ERRORS IN THE DIAGNOSIS AND TREATMENT OF PULMONARY TUBERCULOSIS

Muhammad Babar Khan, *Muhammad Tahir, Shaukat Mehmood Qureshi, H.M. Ashraf

Combined Military Hospital Multan, *Combined Military Hospital Mailsi

ABSTRACT

Objective: The objective of this study was to evaluate the causes of treatment failures in patients diagnosed as pulmonary tuberculosis and started on ATT by general practitioners and general physicians.

Patients and Methods: This was a descriptive observational study conducted at CMH Multan from 1st August 2004 till 31st July 2006. It included patients of all ages and both sexes. All of these patients received ATT for more than 2 months but failed to respond. All relevant investigations including sputum microscopy/culture sensitivity, bronchoscopy and CT scan chest were carried out.

Results: Total numbers of patients registered were 48. There were 27 males and 21 females and the mean age of patients was 42.75 years. Of these, 58.33 % (n=28) were wrongly diagnosed. 25.02% (n=12) did not show proper compliance. 10.41% (n=5) were prescribed inadequate dosage. While 6.25 (3) were suffering from MDR-tuberculosis. Chronic bronchitis/COPD, bronchiestasis and bronchogenic carcinoma were the commonest disease found in this series.

Conclusion: All TB suspects should have a sputum microscopy done at the earlier stage. AFB culture/sensitivity should be carried out whenever considered necessary. In Sputum smear negative patients high index of suspicion for non tubercular pulmonary diseases should be maintained. DOTS needs to be employed in all patients with active pulmonary tuberculosis.

Keywords: Tuberculosis, MDR-TB, DOTS

INTRODUCTION

Tuberculosis is an infectious disease known to mankind since antiquity. It is estimated that one third of the world population is infected with tubercle bacilli, 8 million people develop the disease and 2 million die of disease each year [1]. Tuberculosis is a disease with diverse manifestations and nonspecific symptoms which can mimic other diseases. This lack of specificity can result in a delayed diagnosis or even a misdiagnosis causing morbidity, mortality and spread of disease [2,3].

Tuberculosis can masquerade as bacterial pneumonia, bronchogenic carcinoma, lymphoma, sarcoidosis, fungal infections, pneumoconiosis and bronchitis / bronchiectasis [4]. At the same time many cases of non tubercular pulmonary diseases are missed and treated unnecessarily as pulmonary tuberculosis. In endemic areas clinical diagnosis only may give an over diagnosis of tuberculosis in up to 32.5% of patients [5]. Low detection of tuberculosis is attributed to inadequate knowledge and incompetence of the general practitioners in interpreting the x-rays and neglect to use other diagnostic procedures like sputum smear examination/culture, sputum cytology, bronchoscopy/biopsy and CT scan chest [6,7].

Sputum smear examination is the corner stone in the diagnosis of pulmonary tuberculosis. However in certain communities' up to 30% of patients are

Correspondence: Col Muhammad Babar Khan, Classified Child Specialist, Combined Military Hospital, Multan.

sputum smear/culture negative. In sputum smear negative patients or those who can not produce sputum fiber optic bronchoscopy has an important role in the diagnosis [8].

At primary care level most cases of pulmonary tuberculosis are diagnosed and treated empirically on the basis of clinical and radiological indicators without recourse to sputum microscopy. A large proportion of tuberculosis patients in high prevalence countries first approach a private practitioner [9]. At primary care level inappropriate drug regimen, often with incorrect combinations and inaccurate doses for the wrong duration are prescribed [10]. Noncompliance with the treatment is considered as the patient's choice and not a problem that must be addressed by the physicians. Poor prescribing habits and inadequate compliance to treatment are main contributing factors in MDR-TB which is a man made problem and is becoming a global threat [11,12].

Universal DOTS remains the ultimate weapon in every country's fight to control tuberculosis. It leads to a rise in the completion rate of TB therapy, a fall in TB incidence and reduction in the prevalence of MDR-TB in the community [13-16].

The objective of this study was to evaluate the causes of treatment failures in patients diagnosed as pulmonary tuberculosis and started on ATT by general practitioners and general physicians.

