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Tuberculosis – Are We Missing the Diagnosis?

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ABSTRACT

We reviewed the 52 new cases of pulmonary tuberculosis diagnosed at Pusat Pakar Utara, Kedah in 1998. It was found that the majority of the patients had symptoms for many years. They had seen many doctors but were not diagnosed. In 40% of the patients, no investigations for tuberculosis were done and in the others tuberculosis was excluded because of negative sputum smear examination. Many had typical history and X-ray changes suggestive of tuberculosis but more sensitive investigations such as sputum culture for Mycobacterium or bronchoscopy were not performed. Cases are presented to illustrate the problems in the diagnosis.

Keywords: Tuberculosis, Diagnosis, smear-negative, Bronchoscopy

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INTRODUCTION

Tuberculosis has never really been eliminated anywhere and now it is creating new crisis around the world. The best way to prevent the disease 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 at the time of diagnosis[1]. 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[2]. The delay in diagnosis is mainly due to incorrect diagnosis by the doctors rather than patients' delay in seeking medical advice[3]. We studied the cases of PTB diagnosed in our hospital in 1998 to highlight the problem.

CASE STUDIES AND DISCUSSIONS

In 1998, 52 cases of PTB were diagnosed in Pusat Pakar Utara, Kedah. Sputum examination for acid-fast bacilli (AFB) by direct smear was positive in 38.5% of cases, and 9.6% had positive sputum culture. In another 42.4% of cases, the diagnoses were made from bronchial washing smear (21.2%) or culture (21.2%). Five patients (with clinically high probability of PTB but either refused or not fit for bronchoscopy) were diagnosed on the basis of a positive response to empirical anti-tuberculous therapy.

The case histories were reviewed particularly looking at the onset of first symptoms suggestive of tuberculosis, previous consultations, diagnosis and investigations. The majority of the patients had a long history of symptoms suggestive of tuberculosis. Almost all patients (90.4%) had seen many doctors before coming to our clinic. In 40.3% of the patients the diagnosis of tuberculosis was probably not considered at all because no investigation was done. In the other 50%, investigations (mostly chest X-ray and/or sputum direct smear alone) were done but were said to be negative for tuberculosis. The following problem areas are identified as the cause of PTB misdiagnosis:

PROBLEM 1: OVER DEPENDENCE ON SPUTUM EXAMINATION BY DIRECT SMEAR

Most patients had sought medical attention early for symptoms suspicious of tuberculosis. However, omission to do the appropriate investigations or referral for an expert opinion led to failure of diagnosis.

Case 1

CSC, a 56-year-old lady first had haemoptysis in 1969. She was seen in the Chest Clinic, apparently sputum AFB by direct smear was negative. In 1990, she had haemoptysis again with fever, loss of appetite and loss of weight. She saw a general practitioner (GP) who suspected tuberculosis and started Rifampicin and Isoniazid (INH). She was then referred to a physician who told her that she was not suffering from tuberculosis and was treated with antibiotics instead. In 1995 she again had cough and since chest X-ray was suspicious

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of tuberculosis she was referred to the Chest Clinic. Again she was told that she did not have PTB. In 1996, she had unresolved pneumonia. Bronchoscopy showed features compatible with PTB. Bronchial washing for AFB direct smear was positive and she was started on anti-TB treatment. She however sought a second opinion from the Chest Clinic and again was told to stop treatment. In 1998, she presented again with severe lethargy and loss of weight. Bronchoscopy was repeated. Bronchial washing for AFB direct smear was again positive. Bronchial washing for culture was also positive for *Mycobacterium tuberculosis* confirming the diagnosis of PTB. She completed anti-TB treatment and since then she had been well (30 years after her first symptoms).

Case 2

RAR, a 30-year-old female factory technician was seen in August 1998 with problem of being unwell for eight months. She also had cough, haemoptysis, and significant loss of weight and loss of appetite. She had seen a few doctors including a private specialist and the Chest Clinic. Chest X-rays and sputum examinations were done but she was told that she did not have tuberculosis. On examination, she was severely emaciated. There were crepitations at both lung apices. The chest X-ray showed severe fibrosis with cavitations in both upper zones, highly suggestive (if not typical) of PTB. Bronchoscopy showed inflammation in both upper bronchi compatible with tuberculosis. Direct smear examination of bronchial washing was positive for AFB. She has much improved after treatment with anti-TB but the chest X-ray showed considerable permanent lung scarring.

The above two cases represent the most common scenario of failure of diagnosis. The patients had typical clinical features and the chest X-ray changes were highly compatible with PTB. They had seen many doctors including specialists but were not treated because sputum direct smears (often of a single specimen) were negative.

In many countries, approximately half of all tuberculosis cases are not bacteriologically confirmed for one reason or another[4]. It is not uncommon to find smear-negative but culture-positive specimens, as high as 70% has been reported especially in the developing countries[4,5]. Bronchoscopy is often helpful in the diagnosis of sputum negative cases[6]. Zainuddin et al. found that out of 74 patients suspected to have smear-negative tuberculosis, bronchoscopy confirmed the diagnosis in 45% of patients[7].

