

Mortality in smear-negative tuberculosis patients in Phalombe.

JCJ Calis, ML Bakker, RB Elens, M Borgdorff, AD Harries

Summary

In two hospitals in Malawi, where HIV prevalence among tuberculosis patients is 80-90%, the treatment outcome in patients registered with smear-negative pulmonary tuberculosis was determined in relation to chest x-ray (CXR) findings and certain laboratory parameters. Of 70 patients who were registered and treated, 32 (46%) were known to have died. Mortality was particularly high in those with a normal / minimally abnormal CXR (62%) and in those with a white cell count of less than $3.5 \times 10^9/l$ (77%). The reasons for this high mortality among patients with smear-negative PTB are not known and requires more research.

Introduction

Malawi is severely affected by a dual epidemic of HIV and tuberculosis (TB). In 1999, the estimated national HIV-seroprevalence rate was 8.8% in the adult general population (source = National AIDS Control Programme). In 2001, the number of TB cases registered nationally was 27,672 (source = National TB Control Programme). As elsewhere in sub-Saharan Africa, TB incidence has increased steeply in the last 15 years, and the presentation of tuberculosis has changed, with an increasing proportion of patients presenting with smear-negative pulmonary TB (PTB) and extra pulmonary TB [1].

In Malawi, smear-negative PTB patients have a high prevalence of HIV infection (up to 90%) and a high mortality (above 30%) during the first year of treatment [2,3]. Studies in Malawi have shown that a significant proportion of smear-negative PTB patients with culture-positive *Mycobacterium tuberculosis* have a normal or minimally abnormal chest x-ray (CXR) [2,4]. Unfortunately culture is not routinely available as diagnostic tool, and therefore the diagnosis of TB in these patients is difficult. The treatment outcome of smear-negative PTB patients with normal CXRs compared with those who have abnormal CXRs has not been well described. The full blood count and erythrocyte sedimentation rate (ESR) can usually be measured in hospital laboratories, and may be useful tools for predicting high mortality in this situation. We therefore carried out a study to i) document the treatment outcome of smear-negative PTB patients, and ii) determine whether the CXR pattern, haemoglobin (Hb), white cell count (WBC) and ESR measurements were determinants of increased mortality.

Methods

A retrospective cohort study was carried out in two mission hospitals (Mlambe and Phalombe Mission Hospital) in the southern region of Malawi. All new smear-negative PTB patients who were registered between 1-1-96 and 31-12-98 were included. The diagnosis had been based on clinical features, i.e. cough for three or more weeks not responding to at least one course of broad-spectrum antibiotics, negative sputum smears and CXR characteristics. Patients had received standard chemotherapy (twelve months of daily isoniazid and ethambutol, with daily streptomycin during the first month).

Smear-negative PTB patients had their CXRs reviewed by two clinical officers and two medical officers. The CXR was classified as either a "TB-CXR" if at least two readers considered it was suggestive of TB based on previously described criteria [3], or a "normal or minimally abnormal" CXR. The case notes were reviewed and the following information was recorded: age, sex, white blood cell count (WBC), haemoglobin and erythrocyte sedimentation rate (ESR). Standardised treatment outcomes according to criteria from the WHO and the International Union against TB and Lung Disease were documented from the TB-register, treatment cards or visits to the patient's home. Mortality was determined using the Kaplan-Meier method, to correct for the loss to follow up. Risk factors for mortality were analysed by odds ratios and adjusted odds ratios using logistic regression.

Results

There were 70 patients, 25 men and 45 women, with a mean age of 32 years. Most patients were over 18 years old (n=67). Twenty-four (34%) patients completed treatment, 32 (46%) patients were known to have died, 12 (17%) defaulted and 2 were still on treatment at the time of the review. During the first month of treatment, 9 patients died (28% of deaths), with 23 (72%) dying during the continuation phase. The Kaplan-Meier corrected mortality rate of the cohort at one and eleven months was 13% and 53% (95% CI 41-66%) respectively.

Mortality was not associated with gender or with age. Risk factors for mortality are shown in the TABLE. Patients with a normal or minimally abnormal CXR had a higher mortality than those who had a TB-CXR. Patients with a lower WBC had a higher mortality than those who had a higher WBC. No significant association was found between mortality and haemoglobin level or ESR.

