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# Gender differences in the clinical diagnosis of tuberculous lymphadenitis—a hospital-based study from Central India

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## KEYWORDS

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## Summary

**Objective:** Tuberculous lymphadenitis can be difficult to diagnose clinically, and as it is thought to be more common in females, we describe here the clinical characteristics of cervical tuberculous lymphadenitis in men and women and compare this with cytology to assess their diagnostic value.

**Methods:** Two hundred and nineteen patients with tuberculous lymphadenitis, aged 14 years or more, who presented with a neck mass to the Department of Pathology, Ujjain Hospital, Ujjain, India were included in the study. The presenting clinical symptoms and signs were compared between men and women and with the cytology of fine needle aspirates from the lymph nodes.

**Results:** Seventy-five percent of the patients were aged between 14 and 35 years, with a male to female ratio of 1:2.1. One or more constitutional symptoms were present in 56.6% of patients on presentation. There were more men with clinical symptoms than women. Fever was the most common manifestation in both gender groups. Fever for more than 30 days, cough, weight loss, and night sweats were significantly more common in men. On cytology, necrotic granulomas were found to be associated with constitutional symptoms.

**Conclusions:** Constitutional symptoms were more frequently reported by men than by women and showed a correlation with necrotic granulomas on cytology.

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## Introduction

The incidence of extrapulmonary tuberculosis (EPTB) has been increasing worldwide over the last few years.<sup>1–3</sup> Peripheral tuberculous lymphadenitis is the most common form

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of the disease,<sup>1,2,4</sup> and is reported to occur in 25–60% of all EPTB cases.<sup>1,2,4,5</sup> Widespread vaccine coverage, HIV infection, and atypical mycobacteria have modified the clinical presentation of the disease in the last decade.<sup>3,6,7</sup> In India, 43% of tuberculous lymphadenitis cases are diagnosed on clinical grounds alone without laboratory confirmation,<sup>8</sup> as these facilities are often not available. Furthermore, even at a center with molecular laboratory facilities, the result of a test will need to be interpreted in the light of the clinical findings. Thus there is a need to update the clinical guidelines for diagnosing tuberculous lymphadenitis and to improve understanding of the pathogenesis.

Tuberculous lymphadenitis is more common in females than in males. Asian women and black women have an increased risk of developing tuberculous lymphadenitis.<sup>9,10</sup> Various studies have reported gender differences in the clinical presentation of pulmonary tuberculosis,<sup>11–14</sup> and similarly one would expect differences in the signs and symptoms of tuberculous lymphadenitis.

Fine needle aspiration (FNA) cytology is usually the first line of investigation in the diagnosis of tuberculous lymphadenitis and has a high diagnostic yield (97%).<sup>15,16</sup> However, laboratory facilities are not available at all centers in developing countries. We were interested in reviewing the clinical parameters of tuberculous lymphadenitis in relation to the morphological changes on cytology.

Patients included in the study were from Ujjain, which is one of the largest districts in Madhya Pradesh in Central India. Madhya Pradesh has a dense rural population and is currently fully covered by the Revised National Tuberculosis Control Program and DOTS program. The prevalence of EPTB varies (3–23%) in the 45 different districts. In Ujjain the prevalence of tuberculosis is 146/100 000 population, and EPTB accounts for approximately 15% of all cases.<sup>11</sup> Until now very little clinical information has been available on lymph node tuberculosis from this region.

The aim of the present study was to describe and compare the symptoms of tuberculous lymphadenitis in men and women in a cohort of patients attending Ujjain Charitable Trust Hospital and Research Centre (UCTHRC), Madhya Pradesh, and to compare the signs and symptoms with the results of cytology to assess their diagnostic value.

## Methods

### Study site

This study was conducted between July 2004 and December 2005 at UCTHRC, a 500-bed referral and teaching hospital in Ujjain, India. UCTHRC receives patients from the city of Ujjain (urban poor and middle class population of 400 000), the Rural Primary Health Centre of the Palwa region serving a population of more than 60 000, and referred patients from Ujjain District Hospital.

### Patients

All inpatients and outpatients with a neck mass, who were referred to the Department of Pathology for FNA cytology, were initially enrolled in the study at the Department of Pathology of UCTHRC when the results of cytology were suggestive of tuberculous lymphadenitis. Detailed

demographic information, clinical history, and examination of all recruited patients were recorded using a pre-designed form by the investigator (MRP) at the time of cytological diagnosis. HIV testing and chest X-ray were also done. Patients were excluded from the study if they were less than 14 years of age, the chest X-ray was suggestive of active pulmonary tuberculosis, and if they were on treatment for tuberculosis or receiving corticosteroids, immunosuppressive, or anti-retroviral therapy.

