EXTRAPULMONARY TUBERCULOSIS IN PENINSULAR MALAYSIA: RETROSPECTIVE STUDY OF 195 CASES

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Abstract. During a 2-year retrospective study, 195 non-HIV-infected patients with extrapulmonary tuberculosis (EPT) were diagnosed at the National Tuberculosis Center, Kuala Lumpur, representing 10% of all patients with tuberculosis. Their mean age was 39 (±SD) 14 years old (range 14-81). The largest age group was 25-34 years, while 78.5% were less than 50 years of age. The subjects were mainly female (50.3%), Malay (49.2%), married (61.5%), resided in Kuala Lumpur (51.0%), and were unemployed (50.3%). Regarding risk factors, they were smokers and/or alcohol users (21.0%), and injecting drug users (IDUs) (5.1%); they also had history of tuberculosis (3.6%) and contact with TB patients (9.2%). Lymphadenopathy was the most common sign (45.6%) shown in the medical records. 42% of x-ray findings (chest, spine, and hip) showed signs consistent with tuberculosis, while histopathology was the most useful diagnostic tool (52.3%) and lymph node was the most frequent specimen used (35.0%) in this study. The three main sites of involvement were lymph nodes (42.6%), miliary and disseminated (19.5%), and pleura (12.8%). The outcome of this study showed 72.8% of these patients had completed treatment for at least 6 months, whilst, only 4.6% of patients were still undergoing treatment, and unfortunately, 22.6% of them showed non-adherence to anti-tubercular therapy at a duration of less than 6 months. However, no MDR-TB or death cases were reported or registered in this study.

INTRODUCTION

Tuberculosis (TB) is an ancient killer disease that can heavily affect both non-HIV and HIV-related individuals. It remains a major challenge worldwide both in terms of disease burden and resistance to conventional antibiotic therapy (Eltringham and Drobniewski, 1998). Tuberculosis is considered among the top 5 communicable diseases reported in Malaysia where the number has been constantly increasing from 12,691 (61%) in the year 1996 to 15,057 (64.7%) by the end of the year 2000. The number of deaths seems to be directly proportional to the nuber of cases, 271 (1.2%) in the year 1996, to 882 (4%) by the end of the year 2000 (Ministry of Health, Malaysia, 2000). Data before the Acquired Immune Deficiency Syndrome (AIDS) era indicated that despite the decline in pulmonary TB, the number of cases of extrapulmonary tuberculosis remained constant (Noertjojo *et al*, 2002). Extrapulmonary tuberculosis has a broad spectrum of clinical manifestations that may be referable to almost any organ system and should be considered in the differential diagnosis of bone, joint, genitourinary tract and central nervous system (CNS) disease (Alvarez and McCabe, 1984). There have been surprisingly few studies on extrapulmonary tuberculosis in non HIV-infected patients in the past two decades. Therefore, we propose this study to identify the nature of extrapulmonary tuberculosis in terms of its current epidemiological pattern, clinical scenario, such as manifestations, laboratories, diagnosis, the role of treatment and most importantly its outcome among non-HIV-infected patients, which definitely aids better understanding and management of this resurgent disease.

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MATERIALS AND METHODS

From January 2001 to December 2002, we retrospectively reviewed 1,903 patients with tuberculosis who were registered at the National Tuberculosis Center (NTBC), Kuala Lumpur, Malaysia. Of these, 195 (10%) were diagnosed as extrapulmonary tuberculosis. Their medical records were reviewed according to our inclusion criteria for study subjects, as follows; (1) HIV-negative patients with anti-HIV status tested by any serological technique, and age ≥ 14 years, (2) all patients who were diagnosed as having developed tuberculosis of organs other than the lungs *eg* pleura, lymph node, abdomen, genito-urinary tract, skin, joints and bone, meninges, etc. Diagnosis was based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extra-pulmonary tuberculosis, followed by a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy (WHO,

