

Clinical presentation and outcome of patients diagnosed with active pulmonary tuberculosis in a large critical care unit

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Abstract

Objective: To examine the presentation and outcome of patients diagnosed with active pulmonary tuberculosis after admission to the intensive care unit (ICU).

Design: New cases of active pulmonary tuberculosis admitted to our critical care unit from January 1999 to January 2006 were identified. Data were collected retrospectively from medical records including demographics, clinical presentation, number of sputum samples, therapy provided and patient outcome.

Setting: Data were collected from the ICU database and microbiology laboratory records.

Patients and participants: Thirty-three patients were diagnosed with active pulmonary tuberculosis. Age was 63 ± 17 , and 60.7% were males. Onset of symptoms averaged 17 days prior to presentation (range: 1-90 days), including fever in 51%, cough in 14%, dyspnea in 8%, night sweats in 6%.

Interventions: Twenty-two patients were treated for tuberculosis during hospitalization. The other 11 were

not diagnosed during hospitalization and were found later to be culture positive.

Measurements and results: The most common ICU clinical diagnosis was community-acquired pneumonia in 54%, followed by aspiration pneumonia in 3%. Out of 161 tracheal aspirates, only 48 (30%) were AFB stain positive and 80 (69%) were culture positive. Out of 33 patients who had at least one positive culture, only 62% were AFB stain positive. Of the 22 patients treated for tuberculosis during hospitalization; 15 (68%) died. Of the remaining 11 who were not diagnosed during hospitalization 7 (64%) died.

Conclusions: Active pulmonary tuberculosis is common in ICU patients. The diagnosis may be confounded by atypical clinical presentation and the lack of sensitive and rapid diagnostic tests. Considering the impact if misdiagnosis and risk of transmission to health care professionals, clinicians must maintain high level of suspicion and a low threshold for respiratory isolation. Newer and more sensitive tests must be developed and utilized.

Key words: Tuberculosis, ICU, retrospective, misdiagnosis.

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Introduction

Tuberculosis can be regarded as a global pandemic with almost 9 million new cases and approximately 2 million deaths each year. (1) An estimated one-third of the population of the world is infected with *Mycobacterium tuberculosis*, and the resultant disease represents a major public health problem. (2) Endemic infection is a major contributor to the annual death rate across the globe. The high morbidity and mortality of tuberculosis is the source of major medical and social problems, especially in developing countries. It is ranked as the seventh highest cause of morbidity worldwide, and ranks even higher in emerging nations. (3,4) Since 1993 tuberculosis has been regarded as a global emergency, and little improvement in the situation has been seen. Minimal resources coupled with a lack of accurate, rapid and cost-effective diagnostic tests have posed a major obstacle to tuberculosis control in nations such as India. (5) Among South East Asian nations India ranks as one of the highest in incidence. India possesses one third of the world's tuberculosis population, with 1.8 million new cases per year, excluding 0.2 million cases in which tuberculosis has developed secondary to HIV. There are two hundred thousand deaths annually from the disease or related complications in India. (3,6,7). Saudi Arabia is considered as an intermediate prevalence area for tuberculosis, probably because of its level of development. (8,9)

With the help of Revised National Tuberculosis Control Program (RNTCP) and World Health Organization (WHO) initiative in terms of Directly Observed Treatment, Short course (DOTS), efficacious treatment of tuberculosis has become relatively simple in early cases. (6) On the other hand, severe fulminating pulmonary tuberculosis remains a challenge. Tuberculosis required intensive care admission a count for 1-3% of all tuberculosis cases. (10,11)

Severe tuberculosis triggers respiratory life-threatening symptoms likely to increase morbidity, and often requires the transfer of patients to the Intensive Care Unit (ICU). Respiratory failure is a leading cause of ICU admissions. Other major causes are adult respiratory distress syndrome (ARDS), organ failure and dissemination of disease. Unfortunately treatment in the ICU during the past five decades has contributed little to reducing the threat of these disease entities. (3,6) On the contrary, admission and treatment in the ICU has produced as a consequence the

under reporting of severe tuberculosis, factors leading to admission, and induced toxicities, with resultant diminished disease awareness. King Fahad National Guard Hospital is an 800-bed tertiary care hospital located in the central region of the Kingdom of Saudi Arabia (KSA), provides multilevel health care for National Guard soldiers and their extended families. It has one of the largest critical care units in the Kingdom serve 40 beds and runs by qualified pulmonary and critical care board certified consultants.

The purpose of our study is to review all cases with active pulmonary tuberculosis admitted to our intensive care unit in a period over six years and to examine the characteristics, presentation, underlying risk factors, outcome of patients and to highlight the possible causes of delaying diagnosis.

Materials and methods

Here we present a retrospective study that was conducted to examine the characteristics and outcomes of patients diagnosed with active pulmonary tuberculosis requiring ICU admission, and to identify potential factors affecting mortality rates.

