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Identification of Mono and Multi-Drug Resistance in Patients with Tuberculous Lymphadenitis Undergoing Excision: A Prospective Observational Study

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Abstract: ***Background:*** Tuberculosis lymphadenitis (TBLN) is a prevalent form of extrapulmonary tuberculosis (TB), particularly in low socioeconomic countries such as Pakistan. The rising burden of drug-resistant TB poses a significant challenge to management, often exacerbated by limited awareness, delayed diagnosis and poor treatment adherence. The objectives of this study were to: 1) identify the frequency of mono- and multi-drug resistance (MDR) among newly diagnosed and relapsed TBLN patients using excisional biopsy with microbiological analysis; and 2) evaluate clinicopathological aspects of TBLN. ***Methods:*** A prospective observational study was conducted on 60 newly diagnosed and previously treated TBLN patients between December 2024 and October 2025 at Dow University Hospital, Karachi, Pakistan. All patients underwent excisional lymph node biopsy, and their tissue samples were sent to the microbiology laboratory for histopathology, culture, and genexpert® MTB/RIF testing. ***Results:*** TBLN was most common in individuals with a mean age of 29.81 years and a female predominance of 61.7%. The majority presented with cervical lymph node swelling 90% and cough 31.67%. Overall, rifampicin resistance was detected in 11.67% of cases, isoniazid resistance in 8.33%, and MDR in 6.67%. Approximately 22.22% of patients had a history of previously treated TBLN, among whom 11.11% had MDR. Comparison between treatment history and the presence of drug resistance did not show a statistically significant correlation (p=0.593, OR=2.15, 95% CI= 0.36–12.80). ***Conclusion:*** A clinically relevant proportion of TBLN patients had mono- and multi-drug resistance. Our findings highlight that histopathological and microbiological evaluation through excisional biopsy is an efficient approach for diagnosing TBLN and detecting drug resistance, supporting its role in accurate and timely diagnosis to combat the disease in endemic settings.

Keywords: Tuberculosis Lymphadenitis, Excisional Biopsy, Drug Resistance, MDR-TB, Rifampicin.

INTRODUCTION

Tuberculosis (TB) is one of the oldest and deadliest infectious diseases (1). It is caused by *Mycobacterium tuberculosis* (MTB) and causes more than a million fatalities every year (1). Globally, extrapulmonary TB accounts for 15-20% of TB cases, with TB lymphadenitis (TBLN) being the most common manifestation (2). TBLN is a chronic granulomatous inflammation of lymph nodes characterized by caseous necrosis and commonly presents with painless enlarged lymph nodes (3). Frequently affected lymph nodes include cervical, axillary, supraclavicular, inguinal and abdominal nodes (3). The associated systemic features may include low-grade fever, cough, malaise, fatigue, night sweats, and weight loss (4). Major risk factors for TBLN include race, sex, HIV infection, pregnancy, diabetes mellitus, vitamin D deficiency and low protein intake (5). A study in Northern Ethiopia revealed that cough and pediatric age are indicators of TBLN, underscoring

the heterogeneity of its clinical presentation (5).

In 2019, 16% of 7.1 million cases of TBLN prevalence were reported worldwide (6,7), with the ratio being higher in children up to 14 years in India (4.4 cases per 1000) and between 30-40% in the United States (6). Pakistan remains one of the highest TB-burden countries, with the World Health Organization (WHO) reporting about 410,000 TB cases and 69,000 TB deaths per year (8). A literature review estimated the prevalence of TBLN in Pakistan to be 37.33%, predominantly affecting individuals between the ages of 14-27 (6).

