

NONTUBERCULOUS MYCOBACTERIAL DISEASE OF THE LUNGS IN SINGAPORE

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ABSTRACT

Information on lung disease due to nontuberculous mycobacteria (NTM) is lacking in Singapore. A review of the records at the Central Tuberculosis Laboratory up to the end of 1988 showed that 23 patients seen between 1976 to 1988 inclusive had cultures which were repeatedly positive for NTM. Of the 23 cases analyzed, 15 were found to have lung disease which could be attributed to NTM. There were 9 males and 6 females with a male to female ratio of 1.5:1. The patients were either middle aged or elderly. The 2 main infective agents were *M avium-intracellulare* and *M kansasii*. Ten (67%) patients had moderately advanced and 5 (33%) had far advanced disease. Concurrent disease of the lung was present in 10 patients (67%). Seven (47%) patients had bronchiectasis, 1 (7%) had both bronchiectasis and chronic obstructive pulmonary disease (COPD) and 2 (13%) had COPD. A past history of pulmonary tuberculosis was present in 10 patients (67%). Lung disease due to NTM is uncommon in Singapore. Treatment failure was attributed to poor compliance, a possibility which could not be excluded in those patients who had adverse reactions.

Keywords: Nontuberculous mycobacteria, lung disease, Singapore.

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INTRODUCTION

The genus mycobacteria include about 40 species of which *M tuberculosis* complex (*M tuberculosis*, *M bovis*, *M africanum* and *M microti*) and *M leprae* are the major pathogens. The other organisms are referred to as nontuberculous mycobacteria (NTM) or environmental mycobacteria as they are found mainly in soil and water. Unlike tuberculosis which is a disease of major public health importance, little attention was paid to diseases caused by NTM. The epidemic of AIDS worldwide has rekindled interest on infections caused by NTM and other opportunistic organisms. Locally, no information is available on the clinical and epidemiological aspects of nontuberculous mycobacterial infection. This paper reports on a retrospective study of 15 patients with nontuberculous mycobacterial disease of the lungs seen over a 13-year period at the Tan Tock Seng Hospital (TTSH) and the Department of Tuberculosis Control.

PATIENTS AND METHOD

The bacteriology records at the Central Tuberculosis Laboratory were reviewed up to the end of 1988. The Central Tuberculosis Laboratory is the main mycobacteriology laboratory in Singapore which provides a service for the isolation, identification and susceptibility testing of mycobacteria. This

service is used by all the hospitals and outpatient clinics in the public and private sector. Patients with persistent niacin negative cultures were identified and their clinical records were retrieved and analyzed. Patients are considered to have lung disease caused by nontuberculous mycobacteria if they fulfilled the following criteria:

- (1) Chest X-ray evidence of recent disease compatible with a granulomatous disease.
- (2) Sputum specimens repeatedly positive for niacin negative mycobacteria over a period of >3 months.
- (3) Same species of mycobacteria isolated from at least 3 consecutive sputum specimens with cultures showing moderate or numerous colonies.

Sputum was cultured on Lowenstein Jensen Medium and incubated at 37°C for 4-8 weeks. Species identification was based on rate of growth, colony morphology, pigmentation, selective media, biochemical and enzyme tests⁽¹⁾. In vitro drug susceptibility tests were based on the absolute concentration method⁽²⁾. Assessment of the selected cases was based on the clinical and radiological findings, sputum bacteriology and response to chemotherapy. The extent of disease was graded into 3 categories: minimal, moderate or far advanced⁽³⁾.

Treatment outcome was classified as (1) improved - when there is clinical and radiological improvement with or without conversion of sputum; (2) stable - when there is no clinical and radiological change following chemotherapy regardless of sputum results; (3) deteriorated - when there is clinical and radiological worsening in spite of chemotherapy.

RESULTS

A total of 23 cases were found to have persistent niacin negative mycobacteria between 1976 to 1988. Fifteen cases were seen at TTSH, 7 cases were seen at the Department of Tuberculosis Control and one case was seen at another hospital. The infective agents identified were *M avium intracellulare scrofulaceum* (MAIS) complex in 10 cases, *M kansasii* in 6 cases, *M fortuitum* in 4 cases, *M chelonae* in 2 cases and *M terrae* in one case. Of the 23 cases, 8 were excluded from analysis because there was no radiological evidence of recent lung disease leaving only 15 cases for analysis.

Causative agents

These are shown in Table I. The main infective agents were as follows: MAIS complex—10 cases (includes 9 cases of *M*

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Table I - Causative Agents

Micro-organism	Cases No. (%)
MAIS Complex	10 (66)
M kansasii	4 (27)
M chelonaei	1 (7)

avium intracellulare infection and one case of M scrofulaceum); M kansasii - 4 cases, and M chelonaei - 1 case.

