MORTALITY OF PATIENTS WHILE ON TREATMENT FOR ACTIVE TUBERCULOSIS

K L Tan, K N Sin Fai Lam, L S Chew

ABSTRACT

In the era of effective antituberculous chemotherapy, some patients with tuberculosis still die while on treatment. The aim of this study was to review deaths occurring in patients while on treatment for active tuberculosis in Alexandra Hospital during the 4-year period from 1991 to 1994. Medical records of 30 such patients were reviewed retrospectively. Twenty-one patients were certified as dying from tuberculosis; in the remaining 9 patients, the principal cause of death was other than tuberculosis. Of the patients who died of tuberculosis, 7 (33.3%) died within a week and 19 (90.5%) died within a month of initiation of antituberculous treatment. Seventeen (81%) were males and 15 (71%) were smokers. All the 21 patients had pulmonary involvement and in 4 patients, there was disseminated disease. Chest roentgenographic findings of bilateral involvement were seen in 16 (76.2%) patients and of cavitary disease in 15 (71.4%) patients. Eighteen (86%) had a positive sputum smear result. Seven patients received corticosteroid cover. In 14 patients who had their weights recorded at initiation of antituberculous treatment, the mean weight was 36.3 kg (range 25.5kg - 47kg). Notable biochemical derangements included hyponatraemia (86%) and hypoalbuminaemia (95%). Plasma cortisol and/or Synacthen stimulation test were performed in 4 patients; none was indicative of adrenal hypofunction. We conclude that death attributed to tuberculosis in patients while on treatment occurs early and is largely due to advanced disease.

Keywords: tuberculosis, death, hyponatraemia, hypoalbuminaemia, adrenal

SINGAPORE MED J 1996; Vol 37: 258-260

INTRODUCTION

The development of specific chemotherapeutic agents has revolutionised the prognosis of tuberculosis, making tuberculosis truly curable and preventable[1]. The mortality rate has declined with the introduction of effective antituberculous chemotherapy[2]. Nevertheless, some patients with active tuberculosis still die while on treatment for their disease.

The aim of this study was to review deaths occurring in patients while on treatment for active tuberculosis in Alexandra Hospital during the 4-year period from 1991 to 1994.

PATIENTS AND METHODS

Medical records of 71 patients who died in Alexandra Hospital over a four-year period from 1991 to 1994 for whom tuberculosis was coded (International classification of disease codes 010-018)[3] in the diagnosis section (as final diagnosis/principal morbid condition or as other diagnosis) of the government hospital inpatient discharge summary were studied retrospectively. Patients with inactive tuberculosis or who were not on treatment for tuberculosis were excluded. Thirty patients who died while on treatment for active tuberculosis were identified. In all thirty patients, the definitive diagnosis of active tuberculosis was substantiated; either a recent positive smear for acid-fast bacilli or a recent positive culture for *Mycobacterium Tuberculosis* or histological or necropsy evidence consistent with tuberculosis.

Characteristics that were studied included age, gender, race, weight, presenting symptoms, concomitant medical conditions, history of smoking, results of laboratory investigations, clinical parameters, extent of disease, treatment, cause of death and mode of death. Pertinent clinical events preceding death were reviewed.

RESULTS

Thirty patients with active tuberculosis died while on treatment in Alexandra Hospital during the 4-year period from 1991 to 1994. Twenty-one patients were certified as dying from tuberculosis. In the remaining 9 patients, the principal cause of death was certified as other than tuberculosis. These were in order of frequency: malignancy (3), bronchopneumonia (2), chronic obstructive pulmonary disease (1), diabetic nephropathy (1), cerebrovascular accident (1) and thyrocardiac disease (1).

Table I lists the age distribution of the 21 patients who died from tuberculosis while on treatment. The mean age was 59 years (range, 35 to 90 years). Seventeen (81%) were male and 4 (19%) were female patients. Table II shows the ethnic origin of the patients who died from tuberculosis while on treatment.

