

## EXTRAPULMONARY TUBERCULOSIS IN LADY READING HOSPITAL PESHAWAR, NWFP, PAKISTAN: SURVEY OF BIOPSY RESULTS

Shafi Ullah, Syed Humayun Shah\*, Aziz-ur-Rehman, Arshad Kamal, Norin Begum, Ghaazaan Khan\*\*  
Departments of Pathology Lady Reading Hospital Peshawar, Ayub Medical College Abbottabad\* and Khyber Medical College Peshawar\*\*

**Background:** Tuberculosis is a disease of poor countries. In the recent years, there has been an increase in the occurrence of extra-pulmonary tuberculosis (EPTB) world over. As very little data is available regarding the situation of EPTB in NWFP, this study was conducted to assess its frequency in various organ systems of the body and to evaluate the role of demographic factors like sex and age in its causation. **Methods:** A total of 525 cases of EPTB diagnosed histopathologically in the Department of Pathology, Lady Reading Hospital Peshawar in the years 2002–2005 were included in the study. Age, sex and sites of biopsies were recorded. **Results:** High female preponderance was noted with a M:F ratio of 1:2. Mean age was 35 years and 70% of the patients were in the age group 15–45 years. Lymph nodes were the most common site of EPTB, involved in 66.4% of the cases. **Conclusion:** EPTB has high rates in females in their reproductive age. Tuberculous lymphadenitis is the most common form of EPTB. High occurrence of EPTB in female population needs immediate attention of tuberculosis control programs.

**Keywords:** Tuberculosis, Extrapulmonary tuberculosis, EPTB.

### INTRODUCTION

Tuberculosis (TB) is a worldwide disease. Annually, about nine million people contract tuberculosis and nearly two million are killed by the disease.<sup>1</sup> The fatal synergy of HIV and tuberculosis, and the emergence of multidrug-resistant *M. tuberculosis* have further contributed to the re-emergence of TB in many parts of the world.<sup>2-4</sup>

The propagation of tuberculosis is directly related to the socioeconomic and hygienic conditions of human populations. Except for the recent increase in the incidence of tuberculosis in the affluent West due to AIDS<sup>5</sup>, tuberculosis is generally a disease of poverty, having a high prevalence in the developing countries.<sup>4-7</sup> Southeast Asia seems to be the most afflicted: 44% of its population is reported to be *M. tuberculosis* infected.<sup>8</sup>

Tuberculosis occurs in both sexes, in all age groups and can affect virtually all organs of the body.<sup>9</sup> Depending upon the anatomical site involved, it has a wide spectrum of clinical presentation.

Broadly, TB may be pulmonary (occurring in lungs) or extrapulmonary (occurring outside the lungs). Extrapulmonary tuberculosis can occur alone or in combination with the pulmonary variety.<sup>10</sup> Whereas the diagnosis of pulmonary tuberculosis (PTB) is relatively easy, EPTB usually presents a diagnostic problem even for the highly experienced physicians. In many cases, biopsy is mandatory for definite diagnosis.

Roughly, 10–20% of tuberculosis cases are extrapulmonary, while among HIV positives it could be around 50%.<sup>11</sup> Depending upon the geographic locality and ethnicity of a population, variations have been reported in various studies regarding the occurrence and frequency of EPTB in the two sexes, in different age groups and also in the organs involved.<sup>11-13</sup>

EPTB is on the increase world over.<sup>11</sup> However, very limited data is available about the situation of EPTB

in the developing countries in general<sup>14</sup> and in our region in particular. Keeping in view this dearth of information about EPTB in NWFP, the present study was conducted for two purposes:

1. To assess if some of the demographic factors like sex and age could act as predisposing factors in the causation of EPTB in our region.
2. To find the frequency of biopsy-proved tuberculosis in various organ systems of the body.

### MATERIAL AND METHODS

It was a prospective study. All the biopsy specimens submitted to the pathology Department, Lady Reading Hospital Peshawar in the years 2002–2005 that were diagnosed as tuberculosis were included in the study. There came out to be 525 such cases. Age, sex and site of biopsy were recorded. The specimens were received and preserved in 10% formalin, processed in routine manner and embedded in paraffin wax. Three-micron thick sections were cut and stained by Haematoxylin and Eosin.<sup>15</sup> The diagnosis was undertaken on morphological grounds. Tissues containing caseating epithelioid cell granulomas were identified as tuberculous. The slides were reviewed by two histopathologists.

