

## ORIGINAL ARTICLE

# Clinical Features and Predictors of a Complicated Treatment Course in Peripheral Tuberculous Lymphadenitis

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**Background/Purpose:** There remains uncertainty regarding the treatment strategy for patients with peripheral tuberculous lymphadenitis (pTBL) in areas endemic for tuberculosis. The purpose of this study was to demonstrate the clinical features and assess the predictors of a complicated treatment course in pTBL.

**Methods:** A retrospective analysis of 97 pTBL patients from January 1995 through to December 2004 was conducted. Patient characteristics with and without a complicated treatment course, defined as prolonged treatment (> 9 months) and/or relapse, were compared for determining the predictors.

**Results:** The disease occurred predominantly in females (57.7%) with a mean age of 37. Most patients (72%) were asymptomatic. Cervical nodes were the most common (72%) manifestations. Fifty-six patients completed a 6–9 month course of therapy without relapse; 28 had a prolonged but complete treatment course, and 13 relapsed within a mean of 8.5 months after treatment (range, 3–42 months; median, 7.8 months). Of 97 pTBL patients, six had enlarged or newly appeared lymph nodes during treatment. Multivariate analysis indicated that low body mass index and bilateral cervical nodes were independent determinants of a complicated treatment course with the odds ratios of 1.2 (95% CI, 1.01–1.41;  $p=0.042$ ) and 3.9 (95% CI, 1.08–14.0;  $p=0.038$ ), respectively.

**Conclusion:** This study found that pTBL is more likely to occur in young female patients. For patients who present with bilateral cervical nodes and low body mass index, a prolonged treatment course to ensure disease control should be considered. [*J Formos Med Assoc* 2008;107(3):225–231]

**Key Words:** clinical features, predictors, treatment course, tuberculous lymphadenitis

Tuberculosis (TB) is the foremost cause of death from a single infectious agent in humans. According to recent estimates, one person is newly infected with TB bacilli every second worldwide, and one third of the global population is currently infected with TB.<sup>1</sup>

Peripheral tuberculous lymphadenitis (pTBL) is a common manifestation of extrapulmonary TB, accounting for about 4.0–5.1% of all TB cases and 20.3–50.0% of extrapulmonary TB.<sup>2–6</sup> Its timely

diagnosis requires a high index of suspicion and histologic and microbiologic analyses due to its indolent clinical characteristics.<sup>1,5,7</sup> American Thoracic Society (ATS) guidelines recommend a 6-month course of therapy for pTBL that consists of a 2-month period of isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA) followed by INH and RIF for an additional 4 months.<sup>8</sup> Although previous studies have demonstrated a high success rate in the treatment of pTBL

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with the 6-month regimen,<sup>9-11</sup> many patients undergo a prolonged treatment course or suffer disease relapse. This study examined the clinical features and assessed the predictors of a complicated treatment course in pTBL patients in Taiwan.

## Methods

### *Study subjects and setting*

This study involved a retrospective analysis of records of both outpatients and inpatients diagnosed with pTBL from January 1995 through to December 2004 at National Taiwan University Hospital (NTUH), a tertiary medical center in Northern Taiwan. Diagnosis of pTBL in all subjects was confirmed by pathology of excised peripheral lymph nodes (LN), including cervical, supraclavicular, axillary and inguinal areas, showing caseating granulomatous inflammation, with or without positive TB culture. Patients who received complete anti-TB therapy and follow-up at our clinics were enrolled into the study. Patients were excluded from the study if they exhibited non-caseating granulomatous disease (such as sarcoidosis), tissue cultures indicating LN yielding non-TB *Mycobacterium* and multidrug resistant TB. As the objective of this study was to verify the effectiveness of anti-TB therapy, patients were not enrolled if they died for reasons other than TB at follow-up pending the completion of the treatment course.

A chart extraction form was used to retrieve demographic data including age, gender, body mass index (BMI), concomitant medical illness and clinical features. The characteristics of LN and constitutional symptoms including fever, sweating, loss of body weight, fatigue and respiratory symptoms were recorded. Initial treatment regimen, adjustment of regimen, treatment duration, drug side effects, microbiologic data with susceptibility tests, and treatment response were also obtained.