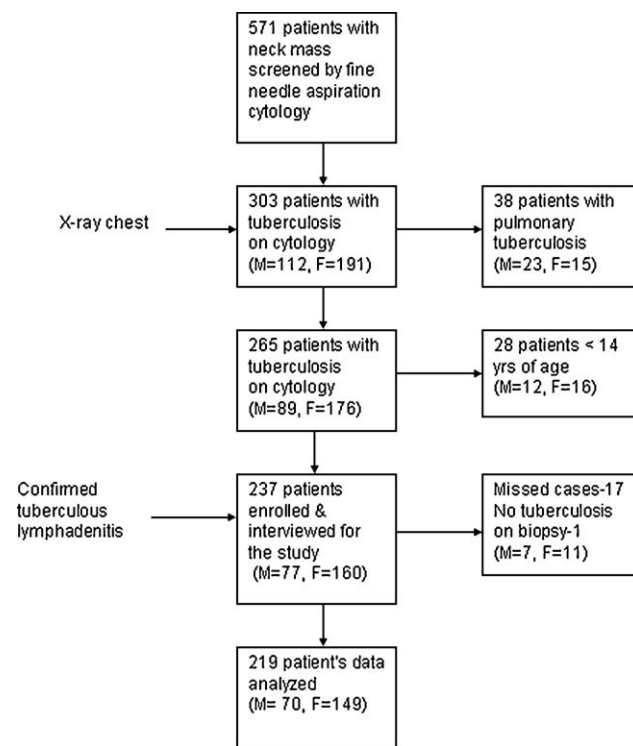
The cytological diagnosis of tuberculous lymphadenitis was confirmed when the lymph gland aspirate or biopsy showed acid-fast bacilli (AFB) on Ziehl–Neelsen (ZN) carbol fuchsin stain, and/or positive *Mycobacterium* culture of lymph gland aspirate/biopsy, and/or caseating granulomas on lymph node biopsy, and/or a good clinical response to treatment after an initial 8 weeks of follow-up.

A lymph node biopsy was performed when the initial diagnosis of tuberculosis on cytology was consistently equivocal or the clinical response to treatment was not satisfactory after 8 weeks. Only the confirmed tuberculous lymphadenitis cases were included in the final analysis.

A total of 571 patients with neck mass were screened by FNA cytology during the study period, of whom 303 were diagnosed as having tuberculous lymphadenitis. Thirty-eight patients with active pulmonary tuberculosis on chest X-ray and 28 patients less than 14 years of age were excluded from the study. Two hundred and thirty-seven patients were thus interviewed and enrolled in the study (Figure 1).

### Fine needle aspirates

Fine needle aspiration from lymph nodes was performed under sterile conditions, using a 21 G needle attached to a



**Figure 1** Flow diagram of all patients referred with cervical lymphadenopathy.

10 ml disposable syringe. A part of the aspirate was used for preparing smears, of which one was stained with Giemsa for cytology and one was stained with ZN for the demonstration of AFB. The other part of the aspirate was sent for culture on Lowenstein–Jensen medium.

On microscopic examination the cytological findings were classified into three patterns according to the amount of necrosis and the number and arrangement of the cells as: (1) non-necrotizing granulomas – epithelioid histiocytes arranged closely in a non-necrotic background of mononuclear inflammatory cells; (2) necrotizing granulomas – necrosis with scattered groups of well formed epithelioid histiocytes and/or giant cells; and (3) necrotic material – mainly necrotic degenerated neutrophils, lymphocytes, and epithelioid histiocytes.

### Ethical considerations

The decision to do aspiration cytology was based on clinical demand and not for the sake of participation in the study. Written informed consent was obtained from each patient. HIV testing was done after pre-test counseling and verbal consent. Patients were ensured of confidentiality, and post-test counseling was offered to patients who wished to know their results.

### Statistical analysis

Data entry and analysis was done using SPSS 11.5 for Windows. Analysis using cross-tabulation was performed to assess relationships among variables. The Pearson Chi-square test was used to compare differences in the prevalence of symptoms among gender groups, age groups, and cytology findings. Multiple linear regression analyses were performed to assess the effect of confounding on outcome variables. Different symptoms were included as dependent variables, and age, sex, and cytology features were included as independent variables in the model to adjust for confounding. Differences were considered statistically significant if  $p \leq 0.05$ .

### Results

A total of 219 patients with a confirmed diagnosis of tuberculous lymphadenitis were included in the final analysis (Figure 1). The cytological diagnosis was confirmed by ZN stain only in two patients, culture only in 15, ZN and culture in 34, lymph node biopsy in 111, and good clinical response to treatment in 74.

