Early Manifestations of Disseminated Mycobacterium avium Complex Disease: A Prospective Evaluation

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A nested case-control study was conducted in two trials of prophylaxis for Mycobacterium avium complex (MAC) infection to describe the specific signs, symptoms, and laboratory abnormalities of MAC disease in AIDS. Patients had ≤200/mm³ CD4 cells and a prior AIDS-defining illness. Of 571 patients, 102 (17.9%) developed MAC bacteremia during a mean follow-up of 256 days. Among cases of MAC disease, 90 were compared with 180 matched controls. Patients with MAC disease were more likely than controls to have lower weights (66.3 vs. 71.1 kg, \( P = .001 \)) and Karnofsky scores (74.3 vs. 84.4, \( P < .001 \)); a higher proportion had fever (48% vs. 26%, \( P = .003 \)), abdominal pain (23% vs. 13%, \( P = .05 \)), decreased hemoglobin levels (10.9 vs. 12.1 g/dL, \( P < .001 \)), and elevated alkaline phosphatase (203 vs. 138 U/L, \( P = .04 \)) and lactate dehydrogenase (334 vs. 280 U/L, \( P = .02 \)) levels. Characteristics of MAC disease that occurred before bacteremia were weight loss (3 months prior), fever (2 months), and anemia and elevated lactate dehydrogenase (1 month). These data suggest that patients have symptomatic MAC disease for several months prior to the occurrence of bacteremia.

Disseminated Mycobacterium avium complex disease is now the most common bacterial infection among persons with advanced AIDS [1–4], and it has been estimated that up to one-fourth of all AIDS patients will acquire this infection during their lifetimes [5]. Despite the occurrence of Mycobacterium avium complex disease in large numbers of patients, its clinical manifestations and natural history have not been well delineated. While retrospective and descriptive studies have reported the signs and symptoms present in persons with M. avium complex disease [1, 3–10], it is not clear which clinical features are due to M. avium complex and which are related to the underlying human immunodeficiency virus (HIV) infection or other concomitant illnesses. Fever, weight loss, night sweats, fatigue, diarrhea, lymphadenopathy, organomegaly, anemia, and elevated liver function values have all been reported as manifestations of disseminated M. avium complex infection. However, all of these signs and symptoms have also been associated with advanced HIV infection itself, as well as with other opportunistic infections and malignancies.

Prior studies of disseminated M. avium complex infection have been limited by the analysis of data from patients in a single geographic region [6–8], the lack of uniform methods for the detection of M. avium complex or standardized definitions of disseminated disease [9, 10], and the lack of a well-matched cohort of patients with similar severity of HIV disease but without M. avium complex infection [7, 8]. To overcome these limitations, we evaluated the occurrence of disseminated M. avium complex disease in patients who were enrolled in the placebo arms of two identical studies of M. avium complex prophylaxis [11]. These patients were from many geographic sites in the United States and Canada, fulfilled standardized eligibility criteria, were followed using uniform definitions of clinical status, and had blood drawn monthly for mycobacterial culture. We were able to evaluate this group of high-risk patients to determine risk factors for disseminated M. avium complex disease. We then created a matched cohort of patients with a similar level of immunosuppression but without disseminated M. avium complex disease in order to differentiate the signs and symptoms associated with M. avium complex disease from those related to HIV infection. The time of onset of these signs and symptoms in relation to the detection of M. avium complex bacteremia and the impact of disseminated M. avium complex disease on survival were evaluated.
Methods

Patients were enrolled in two identical double-blind, placebo-controlled trials of rifabutin for prophylaxis of disseminated M. avium complex disease, as previously reported [11]. For the purpose of this analysis, only patients who were randomly assigned to receive placebo were included. At enrollment, patients were required to be at least 18 years old, have a CD4 lymphocyte count of ≥200/μL, and have a prior AIDS-defining illness [12]. All patients were required to be receiving antiretroviral therapy and prophylaxis against Pneumocystis carinii at study entry. Patients were excluded if either of 2 baseline blood cultures or a baseline stool culture was positive for M. avium complex. They were prohibited from taking any drugs with antimycobacterial activity during the trials. Patients were evaluated every 4 weeks using standardized forms for recording changes in symptoms or physical findings. At each visit, patients had complete blood cell counts and selected chemistry tests performed. Lymphocyte subset evaluations were done every 3 months.

