Pulmonary non-tuberculous mycobacterial disease

M. L. PLIT, M. WOOLF, G. B. MILLER

Summary
We confirmed 3 and identified 7 possible cases of pulmonary non-tuberculous mycobacterial disease. The clinical and radiological features were indistinguishable from those of tuberculosis, although a few thin-walled cavities may have been more suggestive of non-tuberculous disease. Previously described predisposing factors were identified in our patients and included previous fibrocavitating disease, chronic airflow obstruction and bronchiectasis. However, 5 patients had no pre-existing lung disease. The difficulties in treating these patients are discussed and in view of the chronic indolent course, prolonged aggressive polypharmacy is usually not indicated. It is recommended that at least two consecutive sputum specimens be sent for culture and drug resistance testing whenever the disease is suspected. This will help differentiate colonisation from infection and rationalise management.

Until the end of World War II acid-fast bacilli with culture characteristics different from those of Mycobacterium tuberculosis were regarded as unimportant. However, since then it has been realised that these multiresistant mycobacteria constituted the only organisms to be repeatedly isolated from certain patients, some of whom had pulmonary disease indistinguishable from tuberculosis. In the last 20 years, as the incidence of tuberculosis in the USA has declined, so that of non-tuberculous mycobacterial disease (NTMD) has apparently increased.

Stottmeier et al. pioneered the epidemiology of NTMD in South Africa from 1964. A high incidence of M. avium complex has been cultured from pigs with lymphadenitis, the source of infection most likely arising from plant feed. Human skin testing has revealed that about 10% of rural children react exclusively to avian purified protein derivative, while sputum studies have shown that up to 61% of apparently healthy black adults in certain villages harbour non-tuberculous mycobacteria. The presence of infiltration without cavitation which cannot be explained by other disease, and no decrease in the number of colonies within 1 month, or no sputum conversion to negative within 2·4 months after bronchial hygiene; or (iii) isolation of the mycobacteria from biopsy tissue together with histopathological changes compatible with the disease.

Patients and methods
We attempted to identify cases of NTMD referred to Rietfontein Hospital within the past 5 years for treatment of pulmonary tuberculosis. Despite incomplete investigations and record-keeping, we managed to confirm 3 cases and identified a further 7 possible cases according to the diagnostic criteria cited above. M. tuberculosis had not been cultured from any of these patients.

Case 1
The patient was a 45-year-old black man who lost his job as a labourer in an engineering firm when pulmonary tuberculosis was diagnosed in March 1983. Sputum culture at that stage revealed multiresistant mycobacteria but the species was not identified. Despite 12 months' treatment for tuberculosis, which included isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin, his sputum remained positive for acid-fast bacilli and he was then referred to Rietfontein Hospital for further treatment.
On admission he complained of persistent dry cough and weight loss. Clinical examination revealed a thin man with finger-clubbing but no cyanosis. The findings were otherwise normal.
A chest radiograph showed two large, thin-walled cavities and an infiltrate in the right upper lobe. A Heaf test gave a 2+ reaction. Initial sputum culture yielded 20-29 colonies of *M. intracellulare* resistant to isoniazid, pyrazinamide, ethionamide and ethambutol but sensitive to rifampicin and streptomycin.

**Case 2**

The patient was a 53-year-old white man who lost his job as a building construction worker in 1981 when pulmonary tuberculosis was diagnosed after acid-fast bacilli had been seen on sputum microscopy. Despite treatment for 1 year his sputum remained persistently positive and he was then referred to Rietfontein Hospital for possible lobectomy.

On admission he complained of a dry cough and a 6 kg weight loss over the previous 4 months. The rest of the clinical findings were normal.

A chest radiograph showed a large, thin-walled cavity in the right upper lobe. A Heaf test showed a 2+ reaction. Five hundred colonies of *M. intracellulare* resistant to all standard drugs were cultured from the sputum. His original sputum culture a year previously also reported the presence of *M. intracellulare* with the same drug resistance pattern.

