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High prevalence of tuberculosis diagnosed during autopsy examination at Muhimbili National Hospital in Dar es Salaam, Tanzania

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Abstract: The primary aims of tuberculosis (TB) control programmes is early diagnosis and prompt treatment of infectious cases to limit transmission. Failure to diagnose and adequately treat TB could lead to premature death and unrecognized transmission of *Mycobacterium tuberculosis*. The proportion of missed TB cases has not been reported in Tanzania. The objective of this study was to quantify the number of cases of TB identified by autopsy. Deceased morbid bodies from Muhimbili National Hospital were involved. Retrieval of admission, diagnostic and other important records used to manage the patient after admission was done. Demographic information, site and type of disease, past medical history, chest x-ray report, clinical diagnosis and cause of death reported upon death certification were recorded. Lung tissues, lymphnodes and blood clots for HIV testing were collected. Biopsy tissues were processed through Ziehl Nielsen staining and examined by microscopy. The study involved 74 deceased individuals where 56 (75.7%) were males. Information for duration of seeking health care before death was available for 41(55.4%) subjects. Thirty-four (45.9%) cases received diagnosis before death. The main diagnoses were pneumonia 10(13.5%), heart failure 6(8.1%), AIDS-related illnesses 6 (6.8%) and malaria 5 (6.8%). The main clinical findings were wasting (51/74 (68.9%)) and abnormal fluid collection in different body cavities, 61(50.8%). In 24 out of 71(33.8%) biopsies acid fast bacilli (AFB) were detected. Records of lymphnodes examination were available in 63 cases and 22 of them had AFB. Twenty-two (34.9%) from the paratracheal and hilar lymphnodes were observed to have AFB. HIV was detected by ELISA in 19 (33.3%) out of 57 deceased, and 12 (63.2%) of the HIV positive deceased were co-infected with TB. Out of the 22 cases positive for AFB on tissue-biopsies 12 (54.5%) were HIV positive. There is a high number of TB cases diagnosed after death that could not be detected before they died. There is a need for increased awareness and to include postmortem data in the annual statistics of TB for precise reporting of the magnitude of the TB burden in the country.

Keyword: autopsy, tuberculosis, HIV, morbid, autopsy, Tanzania

Introduction

One in ten people that are infected with *Mycobacterium tuberculosis* (MTB) may develop active tuberculosis (TB) at some time in their lives (WHO, 2010). The risk of developing active disease is greatest in the first year after infection, but active disease often does not occur until many years later. The development and progression of the disease are aggravated by HIV infection. In HIV-positive individuals, the risk of development of tuberculosis is dependent upon the CD4+ T cells count. TB often appears when the cell count is still relatively normal so that TB is a common opportunistic infection in HIV infected individuals (Barry & Barnes, 1994). In addition, HIV can activate latent TB causing progression to active TB. In turn, infection with HIV leads to destruction of CD4+ T cells and thus shortens survival of TB infected individuals (Denise, 1999). Early symptoms of active TB can include weight loss, fever, night sweats, and loss of appetite, or they may be vague and unnoticed by

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the affected individual.

In TB control programmes the WHO definition of 'TB deaths' is the number of TB cases dying during treatment, regardless of the cause (WHO, 1993). Untreated one in three patients with TB will die, and for the rest their disease either goes into remission (halts) or becomes chronic and more debilitating with cough, chest pain, and bloody sputum. Symptoms of TB involving areas other than the lungs vary, depending upon the organ affected (Edlin, 1997). In three different studies in the USA, TB was the underlying or a contributing cause of death in up to 50% of TB cases unrecognized until death (Makela *et al*., 1971; Enarson *et al.*, 1978; Mackay & Cole 1984).