Early and accurate detection is crucial for TB control. The commonly used methods for diagnosis are histopathology, mycobacterial culture, genexpert® MTB/RIF, and smear microscopy (9). Excisional biopsy is regarded as the gold standard diagnostic method for TBLN compared to fine needle aspiration cytology (FNAC) (10), as it preserves the lymph node architecture (12). Although it is an invasive procedure, it has the highest sensitivity (80%) and gives a rapid and accurate diagnosis of TBLN as well as a drug resistance profile via mycobacterial culture and drug susceptibility testing (11). The research from Hong Kong identified that 80% of excisional biopsy specimens produced positive culture results, compared to only 17% of fine needle aspiration specimens (11). However, the definite diagnosis of resistance in TBLN is made by culture in the affected lymph node, which gives the resistance pattern for both first- and second-line anti-TB drugs and also confirms the infection by MTB. In contrast, the genexpert® MTB/RIF assay is a fully automated, cartridge-based, and real-time PCR (polymerase chain reaction) system that also confirms the presence of MTB and only rifampicin resistance. The assay employs five overlapping molecular probes to target the rifampicin resistance-determining region (RRDR) of the rpoB gene (13,14). Treatment of TBLN includes first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) and second-line drugs (streptomycin, moxifloxacin, levofloxacin, amikacin) (15).

Currently, the emergence of MDR, or rifampicin resistance, is an important issue (2). In 2018, 186,772 cases of MDR-TB and 156,071 cases of rifampicin resistance were reported (15), and in 2019, 465,000 patients were diagnosed with rifampicin-resistant TB worldwide (16). Research on 'Prevalence and Diagnosis of Rifampicin-Resistant MTB using the GeneXpert® MTB/RIF Assay' at a tertiary care children's hospital, published that there is 4.5% prevalence of MDR-TB in children (18). According to another literature review, it was also observed that escalation in drug resistance in TB due to lack of awareness can be proven to be deadly (16). Drug resistance occurs due to chromosomal mutations that lead to activation of the efflux pump at the bacterial surface, alterations in drug target, enzyme drug inactivation, and impaired drug activation (16). Resistance may also arise in patients from drug-resistant strains due to inadequate regimens, drug malabsorption, and poor adherence to treatment (15). Use of anti-tuberculous therapy for a long time or unwisely switching to second-line drugs can result in paradoxical upgrading reactions (17).

Despite this substantial epidemiological impact of TB in Pakistan, local data describing the clinicopathological features and drug resistance patterns of TBLN remain limited and under-reported; hence, understanding its prevalence and drug resistance patterns is important for an effective diagnostic and therapeutic approach and improving patient outcome to avert the complications, misdiagnosis, and mortality in TB patients. Excisional lymph node biopsy provides both diagnostic and therapeutic intervention; while previous research has focused mainly on clinical presentations and outcomes of TBLN, data integrating excisional biopsy with comprehensive microbiological analysis remains inadequate. Therefore, this prospective observational study aimed to determine the frequency of mono- and multi-drug resistance among newly diagnosed and relapsed (previously treated) TBLN patients using excisional biopsy with mycobacterial culture, and genexpert® testing. Our study also evaluated the clinicopathological aspects of TBLN in an endemic, low-resource setting.

METHODS

Study settings and design

A prospective observational study was conducted at Dow University Hospital, Dow University of Health Sciences (DUHs), Karachi, Pakistan, including the Department of General Surgery and Thoracic Surgery, also known as Ojha Institute of Chest Disease (OICD).

DUHs is a tertiary care hospital with a specialized TB unit (OICD) with over 350 beds. Since its establishment in 1939, it has been one of only three public-sector hospitals in the region providing diagnosis and treatment for TB.

Participants were recruited from both inpatient and outpatient departments over a duration of 11 months, starting from December 2024 to October 2025.

Study Population

All consecutive patients undergoing excisional lymph node biopsy during the study period were screened for eligibility. A total of 283 lymph node excisional biopsies were performed, of which 60 patients (21.2%) were confirmed to have TBLN and constituted the final study cohort.

Inclusion Criteria

1. Age ≥ 14 years.
2. Presence of single or multiple enlarged evident lymph nodes (cervical, axillary, mediastinal, inguinal, or femoral) on clinical examination or radiological imaging.
3. Newly diagnosed, relapsed (previously treated), or currently treated cases of TBLN.
4. Underwent excisional lymph node biopsy with adequate tissue available for pathology, mycobacterial culture, and geneXpert® testing.

