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Clinical and radiological features of pulmonary disease due to culture-positive *M. tuberculosis* or nontuberculous mycobacteria in South African gold miners

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Distinguishing whether pulmonary mycobacterial disease is due to* Mycobacterium tuberculosis *or nontuberculous mycobacteria (NTM) has important clinical and public health implications. There are limited data comparing these groups of patients, particularly from developing countries in the era of HIV infection. South African mineworkers have high rates of tuberculosis (TB), NTM disease and HIV infection. The study took place in a hospital serving four gold mines. All men with a positive sputum mycobacterial culture in 1995 were enrolled. Patients were interviewed, sputum and blood samples obtained and a chest radiograph taken. We compared clinical, laboratory and radiological features in those with TB with those with NTM disease (mainly* Mycobacterium kansasii*). Treatment outcomes are reported for those with pulmonary disease due to* M. kansasii*. The 425 patients with TB and 51 with NTM disease showed no significant difference in HIV status. Of patients with a positive smear, 91.3% (314/344) cultured* M. tuberculosis*. Patients with TB weighed less (p=0.03) and had lower haemoglobin levels (p<0.001). Those with NTM were less likely to have extensive radiographic changes (OR 0.27) than those with TB. Those with NTM were more likely to have silicosis (OR 9.7). Fourteen of the 36 patients with* M. kansasii *pulmonary disease had a positive culture at six months and a further 11 had a positive culture in the follow-up period. Patients with TB had features of more aggressive disease. The current practice of treating smear-positive patients as TB seems reasonable. Treatment failure and relapse were common in those with disease due to M. Kansasii.

Introduction

Pulmonary mycobacterial disease may be due to *Mycobacterium tuberculosis* or nontuberculous mycobacteria (NTM). Differentiating the causative organism has important clinical and public health implications. Infection due to NTM is usually acquired from environmental sources[1] and public health tuberculosis (TB) control measures, such as contact tracing, would thus not be indicated in patients with NTM disease. The treatment regimen for patients with NTM disease differs from that for TB.[1-3] There are limited data comparing a variety of clinical (eg. weight) and laboratory (eg. haemoglobin levels, T-cell counts) findings in these groups of patients.

South African mineworkers have high rates of TB, NTM disease and HIV infection. In a study of risk factors for NTM disease compared to TB in miners, we showed that previous TB treatment, silicosis and longer duration of underground work were more strongly associated with NTM disease than TB.[4] In this paper, we aim to identify clinical, laboratory and radiological features that differentiate patients with disease due to NTM and *M. tuberculosis*. We also report outcome of treatment in those with disease due to *Mycobacterium kansasii*.

Materials and methods

The study was undertaken in a hospital that serves men working on four South African gold mines. A comprehensive TB control programme, including both active (chest radiographic screening and contact tracing) and passive case-finding, is in place. Men with symptoms suggestive of TB are referred from the primary healthcare facilities to the hospital where a diagnosis is made and treatment initiated. TB suspects routinely have three sputum smear examinations; a minimum of one specimen is cultured, and the organism is identified and tested for drug resistance. Treatment for TB comprises two months of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), followed by four months of isoniazid and rifampicin (2HRZE/4HR). Patients with multidrug resistance are treated according to their drug sensitivity pattern. Smear-positive patients are initially hospitalised, after which they report every weekday to the primary healthcare facilities, where directly observed therapy is practised. Smear-positive patients are presumed to have TB and are started on anti-TB therapy (HRZE). Culture results are available after approximately six weeks, at which stage therapy is individualised for NTM patients: patients who are smear-positive have their regimen changed to 2HRZE/4HRE; patients with a negative smear and single NTM culture, who are clinically well, are not treated but are followed up in the routine surveillance system; those who are

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clinically unwell have a second sputum specimen sent for microscopy and culture and are reviewed six weeks later. Patients who do not respond to this first-line treatment have repeat cultures and their regimen is altered according to the organism and drug susceptibility results.

All patients with at least one positive sputum mycobacterial culture in 1995 were prospectively enrolled in the study. Details of the study methods have been previously described.[5] Patients were interviewed, sputum and blood samples obtained and a chest radiograph taken. Weight loss was assessed by subtracting the weight on admission from the highest recorded weight since commencing employment (miners are usually weighed on return from annual leave). Anaemia was defined as a haemoglobin level of <12g/dl.