An autopsy study in Mumbai, India reviewed pulmonary pathology in patients with AIDS, and observed pulmonary pathology in 126 (88%) cases. Among the lesions identified were pulmonary TB in 85 cases (59%) (Lanjewar & Duggal, 2001). A similar but retrospective review of autopsy findings and medical records in 33 HIV-infected children living in a Kenyan orphanage, respiratory disorders were probably the primary cause of death in 21 (64%), in 19 (90%) of whom pyogenic parenchymal lung disease was detected. A presumptive clinical diagnosis of PTB had also been made in 14 (67%) of them; the children also had a history of more than four recurrent acute lower respiratory tract infections per year. Among the 128 patients with chest disease who were enrolled in a study of the pathology and causes of death in a group of predominantly HIV-positive patients in Botswana, TB was reported to be the leading cause of death (Ansari *et al.*, 2002). As TB has become more prevalent, several factors contribute to the continued undiagnosed deaths from TB. Failure of diagnosis of TB has become an increasingly important contributor to deaths from the disease, as it is increasingly associated with HIV infection. The current study was conducted to determine the prevalence of TB diagnosed after death among dead bodies not suspected to have TB at Muhimbili National Hospital in Tanzania.

Materials and Methods

Study setting

The study involved deceased morbid bodies from Muhimbili National Hospital (MNH) in Dar es Salaam Tanzania. The Department of Pathology and Morbid Anatomy of MNH did sample processing based on predetermined inclusion and exclusion criteria. The department provides storage and autopsy services to dead bodies at the hospital and other hospitals in Dar es Salaam. It has qualified morgue technicians and pathologists who routinely offer the services.

Enrollment of study subjects

A pathologist on-duty went through all medical records of the dead bodies that were not presumed to have TB. Inclusion criteria for the study were as follows: a dead body brought to MNH regardless of history of illness, age and sex; a dead body that before death was referred to MNH for further management; a dead body previously hospitalized at MNH whose medical records shows initial clinical presentations to be compatible with pulmonary pathology; a dead body whose stated initial cause of death was not TB; a dead body whose diagnosis was not established; a dead body where the condition had deteriorated unexpectedly during hospitalization; and a dead body with clinical records presenting with symptoms not compatible with pulmonary pathology. Exclusion criteria included dead bodies with clinical records that presented with symptoms not compatible to pulmonary pathology; and being a dead body with no diagnosis of TB before death were the main exclusion criteria of the study cases.

In each case, an investigator made a close follow up and retrieved admission, diagnostic records and other important records that were used to manage the patient after admission. The recorded information included, age, sex, place of birth, site and type of disease, past medical history, chest X-ray report, clinical diagnosis and cause of death upon the death certification. Status at diagnosis was categorized as active or dead and cases were stratified into males or females and major

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disease site.

Collection of specimen and laboratory processing of the specimens

The biopsies included lungs and lymph nodes. This required collection and analysis of samples for HIV-serology status not included on the individual case-report form. Major site of the disease was used to classify patients with more than one pulmonary TB site. The samples were processed for conventional Ziehl-Neelsen (ZN) microscopy examination.

Data analysis

For easy analysis and generation of simple tables for presentation of the findings, the data collected were entered into the computer using SPSS software package. Further analysis using Epi Info 2000 was made to complement the interpretation and presentation of the study information.

Ethical considerations

Before conducting the study, ethical approval was sought from and granted by the Medical Research Coordinating Committee of the National Institute for Medical Research. Administrative permission was also sought from authorities of the Muhimbili National Hospital where the study was conducted. A written consent was obtained from relatives of the deceased meeting inclusion criteria of the study. All refusals by relatives to do the autopsy were respected.

Results

Socio-demographic characteristics of the study subjects

We present the results of autopsy materials from 74 deceased individuals of whom 56 (75.7%) were males. The mean age was 35 years (range= 2-85. Majority of the study subjects 43 (58.1%) were aged between 15 and 44 years. Some basic characteristics of the study subjects are shown in Table 1.