#### Patient details (Table 1)

A female predominance was observed among the 219 patients, with a male to female ratio of 1:2.1. The mean age was 33.9 years, ranging from 14 to 85 years. Seventy-five percent of the patients were aged between 14 and 35 years. The mean age of women was 28 (range 14–50) years and of men was 38 (range 14–85) years; this difference was significant ( $p = 0.051$ ). None of the patients had HIV infection. More men than women had another medical disease ( $p = 0.041$ ).

**Table 1** Demographic and general clinical characteristics of men and women with tuberculous lymphadenitis ( $N = 219$ ).

Characteristics	Men	Women
	( $n = 70$ ) $n$ (%)	( $n = 149$ ) $n$ (%)
Age (years)		
14–19	10 (14.3)	38 (25.5)
20–29	18 (25.7)	69 (46.3)
30–39	17 (24.3)	23 (15.4)
40–49	18 (25.7)	15 (10.1)
50 or more	7 (10)	4 (2.7)
Mean age	38	28
Age range	14–85	14–50 <sup>a</sup>
Origin		
Urban	30 (42.9)	58 (38.9)
Rural	40 (57.1)	91 (61.1)
Occupation		
Unemployed/student	20 (28.6)	91 (61.1)
Farmer/laborer	32 (45.7)	43 (28.8)
Employed	18 (25.7)	15 (10.1)
Associated disease		
Diabetes	6 (8.6)	2 (1.3)
Hypertension	14 (20)	1 (0.7)
Other respiratory disease	6 (8.6)	2 (1.3)
Other	2 (2.9)	0
None	54 (77.1)	145 (97.3) <sup>b</sup>

<sup>a</sup>  $p = 0.051$ .

<sup>b</sup>  $p = 0.033$ ; value adjusted for age and sex.

#### Clinical signs and symptoms at presentation (Table 2)

All patients presented with a neck mass of varying duration (range 4 days to 8 months). The mean duration of a neck mass at the time of presentation was significantly higher in men ( $p = 0.015$ ) with a range of 3 weeks to 8 months, whereas women reported a duration of 4 days to 8 weeks. Constitutional symptoms were present in only 56.6% of the patients. Symptoms were reported either alone or in combination. A history of fever was the most prevalent symptom. Other major clinical symptoms were tiredness, weight loss, night sweats, cough, frequent colds, and loss of appetite. Only a few patients reported cough with expectoration ( $n = 21$ ). The clinical symptoms varied significantly between men and women. Men more often presented with constitutional symptoms than women ( $p = 0.02$ ). They frequently had fever ( $p = 0.001$ ), a long duration of fever ( $>30$  days;  $p = 0.013$ ), cough ( $p = 0.05$ ), weight loss ( $p = 0.02$ ), and night sweats ( $p = 0.03$ ). However, cough was found not to be significant after adjusting for age. No significant differences were found between men and women with regards to frequent colds, weakness, or family history of tuberculosis contact. Women, however, more commonly reported having more than one symptom, although this was not significant after adjusting for age. After controlling for age, sex, and cytology in multiple

linear regression analyses, the prevalence of fever, night sweats, and loss of appetite were found to be significant.

On clinical examination, the lymph nodes from posterior triangle were most commonly involved (106 (48.4%)), followed by the supraclavicular nodes (40 (18.3%)). Bilateral lymphadenopathy was seen in seven (3.2%) and a discharging sinus in three patients (1.4%). Multiple nodes were most frequently found in the posterior triangle (91%;  $p = 0.04$ ), whereas a single palpable lymph node was most often found in the supraclavicular region, and this was commonly seen in women ( $p = 0.04$ ) (Table 2).

### Cytology

On cytology, non-necrotic granulomas were seen in 87 (39.7%) cases, necrotic granulomas in 93 (42.5%) cases, and 39 (17.8%) showed only necrotic material. Clinical symptoms showed a tendency to correlate with the cytology pattern and extent of necrosis after adjusting for age and gender. The frequency of necrotic granulomas was higher in patients who presented with weight loss ( $p = 0.04$ ), fever ( $p = 0.008$ ), loss of appetite ( $p = 0.001$ ), and supraclavicular lymph nodes ( $p = 0.005$ ) (Table 3). Necrotic granulomas and necrotic material on cytology were more commonly observed in men than in women (Table 4).

### Discussion

The clinical manifestations of tuberculous lymphadenitis are thought to be a local manifestation of a systemic disease.<sup>10</sup> Apart from the bacterial factors, the clinical features are influenced by host factors such as age, sex, nutrition, genetics, family history of contact, and the immune competence of

the patient. This leads to varied clinical and morphological presentations.

