Original Report

Significance of Respiratory Isolates of *Mycobacterium avium* Complex in HIV-Positive and HIV-Negative Patients

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ABSTRACT

Objective: *Mycobacterium avium* complex (MAC) is isolated with increasing frequency from respiratory specimens. This study was an attempt to determine the significance of this in human immunodeficiency virus (HIV)-positive and HIV-negative patients.

Methods: A retrospective cohort study was conducted at Bellevue Hospital, a large municipal hospital in New York City, including all patients with two or more respiratory tract specimens positive for MAC during the period January 1996 to October 1996.

Results: Eighty patients met inclusion criteria. Forty-six were HIV-positive, and 34 were HIV-negative. Age, gender distribution, and race were comparable. Cough was a common complaint in all patients, whereas HIV-positive patients were significantly more likely to have fever (19 vs. 2, $P < 0.0001$). Abnormal chest radiographs were common in both groups ($P > 0.8$), although HIV-positive patients were more likely to have diffuse abnormalities ($P < 0.0001$). Focal radiographic findings were similar for both groups; however, there was a trend toward more lymphadenopathy in the HIV-positive group, though this did not reach statistical significance ($P = 0.17$). Notably, patients in both groups frequently had an established concurrent pulmonary diagnosis or evidence of disseminated MAC infection. Patients who were HIV-positive had *Pneumocystis carinii* pneumonia (n = 10), pneumonia (n = 10), and disseminated MAC disease (n = 12); whereas the concurrent disease in HIV-negative patients predominantly was active tuberculosis (n = 13). According to the recent American Thoracic Society-recommended criteria for the diagnosis of pulmonary disease caused by nontuberculous mycobacteria only 7 of 46 HIV-positive patients and 1 of 34 HIV-negative patients met clinical, bacteriologic, and radiographic criteria for pulmonary disease caused by MAC ($P = 0.052$).

Conclusion: *Mycobacterium avium* complex often is cultured from patients with other lung diseases, and its presence in sputum infrequently signifies true disease, though it is more likely to do so in HIV-positive patients.

Key Words: *human immunodeficiency virus,* Mycobacterium avium *complex,* Mycobacterium tuberculosis, *nontuberculous mycobacteria*

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Nontuberculous mycobacteria (NTM) are ubiquitous organisms in the environment. They often are isolated from water and soil, and frequently have been isolated from respiratory tract specimens from persons with and without overt lung disease.[1-3] More often than not, they have been considered airway colonizers rather than true pathogens, although clinical syndromes associated with several NTM are well known and well characterized.[4]

Organisms belonging to the *Mycobacterium avium* complex (MAC) are the most frequently isolated of the NTM in clinical practice in the United States.[3] Increasingly, MAC has been implicated as a true pathogen in both immunocompetent and immunocompromised individuals. This is reflected in the recently updated guidelines for diagnosis of disease attributable to NTM, published by the American Thoracic Society (ATS).[5] It is possible that the apparently increased frequency of recovery of MAC from respiratory samples is related to improved proficiency in isolating and identifying mycobacteria, increased numbers and survival of immunocompromised patients with acquired immunodeficiency syndrome (AIDS), and prolonged survival of patients with underlying severe pulmonary disease. Despite this, the clinical syndromes associated with the isolation of MAC from respiratory tract specimens remain somewhat poorly defined, as many (particularly in patients without AIDS) were characterized when culture techniques and imaging studies were not as sophisticated as those currently routinely available. In addition, many early reports of pulmonary disease attributable to MAC represented highly selected series in which patients were chosen because of clear-cut pulmonary

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syndromes or clinically worsening lung disease. These studies have provided valuable information in terms of defining pulmonary syndromes caused by MAC (including the so-called Lady Windemere syndrome of lingular or middle lobe infiltrates attributable to MAC in elderly women),[6-8] but they have provided somewhat less information regarding the relative frequency of these syndromes compared with the isolation of MAC in respiratory samples in patients in general.

To more completely determine the significance of recovery of MAC from sputum or bronchoscopic specimens, an investigation of the significance of this finding in patients with and without HIV infection was conducted.

