Mycobacterium arupense in Cancer Patients
An Emerging Infection or a Commensal Organism

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Abstract: Mycobacterium arupense is a slow-growing, nonchromogenic, acid-fast bacillus. Its clinical spectrum, epidemiology, and frequency of colonization versus true infection remain unknown. We evaluated the clinical significance of M arupense and positive cultures from cancer patients.

We retrospectively reviewed records of all cancer patients treated at our institution between 2007 and 2014 to identify those who had positive cultures for M arupense. Mycobacterium arupense was identified by sequencing the 16S rRNA and hsp65 genes. A total of 53 patients had positive cultures, 100% of which were isolated from respiratory specimens. Of these, 7 patients met the American Thoracic Society/Infectious Diseases Society of America criteria for a definitive diagnosis of M arupense infection. No relapses of M arupense were no related deaths in either group. Of the included patients, 13 received therapy for M arupense infection and 40 did not. The outcomes of treated and untreated patients did not differ significantly. No relapses of M arupense were observed. In addition, there were no M arupense-related deaths in either group.

In cancer patients, M arupense appears to be mostly a commensal organism rather than a pathogen. Patients who did or did not receive treatment had similar outcomes. Validation of these findings in a larger prospective trial is warranted.

INTRODUCTION

The number of significant nontuberculous mycobacteria (NTM) isolates is increasing in the United States, alongside increasing number of pulmonary infection caused by this type of mycobacterium. Nontuberculous mycobacteria are a large group of organisms, found universally in water, soil,1,2 and bio-aerosols,3,4 which can cause vast array of human disease, particularly severe lung disease in patients with underlying immunocompromising disorders. However, some NTM, such as Mycobacterium terrae and Mycobacterium gordonae, are broadly considered to be nonpathogenic.5–7

One NTM, Mycobacterium arupense, was first identified from clinical specimens in the United States and as a novel species of the genus Mycobacterium in 2006.8 M arupense is a slow-growing, nonchromogenic, acid-fast bacillus that is genotypically related to the Mycobacterium terrae complex, which also includes Mycobacterium kumamotonense, Mycobacterium hibernae, Mycobacterium longiordum, Mycobacterium engbaekii, Mycobacterium senuense, Mycobacterium heraklionense, Mycobacterium nonchromogenica, and Mycobacterium terrae. A 2006 Japanese study successfully isolated several strains of NTM, 1 of which had 16S rRNA and hsp65 gene sequences that were 99.8% and 100%, respectively, similar to those of M arupense.9

Like other NTM, 1 important issue regarding M arupense is whether a positive culture indicates colonization or a possible true infection. To our knowledge, there have been no studies addressing this issue. Although some NTM have been shown to be nonpathogenic, whether this is also the case for M arupense remains unclear. It is important, therefore, to gain more insight into the clinical significance of this organism, especially in immunocompromised patients. We conducted this retrospective study to determine the clinical significance of positive cultures of M arupense from sputum, bronchoalveolar lavage (BAL), or body fluids. We also examined the frequency of colonization versus true infection in cancer patients with positive culture results. Finally, we looked for differences in response and outcomes between treated and untreated patients.

MATERIALS AND METHODS

We retrospectively identified all patients treated at The University of Texas MD Anderson Cancer Center, Houston, TX, from January 1, 2007, through March 5, 2014, who had at least 1 sputum sample, BAL, or sterile body fluid culture that was positive for M arupense. Clinical information about the patients was collected through electronic medical records. We included data on patient demographics, presence of neutropenia, history of stem cell transplant, treatment with chemotherapy and/or radiation therapy within 30 days before or 3 months after positive M arupense culture, coinfection within 7 days of positive culture, duration of antibiotic treatment, presence and type of underlying malignancy, and presence of underlying...
### TABLE 1. Classification of Suspected *Mycobacterium arupense* Infections According to ATS/IDSA Criteria

