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A clinical study of tuberculous cervical lymphadenopathy cases presenting in a tertiary care hospital in M.P.

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Abstract: This study aimed to clinically investigate cases of tuberculous lymphadenopathy in a tertiary care center in Madhya Pradesh. 67 patients with swelling in the neck and clinically diagnosed as Cervical Tuberculous Lymphadenopathy were included. Data was collected through detailed history, physical examination, routine investigations, radiological tests, and FNAC. Most participants were females (56.7%) in the 11-20 years age group (32.8%). Chest X-ray/ CT thorax findings showed infiltrates in 7.5%. Mantoux test was positive in 85.1% participants. FNAC revealed granuloma without caseous necrosis in 80.6% cases, with AFB found in 28%. 91% were treated with ATT only, while 6% were treated with ATT+ART. 28.4% experienced a paradoxical reaction during treatment, with 94.7% undergoing modification of treatment. USG neck at the end of 6 months treatment revealed residual lymph nodes in only 20.9%. 22.4% required an extended duration of treatment. The study concludes that cervical lymph node tuberculosis is the most common form of extra-pulmonary tuberculosis and FNAC is the simplest procedure for diagnosis. The presence of residual LNs after 6 months of anti-tuberculosis treatment does not necessarily indicate recurrence or treatment failure but must be re-evaluated and differentiated from active TB.

Keywords: Tuberculous cervical lymphadenopathy; Residual lymph nodes; FNAC; ATT.

1. Introduction

Tuberculosis (TB) remains one of the top 10 causes of death worldwide, with extra-pulmonary TB accounting for nearly 15-20% of cases and showing no significant decrease in incidence compared to pulmonary TB. In 2019, the estimated global incidence of TB was 10 million [1]. Extra-pulmonary TB can occur in various sites, including the pleura, CNS, lymph nodes, genitourinary system, bones, and joints [2]. In countries with occasional TB prevalence, lymph node TB is the most common form of extra-pulmonary TB [3], with Mycobacterium tuberculosis and occasionally Mycobacterium bovis being the causative agents of tuberculous lymphadenopathy [4,5].

Diagnosing cervical tuberculous lymphadenitis (CTBL) can be challenging, even with the development of new diagnostic methods, especially in patients without a history of TB. Other granulomatous lymphadenitis, such as non-tuberculous mycobacteria, sarcoidosis, toxoplasmosis, tularemia, fungal disease, cat-scratch disease, and neoplasms, should be considered [6,7]. The diagnosis of CTBL necessitates a high index of suspicion, as cervical lymphadenopathy is a common form of extra-pulmonary TB in developing countries like India. The head and neck region is rich in lymphatics, with approximately 300 lymph nodes located in the neck region alone [8]. However, there are many causes of cervical lymphadenopathy, increasing the likelihood of a wrong clinical diagnosis in cases of cervical lymphadenopathy compared to other diseases.

Given these challenges in diagnosis, the present study aims to clinically study cases of tuberculous lymphadenopathy presenting in a tertiary care center in Madhya Pradesh, India. The study will help improve our understanding of CTBL and its clinical presentation, which could aid in developing more accurate diagnostic methods and effective treatments.

2. Materials and Methods

This observational study was conducted in the Department of Respiratory Medicine at R.D. Gardi Medical College in Ujjain, Madhya Pradesh after obtaining approval from the Institutional Ethics Committee over a period of one year. A total of 67 patients who presented to the OPD/IPD of the hospital with swelling in the neck and were clinically diagnosed with Cervical Tuberculous Lymphadenopathy were included in the study after providing consent. Clinically and hemodynamically unstable patients, underage and mentally unfit patients were excluded from the study.

The sample size was calculated to be 67 based on the formula $n = \frac{Z^2 p(100-p)}{d^2}$, taking expected prevalence (p) as 57% [9] and margin of error (d) as 10%.

A detailed socio-demographic and personal history was recorded, and a complete physical examination (both general and systemic) was performed. Basic routine investigations were carried out. Radiological tests, as well as, FNAC were other investigations that were carried out.

3. Statistical Analysis

Data was collected, appropriately coded, and compiled in an MS Excel spreadsheet. Continuous data was expressed in mean and standard deviation. The descriptive representation of data was done in the form of frequencies and percentages, calculated in MS Excel. The graphical representation of data was done using figures and tables. Analytical part was done using appropriate tests of association using SPSS 25 (trial version) software wherever necessary. The level of significance was fixed at 95%. A p-value less than 0.05 was considered statistically significant.