MATERIALS AND METHODS

Reports from the microbiology laboratory at Bellevue Hospital (a large municipal hospital in New York City) were reviewed for respiratory tract isolates positive for MAC during the period from January to October 1996. Mycobacterial cultures are performed using the broth-based MGIT culture system (Becton-Dickinson, Franklin Lakes, NJ) and are speciated with nucleic acid probes (Gen-Probe, San Diego, CA). Patients with two or more sputum cultures or any one bronchoscopy specimen positive for MAC were identified to increase the likelihood of finding patients with true disease as defined in the recently revised ATS guideline.[5]

Having identified patients with deep or multiple respiratory tract specimens positive for MAC, medical records of the patients were reviewed and relevant demographic and clinical data were abstracted. Results of radiographic studies performed at the time of the initial positive MAC culture were reviewed.

Patients were classified as having disease definitely, possibly, or unlikely attributable to infection with MAC organisms, according to the revised ATS criteria for the diagnosis of pulmonary disease attributable to nontuberculous mycobacteria.[5] These criteria include clinical symptoms (cough, fever, fatigue, weight loss, hemoptysis, or dyspnea not accounted for by other pulmonary disease), radiographic findings (cavitation, nodules, or progressive infiltrates on chest radiograph or multiple small nodules or multifocal bronchiectasis on chest computed tomography [CT]), and bacteriologic results (two or more positive sputum cultures, one positive bronchoalveolar lavage (BAL) culture, or one positive culture from a tissue biopsy specimen). Definite disease, as defined by the ATS guidelines, had evidence from all three components. Patients with definite pulmonary MAC were compared to patients in the study who did not fulfill criteria for this diagnosis.

Statistical comparisons of independence were done by chi-square analysis.

RESULTS

Identification and Characterization of Study Population

From January to October 1996, there were 648 respiratory specimens from 319 patients that yielded growth of MAC organisms. Of these 319 patients, 117 met inclusion criteria for the study (two or more sputum samples or one or more bronchoscopy specimens positive for MAC); of these 117, medical records of 80 patients were available for review. This cohort formed the study population. Although there were several charts not available for complete review, using the hospital's computer database, it was possible to ascertain HIV status and radiographic findings for these patients, and the distribution of findings was not different from that among patients for whom complete records were available. However, since complete information was not available for this group, their data were not included in the overall results.

Of the study population, there were 46 (58%) HIV-positive individuals and 34 (42%) HIV-negative individuals. The demographic characteristics of the patients, stratified by HIV serostatus, are shown in Table 1. There were no statistically significant differences between HIV-positive and HIV-negative patients in the demographic features identified, and the demographic characteristics of HIV-positive patients with MAC were not different from those of patients with HIV seen at the hospital in general.

Bacteriology

The number of respiratory specimens yielding MAC from the study cohort of 80 patients was 277; the median number of respiratory cultures positive for each patient in the study was three. Most of the positive MAC cultures

Table 1. Characteristics of Study Patients

Characteristics	*HIV-Positive*	*HIV-Negative*
Total (n = 80)	46	34
Median age (y) (range)	36 (24–48)	41 (19–45)
Gender		
Female (n = 12)	7	5
Male (n = 68)	39	29
Race/ethnicity*		
Asian	0	7
African-American	26*	14
Hispanic	17	9
Caucasian	2	4
HIV risk		
Heterosexual	11	1
Homosexual	6	0
IVDU	19	3
Unknown	12	30
Tobacco history		
Nonsmoker	6	7
Smoker	29	15
Mean CD4 count (cells/mm^3) (range)	21 (0–300)	

*P < 0.01 vs. HIV-negative. IVDU = intravenous drug user.

were obtained from sputum samples (264 samples total). Ten samples were obtained from cultures of BAL fluid or bronchial washings. Two cultures were obtained from transbronchial biopsy specimens, and one was from a mediastinal lymph node aspiration.

Clinical Features of Patients

Cough, chills, and a variety of nonspecific complaints were fairly common among both HIV-positive and HIV-negative patients in the study (Table 2). However, fever was observed more often among HIV-positive patients.

Among concurrent pulmonary diagnoses at the time MAC was isolated from a respiratory sample, tuberculosis and bacterial pneumonia were common in both groups (Table 3). Patients with AIDS also frequently had disseminated MAC infection or *Pneumocystis carinii* pneumonia (PCP). The overall likelihood of having a concurrent pulmonary diagnosis did not differ between HIV-positive and HIV-negative patients.