Table 1: Baseline characteristics of the deceased individuals

Characteristics		Number	Percent
Sex	Male	56	75.7
	Female	18	24.3
Marital status	Single	32	43.2
	Married	39	52.7
	Widow	1	1.4
	Divorced	2	2.7
HIV sero-status	HIV-Positive	38	51.3
	HIV-Negative	19	25.7
	Not known	23	31%

Admission and reasons for admission

Among the 74 cases, 22 (29.7%) were admitted in the hospital before death. Reasons for admission were available for only 19 patients. Serious ill health was the main reason (47.4%) for admission. Other reasons included referral (3), abdominal distention (1), wasting (3), difficulty in breathing (2) and fever (1). Six (31.6%) out of the 19 admitted patients had more than one causes of admission.

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Visit to health facility before death

Information for duration of seeking health care before death was available for 41(55.4%) study subjects. Eighteen (43.9%) had presented to a health facility for the first time for treatment one week before death while a quarter presented to health facility for a duration ranging from 2-12 months. Records for reasons for attending the health facility at which the diseased death was recorded were available for 64 (86.5%) bodies. Thirty-two (43.2%) of the cases were brought dead; 14(18.9%) were referred from lower level health facilities and six (8.1%) had fever. Other reasons included abdominal distention, chest tightness, having no improvement from illness, trauma, recurrence of ill health and malaria.

A total of 34 (45.9%) out of the 74 cases had received diagnosis before death. The main diagnosis was pneumonia 10 (13.5%), heart failure 6 (8.1%), AIDS-related complications (ARC) 6 (6.8%) and malaria 5 (6.8%). Other diagnoses include anemia, liver failure, bronchial asthma, epilepsy and typhoid. Some cases were diagnosed with more than one health problem.

Despite no-one being diagnosed to have TB before death, an assessment to establish if the deceased were examined for TB revealed that 27 (79.4%) undertook a chest X-ray and 13 (38.2%) submitted sputum samples for AFB smear examination. The time interval between death and postmortem ranged from 0 to 22 days whereas 64 (90%) cases were examined within 5 days from death. Wasting was reported as the main physical finding in 51 (68.9%) cases during autopsy (Table 2). Results for condition of body cavities were available for 61 cases, from whom 31 (50.8%) had abnormal collection of the fluids in different body cavities and potential spaces. Abnormal fluid collections included pleural effusion (18; 24.3%), pericardial effusion (10; 13.5%) and peritoneal effusion (3; 4.1%). Most of the para-tracheal and hilar-lymph nodes were observed to be enlarged and discrete. While a few had the para-tracheal and hilar-lymph nodes enlarged and matted (Table 3a), majority of the deceased had normal left and right lungs. Isolated granulation-like lesions milliary and suppurative lesions were also common (Table 3b). Microscopic examination of lungs indicated less malformation and granulation than the lymphnodes biopsies (Table 4).

Table 2: Results of physical examination during autopsy

Examination	**Results**			
Abnormal findings	Yes n (%)	No n (%)	No results n (%)	Total
Wasted body	51(68.9)	19 (25.7)	4 (5.4)	74
Peripheral lymphadenopathy	4 (5.4)	66 (89.2)	4 (5.4)	74
Discharging sinus	1 (1.4)	69 (93.2)	4 (5.4)	74
Deformed chest wall	4 (5.4)	66 (89.2)	4 (5.4)	74

Results of smear microscopy on biopsies taken from 71 deceased bodies were available of which 24 (33.8%) showed acid fast bacilli (AFB). More than half (14; 58.3%) of the AFB positive biopsies were from males. Almost all (95.5% (21/22) of the AFB positive deceased had wasted bodies. Pleural and pericardial effusions were more common among AFB positive bodies than those without, 10 (58.8%) and 5 (29.4%), respectively ($P>0.05$). Sixty three records were available for analysis of AFB status in the lymph nodes. Twenty-two (34.9%) of the paratracheal and hilar lymphnodes were observed to be AFB positive. Although the lung tissues were seen to have much more AFB positive, normal lung histology of the right lower lobe was much more associated with AFB positive (73.9%).