**Case 3**

The patient was a 74-year-old retired boilermaker who was originally investigated in 1980 for fibrocavitating disease of the right upper lobe. *M. intracellulare* resistant to isoniazid, rifampicin, pyrazinamide, ethambutol and thiactazone and partially resistant to streptomycin and ethionamide was cultured. He absconded from the hospital after 5 days and was lost to follow-up.

He was readmitted to hospital in December 1982 complaining of chronic weight loss, productive cough, haemoptysis and grade 3 dyspnoea. He had smoked for 40 years. Clinical examination revealed wasting. His chest was hyperinflated with bilaterally decreased breath sounds and coarse crackles over the right upper lobe. The rest of the findings were normal.

A chest radiograph showed hyperinfiltrated lungs with enlarged pulmonary arteries and right ventricular hypertrophy. The right upper lobe showed dense fibrocavitating disease with volume loss. The left upper lobe showed an infiltrate with multiple small, thin-walled cavities. A Heaf test showed a 2+ reaction, and sputum culture revealed *M. intracellulare* with the same resistance pattern as had been noted in 1980.

The clinical features in a further 7 possible cases of NTMD are listed in Table I. There were 3 men and 4 women, with mean age 50 years (34-75 years). Three were black, 3 white, and 1 was coloured.

**TABLE I. CLINICAL FEATURES IN 7 POSSIBLE CASES OF NTMD**

<table>
<thead>
<tr>
<th>CHEST RADIOGRAPH</th>
<th>Non-cavitating infiltrates and fibrosis</th>
<th>Right basal infiltrate and right pleural fibrosis</th>
<th>Previous lung disease</th>
<th>Sputum culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper lobe cavities</td>
<td>4</td>
<td>2</td>
<td>Previous treatment for tuberculosis</td>
<td><em>M. intracellulare</em></td>
</tr>
<tr>
<td>Previous lung disease</td>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td><em>M. kansasii</em></td>
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<tr>
<td>Nil</td>
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</tbody>
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**Discussion**

The 3 confirmed cases comply with the diagnostic criteria of the American Thoracic Society and Ahn *et al.*

The confirmation of NTMD in a black male is of particular interest in that NTMD has been reported to occur less frequently in this race group. Although the presence of cavitation and the failure to culture *M. tuberculosis* in the possible cases might suggest true NTMD, follow-up sputum cultures in these patients were unfortunately not done and therefore the diagnosis could not be confirmed.

The clinical features of all our cases are indistinguishable from those of tuberculosis except that most of our patients demonstrated a relatively stable course. Although there are no reliable radiological differences between NTMD and tuberculosis, it has been suggested that a single large, thin-walled cavity with little surrounding infiltrate should create a high index of suspicion for NTMD disease. The characteristics of the cavities in patients 1 and 2 in our series would fit this description. There may, however, be a bias towards reporting upper lobe disease and cavitation in studies that have depended upon sputum cultures to establish the diagnosis.

In the study of Albelda *et al.* it was noted that when the diagnosis was made histologically in a subgroup of patients, half the patients had different radiological features including patchy, nodular infiltrates without upper lobe predominance. Some patients also demonstrated small, thin-walled cavities resembling bronchiectasis as was seen in our third case.

**Pathogenesis**

Non-tuberculous mycobacteria are only weakly pathogenic for animals and humans. There is no evidence of person-to-person spread and the ubiquity of the organism in the environment points to an environmental source of human infection. Patients with pre-existing fibrocavitating lung disease such as tuberculosis, pneumoconiosis, bullous emphysema, bronchiectasis and oesophageal disease with chronic aspiration are commonly colonised by these organisms. However, these patients are also predisposed to invasive disease. In 1 of our confirmed cases of NTMD the patient had associated chronic airflow obstruction, but in the other 2 cases there was no evidence of predisposing lung disease. In 4 of the 7 possible cases previous treatment for tuberculosis had been given, although the original diagnosis of tuberculosis could not be confirmed, and 1 showed evidence of bronchiectasis. Immunosuppressed patients with malignant disease and the acquired immunodeficiency syndrome are predisposed to both tuberculosis and NTMD disease.