4. Results

The sociodemographic characteristics of the study population are presented in Table 1. The majority of participants (32.8%) belonged to the age group of 11-20 years, followed by those between 21-30 years (22.4%) and 31-40 years (17.9%). The minimum and maximum age of the participants were 7 and 60 years, respectively, with a mean age of 25.71 years. Female predominance was observed (56.7%) with a male to female ratio of 1:1.31. Most participants were residents of rural areas (62.7%) and belonged to a lower socioeconomic status (64.2%), as per the Kuppuswamy classification. The majority (46.3%) had only received primary school education, while 4.5% were illiterate. 11.9% were addicted to smoking, 9% to tobacco, and 6% to alcohol.

Among those with a positive history of TB, 60% were found to have non-residual lymph nodes, while 40% had residual lymph nodes (Table 2). 81.4% of patients with non-residual lymph nodes and 18.6% with residual lymph nodes did not have any co-morbidity. Among those with diabetes, 50% had residual and non-residual lymph nodes each. Among patients with HIV, 75% had non-residual lymph nodes and 25% had residual lymph nodes. 23.9% of patients were asymptomatic, while the rest had symptoms such as a decrease in appetite (71.6%), weight loss (55.2%), fever (19.4%), cough (14.9%), and pain (7.5%). A large proportion of patients with a decrease in appetite (81.2%), weight loss (75.7%), fever (77%), cough (90%), and pain (80%) were observed to have non-residual lymph nodes (Table 2).

The number, location, site, and characteristics of lymph nodes were studied as presented in Table 3. 76.1% of the population had <=5 lymph nodes, while the rest had >5 nodes. 94% of the study participants had only cervical lymphadenopathy, while axillary (3%) and mediastinal lymphadenopathy (3%) were also observed among the participants. Among those with cervical lymph nodes, 49.3% were located in the upper deep cervical region, followed by 20.9% in the supraclavicular region, 19.4% in the lower deep cervical region, and with the least (10.4%) located in the submandibular region. Most of the nodular swellings (43.3%) were located on the right side, while 28.4% were on the left and both sides, respectively. 79.1% of the lymph nodes were firm in consistency, 76.1% discrete, and 70.1% were fixed. The association between residual/non-residual lymph nodes and lymph node consistency, nodal status, and mobility was also studied. It was noted that lymph node consistency was significantly associated with the presence of non-residual and residual lymph nodes with a p-value of 0.023 (Figure 1).

Investigations were conducted and the results were analyzed as presented in Table 4. The Mantoux test was positive in the majority (85.1%) of the study participants. ESR was elevated in a large proportion, i.e., 91%. Chest X-ray/CT thorax findings were normal in 89.5% of the participants, while infiltrates were found in

7.5% and mediastinal lymphadenopathy was observed in 2%. The association between Chest X-ray/CT thorax findings and the presence of residual/non-residual lymph nodes was studied, and a significant association was found between them with a p-value of 0.012 (Figure 4). On performing FNAC, granuloma without caseous necrosis was observed in the majority (80.6%), while caseous necrosis alone was observed in 19.4%. AFB (Acid-fast bacilli) were found in 28% of cases. Due to the COVID-19 pandemic, CBNAAT could not be carried out in 21 cases as the machines were utilized for COVID-19 tests. However, among the remaining cases, MTB was detected in 16.5%. The association between CBNAAT findings and the presence of residual/non-residual lymph nodes was also studied, but it was found to be insignificant with a p-value of 0.338 (Figure 4). Isoniazid and rifampicin resistance were observed in 1.5% of participants each, while sensitivity was seen in 17.9%. Drug sensitivity by LPA and Liquid culture could not be done in all the patients due to the COVID-19 pandemic, as our hospital had become a DCH (Dedicated COVID Hospital).

The majority of the patients (91%) were treated with ATT only, while 6% were treated with ATT+ART. One patient was treated with H mono therapy, and one patient was treated with a shorter regimen for drug-resistant TB, as seen in Table 5. A paradoxical reaction during the course of treatment was seen in 28.4% of the patients. Among these patients, 94.7% underwent modification of treatment, while one patient did not.