Our study supports previous reports that have shown that more women than men have tuberculous lymphadenitis.<sup>1–4,17</sup> We noted that constitutional symptoms were more common in men than in women. Although these symptoms are similar to those described in pulmonary tuberculosis,<sup>12</sup> the pattern of symptoms is different, and as expected, the traditional markers of tuberculosis such as cough or cough with expectoration, are rare in tuberculous lymphadenitis.<sup>18,19</sup> Women usually have a quiescent presentation or report multiple, vague, and atypical constitutional symptoms. These observations reflect biological, hormonal, social, environmental, or behavioral differences between men and women. Biologically there is a fundamental difference in the immune systems of men and women.<sup>20</sup> Ramathan et al. suggest a hormonal influence on immunity as the underlying cause for the different pattern of disease in women.<sup>21</sup> Socially, in developing countries women often have a low socioeconomic and nutritional status, which can affect the immune response to the disease.<sup>18,21,22</sup> Others have suggested that women are more conscious of their appearance and attend healthcare facilities earlier, while men ignore their disease until it is at a more advanced stage.<sup>12,18,19,23</sup>

There are also differences between men and women with regard to the clinical signs of the disease. Men more frequently have enlarged posterior cervical, submandibular, bilateral, and matted lymph nodes, while women usually have an enlarged unilateral, single supraclavicular node. Dvorski noted similar findings.<sup>24</sup> The group of nodes affected in peripheral lymphadenitis depends on the location of the initial focus of infection, as it is considered part of the primary complex and a manifestation of early post-primary

**Table 2** Clinical symptoms and signs in men and women diagnosed to have tuberculous lymphadenitis.

Clinical characteristics	Men ( $n = 70$ ) $n$ (%)	Women ( $n = 149$ ) $n$ (%)	$p$ -Value <sup>a</sup>
<b>Symptoms</b>			
Fever	43 (61.4)	63 (42.3)	0.001
Duration of fever >30 days	28 (40)	48 (32.2)	0.013 <sup>a</sup>
Weight loss	28 (40)	21 (14.1)	0.02 <sup>a</sup>
Weakness/tiredness	29 (41.4)	49 (32.9)	0.16
Loss of appetite	28 (40)	33 (22.1)	0.07
Night sweat	22 (31.4)	13 (8.7)	0.03
Frequent cold	3 (4.3)	21 (14.1)	0.14
Cough	10 (14.3)	26 (17.4)	0.05 <sup>a</sup>
Cough with expectoration	4 (5.7)	17 (11.4)	0.11
None	19 (27.1)	76 (51.0)	0.02
More than one symptom	14 (20)	65 (43.6)	0.16
Positive family history of TB	3 (4.3)	19 (12.8)	0.10
<b>Signs</b>			
Supraclavicular node	4 (5.7)	36 (24.2)	0.04
Posterior node	38 (54.3)	68 (45.6)	0.43
Solitary node	11 (15.7)	48 (32.2)	0.04
Bilateral	4 (5.7)	3 (2.0)	0.48
Discharge sinus	3 (4.3)	0	0.44

<sup>a</sup>  $p$ -Value not significant after adjusting for age.

**Table 3** Cytology patterns in tuberculous lymphadenitis patients presenting with different constitutional symptoms.

Clinical characteristics	Cytology pattern (N = 219)		
	Non-necrotic granuloma (n = 87)	Necrotic granuloma (n = 93)	Necrotic material (n = 39)
Fever	28 (32.2)	66 (71.0) <sup>a</sup>	12 (30.8)
Duration of fever (>30 days)	28 (32.2)	38 (40.9)	10 (25.6)
Weight loss	11 (12.6)	21 (22.6)	17 (43.6) <sup>b</sup>
Weakness/tiredness	24 (27.6)	38 (40.9)	16 (41.0)
Loss of appetite	4 (4.6)	38 (40.9) <sup>c</sup>	19 (48.7)
Night sweat	12 (13.8)	14 (15.1)	9 (23.1)
Frequent cold	11 (12.6)	9 (9.7)	4 (10.3)
Cough	11 (12.6)	19 (20.4)	6 (15.4)
Positive family history of TB	9 (10.3)	9 (9.7)	4 (10.3)
Supraclavicular	9 (10.3)	14 (15.1)	17 (43.6) <sup>d</sup>
Posterior node	36 (41.4)	64 (68.8)	6 (15.4)
Solitary node	25 (28.7)	23 (24.7)	11 (28.2)

Results are n (%).

<sup>a</sup>  $p = 0.008$ .

