ORIGINAL ARTICLE

Pulmonary Tuberculosis - A Review of Clinical Features and Diagnosis in 232 Cases

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Summary

The diagnosis of pulmonary tuberculosis is often delayed due to atypical clinical features and difficulty in obtaining positive bacteriology. We reviewed 232 cases of pulmonary tuberculosis diagnosed in Kedah Medical Centre, Alor Setar from January 1998 to December 2002. All age groups were affected with a male predominance (Male:Female ratio = 60:40). Risk factors include underlying diabetes mellitus (17.7%), positive family history (16.8%) and previous tuberculosis (5.2%). Nearly half (45.3%) of patients had symptoms for more than one year. Only 22% of patients had typical symptoms of tuberculosis (prolonged recurrent fever, cough, anorexia and weight loss), whilst others presented with haemoptysis, chronic cough, COPD, bronchiectasis, general ill-health, pyrexia of unknown origin or pleural effusion without other systemic symptoms. Fifteen percent of the patients presented with extrapulmonary diagnosis. Ninety percent of the patients had previous medical consultations but 40% had no chest radiograph or sputum examination done. The chest radiographs showed 'typical' changes of tuberculosis in 62% while in the other 38% the radiological features were 'not typical'. Sputum direct smear was positive for acid-fast bacilli in only 22.8% of patients and 11.2% were diagnosed base on positive sputum culture. Sputum may be negative even in patients with typical clinical presentations and chest radiograph changes. Bronchial washing improved the diagnosis rate being positive in 49.1% of cases (24.1% by direct smear and the other 25.0% by culture). In 16.8% of cases, the diagnosis was based on a good response to empirical anti-tuberculosis therapy in patients with clinical and radiological features characteristic of tuberculosis. In conclusions, the clinical and radiological manifestations of pulmonary tuberculosis may be atypical. Sputum is often negative and bronchoscopy with washings for Mycobacterium culture gives a higher yield for diagnosis. In highly probable cases, empirical therapy with anti-tuberculosis drugs should be considered because it is safe and beneficial.

Key Words: Tuberculosis, Pulmonary, Diagnosis, Bronchoscopy

Introduction

In spite of extensive control programme, tuberculosis remains a major public health problem worldwide. In fact, there is a global resurgence of the disease. The key to the overall control of tuberculosis is to cure infectious cases at an early stage. However, the diagnosis is often delayed or missed causing morbidity, mortality and continued spread of the disease. More than 80% of new cases of pulmonary tuberculosis (PTB) are in an advanced stage radiologically at the time of diagnosis[1-3]. Many cases are missed altogether sometimes resulting in deaths. The diagnoses in 31.5% of tuberculosis deaths in Penang Hospital in 1993 were made at autopsy[4]. Even in the United States, 5% of TB deaths were discovered at autopsy[5].

The delay in diagnosis is mainly due to incorrect diagnosis by the doctors rather than patients delay in seeking medical advice[2,6-9]. Patients with active

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pulmonary disease may have multiple emergency department visits, often with non-pulmonary complaints but the diagnosis is often missed although tuberculosis risk factors and symptoms are usually present in these patients[9]. Even in hospitalised patients there is a delay in the diagnosis and treatment[10]. Nearly 30% of culture-positive PTB were missed due to failure to obtain a positive Z-N stain on examination of sputum[11].

Rapid diagnosis therefore depends on the doctor's awareness and recognition of the significance of the patient's symptoms and appropriate investigations. Hence, a continuing awareness of the clinical spectrum of tuberculosis remains important. We reviewed cases of PTB diagnosed in our hospital in 1998 to 2002 to highlight the spectrum of clinical presentations and the diagnostic difficulties.

Materials and Methods

This review included all in-patients and out-patients diagnosed as pulmonary tuberculosis (PTB) at the Kedah Medical Centre, Alor Setar, during the 5-year period from January 1998 to December 2002. Kedah Medical Centre is an 80-bed private hospital with one general physician and one chest physician.