PROBLEM 2: DIAGNOSIS OF "OLD PTB" ON CHEST X-RAY

Case 3

CTC, an 82-year-old man was admitted to the General Hospital in February 1998 for an operation of a perianal lesion. Pre-operative chest X-ray was done and tuberculosis was suspected. He was seen in the Chest Clinic three weeks later but was told to have "old tuberculosis". No sputum examination was done. He was treated with antibiotics and advised to have a repeat chest X-ray after two weeks. However, a few days later, he was admitted to our hospital with severe lethargy and breathlessness. He looked severely emaciated, breathless and ill. Chest X-ray showed bilateral fibrosis in the upper zones with soft opacities and cavitations suggestive of active tuberculosis. Sputum direct smear was positive for AFB.

Quite often, X-rays are reported as "old tuberculosis" based on presence of fibrosis and calcifications. Active tuberculosis should be always be excluded in all cases of "old tuberculosis" on chest X-ray 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 specimen.

PROBLEM 3: PLEURAL EFFUSIONS

Like other extra-pulmonary cases, tuberculous effusions are often difficult to confirm bacteriologically. In a review by Hooi, out of the 49 cases of TB pleural effusion, only 13 cases had positive pleural biopsy, another five had positive pleural fluid culture. About half of the cases were diagnosed on the basis of a positive response to empirical anti-tuberculosis therapy[8]. Therefore empirical therapy with anti-TB is indicated if other causes of pleural effusion have been excluded. The following two cases illustrates this problem very well.

Case 4

MRA, a 39-year-old man was first admitted in 1991 for pain in the right hypochondrium. Chest X-ray showed right pleural effusion with right upper zone consolidation suggestive of tuberculosis. He was referred to the Chest Clinic. Pleural aspiration and biopsy were done. He was told that no tuberculosis was detected. In 1997, he was referred by a general practitioner for cough of 10 months' duration associated with tiredness, fever and breathlessness. Chest X-ray showed thickened pleura in the right hemithorax, mottling and fibrosis in the right upper zone suggestive of 'old TB'. Sputum direct smear examination was negative for AFB and he was

treated symptomatically. In 1998 he was admitted with fever. The chest x-ray showed changes suggestive of pulmonary tuberculosis and sputum examination by direct smear was positive for AFB, confirming the diagnosis seven years after the first presentation.

Case 5

LL, a 79-year-old man was seen in April 99 for feeling unwell. In 1997, he was admitted to a hospital in Sarawak with a left pleural effusion. Apparently pleural aspiration and bronchoscopy were done but no cause was found. Chest X-ray showed consolidation and a small left pleural effusion. Bronchoscopy showed inflammation in the left upper and lower lobes, and the right middle lobe bronchi. Direct smear of the bronchial washing was negative for AFB but TB culture was positive. He improved after treatment with anti-tuberculosis drugs.

PROBLEM 4: BRONCHIECTASIS

Bronchiectasis is inflammation of the bronchi causing weakening of the wall resulting in dilatation, collapse and mucus collection. In our community, tuberculosis is a common cause and should always be excluded by culture of sputum or bronchial washing because sputum direct smear is often negative in these cases.

Case 6

RO, a 69-year-old man was first admitted in 1990 with cough, haemoptysis and breathlessness for about two months. Chest X-ray showed "bronchiectasis" and sputum examination for AFB was negative three times. He was treated with bronchodilators, antibiotics and antitussives. Since then he was frequently seen in the outpatient clinic and was admitted on four occasions for "bronchiectasis". In 1999, he was admitted for herniorraphy. Pre-operative chest X-ray showed "bronchiectasis". On questioning, he admitted to have recurrent haemoptysis. Sputum direct smear was negative for AFB but culture for Mycobacterium was positive. He has much improved since treatment for tuberculosis.

Case 7

AFHH, a 43-year-old man was admitted in June 1999 for fistulectomy of fistula-in-ano. He had chronic recurrent anal stenosis and perianal fistula since 1987 for which he was operated three times. He was referred for chronic wheezing. He was told to have bilateral bronchiectasis and left lobectomy was done in 1977. At the same time, his son was admitted with unresolved pneumonia and bronchoscopy confirmed tuberculosis. On questioning, his mother-in-law also had a history of PTB. Chest-ray was compatible with bronchiectasis. He refused bronchoscopy and was treated empirically with anti-TB drugs. Since then, he has no more chest symptoms or perianal problems.