Table I – Age distribution of patients who died from tuberculosis while on treatment

Age	Number	Percentage	Cumulative %
30 - 39	4	19.0	19.0
40 - 49	3	14.3	33.3
50 - 59	3	14.3	47.6
60 - 69	7	33.3	80.9
70 - 79	2	9.5	90.4
80 - 89	1	4.8	95.2
90 - 99	1	4.8	100
Total patients	21	100	

Department of Medicine
Alexandra Hospital
Alexandra Road
Singapore 159964

K L Tan, MBBS, MRCP (UK)
Medical Officer (Specialist)

K N Sin Fai Lam, MBBCh, FRCP, FAMS
Consultant

L S Chew, MBBS, FRACP
Clinical Associate Professor and Head

Correspondence to: Dr K L Tan
Department of Respiratory & Critical Care Medicine
Singapore General Hospital
Outram Road
Singapore 169608

Table II – Ethnic origin of patients who died from tuberculosis while on treatment

Ethnic origin	Number	Percentage
Chinese	15	71.4
Malay	2	9.5
Indian	2	9.5
Others	2*	9.5
Total patients	21	100

*One Eurasian and one Pakistani

The mean duration of symptoms at presentation was 61 days (range, 1 day to 1 year). Concomitant medical conditions that were present are shown in Table III. Fifteen (71%) patients were smokers. All the 21 patients had pulmonary involvement and in 4 patients, there was disseminated disease. Chest roentgenographic findings of unilateral involvement were seen in 5 (23.8%) patients and bilateral involvement in 16 (76.2%) patients. Fifteen (71.4%) patients had roentgenographic findings of cavitary disease (Table IV). Eighteen (86%) patients had a positive sputum smear result for acid-fast bacilli.

Table III – Concomitant medical conditions and death of tuberculosis patients while on treatment

Condition	Number	Percentage
Chronic obstructive airways disease	10	48
Alcoholism	5	24
Diabetes mellitus	4	19
Cerebrovascular disease	1	5
Ischaemic heart disease	1	5
Malignancy*	1	5

* Adenocarcinoma proven on sputum cytology

Table IV – Chest roentgenographic findings

	Non cavitary	Cavitary
Unilateral	2 (9.5)	3 (14.3)
Bilateral	4 (19)	12 (57.1)

% in parentheses

Anaemia was present in 13 (76.5%) male patients and all 4 female patients who died of tuberculosis while on treatment (Table V). Leucocytosis was seen in 38.1%. The biochemical profile is summarised in Table VI. The notable biochemical derangements include hyponatraemia (86%) and hypoalbuminaemia (95%). None of the patients had both hyponatraemia and hyperkalaemia. Plasma cortisol and Synacthen stimulation test were performed in 3 and 1 patients suspected clinically of hypoadrenalism, respectively; none of the results was supportive of adrenal hypofunction.

Of the patients who died from tuberculosis while on treatment, 7 (33%) and 19 (90%) died within a week and a month, respectively, of initiation of antituberculous chemotherapy (Table VII). Seven patients received corticosteroid cover. In 14 patients who had records of their weights at the initiation of antituberculous treatment, the mean weight was 36.3 kg (range, 25.5-47 kg).

Table VIII summarises the mode of death in the patients who died from tuberculosis while on treatment. Fourteen (66.7%) patients showed no clinical improvement despite treatment and died expectedly of overwhelming tuberculosis. Four patients died of respiratory failure and one of massive hemoptysis. In two patients, death was sudden, unexpected and unexplained. Both patients were relatively young (aged 37 and 46 years respectively) and in both cases, death occurred early (within 48 hours and within 24 hours respectively) of initiation of antituberculous chemotherapy. One patient received corticosteroid cover. Both patients were signed up by the Coroner without necropsies performed.

Table V – Haematologic profile

	Hb (male) (g/dL) n = 17	Hb (female) (g/dL) n = 4	White cell count ($X10^9$/L) n = 21
Normal	13 - 16	11 - 14	4 - 11
Mean	10.9	9.3	11.4
SD	2.43	1.23	4.98
% above range	0	0	38.1
% below range	76.5	100	4.8

Hb = Haemoglobin

Table VI – Biochemical profile of patients who died from tuberculosis while on treatment

	Normal	Mean	SD	% above range	% below range
Na+ (mmol/L)	135 -145	130	7.5	0	86
K+ (mmol/L)	3.5 - 5	3.6	0.76	5	48
Urea (mmol/L)	2.8 - 7.7	15.6	17.1	71	0
Cre (μmol/L)	44 -144	87	56.6	5	5
TP (g/L)	62 - 82	59.6	10.9	0	50
Alb (g/L)	37 - 51	24.7	5.7	0	95
SAP (U/L)	32 - 103	147	134	55	0
Alt (U/L)	7 - 36	31	40	20	0
Ast (U/L)	15 - 33	34	17	40	0

