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Pulmonary Disease Empirically Treated as Tuberculosis-A Retrospective Study of 107 Cases

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Summary

Pulmonary disease is sometimes treated empirically as tuberculosis (TB) in the absence of microbial confirmation if the clinical suspicion of active TB is high. In a country of relatively high TB and low HIV burden, we retrospectively studied 107 patients (69.2% male; mean age (SD): 45 (17) years) who received empirical anti-TB treatment for intrapulmonary opacities or pleural effusions suspected of active TB in our hospitals between 1998 and 2002. The diagnosis of definite or probable 'smear-negative' pulmonary TB was made based on treatment outcome at two months with rifampicin, isoniazid, pyrazinamide and ethambutol (or streptomycin). At this end-point, 81 patients (84.4%) had both clinical and radiological improvement (definite cases), 12 (12.5%) had clinical improvement alone and 3 (3.1%) had radiological improvement alone (probable cases). Confirmation of acid-fast bacilli was subsequently obtained in 12 patients (all definite cases) from culture of initial pulmonary specimens. Eleven patients (10.5%) were diagnosed as 'non-TB' based on absence of both clinical and radiological improvement or discovery of another cause for the pulmonary condition at or before this two-month study end-point. In the 'non-TB' group, 2 had carcinoma, 2 had HIV-related pulmonary diseases, 1 had bronchiectasis, while in 6 causes were indeterminate. Six (6.3%) and 3 (27.3%) patients reported adverse effects from anti-TB drugs from the 'TB' and 'non-TB' groups respectively. Our findings suggest that empirical anti-TB treatment is an acceptable practice if clinical suspicion is high in patients coming in our region.

Key Words: Pulmonary tuberculosis, Smear-negative, Empirical treatment, Malaysia

Introduction

In the absence of microbial confirmation, empirical treatment with anti-tuberculous (TB) drugs in unexplained lung opacities or pleural effusions when clinical suspicion is high is practiced by many [1,2,3,4]. Untreated 'smear negative' patients or those whose treatment are delayed have high morbidity and mortality, and as such, empirical chemotherapy can be life saving [5,6,3]. However, the practice can lead to the danger of exposing inappropriately treated patients unnecessarily to the toxicity of anti-TB drugs [7,8], and the delaying of the diagnosis and treatment of underlying pulmonary conditions that may have serious clinical consequences.

Malaysia is a multiracial country with a notification rate for TB at 68.1 per 100 000 population and with an estimated incidence at 112 per 100 000 population [9,10]. The World Health Organization has categorized Malaysia as a region of intermediate high TB burden[9]. Prior to HIV epidemic, there was an estimated 1.22 cases of 'smear negative' pulmonary or extrapulmonary TB to every 'smear positive' case[3] and this probably still

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holds true for countries with low prevalence of HIV such as Malaysia[9]. Local Malaysian studies have shown that TB is a common cause of pleural effusions particularly in patients aged below 50 years old [11,12]. Thus, empirical chemotherapy for unexplained lung or pleural disease is an accepted practice in acid-fast bacilli (AFB) smear-negative cases or non-sputum producers whenever the clinical and radiological presentations are suggestive of active TB. Moreover, the lack of access to the microbiology laboratory or bronchoscopy service in some district areas requires that such approach be adopted. To investigate the treatment outcome of such a practice, we conducted a retrospective study of patients being empirically treated in our hospitals.

Materials and Methods

Case records between 1998 and 2002 located in the TB Clinics of an 800-bed state teaching hospital (Seremban Hospital) and a 300-bed district general hospital (Kuala Pilah Hospital) were hand-searched for patients who received empirical anti-TB treatment for pulmonary disease. Patients included were those who received treatment based on clinical and radiological grounds alone without any microbial confirmation of AFB or tissue histology findings of granuloma on sampled pulmonary specimens (sputum, bronchial washing/BAL or pleural aspirates /biopsies). Our standard criteria for commencing patients with empirical anti-TB treatment were absence or poor response to at least 2 different courses of anti-microbial antibiotics over a month period and smear-negative sputum for at least two occasions. Excluded were patients with incomplete follow-up for whatever reasons, those who were transferred to other hospitals for completion of treatment, and those whose TB were 'extra-pulmonary'.