USG neck was performed at the end of 6 months of treatment, and residual lymph nodes were observed in only 20.9% of the participants. The mean age of the participants with residual lymph nodes was 19.429$\pm$10.23, and among those with non-residual lymph nodes was 27.377$\pm$14.01. At the end of 6 months, FNAC was done in 12 patients, of whom the majority showed no granuloma while the remaining showed caseous necrosis. In 55 patients, FNAC was not applicable (NA) because the lymph nodes resolved with treatment. 77.6% of the patients received treatment for the normal duration, while the remaining 22.4% required an extended duration of treatment. The association between the duration of treatment and the presence of residual/non-residual lymph nodes was found to be significant with a p-value of 0.000 (Figure 5). Surgical incision/Incision and Drainage was advised in 9% of the study participants, while in the rest, resolution was obtained by chemotherapy alone.

Table 1. Distribution of study participants on the basis of socio-demographic variables

Socio demographic variables		Frequency (N)	Percentage (%)
Age group	<=10 years	8	11.9%
	11 -20years	22	32.8%
	21 -30years	15	22.4%
	31 -40years	12	17.9%
	41 -50years	6	9.0%
	>50 years	4	6.0%
Gender	Male	29	43.3%
	Female	38	56.7%
Residence	Urban	25	37.3%
	Rural	42	62.7%
Socio-economic status	Lower	43	64.2%
	Lower Middle	19	28.4%
	Higher middle	5	7.5%
Education	Graduate	9	13.4%
	High school	19	28.4%
	Intermediate	3	4.5%
	Middle school	2	3%
	Primary school	31	46.3%
	Illiterate	3	4.5%
Addiction	Smoking	8	11.90%
	Alcohol	4	6.00%
	Tobacco	6	9.00%
	None	49	73.10%

Table 2. Distribution of study participants on the basis of lymph node findings and association with various parameters

Parameters		Non-Residual Lymph nodes		Residual Lymph nodes		p-value
		Frequency (N)	Percentage (%)	Frequency (N)	Percentage (%)	
Previous history of TB	No	50	80.6%	12	19.4%	0.275
	Yes	3	60.0%	2	40.0%	
Presence of co-morbidities	DM	2	50.0%	2	50.0%	0.321
	HIV	3	75.0%	1	25.0%	
	None	48	81.4%	11	18.6%	
Symptoms	Asymptomatic	11	68.7%	5	31.3%	
	Decrease in appetite	39	81.2%	9	18.8%	
	Weight loss	28	75.7%	9	24.3%	
	Fever	10	77.0%	3	23.0%	
	Cough	9	90%	1	10%	
	Pain/tenderness	4	80%	1	20%	

Table 3. Distribution of study participants based on number, location, site and characteristics of lymph nodes

Parameters on 1st hospital visit		Frequency (N)	Percentage (%)
Lymph node number	<=5	51	76.1%
	>5	16	23.9%
Various sites of lymphadenopathy	Only Cervical	63	94.0%
	Cervical+Axillary	2	3.0%
	Cervical+Mediastinal	2	3.0%
Site of cervical lymphadenopathy	Lower deep cervical	13	19.4%
	Sub-mandibular	7	10.4%
	Supraclavicular	14	20.9%
	Upper deep cervical	33	49.3%
Nodular swelling laterality	Bilateral	19	28.4%
	Left side	19	28.4%
	Right side	29	43.3%
Lymph node character	Firm	53	79.1%
	Soft	14	20.9%
	Discrete	51	76.1%
	Matted	16	23.9%
	Fixed	47	70.1%
	Mobile	20	29.9%

Table 4. Distribution of study participants based on the various investigations and their results

Investigations		Frequency (N)	Percentage (%)
Mantoux test	Negative	9	13.4%
	Notdone	1	1.5%
	Positive	57	85.1%
ESR	Normal	6	9.0%
	Raised	61	91.0%
Chest X-ray/ CT thorax	Infiltrate	5	7.5%
	Mediastinal lymphadenopathy	2	3%
	Normal	60	89.5%
FNAC	Caseous necrosis	13	19.4%
	Granuloma without caseous necrosis	54	80.6%
	AFB	19	28.0%
CBNAAT	MTB Detected	11	16.5%
	MTB Not detected	35	52.2%
	Not done	21	31.3%
Drug susceptibility Testing 'S'/ 'R'	Notdone	53	79.1%
	ResistanceforIsoniazid	1	1.5%
	Resistancefor Rifampicin	1	1.5%
	Sensitive	12	17.9%

Table 5. Distribution of study participants on the basis of treatment provided and its modifications

