Pulmonary disease due to *Mycobacterium malmoense* in British Columbia

Mohamed S Al-Moamary MRCP, William Black MB FRCP,
Kevin Elwood MB BCH MRCP (UK) FRCP

*Division of Tuberculosis Control and the Provincial Laboratory, British Columbia Centre
for Disease Control, Vancouver, British Columbia*

MS Al-Moamary, W Black, K Elwood. Pulmonary disease due to *Mycobacterium malmoense* in British Columbia. *Can Respir J* 1998;5(2):135-138.

Mycobacterium malmoense was first described in northern Europe and the United Kingdom in 1977. Since then, reports have appeared with increasing frequency. Cases have, however, rarely been reported from the United States, and, until now, none have been reported in Canada. This may reflect either true low prevalence of the disease or under-diagnosis by laboratories due to slow growth of the organism. This report describes a case of pulmonary disease caused by *M malmoense* in a 44-year-old man from British Columbia who was successfully treated with an 18-month course of conventional antituberculous drugs combined with a macrolide. This is the first report of this disease in British Columbia and, to our knowledge, in Canada.

Key Words: Atypical mycobacteria, *Mycobacterium malmoense*, Pulmonary disease

Maladie pulmonaire causée par *Mycobacterium malmoense* en Colombie-Britannique

RÉSUMÉ : *Mycobacterium malmoense* a été décrit pour la première fois en Europe du Nord et au Royaume-Uni en 1977. Depuis, les cas rapportés sont de plus en plus fréquents. Toutefois, les cas rapportés des États-Unis sont rares et, jusqu'à maintenant, aucun cas n'avait été rapporté au Canada. Ceci peut refléter soit la vraie prévalence de la maladie ou le fait qu'elle est sous-diagnostiquée dans les laboratoires à cause de la lenteur de la croissance de l'organisme en question. Le présent article décrit un cas de maladie pulmonaire causée par *M. malmoense* chez un homme de 44 ans de la Colombie-Britannique qui a été traité avec succès pendant 18 mois avec des médicaments antituberculeux habituels combinés à un macrolide. C'est la première fois que l'on rapporte un cas de cette maladie en Colombie-Britannique et, à notre connaissance, au Canada.

M*ycobacterium malmoense* is a slow growing, non-pigmented atypical mycobacterium. It was first described in 1977 by Schroder and Juhlin (1) who reported four cases of pulmonary disease from Malmo, Sweden, hence its name. Since then, *M malmoense* has been reported with increasing frequency in northern Europe and the United Kingdom, and is the second most common cause of atypical mycobacterial infection in Sweden (1,2). In the United

States, fewer than a dozen cases have been reported (3). This paper describes the first reported case of pulmonary disease due to *M malmoense* in Canada.

CASE PRESENTATION

In September 1993, a 44-year-old man presented with dyspnea and chronic productive cough of several weeks duration associated with poor appetite and weight loss of

Correspondence and reprints: Dr Kevin Elwood, British Columbia Centre for Disease Control, Division of Tuberculosis Control, 655 West 12th Avenue, Vancouver, British Columbia V5Z 1L8. Telephone 604-660-6102, fax 604-660-1950, e-mail kevin.elwood@bccdc.hnet.bc.ca

Figure 1) Initial chest roentgenogram showing right upper lobe cavitation, parenchymal densities and bilateral upper lobe bullae

13.6 kg over 18 months. He denied any history of hemoptysis, fever or night sweats. He had smoked two packs of cigarettes per a day for several years and gave a history of mild asthma controlled with occasional salbutamol inhalations. He had previously abused alcohol but had abstained for eight years before presentation. He was born in northern England, emigrated to Canada at the age of 14 and lived in the interior of British Columbia. Several years earlier he had worked as a ship's radio operator. During that period, he had six months' exposure to a sailor with chronic cough who was originally from Malmo, Sweden.

Initial chest x-ray showed focal right upper lobe densities, right upper lobe cavitation and probable bilateral apical bullae (Figure 1). Human immunodeficiency virus (HIV) serology was negative. Multiple sputum smears were positive for acid-fast bacilli. A presumptive diagnosis of active pulmonary tuberculosis was made. Standard antituberculous treatment was initiated with isoniazid 300 mg, rifampin 600 mg and pyrazinamide 1500 mg daily. Tuberculin skin test was negative to 5 U of Tuberculin Purified Protein Derivative (Connaught Laboratories Limited).