Radiographic Findings

Abnormal radiographic findings were common in both HIV-negative and HIV-positive patients (Table 4). Patients with AIDS were more likely to have diffuse infiltrates, probably reflecting the high incidence of *P. carinii* pneumonia in this group. Several patients obviously had more than one abnormality noted on chest radiograph.

Thirty-two of the 80 patients in the cohort had CT scans of the chest, and these results also were reviewed. In general, CT findings were similar to those seen on plain chest radiographs. However, CT scans identified 13 patients with mediastinal adenopathy (10 of whom were HIV-positive), whereas this finding was noted on the plain films of only nine patients.

Diagnostic Classification of Patients

After review of the above data on a case-by-case basis, the patients were classified into two groups: those with definite evidence of MAC pulmonary disease (based on the ATS guidelines) or those not meeting the diagnostic criteria. Table 5 presents these classifications along with the summary characteristics of the patients in the two categories. Of the 80 patients in the study, only eight (10%) could be classified as having definite pulmonary MAC disease. Of these, seven were HIV-positive and only one was HIV-negative. Overall, only 1 of 34 (3%) HIV-negative patients with multiple positive sputums or BAL cultures met ATS criteria for pulmonary MAC. Of patients with AIDS, 7 of 46 (15%) HIV patients met ATS criteria, although three of the seven also had disseminated infection, as evidenced by positive blood cultures for *M. avium* complex, so that only 4 of 46 (8.7%) could be said to have isolated MAC pulmonary disease. The patients with MAC cultured from both blood and sputum not classified as having MAC lung disease had another pulmonary diagnosis that was believed to explain the radiographic abnormalities. These diagnoses were: PCP, bacterial pneumonia, tuberculous adenitis, and herpes pneumonitis. Three had no radiographic findings at the time of the positive sputum cultures. Of the seven HIV-positive patients who met criteria for MAC pulmonary disease, all but one had CD4+ cell counts of less than 40/mm^3 (mean: 33/mm^3; range: 0–130/mm^3).

Interestingly, of the cohort of 80 patients, 16 had sputum smears that were positive for acid-fast bacilli. Of these, only one occurred in a patient ultimately deemed to have true MAC pulmonary disease. Thus, a positive sputum smear was not predictive of MAC pulmonary disease in this cohort.

Patients with definite MAC pulmonary disease had chest radiographs that most often demonstrated mediastinal

Table 2. Symptoms Reported by Patients

Symptoms	*HIV-Positive*	*HIV-Negative*
Fever (n = 21)	19*	2
Cough (n = 14)	9	5
Chills (n = 10)	9	1
Night sweats (n = 8)	7	1
Change in sputum (n = 7)	3	4
Weight loss (n = 6)	5	1
Anorexia (n = 3)	2	1
Hemoptysis (n = 2)	1	1
Dizziness (n = 2)	2	0
Fatigue (n = 1)	1	0
Other (n = 3)	2	1

*P < 0.01 vs. HIV-negative; all others not significant.

Table 3. Concurrent Pulmonary Diagnoses

Diagnosis	*HIV-Positive*	*HIV-Negative*
Asthma exacerbation (n = 3)	2	1
P. carinii pneumonia (n = 10)	10*	0
Pneumonia (n = 13)	10	3
Tuberculosis		
Active (n = 20)	7	13
Inactive (n = 5)	2	3
Sarcoidosis (n = 1)	0	1
Herpes pneumonitis (n = 1)	1	0
Acute bronchitis (n = 6)	4	2
COPD (n = 1)	0	1

*P < 0.05 vs. HIV-negative; all others not significant. COPD = chronic obstructive pulmonary disease.

Table 4. Chest Radiograph Findings

Findings	*HIV-Positive*	*HIV-Negative*
Normal (n = 14)	8	6
Bronchiectasis (n = 2)	1	1
Cavity (n = 3)	1	2
Diffuse infiltrate (n = 20)	18*	2
Focal infiltrate (n = 23)	10	13
Lymphadenopathy (n = 9)	7	2
Nodules (n = 11)	5	6

*P < 0.05 vs. HIV-negative; all others not significant.