All patients were followed-up for at least 1 year after the completion of treatment to verify disease relapse. The first episode of relapse was recorded if more than one occurred in the same patient. Based on clinical scenarios of treatment course,

patients were divided into two groups: uncomplicated and complicated. *Uncomplicated* was defined as disease cured after a 6-9-month course of anti-TB therapy with diminished (< 1 cm) or disappeared LN and no evidence of relapse for 1 year post-treatment. *Complicated* was defined as patients with: (1) prolonged treatment course exceeding 9 months; (2) treatment failure defined as LN persisting throughout the treatment course without decreasing in size; or (3) relapse defined as cure of disease after a 6-9-month anti-TB therapy but new appearance of LN after completing treatment and diagnosis and confirmed by pathology and/or culture results.<sup>5,7,8,12</sup>

### *Statistical analysis*

Data were expressed as mean  $\pm$  standard deviation and range, and for data with skewed distribution as median and range. The  $\chi^2$  test was used for categorical variables, and Fisher's exact test (if appropriate) and Student's *t* test for continuous variables. Exploratory analysis of predictors for a complicated treatment course was performed by comparing patient characteristics between the two groups. Univariate analysis was performed to determine potential predictors of a complicated treatment course. If variables were unavailable for more than 25% of patients, only number and ratio were presented instead of statistical analysis. All potential predictors were included in the full model for exploratory analysis. Multivariate logistic regression was used to assess predictors of a complicated treatment response. Stata Statistical Software version 8.0 (Stata Corp., College Station, TX, USA) was used for statistical analysis. All tests were two-sided, and a *p* value < 0.05 was considered statistically significant.

## Results

### *Patient demographics*

Within a 10-year period, 119 pTBL patients were identified, representing 3.1% of all TB cases (*n* = 3811) diagnosed at NTUH. Twenty-two were excluded from the analysis, 15 received no treatment,

**Table 1.** Demographic data of enrolled patients\*

	Total (n=97)	Uncomplicated <sup>†</sup> (n=56)	Complicated <sup>†</sup> (n=41)	p
Age (yr)	37 ± 15.5 (97, 7–74)	38 ± 17.0 (56, 7–74)	34 ± 13.0 (41, 15–73)	0.192
Male	41/97 (42)	25/56 (45)	16/41 (39)	0.679
Previous TB	29/94 (31)	14/54 (26)	15/40 (38)	0.264
HIV positive	21/64 (33)	9/35 (26)	12/29 (41)	
Immunocompromised <sup>‡</sup>	8/97 (8)	5/56 (9)	3/41 (7)	0.999
BMI (kg/m <sup>2</sup> )	21.1 ± 3.38 (87, 15.9–31.5)	21.9 ± 3.60 (51, 16.3–31.5)	20.0 ± 2.74 (36, 15.9–26.8)	0.006

\*Data are presented as mean ± standard deviation (n, range) or n/N (%); <sup>†</sup>see text for definitions of uncomplicated and complicated groups; <sup>‡</sup>chronic liver disease, renal disease, diabetes, alcoholism or steroid use. TB = tuberculosis; HIV = human immunodeficiency virus; BMI = body mass index.

**Table 2.** Clinical presentations and treatment course\*

	Total (n=97)	Uncomplicated <sup>†</sup> (n=56)	Complicated <sup>†</sup> (n=41)	p
Constitutional symptoms <sup>‡</sup>	27/97 (28)	13/56 (23)	14/41 (34)	0.259
Active pulmonary TB	19/96 (16)	6/55 (10)	13/41 (25)	0.002
Sites of TB other than LN	27/96 (28)	9/55 (16)	18/41 (44)	0.005
Biopsy to treatment (d)	27 ± 29.3 (97, –34–133)	30 ± 26.3 (56, –25–133)	25 ± 34.7 (41, –34–121)	0.441
Initial 4-drug regimen <sup>§</sup>	80/97 (82)	45/56 (80)	35/41 (85)	0.597
Regimen adjusted due to drug side effects	30/97 (31)	15/56 (27)	15/41 (37)	0.375

\*Data are presented as n/N (%) or mean ± standard deviation (n, range); <sup>†</sup>see text for definitions of uncomplicated and complicated groups; <sup>‡</sup>fever, sweats, body weight loss, fatigue and airway symptoms; <sup>§</sup>rifampin, isoniazid, ethambutol, pyrazinamide. TB = tuberculosis; LN = lymph nodes.

five were lost to follow-up, and two died during treatment due to non-TB causes. Ninety-seven (56 female, 41 male) patients were enrolled in the study.