Patients had a single blood culture for mycobacteria done at each monthly visit. All cultures were processed at one of two central laboratories using broth radiometric techniques [13]. Patients who were found to have M. avium complex bacteremia were classified as having disseminated disease. These patients were reevaluated every 1–3 months thereafter and received antimycobacterial therapy at the discretion of their care provider.

To determine the impact of disseminated M. avium complex disease on various clinical and laboratory parameters, we developed a matched cohort of patients who were participating in the study but who did not develop disseminated M. avium complex (controls) disease. As an initial step in developing this control cohort, a proximate CD4 cell count was determined for patients with disseminated M. avium complex disease (cases) and was defined as the CD4 cell count nearest to, but not later than, the time of disseminated M. avium complex disease. Furthermore, the proximate CD4 cell count had to be taken no longer than 90 days before the time M. avium complex bacteremia was first detected. For each case, the proximate CD4 cell count and the number of days from the proximate CD4 cell count to the detection of M. avium complex bacteremia (“M. avium complex lag”) were calculated. Controls were chosen for each case by finding a patient at the same investigational site who did not develop disseminated M. avium complex disease but who had a CD4 cell count similar (±10) to that of the case. For the control, the time of “equivalent M. avium complex” was the date of the matching CD4 cell count plus the M. avium complex lag. Therefore, the time of equivalent M. avium complex would be the same as the baseline time or time the blood was drawn for culture from patients with M. avium bacteremia. This process was repeated to create 2 controls for each case.

The focus of the statistical analyses was to compare cohorts of patients who did and did not develop M. avium complex bacteremia with respect to characteristics that were possibly associated with M. avium complex bacteremia. Comparisons with respect to quantitative variables were made using the Wilcoxon rank sum test or the t test. Categorical variables were compared using either the χ²- or Fisher’s exact test. Kaplan-Meier methodology with a log-rank test was used to compare the groups with respect to survival.

Results

Patients were recruited from February 1990 through January 1992 at 73 centers in the United States and Canada; 580 were randomized to receive placebo within the 2 studies. These patients were predominantly male (97%) and white (88%), and they had a mean age of 37.7 years (±8.1). The average patient had been diagnosed with AIDS for slightly over 1 year, and the mean and median CD4 cell counts of the population were 56 and 36/mm³, respectively.

Of the 580 patients, 9 had M. avium complex bacteremia at enrollment and were removed from further analysis, leaving 571 who were evaluated monthly. During a mean length of follow-up of 256 days, 102 (17.9%) of the patients developed M. avium complex bacteremia, while 469 (82.1%) did not. Using Kaplan-Meier methodology, the 1-year incidence of M. avium complex bacteremia was 24.6% for the entire cohort [11]. When determined by CD4 cell subsets at baseline, the 1-year incidence of disseminated M. avium complex disease was 33.6% for persons with CD4 cell counts of 0–25/mm³, 22.8% for persons with CD4 cell counts of 26–50/mm³, 35.6% for persons with CD4 cell counts of 51–75/mm³, 2.9% for persons with CD4 cell counts of 76–100/mm³, and 9.4% for persons with CD4 cell counts >100/mm³.

The enrollment characteristics of the patients who did and did not develop disseminated M. avium complex disease are shown in table 1. Patients who developed disseminated M. avium complex bacteremia had substantially lower mean CD4 cell counts at baseline than those who did not (35 vs. 61/mm³). In addition, those who developed M. avium complex bacteremia had statistically significantly lower weights and total white blood cell counts, although the absolute differences were small. In addition, patients who developed M. avium complex disease had small but significantly higher values for serum glutamic-oxaloacetic transaminase (SGOT), bilirubin, and alkaline phosphatase at baseline. There were no differences between persons who acquired M. avium complex disease and those who did not with respect to age, race, or sex, although relatively few women or nonwhite persons were enrolled (data not shown).