PROBLEM 5: CHRONIC OBSTRUCTIVE AIRWAY DISEASE (COPD)

Another mode of presentation where the diagnosis of PTB is often missed are patients who presented with recurrent coughing, breathlessness and wheezing often diagnosed as asthma or COPD. This group of patients is often more difficult to diagnose because the patients are usually elderly, cannot produce good sputum specimen, and often too ill for bronchoscopy. In this situation, empirical therapy sometimes gives a very gratifying outcome like this case:

Case 8

FT, a 60-year-old lady was admitted with severe respiratory failure. Apparently she had been admitted frequently to another hospital with diagnosis of chronic lung disease for the past few years. In the past few months she was bed-ridden. On admission, she was very ill, emaciated, and in respiratory failure (ECG showed p-pulmonale). Chest X-ray showed hyperinflation with "bronchiectasis" and "pneumonitis". Sputum smear for AFB was negative and she was too ill for bronchoscopy. She was treated empirically, improved and walked home after one week. Four weeks later, the result of sputum TB culture was positive confirming the diagnosis.

However, in others the diagnosis is too late as illustrated by this case:

Case 9

OSH, a 70-year-old Chinese man was referred from a district hospital with acute exacerbation of COPD, which was diagnosed about one year ago. Physical examination revealed hyperinflated chest with generalised crepitations and rhonchi. Chest X-ray showed hyperinflated lungs with mild "pneumonitis". Sputum direct smear for AFB was negative. He was treated with bronchodilator. By the next day, he improved and took self-discharge. He was advised bronchoscopy but refused. Three weeks later, sputum culture for Mycobacteria was positive. On contacting the family it was learnt that the patient was readmitted but died in the district hospital.

PROBLEM 6: EXTRAPULMONARY TUBERCULOSIS

About 11% of all TB cases are extrapulmonary[9]. The diagnosis of these cases is the most difficult

because of the non-specific clinical features, normal chest X-rays and difficulty in obtaining specimen. Patient may refuse biopsy or the histopathology may be misleading. This is illustrated by this case:

Case 10

HA, a 30-year-old housewife had right cervical lymphadenopathy for two months. Histopathology of excision biopsy was reported as "Cellulitis with pseudocystic changes, not suggestive of tuberculosis". However, culture of tissue biopsy for M. tuberculosis was positive, and patient responded well to anti-TB drugs.

Case 11

JJ, A 21-year-old medical student had incision and drainage done in June 1992 for abscess of the scrotum and perianal region of six months' duration. Since then, he had chronic discharging sinus. Fistulectomy was done in August 1992 and repeated in August 1994. The histopathology showed acute on chronic proctitis. His did not respond to antibiotics including metronizale. He was also seen in the Chest Clinic a few times for cough and chest pain but investigations for tuberculosis was negative. In September 1994 (more than two years later), sputum and anal discharge sent for Polymerase Chain Reaction (PCR) were positive for Mycobacterium tuberculosis. The chest problems and the perianal sinuses cleared after treatment for tuberculosis.

PROBLEM 7: FAILURE TO START EMPIRICAL THERAPY

Like pneumonia due to other organisms, 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. In such patients in whom the probability of tuberculosis is high, empirical therapy is very rewarding as illustrated by this case:

Case 12

AS, a 67-year-old lady was admitted in November 1998 with lethargy, fever, loss of weight and appetite and dehydration. She had a history of frequent admissions to hospital with arthritis and chronic bronchitis and now bed-riddened for a few months. On admission, she was a fragile elderly lady, emaciated, febrile, dehydrated, breathless and pale. There was severe kyphosis and both lower limbs were in flexion deformity. Chest X-ray showed bilateral infiltrations and cavitations in both upper zones and pleural calcifications in the right lower zone highly suggestive of active tuberculosis. X-ray spine showed osteoporosis and wedge compression of lumbar spine. Clinically, she had a very high probability of suffering from active tuberculosis. However, she could not produce sputum and was too ill for bronchoscopy. She was started on anti-TB treatment empirically. Within one week, she improved and was able to walk with support. After one month, she was well and could walk without support.

CONCLUSION AND RECOMMENDATION

Many cases of tuberculosis are missed and the diagnosis is often delayed causing morbidity, mortality and spread of the disease. The main cause of the delay in the diagnosis of PTB is not because of the delay by the patients in seeking medical advice. In many cases, it is the doctors who failed to make the correct diagnosis and do the appropriate investigations. When PTB is suspected, they tend to depend too heavily on the non-sensitive sputum direct smear examination to confirm the diagnosis. Even patients with classical features of PTB are often left untreated because of negative sputum smear examination for AFB.

Sputum culture for *M. tuberculosis* or bronchoscopy, which is more likely to give positive results, should be more frequently done. In clinically highly probable cases where bacteriological confirmation is not possible, empirical treatment with the current chemotherapy is recommended because it is safe and would prevent spread, morbidity and mortality. Studies have found that 58 - 63% of smear-negative cases developed bacteriologically confirmed pulmonary tuberculosis during a follow-up period of three to 58 months[10,11]. Patients who received a course of antituberculous therapy were 90% less likely to develop reactivation than those who were not treated[12]. Thus, a course of chemotherapy affords considerable protection against future morbidity.

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