PATIENTS AND METHODS

This study is a descriptive study. It was conducted at the Pulmonology Department of Combined Military Hospital Multan. The duration of study was from 1st August 2004 till 31st July 2006 (two years). The study population was the army personnel, their relatives and civilian patients who visited the hospital for private treatment. It included patients of all ages and both sexes. Patients in the study were either referred by general practitioners/general physicians or reported themselves to pulmonology outpatient department. They were all labeled as cases of

pulmonary tuberculosis. All of these patients received ATT from general practitioners and general physicians for two or more months Furthermore there was no subjective or objective improvement in the clinical condition after ATT. The chest x-rays were either unchanged or lesions showed progression.

The study excluded the patients who used ATT for less than 2 months and patients with other co morbid conditions All these patients were further worked up with detailed history of the onset of the illness, the initial symptoms, investigations done, type and duration of medicines used and response to treatment. The patients were then ordered relevant investigations such as sputum smear examination, sputum culture / sensitivity bronchoscopy, bronchial biopsy / transbronchial biopsy for histopathology, CT scan chest etc. The causes of treatment failure once established were noted down and the patients were thoroughly briefed about the further course of treatment.

RESULTS

A total of 48 patients met the inclusion criteria for the study. There were 27 (56%) males and 21 (44%) females. The age ranged between 13 to 68 years with mean age of 42.75 years. The patients included the serving soldiers, their dependents and civilian patients. Most of the patients were referred to pulmonology department by various general practitioners and general physicians with the complaint that response to ATT was not adequate. There was a few patients who themselves reported for review of their treatment. All the patients took ATT for more than 2 months.

On detailed history, examination and investigations it was found that most of the patients (n=28) were wrongly diagnosed. These patients were commenced on ATT on the basis of history and chest radiography only. The chest radiographs in all the above cases were not reported upon by a qualified radiologist. The patients were not

investigated any further. In some patients (n=12) although the treatment was started correctly but enough time was not given in explaining to the patients the nature of the illness and the importance of prolonged ATT. Hence such patients were not motivated enough and they stopped the treatment on slight improvement of their clinical condition, resulting in resurgence of their disease. In 5 patients the dose prescribed was less than the required dose according to the body weight and lastly 3 patients who did not respond to the treatment were suffering from multi-drug resistant (MDR) tuberculosis (table-1).

It is obvious from these results that most of the patients who did not respond to ATT after using it for more than 2 months were those who were wrongly diagnosed (58.33%).

The patients who wrongly diagnosed were extensively investigated to reach a confirmed diagnosis. The investigations included repeat chest radiography, sputum microscopy, sputum culture/sensitivity, bronchoscopy, histopathology, computerized tomogram scan etc. The final diagnoses of these patients are tabulated (table-2). It is obvious from the above table that there was a wide variety of diagnosis. Chronic bronchitis, bronchogenic carcinoma and bronchiectasis were the most frequent diseases seen in this series.

All the patients included in the study once diagnosed were briefed in detail about their disease and were treated accordingly. Those who were confirmed to be suffering from pulmonary tuberculosis but did not respond to treatment due to inadequate dose or due to the poor compliance were prescribed ATT in correct dose and were briefed in detail about the usefulness and duration of therapy. The patients suffering from MDR TB were treated accordingly as per protocol.

DISCUSSION

The symptoms of tuberculosis are protean and non specific. This lack of specificity can result in a delayed diagnosis or even a misdiagnosis [2]. It is a disease with diverse manifestations which can mimic other diseases. The diagnosis of pulmonary tuberculosis is often delayed due to atypical clinical features and difficulty in obtaining positive bacteriology. [17] Bacteriology is the gold standard for diagnosis of tuberculosis [18]. Early recognition of patients with active tuberculosis is crucial to limit transmission of mycobacterium tuberculosis. Delayed diagnosis leads to delayed treatment and prolongs the transmission of infection in the community. Late treatment also jeopardizes recovery and cure of patients [19]. Tuberculosis can masquerade as bacterial pneumonia, bronchogenic carcinoma, lymphoma, sarcoidosis, fungal infection, pneumoconiosis, bronchiectasis and asthma [4]. Erroneous diagnosis of tuberculosis instead of other diseases can also be made. Many cases of nontubercular pulmonary diseases are missed causing morbidity and mortality [20].