| ATS/IDSA Category | Total N = 53 N (%) | Treatment N = 13 N (%) | No Treatment N = 40 N (%) | P Value * |
|-------------------|--------------------|------------------------|---------------------------|-----------|
| Definitive        | 7 (13.2)           | 2 (15.4)               | 5 (12.5)                  | 0.96      |
| Probable          | 14 (26.4)          | 4 (30.8)               | 10 (25.0)                 |           |
| Possible          | 29 (54.7)          | 7 (53.8)               | 22 (55.0)                 |           |
| Colonization      | 3 (5.7)            | 0 (0.0)                | 3 (7.5)                   |           |

ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America.
*P < 0.05 was considered statistically significant.

### TABLE 2. Baseline Characteristics of Patients in the 2 Study Subgroups

| Characteristics                                      | Total N = 53 N (%) | Treatment N = 13 N (%) | No Treatment N = 40 N (%) | P Value * |
|------------------------------------------------------|--------------------|------------------------|---------------------------|-----------|
| Median age (years) (range)                           | 58 (14–79)         | 57 (16–70)             | 59 (14–79)                | 0.35      |
| Sex, male                                            | 28 (52.8)          | 9 (69.2)               | 19 (47.5)                 | 0.17      |
| Type of cancer                                       |                    |                        |                           | 0.64      |
| Hematologic                                          | 22 (41.5)          | 5 (38.5)               | 17 (42.5)                 |           |
| Solid tumor                                          | 25 (47.2)          | 8 (61.5)               | 17 (42.5)                 |           |
| Both                                                 | 4 (7.6)            | 0 (0.0)                | 4 (10.0)                  |           |
| No cancer                                            | 2 (3.8)            | 0 (0.0)                | 2 (5.0)                   |           |
| History of SCT                                       | 9 (17.0)           | 1 (7.7)                | 8 (20.0)                  | 0.42      |
| Type of SCT                                          |                    |                        |                           |           |
| Autologous                                           | 3 (5.7)            | 0 (0.0)                | 3 (7.3)                   |           |
| Allogeneic                                           | 6 (11.3)           | 1 (7.7)                | 5 (12.5)                  |           |
| Chemotherapy within 30 days prior to or 3 months     | 30 (56.6)          | 9 (69.2)               | 21 (52.5)                 | 0.29      |
| after positive culture                               |                    |                        |                           |           |
| Radiotherapy within 30 days prior to or 3 months     | 11 (21.2)          | 5 (38.5)               | 6 (15.4)                  | 0.12      |
| after positive culture                               |                    |                        |                           |           |
| Underlying lung disease                              | 10 (20.0)          | 3 (25.0)               | 7 (18.4)                  | 0.69      |
| Source of *M. arupense* culture                      |                    |                        |                           | 0.50      |
| BAL or BW                                            | 28 (52.8)          | 9 (69.2)               | 19 (47.5)                 |           |
| Sputum                                               | 24 (45.3)          | 4 (30.8)               | 20 (50.0)                 |           |
| One sputum                                           | 22 (41.5)          | 4 (30.8)               | 18 (45.0)                 |           |
| Two sputum                                           | 2 (3.8)            | 0 (0.0)                | 2 (5.0)                   |           |
| Pleural fluid                                        | 1 (1.9)            | 0 (0.0)                | 1 (2.5)                   |           |
| Coinfections within ± 7 days from positive culture   | 26 (49.1)          | 8 (61.5)               | 18 (45.0)                 | 0.30      |
| Duration of antibiotic treatment Median days (range)  | 38 (3–295)         | 38 (3–295)             | NA                        |           |
| Neutropenia                                          | 7 (13.2)           | 2 (15.4)               | 5 (12.5)                  | >0.99     |
| Clinical symptoms                                    | 52 (98.1)          | 13 (100.0)             | 39 (97.5)                 | >0.99     |
| Fever                                                | 28 (52.8)          | 5 (38.5)               | 23 (57.5)                 | 0.23      |
| Cough                                                | 41 (77.4)          | 8 (61.5)               | 33 (82.5)                 | 0.14      |
| Productive cough                                     | 31 (58.5)          | 6 (46.2)               | 25 (62.5)                 | 0.30      |
| Hemoptysis                                           | 8 (15.1)           | 2 (15.4)               | 6 (15.0)                  | >0.99     |
| Weight loss                                          | 14 (26.4)          | 3 (23.1)               | 11 (27.5)                 | >0.99     |
| Chest pain                                           | 13 (24.5)          | 5 (38.5)               | 8 (20.0)                  | 0.27      |
| Fatigue                                              | 25 (47.2)          | 6 (46.2)               | 19 (47.5)                 | 0.93      |
| SOB/dyspnea/tauchynpena                              | 34 (64.2)          | 9 (69.2)               | 25 (62.5)                 | 0.75      |
| Night sweats                                         | 10 (18.9)          | 2 (15.4)               | 8 (20)                    | >0.99     |