Exclusion Criteria

1. Pregnant women.
2. Incomplete clinical and laboratory records.
3. Declined or unavailable informed consent.

Study tool and data collection

Data was collected using a questionnaire-based survey (1,3,8), which was drafted after conducting a literature search using keywords such as "TBLN," "MDR-TB," "drug resistance," "excisional biopsy," "culture," "genexpert," and more. The questionnaire was divided into 2 sections; the first part consisted of socio-demographic variables, including medical record (MR) number, age, sex, marital status, addictions, co-morbidities, and previous TB exposure, and the second section provided the information on symptoms, investigations and treatment outcomes under the heading 'Diagnostic Approach'. The structured questionnaire was pretested on a sample representing 5% of the targeted population to assess its consistency before the original data collection.

The survey was conducted in the participant's native language, in the presence of trained postgraduates and medical officers, after obtaining the informed consent.

Diagnostic Intervention and Laboratory Methods

During the study period, all selected patients underwent detailed clinical and radiological evaluation before the biopsy. Excisional biopsy of the lymph node was performed under general or local anesthesia using standard aseptic protocol after informed consent. Biopsy specimens (tissue samples) were forwarded to the microbiology lab in formalin for histopathological examination and in saline (0.9%) for microbiological analysis (culture and genexpert®) (7). Sterilization was ensured to avoid contamination throughout the process.

Histopathological examination was performed on hematoxylin and eosin (H&E) stained sections by an experienced histopathologist at DUHs. Histopathology was categorized into four groups: (i) well-formed granulomas without necrosis, (ii) well-formed granulomas (predominantly) with necrosis, (iii) ill-formed granulomas with necrosis, and (iv) caseous necrosis without granuloma, for classification purposes (21).

For mycobacterial culture specimens, two slopes of Lowenstein-Jensen (LJ) medium and one Mycobacteria Growth Indicator Tube (MGIT 960; Becton Dickinson, Sparks, MD, USA) were inoculated for the detection of MTB and drug pattern (19). Genexpert® was performed according to manufacturer protocols to detect MTB and rifampicin resistance (20). Laboratory reports were typically issued within 24–72 hours for genexpert® results, 10–14 days for histopathology, and 6-8 weeks for culture reporting.

Statistical analysis

Sample size was calculated using OpenEpi version 3.01 (22). Based on a previous study, a 2.819% prevalence of TBLN was reported in Pakistan (23); with a 97% confidence level and a 5% margin of error, the computed sample size was 52. After adding a 10% expected non-response rate, a minimum sample size of 57 was obtained. Later, during the study period three additional patients who fulfilled the eligibility criteria were also included, resulting in a final analyzed sample of 60 patients with confirmed TBLN. All the data that was tabulated on the Google Form was then reviewed and transferred into a Microsoft Excel sheet. The data was analyzed using IBM SPSS Statistics version 30. Descriptive statistics were used to summarize the data. Categorical variables such as sex, smoking status, drug resistance were presented as frequencies and percentages, while mean ± standard deviation was reported for continuous variables such as age. Drug resistance patterns were compared between newly diagnosed and previously treated patients using univariate analysis. Fisher's exact test and odds ratio (OR) with 95% confidence intervals (CIs) were also calculated to assess the association between treatment history and drug resistance. Statistical significance was defined at p-value ≤0.05.

Ethical considerations

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of DUHs. The reference number is *IRB-3722/DUHS/Approval/2024/12*. The study was reviewed and approved by an ethical review board to ensure compliance with relevant ethical standards, minimizing harm and protecting participant's rights. Written informed consent was obtained from all participants. All methods were conducted strictly in compliance with the guidelines and regulations of the *Declaration of Helsinki*.