The aim of this study was to investigate the causes of lack of response to ATT in patients diagnosed as pulmonary tuberculosis and started on anti tuberculosis treatment. It was found that most of the patients who did not respond to ATT after using it for more than 2 months were those who were wrongly diagnosed. There was a wide variety of diagnoses. Chronic bronchitis, bronchogenic carcinoma and bronchiectasis contributed mainly to diagnosis. There are many studies in the literature in which erroneous diagnosis of tuberculosis was made. In a study carried out by Szczuka I et al. in Poland false diagnosis of pulmonary tuberculosis was found in 63 out of random sample of 560 patients registered in 1993 [7]. All of these patients were sputum smear negative. Among the 63 patients with false diagnosis of tuberculosis, there were 15 cases with lung cancer, 15 cases with pneumonias, 15 cases with diseases of circulatory system with abnormal chest x-rays, 8 cases with old post tuberculous changes in the lung considered as relapse, 4 cases of bronchiolitis obliterans

with organizing pneumonia, 3 cases of sarcoidosis and 1 case of aspergillosis in a post TB cavity. The most serious errors were those related to failure in diagnosing (or too-late diagnosis) lung cancer. The main source of error was false interpretation of radiological data and neglect to utilize other diagnostic procedures like sputum culture, cytology, CT scan, and bronchoscopy. Apart from clinical assessment, the main basis for diagnosis of tuberculosis was chest radiography. In another Polish study Klinika AM et al. basing on the analysis of 1351 medical records, found that pulmonary TB and lung cancer were co-existent in 224 cases [21]. Erroneous diagnosis of tuberculosis instead of lung cancer was made in 35 patients (1 % of all tuberculosis cases).

Transbronchial lung biopsy is useful diagnostic method for diffuse pulmonary diseases e.g; sarcoidosis, organizing pneumonia, neoplastic infiltrates of lung and tuberculosis. In a study carried out by He LX in China 65 cases of bronchopulmonary tuberculosis simulating lung cancer were diagnosed by fiber bronchoscopy [22]. Bronchoscopic biopsy provides an effective method in the differential diagnosis of tuberculosis and cancer of lung. Because lung cancer may be similar to tuberculosis not only in clinical symptoms but also in x-ray manifestations, it is sometimes misdiagnosed. Mamiliaev RM in his paper presented data on 25 patients who were misdiagnosed as having focal pulmonary tuberculosis [23]. Gill G V et al. presented data of six patients in his article in which tuberculosis was wrongly diagnosed [24]. The patients were all blacks from areas of high TB prevalence and treatment for presumed tuberculosis was instituted without bacteriological confirmation. There was a delay of up to 2 years before the correct diagnosis was made involving much morbidity and unnecessary treatment. Because TB is over diagnosed in endemic areas, bronchoscopy is recommended for all cases of pneumonias with delayed resolution [25]. It has been recommended that fiber optic bronchoscopy be performed early in heavy smokers and patients more than 50 years of age with slow or non resolving pneumonia.

Three cases (6.25%) in our study did not respond to the first line anti TB treatment because of multi drug resistant bacilli. MDR tuberculosis is defined as simultaneous resistance to at least rifampicin and INH with or without resistance to other drugs [26]. The emergence of multi drug resistant tuberculosis is becoming a global threat. There is a real danger that tuberculosis may be incurable once more if the current trend of growing drug resistance is not checked. Inconsistent or inadequate treatment of TB has been the main cause of MDR-TB [27,28]. Resistance of Mycobacterium tuberculosis is a man-made amplification of spontaneous mutation in the genes of tubercle bacilli. Resistance rates are high when treatments approaches are inappropriate, incorrect regimens are used, there is poor adherence to treatment, rates of treatment completion are low and therapy is not directly observed [29-31]. Measures to improve treatment completion rates are urgently required. The most effective strategy for ensuring completion of therapy is directly observed therapy in which a health care worker is present when the patient takes his or her medication [14-16]. The problem of MDR-TB is on the rise in Pakistan due to multiple factors. In a study carried out by Butt T et al. in Rawalpindi in which resistance pattern of Mycobacterium tuberculosis isolates was evaluated, it was seen that 15% of the isolates were resistant to a single drug and 28% were multi drug resistant [32]. In an other study carried out by Rasul S and colleagues, acquired drug resistance was found to be much higher than the primary resistance [33]. Primary MDR was 7.31% and acquired MDR was 25.7%. In a study carried out by Almani SA et al. multi resistant TB was found in 24.44% isolates [34]. Yet in another study by Karamat A K et al. multi drug resistance was found in 13.66% isolates [35]. There is a need to establish centers at a number of places all over the country with professionals trained to