An attempt was made to obtain two specimens for mycobacterial culture from each patient, prior to commencing treatment, on different days, to reduce the possibility of laboratory contamination. Sputum smears, using fluorescent microscopy with auramine stain, were performed according to standard methods. Sputum specimens were inoculated into Bactec 12B vials after decontamination. Isolates of acid-fast bacilli were identified using DNA-RNA hybridisation (Gen-Probe AccuProbe, San Diego, California, USA) for *M. tuberculosis*, *M. kansasii* and *Mycobacterium avium* complex. Standard biochemical tests and morphological assessment on a Lowenstein-Jensen slope were used to identify all other species.[6] Pulmonary TB was diagnosed if at least one sputum culture grew *M. tuberculosis*. The diagnosis of pulmonary NTM disease was made in patients with at least two sputum cultures that were positive for the same nontuberculous mycobacterium.

Postero-anterior chest radiographs, taken at diagnosis, were read jointly by two readers blinded to the culture result, HIV status and clinical data. To assess extent of radiographic changes each lung was classified into upper, middle and lower zones. Severity was classified as minimal if there was slight to moderate involvement in one or both lungs, but the total extent of lung affected did not exceed one zone; moderate if multiple zones were affected but with intervening areas of normal lung; and extensive if multiple zones were affected with minimal normal lung present. Radiographs were considered to be typical of TB if there were predominantly upper zone infiltrates/fibrocavitation or miliary disease. A radiograph was considered atypical if changes, including cavitation, were present predominantly in the lower lung fields, if there was isolated hilar and/or mediastinal lymphadenopathy, if there was lobar consolidation or if there were no changes. Silicosis was recorded as present (International Labour Office (ILO) category 1/1 or higher), possible (ILO category 1/0 or 0/1) or absent (ILO category 0/0 or 0/-).[7]

T-cell analysis was determined by flow cytometry using SimulSet monoclonal antibodies and FACSort (Becton Dickinson, San Jose, California, USA). Relative levels of CD4+ and CD8+ lymphocytes expressed as percentages of total lymphocytes, which are less variable than absolute counts, were used.[8] A CD4 percentage of >28% corresponds to an absolute CD4 count of >500/uL, 14-28% corresponds to 200-499/uL and <14% to <200/uL.[9]

Treatment outcomes for subjects with TB have been discussed in detail previously.[5] For the purposes of this paper, outcomes in those subjects who had pulmonary disease due to *M. kansasii* are reported. Sputum was cultured six months after enrolment into the study and subjects were followed through the routine follow-up system until October 1998.

Ethics approval was obtained from the University of the Witwatersrand and the London School of Hygiene and Tropical Medicine.

Data were entered and analysed using Epi-Info 6.02 (WHO, Geneva and CDC, Atlanta) and STATA 5.1 (Stata corporation, Texas). Continuous variables were compared using the t-test. Categorical variables were analysed using the chi-squared test if binary or the chi-squared test for trend if ordinal. In addition to the crude odds ratios (ORs) obtained from the univariate analysis, a logistic regression analysis was undertaken, in which each clinical manifestation was adjusted for factors previously identified as being linked to the development of TB or NTM disease (previous TB treatment, silicosis, years working underground and alcohol consumption).[4] Age and HIV status were included in the model *a priori*.

Results

During 1995, 505 men had a sputum specimen that was positive on mycobacterial culture. Of these, 425 specimens grew *M. tuberculosis* alone and 51 had two or more positive NTM cultures (NTM disease). The remaining 29 patients were excluded from the analysis: sputum from seven patients grew both *M. tuberculosis* and an NTM on the same specimen (mixed infections) and in 22 patients there was a single positive NTM culture. In these mines, the period prevalence of pulmonary TB in 1995 was 1515 per 100 000 population (432/28 522) and that for NTM disease was 179 per 100 000 population (51/28 522).

The spectrum of NTM organisms cultured is shown in Table 1. *M. kansasii* was the predominant organism (67%). Forty-eight of 51 NTM patients had the same NTM organism on all cultures while in three patients one culture isolated a mixture of *M. kansasii* and MAI. Over half of the NTM patients had a history of TB treatment. Eighteen (35.3%) of the 51 patients with NTM disease were HIV-infected. The various NTM species were cultured in both HIV-positive and -negative patients, except *Mycobacterium abscessus* where both patients were HIV-negative.