The ethnicity of all patients was Chinese. Fifty-six patients (uncomplicated group) were followed-up for a mean of 44 months (range, 12–116 months). Forty-one patients (complicated group) received a mean of 13.6 months (range, 10–26.5 months) of anti-TB therapy, 13 of whom relapsed with a mean elapsed time of 8.5 months (range, 3–42 months; median, 7.8 months). No patient in the complicated group experienced treatment failure. The cure rate was 87% (84/97).

Age distribution was mostly in the 30–39 years old stratum (33%), followed by 20–30 (24%), 40–49 (11%), ≥ 60 (11%), 50–59 (9%), 10–19 (8%) and 0–9 (4%), respectively. Anti-human immunodeficiency virus (HIV)-infected patients had a mean CD4 count of 79/mm<sup>3</sup>, of whom 81%

(17/21) had acquired immune deficiency syndrome (AIDS), indicated by CD4 count < 200/mL and/or appearance of opportunistic infections. Univariate analysis revealed that only initial BMI significantly differed ( $p=0.006$ ), indicating its potential value as a predictor of a complicated treatment course (Table 1).

#### Clinical presentations and treatment course

Table 2 summarizes the clinical features and treatment course for all subjects. Constitutional symptoms were observed in 76% (16/21) of HIV-infected patients and in 12% (5/43) of non-HIV infected patients. Pulmonary involvement was more common (57%) in HIV-infected patients. Chest radiography revealed fibrocalcified lesions in 10% of patients, mediastinal lymphadenopathy in 5%, mild infiltration in 10%, advanced (caseating infiltration or cavitation) and miliary

**Table 3.** Characteristics of lymph nodes and microbiologic results

	Total (n = 97)	Uncomplicated <sup>†</sup> (n = 56)	Complicated <sup>†</sup> (n = 41)	p
Positive AFS of LN	30/96 (31)	14/56 (25)	16/40 (40)	0.126
Positive culture of LN	37/53 (70)	18/26 (69)	19/27 (70)	
Any resistance in drug susceptibility	6/53 (11)	0/26 (0)	6/27 (22)	
Characteristics of LN				
Duration (d)	194 ± 363.2 (91, 7–1800)	220 ± 395.7 (52, 7–1800)	160 ± 316.4 (39, 14–1800)	0.424
Size (cm)	3.0 ± 1.88 (95, 0.6–10)	2.8 ± 1.76 (54, 0.6–10)	3.2 ± 2.02 (41, 1–8)	0.316
Bilateral cervical node distribution	20/97 (21)	7/56 (13)	13/41 (32)	0.025
Tenderness	33/88 (37)	19/50 (38)	14/38 (37)	0.999

\*Data are presented as n/N (%) or mean ± standard deviation (n, range); <sup>†</sup>see text for definitions of uncomplicated and complicated groups. AFS = acid-fast stain; LN = lymph nodes.

lesions in 6% and TB pleurisy in 2%; all others (67%) were normal.

Six (5 in complicated group) of 97 patients had enlarged or newly appeared LNs during the course of treatment at an average of 2.5 months (range, 2.0–5.5 months) after initiating therapy. Three of five patients in the complicated group underwent surgical intervention; all were found to have granuloma pathologically, but only one was culture-positive for *Mycobacterium tuberculosis*. Residual nodes were observed in eight patients, four in each group. Three (1 in uncomplicated group, 2 in complicated group) had local abscess formation; otherwise, none developed local complications such as ulceration or sinus drainage.