A standard questionnaire was used to collect data on patients' demographics and clinical characteristics, their clinical presentations, investigations of inflammatory indices (total white cell count and erythrocyte sedimentation rate), results of Mantoux test, and side effects, if any, of anti-TB drugs. The treatment outcome was based at two months of quadruple chemotherapy with rifampicin, isoniazid, pyrazinamide and ethambutol (or streptomycin). A patient was considered to have 'definite' pulmonary TB if there were both clinical and radiological improvement or culture of AFB from initial pulmonary specimens. A patient was considered to have 'probable' pulmonary TB if there was either clinical or radiological improvement and that complete anti-TB treatment was carried out to six or nine months. A patient was diagnosed to be 'non-TB' if there was no improvement of any of the above mentioned at two-months study end-point and that anti-TB treatment was terminated, or alternatively another cause for the pulmonary condition was discovered at or before this time. Clinical and/or radiological improvement have been used in previous studies as a means of establishing the diagnosis 'smear negative' pulmonary TB [13,14,15]. Side effects of anti-TB drugs were categorized into major or minor. A major side effect was defined as one that was sufficiently severe to have caused interruption or change of treatment regime. A minor side effect was defined as one that did not cause interruption or change of treatment regime.

Statistical analysis

Fisher's exact test was used to analyze categorical data and student's t test for continuous variables. All significance tests were two-tailed and p value less than 0.05 was considered significant. All analysis was carried out on SPSS Version 11.0 for Windows.

Results

Data from 107 eligible patients [69.2% male; mean age (SD) 45 (17) years; 55.1% Malays, 28.0% Chinese, 10.3% Indians, 6.5% of other ethnicity; 62.6% from Seremban Hospital, 37.4% from Kuala Pilah Hospital] were analyzed. Sputum was collected in 96 patients (89.7%), bronchoscopy washings/lavage in 11 patients (10.3%) and pleural aspirates/biopsies in 6 patients (5.6%). No microbial specimens were collected in 10 patients (9.3%). In 12 patients, AFBs were subsequently cultured in sputum (n=10) and pleural aspirates/biopsies (n=2).

Eighty-one (84.4%) and 15 patients (15.6%) had definite and probable pulmonary TB respectively. Eleven patients (10.5%) did not have pulmonary TB. In those with probable TB, 12 patients (12.5%) had clinical improvement alone and 3 patients (3.1%) had radiological improvement alone (Figure 1). In the 'non-TB group', 2 patients had carcinoma, 2 had HIV-related pulmonary diseases, 1 had bronchiectasis, and 6 whose causes were indeterminate (Table I).

The demographics and clinical characteristics of patients in the 'definite TB', 'probable TB' and 'non-TB' groups were generally comparable (Table II). The mean age was in the middle age range with

predominance of men in all groups. The distribution of ethnic groups in all groups was similar with Malay and Chinese forming the two larger groups followed by Indians. There were 7 patients from other undefined ethnic groups (5 from Indonesia, 2 from minority native groups of Malaysia), whom all belonged to the 'definite TB' group. There were no significant differences in non-HIV related comorbidity between all groups. The comorbidity comprised of treated colorectal carcinoma (n=2), Hepatitis B infection (n=1), splenectomy (n=1), end-stage renal disease (n=3), diabetes mellitus (n=1), alcohol dependence (n=4), and non-HIV intravenous drug users (n=3). In our study, there were only 6 patients with known positive HIV status- 4 in the 'definite TB' group while the other 2 in the 'non-TB' group. In all groups, the proportions of patients treated in the Seremban or Kuala Pilah Hospital were comparable.