In order to differentiate the clinical and laboratory abnormalities of the patients who developed disseminated M. avium complex disease from changes due to underlying HIV infection or other concomitant diseases, a matched cohort was developed as described in Methods. Of the 102 patients with disseminated
M. avium complex disease, 90 had a CD4 cell count taken ≤90 days before the development of M. avium complex disease. Each of the 90 patients with disseminated M. avium complex disease, although these differences were not statistically significant, were apparent as early as 3 months before the onset of M. avium complex disease; abdominal pain, fatigue, a lower Karnofsky score, and an elevated alkaline phosphatase level only became statistically more common in patients with disseminated M. avium complex disease at the time the first blood culture was positive. Night sweats and diarrhea appeared to become associated with M. avium complex disease at the time of bacteremia.

The impact of M. avium complex bacteremia on survival was evaluated using individuals in the disseminated M. avium complex disease and control cohorts (figure 1). The median survival from the time of the initial positive blood culture was 264 days for those with disseminated M. avium complex and 592 days from the time of equivalent M. avium for controls who did not develop disseminated M. avium complex disease (P < .01).

### Discussion

This prospective evaluation provided a unique opportunity to define the early manifestations of M. avium complex disease in individuals with HIV infection. A large number of high-risk patients were followed with monthly mycobacterial blood cultures in multiple geographic sites throughout the United States and Canada. Even more important, the presence of a

| Table 1. Risk factors for disseminated M. avium complex (MAC) bacteremia. |
|-----------------------------|-----------------------------|-----------------------------|
| Enrollment characteristic   | Bacteremia (n = 102)        | No bacteremia (n = 469)     |
| (means)                     |                             |                             |
| Age (years)                 | 38.0                        | 37.6                        | NS             |
| Weight (kg)                 | 68.8                        | 72.1                        | .02            |
| Karnofsky score (%)         | 87.9                        | 89.1                        | NS             |
| CD4 cell count (mm³⁻¹)      | 34.6                        | 60.7                        | <.001          |
| Hemoglobin (g/dL)           | 12.2                        | 12.5                        | .06            |
| WBCs (×10⁹/L)               | 2.7                         | 3.5                         | <.001          |
| Platelets (×10¹⁰/L)         | 200                         | 205                         | NS             |
| SGOT (U/L)                  | 51                          | 46                          | .02            |
| SGPT (U/L)                  | 53                          | 48                          | NS             |
| Bilirubin (mg/dL)           | 0.46                        | 0.28                        | .01            |
| Alkaline phosphatase (U/L)  | 116                         | 108                         | .03            |

NOTE: WBCs, white blood cells; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamate-pyruvate transaminase; NS, not significant.
Table 3. Time course of signs, symptoms, and laboratory abnormalities associated with disseminated M. avium complex (MAC) disease of cases versus controls.

<table>
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<th>At time of MAC infection</th>
<th>1 month prior</th>
<th>2 months prior</th>
<th>3 months prior</th>
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<td>Controls</td>
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<td>Cases</td>
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</table>

NOTE. NS, not significant (P > .10); LDH, lactate dehydrogenase. * Mean values.

A matched cohort of patients with equally severe immunosuppression allowed the impact of disseminated M. avium complex disease to be distinguished from other changes related to advanced HIV infection. Overall, the 1-year incidence of M. avium complex bacteremia was 24.6%, with the highest 1-year rates for individuals with <75 CD4 cells/mm³. This incidence is similar to that reported by others [7, 9, 14].

The only clinically important predictor of the development of M. avium complex bacteria was the CD4 lymphocyte count at baseline. Patients who developed disseminated M. avium complex disease had significantly lower mean CD4 cell counts (35 vs. 61/mm³) than persons who did not (table 1). Several other characteristics were also correlated with the development of M. avium complex disease; however, the small differences in values are not likely to be clinically useful. As a group, persons who became infected with M. avium complex weighed less at baseline (68.8 vs. 72.1 kg). In addition, there were statistically significant elevations in liver function values in persons who developed M. avium complex disease, although the absolute differences in levels of SGOT, bilirubin, and alkaline phosphatase were small. In other series, anemia has been associated with an increased risk of developing M. avium complex bacteremia; however, in our study, the baseline hemoglobin level was only marginally lower in patients who developed M. avium complex bacteremia (12.2 vs. 12.5 g/dL, P = .06).