Parameters		Frequency (N)	Percentage (%)
Treatment	Hmono	1	1.5%
	ATT Only	61	91%
	ATT with ART	4	6%
	Shorter regimen	1	1.5%
Paradoxical reaction during treatment	Seen	19	28.4%
	Not seen	48	71.6%
Modification of treatment in those with paradoxical reaction (n=19)	Modified	18	94.7%
	Not-modified	1	5.3%

Table 6. Distribution of study participants based on parameters analysed at the end of completion of treatment

Parameters		Frequency (N)	Percentage (%)
USG neck findings at end of 6 months treatment	Residual lymph node	14	20.9%
	Mean age = 19.429±10.23		
	Non Residual lymphnode	53	79.1%
	Mean age = 27.377±14.01		
FNAC findings at end of 6 months treatment	NA	55	82.1%
	Caseousnecrosis	5	7.5%
	Nogranuloma	7	10.4%
Total duration of treatment	Extended duration	15	22.4%
	Normal duration	52	77.6%
Treatment other than chemotherapy	Surgical excision	6	9%
	Incision and drainage	6	9%

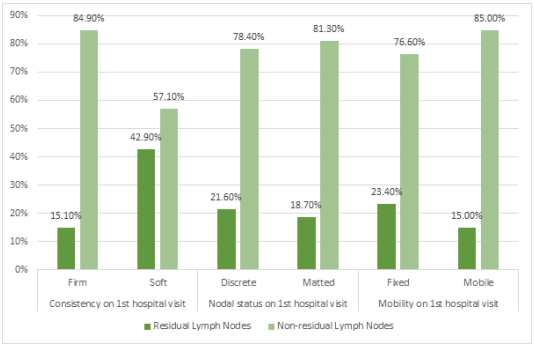

Figure 1. Association between consistency, nodal status and mobility of lymph nodes and presence of residual/ non-residual lymph nodes (Lymph node consistency was significantly associated withpresence of residual/non-residual lymph node with p=0.023)

Figure 2. Leftsideof neckshowinglymphnodeabscess

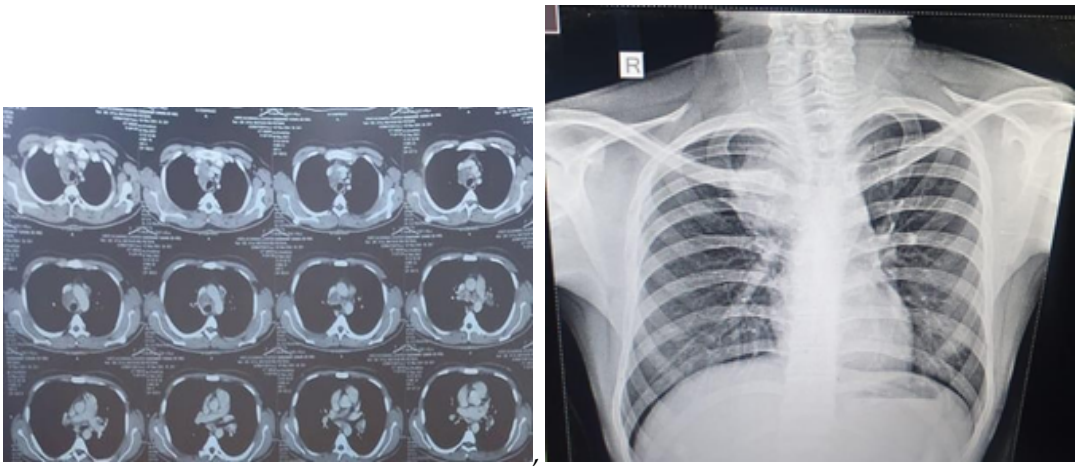

Figure 3. ChestxrayandHRCTthoraxshowingmediastinallymphadenopathy (Chest x ray/ CT thorax finding were significantly associated with presence of non-residual/ residual lymph nodes with p=0.012. Association between CBNAAT findings and presence of non-residual/ residual lymph nodes was insignificant with p=0.338)

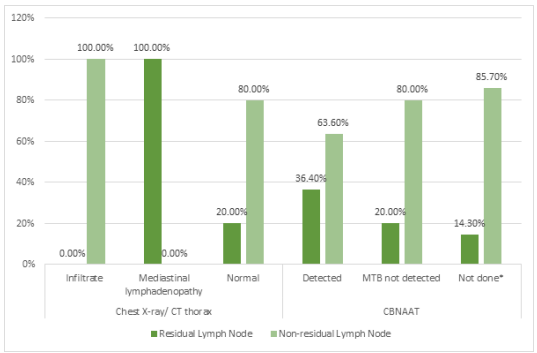

Figure 4. Association between Chest X-ray/ CT thorax and CBNAAT findings and presence of residual/ non-residual lymph nodes