### RESULTS

A total of 525 tissue specimens contained caseating epithelioid cell granulomas and the diagnosis of tuberculosis was made. Record regarding the gender, age and site of biopsy are summarized in Tables 1–8. The number of male patients was 176 while that of female patients was 349 (Table-1) with a M:F ratio of 1:2. The ages ranged from 1–80 years. The mean age was 35 years. Out of the whole series, 82 cases (16%) were below 15 years, 369 cases (70%) were from 15–45 years and 74 cases (14%) were over 45 years of age (Table-2).

**Table-1: Sex Distribution**

Sex	Number of Cases	%
Male	176	33.52
Female	349	66.48
Total	525	100

**Table-2: Age Distribution, both sexes**

Age	Number of Cases	%
Below 15 Years	82	15.62
15-45 Years	369	70.28
Above 45 Years	74	14.10

**Table-3: Age Distribution, females**

Age	Number of Cases	%
Below 15 Years	53	15.18
15-45 Years	249	71.35
Above 45 Years	47	13.47

**Table-4: Age Distribution, males**

Age	Number of Cases	%
Below 15 Years	29	16.48
15-45 Years	120	68.18
Above 45 Years	27	15.34

Out of 525 cases, 349 cases (66.4 %) occurred in lymph nodes, 49 (9.3%) in skeletal system including spine, 35 (6.7%) in skin and subcutaneous tissue, and 33 (6.3%) in GIT including mesentery/peritoneum. Pleural TB was seen in 23 (4.4%) cases. Male and female genital systems revealed tuberculosis in 12 (2.3%) and 11 (2%) cases respectively. In each of the remaining systems, tuberculosis was found only in less than 1% of the cases (Table-5). There were some differences in the distribution of tuberculosis in the two sexes. Details are given in Table-6 and 7. Mean ages for different systems are summarized in Table-8.

**Table-5: Distribution according to system/site of biopsy: Both Sexes**

System involved	No. of Cases	%
Lymph Nodes	349	66.4
Skeletal System	49	9.3
Skin and Subcutaneous Tissue	35	6.7
GI Tract, Mesentery and Peritoneum	33	6.3
Male Genital System	12	2.3
Female Genital System	11	2.0
Urinary System	5	1.0
Pleura	23	4.4
Female Breasts	3	0.6
CNS	2	0.4
Eye	2	0.4
Pericardium	1	0.2
<b>Total</b>	<b>525</b>	<b>100</b>

**Table-6: Distribution according to system/site of biopsy: Males**

System involved	No. of Cases	%
Lymph Nodes	102	58.0
Skeletal System	14	7.9
Skin and Subcutaneous Tissue	17	9.7
GI Tract, Mesentery and Peritoneum	14	7.9
Pleura	12	6.8
Male Genital System	12	6.8
Urinary System	3	1.7
CNS	1	0.6
Pericardium	1	0.6
<b>Total</b>	<b>176</b>	<b>100</b>

**Table-7: Distribution according to system/site of biopsy: Females**

System involved	No. of Cases	%
Lymph Nodes	247	70.7
Skeletal System	35	10.0
Skin and Subcutaneous Tissue	18	05.2
GI Tract, Mesentery and Peritoneum	19	05.4
Pleura	11	03.2
Female Genital System	11	03.2
Urinary System	2	0.6
CNS	1	0.3
Breasts	3	0.8
Eye	2	0.6
<b>Total</b>	<b>349</b>	<b>100</b>

**Table-8: Mean Age for different Systems**

System involved	Mean Age (Years)
General	35
Lymphoid System	27
Skeletal System	34
Skin and Subcutaneous Tissue	31
GI Tract, Mesentery and Peritoneum	42
Pleura	41
Female Genital System	28
Male Genital System	42
Female Breasts	49

## DISCUSSION

The study is based on histopathological examination of biopsy specimens and indicates only approximate frequency of extrapulmonary tuberculosis in the population. The reason is that some cases of EPTB are not diagnosed by histopathological methods. For example, many cases of pleural tuberculosis are diagnosed by the examination of the pleural aspirate and are not included in our study. The less number of cases from CNS in our series is again due to the fact that many cases of neurotuberculosis, meningitis being the commonest in the category,<sup>9</sup> are generally diagnosed by methods other than biopsy.<sup>16,17</sup> Also, in some published series, spinal tuberculosis has been included in CNS tuberculosis<sup>18</sup>. In our series, we have grouped spinal TB with skeletal system and pleural TB is categorized as extrapulmonary. This is done according to the European consensus on surveillance of tuberculosis.<sup>19</sup>