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Table 3: Results of lymph node and lung examination during autopsy

a) Condition of the lymph nodes

	Normal size	**Enlarged and discrete**	**Enlarged and matted**	**Others**	**No response**
	n (%)	n (%)	n (%)	n (%)	n (%)
Para-tracheal lymphnodes	42 (56.8)	19 (25.7)	5 (6.8)	4 (5.4)	4 (5.4)
Hilar-lympnodes	40 (54.1)	22 (29.7)	4 (5.4)	3 (4.1)	5 (6.8)

b) Appearance of the lungs

	Normal looking	**Isolated granulation-like lesions**	**Milliary lesions**	**Suppurative Lesions**	**Others**
Right lung	50 (67.6)	7 (9.5)	3 (4.1)	4 (5.4)	10 (13.6)
Left Lung	56 (75.7)	3 (4.1)	3 (4.1)	2 (2.7)	10 (13.6)

Nineteen (33.3%) out of 57 deceased were HIV positive, most of whom were co-infected with TB (12; 33.3%. Twelve (54.5%) of the 22 AFB positive deceased were HIV positive. The proportion of HIV positive among individuals with AFB positive was significantly higher than in those with AFB negative ($P<0.05$). Much of the AFB were observed to be located in paratracheal and hilar-lymphnodes, 28.1% (18/64) and 30.8% (20/65), respectively. Similarly, the right lobe and left upper lobes of the lungs were reported to have more AFB 20.3% (14/69) and 15.7% (11/70), respectively.

Table 4: Histological findings through microscopy examination

		Normal histology	**With well formed granulation**	**With poorly formed granulation**	**With suppurative inflammation**
	(N)	n (%)	n (%)	n (%)	n (%)
Para tracheal lymph nodes	62	36 (58.1)	7 (11.3)	13 (20.9)	6 (9.7)
Hilar lymph nodes	63	38 (60.3)	12 (19.0)	10 (15.9)	3 (4.8)
Right Upper Lung	66	46 (69.7)	7 (10.6)	6 (9.1)	7 (10.6)
Right middle lobe	66	52 (78.8)	5 (7.6)	4 (6.1)	5 (7.6)
Right lower lobe	64	53 (82.8)	4 (6.3)	3 (4.7)	4 (6.3)
Left Upper lobe	67	55 (82.1)	7 (10.4)	4 (6.0)	1 (1.5)
Left lower lobe	67	58 (86.6)	4 (6.0)	4 (6.0)	1 (1.5)

Discussion

A successful TB control programme requires basic clinical and public health management to be performed efficiently and consistently. In Tanzania, the National TB/Leprosy programme (NTLP) of Ministry of Health and Social Welfare notifies all cases of active tuberculosis. But most such cases come to the attention of the programme when they seek help from the health system for their symptoms, i.e. through passive case finding. An annual report of the program records all TB cases

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that have been diagnosed before the patient dies. This is done through analysis of clinical specimens submitted to the laboratories for the diagnosis of TB. Our findings show that among the individuals who received diagnosis prior to death, chest X-ray was frequently used. This could be explained by the large number of individuals presenting with pneumonia, a condition with some symptoms in common with TB. Wasting, pleural and pericardial effusions were major findings among AFB positive deceased. Xie *et al*. (1992) and Williams *et al*. (2000) reported that death due to TB is uncommon in patients while on treatment and that the main reason for death due to TB is that some patients are not diagnosed, and therefore not treated, before they die of the disease.