Na+ = Sodium, K+ = Potassium, Cre = Creatinine
TP = Total protein, Alb = Albumin, SAP = Alkaline phosphatase,
Alt = Alanine aminotransferase, Ast = Aspartate aminotransferase

NB: Liver function test records were available for 20 out of the 21 patients

Table VII – Time of death from the start of treatment for tuberculosis

	Number	Cumulative %
1 to ≤ 7 days	7	33.3
> 7 days to ≤ 1 month	12	90.5
> 1 month to ≤ 2 months	1	95.2
> 2 months	1	100

Table VIII - Mode of death

Overwhelming tuberculosis, expected	14	(66.7%)
Respiratory failure	4	(19 %)
Massive hemoptysis	1	(4.8%)
Sudden, unexpected, unexplained	2	(9.5%)

% in parentheses

DISCUSSION

Tuberculosis is an important cause of death in Singapore,

accounting for 0.8% of all deaths and a mortality rate of 3.9 cases per 100,000 population in Singapore in 1993[4].

Death due to tuberculosis is potentially preventable, provided that patients are diagnosed promptly and treated early. The most striking finding of this study was that death attributed to tuberculosis in patients while on treatment occurred early and was largely related to extensive disease present at time of diagnosis and institution of treatment.

In our series, 90.5% of the patients who succumbed to tuberculosis while on treatment, died within a month of commencement of antituberculous chemotherapy. Our findings are in agreement with the other described series by Humpries et al[5], who found that 69% of the patients died within the first month of chemotherapy; and that of HJ Xie et al[6], who found that 87% of the patients died within 3 months of commencement of therapy.

As in other series[7], a marked preponderance of males was observed among those who died while on treatment. Unlike most other studies[5-7] which show death from tuberculosis to be associated with advancing age, approximately half of our patients who died from tuberculosis while on treatment were below 60 years. Our findings do not concur with the study by Davis et al[8] who found that approximately 50% of deaths among patients who have tuberculosis were due to concomitant medical problems not directly related to tuberculosis. This could be attributed to the primarily elderly population in his study, in which one would expect an increased incidence of underlying arteriosclerotic, cardiovascular and chronic obstructive pulmonary disease.

Significant predictors of death while on treatment for tuberculosis has been shown by Xie et al[6] to include the extent of disease and sputum smear positivity for acid fast organisms. In a stepwise multivariate discriminant analysis, death from tuberculosis was found by Humphries et al[5] to be significantly associated with radiographic extent of disease before treatment, extent of cavitation and a positive sputum smear result. It was not surprising therefore, in this series, that most patients who died had extensive disease, either advanced pulmonary or disseminated tuberculosis.

Eighty-six percent of our patients who died while on treatment for tuberculosis had hyponatraemia, a well recognised feature of pulmonary tuberculosis and attributed to inappropriate secretion of antidiuretic hormone[9]. The other notable biochemical abnormality was hypoalbuminaemia, present in 95% of our patients who died while on treatment. Hypoalbuminaemia may reflect either malnutrition, or more likely severity of disease[10].

In the literature, much has been written regarding adrenal function in active tuberculosis[11-15]. Adrenocortical insufficiency is uncommon in patients with pulmonary tuberculosis. Suboptimal cortisol responses to Synacthen usually reflect a hyperstimulated basal level secondary to stress[15]. Of the four patients who had plasma cortisol or Synacthen stimulation test performed, none of the results was supportive of hypoadrenalism.

Ellis and Webb[16] first highlighted the presence of a proportion of patients who died suddenly and unexpectedly, in the early stages of apparently effective chemotherapy, in whom necropsy confirmed the presence of localised pulmonary tuberculosis but failed to provide an adequate reason for the sudden death. The occurrence of unexplained death within a few weeks of commencing therapy was postulated to be possibly due to a Herxheimer-type reaction.