RESULTS

During the study, a total of 60 patients with confirmed TBLN were included. The mean age of the study population was 29.81 ± 16.26 years, with the highest

prevalence observed in the 14–24 year age group (48.33%). A female predominance of 61.67% (n=37) was noted, while 38.33% (n=23) were males. Nearly half of the participants were married 48.33% (n=29), followed by single individuals 46.67% (n=28). The majority had no documented co-morbidities, 76.67% (n=46), but among the remaining proportion, hypertension 13.33% (n=8) and diabetes mellitus 11.67% (n=7) were the most common. Similarly, most of them reported no addictions, 76.67% (n=46), followed by smoking, mostly seen in 16.67% (n=10) of patients.

Cervical lymphadenopathy was the most common site of involvement and clinical presentation, observed in 90% (n=54) of patients, followed by mediastinal 6.7% (n=4) and axillary 3.33% (n=2) lymph nodes.

Systemic symptoms were infrequently reported. Cough was the most common associated symptom in 33.33% (n=20) of cases, while fever, night sweats and malaise were each present in 11.67% (n=7) of patients. Histopathologically, four categories of describing TBLN were used; the most common in our setup was well-formed granulomas (predominantly) with necrosis in 71.67% (n=43) of these cases. Ill-formed granulomas with necrosis were more frequent than non-necrotizing granulomas (16.67% (n=10) versus 8.33% (n=5), respectively). Caseous necrosis with no granuloma was found in the least number of patients, that is, 3.33% (n=2).

Table 1. Clinicopathological Characteristics of the TBLN Population

Variable	Frequency (n)	Percentage (%)
Age Group (Years)		
	29.81 ± 16.26	
14-24	29	48.33
25-34	14	23.33
35 & above	17	28.33
Gender		
Male	23	38.33
Female	37	61.67
Marital Status		
Single	28	46.67
Married	29	48.33
Widow/Divorced	3	5
Co-morbidities		
None	46	76.67
Hypertension	8	13.33
Diabetes	7	11.67
Heart disease	2	3.33
COPD	1	1.67
Symptoms		
Cough		
Yes	20	33.33
No	40	66.67
Fever		
Yes	7	11.67
No	53	88.33
Malaise		
Yes	7	11.67
No	53	88.33
Night sweating		
Yes	7	11.67
No	53	88.33

Weight Loss		
Yes	6	10
No	54	90
Dyspnea		
Yes	5	8.33
No	55	91.67
Addictions		
None	46	76.67
Smoking	10	16.67
Pan	7	11.67
Gutka	4	6.67
Naswar	2	3.33
Lymph Node Type		
Cervical	54	90.0
Mediastinal	4	6.67
Axillary	2	3.33
Histopathology Type		
Well-formed granulomas with no necrosis	5	8.33
Well-formed granulomas (predominantly) with necrosis	43	71.67
Ill-formed granulomas with necrosis	10	16.67
Caseous necrosis with no granuloma	2	3.33

Resistance to first-line anti-tuberculous drugs was identified in a subset of patients. Rifampicin resistance was detected in 11.67% (n=7) of patients, while isoniazid resistance was documented in 8.33% (n=5). MDR-TB was present in 6.67% (n=4) of cases. All patients were sensitive to ethambutol, and resistance to pyrazinamide was rare, 1.7% (n=1). Overall, the majority demonstrated sensitivity to first-line drugs.

Table 2 (a). Results of Investigation with Drug Characteristics - Mycobacterial Culture (n=60)

Drugs	Frequency (n)	Percentage (%)
Rifampicin		
Resistance	7	11.67
Sensitive	53	88.33
Isoniazid		
Resistance	5	8.33
Sensitive	55	91.67
Ethambutol		
Resistance	0	0
Sensitive	60	100
Pyrazinamide		
Resistance	1	1.67
Sensitive	59	98.33
Rifampicin & Isoniazid (MDR)		
Resistance	4	6.67

In contrast, geneXpert® MTB/RIF detected rifampicin resistance in 10% (n=6) of cases, while in 68.33% (n=41), it was not detected by the assay. However, 8.33% (n=5) of cases were indeterminate, indicating the inability of the assay to conclusively determine rifampicin resistance.