handle the emerging problem of MDR. Each center must be equipped with adequate facilities for susceptibility testing, so that resistance pattern can be ascertained and treatment regimen tailored accordingly. DOTS strategy along with acquiring Government commitment, case detection by sputum microscopy, a regular supply of anti tuberculosis drugs and standardized recording and reporting system can eliminate multi drug resistant tuberculosis [13-16,36]. Drug susceptibility testing and second line drugs are not cost effective because of limited resources. Without treatment multi drug resistant strains can spread rapidly with in vulnerable population. Patients infected with multi drug resistant TB are difficult to cure and treatment is much more toxic and expensive [11,12].

Five (10.4%) patients in our study were prescribed inadequate dosage of anti tuberculosis drugs by the general practitioners that led to failed response. A global situation assessment report by WHO suggested that delays in establishing a diagnosis are common [2,13]. This survey and other studies have shown that clinicians who work in the private sector often deviate from standard internationally recommended management practices. These deviations include under utilization of sputum microscopy and over reliance on radiography for diagnosis. The private practitioners do not keep themselves current with recent guidelines and prescribe inadequate drug regimen. ATT is available over the counter without prescription, therefore easily accessible for misuse by unqualified practitioners and even by the patients themselves. In addition many practitioners use non recommended drug regimen with incorrect combinations of drugs and mistakes in both drug dosage and duration of treatment [9,10,37].

Poor compliance to the prolonged ATT was seen in 12 (25.02%) patients. This is due to the fact that it is uncommon for private practitioners to be able to assess adherence to

Table-1: Various causes of treatment failures.

Causes	No. of patients	%age
Diagnoses other than pulmonary TB	28	58.33
Inadequate dosage	5	10.41
Improper compliance	12	25.0
Multi drug resistance TB	3	6.25
Total	48	100

Table-2: Breakdown of cases which were wrongly diagnosed as pulmonary tuberculosis.

Causes	No. of patients
Chronic bronchitis/COPD	5
Bronchiectasis	4
Bronchogenic carcinoma	5
Sarcoidosis	3
Pneumoconiosis	3
Old healed lesion	3
Mitral stenosis	2
Aspergilloma	1
Pleural effusion / congestive cardiac Failure	2
Total	28

the treatment regimen and correct poor adherence when it occurs. Patient noncompliance with treatment is common place, made worse by low income, competing family needs and non concern by private physicians, who consider noncompliance with treatment as the patient's choice and not a problem that must be addressed by the physician [37]. Substandard care will result in poor patient outcome, continued infectiousness with transmission of Mycobacterium tuberculosis to family and other community members and generation and propagation of drug resistance. A study was carried out by Uplekar M et al., the objective of which was to understand TB management practices among the private medical practitioners and the behaviors of the patients towards their treatment [38]. It was noted that the first source of help for 86% of patients was a private practitioner. The diagnostic and treatment practices of private practitioners were inadequate. 15% did not consider sputum examination to be necessary. The treatment adherence rate among the patients in private clinics was 59%. Another

study by Arif K et al. reflects poor awareness of WHO guidelines and low compliance among physicians and a high loss to follow up [39]. Only 23% of patients had a diagnostic bacteriological sputum smear examination. No sputum smear test was conducted during treatment. Over 70% patients were lost to follow up, more than half of these during the intensive phase. There is a need to educate private practitioners and their TB patients.