Patient characteristics

There were 9 males and 6 females with an age range of 42 to 88 years and a mean age of 66.4 years. All the patients were Chinese. The mean ages of patients in the M kansasii group and M avium intracellulare complex group were 74.5 years and 63.2 years respectively.

Table II - Pre-existing Lung Disease

Disease	Cases No. (%)
History of PTB	10 (67)
Bronchiectasis	7 (47)
COPD & Bronchiectasis	1 (7)
COPD	2 (13)

Pre-existing Disease - Table II

Pre-existing disease was present in 10 patients (67%). Seven (47%) had underlying bronchiectasis, 1 (7%) had both bronchiectasis and chronic obstructive pulmonary disease (COPD), 2 (13%) had COPD. Ten had a past history of pulmonary tuberculosis (67%). A past history of pulmonary tuberculosis or a concurrent disease was present in 87% of cases.

Table III - Radiologic Extent of Disease & Cavitation

Extent	Cases No. (%)
Moderately advanced	10 (67)
Far advanced	5 (33)
Cavitation	8 (53)

Extent of Disease - Table III

Ten (67%) had moderately advanced and 5 (33%) had far advanced disease. Cavitation was present in 8 patients (53%). Pulmonary disease was unilateral in 7 (47%) patients and bilateral in 8 (53%) patients.

Drug Susceptibility Tests

Susceptibility tests were done against the following drugs: streptomycin, isoniazid, ethambutol, ethionamide and kanamycin. Susceptibility test to rifampicin was not available prior to 1985.

M kansasii (n = 4)

Of the 12 isolates tested, 100% showed resistance to isoniazid, 100% to streptomycin, 33% to ethambutol; 0% to ethionamide and 60% to kanamycin.

MAIS complex (n = 10)

Thirty isolates were tested and 100% showed resistance to isoniazid, 87% to streptomycin, 87% to ethambutol, 14% to ethionamide and 17% to kanamycin.

M chelonaei (n = 1)

Resistance was present to isoniazid, streptomycin, ethambutol, ethionamide and kanamycin in all 3 isolates tested.

Treatment and Outcome

M kansasii

M kansasii was the cause of disease in 4 patients (3 males, 1 female). All had moderately advanced disease. One patient, a vagrant was irregular with chemotherapy which was given for one year; another patient who had a rash and itchiness defaulted from treatment after 7 months of chemotherapy. The disease deteriorated in both patients. The third patient with moderately advanced disease and bronchiectasis was given treatment for 2 months and then discontinued because of her advanced age and absence of distressing symptoms. The disease remained stable during follow-up for 29 months. The fourth patient was a case of COPD with poor lung function. She improved with chemotherapy showing radiological clearing and sputum conversion. However, she died 5 months after starting chemotherapy from respiratory failure. Of the 4 patients, one improved, 2 deteriorated and one had stable disease in spite of receiving only 2 months of treatment.

The patients were treated with a combination of isoniazid, rifampicin, ethambutol. An additional drug such as streptomycin or kanamycin was given initially before species identification was known.

MAIS Complex

Disease due to MAIS complex was found in 10 patients (6 men, 4 women). Six had moderately advanced and 4 had far advanced disease, 6 had cavitation and 5 had bronchiectasis. Unilateral disease was present in 3 patients and bilateral disease in 7 patients.

The main drugs used in chemotherapy were isoniazid, rifampicin, ethambutol, kanamycin, ethionamide and pyrazinamide. Three patients were treated with isoniazid, rifampicin, ethambutol for 1½ to 2 years with ethionamide or kanamycin added to the regimen in 2 patients. Six patients were treated with rifampicin and ethambutol or rifampicin and isoniazid for 1½ to 2½ years supplemented with ethionamide and an initial course of kanamycin. One 83-year-old patient received treatment with rifampicin, ethambutol and isoniazid for 6 weeks after which treatment was discontinued because of side effects.

Improvement was noted in 2 patients, in one patient the disease remained stable and in 7 patients the disease deteriorated. Sputum did not convert in all patients. Overall, there was a satisfactory response in 30% of cases. The mean duration of follow-up was 3.5 years in 8 patients (range 1 to 7 years). Two patients defaulted after chemotherapy. Five patients had side effects to drugs but treatment was interrupted in only 3 patients.

M chelonaei

There was only one case of lung disease due to M chelonaei subspecies abscessus. The patient had underlying bronchiectasis. She failed to respond to a course of isoniazid, ethambutol, rifampicin, ethionamide plus kanamycin given initially.