The overall M: F ratio in our series is 1:2. This finding is in accordance with several other studies.<sup>10,20,21</sup> The reason for this female preponderance is elusive but it is likely that both biological sex differences and sociocultural risk factors related to gender roles make women more vulnerable to the disease. In a male dominated society like that of *Pakhtuns*, the socioeconomic status of woman is even more pathetic. It is a common practice in *Pakhtun* and Afghan societies that females generally take their meals after the males have finished. Also, for emotional reasons, mothers would feed their kids first on the expense of their own nutrition. This differential access to food by females could cause relatively more malnutrition in females as

compared to males.<sup>7</sup> The other likely socio-cultural factors could be high female illiteracy, female economic dependency and their poor access to health care. The increased likelihood of females with tuberculosis presenting with an extra-pulmonary disease manifestation is particularly pronounced in the reproductive age i.e. in 15–45 years age group. It suggests that endocrine factors might play a role. In a study performed as far back as 1940, female predominance in EPTB was associated with hormonal changes.<sup>22</sup> Reproductive burden in females associated with pregnancy, parturition, abortion and lactation may also be significant. Particularly early marriages, teen-parenting, multigravidity with less time interval between successive pregnancies and lactational stress may impair immunity resulting in higher predisposition to tuberculosis. In a study conducted in India,<sup>23</sup> it was found that females had up to 130% higher risk of progressing from TB infection to disease between the ages of 10 and 44 years. A higher rate of progression from infection to disease among reproductive age women has been described in some studies.<sup>24</sup> Thus, in our environments, female gender and age between 15–45 years are two important predisposing factors for EPTB.

In addition to host factors, genetic polymorphism of *M. tuberculosis* has important clinical consequences.<sup>25,26</sup> High female predilection in certain world regions may be a function of some genetic variations of the organism. In one study conducted in Madagascar,<sup>27</sup> the clustering rate was found to be significantly higher in female patients than in male patients suggesting that Malagasy women were more likely to progress to disease after infection than men. However, this concept has yet to be explored.

Regarding the frequency of EPTB in different age groups, there are differences among various studies.<sup>21,28</sup> In our study, about 70% of the cases are in the age group 15–45. The remaining 30% of the cases are equally distributed in the age group below 15 years and above 45 years. Such distribution of the disease, the dynamics of which is not properly understood, is in accordance with some other studies.<sup>21</sup> In females, some factors have already been discussed. In males such factors are more difficult to make out. Again biological factors are probable. Exposure to unhealthy working conditions in this age group in the proletariat class may play some role in the pathogenesis of both pulmonary and extrapulmonary tuberculosis.

In our study, the lymph nodes were the most common site of EPTB, observed in 66% of cases. Some studies have suggested a variable localization of EPTB in the body. In Hong Kong,<sup>10</sup> the most common site of EPTB was the pleura, followed by the lymph nodes whereas in one study in USA,<sup>29</sup> bones and/or joints were the most common sites. Results of our study are comparable to many other studies<sup>13,30-32</sup> which reported highest frequency of lymph node involvement. Cervical

adenopathy is most common, but inguinal, axillary, mesenteric, mediastinal, and intramammary involvement all have been described.<sup>33</sup> Likely, TB organism may have tropism for lymph nodes. The other reason for such high frequency may be that tuberculous of lymph nodes lead to their enlargement which is clinically quite obvious, consequently with early and easy diagnosis. Other forms of EPTB may be more difficult to diagnose and many may remain unexplored.

Our frequency of some other sites is to a great degree in agreement with other studies.<sup>34</sup> Disagreement in different studies regarding variations in the frequency of EPTB in different anatomic sites is difficult to explain. However, these differences suggest that the dynamics of extrapulmonary tuberculosis epidemiology may be specific to geographic location and population; more population-based studies in different geographic regions are needed.

## CONCLUSION

1. EPTB is significantly more common in females, specially in their reproductive age and need the attention of tuberculosis control programs.
2. Lymphadenitis is the most common form of EPTB in our region.
3. A more comprehensive study, integrating all methods of diagnosis, is needed to determine the exact occurrence of extrapulmonary tuberculosis in our population.

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### Address for Correspondence:

**Dr. Shafi Ullah**, Abasin Hospital, Opposite Attock Petrol Pump, Michni Road, Shabqadar Bazar, Shabqadar, Tehsil and District Charsadda, NWFP, Pakistan. Tel: +92-91-6281864  
**Email:** Shafiullajan@yahoo.com