DOTS was devised to address the tendency of patients to noncompliance with the long course of treatment necessary to achieve the cure of TB. DOTS refers to a method of treatment virtually unique to TB in which each prescribed dose of oral medication is swallowed under the observation of a supervising person, usually a health professional. DOTS has been the most significant advance in the treatment of TB. It leads to a rise in the completion rate of TB therapy, a fall in TB incidence and a reduction in the prevalence of MDR-TB in the community [14,15].

CONCLUSION

Sputum microscopy remains the most important investigation once the diagnosis of pulmonary TB is entertained. Under utilization of sputum microscopy and over reliance on radiography for diagnosis of TB by the general practitioners should be discouraged. Sputum culture and sensitivity testing must be requested whenever considered necessary. Negative smears should prompt sputum induction or bronchoscopy. Chest x-rays should be interpreted by qualified radiologist. In case of doubt all relevant investigations including CT scan chest, tissue biopsy/histopathology should be undertaken to exclude any other disease which can mimic pulmonary TB.

Every patient with active pulmonary tuberculosis must be treated with DOTS. Importance of the education of health professionals along with patient motivation can not be overemphasized. Regional centers at multiple sites with state of the art culture and sensitivity facilities should be established to handle the emerging problem of MDR.

REFERENCES

1. Dye C, Scheela S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of Tuberculosis: Estimated incidence, prevalence, and mortality by country. WHO global surveillance and monitoring project. *J Am Med Assoc* 1999; 282: 677-86.

2. Wandwalo ER, Morkve O. Delay in tuberculosis case finding and treatment in Mwanza, Tanzanzia. *Int J Tuberc Lung Dis* 2000; 4(2): 133-138.

3. Small PM, Fujiwara PI. Management of tuberculosis in the United States. *N Eng J Med* 2001; 345: 189-200.

4. Teo SK. Tuberculosis-Barriers to early diagnosis. *Singapore Med J* 2002; 43(4): 169.

5. Avijgan M. Specificity and sensitivity of clinical diagnosis for chronic pneumonia. *East Mediterr Health J* 2005; 11(5/6): 1029-1037.

6. Sengupta A, Nundy S. The private health sector in India. *Br Med J* 2005; 331: 1157-1158.

7. Szczuka I, Pawlicka L, Kus J, Leowski J, Roszkowski K. Analysis of diagnostic errors and recommendations of diagnostic procedures in bacteriologically negative pulmonary tuberculosis. *Pneumonol Allergol Pol* 1998; 66(1-2): 17-23.

8. Yuksekol I, Bal S, Ozkan M, Balkan A, Bedrihan I, Tozkoparan E. The value of fiber optic bronchoscopy in the diagnosis of smear negative pulmonary tuberculosis. *Tuberk Toraks* 2003; 51(4): 405-9.

9. Uplekar M, Pathania V, Raviglione M. Private practitioners and public health. Weak links in tuberculosis control. *Lancet* 2001; 358: 912-916

10. Shah SK, Sadiq H, Khalil M, Noor A, Rasheed G, Shah SM, et al. Do private doctors follow national guidelines for

managing tuberculosis in Pakistan? East Mediterr Health J 2003; 9: 776-88.

11. Surendra K Sharma, Alladi M. Multi drug resistant tuberculosis. A menace that threaten to destabilize tuberculosis control. *Chest* 2006; 130: 261-272.

12. Nettleman, M.D. Multi drug resistant tuberculosis: News from the front. *J Am Med Assoc* 2005; 293: 2788-90

13. WHO. *In global tuberculosis control: Surveillance, planning and financing.* Geneva: World Health Organization; 2006. p. 242.

14. Sharma SK, Liu JJ. Progress of DOTS in global tuberculosis control. *Lancet* 2006; 367: 951-952.

15. Frieden TR, Munsiff SS. The DOTS strategy for controlling the global tuberculosis epidemic. *Clin Chest Med* 2005; 26: 197-205.

16. Lilia PM, William RJ. Preventing multi drug resistant tuberculosis and errors in tuberculosis treatment around the globe. *Chest* 2000; 117; 620-623.