The clinical data, microbiology laboratory records and the chest radiograph findings were reviewed. The symptoms, duration of illness, underlying diseases, previous consultations and investigations were recorded. In our hospital, all patients suspected of tuberculosis had a chest radiograph done. If available, sputum was sent for microscopy (direct smear) for acid-fast bacilli (AFB). Fibreoptic bronchoscopies were performed in cases where sputum analysis was negative or unavailable. Screening for HIV infection was done in all patients before bronchoscopy. Bronchoscopy would not be done if the HIV test was positive. For those patients who were unfit or refused bronchoscopy, sputum (if available) was sent for mycobacterium culture. If the clinical features, radiological changes and findings on bronchoscopy (if performed) showed high probability of PTB, they were put on empirical anti-tuberculosis therapy. PTB was diagnosed if there was good and sustained clinical and radiological improvement.

Results

In the 5-year period, a total of 232 cases of pulmonary tuberculosis were diagnosed. In the same period, 24 cases of extra-pulmonary tuberculosis were also detected but they were not included in this review.

Age and Sex: The age and sex distribution of the patients is shown in Figure 1. All age groups were affected. The peak incidence was in the 61-70 age groups. Overall, there was a predominance of male patients (Male:Female = 60:40). However, in patients younger than 40 years, there was a female predominance (2:1) whereas in older patients the ratio was reversed (1:2.2).

Associated illness and risk factors (Table I)
Ninety-nine patients (42.6%) had risk factors or associated illness. Forty-one patients (17.7%) had diabetes mellitus and thirty-nine patients (16.8%) had a family history of tuberculosis (including eleven patients (4.7%) who had both diabetes and positive family history). Patients were often not forthcoming with family history until the diagnosis of PTB was confirmed. Twelve patients (5.2%) had a history of previous treatment for tuberculosis. The other associated illness included two cases of lung cancer, one case each of ischaemic heart disease, endocarditis, carcinoma of the larynx and pregnancy. Only one HIV-related case was recorded (The patient also had diabetes and cardiomyopathy with congestive heart failure).

Duration of symptoms
Most of the patients had a long history of symptoms compatible with PTB. Nearly half (45.3%) of the patients had symptoms for more than one year. The duration from onset of first symptoms to the time of diagnosis is shown on Table II. In 16 cases, the time of onset was undetermined because the patients presented with other medical or surgical diagnoses and had no symptoms to suggest tuberculosis even on direct questioning.

Clinical presentation
The types of presentation were classified into clinical groups (considering their symptoms, signs and chest radiographic changes), rather than into single symptomatology. The distribution of cases according to clinical presentation is shown in Table III.

History of previous consultations or investigations
Although the patients had a long history of illness and the majority had sought medical attention, the diagnosis of PTB was not made because of negative investigations (usually chest x-ray or sputum direct smear only). In

half of the cases, no investigations were performed previously (Table IV).

Chest radiography and methods of diagnosis

The chest radiographic findings and methods of diagnosis are shown in Table V. The chest radiographs showed 'typical' changes of tuberculosis in 62% of patients while in the other 38% the radiological features were 'not typical'. Sputum direct smear was positive in only 22.8% of patient and 11.2% were diagnosed on sputum culture. Bronchial washing was positive in 49.1% (24.1% by direct smear and 25.0% by positive culture only). In 16.8% of cases without microbiological confirmation, the diagnosis was made on the basis of highly suggestive clinical and radiographic features and a significantly good response to empirical anti-tuberculosis therapy.

Laboratory findings:

Blood investigations were not done in all patients. Anemia (Hb<11.0g/dl) was present in 21.4% (42/196) of cases. White cell counts of more than 11.0 x 10^9/dl was seen in 28.3% (43/152). The erythrocyte sedimentation rate (ESR) was less than 40mm/hr in 29.9% (32/107) cases; 40-100mm/hr in 46.7% (50/107) and more than 100 mm/hr in 23.4% (25/107) cases. Interestingly, we noted that 26% (37/143) of the patients had high platelet counts of more than 400 x 10^9/dl. The platelet counts did not correlate with the haemoglobin level or white cell count.

