Pulmonary Cavity From Mycobacterium malmoense in an HIV-Infected Patient: Complicated by Bronchopleural Fistula

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We present a case of M. malmoense and HIV co-infection complicated by aspergilloma leading to bronchopleural fistula with intractable pneumothorax and pleural aspergillosis, ultimately requiring surgical intervention. Treatment guidelines for M. malmoense are reviewed, literature regarding M. malmoense and HIV co-infection is reviewed, and the epidemiology of M. malmoense in North America is discussed.

Keywords. bronchopleural fistula; HIV; Mycobacterium malmoense.

Mycobacterium malmoense is an atypical mycobacterial strain first discovered in Sweden in 1954. The incidence of M. malmoense infection has been rising since the 1980s; yet, outside of northern Europe, infection is extremely rare. The first case of pulmonary M. malmoense infection in North America was reported in 1984 [1]. Most patients who develop M. malmoense infections have structural lung disease that compromises immunity, such as chronic obstructive pulmonary disease (COPD). Infection is associated with contaminated water or soil; no interpersonal communication of infection has been reported [2]. Disseminated disease is rare and has only been observed in severely immunocompromised patients, such as those with AIDS. Due to the progressive nature of the infection, timely diagnosis and appropriate management of M. malmoense infections are essential. However, because the clinical presentation is very similar to that of tuberculosis, patients can be easily misdiagnosed and improperly treated.

CASE REPORT

The patient is a 63-year-old African American male with medical history significant for long-standing HIV infection (most recently treated with raltegravir, emtricitabine, and tenofovir; CD4 >600 and viral load undetectable), hepatitis C, and cirrhosis. He presented with a 15–20-lb weight loss, nonproductive cough, and right-sided chest pain; he denied fever, chills, or night sweats. The remainder of review of systems was unremarkable. Chest imaging, including computed tomography (CT), demonstrated a new 4.8-cm right upper lobe cavitary lesion with multiple nodular cavitary foci as well as left-sided pulmonary nodules (Figure 1). Samples from bronchoscopy with bronchoalveolar lavage (BAL) and postbronchoscopy sputum were all positive on acid fast bacilli (AFB) stain. Nucleic acid amplification testing (GeneXpert) on BAL and sputum samples was negative for Mycobacterium tuberculosis (MTB). Fungal cultures and serum galactomannan were negative. Given the high negative predictive value of polymerase chain reaction for MTB infection on an AFB-positive sputum sample, MTB infection was thought to be unlikely. The patient was treated for nontuberculosis mycobacterium (NTM). Due to concerns for drug interactions with his antiretroviral medication, a regimen of rifabutin, azithromycin, and ethambutol was selected after discussions with several consulting services. This regimen was initially complicated by gastric intolerance; however, this was abrogated by stepwise addition of these medications.

Samples were sent to Charles River Laboratories (Newark, DE) for culture and microbial identification via DNA sequencing. All sputum and BAL samples were identified as Mycobacteria malmoense. Based on this, the rifabutin was changed to rifampin, and the other medications were continued (rifampin 600 mg, ethambutol 800 mg, and azithromycin 500 mg daily). Hepatitis C treatment was deferred due to concern for hepatotoxicity and side effects. After 15 months of therapy, sputum cultures were continually negative for M. malmoense; however, the cavity persisted on chest imaging.

Twenty-four months after initial presentation, the patient was admitted with a 4-day history of progressive dyspnea and nonproductive cough. Chest CT then demonstrated a right-sided hydropneumothorax. Placement of a chest tube yielded 400 cc of purulent fluid. After 2 weeks, the air leak persisted; repeat chest CT demonstrated a tract fistula between the cavity lesion and pleura. Pleural fluid from his chest tube grew Aspergillus fumigatus, as did bronchial washings obtained from repeat bronchoscopy. Antifungal coverage with amphotericin was begun initially because of concern for pleural aspergillosis and potential interaction with the antitubercular agents.
However, as all mycobacterial cultures from this admission and during the previous nine months were negative, antimycobacterial agents were discontinued and antifungal therapy was changed to voriconazole.

The bronchopleural fistula ultimately failed to close with conservative measures. He underwent a right upper lobectomy and right chest reconstruction with latissimus and serrated anterior muscle flaps. He recovered slowly from these interventions and required long-term voriconazole treatment.

DISCUSSION

This case describes a rare mycobacterial infection (*M. Malmoense*) and subsequent cavitary lesion in an immunocompromised host. The infection was clinically significant per American Thoracic Society guidelines, based on imaging and positive culture obtained via bronchoscopy [3]. He responded well to therapy, only to develop a secondary fungal infection, which spread from his cavitary lesion to his pleura via a fistula that was responsible for a chronic pneumothorax. Despite several attempts to mitigate his condition with endobronchial valves and percutaneous plugging, definitive treatment ultimately required lobectomy and chest wall reconstruction.