Sputum samples were processed in the mycobacteriology laboratory of the British Columbia Centre for Disease Control, Vancouver, British Columbia by using standard methods (4). A nonphotochromogenic, nontuberculous mycobacterium (NTM) species was isolated on several occasions after incubation periods ranging from 21 to 28 days. Isoniazid and pyrazinamide were discontinued, and clarithromycin plus ciprofloxacin were added. Subsequent tests at the Laboratory Centre for Disease Control, Ottawa, Ontario con-

Figure 2) Follow-up chest roentgenogram on completion of therapy showing postsurgical stapling and radiological improvement

firmed the isolates to be *M malmoense*. It grew at 25°C and 37°C but not at 42°C, hydrolyzed Tween (DIFCO Laboratories, Michigan) and gave a characteristic pattern when tested by high performance liquid chromatography.

Drug susceptibility testing revealed the organism to be sensitive to rifampin, ethambutol, streptomycin and clarithromycin but resistant to isoniazid and ciprofloxacin. Treatment was altered to ethambutol 800 mg, clarithromycin 500 mg twice daily and rifampin 600 mg.

Eleven months after initiation of treatment, the patient developed a left-sided pneumothorax. Due to a persistent air leak, apical decortication and excision of bullae by video-assisted thoracoscopy were carried out. An elective bullectomy and apical pleurectomy were also done on the right side several months later. Despite clear radiological improvement before surgery, necrotizing granulomas were identified in a lung biopsy specimen taken at operation, which stained positive for acid-fast bacilli. Similar findings were described in the adjoining right pleural biopsy. The lung tissue was unfortunately not sent for culture.

The patient responded symptomatically with improvement in cough, dyspnea and weight loss. He also responded radiologically (Figure 2). There was no evidence of recurrence at two years' follow-up, and all cultures became negative. The patient was subsequently lost to follow-up.

DISCUSSION

The case reported here fulfils the American Thoracic Society criteria for the diagnosis of pulmonary disease caused by NTM (5). Our patient had focal radiological changes,

acid-fast bacilli seen on multiple sputum samples and cultures that grew *M malmoense* in the absence of other pathogens. The opportunity offered at surgery of obtaining lung tissue with subsequent demonstration of acid-fast organisms in necrotizing granulomas confirmed the diagnosis. This case is, to our knowledge, the first reported case in Canada. The relative rarity of *M malmoense* infection in North America compared with Europe has been commented upon by others (2,6). Although the organism may take eight to 12 weeks to grow, most cultures are positive at eight weeks. The epidemiological differences noted above are more likely to be due to differences in the environmental prevalence of the organism than to differences in laboratory practice. In our case, the diagnosis was facilitated by growth occurring in less than 28 days. However, because 70% to 80% of isolates are considered significant (2,7), and because it is the practice of the Provincial Laboratory to pursue growth by prolonged incubation if necessary, cases that failed to grow within the standard incubation period were unlikely to have been missed in the past.

Antimicrobial susceptibility patterns of *M malmoense* are variable and, as with other NTMs, show poor correlation between in vitro results and clinical response (7). The organism is usually resistant to isoniazid and pyrazinamide, and sensitive to rifampin and streptomycin. The omission of ethambutol from the standard antimycobacterial regimen has been associated with an unfavourable course, and higher relapse rates have been reported with regimens of less than 18 months (7,8). Other drug choices, based on in vitro sensitivity tests, including second-line drugs, were not as effective (7).

Pronounced in vitro synergism has been demonstrated for the combination of ethambutol with ciprofloxacin, amikacin and rifampin (8). A minority of cases require partial or total lung resection because of poor clinical response or drug resistance (7,8). Our patient completed an 18-month course of ethambutol, rifampin and clarithromycin with satisfactory clinical and radiological response, which is consistent with the current experience in the literature (7,8).

Pneumothoraces have been considered a possible predisposing factor for pulmonary disease due to *M malmoense* (9), but in this case the pneumothorax probably resulted from the underlying bullous disease. The patient grew up in northern England, an area with a high prevalence of disease due to *M malmoense*, and he described contact with a sailor from Malmo, Sweden. The clinical significance of this, although a noteworthy coincidence, is questionable because person to person transmission of *M malmoense* is not thought to occur (10). The source of the infection is assumed to be the environment, with the bacteria entering human hosts via contaminated water and soil (11,12), although a water source was considered unlikely in a large series of cases from Scotland (2). Indeed, the organism has only been infrequently recovered from the environment, which may reflect difficulty in culturing the organism (13). It has also been isolated from the stools of healthy Europeans, raising the possibility that it may be commensal (14).