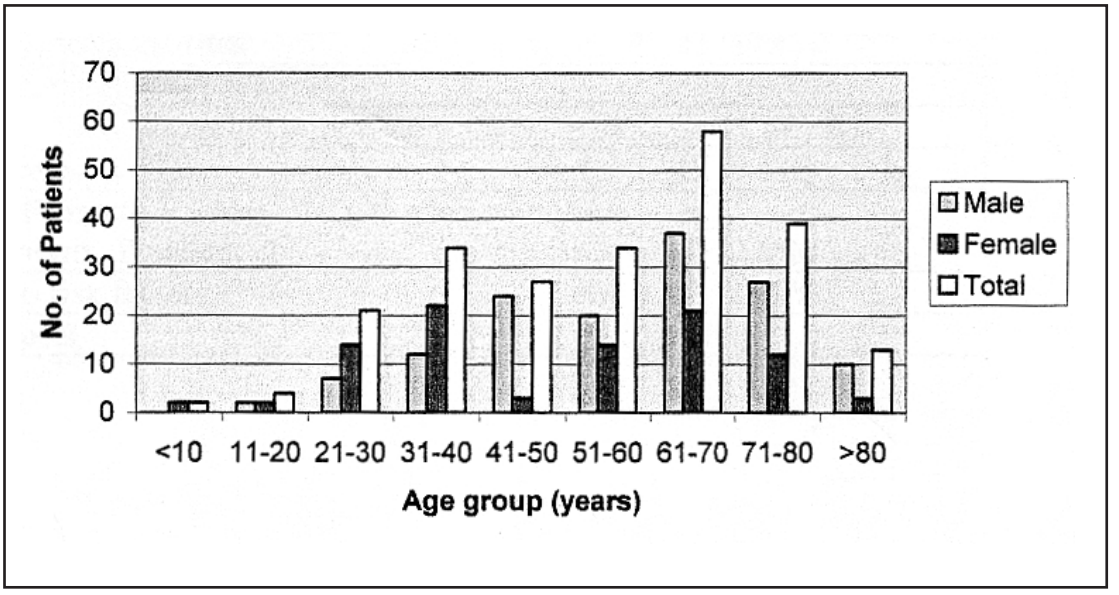

Fig. 1: Age and sex distribution

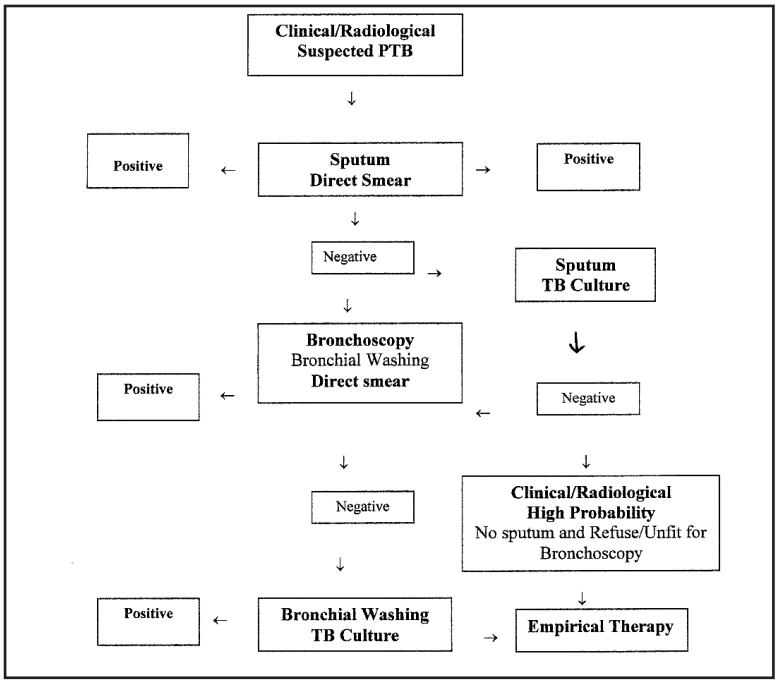

Fig. 2: Suggested algorithm for diagnosis of pulmonary tuberculosis

Table I: Risk factors or underlying diseases

Associated illness/Risk factors	No. of cases (%)
Diabetes mellitus	41 (17.7%)
Family/contact history	39 (16.8%)
Diabetes and Family history	11 (4.7%)
Previous PTB	12 (5.2%)
Others: (Ca Lung, IHD, Endocarditis, Ca Larynx, Pregnancy)	7 (2.5%)
No risk factor	133 (57.8%)
Total	**232**