We reviewed the records of patients age of 18 and over with a diagnosis of severe tuberculosis admitted to the ICU in our hospital between January 1999 and January 2006. Patients who had been newly diagnosed with tuberculosis were retrospectively identified from the ICU database, medical records and laboratory documents for inclusion in the study.

Cases of active tuberculosis were defined as positive culture for *Mycobacterium tuberculosis* in the sputum, tracheal aspirate or broncho-alveolar lavage (BAL). We excluded all patients who are known to have pulmonary tuberculosis before ICU admission or the cases, which diagnosed on the bases of clinical judgement only.

Using our standard ICU database, microbiology laboratory records and other referenced documents, patient related information and relevant data were collected. Data collected from medical records included demographics and characteristics of patients, clinical presentation, diagnostic procedures employed, test results, reasons for ICU admission, diagnosis during ICU admission, medical

history, co-morbidities, therapy administered and eventual outcomes. Data are expressed numerically, with percentages of groups where applicable. Variations within categories are shown as means with ranges where appropriate. Comparative data between characteristics are displayed, and data are summarized as tables as well as in text.

Results

Patient characteristics

The numbers of patient diagnosed as pulmonary tuberculosis based on at least one positive sputum culture over period from January 1999-January 2006 were 33 patients. This represented a small fraction of the total number of admissions to the ICU during the six-year period covered by our study. Within the cohort of 33 patients, 20 (60.7%) were male, and 13 (39.3%) female. The mean age of all patients was 63 ± 17 years.

Clinical presentation

The mean time lapse between onset of symptoms and presentation at the hospital was $17 \pm \text{SD}$ days, OR average 17 days, ranging from one to 90 days. Symptoms at presentation were varied. Fever was reported in 51% of patients at the time of admission. Other symptoms included cough (14%), dyspnea (8%), night sweats (6%) and fatigue in 21% of cases. Other less common symptoms, including hemoptysis, weight loss, severe respiratory insufficiency, anemia, and elevated WBC count. Symptoms were clinically assessed by the physician present in the ICU at the time of admission. Symptoms are summarized in **Table 1**.

Treatment was initiated on the basis of the clinical diagnosis made during admission to the ICU in 18 (54%) patients. The initial diagnosis at the time of admission to ICU was as followings: community-acquired pneumonia 19 patients (57%), congestive heart failure 4 patients (12%), two patients had liver failure, and one patient had aspiration pneumonia. Other diagnoses included severe anemia, pulmonary embolism, severe ascitis, malignancy, and sepsis. Also three patients in addition to pulmonary tuberculosis had extra pulmonary tuberculosis, in form of meningitis, peritonitis and colitis.

Laboratory/microbiology testing

A total of 161 tracheal aspirates were withdrawn for microbiological testing from the 33 admitted patients. It accounted for 5 tracheal aspirate collections per patient at different time periods. Of the 161 tracheal aspirates 48 (30%) were stain positive for acid fast bacilli (AFB), eighty were culture positive aspirates. Among the 33 total patients who had at least one positive culture, 62% were AFB stain positive.

Patient outcomes

A total of 22 (67%) patients were treated for tuberculosis during hospitalization based on positive AFB and positive *Mycobacterium tuberculosis*. An additional 11 (33%) patients were diagnosed as tuberculosis based on positive *Mycobacterium* culture later on either post discharge from hospital or post death. A majority of these patients required mechanical ventilation to assist respiration. Among 22 patients treated for tuberculosis 15 (68%) died during hospitalization and 7 improved and listed as survivors. Among the 11 patients who were diagnosed as tuberculosis at later stage, 7 (64%) died before they received anti tuberculosis therapy. Outcomes are summarized in **Table 2**.

Causes of death

In all patients who died, severe tuberculosis and related complications were the primary cause of death. Seven patients who later were found to be culture positive died because of delayed diagnosis multiple organ failure and septic shock (refractory "severe" tuberculosis).

Discussion

The purpose of this retrospective analysis was to evaluate the clinical presentation and mortality associated with patients with tuberculosis who were admitted to the ICU. The records of a total of 33 patients with tuberculosis requiring admission to the ICU during a period of six years were analyzed. The mortality rate among these patients was high, 22 (67%) of the total. Respiratory failure requiring mechanical ventilation was the most common cause for

mortality.

The mean age of the patients in this analysis was 63 years, which was somewhat higher than that reported in other similar studies. In those studies the mean ages were 41 (7) and 59 (12) years. Ranges were from 40 to 80 years, consistent with published studies. (13) Advanced age was in general more associated with co-morbid conditions, which plausibly might be considered the cause of mortality in cases of tuberculosis. Gender distribution was in line with data from previous studies (14) as males (60.7%) were seen more often with severe pulmonary tuberculosis than females (39.3%). One possible explanation for this disparity might be the higher exposure of males to droplet infections due to a greater prevalence of outdoor occupations. Aggravating factors such as smoking, exposure to air pollutants and industrial exposure may also predispose males to tuberculosis.