There were no significant differences between all groups in their radiological and clinical presentations (Table III). More than 70% of patients in both groups presented with intrapulmonary opacities alone while a much smaller proportion had pleural effusion alone. Seven patients from the 'definite TB' (n=6) and 'probable TB' groups (n=1) had both pulmonary opacities and pleural effusions, compared to none in the 'non-TB' group. Cough was the commonest respiratory symptoms in all groups while haemoptysis was the second commonest symptoms in the 'definite TB' and 'probable TB' groups. Dyspnoea and pleuritic pain were not a common complaint with fewer than 20% in all groups reporting these. A small proportion of patients in all groups had no respiratory symptoms whatsoever.

In all groups, a large proportion of patients had systemic symptoms of fever, anorexia and weight loss while a much small proportion reported night sweats. The latter were only reported in the 'definite TB' and 'probable TB' groups. Twenty-four patients (25%) in the 'definite TB' (n=21) and 'probable TB' groups (n=3), and 1 patient (9.1%) in the 'non-TB' group had no systemic symptoms whatsoever. The proportions of patients previously treated for pulmonary TB or having a family or personal history of contact with infected TB individual were comparable in all groups (Table III).

The results of ESR were available in only 58 patients. In these patients, whether normal or high values, they were not significantly different between the three groups. Similarly, results of total WCC were available in only 48 patients and they were not significantly different between the groups. The results of Mantoux test were available in even fewer patients (n=38). Of these, only 1 patient in the 'non-TB' group had this test report. Over 70% of the patients in the 'definite TB' group and 50% of patients in the 'probable TB' group had negative Mantoux result (Table IV).

Nine patients (8.4%) reported side effects from anti-TB drugs with 6 patients (6.3%) coming from the 'definite TB' group and 3 patients (27.3%) from the 'non-TB' group. The difference between the two groups is statistically significant (p=0.045). Of the 6 patients in the 'TB' group, 4 had minor side effects and 2 had major. All 3 patients in the 'non-TB' group had minor side effects only. The minor side effects reported were pruritus (n=3), nausea and vomit (n=3), macular rash (n=1), giddiness (n=1) and joint pain (n=1). Major side effects were severe pruritus (n=1) and jaundice (n=1).

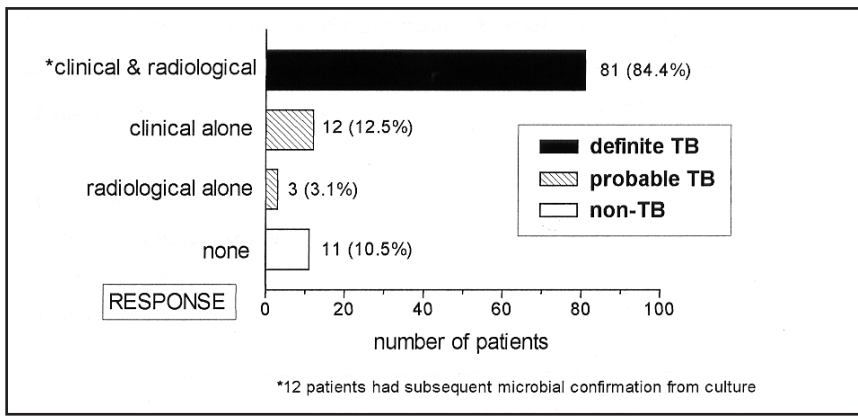

Fig 1: Classification of definite, probable or non-TB based on treatment outcome at two months in patients empirically treated (n=107)

Table I: Causes of pulmonary diseases in 'non-TB' group

Causes	Number
Carcinoma	2*
HIV-related lung diseases	2
Bronchiectasis	1
Indeterminate causes	6