2002). Throughout this study, socio-demographic profiles, clinical presentations and investigation results, treatment medications and duration, patient compliance with therapy, and outcome of therapy response were also enlisted in the standardized data collection sheet. Multidrug resistant tuberculosis (MDR-TB) was defined as resistance to at least 1 and/or 2 important drugs, isoniazid (INH) and/or rifampicin (RF). Defaulter was defined, in accordance with the World Health Organization, as a patient who did not collect medication for 2 months or more any time after registration. The criteria for monitoring response to treatment were improvement of clinical symptoms and signs, x-ray or related laboratory findings when compared to baseline, with compliance to therapy for at least 6 months.

Statistical analysis

The data were analyzed using the statistical software, SPSS version 10 (SPSS Inc, Chicago, USA). Data with quantitative variables were expressed by mean (±SD) and range, while qualitative variables were estimated by frequency and percentage.

RESULTS

Table 1 illustrates the socio-demographic characteristics of the study subjects at the time of diagnosis. The mean age was 39 (±SD) 14 years (range 14-81). The largest age group was 25-34 years old, and 78.5% were less than 50 years of age. Subjects were mainly female (50.3%), the Malay (49.2%), married (61.5%), resident in Kuala Lumpur (51.0%) and unemployed (50.3%). Regarding risk factors, they were smokers and/or alcohol users (21.0%), and injecting drug users (IDUs) (5.1%), moreover, they also had a history of previous tuberculosis (3.6%) and contact with TB patients (9.2%).

At the time of diagnosis, 48.2 and 43.1% of patients had positive BCG status and tuberculin skin test (≥ 10 mm), respectively. Lymphadenopathy was the most common sign (45.6%) shown in the medical records; 33.3% was at the cervical, and 5.1% at the supraclavicular regions. Forty-two percent of x-ray findings included chest/miliary, spine and hip showed signs consistent with tuberculosis, while histo-pathological examination was the most useful tool (52.3%) still routinely available for confirmation of extrapulmonary tuberculosis, the lymph node was the most frequent specimen used (35.0%) in this study, as shown in Table 2.

Among 1,903 patients with tuberculosis, 195 (10%) non-HIV infected patients were diagnosed with extrapulmonary tuberculosis. Lymphatic, miliary/ disseminated, pleural and osteoarticular involvement were the most common, as shown in Table 3. The result of this study showed 72.8% of these patients completed

Table 1
Socio-demographic characteristics of 195 patients.

Variables	No. of patients (%)
Range of age = 14-81 years	
Mean ± SD = 39 ± 14 years	
Sex ratio (M:F) = 1:1	
Age group (year)	
15-24	29 (15.0)
25-34	61 (31.3)
35-44	41 (21.0)
45-54	37 (19.0)
≥ 55	27 (13.8)
Sex	
Male	97 (49.7)
Female	98 (50.3)
Race	
Malay	96 (49.2)
Chinese	39 (20.0)
Indian	34 (17.4)
Other[a]	26 (13.3)
Marital status	
Single	75 (38.5)
Married	120 (61.5)
Address	
Kuala Lumpur	99 (51.0)
Outsider	96 (49.0)
Occupation	
Laborer	47 (24.1)
Non-laborer	50 (25.6)
Unemployed	98 (50.3)
Determining factors	
Smoking and/or alcohol	41 (21.0)
Intravenous drug user	10 (5.1)
Concomitant illness: diabetes mellitus	9 (4.6)
Case category	
New case	188 (96.4)
Relapse (previous history of TB-lymph node or heart)	5 (2.6)
Return after default (previous history of pulmonary TB)	2 (1.0)
History of contact with tuberculosis patient	18 (9.2)

[a] Other: foreigners who were classified as persons with foreign nationality and persons with first and/or family names that were clearly not Malaysian.

Table 2
Clinical presentations and investigation results at first entry.