17. Ismail Y. Pulmonary tuberculosis-a review of clinical features and diagnosis in 232 cases. *Med J Malaysia* 2004; 5(1): 56-64.

18. Colebanders R, Bastian I. A review of the diagnosis and treatment of smear negative pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2000; 4:97-107.

19. Thomas RF, Trimothy RS, Sonal SM, Catherine JW and Christopher D. Tuberculosis. *Lancet* 2003; 362: 887-899.

20. Ismail Y. Tuberculosis – are we missing the diagnosis. *Singapore Med J* 2003;43(4):172-176

21. Klinika C, Pluc AM, Wroclawiu. Tuberculosis and lung cancer. *Pneumol Allergol Pol* 1991; 59(1-2): 48-54.

22. He LX. Differential diagnosis between tuberculosis and cancer of lung. Analysis of 65 tuberculosis cases diagnosed by fiber bronchoscopy. *Zhonghua Jie He He Hu Xi Za Zhi* 1991;14(2): 69-70.

23. Mamiliaev RM. X-ray differential diagnosis of focal tuberculosis and peripheral lung cancer. Proble Tuberk 1998;6:52-3.

24. Gill GV, Krige LP, Pelly MD. Overdiagnosis of tuberculosis. Case reports. *S Afr Med J* 1983; 63(24): 933-5.

25. Menendez R, Perpina M, Torres A. Evaluation of non- resolving and progressive pneumonia. *Semin Respir Infect* 2003; 18(2): 103-111.

26. Karamat AK, Hayat S, Butt T, Abbasi S. Multi drug resistant tuberculosis. *Pak Armed Forces Med J* 2000;50(2):114-6.

27. Tahaoglu K, Torun T, Sevim T, Atac G, Kir A, Karasulu L et al. The treatment of multi drug resistant tuberculosis in Turkey. *N Eng J Med* 2001;345(3):170-174.

28. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis: Common errors and their association with the acquisition of drug resistance. *J Am Med Assoc* 1993; 270: 65-8.

29. Kordy FNS, Althawadi S, Alrahji AA. Drug resistance pattern of Mycobacterium tuberculosis in Riyadh, Saudi Arabia. *Int J Tuberc Lung Dis* 2004; 8(8): 1007-1011.

30. Farmer PE, Furin JJ, Shin SS. Managing multi drug resistant tuberculosis. *J Respir Dis* 2000; 21: 53-56.

31. Hopewell PC, Migliori GB, Raviglione MC. Tuberculosis care and control. *Bulletin of WHO* 2006; 84(6): 428.

32. Butt T, Ahmed RN, Kazmi SY, Rafi N. Multi drug resistant tuberculosis in Northern Pakistan. *J Pak Med Assoc* 2004; 54(9): 469-72.

33. Rasul S, Shabbir I, Iqbal R, Haq MU, Khan SU, Saeed S, Mirza N. Trends in multi drug resistant tuberculosis. *Pak J Chest Med* 2001; 7(3): 21-8.

34. Almani S A, Memon NM, Qureshi AF. Drug resistant tuberculosis in Sindh. *J Coll Physicians Surg Pak* 2002; 12(3): 136-139.

35. Karamat AK, Rafi S, Abbasi S. Drug resistance in Mycobacterium tuberculosis. *J Pak Med Assoc* 1999; 49(11): 262-5.

36. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F et al. Community based therapy for multi drug resistant tuberculosis in Lima, Peru. *N Engl J Med* 2003; 348: 119-28.

37. Sbarbaro J A. Multi drug resistant tuberculosis. It is time to focus on the private sector of medicine. *Chest* 1997; 111: 1149-1151.

38. Uplekar M, Juvekar S, Rangan S, Nunn P. Tuberculosis patients and practitioners in private clinics in India. *Int J Tuberc Lung Dis* 1998; 2(40): 324-9.

39. Arif K, Ali SA, Amanullah S, Siddiqui I, Khan JA, Nayani P. Physicians compliance with national tuberculosis guidelines. A university hospital study. *Int J Tuberc Lung Dis* 1998; 2(3): 225-30.