BAL = bronchoalveolar lavage, BW = bronchial wash, NA = not applicable, SCT = stem cell transplant, SOB = shortness of breath.
*P < 0.05 was considered statistically significant.
†One patient was lost to follow-up.
‡Three patients were lost to follow-up.
§Two patients were lost to follow-up.
lung disease. In addition, we collected information about the sample source (BAL or bronchial wash, pelvic fluid, sputum, or pleural fluid), quantity of samples, and clinical symptoms (fever, cough, sputum production, hemoptysis, weight loss, chest pain, fatigue, shortness of breath, dyspnea, tachypnea, and night sweats). This study was approved by the institutional review board.

**Diagnosis and Definitions**

Definitive cases of *M. arupense* were identified according to American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria, which require sputum specimens of at least 3 early morning specimens on different days and must be analyzed for acid-fast bacilli. Other disorders, such as tuberculosis, must be excluded. The presence of cavitary in chest radiography or high-resolution computed tomography of the chest mostly, but not exclusively, shows the following characteristics: this wall cavity, more contiguous spread of disease but less bronchogenic, and more involvement of the pleura over the involved area of the lungs. According to ATS/IDSA, each of these criteria is equally important and all must be met to make a definitive diagnosis of NTM infection.

Cases were classified as “probable” when patients met the following criteria: clinical symptoms consistent with the site of the infection (e.g., cough in patient with suspected respiratory infection); atypical radiological findings (including pleural effusion or nonspecific infiltrates); positive culture results from at least 2 separate sputum samples or 1 BAL or other sterile body fluid; and appropriate exclusion of coinfection. We considered cases to be “possible” if patients showed any clinical symptoms or positive radiological findings, positive results from 1 sputum culture, BAL, or other sterile body fluid culture even though a coinfection was present. Colonization was considered when patients displayed no clinical symptoms or no positive radiological findings and had positive culture results from 1 sputum culture, BAL, or other sterile body fluid culture. *M. arupense* had been identified by sequencing the MT-RNR2 (16S rRNA) and hsp65 genes. The recent widespread use of PCR and gene sequencing offers the most accurate identification of rapidly growing mycobacteria species. Frequently analyzed genes include the 16S rRNA gene, hsp65, rpoB, and others; all these genes are highly conserved throughout bacterial evolution, but are variable enough to allow species identification.

We compared the outcomes of 2 evaluable groups totaling 44 patients. Ten patients were lost to follow-up: 2 in the treated group and 8 in the untreated group. Those patients were not included in the outcome analysis. We compared outcomes for 2 subgroups: patients who received treatment for NTM infections and those who did not. We reviewed follow-up data for both groups for 3 months and classified clinical and radiological outcomes as “improvement,” “worsening,” or “no change.” We also tracked microbiological eradication for up to 1 year, relapses for up to 6 months from negative culture, and death within 6 months of NTM diagnosis.