(b) Result of Investigation with Drug Characteristics - GeneXpert® MTB/RIF (n=60)

Rifampicin Resistance	Detected	Indeterminate	Not detected
Frequency (n)	6	5	49
Percentage (%)	10	8.33	81.67

Patients with a history of prior TB (n=9) demonstrated a higher frequency of drug resistance 22.22% (n=2), compared with newly diagnosed patients, 11.53% (n=6). MDR was identified in both groups, accounting for 5.88% (n=3) in newly diagnosed patients (n=51) and 11.11% (n=1) of relapsed patients. Comparison between treatment history and the presence of drug resistance did not demonstrate a statistically significant association (Fisher's exact test, *p=0.593, OR=2.15, 95% CI= 0.36–12.80*). The odds of drug resistance were higher in relapsed cases (0.286) than in newly diagnosed cases (0.133).

Table 3. Association Between Newly Diagnosed and Relapsed (Previously Treated) Cases with the Outcome of Drug Resistance Pattern (n=60)

		Sensitive	Rifampicin Resistance	Isoniazid Resistance	Rifampicin & Isoniazid Resistance (MDR)
Previously treated cases (n)		7	2	1	1
Newly diagnosed cases (n)		45	5	4	3

DISCUSSION

TBLN remains a significant challenge in several developing countries, including Pakistan (1,3). The emergence of mono- and multi-drug resistant TB complicates the management of TBLN, leading to delays in diagnosis, treatment failures, and increased morbidity (18). This prospective observational survey evaluated the clinicopathological characteristics of TBLN and identified the drug resistance pattern using excisional biopsy, histopathology, mycobacterial culture, and geneXpert® MTB/RIF assay.

This study highlights several important epidemiological and clinical observations **[Table 1]**. The majority of our patients were younger, between the ages of 14-24, accounting for about 48.33% of cases. These findings align with prior studies in Pakistan indicating a high burden among the younger population (6). Females were more commonly affected than males (61.67% vs. 38.33%), which contrasts with a retrospective study from Ethiopia where male predominance was observed (3). While other researchers have reported TBLN co-infection with diseases such as HIV (5,17), the majority of our patients were previously healthy and had no known co-morbidities and addictions. These findings suggest that while demographic factors provide context for understanding population susceptibility, they may not independently predict TBLN and reflect the possibility of sociocultural, nutritional and healthcare-seeking differences in endemic areas, emphasizing the need for comprehensive diagnostic approaches regardless of patient characteristics. The most common clinical presentation was enlargement of cervical lymph nodes (90%) and cough (33.33%), as shown in the **[Table 1]**, while systemic symptoms were relatively uncommon. Studies conducted in Africa and Bangladesh have also reported a similar finding (3,5). Unlike the research conducted in Qatar and Malaysia, where night sweats were the most frequent presenting symptom, and Denmark and Malaysia, where constitutional symptoms were more frequent (26,27,28). These findings suggest that TBLN may present without classical systemic symptoms, potentially leading to misdiagnosis. The well-formed granuloma with necrosis was most commonly observed in histopathological examination. This finding aligns with the previous research conducted in Saudi Arabia (29) that highlights the diagnostic importance of histopathology in TBLN cases.