#### *Characteristics of LNs, microbiologic and laboratory results*

Patients in the complicated group had more bilateral cervical LNs ( $p = 0.025$ ). Median duration from development of mass to diagnosis of pTBL was 3.5 months (range, 0.25–60 months). In HIV-infected patients, lymphadenopathy was of shorter duration with a mean of 47 days versus 310 days in non-HIV infected patients. The neck region was the most common site of lymphadenopathy. Cervical, submandibular, supraclavicular, axillary and inguinal nodes were noted in 72%, 14%, 12%, 8% and 2% of patients, respectively. Only 54.6% of surgical specimens were sent for TB culture, and the yield rate was 70% positive for TB. Cultures

from HIV-infected patients had a higher percentage of TB positivity than cultures from non-HIV-infected patients (93% vs. 52%,  $p = 0.01$ ). As Table 3 shows, resistant strains were all identified in the complicated group, including two strains that were resistant to EMB, two to streptomycin (SM), one to INH and one to RIF. Laboratory findings revealed mild anemia with hemoglobin of  $12.0 \pm 2.1$  g/dL and  $11.6 \pm 2.0$  g/dL and mildly elevated lactate dehydrogenase of  $545.0 \pm 422.8$  U/L and  $447.0 \pm 155.5$  U/L in uncomplicated and complicated groups, respectively. Other data, including albumin and cholesterol levels, were nonspecific. None of the differences in laboratory findings approached statistical significance.

#### *Multivariate analysis of predictors of a complicated treatment response*

Results of univariate analysis indicated that BMI, TB involving other sites, active pulmonary TB and bilateral cervical node distribution were potential predictors. Due to the close relationship between active pulmonary TB and TB involving other sites, only the former was deemed a potential predictor. Age and gender were also analyzed in the full model. The results showed that both low BMI and bilateral cervical node distribution were independent determinants of complicated treatment course with odds ratios of 1.2 (95% CI, 1.01–1.41;  $p = 0.042$ ) and 3.9 (95% CI, 1.08–14.0;  $p = 0.038$ ), respectively (Table 4).

**Table 4.** Multivariate analysis for predictors of complicated treatment course

	Odds ratio	95% confidence interval	<i>p</i>
Age	1.00	0.97–1.03	0.701
Gender	0.57	0.21–1.57	0.279
Body mass index*	1.19	1.01–1.41	0.042
Active pulmonary TB	1.88	0.53–6.76	0.329
Bilateral cervical LN	3.88	1.08–14.0	0.038

\*Risk ratio is presented as per unit decrease of kg/m<sup>2</sup>. TB = tuberculosis; LN = lymph nodes.

## Discussion

The findings of this study indicated that lower BMI and bilateral cervical lymphadenopathy were predictors of a complicated treatment course in pTBL patients. The ATS guidelines for pTBL were also found to be applicable in TB endemic areas, and treatment response of pTBL resembled that of pulmonary TB.

Due to the indolent nature of pTBL, patients often seek medical treatment only after several months of development. From 1995 to 2002, the incidence of TB in Taiwan increased from 50 to 74.6 per 100,000 persons, representing 11,000–16,000 new cases yearly.<sup>13</sup> Although the results are partially explained by the strict regulation by National Health Insurance Policy since 1997, the annual incidence of TB is still high according to the Centers for Disease Control in Taiwan. This increased incidence accounts for the high prevalence of TB infection history in the study population. Also consistent with previous reports<sup>5,6,12,14–16</sup> was the predominance of young adult female subjects with pTBL. The higher proportion of young adults suggests that TB lymphadenitis is an entity of early post-primary TB reactivation.<sup>12</sup>

Several studies have described the association between development of TB and impaired host immunity.<sup>2,17–22</sup> HIV infection was the most commonly mentioned, in which CD4 counts were usually <50/mm<sup>3</sup>.<sup>1,2,7,17</sup> The clinical features of TB in HIV-infected patients dramatically differed from those in immunocompetent hosts.<sup>18–20</sup> Most reflected a clinical syndrome of HIV infection rather than of TB infection. The results of this study indicated that HIV-infected patients had

a shorter course of development of lymphadenopathy, higher positive TB culture rates and more frequent pulmonary involvement. These findings may have been due to the heavy burden of TB bacilli with rapid spread under the condition of impaired immune defense.