DISCUSSION

Nontuberculous mycobacteria are also known as environmental mycobacteria because they are found in water (natural as well as piped water), soil, house dust and food such as raw milk, eggs and meat. They are normally saprophytes but can become pathogenic when there is a breakdown of the host defence mechanism. NTM can cause localized disease of the skin, lymph nodes, lung or become widely disseminated especially in immunocompromised patients. Being ubiquitous, they can contaminate sputum or other clinical specimens. Therefore, an isolated positive sputum culture is not clinically significant. As the organism can colonize the respiratory tract

without causing disease, care must be taken in the interpretation of the bacteriological results. Lung disease due to NTM should be diagnosed only when the same species is isolated repeatedly over a prolonged period in the presence of a recent pulmonary lesion which did not respond to antibiotic therapy.

Nontuberculous mycobacterial disease of the lung appears to be uncommon in Singapore as there were only 15 cases diagnosed between 1976 to 1988 inclusive, compared with 20,300 new cases of pulmonary tuberculosis seen at the Tan Tock Seng Hospital and the Department of Tuberculosis Control over the same period. The notification rate of pulmonary tuberculosis is still relatively high in Singapore compared with the developed countries although it had declined from 118 per 100,000 population in 1976 to 58 per 100,000 in 1988⁽⁴⁾. In countries where tuberculosis has become very uncommon, the number and proportion of cases with NTM disease have increased in relation to pulmonary tuberculosis.

In the present study, *M avium intracellulare* and *M kansasii* were the 2 main organisms causing lung disease. In one patient, *M chelonae* subspecies *abscessus*, which is an uncommon cause of lung infection, was isolated⁽⁵⁾. In common with other reports^(6,7) the patients in this series belong to the older age group and there is a male preponderance. A local risk factor such as a pre-existing lung disease is usually present. In this study, the patients were found to have healed tuberculous lesions, bronchiectasis, and COPD. There were no cases of pneumoconiosis or lung cancer. As most of the patients were seen many years ago, examination for HIV was not done. In only one patient with infection due to *M scrofulaceum*, examination for HIV was negative.

The response to chemotherapy is unsatisfactory in both groups of patients (*M kansasii* and MAIS complex). The small number of patients made it very difficult to assess whether the extent of disease and the presence of underlying disease could have affected the treatment outcome. A high percentage of patients developed drug reaction in the MAIS complex group. Of the eight patients who received second line in addition to primary drugs, 5 developed adverse reactions and in 3 patients, chemotherapy was interrupted. The possibility of poor compliance in the patients with drug reactions could not be excluded.

The recommended treatment for NTM disease of the lung is based on chemotherapy with a combination of standard drugs such as ethambutol, rifampicin, isoniazid and streptomycin^(8,9). Patients with *M kansasii* infection of the lung should be treated for 15 months using a regimen of rifampicin, ethambutol and isoniazid⁽⁷⁾ although 12 months of chemotherapy has also been reported to be effective⁽¹⁰⁾. The organisms belonging to the MAIS complex are usually resistant to all primary drugs. However, it is generally accepted that the results of in vitro susceptibility tests for NTM may not be applicable to the nontuberculous mycobacteria as these organisms are compared with a strain of drug sensitive *M tuberculosis*. In addition, it is postulated that while the organisms may be resistant to a single drug,

they may be susceptible to 2 or more drugs given in combination because of synergistic action⁽⁹⁾. Hence patients with infection caused by MAIS complex are treated with a combination of isoniazid, rifampicin and ethambutol supplemented with streptomycin during the first 3 months or longer. The total duration of chemotherapy is 18 to 24 months^(8,11). When a combination of 5 or 6 drugs is given, there is a higher incidence of drug toxicity⁽¹²⁾. This regimen is usually recommended for patients with extensive or progressive disease who have failed to respond to the standard drugs. In view of the higher incidence of drug toxicity with a 5-drug combination, treatment with first line drugs for a longer duration of 3 years or more has been advocated⁽¹³⁾. *M chelonae* is resistant to all antituberculosis drugs. Recommended treatment includes using a combination of amikacin and cefoxitin or either erythromycin or imipenem depending on the in vitro susceptibility tests.

CONCLUSION

Lung disease caused by nontuberculous mycobacteria is uncommon in Singapore. The 2 main aetiologic agents are *M avium intracellulare* and *M kansasii*. Patients affected are middle aged or elderly, with a higher proportion of males. About 70% of patients have a pre-existing lung disease and there was a past history of pulmonary tuberculosis in 67% of cases.

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