Table 5. Characteristics of Patients by Diagnostic Category

	MAC Lung Disease (n = 8) (10%)	*No Definite MAC Lung Disease (n = 72) (90%)*
HIV status		
Negative	1 (12.5)	33 (46.0)
Positive	7 (87.5)	39 (54.0)
Symptoms		
Fever	6 (75.0)	15 (21.0)
Weight loss	2 (25.0)	4 (5.5)
Chills	2 (25.0)	8 (11.1)
Cough	3 (37.5)	11 (15.0)
Night sweats	1 (12.5)	7 (9.7)
Radiographic findings		
Normal	0 (0)	14 (19.4)
Diffuse nodular opacities	5 (62.5)	15 (20.8)
Lymphadenopathy	3 (37.5)	6 (8.3)
Bronchiectasis	0 (0)	2 (2.7)
Focal opacities	1 (12.5)	31 (43.0)
Cavitary lesions	1 (12.5)	2 (2.7)
Other diagnoses		
Pneumonia	0	13 (18.0)
Tuberculosis		
Previous	0	5 (6.9)
Current	0	20 (27.7)
PCP	0	10 (13.8)
Bronchitis		6 (8.3)
Asthma exacerbation		3 (4.1)
COPD		1 (1.4)
Herpes pneumonitis		1 (1.4)
Sarcoid		1 (1.4)
Pulmonary fibrosis		2 (2.7)
Disseminated MAC	3	9 (12.5)

MAC = *Mycobacterium avium*; HIV = human immunodeficiency virus; PCP = *Pneumocystis carinii* pneumonia; COPD = chronic obstructive pulmonary disease.

lymphadenopathy or focal nodular infiltrates, which might mimic pulmonary tuberculosis (Figures 1 and 2). This was in contrast to patients who did not fulfill criteria for pulmonary MAC disease; these patients more often had normal chest radiographs or focal opacities typical of routine bacterial pneumonia. Fever and cough were the most common clinical complaints in patients with definite disease, but these symptoms also were common in patients with airway colonization with MAC and other pulmonary diagnoses. This is not surprising given the nonspecific nature of these complaints.

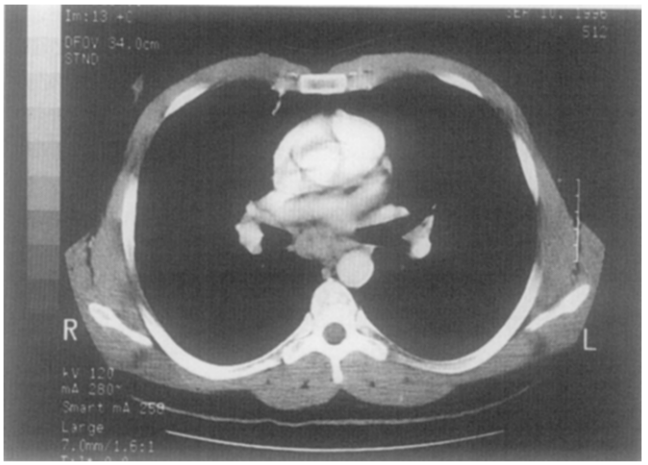

Figure 1. Chest computed tomography scan of an HIV-positive patient (CD4+ cells = 20/mm^3) with five induced sputum samples culture positive for MAC and no evidence of any other cause of pulmonary disease. Note evidence of a right middle lobe infiltrate.

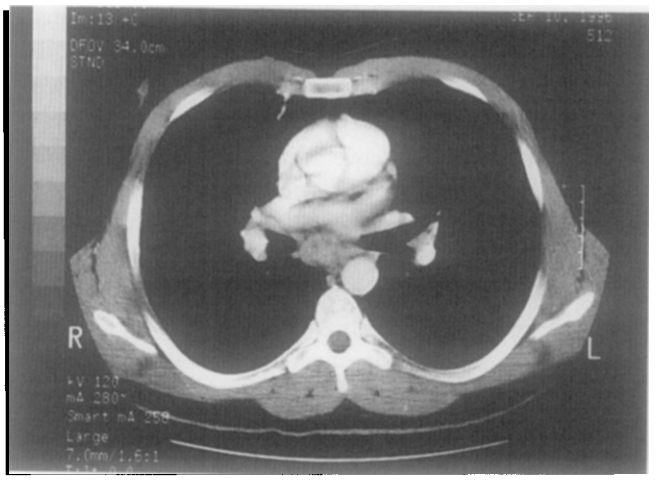

Figure 2. Computed tomography scan of the chest of a patient with mediastinal lymphadenitis caused by *M. avium* complex. Mediastinal view shows enlarged subcarinal lymph node with central necrosis.