TB resistance to first-line drugs is classified as mono-drug resistance, while resistance to both rifampicin and isoniazid is classified as MDR-TB (16,24). A research in Pakistan reported a low rifampicin resistance rate, with only 5 out of 110 patients testing positive for rifampicin resistance (15), in contrast to our study's findings of a 11.67% rifampicin resistance rate among TBLN-positive cases in mycobacterial culture, as presented in **[Table 2a]**. These findings are also comparable to a previous study (29) which reported 10.7% TBLN resistance cases. While MDR-TB was also

observed in 6.67%. The presence of MDR-TB in both newly diagnosed and previously treated patients emphasizes the ongoing transmission of resistant strains, indicating the rise of resistance from prior exposure. According to the WHO, Xpert MTB/RIF and Xpert Ultra (genexpert®) are the initial tests recommended for diagnosing pulmonary and extrapulmonary TB (15,18). It also detected a similar proportion of rifampicin resistant cases compared with culture. However, a clinically relevant number of cases (8.33%) yielded indeterminate results on genexpert®, which could be due to low bacterial load, poor sample quality or machine malfunctions **[Table 2b]**. This observation signifies the value of integrating molecular analysis with culture based tests, especially for TBLN, to avoid misclassification of drug resistance. Even though a study in Addis Ababa showed a higher detection rate of positive TB cases using Xpert MTB/RIF, implying differences in detection rates across different populations (2). Additionally, genexpert® MTB/RIF, while highly reliable for detecting rifampicin resistance, cannot detect isoniazid resistance without additional molecular testing, and culture-based drug susceptibility testing, although accurate, is time-consuming delaying treatment decisions.

In this cohort, mono-drug resistance and MDR-TB were found in both new and relapsed cases, which suggests that both primary and acquired drug resistance existed during the course of TBLN. Even so, the majority of patients (52) were newly diagnosed, with no prior history of TBLN **[Table 3]**, but drug resistance was observed to be higher among relapsed TBLN patients, implying inadequate or prior incomplete treatment for the development of drug-resistant strains. However, the comparison between the two groups was not statistically significant, likely due to the limited sample size.

The key strength of this study is its prospective observational design and use of excisional biopsy with comprehensive microbiological analysis for diagnosing TBLN and identifying drug resistance patterns. However, several limitations of this study should be acknowledged. The single-center design and relatively small sample size (total n=60, original 57 + 3 additional participants) may limit the generalizability and reduce the statistical power to detect significant associations, especially in subgroup analyses. Selection bias may have been observed due to the exclusion of patients who did not provide consent, had financial difficulties, were non-compliant with lab tests and treatment or had misplaced samples. These factors may have impacted the quality and reliability of our findings.

Therefore, it is advisable for future research studies to conduct larger, multi-center cohorts among diverse populations to determine predictive factors and resistance patterns in TBLN and use genomic sequencing to identify resistance-conferring mutations in TB strains and, explore the mechanisms behind drug resistance, in Pakistan or other endemic areas to develop new strategies for combating TB.

CONCLUSION

To conclude, the study demonstrates a significant burden of mono- and multi-drug resistance with considerable variation in demographic characteristics among TBLN patients. Rifampicin resistance and MDR were identified in a notable number of cases, in previously treated as well as newly diagnosed patients. Clinically, TBLN predominantly affected young individuals and presented as isolated cervical lymphadenopathy, in the absence of prominent systemic symptoms.

Excisional lymph node biopsy enabled early and accurate detection of drug resistance, highlighting its diagnostic value beyond cytology-based approaches, particularly in patients lacking classical systemic symptoms. This points out the need for enhanced monitoring, early detection, and strict adherence to treatment guidelines to mitigate further resistance development. More extensive research is also recommended to refine management. These insights are essential for improving patient outcomes and guiding public health strategies in TB-endemic, resource-limited countries.

DECLARATION

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Authors: All authors contributed equally to the conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing the original draft, and editing the review draft of this research.

ABBREVIATIONS

Tuberculosis (TB)
TB lymphadenitis (TBLN)
Mycobacterium tuberculosis (MTB)
Multidrug resistant TB (MDR-TB)
World Health Organization (WHO)
Fine needle aspiration cytology (FNAC)
Ojha Institute of Chest Disease (OICD)

Lowenstein-Jensen (LJ)
Mycobacteria Growth Indicator Tube (MGIT)
Hematoxylin and eosin (H&E)
Institutional Review Board (IRB)

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