The clinical and laboratory features of the NTM patients were compared with those with pulmonary TB (Table 2). The age distributions were similar. The mean weights on admission were 60.5 kg and 58.3 kg in those with NTM and TB, respectively (p=0.03). Of patients with a positive smear, 91.3% (314/344) cultured *M. tuberculosis*. The mean haemoglobin was 13.6 g/dl in patients with NTM and 12.7 g/dl in those with TB (p<0.001). In patients with NTM, 52.9% had previously taken anti-TB treatment compared to 25.4% of TB patients (p<0.001).

Comparison of radiological features in patients with NTM and TB is shown in Table 3. Examples of the spectrum of chest radiographic changes in patients with NTM disease and TB are shown in Figures 1-3. One patient with NTM (2.0%) and eight with TB(1.9%) had no changes on chest radiograph. None of these patients had previous TB treatment, and all but two (both TB patients) were HIV-

Table 1: **NTM organism, history of TB treatment, HIV status and degree of immunosuppression in 51 gold miners**

	Total n	(%)	Previous TB n	HIV- positive n	CD<14%* n
M. kansasii	34	(66.7)	15	11	4
MAI	9	(17.6)	7	4	4
M. abscessus	2	(3.9)	2	0	-
M. scrofulaceum	3	(5.9)	1	2	0
Mixed *MK/MAI*	3	5.9	2	1	1
Total	51		27	18	9

* In HIV- positive subjects. CD4 of <14% corresponds to CD4 count of <200 cells/L. CD4 not available on one patient with *M. kansasii* infection

Table 2: **Comparison of clinical and laboratory features in patients with NTM disease and pulmonary TB**

	NTM n=51 n	%	TB n=425 n	%	Crude OR	95% CI	P value	Adjusted* OR	95% CI	P value
Clinical										
Admission weight n=473										
<55kg	11	21.6	117	27.7	1		0.02	1		0.02
55-64kg	23	45.1	235	55.7	1.0	0.49-2.2		1.00	0.44-2.25	
≥65kg	17	33.3	70	16.6	2.6	1.1-5.9		2.88	1.18-7.06	
Weight loss n=458										
Stable/ gained weight	4	8.2	38	9.3	1		0.1	1		0.06
1-4kg	26	53.1	161	39.4	1.5	0.50-4.7		1.27	0.40-4.04	
5-9kg	13	26.5	110	26.9	1.1	0.34-3.7		0.85	0.24-2.98	
≥10kg	6	12.2	100	24.4	0.57	0.15-2.2		0.46	0.11-1.84	
Laboratory										
Sputum smear n=476										
Negative	21	41.2	111	26.1	1			1		
Positive	30	58.8	314	73.9	0.51	0.28-0.92	0.03	0.39	0.20-0.76	0.006
HIV n=475										
Negative	33	64.7	217	51.2	1			1		
Positive	18	35.3	207	48.8	0.57	0.31-1.1	0.07	0.67	0.35-1.29	0.2#
CD4% (in HIV+) n=215										
>28%	9	52.9	94	47.5	1		0.4	1		0.4
14-28%	7	41.2	75	37.9	0.97	0.35-2.8		0.77	0.24-2.45	
<14%	1	5.9	29	14.6	0.36	0.04-3.0		0.40	0.05-3.51	
Anaemia n=458										
No	41	85.4	257	62.7	1			1		
Yes	7	14.6	153	37.3	0.29	0.13-0.66	0.003	0.30	0.13-0.72	0.007

* Adjusted for risk factors: age, HIV status, previous TB treatment, silicosis, years working underground and alcohol consumption
# Adjusted for age, previous TB treatment, silicosis, years working underground and alcohol consumption

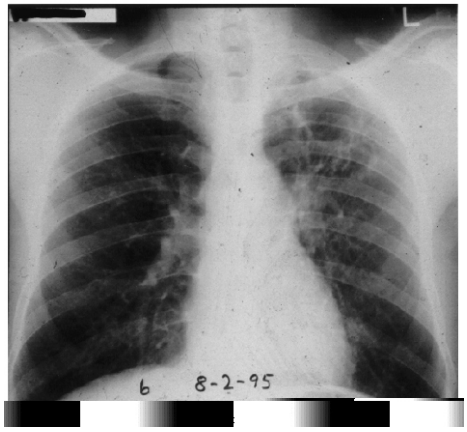

Figure 1: **Chest radiograph of a patient with numerous positive cultures for *M. kansasii*, showing features typical of TB**