At the onset of M. avium complex bacteremia, there were fewer signs and symptoms than have been reported by others (table 2). For example, in our group, only 48% of patients had fever, and 24% had night sweats. In a study of 114 patients with disseminated M. avium complex disease reported from Atlanta, 84% had fever and 44% had night sweats at diagnosis [15]. In a compilation of symptoms reported from 10 reported studies, Benson and Ellner [4] found that 87% of persons with disseminated M. avium complex disease had fever and 78% had night sweats [4]. The fact that fewer patients in our cohort had fever and night sweats suggests that patients in our study were diagnosed early in their disease because of the monthly culture of blood for mycobacteria. This is supported by the high frequency of asymptomatic patients. The abnormalities in signs and symptoms shown in table 2 may more accurately reflect the abnormalities that present at the onset of disseminated M. avium complex disease than in series reporting abnormalities in persons who may have had M. avium complex infection for some time prior to diagnosis. Another indication that our patients may have been diagnosed earlier in their disease is that we found the hemoglobin levels to be substantially higher in our patients than in patients in other studies. Our patients had a mean hemoglobin concentration of 10.9 g/dL at the time of initial diagnosis of M. avium complex bacteremia, while others have reported that 85% of patients have a hemoglobin concentration of <8.5 g/dL [4]. Other abnormalities reported as being associated with M. avium complex disease include weight loss and fatigue, reported for >60% of our patients, and abdominal abnormalities (including pain and diarrhea), found in about one-fourth to one-third of our patients.

To differentiate the symptoms associated with M. avium complex disease from symptoms due to other HIV-related abnormalities in patients with equally advanced HIV disease, we matched cases of M. avium complex disease with controls by CD4 cell count. CD4 cell counts were used as the most powerful single predictor of HIV disease progression, as virus load measurements were not available for this cohort. The data in table 2 demonstrate that many of the signs and symptoms associated with M. avium complex disease occur in individuals at the same stage of HIV disease but without M. avium complex infection. Despite the overlap of abnormalities between the 2 groups, this study prospectively confirmed the association between disseminated M. avium complex disease and weight loss, abdominal pain, fever, night sweats, anemia, a low Karnofsky score, and an increase in level of serum alkaline phosphatase. Such associations have previously been reported only from cross-sectional and cohort studies and are assumed to
Figure 1. Probability of survival following diagnosis of M. avium complex (MAC) bacteremia. Patients with MAC infection (dashed line) had shorter survival time (median, 264 days) than controls (solid line; median, 591 days) \( (P < .01) \).

represent manifestations of disseminated M. avium complex disease because they have not been reported to be predictors of disease. Moreover, those studies did not differentiate the symptoms of M. avium complex infection from those of other HIV-associated illnesses and may have combined persons with early- and late-stage M. avium complex disease. The present study, where patient blood was cultured monthly, identified disseminated M. avium complex disease and its associated abnormalities at the onset of dissemination. An elevated serum LDH level was also associated with disseminated M. avium complex disease. Although not previously reported in association with M. avium complex disease, LDH level has been noted to be a harbinger of P. carinii pneumonia in patients with AIDS [16]. The clinical relevance of LDH as a marker for M. avium complex disease remains to be elucidated.

The pathophysiology of M. avium complex disease has not been well studied. It appears that this disease is acquired from the environment through the gastrointestinal tract or, less commonly, the lung [4, 5]. Foci of localized infection in the gastrointestinal or respiratory tract eventually produce bacteremia, which then spreads disease to internal organs, such as the spleen and bone marrow. Bacteremia may be transient at first, but soon becomes persistent, and the number of mycobacteria in the blood increases over time [17–19]. Thus, M. avium complex disease in the absence of bacteremia or associated with bacteremia of low titer is associated with early disease, while multiorgan system involvement and high-titer bacteremia are associated with long-standing disease. Such long-standing disease is associated with greater morbidity, poorer response to antimycobacterial agents, and shorter survival [15].