While the primary aim of TB control programmes is early diagnosis and prompt treatment of infectious cases to limit transmission, these broad outcome measures do not provide detailed insight into the pathways of clinical care or identify reasons for missing the targets (van der Werf *et al*., 2007). Methods of TB diagnosis have not changed significantly for many decades; resting primarily on clinical history, clinical examination, chest radiograph (CXR), sputum smear and culture. Despite this long experience, there is overwhelming evidence that TB diagnosis is prone to significant error (Linell & Ostberg, 1966). Misdiagnosis occurs both if TB is missed and if TB is over-diagnosed. This is partly supported by the presented findings in our study where despite that more than half of the study subjects having presented to formal health care prior to their death, none was neither suspected nor diagnosed to have TB as required. A recent South African study found 21% of adults dying in hospital with a pre-mortem diagnosis of TB had no TB at autopsy (Martinson *et al*., 2007), while a study conducted in Italy, 36% of deceased AIDS patients with clinical diagnoses of TB had no evidence of TB at autopsy (Monforte *et al*., 1996). On the other hand, and of more concern to public health, are studies similar to ours conducted in the USA that suggest 5% of notified TB cases are diagnosed only after death (Rieder *et al*., 1991; DeRiemer *et al*., 1999), plus several large autopsy studies showing that TB is missed in life in 18-54% of cases with pathological evidence of active TB (Sarode et al., 1993; Rowińska-Zakrzewska *et al.,* 1995; Murray *et al*., 2007). Our findings show that many of the assessed patients presented with symptoms that could have prompted clinicians to consider a thorough screening for TB. Other indications of the possibility to diagnose TB existed in most of the study patients, as about one third of all the study cases were admitted in the hospital and about 46% received some diagnosis before their death. Clinicians therefore had opportunity to initiate investigations and treatment, and in many cases to monitor the response to treatment. Furthermore, we found that at least 44% of the cases made contact with medical services before death.

Although our study did not aim at assessing the operational implication of undiagnosed TB before death, one can easily think of the effects of other patients who are admitted in hospital with those with undiagnosed TB. This can also be an important source of the infection for the healthcare workers. Missing the diagnosis of TB can have major consequences, both for the patient and the public at large. In a review on the biosafety considerations for autopsies, Nolte *et al*. (2002) found that the occupational rate of TB amongst pathologists involved in the performance of autopsies was 10% compared to 1% in clinicians and 4% in pulmonary and TB specialists. Diagnosis at autopsy reveals a substantial health risk to hospital staff contacts in addition to contacts in the community before death. As the current study was conducted in a major referral hospital in the country, it is not appropriate to attribute the failure to diagnose the disease with the lack of experience of medical professionals despite of suspicious symptomatology.

Our findings highlight a number of important operational and programmatic issues. There are some un-answered questions that may need further systematic studies. The findings that AFB was much more localized in the right lower lobe of the lungs and in both the paratracheal and hilar lymphnodes poses a question of whether this plays any role in failure to diagnose TB. While there were more males diagnosed to have TB than females, the role of age and sex profile reported in this study was not different from the general trends in notification of TB in the country (MOH&SW, 2010).

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The findings emphasize the importance of reporting undiagnosed TB in order to improve intervention strategies through adequate clinical, laboratory and x-ray investigations. Our results have also shown that TB can be missed if it is not considered as a possibility. The failure to diagnose TB prior to the patient's death might be contributing to the increase in TB infections in the country. The findings are expected to foster an increased awareness of the continuing presence of TB in the community.

Our study had some limitations. We did not have culture and sensitivity testing of the samples for mycobacteria. While multiple causes of death may act simultaneously, the cause of death could not be determined accurately especially for cases whose death occurred outside the study hospitals. A serious factor to the low total number of cases in our study was the refusal by family members to consent for post mortem following a relative's death.

The selected autopsies done at the National Hospital revealed a high prevalence of undiagnosed TB. This may have contributed to unnecessary deaths among the study cases because of failure to timely diagnose and treat. The findings appeal for increased awareness and to inclusion of postmortem data in the annual TB statistics precise reporting of the magnitude of the TB burden in the country.

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