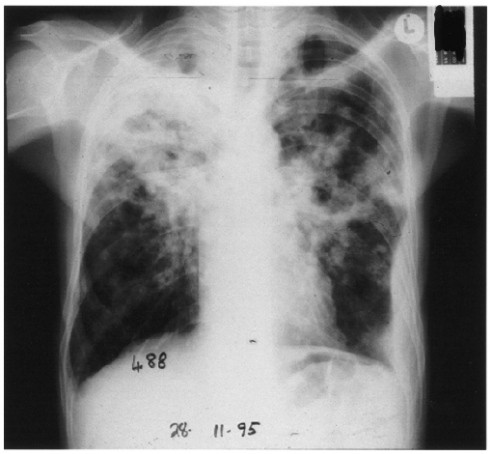

Figure 2: **Extensive bilateral cavitary pulmonary TB**

Table 3: **Comparison of chest radiographic findings in patients with NTM disease and pulmonary TB**

	NTM n=51(10.8%)		TB n=422(89.2%)		Crude OR	95% CI	P value	Adjusted* OR	95% CI	P value
	n	%	n	%						
Extent of changes										
Nil / Minimal change	17	33.3	96	22.8	1		0.3	1		0.007
Moderate change	20	39.2	207	49.1	0.55	0.27-1.1		0.27	0.12-0.60	
Extensive change	14	27.5	119	28.2	0.66	0.31-1.4		0.27	0.11-0.66	
Pattern										
Typical	41	80.4	356	84.4	1			1		
Atypical	10	19.6	66	15.6	1.32	0.63-2.8	0.5	2.09	0.87-5.03	0.1
Cavitation										
No	19	37.3	232	55.0	1			1		
Yes	32	62.7	190	45.0	2.06	1.1-3.8	0.02	1.29	0.62-2.54	0.5
Upper zone involvement										
No	5	9.8	4.0	9.5	1			1		
Yes	46	90.2	382	90.5	0.96	0.36-2.3	0.9	0.56	0.19-1.7	0.3
Silicosis										
No	37	72.5	357	1				1		
Possible	11	21.3	63	14.9	1.69	0.81-3.5	0.2	1.36	0.62-2.98	0.8
Yes	3	5.9	3	0.7	9.65	1.8-51	0.001	12.6	2.22-71.3	0.004
Unilateral										
No	36	73.5	303	73.5	1			1		
Yes	13	26.5	109	26.05	1.00	0.51-2.0	1.0	1.55	0.72-3.31	0.3
Side										
Left	4	30.8	45	41.3	1			1		
Right	9	69.2	64	58.7	1.58	0.46-5.5	0.5	0.77	0.17-3.62	0.7
Pleural involvement										
No	39	76.5	322	76.3	1			1		
Yes	12	23.5	100	23.7	1.00	0.50-2.0	1.0	0.70	0.33-1.49	0.3
Fibrosis										
No	36	70.6	311	73.7	1			1		
Yes	15	29.4	111	26.3	1.18	0.62-22	0.6	0.64	0.31-1.35	0.2

* Adjusted for risk factors: age, HIV status, previous TB treatment, silicosis, years working underground and alcohol consumption

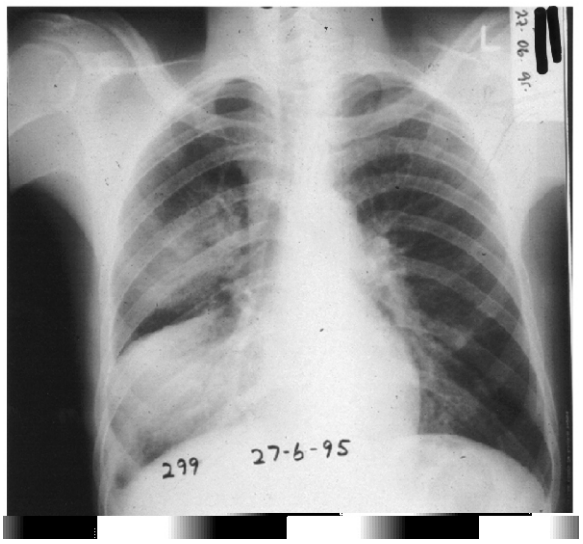

Figure 3: **Atypical radiographic presentation of pulmonary TB in an immunocompromised patient**