**Statistical Analysis**

Categorical variables were compared using Chi-square or Fisher’s exact tests, as appropriate. Continuous variables were compared using the Wilcoxon rank-sum test. All tests were 2-sided, and *P < 0.05* was considered to be statistically significant. The statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

**RESULTS**

We retrospectively identified 53 patients treated at The University of Texas MD Anderson Cancer Center from January 2007 through March 2014 who had at least 1 sputum sample, BAL, or sterile body fluid culture that was positive for *M. arupense*. Thirteen patients had been treated for *M. arupense* infection and 40 patients had not. Depending on the sensitivity of the isolated organisms to antitubercular drugs, treatment included clarithromycin, rifabutin, and ethambutol. Seven (13.0%) patients met the ATS/IDSA criteria for a definitive diagnosis of NTM disease, of whom 2 had been treated. Fourteen (25.9%) cases were classified as probable, of whom 4 had been treated. Twenty-nine (54.7%) cases were identified as colonization; 7 of these had been treated. Of 3 cases classified as colonization, none had been treated (Table 1).

**TABLE 3. Comparison of Clinical, Microbiological, and Radiographic Outcomes of the Treated and Untreated Groups**

| Evaluable Cases         | Total (N = 43) N (%) | Treatment (N = 11) N (%) | No Treatment (N = 32) N (%) | P Value* |
|-------------------------|----------------------|-------------------------|-----------------------------|----------|
| Symptom follow-up in 3 months | 43 (9.3)             | 11 (0.0)                | 32 (12.5)                   | 0.62     |
| No change               | 4 (9.3)              | 0 (0.0)                 | 4 (12.5)                    |          |
| Improvement             | 27 (62.8)            | 7 (63.6)                | 20 (62.5)                   |          |
| Worsening               | 10 (23.3)            | 3 (27.3)                | 7 (21.9)                    |          |
| Mixed                   | 2 (4.7)              | 1 (9.1)                 | 1 (3.1)                     |          |
| Radiology follow-up in 3 months | 39 (17.9)         | 9 (11.1)                | 30 (20.0)                   | 0.91     |
| No change               | 7 (17.9)             | 1 (11.1)                | 6 (20.0)                    |          |
| Improvement             | 22 (56.4)            | 6 (66.7)                | 16 (53.3)                   |          |
| Worsening               | 9 (23.1)             | 2 (22.2)                | 7 (23.3)                    |          |
| Mixed                   | 1 (2.6)              | 0 (0.0)                 | 1 (3.3)                     |          |
| Microbiology follow-up in 3 months | 26 (96.2)         | 6 (100.0)               | 19 (95.0)                   | >0.99    |
| Microbiology eradication within 1 year | 25 (96.2)         | 6 (100.0)               | 19 (95.0)                   |          |
| Relapse within 6 months after negative culture | 1/24 (4.2)        | 1/5 (20.0)              | 0/19 (0.0)                  | 0.21     |
| Death within 6 months of *M. arupense* diagnosis | 13 (30.2)         | 3 (23.1)                | 11 (34.4)                   | 0.46     |

*P < 0.05 was considered statistically significant.

One patient was lost to follow-up.
Our results indicate that the baseline clinical characteristics of the treated and untreated groups did not differ significantly (Table 2). Patients’ underlying malignancies were divided nearly equally between solid (47.2%) and hematological (41.5%) malignancies, and 17.0% had a history of stem cell transplant. *Marupense* was mostly (100% of cases) recovered from respiratory specimens: 52.8% from BAL or bronchial wash, 45.3% from sputum, and 1.9% from pleural fluid. Symptom burden was similar in the treated and untreated groups, as shown in Table 2.