* 1 small cell carcinoma, 1 metastatic carcinoma of unknown origin

Table II: Patients' demographics and clinical characteristics

	Definite TB	Probable TB	Non-TB
n	81	15	11
Mean age, yrs (SD*)	45 (16)	46 (20)	46 (14)
Age			
<25 yrs	9 (11.1%)	3 (20.0%)	1 (9.1%)
25-50 yrs	39 (48.1%)	6 (40.0%)	4 (36.4%)
>50 yrs	33 (40.7%)	6 (40.0%)	6 (54.5%)
Male, n	55 (67.9%)	11 (73.3%)	8 (72.7%)
Ethnic groups			
Malays	45 (55.6%)	7 (46.7%)	7 (63.6%)
Chinese	20 (24.7%)	7 (46.7%)	3 (27.3%)
Indians	9 (11.1%)	1 (6.7%)	1 (9.1%)
Others	7 (8.6%)		0
Non-HIV related comorbidity**	12 (14.8%)	1 (6.7%)	2 (18.2%)
HIV status positive	4 (4.9%)	0	2 (18.2%)
Original hospital			
Seremban Hospital	49 (60.5%)	11 (73.3%)	7 (63.6%)
Kuala Pilah Hospital	36 (39.5%)	4 (26.7%)	4 (36.4%)

*SD= standard deviation

**Non-HIV related comorbidity were treated colorectal carcinoma (2), Hepatitis B infection (1), splenectomy (1), end-stage renal disease (3), diabetes mellitus (1), alcohol dependence (4), non-HIV intravenous drug user (3).

#p>0.05 between comparisons of all variables

Table III: Patients' radiological and clinical presentations*

	Definite TB	Probable TB	Non-TB
Radiological			
Intrapulmonary opacity	64 (79.0%)	13 (86.7%)	8 (72.7%)
Pleural effusion	11 (13.6%)	1 (6.7%)	3 (27.3%)
Both opacity & effusion	6 (7.4)	1 (6.7%)	0
Respiratory symptoms			
Nil	4 (4.9%)	3 (20.0%)	2 (18.2%)
Cough	72 (88.9%)	12 (80.0%)	9 (81.8%)
Haemoptysis	31 (38.3%)	5 (33.3%)	1 (9.1%)
Dypsnoea	13 (16.0%)	2 (13.3%)	2 (18.2%)
Pleuritic pain	5 (6.2%)	2 (13.3%)	1 (9.1%)
Systemic symptoms			
Nil	21 (25.9%)	3 (20.0%)	1 (9.1%)
Fever	38 (46.9%)	7 (46.7%)	6 (54.5%)
Anorexia	43 (53.1%)	9 (60.0%)	6 (54.5%)
Night sweats	16 (19.8%)	2 (13.3%)	0
Weight loss	45 (55.6%)	6 (40.0%)	8 (72.7%)
Previously treated for TB	10 (12.3%)	4 (26.7%)	2 (18.2%)
Personal or family history of TB contact	16 (19.8%)	3 (20.0%)	1 (9.1%)

*p>0.05 between comparisons of all variables

Table IV: Blood indices of inflammation and Mantoux tests*

	Definite TB	Probable TB	Non-TB
ESR (n=58)			
Normal	12 (28.6%)	3 (30.0%)	1 (16.7%)
High	30 (71.4%)	7 (70.0%)	5 (83.3%)
Total WCC (n=48)			
Normal	21 (65.6%)	7 (70.0%)	4 (66.7%)
High	11 (34.4%)	3 (30.0%)	2 (33.3%)
Mantoux Test (n=38)			
Positive	7 (24.1%)	4 (50.0%)	0
Negative	22 (75.9%)	4 (50.%)	1 (100%)

ESR=Erythrocyte Sedimentation Rate. Normal male value ≤ age [years] divided by two; normal female value ≤ age [years] plus 10 divided by two.
WCC=White Cell Count
Positive Mantoux test= skin induration ≥ 15 mm diameter
Parenthesis in first column =the number of patients who had these investigations available
*p>0.05 between comparisons of all variables

Table V: Frequency of side effects from anti-TB therapy

	Definite TB	Probable TB	Non-TB
Present (n=9, 8.4%)*	6 (6.3%)	0	3 (27.3%)
Severity			
Minor	4 (4.2%)	-	3 (27.3%)
Major	2 (2.1%)	-	-