Discussion

This study shows a high mortality in smear-negative PTB-patients in two mission hospitals in Malawi. Mortality rates were particularly high in patients with a normal or minimally abnormal CXR and in those with a WBC $< 3.5 \times 10^9/l$. This study was not designed to assess the reasons for this high mortality. A high proportion of patients probably had HIV infection [2], and this may be an important explanation for the high death rates [1,2].

There are some limitations to this study. First, it was retrospective, making it impossible to determine HIV status. Use of the WHO clinical staging system might have helped, but unfortunately this was also not recorded in the case notes. Second, it is not possible to be certain of the diagnosis of patients registered as smear-negative PTB. Some of the patients with a normal or minimally abnormal CXR may have had diseases other than TB. However, under routine conditions these patients are registered and treated for TB, consuming resources from the National TB Control Programme. Third, the accuracy of reported death rates can be questioned. Nearly 20% of patients defaulted from treatment, and previous studies have shown that a significant proportion of patients who default in fact have died [5].

Although the interpretation of the CXR in such circumstances is difficult, it appears to be useful in predicting treatment outcome. The poor prognosis of culture-positive patients with a normal or minimally abnormal CXR is likely to be due to advanced HIV infection [6], and the high mortality associated with a low WBC may be because leukopaenia is associated with a poor prognosis in HIV-positive individuals in general [7]. The reasons why a normal CXR or a low WBC are associated with high

mortality are unknown – for example, wrong diagnosis or pulmonary TB associated with severe immunodeficiency – and could be considered as a useful area for more research.

Authors:

- JCJ Calis¹, ML Bakker¹, RB Elens², M Borgdorff³, AD Harries⁴
 1. Academic Medical Center, University of Amsterdam, Netherlands
 2. Holy Family Mission Hospital, Phalombe, Malawi
 3. Royal Netherlands Tuberculosis Association (KNCV), The Hague, The Netherlands
 4. National Tuberculosis Control Programme, Ministry of Health & Population, Lilongwe, Malawi

Address for Correspondence: AD Harries, C/o British High Commission, PO Box 30042, Lilongwe 3.

Email: adharries@malawi.net

References

1. De Cock KM, Soro B, Coulibaly IM, Lucas SB. Tuberculosis and HIV infection in sub-Saharan Africa. *JAMA* 1992;268:1581-1587.
2. Hargreaves NJ, Kadzakumanja O, Phiri S, et al. What causes smear-negative pulmonary tuberculosis in Malawi, an area of high HIV seroprevalence? *Int J Tuberc Lung Dis*. 2001;5:113-22.
3. Banda H, Kang'ombe C, Harries AD, et al. Mortality rates and recurrent rates of tuberculosis in patients with smear-negative pulmonary tuberculosis and tuberculous pleural effusion who have completed treatment. *Int J Tuberc Lung Dis*. 2000; 4:968-74.
4. Harries AD, Banda HT, Boerree MJ, et al. Management of pulmonary tuberculosis suspects with negative sputum smears and normal or minimally abnormal chest radiographs in resource-poor settings. *Int J Tuberc Lung Dis* 1998; 2: 999-1004.
5. Kruyt MLL, Kruyt ND, Boeree MJ, Harries AD, Salaniponi FML, van Noord PA. True status of smear-positive pulmonary tuberculosis defaulters in Malawi. *Bull World Health Organization* 1999; 77: 386 – 391.
6. Greenberg SD, Frager D, Suster B, Walker S, Stavropoulos C, Rothpearl A. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology* 1994; 193: 115-9.
7. Lindan CP, Allen S, Serufilira A, et al. Predictors of mortality among HIV-infected women in Kigali, Rwanda. *Annals of Internal Medicine* 1992; 116: 320-8.

Table: Mortality of smear-negative tuberculosis patients

Parameter	Number	Died	Mortality (corrected Kaplan-Meier)	Odds Ratio (95%-CI)
All	70	32	53%	
No-TB CXR	45	25	62%	1.9 (1.03-3.4)
TB CXR	25	7	33%	1
WBC Less than 3,5	15	9	77%	5.1 (1.5-17.7)
WBC 3.5-10.4	32	15	53%	3.5 (1.01-12.3)
WBC 10.5 and more	15	2	15%	1

*** Not all patients had measurements of the WBC (89%).**



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