Clinical presentations	No. of patients (%)
Symptoms	
Loss of appetite and weight	82 (42.1)
Cough	80 (41.0)
Fever	70 (36.0)
Pain (chest, loin, knee, hip, flank, back, abdomen, and neck)	43 (22.1)
Sputum	35 (18.0)
Dyspnea	25 (13.0)
Hemoptysis	17 (8.7)
Dysphagia	1 (0.5)
Other	1 (0.5)
Signs	
BCG vaccination status	
Yes	94 (48.2)
No	51 (26.2)
No information	50 (25.6)
Tuberculin skin test (Mantoux test)	
≥ 10 mm	84 (43.1)
< 10 mm	29 (15.0)
No information	82 (42.1)
Lesion or swelling (abscess or lump)	11 (5.6)
Hoarseness of voice	3 (1.5)
Hematuria	3 (1.5)
Blurring of vision	4 (2.0)
Lymphadenopathy	89 (45.6)
Cervical	65 (33.3)
Supraclavicular	10 (5.1)
Axilla or mediastinal	5 (2.5)
Mixed (at least 2 sites)	9 (4.6)
Investigation results	
ESR	
> 10 mm at the first hour	158 (81.0)
< 10 mm at the first hour	17 (8.7)
Not recorded	20 (10.3)
X-ray findings	
Chest: not available	4 (2.1)
normal finding	108 (55.4)
abnormalities (pleural effusion and parahilar cyst)	26 (13.3)
Miliary	38 (19.5)
Spine	15 (7.7)
Hip	3 (1.5)
Other results (CT scan, MRI, ultra-sound, echocardiogram, PCR and opthalmoscopic examination)	20 (10.3)
Sputum smear positive for AFB	
Positive	12 (6.2)
Negative	167 (85.6)
No information	16 (8.2)
Sputum culture positive for *M. tuberculosis*	
Positive	20 (10.3)
Negative	151 (77.4)
No information	24 (12.3)
Fluid analysis (smear, culture and biochemical analysis)	
Positive	17 (8.7)
No information	178 (91.3)
Tissue biopsy	102 (52.3)
Positive	101 (51.8)
Lymph node	68 (35.0)
Pleura	9 (4.6)
Spine	5 (2.6)
Other	19 (9.7)
Negative	1 (0.5)
No information	94 (48.2)

treatment of at least 6 months, whilst only 4.6% of patients were still undergoing treatment; 22.6% showed non-adherence to anti-tubercular therapy at a duration of less than 6 months. However, no MDR-TB or deaths was reported or registered in this study, as illustrated in Fig 1.

Lymph node tuberculosis

Tuberculous lymphadenitis was the most frequent extrapulmonary tuberculosis in 83 (42.6%), with predominant cervical lymph node involvement; moreover, it was more common in females (M:F = 27:54) than males. The diagnosis of lymph node TB was confirmed by typical histopathological examination in 68 (82%) cases and by a high index of suspicion of clinical s/s and/or positive tuberculin skin test in 14 (17%) of cases. Seven (3.6%) patients were still undergoing anti-tubercular therapy, but 13 (6.7%) were lost to follow-up with no evidence of relevant drug adverse reaction or resistance. Otherwise, all other patients (included 4 relapse cases) completed treatment of at least 6 months' duration.

Miliary and disseminated tuberculosis

We found 38 (19.5%) patients, 36 had miliary tuberculosis, miliary and TB-spine (1 case), and miliary with TB-meninge, liver, and bone marrow (1 case). All were diagnosed on the basis of clinical s/s and radiological finding. Eleven, 18, and 9 patients were confirmed bacteriologically by sputum smear for AFB, culture for *M. tuberculosis*, or both, respectively. Only 1 case was diagnosed by cerebrospinal fluid for *M.*

Table 3
Disease location of extra-pulmonary tuberculosis of 195 patients.