Minor side effects were pruritus (3), nausea & vomit (3), macular rash (1), giddiness (1) and joint pain (1). Major side effects were severe pruritus (1) and jaundice (1).
*p=0.045 between the definite TB and non-TB groups of overall frequency

Discussion

In a retrospective study, we have shown that a large proportion of the studied patients who were treated empirically for pulmonary TB on clinical and radiological grounds responded positively at the end of two months' treatment with quadruple anti-TB drugs. About 10% had different diagnoses or had their treatment terminated at two months due to absence of therapeutic response or discovery of the underlying diseases explaining the pulmonary conditions. This study was conducted in a population of relatively high TB burden but whose HIV prevalence is low [9].

The annual figures of patients being treated for TB in both the hospitals are between 450 and 500 with the proportion of patients treated empirically around 2 to 5%. The therapeutic success of anti-TB chemotherapy can be reliably determined after two months' of intensive treatment with triple or quadruple anti-TB drugs in most 'smear-negative' cases and such diagnostic criteria has been used in studies researching 'smear-negative' pulmonary TB [13, 14, 15]. Our division between 'definite TB' and 'probable TB' is considered necessary because as a hospital policy, 'smear-negative' pulmonary specimens (especially in the context of sputum) were not routinely sent for culture unless specifically requested by attending clinicians. As a result, a majority of empirically treated cases could not be verified by subsequent culture findings. Therefore, the 'gold standard' of diagnosing 'smear-negative' pulmonary TB falls back on clinical and radiological improvement. We seek to ensure the results are valid by limiting the 'definite TB' cases to those with both clinical and radiological improvement while to those whose improvement was one alone as 'probable TB' cases. In the latter, they can still be genuine TB cases and as such, the attending clinicians then had decided to treat the patients fully. For example, in the 3 patients who had only radiological improvement, 2 did not have clinical symptoms (either respiratory or systemic) to begin with. Therefore, any improvement would have to be radiological alone. In the 12 patients with clinical improvement alone, the lack of radiological improvement may be contributed by fibrosis or bronchiectasis that frequently accompanies active pulmonary TB, or simply a delay response of more than two months. Therefore, clinical improvement alone would have been sufficient to clinch the diagnosis of 'smear negative' TB.

In the 11 patients (10.3%) that were 'not TB', 2 patients had carcinoma. Although review of their notes showed that their disease were already advanced and inoperable at the outset, it still raises the question whether empirical treatment had been inappropriately initiated and therefore had delayed diagnosis and treatment of their true conditions. In 6 patients, there were no clear diagnosis of their pulmonary diseases and it is therefore difficult to ascertain whether anti-TB treatment has been appropriate or not. It is conceivable that in some whose initial mycobacterium load is high, clinical or radiological improvement could only become apparent after more than two months of treatment.

The clinical characteristics of patients in the 'TB' and 'non-TB' group were generally comparable. There was also no difference in outcome of success whether empirical treatment was initiated in the state teaching hospital or the district hospital. The practice of empirical treatment is common among HIV patients with suspected pulmonary TB because of low yield in attempts at isolating AFB from pulmonary specimens [3].

In our study, patients with positive HIV status are few and it probably reflects the relatively low prevalence of HIV infection or testing in our population.