DISCUSSION

This study was performed to determine the frequency and significance of multiple respiratory tract specimens that yielded growth of *M. avium* complex organisms. The study produced several interesting findings. In a 10-month period, the hospital laboratory reported a large number of positive cultures from respiratory specimens that grew MAC isolates: 648 from 319 patients. This far exceeds the number of cultures positive for *Mycobacterium tuberculosis* (or any other nontuberculous mycobacteria) identified in the hospital during the same period. In fact, such a high rate of recovery of MAC seems to represent a relatively recent trend, though precise data on the frequency of recovery of MAC are difficult to obtain, because disease attributable to *M. avium* complex is not a reportable condition in the United States.[2,3] The increasingly high rates of recovery of MAC may be related to several factors, including a higher prevalence of this organism in the environment (particularly in water supplies), higher rates of person-to-person transmission (though historically this mode of spread has not been considered to be likely), and possibly the use of more sensitive broth-based culture techniques.

Despite the frequency of recovery of MAC in sputum samples, only a minority of patients met ATS criteria for diagnosis of actual pulmonary disease attributable to MAC. In fact, many of the patients had other pulmonary

illnesses at the time of evaluation for MAC. In this light, the range of symptoms and radiographic findings in the present cohort should not be taken to represent MAC-specific findings, and the reader is cautioned always to consider alternate diagnoses in patients from whom MAC is recovered in a respiratory sample. Interestingly, a diagnosis of MAC was more likely in patients with HIV infection than in immunocompetent hosts. Although MAC bacteremia is a well-described source of morbidity and mortality in patients with AIDS,[9] MAC pulmonary disease, particularly without evidence of disseminated infection, occurs less frequently. In fact, previous studies report that isolated MAC pulmonary disease in patients with AIDS is unusual.[10-12] The authors of a previous study identified 53 patients with HIV infection with multiple sputum cultures positive for MAC in a 24-month period. Of these, five (9.4%) were determined to have pulmonary disease without dissemination, a frequency remarkably close to that found in the present study. Strikingly however, the patients in the present study were identified in less than half the time it took to assemble a cohort in the previous report, perhaps indicating regional differences in the importance of this pathogen.[12]

The significance of pulmonary MAC disease as an isolated cause of morbidity and mortality is not well described, and the pathologic or cause-and-effect relation between pulmonary MAC infection and disseminated disease is not well defined. Whereas respiratory colonization with MAC seems to be a predictor of the development of disseminated disease, the frequency of pulmonary involvement in disseminated disease has been reported to range only between 1.3% and 8.5%.[10-14]

Radiographic findings in MAC pulmonary disease associated with HIV infection differ markedly from the classic findings associated with the so-called Lady Windemere syndrome.[8] In the present study, the most common radiographic findings were mediastinal adenopathy or nodular infiltrates. This also differs from recently described patterns of a "tree in bud" appearance linked to bronchiolitis associated with MAC infection that often occurs with bronchiectasis.[15-20] The nodular disease and mediastinal adenopathy can certainly mimic the manifestations of disease caused by *M. tuberculosis* in patients with HIV infection,[21] and clinicians should consider both mycobacteria when these radiographic findings are accompanied by the report of a positive acid-fast smear from a respiratory sample. In such cases, a nucleic acid amplification assay may be helpful in rapidly distinguishing *M. tuberculosis* from *M. avium* complex organisms.[22]

Most of the HIV-infected patients in whom a diagnosis of pulmonary MAC disease was made had advanced AIDS, as manifested by the low CD4+ T-cell counts. In this regard, these patients are similar to those at risk of developing disseminated MAC, which usually occurs with CD4+ T-cell counts of less than 50/mm^3.[9,23,24]

CONCLUSION

It has been demonstrated that isolation of MAC from respiratory samples is now common, and many of the patients have multiple sputum cultures positive for *M. avium* complex. However, despite this apparent increased frequency of recovery of MAC, most patients from whom this organism is recovered do not meet ATS criteria for definite pulmonary disease. Although isolated pulmonary MAC disease is still uncommon in patients with HIV infection, it should be in the differential diagnosis of radiographic abnormalities and a positive acid-fast smear in this patient population.

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