Disease location	No. of patients (%)
Lymph node	83 (42.6)
Cervical	59 (30.3)
Supraclavicular	10 (5.1)
Axilla or mediastinal	5 (2.6)
Mixed	9 (4.6)
Miliary/disseminated	38 (19.5)
Pleura	25 (12.8)
Osteoarticular (bone/joint)	24 (12.3)
Spine	20 (10.3)
Hip	3 (1.5)
Knee	1 (0.5)
Genito-urinary tract	8 (4.1)
Bladder	4 (2.1)
Testes	2 (1.0)
Kidney	1 (0.5)
Ovary	1 (0.5)
Abdomen	6 (3.1)
Peritoneum	4 (2.1)
Intestine	1 (0.5)
Liver	1 (0.5)
Others	12 (6.2)
Eye	4 (2.1)
Skin	4 (2.1)
Heart	2 (1.0)
Breast	1 (0.5)
Skeletal muscle	1 (0.5)

tuberculosis. Three out of 16 patients who were lost to follow-up had adverse drug reactions in less than 6 months' therapy. Another 22 (11.2%) patients successfully completed treatment.

Pleural tuberculosis

Twenty-five (12.8%) patients with pleural tuberculosis were notified in this study; definite diagnoses (pleural biopsy and/or fluid analysis) were made in 20, and presumptive diagnoses (s/s and CXR finding) were made in 5. In the duration of less than 6 months' therapy, 1 (0.5%) out of 4 patients who defaulted during therapy had developed adverse drug reaction, while only 1 patient in this category was still undergoing treatment. It is interesting to mention that 20 patients responded well to standard ATT.

Osteoarticular (bone-joint) tuberculosis

In 24 (12.3%) patients, spinal tuberculosis 20 (10.3%) was the most common extrapulmonary tuberculosis, followed by the hip joint (3; 1.5%) and knee joint (1; 0.5%). Equal sex distribution was observed in these patients. Most of TB-bone/joint cases came with the presenting symptom of pain, back, hip, knee and neck (19 patients), weakness (3 patients), and paresthesia (2 patients). Eight patient diagnoses were confirmed by histological examination, and 16 cases were diagnosed by clinical s/s and/or radiological imaging (x-ray, CT scan, or MRI). Only 5 (2.6%) were lost to follow-up and 1 of them developed drug-induced hepatitis. Nineteen (including 2 patients who returned after defaulting) completed treatment of at least 6 months, and interestingly, more than half of patients 11/19 (58%) were treated for at least 1 year with ATT.

Genito-urinary tuberculosis

There were 8 cases of genito-urinary tuberculosis; bladder (4 cases), testes/epididymis (2), kidney (1), and ovary (1). Definite diagnoses were made by histological examination and/or fluid analysis in 6 cases, while 2 cases were diagnosed by clinical s/s and/or ultrasound. Seven patients effectively responded well to therapy, and only 1 patient defaulted treatment.