positive. Patients with NTM and TB had similar radiological findings in terms of features typical of TB, upper zone involvement, unilateral disease, left or right-sided changes, pleural involvement and fibrosis. Patients with NTM were more likely to have radiographic features of silicosis. After adjustment for age, HIV status, previous TB treatment, silicosis, years working underground and alcohol consumption, those with NTM were less likely than TB patients to have moderate to extensive radiological changes. The association with cavitation seen on univariate analysis was confounded by previous TB treatment.

Of 36 cases with *M. kansasii* pulmonary disease, 14 had a positive culture for *M. kansasii* six months after study entry in 1995. A further 11 were known to have had a positive culture in the follow-up period. Thus, 25 of 36 (69%) cases were known to have failed treatment. Five men later developed TB. One HIV-positive man died 4½ months after diagnosis and a further four men (two HIV-positive) died during follow-up.

Discussion

In developed countries, with the spread of the HIV epidemic, disease attributable to NTM has increased both in actual numbers and as a proportion of all mycobacterioses.[3] The major burden of the HIV epidemic, however, is in developing countries, particularly in sub-Saharan Africa, and this has resulted in an increased incidence of both pulmonary and extrapulmonary TB.[10] Disease due to NTM is potentially a cause of morbidity and mortality in African patients with advanced immunosuppression.

The rates of TB and pulmonary NTM disease in this population of gold miners are extremely high. In a previous prospective cohort study in a South African gold mining workforce, the incidence of NTM disease (meeting the ATS case-definitions of definite disease and excluding chronic cases) was 47.6 per 100 000 employee years.[11] The prevalence of NTM disease in the mines in 1995 in this study (179 per 100 000 population) is higher, but case definitions

differed and all cases (new and previous treatment) were included. The spectrum of NTM organisms, and the predominance of *M. kansasii* infection, are similar in the two settings.[12] Similarly, periodic surveys in the 1980s, prior to the HIV epidemic, from one mine hospital showed that the commonest NTM organism was *M. kansasii* (79%), with *M. scrofulaceum*, *M. intracellulare, M. fortuitum* and *M. terrae* were also isolated.[13]

There is geographical variation in the prevalence of NTM disease and the mycobacterial species responsible for infection.[1] It is estimated that in Great Britain, between 1952 and 1978, there were approximately 200 cases of infection with atypical mycobacteria per year, an incidence of 0.4 per 100 000 population, most often due to *M. kansasii*.[14] In the United States in the early 1980s, prior to the HIV epidemic, the prevalence of NTM pulmonary disease was estimated to be 1.8 per 100 000 population.[15] In Japan, where pneumoconiosis is the most prevalent occupational disease, NTM incidence rates have been estimated at 1.7 cases per 100 000 population per year, with 90% of disease due to MAI.[16] Incidence is high in some areas of the Czech Republic (12.4 per 100 000), which may be linked to contaminated water.[17] In developing countries, national rates of NTM disease are usually unavailable, as cultures on suspected TB patients are often not routinely performed. Reported rates of TB therefore probably include a proportion of NTM patients. In a 1989-1990 cross-sectional study in Nigeria, of the 188 patients with a positive sputum mycobacterial culture, 73% cultured *M. tuberculosis*, with *M. kansasii* being the most common NTM.[18] In Guinea-Bissau (1992-1993), 17 (8%) of positive sputum cultures from 206 patients isolated MAC.[19]

In countries with a high incidence of TB, the proportion of mycobacterial cultures that isolate NTM is generally low. In 1977, of 4 923 positive mycobacterial cultures at the South African Institute for Medical Research, 2.1% cultured NTM strains.[20] In contrast, in the United States, the rate of disease attributable to *M. avium* is approximately 13% that of pulmonary TB.[3] In our study, of all cases with mycobacterial disease, 11% had disease due to an NTM. Similar proportions were found in other mines in the 1980s (8-12% in patients with a first episode of disease and 21% in those with relapse)[13] and more recently (11.5% and 19.5%, respectively).[12]