With regards to the clinical and radiological presentations, all three groups were comparable. However, none of the patients in the 'non-TB' group had radiological involvement of both intrapulmonary opacity and pleural effusion, or night sweats on presentation. Also, haemoptysis was only present in 1 patient in the 'non-TB' group compared to 36 in the 'definite TB' and 'probable TB' groups. These features may be used as favoring pulmonary TB, although they remain non-specific. History of previously treated for TB, or personal or family history of TB contact, are often used by clinicians in supporting the use of empirical treatment. We have shown that this information was not particularly discriminating. Similarly, ESR and total white cell count as indices of inflammation that are useful in deciding the nature of infection/inflammation of pulmonary disease, were not helpful in discriminating 'TB' from 'non-TB' disease. Only 1 patient in 'non-TB' group had Mantoux test available for our study and the result was negative. Over 76% of patients in 'TB group' had negative Mantoux tests indicates that in our study population, Mantoux test was a poor predictor of active TB disease. Yaacob et al [16] have shown that in a large teaching hospital in north Malaysia peninsular, only 42% of 468 cases of active TB infection had positive Mantoux tests. The authors suggest that the low sensitivity of skin testing may be attributed to the differences in tuberculin test profiles among various ethnic communities. The cut-off point for positive skin test practiced in our clinics is 15mm diameter. This is probably appropriate in Malaysia population where BCG vaccination is required for all.

Studies have shown that severe drug toxicity compelling a change or interruption in anti-TB treatment regime is as high as 10% [7, 8]. Our study recorded an overall side effect incidence of 8.4% from anti-TB chemotherapy and a major side effect incidence of 2.1%. All major side effects occurred in the 'definite TB' group but in terms of overall side effects, there was a significantly higher incidence in the 'non-TB' compared to the other groups. This suggests that patients inappropriately started on anti-TB chemotherapy are exposed to the same or even higher risk of developing side effects from treatment. Our finding reiterates the importance of careful consideration regarding the risk/benefit of introducing empirical anti-TB treatment on the part of the attending clinician.

In any retrospective study, accuracy of collected data is hugely dependent on the clarity and adequacy of case records. TB control and treatment programme in Malaysia has been centrally administered by the Ministry of Health Malaysia for many years now issued clear directives on case recording, case reporting and contact tracing. As a result, the records in all TB clinics are largely standardized with clear documentation of clinical details specifically required for all registered patients. Our data collection was based on these records. However, investigations such as ESR, total WCC and Mantoux test were not routine standard investigations for all registered patients. This reality has been reflected in our data collection. The low frequency of ordering these tests in the empirically treated group of patients suggests that many treating clinicians do not use them in their process of decision making. The reduced number of available test results in more than half our patients has significantly reduced the power of our study with regards to understanding of their values in predicting outcome for empirical treatment of unexplained pulmonary diseases.

One important consideration for our study is the exclusion of empirically treated patients with incomplete follow-up. While it is clear that many were transferred out of the district to be treated in another government TB clinic, there were some who defaulted follow-up for no known reasons and tracings them was unsuccessful. In all these cases, it is not known whether empirical chemotherapy was successful or not, or whether they had developed serious adverse effects from the drugs that had led to their defaulting follow-up. However, the number is small and is unlikely to cause significant deviation to the findings in our study.

Empirical treatment with anti-TB drugs in 'smear negative' patients is an accepted practice in many places. Many studies have addressed the question on how to increase the clinical prediction of 'smear negative' pulmonary TB [17,4,13]. While our study does not address the criteria on which clinicians decided to introduce empirical anti-TB chemotherapy, the findings add to the pool of evidence for the effectiveness of such an approach in a population of relatively high TB burden. Such practice outside regions of high TB prevalence may not be appropriate depending on the disease behaviour in the community, the HIV prevalence, pattern of drug resistance, and other local

factors [3]. It is however important to consider that the global incidence of TB is increasing, and inadequate case-detection and cure rates have been identified as reasons for this mounting burden [18,19]. Therefore, there should be an increased awareness of the possibility of TB in unexplained or poorly resolving pulmonary disease on the part of the attending clinician. The rapid spread of Severe Acute Respiratory Syndrome across all international boundaries clearly illustrates the ease with which some infections transmit from one place to another especially when aerosol spread is involved [20]. However, it remains important to emphasize that empirical anti-TB treatment should only be started after careful consideration and preferably following discussion with a chest specialist or an experienced physician. These considerations include disease severity and its immediate threat to life and public (especially young children at home); urgency of commencing treatment, comorbidity (including HIV) associated with the patient; and availability of or access to appropriate diagnostic resources.

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