Previous studies indicate that BMI is lower in pulmonary TB patients than in healthy controls.<sup>23,24</sup> BMI is also known to be lower in HIV-infected adults with TB infection than in non-HIV-infected adults.<sup>25</sup> The lower BMI reflects the magnitude of malnutrition that is closely related to the integrity of immune defense.<sup>26</sup> Another finding of the current study is that patients with bilateral cervical node distribution are more likely to have a complicated treatment course. The same findings can be observed in patients with TB in other sites including pulmonary involvement. Together, these data imply that either the extent of TB infection or the burden of TB bacilli is attributable to an unsatisfactory treatment course.

The presentations in these patients were mostly asymptomatic except for slowly enlarging, painless cervical masses. Physical examination typically revealed firm, discrete or confluent masses. These findings are consistent with those of previous studies, except for a drain sinus tract that was noted in 5–10% of patients, and some who presented with fistula.<sup>7,27,28</sup> Since pTBL is indolent in nature, excessive delay in diagnosis or treatment is not uncommon.<sup>29,30</sup> The diagnosis of patients in this study was based on pathologic findings of excised LNs and/or tissue cultures. In certain situations, a surgical procedure might postpone treatment due to pending pathology results. Culture results also require a delay of several weeks. The tuberculin

skin test has been proposed as a diagnostic tool for pTBL.<sup>5</sup> However, this test was not performed because massive Bacillus Calmette-Guérin vaccination and the high prevalence of TB infection history in the general population makes the test less useful. Culture for *Mycobacterium spp.* is a critical step in treating TB infection. However, surgical specimens are rarely sent for microbiologic culture, which highlights the need to implement a standard procedure for managing pTBL.<sup>5,7,12</sup>

ATS guidelines indicate that a 6-month regimen consisting of INH and RIF is effective for TB treatment, and a 9- to 12-month regimen is needed for infection in the central nervous system.<sup>8</sup> Due to the high incidence of INH resistance (4.7–12.0% of primary resistance) in Taiwan,<sup>13</sup> the treatment strategy for newly diagnosed TB is comprised of a four-drug (INH, EMB, RIF, PZA) regimen for the initial 2 months followed by INH, EMB and RIF for an additional 4 months.<sup>31</sup> Further, the ATS guidelines indicate that prolongation of therapy should be considered if clinical improvement is slow.<sup>8</sup> However, the categories *slow to respond* and *paradoxical response* are not clearly distinguishable, especially in pTBL. In this study, 6% of cases had enlargement or newly appearing LNs during initial treatment. A literature review of pTBL<sup>5,6,10–12,14–17</sup> disclosed that newly appearing LNs, enlargement of existing nodes or nodes becoming fluctuant occurs in up to 20% of pTBL patients at a mean of 3.5 months after the initiation of therapy.<sup>5,10,12,32</sup> Residual nodes were also noted in 4–10% of cases after completion of therapy, although most of them were free from microbiological relapse.<sup>5,6,12,17,32</sup> The overall cure rate was 89–100%, but treatment duration, even in recent decades, usually exceeds 6 months. It is crucial that clinicians carefully differentiate between post-therapy paradoxical expansion and treatment failure. Otherwise, patients may be subject to a higher risk of anti-TB drug-related side effects.

There are several limitations to this study. First, the incidence of pTBL might have been underestimated due to cases detected by fine needle aspiration not being enrolled. Second, due to the unavailability of certain biochemical data, the

effects of these criteria on complicated treatment course was not analyzed, and only patient characteristics were considered. Third, treatment strategies depend on the judgment of the clinicians, and misclassification of treatment response might occur. Finally, most of our patients did not receive directly observed treatment strategy (DOTS); thus, possible lack of adherence to treatment may have played a role in determining patient outcome.

In conclusion, this study of the clinical features and treatment course of pTBL patients indicate that young adult females with asymptomatic cervical lymphadenopathy should be examined for pTBL, especially in TB endemic areas. The relatively low proportion of surgical specimens being sent for mycobacterial culture highlights the need to implement a standard procedure for managing pTBL. A prolonged treatment course should be considered in patients who present with bilateral cervical nodes and low BMI to ensure disease control.

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