated techniques like culture and molecular assays [43].

Radiological techniques (CT and MRI) provide a non-invasive, fast, and reliable method for the initial diagnosis of tuberculous lymphadenopathy. According to the Index TB guidelines, Chest X-ray should be done in all symptomatic lymph node tuberculosis (LNTB) patients and CT scan or USG should be advised to supplement diagnosis in abdominal LNTB especially in HIV patients [44]. The lymph nodes may be initially homogenous but with disease progression, they develop central necrosis and are easily detected in CT and MRI images with or without contrast [45]. In this study, the sensitivity and specificity of radiological techniques were found to be approximately 83% and 93% respectively. In a study conducted by Jong *et al*. it was seen that radiological technique combined with FNA could be highly sensitive (98%) and specific (95%) in diagnosing tuberculous lymphadenopathy [46]. This corresponds to the current study.

In this study, the authors have found no statistically significant (p= .325892 i.e. > .05) association between smear positivity and presence of granuloma in histopathological examinations. This reflects the fact that many of the AFB negative cases may have tuberculous lymphadenopathy and will be evident by the presence of granuloma in histopathological examinations. A study done by Deitel *et al*. showed similar results where 10 out of 23 cases were AFB smear-positive but 19 out of them showed granuloma (McNemer Chi-square statistics is 9.0000 i.e. p> .05) [47]. Their study results are in harmony with this current study.

Similarly, this study has found no statistically significant (p=.782252 i.e. >.05) association between smear positivity and radiological characteristics of tuberculous lymphadenopathy. The sensitivity of smear microscopy relies on the quality and source of the sample [48]. Due to this low sensitivity (46-78%) of AFB smears by Z-N staining smear-negative cases should be screened by various radiological techniques that will increase the overall diagnostic sensitivity [49, 50].

Various demographic and socio-economic characteristics of those presumptive tubercular lymphadenopathy cases were analyzed in this study. The only characteristics which were found to be statistically significant and associated with laboratory-confirmed tuberculous lymphadenopathy cases were history of contact with pulmonary TB (PTB) (p= .009734 i.e. ≤.05) and habit of cigarette smoking (p= .01965. i.e. ≤.05). A study was done by Khan *et al*. also found smoking as a significant risk factor along with other statistically significant risk factors like alcoholism, diabetes mellitus, HIV, age, sex, employment, and marital status were not found as statistically significant risk factors [51]. Their study results are in harmony with this current study.

Contact with a patient with active pulmonary tuberculosis or a previous episode of pulmonary tuberculosis may be associated with tuberculous lymphadenopathy as seen in studies conducted by various authors like Khajanchi *et al*., Collu *et al*. and Nanda *et al*. [52-54]. In this study, we have also found a statistically significant association (p= .009734 i.e ≤.05) between contact with PTB cases and laboratory-confirmed cases of tuberculous lymphadenopathy which corresponds to findings of those authors.

VII. CONCLUSION-

Tuberculosis continues to be an important cause of lymphadenopathy in the young population and involvement of the cervical lymph nodes is the most common clinical presentation. Female predominance was seen among patients with tuberculous lymphadenitis. Although cervical nodes are commonly involved, lymphadenopathy involving lymph nodes of other anatomical sites are needed to be analyzed for tubercular etiology. Most of the cases of tubercular lymphadenopathy maybe smear-negative in Z-N staining and are easily misdiagnosed. The diagnosis needs to be supplemented by other diagnostic modalities like FNA and excision biopsy, radiological techniques like USG, CT scan, or MRI and molecular techniques like CBNAAT. The combination of various diagnostic modalities along with Z-N stain highly increases the sensitivity and specificity. Contact with an active PTB case and smoking habits are found to be significant risk factors and were to be avoided to prevent such infections.

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