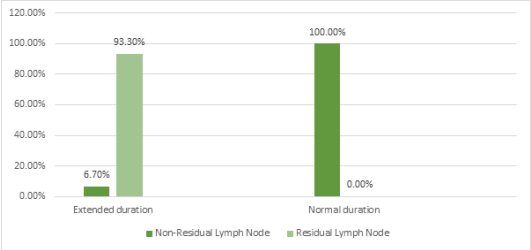

Figure 5. Association between duration of treatment and presence of residual/ non-residual lymph nodes (Association between the duration of treatment and presence of residual/ non-residual lymph nodes was found significant with p-value=0.000)

5. Discussion

Most of the participants (32.8%) in the present study belonged to the age group of 11-20 years, followed by 22.4% between 21-30 years and 17.9% between 31-40 years. In a study by Biswas et al. [10], 19 out of 30 cases were in the age group between 11 and 30 years. In another study by Majeed et al. [11], of 96 cases, 31 cases were in the age group between 21 and 30 years. In this younger age group, the lymphatic system plays an important role, and the lymph nodes act as a powerful second line of defense in preventing the infection, but undernourishment and malnutrition are predisposing factors for the development of TB. Female predominance was observed (56.7%) in the present study, with a male-to-female ratio of 1:1.31. It was found to be 1.7:1 by Biswas et al. [10] and 1.6:1 by Majeed et al. [11]. The increased incidence in females may be due to the wide prevalence of malnourishment, lack of education, early marriage, pregnancy, large families, not giving priority to own health, and poor socioeconomic conditions. Most were residents of rural areas (62.7%) and belonged to a lower socioeconomic status (64.2%), as per the Kuppuswamy classification, in the present study. Biswas et al. [10] found that 60% belonged to a lower socioeconomic status. The main contributing factor for the higher preponderance of TB in low socioeconomic status is due to overcrowding, poor ventilation, unhygienic living conditions, poverty, and malnutrition.

In the present study, among those with a positive history of TB, most (60%) were found to have non-residual lymph nodes, while the remaining 40% had residual lymph nodes. Among those with diabetes, 50% had residual and non-residual lymph nodes each. Among patients with HIV, 75% had non-residual lymph nodes and 25% had residual lymph nodes. In a study by Seok et al. [12], diabetes was seen in 6.7%, chronic renal failure in 4.2%, cardiovascular disease in 15.2%, and hematological malignancy in 2.4% of cases. It was observed in the present study that 23.9% of patients were asymptomatic, while the rest had symptoms such as decreased appetite (71.60%), weight loss (55.20%), fever (19.40%), cough (14.90%), and pain (7.5%). Also, a large proportion of the patients with the above symptoms were observed to have non-residual lymph nodes. Jha et al. [13] reported weight loss in 14.3% of cases, fever in 10.7%, cough in 10.7%, and pain in 7.3%. Cough is usually not a feature of tuberculous adenitis, and if present, it is probably due to an associated upper respiratory infection or may be a symptom in patients with mediastinal lymphadenopathy. Pain is due to stretching of the covering LN capsule or stretching of deep fascia of the neck by the enlarging lymph nodes. Pain is more if a secondary infection is present.

As observed in the study, a large percentage (76.1%) of the population had 5 or fewer lymph nodes. Lymph nodes were found to be firm in consistency (79.1%), discrete (76.1%), and fixed (70.1%). Consistency was significantly associated with the presence of non-residual and residual lymph nodes (p-value=0.023). A previous study by Salman et al. [14] found that 66% of lymph nodes were soft in consistency, while 34% were firm. Additionally, 28% of lymph nodes were discrete, while 72% were matted. Fixed lymph nodes were present in 70% of cases, and mobile lymph nodes were present in 30%.