Table II: Duration of illness from onset of first symptoms to diagnosis of pulmonary tuberculosis

Duration of illness	No. of cases (%)
Less than 2 weeks	19 (8.2%)
2 weeks to 1 month	24 (10.3%)
1 to 3 months	41 (17.7%)
3 to 6 months	19 (8.2%)
6 months to 1 year	31 (13.4%)
1 to 5 years	43 (18.4%)
5 to 10 years	24 (10.3%)
More than 10 years	15 (6.5%)
Undetermined	16 (6.9%)
Total	**232**

Table III: Clinical presentations in 232 cases of pulmonary tuberculosis

Clinical Presentation	Total Cases
Typical of tuberculosis - Combinations of prolonged fever, cough (with or without haemoptysis), anorexia, weight loss	52 (22.4%)
Haemoptysis - Cough out blood (once or recurrent) but without other systemic symptoms tuberculosis or evidence of bronchiectasis	29 (15.0%)
Chronic cough: Undiagnosed cough (more than one month) but without systemic symptoms	24 (10.3%)
COPD: Diagnosed chronic obstructive airway disease or recurrent cough and breathlessness with clinical findings suggestive of airway obstruction.	22 (9.5%)
Pneumonia: Acute fever and cough (less than 2 weeks).	21 (9.1%)
Bronchiectasis: Diagnosed bronchiectasis or chronic productive cough with chest x-ray compatible with basal bronchiectasis.	15 (6.5%)
General ill-health: Prolonged illness with fever, anorexia, weight loss without respiratory symptoms	10 (4.3%)
Pyrexia of unknown origin - Fever of more than 2 weeks, without respiratory symptoms	7 (3.0 %)
Pleural effusion: Symptomatic pleural effusion (Pain or breathlessness), without significant systemic features	7 (3.0%)
Asthma: Diagnosed asthma or acute airway obstruction	5 (2.1%)
Hoarse voice/Sorethroat: All presented to the ENT	5 (2.1%)
Others (extrapulmonary presentations): This includes lympadenopathy (7), inguinal hernia (4), perianal abscess (3), arthritis (3), routine medical examination (3) appendicitis (2) anemia (2) and one case each of pneumothorax, acute gastroenteritis, gastric ulcer, acute myocardial infarction, congestive heart failure, backache, motor vehicle accident, brain 'tumour', paraparesis, fracture hip, and Parkinson's disease (On questioning, 19 patients had symptoms of PTB).	35 (15.0%)
Total	**232**

Table IV: Previous consultations or investigations

History of previous consultations or investigations	Number of cases (%)
No previous medical consultations	23 (9.8%)
Had medical consultations but no history of CXR or sputum examination	94 (40.6%)
Had investigations done but no PTB diagnosis	115 (49.6%)
CXR and sputum examination	65
CXR only	39
Bronchoscopy	7
Other specimen (pleural aspiration etc)	4
Total	**232**

Table V: The method of diagnosis in relation to chest x-ray changes

Chest x-ray changes	AFB	Sputum Culture	Bronchial AFB	Washing Culture	Empirical Therapy	Total
Infiltrates, ± Fibrosis, Cavitations both upper lobes	23	10	21	12	10	76 (32.7%)
Infiltrates, ± Fibrosis, Cavitations right upper lobe	19	3	12	8	5	46 (19.8%)
Infiltrates, ± Fibrosis, Cavitations left upper lobe	4	3	8	5	1	21 (9.0%)
Pneumonia (Mid or lower zone lobar consolidations or diffuse infiltrates)	2	3	8	7	4	24 (10.3%)
Bronchiectasis (Mid or lower zones)	2	3	3	12	8	28 (12.1%)
Pleural effusions	0	0	1	3	11	15 (6.4%)
"Old PTB" Chronic changes	3	4	1	5	0	13 (5.6%)
Miliary changes	0	0	1	6	0	7 (3.0%)
Abscess (middle/lower lobe)	0	0	1	1	0	2 (0.9%)
Total	**53 (22.8%)**	**26 (11.2%)**	**56 (24.1%)**	**58 (25.0%)**	**39 (16.8%)**	**232**