Abdominal tuberculosis

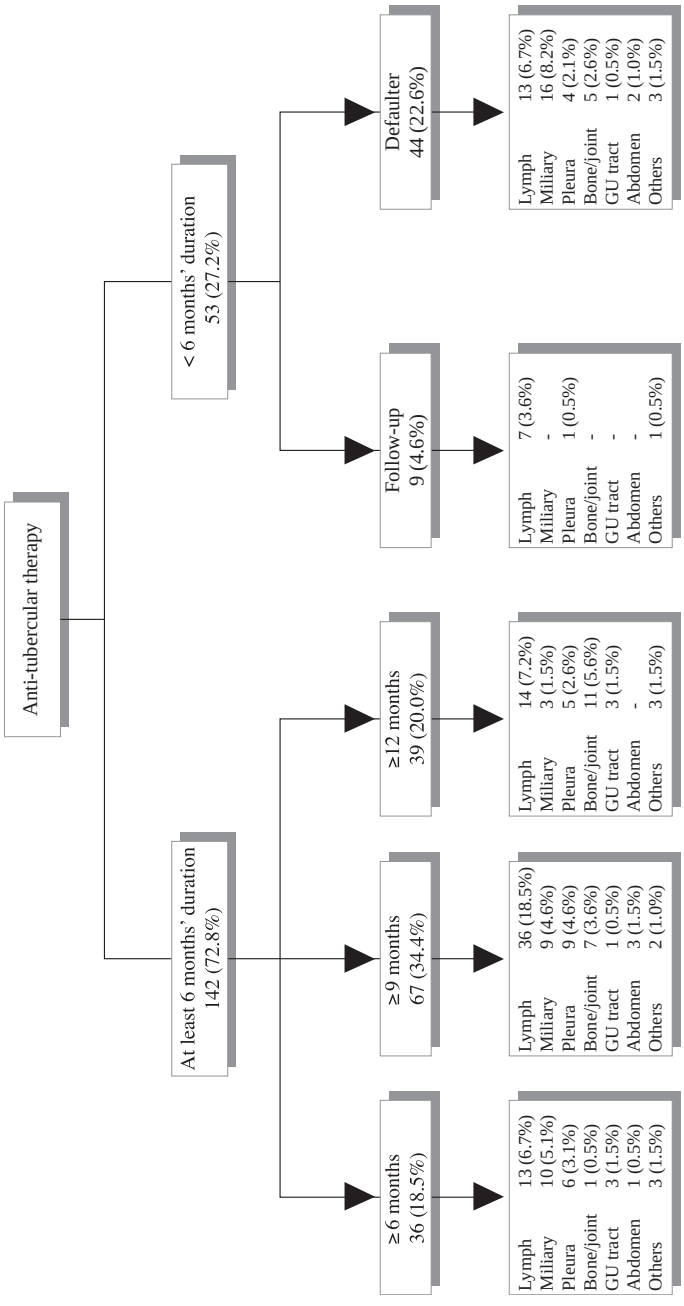
Out of 6 cases, tuberculous peritonitis was the most common (4 cases), followed by intestine (1) and liver (1). Definite diagnoses (tissue biopsy and/or fluid analysis) were made in 5 cases and only 1 case was diagnosed on the grounds of high clinical suspicion. Four patients were successfully treated with ATT, while 2 cases were lost to follow-up.

Others

Twelve cases (6.2%) developed other forms of extrapulmonary tuberculosis: eye (4 cases), skin (4), heart (2), skeletal muscle (1), and breast (1). Half of the cases were confirmed by tissue biopsy and the other half were diagnosed either by opthalmoscopic examination (4 cases) or echocardiogram (2 cases). Two-thirds of these patients completed treatment and the other 1/3 defaulted during treatment.

DISCUSSION

Over the last 2 decades, the incidence of extrapulmonary tuberculosis in developed countries has remained relatively constant, despite a progressive fall in the number of reported cases of pulmonary tuberculosis (Farer *et al*, 1979; Dwyer *et al*, 1987; Rieder *et al*, 1990). Tuberculosis is still a major public health problem in Malaysia. From this study, the frequency distribution of extrapulmonary tuberculosis was 10% for all cases of tuberculosis. This finding is



Anti-tubercular regimen: EHRZ+RH2: 160(82.1%); HRZ+RH2: 15(7.7%); SHRZ+RH2: 7(3.6%) and others 8(4.1%).

Fig 1- The diagram of anti-tubercular therapy and outcome of these patients.

supported by previons reports (Mehta *et al*, 1991; Hayati *et al*, 1993; Noertjojo *et al*, 2002; Sachdeva *et al*, 2002), however, few other studies showed figures higher than ours (Dolberg *et al*, 1991; Fernandez Jorge *et al*, 1995; Denis-Delpierre *et al*, 1998; Lado Lado *et al*, 2000). The variation in the rate of EPT could be generally due to changes in the patients with tuberculosis, the accuracy in term of early diagnosis, and appropriate investigations and treatment. Moreover, extrapulmonary tuberculosis rapidly progresses by nature, and is potentially fatal but usually treatable condition. Therefore, diagnostic procedures should seek earlier detection in any suspected cases, before final diagnosis.