We demonstrated the broad spectrum and overlap of clinical features of pulmonary disease due to NTM and *M. tuberculosis*. Even though we studied a broader range of clinical, laboratory and radiological features than in previous studies, we did not find any pathognomonic features that indicated whether the patient had TB or NTM disease. However, those with TB were more likely to weigh less, have lower haemoglobin levels and have more extensive radiographic changes, suggesting more aggressive disease. Furthermore, by adjusting for known risk factors, it was possible to estimate whether the difference in clinical features was a feature of the underlying disease process or a manifestation of a particular risk factor. For example, patients with NTM disease weighed more than those with TB, independent of HIV status; and, after controlling for risk factors including previous TB treatment, HIV status and silicosis (all of which may influence radiographic features), those with TB had more extensive chest radiographic changes.

The wide spectrum of clinical disease due to NTM ranges from infected bullae that heal spontaneously to progressive destructive lung disease.[3] Signs and symptoms are variable and are often non-specific, including chronic productive cough, fatigue, fever, haemoptysis, dyspnoea and weight loss.[1] Although the chest radiographic features of NTM pulmonary disease often mimic those of TB, other radiological appearances have been described.[21-24] Studies comparing these patients report that haemoptysis[25] and unilateral right-sided radiographic changes with lower lobe involvement with smaller cavities [21,26] were more common in those with NTM disease. In a retrospective case series, comparison of radiological features in patients with disease due to *M. kansasii* or *M. tuberculosis* found that those with the NTM were more likely to have radiographs showing focal scarring, silicosis and old cavitation.[27] As in our study, they were less likely to have extensive radiological changes. Our findings concur with previous reports[21-24,26] that the chest radiograph is unhelpful in differentiating between TB and NTM disease. Patients with pulmonary TB may have a normal appearance on chest radiograph[28] and the presence of chest radiographic changes as a necessary criterion for NTM disease has been challenged, particularly in patients with AIDS.[22,23]

A previous prospective study in a gold mine found that miners develop *M. kansasii* disease at an early stage of HIV infection and that disease prevalence is independent of HIV status.[29] Similarly, we found that those with NTM were less often HIV-positive than those with TB and that few (4/34) of our HIV-positive patients with disease due to *M. kansasii* were severely immunocompromised.

Using a short-course regimen, treatment outcomes were poor for those with disease due to *M. kansasii*, with over two-thirds of patients having positive cultures at six months and in the subsequent follow-up period. Some of these men also had *M. tuberculosis* during follow-up with important clinical implications, viz. there should be a high index of suspicion of TB even if a previous culture grew an NTM. Comparison of treatment outcomes between studies is difficult, since they have different diagnostic criteria, patient characteristics (including proportion with HIV infection), treatment regimens and length of follow-up. Different studies have reported cure rates of 46% to 83%,[11,27] and relapse rates of 8% to 10%.[17,30]

This study highlights the diagnostic challenge of pulmonary mycobacterial disease in the era of the HIV pandemic. The study design and setting have a number of strengths: a large number of cases were diagnosed in a one year period; all patients, regardless of severity of disease, present to the same medical facility; the well-resourced medical services with availability of multiple sputum cultures make diagnosis more likely than in other developing country settings, and there were few missing data. Furthermore, there was systematic and prospective data collection and the same diagnostic work-up for those with possible TB or NTM disease. Although the minerkers were all silica-exposed men, the results presented adjust for risk factors, such as age, HIV status and silicosis and may be applicable to settings other than the mine environment.

With the large burden of mycobacterial disease seen in developing countries, a practical approach to the diagnosis

and management of patients is needed. Clearly the approach will be determined by the availability of resources and facilities. An important indicator was that those with NTM disease were less likely to be smear-positive than patients with TB. In this setting, with approximately 90% of all mycobacterial cultures culturing *M. tuberculosis*, the predictive value of a positive smear being TB was 91%. Thus, treating all smear-positive patients as TB, in settings with high rates of TB and where culture facilities are unavailable, seems appropriate. Comparison of patients with NTM disease and TB reinforces World Health Organization guidelines, with emphasis on smear-positive cases and treating all cases as TB in developing countries.

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