**Management and prognosis**

The management of NTMD cannot be based on treatment principles applicable to tuberculosis, because of widely differing patterns of drug resistance and disease progression. Furthermore, there are no controlled studies of treatment for NTMD. Many patients with NTMD have a chronic, indolent course and aggressive polypharmacy may be worse than the disease itself because of prolonged treatment and a high incidence of drug side-effects. Rational therapy can therefore be undertaken only when the mycobacterial species and the drug resistance pattern have been identified. The potential benefits of treatment must then be weighed against the clinical state of the patient and evidence of disease progression. *M. kansasi* has a drug sensitivity pattern similar to that of tuberculosis and treatment response is excellent with few relapses when isoniazid, ethambutol and rifampicin are included in the drug regimen. The optimum duration of treatment...
is unknown but it has been suggested that multiple drug regimens be continued for 18–24 months, or for at least 6 months after culture has become negative.1,2,12,19,20

The treatment of *M. intracellulare* is more difficult. Despite multiple drug resistance patterns, resistance is often not total in that partial effectiveness of one drug may render the action of a second or third drug more effective.2 For example, in our first case culture still showed sensitivity to rifampicin and streptomycin and in our second case organisms were partially sensitive to streptomycin and ethionamide. Initial treatment with up to five drugs is suggested, including isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol.2,12,12,21,22 Other possible alternatives include ethionamide, kanamycin, capreomycin, erythromycin and the newer-generation cephalosporins.23 The development of a new rifamycin derivative, ansamycin (Rifabutin), is particularly promising and may herald a new generation of more effective drugs against NTMD.24 One study reported a sputum conversion rate to negative in only 30–50% of patients even when rifampicin was included in the treatment regimen.9 There is frequent relapse and resistance to every drug is common, as was seen in our first case.12

If the disease is localized, early surgery is recommended.1,8,12,21 However, reports of selected patient populations indicate that the results of surgery with postoperative drug therapy are disappointing in that only about 60% of patients or less have lasting remissions.19

As most cases run an indolent course, the indications for ongoing treatment should be periodically reassessed. If sputum converts to negative and the patient is relatively asymptomatic without any disease progression, treatment should be continued for at least 1 year further.2 If spura are persistently positive but the patient remains stable, the drugs should be discontinued, and if withdrawal leads to recurrent symptoms, treatment should probably be restarted.2 These patients have often been on treatment for months anyway before the culture result becomes available. For example, it took up to 7 months before we received the final culture reports on some of our patients.

Our first patient had received multiple drug therapy for 21 months with partial radiological improvement. However, sputum cultures remained persistently positive and it was decided to discontinue treatment and periodically reassess for clinical relapse.

Our second patient had already been treated for 1 year and in view of spontaneous symptomatic improvement when treatment was stopped, it was decided not to recommence specific therapy. Right upper lobe necosity might have been a viable treatment alternative.

Our third patient did not receive specific therapy since his symptoms were mainly related to chronic airflow obstruction and he was unlikely to comply with a treatment programme anyway.

It is worth emphasising that the disappointing results of treatment reported in the literature may be biased towards a selected referral population with more advanced disease.2,5,22 Neither age, sex nor race appeared to influence the prognosis.6 A poor prognosis has been associated with other serious diseases9 and the fact that in one series 84% of patients ultimately died from causes other than NTMD, should caution against aggressive, indefinite treatment.8

**Conclusion**

Although the prevalence of NTMD in the developing world appears to be low,3 the potential harm that misdiagnosis may do to the individual patient should not be underestimated. These patients may be labelled as 'chronic tuberculosis' and subjected to prolonged treatment with multiple potentially toxic and ineffective drugs, while the true disease progresses. For example, 2 of our confirmed cases of NTMD were treated for almost 2 years before the correct diagnosis was made. During this time they remained unemployed and were falla­ciously regarded as potentially infectious, necessitating social isolation. We recommend that whenever tuberculosis is sus­pected and facilities permit, the initial sputum should be sent for mycobacterial culture. Sputum culture should be repeated with drug resistance testing whenever the sputum remains persistently positive on microscopy despite multiple drug therapy, or if NTMD is initially reported. This approach will differentiate tuberculosis from NTMD and, if NTMD is identified, help distinguish colonisation from disease, thus promoting rational treatment decisions.

**REFERENCES**