<sup>b</sup>  $p = 0.04$ .

<sup>c</sup>  $p = 0.001$ .

<sup>d</sup>  $p = 0.005$ .

tuberculosis.<sup>9</sup> The triad of multiplicity, matting, and caseation helps in reaching a diagnosis of tuberculous lymphadenitis in many cases, but it is not the most common presentation in women.

As cytology is used as the first line of investigation to diagnose clinically suspected tuberculous lymphadenitis, we made an attempt to correlate the cytological spectrum of the disease with the clinical features to improve the characterization of symptoms. There was a relationship between the presence of granulomas, degree of caseous necrosis, and clinical manifestations. Patients presenting with systemic symptoms showed more extensive necrosis than patients with no systemic symptoms. It is believed that the delayed type hypersensitivity (DTH) reaction seen in tuberculosis is responsible for the clinical symptoms, which are caused by various cytokines released from the site of tissue damage.<sup>25,26</sup> DTH mediates a systemic reaction via cytokines such as tumor necrosis factor (TNF)- $\alpha$ , interferon (IFN)- $\gamma$ , or interleukin (IL)-1, which are locally increased at the site of granulomatous inflammation in response to the immune challenge.<sup>25</sup> Verbon et al. demonstrated higher levels of cytokines IFN- $\gamma$  or IL-6 in patients with active tuberculosis presenting with fever, anorexia, and malaise.<sup>17</sup> Morphologically DTH is signaled by the presence of caseous necrosis in the center of the granuloma.<sup>25,27</sup> Thus the amount of casea-

tion appears to influence the clinical manifestations of the disease. Granulomas formed show different degrees of organization depending on the immune status. It is proposed that a good cell-mediated immune response results in granulomas with minimal necrosis and few if any clinical symptoms, whereas a poor cell-mediated immune response results in scattered epithelioid macrophages with massive necrosis and frequent and severe clinical manifestations.<sup>27</sup> In pulmonary tuberculosis it has also been reported that symptoms are more common in patients with progressive lung lesions.<sup>13</sup> In our study the symptoms were more prominent in patients with necrosis and this probably reflects the pathology of the disease.

In India, and other resource-poor countries, most cases of tuberculous lymphadenitis are diagnosed and treated on the basis of clinical suspicion alone. This study thus looked at the symptoms in patients who presented with tuberculous lymphadenitis to a center in India where routine pathology services are available. More advanced technology such as PCR was not available and the diagnosis was therefore based on the clinical signs, culture, and the presence of necrotizing granulomas on cytology. This also remains the most common method used to diagnose tuberculous lymphadenitis in the developed world. However, in a resource-poor setting, it is difficult to decentralize the special diagnostic services at district level. Thus the clinical criteria used to diagnose tuberculous lymphadenitis should be improved. This will reduce the referral time to the tuberculosis diagnostic and treatment unit and hence decrease morbidity, mortality, and over-treatment.

Being a hospital-based study our patient population was partially selected. Most of our patients were from the out-patient department, but our cohort also included hospitalized patients. Also, the limited number of patients enrolled restricts the evaluation of the true value of a well-defined symptom-based approach to diagnose tuberculous lymphadenitis. However, our study gives an insight into gender differences in symptomatology in the most common form

**Table 4** Cytology pattern of tuberculous lymphadenitis in men and women.

Cytology pattern <sup>a</sup>	Men (N = 70) n (%)	Women (N = 149) n (%)
Non-necrotic granuloma (n = 87)	18 (25.7)	69 (46.3)
Necrotic granuloma (n = 93)	38 (54.3)	55 (36.9)
Necrotic material (n = 39)	14 (20)	25 (16.8)

<sup>a</sup>  $p = 0.04$ .



of extrapulmonary tuberculosis and it provides the background for a community study for a better symptom-based diagnostic approach, particularly in resource-limited settings. Our study also raises a few important issues. Firstly, the clinical manifestations of tuberculous lymphadenitis are to some extent sex-dependent and this aspect should be considered, especially in developing countries, during the clinical evaluation of patients. The laboratory findings should be interpreted together with the clinical picture to reach an accurate diagnosis. There is clearly a need for better diagnostic laboratory tests, especially in paucibacillary extrapulmonary cases. Secondly, the immune reactions taking place at a cellular and molecular level, morphologically seen in the form of granulomas and caseation of a diseased node, influence the clinical profile of a patient.

In conclusion, we found that constitutional symptoms in tuberculous lymphadenitis are more commonly reported by men than by women, and the degree of necrosis on cytology correlates with the presence of constitutional symptoms.

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*Conflict of interest:* No conflict of interest to declare.

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