Henriques and colleagues (10) retrospectively studied

the records of 221 patients with various infections caused by *M malmoense* from 1968 to 1989. *M malmoense* was isolated from the respiratory tract of 171 patients (77%) and the lymph nodes of 36 patients (16%). Most of the former individuals were adults with a mean age of 62 years, and the latter were children. In this respect the organism resembles *Mycobacterium avium-intracellulare* in that it tends to affect 'old lungs and young glands'. The majority of pulmonary disease due to *M malmoense* occurs in patients with pre-existing lung diseases such as chronic obstructive pulmonary disease, tuberculosis, carcinoma of the lung and pneumoconiosis, and in combination with aspergillus lung disease (15). In a cluster of cases in Scotland, 95 of 1005 mycobacterial isolates were due to *M malmoense*, and the majority (76%) were considered clinically significant. These cases were not attributed to the high local prevalence of HIV, although it has occurred in this setting (2,16).

Evans and colleagues (17) reported that the roentgenographic findings in 16 patients with proven pulmonary infections due to *M malmoense* were different from those due to *Mycobacterium tuberculosis* (17). Pulmonary disease due to *M malmoense* was more likely to have cavities larger than 6 cm in diameter, air-fluid levels within the cavities, loss of lung volume and coexistent pneumoconiosis. However, these differences are unlikely to be sufficient to allow a specific diagnosis on the basis of roentgenographic changes alone.

Although our patient responded to a regimen of conventional antituberculous drugs and a macrolide, the optimal regimen for this disease is not known. Reasonable response rates have been observed with isoniazid, rifampin and ethambutol, irrespective of sensitivities (7). Because conventional antituberculous medication may not always be effective, the potential efficacy of newer alternative drugs, such as quinolones, macrolides and rifabutin, needs to be determined. Single drug susceptibility testing may not be sufficient to aid therapeutic decisions because synergism has been demonstrated for combinations of ethambutol, ciprofloxacin, rifampin and amikacin (8). We cannot comment on the role of clarithromycin in the treatment of our patient because he may have responded to conventional antituberculous therapy. Clearly, the inclusion of these newer agents will have considerable cost implications underlying the need for trials from high prevalence countries to guide decisions on length of therapy and the optimal, most cost effective regimens.

REFERENCES

- Schroder K, Juhlin I. *Mycobacterium malmoense* sp. Nov J Syst Bacteriol 1977;27:241-6.
- Bollert F, Watt B, Greening A, Crompton G. Non-tuberculous infection in Scotland: a cluster in Lothian? Thorax 1995;50:188-90.
- Alberts W, Chandler K, Solomon D, Goldman A. Pulmonary disease caused by *Mycobacterium malmoense*. Am Rev Respir Dis 1987;135:1375-8.
- Murray PR, ed. Manual of Clinical Microbiology. Washington: American Society of Microbiology, 1995.
- Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am Rev Respir Dis 1990;142:940-53.
- Good R, Snider D Jr. Isolation of nontuberculous mycobacteria in the United States. J Infect Dis 1982;146:829-33.
- Banks J, Jenkins P, Smith A. Pulmonary infection with *Mycobacterium*

- malmoense*: a review of treatment and response. Tuberculosis 1985;66:197-203.
 8. Hoffner S, Hjelm U, Kallenius G. Susceptibility of *Mycobacterium malmoense* to antibacterial drugs and drug combinations. Antimicrob Agents Chemother 1993;37:1285-8.
 9. France A, Mcleod D, Calder M, Seaton A. *Mycobacterium malmoense* infections in Scotland: an increasing problem. Thorax 1987;42:593-5
 10. Henriques B, Hoffner S, Petrini B, Juhlin I, Wahlen P, Kallenius G. Infection with *Mycobacterium malmoense* in Sweden: Report of 221 cases. Clin Infect Dis 1994;18:596-600.
 11. Hoffner S. Pulmonary infections caused by less frequently encountered slow-growing environmental Mycobacteria. Eur J Clin Microbiol Infect Dis 1994;13:937-41.
 12. Saito H, Tomioka H, Sato K, Tasaka H, Dekio S. *Mycobacterium malmoense* isolated from soil. Microbiol Immunol 1994;38:313-5.
 13. Hoffner SE, Henriques B, Petrini B, Kallenius G. *Mycobacterium malmoense*: an easily missed pathogen. J Clin Microbiol 1991;29:2673-4.
 14. Portaels F, Larsson L, Smeets P. Isolation of mycobacteria from healthy persons' stools. Int J Lepr 1988;56:468-71.
 15. Bollert FG, Sime PJ, MacNee W, Crompton GK. Pulmonary *Mycobacterium malmoense* and aspergillus infection: a fatal combination. Thorax 1994;49:521-2.
 16. Falkinham JO. Epidemiology of infection by nontuberculous mycobacteria. Clin Micro Rev 1996;9:177-215.
 17. Evans A, Crisp A, Colville A, Evans S, Johnston I. Pulmonary infections caused by *Mycobacterium malmoense* and *Mycobacterium tuberculosis*: comparison of radiographical features. AJR Am J Roentgenol 1993;161:733-7.
-
-