In this case, the patient had several concomitant infections that required simultaneous treatment and careful adjustment of treatment regimens. On initial presentation, we considered standard HRZE therapy to treat for active tuberculosis; however, we instead chose rifabutin, azithromycin, and ethambutol as a second-line therapy to avoid drug interactions with his antiviral medications. Once cultures revealed *M. malmoense*, we switched from rifabutin to rifampin, per British Thoracic Society guidelines [4]. The patient had been on his current HIV therapy (raltegravir, emtricitabine, and tenofovir) for years with good viral suppression (CD4 >600 and an undetectable viral load). Because rifampin increases the hepatic metabolism of raltegravir, we increased the raltegravir from 400 mg to 800 mg twice daily; this was well tolerated by the patient and maintained viral suppression throughout treatment. Another important consideration in this case was the chronic hepatitis C infection; again, with the input of several consulting services, we decided to defer treatment of the hepatitis C until antimycobacterial therapy was completed due to concern for hepatotoxicity and other side effects.

Treatment of *M. malmoense* consists of a rifamycin and ethambutol, with the option of isoniazid [3]. Clarithromycin and ciprofloxacin have been studied as adjunctive therapies and have thus far demonstrated no benefit and potential extra side effects [5]. An important caveat to current guidelines is that they are explicitly for HIV-negative patients; no studies have been performed in HIV-positive individuals.

Antibiotic resistance is an important concern given the prolonged course of treatment and slow progression of *M. malmoense* infection. Drug susceptibility testing (DST)—remains an area of ongoing research in *M. malmoense* infection, with the potential to help guide appropriate antibiotic selection early in treatment. Within the DST literature, a distinction is made between rapid-growing organisms (≤7 days for culture positivity) and slow-growing organisms (>7 days for culture positivity). Time to culture positivity for *M. malmoense* in liquid medium with a standard protocol optimized to detect atypical mycobacterial isolates is ~15 days [6]. There is a clear role for DST in *M. tuberculosis*; however, DST in NTM remains an area of active research [3–5]. Current guidelines recommend DST for selected rapid-growing species, including *M. abscessus, M. chelonae*, and *M. fortuitum* [3]. However, in many NTM species, especially slow-growing NTM (including *M. malmoense*), a significant divergence between phenotype in vitro and in vivo has been appreciated [3, 7]. A recent meta-analysis showed
a poor treatment response rate, at 54%, with a high all-cause mortality rate (34%–54%) in patients treated for *M. Malmoense* [8]. The difficulty in determining susceptibility in NTM stems from the lack of a universally accepted laboratory protocol that is optimized for slow-growing organisms. For this reason, a recent study of *M. malmoense* did not include DST in its study design. In our case, DST was not performed but would have been considered had the patient not improved clinically. Our patient received rifampin, ethambutol, and azithromycin for a total of 24 months (negative sputum cultures for >9 months); in this individual, antimycobacterial therapy was successful, as there was no evidence of mycobacterial species on subsequent sputum samples or from excised lung tissue.

In this case, the patient had long-standing HIV infection that was well controlled on antiretroviral medications. Little is known about what role, if any, HIV infection plays in the pathogenesis of *M. malmoense* infection. Despite the prevalence of *M. malmoense* in northern Europe, few cases of HIV and *M. malmoense* co-infections have been reported; several case reports published in the 1990s described patients with fulminant HIV infection (CD4 counts <100) and co-infection with *M. malmoense* [9–12]. In each of these cases (6 total), *M. malmoense* was identified on culture, but all had other identified infections. Two of the 6 improved with treatment. Only 1 patient had pulmonary symptoms and met criteria for clinically significant infection. With the advent of antiretroviral medications, there has only been 1 report of an HIV-infected patient with concomitant *M. malmoense* infection (disseminated cutaneous disease) [13]; this patient had a CD4 count of 477 with antiviral therapy and responded well to treatment. Clearly, further study is needed to determine the effect of HIV and *M. malmoense* co-infection on disease pathogenesis.

*M. malmoense* remains a rare infection in the United States, despite its increasing prevalence in northern Europe. Determining the true prevalence of *M. malmoense* infections in the United States has been difficult. In 1979 and 1980, 2 and 12 cases, respectively, were reported in the United States [14]. Another survey demonstrated 11 in 1992, 35 in 1993, and 27 in 1994 [15]. A recent study reviewed 1865 patients identified with nontuberculous mycobacterium identified 1 *M. malmoense* isolate [16]. Since these earlier surveys, the prevalence of pulmonary NTM has exploded, increasing by 135% from 1997 to 2007 [17]. This has been primarily attributed to *M. avium* infection; however, there has been no effort to quantify rates of *M. malmoense* infection. For example, in Canada, *M. malmoense* had not been previously reported, and no isolates were found in 2400 samples positive for NTM over 10 years [18]; however, 3 cases of *M. malmoense* have recently been reported [19, 20]. These findings suggest that *M. malmoense* infection is either increasing and/or it is being identified more frequently. In either case, practitioners should be aware of NTM and its clinical similarity to tuberculosis, especially as appropriate diagnosis is essential for proper treatment.

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