Clinical symptoms had improved at 3-month follow-up in 7 (63.6%) treated patients and 20 (62.5%) untreated patients ($P = 0.62$) (Table 3). Similarly, radiological findings showed improvement in 6 (66.7%) and 16 (53.3%) of the patients in the treated and untreated groups, respectively ($P = 0.91$). There were no relapses of *Marupense* infection among patients in the untreated group. However, there was 1 (20%) relapse in the treated group reported at 6-month follow-up. There were no *Marupense*-related deaths in either group (Table 3).

### DISCUSSION

Our results suggest that *Marupense* is usually a colonizer, not a true infection, in the respiratory system and that it usually does not require treatment even in patients with cancer. Our data showed no differences in either response or outcomes between the subgroup treated for *Marupense* and the untreated subgroup. We expected that certain baseline characteristics, such as immunocompromised status, type of malignancy, neutropenia, and stem cell transplant, might have an impact on outcomes, but we found no significant differences in outcomes according to these characteristics in either the treated or untreated groups. In addition, the symptom burdens for the 2 groups were comparable.

Our conclusion is further supported by the low proportion of patients whose diagnosis of *Marupense* infection was definitive according to ATS/IDSA criteria—only 13%. The majority of cases (61%) were considered to be possible infections or colonizations. Moreover, even among the small group of definitive
cases, the outcomes were not affected by whether patients received antimicrobial therapy. These results suggest that there is no clear benefit in treating M. arupense, especially when it is recovered from respiratory specimens. Since its isolation in 2006, there have been only 9 reports of recovery of M. arupense from clinical samples all over the world, 75% of which were recovered from patients with osteoarticular symptoms, mostly following an injury or a history of corticosteroid use (Table 4).^{11–13} They include 4 cases of tenosynovitis of the hand, 1 case of osteomyelitis of the wrist, 1 case of pulmonary infection in an immunocompetent patient, 1 case of pneumonia and 1 case of bacteremia in an HIV-positive patient, and 1 case of large joint (knee) acute arthritis. The most recent case, reported by Seidl and Lindeque^{14} in September 2014, is the first known case of large joint infection caused by M. arupense, in a 69-year-old woman with no known immunocompromising concurrent conditions. Only 1 case of pulmonary infection caused by M. arupense in an immunocompetent patient has been reported, although this patient had also been diagnosed with an underlying kidney tumor. In fact, based on ATS/IDSA criteria, that case most likely should have been classified as a probable infection.

In this study, we report the largest number of patients with positive respiratory specimens of M. arupense. Our cases were all recovered from pulmonary specimens. Most of them were categorized as probable (26.4%) or possible (54.7%). Based on our review of the literature and the results of this present study, it is possible that M. arupense mostly causes osteoarticular disease, and when it is recovered from respiratory specimens, it is most likely a colonizer. M. arupense is genotypically related to the M. terrae complex, which is, for the most part, considered to be a nonpathogenic group of organisms.

Our study has 3 major limitations. First, most of our studied cases were categorized as possible infections. Because of the small number of definitive cases in our patient population, our results may be difficult to generalize. We adjusted for this possibility by combining the definitive cases and the probable cases into 1 group (N = 21), but we still found no significant difference between the treated and untreated cases (P = 0.54). Therefore, our results must be confirmed in a larger study. Second, our study is a retrospective study with no control group for comparison. Larger prospective studies are needed to validate our findings and to determine whether M. arupense causes any definitive pulmonary infections that require treatment and how often it causes extrapulmonary disease, such as osteoarticular infection. Third, there is no standard, well-established, effective therapy for M. arupense infection, so we had to rely on the tested sensitivity of the organism to determine the appropriate therapy.

In conclusion, M. arupense recovered from respiratory specimens is most likely a colonizer, not a pathogen, even in immunocompromised patients. Nonetheless, clinical management should be considered on a case-by-case basis. Further larger prospective studies need to be conducted to determine whether M. arupense can cause definitive pulmonary infections that require treatment and how often it causes extrapulmonary disease such as osteoarticular infections.

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