In our study earlier presentation to the hospital also was observed in comparison to other studies. While the range was rather broad, one to 90 days from onset of symptoms to hospital admission, the mean duration was only 17 days until admission to the ICU. There were fewer patients with delayed presentation. The mortality rate of 67% might be indicative of an association between early presentation and mortality. (15) This may well be a logical conclusion since patients with severe and uncontrolled symptoms leading to early ICU admission would tend toward a higher rate of mortality. In a meta-analysis of the effect of initial drug resistance and treatment regimen on tuberculosis treatment outcomes from studies published in English from 1965 to 2007, it was concluded that treatment outcomes were substantially worse in the presence of initial drug resistance, which has important implications in resource-limited settings in which drug resistance is prevalent. (16) Among the patient cohort in our study fever was the most common clinical symptom observed upon presentation to the hospital, and was seen in one-half (51%) of patients. Fever was indicative of a high grade of infection that required immediate attention. Cough, dyspnea and other respiratory symptoms were seen in approximately 27% of cases, as would be expected in pulmonary conditions. (17) Hemoptysis was a symptom of primary concern, although seen in a relatively small number of patients.

The clinical diagnosis that was the primary contributing factor to mortality was community-acquired pneumonia, seen in 54% of cases. This is a predominant condition in developing countries such as India. (18) A common cause of pneumonia was nosocomial infection from *Streptococcus pneumoniae*, requiring mechanical ventilation. It is probable that debilitating factors such as alcoholism or anemia are contributory. Aspiration of sputum leading to aspiration pneumonia was a less common diagnosis in the study. Similar findings have been reported in other studies. (12,19)

Laboratory and microbiological testing were carried out as confirmatory to the clinical presentation. (20) From a total of 161 tracheal aspirates, 48 were seen as gram stain positive for AFB (30%) excluding others as negative. Cultures were observed to be more sensitive than staining in 69% of total aspirates, including cases that were found negative with gram staining. Cultures are more specific in diagnosing early stage tuberculosis. (21)

Mortality among patients during hospitalization was higher among treated patients than the non-treated group. Twenty-two patients with an early diagnosis, admitted to the ICU and treated had a somewhat higher rate of mortality. Eleven non-treated patients who were diagnosed later on with tuberculosis were treated empirically. Seven of them died. These patients suffered from underlying tuberculosis but received treatment for pneumonia. This ultimately resulted in respiratory failure. This result illustrates the deleterious effect of delayed or missed diagnosis. Delay in diagnosis is significant to both disease prognosis at the individual level and transmission within the community. This corresponds to previous studies. (22,23) With the emergence of HIV with tuberculosis co-infection, it is of primary importance to conduct laboratory evaluations to rule out life threatening compounding of conditions. (24) Suppression of the immune system is the basic cause of HIV-tuberculosis co-infection. In this study there was no case of HIV-tuberculosis co-infection, despite the fact that it was conducted in a developing nation. (25) Major advances that would carry tuberculosis diagnosis and treatment to a new level have not yet been realized. While there has been some progress, accelerated advances are needed. Despite the overwhelming global burden of tuberculosis and the overall low rates of diagnosis,

conventional approaches in general continue to rely on tests that have major limitations. One of the primary reasons for this is the lack of a sensitive method for reliable diagnosis, especially in HIV-positive patients. Clinical trials will be necessary to identify and demonstrate the efficacy of new diagnostic methods. These trials must be conducted in the geographical areas where they will be used, specifically in developing countries with high incidences of tuberculosis. (26,27)

The small sample size in this study may possibly have limited the statistical significance of some of the findings. Also, retrospective analyses such as this are dependent on available data. This is a major disadvantage in retrospective study design. A larger prospective study should be undertaken to confirm these findings on clinical presentations and outcomes of patients with active pulmonary tuberculosis.

Conclusion

In emerging nations infections such as tuberculosis requiring intensive care are not uncommon. Clinician awareness of the symptomatology and contributory factors of the disease is vital. Diagnoses may be challenged by atypical clinical presentations along with the lack of sensitive and rapid diagnostic tests. Early diagnosis of tuberculosis can reduce the health burden and mortality among an expanded stratum of the population. As was seen in this study, late or missed diagnoses resulting in non-treated cases are contributory to unnecessary morbidity and mortality. It will be important to develop and utilize novel, more sensitive and specific tests. Considering the serious impact of missed or delayed diagnoses and the risk of transmission to health care professionals, clinicians must maintain a high level of suspicion and a low threshold for respiratory isolation to combat tuberculosis.

Table 1. Symptoms at presentation (33 patients)

Symptoms	%
Fever	51
Cough	14
Dyspnea	8
Night sweats	6
Less common symptoms (fatigue, hemoptysis, weight loss, severe respiratory insufficiency, anemia, elevated WBC)	21

Table 2. Patient outcomes

Treatment/Outcome	Number of patients (n=33)	%
Treated for TB during hospitalization	22	67
Treated according to clinical diagnosis non-TB*	11	33
Deaths during hospitalization, TB treated pts	15	68
Survivors, TB treated pts	7	32
Deaths, non-TB treated pts	7	64

Legend: *Found later to be culture positive for TB

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