The limitation of our study arises from potential inaccuracies in death certification in patients said to have died as a direct result of tuberculosis. Published reports[7,17-21] have shown inaccuracies in death certification to be apparently common. Heng et al[21] evaluated the accuracy of tuberculosis death certification in Singapore and found that only 56% of active tuberculosis certified by hospital doctors were correct.

In conclusion, death attributed to tuberculosis in patients while on treatment occurs early and is largely due to extensive disease. If patients present at an earlier stage, prompt diagnosis and early institution of treatment may prevent some of these deaths.

ACKNOWLEDGEMENTS

The authors would like to thank Miss Shanta Sockalingam and Mr Chua Tong Yan of the Medical Records Office for their assistance.

REFERENCES

1. Johnston RF, Wildrick KH. The impact of chemotherapy in the care of patients with tuberculosis. Am Rev Respir Dis 1974; 109:636.
2. Grzybowski S, Enarson DA. The fate of cases of pulmonary tuberculosis under various treatment programmes. Bull Int Union Tuberc 1978; 53: 70-5.
3. International classification of diseases (1975 Revision). Manual of the international statistical classification of diseases, injuries and causes of death. Geneva: World Health Organization, 1977.
4. Epidemiology Unit, Communicable Disease Centre, Ministry of Health, Singapore. Communicable disease surveillance report 1993.
5. Humphries MJ, Byfield SP, Darbyshire JH, Davies PDO, Nunn AJ, Citron KM, et al. Deaths occurring in newly notified patients with pulmonary tuberculosis in England and Wales. Br J Dis Chest 1984; 78: 149-58.
6. Xie HJ, Enarson DA, Chao CW, Allen EA, Grzybowski S. Deaths in tuberculosis patients in British Columbia, 1980-1984. Tuber Lung Dis 1992; 73: 77-82.
7. Hong Kong Chest Service/British Medical Research Council. Survey of deaths in Hong Kong attributed to tuberculosis during a five-year period. Tubercle 1984; 65: 253-61.
8. Davis CE, Carpenter JL, McAllister CK, Bush BA, Ognibene AJ. Tuberculosis. Cause of death in antibiotic era. Chest 1985; 88: 726-9.
9. Shalhoub RJ, Antoniou LD. The mechanism of hyponatraemia in pulmonary tuberculosis. Ann Intern Med 1969; 70: 943-62.
10. Morris CDW, Bird AR, Neil H. Hematological and biochemical changes in severe pulmonary tuberculosis. Q J Med 1989; 73: 1151-9.
11. Ellis ME, Tayoub F. Adrenal function in tuberculosis. Br J Dis Chest 1986; 80: 7-12.
12. Barnes DJ, Naraqi S, Temu P, Turtle J. Adrenal function in patients with active tuberculosis. Thorax 1989; 44: 422-4.
13. Sarma GR, Immanuel C, Ramachandran G, Krishnamurthy PV, Kumaraswami V, Prabhakar R. Adrenocortical function in patients with pulmonary tuberculosis. Tubercle 1990; 71: 277-82.
14. York EL, Enarson DA, Norbert EJ, Fanning FA, Sproule BJ. Adrenocortical function in patients investigated for active tuberculosis. Chest 1992; 101: 1338-41.
15. Chan CH, Arnold M, Mak TW, Chan RW, Hoheisal GB, Chow CC. Adrenocortical function and involvement in high risk cases of pulmonary tuberculosis. Tuber Lung Dis 1993; 74: 395-8.
16. Ellis ME, Webb AK. Cause of death in patients admitted to hospital for pulmonary tuberculosis. Lancet 1983; 1: 665-7.
17. Khoury SA. Death certificates and tuberculosis register cards. Am Rev Respir Dis 1971; 104: 936-7.
18. Allan WGL, Snell NJC, Hill LE, Fayers PM, Scadding JG, Fox W. A survey of deaths in Hong Kong attributed to tuberculosis. Tubercle 1981; 62: 1-11.
19. Simmonds FAH. The causes of death in pulmonary tuberculosis. Tubercle 1963; 44: 230-40.
20. Research Committee of the British Thoracic and Tuberculosis Association. A survey of tuberculosis mortality in England and Wales in 1968. Tubercle 1971; 52: 1-18.
21. BH Heng, KK Tan, KW Chan, TH Tan. An evaluation of 1987 tuberculosis deaths in Singapore. Singapore Med J 1990; 31: 418-21.