In the present study, cervical lymph nodes were found to be located in the upper deep cervical region (49.3%), supraclavicular region (20.9%), lower deep cervical region (19.4%), and submandibular region (10.4%). The right side was more commonly affected (43.3%) than the left side (28.4%) or both sides (28.4%). Lower deep cervical nodes were least commonly involved in a study by Biswas et al. [10]. The posterior triangle nodes were the most commonly affected (42%) followed by the upper deep cervical nodes (16%) in a study by Maharjan et al. [15]. Seok et al. [12] observed that the right side was affected in 58.8% of cases, the left side in 35.8% of cases, and both sides in 8.5% of cases. This is likely because the lymphatics of the right lung and the

lower lobe of the left lung typically drain to the right supraclavicular lymph nodes and then upwards to the right lower cervical chain.

In the present study, most participants (94%) had only cervical lymphadenopathy, while axillary (3%) and mediastinal lymphadenopathy (3%) were also observed. Dandapat et al. [16] found cervical region involvement in 70% of cases, axillary involvement in 6% of cases, inguinal involvement in 9% of cases, and multiple-site involvement in 15% of cases. Subrahmanyam et al. [17] found tuberculous cervical lymphadenopathy in 93.3% of cases, axillary involvement in 3.8% of cases, and inguinal lymph node TB in 2.9% of cases.

During the initial diagnostic work-up, granulomatous lesions without caseous necrosis were observed in 80.6% of cases, while caseous necrosis was observed in 19.4% of cases. Mudassar et al. [11] found that 69% of cases had granulomatous lesions without caseous necrosis, while 31% had caseous necrosis. ZN stain for AFB of lymph node aspirate was found to be positive in 28.4% of cases in the initial evaluation. In the study by Seok et al. [12], AFB was positive in 20.8% of cases.

Mantoux test was positive in the majority of study participants (85.1%), and ESR was raised in 91% of cases. Chest X-ray/CT thorax findings in 7.5% of cases suggested infiltrates, and in 2% of cases, mediastinal lymphadenopathy was observed. There was a significant association between Chest X-ray/CT thorax findings and the presence of residual/non-residual lymph nodes (p-value=0.012). Jha et al. [13].

In the present study, ATT CAT 1 (HRZE) was given to 97% of patients based on microbiological, histopathological, radiological, and clinical findings. 1.5% [1] were resistant to isoniazid and 1.5% (1) to rifampicin. ATT with ART was given to 4 patients (6%) who were HIV positive. The MDR shorter regimen was given for rifampicin resistance and the H mono regimen was given for isoniazid resistance. A paradoxical reaction was observed in 19 (28.4%) cases. AvanishGandhare et al. [20] reported a paradoxical reaction in 20% of patients during or after treatment cessation, while Seok et al. [12] reported a paradoxical reaction during treatment in 23.0% of patients. This reaction has been attributed to an immune response to dying M. tuberculosis organisms. Treatment for paradoxical reaction was given along with ATT in 18 out of 19 cases, with steroids and anti-inflammatory drugs, and treatment duration was increased. Seok et al. [12] reported that among 320 patients, 12 were treated with steroids and NSAIDs.

In the present study, a USG neck was performed at the end of 6 months of treatment. 20.8% had residual lymph nodes. FNAC was performed in such patients, and caseous necrosis was observed in 7.5%, while others had no sign of tuberculosis. This suggests that all residual lymph nodes do not indicate treatment failure, and patients were closely followed up as many of these nodes were expected to resolve over time. In the present study, the total duration of treatment was significantly associated with the presence of non-residual/residual lymph nodes with $p<0.05$. Lymphadenopathy resolved in 77.6% of patients after 6 months of treatment but persisted in 22.4% of patients, while in the study by Seok et al. [12], extended treatment for a long period was given in 20% of patients. In our study, 6 (9%) patients underwent surgical excision, and 6 (9%) patients underwent non-dependent incision and drainage, whereas Maharajan et al. [15] reported that 4.8% of patients were advised for surgical excision, and Salman et al. [14] reported that 18% of patients had surgical excision. Jha et al. [13] found that 7.8% of patients were advised for surgical excision and 3.5% for non-dependent incision and drainage. With the advancement in chemotherapy, the role of surgery is limited to drainage of cold abscess, excision biopsy of affected lymph nodes, and excision of residual lymph nodes.

6. Conclusion

Cervical lymph node tuberculosis is the most common form of extrapulmonary tuberculosis. FNAC is the most common and simple procedure to diagnose lymph node tuberculosis. The presence of residual LNs after 6 months of anti-tuberculosis treatment in patients with cervical tuberculosis lymph node does not necessarily indicate recurrence or treatment failure but must be re-evaluated and differentiated from active TB.

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