Discussion

There has been considerable alarm at the recent increase in the incidence of tuberculosis all over the world. Implicated in this increase has been the impact of HIV infection, an increase in immigrants from areas of high prevalence and a decrease in vigilance which led to underfunding of tuberculosis control programmes. In this study, only two patients were immigrants and there was only one HIV-related case of PTB. However, it is noted that bronchosopy was not done in patients who were HIV-positive and this may have underestimated the HIV-related PTB in our series.

Diabetes mellitus is the commonest underlying risk factor. The relative risk of developing PTB in non-insulin dependent diabetes mellitus (NIDDM) is 5 to 7 times than the general population[12,13]. In the insulin dependent diabetes mellitus (IDDM), the risk is as high as 26 times[12]. It is therefore recommended that all patients with diabetes should undergo routine chest x-ray examination at diagnosis and whenever they developed prolonged cough, fever or unexplained ill-health. PTB should be suspected even if the radiological features are atypical because in diabetics, there is an increased frequency of non-classical changes particularly lower lung field involvement[14,15].

The male predominance in pulmonary tuberculosis is well recognised. It had also been shown in other reviews in Malaysia, Ireland, Britain and United States1[16-20]. So far no undisputed explanation has been forwarded for this finding.

The onset of PTB by nature is insidious, resulting in late diagnosis. Patients with active PTB may have multiple emergency department visits[9]. About 23% of our patients had symptoms for more than 5 years before diagnosis was made. Most of them had earlier consulted other medical practitioners but no chest radiograph or sputum analysis was done. In many cases, the diagnosis was excluded because of negative sputum direct smears. It is imperative that a high index of suspicion be maintained in order not to miss such cases. This is especially so if the same patient had persistent complaints but without a definitive diagnosis.

The clinical manifestations of PTB are protean and non-specific. We propose to classify the presentations into clinical groups based on the combination of history, symptoms and radiological features as in Table IV. Classic symptoms of prolonged cough and fever are insensitive predictors of tuberculosis. Only 22.4% of our patients had classic symptoms of PTB. This finding is similar to that reported by Miller et al[20].

Twelve percent of our patients presented with haemoptysis without other symptoms. This does not include some patients who had undiagnosed haemoptysis many years earlier but now having other features of PTB. In our community, pulmonary tuberculosis and post-tuberculosis bronchiectasis are the most common causes of haemoptysis[21].

Twelve percent of our patients presented with clinical and radiographic changes suggestive of bronchiectasis. In half of them, bacteriological confirmation were unsuccessful but the patients had a significant response to empirical therapy with anti-TB drugs. These patients may have endobronchial tuberculosis which often have negative bacteriology[22]. Bronchial biopsy may be needed to confirm the diagnosis in these cases[23], but the procedure was not done in our cases for fear of bleeding.

Another group of patients in whom the diagnosis of PTB was often missed were patients who presented with recurrent cough, breathlessness and wheezing. About 10% of our patients presented in this manner. They were often diagnosed as having asthma or COPD but the symptoms resolved after treatment with anti-tuberculosis therapy. This group of patients is often more difficult to diagnose because they are elderly, cannot produce good sputum specimen, and often too ill for bronchoscopy.

Tuberculous effusions are often difficult to confirm bacteriologically. In a review by Hooi, out of the 49 cases of tuberculous pleural effusion, only 13 cases had positive pleural biopsy, another 5 had positive pleural fluid culture. About half of the cases were diagnosed on the basis of a positive response to empirical anti-tuberculosis therapy[24]. Therefore empirical therapy with anti-tuberculosisdrugs is indicated if other causes of pleural effusion have been excluded.