To examine these time-dependent changes, we compared the clinical and laboratory characteristics of the patients with disseminated M. avium complex disease with those of the control cohort at each month, from 5 months before to the initial diagnosis of M. avium complex bacteremia (table 3). Using this technique, we were able to define the time at which significant differences occurred between the cases and controls for each individual characteristic.

Patients with disseminated M. avium complex disease had a clinical prodrome that was identifiable 3 months before the first positive blood culture. Such patients had a significant loss of weight compared with the controls at this point, which continued to the time of dissemination. One to 2 months prior to the first detection of M. avium complex in the blood, patients
reported more fever, and lower hemoglobin and higher LDH levels could be detected. Many of the other abnormalities associated with disseminated *M. avium* complex disease, including a lower Karnofsky score, abdominal pain, night sweats, diarrhea, and an elevated level of alkaline phosphatase could be detected only at the time of dissemination. Thus, it appears that most of the manifestations of disseminated *M. avium* complex disease appear closely before or at the time of initial *M. avium* complex bacteremia. However, the occurrence of fevers and weight loss 2–3 months before the first positive blood culture suggests that localized disease is present well before bacteremia. This is consistent with animal models of disseminated *M. avium* complex disease [20, 21] and observations at autopsy that *M. avium* complex is found in intestines, liver, and spleen in most patients who die of disseminated *M. avium* complex disease. An autopsy study failed to identify sites of localized disease in some patients, but this failure may have been due to a treatment effect with antimycobacterial agents [17].

Early in the AIDS epidemic, some believed *M. avium* complex to be predominately a marker of severe immunosuppression, rather than a disease with substantial attributable mortality [22]. In part, this belief was founded on the observation that survival time of those with and without *M. avium* complex infection was quite short. We found survival to be approximately half as long in patients with disseminated *M. avium* complex (median, 264 days) as in controls (median, 592 days). Because many of our patients with *M. avium* complex infection were treated with antimycobacterial agents, the true survival of patients with untreated *M. avium* complex infections may in fact be shorter, as treatment of this disease has been shown to lengthen survival [14, 23, 24]. The survival of our patients with *M. avium* complex disease was substantially longer than that of largely untreated patients in a prior observational study [7] (median survival, 134 days); such longer survival is likely due to both earlier detection and antimicrobial therapy, as well as other improvements in HIV-related care.

This large, multisite study demonstrates that disseminated *M. avium* complex disease occurs in a high percentage of patients with severe immunosuppression who do not receive prophylaxis. There were no useful clinical predictors of dissemination other than a low CD4 lymphocyte count. Prior history of an opportunistic infection is also an important predictor [7], but we were unable to examine this factor because all patients in our study had a prior AIDS-defining illness. Many of the signs and symptoms that have been associated with *M. avium* complex infection are present in patients with equally advanced HIV disease without *M. avium* complex infection. Weight loss, anemia, and fever are, however, harbingers of *M. avium* complex bacteremia. Night sweats, diarrhea, abdominal pain, and elevated levels of alkaline phosphatase, which are frequently associated with disseminated *M. avium* complex in the literature, occur coincident with the detection of mycobacteria in the blood.

These results have several important implications for patients with advanced AIDS. First, such patients have a high risk for *M. avium* complex disease and should receive prophylactic antibiotics. Second, because such patients have fever and weight loss from *M. avium* complex infection prior to the occurrence of bacteremia, examination of tissues for evidence of *M. avium* complex may be warranted when blood cultures are negative; biopsy of the gut or liver may be useful, but stool culture is not [25]. Third, when *M. avium* complex infection is suspected, blood should be cultured monthly to detect mycobacteria at the earliest possible time because early detection of *M. avium* complex disease is associated with fewer symptoms and longer survival. Fourth, because fever and weight loss from other causes are common in persons with advanced AIDS, we do not recommend presumptive treatment for *M. avium* complex disease. Improved methods for early diagnosis of *M. avium* complex disease are needed.

Acknowledgments

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References