The demographic patterns of these patients clearly showed that, for age distribution, extrapulmonary tuberculosis is acquired in the early teens and tends to increase with age (25-34 years), then decline as one becomes older. The Malays were not only the major ethnic group, but also had the highest frequency of EPT-lymph node, miliary, pleura, and spine when compared with the others in this study. Furthermore, unfavorable social conditions, such as marital status, unemployment, smoking and alcohol, intravenous drug use, and history of previous exposure and contact with tuberculosis showed similar results to other studies (Fernandez Jorge *et al*, 1995; Fain *et al*, 2000). In this context, we conclude that socio-demographic differences are more important contributing factors to the gradual increase in the course of disease.

In the majority of cases, the method of diagnosis was histology (102/195; 52%), particularly in TB-lymph node (68/83; 82%) in this study, not only to confirm diagnosis but also to differentiate tuberculosis from malignancy or other metastatic forms. We noted that 84/195 (43%) of these patients had positive tuberculin skin tests, which were also more common in TB-lymph node (51/83; 62%). Therefore, we concluded that tuberculin skin tests should be performed on all individuals suspected of tuberculosis which is supported by an earlier work (Elder, 1992), but contrary to others (Yaacob, 1990; Qari, 2002). Even though both sputum for smear and culture were performed in most cases, positive results were not encouraging; however, no relevant drug resistance was found from culture and sensitivity testing. This study showed that abnormalities by x-ray findings were directly proportional to the number of sites involved. Meanwhile, we should not dismiss extrapulmonary tuberculosis, even in the case of normal x-ray findings.

Tuberculous lymphadenitis was the most common extrapulmonary tuberculosis (43%) with predominant cervical lymph node involvement and in females. These findings are supported by previous studies (Tan, 1988; Shimoide *et al*, 1994; Huang *et al*, 2000; Chan-Yeung *et al*, 2002; Ebdrup *et al*, 2003). However, pleural tuberculosis was the most common, as found in other studies (Haegi, 1987; Ramos *et al*,1995; Ozbay and Uzun, 2002; El-Sony *et al*, 2003).

In general, the role of treatment in extrapulmonary tuberculosis is as important as in pulmonary TB or even greater. However, there have been comparatively few clinical trials on the treatment of extrapulmonary disease. Overall, 73% of these patients were successfully treated with at least a short course of anti-tubercular therapy and without evidence of relapse. This finding agrees with previous reports (Monie *et al*, 1982; Dutt *et al*, 1986; Dutt and Stead, 1989). Thirty-three percent of cases were treated for ≥ 9 months of ATT, which shows that patients appear to be more compliant or adherent to therapy and eventually can prevent the recurrence of tuberculosis. Interestingly, we found that the 12-month courses of ATT were practically given, as seen in the majority of patients with osteoarticular tuberculosis, which was also recommended by other investigators in the literature (Newton *et al*, 1982; Pertuiset *et al*, 1999). Unfortunately, 23% of all cases were lost to follow-up before completing anti-tubercular therapy. Therefore, we strongly recommend that measures should be adapted for the therapeutic management of these patients (Fain *et al*, 2000) in order to enhance the effectiveness of the national tuberculosis control program.

Based on our findings, extrapulmonary tuberculosis is still gaining attention and has not yet disappeared from Malaysia. Predisposing factors seem to play contributing roles in the cause of disease. The most common site of involvement was the lymph node, followed by miliary and disseminated, pleura, skeleton, genitourinary tract, abdomen and others, respectively. The duration of treatment varied from 6 to 12 months, depending on the site of involvement. No primary drug resistance or death was notified in this study.

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