Fifteen percent of our patients presented with non-pulmonary complaints. Sokolove et al. reported that patients with active PTB may have multiple emergency room visits, and often have non-pulmonary complaints (medical but non-pulmonary 33%, infectious but non-pulmonary 41%, traumatic/orthopedic 12%) but often missed although tuberculous risk factors and symptoms are usually present (86%) in these patients[9].

The chest radiograhph is abnormal in the majority of cases but classical PTB changes only occur in 63% of cases. Quite often, x-rays are reported as 'old tuberculosis' based on the presence of fibrosis and calcifications without excluding active disease. This is one of the common reasons for missed diagnoses[25]. Active tuberculosis should always be excluded in all cases of 'old tuberculosis' on chest radiograph particularly in patients with no previous treatment of tuberculosis. If possible bronchoscopy should be carried out since most of these patients cannot produce good sputum specimens.

In many countries, approximately half of all tuberculosis cases are not bacteriologically confirmed for one reason or another[26]. It is not uncommon to find smear-negative but culture-positive specimens, as high as 70% has been reported especially in developing countries[26,27]. The incidence of smear positivity ranged from 32 to 55.3% and culture positivity form 70% to 96% of patients[28,29]. Therefore sputum culture for mycobacteriua should be performed in suspected cases if sputum is negative.

The finding of positive Zeihl-Nelson staining of sputum smear in this study (22.8%) is notably lower than in other reports. There are a few explanations for this finding. Firstly, most of our patients were investigated as outpatients with a single sputum specimen only. Secondly, many patients with symptoms of tuberculosis would have been detected earlier in government institutions if sputum were positive and only those with negative sputum would seek a second opinion in private hospitals.

A wide range of molecular techniques which amplify Mycobacterial nucleic acids are currently under evaluation for the rapid diagnosis of tuberculosis but unfortunately the increased sensitivity is not always associated with increased specificity. The tests are also currently too costly. Therefore their role in the routine diagnosis remains undefined[30].

Our experience suggests that bronchoscopy with culture of the bronchial washings is very useful when sputum analysis is unhelpful. Forty-nine percent of our patients had positive bronchial washing smears or cultures. Similar findings had been reported by many authors[31-34].

Bacteriological confirmation of pulmonary tuberculosis is not always possible. Some patients are too ill while many others refuse invasive investigations such as bronchoscopy or biopsy because of fear or for financial reasons. Studies have found that 58 - 63% of smear-negative cases developed bacteriologically confirmed pulmonary tuberculosis during a follow-up period of 3-

58 months[35,36]. Patients who received a course of antituberculous therapy were 90% less likely to develop reactivation than those who were not treated[37]. Smear-negative PTB appear responsible for about 17-28% of tuberculous transmission[38,39] and may cause as many death as smear-positive cases (22% Vs 26%)[40]. In such patients in whom the probability of tuberculosis is high, empirical therapy should be initiated. Similarly, empirical therapy should be started while awaiting results of culture to avoid disease progression and mortality[11].

Conclusion and Recommendation

The onset of PTB is gradual and insidious, and the symptoms are unremarkable and non-specific resulting in delay in diagnosis resulting in morbidity, mortality and continued spread of the disease. Only about 20% of patients had 'typical manifestations' of PTB. Others may present with haemoptysis, obstructive airway disease, prolonged cough, pleural effusion, pneumonia or non-pulmonary symptoms. The chest radiographs are not typical in about 40% of cases. High index of suspicion for tuberculosis among medical practitioners is necessary so that the diagnosis is not missed. It must also be stressed that even in highly typical cases, sputum smear is not always positive. Bronchoscopy is a useful tool to collect specimen for smear and culture of the bronchial washing for Mycobacterium. In those cases with high clinical probability of tuberculosis, where bacteriological confirmation is not possible, empirical treatment is recommended because it is safe and would prevent spread, morbidity and mortality. Figure 2 shows a suggested algorithm for diagnosis of patients with suspected tuberculosis.

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